PD-AAL-494-A1 931-0045 931-0045-7

Appendix 6A, Ch 6
Page 4 (TM 3:1)

AGENCY FOR INTERNATIONAL DEVELOPMENT
PROJECT PAPER FACESHEET
TO BE COMPLETED BY ORIGINATING OFFICE

1. TRANSACTION CODE (*"X" appropriate box*)
☐ Original ☒ Change ☐ Add ☐ Delete

PP
DOCUMENT CODE 3

2. COUNTRY/ENTITY: Interregional GTS-KPA 19

3. DOCUMENT REVISION NUMBER: 1

307A

4. PROJECT NUMBER: 931-11-560-045

5. BUREAU: a. Symbol TAB; b. Code 6

6. ESTIMATED FY OF PROJECT COMPLETION: FY 80

7. PROJECT TITLE - SHORT (*stay within brackets*): Development of Vitamin Delivery Systems

8. ESTIMATED FY OF AUTHORIZATION/OBLIGATION: a. INITIAL mo. 7 yr. 4; b. FINAL FY 79

9. ESTIMATED TOTAL COST ($000 or equivalent, $1 =)

a. FUNDING SOURCE	Operational YEAR FY 76 b. FX	c. L/C	d. Total	ALL YEARS e. FX	f. L/C	g. Total
AID APPROPRIATED TOTAL	645		645	4089		4089
(Grant)	(645)	( )	(645)	(4089)	( )	(4089
(Loan)	( )	( )	( )	( )	( )	(
Other U.S. 1.						
Other U.S. 2.						
HOST GOVERNMENT						
OTHER DONOR(S)						
TOTALS	645		645	4089		4089

10. ESTIMATED COSTS/AID APPROPRIATED FUNDS ($000)

a. Appropriation (Alpha Code)	b. Primary Purpose Code	c. Primary Tech. Code	Thru FY 75 d. Grant	e. Loan	FY 76 f. Grant	g. Loan	FY 77 h. Grant	i. Loan	ALL YEARS j. Grant	k. Loan
FN	320	320	106		645		1300		4089	
TOTALS			106		645		1300		4089	
11. ESTIMATED EXPENDITURES			41		645		1300			

12. PROJECT PURPOSE(S) (*stay within brackets*) ☐ Check if different from PID/PRP

To assist LDCs in implementing programs for alleviating Vitamin A deficiency.

13. WERE CHANGES MADE IN BLOCKS 12, 13, 14, or 15 OF THE PID FACESHEET? IF YES, ATTACH CHANGED PID FACESHEET.
☐ Yes ☐ No

14. ORIGINATING OFFICE CLEARANCE

Signature: [signature]

Title: Martin J. Forman
Director, TA/N

Date Signed: mo. 1 day 16 yr. 76

15. Date Received in AID/W, or For AID/W Documents, Date of Distribution: mo. day yr.

AID 1330-6 (7-75)

PROJECT SUMMARY

1. Basic Identification and Fiscal Data

Project Title:	Evaluation of a fortification program to control Vitamin A Deficiency in the Philippines
New or Extension:	New
Contractor and Address:	Cornell University, Ithaca, New York
Principal Investigator:	Michael C. Latham, M.D.
Duration:	3 years
Total Estimated Cost:	$145,181
Funding by Fiscal Years:	FY 1978 - $40,572 FY 1979 - $57,618 FY 1980 - $46,991

AID Project Manager and Sponsoring Office: John I. McKigney
Office of Nutrition

2. Abstract

Xerophthalmia due to vitamin A deficiency is the major cause of childhood blindness in the Philippines and several other Asian countries. An initial collaborative pilot study between Cornell University and Philippines government institutions determined vitamin A fortification of monosodium glutamate (MSG) to be the most suitable of three possible approaches to the reduction of xerophthalmia and vitamin A deficiency in the test communities located in Cebu province, where low levels of this taste enhancer are used.

The results on Cebu have led to recommendations for a national program to control vitamin A deficiency in the Philippines. These recommendations call for a national program of vitamin A fortification of MSG after a pilot trial in 2 or 3 provinces, and the careful evaluation of its effectiveness. The current proposal is to conduct this trial, and to plan for a national program.

The objectives of the proposed project are to (a) evaluate the feasibility, effectiveness, economics of vitamin A - fortified MSG distribution through normal commercial channels, (b) allow a reasonable prediction of the likely effectiveness of a national vitamin A fortification program, and (c) assist the Philippine Government in planning and initial implementation of the national program.

MEMORANDUM

TO : Research Advisory Committee

THRU : Miloslav Rechcigl, TA/RES

FROM : J. McKinney, for Irwin Hornstein, TA/N

SUBJECT: Research proposal entitled "Evaluation of a fortification program to control vitamin A deficiency in the Philippines.

The attached proposal has been submitted to the Office of Nutrition (TA/N) by Michael C. Latham, M.D., Professor of International Nutrition, Cornell University. The proposed research is based on the results of a collaborative study underway in the Philippines since 1973 and the Cebu Institute of Medicine, The Nutrition Center of the Philippines and Cornell University. Prior activities (described in Appendix I of the proposal) consisted of a detailed investigation of the prevelance and underlying causes of xerophthalmia in 12 communities on the island of Cebu, testing the effectiveness of three intervention strategies, and determining their cost effectiveness.

The study has received prior funding from A.I.D. in the form of a small research project grant to support statistical analysis of epidemiological data and the cost effectiveness of the alternative intervention approaches. The major funding source for the prior and proposed activities is the Philippines Government. WHO and UNICEF have also provided assistance. The funding requested of AID in the present proposal would basically underwrite Cornell University involvement in project planning, progress review, within-U.S. validation of serum vitamin A determinations, data analysis and preparation of reports.

If approved, this research study will be funded as an activity within the TA/N project entitled "Development of Vitamin A Delivery Systems" (Project paper and minutes of 12/16/75 Research and Development Committee (R&DC) meeting attached). The basic purpose of the Vitamin A Delivery Systems project is to implement a commitment made by the U.S. Secretary of State at the World Food Conference in 1974 to combat vitamin A deficiency throughout the developing areas of the world. AID was assigned the lead role. To assure that the program is a worldwide cooperative effort an "International Vitamin A Consultative Group" (IVACG) has been formed through the initiative of TA/N. The Philippines study embodies several of the major priority activities and needs identified in the TA/N project paper and R&DC recommendations. The research goals, evaluation approaches, and the host country/U.S. institutional relationship are consistent with Agency policy, recommendations 8.2, 8.3 and 8.4 of the report of a Joint WHO/USAID meeting on Vitamin A deficiency and Xerophthalmia (copy attached) and recommendations 9, 11 and 12 of the International Vitamin A Consultative Group Guidelines for the Eradication of Vitamin A Deficiency and Xerophthalmia (copy attached).

If the study is successful ,the results will have immense potential for use in other parts of the world. Several Asian countries will be in a position to directly apply the Philippine results. The research has relevance beyond both the food vehicle and the health problem being tested. It will demonstrate a means of fortification and of its evaluation which will have relevance to other nutritional deficiency diseases, using a number of food vehicles. Thus, the outcome of this study could have a significant influence on the future planning by AID and developing country governments of national programs for the prevention of vitamin A deficiency and resulting blindness.

The comments of three independent investigators who reviewed the proposal are also attached.

THE PENNSYLVANIA STATE UNIVERSITY
118 HENDERSON HUMAN DEVELOPMENT BUILDING
UNIVERSITY PARK, PENNSYLVANIA 16802

College of Human Development
Division of Biological Health

Area Code 814
865-3447

August 18, 1977

Dr. John I. McKigney
Health Scientist Administrator
Office of Nutrition
T.A.B.-A.I.D.
Department of State
Washington, D.C. 20523

Dear John:

I have reviewed the proposal submitted by Professor Michael C. Lathan titled, "Evaluation of a Fortification Program to Control Vitamin A Deficiency in the Philippines." In considering the proposal, I have also reviewed a copy of the final report of the initial study recently completed in the Philippines. I concur with Dr. Lathan's contention that the study proposed is a logical next step in the ultimate goal of establishing a national program for reducing the prevalence of vitamin A deficiency in the Philippines.

Justification for the Project

There is little doubt but that vitamin A deficiency is a serious public health problem at least in parts of the Philippines, particularly in Cebu where the initial project was done. There is indication that the problem is widespread throughout the Philippines but there is need for additional documentation. The proposed study would provide some added documentation in three additional areas of the Philippines. This is especially important because of a recent report of a study sponsored in part by the Helen Keller International that indicated a lesser problem in some areas near Manila.

The initial study did not quantitatively evaluate consumption patterns for MSG, particularly those foods that contain the fortified product and how these are distributed among family members. There is little doubt from results of the first study that the vulnerable child population did receive the product in Cebu since blood values rose. However, there is no assurance that the dietary practices in that province have a wider application and such information would be important for designing a nationwide program. For this reason, the present proposal would add needed additional information onto this question.

Additionally, Cebu was thought to have a low utilization of MSG. If indeed this proves true and utilization is greater in other provinces, then there may be need for additional consideration of levels of fortification and possible toxicities.

Critique of the Design and Methodology

The goals of the study are (a) to allow a reasonable prediction of the likely effectiveness of the national vitamin A fortification program, and (b) evaluate the feasibility, cost, and effectiveness (based on serum vitamin A levels) of MSG fortification covering the whole population in two or three separate provinces. The goals of the proposal are certainly justified. The question is whether or not the study sites selected are sufficiently representative of the many and diverse islands and cultures of the Philippines to assure the results will provide an adequate base for a national program. This may be true, but the proposal does not go into sufficient detail as to the justification for the provinces selected to evaluate this. It would be useful if additional narrative were developed which outlined in greater detail the rationale for choosing the particular provinces for study and how the characteristics in the selected provinces relate to other areas of the Philippines in order to evaluate the extent of the transferability of the results. It is realized that the investigators plan to undertake a concurrent study of the utilization of MSG in the rest of the Philippines.

Methodology

1. The methodological approach toward evaluation of the effectiveness of the program is only sketchily described in the proposal. It would be useful to have greater detail in study design, although it is realized that many of these details of sample size and selection must be worked out later as appropriate to the particular site selected. Nonetheless, to really understand whether the vehicle is appropriate in reaching the most vulnerable population group, it would be useful to have more clearly delineated the methodology to be used in detailed studies of distribution of fortified products within families by age group and sex.

2. The proposal to determine shelf-life by using a specially coded number is indeed a good one. It would also seem important to determine what foods MSG is added to and whether or not left-overs from these foods are usual and if so, how are they stored. This information might be important in determining long-range bioavailability of the nutrified MSG and products made from it.

3. In the provinces selected for study, the fortified MSG is distributed free to participants. Presumably the utilization would not change should the users have to purchase the product. A small substudy to confirm this assumption would be useful.

Significance of the Project

An effective low-cost intervention approach to reducing the magnitude of vitamin A deficiency in the Philippines, as well as in Southeast Asia,

is indeed needed. Identifying suitable products capable of being nutrified for this purpose seem to be a reasonable approach and potentially a transferable technology to other countries in Southeast Asia where the problem also exists. Therefore, the proposed project is indeed most significant and relevant to the goals of the USAID.

Potentially, MSG as an effective vehicle for improving vitamin A nutriture may also serve as a vehicle for other nutrients known to be minimally consumed in the Philippines and elsewhere in Southeast Asia. The project, therefore, does have potential significance beyond that of vitamin A nutrification alone.

Budget

The budget for the project appears reasonsble for the magnitude of work envisaged.

Investigators and Resources

The investigators are experienced professionals who have amply demonstrated their ability to successfully conduct the kind of study proposed.

The personnel and technical resources are available and adequate for conduct of the study.

Summary

I recommend approval of the proposal for support by AID. However, the proposal could be greatly strengthened if it included a more specific description of methodology to be used, particularly for evaluation of the programs' effectiveness. For example, a more careful study to document dietary intake of subjects on whom blood samples are drawn for evaluation of serum levels would provide information on consumption of the fortified product rather than other food sources as the likely reason for change in blood values.

Sincerely,

Barbara A. Underwood

Barbara A. Underwood, Director
Division of Biological Health

BAU/jk

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Dr. John I. McKigney, AID

DATE: August 16, 1977

FROM : Dr. J. G. Bieri

SUBJECT: Comments on Application "Evaluation of a fortification program to control vitamin A deficiency in the Philippines," from M. C. Latham.

This application is based on the apparently successful demonstration in the past three years that fortification of monosodium glutamate (MSG) with vitamin A can significantly elevate blood vitamin A levels in a Philippine population (Cebu project). It is now proposed to (1) essentially repeat the first study on a larger scale and (2) make cost-benefit estimates for eventually fortifying the entire Philippine population and (3) begin assisting the Philippine government in the national fortification program.

Although the general goals of the proposal are laudable, i.e., improvement of the vitamin A status of the Philippine population, especially for children, there are a number of deficiencies in the proposal that would appear to require both clarification and perhaps modification.

The actual intervention program proposal is presumably a mock-up of the earlier feasibility study. In the latter, it is stated that 1715 children and 626 households provided baseline data prior to the intervention, but no figures are given for the numbers in the follow-up. In the present proposal, it is stated that three provinces will be used for the MSG fortification. One would like some numerical estimates of the population to be covered and the number of individuals and households to be surveyed before and after the supplementation. Only with such figures for comparison with the feasibility study (Cebu) can a sound judgment be made as to whether or not the population and sampling are of sufficient size to provide data which can be used for the national projections.

It is proposed that during years 2 and 3, planning will be undertaken for the national vitamin A fortification project, based on the first 12 months evaluation in the 3 pilot provinces. This seems to have several assumptions that are taken for granted. First, it assumes that the results of the first year will be positive, and second it implies that the data from the first year's intervention will be available in a form which will permit the assumed positive evaluation. In a program of this magnitude, it would appear that at least six months and perhaps a year or more may be required for gathering and analyzing the data. These time relationships should be more clearly and realistically delineated in the light of experience from the feasibility study (Cebu).

It would seem premature to begin planning the national program before the results from the three provinces are clearly available. If the investi-

gator feels that the data after the first 12 months will be conclusive enough to justify beginning the planning for the national program, why should the three-province study continue into the second and third years?

With regard to the biochemical evaluation of vitamin A status, I concur that plasma retinol binding protein (RBP) determinations would not be worth the effort and expense. Plasma vitamin A values by the method proposed should adequately indicate the effectiveness of the nutritional intervention.

In summary, the results from the Cebu study are the most promising in indicating a satisfactory intervention technique. I believe the proposed three-province study should be conducted but that the quantitative aspects of sampling and population need to be provided in order to be assured of the adequacy of the numbers. Planning for the national program probably should be minimized during the second year and delayed until the third or fourth years. The budget seems entirely reasonable for the U.S. contribution to a program which will be largely supported by the Philippine government.

THE NUTRITION FOUNDATION, INC.
480 FIFTH AVENUE • NEW YORK N Y 10017 • 212 687-4830

September 4, 1977

Dr. John McKigney
Nutrition Advisor
Agency for International Development
Office of Nutrition
Washington, D.C. 20523

Dear Dr. McKigney:

I have reviewed the earlier draft application to USAID from Cornell University entitled "Evaluation of a Fortification Program to Control Vitamin A Deficiency in the Philippines", Michael Latham, principal investigator, and the application dated August 6, 1977. As I have indicated verbally to you in Quebec at the WHNC meeting, I feel that this program deserves support. After re-studying the proposal of August 6th, I have the following recommendations and comments:

1) I recommend approval and support at approximately the requested level for the three-year period as projected (i.e., total cost approximately $145,181.)

2) I suggest for consideration a few specific additions to the plan indicated (vide infra).

Reasons for approval include those clearly indicated in the background reviewed in the application--the problem is a demonstrated need in a country. There are methods that promise to be successful in control. The institution and personnel involved are ones that can effectively launch an effective national program and successfully evaluate its effectiveness; there are good background data upon which to plan, and the work proposal is feasible and resources requested reasonable.

As to my specific suggested additions and comments under 2:

a) On page 18, information (and observations) to be obtained should include that concerning the cooking use in the household studied of MSG, whether it is added to food given to infants and young children, is there any change in consumption during pregnancy?

Sales information from local stores should be obtained to supplement other information re amount of MSG used locally by families. The information gatherer should actually make a pantry survey to verify the supplies in the home.

b) On page 18, information on "other food items" should be of such systematic nature that it permits identification of any major changes in the food sources of vitamin A and carotene.

c) The monitoring of keeping qualities of fortified MSG--and of the actual use of fortified MSG--should include obtaining samples from the local stores and from households during the course of the study and analyzing these for vitamin A. This will provide essential data on stability under field conditions.

d) Importantly, I feel that other measures should simultaneously be initiated to build a broad program of increased intake of vitamin A and to protect the high-risk child. Such programs will not invalidate the anticipated evaluation of fortified MSG. There should be two actions. One, routine administration of hospitals, out-patient clinics, and so forth, of a protective oral dose of vitamin A (100,000-200,000 I.U. orally) to any child with suggestive ocular lesions or with malnutrition (PCM) and/or significant diarrheal disease; Two, educational and extension work should proceed as the "public health and horticulture intervention" (noted on page 5) since neither of these have effected an increment in serum vitamin A in the Cebu study. They will do so very slowly, if at all, and not likely induce measurable differences in blood levels in less than 1-2 years. They should be initiated, however.

e) There should be systematized data gathering concerning the eye lesions, blood levels and other relative information continuously on children (6 months to 5 or 6 years of age) brought into clinics, out-patient clinics, out-patient clinics, or hospitalized within or from the study area.

f) Observations on ophthalmologic conditions should be made both with and without (before) use of the stain (page 24).

g) Where will serum retinol be done? It is feasible to do these in the country and I assume such is planned.

As to RBP, this will be of greatest value in cases with quite low serum retinol level to distinguish PCM effect from "simple" avitaminosis A.

There are several other excellent resource personnel in the Philippines--Dr. Florentino, for example, who could be of great usefulness in this study.

I trust these comments will be helpful. Sorry that I did not understand that you needed this written critique immediately. I understood that you needed it by October. As you know, I was in Europe since the Quebec meetings.

My best personal regards.

Sincerely,

William J. Darby

William J. Darby

WJD/ed

AID APPLICATION

~~DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE~~

PROTECTION OF HUMAN SUBJECTS ASSURANCE/CERTIFICATION/DECLARATION

[X] ORIGINAL [ ] FOLLOWUP [ ] REVISION

[ ] GRANT [X] CONTRACT [ ] FELLOW [ ] OTHER

[X] NEW [ ] RENEWAL [ ] CONTINUATION

APPLICATION IDENTIFICATION NUMBER *(If known)*

STATEMENT OF POLICY: Safeguarding the rights and welfare of subjects at risk in activities supported under grants and contracts from DHEW is primarily the responsibility of the institution which receives or is accountable to DHEW for the funds awarded for the support of the activity. In order to provide for the adequate discharge of this institutional responsibility, it is the policy of DHEW that no activity involving human subjects to be supported by DHEW grants or contracts shall be undertaken unless the Institutional Review Board has reviewed and approved such activity, and the institution has submitted to DHEW a certification of such review and approval, in accordance with the requirements of Public Law 93-348, as implemented by Part 46 of Title 45 of the Code of Federal Regulations, as amended, (45 CFR 46). Administration of the DHEW policy and regulation is the responsibility of the Office for Protection from Research Risks, National Institutes of Health, Bethesda, Md 20014.

1. TITLE OF PROPOSAL OR ACTIVITY

"Evaluation of a Fortification Program to Control Vitamin A Deficiency in the Phillipines

2. PRINCIPAL INVESTIGATOR/ACTIVITY DIRECTOR/FELLOW

Professor Michael C. Latham. M.D. - Program in International Nutrition

3. DECLARATION THAT HUMAN SUBJECTS EITHER WOULD OR WOULD NOT BE INVOLVED

[ ] A. NO INDIVIDUALS WHO MIGHT BE CONSIDERED HUMAN SUBJECTS, INCLUDING THOSE FROM WHOM ORGANS, TISSUES, FLUIDS, OR OTHER MATERIALS WOULD BE DERIVED, OR WHO COULD BE IDENTIFIED BY PERSONAL DATA, WOULD BE INVOLVED IN THE PROPOSED ACTIVITY. (IF NO HUMAN SUBJECTS WOULD BE INVOLVED, CHECK THIS BOX AND PROCEED TO ITEM 7. PROPOSALS DETERMINED BY THE AGENCY TO INVOLVE HUMAN SUBJECTS WILL BE RETURNED.

[X] B. HUMAN SUBJECTS WOULD BE INVOLVED IN THE PROPOSED ACTIVITY AS EITHER: [ ] NONE OF THE FOLLOWING OR INCLUDING: [X] MINORS, [ ] FETUSES, [ ] ABORTUSES, [ ] PREGNANT WOMEN, [ ] PRISONERS, [ ] MENTALLY RETARDED, [ ] MENTALLY DISABLED. UNDER SECTION 6. COOPERATING INSTITUTIONS, ON REVERSE OF THIS FORM, GIVE NAME OF INSTITUTION AND NAME AND ADDRESS OF OFFICIAL(S) AUTHORIZING ACCESS TO ANY SUBJECTS IN FACILITIES NOT UNDER DIRECT CONTROL OF THE APPLICANT OR OFFERING INSTITUTION.

4. DECLARATION OF ASSURANCE STATUS CERTIFICATION OF REVIEW

[ ] A. THIS INSTITUTION HAS NOT PREVIOUSLY FILED AN ASSURANCE AND ASSURANCE IMPLEMENTING PROCEDURES FOR THE PROTECTION OF HUMAN SUBJECTS WITH THE DHEW THAT APPLIES TO THIS APPLICATION OR ACTIVITY. ASSURANCE IS HEREBY GIVEN THAT THIS INSTITUTION WILL COMPLY WITH REQUIREMENTS OF *DHEW Regulation 45 CFR 46*, THAT HAS ESTABLISHED AN INSTITUTIONAL REVIEW BOARD FOR THE PROTECTION OF HUMAN SUBJECTS AND, WHEN REQUESTED, WILL SUBMIT TO DHEW DOCUMENTATION AND CERTIFICATION OF SUCH REVIEWS AND PROCEDURES AS MAY BE REQUIRED FOR IMPLEMENTATION OF THIS ASSURANCE FOR THE PROPOSED PROJECT OR ACTIVITY.

[X] B. THIS INSTITUTION HAS AN APPROVED GENERAL ASSURANCE (DHEW ASSURANCE NUMBER G0063) OR AN ACTIVE SPECIAL ASSURANCE FOR THIS ONGOING ACTIVITY, ON FILE WITH DHEW. THE SIGNER CERTIFIES THAT ALL ACTIVITIES IN THIS APPLICATION PROPOSING TO INVOLVE HUMAN SUBJECTS HAVE BEEN REVIEWED AND APPROVED BY THIS INSTITUTION'S INSTITUTIONAL REVIEW BOARD IN A CONVENED MEETING ON THE DATE OF 8/8/77 IN ACCORDANCE WITH THE REQUIREMENTS OF THE *Code of Federal Regulations on Protection of Human Subjects (45 CFR 46)*. THIS CERTIFICATION INCLUDES, WHEN APPLICABLE, REQUIREMENTS FOR CERTIFYING FDA STATUS FOR EACH INVESTIGATIONAL NEW DRUG TO BE USED (SEE REVERSE SIDE OF THIS FORM).

THE INSTITUTIONAL REVIEW BOARD HAS DETERMINED, AND THE INSTITUTIONAL OFFICIAL SIGNING BELOW CONCURS THAT:

EITHER [X] HUMAN SUBJECTS WILL NOT BE AT RISK; OR [ ] HUMAN SUBJECTS WILL BE AT RISK.

5. AND 6. SEE REVERSE SIDE

7. NAME AND ADDRESS OF INSTITUTION

Cornell University
Ithaca, New York 14853

8. TITLE OF INSTITUTIONAL OFFICIAL

Chairman, University Committee on Human Subjects

TELEPHONE NUMBER

607-256-5014

SIGNATURE OF INSTITUTIONAL OFFICIAL

DATE

1977

HEW-59 (Rev. 4-75)

ENCLOSE THIS FORM WITH THE PROPOSAL OR R

5. INVESTIGATIONAL NEW DRUGS - ADDITIONAL CERTIFICATION REQUIREMENT

***SECTION 46.17 OF TITLE 45 OF THE** Code of Federal Regulations states, "Where an organization is required to prepare or to submit a certification . . . and the proposal involves an investigational new drug within the meaning of The Food, Drug, and Cosmetic Act, the drug shall be identified in the certification together with a statement that the 30-day delay required by 21 CFR 130.3(a)(2) has elapsed and the Food and Drug Administration has not, prior to expiration of such 30-day interval, requested that the sponsor continue to withhold or to restrict use of the drug in human subjects; or that the Food and Drug Administration has waived the 30-day delay requirement; provided, however, that in those cases in which the 30-day delay interval has neither expired nor been waived, a statement shall be forwarded to DHEW upon such expiration or upon receipt of a waiver. No certification shall be considered acceptable until such statement has been received."*

INVESTIGATIONAL NEW DRUG CERTIFICATION

TO CERTIFY COMPLIANCE WITH FDA REQUIREMENTS FOR PROPOSED USE OF INVESTIGATIONAL NEW DRUGS IN ADDITION TO CERTIFICATION OF INSTITUTIONAL REVIEW BOARD APPROVAL, THE FOLLOWING REPORT FORMAT SHOULD BE USED FOR EACH IND: (ATTACH ADDITIONAL IND CERTIFICATIONS AS NECESSARY).

- IND FORMS FILED: ☐ FDA 1571, ☐ FDA 1572, ☐ FDA 1573
- NAME OF IND AND SPONSOR _____
- DATE OF 30-DAY EXPIRATION OR FDA WAIVER
  (FUTURE DATE REQUIRES FOLLOWUP REPORT TO AGENCY) _____
- FDA RESTRICTION _____
- SIGNATURE OF INVESTIGATOR _____ DATE _____

6. COOPERATING INSTITUTIONS - ADDITIONAL REPORTING REQUIREMENT

SECTION 46.16 OF TITLE 45 OF THE *Code of Federal Regulations* IMPOSES SPECIAL REQUIREMENTS ON THE CONDUCT OF STUDIES OR ACTIVITIES IN WHICH THE GRANTEE OR PRIME CONTRACTOR OBTAINS ACCESS TO ALL OR SOME OF THE SUBJECTS THROUGH COOPERATING INSTITUTIONS NOT UNDER ITS CONTROL. IN ORDER THAT THE DHEW BE FULLY INFORMED, THE FOLLOWING REPORT IS REQUESTED WHEN APPLICABLE.

USE FOLLOWING REPORT FORMAT FOR EACH INSTITUTION OTHER THAN GRANTEE OR CONTRACTING INSTITUTION WITH RESPONSIBILITY FOR HUMAN SUBJECTS PARTICIPATING IN THIS ACTIVITY: (ATTACH ADDITIONAL REPORT SHEETS AS NECESSARY).

INSTITUTIONAL AUTHORIZATION FOR ACCESS TO SUBJECTS

- SUBJECTS: STATUS (WARDS, RESIDENTS, EMPLOYEES, PATIENTS, ETC.) _____

  NUMBER _____ AGE RANGE _____

  NAME OF OFFICIAL (PLEASE PRINT) _____

  TITLE _____ TELEPHONE _____

  NAME AND ADDRESS OF COOPERATING INSTITUTION _____

- OFFICIAL SIGNATURE _____

NOTES: *(e.g., report of modification in proposal as submitted to agency affecting human subjects involvement)*

RETURN IT TO REQUE

AID

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

☐ GRANT ☒ CONTRACT ☐ FELLOW ☐ OTHER

PROTECTION OF HUMAN SUBJECTS ASSURANCE/CERTIFICATION/DECLARATION

☒ ORIGINAL ☐ FOLLOWUP ☐ REVISION

☒ NEW ☐ RENEWAL ☐ CONTINUATION

APPLICATION IDENTIFICATION NUMBER *(If known)*

STATEMENT OF POLICY: Safeguarding the rights and welfare of subjects at risk in activities supported under grants and contracts from DHEW is primarily the responsibility of the institution which receives or is accountable to DHEW for the funds awarded for the support of the activity. In order to provide for the adequate discharge of this institutional responsibility, it is the policy of DHEW that no activity involving human subjects to be supported by DHEW grants or contracts shall be undertaken unless the Institutional Review Board has reviewed and approved such activity, and the institution has submitted to DHEW a certification of such review and approval, in accordance with the requirements of Public Law 93-348, as implemented by Part 46 of Title 45 of the Code of Federal Regulations, as amended, (45 CFR 46). Administration of the DHEW policy and regulation is the responsibility of the Office for Protection from Research Risks, National Institutes of Health, Bethesda, Md 20014.

1. TITLE OF PROPOSAL OR ACTIVITY

"Evaluation of a Fortification Program to Control Vitamin A Deficiency in the Phillipines

2. PRINCIPAL INVESTIGATOR/ACTIVITY DIRECTOR/FELLOW

Professor Michael C. Latham, M.D. - Program in International Nutrition

3. DECLARATION THAT HUMAN SUBJECTS EITHER WOULD OR WOULD NOT BE INVOLVED

☐ A. NO INDIVIDUALS WHO MIGHT BE CONSIDERED HUMAN SUBJECTS, INCLUDING THOSE FROM WHOM ORGANS, TISSUES, FLUIDS, OR OTHER MATERIALS WOULD BE DERIVED, OR WHO COULD BE IDENTIFIED BY PERSONAL DATA, WOULD BE INVOLVED IN THE PROPOSED ACTIVITY. (IF NO HUMAN SUBJECTS WOULD BE INVOLVED, CHECK THIS BOX AND PROCEED TO ITEM 7. PROPOSALS DETERMINED BY THE AGENCY TO INVOLVE HUMAN SUBJECTS WILL BE RETURNED.)

☒ B. HUMAN SUBJECTS WOULD BE INVOLVED IN THE PROPOSED ACTIVITY AS EITHER: ☐ NONE OF THE FOLLOWING, OR INCLUDING: ☒ MINORS, ☐ FETUSES, ☐ ABORTUSES, ☐ PREGNANT WOMEN, ☐ PRISONERS, ☐ MENTALLY RETARDED, ☐ MENTALLY DISABLED. UNDER SECTION 6. COOPERATING INSTITUTIONS, ON REVERSE OF THIS FORM, GIVE NAME OF INSTITUTION AND NAME AND ADDRESS OF OFFICIAL(S) AUTHORIZING ACCESS TO ANY SUBJECTS IN FACILITIES NOT UNDER DIRECT CONTROL OF THE APPLICANT OR OFFERING INSTITUTION.

4. DECLARATION OF ASSURANCE STATUS/CERTIFICATION OF REVIEW

☐ A. THIS INSTITUTION HAS NOT PREVIOUSLY FILED AN ASSURANCE AND ASSURANCE IMPLEMENTING PROCEDURES FOR THE PROTECTION OF HUMAN SUBJECTS WITH THE DHEW THAT APPLIES TO THIS APPLICATION OR ACTIVITY. ASSURANCE IS HEREBY GIVEN THAT THIS INSTITUTION WILL COMPLY WITH REQUIREMENTS OF *DHEW Regulation 45 CFR 46*, THAT IT HAS ESTABLISHED AN INSTITUTIONAL REVIEW BOARD FOR THE PROTECTION OF HUMAN SUBJECTS AND, WHEN REQUESTED, WILL SUBMIT TO DHEW DOCUMENTATION AND CERTIFICATION OF SUCH REVIEWS AND PROCEDURES AS MAY BE REQUIRED FOR IMPLEMENTATION OF THIS ASSURANCE FOR THE PROPOSED PROJECT OR ACTIVITY.

☒ B. THIS INSTITUTION HAS AN APPROVED GENERAL ASSURANCE (DHEW ASSURANCE NUMBER G0063) OR AN ACTIVE SPECIAL ASSURANCE FOR THIS ONGOING ACTIVITY, ON FILE WITH DHEW. THE SIGNER CERTIFIES THAT ALL ACTIVITIES IN THIS APPLICATION PROPOSING TO INVOLVE HUMAN SUBJECTS HAVE BEEN REVIEWED AND APPROVED BY THIS INSTITUTION'S INSTITUTIONAL REVIEW BOARD IN A CONVENED MEETING ON THE DATE OF 8/8/77 IN ACCORDANCE WITH THE REQUIREMENTS OF THE *Code of Federal Regulations on Protection of Human Subjects (45 CFR 46)*. THIS CERTIFICATION INCLUDES, WHEN APPLICABLE, REQUIREMENTS FOR CERTIFYING FDA STATUS FOR EACH INVESTIGATIONAL NEW DRUG TO BE USED (SEE REVERSE SIDE OF THIS FORM).

THE INSTITUTIONAL REVIEW BOARD HAS DETERMINED, AND THE INSTITUTIONAL OFFICIAL SIGNING BELOW CONCURS THAT:

EITHER ☒ HUMAN SUBJECTS WILL NOT BE AT RISK; OR ☐ HUMAN SUBJECTS WILL BE AT RISK.

5. AND 6. SEE REVERSE SIDE

7. NAME AND ADDRESS OF INSTITUTION

Cornell University
Ithaca, New York 14853

8. TITLE OF INSTITUTIONAL OFFICIAL	TELEPHONE NUMBER
Chairman, University Committee on Human Subjects	607-256-5014
SIGNATURE OF INSTITUTIONAL OFFICIAL	DATE
[signature]	8/8/77

HEW-596 (Rev. 4-76)

ENCLOSE THIS FORM WITH THE PROPOSAL OR RETURN IT TO REQUESTING AGENCY. Duplicate

5. INVESTIGATIONAL NEW DRUGS - ADDITIONAL CERTIFICATION REQUIREMENT

SECTION 46.17 OF TITLE 45 OF THE Code of Federal Regulations states, "Where an organization is required to prepare or to submit a certification . . . and the proposal involves an investigational new drug within the meaning of The Food, Drug, and Cosmetic Act, the drug shall be identified in the certification together with a statement that the 30-day delay required by 21 CFR 130.3(e)(2) has elapsed and the Food and Drug Administration has not, prior to expiration of such 30-day interval, requested that the sponsor continue to withhold or to restrict use of the drug in human subjects; or that the Food and Drug Administration has waived the 30-day delay requirement; provided, however, that in those cases in which the 30-day delay interval has neither expired nor been waived, a statement shall be forwarded to DHEW upon such expiration or upon receipt of a waiver. No certification shall be considered acceptable until such statement has been received."

INVESTIGATIONAL NEW DRUG CERTIFICATION

TO CERTIFY COMPLIANCE WITH FDA REQUIREMENTS FOR PROPOSED USE OF INVESTIGATIONAL NEW DRUGS IN ADDITION TO CERTIFICATION OF INSTITUTIONAL REVIEW BOARD APPROVAL, THE FOLLOWING REPORT FORMAT SHOULD BE USED FOR EACH IND: (ATTACH ADDITIONAL IND CERTIFICATIONS AS NECESSARY)

- IND FORMS FILED: ☐ FDA 1571, ☐ FDA 1572, ☐ FDA 1573
- NAME OF IND AND SPONSOR _____
- DATE OF 30-DAY EXPIRATION OR FDA WAIVER _____
  (FUTURE DATE REQUIRES FOLLOWUP REPORT TO AGENCY) _____
- FDA RESTRICTION _____
- SIGNATURE OF INVESTIGATOR _____ DATE _____

6. COOPERATING INSTITUTIONS - ADDITIONAL REPORTING REQUIREMENT

SECTION 46.16 OF TITLE 45 OF THE *Code of Federal Regulations* IMPOSES SPECIAL REQUIREMENTS ON THE CONDUCT OF STUDIES OR ACTIVITIES IN WHICH THE GRANTEE OR PRIME CONTRACTOR OBTAINS ACCESS TO ALL OR SOME OF THE SUBJECTS THROUGH COOPERATING INSTITUTIONS NOT UNDER ITS CONTROL. IN ORDER THAT THE DHEW BE FULLY INFORMED, THE FOLLOWING REPORT IS REQUESTED WHEN APPLICABLE.

USE FOLLOWING REPORT FORMAT FOR EACH INSTITUTION OTHER THAN GRANTEE OR CONTRACTING INSTITUTION WITH RESPONSIBILITY FOR HUMAN SUBJECTS PARTICIPATING IN THIS ACTIVITY: (ATTACH ADDITIONAL REPORT SHEETS AS NECESSARY).

INSTITUTIONAL AUTHORIZATION FOR ACCESS TO SUBJECTS

- SUBJECTS: STATUS (WARDS, RESIDENTS, EMPLOYEES, PATIENTS, ETC.) _____

  NUMBER _____ AGE RANGE _____

  NAME OF OFFICIAL (PLEASE PRINT) _____

  TITLE _____ TELEPHONE _____

  NAME AND ADDRESS OF COOPERATING INSTITUTION _____

- OFFICIAL SIGNATURE _____

NOTES: *(e.g., report of modification in proposal as submitted to agency affecting human subjects involvement)*

NOTATIONS:

1. This PP revision proposes an increase in total funding level of the project from the original approved level of $668,000. The revised total funding level of $4 million will provide for the expansion of activities in response to the Secretary of State's initiative made at the World Food Conference.

2. The Research and Development Committee discussed and endorsed this PP revision at its December 15, 1975 R&DC meeting.

PROJECT AUTHORIZATION:

1. Conditions of Approval

The total project is approved in principle, with funding not to exceed $2.6 million, from FY 74 through FY 78. This approved funding level provides partial funding in the amount of $590,000 for FY 78, with remainder of funding for that fiscal year and beyond contingent upon an in-depth evaluation scheduled for the Spring of 1977 and a revised Project Paper thereafter.

A. Originating Office

Drafter: Dr. Irwin Hornstein, TA/ [signature] date 4/27/7

B. Clearances:

TA/PPU, Carl R. Fritz [signature] date 4/28/76
PPC/DPRE, Arthur Handly [signature] date 5/5/76
AA/PPC, Philip Birnbaum [signature] date 5/10/76

C. Approval:

AA/TA, Curtis Farrar [signature] date 5/6/76

DA/AID, John E. Murphy [signature] date 5/11/76

This PP revision proposes an increase in the total funding level of the project from the original approved level of $668,000. The revised total funding level of $4 million will provide for the expansion of activities in response to the Secretary of State's initiative made at the World Food Conference.

INTRODUCTION

Vitamin A deficiency is said to be the biggest single cause of preventable blindness in many of the developing countries. Extensive studies have established the widespread distribution of this deficiency-particularly in pre-school age groups in South East Asia, The Middle East and Latin America. It has been estimated that at least 80,000 children below the age of 4 become blind every year because of avitaminosis A. Furthermore blindness is but the "tip of the iceberg". Vitamin A deficienc inhibits growth, increases susceptibility to infection and can lead to death particularly when associated with protein/calorie malnutrition.

As a result of technological developments over the past several years, low cost approaches are now available to address the problem. The administration of massive periodic doses of vitamin A is considered an effective ermegency measure for overcoming the deficiency. Vitamin A fortification of food staples may be the most economical and socially acceptable long-term method for assuring that vitamin A requirements are met. Vitamin A programs utilizing massive periodic doses and/or vitamin A fortification have been equally under utilized on a national scale. Fragmented efforts have been made in the developing countries to establish programs but to date these efforts have been uncoordinated at the national level. This program is being proposed with the hope that AID can serve as the catalyst for coordinating and implementing worldwide efforts in vitamin A programming.

A. Statement of Goal

1. The Goal

To minimize the effects of malnutrition by instituting appropriate systems for the delivery of vitamin A to preschool children in LDCs.

2. Measurement of Goal Achievement

a) Decrease in vitamin A deficiency among preschool children.
b) Decrease in new cases of xeropthalmia.

3. Assumptions About Goal Achievement

a. Methodologies for administering vitamin A by the massive dose technique are available.

b. Techniques for fortifying food staples with vitamin A are either available or can readily be developed.

c. Mass delivery of vitamin A to target groups can either be "piggy-backed" on to existing distribution systems or new innovative systems can be developed.

d. The efforts of all concerned groups can be coordinated to achieve maximum benefits at relatively small costs.

f. Cost estimates can be made from studies in Bangladesh and Pakistan. In Bangladesh, the one country where a nationwide "massive-dose" program has been attempted, the yearly cost is approximately $300,000. The program hopes to reach 15,000,000 children 0-6 years of age semi-annually Vitamin A capsules containing 200,000 I.U. cost about $10/thousand. The capsules are distributed by piggy-backing an existing malaria control system that reaches virtually every household in Bangladesh. The cost of distribution is absorbed by the Bangladesh government.

The cost of vitamin A fortification is similar in magnitude. AID/W through its PASA with USDA has developed a technique for the fortification of tea with vitamin A. Children drink tea at a very early age in India, Pakistan, Bangladesh, and Ceylon. Tea can therefore provide an appropriate vehicle for carrying vitamin A to the target group in these countries. The cost of fortifying tea as a large scale on-going progr in Pakistan has been calculated. The capital cost for providing sufficient capacity to produce all the vitamin A/tea concentrate to fortify 90,000,000 pounds of tea per year is only $60,000. The cost for fortifying the total supply of 90,000,000 pounds of tea per year is approximately $500,000 and $350,000 represents the import cost for vitamin A. The increase in the cost of vitamin A fortified tea per pound would be less than one percent the price of tea.

B. Statement of Purpose

1. To assist LDCs in implementing programs for alleviating vitamin A deficiency.

2. Conditions Expected at End of Project

a. An assessment of extent of vitamin A deficiency in approximately twelve countries.

b. A surveillance methodology based on easily available indicators that will predict where and when vitamin A deficiency will become a problem.

c. Development of the appropriate vitamin A techniques to be utilized (massive doses, fortification, nutrition education or a combination) in these countries.

d. Implementation of appropriate programs in at least 5 of these 12 countries

e. Coordination of efforts by donor agencies in implementing vitamin A programs in LDCs. (This will be accomplished through a consultative group consisting of members of AID, WHO/PAHO, FAO, UNICEF, the World Bank and private donors such as the American Foundation for the Overseas Blind. The group would convene at least on an annual basis. The group would provide guidance (a) regarding needed research and field programs, (b) possibilities for joint funding of major programs, and (c) the need for workshops or seminars. This coordinating activity would minimize duplication of research projects, encourage execution of major projects that would be beyond the financial scope of any one organization and insure dissemination of information and new knowledge to concerned organizations.)

* This will be part of an integrated and planned national nutrition effort.

3. Basic Assumptions About Achievement of Purpose

a. Blindness caused by vitamin A deficiency can be prevented by the use of one or more existing technologies for supplying vitamin A to the vulnerabl preschoolers.

b. Mass delivery of vitamin A to the target group can in many instances be based on utilization of existing distribution systems. (e.g. use of malaria control systems for delivery of semi-annual massive doses of vitamin A)

C. Statement of Project Outputs

Outputs

a. The development of country specific procedures for determining: (1) the extent of blindness due to vitamin A deficiency, (2) the techniques to be implemented for alleviating the deficiency, (3) the methodology to use for evaluating effectiveness of programs, and (4) the techniques to be utilized to maintain effective surveillance programs.

b. LDC personnel trained to carry on in-country vitamin A programs.

c. Information relative to the progress of vitamin A programs disseminated to LDCs and other donor agencies.

d. Bio-chemical method of detection of vitamin A deficiency in target grc

2. Output Indicators

Established avitaminosis A programs at the national level in several countrie utilizing the methodologies developed for (a) assessing extent of deficiency numerically and geographically, (b) supplying vitamin A in appropriate form to target groups, (c) evaluating effectiveness of programs and (d) maintainin effective surveillance programs.

3. Basic Assumption About Production of Outputs

a. Each country must be considered as a separate problem. Analysis of needs and resources (government/private) will lead to the development of an appropriate system in a specific country for the mass delivery of vitamin A to target groups.

b. Implementation of at least 5 projects will demonstrate that a relatively low-cost approach can be undertaken on a national scale and yield tangib and beneficial results by reducing blindness caused by vitamin A deficie within a relatively short period of time.

Statement of Project Inputs

1. Inputs

a. Expert groups to provide guidance to AID in determining program planning.

b. Team(s) of experts to develop specific country programs.

c. Seminars, workshops site visits to disseminate information to LDCs and coordinate efforts of donor agencies.

d. Training program for LDC personnel.

e. Development of bio-chemical method for determining degree of vitamin A deficiency.

2. BUDGET (X $1000)

	FY 74	FY 75	FY 76	FY 77	FY 78	FY 79	TOTAL
Planning & Coordination	-	-	30	30	30	30	120
Prevalence Surveys & Surveillence	-	-	120	240	240	120	720
Assay & Other Technical Development	-	-	30	50	50	-	130
Field Demonstrations	-	-	100	600	500	300	1500
Education (KAP)	-	-	25	150	123	100	398
Evaluation of Methodologies & Preparation of Project Compendium	-	66	300	150	200	200	916
Workshop & Conference	40	-	-	45	-	75	160
Dissemination of Information	-	-	-	10	10	10	30
Consultant Group(s) (Including experts)	-	-	25	25	25	25	100
GRAND TOTAL	40	66	630	1300	1178	860	4074

3. Basic Assumptions About Management of Inputs

a. Existing technologies for delivering vitamin A to target groups can be adapted to meet the diverse conditions existing in the LDCs.

b. USAID Missions, LDC public and private sectors, and donor agencies includir WHO/PAHO, FAO and UNICEF will support programs designed to meet vitamin A requirements of LDC populations.

Rationale

The tragedy of blindness extends beyond the individual and his immediate family. It represents a loss of potential talent and creates an economic burden for society. Cumulatively, 80 to 100,000 new cases per year of blindness caused by vitamin A deficiency may mean 2 to 3 million blind who must be cared for in the LDCs at any given time.

Reduction of Xerophthalmia induced blindness would afford a dramatic demonstration of the effectiveness of improved nutrition on health and could serve to encourage LDC nutrition planning on a national scale.

This program is being proposed (a) with the knowledge that methods for alleviating vitamin A deficiency worldwide are available; (b) with the belief that proper implementation of programs and coordination of efforts by the LDCs, AID and other donor agencies can lead to at least a 75% reduction in new cases of blindness attributable to vitamin A deficiency, (This prediction assumes that at least 75% of the target group can be reached on a continuing basis in a given LDC within 3 years after the introduction of a comprehensive vitamin A program.) and (c) with the hope that AID can serve as the catalyst for coordinating worldwide efforts and for developing proper implementation procedures.

In addition, an all out effort to overcome vitamin A deficiency ties in with AID's program on breeding cereals and legumes that are superior in protein quality and quantity. Children in the LDCs not only suffer from protein/calorie malnutrition but from concomitant vitamin and mineral deficiencies. Thus, if a new variety of grain, e.g. opaque-2 corn, is introduced, the available protein in the child's diet will increase appreciably. This increase in protein will tend to promote growth and increase the demand for vitamin A. If the child is borderline in vitamin A, this added stress could throw the child into a state of vitamin A deficiency. If one looks at the entire food system it becomes obvious the one intervention may create problems that should be addressed simultaneously on other fronts. Thus, the proposed vitamin A program could be a necessary adjunct to programs designed to improve dietary protein thru the introduction of new crop varieties.

In order to properly define AID's role in avitaminosis A program planning, an ad hoc expert group was convened prior to the initiation of the project. This group included representatives from donor agencies as well as experts in vitamin A technology and programming. The group provided preliminary advice needed to initiate AID's proper role in the area. Their recommendations included:

-- AID should support countries interested in initiating vitamin a programs. AID, through an appropriate mechanism, could provide a person or a team to determine in a given country any or all of the following: (a) incidence of vitamin A deficiency, (b) geographical areas where the deficiency exists, (c) appropriate short and long term measures to be instituted, (d) the most appropriate delivery systems for bringing together the treatment and the target and (e) a methodology for evaluating the efficacy of the program.

-- Demonstration projects should be established, if needed, to evaluate the effectiveness of proposed intervention programs such as massive oral doses of vitamin A. Evaluations should include a determination of the cost effectiveness of the program--and if possible a comparison with alternate intervention strategies

-- AID should endorse and encourage the cooperation of Voluntary Agencies in adding a vitamin A component to their nutrition programs.

Course of Action.

The steps required to implement a program for the alleviation of vitamin A deficiency in a country or region include the following:

a. an analysis of the numerical and geographic extent of vitamin A deficiency,

b. adoption or development of suitable technologies for overcoming vitamin A deficiency in the specified area, and

c. developing vitamin A delivery systems tailored to fit the specific constraints and opportunities existing with the area for reaching the preschool child.

The first step--the determination of the extent of vitamin A deficiency--not only locates the regions in a given LDC where the vitamin A problem is most serious but also serves to provide a baseline for measuring the decrease in avitaminosis A as the program continues. Quantitative base line data is however seldom available in the LDCs; and in most cases, it will be necessary to teach the survey teams how to recognize early clinical signs of vitamin A deficiency in order to obtain the required data.

The second step--the mix of technologies to be utilized may include one or more of the following:

a. Periodic distribution of high potency vitamin A capsules to the most vulnerable groups.

b. Fortification with vitamin A of food staples which are widely available to vulnerable groups.

c. Nutrition education to encourage the production and consumption of foods with high carotene content such as dark green vegetables.

The first alternative may be considered an effective emergency measure for overcoming existing deficiencies. Fortification is a preventive measure that if "doable" requires no action on the part of the consumer. Measures designed to modify food habits require understanding and cooperation on the part of the consumer and their major impact may be quite long range.

The third step--the choice of delivery system(s) may e.g. piggy back an existing health delivery system. Thus in Bangladesh distribution of high potency vitamin A capsules was superimposed on an existing malaria control program. Evaluation of the programs will be continuous throughout the life of the project.

The Implemen

Backgrou

Considerable spade work has been done by TA/N prior to the submission of this "PROP". The implementation plan per se is a follow up to these initial efforts. Work to date is summarized and implementation plan follows.

In FY '74 a "vitamin A expert group" was established on an ad hoc basis. Included in this group were individuals with specific expertise in vitamin A research and development of applied programs plus representatives from the U.N., PAHO, the American Association for Overseas Blind, etc. In May 1975 the "ad Hoc" group was formalized into the International Vitamin A Consultative Group (IVACG) with the function of recommending tasks to the member agencies. This approach will serve to (1) minimize duplication of effort, (2) encourage execution of major projects that otherwise would be beyond the financial means of any one organization, and (3) to insure the dissemination of information and new knowledge to concerned organizations and individuals.

The provisional goals of the group are the following:

-- To encourage the coordination of vitamin A programming and research activities worldwide.

-- To provide for the establishment of a clearinghouse for the collection and dissemination of information on vitamin A activities.

-- To sponsor workshops, symposia and seminars that will help encourage the implementation of Vitamin A programs.

In FY '74 a comprehensive review of the "state of the art" with respect to vitamin A requirements, deficiencies, diagnostic criteria, ongoing programs and available technology was prepared. The three-volume status report will serve as a base for future programming and is being made available to scientists, institutions and donor agencies engaged in vitamin A programming.

A less technical monograph providing a condensed version of the contents of the three-volume set is in preparation. This will be made available to non-technical but concerned workers in the vitamin A field.

In the latter half of 1974 a joint WHO/AID conference was held. Its goal was to develop specific recommendations that would serve as a basis for vitamin A programming and research, both by AID and other funding agencies.

Plan

(a) LDC Involvement and Commitment: To date, all Agency vitamin A activities in LDCs involve in-country institution and/or host government participation. Current project activities have or will start in Guatemala, Sri Lanka, Philippines, El Salvador, Haiti and Indonesia. In each of these countries, host government or in-country institution personnel and equipment serve as a significant or total part of the field team. Commitment to delivery programs depend on the type of ongoing activity. In the case of Guatemala, the government is strongly committed and has initiated a national program of vitamin A fortification of sugar. Whereas, in El Salvador, commitment to delivery program is predicated on the interpretation of data collected from an in-country prevalence survey.

Selection of these countries for program activities is based on host government and/or in-country institution requests or via a U. S. institutional collaboration which has had prior sanction from the LDC government. Moreover, all host governments indicated firm or conditional commitment to a vitamin A program.

During FY '76 a determination will be made of LDCs interested in initiating vitamin A programs, and a clearinghouse for dissemination of information concerning vitamin A activities will be established.

(b) Education Component: Educational programs are being developed that will both inform and elicit response in the populations to the signs of vitamin A deficiency, and instruct and encourage them to produce and/or consume foods rich in vitamin A. Educational materials and instructional procedures are to be worked out for different age, population, occupational, and professional groupings. Currently, a specific activity in this field is being carried out by the American Federation for Overseas Blind in conjunction with the Nutrition Foundation.

In addition, in each country selected LDC para-medicals will be trained in the identification of clinical signs of vitamin A deficiency. These personnel will be used in conducting prevalence surveys and surveillance programs. In all field operations LDC personnel will gain from on-the-job training.

(c) Research Component: Research will be initiated in support of field activity needs. Examples include (a) improved biochemical methods for the determination of vitamin A status under field conditions; (b) factors which contribute to the development of vitamin A deficiency and keratomalacia in the preschool population; (c) improved methods for delivering vitamin A to target groups.

Activity*KP: 2--Reaching the Pre-School Child
Project Development of Vitamin A
No. 560-0457 Title Delivery Systems

Contract/PASA
No. _____ Name Irwin

Project Manager Hornstein Extension 29771

Contract/PASA
Officer _____ Extension _____

TAB - GENERAL TECHNICAL SERVICES

FY 1975 Interregional Program Budget Review
Project and Budget Analysis Matrix

Major Country/Countries
Worldwide

BEST AVAILABLE COPY

Obligation: Begin FY 1974 End FY
Work Begin FY 1974 End FY
PROP Status: PROP approved thru F
New/Revised Required in FY

Estimated Submission Date Nov (Month)

Evaluation Schedule June (Month) - 1976 (Year)

Narrative

Purpose:

Assist LDCs in (a) analyzing the extent of vitamin A deficiencies, (b) adapting and/or developing technologies for overcoming Vit. A deficiency, (c) adapting and/or developing delivery systems for reaching the target group (d) implementing programs for alleviating Vit. A deficiency.

Outputs:

The development of country specific procedures for determining the extent of blindness due to vitamin A deficiency, the techniques to be implemented for alleviating the deficiency, the methodology to use for evaluating effectiveness of programs.

Indigenous personnel trained to carry on in-country Vitamin A programs.

Information relative to the progress of vitamin A program disseminated to LDCs and donor agencies.

Improved method of detection of vitamin A deficiency in target groups.

Inputs: Funding of:

Expert groups to provide guidance to AID in determining proper program planning.

Team(s) of experts who will develop specific country programs.

Programs for implemention(s) and evaluation(s) of vitamin A programs.

Seminars, workshops, site visits, etc. to disseminate information to and coordinate efforts of donor agencies.

Establishment of a clearinghouse for the collection and dissemination of information on vitamin A activities.

Objectively Verifiable Indicators

B2 End of Project Status:

a. Assessment of extent of Vit. A deficiency in 12 countries.
b. Development of methodologies to be used in these 12 countries for combatting avitaminosis A.
c. Programs carried out in 2 countries.
d. Coordinated efforts by donor agencies in combatting Vit. A deficiencies in LDCs.
e. Development of surveillance methodology that will predict where and when vitamin A deficiency will become a problem.

C2 Output Indicators:

Established Avitaminosis A programs at the National level in several countries utilizing the methodologies developed for assessing extent of deficiency, supplying Vitamin A in appropriate form to target groups, evaluating effectiveness of program, and maintaining effective surveillance programs.

B2 Budget Summary (in thousands of dollars)

	(1) Personnel Dollars	(1) PY	(2) Participants Dollars	(2) PY	(3) (Commodities)	(4) Total Dollars	(4) PY	(5)
All Prior Years								
1. Thru FY 1972								
2. Actual FY 1974	40	10				40	10	
3. Estimated FY 1975	60	16			6	66	16	
4. Proposed FY 1976	580	142			65	645	142	
5. All Other	3270	785			68	3338	785	
6. Total	3950	953			124	4089	953	

Important Assumptions and Progress to Date

B3. Assumptions for Achieving Purpose:

a. Blindness caused by Vit. A deficiency c prevented by the use of techniques (ada developed) for delivering Vit. A to vul pre-schoolers.
b. Mass delivery of Vit. A to the target p in many instances be based on utilizati existing distribution systems.

B4 Progress to date:

C3 Assumption for Achieving Outputs:

a. Analysis of needs and resources (governm will lead to the development of an approp in a specific country for the mass delivery to target groups. b. Implementation of o projects will demonstrate that a relatively approach can be undertaken on a national s tangible and beneficial results.

C4 Progress to date:

A compendium completed on the current stat art in the technology, deficiency status worldwide programming efforts on vitamin A completed. Prevalence surveys being conduc and planned for El Salvador. Evaluation o vitamin A fortification program being con Guatemala. Field demonstration activities Haiti and Indonesia.

Geographic Area, Area of Concentration, or Field Support

d. A contract will be established with an appropriate institution to provide, upon AID request, an expert team to determine in a given LDC any or all of the following: (1) incidence of vitamin A deficiency, (2) geographical areas where the deficiency exists, (3) appropriate short and long term measures to be instituted, (4) the most appropriate delivery system for bringing together the treatment and target, and (5) a methodology for evaluating the efficacy of the program.

Three or four countries will be surveyed in each of FY '76, FY '77, and FY '78.

e. Through an appropriate contract (not necessarily with the same institution) demonstration projects will be established to evaluate the effectiveness of the proposed intervention programs. It is assumed that a minimum of 3 years will be required for each study. Evaluation will include a determination of the cost effectiveness of the program.

Five such demonstration projects will be initiated. Two in each of FY '76 and FY '77 and one in FY '78. Each to run for 2-3 years.

At the completion of the initial studies (in FY '77 or '78) and remaining studies in FY '79 conferences will be held to summarize the results of the projects to concerned institutions and agencies to further promote implementation of vitamin A projects.

The plan as outlined will support the Secretary of State's position formulated at the November 1974 World Food Conference in Rome. Dr. Kissinger stressed the need for immediate campaigns against blindness due to vitamin A deficiency and stated that the United States was prepared to initiate a multi-million dollar program for this purpose. Recommendations to eradicate this nutritional problem were included in the resolutions adopted at the Conference.

EVALUATION

In June 1975 a PAR was prepared covering the progress of project activities in the following areas: (1) the effectiveness of fortifying sugar with vitamin A (INCAP); (2) the development of new biochemical diagnostic techniques for determination of vitamin A deficiency; and (3) the formation of the International Vitamin A Consultative Group to coordinate research and operational programs. A PAR will be submitted in June 1976 to cover the current status of these activities and new activities initiated in FY 76.

An in-depth evaluation will be conducted in April 1977. This evaluation will be a comprehensive review and will include outside experts as members of a panel. Funding beyond FY 78 will be based on the results of this evaluation.

An informal evaluation will be conducted periodically on the sub-projects. This will include a review of quarterly reports and visits to the contractors' facilities. A tentative schedule for the informal evaluation of sub-projects is as follows:

June 1976 - Nutrition Foundation (IVACG)

July 1976 - Vitamin A Prevalence Survey in Sri Lanka (CDC)

January 1977 - Fortification of Sugar with Vitamin A (INCAP)

February 1977 - New biochemical diagnostic techniques for Vitamin A Deficiency (MIT)

MAY 10 1976

ACTION MEMORANDUM FOR THE DEPUTY ADMINISTRATOR

THRU: ES

FROM: AA/PPC, Mr. Philip Birnbaum

Problem: Your approval is required for a revision and increase in funding of the TA Bureau project, "Development of Vitamin A Delivery System," from an approved total funding level of $668,000 to a new level of $4,089,000.

Discussion: This Technical Assistance Bureau (TAB) activity was initiated in FY 74 as a five year program with the purpose to assist LDCs in implementing programs for alleviating vitamin A deficiency. The program supports development of:

(1) Country specific procedures for determining:
   a) extent of blindness due to vitamin A deficiency
   b) techniques to be implemented for alleviating the deficiency
   c) methodologies to use for evaluating effectiveness of programs and
   d) techniques to be utilized to maintain effective surveillance programs.

(2) LDC personnel trained to carry on in-country vitamin A programs.

(3) Biochemical method of detection of vitamin A deficiency in target population groups.

(4) Information relative to the progress of vitamin A programs for dissemination to LDCs and donor agencies.

In 1974, A comprehensive review of the state of the art was held with respect to vitamin A. A three volume status report outlining vitamin A requirements, deficiencies, diagnostic criteria, ongoing programs and available technology was prepared and distributed to scientists, institutions and donor agencies dealing with vitamin A programming.

AID has provided a grant to WHO in support of a conference on vitamin A deficiency, which was held in November 1974. A technical report on the conference was reviewed by AID last May, and is now being printed for worldwide distribution.

In 1975, a contract with the Institute of Nutrition of Central America and Panama in Guatemala for the evaluation of vitamin A foritification of sugar was signed. Initial six month funding was provided. INCAP reported data on feasibility of conducting project evaluation in Guatemala and Costa Rica. These findings were submitted in November 1975 and reviewed by TAB and consultants. The result of this review was the elimination of Costa Rica as a project site, and the addition of El Salvador as a potential

new site. The project is continuing with funding for the next 20 months.

The International Vitamin A Consultative Group was officially formed in May, 1975, at the U.N. Headquarters. A second meeting of IVAGG was held in Haiti in March 1976. The members reviewed vitamin A problems existing in the world and made recommendations for pursing activities for combatting vitamin A deficiency. Draft guidelines have been prepared and will be published in July.

The original PROP (attached) was approved in FY 1974 at a total cost of $668,000. TAB, to date, has obligated $468,000 and anticipates an additional obligation of $284,000 during FY 1976 if the expanded proposal is approved. This acceleration over the original program has resulted from the added support given the program by the Secretary of State's position presented at the World Food Conference in Rome, November 1974. Dr. Kissinger stressed the need for immediate campaigns against blindness due to vitamin A deficiency and stated that the United States was prepared to initiate a multi-million dollar program for this purpose. The World Food Conference included in its resolution a recommendation to eradicate this nutritional problem.

The increase in funding level requested for this program is in response to the worldwide concern in the problem of vitamin A deficiency and resulting blindness. Vitamin A surveys originally were planned for 6-8 countries, however this will be increased to 10-12 countries. Implementation of appropriate vitamin A delivery systems will increase from 2 to 5 countries.

The proposed PP revision was discussed and endorsed by the Reseach and Development Committee on December 16, 1975. Major issues focused on LDC involvement, criteria for selecting LDC, field research, and cost effectiveness. (See Attachment B: Informal Minutes of R&DC Meeting, 12/16/75). The R&DC comments and suggestions were incorporated in the PP revision which again was circulated to the R&DC for optional comments. No other issues were raised regarding this project.

PPC subsequently questioned whether the project should be approved in the full proposed amount of $4,089 million through FY 1979. We agreed with TAB on a joint recommendation that the total project be approved in principle but that funding be limited to an amount not to exceed $2.6 million. This funding level provides partial funding in the amount of $590,000 for FY 78 with the remainder of funding for that fiscal year and beyond contingent upon an indepth evaluation in 1977 and a revised project paper which includes the recommendations therein.

Funds for this project are included in the Activity Data Sheets, "Reaching the Pre-School Child," p.33 of the FY 1976 C Interregional Book and p.37 of the FY 1977 CP Interregional Book.

Recommendation: That you approve the attached Project Paper Revision in principle, with the condition that funding is limited at this time to a total of $2.6 million with funding beyond FY 78 contingent upon an in-depth evaluation and revised project paper which reflects that review. Language in corporating this cavaet is included on page 1A for your review and approval. We recommend that you approve this PP Revision by signing page 1A of the PP.

Attachments:

A. PROP - Development of Vitamin A Delivery Systems

B. Informal Minutes of the Reseach and Development Committee Meeting, 12/16/75.

Clearances:

AA/TA:CFarrar CF date 5/6/76
GC:WWarren date
GC/TFHA:ARichstein date
PPC/DPRE:AHandley date

TA/PPU:ECMcLeod:TA/N:SGKahn:asj:4/28/76

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

Projects: 1. Development of Vitamin A Delivery Systems, GTS, KPA #9 - 045

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

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

for both the Vitamin A Delivery System and the Combatting Iron Deficiency Anemia projects.

1. LDC involvement and commitment and criteria for selecting LDC.
2. Education component.
3. LDC institution for continuation of surveillance of the problem.
4. Increase level of funding for field research.
5. More specificity on alternatives for what is to be tested.
6. Cost effectiveness.

August 6, 1977

Application to U.S.A.I.D. from

Cornell University

Ithaca, New York 14853

for support for research and project entitled:

Short title: "Fortification to control vitamin A deficiency"

Full title: "Evaluation of a fortification program to control vitamin A deficiency in the Philippines"

Principal Investigator:

Professor Michael C. Latham, M.D.
Director, Program in International Nutrition
Professor of International Nutrition
Cornell University, Ithaca, New York 14853

Date of Submission: August 12, 1977

Proposal Starting Date: January 1, 1978

Completion Date: December 31, 1980

Signed: _____
Thomas R. Rogers, Director
Office of Academic Funding
123 Day Hall

Signed: _____
Dr. Michael C. Latham
Principal Investigator
127 Savage Hall

Abstract and Summary

Xerophthalmia, due to vitamin A deficiency, is the major cause of childhood blindness in the Philippines, and in several other Asian countries. When severe, the condition carries with it a high case fatality rate. Yet it is a preventable condition.

A collaborative study on vitamin A deficiency was begun in the Philippines in 1973, and is continuing. The institutions involved are the Cebu Institute of Medicine, the Nutrition Center of the Philippines, and Cornell University.

The first year of work consisted of a detailed investigation of the prevalence and underlying causes of xerophthalmia in 12 different communities on the island of Cebu in the Philippines. On the basis of the findings of this investigation, three different intervention strategies were designed, each one believed to have a good chance of controlling xerophthalmia and vitamin A deficiency. These interventions were (a) the provision every 6 months of 200,000 IU of vitamin A to all children, (b) a public health and horticulture intervention, and (c) a fortification program.

Each of these interventions was introduced separately into four different areas, two urban and two rural. All 12 areas surveyed were therefore covered. The data collected in the prevalence survey served as the baseline for the evaluation of the effectiveness of two years of intervention in each area.

All three interventions were associated with a marked reduction in eye signs of xerophthalmia. However only the fortification program was associated with a significant and important rise in serum vitamin A levels. The cost of each intervention and its suitability for a national program were carefully studied.

As a result of this, recommendations have been made for a national program to control vitamin A deficiency in the Philippines. These recommendations call for a national program of vitamin A fortification after a pilot trial in 2 or 3 provinces, and for the careful evaluation of its effectiveness. The current proposal is to conduct this trial, and to plan for a national program.

In the Cebu study the only suitable vehicle for fortification was found to be Monosodium Glutamate (MSG), a seasoning almost universally used by families in the Philippines and in some other Asian countries. In Cebu consideration was given to fortifying many different foods but none satisfied the criteria generally accepted as necessary for a fortification program. In contrast, MSG was found to be almost daily used by families, it is present in foods like soups and stews which are fed to children, it can be fortified without undue change to the product and without an increase in price, and most importantly, the product passes through a manufacturing process where vitamin A can be added. Nearly all the MSG in the Philippines is made by one manufacturer.

Cebu, where the earlier intervention project was so successful, is considered by the distributor to be an area of low utilization of MSG when compared with Greater Manila and with the rest of Luzon which are the most heavily populated areas of the Philippines. Both these areas use more MSG per head than does Cebu.

The proposed project is (a) to evaluate the feasibility, effectiveness and cost of a vitamin A fortification in three different Philippine provinces, (b) to undertake investigations to allow a reasonable prediction of the likely effectiveness of a national vitamin A fortification program, and (c) to plan and assist with the implementation of a national vitamin A fortification program.

The project is again a collaborative one, and will last three years. It is believed that it will markedly reduce vitamin A deficiency, xerophthalmia and blindness in three provinces, and will contribute to the early control of this serious public health problem in the Philippines.

This is to certify that this proposal has not been submitted to any other sponsor in whole or in part for their support.

Michael C. Latham

Dr. Michael C. Latham
Principal Investigator

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B. Relevance of Proposed Work to A.I.D.

(1) The problem and its pertinence to A.I.D.'s mission

Xerophthalmia, due to a deficiency of vitamin A, is the major cause of childhood blindness in the Philippines, and in several other Asian countries. It is responsible for a good deal of morbidity. Keratomalacia, which is a severe form of advanced xerophthalmia, carries with it a high case fatality rate. The U.S. government, aware of this devastating yet preventable form of malnutrition, has pledged support for efforts to control vitamin A deficiency.

At the World Food Conference in Rome vitamin A deficiency and nutritional anemias were singled out as nutritional problems amenable to control and ones which the U.S. would help countries to address. The responsibility for fulfilling this U.S. commitment will fall largely on U.S.A.I.D.

A project in Cebu by our group was one of the most detailed studies of the prevalence and underlying causes of xerophthalmia ever undertaken. The subsequent evaluation of three alternate strategies to control vitamin A deficiency is also unique. The results of these two studies are now available, and the logical next step is to move to test the control of vitamin A deficiency in much larger geographic areas of the Philippines. Authorities in the Philippines are keen to see the introduction of fortification in three provinces prior to a national program.

The collaborative study relating to vitamin A deficiency was begun in Cebu in the Philippines in 1973. This is a joint project of the Cebu Institute of Medicine and Cornell University, with in the latter years assistance from the Nutrition Center of the Philippines. The project has received support from the National Science Development Board of the Philippines (the major donor), W.H.O., UNICEF, Cornell University as well as

U.S.A.I.D. Technical assistance was provided by Hoffmann-La Roche of Nutley, New Jersey.

The first part of the study consisted of an investigation of the prevalence of xerophthalmia and vitamin A nutritional status, and of the determinants and related etiological factors in 12 different barrios or communities, three each in four distinct ecological zones, half urban and half rural.

One thousand seven hundred and fifteen children aged 1 to 16 years were examined. Clinical, biochemical and anthropometric data were collected from the children. Dietary and socioeconomic information was obtained from the households. Forty-seven percent of the children had deficient or low serum vitamin A levels and 6.3 percent had clinical eye signs associated with xerophthalmia. Multivariate statistical techniques were used to examine factors possibly associated with vitamin A deficiency in the different areas. A report of this phase of the study is available.

On the basis of these findings three different intervention strategies were designed, each one believed to have a good chance of controlling xerophthalmia and vitamin A deficiency. These interventions were (a) the provision every 6 months of 200,000 IU of vitamin A (the "massive dose capsule" intervention); (b) a "public health and horticulture intervention"; and (c) the fortification of monosodium glutamate (MSG) which is a seasoning almost universally used by families in the Philippines (the "MSG fortification" intervention).

Each of these interventions was introduced separately into four different areas, two urban and two rural. All 12 areas surveyed were therefore covered. The data collected in the prevalence survey served as the baseline for the evaluation of the effectiveness of the three different interventions.

All three interventions were associated with a marked reduction in the eye signs of xerophthalmia. However only the MSG fortification was associated with a significant rise in serum vitamin A levels. Mean serum vitamin A levels were 21.3 mcg/100 ml before the fortification and 28.5 mcg/100 ml after it. Especially gratifying was the fact that those with deficient and low serum vitamin A levels had the most dramatic rises. In those who had been "deficient" the serum vitamin A went from a mean of 6.4 to a mean of 25.4 mcg/100 ml.

The cost and effectiveness of the three interventions was carefully examined. As a result of this, recommendations have been made for a national program to control vitamin A deficiency in the Philippines (Appendix I, Chapter V). These recommendations call (a) for the eventual fortification with vitamin A of all MSG in the Philippines, after a pilot trial in two or three provinces, (b) for the adoption through existing health and agricultural services of certain limited parts of the other two interventions.

The present request is for funds to assist with the next stage of the MSG fortification program. The clear understanding is that if this proves to be feasible and effective then a national program will follow. Two allied projects will be undertaken as follows:

(a) A study to allow a reasonable prediction of the likely effectiveness of a national vitamin A fortification program, and

(b) An evaluation of the feasibility, cost and effectiveness (based on serum vitamin A levels) of MSG fortification covering the whole population in 2 or 3 separate provinces.

This proposal is a request for financial support for these projects, which are the logical last stepping stones prior to a national program.

The national program will, we believe, be of very low cost since the manufacturer is willing to replace a small portion of the MSG in each packet with the vitamin A pre-mix, and not add to the cost of the product as retailed. The only government cost will be in monitoring and evaluation. The results from Cebu suggest that a national program will be highly effective, both in raising serum vitamin A levels in children at risk and in reducing very quickly the eye signs of xerophthalmia. If successful, blindness resulting from vitamin A deficiency could be almost eliminated in the Philippines. The projects although here labeled as research projects will in all likelihood play a major role in preventing vitamin A deficiency, xerophthalmia and resulting blindness in the three provinces in which the work will be conducted.

This project when successfully completed will have demonstrated the effectiveness of a technical solution to a major social and public health problem of the Philippines, and of many other third world countries. It will have increased the capability of the Government and Agencies of the Philippines to control the scourge of vitamin A deficiency which is a major cause of blindness. By so doing it will have satisfied some of the main purposes of A.I.D. research support.

(2) Potential utilization of research results in other developing countries

The results of the work in the Philippines do have immense potential for use in other parts of the world. Indonesia with its huge population and with a major problem of blindness due to vitamin A deficiency has already indicated an interest in the proposed work in the Philippines. Other countries are also likely to use the results. The research has relevance beyond both the vehicle (MSG) and the health problem (vitamin A

deficiency). It will demonstrate a means of fortification and of its evaluation which will have relevance to other deficiency diseases using a number of food vehicles.

It is now widely agreed that except for protein-calorie malnutrition many of the nutritional problems of developing countries might most quickly and easily be solved or alleviated using fortification rather than programs which address food availability, eating habits, and economic problems. Certainly fortification also is likely to be the most cost-effective intervention if it can be successfully carried out.

Despite this there are not very many examples of good demonstration projects of the effectiveness of fortification in third world countries with the exception of salt iodization to control endemic goitre. Such demonstrations are necessary, and need to be carefully planned, well executed and then adequately evaluated. The present project will attempt to do this.

(3) Philippine participation in proposed research

As indicated in this application the proposed project follows three years of collaboration between Cornell University, the Cebu Institute of Medicine, and the Nutrition Center of the Philippines.

In the present project the participation of these two Philippine institutions will be extensive. Tomas Fernandez, M.D., of the Cebu Institute of Medicine, and Florentino Solon, M.D., Executive Director of the Nutrition Center of the Philippines, will be our main collaborators. The Philippine National Nutrition Council which is the official policy making and coordinating body in all work related to nutrition in the Philippines is supporting the project. Dr. Solon is the Executive Director of both the Philippine National Nutrition Council and the Nutrition Center of the Philippines.

These Philippine organizations will provide the major assistance to the project. They will make all arrangements with provincial governors, mayors and officials; they will ensure that local facilities are available; they will provide field workers; and they will use their laboratories or ones with which they work for all biochemical determinations.

Jointly with Cornell they have been involved in the agreements reached with Union Chemicals (Manila) for the fortification or nutrification of MSG and with Hoffmann-La Roche of Nutley, New Jersey for technical assistance.

Dr. Florentino Solon who directs all government nutrition efforts in the Philippines is continuing to take an active role in the project. Dr. Solon has close relations with First Lady Mrs. Emelda Marcos who is Patron of the Nutrition Center of the Philippines and who takes a continuing interest in its work. President Marcos has also frequently expressed his commitment to the nutrition programs in the Philippines. This political support has been a very important factor in the innovative and exciting nutrition programs now being launched in the Philippines.

(4) Environmental effects

The proposed project is not believed to have any adverse environmental effects.

(5) Effects on other concerns of A.I.D.

The improvement of health and nutrition is generally believed to be a prerequisite to the successful acceptance of family planning and child spacing. Malnutrition is a major contributor to morbidity and mortality in the Philippines and other developing countries. It is often stated that over 50 percent of child morbidity and mortality is related to malnutrition.

Xerophthalmia due to vitamin A deficiency has its major clinical effects on the eyes. But work in a number of countries shows that young children with serious xerophthalmia have a very high mortality rate from this disease. Children who survive, but who are blinded by xerophthalmia, also have a very much higher mortality rate than do normal children.

Any program which will control this devastating disease will provide families with an increased confidence that children are likely to survive in health. This may be a prerequisite to acceptance of family planning.

Although the program is aimed mainly at the health of children, it will improve the vitamin A nutritional status of adults, including women. By controlling a serious disease in children it will relieve women both of an anxiety, and of the care of children ill with xerophthalmia. It will also reduce the burden to society of blind people.

The problem of xerophthalmia is associated very closely with poverty. The program will therefore be of greatest benefit to those who live in poverty.

Finally, good sight must surely be regarded as a most important human right. The proposed research, and intervention, will help extend this right to more people in three Philippine provinces and later to the whole nation.

C. Specific Aspects of Proposed Work

(1) Specific objectives

The objectives are as follows:

1. To investigate the utilization of MSG first in three provinces and then nationally to allow a determination of the likely effectiveness of a fortification program in different parts of the Philippines.

2. To evaluate the effectiveness of the fortification of MSG program with vitamin A in three provinces, and on subjects at risk of suffering from vitamin A deficiency, and to test public reaction, etc.

3. To analyze the data from 1. and 2. so as to make predictions of the benefits likely to accrue from a national program, and the costs of the national monitoring and evaluation of the program.

4. To prepare appropriate reports and publications.

5. To assist the Philippines in the establishment of a national vitamin A fortification program, and especially in the means of monitoring and evaluating its effectiveness.

(2) Rationale and background

A detailed report of the preliminary work undertaken over the last several years is attached as Appendix I. This describes the problem of vitamin A deficiency in the Philippines, the original survey of the prevalence of xerophthalmia and its determinants in 12 areas in Cebu, the selection and implementation of three alternate control strategies, the evaluation of their relative effectiveness, and finally the recommendations for future action.

A project to determine the prevalence of xerophthalmia and to evaluate the effectiveness of three alternate intervention strategies to control vitamin A deficiency has been largely completed after three years of work. (Some reports and publications with a little re-analysis of data need still to be undertaken.)

The research has been conducted jointly by the Cebu Institute of Medicine (CIM) and Cornell University's Division of Nutritional Sciences, and more recently with assistance from the Nutrition Center of the Philippines. CIM is one of the seven medical schools in the Philippines. The CIM Director of the project has been Florentino Solon, M.D., who is now Executive Director of the National Nutrition Council and the Nutrition Center of the Philippines. The Cornell involvement is under the direction of Professor Michael C. Latham, M.D., Professor of International Nutrition and Director of the Program in International Nutrition at Cornell University. Tomas Fernandez, M.D., of CIM has been director of the field operations and in charge of the large local staff. Barry Popkin, Ph.D., a Research Associate at Cornell University and an economist, but resident at the University of the Philippines, has had responsibility for much of the data analysis.

The first phase of the study consisted of a large baseline survey of 1,715 children and 626 households in 12 separate locations, 6 urban and 6 rural. The survey provided data on the prevalence of vitamin A deficiency and xerophthalmia (using clinical, biochemical, and dietary measures) and on numerous health, social, economic and related factors (see Appendix I for detailed findings).

As a result of an analysis of the baseline survey three different intervention strategies were designed. Each one of these was believed to be likely to improve vitamin A nutritional status in the selected areas. Each was planned for introduction separately in four different areas. Consideration was given to having a similar number of control areas where no intervention would be introduced but the investigators and their advisors agreed that for ethical and other reasons this should not be done.

The three interventions consisted of (1) a massive dose vitamin A capsule (200,000 IU of vitamin A) provided every 6 months to all children in 4 areas, 2 urban and 2 rural; (2) a public health and horticulture intervention designed to control related diseases, to insure availability of health care and early treatment, and to encourage greater production and consumption of vitamin A (mainly carotene) rich foods in 4 areas, 2 urban and 2 rural; and (3) a fortification program in which universally used packets of the popular seasoning monosodium glutamate (MSG) were enriched or nutrified with vitamin A and supplied to families in 4 areas, 2 urban and 2 rural.

A large local staff were responsible under Dr. Fernandez for the continual implementation of these three interventions in each of the 12 areas, and for periodic examination of the study children. The Cornell participants were closely involved in the design, in following the interventions, and in all policy decisions, and they took responsibility for the analysis of the huge amount of data generated first from the baseline study, and then from the longitudinal study of 1,715 children. A very large number of variables were included in the analysis. These also included cost figures to allow for a cost effectiveness analysis to be undertaken. Dr. Popkin also undertook a lengthy benefit-cost analysis of the data. Various statistical techniques were used for this study including both descriptive and multiple regression analyses.

The evaluation reveals that all three interventions have had a good effect by reducing significantly the active clinical signs of xerophthalmia. The fortification of MSG with vitamin A was the only one of the three interventions which markedly raised serum vitamin A levels. In the four MSG areas the mean serum vitamin A levels were 21.3 mcg/100 ml before intervention and 28.5 mcg/100 ml after the intervention. Particularly

striking was the fact that the high risk children receiving fortified MSG benefitted most in terms of rises in serum vitamin A levels. Those who were "deficient" before the intervention had a mean serum vitamin A level of 6.4 before and of 25.4 mcg/100 ml after, and those who were "low" had a mean serum vitamin A level of 14.4 before and of 28.8 mcg/100 ml after the intervention. Serum vitamin A determinations are generally accepted as the most objective available means of evaluating vitamin A nutritional status.

A report some 100 pages in length has been prepared and this provides details of the investigation. Some extensive sections of this are included in the report attached here. A scientific paper on the baseline survey has been accepted for publication in the American Journal of Clinical Nutrition. A short article on the project appeared in the Xerophthalmia Club Bulletin. A detailed report was made of the project at the meeting of the International Vitamin A Consultative Group held at the World Health Organization Headquarters in Geneva, Switzerland in May 1977. Dr. Fernandez and Dr. Latham both attended that meeting. A number of other papers and reports are at various stages of preparation.

In February 1977 Dr. Solon, Dr. Fernandez and Dr. Latham presented the findings of the intervention study to a large meeting of the National Science Development Board of the Philippines, who had invited many leading nutritionists, health workers, ophthalmologists, agricultural specialists, and persons from the international agencies (including U.S.A.I.D.) to attend and to comment. At this meeting the data were presented, and recommendations were made for steps that would lead to a national program to control vitamin A deficiency in the Philippines. Those recommendations are included in the report attached.

The present application is to facilitate the implementation of these recommendations which are expected to lead to a national program. In general the recommendations call eventually for a national program of enrichment with vitamin A of all MSG in the Philippines, and concurrently for the introduction of some aspects of the other two interventions into national health and agricultural activities.

The investigators believed (and this was generally agreed to) that two steps were necessary prior to a national program being implemented. These were:

1. An investigation of the utilization of MSG in the Philippines so as to predict who would benefit, and who would be missed in a national program of vitamin A fortification of MSG.

2. The implementation of an MSG fortification program in three different provinces of the Philippines in order to determine feasibility, public reaction, and especially to monitor its effects on serum vitamin A levels.

This proposal requests support for certain aspects of these two related projects which will be undertaken by Cornell University under the direction of Dr. Michael C. Latham. The two projects will be phased into a national MSG fortification program towards the end of the project. There will therefore be three major activities, the first two will be concurrent, and will begin early. The activities are:

1. Utilization of MSG in the Philippines.
2. Evaluation of MSG fortification in 3 provinces.
3. Phasing in of a national vitamin A fortification program.

(3) Literature review

A thorough literature review with an extensive bibliography and list

of references was prepared during the earlier phases of work when we were evaluating three alternate strategies to control xerophthalmia. That review is included as Appendix II with its references.

Since that time there has been published the Report of a Joint WHO/USAID Meeting. This is entitled "Vitamin A Deficiency and Xerophthalmia" and is WHO Technical Report Series No. 590, 1976 (1). Both Dr. Latham (the Principal Investigator) and Dr. Solon (the Project Director) served on the group that prepared the report. It provides a useful "state of the arts" review on xerophthalmia, it recommends a new classification of clinical signs of vitamin A deficiency, it suggests criteria for community diagnosis of xerophthalmia and it provides a detailed discussion on prevention.

Almost at the same time the International Vitamin A Consultative Group (IVACG) produced a useful booklet entitled "Guidelines for the eradication of vitamin A deficiency and xerophthalmia" (2). The Principal Investigator is a member of IVACG and served as Chairman of its Research Working Group which prepared one section of this publication.

These two publications both suggest that fortification of suitable products may offer a sound means of controlling vitamin A deficiency and they provide useful guidelines. These have been followed in the proposal here.

Fortification has been practiced extensively for a long time, with vitamin A added to such products as margarine in North America, Europe and elsewhere, and to various powdered and preserved milk products. These measures have not been aimed primarily to control xerophthalmia on a national or regional basis but rather to ensure that vitamin A was present when a food like butter was substituted for by use of margarine; or when fresh milk was replaced by preserved milk products.

Up to a few years ago it seemed that most hope for a dramatic reduction in xerophthalmia was pinned onto the strategy of providing a massive dose (usually 200,000 IU) to young children every 6 months. Major programs were launched in Bangladesh and India (3), trials were undertaken in Central America and Indonesia, and we included this method as one of our three intervention strategies in Cebu in the Philippines (4).

There is now some disillusionment about this strategy for a number of reasons. These include the fact that a delivery system has to be established, and this may be very costly; most delivery systems miss a number of children at the time that first dose is given and miss increasing percentages of children when subsequent doses are administered, and the missed children may be those at greatest risk of developing xerophthalmia; and the interval of 6 months between doses does not appear to maintain satisfactory levels of serum vitamin A for the whole period.

Fortification of sugar with vitamin A has been made mandatory in Guatemala and some other Central American countries. The program in Guatemala is being carefully monitored by a team at INCAP (5). Other vehicles for fortification with vitamin A are being considered but no program is believed to be as advanced as those in Central America, or to have been evaluated as thoroughly as in the Cebu project in the Philippines.

For a more comprehensive literature review prepared for the Philippine project please refer to Appendix II.

(4) General experimental design

Two provinces have been selected. These are the island of Marinduque which is fairly typical of the heavily populated middle sized islands, and the second is Nueva Viscaya on the major island of Luzon. A third province will soon be selected. In each province a random sampling technique will

be used to select an appropriate number of municipalities, and of barangays within each municipality for study. Each municipality and each barangay will have an equal chance of being selected. In each of the selected barangays a random selection of households will be made to provide the appropriate number of families. A trained interviewer will visit each household and use a questionnaire to assess the utilization of MSG by the family and by each household member. Other relevant information will be collected. The questionnaire will be designed so that the family are asked about their utilization of salt, sugar, other food items, as well as MSG so as not to draw special attention to MSG. The foods and dishes to which MSG are customarily added will be identified.

Details will be obtained from Union Chemicals (Manila) regarding their distribution of MSG. They provide 95 percent of the MSG used in Philippine households. With their assistance the length of time between manufacture and consumption will be determined. A code identification of date of manufacture will be put on certain MSG packets. The packets being used in the households will then provide data on when these were manufactured. Similarly in the small shops (the "sari-sari" stores) packets with the date code will be examined. The reason for this is that vitamin A potency in fortified products including MSG is reduced over time. It has been determined that most of the potency is present one year after fortification but it is important to know the usual length of time between fortification and consumption.

Union Chemicals have agreed to cooperate with all aspects of the study. They have agreed that fortification can be undertaken by them, and that the cost of the product at retail will not be increased.

In the selected barangays a subsample of families perhaps one in five

Up to a few years ago it seemed that most hope for a dramatic reduction in xerophthalmia was pinned onto the strategy of providing a massive dose (usually 200,000 IU) to young children every 6 months. Major programs were launched in Bangladesh and India (3), trials were undertaken in Central America and Indonesia, and we included this method as one of our three intervention strategies in Cebu in the Philippines (4).

There is now some disillusionment about this strategy for a number of reasons. These include the fact that a delivery system has to be established, and this may be very costly; most delivery systems miss a number of children at the time that first dose is given and miss increasing percentages of children when subsequent doses are administered, and the missed children may be those at greatest risk of developing xerophthalmia; and the interval of 6 months between doses does not appear to maintain satisfactory levels of serum vitamin A for the whole period.

Fortification of sugar with vitamin A has been made mandatory in Guatemala and some other Central American countries. The program in Guatemala is being carefully monitored by a team at INCAP (5). Other vehicles for fortification with vitamin A are being considered but no program is believed to be as advanced as those in Central America, or to have been evaluated as thoroughly as in the Cebu project in the Philippines.

For a more comprehensive literature review prepared for the Philippine project please refer to Appendix II.

(4) General experimental design

Two provinces have been selected. These are the island of Marinduque which is fairly typical of the heavily populated middle sized islands, and the second is Nueva Viscaya on the major island of Luzon. A third province will soon be selected. In each province a random sampling technique will

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In the selected barangays a subsample of families perhaps one in five

will be used to provide the baseline data for evaluation. All preschool age children (aged 1-6 years), some school age children, and a sample of lactating women and other adults will be used to get determinations of serum vitamin A. Clinical eye examinations will be made on the preschool children. This will include use of the new eye-staining technique of Sauter (using either Rose Bengal or Lissamine Green stain) for conjunctival xerosis.

Soon after the completion of the collection of baseline data, all MSG introduced in the three provinces will be fortified with vitamin A. It is intended to add 15,000 IU of vitamin A for each 2.4 gram packet of MSG. This was the same amount used in the Cebu study, and found to be acceptable and effective. An investigation will be made to monitor the acceptability and use of the fortified MSG in the three provinces.

Twelve months, and again 24 months, after the baseline survey an equal number of subjects matched for age, sex, etc. (but not necessarily the same subjects) will be examined in the same way. Blood will be collected for serum vitamin A determinations and clinical eye examinations conducted as before. These new data will be utilized to evaluate the effectiveness of the MSG fortification, or nutrification, program in each of the three provinces.

It is predicted that the distribution of serum vitamin A levels will shift upwards (see WHO publication) perhaps from a mean around 20 mcg/100 ml to a mean of 30 mcg/100 ml after two years but with the curve of the distribution rather similar at each period but shifted markedly to the right away from zero. This is now accepted as the best means of evaluating the effectiveness of a vitamin A fortification program. Similarly it is predicted that clinical signs of xerophthalmia in those examined will be

markedly reduced. The use of the eye staining technique will be evaluated and compared with regular clinical examinations.

Concurrent with the interventions in the three selected provinces, a study will be undertaken of the utilization of MSG in the rest of the Philippines. Techniques similar to those used to gauge MSG utilization in the three fortification provinces will be used in the other Philippine provinces. However fewer municipalities, barangays and households will be surveyed.

During year 2 and 3 of the present project, planning will be undertaken for a national vitamin A fortification project. This will be based on the first 12 month evaluation in the 3 pilot provinces and on the national MSG utilization survey. A meeting will be called in year 2 for the purpose of making detailed proposals for the national program. Various responsible and knowledgeable persons in the Philippines will be invited to this meeting. An outside consultant* will be invited to participate and provide advice. Recommendations will be expected on how and when to proceed with a national program; the appropriateness of the level of nutrification used in the three provinces; a prediction of the likely effectiveness; proposals for control of xerophthalmia in groups of the population not likely to benefit from MSG fortification.

Serum vitamin A determinations will be undertaken in the Philippines. On a sub-sample of the sera duplicate determinations will be performed at a laboratory in the U.S., probably at Cornell University, to validate the results.

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* Dr. Guillermo Arroyave of INCAP in Guatemala may be the logical choice. He is responsible for vitamin A fortification of sugar in several Central American countries.

Cornell University will take a large share of responsibility for the data analysis on which the evaluation is dependent. A Research Associate will be employed by Cornell University who will be stationed in the Philippines. He or she will be a person with a good knowledge of nutrition and with experience and capability of data analysis and computer techniques.

The proposed project is the logical next step following the previous study investigating the effectiveness of three alternate strategies to control vitamin A deficiency.

The chances of success seem high because the evaluation in Cebu has shown that fortification is feasible, it is well accepted by the public, it does not add cost to families involved, and it is effective both in reducing eye lesions due to vitamin A deficiency and in raising serum retinol (vitamin A) levels. These are agreed to be the best means of evaluation.

(5) Specific research methodologies and techniques

Introduction

An important objective of the present project is to monitor and evaluate the effectiveness of a vitamin A fortification in three provinces, as a step on the way to a national fortification program.

In each province baseline data will be collected from a suitably designed sample of children and a limited number of adults prior to the intervention. Data will include the utilization of MSG, serum vitamin A levels and prevalence of ocular signs.

Protection of individuals and informed consent

Care will be taken to safeguard the rights and welfare of human subjects involved in the project. At all times families, including parents of children, will be informed about the purposes of the program and the

procedures to be used. The benefits to result from the program will also be explained. Whenever eye signs or low serum vitamin A levels are detected appropriate treatment will be given. Similarly the medical team examining subjects will provide simple medical treatment for other conditions and will where necessary refer cases to the appropriate medical authorities. No pressure will be put on families to participate against their will.

Evaluation of effectiveness

Follow-up surveys will be performed at 12 month intervals, using an independent sample of children matched with the baseline sample, and measuring the same parameters in order to measure the effectiveness of the fortification program. In follow-up surveys persons with active clinical signs of xerophthalmia and with deficient and low serum vitamin A levels will receive treatment as early as possible, in the same way as in the baseline survey.

The infrastructure to be used at the local level are the rural health units (RHU's) and the municipal and barangay health and nutrition workers.

Sampling and data analysis

Although it would be most desirable from the purely theoretical point of view to draw a sample from the whole province, this may not always be feasible in all provinces (it will be possible in Marinduque). The main reasons for this not being practical include for example that blood samples from outlying barangays would have to be frozen and transported over long distances to the laboratory. Care however will be exercised to sample from areas which are representative of the whole province, in order to avoid or limit the introduction of biases, while remaining within the constraints imposed by the logistics of the field work.

The sample size to be drawn from each area will be determined on a rational basis using statistical advice provided by a WHO Consultant Biostatistician (Dr. S. P. H. Mandel, Professor of Mathematical Statistics, University of Otago, New Zealand).

The sampling plan for the selection of subjects for the monitoring and evaluation will consist of a multi-stage cluster sampling design, with the municipality, barangay and household constituting the primary, secondary and tertiary sampling units respectively.

An appropriate information system for the collection, collation, storage, retrieval and analysis of data is being designed. As far as possible fairly basic statistical procedures will be used for the analysis of the data. Multivariate statistical techniques will be sparingly used.

The actual sample size will be based on initial findings of prevalence and variability. Sample sizes required for specified widths (λ) of say the 95 percent confidence interval for estimating a prevalence ratio will be estimated. Statistical advice has been obtained to help determine the needed sample size capable of detecting minimum practical effects of the intervention. The prior work in Cebu is helpful in providing an estimate of the order of magnitude of effects of intervention.

Data collected will be keypunched and set up for computer analysis. The Cornell Research Associate will take major responsibility for the data analysis. The IBM 370-145 Computer of Meralco in Manila will be used for much of the analysis, and certain analyses will be done on the Cornell computer (also an IBM 370).

Eye examinations and serum vitamin A determinations

Similar techniques will be used as in the xerophthalmia project in

Cebu both for the eye examinations and for determination of serum vitamin A levels.

Eyes will be examined by a physician trained to recognize eye signs related to xerophthalmia and to make differential diagnosis for other conditions. Regular and frequent standardization will be checked for observer consistency. The only new technique which is being considered for use is the staining procedure proposed by Sauter (6), and now tested in India by Reddy (7), and used in studies in Kenya, Indonesia and Guatemala. This consists of putting a small drop of either Rose Bengal or Lissamine Green stain in the eye. This method makes the diagnosis of conjunctival xerosis much easier.

Serum retinol levels will be determined in the laboratory using the standard Trifluoracetic acid method widely used and as recommended in the ICNND Manual on Nutrition Surveys.

Recently it has become apparent that there is a close correlation between plasma levels of vitamin A and of retinol binding protein (RBP). In vitamin A deficiency plasma levels of holo RBP fall and RBP accumulates in the liver indicating the intimate relationship of RBP with retinol in plasma (8). Consideration has been given to using RBP determinations as a further means of evaluation. At present no final decision has been made but in general it is believed that this will complicate the project without necessarily producing any great advantages.

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D. Facilities and Resources

(1) Facilities

The facilities of the Nutrition Center of the Philippines, of Cornell University and of CIM are available and adequate for the project. Whenever necessary other facilities will also be utilized. Computer facilities necessary for the analysis of the data are available both in Manila and in Ithaca.

The Nutrition Center of the Philippines (NCP) in Manila will take overall responsibility for the implementation in the three provinces. The Philippine National Nutrition Council (NNC) will make decisions concerning a national program. Dr. Florentino Solon, the Director of the overall vitamin A project, is also Executive Director both of the NCP and NNC. These organizations have a headquarters building in Makati (near Manila) with a full range of facilities. NCP has staff in the provinces, and is working in most municipalities.

The Cebu Institute of Medicine is one of seven medical schools in the Philippines. It has the usual number of medical departments. The laboratory was used for doing serum vitamin A and other determinations for the Cebu project.

Other Philippine institutions such as the Food and Nutrition Research Institute (Director: Dr. Carmen Intengan) will also be used where necessary.

Dr. Engel, Nutrition Adviser to U.S.A.I.D. in Manila (on loan from V.P.I.) has been consulted about the project, and will provide advice and support.

(2) Personnel

Principal Investigator - Professor Michael C. Latham, M.D. (C.V. follows).

Director of Overall Project - Florentino Solon, M.D., Executive Director, Nutrition Center of the Philippines and Philippines National Nutrition Council (C.V. follows).

Associate Director of Project - Tomas Fernandez, M.D., Cebu Institute of Medicine (C.V. follows).

Cornell will employ a full-time Research Associate who will spend most of his/her time in the Philippines. A Cornell Research Assistant will also work part-time on the project. A part-time computer programmer will be employed in the Philippines.

Curriculum Vitae

Name: Michael Charles Latham

Present Position: Professor of International Nutrition, Cornell University

Address: Graduate School of Nutrition, Cornell University, Ithaca, New York 14850 (Telephone (607) 256-3041)

Education:
1946 First Class Matriculation
1949 Bachelor's Degree, Trinity College, University of Dublin
1952 Graduated from Medical School, University of Dublin
1958 Diploma of Tropical Medicine and Hygiene, London University
1965 Master of Public Health, Harvard University
1973 Fellow, Faculty of Community Medicine, Royal College of Physicians, London (Honorary)

Degrees: B.A., M.B., B.Ch., B.A.O. (Dublin); D.T.M. and H. (London); M.P.H. (Harvard); F.F.C.M. (London)

Distinctions: Awarded O.B.E. by H. M. Queen Elizabeth II for "distinguished service in Tanzania."
Elected Fellow, Faculty of Community Medicine of Royal College of Physicians, England, 1973

Previous Positions:

1952-53: House Surgeon, High Wycombe Hospital, England
1953-54: Visitor Exchange Fellow at Methodist Hospital, Los Angeles, California
1954-55: Senior House Officer, North Middlesex Hospital, London
1955-64: Medical Officer and later Medical Officer in Charge, Nutrition Unit, Ministry of Health, Tanzania
1964-68: Research Fellow, Research Associate and Assistant Professor of Nutrition, Department of Nutrition, Harvard University
1968-Present: Professor of International Nutrition, Cornell University, and Director of the Program in International Nutrition

Consultant and Allied Duties:

Nutrition Consultant to W.H.O., F.A.O., UNICEF and the Peace Corps; Panel Vice-Chairman and Consultant, White House Conference on Food, Nutrition and Health 1969; Associate Editor of "Nutrition Reviews"; F.A.O. Correspondent on Food Habits and Food Behavior; Member of National Academy of Sciences/National Research Council Committee on International Nutrition Programs; Committee Member National Academy of Sciences Executive Committee on Problems of Pest Control; Editor Cornell/MIT International Nutrition Policy Series; Served on PAG Committee on Milk Intolerance; Associate Member of the Faculty of the Cornell Institute of Food Science and Marketing

Membership of Professional Associations:

Fellow, Royal Society of Tropical Medicine and Hygiene
Fellow, American Public Health Association
Member, Nutrition Society (London)
Member, American Institute of Nutrition
Member, International College of Tropical Medicine
Member, British Medical Association
Member, American Society for Clinical Nutrition
Member, American Association for the Advancement of Science
Member, Xerophthalmia Club
Member, Society for Nutrition Education

Publications: Author and co-author of approximately 85 publications including four books.

Michael C. Latham
Professor of International Nutrition
Cornell University
Ithaca, New York

April 1977

Publications

A. Books

(1) "Human Nutrition in Tropical Africa" (1965) M. C. Latham. Published by FAO, Rome, for Joint FAO/WHO/UNICEF Project. 260 pp., 68 figs. Second printing 1968; Third printing 1969; Fourth printing 1970; Fifth printing 1973. French edition 1971.

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CURRICULUM VITAE

NAME: Florentino S. Solon

PRESENT POSITION: Executive Director, Philippines National Nutrition Council
Executive Director, Nutrition Center of the Philippines

ADDRESS: Office: Nutrition Center of the Philippines, Population Center Building, South Superhighway, Makati, Rizal, Philippines

EDUCATION: 1956 - Doctor of Medicine - University of Santo Tomas
1964 - Master of Public Health - University of the Philippines
1966 - Diploma in Nutrition - London University
1966 - Certificate in Applied Nutrition - Ibadan University, Nigeria, Africa

DEGREES: M.D. (UST) M.P.H. (UP) DIP.NUTR. (London)

PREVIOUS POSITIONS:

Municipal Health Officer, Carmen, Cebu 1957-1963
Medical Nutritionist II, Regional Health Office No. 6, 1964-1966
Mental Hygienist, Southern Islands Hospital (Medical Specialist II)
Chief of Consultants, Regional Health Office No. 6, Cebu City
Chairman, Department of Preventive and Social Medicine, Cebu Institute of Medicine

CONSULTANT DUTIES:

Philippine Medicare Commission Phase II
Philippine Applied Nutrition Programs

DISTINCTIONS:

1. Most Outstanding MHO - by Cebu Medical Society (CMS) 1962
2. Most Outstanding MHO - by the Association of Municipal Health Officers of the Philippines 1963
3. Certificate of Scholastic Excellence (in M.P.H. course) by University of the Philippines PHI KAPPA PHI - 1964
4. Community Development Award - by CMS - 1969
5. Most Exemplary Young Citizen of Cebu (in Medicine) TEYC 1969
6. Science Awardee (1970) for Pioneering Establishment of Malnutrition Ward - by Philippine Association for the Advancement of Science
7. 125th Lecturer of the Don Luis Cuerrero Memorial Lecture - University of Santo Tomas, College of Medicine - July 1970
8. Most Outstanding Physician for the CMS - by the Philippine Medical Association - 1971
9. Delegate to the First Asian Nutrition Congress, Hyderabad, India 1971
10. UST Centennial Community Service Award - 1971
11. Makati Rotary Award for Community Service - 1972

MEMBERSHIP OF PROFESSIONAL ASSOCIATIONS:

Member, International Union of Nutritional Sciences
Member, Xerophthalmia Club (International)
Member, Philippine Association of Nutrition
Member, Philippine Medical Association
Councilor, Cebu Medical Society
Member, Philippine Association of Medical Colleges

ARTICLES WRITTEN:

1. The Presenting Symptoms of the 1st 150 Mental Cases Seen in Cubao Mental Health Clinic (Thesis, M.P.H. - U.P. - 1964)
2. The Community and Hospital Infection, Southern Medical Journal - 1964
3. The Daily Requirement for Ascorbic Acid (Read at Nutrition Seminar London University - 1966)
4. Recent Trends in Nutrition, Southern Medical Journal - 1968
5. Food and Food Values, Southern Medical Journal - 1968
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8. Training of Medical Interns in Comprehensive Community Medicine CMS Bulletin - 1969
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10. Community Medicine in a Rural Setting, Journal of the Manila Medical Society - September 1970
11. Experience in the Training of Medical Interns and Nurses in the Delivery of Health Care in the Philippines, Philippine Hospital Association Journal - September 1971
12. The Role of Community Medicine in Medical Education Proceedings of the Second National Medical Education Seminar on Community Medicine, Association of Korean Colleges - May 1972
13. The Status Vitamin A Deficiency in the Philippines - Country Report, Meeting on Prevention of Blindness in Southeast Asia, Hyderabad, India - March 1972
14. Organizing the Community for Nutrition Programs, Nutrition Education Conference, Guadalajara - 1972
15. Field Training of Medical and Health Personnel in Nutrition, International Nutrition Congress, Mexico - 1972

CURRICULUM VITAE

NAME: Tomas L. Fernandez

PRESENT POSITION: Coordinator, Cebu Institute of Medicine-Community Medico-Social Services.

Faculty member, Department of Preventive and Social Medicine, CIM

ADDRESS: Cebu Institute of Medicine, Cebu, Philippines

MARITAL STATUS: Married with two children

EDUCATION: 1961 - Associate in Arts, University of San Carlos

1966 - Doctor of Medicine, Cebu Institute of Medicine

1971 - Masters of Public Health, University of the Philippines

DISTINCTION: Scholastic Gold Medal Philippine Public Health Association, SEAMCO Educational Tour

PREVIOUS POSITIONS: 1966-1969 Faculty Department of Microbiology, CIM

1969-present Faculty Department of Preventive and Social Medicine, CIM

1973-1977 Field Director CIM-Cornell Vitamin A Project

(3) Other research contracts and grants received by Principal Investigator

(a) National Dairy Council grant to investigate the relationship of lactose intolerance to milk intolerance, 1975-1977. Total grant $8,154.

(b) U.S.A.I.D. funding for project entitled "Evaluation of three alternate strategies to prevent xerophthalmia in children in the Philippines". 6/1/76 - 9/1/77. Total grant $19,000.

(c) Hatch Funds grant to investigate lactose intolerance in New York State and the significance of this for the dairy industry. 1973 to 1975.

(d) U.S.A.I.D. contract, Nutrition Policy and Planning Workshop for Africa. 3/1/76 - 7/31/76. Total grant $67,000.

(e) World Bank support to conduct research in Kenya on (1) the relation of nutrition and health to worker productivity, and (2) the effect of roundworm infection on nutritional status in children. 1975-1977. Total grant $35,000.

E. Budget Information and Estimates

(1) Estimated total funding requested of A.I.D.

Year 1	$40,572.00
Year 2	57,618.00
Year 3	46,991.00
Total	$145,181.00

(2) Financial contributions and cost sharing

The time and effort of the Principal Investigator is a cost to be borne by Cornell University. It is expected that Dr. Latham will devote 10-20% of his effort to the project. The contribution in terms of salary and fringe benefits is approximately $18,000.00 (at 15% of effort).

The Project Director and the Cebu Institute of Medicine Associate Director will also not receive salaries or wages from this grant. Dr. Solon is expected to devote 10% of his effort and Dr. Fernandez 30% of his effort to the project. The value of this over three years is estimated to be around $20,000.00.

The Nutrition Center of the Philippines and the Philippine National Nutrition Council will carry the costs of the field work including medical, health and nutritional staff; of all laboratory determinations; of getting questionnaire information; and of work in the actual fortification of the product. The costs of none of these items are requested in the budget for this project. The estimated cost of this aspect is $110,000.00 over the 3 years.

Facilities and staff of the various institutions involved (Cornell, CIM and NCP) including office space, libraries, laboratories etc. will be available at no cost to the project. The value of this cannot easily be estimated.

(3) **Detailed budget by year**

Year 1 Jan. 1, 1978 - Dec. 30, 1978	**Amount U.S. $**
(1) Salaries	
Principal Investigator (Dr. Latham)[1] Cornell University	Nil
Project Director (Dr. Solon)	Nil
CIM Associate Director (Dr. Fernandez)	Nil
Cornell Research Associate[2] (10 months at $1200.00 p.m.)	12,000.00
Computer Programmer in the Philippines (6 person months at $200.00 p.m.)	1,200.00
Secretary in the Philippines (6 person months at $120.00 p.m.)	720.00
Cornell Research Assistant (to work in Philippines summer 1978)	1,070.00
21.5% fringe benefits of $12,000.00 Cornell salaries and wages (other than students)	2,580.00
(2) Consultant fees and expenses (20 days at $100.00 p.d.)	2,000.00
(3) Non-expendable equipment	Nil
(4) Expendable equipment and supplies[3] (including office expenses)	2,000.00
(5) Travel and subsistence	
(a) Two round-trip (Principal Investigator and Research Assistant) and one one-way Ithaca-Manila	5,000.00
(b) Local travel in Philippines	600.00
(c) Per diem[4]	1,200.00

Year 1 (continued)

	Amount U.S. $
(6) Publication costs and communications[5]	
Journal articles, preparation of reports, reporting at meetings, etc.	2,000.00
(7) Other direct costs[6]	
Key punching, computer, statistical analysis, etc.	3,000.00
(8) Total Direct Costs	33,370.00
(9) Indirect costs 55.1% of Cornell salaries off campus ($13,070.00)	7,202.00
(10) Grand Total	$40,572.00

Year 2 Jan. 1, 1979 - Dec. 30, 1979	Amount U.S. $
(1) Salaries	
Principal Investigator (Dr. Latham)[1] Cornell University	Nil
Project Director (Dr. Solon)	Nil
CIM Associate Director (Dr. Fernandez)	Nil
Cornell Research Associate[2] (12 months at $1300.00 p.m.)	15,600.00
Computer Programmer in the Philippines (6 person months at $250.00 p.m.)	1,500.00
Secretary in the Philippines (12 person months at $150.00 p.m.)	1,800.00
Cornell Research Assistant	5,200.00
21.5% fringe benefits of $15,600.00 Cornell salaries and wages (other than students)	3,354.00
(2) Consultant fees and expenses (10 days at $100.00 p.d.)	1,000.00
(3) Non-expendable equipment	Nil
(4) Expendable equipment and supplies[3] (including office expenses)	2,500.00
(5) Travel and subsistence	
(a) Three round-trips U.S.-Manila (Principal Investigator, Consultant, Research Assistant) and one round-trip Manila-Ithaca	8,000.00
(b) Local travel in the Philippines	600.00
(c) Per diem[4]	1,400.00

Year 2 (continued)

	Amount U.S. $
(6) Publication costs and communications[5]	
Journal articles, preparation of reports, reporting at meetings, etc.	1,500.00
(7) Other direct costs[6]	
Key punching, computer and statistical analysis, etc.	3,000.00
(8) Total Direct Costs	45,454.00
(9) Indirect costs 69% of Cornell salaries on campus (of $5200.00) and 55.1% off campus (of $15,600.00)	12,164.00
(10) Grand Total	$57,618.00

Year 3 Jan. 1, 1980 - Dec. 31, 1980	Amount U.S. $
(1) Salaries	
Principal Investigator (Dr. Latham)[1] Cornell University	Nil
Project Director (Dr. Solon)	Nil
CIM Associate Director (Dr. Fernandez)	Nil
Cornell Research Associate[2] (8 months at $1400.00 p.m.)	11,200.00
Computer Programmer in the Philippines (4 person months at $300.00 p.m.)	1,200.00
Secretary in the Philippines (4 person months at $180.00 p.m.)	720.00
Cornell Research Assistant	6,000.00
21.5% fringe benefits of $11,200.00 Cornell salaries and wages (other than students)	2,408.00
(2) Consultant fees and expenses (20 days at $100.00 p.d.)	2,000.00
(3) Non-expendable equipment	Nil
(4) Expendable equipment and supplies[3] (including office expenses)	2,000.00
(5) Travel and subsistence	
(a) Two round-trips Ithaca-Manila (Principal Investigator and Research Assistant) and one one-way Manila-Ithaca (Research Associate)	5,000.00
(b) Local travel in the Philippines	400.00
(c) Per diem[4]	1,200.00
(6) Publication costs and communications[5]	
Journal articles, preparation of reports, reporting at meetings, etc.	2,500.00

Year 3 (continued)	Amount U.S. $
(7) Other direct costs[6]	
Key punching, computer and statistical analysis, etc.	2,500.00
(8) Total Direct Costs	37,128.00
(9) Indirect costs 69% of Cornell salaries on campus (of $6000.00) and 55.1% off campus (of $11,200.00)	9,863.00
(10) Grand Total	$46,991.00

Total Direct Costs	
Year 1	$ 33,370.00
Year 2	45,454.00
Year 3	37,128.00
Total	$115,952.00
Total Indirect Costs	
Year 1	$ 7,202.00
Year 2	12,164.00
Year 3	9,863.00
Total	$29,229.00
Grand Total (Direct and Indirect)	
for 3 year study	$145,181.00

[1] Dr. Latham is expected to devote 10 to 20 percent of effort to the project but no reimbursement for salary is being requested.

[2] Cornell Research Associate will be based in the Philippines but will be entitled to Cornell fringe benefits.

[3] Approximately 50% to be spent in the Philippines and 50% at Cornell.

[4] Per diem is for those travelling away from the duty station, mainly from U.S. to Philippines.

[5] Will be spent mainly at Cornell.

[6] About 70 percent is expected to be spent in the Philippines and 30 percent at Cornell.

APPENDIX I June 30, 1977

Report on:

"Research to determine the cost and effectiveness of alternate means of controlling vitamin A deficiency"

and

"Evaluation of three alternate strategies to prevent xerophthalmia in children in the Philippines"

Supported by U.S.A.I.D.

Principal Investigator: Michael C. Latham, Cornell University

Prepared by:

Florentino Solon, M.D., M.P.H., Executive Director, National Nutrition Council and Nutrition Center of the Philippines.

Tomas Fernandez, M.D., M.P.H., Project Field Director, Cebu Institute of Medicine.

Barry Popkin, Ph.D., Research Associate, Cornell University and Rockefeller Fellow, University of the Philippines, Department of Economics.

and

Michael C. Latham, M.D., M.P.H., D.T.M. and H., Professor of International Nutrition, Cornell University (Principal Investigator U.S.A.I.D. Contracts No. AID/ta-C-116 and AID/it-C-1319)

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Preface

This report to U.S.A.I.D. constitutes the final report in respect to "Research to determine the cost and effectiveness of alternate means of controlling vitamin A deficiency" and "Evaluation of three alternate strategies to prevent xerophthalmia in children in the Philippines".

These projects in the Philippines received support from U.S.A.I.D. for the Cornell component. Other financial assistance was received from the National Science Development Board of the Philippines and from the World Health Organization in Geneva. UNICEF donated vitamin A capsules and Hoffmann-La Roche provided valuable technical assistance. Union Chemicals (Manila), the Philippine associate of the Ajino Moto Company of Japan, cooperated with the team in the fortification of their product.

Assistance has been received from numerous people in all these organizations and in others during the three years of the project. We are grateful to all of them and to the staff of the Office of Nutrition of U.S.A.I.D., all of whom made the completion of the task possible. The government of the Philippines and the Nutrition Center of the Philippines provided cooperation. Above all we are extremely thankful to the families in the 12 barangays in Cebu who were central to the study and whose patience, cooperation and friendliness were essential and much appreciated. We believe that the help of all of these will contribute to the control of vitamin A deficiency and a scourge of blindness in the Philippines.

CHAPTER 1

INTRODUCTION

This pilot project attempts to systematically determine the best programs for eliminating xerophthalmia in the Philippines. The goals are to:

1. Determine the magnitude of xerophthalmia, or severe vitamin A deficiency in one region in the Philippines;
2. Understand the relative importance of the various factors associated with xerophthalmia;
3. Design optimal programs for eliminating and preventing xerophthalmia for different ecological conditions; and
4. Determine the nutritional and economic effects of each program after the programs have operated for one and one-half years.

The need for systematic planning to develop useful strategies and programs for combatting malnutrition has become widely recognized in recent years. This stems partially from the major changes in the perspective on human resource development and the numerous technological breakthroughs which have led to renewed interest in specific nutrition interventions. Further, planners have become increasingly aware of the developmental efforts of the previous decades which have benefited not those most in need, but the middle and upper classes of society. These previous investment-oriented developmental

approaches ignored the issues of employment, income distribution and other major welfare issues such as nutrition.

This interest in nutrition has meant that more efforts are being directed towards developing effective nutrition strategies. This would ideally include four steps: (1) a determination of the magnitude of the general or specific nutrition problem; (2) an understanding of the importance of various determinants of this nutrition problem; (3) an analysis of the optimum means of eliminating, alleviating, or preventing the problem; and (4) an evaluation of the health, nutritional and economic benefits resulting from its elimination.

The 1970's represent the decade of equity considerations for many interested in the development of low income nations. Attention is being focused on directly reaching those most in need through various health, nutrition and other programs as well as through enhanced employment opportunities, etc. The term rural development is often used to represent the confluence of all these interests as it relates to rural areas. It is recognized that in the past many developmental programs intended to reach the bottom 30, 40 or even 50% of the population simply have not met this goal.

At the same time, advances in agricultural, nutritional, and health technology have allowed some nutrition intervention programs to be developed within the present framework of most low-income nations without waiting for major economic transitions to take place. Examples of this are the Green Revolution and malaria eradication. In the nutrition area, recent advances

in fortification and synthetic nutrient technology provide exciting new possibilities. For instance, minimal costs are involved in the fortification of salt with iodine or the provision of children with massive dose of capsules of vitamin A.

The Nutrition Planning Process and This Pilot Project

The first step was the determination of the general nutrition problem. This included the identification of the particular segment of the population affected (age, sex, rural/urban, etc.) on the island of Cebu through the use of household and individual dietary surveys; biochemical, anthropometric, and clinical/medical examinations.

The second stage proceeded at two levels. One level examined the various factors related to xerophthalmia in a strict cause-and-effect framework. The nutritional problems were viewed as an aspect of health and examined for the medical, environmental, as well as nutritional factors. This analysis determined where nutrition intervention can take place.

The second level considered the possible nutrition interventions with other non-nutrition programs. To maximize or improve the nutritional status of a population or any target group, numerous points in a social system need to be examined. There are many ways to improve the nutritional status without direct nutritional intervention. Some of these are: the provision of jobs; subsidization of food through price manipulation or direct distribution; technological change to improve the yields or nutritional content of various food crops; and the elimination of infectious diseases which interact synergis-

tically with food ingestion to increase dietary needs or to cause malabsorption. It must be determined how intervention, through these and other non-nutritional approaches, would substitute for or be complementary with direct nutritional intervention such as child feeding or fortification programs.

Once the link between the various forms of development and nutritional change are made, the point of nutritional intervention is determined. Often, of course, nutrition intervention programs will not be as meaningful in the broad context of national development as other developmental programs will be. It is important that the nutritional programs not be developed in a vacuum.

CHAPTER II

BRIEF BACKGROUND OF VITAMIN A DEFICIENCY*

A. Introduction

In natural situations a pure vitamin A deficiency seldom exists as an isolated condition, especially in Asia. Rarely does the deficiency of Vitamin A occur without the presence of other nutritional deficiencies or in conjunction with other disease. Many forms of malnutrition occur in the presence of infectious and parasitic diseases which often are interacting synergistically with malnutrition. Thus the conditions of interest here, xerophthalmia and keratomalacia, occur concurrently with dietary deficiencies such as protein, calories and riboflavin and with diarrhea and other forms of infectious or parasitic disease. Vitamin A deficiency produces a variety of pathological lesions but this study is concerned chiefly with the deficiency as it relates to the eye and to the resultant blindness, mortality and morbidity which are the most significant consequences of this deficiency.

Xerophthalmia is the general syndrome which covers all eye lesions and the general public health problem implied in vitamin A deficiency. The affix xero- suggests a dryness, lusterless condition of the eyeball. Keratomalacia relates to the softening of the cornea with ulceration and loss of vision. The root malacia differs from xero as it is the weakening, softening and melting process which follows xerophthalmia. This last stage of xerophthalmia may develop very rapidly.

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*This discussion represents the synthesis of many scientific papers dealing with various aspects of vitamin A and xerophthalmia. A more detailed study will document these sources at a later date.

Vitamin A includes the preformed vitamin A (retinol) or the pro-vitamins A or carotenoids. Preformed A is ready for utilization by man while the preformed carotenes must be converted to vitamin A in the intestines of man. It should be noted that the preformed A is four to six times as efficient as the beta carotene in that much of the beta carotene is lost in the process of absorption and conversion before it can be utilized by the human organism.

B. Consequences of xerophthalmia

A deficiency of vitamin A affects many central life processes of the human organism. Many of these relationships may have important economic manifestations which will be discussed later. The following are some of the relationships:

a) Resistance to infection - a deficiency lowers the resistance to infection in general and especially lowers the integrity of the epithelial tissues. Vitamin A is synergistic with almost all infectious diseases in which the relationship has been studied. Children and adults with xerophthalmia are highly susceptible to infections, particularly the respiratory and genito-urinary systems.

b) Reproduction - vitamin A is essential for the normal functioning of the reproductive system;

c) Utilization of dietary protein - The addition of vitamin A increases the utilization of protein. On the other hand, a deficiency of vitamin A may reduce food intake and growth.

d) Visual cycle - vitamin A is essential in the formation of rhodopsin. Rhodopsin is important for vision in dim light. Furthermore, blindness is a common occurrence for those who have suffered from xerophthalmia. Often the lesions are asymmetric; the numbers of people blind in both eyes and one eye is about equal. Disagreement exists on this point. In one study, among the survivors of xerophthalmia, 27% were blind, 59% had greatly reduced vision and only 14% had undamaged eyes. McLaren estimated that a minimum of 1 in 800 children surviving the age of 5 in Indonesia would be totally blind from xerophthalmia.

e) Mortality - vitamin A deficiency greatly increases the mortality rate of children. Between 25 to 60 percent of those with xerophthalmia die. Observations in India suggest 50 per cent survive while in areas of North Africa survival may be a rarity. At the same time, many children with xerophthalmia die of kwashiorkor or nutritional marasmus who might otherwise survive and become blind.

C. Nutritional and Biochemical factors

Two of the key processes which determine the effects of dietary intake over time on the human organism's vitamin A nutriture are the absorption and conversion of the preformed beta carotene. The biosynthesis (conversion) of vitamin A from beta carotene takes place mainly in the intestinal mucosa,

during the absorption of dietary B-carotene. The presence of various diseases interferes with this absorption process of either carotene or vitamin A. Acute febrile infectious disease and perhaps also diarrheal disease have a trigger effect, which cannot always be explained by depletion.

Basically the provitamin A (carotenoids) is converted into retinol(vitamin A) and then absorbed. Fat affects the amount of carotene absorbed since vitamin A is a fat soluble vitamin. Protein deficiency markedly depresses the intestinal conversion of beta-carotene. After absorption, the nutrient is either utilized or stored. A study carried out in India showed that mild protein calorie malnutrition does not impair the absorption of beta-carotene. Protein is necessary for the utilization of the vitamin A and is also responsible for the transport of this A (retinol) in human plasma while vitamin E affects the utilization and also the storage of the A in the liver. Scientists are finding that some vitamin A is stored in skin and muscle.

Previously it was mentioned that vitamin A affects protein metabolism, reducing the utilization of the ingested protein. A severe protein deficiency may prevent vitamin A from reaching the liver and keep the remaining reserves unavailable to the other tissues of the body for utilization. This does not mean kwashiorkor or xerophthalmia will necessarily occur concrrently. Rather, this means programs which provide protein and subsequently accelerate the rate of growth in children, may produce the appearance of xerophthalmia.

An unrelated but important factor is the effect of maternal nutriture. Poor maternal vitamin A nutriture results in a low storage in the unborn child and a low content of vitamin A in the mother's breast milk.

There are several biochemical indicators of vitamin A nutritional status. The clinical indicator used in this study is the xerophthalmia ranking discussed in the introduction. The amount of vitamin A stored in the liver can be determined by a biopsy of liver tissue taken with a biopsy needle injected into this organ. Although this test is very useful, it may be painful, it produces side effects and complications in some patients and was not utilized. It is not a field test. Determinations of the levels of vitamin A (retinol) and of carotene in the serum (plasma) are the two basic methods. Also there is some evidence of a poor correlation between vitamin A in the liver and the plasma unless the deficiency is very severe. The same is true for clinical symptoms of vitamin A deficiency and serum A levels. Part of the explanation may be the storage of vitamin A in the skin and muscle.

The serum carotene, on the other hand, reflects recent dietary intake. Beta-carotene is not stored for very long; it is converted to vitamin A. The finding of low carotene levels is informative as to the type of diet consumed over recent weeks and months. There is a problem with the serum carotene because more of the carotenes are not converted to retinol.

The guidelines for interpreting the biochemical data are supplied by the Interdepartmental Committee on Nutrition for National Development. These are found in Table 1.

Table 1 Biochemical Data Interpretation*
ICNND

	Deficient	Low	Acceptable	High
1. Plasma vitamin A ug/100 ml	10	10-19	20-49	≥50
2. Plasma carotene ug/100 ml		20-39	40-99	≥100
Pregnant women				
Trimester 1		20-39	40-99	≥100
Trimester 2		30-79	80-199	≥ 200
Trimester 3		40-79	80-249	≥250

*Serum levels of nutrients in children do not differ appreciably from those of adults.

D. Dietary Aspects

In the previous discussion, vitamin A sources were described as retinol and as carotenoids. The main carotenoid is beta-carotene. The importance of these distinctions lies in the relative effectiveness in each in providing the necessary biological activity for the human body.

The carotenoids are not utilized as efficiently as retinol by the human body. The standard relationship is 1 ug beta-carotene equals .167 ug retinol or beta-carotene is one-sixth as efficient as retinol. The other carotenoids are much less efficient than beta-carotene and are given a retinol equivalence of one-twelfth. The other standard of measurement for vitamin A activity is International Units (IU). One I.U. of vitamin A is equivalent to 0.3 ug of retinol.

These relationships are significant, especially when carotenoids provide 65-95% of the total vitamin A activity in the diets of the developing areas. The principal sources of vitamin A in the diets of developing areas are fruits and vegetables—predominantly the green leafy and yellow vegetables.

Sources of Vitamin A

Foods containing previtamin A as retinol are fairly expensive and consumption may be prohibited by religious or cultural mores. It occurs widely in animal tissues, especially in the livers where it is stored. The fat content of the meat, milk or fish may be important; the retinol is often found in these tissues. Thus lean meat or fish and milk from which the fat has been skimmed are almost devoid of vitamin A. While

fish provide an excellent source of vitamin A, sun dried fish loses most of its vitamin A value. "Eggs are an excellent source of retinol and may prove to be a practical method of supplementing vegetable diets."

Beta-carotene is found in all the green parts of plants. Green leafy vegetables, such as the young leaves of Ipomoea (sweet potato and swamp cabbage), cassava, amaranth, horse-radish, etc. are rich sources of carotenes. ...Fresh immature legumes (green string beans, lima beans, peas, etc.) before they reach the mature dried stage (grain legumes) are also good sources of both proteins and carotenes. Breast milk is another important vitamin A (preformed) source. For infants breast feeding is of unquestionable importance in forestalling vitamin A deficiency.

Beta-carotene is also found in abundance in red palm oil, carrots, mangoes, papayas and other yellow vegetables and fruits. Red palm oil, a very rich source of beta-carotene is extensively produced in West and Central Africa and parts of the Far East. It is often used to treat xerophthalmia. Coca, consumed in the highland areas of Bolivia, has a high carotene A content.

Carotene and retinol are relatively stable towards heat and in the canning and processing. In some cases such as carrots the foodstuff must be cooked to release all of the carotene. At the same time traditional techniques such as the drying of leaves and the storage of vegetables such as squash do not lead to a loss of carotene. Extensive exposure to the sun (e. g., sun dried fish appears to be the major cause of carotene or retinol loss.

Often the main staple determines the diet content of vitamin A. When it provides little or no carotene as in the case of rice and white corn, the incidence of xerophthalmia is very high. Thus the rice-eating populations of Asia and the Far East usually consume lower amounts of carotene than do those whose staple is yellow maize, sweet potatoes or millet.

Requirements

The requirements for vitamin A, expressed in weights of ug, vary by age and sex. The recommended daily amount of retinol for an adult is 750 ug (micrograms). An amount as low as 390 ug retinol per day is required to prevent visual symptoms of vitamin A deficiency in adults. During pregnancy the recommended daily allowances (RDA) remain constant; however, lactating women have an RDA of 1200 ug retinol per day. Growth requirements are greater for infants. At the end of three and five months 420 ug/day or about 65 ug/kg. and 50 ug/kg, respectively are recommended. Table 2 reports the recommended levels of retinol.

Table 2

Recommended Intake of Retinol at Various Ages

Age	Recommended intake ug retinol per day	International units	Age	Recommended intake ug retinol per day	I. U.
0-6 months	1/		7-9 years	400	1333
6-12 months	300	1000	10-12 years	575	1917
1 year	250	833	13-15 years (boys-girls)	725	2417
2 years	250	833	16-19 years (boys-girls)	750	2500
3 years	250	833			
4-6 years	300	1000	Adults (man-woman)	750	2500

Note: For diets containing both carotene and retinol, adjustment must be made as described in the text.

1/ For infants 0-6 months, it is accepted that breast feeding by well-nourished mother is the best way to satisfy the nutritional requirements for vitamin A.

E. Etiological Relationships

The incidence of xerophthalmia differs from area to area. with the same vitamin A dietary intake. The causes of this disease are complex and vary seasonally and by age and sex as these factors are related to food supply, disease, poverty and urbanization and numerous cultural forces. This section summarizes these factors, in particular the issue of age and sex.

A common profile begins with the pre-school child who is undernourished but does not display clinical symptoms of xerophthalmia or any other form of malnutrition. Then the child becomes infected with a serious gastrointestinal or respiratory infection at the age of 3 which precipitates xerophthalmia. A month later the child's vision becomes blurred and the mother takes the child to a local clinic 20 miles away. But, it is too late. The child's condition is irreversible and eyesight in both eyes is lost.

Dietary factors

A low intake of vitamin A or carotene can be consumed by a child or by the infant because the milk of the mother is low in these nutrients. In Java, the vegetables and young pulses are placed in a soup (sajur) along with peppers and other spices. This soup is very spicy and many children refuse to eat it. Thus, the children consume very little carotene. In some areas in Java among the poor there are periods right before the rice harvest when no sources of carotene are available and the dietary-related incidence of xerophthalmia is high. In Europe, xerophthalmia used to appear in the spring after the provitamin A reserves were exhausted at the end of a greenless winter.

Other examples of dietary causes are kwashiorkor and the resultant effects on the metabolism of vitamin A, a low intake of dietary fat lowering the intestinal absorption of all forms of vitamin A (especially the carotenes), and a maldistribution of food in the family resulting in the good sources of retinol and beta-carotene being given to the child very sparingly. In one study of 180 children with xerophthalmia, 90% of the children were classified as malnourished.

Disease

The direct effects of various diseases on the absorption of retinol and carotene were already highlighted. Most authors associate the average case of xerophthalmia, especially keratomalacia, with diarrhea, measles, tuberculosis, hookworm, fever or ascaris. The diarrhea months occur simultaneously with the highest incidence of xerophthalmia cases in Japan, Korea, South Asia, and the Near East and North Africa. Often the onset of diarrhea leads to a reduced diet of rice, barley water tea or herb infusions. This exacerbates the problem. Xerophthalmia cases frequently come in waves. These prove to depend rather more on epidemiological variation of the contagious diseases of childhood than on seasonal variation of food intake. Some conflicting evidence on the relationship between xerophthalmia and diarrhea has been presented.

The best documentation of the effects of various diseases on the incidence of xerophthalmia was a study done in North Vietnam. Two distinct periods with a high incidence occurred. In the hot summer months there were numerous cases of intestinal infection. In October to December, the cold season, the inci-

dence of respiratory infection was high. The incidence of xerophthalmia related directly to these diseases and was highest during these two periods. Measles, tuberculosis, ascaris and giardia are some of the diseases which can increase the incidence of xerophthalmia. Most of this information has come from studies of children admitted to hospitals and has not followed children over a period of time. Thus these associations might be spurious in the sense that these diseases do not trigger xerophthalmia. It is, of course, possible that xerophthalmia triggers them.

Poverty

Xerophthalmia is felt to be a poor man's disease. Rarely is a case found among middle income or rich children. For example in Jogjakarta, Indonesia, Oomen collected 11,000 case histories (of xerophthalmia) from the free clinics, but not one while scanning thousands of records of paying patients.

Urbanization

The rapid urbanization of the past several decades has produced hundreds of squatters colonies and slum areas in large and small metropolitan areas. Alternately termed bustees, jhuggi, jhonpris, urban barrios, or shanty towns, these urban villages or squatters colonies are the scene of some of the most seriously malnourished children. The existence of most inhabitants in the urban villages is marginal; the chief occupations are the crafts of basket-weaving, clothes washing, etc., and similar marginal urban occupations such as pulling rickshaw, or selling sugar water on a corner. Often their destitution forces them to resort to begging.

These people carry their old food habits with them to the cities. They often will consume only the same grains, fruits and vegetables which they had available in their villages. Grains are obtained, though they may be much more expensive. These staples will be purchased first. However, the more perishable fruits and vegetables often cannot be obtained. When they are available, the quantity purchased is much less than that same family would have consumed in rural areas. Another factor is important. In rural areas, many of the fruits and vegetables are consumed with little or no cost. When a price is placed on these foods, families are most likely to consume less of them and more of their staple food which is usually low in carotene.

The unavailability of fruits and vegetables in the urban market is a second factor in the different levels of consumption of these foods in urban and rural areas. In the Philippines fruits and vegetables are usually produced as a cash crop by the Chinese. Most often farmers normally produce only for their own consumption.

There are detrimental social forces which become important in urban areas. The advertising of commercial food induce many families to purchase these much more expensive foods and their nutritional status suffers. Or, the mother may be forced to work and be unable to breast feed the baby. The substitute of powdered milk or other forms of baby milk is diluted or fed in smaller quantities to the child. Often the skimmed milk is not fortified to replace the retinol lost with the skimmed-off fat.

Before World War II xerophthalmia attracted much attention in Singapore where it was related to the use of artificially fed infants. For a long time the powdered skimmed milk sent to developing areas from the U.S. through Public Law 480 was not fortified. Now U.S. exports of powdered skimmed milk are fortified with vitamin A.

Age-Sex

Incidence of xerophthalmia trends in age rates are the same for males and females. The peak incidence is during the third year. The incidence is much higher among males; this gap increases with age. The statistics vary slightly but the general ratios are about 58% males: 42% females for preschool children age 2-5; 85% males: 15% females, ages 10-13; and 87% males: 13% females, ages 14-24. Oomen and Ten Doesschate feel this bias toward the male sex (higher incidence of xerophthalmia) is an intrinsic factor just as is the relationship between xerophthalmia and protein malnutrition.

In the geography of xerophthalmia, climate plays a role far different from what one would suspect. The humid, rich and green tropics where carotene sources are plentiful, especially in the Far East often have a high incidence of xerophthalmia. These also are the rice-eating areas and the areas with the greater incidence of gastrointestinal infection. Also these are the poor and more highly populous areas.

A very high incidence is found in the slums of Manila and Cebu City, Saigon, Dacca and the large cities of Southern India such as Madras and Hyderabad.

Among the regions of the world the most prevalent and serious problem is found in South and Eastern Asia, the Far East, North Africa, and parts of the Near East. And a less serious problem is found in Central and South America, and North Asia and East Africa. The lowest incidence in the developing world is in West Africa where cooking in red palm oil is common. Few cases are found in the Caribbean.

CHAPTER 3

VITAMIN A DEFICIENCY IN CEBU

A. Survey Design

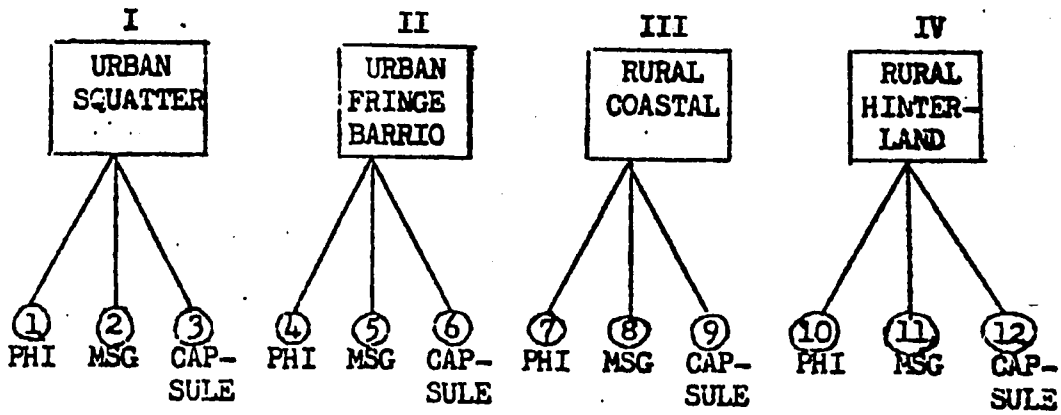
The survey was conducted in four ecological zones: urban squatter and slum areas; urban barrios (fringe of cities); coastal barrios; and hinterland semi-mountainous barrios. These areas were selected because they represented four major economic and nutritional geographic groupings in terms of diet, market accessibility, sanitary conditions, labor markets, etc. This means each area may have different public health problems or have the same problems caused by different factors. Furthermore, the delivery systems for public services such as health and nutritional care may be very different.

Three separate areas were selected in each zone. This was done so three different programs could be run concurrently in separate areas within each ecological zone. Also the representativeness of the survey data is better. This design is shown in Figure 1 for three possible programs in each zone. There were approximately 100 children aged 1-6 and 40 children aged 7-15 selected from each of the twelve areas for a sample population of about 1700 children. Stratified sampling procedures were followed by obtaining the necessary socioeconomic, clinical and biochemical information from each child and his/her family. Each barrio was separated into ten sections and subsamples of ten children 1-6 and four children 7-16 were taken per section.

Figure 1

RESEARCH DESIGN

FOUR ECOLOGICAL ZONES



12 AREAS

EACH ZONE

DIFFERENT ECONOMIC, HEALTH, DIETARY CONDITIONS

SAMPLING BASIS

NO COMMUNICATIONS BETWEEN 12 AREAS ACCESSIBLE

SIZE: OVER 300 FAMILIES EACH

B. Demographic and Socioeconomic Background of Sample Population

Nestled in the middle of the 7,000 Philippine Islands is Cebu — the center of trade and commerce for the central section of the Philippines and Cebu City, the second largest metropolitan in the country. The cultural heritage of Cebu is rich and old. It was a major port of commerce with Chinese, Cambodian (Sawankhalok), Siamese, and Arab traders centuries ago. It enjoys the distinction of being visited by the Portuguese explorer, Fernando de Magellan, in 1521. Indeed Magellan was killed by Lapulapu, a warrior-hero there. The Spanish era began as Cebu's (Zubu then) Rajah and his wife were baptized as Christians.

Since that time people in Cebu City have developed from a fishing and trading center into a busy center of education, industry, and commerce. The metropolitan population is close to a half million people who are especially famous for their very sweet mangoes.

Cebu has a moderate climate with about 70 inches of rain a year. It is sheltered by islands on all sides and does not suffer from the serious typhoons which affect many of its neighbors. Coconut and corn are the principal agricultural products on this elongated mountainous island. It is one of the most densely populated areas in the Republic of the Philippines.

The twelve barrios and squatter areas included in this study are located in and on the fringes of Cebu City, and up to 60 miles south of the city. They vary in topography from hinterland barrio which has many houses nestled on the top

of mountains to the beautiful coastal barrios to some squatter areas which can get semi-flooded during the mild monsoon season.

The sample population is quite homogeneous. Over 95% of the sample is Roman Catholic and most of the remainder adhere to religious groups which have split off from the main Catholic Church for political reasons. Other than 1-2% of the people who have Chinese, Moslem, or Spanish (Mestizo) background, the rest fall into a Filipino ethnic group. No big cultural differences separate these groups like one would find in India between two castes in the same village. Cultural differentiation based on caste allowed Levinson to understand many behavioral characteristics based on whether a household was a Jat or a Ramdasia. Among the Cebuano sample, no ethnic, occupational or income group held to a pattern similar to those found in other regions in India and so many other countries. Similar differences would be expected in the Negrito and Moslem areas in the Philippines. The belief and other behavioral patterns which exist in the sample population appear to be based on numerous other factors which do not allow a simple delineation of groups.

The population is young. Of the persons studied in the 662 families, the majority are under 12 years of age and 64.25% are younger than the age of 20. Partially this is the result of the more rapid population growth of the Philippines. However, the sampling techniques of accepting only families with at least one child younger than seven was important in producing such a young sample. According to the 1970 Philippine census, only 53.15% of the population was younger than 20.

The rapid Filipino growth rate results in large family sizes. Among the sample the average family has 6.14 members. The inclusion of relatives and other non-nuclear family members who live in the same house raises this average to 6.77 peoples per household. The size of families is larger in the rural areas (see Table 3). Also both the family and household size increases with rising incomes. Income quartile 1 represents 25% of the families in terms of their family income while quartile 4 represents the 25% with the highest income.

The sample population is very poor. The average household per capita income is $71. The incomes are highest in the rural coastal barrios and lowest in the squatter areas (Table 4). There is a large increase in per capita income between the first three and the fourth income quartiles. This is representative of the large income disparity between the rich and the poor in this region. These income quartiles group the households according to their relative position within their own zone. Thus the income range of each quartile varies from zone to zone. This quartile breakdown into about 165 families per quartile or 40 per quartile per zone is used frequently in this analysis to allow us to understand the distribution of various factors between income classes.

The sources of this household income for the total sample are found in table 5. Credit and other forms of deficit financing were not included in this income data which are the basis for all preceding discussions of income. The first interesting issue is that 75% of the families have a household income less than $454.73. This is surprisingly similar to the results from

Table 3 Size of Family and Household
(Average number)

	Family size	Household size
Urban		
Squatters	5.92	6.66
Barrio	6.10	6.69
Rural		
Coastal	6.27	6.87
Hinterland	6.30	6.89
Total	6.14	6.77
Income quartile		
1	4.83	5.30
2	6.47	6.99
3	6.50	7.14
4	6.78	7.67
Total	6.14	6.77

Table 4 Total Household Income Per Capita*
(U.S. Dollars)

Income quartile	Area				
	Urban		Rural		Total
	Squatter	Barrio	Coastal	Hinterland	
1	12	14	17	21	16
2	45	42	49	38	44
3	68	64	85	67	71
4	128	169	181	136	153
Total	63	72	83	66	71

* Includes all cash and in-kind income sources but excludes three families from quartile 4 with incomes greater than 20,000.

Table 5 Sources of Total Household Income (per year in U.S. dollars), Total Population

Income Quartile	In-kind Income[a] Garden Total	Garden % total income	Farming Total	Farming % total income	Fishing Total	Fishing % Total income	Cash Income Farming Total	Farming % Total income	Fishing Total	Fishing % total income	Business Total	Business % Total income	Contributions from other household members Total	Contributions % total income	Total house-hold income	Per Ca-pita Income
First	8.99	9	5.36	5	1.49	1	-2.50	-2[b]	1.84	2	67.25	67	18.04	18	100.46	16.01
Second	10.10	4	4.57	2	5.53	2	1.00	0	5.35	2	240.97	87	10.39	4	277.90	43.91
Third	14.06	3	7.23	2	6.41	1	1.19	0	8.04	2	403.60	89	14.20	3	454.73	70.68
Fourth	21.42	2	10.15	1	10.39	1	3.39	0	20.06	2	925.04	90	37.27	4	1027.72	153.11
Total	13.61	3	6.82	1	5.93	1	.76	0	8.78	2	407.13	88	19.92	4	462.94	70.59

a/ A major value of in-kind income in Philippine government statistics, the rental value of owner-occupied homes were not included in this study. This group represent about 1/3 of the in-kind income of the Philippines in 1971 (10, 139-E).

b/ All negative values are the result of all costs being attributed to the farming and fishing cash income during the coding process and not being allocated proportionately to the in-kind aspect.

a 1971 Filipino government study of income. In 1971, 74.3% of the Eastern Visayan families had an income less than $448. Second, it is interesting to note the decline in the relative contribution of in-kind income, especially from the garden as household income increases. In the first quartile, 15% of the income is from in-kind (home production) sources and in the fourth quartile, only 4% comes from these sources. Also the contribution of household members who do not belong to the nuclear family declines from 18% in quartile 1 to 4% in quartile 4. These are relative decreases, while the absolute contribution of in-kind and nonfamily member contributions to household increases as income increases.

The fathers have more education than the mothers but the differences are smaller than is found between males and females in most Asian countries. Most of the parents have 3-7 years of schooling. The urban parents, in general, are more educated than the rural ones. (Table 6)

The last issue is the description of the wealth of this population. Given the low incomes it is not surprising that most of these families possess few expensive items. Traditionally land has been perceived as a key factor in the wealth of most Filipino families. In the more densely populated island of Cebu, we would expect this to delineate clearly the economi position of most families. This does happen for the richer families. The difference in average land owned by the first three quartiles and the fourth quartile is almost one-half hectare or greater than one acre (Table 7). The difference

Table 6 Distribution of Mothers by Education Level
(percent)

Education level (years of schooling)	Area: Urban Squatter	Urban Barrio	Rural Coastal	Rural Hinterland	Total
None	13.1	12.9	7.0	16.6	12.5
1-2	7.4	3.5	5.1	8.9	6.2
3-4	12.5	28.8	26.6	29.3	24.0
5-7 a/	39.2	23.5	36.7	26.1	31.4
8-9	11.4	10.0	10.1	6.4	9.5
10-11 b/	8.0	10.0	7.0	7.0	8.0
College c/	8.5	11.2	7.6	5.7	8.3
Total	100.0	100.0	100.0	100.0	100.0

Distribution of Fathers by Education Le el
(percent)

Education level (years of schooling)	Area: Urban Squatter	Urban Barrio	Rural Coastal	Rural Hinterland	Total
None	13.1	12.4	12.0	12.7	12.7
1-2	3.4	10.6	4.4	12.7	7.7
3-4	14.2	14.1	19.6	26.1	18.3
5-7 a/	24.4	24.7	31.0	24.8	26.1
8-9	14.2	12.4	12.7	11.5	12.7
10-11 b/	17.0	15.3	8.2	8.3	12.4
College c/	13.6	10.6	12.0	3.8	10.1
Total	100.0	100.0	100.0	100.0	100.0

a/ Equivalent to grade school graduate
b/ Equivalent to high school graduate
c/ One or more years of college

Table 7 Total Land Ownership (hectares)

Income quartiles	Urban Squatter	Urban Barrio	Rural Coastal	Rural Hinterland	Total
1	.0	.574	.051	.042	.167
2	.324	.070	.0	.029	.112
3	.045	.148	.110	.170	.117
4	.888	.512	.174	.779	.594
Total	.310	.324	.083	.255	.246

is even greater for the families in the top 10% income group (10th decile). Each of these families own about 1 hectare. Other forms of wealth are distributed among a small minority. Ownership statistics show that: 71% own their house with 80% paying no rent; only 34.1% own any type of furniture other than simple benches; 5.7% own a kerosene, gas or electric stove; 2.3% own a radio; 21.9% own a sewing machine; 2.3% own motor bikes and 5.1% own bicycles.

C. Xerophthalmia in Cebu

1. Definition of Xerophthalmia

Xerophthalmia literally means "dry eye" and in this restricted sense is a term used exclusively by ophthalmologists to describe the changes in the eye that occur when the secretions of the paraocular glands of the goblet cells of the conjunctiva dry up, leading to discontinuity of the fluid films usually present over the surface of the conjunctiva and cornea. This dessication may result from a variety of clinical conditions, but the xerosis or dryness consequent upon Vitamin A deficiency is by far the most common and important cause.

In a broader sense, and in a public health content, the term xerophthalmia was chosen to apply to the syndrome of severe Vitamin A deficiency.

For many years there has been a need for a classification of xerophthalmia to permit clearer reporting of the various eye changes generally agreed to be characteristic of the condition. The first classification scheme to gain some degree of general acceptance was that proposed by ten Doesschate which was based on a scheme commonly used in Indonesia. The baseline figures of this study was accordingly classified adcording to this (Table 8).

This classification was subsequently expanded to include also night blindness and corneal sequelae (Table 9). This was done in view of the diffculty in attaining desired objectivity of ocular findings especially in the category of conjunctival xerosis.

Serum A values were classified according to ICNND standards described earlier in this report.

2. Criteria for Community Diagnosis of Xerophthalmia and and Vitamin A Deficiency

Application of the classification alone for the purpose of arriving at a conclusion as to whether or not a xerophthalmia problem of public health magnitude exists in a community has several shortcomings. Certain of the indicators lend themselves more readily than others to field use. XIA, conjunctival xerosis, is especially liable to misinterpretation. In the absence of other indicators a decision about the presence or absence of conjunctival xerosis is highly subjective. The classification alone provides no indication as to how serious the situation may be in comparison with past experience and conditions elsewhere. Some criteria, admittedly arbitrary, that, when fulfilled, suggest a problem of public health magnitude might be useful. The new classification is based on only one method of examination for assessing Vitamin A status — i.e., clinical. Incorporation of biochemical assessment is desirable to provide additional information of an independent nature for community diagnosis of xerophthalmia and Vitamin A deficiency.

The following point prevalence rates are suggested as criteria:

Clinical

X1B in more than 2.0% of the population at risk

X2 + X3A + X3B in more than 0.01% of the population at risk

XS in more than 0.1% of the population at risk

Biochemical

Plasma Vitamin A level of less than 10 mcg/100 ml in more than 5.0% of the population at risk

In a vulnerable population the presence of one or more of the three clinical criteria should be considered as evidence of a xerophthalmia problem. The biochemical criterion is only indicative of significant Vitamin A deficiency and may be used alone if the objective is to improve Vitamin A status. The value of corroborative evidence of more than one indicator has to be stressed.

3. Prevalence of Xerophthalmia

Classification of clinical signs according to the scheme proposed by ten Doesschate gave a very high prevalence of conjunctival xerosis qualified only as conjunctival wrinkling. This was a problem that clearly emphasized the need for extreme objectivity of clinical signs and the need for association of wrinkling with other signs, which, together will be highly suggestive or indicative of conjunctival xerosis.

Table 8
Prevalence of Xerophthalmia - Old Classification
per cent

CLASSIFICATION	PREVALENCE
X0 - Only nightblindness present	0.1%
X1 - Conjunctival xerosis (dryness) with or without nightblindness, with or without Bitot's spots	66.4%
X2 - Corneal xerosis, reversible changes of corneal epithelium	0.6%
X3A - Irreversible corneal changes, loss of substance, perforations	0.0%
X3B - Softening of parts of cornea (Keratomalacia)	0.0%
X4 - Scars, blindness, large or total whiteness of eye	0.2%

N = 1715

The new classification emphasized descriptive categories and had taken into account the need for the categories to indicate severity of the problem. The baseline figures were subsequently reclassified according to this and so many of those cases previously identified as conjunctival xerosis on the basis of wrinkling alone, were excluded.

Detailed description of signs in this classification is attached as Appendix I.

Table 9
Prevalence of Xerophthalmia - New Classification
per cent

CLASSIFICATION	SIGNS - PRIMARY	PREVALENCE
X1A	Conjunctival xerosis	2.0%
X1B	Bitot's spots with conjunctival xerosis	1.7%
X2	Corneal xerosis	0.5%
X3A	Corneal ulceration with xerosis	0.0
X3B	Keratomalacia	0.0
	SIGNS - SECONDARY	
XN	Night blindness	1.8%
XF	Xerophthalmia fundus	-
XS	Corneal scars	0.3%

N = 1715

The magnitude under the category X1A represents those cases with wrinkling and pigmentation only and were included in that these were the only ones with a plurality of signs that make up the syndrome of X1A, although admittedly, not the majority that is required.

A total of 4.2% showed primary signs and some 2.1% showed secondary signs, or a total prevalence of 6.3% for all categories of both active and non-active clinical xerophthalmia.

Serum A values classified according to ICNND standards showed some 57% of the sample with deficient and low levels, 40% normal and only 3% with high levels (Table 10). It is recognized that serum A levels are affected by a host of factors like recent intake and disease and that expectedly, there would

be children with low serum A values but without clinical signs of xerophthalmia and those with clinical signs but with high serum values.

The serum A values were therefore not treated independently but in association with other data collected; more significance was attached to the mean values in the ecologic groups prior to and after the use of intervention methods rather than to individual measurements.

Table 10 Distribution of Serum A per cent

mcg/100 ml	ICNND Category	Baseline
below 10	Deficient	17
10-19	Low	40
20-49	Normal/Acceptable	40
50 plus	High	3

It will be recalled that the first objective of the study was to determine the magnitude of the problem of xerophthalmia and that from a public health point of view certain criteria have to be fulfilled. The application of such criteria to baseline figures showed that two of the clinical and the sole biochemical criteria were more than fulfilled satisfactorily; the combined magnitudes of corneal xerosis, Keratomalacia, and corneal scars, and deficient serum A levels exceeded the criteria figures of 0.01%, 0.1% and 5% of the population at risk.

Table 11

Baseline Survey Results vs. Criteria for Diagnosis of Xerophthalmia and Vitamin A Deficiency

CRITERIA	BASELINE
Clinical	
1 X1B > 2.0%	1.7%
2 X2 + X3A + X3B > 0.01%	0.5%
3 XS > 0.1%	0.3%
Biochemical	
Serum A < 10 mcg/100 ml > 5%	17%

4. Analysis of Related Factors

a. Ecology

In general, xerophthalmia was found to be more prevalent in the urban than in rural areas. The highest prevalence was found in the urban squatter areas and the lowest in the rural coastal areas (Table 12).

Table 12

Prevalence of Ocular Xerophthalmia by Ecologic Zone
per cent

Urban	
Squatter	10.6
Barrio	6.9
Rural	
Coastal	3.9
Hinterland	4.1

N = 1715

When ocular xerophthalmia is matched with serum levels, the similar ecologic relationships are obtained (Table 13). This means that the figures represent those cases with both clinical signs and either low or deficient serum A levels

Table 13

Prevalence of Xerophthalmia : Clinical Signs Plus Low or Deficient Serum A Levels

Urban	
Squatter	6.0
Barrio	3.5
Rural	
Coastal	2.9
Hinterland	2.9

N = 1715

b. Sex

A higher prevalence of xerophthalmia was found among males than among females for all age groups studied and the difference is more pronounced in the older children. (Table 14)

Table 14
Prevalence of Xerophthalmia: Clinical Signs Only by Sex and Age per cent

	1-6 years	7-16 years
Boys	6.2	11.4
Girls	5.5	4.4

N = 1715

Matching the clinical signs with low or deficient serum A levels shows a similar male preponderance of xerophthalmia, which is again true for all age groups (Table 15). Reasons for sex differences in the prevalence of xerophthalmia might be differential vegetable consumption patterns and certain cultural factors.

Table 15

Prevalence of Xerophthalmia: Clinical Signs Plus Low or Deficient Serum A Levels by Sex, Age and Zone
per cent

Zone	AGE GROUPS					
	1-6 years		7-16 years		Total	
	Male	Female	Male	Female	Male	Female
Urban						
Squatter	4.3	5.1	12.7	4.3	7.2	4.8
Barrio	3.7	3.9	1.9	4.4	3.1	4.0
Rural						
Coastal	4.1	2.9	3.1	0.0	3.8	2.0
Hinterland	3.4	2.1	5.5	1.4	4.1	1.8
Total Average	4.0	3.5	5.9	2.6	4.5	3.2

N = 1715

c. Age -

A peak prevalence of xerophthalmia showed in the 4-6 years age group and another in the 14-16 years age group (Table 16). The former could be reflective of deficient intake occasioned by inadequate supplementation and frequency of diseases while the latter could be due to increased demands with adolescent growth spurts.

Table 16

Prevalence of Xerophthalmia by Age : Clinical Signs

Plus Low or Deficient Serum A Levels
per cent

ZONE	AGE GROUPS 1-3	4-6	7-9	10-13	14-16
Urban					
Squatter	2.7	7.1	6.3	9.6	11.8
Barrio	3.5	4.1	5.3	2.0	0.0
Rural					
Coastal	0.0	7.0	1.9	1.6	0.0
Hinterland	0.7	4.8	4.2	1.6	8.3
Total	1.7	5.7	4.5	3.6	5.2

N = 1715

d. Income

An inverse relationship was seen between the prevalence of xerophthalmia and income quartiles. As a whole, the prevalence is higher among the poor than among the rich (Table 17).

Table 17

Prevalence of Xerophthalmia by Income Quartiles: Clinical Signs Plus Low or Deficient Serum A Levels
per cent

INCOME QUARTILE	ECOLOGICAL ZONE				
	URBAN		RURAL		TOTAL
	Squatter	Barrio	Coastal	Hinterland	
1	5.8	10.5	2.6	2.0	4.7
2	6.8	3.1	1.8	3.4	3.9
3	7.0	0.9	1.1	5.5	3.7
4	3.6	0.0	6.1	1.2	2.8

N = 1715

e. Employment of the Mother

Children of working mothers were found to have a higher prevalence of xerophthalmia (Table 18 This probably represents a loss of mother's child care time in general.

Table 18

Prevalence of Xerophthalmia and Employment of Mother
per cent

Zone	Not Employed	Employed
Urban		
Squatter	5.8	6.6
Barrio	3.3	4.1
Rural		
Coastal	3.2	2.1
Hinterland	2.5	4.0
Total	3.8	4.0

It was likewise found that a higher prevalence of xerophthalmia obtains for children of working mothers only in the lower income quartiles while the converse was true for the higher income families (Table 19). This could mean a loss of child care time for the poor which could not be compensated by an increase in income, while among the rich, time substitutes could be purchased with the income increase.

Table 19

Prevalence of Xerophthalmia by Income Quartile

and Employment of Mother
per cent

Income Quartile	Non-Employed	Employed
1	3.4	5.9
2	3.6	3.9
3	4.4	1.4
4	3.8	2.9

f. Factors Affecting Vitamin A Intake

1) Garden

A positive garden effect on Vitamin A intake was seen in the rural areas while a negative effect obtained for urban areas (Table 20). This could be due to increased consumption of garden produce in the rural areas while a strong market orientation in the urban areas could very well encourage selling of produce rather than consumption.

Table 20

Comparison of Child's Average Daily Vitamin A Intake

Based on Whether or Not Household Have Garden

Zone	IU Have Garden	IU No Garden
Urban		
Squatter	388	563
Barrio	467	963
Rural		
Coastal	642	121
Hinterland	1860	861

N = 130

2) Employment of Mother

An increase in the average daily Vitamin A intake was seen in the urban areas when the mother works but the reverse was true for the rural areas (Table 21). This could mean increased expenditures for food when the urban mother works, but in the rural areas the effect of work may well cause a loss of child care time.

Table 21

Comparison of Child's Average Daily Vitamin A Intake

Based on Whether or not Mother is Employed

Zone	IU Employed	Non-Employed
Urban		
Squatter	725	428
Barrio	1174	337
Rural		
Coastal	503	647
Hinterland	813	2164

N = 130

3) Diseases

In general, the presence of either mild or severe disease was associated with increased intake of Vitamin A (Table 22). This probably reflects better child care in the home when mild disease is present and institutional care in the case of severe disease — both conditions producing increased intakes of Vitamin A.

Table 22

Relationship between average daily Vitamin A Intake and Child's Disease Pattern

IU

Zone	Mild Disease		Severe Disease	
	Absent	Present	Absent	Present
Urban				
Squatter	614	431	508	504
Barrio	477	658	841	167
Rural				
Coastal	709	466	613	505
Hinterland	1038	1124	779	3133
Total	920	1123	679	963

CHAPTER IV

ALTERNATE MEANS OF CONTROLLING VITAMIN A DEFICIENCY

A. Introduction

In ancient Egypt, ox liver or the liver of a cock would have been prescribed for night blindness. Jeremiah of Biblical fame would have prescribed grass for the wild asses whose vision failed. Progress toward preventing xerophthalmia, though slow, has accelerated in recent decades. Large scale production by chemical synthesis of Vitamin A began in the 1950's and today hundreds of forms of the carotenes are available. At the same time, techniques of communication and food fortification have advanced rapidly. Radio, TV, advanced forms of marketing, vitamin A fortification in all forms in butter, margarine, milk, etc. are extant. Another factor in reducing the deficiency is the conquest in many countries of infections and parasitic diseases as smallpox and hookworm. Thus, the technology exists and the primary question becomes the delivery system.

The foremost aspect for consideration in the design of alternate means would understandably be practical and technical feasibility for nationwide application. The possibility of integration into existing health programs and cost-benefit ratios would likewise be considered.

In the light of these aspects several possibilities were considered, viz.,

1) Educational programs aimed at increased consumption of Vitamin A sources
2) Horticulture and related production activities
3) Prevention and control of infectious and parasitic diseases
4) Periodic massive dose program
5) Food fortification

Educational programs for increased consumption of Vitamin A sources, horticulture and disease prevention and control were deemed integral components of existing basic health services in the Rural Health Unit and obviously only needed emphasis and orientation towards the problem of xerophthalmia. For this reason, these three were lumped together as Public Health Intervention, to which a fourth component, the Botica sa Baryo was added.

Periodic massive dose program was considered very acceptable in the light of the experience of other countries and the availability of the massive dose capsules.

Food fortification is widely practiced and the requisites for such a program were found available.

A. Public Health Intervention - PHI

The working principles behind this intervention aimed to control Vitamin A deficiency through the following mechanisms:

1) control and prevent infectious and parasitic diseases, thus minimizing demands and losses of Vitamin A, lessening the probability of predisposition to xerophthalmia and early identification of clinical cases, and improvement of general health status

2) horticulture program aimed at increased home production of sources of Vitamin A which could consequently increase income and consumption especially as related to nutrition education

3) nutrition education to create awareness of and concern for the problem of xerophthalmia, the role of the family in the identification, treatment and prevention, appreciation of common Vitamin A sources and the unpleasant consequences of xerophthalmia

a) Mechanics

The operating methodologies of the PHI involved weekly one-day visits to the area by a health team composed of one physician and three paraprofessional health workers (Family Health Aides). Services included morbidity clinics, deworming, establishment of a Botica sa Baryo (village cooperative pharmacy), training of Medical Auxiliary Workers (MAW), environmental sanitation with emphasis on water purification and sanitary toilets, horticulture and establishment of a community organization (Barangay Network) to serve as channel for education, for monitoring of vital events and for program implementation. The details are attached as Appendix II.

b) Performance

Accomplishments over a 52-week period included the following:

1) 3,696 consultations
2) deworming of some 250 sample children
3) home gardens in some 49% of sample families
4) sanitary toilets in 30% of sample families
5) Intensive Family Care (IFC) for some 45% of sample families

c) Effect on Xerophthalmia

Obviously, the period of implementation was too short to allow for valid conlusions to be made as to the efficacy and efficiency of the PHI. While the effects desired are expectedly lasting, they usually take some time in coming, and are never dramatic. Nevertheless, a measurement had to be made of its impact on the problem, xerophthalmia.

It should be mentioned here that the effects of the interventions are measured on active clinical xerophthalmia, made up of the categories XN, X1A, X1B, X2 and X3. Corneal scars, XS being sequelae are not included, as well as X1A represented in this series as mere conjunctival pigmentation, for the reason that the other signs needed for the X1A syndrome are lacking.

Public Health Intervention was found to have reduced the prevalence of active clinical xerophthalmia by an average of about 44% (Table 23).

Table 23

Effect of PHI on Active Clinical Xerophthalmia

per cent

Category	Before	After	Change	
XN	2.1	1.1	-1.0	(48%)
X1B	3.0	1.6	-1.4	(47%)
X2	0.4	0.2	-0.2	(50%)
X3	0.0	0.2	+0.2	
Total Active Signs	5.5	3.1	-2.4	(44%)

d) Effect on Serum A levels

The changes in serum A levels before and after the PHI were a reduction of the mean serum A value and an increase in the percentage of sample children with low and deficient serum A levels (Table 24).

Table 24 Effect of PHI on Serum A Level

	Before	After	Change
Mean Serum A mcg/100 ml	18.4	16.5	-1.7 mcg
% with low and Deficient Serum A levels	65	75	+ 10 percentage points

C. Massive Dosage Capsule Program

It is recognized that about 30-50% of a 200,000 IU dose of Vitamin A is stored by the body, and the protection period for a growing child has been calculated to be about 100 days. Man is usually susceptible to the blinding effects of Vitamin A deficiency only during childhood. On the basis of these observations periodic massive dosage programmes have appeared to be a feasible control measure.

Experience in countries like Jordan, India, Bangladesh, Indonesia and El Salvador showed that oral dosing with 200,000 IU of retinyl palmitate in oil once every 6 months produced remarkable reduction in the prevalence of eye lesions and caused no serious acute hypervitaminosis symptoms.

The objective in utilizing this approach was not to question the results of other workers but rather to try out modes of distribution in an effort to come up with a conceivably efficient system of reaching the vulnerable groups.

a) Mechanics

Four distribution strategies were drawn up and implemented in four physically separate areas, namely:

1. Barangay or Village Council
2. School Teachers
3. Youth Groups
4. Health Team (1 physician and 3 Family Health Aides)

The community was prepared through distribution of information leaflets dwelling on what the capsule contained, what it was for, who will receive them, how often, who will distribute them and so on.

The distributors were prepared in that they were thoroughly briefed on the capsule, the strategies, forms to be filled and reporting. Details like how the capsule will be administered were likewise given. All necessary supplies were issued to distributors prior to each distribution.

The flow charts for each strategy are attached as Appendix III.

b) Distribution Performance

Analysis of the strategies showed that the health team reached more children per person-day than any of the other three, followed by the youth groups (Table 25). While the strategy using school teachers looked very poor, it should be mentioned here that most of the reactions from the capsule were observed in this area and caused subsequent refusals.

Table 25

Analysis of Capsule Distribution Strategies

Strategy	Dosing	Cooperators	Days	Target	Number Reached	Reached Per Person-Day
I Village Council	1	10	4	1136	950	23.75
	2	10	3		1113	37.10
	3	6	6		395	10.97
	Average	8.66	4.33		819.33	21.85
II School Teachers	1	6	5	829	815	27.16
	2	6	2		634	52.83
	3	10	7		403	5.75
	Average	7.33	4.66		617.33	18.07
III Youth Groups	1	6	6	791	791	21.97
	2	7	4		791	28.25
	3	6	3		744	41.33
	Average	6.33	4.33		775.33	28.29
IV Health Team	1	4	4	768	729	45.56
	2	4	4		753	47.06
	3	4	3		755	46.25
	Average	4	3.66		744	46.37

c) Reactions

Some 3.4 per cent of capsule recipients had reactions six to twenty-four hours after the ingestion of the capsule. A few of the reactions lasted for about two days. The most common were vomiting, headache, and fever (Table 26). One child passed out worms. These reactions were an important factor in the increase of the refusal level especially in the rural coastal area where the reaction rate was highest to the first capsule distribution. Many children affected by the first capsule refused the second and the third. Neighbors of these children also had understandably higher refusal rates.

The reactions may relate to Serum A levels. It could be that children with very low initial serum A levels absorbed much higher amounts of retinyl palmitate and hence had reactions.

Table 26

Frequency of Reactions to Mass Dosage Capsule

	During First Deliver per cent
Vomiting	0.8
Headache	0.4
Fever	0.4
Abdominal Pain	0.2
Vomiting and abdominal pain	0.4
Multiple or unclassified reactions	1.2
TOTAL	3.4%

d) Effect on Xerophthalmia

The massive dosage capsule program reduced nightblindness and Bitot's spots by about 70 per cent and eliminated all cases of corneal xerosis. Overall, the capsule program reduced the prevalence of active clinical xerophthalmia by about 73 per cent (Table 27).

Table 27

Effect of Massive Dosage Capsule on Active Clinical Xerophthalmia

Category	Before (per cent)	After (per cent)	Change	
XN	1.7	0.5	-1.2	(70%)
X1B	0.7	0.2	-0.5	(70%)
X2	0.2	0.0	-0.2	(100%)
X3	0.0	0.0		
Total Active Signs	2.6	0.7	-1.9	(73%)

e) Effect on Serum A Levels

A technical problem arose during the evaluation period due to the delayed arrival of reagents ordered from outside the country causing delay in the Serum A analysis which was finally done some five (5) months after the last capsule distribution. This could have a bearing on the Serum A profile

that was obtained (Table 28). The mean serum A value dropped by about 0.9 mcg from baseline to evaluation and the percentage of children with low and deficient serum A levels increased by some seven (7) percentage points.

Table 28

Effect of Massive Dosage Capsule on Serum A Levels

	Before	After	Change
Mean Serum A mcg/100 ml	19.9	19.0	-0.9 mcg
% with low and Deficient Serum A levels	57	64	+7 percentage points

D) MSG Fortification Program

Fortification of foods with appropriate amounts of Vitamin A has the advantage of reaching all those who consume the fortified food and requires neither the active participation of the population nor an elaborate and costly delivery system. The problem however, is to select a food vehicle for fortification that meets the following requisites:

1. it is widely consumed especially by children at ris
2. passes through a manufacturing process where fortification is feasible
3. shows little variation in per capita consumption
4. organoleptically suitable for fortification
5. the fortified food product should be stable

a) Mechanics

To determine which food or combination of foods could provide the role of universal carrier, information on the frequency of intake, method of cooking, and method of obtaining a variety of food was collected. Potential carriers included rice, corn grits, white refined and brown sugar, salt, chocolate, coffee, margarine, monosodium glutamate (MSG), soft drinks, biscuits, breads and other flour-based foods.

The mother was asked the frequency of the consumption of each potential carrier item for each child. Table salt, MSG and biscuit, bread and other flour-based products were consumed most frequently (Table27). Much of the salt was obtained from evaporating sea water in the sun. This process does not readily lend to fortification. The other items were obtained through commercial outlets. Biscuits, bread and other flour-based products could be fortified satisfactorily except that sources of flour and/or biscuits and bread are numerous such that control on a national basis would be expectedly difficult. MSG is produced and marketed by two leading locally-based firms but about 90% of the market is controlled by only one company.

Table 29

CHILDREN REACHED WITH POTENTIAL FORTIFIED FOOD

AT LEAST ONCE A WEEK

Food Item	Percentage Who Consume This Item
Rice	38
Corn Grits	93
Refined White Sugar	63
Table Salt	95
Margarine	39
M S G	94
Biscuit/Bread	97

N = 1779

A further study showed that the families surveyed consumed an average of two 2.4 gram packs of MSG daily, added to the usual food. Examination of the MSG and the process of manufacture showed that this item fulfilled the criteria for fortification.

The leading local MSG manufacturer agreed to provide the required MSG for the study and the process for fortification as soon as the U.S. pharmaceutical company provided the Vitamin A.

Each 2.4 gram packet was fortified with 15,000 IU of Vitamin A and testing of contents and loss rates in storage at different temperatures was done on samples sent to laboratories in the U.S. and in Switzerland. The results showed

that at maximum Philippine temperatures and after one year storage, the average content per packet was 11,600 IU.

The fortified MSG was distributed to sample families on a two-pack day rate on a weekly basis. Empty packets were subsequently collected and replaced with new packs every week for at least one year.

Initial reactions to the fortified MSG as surveyed included the following:

1. improves the taste of cooked foods better than commercial MSG
2. children consumed more of the food
3. food has "vitamin" smell
4. regulates bowel habits
5. improves sleep

Of course these are merely expressions of subjective observations after the initial use of MSG. Some of these may very well be entirely unrelated to consumption of fortified MSG.

b) Effect on Xerophthalmia

The fortified MSG program eliminated most of the cases of nightblindness and the majority of corneal xerosis and Bitot's spots with conjunctival xerosis (Table 30). Overall, the effect on active clinical xerophthalmia was a reduction by about 77%.

Table 30

Effect of MSG Fortification on Active Clinical

Xerophthalmia
per cent

Category	Before	After	Change
XN	1.6	0.2	-1.4 (88%)
X1B	1.4	0.5	-0.9 (64%)
X2	0.9	0.2	-0.7 (78%)
X3	0.0	0.0	
Total Active Signs	3.9	0.9	-3.0 (77%)

c) Effect on Serum A Levels

The mean serum A value increased by about 8 mcg between baseline and evaluation and the percentage of children with low and deficient serum A levels decreased by some 14 percentage points (Table 31). This reflects a general improvement of the status of Vitamin A nutriture.

Table 31

Effect of MSG Fortification on Serum A Levels

	Before	After	Change
Mean Serum A mcg/100 ml	21.4	29.4	+8 mcg
% with low and Deficient Serum A levels	51	37	-14 percentage points

E. Summary

All the three interventions produced an impact on the problem of Vitamin A deficiency. Overall, for the three methods, active clinical xerophthalmia was reduced by about 57% (Table 32). The general effect on Serum A levels was actually an improvement although small. The overall mean for Serum A values for all zones, all interventions was estimated to be about 19.9 mcg/100 ml for baseline and 21.6 mcg/100 ml for evaluation or an increase of about 8.5 per cent.

There are several aspects to be considered in evaluating the effects of interventions. First, PHI effects may not be expected in as short a period as one year. Second, the technical problem of reagents may have affected serum A values in the capsule areas. Thirdly, there is the possibility that a general economic deterioration may be presently obtaining and may therefore be reflected in the parameters used.

It is clear, however, that the interventions produced impact in areas which affect xerophthalmia indirectly as improvement of nutritional status, increased awareness, and other health factors.

Table 32

Overall Effects of All Interventions on Active Clinical Xerophthalmia

per cent

Category	Before	After	Change
XN	1.8	0.6	-1.2 (67%)
X1B	1.7	0.8	-0.9 (53%)
X2	0.5	0.1	-0.4 (80%)
X3	0.0	0.2	+0.2
Total Active Signs	4.0	1.7	-2.3 (57%)
	N = 1715	N = 1667	

CHAPTER V

RECOMMENDATIONS FOR A NATIONAL POLICY

Recommendations for a national policy to deal with the problem of vitamin A deficiency should be based on answers to the following questions:

1. Is there a sufficiently serious problem to justify action?
2. Has there been an examination of possible intervention strategies?
3. Which one, or combination, of these intervention strategies is likely to be most effective?
4. How feasible will it be to introduce such a national strategy?
5. What will the costs be of such an intervention, what is the effectiveness likely to be, and who will benefit?
6. Are there any preliminary investigations that need to be undertaken prior to introducing a national intervention program?
7. What methods should be used to monitor and evaluate the effectiveness of the program?
8. Can the intervention be used to produce benefits, other than on vitamin A deficiency?

(1) Extent and seriousness of the problem

The baseline study in Cebu clearly indicates a very high prevalence of deficient and low serum vitamin A levels, and the presence of significant numbers of children with clinical signs of xerophthalmia. Our findings are supported by the extensive surveys of the Food and Nutrition Research Institute which also showed a high prevalence of low serum vitamin A levels and a large percentage of persons on diets deficient in Vitamin A. Cases of keratomalacia often leading to total or partial blindness, or death are frequently seen in hospitals in Cebu and elsewhere.

It should be noted that countries such as Guatemala have introduced national vitamin A fortification programs even though clinical evidence of xerophthalmia is rare and mean serum vitamin A levels are higher than in the Philippines.

(2) Examination of possible interventions

As stated we have evaluated three intervention strategies namely the massive dose capsule, fortification, and a public-health-hoticulture intervention. These are the principal methods of control suggested by the WHO Report on Xerophthalmia.

In the case of fortification our investigation indicated that MSG was the most suitable food product for fortification.

(3) Which intervention, or combination of interventions is likely to be most effective?

Based solely on the criteria of effectiveness in (a) raising serum vitamin A levels and (b) reducing active clinical

signs of xerophthalmia it is clear that MSG fortification is the most effective intervention. It served to raise the level of serum vitamin A from a mean of 21.3 mcg/100 ml. (Table 33). The serum vitamin A levels of the group who were initially classified as "deficient" rose from a mean of 6.4 to 25.4 mcg/100 ml. an increase of 19 mcg/100 ml. (Table 34). A similar impressive rise was shown in those classified as "low". In an examination of those with active clinical signs of xerophthalmia these dropped from 3.9 per cent to 0.9 per cent following MSG fortification. The difference is significant at .001 level (Table 35). MSG fortification lowered by 77 per cent the percentage of children with active clinical signs. That is, for every 100 children who had active signs before MSG fortification only 23 would have signs after 12-18 months.

There were positive effects also resulting both from the high dose capsule and public-health-horticulture intervention. These effects were less marked on vitamin A nutritional status than were those resulting from the MSG intervention. The public-health-horticulture intervention has benefits of several kinds on nutrition and health factors other than vitamin A deficiency. These benefits such as on child growth are not produced either by MSG fortification or the high dose capsule.

We recommend as a result of the study in Cebu that serious consideration be given to a national program of MSG fortification with vitamin A. We believe that this would be feasible, would produce marked benefits and would be of low cost.

We recommend also that elements of the other two interventions namely the high dose capsule and the public-health-horticulture approaches be incorporated where appropriate into existing government health and agricultural programs. For example we recommend that physicians and health workers be made more aware of the vitamin A problem and of the diagnosis and classification of xerophthalmia, and that they have available high dose capsules for use in children with, or at high risk of developing, xerophthalmia. We recommend that capsules containing 100,000 IU rather than 200,000 IU be used, at three rather than six months intervals.

A list of risk factors will be drawn up by the National Nutritional Council through its Xerophthalmia Committee for dissemination by the Department of Health.

(4) Feasibility of introduction of proposed national program

The pilot trial of MSG fortification and its successful use in the four areas in Cebu indicates that the method is feasible. With technical assistance from Hoffman-La Roche, Inc. a suitable product was formulated, and its stability and lasting quality tested. Subsequently with the help of Union Chemicals (Manila) the vitamin A was mixed with Aji-no-moto MSG. There were no problems of palatability. The product was well accepted and was used for 12-18 months in the field.

Moving to a national program would present no new forseeable technical problems and would involve mainly a major change in the scale of the operation.

Consideration would need to be given as to whether an attempt would be made to secure voluntary agreement from the two manufacturers to add vitamin A to their MSG, or whether to introduce legislation for mandatory fortification of MSG with vitamin A. The possibility that some unfortified MSG in different packages be available on a small scale for those deliberately choosing to avoid the vitamin A enriched product deserves consideration.

The use of high dose capsules in the health centers and hospitals, the training of health personnel, and certain horticultural activities would be suggested to the Health and Agricultural Departments.

(5) Cost, effectiveness and beneficiaries

The costs of such a program will be relatively small. We believe that it might be feasible for such a national program to be introduced without any cost either to the government (other than that of monitoring and evaluation) or to the general public. The cost to the manufacturers would be relatively small in relation to their overall business. The major initial expense would be for a Nauta Mixer (estimated cost $22,000) and the only recurrent costs would be the staff to supervise the operation. It is proposed that vitamin A (retinol palmitate) plus the flow enhancing agent (silicon dioxide) be added to replace a small quantity of MSG in each packet, and not be in addition to the 2.2 grams of MSG currently in each packet. The fortified packet of MSG would then contain approximately 2.1 grams of MSG and 0.1 gram of

the vitamin A - agent mixture. Because the cost of the vitamin A - agent mixture is not significantly different from that of MSG, the final cost to the purchaser of fortified MSG would be the same as for currently unfortified MSG, namely 5 centavos for 2.2 grams of product.

If there is no increase in the total number of packets purchased, then the total national consumption of MSG, and that consumed per family, would be slightly reduced i amount (by an average of approximately 4 per cent). The total revenue accruing to the manufacturers and retailers would also remain unchanged by the program.

Our review of the literature and consultation with a number of authorities satisfies us, that the dangers of toxicity either from the MSG or from the vitamin A are negligible. One of the advantages of MSG, like salt (and unlike sugar, tea and other suggested vehicles for fortification) is that persons currently using MSG are unlikely to increase their consumption of the product to any great degree. MSG if used daily by a family is used to the same extent whether the family is in the upper or lower income groups. Toxicity from excess consumption of vitamin A would not occur from fortification of MSG at the suggested levels, for the same reason that toxicity has not been reported as a result of vitamin A fortification of margarine and other foods in Europe or North America.

The effectiveness of a national program of MSG fortification can be predicted from the Cebu experiment. It will however vary according to the level of utilization and prevalence of vitamin A deficiency in each area of the country. If the situation in the island of Cebu is taken to be representative of the Philippines both with regard to the prevalence of vitamin A deficiency and the utilization of MSG then a national program could be predicted to result in the following benefits:

(a) Raising of serum vitamin A levels of children by 7.2 mcg/100 ml., and

(b) a reduction by 77 per cent of the active clinical lesions of vitamin A deficiency or xerophthalmia in the first year of the program.

The program also would be expected to diminish to a great extent both blindness and mortality resulting from xerophthalmia in the Philippines. The main beneficiaries of the program would be children at risk of vitamin A deficiency especially young children in the low socio-economic group of the population. But adults and older children would also benefit in that their intakes of vitamin A would increase as a result of the program, and would more often than now reach the RDA levels.

The program of vitamin A fortification would also be supplemented by the suggested Public Health and horticulture intervention including the controlled use of high dose capsules of vitamin A. This additional action would be expected to have benefits beyond that of the MSG fortification program.

(6) Needed preliminary investigations

The high rate of consumption of MSG in the Philippines makes it certain that the program would benefit many millions of families. However, though not essential, investigations would be warranted of MSG use in the different regions and provinces of the Philippines, by different age groups and by different segments of the population. Such an investigation could quite simply and rapidly be undertaken during the period while manufacturers were gearing up for the fortification program. The MSG utilization survey might form the basis for a future monitoring and evaluation system.

Negotiations and investigation of the acceptability of the proposals to the manufacturers would be necessary. Similarly a determination would have to be made of the availability of the necessary quantities of retinol palmitate. Only then could a prediction be made of the date of implementation of a national program.

(7) Monitoring and evaluation

It is proposed that a national program be monitored to obtain regular data on the utilization both of the vitamin A fortified MSG, and also on the Public Health Intervention including the capsule distribution. Tests would be conducted to determine the average length of time between fortification in the factory and eventual purchase and utilization by the consumer in the provinces.

The total utilization of fortified MSG per year in each province would be monitored. The use of MSG at risk groups would also be assessed.

A small sample of subjects, mainly children, in each region would be carefully selected for the purposes of program evaluation. Evaluation would rely mainly on serum vitamin A levels of these subjects prior to the initiation of the program, and at 12-month intervals thereafter. At the same time the Department of Health would be asked to maintain statistics on cases of xerophthalmia and keratomalacia in selected government hospitals. The Malnutrition Registry maintained by Rural Health Units and Government Hospitals would also be used to evaluate the program's effectiveness.

(6) Use of the intervention to produce other benefits

Fortification of MSG with vitamin A cannot be expected to produce other benefits besides its effects on vitamin A nutritional status.

However because MSG is so widely utilized by the population in the Philippines consideration should be given to fortifying this product with other nutrients which are deficient in Filipino diets. The obvious candidate for consideration would be iron, because iron deficiency anemia is very prevalent in the country. Another possibility would be iodine. Goiter though less prevalent than anemia remains an important public health problem.

The Hoffman-La Roche Company have been consulted about the possible combination of vitamin A and iron in MSG. They are prepared to provide technical assistance. It is possible that unforseen difficulties will arise in selecting an iron compound which is both suitable for combination with MSG and vitamin A, and one which also well absorbed. If a combination of iron and vitamin A proves difficult, then it may be recommended that alternate packets of MSG be fortified separately with vitamin A and with iron. Then a consumer purchasing for example 4 packets of MSG would take home two containing added vitamin A and two containing added iron.

The Public-Health-Horticulture intervention proposed could be expected to have long term benefits on morbidity, mortality, nutritional status, and food consumption.

Conclusions

The proposals and recommendations contained in this report are those of the Principal Investigator and Co-Researchers of this NSDB supported Research Project. They are based on a detailed review of the results of the research, and an understanding from experience of three different types of intervention.

Prior to any final decision to implement these proposals they will need to be widely discussed and reviewed by knowledgeable experts both in and outside the Philippines.

Table 33

EFFECTS ON SERUM VITAMIN A LEVELS OF MSG FORTIFICATION

COMPARED WITH OTHER INTERVENTIONS

	Non MSG Group mcg/100 ml.	MSG Group mcg/100 ml.
BEFORE	19.3	21.3
AFTER	17.9	28.5
CHANGE	-1.4	+7.2

Table 34

EFFECT OF MSG FORTIFICATION ON SERUM VITAMIN A LEVELS

USING ICNND CLASSIFICATION

	mcg/100 ml.	N
DEFICIENT (Below 10 mcg)		
Before	6.4	71
After	25.4	63
Change	+19.0	
LOW (10-19 mcg)		
Before	14.4	173
After	28.8	139
Change	+14.4	
ACCEPTABLE (20-49 mcg)		
Before	29.3	216
After	27.8	173
Change	-1.5	
NORMAL (50+ mcg)		
Before	57.9	14
After	53.6	14
Change	-4.3	

Table 35

PRESENCE OF ACTIVE CLINICAL SIGNS OF XEROPHTHALMIA

BEFORE AND AFTER FORTIFICATION OF MSG

		BEFORE	AFTER	CHANGE	PERCENT REDUCTION IN CLINICAL SIGNS
		%	%	%	
XN	Night blindness	1.6	0.2	-1.4	88%
X1B	Bitot's spots with xerosis	1.4	0.5	-0.9	64%
X2	Corneal xerosis	0.9	0.2	-0.7	78%
X3	Keratomalacia	0	0	0	-
	TOTAL ACTIVE SIGNS	3.9[1/]	0.9[1/]	-3.0[1/]	77%

NOTE: X1A not included. WHO Report states "conjunctival xerosis - X1A not recommended for community diagnosis."

XS - Corneal scars are not active lesions.

[1/] Chi Square significant at .001 level.

CHAPTER VI

SUMMARY

Vitamin A is a necessary nutrient for man and animals. In the absence of an adequate dietary intake of Vitamin A, or of its carotenoid precursors, for a significant period, a number of abnormalities appear in experimental animals. These include loss of appetite, loss of weight, increased keratinization of epithelial tissues, a reduced frequency of mucus-secreting cells, and a negative nitrogen balance. As the deficiency becomes progressively more severe, stomach emptying becomes defective, nervous disorders of balance and motor skills appear, and nightblindness, eye lesions, and then blindness occur. Resistance to infection is much reduced and the reproductive process is disrupted. Death ultimately ensues.

In man, and particularly in children, Vitamin A deficiency most commonly and prominently affects the eyes, both externally by disrupting the epithelia of the cornea and conjunctiva, and internally by lowering the sensitivity of the retina to light. The former condition is known as xerophthalmia, and the latter as night blindness. In severe Vitamin A deficiency, blindness can result from ulceration of the cornea, keratomalacia and corneal opacity. Vitamin A deficiency, usually accompanied by protein-energy malnutrition, is also linked with an increased frequency of infection and with defective immunological defense mechanisms. Although all of the reported

effects of vitamin A deficiency in experimental animals have not been confirmed in man, the deficiency does seem to follow the same general pattern in all species studied and ultimately it affects adversely essentially all tissues of the body.

The Cebu Project

This was a collaborative venture of the Cebu Institute of Medicine in Cebu City and Cornell University in New York. Started in July 1973, the project set the following goals for a three-year study period:

1. Determine the magnitude of the problem of Vitamin A deficiency
2. Understand the relative importance of the various factors associated with xerophthalmia
3. Design optimal programs for eliminating and preventing xerophthalmia for different ecological conditions.
4. Determine the nutritional and economic effects of each program after the programs have operated for one year.

Some 1715 sample children aging 1-16 were drawn randomly from 600-odd sample families in four representative Philippine ecologic zones, namely urban squatter, urban fringe barrio, rural coastal and rural hinterland barrios. Clinical, biochemical and anthropometric data were collected from the children and dietary and socioeconomic information were obtained from the households.

The prevalence of xerophthalmia was found to be about 6.3% out of some 1715 children and 57 percent had low and deficient serum A levels. The figures for prevalence exceeded those set in the criteria for public health problems.

Xerophthalmia was found to be more prevalent in the urban than rural areas, affected males more than females, showed prevalence peaks in the 4-6 and 14-16 years age groups, affected children in lower income families more than the children of rich families and was more prevalent among children of working mothers especially in the poor families.

Gardens produced a positive effect in the rural areas and a negative effect in the urban areas insofar as Vitamin A intake was concerned. Working mothers in urban families produced increased intakes of Vitamin A while the converse was observed in the rural areas. In general, the presence of either mild or severe disease was associated with an increase in the Vitamin A intake.

The alternate methods of controlling Vitamin A deficiency that were used were a public health disease elimination and horticulture program, massive dosage capsule program and fortification of monosodium glutamate. The overall effects of the three programs were a reduction of the prevalence of active clinical xerophthalmia by about 57% and a marginal improvement of the mean serum A value. Comparison of individual interventions showed that the MSG fortification program produced the best

results in terms of improvement of serum A levels and reduction of active clinical xerophthalmia.

Tentative recommendations for a national policy include a multiple intervention approach to the solution of the problem, integrations of some intervention programs into existing health services and involvement of other governmental agencies such as the agriculture and education departments.

Appendix 1.

Cost analysis, effectiveness parameters and benefit cost analysis

Cost Analysis

Three programs were being carried out for the prevention and elimination of xerophthalmia. These programs are:

(a) Distribution of massive dosage vitamin A capsules to children age 1-15, every six months,

(b) Fortification of MSG with vitamin A, and

(c) The comprehensive Public Health Intervention (PHI)

The specific cost components of each program will be spelled out first.

(a) Capsule Intervention

There are only two components in the cost of this program, namely the cost of the capsules and the cost of delivery. Should the people be required to pay for the capsules, then this would fall under private cost. But since this is not done in the program, all costs are treated as social costs. The total social cost per distribution per barrio for this program is therefore:

$$C_c = nA + D$$

Where C_c = total social cost per distribution

A = cost per capsule

n = total number of capsules dispensed

D = delivery cost

and $D = P_c + F_c$

where P_c = 1 day salary + travel allowance for 1 physician to train distributor

F_c = incentives for distributors

One distribution is needed every six months which means that two distributions are needed per year. The cost per capsule was ₱0.086.[1/] This calculation is the prorated expense of buying a much larger shipment.

Social cost per distribution per barrio

1.	Cost of capsules (₱0.086 x 900)		₱ 77.40
2.	Delivery cost		
	a) one day salary plus travel allowance for one physician to train distributors for each delivery		40.00
	b) incentives for distributors		110.00
	cooperation	₱50.00	
	distributors	60.00	
		Total	₱227.40

Therefore, Total Social Cost Per Year = ₱227.40 x 2 = ₱454.80

(b) Fortification of MSG

Assume that the price of MSG is not increased due to fortification and the marginal cost is subsidized by the government. It follows therefore that private cost is zero and only the total social cost is considered. Economics of scale are involved here and this will be taken into consideration. That is, there is a large fixed cost which can serve many thousands of families. We assume full use of this fixed cost and use as our cost only a prorated portion of that cost. Cost components for this program include:

Nauta Mixer (a new one will be needed every 12.5 years)

Roche Palmitate 250-SD

1/ This cost is based on the reimbursable procurement plan of UNICEF. These 1975 cost figures are the amount the Philippine government would pay UNICEF to purchase, package and ship the drugs and dietary supplements from Copenhagen. Mr. Peter Bailey is thanked for providing us with this information. Conversion from U.S. dollar to peso values is based on $1.00 = ₱7.40.

Silicon Dioxide

Cost of personnel needed to do the mixing

2 workers

1 laboratory technician

Only social costs are required for the vitamin A and other fortification equipment. The basic process suggested is the most expensive one available. A Nauta mixer is used to combine the MSG with the Roche Palmitate 250-S.D. A flow-enhancing agent, silicic acid (silicon dioxide) is added to the vitamin A and MSG during the mixing process. The Nauta mixer handles 11,000 pounds per shift. The material and equipment input requirements for two shifts which will produce daily 10,000 kilograms of MSG or 4,545,000 packages of 2.2 grams MSG per package are:

(1) 1 Nauta mixer = $22,000 Manila CIF. This includes all transportation, insurance, etc. It will be used for 12.5 years and 220 days per year.[1/]

(2) 15,000 IU of vitamin A per 2.1 gram package. When 1 gram of Roche Palmitate 250-SD contains 250,000 IU of retinol palmitate, 250 kg of Roche Palmitate are needed per day.

(3) The Roche Philippines personnel estimate that 5 kilograms of silicic acid are needed per 500 kilograms of MSG so 100 kilograms of silicic acid are required daily.

The total cost of production of 22,000 lbs/day or 10,000 kg/day for 220 working days in a year are:

1/ The Nauta mixer is felt to be more expensive than a tumble mixer which the Roche Manila persons felt could be used. A comparable tumble mixer costs $5000. Mr. Otto of Roche Philippines is thanked for providing us with most of this cost data.

	Year 1
1. Nauta Mixer (Price = US$22,000 or ₱162,800)[1/]	₱ 162,800
needs a new one every 12.5 years	
2. Roche Palmitate 250-SD (yearly)	
needs 55,000 kg[2/]	
at price US$12/kg or ₱88.80/kg[1/]	4,884,000.00
3. Silicic acid (yearly)	
needs 48,400 lbs/year at price US$.65/lb	
or ₱4.81/lb[1/]	232,804.00
4. Personnel needed to do the fortification	
(yearly) 2 workers (₱25/day)	11,000.00
1 laboratory technician (₱25/day)	5,500.00
Total	₱ 5,296,104.00

A barrio with 300 households requiring two 2.4 gram packs of MSG per day needs 1,156.32 lbs of MSG per year, will require only a cost for the first year of ₱1,271.06. For the second year, the cost per barrio will be ₱1,231.99.

(c) Public Health Intervention (PHI)

Private costs of this program would include the following:

C_1 = cement, housing materials and value of time (opportunity cost) needed for toilet construction

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1/ The conversion rate used was ₱7.40 = US$1.

2/ Tests conducted by Hoffmann-La Roche and Co. in Basley and Nutley show that storage of the MSG fortified with retinol palmitate results in a loss of vitamin A. The biggest loss appears between 0 and 6 months. In the following 8 months, the loss appears smaller. This would lead to a slight increase in the amount of vitamin A placed in each packet and slightly increase the costs laid out above; however the Roche person in charge of this project in the Philippines, Mr. Otto, felt a slight reduction in the amount of MSG placed in each packet would be the more likely result. In either case, the social costs would increase. We feel these studies are conclusive enough to state our fortification costs figures may be underestimated by 5-10%.

C_2 = share in establishing and maintaining Botica sa Baryo

C_3 = value of additional time spent on home gardening over and above that which the household members spend in home gardening before the intervention program. Because the vegetables that the program is encouraging the people to plant do not need very much caring and there was a large gardening time before this program began, this variable is assumed to be zero.

C_4 = value of time needed for preparing, feeding children vitamin rich food, attending nutrition education classes. Because it is very difficult to separate out the program effect from the daily chores of the household without much more detailed time data, this variable will not be included in the computation.

The cost of PHI per household is therefore:

$$C_{PHIi} = \sum_{j=1}^{4} Cj$$

where i = refer to household i

C_{PHIi} = private cost of PHI program per household

C_j = cost component j

The social cost of PHI consists of the summation of all private costs plus the following additional costs:

S_1 = salary for one physician, three FHAs and one horticulturist

S_2 = travel allowance for one physician, three FHAs and one horticulturist

S_3 = TB drugs given out to children with TB

S_4 = subsidized vitamins and other drugs

S_5 = antihelminthics for deworming

S_6 = seeds, cuttings, and fertilizer for home gardening

S_7 = education materials

S_8 = training costs for the FHAs and these include a physician, materials and FHA stipends. Again economy of scale considerations mean we consider that one physician can train 15 FHAs; consequently we prorate the expenses of the physician.

S_9 = water-seal bowl frame

S_{10} = equipments and materials for medical kit. These are normally included in the set-up of a health clinic and will be excluded from the costs of the program. We are considering that this program will be added to an existing program and the cost considerations must include only the marginal costs for the service, supplies and training of the PHI.

S_{11} = opportunity cost of MAW for attending training and helping the health team. This is included as a cost because it is the experience that in places where there are more work opportunities, it is very hard to get volunteers to help the health team. So clearly, a value should be assigned to the time that the MAWs spend in helping the health team.

S_1 to S_{10} are direct social costs while S_{11} is an indirect social cost. The total social cost of PHI program is:

$$S_{PHI} = \sum_{i=i}^{n} C_{PHIi} + \sum_{j=1}^{11} S_j$$

where S_{PHI} = total social cost of PHI program per barrio

S_j = cost component j, j = 1, 2, ... 11

i = 1, 2, ... n number of households

In computing the specific costs of each program several assumptions are made. First, we assume the target population of 300 households in each barrio will have 3 children per household. Second, we calculate the costs by assuming meaningful economies of scale would be part of any national health or nutrition program. For instance, this means that the cost of the vitamin A A + E mass dosage capsules is based on a large purchase and more family health aides than are found in this program could be trained for the same fixed costs. Third, the value of time which represents additional or marginal time is included which means the time for gardening was excluded as this was done before the PHI project was introduced but the time for building a new water seal toilet was included. Fourth, our costs are based on the present salary structure and nature of medical technology. For example, new TB chemotherapy which is more cost-effective but unused at present in the Philippines will not be included.

Public Health Intervention

	Year 1	Year 2
I. Private Cost Per Household		
A. Toilet construction (first year only)		
a) cement for flooring (½ bag)	₱ 7.35	-
b) water-seal bowl (labor plus cement)	3.00	-
c) housing materials to build house for the waterseal toilet	10.00	-
d) value of time (3 days)	24.00	-
- this is the opportunity cost for spending time in constructing the toilet instead of doing something else. Minimum wage of ₱8.00/day is used as the basis of computation.		
B. Share in establishing and maintaining Botica sa Baryo	1.00	-
It is assumed here that an initial capital of ₱300 is needed for the setting up of Botica sa Baryo and once it is set up, its operation will be maintained through the proceeds from sales.		
Total private cost per household	₱45.35	-
These costs are only for the first year of the PHI.		
II. Social Cost Per Barrio		
A. Salaries (yearly)		
a) Physician (one day per week, 52 days per year)	1,627.00	1,627.00
- computation based on the present salary of a RHU physician which is ₱9,756 per annum (p.a.)		
b) 3 FHAs (one day per week, 52 days per year)	2,433.60	2,433.60
- computation based on the salary of a RHU midwife which is ₱4,860 p.a.		
c) horticulturist (one week per year)	150.00	150.00

	Year 1	Year 2
B. Travel Allowances (yearly)		
- computed as ₱6.00/day		
a) Physician (52 days per year)	312.00	312.00
b) 3 FHAs (52 days per year)	936.00	936.00
c) horticulturist (6 days per year)	36.00	36.00
C. TB drugs (INH) given out to children with TB	53.75	5.00
Incidence of TB as gathered from the baseline survey is 0.6%. This implies that in a barrio 900 children in the target age group, around 5.4 children will have TB. The cost of supplying 5.4 children with INH for one year is the cost included in this category for the first year. From the second year and after, the cost of treatment will be based on ½ child per year.		
D. Subsidized vitamins and other drugs (yearly)	237.50	237.50
The costs for this category are computed based on the total vitamins and drugs given out free to the sample population during the intervention period. Prices are based on the reimbursable procurement costs from UNICEF.		
E. Antihelminthics for deworming (yearly)	250.00	250.00
F. Seeds, cuttings and fertilizer for home gardens	80.00	40.00
For the first year, cost figure is based on the costs of seeds, fertilizers that the project gives out to the sample population. For the second year and after, only half the amount of the first year is included.		
G. Education materials (biannually)	20.00	-
H. Water-seal bowl frame (first year only)	5.00	-
I. Training of FHAs (one week every 5 years)		
a) Physician	40.70	-
b) Materials	10.00	-
c) Stipends for FHAs	144.00	-
J. Opportunity cost of MAWs for attending training and helping the health team (yearly)	936.00	936.00
Computation based on an average of 3 MAWs helping the health team for around		

	Year 1	Year 2
6 hours per week. Taking the minimum wage of ₱8.00/day for an eight-hour working day as the value of time, the opportunity cost of 3 MAWs is therefore ₱18.00 per week.		
K. Total private cost per barrio	13,605.00	-
Computed by multiplying the total private cost per household by the total number of households in the barrio.		
Total Social Cost	₱20,876.55	₱6,963.00

Table 36 provides a summary of the present value of the private and total societal costs for each program. The present value of the costs for each program are calculated for a 5-year and a 15-year program. Note the smaller differentials between each program's costs over the 15-year period. The costs each year are based on reaching all the children in any area. Equal costs are assumed for each ecological zone. If this is an urban-based delivery system, there will be slight overstatement of the urban area transportation costs. The 15-year costs are the ones which will be used in the determination of the benefit-cost ratios.

The Effectiveness Parameter

The parameter Mj is the effectiveness in eliminating or preventing the various problems associated with xerophthalmia. Thus, we must consider the effectiveness of eliminating the X which exists and of preventing new cases of X. This is not quite the same thing as examining the reduction in xerophthalmia prevalence rates. The reason is that children with X both before and after a program are probably more likely to become blind or die. The available prevalence and change of status data are used to determine Mj.

These programs are designed for a longer period of protection and should not be judged on the basis of an evaluation conducted 6-18 months after the programs began. A more realistic 5 to 15-year period is needed. Given this understanding, the first step will be to determine the effectiveness of each program in preventing blindness and death and in eliminating old cases and preventing new cases of less severe forms of X and the concurrent external effects of these less severe more prevalent C. Table 36 presents the predicted X prevalence rates at the beginning and end of the intervention programs. These rates plus the serum A level and

TABLE 36a THE PREVALENCE OF XEROPHTHALMIA BEFORE AND AFTER THE INTERVENTION PROGRAMS BASED ON THE PREDICTED VALUES OF XEROPHTHALMIA FOR CHILDREN AGED 1-16[1/]

	URBAN SQUATTER			RURAL COASTAL		
	Before	After	Change	Before	After	Change
PHI	.10	.13	+.03	.01	.06	+.05
MSG	.07	.05	-.02	.06	.03	-.03
CAPSULE	.03	.08	+.05	.02	.12	+.10

1/ The predicted values are based on the regression results for each age group as described in Table C5.17. The aggregate values are weighted averages derived from the relative proportion of boys and girls in the 1-6 and 7-16 age groups.

TABLE 36b PRESENT VALUES OF TOTAL SOCIAL BENEFITS

(Values in Pesos)

Zone Discount Rate	Urban Squatter	Rural Coastal
8%	225,041	151,394
15%	68,519	50,440

ocular signs associated with each program are used to determine the Mij rates.

The capsule program eliminated most of the ocular signs and very few ones occur. In the period studied, the ocular signs which were found are of a less serious nature and affect only the conjunctiva. The clinical data were collected 2 months after the capsule was delivered and it is possible that the less than 6-month protection afforded by the capsule may lead to more serious complications by the end of six-months. We assume all blindness and death associated with X will be prevented but that the high prevalence level of less serious X will occur for the final three months of the six-month period. For the first three months, eight percent of the children will still have X. There is the possibility that the capsule delivery system will break down more with time and these Mij rates may be too high. At this time, we assume only 4% and 5% of the capsule children in the squatter and coastal barrios have the possibility of getting X. This means the effectiveness level of Ma and Mnox for the capsule is only about 75%. This represents a 90% reduction for the first three months and a .43% reduction in the amount of X for the final three months.

The MSG fortification promises a much higher level of protection. The large increase in serum A levels after a 10-month period of use mean the higher prevalence of ocular signs which were found after 6 months would have declined by the same period in which the serum A data were collected. MSG fortification affords complete protection against both blindness and death and we assume the effectiveness against morbidity will improve. Still some children would never receive MSG if it were provided only through commercial outlets; thus, 100% effectiveness can never be

obtained. The morbidity level will decline to 1% in both coastal barrios and the squatter areas. This means an effectiveness level against less serious forms of X of about .85 and .83 in these areas, respectively. This is based on the reduction in the initial prevalence levels of X in the MSG areas.

The PHI program is more difficult to evaluate. While it has had the same positive impact on the vitamin A intake of children, and provided significant other health and nutritional benefits, the prevalence of X has increased. About 15% of the children still had ocular signs and a few were of a more severe nature (Table 5.2). Given the availability of medical personnel in each area plus the visit of the FHA's and the work of the MAW's, we assume no deaths associated with X will occur. It is, however, slightly possible that a child may become blind because the serum A levels have decreased and some severe ocular signs occurred. The nutrition education programs which have explained the effects of X-related signs and the importance of consuming leafy vegetables to PHI households should become more effective over time. Nevertheless, there is the possibility that some families will not follow the advice of the MAW's, FHA's and doctors and children will go blind. Others will not be reached at all by the PHI. The X morbidity levels are expected to be slightly lower after the PHI program has run for several more years. Thus, we can assume an effectiveness level against X of only about .50 in each PHI area.

The weighing of the Mij's to produce Mj is based on the net economic value of eliminating each problem in each zone. In the squatter areas, the weights for blindness, death, morbidity and external benefits are .12, .14, .66 and .08, respectively. In the coastal area where the probability of having X was lower, the weights are .06, .09, .33 and .52,

respectively. The weighted Mj's are presented in the last column in Table 37.

The effectiveness parameter Mj is a crucial variable but unfortunately, we are able to estimate it with much less precision than the economic costs and possibly even the economic benefits.

TABLE 37 THE EFFECTIVENESS PARAMETER

EFFECTIVENESS FOR EACH PROBLEM

	morbidity Group A	blindness Group b	death Group d	external benefits Group nox	Overall Effectiveness Mj
Residents of Squatter Areas					
PHI	.50	.98	1.00	.50	.59
MSG	.85	1.00	1.00	.85	.97
CAPSULE	.75	1.00	1.00	.75	.82
Residents of Coastal Barrios					
PHI	.50	.98	1.00	.50	.58
MSG	.83	1.00	1.00	.83	.99
CAPSULE	.75	1.00	1.00	.75	.79

Benefit-cost Analysis

Benefit-cost ratios are a major criteria for project selection. It is always desired that the ratio be greater than one. This criteria presents an incomplete picture in cases in which complex benefits and costs, many of which are intangible, exist. Moreover, most of these analyses limit the scope of their benefits and do not examine many of the secondary effects of their projects. Since the private costs are either very near zero (for two of the programs), it is not useful to present benefit-cost ratios.

The social benefit-cost ratios presented in Table 38 are quite large. Using a discount rate of 8%, these ratios indicate a large benefit to society. The social benefit-cost ratios (BCR) are more important for socio-economic decision-making. In the squatter areas, they clearly indicate the superiority of the capsule program on the basis of costs and benefits related to X as all three programs have BCR's above 1, indicating net economic gains to society from any of these programs. In the coastal areas, the private earning of each cohort are much lower than in the squatter areas and the BCR's are much lower. In fact,the BCR for the PHI is below 1.

In both zones, the capsule program has a higher BCR than the MSG fortification. These differences get much smaller as the discount rate increases from 8% to 15%. Similarly, the increase in the discount rate lowers the BCR of the PHI in both zones.

TABLE 38 SOCIAL BENEFIT-COST RATIOS

Treatment Group	Benefits		Costs		Mij	Benefit-Cost Ratio		Level of Effectiveness Needed for Benefit-Cost Ratio to Equal 1	
	8%	15%	8%	15%		8%	15%	8%	15%
URBAN SQUATTER	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
PHI	225041	151394	98078	80448	.59	1.35	1.11	.44	.53
MSG	225041	151394	11439	8333	.97	19.1	17.6	.05	.06
CAPSULE	225041	151394	4203	3059	.82	43.9	40.6	.02	.02
RURAL COASTAL									
PHI	151394	50444	98078	80448	.58	0.89	0.36	.65	never
MSG	151394	50444	11439	8333	.99	13.1	6.0	.08	.17
CAPSULE	151394	50444	4203	3059	.79	28.5	13.0	.03	.06

The Effectiveness Parameter M

It is most useful to examine how small the effectiveness parameter would have to be for the benefits of the program to equal the costs. For the PHI, Mj would have to equal .53 in the squatters area which is only somewhat smaller than the actual estimated effectiveness level of .59. In one case of the rural coastal barrios at the high discount rate, the PHI costs are greater than the benefits and no adjustments are possible. The effectiveness levels of the fortification and capsule programs would have to be very low. They would have to be .5 to .17 for the fortification and .2 to .06 for the capsule for the costs to equal the benefits.

Other Considerations: Unmeasured and Intangible Benefits

The BCR's for the PHI have been very low. Additional nutritional and health benefits will accrue to children and areas covered by the PHI. The present private and social benefits have not included the benefits which accrue for the elimination of TB and other diseases, the increases in nutritional status, the immunization of children and even the less tangible development of barangay organizations. Community participation in the treatment of community health problems was an important element in the PHI and must not be neglected. This is one of the major differences between the PHI and other health programs. Are these additional unmeasured benefits greater than the unmeasured costs? The best approach may be to consider if the ₱30000 difference between the PHI costs-benefits in the coastal barrios are worth these additional tangible and intangible benefits.

Secondary Effects

This analysis has been based on partial equilibrium analysis. Changes in the relative prices of the various production factors have been ignored because they represent only a transfer effect.

The visibility of the PHI is important as this program is more likely to be associated with concurrent social changes. Demographers and other social scientists often argue that the low visibility and lack of social change involved with the malarial eradication and other mass public health campaigns for the past 3-5 decades did not lead to shift in social attitudes necessary for concomitant fertility declines. The high visibility of the PHI may be an important aspect of the functioning of this program.

The goal is the selection of the program which will be most meaningful to the Philippines. The benefit-cost ratio and the other important Filipino development priorities such as participation of local people in the implementation of the program and the development of "home gardens" have been discussed. The BCR can be viewed as a tool which converts the goal of maximization of economic benefit into a constraint that the BCR be greater than or equal to one. Then the broader developmental goals can be examined.

All three programs have BCR's greater than one in the squatter areas, even with the more conservative 15% discount rate. The BCR for the PHI in the coastal areas is well below one. There are a number of important considerations. First for a minimal marginal cost, the PHI program could distribute capsules which would clearly enhance its effectiveness in eliminatin old X and preventing new X. Second, the PHI is providing significant other benefits. There was meaningful popular participation in the program though interest did wane at times and there were meaningful relative improvements in the level of diseases, parasites, and nutritional status and a reduction in third degree malnutrition, associated with the PHI treatment compared to the other programs. It is hard to disregard a program with these multiple benefits, especially when the PHI is contrasted with the simpler fortification and capsule program which can only provide vitamin A.

If budget constraints are severe, both the capsule and the MSG fortification are attractive programs. It is important to note that MSG could also be fortified with other items. In the case of the Philippines, iron and iodine would be prime candidates. At the same time, other items could be fortified which would increase the effectiveness of a fortification program. It is, in fact, very wise to fortify several items to insure that a minimal level of protection is provided to each child.

The capsule program has very attractive high BCR's, but its effectiveness level is low. Moreover, it requires a superb delivery system and this is too demanding on manpower and other resources to provide just a capsule as the benefit. It may be much more advantageous to use the capsule as an element of other programs and to provide it as part of the curative process in health centers.

Appendix 2

PUBLIC HEALTH INTERVENTION

Policies on the Delivery

A. Over-all Policies/Guidelines

1. The four barrios will receive the same program of intervention
2. The PHI will be delivered by an intervention team consisting of:
   a) one physician
   b) 3 interviewers who assume the roles of multipurpose health worker
   c) one horticulture expert
3. The intervention team will visit each barrio only once a week and will spend a minimum of eight hours per visit.

B. Priority Setting

1. The four barrios will have the same priority rank and will receive PHI of equal intensity.
2. PHI is primarily delivered to the 300 numbered and listed houses.
3. Sample families will have the highest priority rank in the delivery
4. Families within the geographic limits of the barrio but do not belong to the 300 numbered and listed houses are classified under the lowest priority rank and will receive only unstructured health care.

C. Strategy

1. Initial Delivery

a) The initial delivery will be in the form of a massive, segmental (project by project) approach.

b) The following projects are delivered initially:

1. Deworming project
2. Immunization project
3. TB Control project

c) The initial delivery will conform with the priority setting. The initial projects will be delivered to 50% of the total target population and one-half of these should be sample children.

d) Each of the initial projects will be alloted four barrio visits or a total of 32 hours.

e) The Medical Auxiliary Workers Training Program will be started during the initial delivery. Training will be supervised by the team physician and training is described in the MAW Training Manual.

f) The Botica sa Baryo is included in the initial delivery. The initial capital of ₱200.00 will be loaned by CIM-CU to the community and will be repaid from profits generated by the operation of the Botica sa Baryo.

The Botica sa Baryo will be managed and controlled by the Botica sa Baryo Committee of the Barrio Council composed of the following:

1. Barrio Captain as Chairman
2. Barrio Secretary
3. Barrio Treasurer
4. Barrio Auditor
5. CIM-CU Physician

The operation of the Botica sa Baryo and the functions of the Committee are described in the Botica sa Baryo Manual.

2. Subsequent Delivery

a) The subsequent delivery will be programmed in the context of the Service Model.

<u>The Service Model</u>

1. The delivery of PHI to targetted families

The targetted families will conform with the priority setting namely:

1st priority - sample families

2nd priority - families from the 300 numbered and listed houses

3rd priority - families from within the barrio but without house numbers

2. The team physician will have the following work pattern and time distribution.

50% (4 hours) - morbidity clinic

25% (2 hours) - M.A.W. training

25% (2 hours) - Lecture to groups in the community

3. The three Family Health Aides will devote 100% of their time delivering PHI to targetted families with

the following work pattern and time distribution:

50% - 1st priority family

30% - 2nd priority family

20% - 3rd priority family

4. Each Family Health Aide will devote a maximum of two hours per family during the delivery of PHI.

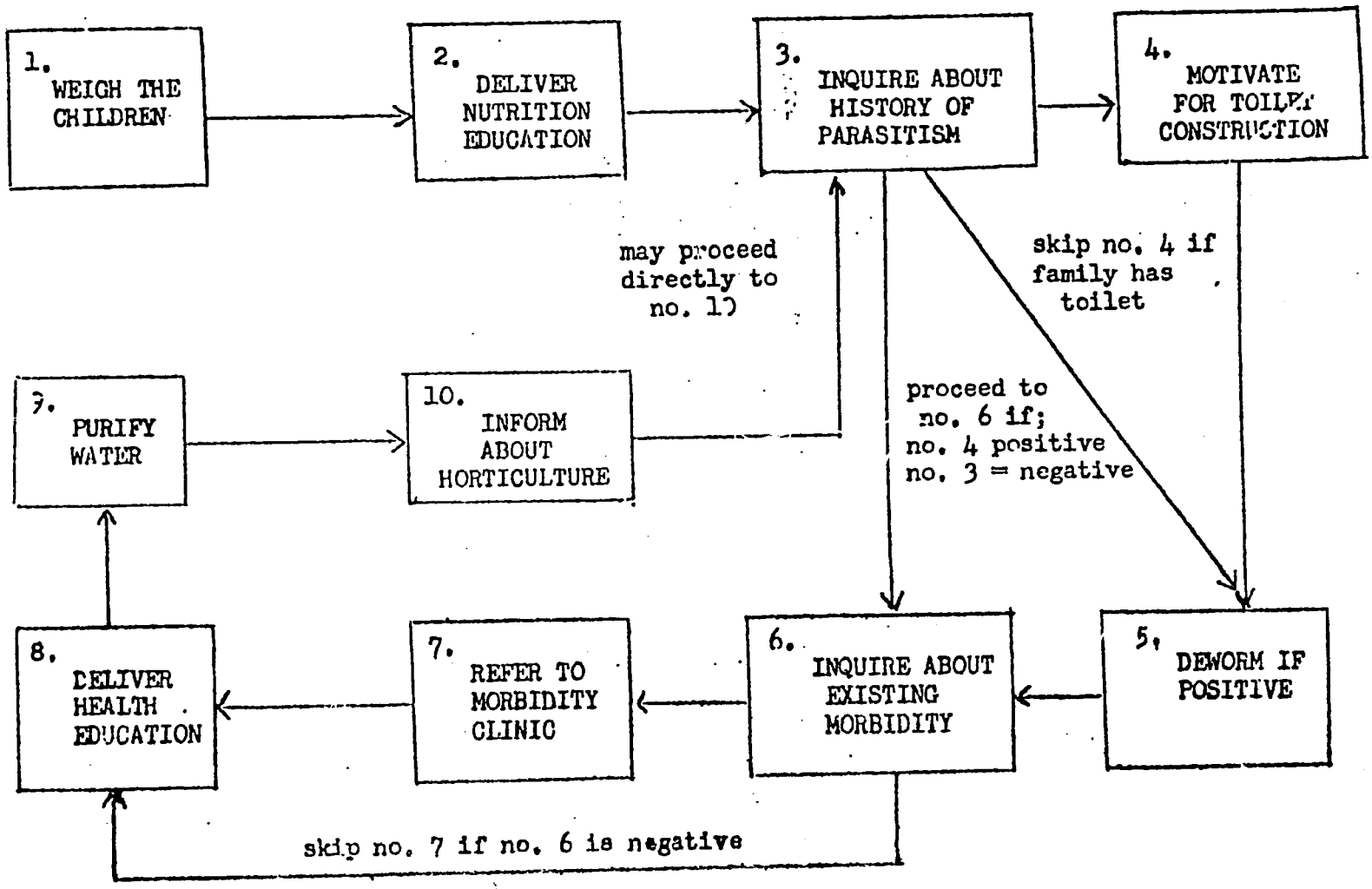
APPENDIX II

INTENSIVE FAMILY CARE

METHODOLOGY FLOW CHART

. if normal weights

reinforce nutritional habits



Guidelines for Intensive Family Care

No. 1 Weigh the Children

Weights:

A. There are children in the household

Steps:

a. Obtain ages of children

b. Weigh the children and assess their nutritional status using table of standard weights.

1. Family with infants (birth to 2 yrs.) and underweight children - deliver nutritional education (No. 2), etc.

2. Family without infants but with underweight children - start directly with part III of No. 2 (Nutrition Education)

3. Family without infants and with normal weight children - starts with part III of No. 2, etc. stressing ill effects of improper health practices.

c. Motivate for Family Planning

B. There are no children in the family

Steps: a) go to 8 - deliver health education

b) go to 9 - purify water

c) go to 10 - inform about horticulture

No. 2 Deliver Nutrition Education

I. Infant Feeding

A. Breast Feeding (Encourage all mothers to breast feed)

1. importance (complete, convenient, safe, cheap)
2. breast care
3. duration and schedule
4. burping

B. Bottle Feeding (Only for mothers who cannot breast feed)

1. hygiene measures:

   - clean bottle) prevent GIT disorders (kalibang)
   - boiled water)

2. formula

   - use evaporated milk - dilution based on age
   - emphasize disadvatages of condensed milk - at high dilution

C. Supplementary Feeding - *starts at four months of age (small amount of vegetables, meat soups, mashed vegetables, etc.)

1. Dilis powder or mongo powder
2. Preparation

   Mashing and straining:

   a. Vegetables
   b. Fruits
   c. Rice
   d. Tubers

Principles:

1. Commonly used foods
2. Hygiene
3. Balance meal
4. Palatability

II Weaning

- gradual

· milk must be part of child's diet

· protein-rich foods (mongo, dilis, etc.) that are inexpensive and readily available

III Weight - Index of growth and development

1. Visual: (Charts)

   To compare normal and retarded development

2. Importance:

   a. Weight in direct proportion to and nutritional practices

      if weight is low - not getting enough of right foods

      or stationary - disease process going like parasitism

   b. Weight reflects growth and developmental status of child.

   c. Serial weighing - adequate gauge in determining growth pattern.

IV Malnutrition

A. Visual (Cases)

B. Types (Bring pictures to illustrate)

   1. Marasmus

   2. Kwashiorkor

   3. Vitamin A deficiency - night blindness

C. Effects

1. physical and mental (brain) retardation

physical - thin, presence of pigmentation, edema, etc.

mental - slow comprehension

irritability

decrease work efficiency

2. susceptibility to infection - drain in money

Solution: Balance foods (Protein, carbohydrates, fat) and Vegetables

Motivate for home gardening to produce basic foods

No. 3 Inquire about history of Parasitism

No. 4 Motivation for Toilet Construction

A. If the children are positive for parasites (by history or stool examination)

Steps: 1. Explain the presence of parasitism as due to lack of a santiary toilet - demonstrate how a child gets the parasite (simplified parasite cycle of life)

2. Mention the other excreta transmitted diseases and d escribe them,

3. Inquire whether any member of the family has been sick with these diseases.

if YES: Point out the presence of these diseases in the family as due to the lack of a sanitary toilet. Also point out that this can be due to lack of blind drainage or improper garbage disposal.

if NO: Inquire whether any member of the family has ever been sick of diarrhea. if yes - then attribute this disease to lack of blind drainage or improper excreta disposal.

4. Teach and encourage the family to:

a. build a sanitary toilet

b. construct a blind drainage

c. dispose garbage properly

B. If the children are negative for parasites:

Steps: 1. Inquire about incidence of diarrhea and other diseases.

2. Explain that water becomes contaminat with bacteria when:

- there are no toilets
- improper drainage system
- improper garbage disposal

3. Then teach and encourage the family t

a. build a sanitary toilet

b. construct a blind drainage system

c. dispose garbage properly

No. 5 Deworm if Positive

No. 6 Inquire about existing morbidity

No. 7 Refer to Morbidity Clinic

No. 8 Deliver Health Education

Topics:

I. Introduction to Communicable Disease Control

A. Briefing of respondents on general results of stool and blood examination of sample children.

B. Information regarding the avoidance and control of certain diseases which easily occur in children and even adults, stressing the importance of knowledge of these diseases.

C. Illustration and discussion of the Communicable Diseases transmitted by the 4 F's:

1. Food
2. Fingers
3. Flies
4. Feces

D. Driving home in minds of Audience the necessity of cleanliness on the four F's.

II. Discussion of Four Common Communicable Diseases Namely:

1. Dysentery (Dysenteria)
2. Cholera (El Tor)
3. Typhoid (Typhus)
4. Intestinal Parasitism (Bitok)

III. Discussion of the general evolution of the specific disease process:

1. Ex. Dysentery:

1. child plays in ground, thus makes hand dirty
2. child eats fruits without washing
3. in evening, child has minimal diarrhea

4. or if day child's appetite not affected therefore, eats more unclean foods
5. so child diarrhea recurs and becomes worst. Also there is accompanying abdominal pain and fever.

2. Discuss also other diseases patterned after dysentery

IV. A. Sources and Causes of Communicable Diseases through
1. Water contamination
2. Food, Flies, Fingers, and Feces

B. Control by:
1. Water chlorination
2. Construction of toilets
3. Construction of proper drainage
4. Sanitary disposal of garbage
5. Environmental sanitation

No. 9 Purify Water

Steps:
1. Inquire about the source of water
2. Inquire about diarrhea
3. Mention the water-borne diseases - cholera, typhoid, and dysentery
4. Explain that water-borne diseases are due to water contaminated with bacteria (reinforce with environmental ssnitation)
5. Mention chlorination as a method of eliminating these bacteria found in water
6. Teach how to chlorinate water
7. Encourage the practice of water chlorination.

No. 10 Inform about Horticulture

I. Discuss the importance of Horticulture

A. Its relation to good nutrition

1. essential nutrients derived from home garden products

2. freshness

3. economic reason - affords savings

II. Mechanics of Horticulture Program

A. For households with existing home gardens:

1. Check the size and locations of home gardens - campaign for more and bigger home gardens

2. Find out varieties of garden plants - promote the raising of malunggay, agbate, gay, etc.

3. Five technical advices:

a. how to make and prepare a seed box or seed bed with subsequent sowing of seeds.

b. preparation of plots for transplanting

c. encourage the proper use of locally available fertilizer i.e., horse, cow or carabao manure, chicken dungs.

d. care for growing plants including chemical treatment, weeding if possible.

B. Households without Existing Home Garden (with available space)

1. Find out the reasons for the absence of home gardens

a. presence of stray animals - let the owner of such animals tie the animals or encourage the farmer to fence with available materials such as kagingking, salirap, etc.

b. lack of personnel

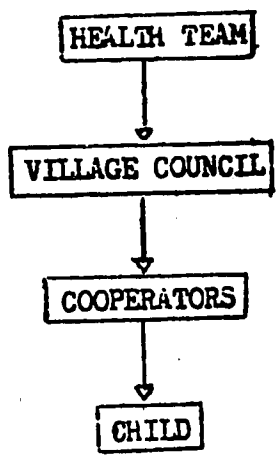
C. Households without available space for home Gardens -

Encourage use of seed boxes, cans for such purpose.

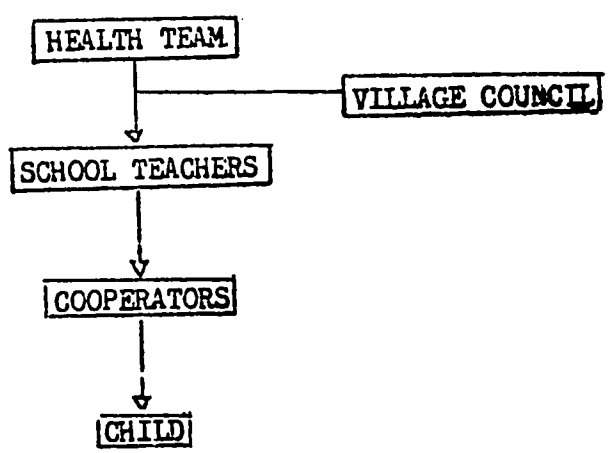
Appendix 3

CAPSULE DISTRIBUTION STRATEGIES

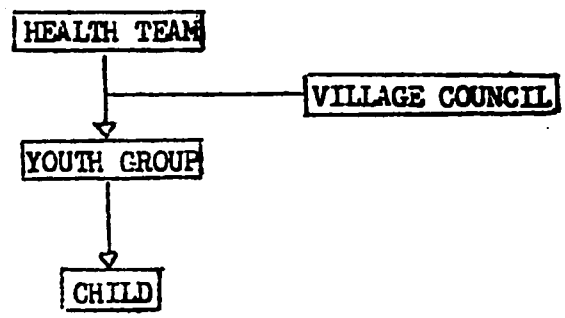
STRATEGY I BARANGAY OR VILLAGE COUNCIL



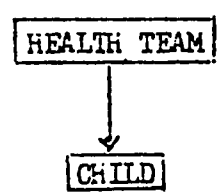
STRATEGY II SCHOOL TEACHERS



STRATEGY III YOUTH GROUPS



STRATEGY IV HEALTH TEAM



Appendix 4

Persons and officials involved in the Project:

FIRST YEAR

A. CORNELL UNIVERSITY

1. Dr. Michael C. Latham - Co-Associate
2. Dr. Barry Popkin - Co-Associate

B. CEBU INSTITUTE OF MEDICINE

1. Dr. Jacinto Velez - President, CIM
2. Dr. Constancio Camomot - Dean, CIM
3. Dr. Ibarra T. Panopio - Consultant Pathologist
4. Dr. Jesus Ravanes - Consultant Ophthalmologist
5. Miss Erlinda Pestaño - Consultant Nutritionist
6. Mr. Gustavo Sasis - Consultant Horticulturist
7. Mrs. Lydia Adlawan - Medical Technologist
8. Mr. Clemente Historillo - Medical Technologist
9. Miss Nanette Jabonero - Medical Technologist
10. Miss Veronica Vocal - Clerk-Typist
11. Mr. Nicasio Setrina - Driver

C. VITAMIN A STAFF

1. Dr. Florentino S. Solon - Project Director
2. Dr. Tomas L. Fernandez - Deputy Director
3. Dr. Jeremias U. Murillo - Co-Investigator
4. Dr. Asuncion V. Arong - Research Physician
5. Dr. Joseph D. Graciosa - Research Physician
6. Dr. Exequiel D. Pilones - Research Physician
7. Mrs. Mercedes A. Solon - Research Assistant
8. Miss Milagros P. Naputo - Research Assistant
9. Mrs. Victoria B. de la Peña - Research Assistant
10. Mrs. Ruperta A. Caballes - Medical Technologist
11. Miss Guillerma Lampayan - Medical Technologist
12. Miss Adiel A. Macavinta - Clerk-Typist
13. Miss Marcelina Chan - Clerk-Typist
14. Mr. Pedro Nellas - Clerk-Driver
15. Mrs. Celsa C. Pono - Health Educator
16. Miss Carmen Logroño - Interviewer
17. Mrs. Josefina Padilla - Interviewer
18. Mr. Bienvenido Holganza - Interviewer
19. Mrs. Mirasol Abaquita - Interviewer
20. Miss Anita Densing - Interviewer
21. Miss Lorna Fortuna - Interviewer
22. Miss Ma. Lisa Gorres - Interviewer
23. Miss Luzviminda de Guzman - Interviewer
24. Mrs. Florenda C. Labuga - Interviewer

SECOND YEAR

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1.	Dr. Michael C. Latham	- Co-Associate
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B. CEBU INSTITUTE OF MEDICINE

1.	Dr. Jacinto Velez	- President, CIM
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3.	Dr. Ibarra T. Panopio	- Consultant Pathologist
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5.	Mr. Gustavo Sasis*	- Consultant Horticulturist
6.	Mrs. Lydia Adlawan	- Medical Technologist
7.	Mr. Clemente Historillo	- Medical Technologist
8.	Miss Nanette Jabonero	- Medical Technologist
9.	Mr. Nicasio Setrina	- Driver

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5.	Dr. Exequiel D. Pilones	- Research Physician
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7.	Mrs. Victoria de la Peña	- Research Assistant
8.	Mrs. Ruperta Caballes	- Medical Technologist
9.	Miss Guillerma Lampayan	- Medical Technologist
10.	Mrs. Marietta Ebo	- Research Aide
11.	Mr. Bernard Lanutan	- Research Aide
12.	Miss Godiva T. Sa-a	- Clerk-Typist
13.	Mr. Pedro Nellas*	- Clerk-Driver
14.	Mrs. Celsa Pono	- Health Educator
15.	Mrs. Carmen Logroño	- Interviewer/Family Health Aide
16.	Mrs. Josefina Padilla	- Interviewer/FHA
17.	Mr. Bienvenido Holganza	- Interviewer/FHA

*First six months only.

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1.	Dr. Michael C. Latham	- Co-Associate
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3.	Miss Amanda Te	- Research Assistant
4.	Mrs. Susan Ybañez-Gonzalo	- Research Assistant
5.	Mr. Eduardo Reyes	- Programmer
6.	Mrs. Leticia Buela-Dizon	- Secretary, AA

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3.	Dr. Ibarra T. Panopio	- Consultant Pathologist
4.	Dr. Jesus Ravanes	- Consultant Ophthalmologis
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7.	Miss Nanette Jabonero	- Medical Technologist
8.	Mr. Nicasio Setrina	- Driver

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5.	Dr. Exequiel D. Pilones	- Research Physician
6.	Miss Milagros P. Naputo	- Research Assistant
7.	Mrs. Victoria B. de la Peña	- Research Assistant
8.	Mrs. Ruperta Caballes	- Medical Technologist
9.	Miss Guillerma Lampayan	- Medical Technologist
10.	Miss Charito Miranda	- Medical Technologist
11.	Mrs. Marietta Ebo	- Research Aide
12.	Mr. Bernard Lanutan	- Research Aide
13.	Miss Godiva T. Sa-a	- Clerk-Typist
14.	Mrs. Celsa Pono	- Health Educator
15.	Mrs. Carmen Logroño	- Interviewer/FHA
16.	Mrs. Josefina Padilla	- Interviewer/FHA
17.	Mr. Bienvenido Holganza	- Interviewer/FHA
18.	Miss Rosario Cabigon	- Medical Technologist
19.	Miss Aurora Saniel	- Medical Technologist
20.	Mrs. Emiliana Canque	- Interviewer
21.	Mrs. Josefa Chan	- Interviewer
22.	Miss Terencia Magallon	- Interviewer
23.	Miss Pacita Rosafa	- Interviewer
24.	Mrs. Nenita Sotto	- Interviewer
25.	Mrs. Purita Titong	- Interviewer
26.	Mr. Natalio Villahermosa, Jr.	- Interviewer
27.	Miss Fe Villarico	- Interviewer
28.	Miss Rosario P. Soriaga	- Training Coordinator
29.	Mr. Cesar Bugtai	- Horticulture Assistant
30.	Mr. Nonoy Ceniza	- Horticulture Assistant
31.	Mr. Generoso Pena	- Science Aide

Appendix 5

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APPENDIX II

A BACKGROUND DISCUSSION OF VITAMIN A DEFICIENCY AND KEY FACTORS RELATED TO IT

a. Introduction

In natural situations a pure vitamin A deficiency seldom exists as an isolated condition, especially in the Third World (Oomen, 1969). Rarely does the deficiency of vitamin A occur without the presence of other nutritional deficiencies or in conjunction with other disease. Many forms of malnutrition occur in the presence of infectious and parasitic diseases which often are interacting synergistically with malnutrition. Thus, the conditions of interest here, xerophthalmia and keratomalacia, occur concurrently with dietary deficiencies such as protein, calories and riboflavin and with diarrhea and other forms of infectious or parasitic disease. Vitamin A deficiency produces a variety of pathological lesions but this study is concerned chiefly with the deficiency as it relates to the eye and to blindness which is one of the most significant consequences of this deficiency.

Xerophthalmia is the general syndrome which covers all eye lesions and the general public health problem implied in vitamin A deficiency. The affix, xero-, suggests a dryness, lusterless condition of the eyeball. More specifically, it relates to a dryness of the conjunctival and corneal epithelia. Keratomalacia relates to the softening of the cornea with ulceration and loss of vision. The root, malacia, differs from xero as it is the weakening, softening and melting process which follows xerophthalmia. Keratomalacia is a special manifestation of xerophthalmia. This last stage of xerophthalmia may develop very rapidly.

The clinical aspects of xerophthalmia have been divided into four stages--stages which do not encompass all essential manifestations of the syndrome but are as complete as is possible (Xerophthalmia 1, p. 2; Ten Doesschate).

Stages of Xerophthalmia

X_0 - only night blindness present

X_1 - conjunctival xerosis (dryness) with or without night blindness, with or without Bitot's Spots

X_2 - corneal xerosis, reversible changes of corneal epithelium (cover)

X_3 - a) irreversible corneal changes, loss of substance, perforations

b) softening of parts of cornea (keratomalacia)

X_4 - scars, blindness, large or total whiteness of eye

Vitamin A includes the preformed vitamin A (retinol) and the provitamins A or carotenoids. Preformed A, found in foods of animal origin, is ready for utilization by man, while the preformed carotenes from vegetable sources must be converted to vitamin A in the intestines of man. It should be noted that the preformed A is many times as efficient as the beta carotene in that much of the beta carotene is lost in the process of absorption and conversion before it can be utilized by the human organism.

b. Consequences of Xerophthalmia

A deficiency of vitamin A affects many central life processes of the human organism. Many of these relationships may have important economic manifestations which will be discussed later. The following are some of the relationships:

a) Resistance to infection - a deficiency lowers the resistance to

infection in general, and especially lowers the integrity of the epithelial tissues (Roels, 1969, p. 906). "Vitamin A is synergistic with almost all infectious diseases in which the relationship has been studied. Children and adults with xerophthalmia are highly susceptible to infections, particularly the respiratory and genito-urinary systems" (Taylor, p. 213).

b) Reproduction - vitamin A is essential for the normal functioning of the reproductive system;

c) Utilization of dietary protein - the addition of vitamin A increases the utilization of protein. On the other hand, a deficiency of vitamin A may reduce food intake and growth (Roels, 1969, p. 905).

d) Visual cycle - vitamin A is essential in the formation of rhodopsin. Rhodopsin is important for vision in dim light. Furthermore, blindness is a common occurrence for those who have suffered from xerophthalmia. Often the lesions are asymmetric; the numbers of people blind in both eyes and one eye is about equal (Oomen, 1964 (b), p. 307). Disagreement exists on this point. Some researchers feel the effects are symmetric (Goldsmith, p. 401). In one study, among the survivors of xerophthalmia, 27% were blind, 59% had greatly reduced vision, and only 14% had undamaged eyes (McLaren, 1963, p. 214). McLaren estimated that a minimum of 1 in 800 children surviving the age of 5 in Indonesia would be totally blind from xerophthalmia (ibid).

e) Mortality - vitamin A deficiency is associated with a high mortality rate among children (Roels, 1969, p. 907). Between 25 to 60 percent of those with xerophthalmia die (McLaren, 1963; Oomen,

1964(b)). Observations in India suggest 50 percent survive, while in areas of North Africa survival may be a rarity (Oomen, 1964(b), p. 36-41). At the same time, many children with xerophthalmia die of kwashiorkor or nutritional marasmus who might otherwise survive and become blind.

c. Nutritional and Biochemical Factors

Two of the key processes which determine the effects of dietary intake over time on the human organism's vitamin A nutriture are the absorption and conversion of the preformed beta carotene. "The biosynthesis (conversion) of vitamin A from beta-carotene takes place mainly in the intestinal mucosa, during the absorption of dietary β-carotene" (Goodman, p. 963). The presence of various diseases interferes with this absorption process of either carotene or vitamin A. "Acute febrile infectious disease and perhaps also diarrheal disease have a trigger effect which cannot always be explained by depletion" (Oomen, 1969, p. 1104). Ascaris may utilize carotene. It is believed that the ascaris (roundworm) can convert carotene to vitamin A in its intestinal wall.

Basically the provitamin A (carotenoids) is converted into retinol (vitamin A) and then absorbed. Fat affects the amount of carotene absorbed since vitamin A is a fat soluble vitamin (National Institute of Nutrition, p. 65). Protein deficiency markedly depresses the intestinal conversion of beta-carotene. After absorption the nutrient is either utilized or stored. A study carried out in India showed that mild protein-calorie malnutrition does not impair the absorption of beta-carotene (Lele). Protein is necessary for the utilization of the vitamin A and is also responsible for the transport of this A (retinol) in human plasma while vitamin E affects the utilization and also the storage of the A in the liver (Roels,

1969, p. 904). Scientists are finding that some vitamin A is stored in skin and muscle (Olson).

Previously it was mentioned that vitamin A affects protein metabolism, reducing the utilization of the ingested protein. A severe protein deficiency may prevent vitamin A from reaching the liver and keep the remaining reserves unavailable to the other tissues of the body for utilization (Arroyave, 1969). This does not mean kwashiorkor or xerophthalmia will necessarily occur concurrently. Rather, this means programs which provide protein and subsequently accelerate the rate of growth in children. may produce the appearance of xerophthalmia (ibid).

An unrelated but important factor is the effect of maternal nutriture Poor maternal vitamin A nutriture results in a low storage in the unborn child and a low content of vitamin A in the mother's breast milk.

There are several biochemical indicators of vitamin A nutritional status. The clinical indicator used in this study is the xerophthalmia ranking discussed in the introduction. The amount of vitamin A stored in the liver can be determined by a biopsy of liver tissue taken with a biopsy needle injected into this organ. Although this test is very useful, it may be painful, it produces side effects and complications in some patients, and was not utilized. It is not a field test. Determinations of the levels of vitamin A (retinol) and of carotene in the serum (plasma) are the two basic methods (Interdepartmental, 1969). Also, there is some evidence of a poor correlation between vitamin A in the liver and the plasma unless the deficiency is very severe. The same is true for clinical symptoms of vitamin A deficiency and serum A levels. Part of the explanation may be the storage of vitamin A in the skin and muscle (National Institute of Nutrition, p. 64).

The plasma or serum A test represents vitamin A nutriture over a period of time because considerable vitamin A can be stored and long periods are required for its depletion. Seasonal fluctuations affect the supply of food containing vitamin A or its precursor, carotene, but do not necessarily affect the serum A. Thus, this index is often uncorrelated with recent dietary intakes.

The serum carotene, on the other hand, reflects recent dietary intake. Beta-carotene is not stored for very long; it is converted to vitamin A. The finding of low carotene levels is informative as to the type of diet consumed over recent weeks and months. There is a problem with the serum carotene because more of the carotenes are not converted to retinol. Biochemical levels are indicative of the nutritional well-being of a person; however, often values reflecting a given level of health vary significantly between each person.

d. Dietary Sources

In the previous discussion, vitamin A sources were described as retinol and as carotenoids. The main carotenoid is beta-carotene. The importance of these distinctions lies in the relative effectiveness in each in providing the necessary biological activity for the human body. The carotenoids are not utilized as efficiently as retinol by the human body (Aykroyd, p. 68). The standard relationship is 1 µg beta-carotene equals .167 µg retinol or beta-carotene is one-sixth as efficient as retinol (Joint, p. 24-25). The other carotenoids are much less efficient than beta-carotene and are given a retinol equivalence of one-twelfth. The other standard of measurement for vitamin A activity is International Units (IU). One IU of vitamin A is equivalent to 0.3 µg of retinol.

These relationships are significant, especially when carotenoids provide

65-95% of the total vitamin A activity in the diets of the developing areas (Joint, p. 6-8). The principal sources of vitamin A in the diets of developing areas are fruits and vegetables--predominantly the green leafy and yellow vegetables. Table 1 gives the estimated distribution of the sources of vitamin A activity in various foods.

Sources of Vitamin A

Foods containing previtamin A as retinol are fairly expensive and consumption may be prohibited by religious or cultural mores. It occurs widely in animal tissues, especially in the livers where it is stored. The fat content of the meat, milk or fish may be important; the retinol is often found in these tissues. Thus, lean meat or fish and milk from which the fat has been skimmed are almost devoid of vitamin A. While fish provide an excellent source of vitamin A, sun dried fish loses most of its vitamin A value. "Eggs are an excellent source of retinol and may prove to be a practical method of supplementing vegetable diets" (Joint, p. 57).

Beta-carotene is found in all the green parts of plants. "Green leafy vegetables, such as the young leaves of Ipomoea (sweet potato and swamp cabbage), cassava, amaranth, horseradish, etc., are rich sources of carotenes....Fresh immature legumes (green string beans, lima beans, peas, etc.) before they reach the mature dried stage (grain legumes) are also good sources of both proteins and carotenes" (Joint, p. 57). Figure 2 shows many of these sources. Breast milk is another important vitamin A (preformed) source. For infants breast feeding is important in forestalling vitamin A deficiency (van Veen, 1974).

Beta-carotene is also found in abundance in red plam oil, carrots, mangoes, papayas and other yellow vegetables and fruits. Red palm oil, a very rich source of beta-carotene is extensively produced in West and

Table 1. ESTIMATED DISTRIBUTION OF SOURCES OF VITAMIN A ACTIVITY (AS IU) IN VARIOUS FOODS

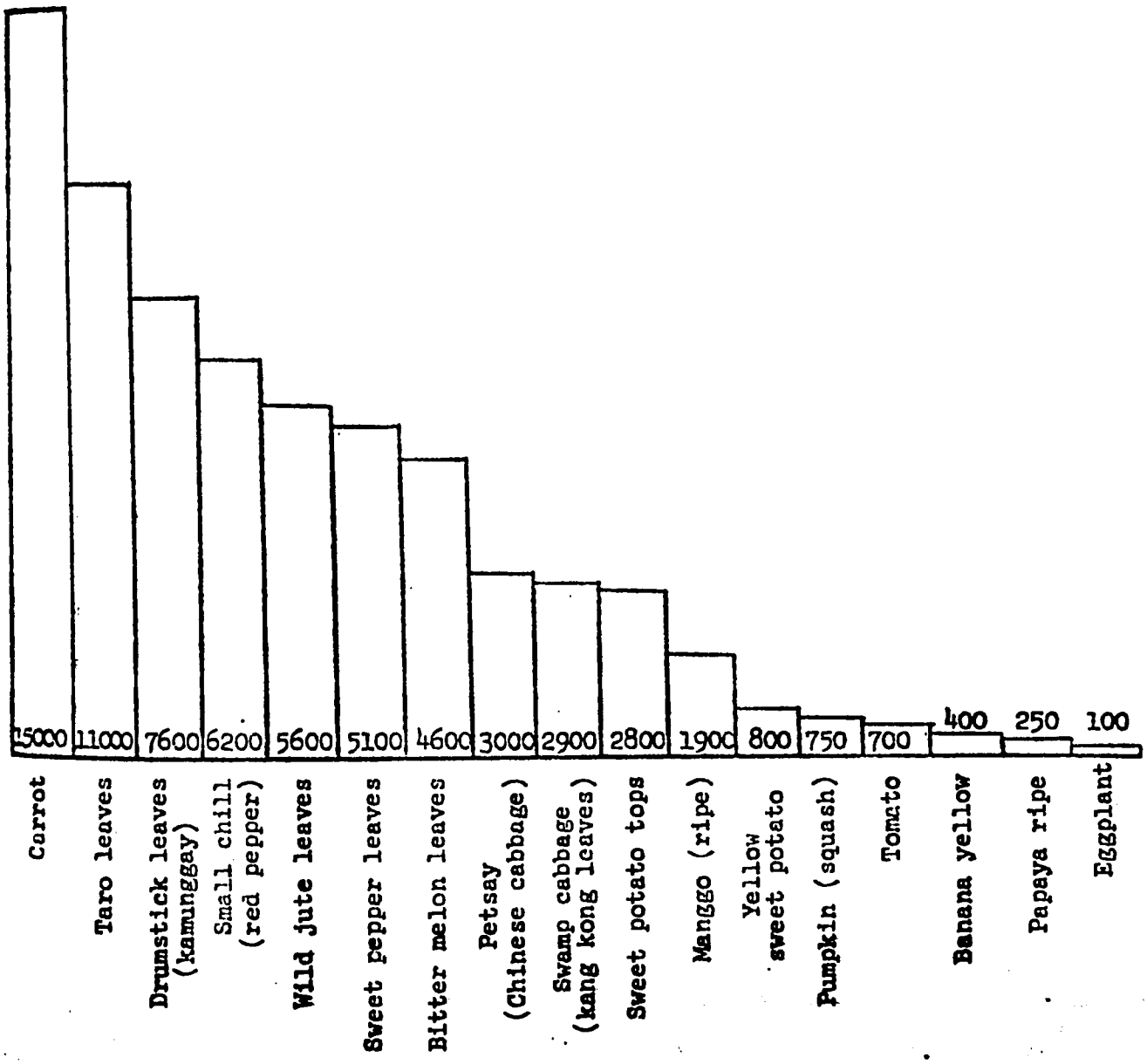
Source	From retinol	β-carotene	Other carotenoids
Animal origin			
Meat and meat organs	90	10	
Poultry	70	30	
Fish and shellfish	90	10	
Eggs	70	30	
Milk and milk products	70	30	
Animal or fish oil	90	10	
Plant origin			
Cereals			
Maize, yellow		40	60
Others		50	50
Legumes and seeds		50	50
Vegetables			
Green vegetables		75	25
Deep yellow (carrots, sweet potatoes - deep orange type, etc.)		85	15
Sweet potatoes - pale type		50	50
Fruits			
Deep yellow (apricot, sapote etc.)		85	15
Other fruits		75	25
Vegetable oils			
Red palm oil		65	35
Other vegetable or seed oils		50	50

Source: Joint FAO/WHO

Figure 2. CAROTENE CONTENT OF FOODS[a]

a/ Approximate provitamin A content of some leafy and yellow vegetables and fruits, International Units per 100 grams (as purchased).

Source: UNWHO Western Pacific Region, p. 26.



Central Africa and parts of the Far East. It is often used to treat xerophthalmia and in some cases as a dietary supplement to prevent xerophthalmia (Roels; UNICEF). Coca, consumed in the highland areas of Bolivia, has a high carotene A content.

Carotene and retinol are relatively stable towards heat and in the canning and processing. In some cases, such as carrots, the foodstuff must be cooked to release all of the carotene. At the same time, traditional techniques such as the drying of leaves and the storage of vegetables, such as squash, do not lead to a loss of carotene. Extensive exposure to the sun (e.g., sun dried fish) appears to be the major cause of carotene or retinol loss.

Often the main staple determines the diet content of vitamin A. When it provides little or no carotene as in the case of rice and white corn, the incidence of xerophthalmia is very high (van Veen, 1947). Thus, the rice-eating populations of Asia and the Far East usually consume lower amounts of carotene than do those whose staple is yellow maize, sweet potatoes or millet.

Requirements

The requirements for vitamin A, expressed in weights of µg, vary by age and sex. The recommended daily amount of retinol for an adult is 750 µg (micrograms). An amount as low as 390 µg retinol per day is required to prevent visual symptoms of vitamin A deficiency in adults (Joint). During pregnancy the recommended daily allowances (RDA) remain constant; however, lactating women have an RDA of 1200 µg retinol per day. Growth requirements are greater for infants. At the end of three and five months 420 µg/day or about 65 µg/kg and 50 µg/kg, respectively, are recommended. Table 2 reports the recommended levels of retinol.

Table 2. RECOMMENDED INTAKE OF RETINOL AT VARIOUS AGES

Age	Recommended intake µg retinol per day	International units	Age	Recommended intake µg retinol per day	International units
0-6 months	1/		7-9 years	400	1333
6-12 months	300	1000	10-12 years	575	1917
1 year	250	833	13-15 years (boys-girls)	725	2417
2 years	250	833	16-19 years (boys-girls)	750	2500
3 years	250	833			
4-6 years	300	1000	Adults (man-woman)	750	2500

1/ For infants 0-6 months, it is accepted that breast feeding by well-nourished mothers is the best way to satisfy the nutritional requirements for vitamin A.

Source: Joint FAO/WHO Expert Group, p. 22.

Few diets consist purely of retinol. These recommendations are corrected for the consumption of beta-carotene at various levels (Joint). The basis for many of these recommended levels is poor (van Veen, 1974). This is especially true for children and adolescents.

e. Fruit and Vegetable Consumption, Home Production and Preference Patterns

Carotene food sources contribute 50-90% of the vitamin A intake of persons in most low income nations. Because of the high carotene content of many fruits and vegetables, this group of foods contributes a disproportionate amount of this carotene relative to the small amount of money spent on them. For example, the bottom 2 deciles of Indians spend about 12% of their expenditures for a group of foods which include fruits and vegetables along with beverages and condiments (B. Desai). In many regions, fruits and vegetables are either picked from the abundant foliage or produced in farms or home gardens. In general, however, it apperas that there is little significance given to consuming them outside the Chinese culture.

Some of the cultural and sociological studies conducted in Asia were reviewed in an attempt to understand the types of belief patterns which would affect fruit and vegetable consumption. In general, they are not classified as a main food which for Malaysians and Filipinos includes only the staple rice or corn (Polson; Wolff). Along with fish, meat and eggs vegetables are classified as a viand.

A series of studies have shown that these carotene-rich fruits and vegetables are often withheld from children (McKay). In a N.E. village in the Visayan island of Leyte (near Cebu), "fruits, other than bananas, and vegetables are rarely fed to the child. Because of existing food prejudices it is inconceivable to many women that they are important" (Nurge, p. 92). In total, Nurge found "that historically, the weanling was not fed fruit,

vegetables, meat or fish" (p. 95). It is unclear if the onset of diarrhea which is often caused by the consumption of these foodstuffs was the reason for these taboos.

The most damaging belief pattern is the practice of limiting common fruits and vegetables for children with eye problems (McKay, p. 70-71). In one rural Malay area the consumption of "cooling" fruits and vegetables (mainly carotene-rich) was prohibited for the xerophthalmic child because these would irritate worms which "then migrate into the eyes causing night-blindness....and finally blindness" (P. Chen, p. 234).

The discussion of home production of fruits and vegetables will center on the role of home gardening because of the small amount of cropland planted to fruits and vegetables in most areas. There is little tradition of home gardening in most parts of the world. This partially relates to the small consumption of vegetables and fruits by these people. Exceptions are the Indonesian, Japanese and Chinese diets. For example, one study in the densely populated island of Java found that home gardens cover about 20% of the arable land (Van Eijnatten). This was reported in 1949 and an earlier study on the same area gave a figure of close to 15% of the cultivated land (Ochse).

Aside from taste and economic pressures, several other social factors are important in explaining the small proportion of the population which engages in home gardening. Fernandez found that in some urban squatters areas where space for gardening was available, fear of eviction prevented the development of home gardens. Many families often will not garden near their houses as they would be destroyed by neighbors' foraging goats and pigs. Also, theft or the fear of theft prevents many families from developing garden plots.

Many of these social constraints can be changed. In some areas, low-income farmers in West Africa and the Philippines have been induced to grow meaningful home gardens (Van Eijnatten). In many cases, this only will happen when some cash can be earned.

In the Philippines a major campaign has been launched by the First Lady, Mrs. Imelda Marcos, to increase the practice of home gardening. In some areas this has led to considerable interest in the cultivation of small home gardens. In many other areas the lack of a tradition of gardening coupled with the dearth of seeds, water and good land has prevented meaningful adoption of this program.

A second factor in the Philippines has led to increased interest in vegetable production and home gardening. This has been the vegetable breeding program at the University of the Philippines College of Agriculture (UPCA) at Los Banos and the multiple cropping project developed first at the International Rice Research Institute (IRRI) by Dr. Richard Bradfield and then at the UPCA. For example, the UPCA has a pilot project in several villages in Laguna Province in the island of Luzon. In these villages the production of a variety of vegetable and fruit vegetables appears to have increased significantly. In this project the farmers have shown a great desire to produce for commercial channels (e.g., A. A. Gomez).

The breeding program has helped to develop new varieties of higher yielding and more disease resistant vegetable varieties. It has also begun to deal with more specific problems such as the inability of tomatoes to bear fruit in warmer climate and the lack of seeds and cuttings (Munger; National Food and Agricultural Council).

The multiple cropping goal is the continuous cultivation of land during the seasons in which the staple or main crop is not grown and also the

use of unused portions of the land during the prime growing seasons. The purpose is to utilize scarce land and labor more efficiently. For example, after the rice season the puddled land could be used for the growth of a variety of crops such as sweet potatoes. The result of both these efforts will be an increased emphasis on vegetables in agricultural planning in the Philippines and a greater availability of high quality varieties. Some of these breeding and selection efforts have been transferred to the newer Asian Vegetable Research and Development Center in Shanhua, Taiwan.

A third element has been the Applied Nutrition Programs in the schools. They have produced school garden programs over the past 5-15 years. While it is difficult to weigh their effects since few evaluations have been completed, undoubtedly they will make it easier for home gardening programs to be developed in any nation in the world where these UNICEF-sponsored programs exist (e.g., G. Desai).

In the past the research neglect of tropical horticultural crops other than those for export-oriented cash crops (citrus, banana, pineapple, etc.) has been serious. When research has been conducted, it is usually tied to the crops preferred by the more Western-oriented segments of the population. These are the cabbages, tomatoes, eggplants, etc. toward which the Western-trained agricultural scientists have become oriented. Moreover, little consideration has been given to the carotene contribution even when deficiencies in this nutrient are important in their countries.

Economic and carotene yields for a variety of vegetables were studied to determine how meaningful the carotene contribution of a home garden could be. Yield data collected from home gardens in Java and commercial and experiment station vegetable crops in the Philippines are compared in terms

of their carotene production in table 3. Yields were computed on a daily basis. While tropical climates do permit multiple and even continuous cropping, crops must be varied over the seasons. It should be noted that these yield levels for the home garden can come only after several years of gardening. The initiation of such a garden is slow in areas where none exist; the surface around the houses is usually compacted, eroded and leached. The possibility of high fertility exists and can come with the build-up and care resulting from plant growth (Van Eijnatten, p. 7-8). Yields per unit of time per land unit are appropriate for tropical climates (Munger). The small size of 18.5 square meters was selected as this was the average of home gardens found in Cebu in 1973. In Africa, Van Eijnatten found an average home garden was 26 square meters.

These results can be compared with the recommended daily allowance (RDA's) of vitamin A. The Javanese home garden, whose yields are expected to be closest to the home gardens in Cebu, provide an annual amount of vitamin A equivalent to about 16% of a 3-year old child's annual needs of 833 IU. If a family with two children aged 3 and 5 gave all the vitamin A to these children, wasted none in preparation, and had to meet 50% of their RDA's throughout the year, they would need about 916 IU daily. Many of the experimental results met this requirement.

A more realistic requirement for the average family of seven (ages 1, 3, 5, 6, and 10, and 2 adults) would be for 33% of its vitamin A to be obtained from the home garden. If it wastes only 20% of the vitamin A between production and final consumption, it would require about 4300 IU of vitamin A each day. The commercial garden in Java, the sweet potato yield (tips plus root), the mung bean pods, and both the swamp and Chinese cabbage yields are adequate. Most of these are based on experimental and

Table 3.

YIELD OF VEGETABLES

Product	Days to last harvest	Economic yield/day/ha[a] Kg	Vitamin A/ 100 g IU	Daily yields of vitamin A/ 18.5 sq. meters
1. Swamp cabbage	30	333	4825	29711
1. Chinese cabbage[b]	60	283	3600	18852
2. 1972 Philippine average--all vegetables	c/	12	3350	740
3. Bush sitao (green edible pod)	77	156	570	1645
3. Mung bean (edible pod)	67	229	1141	4834
3. Sweet potato roots	120	208	1025	3941
tips		69	5565	6590
				10531
3. Cauliflower	49	122	95	215
4. Home garden mixture in Java	c/	2	3350	130
4. Market gardens in same Java area	c/	68	3350	5328
4. Intensive market gardens (Java)	c/	205	3350	12710
5. Tomato	85	165	735	2244

Sources: The vitamin A data was obtained from the Food Composition Table, Food and Nutrition Research Center, Manila, 1968. All the figures are based on Philippine equivalents.

1. Field trials by Dr. Ruben L. Villareal, U.P.C.A. (National Food and Agricultural Council).
2. National Food and Agricultural Council.
3. Data from field trials by Dr. Hunry Munger, R. Villareal at U.P.C.A., 1969 (Munger).
4. Van Eijnatten, p. 22-24.
5. Villareal, Table 5, U.P.C.A. field trials.

a/ This yield is actual economic yield divided by length of growing period.
b/ It is assumed that pre-transplant growth requires no space and that maximum yield is obtained (Villareal, p. 15).
c/ Yields were only supplied on an annual basis.

selective growing conditions. Nevertheless this does point out that there are possibilities of increasing these vitamin A yields if the carotene content and/or economic yields could be increased for the home gardens. Most of the calculations in table 3 overstate the yields as no time was given for between crop preparation of soil. The Philippine average yield and the Javanese data are based on the more representative year-long averages.

f. Etiology and Geography of Xerophthalmia

The incidence of xerophthalmia differs from area to area with the same vitamin A dietary intake. The causes of this disease are complex and vary seasonally and by age and sex as these factors are related to food supply, disease, poverty and urbanization, and numerous cultural forces. This section summarizes these factors, in particular the issues of age and sex.

A common profile begins with the pre-school child who is undernourished but does not display clinical symptoms of xerophthalmia or any other form of malnutrition. Then the child becomes infected with a serious gastrointestinal or respiratory infection at the age of 3 which precipitates xerophthalmia. A month later the child's vision becomes blurred and the mother takes the child to a local clinic 20 miles away. It is too late, however, as the child's condition is irreversible and eyesight is lost or the child dies.

Dietary factors

An inadequate amount of vitamin A or carotene is often consumed by a child. For example, in Java the vegetables and young pulses are placed in a soup (sajur) along with peppers and other spices. This soup is very spicy and many children refuse to eat it (van Veen, 1947, p. 670). In some areas in Java among the poor there are periods right before the rice harvest when no sources of carotene are available and the dietary-related incidence of xerophthalmia is high (ibid., p. 671). In Europe, xerophthalmia used to appear in the spring after the provitamin A reserves were exhausted at the end of a greenless winter (Oomen, 1969, p. 1103).

Other examples of dietary causes are the presence of kwashiorkor with the resultant effects on the metabolism of vitamin A, a low intake of dietary fat which lowers the intestinal absorption of all forms of vitamin A (especially the carotenes), and a maldistribution of food in the family which results in inadequate vitamin A nutriture for the boys or the child aged 2-8. In one study of 180 children with xerophthalmia, 90% of the children were classified as malnourished (Fernandez).

Disease

The direct effects of various diseases on the absorption of retinol

and carotene were already highlighted. A case of xerophthalmia may be associated with diarrhea, measles, tuberculosis, hookworm, fever or ascaris. The diarrhea months occur simultaneously with the highest incidence of xerophthalmia cases in Japan, Korea, South Asia, and the Near East and North Africa (Oomen, 1964(b), p. 5). Often the onset of diarrhea leads to a reduced diet of rice, barley water, tea or herb infusions which exacerbates the problem. "Xerophthalmia cases frequently come in waves. These prove to depend rather more on epidemiological variation of the contagious diseases of childhood than on seasonal variation of food intake" (Oomen, 1972, p. 167). Some conflicting evidence on the relationship between xerophthalmia and diarrhea has been presented (Oomen, 1973).

The best documentation of the effects of various diseases on the incidence of xerophthalmia was a study done in North Vietnam. Two distinct periods with a high incidence occurred. In the hot summer months there were numerous cases of intestinal infection. In October to December, the cold season, the incidence of respiratory infection was high (ibid.). The incidence of xerophthalmia related directly to these diseases and was highest during these two periods. Measles, tuberculosis, ascaris and giardia are some of the other diseases which can increase the incidence of xerophthalmia. Most of this information has come from studies of children admitted to hospitals and has not followed children over a period of time. Thus, these associations might be spurious in the sense that these diseases do not trigger xerophthalmia. It is, of course, possible that xerophthalmia triggers some of them.

Poverty

Xerophthalmia is felt to be a poor man's disease. Rarely is a case found among middle income or rich children. For example, in "Jogjakarta,

Indonesia, Oomen collected 11,000 case histories (of xerophthalmia) from the free clinics, but not one while scanning thousands of records of paying patients (Oomen, 1964(b), p. 5).

Urbanization

The rapid urbanization of the past several decades has produced hundreds of squatters colonies and slum areas in large and small metropolitan areas. Alternately termed bustees, jhuggi jhonpris, urban barrios, favellas or shanty towns, these urban villages or squatters colonies are the scene of some of the most seriously malnourished children. The existence of many inhabitants in these urban villages is marginal; their chief occupations are the crafts of basket weaving, clothes washing, etc., and similar marginal urban occupations such as pulling rickshaw, or selling sugar water on a corner. Often their destitution forces them to resort to begging.

These people may carry their old food habits with them to the cities. They often will consume only the same grains, fruits and vegetables which they had available in their villages. Though they may be much more expensive, their traditional staples will be purchased first. The more perishable fruits and vegetables often cannot be obtained. When they are available, the quantity purchased is much less than that same family would have consumed in rural areas. Another factor is important. In rural areas, many of the fruits and vegetables are consumed with little or no cost. When a price is placed on these foods, families are more likely to consume less of them and more of their staple food which is usually lower in total vitamin A contribution.

Some detrimental social forces gain in importance in urban areas. The advertising of commercial foods induce many families to purchase these much more expensive foods and their nutritional status suffers (Popkin,

1973(b)). Or, the mother may be forced to work and be unable to breast feed the baby. The substitute of powdered milk or other forms of baby milk is diluted or fed in smaller quantities to the child. Often the skimmed milk is not fortified with vitamin A to replace the retinol lost with the skimmed-off fat.

Before World War II the presence of xerophthalmia attracted much attention in Singapore where it was related to the use of artificially fed milk (Oomen, 1964(b), p. 11). For a long time the powdered skimmed milk sent to developing areas from the U.S. through Public Law 480 was not fortified. Now U.S. exports of powdered skimmed milk are fortified with vitamin A.

Age-Sex

Incidence of xerophthalmia trends in age rates are the same for males and females. The peak incidence is felt by some to be during the third year (Oomen, 1969). The incidence is much higher among males and this sex differentiation has been found to increase with age. The statistics vary slightly but the general ratios are about 58% males : 42% females for preschool children aged 2-5; 85% males : 15% females, ages 10-13; and 87% males : 13% females, ages 14-24 (ibid.; McLaren, 1963, p. 213). Oomen and Ten Doesschate feel this higher incidence of xerophthalmia among males may be an intrinsic factor just as is the relationship between xerophthalmia and protein malnutrition (Oomen, 1973, p. 207-208). A discussion of the incidence at various ages follows:

a) Age 0-12 months--the incidence is rare among this group. The chief cause will be the disruption or cessation of breast feeding. It is also related to poor vitamin A nutriture of the mother which leads to a low storage in the neonate and low vitamin A content in the breast milk. In Denmark in the

early 1900's, many cases of xerophthalmia occurred in this age group (McLaren, pp. 198-199). The Oriya of India are another group in which xerophthalmia has been prevalent among infants (van Veen, 1974).

b) Age 1-5 years--the sudden cessation of breast feeding may be associated with the onset of gastrointestinal problems and a higher prevalence of xerophthalmia (McLaren, 1963). This could be caused by a new pregnancy and strong mores against breast feeding a child during this pregnancy (ibid.). Or the child may be fed only rice porridge after weaning as is done in Bali. Most people feel the peak is in the third year and that most cases of xerophthalmia occur between the ages of 2-4 (later than the peak incidence of kwashiorkor). This is because breast feeding develops a large storage of vitamin A which protects the child's vitamin A nutrition for a long time (ibid., p. 203). After the stored vitamin has been used, direct dietary effects or, more likely, the combination of some parasitic or infectious diseases and low dietary intake may lead to xerophthalmia.

c) Age 5-15 years--only 10% of the cases occur among this age group and they are usually less severe (ibid). In one study of 1678 children, 25% of the cases of xerophthalmia were found in this age group (Fernandez). Lower growth requirements and greater resistance to various diseases are probably the more important reasons for this. Older children have been ignored in most recent discussions of X, and most preventive programs are oriented toward children aged 1-6.

An appraisal of older nutrition surveys completed in 1962-64 by the ICNND in Northeast Brazil and Bangladesh also showed a high prevalence of X among children aged 7-16 (Interdepartmental Committee on Nutrition for National Defense, 1965 and 1966).

d) Adults--the instances of xerophthalmia are very rare except in nursing mothers because the vitamin A requirements during lactation are much greater. Night blindness may be found but rarely does blindness occur. Among a few adults, cirrhosis of the liver leads to an impairment of the storage of retinol in the liver and can cause xerophthalmia. Intestinal malabsorption from conditions such as steatorrhea is another cause.

The onset of blindness occurs primarily in the under five group. This differentiates xerophthalmia-caused blindness from many other major causes. In most areas, trachoma does not affect preadolescents (Oomen, 1964(b), p. 2). Cataracts and glaucoma usually occur among adults. Smallpox produces very localized incidence of blindness and is easily identified because of the residual pockmarks. Thus, a high percentage of blindness under the age of 15 usually indicates the presence of xerophthalmia. "In a carefully conducted study in East Java, Indonesia (by J. Ten Doesschate), it was found that in blind children under 5 the cause of blindness was xerophthalmia in 75 percent of the boys and 62 percent of the girls" (Xerophthalmia 2, p. 1). Identification is not always this simple. For example, Ms. Cheryl Bliss has been studying the role of xerophthalmia in "Luapula blindness" in Zambia. The various ways of identifying the causes of blindness in this valley produce very conflicting hypotheses about the cause of

blindness and it is possible that a quite unique syndrome exists outside of any previously known by medical science (personal communication, Ms. Bliss, Cornell).

Geography

In the geography of xerophthalmia, climate plays a role far different from what one would suspect. The humid, rich and green tropics where carotene sources are plentiful, especially in the Far East, often have a high incidence of xerophthalmia. These are the rice-eating areas and the areas with high incidence of gastrointestinal infection. Also, these are the poor and more highly populous areas.

A very high incidence is found in the slums of Manila and Cebu City, Saigon, Dacca and the large cities of Southern India, such as Madras and Hyderabad.

Among the regions of the world the most prevalent and serious problem is found in South and Eastern Asia, the Far East, North Africa, and parts of the Near East. And a less serious problem is found in Central and South America, and North Asia and East Africa. The lowest incidence in the developing world is in West Africa where cooking in red palm oil is common. Few cases are found in the Caribbean.

Seasonality

Seasonality does not refer to the lagged relationships between diseases, nutritional deficiencies and the onset of X. Rather it includes the seasonal patterns of production, consumption, employment, savings and dissavings, rainfall, temperature, diseases, etc. In relation to the effects of seasonal patterns on xerophthalmia (X), the following factors are important:

1. Changes in food production and employment lead to scarcity

of key foodstuffs and the resultant higher prices. Preharvest famine and under- and unemployment are two results (e.g., Mellor, 1970; Oshima).

2. Changes in the rainfall, especially the onset of rainy seasons or monsoonal conditions, often result in diarrhea epidemics.
3. The temperature and humidity cycles can lead to periods in which respiratory and bronchial infections are more predominant.
4. The production of important "protective" horticultural plants may also fluctuate with these climate variations.
5. Increased consumption of calories and proteins may lead to spurts in growth which, in turn, could exacerbate the deficiency of vitamin A and lead to X (Sinha).

The importance of each of these seasonal factors are accentuated on the subsistence sector which depends on agricultural production and employment. Conversely, they are integrated in the cash or industrial sector which has more access to steady employment and also to commodities grown in other climate regions. Other factors, especially the role culture plays in savings and consumption patterns, are important. Two interesting discussions of seasonality are by Oomen and Ten Doesschate, and Sinha and Bang. The latter is based on community data.

The patterns of X vary markedly from one geographic area to another and fluctuate on an annual basis; however, the seasonal patterns of the incidence of X appear to prevail each year (Oomen, 1973). Studies on the effects of season are unavailable for rural populations. Data for urban populations represent a dramatic seasonal effect of X which could be even greater in the rural areas. For example, in Bangalore, South India, "the

seasonal prevalence (of X) in April to July was attributed to the scarcity of green vegetables and milk in that season and to the prevalence of summer diarrhea" (ibid., p. 209). In Hanoi, on the other hand, two distinct seasonal patterns are found. In October-November, a cold season leads to numerous diseases, and in April-July the warm summer season. The quick increases and decreases in the prevalence of X in Hanoi indicated the likely effects of disease. In Bangalore the changes were more gradual and point to the greater importance of vitamin A deficiency.

In Indonesia, the peak period is the dry season when only rice was available and the lowest incidence occurred in the wet seasons when green vegetables and fruits were available. In East Java (Surabaya), July is the peak month, while in West Java (Bandung), May is the peak month. The seasonal variations are more pronounced in Surabaya. It was felt that only the dietary aspect was significantly better during the low X wet season, while diet was only one of the factors explaining the peak incidence in the dry season (ibid., p. 213).

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Supplementary Information

for Application:

"Evaluation of a Fortification Program to Control

Vitamin A Deficiency in the Philippines"

Principal Investigator:

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I. MSG Utilization in Various Provinces of the Philippines and Plans for a National Program to Control Xerophthalmia

This supplementary information is provided now because a small study to examine MSG utilization in two provinces was being conducted at the time of submission of the research proposal. Preliminary results are now available.

The planned research is only a part of a plan to control vitamin A deficiency, xerophthalmia, and blindness due to this cause. The project which will evaluate the effectiveness of MSG fortification in three provinces, is designed to help the Philippines move expeditiously to a national program to control an important public health problem. The research should not be allowed to stray from these objectives. It should be remembered that in many countries, including the United States, fortification has been introduced with no, or minimal evaluation, and this is so also in most European countries. Any attempt to conduct studies and evaluations of such programs are highly desirable but should not be allowed greatly to delay or hinder the applied aspects of the program. Similarly it might be considered desirable to get reliable and detailed national data on vitamin A intakes, serum vitamin levels, clinical evidence of xerophthalmia, and MSG utilization before moving ahead with fortification. This may be desirable but it is not practicable for the whole of the Philippines. It should be recalled that the U. S. national nutrition survey became a 10 state survey, and there was not very much evidence that these 10 states would really be representative of the position in the other 40 states. Fortification either by legislation or without has been instituted without surveys or evaluation.

In the Philippines we have figures to show the distribution of MSG

in different geographic areas. This suggests that families in all regions of the Philippines use MSG. Greater Manila is a high use area; the rest of the island of Luzon is a moderately high use area; and the other regions (including Cebu) are moderate users.

In Cebu our study showed that 94 percent of families use MSG one or more times per week, and in over 90 percent of cases this went into food consumed by young children and other members of the family. It was added especially to soups and stews, where it would be present in the liquid portion consumed by the youngest children. The mean consumption of MSG in Cebu was 2.4 grams per day for a family of 5. It was on the basis of this that decisions were made concerning levels of fortification.

Testing was done by Hoffmann-LaRoche of loss rates of vitamin A as a result of storage under conditions similar to the Philippines. These results showed that losses were relatively small. Earlier tests had been done on the product as added to typical foods including soups and stews.

Leftover foods are generally consumed the same or the next day, in part because of high temperatures and the lack of refrigeration. No significant loss of vitamin A would be likely to result from this.

A small study was conducted in June, July and August 1977 by David Williamson of Cornell University and workers from the Nutrition Center of the Philippines to obtain data on MSG utilization in the provinces of Marinduque and Nueva Viscaya. These are two of the provinces proposed for inclusion in the MSG fortification program. This small study was conducted under the direction of the Principal Investigator (Dr. M. C. Latham) from Cornell and Dr. Florentino Solon from the Philippines.

The full analysis of the data from this study has not been completed. However the results show that MSG is widely used and suggest that as in

Cebu, fortification is likely to be beneficial. In the province of Marinduque 90% of households had used MSG in the 24 hours before interview. The mean household consumption of MSG was 1.9 grams per day. The mean daily consumption for children aged 1-3 years was found to be 0.18 grams of MSG.

In Nueva Viscaya 77% of households had consumed MSG in the previous 24 hours and 74% of children aged 1-3 years had consumed it. (This rate of consumption in the last 24 hours almost certainly means that a much higher percentage of households consume MSG regularly.) The amounts of MSG consumed per household were a little higher in Nueva Viscaya than in Marinduque. The mean household consumption of MSG was 2.8 grams per day. It was estimated that children aged 1-3 years of age were consuming approximately 0.27 grams per day. MSG in all provinces is sold in packets of 2.4 grams at a price of 10 centavos (approximately 1.2 U.S. cents). In the Cebu study MSG was fortified or nutrified with 15,000 IU of vitamin A per 2.4 gram packet of MSG. If MSG in Marinduque and Nueva Viscaya are fortified with this level of vitamin A, then children in the former province will receive a mean of 1,125 IU of vitamin A and in the latter province 1,800 IU per day from this source. This is on the assumption that the 136 households interviewed in Marinduque and the 200 households in Nueva Viscaya are typical of the province. These calculations are based on those families using MSG during the 24 hours prior to the survey. The data here suggest that MSG is purchased in these two provinces in amounts not very different from Cebu.

The data collected will be further analyzed. This study was a preliminary one to obtain information to assist with planning of the proposed intervention and evaluation.

Representativeness of the three provinces

The three provinces selected for this study will be representative of different geographic areas, and could be considered to reflect rather varied provinces. Marinduque is in the central Philippines. It has some small towns but is mainly rural. It is compact with good communications, and is densely populated. Nueva Viscaya is to the far north in Luzon with few large towns, some very rugged and inaccessible country, and is less densely populated than Marinduque or Cebu. Communications in much of the province are quite poor. Cebu, if it is chosen as the third province, is extremely varied. It includes the second largest city with squatter areas and slum settlements, it has coastal fishing villages, and a scattered hinterland population. It is in the southern Philippines and unlike the other two provinces (where rice is the principal food crop) the main staple food in Cebu is maize (corn) and cassava is also widely grown.

Therefore although it cannot be stated that these three provinces are truly representative of all the provinces in the Philippines, no other three provinces would be more representative. They are varied; they do include urban and rural, coastal and hinterland, accessible and non-accessible; north central and south; etc.

Preparations for a national program

It is proposed that while the fortification of MSG with vitamin A is evaluated in the three selected provinces (Marinduque, Nueva Viscaya and perhaps Cebu) data will be gathered on MSG utilization in other provinces of the Philippines. This exercise will be undertaken mainly in year 2 and 3, and will form a part of the preliminary planning for a possible national program. It is realized that a national plan cannot be prepared on the basis of the first year of intervention in the three

provinces, and that data analysis takes time. However it does appear to be justified to begin to gather data and to be making plans so that there is not a long delay between the completion of work in the three provinces and, if the results justify it, the implementation of a national program.

The decision to act in this way may appear to be making unjustified assumptions that the fortification program will yield positive results. This is not so. No national program will be recommended without a careful review of the results of the three province intervention. However the policy makers are keen to see action. The research team therefore need to obtain information on MSG utilization, to consider strategies, and to have tentative or alternative national plans formulated, so that there is a minimum of delay between completion of the present study and some kind of a national program to control vitamin A deficiency. The planners are quick to point out that children are going blind each year, and that therefore delays are costing lives and increasing the blind population.

It is also necessary to state emphatically that MSG fortification is not the only action that the Philippine government will undertake to combat vitamin A deficiency. As a result of the Cebu experiment (See Page 68, Appendix 1 of application) we recommended that certain aspects of the other two interventions be adopted by the government. These include the availability and use of vitamin A capsules by physicians and health workers in all health units for children regarded as at high risk for xerophthalmia. These would include all children with second and third degree malnutrition, young children with other chronic diseases, all children in families where children have been found to have PCM or evidence of xerophthalmia, all children with measles and whooping cough, etc. Recommendations were also made concerning a program to make physicians

and health workers more aware of vitamin A deficiency and its control. Similarly agricultural extension activities should include a stress on the production of carotene rich fruits and vegetables. To some extent this is already being done in the First Lady's Green Revolution Project, and various nutrition programs.

Clearly these kinds of measures are needed if vitamin A deficiency is to be fully controlled. Reliance should not, and will not, be placed on fortification alone.

In Cebu 1,715 children were examined in the baseline study and 1,667 of these were examined again at the end of the intervention. All three interventions had a good effect in reducing active clinical eye signs of xerophthalmia (See Page 64, Table 32, Appendix I of application). The MSG fortification was the only one of the three strategies that was associated with a significant and good rise in serum vitamin A levels, and it is the only one of the three interventions which can relatively easily and cheaply be introduced nationally. But the adoption of various aspects of the other strategies will be encouraged, and implemented where possible as long term measures to reduce the prevalence of vitamin A deficiency. This is the definite intention of Dr. Solon and the research teams, and also of the Philippine authorities.

II. Evidence of Vitamin A Deficiency and Xerophthalmia Elsewhere in the Philippines

Large and detailed nutrition surveys have been conducted in the Philippines over the years by the Philippine Food and Nutrition Research Centre (now named the Food and Nutrition Research Institute). These surveys have consistently shown that a large section of the population in all the regions surveyed have diets providing amounts of vitamin A far below recommended dietary allowances. The mean vitamin A intake in these surveys is around only 50 percent of the Recommended Dietary Allowances. Similarly blood taken for determination of serum vitamin A levels has shown that low and deficient serum retinol levels are common especially in young children. The FNRI surveys showed 47 percent of subjects with low or deficient serum vitamin A levels. As in all surveys which are cross-sectional, and therefore measure point prevalence of clinical conditions, the percentage of children with severe eye lesions due to xerophthalmia appear to be small. But reported rates are consistent with there being a serious problem in nearly all of the regions of the Philippines that have been surveyed, and surveys have been widely conducted.

The recent xerophthalmia study conducted by the American Foundation for the Overseas Blind (now the Helen Keller Foundation) also indicates a "significant public health problem" of xerophthalmia in Luzon. The investigation was undertaken in 2 slum areas of Greater Manila and in a fishing barangay named Hagonoy on the island of Luzon (the main Philippine island on which Manila is situated). Clinical eye examinations were conducted but blood was not examined for vitamin A. Of 2,666 children examined 4 percent had clinical eye signs of xerophthalmia. The study showed a much higher prevalence of these signs in children whose weight for age was low compared with well grown children. The prevalence of eye signs

was 14.3 in those children whose weight for age was below 60 percent of the standard.

Dr. Florentino Solon, Director, Nutrition Centre of the Philippines, reports that serious cases of xerophthalmia, many leading to blindness, are frequently seen in the pediatric and malnutrition wards in all parts of the Philippines where the centre is active.

There is therefore overwhelming evidence that xerophthalmia is an important public health problem, and is not confined to Cebu where the earlier study was undertaken.

III. Statistical Analysis, Sampling Considerations, and Some Study Design Questions

It should be noted that Dr. S. P. H. Mandel has worked as a WHO Consultant to the vitamin A project, and he will continue to serve as a Consultant for the new project. Dr. S. P. H. Mandel is Professor of Mathematical Statistics and Director of the Biometrics Unit at the University of Otago in New Zealand. Prior to this he worked for WHO in Geneva, and before that was on the faculty of the School of Public Health of Tulane University in New Orleans.

Dr. Mandel spent 5 weeks in January and February 1977 in the Philippin to review the findings of the Cebu study and to advise on future action relating to the combat of vitamin A deficiency. The Principal Investigator (MCL), Dr. Florentino Solon, and Dr. Tom Fernandez worked closely with Dr. Mandel in Manila.

In consultation with Dr. Mandel during this period, preliminary plans were made for the next stage of work including the proposed three province intervention with vitamin A fortified MSG. At our request Dr. Mandel produced five short papers to assist with sampling and statistical analysis questions in future work, if the authorities in the Philippines decided to move ahead. These five papers were:

A. Sample size for estimating prevalence

B. Sample size for detecting minimum practical effects of interventions

C. Significance of the difference between prevalences

D. Significance of the difference between means

E. Confidence intervals of prevalence rates.

These five papers are attached to this document, and provide some of the basis on which work is planned.

Dr. Mandel will serve as a Consultant to the three year project. He will provide continuing advice to statisticians in the Philippines employed by the Nutrition Center of the Philippines and the National Nutrition Council of the Philippines, one of whom will be assigned to work with the new project from the beginning. Some of these statisticians are currently involved in the sampling design for both nutritional surveillance and for a nutritional profile of preschoolers in the Philippines. This latter has been using a three stage cluster sampling technique in selected provinces.

It should be stressed here that the employment of statisticians and the actual sampling are mainly the responsibility of the Philippine component of the present project. Sampling will be done with input, consultation and agreement from us. But other than under the heading of consultants no budgetary provision is included in this proposal for this aspect, just as none is included for the other major Philippine contribution which is the actual implementation of the MSG fortification.

At Cornell the Principal Investigator has discussed the design and sampling procedures with Dr. Philip McCarthy, Professor of Economic and Social Statistics, who is generally regarded as one of the foremost U.S. experts on statistical sampling techniques. Discussions were also held with Dr. Paul Velleman, Assistant Professor of Statistics. These and others at Cornell will provide continuing advice as needed. However the responsibility for the final sample design and for decisions concerning the drawing of the sample will be made based on advice from Dr. Mandel and statisticians in the Philippines who are directly involved with the project.

The Principal Investigator and the Co-investigators in Manila believe

that the formulation of a sample design and details of how the sample are to be drawn, constitute the first part of the project and should be integrated with it. There is a strong belief that this is a task of such importance and the inclusion of statisticians so important, that it should not be relegated to something that is done vaguely before the start of the project, mainly for the purposes of a grant application. In fact the design of a sampling plan is a time consuming task which needs to be carefully done using the census data for each province, a variety of other data from the municipalities and finally the barangay (village) household lists that are kept in the provinces. We believe that it would be underplaying the role and involvement of the statisticians to expect this exercise to be completed prior to the beginning of the project. It should be a part of the project, and the statisticians involved are to play as important a role in the project as will the doctors drawing blood and examining eyes, or the laboratory pathologists and technicians making blood determinations. All of these persons are, as in the previous Cebu project, a part of the Philippine commitment, and not included in this U.S.A.I.D. application.

It is proposed that each municipality and that each barangay within the selected municipalities will have an equal chance of being selected within the three provinces. Where municipalities and barangays in a particular province are rather uneven in size, then sample municipalities and barangays will be selected with probabilities proportional to their population. The sampling plan developed in the first stage of the project will include a means of ensuring that some school age children and lactating women are included, as well as the preschool age children mentioned in the proposal.

Consideration is being given (at the suggestion of Professor McCarthy) for drawing two or three samples in 1978, one for use in the baseline and the others for the follow-up. The advantages of doing this seem to be considerable. Precise matching will not be necessary, but there will be some advantage in using a design which ensures that similar numbers of preschool age children, school children and lactating women are included each year.

To obtain information regarding the utilization of MSG in the other provinces in the Philippines consideration will be given to utilizing existing or proposed sampling frames. These include the World Fertility Survey, the household sample survey, and the samples from the plan for nutritional surveillance or for the construction of a nutritional profile of preschoolers. These latter two are a part of national nutrition activities. It should be stressed here that most countries including the United States have introduced fortification without any such investigation using sampling techniques to determine the utilization of fortified foods in the nation. It might be unrealistic to expect of the Philippines something that is not done in much wealthier and more industrialized countries. Therefore the proposal for national studies will have to be realistic in terms of what is feasible and what can be afforded financially. If the project in the three provinces is well evaluated and shows positive results, then a national program is likely to be benëficial to those using similar amounts of MSG in other parts of the Philippines. A huge and costly effort to predict exactly what the benefits will be in each corner of the Philippines may not be absolutely necessary. It is surely sufficient and desirable that a reasonable effort be made to estimate likely benefits in provinces other than the three included in the present project.

Sampling will be as objective as is feasible. In the province of Marinduque the research workers are confident that no constraints need be placed on drawing a sample from the whole province. However for Nueva Viscaya this may not be feasible for a variety of practical reasons as outlined in the proposal. For the third province we hope that it will be feasible. This problem was reviewed by Dr. Mandel, the consultant statistician, and the suggestions contained in the proposal come from him. If in Nueva Viscaya province for example there is one barangay that is inaccessible, and a second that for security reasons is unsafe, then these will not be utilized. These constraints clearly then make final statemen about the province in part invalid. In this case the research team will take care to define their universe accordingly in the sampling plan, and in the final report. It should be kept in mind that this is a project involving communities of people, and not caged animals, and that it is one which will hopefully lead to actions which will improve the public health of significant numbers of people but not all people in all provinces. Practical considerations in some cases have to take precedence over ideal research design. This we believe does not invalidate results provided we are always honest, and with the help of statisticians, indicate in our plans and in our reports how far we deviated from an ideal theoretical sampling plan.

The variables that will be measured in the baseline survey and in the follow-up surveys are:

1. Serum vitamin A levels measured in micrograms per 100 ml.

2. Presence or absence of clinical signs of vitamin A deficiency using the WHO classification.

3. Presence or absence of conjunctival staining after instillation

of one drop of lissamine green into each eye. Positive staining will be graded I to IV (using the procedure of Sauter).

The statistical determinations of the significance of changes in point prevalence of these variables will be done using the techniques suggested by our Consultant, Dr. Mandel (See Technical Appendix C attached) For example in the case of active clinical signs of xerophthalmia a Chi-square test will be applied to find the level of significance of changes between baseline and follow-up surveys. The use of non-parametric procedures will probably be limited to sub-studies which may be done and which are not central to the present proposal nor included in it.

This will include a sub-study in which family (and where possible individual) dietary intakes will be obtained from all persons in the sample. The technique utilized will be the 24 hour dietary recall method. This will allow the research team to have data on consumption of MSG in the baseline and at subsequent surveys, and also consumption of other foods. Changes particularly in consumption of vitamin A and carotene containing foods will be determined in this way. These food consumption data collected will also include information on foods to which MSG is added, the cooking procedures of those dishes to which the MSG is added, and of course who consumes the food. This will supplement the considerable information already collected concerning the use of MSG in the three provinces. It will also provide information which may assist in judging whether dietary changes in the province, between baseline and subsequent surveys have influenced the results.

Serum vitamin A determinations

The serum vitamin A determinations will, as indicated in the proposal, be conducted in the Philippines, using the laboratory of the Cebu Institute

of Medicine (previously used for the Cebu study) and a laboratory in Manila (probably that of the Food and Nutrition Research Institute). The micro procedure will be used. In this 0.1 to 0.2 ml of plasma are required. This means that blood is collected from a finger prick and not from the child's vein. This is a less traumatic and an easier procedure. The Carr-Price reaction using trifluoracetic acid will be used. This method has several advantages including relative simplicity and a single direct reading analysis. It is also unaffected by fluorescent contaminants, and its sensitivity is generally considered adequate. Great care will be exercised to ensure proper storage and the use of reliable standards of crystalline vitamin A. As a means of quality control it is intended that duplicate plasma samples be collected in a sub-sample of subjects. These will be shipped to the U.S. for serum vitamin A determinations probably in laboratories at Cornell University.

Blood samples (around 0.3 ml) will be collected in non-clotting capillary tubes, and immediately centrifuged. The clear plasma will be separated and stored on ice in the dark. As soon as possible thereafter they will be quickly frozen. The frozen samples will be shipped periodically to the laboratory where the determinations are to be made. The stored frozen samples will be kept in closed containers in the dark, and will be analyzed usually within 1 week of collection and always within 2 weeks.

TECHNICAL ANNEX

SAMPLE SIZE FOR ESTIMATING PREVALENCES

How to estimate the sample size that is needed when you want to estimate the prevalence of a condition with a specified level of precision.

Some baseline surveys may be carried out to establish the extent of the problem of vitamin A deficiency and xerophthalmia in a given area. In such a situation the objective is to estimate the prevalence of the condition (active clinical signs or low serum vitamin A levels) to within a specified level of precision; thus for example the investigator may want to select a sample size which is sufficiently large so that the width of the 95% confidence interval does not exceed say 5 percentage or 10 percentage points or any other required level of precision.

The width λ of the 95 percent confidence interval is given by the equation

$$\lambda = 2 \times 1.96 \sqrt{\frac{g\pi(1-\pi)}{m}} \qquad \text{(1A)}$$

where m is the sample size, π is the "true" population prevalence of the condition of interest, and g is the clustering coefficient identified in Technical Annex B which is introduced in those situations where the ultimate sampling unit is the household rather than the child itself, and which compensates for the intra-cluster correlation between children within the same household. In those surveys in which children are actually sampled at random, the clustering coefficient g would be assigned the value 1; in most practical situations, however, households are sampled and all eligible children in the sampled households are included in the sample, in which case the clustering coefficient is assigned a value greater than one. Solving equation (1A) for m we obtain

$$m = 15.37 \frac{g\pi(1-\pi)}{\lambda^2} \qquad \text{(2A)}$$

In some situations π is unknown, in which case we have to substitute the value 1/4 for the expression $\pi(1-\pi)$, which is its maximum value attained when $\pi = 50\%$. In other situations the investigator can make an educated guess that π has the value, for example, 0.3 and in those cases that estimated value of π should be used in equation (2A).

Assuming that π is unknown, and substituting the value 1.92 for the clustering coefficient g on the basis of the rationale set out in Technical Appendix B we obtain a working equation

$$m = \frac{15.37 \times 1.92 \times 0.25}{\lambda^2}$$

i.e.

$$m = \frac{7.38}{\lambda^2} \qquad \text{(3A)}$$

The investigator then simple has to specify the required level of precision λ in order to obtain the necessary sample size.

Some typical values of m as a function of λ are set out in Table 1A below.

TABLE 1A Sample sizes required for specified widths (λ) of the 95% confidence interval for estimating a a prevalence ratio in a given area (clustering coefficient $g=1.92$, $\pi(1-\pi)=0.25$)

λ	m	m*
0.30	82	69
0.25	119	100
0.20	185	155
0.15	328	276
0.10	738	620
0.05	2952	2480

It should be noted that these sample sizes are considerably reduced when an estimate of λ is known; for example, if λ is estimated to be around 30% then the sample sizes have the values shown in the right-hand column (for purposes of comparison) of Table 1A, m*.

Tables like Table 1A can be generated for levels of precision of estimates based on 99% confidence intervals; the only modification that has to be made is to replace the quantity 1.96 in equation (1A) by the quantity 2.58.

Adjustment for large sampling fractions

Tables 1A and 2B have been prepared with the assumption that the number of children in the sample is a small fraction, one-tenth or less of the total number of children living in the area being surveyed. In some cases this assumption may not be valid, and the sampling fraction may exceed one-tenth of the children living in the area being surveyed. If this happens, an adjustment should be made to the sample size.

Following Cochran (1963), if m is the sample size estimated from either Table 1A or 2B and M is the total number of eligible children living in the survey area, then a corrected sample size m_o, adjusted for the large sampling fraction, is given by the equation

$$m_o = \frac{m}{1 + \frac{m}{M}} \qquad (4A)$$

Thus, for example, if it is thought that the prevalence of the condition of interest in the survey area is about 30%, and the investigator wants to estimate that prevalence to a level of precision which will be within 10 percentage points of the true value at the 95% confidence level, then we see from Table 1A that m = 620 children. If in addition the total number of eligible children in the survey area is, say, 1500 then equation (4A) reveals that the number of children must be sampled is

$$m_o = \frac{620}{1 + \frac{620}{1500}} = 439 \text{ children} .$$

SAMPLE SIZE FOR DETECTING MINIMUM PRACTICAL EFFECTS OF INTERVENTIONS

How to estimate the sample size that is needed when you want to be $(1-\beta)\%$ confident that you will not fail to detect, at level of significance α, a specified minimum effect of an intervention.

The investigator must be able to state that unless an intervention produces a change in the prevalence of a condition which is at least as big as a specified minimum value, then the intervention is not of any practical importance. How he arrives at this decision is a complex matter, but cost benefit analyses can be useful in this respect. However, we need this quantity which we shall call Δ as a basis of the calculations which follo Thus the investigator says if the intervention experiment shows us a change which is less than Δ percentage points then the intervention will be considered not to have been effective; if on the other hand there is an improvement of more than Δ percentage points the intervention will be considered effective and recommendations that the intervention be implemented on a wider scale may be issued.

The quantity Δ is thus critical, and a lot of thought, discussion and cost benefit analysis should be directed to its specification. Perhaps Δ has to be set arbitrarily when there is no underlying rationale whatsoever; in those situations it is suggested that Δ should be selected from the set of values 5, 7.5, 10, 15, 20, 25 and 30 percentage points respectively, although other values within or outside the range may be considered appropriate.

The quantity $\delta = p_1 - p_0$, where p_0 is the observed sample prevalence before the intervention is implemented and p_1 is the observed sample prevalence at a specified point in time after implementation, is a random variable. Two assumptions underly the following calculations:

(1) probabilities may be approximated with reasonable accuracy by the normal distribution, this is a reasonable assumption, supported in theory by the Central Limit Theore and will hold provided the prevalences are based on a reasonably large number of children and that the prevalence are not near zero or near 1.

(2) $\sigma^2(\delta)$ = estimated variance of the random variable

$$= g\{\pi_0(1-\pi_0) + \pi_1(1-\pi_1)\}$$

where m is number of children (sample size) to be estimated, π_0 and π_1 are the "true" prevalences in the population before and after the intervention respectively, and g is a clustering coefficient to compensate for the increase in variance arising from within household correlations in vitamin A deficiency status of children, and to a lesser extent, and where applicable, from correlations between households within primary sampling units Assumption (2) is part fact and part assumption in that we are using the standard formula for the variance of the difference between two proportions. The assumption comes in as we shall see when we have to set a value for the clustering coefficient g.

From those two assumptions the formula for the estimate m of the required number of children is then easily developed, because it follows from them that δ is a random variable which is normally distributed around the mean value $(\pi_1-\pi_0)$ and with standard deviation equal to $\sqrt{g(\pi_0(1-\pi_0)+\pi_1(1-\pi_1))}$. Now we want to arrange things so that, in the event that $\pi_0 = \pi_1 = \pi$ say (this is the expression of the null hypothesis that the intervention has no effect), the probability that $\delta>\Delta$ by chance effects alone is less than some value α selected by the investigator; (the chosen value of α corresponds to the "level of significance" in classical hypothesis testing situations, and a value is usually selected from the set

$$\alpha = 0.10,\ 0.05,\ 0.025,\ 0.01,\ 0.005,\ 0.001 \text{ etc.}$$

Let z_α denote the value for which the probability that a standard normal random variable exceeds z_α is equal to α that is to say $P\{Z>z_\alpha\}=\alpha$ where Z is a standard normal random variable $N(0,1)$ then it follows that we must arrange that

$$z_\alpha = \frac{\Delta}{\sqrt{\frac{2g}{m}\,\pi(1-\pi)}}$$

which when rearranged to make it explicit for m becomes

$$m = \left(\frac{z_\alpha}{\Delta}\right)^2 2g\pi(1-\pi)$$

This last equation is still not suitable for the purpose of calculating m, because the right hand side contains the unkno. parameter π. To overcome this difficulty we take advantage of the fact that since the expression $\pi(1-\pi)$ has a maximum value of $\frac{1}{4}$ achieved when $\pi = \frac{1}{2}$ so that we can obtain a conservative estimate of m from the equation

$$m = \frac{g}{2}\left(\frac{z_\alpha}{\Delta}\right)^2$$

Two quantities remain to be identified. The values of z_α are simply extracted from tables of the standardized normal random variable and are given in Table 1 below for conventional values of α:

TABLE 1B Values of z_α for conventional values of α

α	0.1	0.05	0.025	0.01	0.005	0.001
z_α	1.23	1.64	1.96	2.33	2.58	3.09

The clustering coefficient g presents some special problems and a certain amount of guess work is needed. Experience with immunization surveys in the U.S. has shown that for immunization status clustering coefficients for children aged 1-4 years averaged around 1.59, while for children in the age-group 5-14 years they averaged around 2.58 (reference: R.E.Serfling and Ida L. Sherman "Attribute Sampling Methods for Local Health Department's"U.S. Department of Health, Education and Welfare, Public Health Service). Since the Cebu City sample was designed so as to include two children aged 1-6 for every one child aged 7-15, it seems reasonable to select for our purposes a value

for the clustering coefficient g obtained as follows:

$$g = \frac{2 \times 1.59 + 2.58}{3} = 1.92$$

so that finally

$$m = 0.96\left(\frac{z_\alpha}{\Delta}\right)^2$$

and since the remaining quantities on the right hand side namely z_α and Δ are at the discretion of the investigator we now have a working equation. Thus, for example, if the investigator selects

$\alpha = 0.05$ and $\Delta = 25\%$ then

$$m = \frac{0.96 \times 1.64 \times 1.64}{0.25 \times 0.25} = 42 \text{ children .}$$

Table 2 below gives values of m for the different combinations of values of Δ and α .

TABLE 2B Values of m for different combinations of Δ and α

Δ	α	m
30	0.10	18
	0.05	29
	0.025	45
	0.01	58
	0.005	72
	0.001	102
25	0.10	26
	0.05	42
	0.025	60
	0.01	84
	0.005	103
	0.001	147
20	0.10	40
	0.05	65
	0.025	93
	0.01	131
	0.005	160
	0.001	230
15	0.10	70
	0.05	115
	0.025	164
	0.01	232
	0.005	285
	0.001	408
10	0.10	158
	0.05	259
	0.025	369
	0.01	522
	0.005	640
	0.001	917

Table 2B cont.... Values of m for different combinations of Δ and α

Δ	α	m
7.5	0.10	280
	0.05	460
	0.025	656
	0.01	927
	0.005	1 137
	0.001	1 630
5	0.10	630
	0.05	1 033
	0.025	1 476
	0.01	2 085
	0.005	2 557
	0.001	3 665

The power of procedure

Let $\Delta_T = \pi_1 - \pi_0$

represent the true effect of the intervention and let Δ represent as before the minimum effect of interest of the intervention. Then it can be shown (reference Serfling and Sherman (19[illegible])) that

$$z_{1-\beta} = (\Delta - \Delta_T)\sqrt{\frac{2m}{g(1-\Delta_T^2)}}$$

and substituting $g = 1.92$ as before gives the working formula

$$z_{1-\beta} = (\Delta-\Delta_T)\ \frac{1.04m}{(1-\Delta_T)^2}$$

This equation enables us to calculate the probability of detecting a true effect Δ_T of any given magnitude for selected values of m and Δ. Thus for example if $\Delta = 0.25$ is selected as the minimum effect of interest of the interventi the level of significance is selected at $\alpha = 0.05$ then from Table 2B the sample size m must be 42 children. If in fact the true effect of the intervention is $\Delta_T = 0.40$ then we can calculate the probability of detecting that effect at level of significance $\alpha = 0.05$ as follows:

$$z_{1-\beta} = -0.15\ \sqrt{\frac{1.04 \times 42}{0.84}}$$

$$= -0.15 \times \sqrt{52} = -1.08$$

and the value of $(1-\beta)$ corresponding to $z_{1-\beta} = -1.08$ is 86%

This means there is an 86% chance of detecting a true effect $\Delta_T = 0.40$ with a sample size $m = 42$ at the 5% level of significance. Similar calculations can be made for all combinations of Δ, α and m shown in Table 2B.

Note: for the accuracy of these calculations

$m(\Delta) \doteq 1/4\ m(1/2\Delta)$.

The discussion about power is more of academic interest, and is therefore not enlarged upon further, because in all practical situations the quantity Δ_T is unknown. But it is helpful to be able to assess the probabilities of detecting various true effects of an intervention for selected sample sizes.

SIGNIFICANCE OF THE DIFFERENCE BETWEEN PREVALENCES

Testing the significance of the differences between several classes with respect to a polychotomous random variable, such as the prevalence of active clinical signs of xerophthalmia or of deficient and low serum vitamin A levels.

Suppose there are r classes of interest and a response random variable which can fall into any of s categories; this situation is represented schematically in Table C1 below:

TABLE C1 — Observed number of experimental units in each class/response category

Class	Response 1	2	3	....	s	Totals
1	0_{11}	0_{12}	0_{13}	....	0_{1s}	S_1
2	0_{21}	0_{22}	0_{23}	....	0_{2s}	S_2
3	0_{31}	0_{32}	0_{33}	....	0_{3s}	S_3
.						
.						
.						
r	0_{r1}	0_{r2}	0_{r3}	....	0_{rs}	S_r
Totals	R_1	R_2	R_3	....	R_s	T

In Table C1

$$S_1 = 0_{11} + 0_{12} + 0_{13} + --- + 0_{1s} \text{ etc.}$$

$$R_1 = 0_{11} + 0_{21} + 0_{31} + --- + 0_{r1} \text{ etc.}$$

and

$$T = S_1 + S_2 + S_3 + --- + S_r = R_1 + R_2 + R_3 + --- + R_s$$

Form $E_{ij} = \dfrac{S_i \times R_j}{T}$

and

$$\chi^2 = \sum_{i=1}^{r} \sum_{j=i}^{s} \frac{(0_{ij} - E_{ij})^2}{E_{ij}} \qquad (C1)$$

and compare the result with critical value for chi-square with $(r-1)(s-1)$ degrees of freedom.

In many practical situations, the number of classes is 2, and the number of response categories is 2, so that this case is worthy of special consideration. It arises whenever the significance of the difference between two proportions (or prevalence ratios) is being tested (look for example to Table F3). In this case we can represent the situation schematically as in Table C2.

TABLE C2 Number of experimental units observed in each class/response category (2 x 2 contingency table)

Class	Response 1	2	Total
1	a	b	a+b
2	c	d	c+d
Total	a+c	b+d	a+b+c+d

If we apply equation (C1) above to Table C2, then we obtain, after a little gentle algebra

$$\chi^2 = \frac{(a+b+c+d)\ (ad-bc)^2}{(a+c)\,(b+d)\,(a+b)\,(c+d)} \qquad \text{(C2)}$$

and ordinarily a refinement is introduced (known as Yates' correction for continuity) which modifies equation (2) into the form

$$\chi^2 = \frac{(a+b+c+d)\{\,|ad-bc| - 1/2\ (a+b+c+d)\}^2}{(a+c)\,(b+d)\,(a+b)\,(c+d)} \qquad \text{(C3)}$$

In this case, chi-square has one degree of freedom, and the difference between the two proportions $\frac{a}{a+b}$ and $\frac{c}{c+d}$ is significant

at the 5% level whenever $\chi^2 > 3.84$

at the 1% level whenever $\chi^2 > 6.63$

at the 0.5% level whenever $\chi^2 > 7.88$

at the 0.1% level whenever $\chi^2 > 10.86$

As an example, we can look at Table F3. There were 45 active clinical signs of xerophthalmia out of a total of 1161 examined before the intervention with fortified MSG giving a prevalence of 3.9 percent; and there were 10 active clinical signs out of 1161 after the intervention giving a prevalance of 0.9 percent.

Substituting these numbers in Table C2 and equation (C3), we have

$a = 45$ $\qquad$ $b = 1161$

$c = 10$ $\qquad$ $d = 1161$

and making the calculation which is easily verified we obtain $\chi^2 = 21.4$ so that the difference is highly significant, at better than the 0.1% level of significance as is stated in the footnote of Table F3.

In some situations it cannot be assumed that the basic data follow the normal distribution. Those situations can be handled by means of non-parametric procedures which make no assumptions about the distribution of the data. The disadvantage of the non-parametric procedures is that they are generally less powerful than the one based on Students' t, that is they are less likely to detect the effectiveness of an intervention as significant when in fact the intervention has had a significant effect.

Examples of non-parametric procedures which can be used if necessary are sign tests and rank tests. These will not be discussed here.

SIGNIFICANCE OF THE DIFFERENCE BETWEEN MEANS

Testing the significance of the difference between the means of two groups with respect to a continuous (normally distributed) random variable, such as vitamin A intake and serum vitamin A level.

Suppose we have two randomized groups of children who are being examined for a specified response such as vitamin A intake or serum vitamin A level. This is the situation when serial cross-sectional surveys are done as has been proposed in the body of this report.

Let n_1 be the number of children in the first group, n_2 the number in the second group and let the individual response of each child be denoted by

$$X_1, X_2, X_3, \ldots, X_{n_1} \quad \text{and} \quad Y_1, Y_2, Y_3, \ldots, Y_{n_2} \quad \text{respectively.}$$

Form $\bar{X} = 1/n_1 \{X_1 + X_2 + X_3 + \ldots X_{n_1}\}$

and

$$\bar{Y} = 1/n_2 \{Y_1 + Y_2 + Y_3 + \ldots + Y_{n_2}\}$$

Thus $\bar{X}$ represents the mean level of serum vitamin A at baseline, i.e., before intervention and $\bar{Y}$ represents the mean level of serum vitamin A at follow up some time after the intervention with fortified MSG. We are going to conclude that the intervention has been effective whenever we find that the difference $\bar{Y} - \bar{X}$ is positive and large. Look for example to Table F1 and the text of Appendix F where the conclusion that MSG fortification has been an effective intervention is based on the statistics $\bar{X} = 21.3$ mcg/100 ml., $\bar{Y} = 28.5$ mcg/100 ml. and $\bar{Y} - \bar{X} = 7.2$ mcg/100 ml.

To test the statistical significance of such a difference between the means of two randomized groups form the statistic

$$t = \frac{(\bar{Y} - \bar{X}) \sqrt{n_1 n_2 (n_1 + n_2 - 2)}}{\sqrt{(n_1+n_2)\{\sum_{i=1}^{n_1} (X_i - \bar{X})^2 + \sum_{j=1}^{n_2} (Y_j - \bar{Y})^2\}}}$$

and compare the value of this statistic against the critical values of Students' t with (n_1+n_2-2) degrees of freedom. These values can be extracted from the appropriate statistical table found for example in the Documenta Geigy Scientific Tables.

Sometimes it is useful to attach confidence intervals such that one can assert with 95% (or 99%) confidence that the effect of the intervention has been to increase the mean level of serum vitamin A by not less than L mcg/100 ml and by not more than U mcg/100 ml. These lower and upper confidence limits are calculated from the equations

$$L = (\bar{Y}-\bar{X}) - t_\alpha\sqrt{\frac{n_1+n_2}{n_1 n_2 (n_1+n_2-2)}\left\{\sum_{i=1}^{n_1}(X_i-\bar{X})^2 + \sum_{j=1}^{n_2}(Y_j-\bar{Y})^2\right\}}$$

$$U = (\bar{Y}-\bar{X}) + t_\alpha\sqrt{\frac{n_1+n_2}{n_1 n_2 (n_1+n_2-2)}\left\{\sum_{i=1}^{n_1}(X_i-\bar{X})^2 + \sum_{j=1}^{n_2}(Y_j-\bar{Y})^2\right\}}$$

in which t_α is the critical value of Students' t with (n_1+n_2-2) degrees of freedom at the 5% and 1% levels for 95% and 99% confidence limits respectively.

In longitudinal studies the situation is different. In that situation there is one randomized group of children measured at baseline and at follow up, and a more powerful statistical analysis is based upon the statistics d_i which measure the change in the response of the ith child between the baseline and the follow-up survey. Thus if X_1 is the serum vitamin A level of the first child at baseline and Y_1 is the corresponding value for that child at follow up, then $d_1 = Y_1 - X_1$ and we are interested in the data set denoted by

$$d_1, \quad d_2, \quad d_3, \ \ldots \ d_n$$

where n is the number of children in the longitudinal study.

Form the mean

$$\bar{d} = \frac{1}{n}\{d_1 + d_2 + d_3 + \ldots + d_n\}$$

and we are going to conclude that the intervention has been effective if $\bar{d}$ is positive and large.

To test the statistical significance of the change represented by $\bar{d}$, form the statistic

$$t = \frac{\bar{d}\sqrt{n(n-1)}}{\sqrt{\sum_{i=1}^{n}(d_i-\bar{d})^2}}$$

and compare the value of this statistic against the value of Students' t with $(n-1)$ degrees of freedom.

The lower and upper confidence limits are calculated from the equations

$$L = \bar{d} - \frac{t_\alpha}{\sqrt{n(n-1)}}\sqrt{\sum_{i=1}^{n}(d_i-\bar{d})^2}$$

$$U = \bar{d} + \frac{t_\alpha}{\sqrt{n(n-1)}}\sqrt{\sum_{i=1}^{n}(d_i-\bar{d})^2}$$

respectively, where t_α has the same connotation as in the discussion above of two randomized groups, except that the degrees of freedom in this case are $(n-1)$.

TECHNICAL ANNEX E

CONFIDENCE INTERVALS FOR PREVALENCE RATES

Prevalence rates (which are actually proportions) should normally be accompanied by confidence intervals. Thus for example if we look at Table F3 the total prevalence of all active clinical signs of xerophthalmia before intervention for fortified MSG was found to be 3.9% among the children sampled; but one is actually more interested in the prevalence of those clinical signs in the whole population of children from which the sample children were drawn. That (population) prevalence may be higher than 3.9% or lower than 3.9%. Approximate estimates of lower and upper confidence limits for the actual population prevalence can be obtained from the equations

$$L = p - 1.96\sqrt{\frac{p(1-p)}{n}}$$

and

$$U = p + 1.96\sqrt{\frac{p(1-p)}{n}}$$

for the lower and upper 95% confidence limits respectively, and from

$$L = p - 2.58\sqrt{\frac{p(1-p)}{n}}$$

$$U = p + 2.58\sqrt{\frac{p(1-p)}{n}}$$

where p is the observed prevalence in the sample and n is the number of children in the sample.

Referring to the example of prevalence of active clinical signs of xerophthalmia before and after intervention with fortified MSG (Table F3), the prevalence figures are based on samples of size $n = 1161$. Thus for the prevalence before intervention we have, using the 95% level of confidence for example

$$L = 0.039 - 0.011 = 2.8\%$$

and

$$U = 0.039 + 0.011 = 5.0\%$$

and for the prevalence after intervention

$$L = 0.009 - 0.005 = 0.4\%$$

and

$$U = 0.009 + 0.005 = 1.4\%$$

The fact that the lower confidence limit (2.8%) for the prevalence before the intervention is higher than the upper confidence limit for the prevalence after the intervention (1.4%) highlights the fact that the change in prevalence is a real change, and not one that could be ascribed to chance factors.

The confidence limits calculated by these formulae are approximate ones. Exact confidence limits can be found in sets of statistical tables (Documenta Geigy Scientific Tables contain excellent binomial confidence interval tables).

IV. The Question of Toxicity of Vitamin A and of MSG

This brief supplementary information is provided to make it clear that questions of toxicity have been considered both in the Cebu study and when planning the present project.

(1) Vitamin A toxicity

Vitamin A is a fat soluble vitamin, and if taken in excessive doses is not excreted from the body and can cause toxicity. The condition of hypervitaminosis A is, however, very rare. It has usually occurred with over medication with a vitamin preparation either medicinally or as a product such as cod-liver or halibut liver oil, and only when these products were taken in large doses over a long period of time. The signs and symptoms of toxicity include lethargy, malaise, abdominal pain and excessive sweating. Increased intracranial pressure and edema may occur.

Although the amount needed to cause toxicity must vary, and is not accurately known, there is good evidence that very high intakes over long periods would be needed.

As a result cases of hypervitaminosis A are still rare even in countries such as the United States where many different foods are fortified with vitamin A, where large numbers of families consume vitamin preparations often well beyond recommended doses, where "health food stores" encourage the purchase for children of cod liver oil and other preparations rich in vitamin A, and where it is increasingly believed by the public that megavitamin therapy is an answer to much ill health. Carotenemia due to an excessive intake of carotene rich foods is commoner but less serious than hypervitaminosis A. It will not occur as a result of vitamin A fortification.

At the present time in the United States one small serving of many

breakfast cereals will provide a child with 1,250 IU of vitamin A. This is rather similar to the amount that children in Marinduque and Nueva Viscaya will get from their MSG at the levels of current consumption using vitamin A fortification at the level used in Cebu. A person in the U.S. who for breakfast consumed a large helping of a fortified cereal, two eggs, and toast with 24 grams of margarine on it would receive 4,600 IU of vitamin A at this one meal, 3,500 IU of this in fortified products. This illustration is to indicate that fortification in the U.S. is in operation at levels similar to that proposed for the Philippines, but in many different foods and in a population not usually deficient in vitamin A, and one in which vitamin pills are much more widely used. Yet the U.S. has not established a program either to evaluate the benefits of fortification nor to monitor possible toxicity. The risks of hypervitaminosis A seem to be higher in the U.S. than in the proposed Philippine program.

In Central America (Guatemala and at least two other countries) sugar is now being fortified with vitamin A as part of a program to combat vitami A deficiency. In Guatemala, for example, legislation has been passed, all sugar sold is now fortified and it contains about 7,000 IU vitamin A per 100 grams sugar. This intervention is being carefully evaluated by INCAP. Preliminary research at INCAP, and discussions with scientists there and at international meetings suggest that the dangers of hypervitaminosis A from this program are negligible or non-existent. No cases of toxicity have yet been reported. It should be kept in mind that sugar consumption can vary widely, and that many young children have a very sweet tooth.

We are convinced that MSG utilization in the Philippine homes does not have a wide variation each day, for those who use it regularly. The variation, especially upwards, will not be nearly as great as with sugar

(in Central America) or breakfast cereals, margarine and other fortified foods in the U.S. Our data suggest that when families of about 5 persons use MSG, they usually use one 2.4 gram packet, and occasionally 2 such packets per day. MSG, like salt or pepper, and unlike sugar, is not a product which is likely to be consumed in excess by young children.

The margin of safety with vitamin A intake is so high that vitamin A toxicity as a result of fortification of MSG at the levels suggested is virtually impossible.

In the Philippines the MSG is added to foods being cooked. These include the soups, stews, relishes, curry like dishes, etc. These foods are then eaten with rice, maize, cassava or some other staple. The proportion of these foods (to which MSG is added) consumed by each member of the family is usually proportional to his or her calorie or energy intake. Therefore if a child of 2 years of age is consuming 7.5 percent of the total family calories, he or she is likely to get 7.5 percent of the vitamin A enriched MSG. There is no way that this child can get say 50 percent of the MSG. If the child is getting 7.5 percent of the MSG or approximately 0.2 grams, he or she will receive 1,125 IU of vitamin A from the MSG that day. This is a desirable amount, being about 60 percent of the Philippine RDA for vitamin A for a 1-3 year old child. A review of the vitamin A literature suggests that several times this dose would still be perfectly safe.

We have collected data on MSG utilization in Cebu, Marinduque and Nueva Viscaya in sampled households. A hypothetical (but fairly typical) household might consist of four children and the two parents. The likely consumption of MSG and vitamin A is presented in Table 1.

These levels of intake are desirable and have a wide margin of safety. The FNRC surveys and our own data from Cebu suggest that very many persons

Table 1. Hypothetical Filipino family of 6 persons consuming one 2.4 gram packet of MSG fortified with 15,000 IU vitamin A

(Note: Mean household size was 6.5 in Marinduque and 6.7 in Nueva Viscaya surveys)

Ages (years)	% of MSG consumed	Vitamin A obtained (IU)	RDA for vitamin A (IU)
3	10	1500	2000
6	15	2250	3000
8	15	2250	3000
16	20	3000	4000
40	20	3000	4000
45	20	3000	4000

in the Philippines are consuming less than 60 percent of their RDA for vitamin A. In most regions of the Philippines about 80 percent (and sometimes more) of the vitamin A activity is from carotene, and less than 20 percent from pre-formed vitamin A.

(2) MSG toxicity

There is an enormous literature on MSG, and much disagreement about its possible toxicity.

In the Philippines MSG is now very widely sold and utilized. In Cebu the number of families not using MSG during the week prior to questioning was 6 percent and those not using salt the previous week was 5 percent. People in much of South East Asia including Japan and Indonesia also use MSG in a similar manner, frequency and amount. So whether the U.S. believes that this is a healthful or harmful food habit, it is an extremely prevalent one. The program to fortify or nutrify MSG in the Philippines is in no way done to try to encourage MSG consumption, nor to increase its utilization. MSG was chosen simply as the only possible vehicle for fortification meeting accepted criteria. There is no doubt that whether it is nutrified or not the people will continue to consume it.

The question to be asked is whether nutritionists and health workers should recommend fortification of a product which they do not regard as a good healthful food. If the food or product is currently widely consumed and if it is non-toxic, then we believe there is justification in fortifying it especially when as in the Philippines case, there is no other suitable vehicle for the nutrient, and where there is evidence that the particular nutrient deficiency is a serious public health problem. People can (and will) debate as to whether MSG is resulting in any ill health in the Philippines, but all will agree that xerophthalmia is a serious health problem there.

Before discussing what is known about MSG toxicity it might be useful to return to the examples of fortification in the U.S. and in Central America. In the U.S. (and in many other countries) table salt is fortified with iodine. There is much evidence to associate salt intake with hypertension and other health problems (it is now estimated that some 25 million Americans have hypertension). Yet there is not much feeling in the U.S. that fortification of salt encourages its increased consumption, and therefore contributes to serious disease. In Central America and elsewhere sugar intake is associated with dental caries, and high sugar intakes might contribute to other forms of malnutrition because white sugar provides calories but no other nutrients. Arroyave (1) and his colleagues at INCAP do not believe that vitamin A fortification of sugar (and soon iron might also be added) will lead to an increased use of sugar, and therefore to conditions associated with high sugar intakes.

L-Glutamic acid is an amino acid which occurs naturally in proteins of animal and vegetable origin. Glutamic acid and its salts including Monosodium glutamate share similar physical properties. MSG is a food additive or ingredient which officially is GRAS (Generally Regarded as Safe) as listed in the U.S. Code of Federal Regulations (2). MSG has been used as a food seasoning in Asia for several centuries. In industrialized Asian countries with good health services, such as Japan, it is widely consumed and is not considered hazardous to health.

It appears that most of the glutamic acid or its salts consumed is transaminated and absorbed as alanine and a-ketoglutaric acid. Acute toxicity data on MSG in rats suggest that the oral LD_{50} of MSG varies between 14.5 and 19.0 g per kg of body weight (3). Many studies using parenteral administration (injections) of MSG have suggested that this

results in CNS lesions. Olney (4) in a series of papers has been the most prolific and vehement critic of MSG and its safety, but his work too is based mainly on the injection of mice and other laboratory animals with MSG often in very high doses (5). A number of other scientists have conducted similar studies, and in contrast most find no specific effects in mice (6), monkeys (7,8) and other animals.

In humans there are two main types of response that have been reported. These are first, the so called Chinese Restaurant Syndrome (CRS) and the second is an allergic reaction probably to some substance in the materials (such as beets) from which the glutamate was prepared. CRS apparently occurs within an hour of consumption of MSG in sensitive individuals. From the reports it appears to occur in those consuming very large doses of MSG (several grams) on an empty stomach. The symptoms and signs include headache, tightness of the neck, flushing of the face, and sometimes abdominal pain and nausea. These symptoms are short-lived and temporary, most of them disappearing within one hour, although headache is said to be longer lasting in some individuals. One study in Boston which was completely uncontrolled reported CRS in 25 percent of persons exposed to Chinese Restaurant food (9), but controlled double blind studies by others have usually shown no differences in symptoms between control and MSG treated groups (10,11).

Animal and human studies and reports over the years have associated administration of oral glutamic acid with accelerated learning in rats and improved intelligence in mentally retarded children. In general this is regarded as unproven but some scientists still believe that cognitive behavior is positively affected (12). The use of high doses of MSG to treat mental retardation has not resulted in toxicity.

A thorough review of the literature on MSG toxicity was made by us prior to the Cebu study. Our group has still followed the research being undertaken, and we have a continuing computer literature search on MSG toxicity.

We conclude that MSG does not present a biological hazard because (1) glutamic acid comprises about 20 percent of the amino acids in proteins that we consume (and Americans consume much higher levels of protein than do Filipinos), (2) in experimental animals oral LD_{50} values for MSG are very high, (3) children being treated with oral glutamic acid for mental retardation tolerate doses of 50 grams daily for long periods with no evidence of harmful effects, (4) MSG has been used as a food additive for many years in countries such as Japan with no evidence of toxicity, and (5) mammals including man have physiological protective mechanisms against excess absorption from the gut.

Our recommendation for fortification of MSG is not designed to alter in any way the present consumption of MSG by families in the Philippines. Its hazards are, if they exist, certainly less than those of salt and sugar now used for enrichment purposes in other countries. The risk of toxicity from MSG we believe is minute. In contrast, the risk of morbidity, blindness and death from vitamin A deficiency in the Philipiines is high, and therefore any steps to control xerophthalmia deserve support.

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