PD-AAY-647

International Center for Epidemiologic and Preventive Ophthalmology

Vitamin A Program

Annual Report
October 1, 1987 - September 30, 1988

This report was prepared under Cooperative Agreement No. DAN 0045-A-5094-00 between the International Center for Epidemiologic and Preventive Ophthalmology, The Johns Hopkins University, and the Office of Nutrition, Bureau for Science and Technology, United States Agency for International Development.

1.0. Introduction

During fiscal year 1987-88, ICEPO made major preparations for two large vitamin A/mortality trials scheduled to begin in 1989. In Nepal, A Memorandum of Agreement was signed with the Nepalese government, the study site was selected, and other operational plans were made. In Ethiopia, a Memorandum of Intent to Collaborate was signed with the University of Addis Ababa, preliminary field visits were made, meetings were held with UNICEF, WHO, and other potential collaborating agencies, and a protocol was developed.

We have continued to provide technical assistance to Indonesian and Filipino scientists in their efforts to further elucidate the impact of vitamin A on morbidity and mortality and establish vitamin A deficiency control programs. New collaboration was begun in Truk and the Marshall Islands where xerophthalmia was reported for the first time.

In Baltimore, the data processing unit was expanded to meet the demands of the mortality trials in Nepal and Ethiopia. In addition developmental research continued to establish and refine conjunctival impression cytology (CIC-A) as a practical tool for assessment of vitamin A status. The first training manual for CIC-A was published as was the revised African Xerophthalmia Recognition Card in four additional languages.

2.0. Country Programs

2.1. Nepal

A community based vitamin A mortality study will be launched in 1989 in the Terrai region of Nepal. During FY87-88, two major trips were made in preparation for the study. In March, Dr. West visited Nepal to negotiate an agreement of collaboration with the National Society for Prevention of Blindness (NSPB). A five year Memorandum of Agreement was signed on March 13, 1988.

In July, Drs. West and Sommer and Joanne Katz continued in-country preparation. A Letter of Understanding was signed between the NSPB and ICEPO. The USAID/Kathmandu office was repeatedly visited and briefed on study plans. Ethical review was initiated with the Medical Research Committee of Nepal, and is expected to be completed by December. Ethical clearance was obtained from The Johns Hopkins Medical Institutions Joint Committee on Clinical Investigation in September 1988. ICEPO staff visited the study area where they identified the field headquarters site, and made plans for construction of the local facilities. Computers originally purchased for the Philippines trial were shipped from Manila and arrived safely in Nepal. Vehicles and other equipment were ordered. An expatriate field coordinator was hired (ex-Peace Corps volunteer with 14 years experience in Nepal).

The tragic earthquake which struck Nepal in August, fortunately did not cause extreme damage in the study area. However, major roadways were interrupted and demand for construction has increased, which may delay start-up of the study

by 2-3 months. Dr. West (Project Scientist) will move to Nepal in January, 1989. Formal field work will begin April-May 1989. The Nepali co-PI is Dr. Pokhrel, Director of the Nepal Eye Hospital and the Nepal Society for the Prevention of Blindness, with whom this study is being carried out.

2.2. Ethiopia

2.2.1. Community Based Vitamin A Mortality Study.

Progress has been made in planning for a large randomized community trial to assess the impact of vitamin A supplementation on infant and child mortality in southern Ethiopia as a basis for extrapolating vitamin A/mortality findings to Africa. The project will be a collaborative effort of the Faculty of Medicine, Addis Ababa University, The Ethiopian Nutrition Institute (ENI), and ICEPO. A Memorandum of Intent to Collaborate was signed by the faculty of medicine of Addis Ababa University and ICEPO in June of 1987. Follow up discussions were held at the December IVACG meeting in Addis Ababa between Drs. Sommer and Tielsch, the faculty of the University and the ENI. At this meeting a joint protocol was developed.

Dr. Hagos Beyene, a pediatrician at Addis Ababa University is the local director of the study. Dr. Wondu Alemayehu, a member of the Addis Ababa University department of Ophthalmology, will co-direct the study. Dr. Alemayehu graduated from ICEPO's Joint Preventive Ophthalmology/MPH program at The Johns Hopkins University in May, 1988.

From June 30-July 10, Dr. Sommer and Jean Humphrey visited Ethiopia to continue plans for the project. A study site was selected in 2 subdistricts in northern Bale region, and 2 subdistricts in southern Arsi region, and will be headquartered in Dodola, on the main road through Bale near the Arsi border. This area is a monocrop region in which people rely entirely on one grain, usually barley or wheat. The only usual dietary source of vitamin A is milk, which is now chronically in short supply due to recurrent drought with consequent loss of dairy cattle.

Meetings were held with Mr. Assefa, Director of the MOH Blindness Prevention Program, and Vice Minister Getachew, of the MOH both of whom were supportive and pleased with the study site selected. Several meetings were held with representatives of UNICEF who pledged UNICEF administrative and logistical support, including two vehicles. Project goals were also discussed with Willard Pearson, new USAID country director and Gladys Gilbert, USAID Health/Nutrition.

Professor Demissie Habte, Dean of the Medical School, Addis Ababa University remains strongly supportive of the project. A visit was made to the ENI where laboratory facilities include an HPLC, potentially capable of the serum retinol analysis required by the study.

Implementation of the project depends on obtaining funds for in-country costs from non-USAID sources. On February 27 a revised research proposal entitled "Impact of Vitamin A Supplementation on Childhood Morbidity and Mortality in Ethiopia" was submitted to the Canadian International Development Research

Center (IDRC) by Addis Ababa University. In June, 1988 Drs. Sommer, Tielsch, Alemayehu, and Beyene and Dr. Peter Greaves of UNICEF met with IDRC representatives in Ottawa, Canada for further discussion. A subsequent revision of the proposal was submitted with additional clarification in September, 1988. The project has been cleared by ethical review committees at Johns Hopkins, and the University of Addis Ababa.

2.2.2. Hospital Based Acute Respiratory Infection (ARI) Trial

Plans were developed and training carried out for a hospital-based study at Black Lion Hospital in Addis Ababa to assess the impact of vitamin A on ARI-related mortality. The trial is due to begin in October, 1988. Inpatient cases with ARI will be randomized to receive a high dose vitamin A capsule or placebo and then followed for vital outcome. Various clinical parameters will be assessed throughout hospitalization. ICEPO developed the protocol in collaboration with Dr. Hagos, has provided training in conjunctival impression cytology (CIC-A) and the required supplies, will serve as a standardization center for a subsample of CIC-A and serum specimens, and will assist local investigators in the analyses and reporting of results.

2.3. The Philippines

In 1987, at the recommendation of ICEPO, Filipino Secretary of Health, Dr. Alferdo Bengzon established a National Vitamin A Coordinating Council to initiate, promote, and oversee all facets of the vitamin A control program throughout the country. ICEPO

is collaborating in four of these vitamin A projects: 1) a nationwide vitamin A status survey incorporating CIC-A; 2) a multi-center hospital-based study assessing the impact of vitamin A supplementation on mortality due to measles and respiratory infection; 3) a community-based clinical trial on the relative safety of two alternative vitamin A doses; and 4) a program to consider a national plan of monosodium glutamate (MSG) fortification with vitamin A.

2.3.1. Nationwide Vitamin A Status Survey

This study is a collaborative effort of Helen Keller International (HKI) and the Institute of Ophthalmology, University of the Philippines, with technical assistance from ICEPO. Field work was conducted March-July, 1987. A multistage sampling scheme was used to select households from 11 of the 12 regions (region 9 was not considered safe) plus the national capital region of metro Manilla. All children under 6 years in selected households were examined (N=865). Vitamin A status was determined by ocular examination and CIC-A.

ICEPO helped to establish the laboratory for reading CIC-A specimens and has assisted in processing and reading specimens. Data are now being analyzed in Manilla and Baltimore. These surveys will provide the first population-based estimates of the prevalence of subclinical vitamin A deficiency in the Philippines.

2.3.2. Hospital Based Vitamin A/Morbidity Trial

A multi-center hospital-based study is underway to

investigate the impact of vitamin A supplementation on mortality from measles and respiratory illness. ICEPO is collaborating with three hospitals: San Lazaro Hospital (SLH), the National Children's Hospital (NCH), and the Research Institute for Tropical Medicine (RITM). Investigators meet bimonthly under the leadership of Dr. Luluth Lucero to review procedures, solve problems, and review study forms generated in the previous 2 week period.

Four hundred (400) children are being enrolled at RITM and 1000 each at SLH and NCH. As of July, it appears that all centers will need to extend enrollment through next year's measles season to achieve required samples.

ICEPO designed the protocol and is providing technical assistance in analysis of serum specimens and data management. Dr. Keith West met to discuss the study with Dr. Lucero and two other Filipino investigators during his July, 1988 visit. ICEPO will provide training and necessary supplies for CIC-A.

2.3.3. Vitamin A Dosage Safety.

ICEPO collaborated with the Food and Nutrition Research Institute (Ministry of Science and Technology) and Nutrition Unit (Ministry of Health) in conducting a controlled randomized field trial investigating the side effects of two standard large doses of vitamin A (200,000 IU and 100,000 IU) compared to placebo. A preliminary report was prepared for a workshop in Manilla in July. The study found that side effects, particularly nausea, vomiting, and headaches, did result from vitamin A supplementation. Following 200,000 IU, 100,000 IU, and placebo

(containing no vitamin A) nausea and vomiting occurred in 8.8 %, 3.6%, and 2.2% of children, respectively. The report concludes, however, that the benefits derived from vitamin A supplementation outweigh the minor side effects that develop and recommends pursuing a national prophylactic vitamin A program following WHO guidelines[1]. A follow up study to determine whether 200,000 IU actually prolongs prophylaxis compared to 100,000 IU is planned for both the Philippines and for Indonesia.

2.3.4 Philippines Fortification Task Force

In May, 1987, Dr. Sommer wrote to Secretary Bengzon suggesting that the Philippines establish a Task Force to meet with an Indonesian team to share experience, participate in solution of problems in the Indonesia fortification program, and report back to the scientific and policy-making Filipino community. At a meeting on July 10, 1987, the Department of Health (DOH) endorsed creation of such a Task Force.

The Philippine Task Force on Fortification composed of Doctors Consuelo Aranas and Adelisa Ramo (DOH), Ellen Villate (HKI), and Dr. Florencio, visited Indonesia June 18-25, 1988. The recommendations developed from their visit acknowledged the potential for fortification but called for further study to establish MSG food consumption patterns and biologic efficacy of MSG-A fortification.

ICEPO will continue to encourage MSG fortification by providing technical assistance to the scientific and policy

---

[1] For children 2 years and older, 200,000 Iu every 4-6 months; for children less than 2 years, 100,000 IU every 4-6 months.

making communities and by facilitating constructive exchange between Indonesians and Filipinos on this and other preventive strategies.

2.4. Indonesia

2.4.1. Aceh Vitamin A/Mortality Study

The third of eight planned manuscripts reporting the Aceh trial was published during the reporting period: "The impact of vitamin A supplementation on xerophthalmia" **Arch Ophthalmol** 106:218, 1988, (see Appendix A). The paper reports on the dramatic reduction in xerophthalmia due to vitamin A capsule distribution. This analysis also showed that choice of clinical indicator of xerophthalmia will determine the measured level of benefit. History of night blindness is not a sensitive indicator of the impact of vitamin A supplementation when prevalence rates are low, and only the prevalence of new cases of Bitot's spots should be used in comparing rates of xerophthalmia.

The fourth of the planned manuscripts, "Vitamin A supplementation on growth: a randomized community trial" is in **Am J Clin Nutr** 48:1257-1264, 1988, (see Appendix B). This analysis is the first documentation of improved growth following supplementation to an endemically deficient human population.

2.4.2. Conjunctival Impression Cytology-A Study

A case control study and clinical trial were completed in West Java in 1986 which established CIC-A as a important tool in detecting early, subclinical vitamin A deficiency. Two of the papers were published in September and October, 1987. The first

paper "Impression Cytology for Detection of Vitamin A Deficiency" was published in **Arch Ophthalmol** in September 1987 (see Appendix C), and the second paper "Impression Cytology: a practical index of vitamin A status" which derived a 94% specificity and 93% sensitivity of CIC-A in detecting vitamin A deficiency was published in **Am J Clin Nutr** in October, 1987 (see Appendix D). Ms. Lisa Mele will travel to Indonesia in November to work with Dr. Natadisastra on further analysis of the data.

A second phase of this study, was carried out June - September, 1988 evaluating a prototype vacuum applicator for simplifying the obtaining of CIC-A specimens, (see section 4.1.1).

2.4.3. Vitamin A fortification of Monosodium Glutamate (MSG)

A large randomized controlled community trial evaluating the efficacy of vitamin A fortification of MSG was conducted in 1985-86. ICEPO provided technical assistance to the National Research and Development Center (NRDC). The lead authors, Drs. Muhilal and Gantira, each had three month in-residence visits to ICEPO. Analysis were conducted and reviewed, and two manuscripts drafted which will appear in the **Am J Clin Nutr** in November, 1988 (see Appendices E and F).

These studies not only showed dramatic impact of fortification on vitamin A status and xerophthalmia, but also on breastmilk retinol level, hemoglobin concentration, linear growth and mortality.

This work was part of a three year plan of preparation, implementation and economic evaluation of a regional MSG

fortification program currently underway. ICEPO will continue to facilitate the development of this national program.

2.4.4. Vitamin A And Immune Competence.

A randomized controlled trial of the effects of vitamin A supplementation on immunologic status was carried out June - September, 1988 in an area near Bandung. The study is a collaborative project between ICEPO, the Department of Immunology and Infectious Diseases of the Johns Hopkins School of Hygiene and Public Health, the NRDC, and the Cicendo Eye Hospital. Dr. Richard Semba, an ICEPO faculty member, Ms. Deborah Keenum and Ms. Christina Bandera (both medical students at the Johns Hopkins University) worked on the study in Bandung. A total of 240 preschool children were followed for five weeks, 120 with clinical signs of xerophthalmia and 120 matched controls with normal eyes. Following baseline clinical examination, immunologic and hematologic studies, and CIC-A, half of each of the cases and controls were given a 200,000 IU vitamin A capsule, and the other 60 children in each group were not supplemented, serving as controls. Two weeks later, all children were immunized with trivalent polio, attenuated influenza, and DPT vaccines. Final clinical examination and laboratory studies were carried out three weeks later (study week 5) completing the study. Data analysis is underway to address immune status in children with vitamin A deficiency, and determine the impact of vitamin A supplementation on mucosal, humoral, and cell mediated immunity, as well as hematologic parameters and CIC-A.

2.5. Truk, Federated States Of Micronesia

ICEPO began collaboration with staff from the Truk hospital in September, 1987, in carrying out an outpatient clinic survey of vitamin A status among the pediatric outpatient population. ICEPO involvement followed a request from Dr. Michelle Puryear, a USPHS physician, to investigate an apparent rise in the caseload of xerophthalmic children seen in the Truk outpatient clinic.

During the three week period, October 13 - November 6, 1987, a systematic sample of sixty pre-school children were enrolled. Evaluation included physical exam, history of night blindness during the previous month, CIC-A, hematocrit and serum retinol analysis, anthropometry, and diet history for sources of vitamin A. More than half (57%) of these children were CIC-A positive, 17% were nightblind and 5% had bilateral Bitot's spots, suggesting that vitamin A deficiency is an important health problem among these children. In addition, children with abnormal CIC-A had significantly lower hematocrit levels, and a higher prevalence of middle ear infection than CIC-A normal children. This survey is the first quantitative estimate of vitamin A deficiency in Micronesia. Results of this survey have been analyzed and a paper prepared for publication (see Appendix G).

Dr. Keith West visited Truk on July 15-19, 1988 to assist the Truk hospital staff and the Ministry of Public Health Services in planning a statewide xerophthalmia survey, employing CIC-A to assess the prevalence vitamin A deficiency throughout the country.

A case-control study is also planned to investigate the causes and risk factors associated with xerophthalmia in this region. Dr. West will meet with investigators this November.

ICEPO trained two Truk Hospital staff members in CIC-A: Dr. Michelle Puryear, a USPHS pediatrician and PI of the studies, in August, 1987, and Joan Mahoney, M.S., R.D., a registered dietitian working in the Truk Hospital nutrition clinic, in August, 1988.

2.6. Marshall Islands

In the Spring of 1988, Maria Pia Sanchez, a USPHS Child Survival Fellow contacted ICEPO seeking technical assistance after observing a large number of cases of xerophthalmia at Majuro Hospital. Dr. Keith West visited the Marshall Islands, July 13-15, 1988. He gave seminars on vitamin A deficiency to both the medical and nursing staffs, and reviewed plans for two studies: 1) a community-based vitamin A deficiency survey; and 2) a clinic-based case-control study. The community based survey is being carried out in August and September-October, 1988. Vitamin A status will be determined by CIC-A and ocular examination. The evaluation will also include nutritional and morbidity assessment.

A case-control study of risk factors for xerophthalmia will to be carried out at the Majuro Hospital, was also planned during Dr. West's visit. In both Truk and the Marshall Islands abandonment of a traditional diet with increasing dependence on imported processed foods seems to be partly responsible for the apparent emergence of xerophthalmia. ICEPO is providing the

CIC-A supplies, and technical assistance in protocol development, data management and analysis, and reporting.

2.7. Bangladesh

ICEPO provided technical assistance to HKI/Bangladesh and USDA for a pilot project and evaluation for using vitamin A fortified wheat in vulnerable group feeding and food-for-work programs in Bangladesh. Dr. Keith West visited Bangladesh in March, 1988, and met with Dr. Ian Darnton-Hill (HKI- Country Representative) to refine the design and procedural elements, outline a manual of operations, calculate sample size requirements, and outline resource needs for a pilct study. Thirty-five hundred (3500) children are planned to be enrolled and randomly allocated at the union level to receive fortified or unfortified wheat. The future status of this project is presently in question, pending approval by the Ministries of Health, Food, and Relief and Rehabilitation in Bangladesh and upon the primary agencies (MOH and HKI).

2.8. Zambia

ICEPO collaborated with the MOH, and affiliated institutions (National Food and Nutrition Commission, Tropical Diseases Research Centre (TDRC), Flying Doctor Service) in carrying out and analyzing data from a major xerophthalmia survey in the Luapula Valley from August - December, 1985.

Data from this study documents the epidemiology of blindness and xerophthalmia, the latter exceeding WHO criteria for a public health problem. ICEPO developed presentation materials for a

regional xerophthalmia workshop held in Ndola in February, 1988, when study results were presented and plans were initiated for a national vitamin A strategy. Analysis of the data is continuing. Mr. David Mwandu, Deputy Survey Director, is planning a trip to ICEPO for further assistance in data analysis and reporting of results from this survey.

On the basis of the results of the Luapula Valley Survey, FAO has agreed to plan an intervention project in conjunction with UNICEF. ICEPO is assisting in developing follow up plans for prevention of vitamin A deficiency in Zambia.

2.9. Kenya

ICEPO has been providing consultations and visits with Kenyan officials for the past seven years. This input is apparently partially responsible for the resolution passed by the Kenyan Pediatric Association in the spring of 1988, calling for the development of a vitamin A deficiency control program. To develop this program the Association appointed a Vitamin A Task Force to carry out 2-3 years of appropriate research. The task force met for the first time with Dr. Sommer, in Kenya in June and July, 1988.

We anticipate continuing to provide technical assistance to the Task Force as protocols are developed and projects come to fruition in Kenya over the next several years.

3.0. Vitamin A/Bronchopulmonary Dysplasia (non-program funded)

ICEPO has begun collaboration with The Department of Pediatrics, Division of Neonatology, at The Johns Hopkins

Hospital to investigate the impact of vitamin A supplementation on the incidence of BPD and ROP in very low birth weight neonates. Numerous studies have shown that the vitamin A status of premature infants is poor at birth and worsens during the first postnatal week due to difficulties in providing oral or intravenous supplements. Several reports have also indicated that vitamin A deficiency puts these infants at greater risk for developing BPD and respiratory infection.

ICEPO is sharing responsibility for protocol design, serum retinol analysis, data processing and analysis, and manuscript preparation.

This study may elucidate a role for vitamin A in preventing the two major complications of prematurity and will likely also increase understanding of potential mechanisms of vitamin A in influencing risk to respiratory infections. In so doing, it would generate interest in vitamin A among the western medical community, who seem otherwise to be not involved in or concerned about international health issues.

4.0. Vitamin A assessment laboratory

The vitamin A assessment laboratory includes reference and standardization services for CIC-A and serum vitamin A determinations.

4.1. Conjunctival Impression Cytology for Assessment of Vitamin A Status (CIC-A)

The Impression Cytology lab is located in two locations within ICEPO. Staining and mounting are carried out by Mahmood

Farazdaghi in a Wilmer histology lab, while interpretation and cataloging of specimens takes place in the 550 building.

4.1.1. CIC-A Research and Development

Ms. Deborah Keenum, M.A., a medical student and part time research assistant at ICEPO is continuing development of a hand operated vacuum applicator for simplifying obtaining of CIC-A specimens. The applicator standardizes specimen size, improves specimen quality and targeting of samples, is easier to use than the original strip technique, and may improve specificity, sensitivity and inter-observer agreement.

The applicator underwent further testing in Indonesia this year as part of the Immunology Study in West Java (see section 2.4.4.) in June-September, 1988. Data from this investigation are under analysis.

4.1.2. Impression Cytology Training Manual.

The Impression Cytology Training Manual was published in September, 1988 (see Appendix H). The manual reviews the rationale and development of the technique and provides step by step instructions for obtaining, fixing, staining, and interpreting specimens. Interpretation has been simplified by the development of a flow chart with colored photographs of illustrative specimens.

4.1.3. Impression Cytology Training Program

The Center continues to provide training in CIC-A when requested by clinicians and investigators. In addition the

circle of experience with the technique is expanding as those trained at ICEPO become trainers themselves. Among those trained by one of the Centers "graduates" is Dr. Derrick Jelliffe, of the UCLA School of Public Health, who then presented the technique at a conference on nutritional assessment in Pakistan in March, 1988, using teaching slides and materials provided by ICEPO. As a result both UNICEF and USAID/Islamabad have corresponded with ICEPO expressing their interest in exploring the use of CIC-A in various community-based vitamin A surveys and programs in Pakistan.

Dr. Eva Santos, of the Philippines, trained by ICEPO staff in 1987, has since trained several ophthalmologists and primary care physicians in CIC-A, and has conducted several large field studies employing CIC-A to assess vitamin A status in more than 2500 children. Similarly, clinicians in Micronesia (Truk, Marshall Islands) were trained in CIC-A and have or are planning to use it to assess vitamin A status in their respective regions.

Impression cytology was taught to all students in the Joint Program in Preventive Ophthalmology and Public Health at Johns Hopkins during the past academic year.

Ms. Deborah Keenum, wrote and produced a thirty minute video on CIC-A in collaboration with Project Orbis. The video, in combination with the CIC-A training manual will provide excellent instruction to those we can not train in person.

Participants in CIC-A Training.

Denton Cameron, M.D.
Benson Institute
Salt Lake City, UT

Nov. 11, 12, 1987

Dhiren Makdani, Ph.D. Human Nutrition Research Lincoln University Jefferson City, MO	Nov. 11, 12, 1987
Eva Santos, M.D. HKI/Philippines (follow-up training)	Nov. 25, 26, 1987
John Gmunder, Ph.D. Director, Task Force Sight and Life Hoffman La Roche Basle, Switzerland	Nov. 15, 1987
24 Public Health Ophthalmology Fellows	Jan. 30, Feb. 6, 1988
Michael Berman, Ph.D. Assistant Professor, Ophthalmology Johns Hopkins University	Feb. 6, 1988
Dr. Sanjay Shah (former JHU medical student) 2425 Overlook Road No. 2 Cleveland Heights, OH 44106	Feb. 6, 1988
Lori Frost 16 N. Collington Avenue Baltimore, MD 21213	Feb. 6, 1988
Wondu Alemayehu, M.D. Department of Ophthalmology University of Addis Ababa Ethiopia	Aug., 1988
Joan Mahoney, MSRD Nutritionist, Truk Hospital Moen, Truk	Aug. 22, 1988
Laura Kettle Doctoral Student University of Arizona Phoenix, AZ	Oct. 1, 1988

CIC-A training materials and references are sent on request to colleagues. Recipient of CIC-A materials during this reporting period were:

Dr. Zein Ahmed Zein
Dean, Gondor College of Medical Sciences
Gondor, Ethiopia

Dr. M.A. Salisbury
Veterinary Ophthalmologic Research
Schoo of Veterinary Medicine
University of Georgia
Athens, Georgia

Ms. Suzanne Vlakveld
Nutritionist
Niger, Africa

Dr. Emorn Udomkesmalee
Research Nutritionist
Institute of Nutrition
Mahidol University
Bangkok, Thailand

Dr. Heather Goldman
Nutrition/USAID
Islamabad, Pakistan

Dr. Zulfiqar Bhutta
Dept. Pediatrics
Aga Khan University
Karachi, Pakistan

Dr. Anwar Saeed
Nutrition/UNICEF
Islamabad, Pakistan

Laura Kettle
Doctoral Student
Univ. of Arizona
Phoenix, Az

With the publication of the new CIC-A manual, requests for information are expected to accelerate during the next fiscal year.

4.2. Biochemical Reference Laboratory

Since the retirement of Mrs. Agatha Rider in 1986, serum specimens have been analyzed on a temporary basis by her colleague, Ms. Marie Foard at The Johns Hopkins School of Hygiene. New arrangements have now beer made to move the biochemical reference laboratory into the Wilmer Institute through a new collaboration with Dr. Tyl Hewitt This initiative will greatly expand our biochemical capabilities (including HPLC) to support the Center's vitamin A research programs.

5.0. ICEPO Vitamin A Photo Bank

The Center continues to build a slide bank for training, seminars, lectures, and training materials. The Center actively responds to requests for visuals aids on vitamin A deficiency and xerophthalmia from agencies working in the field. During this reporting period slides were made of recent modifications in CIC-A to update this series for teaching and use in the CIC-A Training Manual. Slides from the Photo Banks were also used in developing both the Asian and newly published African Xerophthalmia Recognition Card.

6.0. Data Processing Unit

6.1. Word Processing Integration

During August, 1988, all Wang dedicated word processing machines were "retired" and replaced by Dell System 200 microcomputers for use by this project's faculty and support staff. The integration should dramatically increase efficiency

and help supporting secretarial cost to a minimum. WordPerfect Version 5.0 was installed on these machines and all support staff trained in its use. Large documents (eg. vitamin A-related mailing lists for reprints, reports and updates) that had been created on the Wang machines were converted to WordPerfect format.

The microcomputers were also installed with SciMate, a library reference software package, which now provides immediate access by keyword to the thousands of vitamin A references (both published and unpublished) within the Center.

6.2. Central Computing Facility

Plans are underway to install a Digital Equipment Corporation MicroVAX 3600 Minicomputer running the VAX/VMS operating system. This system will reduce the dependency on the expensive time-sharing system presently accessed at The Johns Hopkins School of Public Health Academic Data Center (ADC). The new system will be housed at ICEPO, configured with two hard disk drives with a combined capacity of 1.2 Gigabytes, a cartridge tape drive capable of storing close to 300 Megabytes on a small cartridge tape, reel-to-reel magnetic tape drive for transferring data from other computer systems, a 600 lines/minutes printer, a six pen color plotter, 2 modems for dialup access, and a variety of software products including programming languages, database management, and statistical packages.

Existing and additional IBM PC AT microcomputers will be linked to the VAX via an Ethernet network, allowing the PCs to act as terminals to the VAX. This allows PC files to be stored

on the VAX and shared between several microcomputer users. In addition, data can be entered to databases residing on the VAX from all microcomputers. An additional VAXStation 3200 minicomputer will be installed to help share the load with the main computer. Using special software the two machines will be closely linked so that they can share resources. The VAXStation also has the capability of producing detailed graphics on screen so that they can be previewed before printing.

Upon installation users will begin transferring data files and programs from ADC to the VAX. This will facilitate cost-efficient analysis of most vitamin A data sets by faculty and collaborating scholars and investigators. Once the investment in this system is made cost becomes a minor issue and no longer an obstacle to full and unhindered analysis of the existing large data sets and those that will be arriving from the Nepal and Ethiopia studies.

7.0. Xerophthalmia Recognition Card.

The updated African Xerophthalmia recognition card was published in September, 1988, in five languages: English, French, Swahili, Chichewa, and Portuguese (see Appendix I). In addition, a photo-only version was printed which will have Amharic text printed in Ethiopia sometime in the future, and other languages should the need arise. Changes were made in keeping with joint WHO/HKI/UNICEF/ICEPO recommendations to include lower respiratory infections as an indication for supplementation and to treat severe malnutrition with one large dose instead of three. Five thousand copies of each were printed

and will be distributed to primary health care workers around the world.

The Asian version is still in use, in English, Indonesian, and Hindi. Thus, the card is now available in eight languages.

8.0. Joint Program in Preventive Ophthalmology and Public Health (PHO Program)

The second quadrennial PHO Course was given during academic year 1987-88. In addition to the thirteen full year students, an additional nine ophthalmologists joined for a shorter three month course. During the year several colleagues lectured, including:

Dr. Bjorn Thylefors, Programme Manager of WHO Prevention of Blindness Program

Dr. Carl Kupfer, Director, NEI

Susan Pettiss, Ph.D. HKI Vitamin A consultant.

Alan Foster, M.D., University of London (presented the Tanzania Vitamin A/Measles study).

Marsha Griffths and Michael Favin, Manoff International (presented vitamin A social marketing).

In addition, the Center's staff gave several lectures on vitamin A: metabolism and function, food sources, impact of deficiency on mortality and morbidity, deficiency control and intervention programs, and methods of status assessment.

Several students developed research protocols dealing with vitamin A deficiency and its prevention.

9.0. Vitamin A Technical Assistance

The following tables summarize the major vitamin A technical

assistance activities rendered by ICEPO to U.S., Foreign, and multi-lateral agencies during the reporting period (individual and informal contacts and assistance are too numerous to mention):

Barbara Underwood, Ph.D. NEI Bethesda, MD	CIC-A teaching slide set for work overseas.
Academy for Educational Development	Provided a summary of current, ongoing vitamin A projects in the Center. Provided vitamin A expertise for a state-of-the art paper on vitamin A projects and nutrition education.
Concern/Bangladesh	Consultation on recommendations for vitamin A treatment of measles and diarrhea.
SCF/Bangladesh	Consultation on recommendations for vitamin A treatment of measles and diarrhea.
Louisiana State Univ.	Consultation to Dr. George Tucks, for a study in Chiang Mai, Thailand, on the effects of vitamin A deficiency on the immune response.
Prevention Magazine Rodale Press	Technical consultation to Linda Miller, editorialist on an article about vitamin A deficiency. (March, 1988 issue).
USAID/Thailand Mission	Vitamin A literature to Mr. Win McKeithen.
Dr. Sibley Hoobler	Vitamin A literature with special reference to Haiti.
University of London Department of Preventive Ophthalmology	Provided copies of Luapula Valley manual of operation, via TDRC.

Cornell Alumni News Letter Ithaca, NY	Provided photograph of child receiving vitamin A capsule for inclusion in an article about J.C. Bauernfiend.
Senator Barbara Mikulski (Maryland)	Provided technical information about vitamin A deficiency to assist Senator Mikulski in working for further congressional support of third world health programs.
Dr. M.K. Sharma Consultant Ophthalmologist Zambia Consolidated Copper Mines	Provision of vitamin A capsules through referral to Task Force Sight and Life
Health, Population, Nutrition USAID/Islamabad, Pakistan	Critiqued protocol for vitamin A hospital-based clinical trial and community assessment.
Dr. Y. H. Yang Seeds for Peace Project Honolulu, Hawaii	Critique of slide presentation promoting horticultural interventions in vitamin A deficiency. Also contributed teaching slides.
Lori Heise Worldwatch Institute	Provided vitamin A publication reprints to assist in work on infant mortality.

10.0. Information Dissemination

Providing current and accurate information about the latest vitamin A research to colleagues and the lay public continues to be an important priority. During this reporting period, a vitamin A mailing list was compiled. The list includes scientific colleagues and legislators who receive periodic mailings on of major vitamin A research.

Other public relation activities during this period included:

The State-of-the-Art paper authored by Drs. West and Sommer: Delivery of Oral Doses of Vitamin A to Prevent Vitamin A Deficiency and Nutritional Blindness was reviewed (and offered in the journal free of charge) in the U.N. SCN News, March 30, 1988, Nos. 1 and 2. Dr. West also contributed a photograph used in the news letter (see Appendix J).

Dr. Sommer was interviewed by a reporter from ASIAWEEK while in the Philippines. The resultant article gave major cover-story treatment to the vitamin A story in their December issue, providing enormous positive and balanced press coverage (see Appendix K).

"20/20" television news program included segments of the Vitamin A/Mortality Story on their twenty year highlight program.

Planning began for a public relations seminar through the Baltimore Council on Foreign Affairs on vitamin A deficiency research and control, through the office of Ms. Cynthia J. Steuart, Director, Office of Public Liaison, USAID, Washington.

Dr. West edited a Manoff paper co-authored by Raisa Smith and Michael Favin entitled Vitamin A an Emerging Key to Child Survival.

Dr. Sommer contributed an article to UNICEF intercom, Oct. 1987: "Staying in sight with Vitamin A," in which he reviewed the WHO/UNICEF joint statement on Vitamin

A supplementation of children with measles (see Appendix L).

11.0. Publications/Presentations/Meetings

11.1. Publications

Sommer A: Staying in sight with vitamin A. **UNICEF INTERCOM**, October 1987, page 11.

Sommer A: Joint WHO/UNICEF Statement. Vitamin A for Measles. **Wkly Epidem** 19:133 1987.

Djunaedi E, Sommer A, Pandi A, Kusdiono, Taylor HR, and the Aceh Study Group: Impact of vitamin A supplementation on xerophthalmia: A randomized community trial. **Arch Ophthalmol** 106:218-222 1988.

Natadisastra G, Wittpenn JR, Muhilal, West KP Jr, Mele L, Sommer A: Impression cytology: A practical index of vitamin A status. **Am J Clin Nutr** 48:695-701 1988.

Natadisastra G, Wittpenn JR, West KP Jr., Muhilal, and Sommer A: Impression cytology for detection of vitamin A deficiency. **Arch Ophthalmol** 105:1224-1228 1987.

Amedee-Manesme O, Luzeau R, Wittpenn JR, Hank A, Sommer A: Impression cytology detects subclinical vitamin A deficiency. **Am J Clin Nutr** 47:875-878 1988.

Djunaedi E, Sommer A, Pandji A, Kusdiono, Taylor HR, and the Aceh Study Group: Impact of vitamin A Supplementation on xerophthalmia: A randomized community trial. **Arch Ophthalmol** 106:218-222 1988.

Wittpenn JR, Natadisastra G, Mele L, Sommer A: Reproducibility of determining vitamin A status by impression cytology. **Ophthalmic Surgery** 19:559-561 1988.

Wittpenn JR, West KP, Keenum DG, Farazdaghi M, Humphrey J, Howard GR, and Sommer A: Training Manual: Assessment of vitamin A status by Impression Cytology. 1988.

West KP, Djunaedi E, Pandji A, Kusdiono, Tarwotjo I, Sommer A, and the Aceh Study Group: The influence of Vitamin A Supplementation on growth: A randomized community trial. **Am J Clin Nutr** 1987 (in press).

Sommer A: Avoidable blindness. **Australian and NZ J Ophthalmol** (in press).

Muhilal, Murdiana A, Azis I, Saidin S, Jahari AB, Karyadi D: Impact of vitamin a fortified MSG on vitamin A status: A controlled field trial. **Am J Clin Nutr** (in press). (ICEPO staff acknowledged).

Muhilal, Permeisih D, Idjradinata YR, Muherdiyantiningsih, Karyadi D: Impact of vitamin A fortified MSG on health, growth, and survival of children: A controlled field trial. **Am J Clin Nutr** (in press). (ICEPO staff acknowledged).

Zeger SL, Edelstein SL: Poisson regression with a surrogate X. An analysis of vitamin A and Indonesia Children's mortality. **Applied Statistics** (in press).

West KP, Howard GR, Sommer A: Vitamin A and Infection: Public Health Implications. **Annual Review of Nutrition** (in press)

Liang KY, Zeger SL: A class of logistic regression models for multivariate binary time series. **J Am Stat Assoc.** (in press). Johns Hopkins University, Dept. of Biostatistics, Tech Rep# 636

Sommer A: Calculating efficiency in the absence of placebo control. (submitted)

Lloyd-Puryear M, Humphrey JH, West KP, Aniol K, Mahoney F, Mahoney J, Keenum DG: Vitamin A deficiency and anemia among Micronesian children. (submitted to **Nutrition Research**)

Tarwotjo I, West KP Jr., Mele L, Nur S, Naurdrawati H, Kraushaav D, Tilden RL, and the Aceh Study Group: Determinants of community-based coverage: periodic vitamin A supplementation. **Am J Public Health** (in press).

11.2. Presentations

Dr. Sommer was the invited EV McCollum lecturer at the FASEB annual meeting, May 1988, Las Vegas. Lecture title: "New Imperatives for an old vitamin (A)."

Dr. Sommer organized and moderated the Martin J. Forman Memorial Lecture at the annual NCIH meeting, May, 1988. The invited lecturer was Professor Ramalingusiakenie.

Two Worldnet United States Information Agency broadcasts were given on Vitamin A and Child Survival. On June 28, 1988, Dr. West presented a seminar with Mr. Bradshaw Langmaid, Deputy Assistant Administrator for Research, Bureau for S&T, USAID with 2-way interlocation in Abidjan, Brazzaville, Liberville, and Niamey and listening pools in 42 countries on July 14, 1988. Dr. Sommer presented with Dr. Nyle Brady, Sr. Assistant Administrator of the Bureau for S&T, USAID, with 2-way interlocution in Monrovia and Lagos, with listening posts in 78 cities throughout the world (see Appendices M and N).

Dr. Sommer participated in a Joint WHO and Task Force Sight and Life Press Conference on May 10, 1988 with a

presentation: "Imperatives for Control of Vitamin A Deficiency" (see Appendix O).

Dr. Sommer gave a foreign press briefing organized by USAID at the Foreign Press Club with John Palmer, executive director of Helen Keller International on February 18, 1988. The briefing focussed on the impact of vitamin A fortification and supplementation programs on child survival. The briefing took place in Washington on February 18. About a dozen foreign press representatives attended the briefing and the transcript was widely distributed through USAID channels.

Dr. Sommer participated in a Manoff-sponsored Voice of American Africa interview. The interview was broadcast in French & English during the first week of February to an estimated listening audience of 20-30 million.

Dr. Keith West gave several presentations on vitamin A deficiency and child survival. Majuro Hospital nursing and medical staffs:

Marshall Islands (July 14, 1988).

Truk Hospital staff

Moen, Truk, FSM (July 17, 1988).

National Institute for Cholera and Enteric Diseases. Calcutta, India (July 22. 1988).

ARVO lectures; May, 1988, Sarasota, Florida

Dr. Richard Semba: "The detection of goblet cell mucin using lectins in patients with mild vitamin A deficiency."

Lisa Mele: Epidemiologic characteristics of xerophthalmia: A case-control analysis.

Dr. John Wittpenn (former ICEPO staff): Vitamin A supplementation: duration of protection as measured by impression cytology (work done while at ICEPO).

Dr. Sommer gave a press conference with Anthony Gambino and the Office of Nutrition sponsored by International Trade and Development Education Foundation in Washington, D.C.

Dr. Sommer presented twice before Congress at the request of Congressmen Tony Hall and Honorable Mickey Leland of House Committee on Hunger.

11.3. Meetings

IVACG, December 1987.

Addis Ababa, Ethiopian

Attended by Drs. Sommer and Tielsch, where they helped organize Ethiopian presentations, and presented their own.

Dr. Sommer, as a member of the IVACG Steering Committee, attended multiple meetings during the reporting period in Washington D.C., London England, and Rome, Italy.

12.0. Staff Travel Summary

Staff:	Dr. James Tielsch
Country:	Ethiopia
Date:	December, 87
Purpose:	Attend IVACG Annual Meeting.

Staff:	Dr. Alfred Sommer
Country:	Ethiopia
Date:	December, 87
Purpose:	Attend IVACG Annual Meeting and continue to lay plans for hospital-based treatment trial and community-based mortality project.

Staff:	Dr. Keith West, Jr.
Country:	Nepal
Date:	February - March, 1988
Purpose:	Planning and signing a Memorandum of Agreement for Vitamin A Mortality Study.

Staff:	Dr. Keith West, Jr.
Country:	Bangladesh
Date:	March, 1988
Purpose:	Planning for vitamin A fortification of wheat trial; provision of technical assistance

Staff:	Dr. Alfred Sommer
Country:	Kenya
Date:	June, 1988
Purpose:	Technical assistance to Kenyan Pediatric Association

Staff:	Dr. Alfred Sommer
Country:	Ethiopia
Date:	June - July, 1988
Purpose:	Planning for vitamin A population-based mortality study and hospital-based treatment trial.
Staff:	Jean Humphrey
Country:	Ethiopia
Date:	June - July, 1988
Purpose:	Planning for vitamin A population-based mortality study and hospital-based treatment trial.
Staff:	Joanne Katz, M.S.
Country:	Nepal
Date:	July - August, 1988
Purpose:	Planning for Vitamin A Mortality Study
Staff:	Dr. Keith West, Jr.
Country:	Micronesia
Date:	July 13 - 15, 1988
Purpose:	Technical assistance to Truk Hospital, FSM and Majuro Hospital, Marshall Island on vitamin A morbidity and surveillance trials.
Staff:	Dr. Keith West, Jr.
Country:	India
Date:	July 21 - 23, 1988
Purpose:	Technical assistance to National Institute for Cholera and Enteric Diseases and Child in Need Institute.

13.0. Vitamin A Program Staff

Professional

Helen Abbey, Sc.D. Biostatistician/Professor

Joseph Canner, B.S. Computer Systems Analyst/Programmer/Analyst

Jean Humphrey, R.D., M.S.P.H. Nutritionist/Research Associate

Joanne Katz, M.S. Biostatistician/Assistant Professor

Deborah Keenum, M.A. Research Assistant

Lisa Mele M.S. Epidemiologist/Research Associate

Agatha Rider Biochemist (retired consultant)

Richard Semba, M.D. Ophthalmologist/Fellow in Preventive Ophthalmology

Alfred Sommer, M.D., M.H.S. Ophthalmologist/Epidemiologist Professor and Center Director

Hugh R. Taylor, M.D. Ophthalmologist/Epidemiologist Associate professor and Center Associate Director

James M. Tielsch, Ph.D. Epidemiologist/Assistant Professor

Keith P. West, Jr., Dr. P.H., R.D. Nutritionist/Assistant Professor and Vitamin A Program Director

Support Staff

Diane Carter, Secretary

Margot Emmett, Secretary

Dawn Follin, Purchasing Assistant

Sharon Lee, Secretary

Rhonda Skinner, Secretary

14.0. Manoff International Subcontract

Please see the biannual report of Manoff International, inc.: Social Marketing of Vitamin A, Biannual Report, September 15, 1987 - March 15, 1988.

15.0. Budgetary Expenditures

(total contract expenditures for period June 1, 1985 - September 30, 1988)

DESCRIPTION	06/01/85 to 09/30/88 AMOUNT
Salaries and Benefits	$1,457,304
Equipment, Supplies, Furnishings (Microvax System and Xerox Machine)	$355,651
Delivery and Postage	$9,484
In-Country Project Costs	$689,552
Subcontracts	$500,000
Printing and Publications	$13,174
Consultants	$12,388
Travel	$235,066
Telephone/Telegraph	$19,301
Computer Charges	$268,699
Indirect Costs	$723,622
	$4,284,241

APPENDIX A

Djunaedi E, Sommer A, Pandji A, Kusdiono, Taylor H, and the Aceh Study Group: Impact of vitamin A supplementation on xerophthalmia: A randomized controlled community trial. **Arch Ophthalmol** 106:218-222 1988.

Reprinted from the Archives of Ophthalmology
February 1988, Volume 106

Impact of Vitamin A Supplementation on Xerophthalmia

A Randomized Controlled Community Trial

Edi Djunaedi, MD; Alfred Sommer, MD; Akbar Pandji, MD; Kusdiono, MD; Hugh R. Taylor, MD; the Aceh Study Group

• **The value of biannual distribution of 200 000 IU of vitamin A in preventing xerophthalmia was assessed in a randomized, controlled community-based trial involving 25 000 preschool children in 450 villages of northern Sumatra. Results indicate that distribution was associated with a dramatic decline in xerophthalmia prevalence; that concurrent controls were critical for distinguishing spontaneous from program-related changes; and that the apparent level of benefit depended on the choice of clinical indicator(s). Night blindness ceases to be an accurate reflection of impact when prevalence rates are low, and comparison of Bitot's spot rates should be confined to new cases of disease.**

(*Arch Ophthalmol* 1988;106:218-222)

Vitamin A deficiency remains a major cause of morbidity and mortality throughout the developing world.[1-4] An estimated 5 million children develop xerophthalmia in Asia yearly—with a quarter million becoming blind.[5,6] Estimates for Africa are less reliable although xerophthalmia alone, or in association with measles, is clearly a major cause of childhood blindness.[7-9]

Periodic administration of massive doses of vitamin A, typically 200 000 IU every six months, remains the most popular, widely implemented means of controlling xerophthalmia.[10,11] Data indicating the effectiveness of this approach are limited to uncontrolled observations,[12] follow-up of treated patients,[6] a small-scale study of thrice-yearly distribution in a single village,[13] an unpublished report of biannual distribution in four villages,[14] and an imaginative attempt to use retrospective analyses to assess a nationwide program.[15,16] The latter study, which inferred that Bangladesh's nationwide program had limited value because the prevalence of Bitot's spots was unrelated to mass-dose vitamin A coverage and xerophthalmia rates were still greater than World Health Organization standards, was hampered by the problems of recall, selection bias, the ecologic fallacy of assuming areas with high and low coverage had similar, inherent baseline risks of xerophthalmia, and the inability to distinguish between new and old (persistent and recurrent) cases of Bitot's spots. A small-scale comparative study of alternative intervention strategies in the Philippines concluded that mass dosing was largely ineffective.[17]

We report herein the first (to our knowledge) large-scale randomized controlled community trial of the efficacy of biannual mass-dose vitamin A prophylaxis in reducing the risk of subsequent xerophthalmia. Results indicate significant benefit, a direct relationship between participation and response, and the importance of prospective, concurrently controlled evaluation and careful choice of clinical indicators.

SUBJECTS AND METHODS

The background and methods have been detailed previously.[3] Continued editing and "cleaning" have resulted in a modest increase in the proportion of subjects with complete records. In summary the study was carried out in 450 villages of northern Sumatra that were randomized to either begin a mass-dose distribution program shortly following baseline examination (program villages, n = 229) or one year later (control villages, n = 221). Health center personnel throughout the study area were instructed in the diagnosis and treatment of xerophthalmia, so the government could compare the effects of "universal" provision to all village children (UNIVAC) with those of "targeted" delivery to children presenting with active disease (TARVAC).

Two study teams, each consisting of an ophthalmologist (team leader), a nurse, an anthropometrist, a dietitian, five enumerators, and a driver, all fluent in the local dialect (Acehenese), visited each village in random order with no knowledge of their program allocation. Enumerators visited every house containing children 0 to 5 years of age; collected socioeconomic, demographic, and medical data; and escorted the children to a central point for their clinical examination. Dates of birth were ascertained by a "local events" calendar.

The ophthalmologist, who examined the children's eyes with a focused light and ×2 loupes, classified abnormalities according to standard diagnostic criteria.[18] Parents were carefully questioned about the pres-

Accepted for publication Oct 2, 1987.

From the Ministry of Health, Government of Indonesia, Jakarta (Drs Djunaedi, Pandji, and Kusdiono); the International Center for Epidemiologic and Preventive Ophthalmology, Dana Center of the Wilmer Institute and School of Hygiene and Public Health, The Johns Hopkins University, Baltimore (Drs Sommer and Taylor); and Helen Keller International, New York (Dr Sommer).

Reprint requests to the International Center for Epidemiologic and Preventive Ophthalmology, Wilmer 120, The Johns Hopkins Hospital, 600 N Wolfe St, Baltimore, MD 21205 (Dr Sommer).

ence of night blindness. A carefully elicited history of night blindness, the presence of Bitot's spots, and the two conditions together are closely correlated with serum vitamin A levels.[19]

All children with xerophthalmia were treated with a large dose of vitamin A and referred to the local health center. Baseline examinations were conducted between September 1982 and August 1983. Follow-up visits were made by the same team in the same sequence nine to 13 months later.

Following baseline examination, the government nutrition service trained a local village volunteer to administer standard capsules supplied by the United Nations Children's Fund (200 000 IU of vitamin A and 40 IU of vitamin E) to every child 1 to 5 years of age by snipping off the capsule's nipple and expressing the contents directly into the child's mouth. Initial distribution took place one to three months following baseline examination; the second distribution took place six to eight months later. The local volunteers were neither trained nor encouraged to carry out other health promotion activities. A special distribution monitor visited each village two to four weeks after the scheduled distribution and interviewed 10% of eligible households. If coverage was less than 80%, the local distributor was encouraged to reach children previously missed.

All data were collected on precoded forms, entered onto diskettes, and shipped to the data management facility at the International Center for Epidemiologic and Preventive Ophthalmology, Baltimore, where the information was processed with the Scientific Information Retrieval (SIR) data management package run on a computer (IBM 4341). Statistical analyses utilized SIR, SAS, SPSS, and GLIM software. Tests for significance and construction of confidence intervals were adjusted for clustering (design effect) associated with randomization by village rather than by individual.[3]

All study procedures were approved by a steering committee consisting of representatives from the Indonesian Center for Nutrition Research, the Directorate of Community Health Services, provincial health authorities, The Johns Hopkins University, Baltimore, and Helen Keller International, New York. All children, regardless of village allocation, received a vitamin A capsule at the concluding examination.

At the baseline examination, 29 493 preschool-age children were enumerated. Follow-up information was available on 26 268, representing 89.3% of those from program (UNIVAC) villages and 88.9% from control (TARVAC) villages. The age and sex distribution of children lacking follow-up information was identical in the two groups.

RESULTS

Details of the initial ocular examination are available on 96% of the cohort of UNIVAC and 95% of

Table 1.—Age-Specific Xerophthalmia Rates at Baseline Examination*

Age, mo	Program (UNIVAC) Villages			Control (TARVAC) Villages		
	No. of Children	XN, No. (%)	X1B, No. (%)	No. of Children	XN, No. (%)	X1B, No. (%)
0-11	1992	0 (0.00)	1 (0.05)	1875	0 (0.00)	3 (0.16)
12-23	1946	5 (0.26)	7 (0.36)	1895	6 (0.32)	10 (0.53)
24-35	2107	31 (1.47)	27 (1.28)	2041	25 (1.22)	21 (1.03)
36-47	2268	31 (1.37)	35 (1.54)	2026	47 (2.32)	44 (2.17)
48-59	1892	30 (1.59)	24 (1.27)	1725	33 (1.91)	41 (2.38)
60+	2720	42 (1.54)	49 (1.80)	2483	42 (1.69)	46 (1.85)
Total†	12 928	139 (1.08)	143 (1.11)	12 058	153 (1.27)	165 (1.37)

*XN indicates history of night blindness; X1B, presence of Bitot's spots as independent criteria.
†Includes three UNIVAC (universal distribution program) and 13 TARVAC (targeted distribution program) children whose ages were unknown.

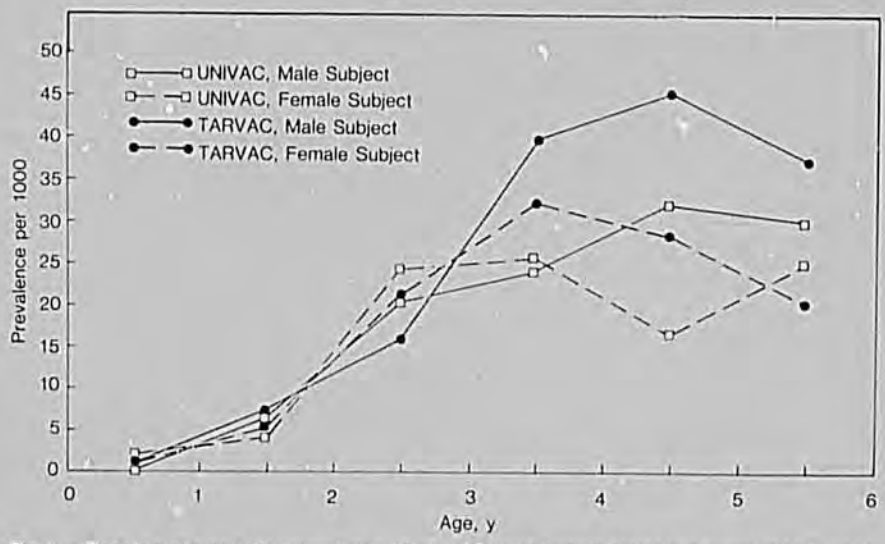


Fig 1.—Baseline age-specific prevalence of active xerophthalmia (night blindness, Bitot's spots, and/or corneal ulceration) among preschool children in UNIVAC (universal distribution program) and TARVAC (targeted distribution program) villages, Aceh, Indonesia.

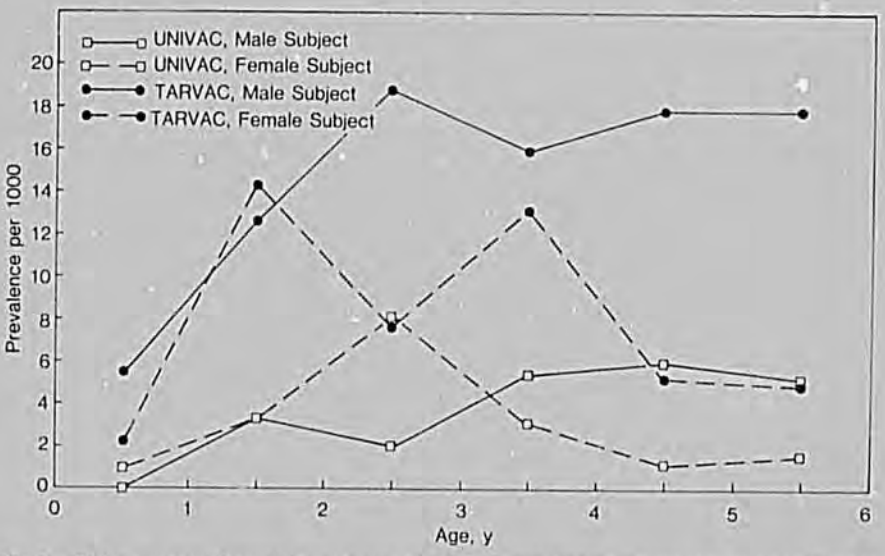


Fig 2.—Follow-up prevalence of new cases of active xerophthalmia among preschool children in UNIVAC (universal distribution program) and TARVAC (targeted distribution program) villages, Aceh, Indonesia. Age is same at baseline examination.

Table 2.—Age-Specific Rate of New Cases of Xerophthalmia at Follow-up Examination*

Age, mo	Program (UNIVAC) Villages			Control (TARVAC) Villages		
	No. of Children	XN, No. (%)	X1B, No. (%)	No. of Children	XN, No. (%)	X1B, No. (%)
0-11	1990	1 (0.05)	0 (0.00)	1887	3 (0.16)	4 (0.21)
12-23	1903	6 (0.32)	3 (0.16)	1874	17 (0.91)	14 (0.75)
24-35	2027	7 (0.35)	2 (0.10)	1990	21 (1.06)	6 (0.30)
36-47	2203	5 (0.23)	3 (0.14)	1996	16 (0.80)	17 (0.85)
48-59	1830	4 (0.22)	2 (0.11)	1672	11 (0.66)	8 (0.48)
60+	2635	4 (0.15)	3 (0.11)	2384	15 (0.63)	10 (0.42)
Total†	12591	27 (0.21)	13 (0.10)	11818	83 (0.70)	59 (0.50)

*XN indicates history of night blindness; X1B, presence of Bitot's spots as independent criteria. Excludes 386 children with xerophthalmia and/or vitamin A receipt at baseline examination.

†Includes three UNIVAC (universal distribution program) and 15 TARVAC (targeted distribution program) children whose ages were unknown.

Table 3.—Relative Risk (RR) of Xerophthalmia*

	Baseline		New Cases at Follow-up	
	RR	$CL_{95\%}$†	RR	$CL_{95\%}$†
XN	1.2	(0.8, 1.8)	3.3	(1.9, 5.7)
X1B	1.2	(0.8, 1.9)	5.0	(2.3, 10.9)
XN, X1B, X3	1.2	(0.8, 1.7)	3.3	(2.2, 5.0)

*Prevalence rate in TARVAC (targeted distribution program) villages divided by prevalence rate in UNIVAC (universal distribution program) villages. XN indicates night blindness; X1B, Bitot's spot as independent criteria; X3, xerophthalmic ulceration; XN, X1B, X3, as mutually exclusive criteria.

†Confidence limits (CL) adjusted for design effect calculated by applying poisson regression with extrapoisson variation to account for natural variability in xerophthalmia rates among villages. The design effect at baseline was conservatively estimated at 3.5, and at follow-up (of new cases) at 1.4.

Table 4.—Prevalence of Bitot's Spots (X1B) at Follow-up in Relation to Bitot's Spot Status at Baseline*

	No Bitot's Spot at Baseline		Bitot's Spot at Baseline	
	No. of Children	X1B, No. (%)	No. of Children	X1B, No. (%)
UNIVAC villages	12277	15 (0.12)	140	20 (14.3)
TARVAC villages	11342	55 (0.48)	160	20 (12.5)

*Results limited to children examined both at baseline and follow-up. UNIVAC indicates universal distribution program of vitamin A; TARVAC, targeted distribution program.

TARVAC children, 12928 and 12058, respectively. The age-specific prevalence of night blindness and of Bitot's spots was similar, rising rapidly from the first to third years of life (Table 1). There were only four cases of xerophthalmic ulceration among UNIVAC children and three among TARVAC children. The rate of active xerophthalmia (night blindness, Bitot's spots, and/or xerophthalmic ulceration as mutually exclusive criteria) was higher among TARVAC than UNIVAC children at baseline, 2.14% vs 1.81%, respectively ($P < .05$). Excess xerophthalmia in control villages was confined to older children, predominantly boys (Fig 1).

Excluding children who received vitamin A at the baseline examination, 93.2% of UNIVAC children reportedly received at least one capsule and 78.1% two capsules from village distributors.[3] Only 1.1% of TARVAC children of the same age reportedly received any capsules and 0.2% received two capsules, presumably when presenting to health centers with active xerophthalmia. A larger proportion of infants in UNIVAC villages received capsules than were eligible under government guidelines: 82.4% received at least one capsule and 61.8% received two capsules, vs 1.1% and 0.1% in TARVAC villages.[3] Coverage rates in UNIVAC villages, therefore, reached target levels.

Ninety-six percent of UNIVAC and TARVAC study cohorts were examined at follow-up, one year later. The prevalence of new cases of active xerophthalmia (eg, among those free of xerophthalmia or receipt of vitamin A at baseline examination) was 0.33% (42/12588) in UNIVAC villages and 1.10% (130/11803) in TARVAC villages, a decline of 82% and 49%, respectively. Almost all the reduction in xerophthalmia prevalence occurred among the older age groups (Table 2, Fig 2), in whom baseline rates were highest to begin with.

The degree of impact varied with the clinical indicator. Between baseline and follow-up, the relative risk of night blindness in TARVAC vs UNIVAC villages increased from 1.2 to 3.3, while for Bitot's spots it increased from 1.2 to 5.0 (Table 3).

The follow-up prevalence rate of night blindness among all study children from UNIVAC villages, regardless of ocular status or treatment at baseline, was only 15% to 20% greater than the prevalence rate of new cases. The follow-up prevalence of Bitot's spots in UNIVAC villages, however, was almost 200% greater than the prevalence rate of new cases, reflecting the impact distribution had on new disease but not on the persistence or recurrence of Bitot's spots among children with previous disease. Bitot's spots were 30 to 100 times more frequent at follow-up among children with Bitot's spots at baseline than among children originally free of disease (Table 4).

COMMENT

The Aceh (Indonesia) study provides a unique opportunity for evaluating the effectiveness of periodic mass-dose vitamin A supplementation in reducing the risk of xerophthalmia. Being a large-scale, randomized, longitudinal, concurrently controlled trial, it avoids many of the limitations of earlier investigations, especially those employing indirect indicators of outcome.[20] It also permits comparison with conclusions that have been reached through retrospective and case-control analyses of point prevalence surveys. Coverage rates were comparable with those reported from other regions, although in usual practice these fall with succeeding distribution cycles.[10,11]

Baseline xerophthalmia rates were slightly (and not statistically) higher in TARVAC than UNIVAC villages. Prevalence rates rose rapidly during the first two to three years of life and were higher in boys, consistent with observations elsewhere.[6,7,16,20,21]

Prevalence rates at follow-up, one year later, were dramatically lower in both groups of villages, proving the

Table 5.—Prevalence of Xerophthalmia in Relation to Capsule Receipt

	Prevalence of Xerophthalmia (Night Blindness and Bitot's Spots)			
	Bangladesh[15,16]		Present Study	
	Capsule Not Received	Capsule* Received	Capsule Not Received	Capsule† Received
XN, No. (%)	... (4.4)	... (2.6)	4/656 (0.61)	22/9484 (0.23)
Relative risk	1.9	1	2.7	1
X1B, No. (%)	... (9.8)	... (8.2)	1/656 (0.15)	11/9484 (0.12)
Relative risk	1.3	1	1.3	1

*History of capsule receipt within the past six months.
†History of receiving one or more capsules during the past ten months.

necessity of concurrent controls for accurate quantification of programmatic impact. Overall, the prevalence in TARVAC villages fell by 49%. This "spontaneous" decline is probably attributable, in part, to the following: historical trends (baseline rates in Aceh were lower than recorded only three years previously,[6] a similar phenomenon being noted throughout many areas of Indonesia [Robert Tilden, MPH, and Dr Muhilal, PhD, oral communication, October 1982]); treatment of (high-risk) children with evidence of xerophthalmia at baseline examination; and the TARVAC approach of sensitizing health center staff to recognize and treat clinical diseases.

Rates did not decline among the youngest controls, presumably because the cohort had aged by one year. Those who had been in... ...ts at baseline, and therefore at low risk of xerophthalmia, were in an older, higher-risk category at follow-up.

The decline in prevalence rates in UNIVAC villages was even more dramatic and was present at every age. The apparent size of the decline and degree of impact depended on the clinical criterion. The prevalence of (new) cases of "active" xerophthalmia (night blindness, Bitot's spots, and/or corneal ulceration) in UNIVAC villages fell by 82% compared with the spontaneous fall in TARVAC villages of 49%. The relative risk of night blindness among TARVAC vs UNIVAC children rose from 1.2 at baseline to 3.3 at follow-up, a smaller change than for Bitot's spots (1.2 to 5.0). There may be a natural limit to the apparent reduction in night blindness rates detectable in routine surveys. Experience indicates that a properly elicited history of night blindness in endemically vitamin A-deficient populations can be a sensitive and specific index of vitamin A status.[6,19] As true prevalence declines, however, the positive predictive value (proportion of all positive histories that represents true cases) falls as well. It is also possible that we witnessed a shift in the severity curve to less prevalent as well as to milder expressions of deficiency.

Sinha and Bang[13] found that 100 000 IU of vitamin A every four months prevented development of Bitot's spots in children previously free of disease but that Bitot's spots recurred, despite prophylaxis, in children who had had Bitot's spots. It is likely that these cases represent localized areas of persistent epithelial metaplasia, largely unresponsive to vitamin A.[22,23] In this study, children with Bitot's spots at baseline had many times the rate of Bitot's spots at follow-up than did other children, despite receiving a therapeutic dose of vitamin A (200 000 IU) at baseline. The rate of recurrent or persistent Bitot's spots was identical in UNIVAC and TARVAC villages, indicating the importance of excluding such cases in evaluating program impact. This no doubt explains much of the apparent lack of program efficacy for Bitot's spots reported from Bangladesh.[16]

Intervention programs rarely have the luxury of recording baseline values, let alone randomized concurrently controlled data, against which their performance can be gauged. Ingenious indirect measures of impact have been suggested, most notably a flattening of the age-related rise in prevalence rates.[20] Such a change was noted in this study, moreso among UNIVAC than TARVAC villages. This finding provides support, in a different country and environment, for the value of this indirect indicator. By itself, however, it does not quantify the degree of improvement, since patterns of age-specified prevalence vary, nor does it permit attribution to the intervention itself.

Impact of capsule distribution in Bangladesh was assessed by comparing capsule receipt status with the presence of xerophthalmia in data from a countrywide prevalence survey.[15,16] Night blindness was only half as frequent among children reporting recent receipt of a vitamin A capsule. The difference in prevalence of Bitot's spots was much smaller. Interpretation of these results is complicated by the self-selection bias involved in choosing to accept a capsule. Those who participate in a program, by receiving a capsule, may differ in many ways (including intrinsic risk of xerophthalmia) from those who do not.[24] For similar reasons, 90% coverage will not necessarily result in an equivalent reduction in xerophthalmia rates: the 10% missed may contain a disproportionate share of all children at risk of disease. Retrospective case-control analyses in Bangladesh and this study yield comparable results (Table 5); in our study, however, the direct technique of comparing baseline with follow-up rates of disease for UNIVAC and TARVAC areas demonstrated that the real degree of programmatic impact was much greater.

In our study and the Bangladesh study[16] some children who reportedly recently received a capsule still had xerophthalmia. In part this may reflect reporting error, in part a residuum of disease in a subset of children with such severe contributory factors (diet, diarrhea, etc) that a single capsule once every six months is inadequate for prevention of (mild) xerophthalmia.[25]

Our study demonstrates that an enormous reduction in disease (82%) is consistent with apparently less dramatic results obtained through a variety of retrospective techniques, that almost half of this reduction may have been spontaneous, and that the choice of clinical indicators will determine, to varying degrees, the apparent level of benefit.

This study was unable to evaluate the effectiveness of periodic massive dosing in preventing corneal ulceration. The study area had been specifically selected for the high rate of active corneal xerophthalmia (night blindness, xerophthalmic ulceration) and xerophthalmic scarring recorded three years previously.[6] Fortunately for the population (and for reasons that remain obscure), the rates had fallen precipitously in the interim. Recent data from India[26] and indirect analyses from Bangladesh,[16] however, provide indirect evidence that high coverage rates may be associated with reduced risk of blindness.

Periodic massive-dose vitamin A supplementation is far from an ideal solution to the problem of vitamin A

deficiency and xerophthalmia. While the capsules are inexpensive, provision is costly and logistically difficult, coverage declines with the drop in enthusiasm accompanying successive rounds, and the children who need the capsule most are probably least likely to receive it.[10,16,24] It was begun as an "emergency, short-term" measure. Unfortunately it remains the predominant intervention strategy and will remain so until fortification and nutrition education take root. It is encouraging to have this additional assurance that mass dosing is effective. The insights provided by this attempt at measuring clinical impact should prove equally relevant to assessing the value of alternative intervention strategies.

This investigation was carried out under cooperative agreement DSAN-CA-0267 between the International Center for Epidemiologic and Preventive Ophthalmology and the Office of Nutrition, US Agency for International Development, State Department, Washington, DC, with additional financial support from Task Force Sight and Life of Hoffman-La Roche, Basel, Switzerland; P. T. Vicks, Indonesia; Ford Foundation, New York and Jakarta; United Nations Children's Fund; and the Asian Foundation for the Prevention of Blindness, Hong Kong.

The Aceh Study Group includes the following professional staff, apart from the authors: A. A. Loeden, MD, PhD; Keith P. West, Jr, Dr PH; Barbara Hawkins, MS; Ignatius Tarwotjo, MSC; Lisa Mele, MS; Robert Tilden, MPH; Daniel Kraushaar, Dr PH; and William Flumenbaum, MA.

References

1. Sommer A, Katz J, Tarwotjo I: Increased risk of respiratory disease and diarrhea in children with preexisting mild vitamin A deficiency. *Am J Clin Nutr* 1984;40:1090-1095.

2. Sommer A, Tarwotjo I, Hussaini G, et al: Increased mortality in mild vitamin A deficiency. *Lancet* 1983;2:585-588.

3. Sommer A, Tarwotjo I, Djunaedi E, et al: Impact of vitamin A supplementation on childhood mortality: A randomised controlled community trial. *Lancet* 1986;1:1169-1173.

4. Muhilal, Soekirman: Dimensi baru dampak program penanggulangan defisiensi vitamin A: Penurunan angka kaskitan dan kematian pada anaka balita. *J Indonesia Nutr Assoc* 1986;11:1-6.

5. Sommer A, Tarwotjo I, Hussaini G: Incidence, prevalence and scale of blinding malnutrition. *Lancet* 1981;1:1407-1408.

6. Sommer A: *Nutritional Blindness: Xerophthalmia and Keratomalacia.* New York, Oxford University Press Inc, 1982.

7. Tielsch J, West KP, Katz J, et al: Prevalence and severity of xerophthalmia in southern Malawi. *Am J Epidemiol* 1986;124:561-568.

8. Sauter JJM: *Xerophthalmia and Measles in Kenya.* Groningen, the Netherlands, Drukkerij Van Denderen, 1976.

9. Foster A, Sommer A: Corneal ulceration, measles and childhood blindness in Tanzania. *Br J Ophthalmol* 1987;71:331-343.

10. West KP Jr, Sommer A: *Periodic Large Oral Dose of Vitamin A for the Prevention of Vitamin A Deficiency and Xerophthalmia: A Summary of Experiences.* Washington, DC, IVACG Report, Nutrition Foundation, 1984.

11. Report of a Joint WHO/UNICEF/USAID/HKI/IVACG Meeting: *Control of Vitamin A Deficiency and Xerophthalmia.* Technical report series 672. Geneva, World Health Organization, 1982.

12. Swaminathan MC, Susheela TP, Thimmayamma BVS: Field prophylactic trial with a single annual oral massive dose of vitamin A. *Am J Clin Nutr* 1970;23:119-122.

13. Sinha DP, Bang FB: The effect of massive doses of vitamin A on the signs of vitamin A deficiency in preschool children. *Am J Clin Nutr* 1976;29:110-115.

14. Tarwotjo I, ten Doesschate J, Gunawan S, et al: *An Evaluation of the Vitamin A Deficiency Prevention Pilot Project in Indonesia.* New York, American Foundation for Overseas Blind, 1976.

15. Cohen N, Rahman H, Sprague J, et al: Prevalence and determinants of nutritional blindness in Bangladeshi children. *World Health Stat Q* 1985;38:317-330.

16. Cohen N, Rahman H, Mitra M, et al: Impact of massive doses of vitamin A on nutritional blindness in Bangladesh. *Am J Clin Nutr* 1987;45:970-976.

17. Solon F, Fernandez TL, Latham MC, et al: An evaluation of strategies to control vitamin A deficiency in the Philippines. *Am J Clin Nutr* 1979;32:1445-1453.

18. Sommer A: *Field Guide to the Detection and Control of Xerophthalmia,* ed 2. Geneva, World Health Organization, 1982.

19. Sommer A, Hussaini G, Muhilal, et al: History of night blindness: A simple tool for xerophthalmia screening. *Am J Clin Nutr* 1980;33:887-891.

20. Vijayaraghavan K, Naider AN, Rao NP, et al: A simple method to evaluate the massive dose vitamin A prophylaxis program in preschool children. *Am J Clin Nutr* 1975;29:1189-1193.

21. Brilliant LB, Pokhrel RP, Grasset NC, et al: Epidemiology of blindness in Nepal. *Bull WHO* 1985;63:375-386.

22. Sommer A, Emran N, Tjakrasudjatma S: Clinical characteristics of vitamin A responsive and nonresponsive Bitot's spots. *Am J Ophthalmol* 1980;90:160-171.

23. Sommer A, Green WR, Kenyon KR: Bitot's spots responsive and nonresponsive to vitamin A: Clinicopathologic correlations. *Arch Ophthalmol* 1981;99:2014-2027.

24. Tarwotjo I, Sommer A, West KP, et al: Influence of participation on mortality in a randomized trial of vitamin A prophylaxis. *Am J Clin Nutr* 1987;45:1466-1471.

25. Periera SM, Begum A: Failure of a massive dose of vitamin A to prevent deficiency. *Arch Dis Child* 1971;46:525-527.

26. Vijayaraghavan K, Sarma KVR, Rao NP, et al: Impact of massive doses of vitamin A on incidence of nutritional blindness. *Lancet* 1984;2:149-151.

Printed and Published in the United States of America

APPENDIX B

West KP Jr., Djunaedi E, Pandji A, Kusdiono, Tarwotjo I, Sommer A, and the Aceh Study Group: Vitamin A supplementation and growth: a randomized community trial. **Am J Clin Nutr** 48:1257-1264 1988.

Vitamin A supplementation and growth: a randomized community trial[1-4]

Keith P West, Jr, DrPH, RD; Edi Djunaedi, MD; Akbar Pandji, MD; Kusdiono, MD; Ignatius Tarwotjo, MS; Alfred Sommer, MD; and the Aceh Study Group

ABSTRACT A randomized community trial was carried out in Aceh, Indonesia, 1982–1984, to assess the impact of semiannual vitamin A (VA) supplementation (60 000 μg RE) on preschool child growth: 229 villages were randomized to VA program and 221 to control status. One thousand thirty-two program and 980 control children aged 1–5 y were assessed and followed for 12 mo. VA program males gained an additional ~110 g weight at age 2–3 y (NS), 190 g at age 4 y ($p < 0.05$), and 263 g at age 5 y over control males ($p < 0.01$). Arm circumference and muscle area expanded 2 mm ($p < 0.05$) and ~36 mm^2 ($p < 0.05$) more per year, respectively, from ages 3 to 5 y of age and more arm fat was retained at every age ($p < 0.05$ at 1 and 3 y) in VA males. There were no group differences in ponderal growth for females or in linear growth for either sex. VA supplementation may improve growth where endemic deficiency exists. *Am J Clin Nutr* 1988;48:1257–64.

KEY WORDS Vitamin A, growth, randomized trial, Indonesia

Introduction

Vitamin A has been known to be required for growth since its discovery in 1913 (1). Deceleration in weight gain is one of the earliest, most reliable events after acute withdrawal of vitamin A from the diet of young animals (2–4), attributed to losses in efficiency in food (5) and, specifically, protein (6) utilization. Prolonged deficiency exhausts circulating and hepatic levels of vitamin A causing complete cessation of growth (7) and subsequent weight loss accompanied by reductions in body fat (6, 8) and deranged protein metabolism (6, 8, 9). Resupplementation with vitamin A restores normal ponderal growth (10–12).

Considerable survey and clinic-based evidence link vitamin A deficiency and its ocular manifestations (xerophthalmia) to stunted linear growth (13–15) and wasting malnutrition (16) in young children though these relationships are not always consistent (17, 18). Cross-sectional survey and clinic-based data do not permit isolating a causal relationship from associations that vitamin A deficiency may share with other growth limiting factors such as protein-energy malnutrition.

Despite the prominence of vitamin A deficiency as the leading cause of blindness among children (14) and as a potentially major determinant of childhood morbidity (19) and mortality (20, 21) in developing countries, its putative role in child growth has been largely extrapolated from animal research. A randomized community trial was carried out in an area of endemic vitamin A deficiency in Indonesia to evaluate the impact of a semiannual vitamin A supplementation program on linear and ponderal growth of preschool children.

Subjects and methods

This growth study formed a part of a large intervention trial in the Province of Aceh, Sumatra, Indonesia, from September 1982 to August 1984 to investigate the impact of vitamin A

[1] From the International Center for Epidemiologic and Preventive Ophthalmology, the Dana Center of the Wilmer Institute, and the School of Hygiene and Public Health, the Johns Hopkins University, Baltimore, MD; the Directorate of Nutrition and National Center for Health Research and Development, Department of Health, Government of Indonesia, Jakarta; and Helen Keller International, New York, NY.

[2] The Aceh Study Group comprises (in addition to authors) Prof AA Loedin, Dr Iman Satibi, Sukarno Nur, Henny Nendrawati, Dr Robert Tilden, Lisa Mele, Dr Daniel Kraushaar, and Dr Hugh Taylor.

[3] Supported by Cooperative Agreement DAN 0045 between the International Center for Epidemiologic and Preventive Ophthalmology, the Johns Hopkins University, and the Office of Nutrition, Bureau for Science and Technology, United States Agency for International Development, with financial assistance from Task Force Sight and Life, PT Vicks, Ford Foundation, UNICEF, Mobil Oil Corporation, and the Asian Foundation for the Prevention of Blindness.

[4] Address reprint requests to KP West, Jr, ICEPO, Wilmer 120, The Johns Hopkins Hospital, 600 N Wolfe St, Baltimore, MD 21205.

Received September 3, 1987.

Accepted for publication January 5, 1988.

supplementation on preschool child health and mortality (21). Briefly, 450 communities in two districts were randomly allocated to vitamin A program (n = 229) and control (n = 221) status. Two ophthalmic field teams, each including an anthropometrist, underwent a 2-mo period of training and standardization before start-up with periodic retraining throughout the 2 y of field work.

At base line ~25 000 children aged 1–5 y were enumerated, interviewed, and examined in study villages. Children with xerophthalmia, acute malnutrition, or other high-risk, morbid conditions were treated with a 60 000-μg RE (200 000 IU) vitamin A capsule (with a second dosage given to parents for the next day as indicated) and referred to local health centers. A systematic subsample of 3283 children presenting to village central sites were selected for anthropometric assessment. Equally distributed between groups were 517 children who had been given vitamin A either for treatment or prophylaxis by the teams at base line and were excluded, leaving 2766 children for growth assessment. After baseline the Government of Indonesia began six-monthly distribution of 60 000-μg RE vitamin A capsules (with 40 mg α-tocopherol equivalents added, UNICEF, Copenhagen) to children aged 1–5 y in program villages as recommended by the World Health Organization (22). Twelve months after base line (two capsule-distribution cycles later), villages in both groups were revisited by the same teams, 22 150 study children (now aged 2–6 y) were reenumerated and examined and parents or guardians were questioned about vitamin A receipt by their children during the previous year.

Follow-up data were complete for 2012 of the 2766 children (72.7%) in the base-line growth-assessment sample (representing 9% of the trial cohort). This number differs slightly from that reported earlier (23) because of the final exclusion of children in both groups who received vitamin A by the teams at base line. Seventeen children (0.6%) died during the interim (7 in the vitamin A group, 10 in the control group), allocation status was indeterminant for 19 (0.7%), sex was unknown for 66 (2.4%), and 652 (23.6%) were missing follow-up anthropometry. At base line children in this last group were nearly identical for age, sex, nutritional status, recent morbidity, household socioeconomic and educational characteristics, and treatment allocation to those followed, suggesting that both groups represented the same underlying population.

Weight of naked or lightly clad children was measured on a suspended Salter spring scale (Salter Industrial Measurement Ltd, West Bromwich, UK) and read to the nearest 0.1 kg after the pointer was completely still for at least 2–3 s. All remaining measurements were independently taken at least three times and their mean was recorded as the observed value. Recumbent length and standing height were measured to the nearest 1 mm at both surveys for children aged < 2 and 2–5 y, respectively, at base line with a portable wooden board (Perspective Enterprises, Kalamazoo, MI) structurally reinforced for increased instrument precision. Left midupper arm circumference was measured with the Zerfas insertion tape (24) at a premarked site half way between the acromion and olecranon processes and read to the nearest 1 mm. Triceps skinfold was measured with a Holtain caliper (Holtain, Ltd, Crosswell, Crymch, UK) and read to the nearest 0.1 mm 2–3 s after its application (25).

Both anthropometrists underwent initial training and standardization (by KPW) at the outset of the study (September 1982), midway through the base-line survey (March 1983) and at the outset of the follow-up survey (September 1983). Approximately 17, 20, and 13 children under age 6 y were available for each session, respectively. Each of the two workers measured the same children within a 15-min period and interworker variance (S^2) was computed by the following equation (26):

$$S^2 = \frac{\sum d^2}{2N} \quad (1)$$

where d^2 equals the component sums of squares associated with replication and N equals the number of children. Estimates of interobserver (technical) error, expressed as a standard deviation, decreased over time with each session: from 7.1 to 4.2 mm for length, 5.3 to 3.0 mm for height, 90 to 20 g for weight, 4.2 to 1.1 mm for arm circumference, and 0.66 to 0.29 mm for triceps skinfold. Intraobserver error was not estimated although this generally tends to be less than that observed between workers (27).

Height (or length), weight, and age data were used with the National Center for Health Statistics (NCHS) reference population (28) to compute percent weight for height (% WH) and height for age (% HA) to reflect levels of wasting and stunting malnutrition, respectively. Arm circumference (AC) and triceps skinfold (TS) measurements were used to derive (in mm^2) the transverse arm (AA), muscle (plus humoral bone) (MA), and fat areas (FA) as estimators of body composition by the following standard formulae (29):

$$AA = AC^2/4\pi \quad (2)$$

$$MA = (AC - \pi TS)^2/4\pi \quad (3)$$

$$FA = AA - MA \quad (4)$$

Although the median follow-up interval for children in both groups was 52 wk (interquartile range, 50–53 wk), all measured growth increment data were annualized by dividing the measured increment by the actual follow-up interval (days) multiplied by 365.

Categorical analyses for differences between groups were based on the chi-square test. Statistical significance of differences in growth between 1-y age groups was assessed by the Student's t test. Least-squares multiple linear regression was used to estimate the vitamin A program effect simultaneously adjusting for minor imbalances in selected base-line characteristics. All analyses were performed using SAS (Statistical Analysis System, Cary, NC).

Study procedures were approved by a steering committee comprising representatives of the National Department of Health and the Provincial Department of Health in Indonesia, the Johns Hopkins University, and Helen Keller International.

Results

Comparability between randomized groups

Age distributions of children in the vitamin A program and control villages were similar (Table 1). Both displayed smaller proportions of children at younger ages and the largest proportion in the sixth year of age. This variation appears to reflect difficulties in gaining access to younger children in this culture for anthropometric measurement and in ascertaining ages of older children in the absence of reliable birth date information (eg, reflecting 5-y digit preference). Both allocation groups were evenly divided by sex with males accounting for 54% and females 46% of study children.

TABLE 1
Age distribution by program allocation, Aceh 1982–84*

Age at baseline	Vitamin A		Control	
y	n	%	n	%
1	182	17.6	171	17.4
2	157	15.2	181	18.5
3	236	22.9	215	21.9
4	208	20.2	170	17.4
5	249	24.1	243	24.8
All ages	1032	100.0	980	100.0

* $\chi^2 = 5.58$ (4 df), $p > 0.2$.

Base-line nutritional status was nearly identical in both groups at each age. Sex-specific comparisons revealed no differences in percent weight for height (Fig 1) or in height for age (Fig 2) except that control males appeared slightly shorter (0.4–1.0% HA) at each age than did vitamin A-program males (female data not shown). No single age difference was statistically significant ($p > 0.1$). Distributions of other nutritional measures (AC, TS, MA, and FA) in age-sex allocation groups were virtually superimposed. Approximately 62% of all 1-y-old children were still breast-feeding irrespective of sex and allocation; the percentage declined rapidly to 5% in the third year of life. In both groups, ~49% reported having a fever during the previous week, 34% a cough, and 8% diarrhea (four or more loose stools/d). These data suggest both groups were comparable at base line in nutritional and health status.

Approximately 92% of all program children reportedly received at least one and 78% received two vitamin A capsules during the year compared to 2% and 1%, respectively, of control village children (likely representing treatment at local health centers).

Vitamin A impact on growth

Males. There were no significant differences in linear growth ($\Delta HT_A - \Delta HT_C$) at any age between vitamin A-program and control males (Table 2). Age-specific linear growth velocities decreased with age in both groups, ranging from ~82 ± 3 (SEM) mm/y for children 1 y to 55 ± 2 mm/y for children 5 y of age at base line (Fig 3A).

Differential ponderal growth ($\Delta WT_A - \Delta WT_C$) appeared at age 2–3 y when program males gained ~110 ± 85 (SED) g/y (unweighted) more than control males ($p > 0.1$). The program difference was greater for older children: 190 ± 78 g at age 4 ($p < 0.05$) and 263 ± 84 g at age 5 ($p < 0.01$) (Table 2). These latter differences represented increases of 6%, 14%, and 18%, respectively, over the weight gain of control males (Fig 3B).

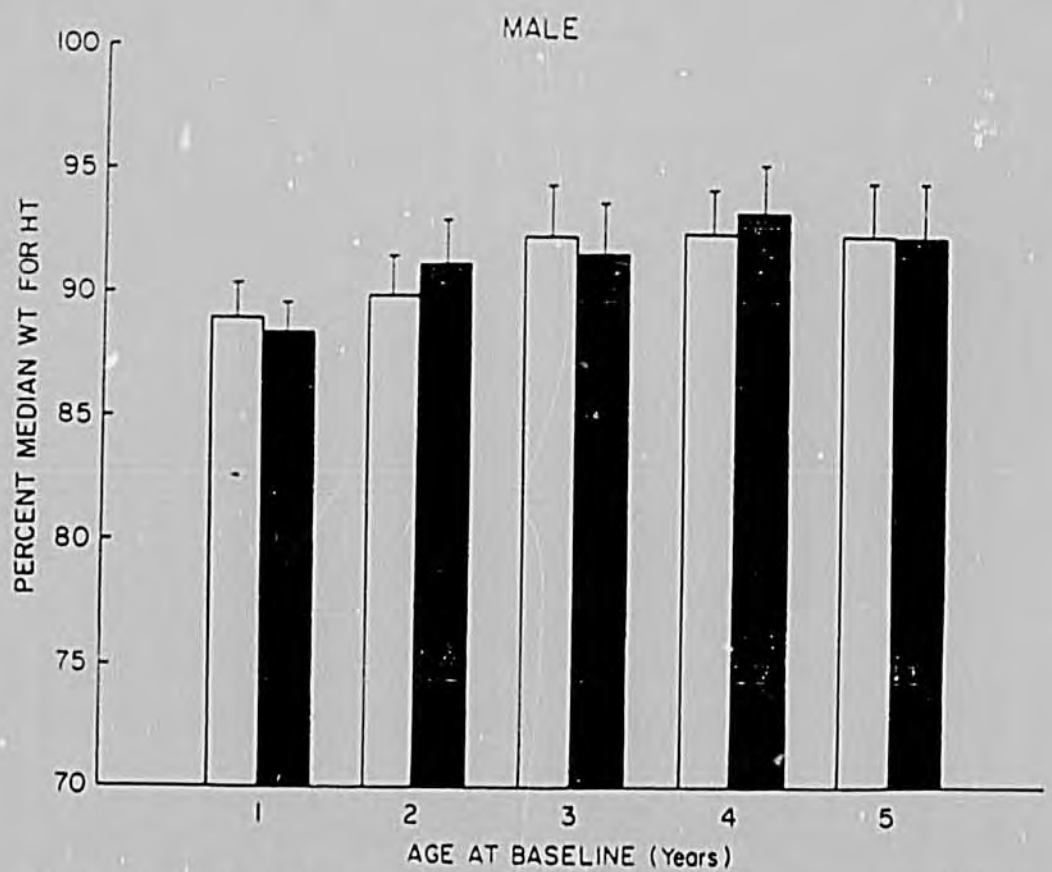


FIG 1. Percent of the NCHS median weight for height (±2 SEM) of Aceh males by allocation and age at base line. Open bars denote vitamin A-program and solid bars control children.

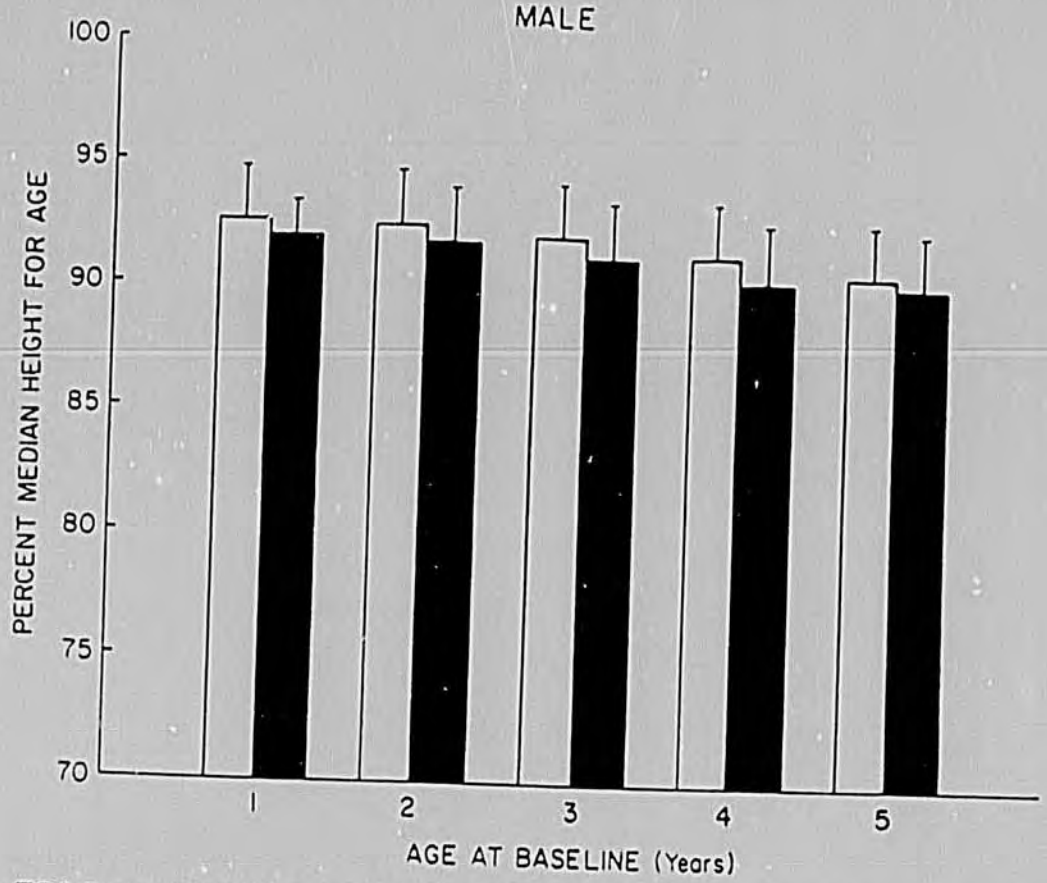


FIG 2. Percent of the NCHS median height for age (±2 SEM) of Aceh males by allocation and age at base line. Open bars denote vitamin A-program and solid bars control children.

A growth effect of vitamin A was also apparent from changes in upper arm indicators. Mean rates of arm circumferential growth were similar in both groups for children aged 1 and 2 y (5 to 6 ± 1 mm/y) but differed among older children (Fig 3C) with program males showing a consistent and statistically significant incremental gain

TABLE 2
Differences ($\bar{D}$) in age-specific annualized growth increments (Δ) between vitamin A-program and control males, Aceh, 1982–84

Age at base line	Number†		Growth measure*									
			$\Delta HT_A - \Delta HT_C$		$\Delta WT_A - \Delta WT_C$		$\Delta AC_A - \Delta AC_C$		$\Delta MA_A - \Delta MA_C$		$\Delta FA_A - \Delta FA_C$	
	A‡	C‡	$\bar{D}$	SED§	$\bar{D}$	SED	$\bar{D}$	SED	$\bar{D}$	SED	$\bar{D}$	SED
y			*mm/y*		*g/y*		*mm/y*		mm^2/y		mm^2/y	
1	94	91	2.8	3.5	−5	108	1.0	1.3	−12	20	31‖	15
2	90	106	2.2	2.7	120	96	0.0	1.0	−10	18	10	13
3	123	117	−0.6	1.9	99	73	2.4¶	0.9	30‖	15	26‖	12
4	113	87	2.0	1.9	190‖	78	2.0¶	0.8	36¶	15	11	13
5	139	126	0.2	2.1	263¶	84	2.5¶	0.8	42¶	15	19	12

* HT, recumbent length (age 1 y at base line) or standing height (≥ 2 y); WT, weight; AC, midupper arm circumference; MA, upper arm muscle area; FA, upper arm fat area.

† Represents maximum number. Up to two children missing data for several age-allocation-measurement specific groups except HT at ages 2 and 3 y for which 2–14 per group are missing data.

‡ A, vitamin A program; C, control.

§ SED, standard error of the difference between means.

‖ $p < 0.05$.

¶ $p < 0.01$.

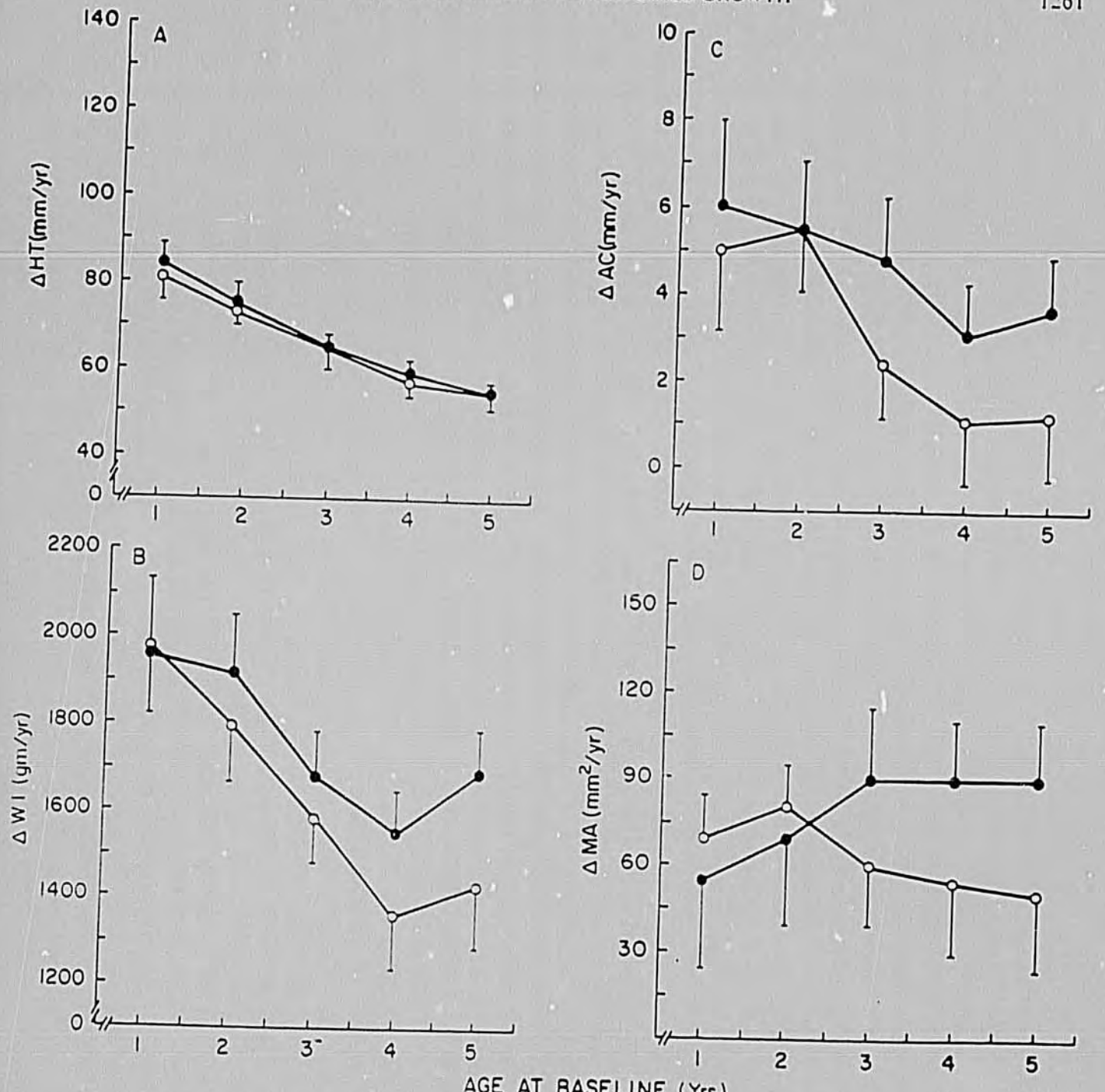


FIG 3. Age-specific annualized growth increments (±2 SEM) of vitamin A program (●) and control (○) males in Aceh, 1982–84: A, length or height (see methods) (ΔHT); B, weight (ΔWT); C, left midupper arm circumference (ΔAC); and D, muscle area (ΔMA).

of ~2 ± 1 mm/y ($p < 0.05$) (Table 2). Increased growth in muscle area ($\Delta MA_A - \Delta MA_C$) among vitamin A program males (30–42 mm²/y) partly accounted for this increment in arm mass (Table 2). Muscle area growth velocities in control males steadily declined from a high of 80 ± 13 mm²/y for 2-y-old males to 49 ± 12 mm²/y for 5-y-old males. In contrast, program males maintained an average annual growth of 90 ± 10 mm² from 3 through 5 y of age ($p < 0.05$) (Fig 3D). Vitamin A program males also retained a slight but consistent arm fat area ($\Delta FA_A - \Delta FA_C$) advantage over control males at each year of age ($p < 0.05$ only at ages 1 and 3 y) (Table 2).

When submitted to multiple-regression analyses, adjusting for the linear effects of minor imbalances in age

TABLE 3
Differences ($\bar{D}$) in age-specific annualized growth increments (Δ) between vitamin A-program and control females, Aceh, 1982–84

Age at base line	Number†		Growth measure*									
			$\Delta HT_A - \Delta HT_C$		$\Delta WT_A - \Delta WT_C$		$\Delta AC_A - \Delta AC_C$		$\Delta MA_A - \Delta MA_C$		$\Delta FA_A - \Delta FA_C$	
	A‡	C‡	$\bar{D}$	SED§	$\bar{D}$	SED	$\bar{D}$	SED	$\bar{D}$	SED	$\bar{D}$	SED
y			*mm/y*		*g/y*		*mm/y*		*mm²/y*		*mm²/y*	
1	88	80	−3.5	4.0	49	102	0.3	1.5	−21	20	−28	20
2	67	75	−0.4	3.6	144	110	2.6	1.5	36	23	27	20
3	113	98	−1.4	1.9	−132	86	−2.3‖	1.0	−38‖	17	−16	14
4	95	83	0.6	2.1	−41	82	0.5	0.9	−2	16	13	15
5	110	117	−0.1	1.9	−11	105	−0.5	0.9	−9	17	−5	13

* HT, recumbent length (age 1 y at base line) or standing height (≥ 2 y); WT, weight; AC, midupper arm circumference; MA, upper arm muscle area; FA, upper arm fat area.

† Represents maximum number. Up to three children missing data for each age-allocation-measurement specific groups except HT for which two to nine per group are missing data.

‡ A, vitamin A program; C, control.

§ SED, standard error of the difference between means.

‖ $p < 0.05$.

within 1-y strata, base-line nutritional status (% WH and % HA), and morbidity (fever, cough, diarrhea), the growth effects of vitamin A supplementation paralleled these bivariate estimates in terms of direction, size, spread, and statistical significance.

Females. Vitamin A supplementation appeared to have no positive impact on linear growth in females (Table 3). Control females grew slightly taller than vitamin A program females at ages 1–3 y ($p > 0.25$) with identical linear growth velocities at older ages. However, in contrast to males, there was also no discernable effect of the vitamin A program on ponderal growth (Table 3). Program females aged 1–2 y gained more weight whereas those aged 3–5 y gained less weight than did control females. No differences reached statistical significance. Growth in upper arm indicators were in general agreement with no consistent, statistically significant program effect from one age group to the next (Table 3). Multivariate adjustment for base-line age, nutritional status, and morbidity did not alter these results.

Discussion

Vitamin A supplementation selectively improved child growth: only the ponderal aspect and only in males after age 2 y. Several different anthropometric measures indicate the effect was stronger at older ages. Weight gain velocity at age 5 y in vitamin A-supplemented males approached 20% over that of control males. Changes in upper-arm fat and muscle areas suggest the increased body mass was due to a sustained advantage in lean body mass growth with greater subcutaneous adipose retention.

These sex-specific results are internally consistent with those from the larger mortality intervention trial that also found the greatest impact among boys. Overall mortality in vitamin A-program villages was reduced 34% (relative risk [RR] = 1.51) but the attributable reduction was 41% in males (RR = 1.69) vs 20% (RR = 1.25) in females (21). The base-line prevalence of active xerophthalmia was also higher in males (30), similar to that previously shown in Indonesia (14) as well as other vitamin A-deficient regions (31–33). In Peru, where vitamin A deficiency appears milder than in Asia, β-carotene (though not retinol) intake was retrospectively linked to attained weight and height but only in males (34).

Mechanisms that would mediate apparent sex differences remain unclear. Principal influences may be cultural in origin because of local differences in dietary vitamin A intake. Filipino male children were estimated to have an 800 IU lower daily intake of vitamin A than females had (35); in Bangladesh preschool males consumed 60 μg RE/d more than females consumed (36). A considerable body of animal research would suggest a metabolic basis underlying a sex difference in response to changes in vitamin A status. During experimental vitamin A depletion, male animals continue to gain weight (37–39) and exhaust liver stores (37) more rapidly than did females, which may predispose males to earlier deceleration in weight gain and exacerbation of xerophthalmia (5, 38–40). After adequate vitamin A repletion, weight gain responds more quickly in male than in female animals (3, 41). These observations suggest that a sex difference may exist in vitamin A storage or utilization quite possibly from differential rates of growth (38).

The absence of a growth effect among 1-y-old children may be related to breast-feeding, which generally continued into the second year of life. Breast milk constitutes a critical source of preformed vitamin A in the weanling diet (36). Presumably, poor vitamin A nutriture would not be growth limiting in the late weaning period or, with sufficient build-up of hepatic reserves, during the first several fully weaned months when total dietary vitamin A intake falls dramatically (36). Extended breast-feeding is associated with protection against mild xerophthalmia

(18, 33, 42) and may, therefore, also protect younger children from poor growth because of vitamin A deficiency. Notably, the stronger effect of vitamin A on growth in older children is consistent with the increased prevalence of xerophthalmia with age in this (30) and other preschool populations (13, 14, 17, 43). This age trend in clinical disease would imply a parallel rise in inapparent vitamin A deficiency as well. Recent studies in Indonesia suggest that 20–25% of older preschool children (3–5 y of age) may harbor physiologically significant, subclinical vitamin A deficiency in regions where only 2–3% of children have xerophthalmia (44).

Semiannual vitamin A supplementation had no apparent effect on linear growth of children at any age for either sex. This was surprising given animal experiments demonstrating cessation of epiphyseal growth within long bones induced by vitamin A deficiency (45–47) and epidemiologic evidence linking mild xerophthalmia to stunted growth in both relatively nonwasted (13, 14, 21) and wasted (16) populations. This same cross-sectional relationship was apparent in Aceh with mildly xerophthalmic children (night blindness and Bitot's spots) across all ages exhibiting a slightly lower base-line height for age than the general population (89.7 vs 91.2%, respectively; $p < 0.001$).

One explanation for this apparent effect on weight but not height may be that mild vitamin A deficiency does not first limit linear growth under such conditions, implying that previous associations have been indirect. In population surveys (31, 48, 49) risk of xerophthalmia was found to be inversely related to socioeconomic status, similar to that frequently observed with protein-energy malnutrition (50). This reflects a close association between vitamin A deficiency and poverty, the latter providing the milieu in which repeated infections and multiple nutritional deficiencies act to stunt growth (36, 51).

Alternatively, milder (subclinical) vitamin A deficiency may limit linear growth but children need more frequent or longer supplementation (> 12 mo) to detect an effect. In marginally nourished children a large, oral dose of vitamin A (60 000 μg RE) appears to elevate serum retinol levels for only 2–3 mo before returning to low base-line or control values (reviewed in 52). Although such pulsing of vitamin A may accelerate ponderal growth, this rather short duration of increased peripheral nutrient availability may not be sufficient to induce more rapid skeletal growth. A recent field trial (53) in West Java, Indonesia, demonstrated increased linear growth in children receiving vitamin A-fortified monosodium glutamate (MSG) through normal market channels compared with children from adjacent control areas where regular MSG was consumed; this suggests that normal linear growth may require an acceptable daily intake of vitamin A over an extended period.

Finally, study conditions do not rule out the possibility that linear growth stunting is caused by more severe vitamin A deficiency. Examining physicians treated and excluded at base line children with xerophthalmia as well as those considered to be at high risk of deficiency (with infection or moderate to severe malnutrition). However, incident xerophthalmia that may have occurred during the year would not be expected to have significantly altered the growth results observed in this large sample of children.

The Aceh study, to our knowledge, provides the first direct test in a human population of the causality of vitamin A in growth. Many questions remain about the underlying mechanisms as well as the conditions that mediate this apparent effect. Analyses were performed on a programmatic, intent-to-treat basis (whether or not children actually received vitamin A at both cycles) because randomization was carried out at the village level. The observed effect may be conservative because nearly 10% of all children reported receiving no vitamin A supplement and > 20% received only one capsule during the interim. The findings suggest that vitamin A prophylaxis programs designed to control nutritional blindness may not only reduce xerophthalmia and mortality (21) but may also improve growth among preschool-aged children. ∎

We gratefully acknowledge Drs George G Graham, Frederick L Trowbridge, and Helen Abbey for their sustained guidance and Lisa Mele for compiling the data base.

References

1. McCollum EV, Davis M. The essential factors in the diet during growth. J Biol Chem 1915;23:231–54.
2. Orr JB, Richards MB. CLXXII. Growth and vitamin A deficiency. J Biochem 1934;28:1259–73.
3. Lamb AJ, Apiwatanaporn P, Olson JA. Induction of rapid, synchronous vitamin A deficiency in the rat. J Nutr 1974;104:1140–8.
4. Anzano MA, Lamb AJ, Olson JA. Growth, appetite, sequence of pathological signs and survival following the induction of rapid, synchronous vitamin A deficiency in the rat. J Nutr 1979;109:1419–31.
5. Mayer J, Krehl WA. Influence of vitamin A deficiency on the gross efficiency of growth and rats. Yale J Biol Med 1948;20:403–5.
6. Patterson JM, McHenry EW, Crandall WA. The physiological properties of vitamin A. Biochem J 1942;36:792–4.
7. Sherman BS. The effect of vitamin A on epithelial mitosis in vitro and in vivo. J Invest Dermatol 1961;37:469–80.
8. Brown EF, Morgan AF. The effect of vitamin A deficiency upon the nitrogen metabolism of the rat. J Nutr 1948;35:425–38.
9. Rechcigl M, Berger S, Loosli JK, Williams HH. Dietary protein and utilization of vitamin A. J Nutr 1962;76:435–40.
10. Baumann CA, Riising BM, Steenbock H. Fat soluble vitamins: XLII The absorption and storage of vitamin A in the rat. J Biol Chem 1934;107:705–15.
11. Lewis JM, Bodansky O, Falk KG, McGuire G. Vitamin A requirements in the rat: the relation of vitamin A intake to growth and to concentration of vitamin A in the blood plasma, liver and retina. J Nutr 1942;23:351–63.
12. Booth VH. Liver storage of vitamin A by male and female rats. J Nutr 1952;48:13–30.
13. Brink EW, Perera WDA, Broske SP, et al. Vitamin A status of children of Sri Lanka. Am J Clin Nutr 1979;32:84–91.
14. Sommer A. Nutritional blindness: xerophthalmia and keratomalacia. New York: Oxford University Press, 1982.
15. Santos LMP, Dricot JM, Asciutti LS, Dricot-d'Ans C. Xerophthal-

mia in the state of Paraiba, northeast of Brazil: clinical findings. Am J Clin Nutr 1983;38:139–44.
16. Cohen N, Measham C, Khanum S, et al. Xerophthalmia in urban Bangladesh. Acta Paediatr Scand 1983;72:531–6.
17. Tielsch JM, West KP Jr, Katz J, et al. Prevalence and severity of xerophthalmia in Southern Malawi. Am J Epidemiol 1986;124: 561–8.
18. West KP Jr, Chirambo M, Katz J, et al. Breast-feeding, weaning patterns, and the risk of xerophthalmia in Southern Malawi. Am J Clin Nutr 1986;44:690–7.
19. Sommer A, Katz J, Tarwotjo I. Increased risk of respiratory disease and diarrhea in children with preexisting mild vitamin A deficiency. Am J Clin Nutr 1984;40:1090–5.
20. Sommer A, Tarwotjo I, Hussaini G, Susanto D. Increased mortality in mild vitamin A deficiency. Lancet 1983;2:585–8.
21. Sommer A, Tarwotjo I, Djunaedi E, et al. Impact of vitamin A supplementation on childhood mortality: a randomized controlled community trial. Lancet 1986;1:1169–73.
22. Report of a Joint WHO/UNICEF/USAID/Helen Keller International/IVACG Meeting. Control of vitamin A deficiency and xerophthalmia. Geneva: World Health Organization, 1982. (WHO technical report series 672.)
23. Indonesia National Blindness Prevention Program. Impact of vitamin A capsule distribution program on xerophthalmia and mortality in Aceh Province, Indonesia 1982–84. Final Report. Jakarta: Ministry of Health, 1987.
24. Zerfas AJ. The insertion tape: a new circumference tape for use in nutritional assessment. Am J Clin Nutr 1975;28:782–7.
25. Tanner JM, Whitehouse RH. Revised standards for triceps and subscapsular skinfolds in British children. Arch Dis Child 1975;50: 142–5.
26. Martorell R, Habicht J-P, Yarbrough C, et al. The identification of evaluation of measurement variability in the anthropometry of preschool children. Am J Phys Anthrop 1975;43:347–52.
27. Gavin JA. The consistency of anthropometric measurements. Am J Phys Anthropol 1950;8:417–26.
28. Hamill PVV, Drizd TA, Johnson CL, et al. NCHS growth curves for children birth–18 years United States. Hyattsville, MD: National Center for Health Statistics November 1977. (DHEW publication [PHS] 78-1650.)
29. Frisancho AR. The norms of upper limb fat and muscle areas for assessment of nutritional status. Am J Clin Nutr 1981;34:2540–5.
30. Djunaedi E, Sommer A, Pandji A, et al. Impact of vitamin A supplementation on xerophthalmia: a randomized controlled community trial. Arch Ophthalmol 1988;106:218–22.
31. Brilliant LB, Pokhrel RP, Grasset NC, et al. Epidemiology of blindness in Nepal. Bull WHO 1985;63:375–86.
32. Cohen N, Rahman H, Spraque J, et al. Prevalences and determinants of nutritional blindness in Bangladeshi children. World Health Stat Q 1985;38:317–25.
33. De Sole G, Belay Y, Zegeye B. Vitamin A deficiency in southern Ethiopia. Am J Clin Nutr 1987;45:750–4.
34. Graham GG, Creed HM, MacLean WC, et al. Determinants of growth among poor children: nutrient intake-achieved growth relationships. Am J Clin Nutr 1981;34:539–54.
35. Solon FS, Popkin PM, Fernandez TL, Latham MC. Vitamin A deficiency in the Philippines: a study of xerophthalmia in Cebu. Am J Clin Nutr 1978;31:360–8.
36. Brown KH, Black RE, Becker S, et al. Consumption of foods and nutrients by weanlings in rural Bangladesh. Am J Clin Nutr 1982;36:878–88.
37. Brenner S, Brookes MCH, Roberts LJ. The relation of liver stores to the occurrence of early signs of vitamin A deficiency in the white rat. J Nutr 1942;23:459–71.
38. McLaren DS. Influence of protein deficiency and sex on the development of ocular lesions and survival time of the vitamin A-deficient rat. Br J Ophthalmol 1959;43:234–41.
39. McLaren DS, Tchaliar. M. Biochemical and hematologic changes in the vitamin A-deficient rat. Am J Clin Nutr 1965;17:131–8.
40. Bieri JG. Comments. Am J Clin Nutr 1969;22:1086–7.
41. Sherman HC, Campbell HL. Stabilizing influence of liberal intake of vitamin A. Proc Natl Acad Sci USA 1945;31:164–6.
42. Tarwotjo I, Sommer A, Soegiharto T, Susanto D, Muhilal. Dietary practices and xerophthalmia among Indonesian children. Am J Clin Nutr 1982;35:574–81.
43. Vijayaraghavan K, Naidu AN, Rao NP, Srikantia SG. A simple method to evaluate the massive dose vitamin A prophylaxis program in preschool children. Am J Clin Nutr 1975;28:1189–93.
44. Natadisastra G, Wittpenn JR, West KP Jr, et al. Impression cytology for detection of vitamin A deficiency. Arch Ophthalmol 1987;105:1224–8.
45. Wolbach SB. Vitamin A deficiency and excess in relation to skeletal growth. J Bone Joint Surg [Am] 1947;29:171–92.
46. Wolbach SB, Hegsted DM. Vitamin A deficiency in the chick: skeletal growth and the central nervous system. AMA Arch Pathol 1952;54:13–29.
47. Baume LJ. Differential response of condylar, epiphyseal, synchondrotic, and articular cartilages of the rat to varying levels of vitamin A. Am J Orthod 1970;58:537–51.
48. Cohen N, Jalil MA, Rahman H, et al. Landholding, wealth and risk of blinding malnutrition in rural Bangladeshi households. Soc Sci Med 1985;21:1269–72.
49. West KP Jr, Katz J, Mzembe C, et al. A survey method to assess fortifiable condiment use by rural households. Nutr Res 1986;6: 719–24.
50. Mason JB, Habicht JP, Tabatabai H, Valverde V. Nutrition surveillance. Geneva: World Health Organization, 1984.
51. Martorell R, Habicht JP, Yarbrough C, et al. Acute morbidity and physical growth in Guatemalan children. Am J Dis Child 1975;129:1296–301.
52. West KP Jr, Sommer A. Delivery of oral doses of vitamin A to prevent vitamin A deficiency and nutritional blindness. Food Rev Int 1985;1:355–418.
53. Muhilal, Permeisih D, Idjradinata YR, Muherdiyantiningsih, Karyadi D. Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial. Am J Clin Nutr 1988;48:1271–6.

APPENDIX C

Natadisastra G, Wittpenn J, West KP Jr., Muhilal, and Sommer A: Impression cytology for detection of vitamin A deficiency. **Arch Ophthalmol** 105:1224-1228 1987.

Reprinted from the Archives of Ophthalmology
September 1987, Volume 105

Impression Cytology for Detection of Vitamin A Deficiency

Gantira Natadisastra, MD; John R. Wittpenn, MD; Keith P. West, Jr, DPH, RD; Muhilal, PhD; Alfred Sommer, MD

• Vitamin A (retinol) deficiency causes blindness, increased morbidity, and mortality among preschool children in many developing nations. Previous studies suggest that impression cytology may represent the first simple, reliable test to detect mild xerophthalmia in young children. We used impression cytology to evaluate and follow up 75 Indonesian preschool children with mild xerophthalmia and an equal number of age-matched, clinically normal neighborhood controls. Results of impression cytology, which were closely correlated with baseline serum vitamin A levels, documented histologic improvement following treatment with vitamin A. Furthermore, results of impression cytology, where abnormal, improved to normal following vitamin A treatment in a significant percentage (23%) of otherwise clinically normal children. Impression cytology appears to detect clinical and physiologically significant preclinical vitamin A deficiency.

(*Arch Ophthalmol* 1987;105:1224-1228)

Accepted for publication May 21, 1987.

From the Cicendo Eye Hospital and University of Padjajaran, Bandung, Indonesia (Dr Natadisastra); the International Center for Epidemiologic and Preventive Ophthalmology, Dana Center of The Wilmer Institute and School of Hygiene and Public Health, The Johns Hopkins University, Baltimore (Drs Wittpenn, West, and Sommer); the Eye Research Institute of the Retina Foundation, Boston (Dr Wittpenn); and the Nutrition Research and Development Center, Bogor, Indonesia (Dr Muhilal).

Presented in part at the Annual Meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Fla, April 29, 1986.

Reprint requests to Wilmer 120, The Johns Hopkins Hospital, Baltimore, MD 21205 (Dr Sommer).

Xerophthalmia, or vitamin A (retinol) deficiency, is the major cause of childhood blindness in many developing countries.[1,2] Mild xerophthalmia (manifested by night blindness, conjunctival xerosis, and/or Bitot's spots) is associated with increased morbidity and mortality.[3-5] Vitamin A supplementation of nonxerophthalmic children reduces mortality, suggesting that subclinical vitamin A deficiency (ie, vitamin A deficiency without ocular manifestations of xerophthalmia) is also associated with increased mortality.[6] The need exists for a relatively simple, objective test of vitamin A status to identify communities in which vitamin A deficiency is prevalent and constitutes a public health problem. Previous studies demonstrated the ability of conjunctival impression cytology to distinguish between a small number of seemingly normal children and those with mild xerophthalmia.[7] We report herein the preliminary results of a much larger prospective, clinical trial correlating the results of conjunctival impression cytology with indexes of clinical and subclinical vitamin A deficiency.

SUBJECTS AND METHODS

The study was performed in central Java at the Cicendo Eye Hospital, Bandung, Indonesia. Children with mild xerophthalmia, ie, a history of night blindness or the presence of conjunctival xerosis with Bitot's spots, were identified in surrounding villages by a trained nurse. Whenever a case was identified, an age-matched control from the same village was also identified. All subjects (patients and controls) were brought to the hospital where they were examined by one of two ophthalmologists to confirm the presence of Bitot's spots in patients and normal eyes in controls. Participation in the study was limited to children aged 36 to 72 months. Seventy-five patients and 74 age-matched controls were identified.

A dietary and disease history was obtained from the parent or guardian of each child. After obtaining parental consent, each child underwent baseline evaluation consisting of an ocular examination, anthropometry, biochemical studies, and impression cytology. All ocular findings were drawn and photographed. Venous blood was obtained and promptly separated, and the serum frozen. Serum vitamin A was analyzed by high-performance liquid chromatography.[8]

Conjunctival impression cytology was performed on each patient using a previously described technique.[7] In summary, this technique consists of applying 5 × 5-mm pieces of cellulose acetate filter paper (HAWP 304F0, Millipore Corp, Bedford, Mass) to the nasal and temporal bulbar conjunctiva of each eye after application of topical 0.5% proparacaine hydrochloride. The filter paper was gently applied to the eye for 3 to 5 s and then removed with a peeling motion. The filter paper with the adherent epithelial cells was immediately placed in a fixative solution prepared by mixing 70% ethyl alcohol, 37% formaldehyde, and glacial acetic acid in a 20:1:1 volume ratio.

Specimens were collected separately from the nasal and temporal quadrants of each eye. After fixation, the specimens were stained with periodic acid-Schiff (PAS) and modified Papanicolaou's stain as described previously.[10] All impression cytologic specimens were examined in masked fashion and staged according to the degree of squamous metaplasia as previously described (Table 1).[8,10] Each child was assigned to the lowest stage (ie, the most normal) found among the four specimens (Fig 1).

All patients received at least 200 000 IU

of oral vitamin A within one week of collection of baseline specimens, as part of a concurrent therapeutic trial.

All children were reexamined one week after their baseline examination. All children then received a second capsule containing 200 000 IU of vitamin A. Follow-up ocular examinations with impression cytology were performed one week, two months, and six months after receiving the second capsule. One hundred twenty-one children (81% of the original sample) remained throughout the six-month follow-up period. Examiners were masked at each examination as to treatment group, previous diagnosis, impression cytologic results, and baseline serum vitamin A level.

For statistical analyses, we used Student's t test for the difference between means and a nonparametric test for monotonic trends.

RESULTS

Baseline Serum Vitamin A Levels

Serum vitamin A levels were obtained at baseline in all but one of the 149 subjects. Levels of serum vitamin A decreased monotonically with increased severity of cytologic abnormality ($P < .002$) (Table 2). Stages 0 and 1, representing normal conjunctival impressions, were associated with mean serum vitamin A levels greater than 0.70 μmol/L (20 μg/dL). Each abnormal stage, ie, stages 2 through 5, was associated with a mean serum vitamin A level significantly less than 0.70 μmol/L (20 μg/dL) ($P < .025$). This trend persisted even after separating the subjects, according to clinical criteria, into patients and controls ($P < .002$) (Tables 3 and 4). All subjects were reclassified into two cytologic groups, normal (stage 0 or 1) and abnormal (stages 2 through 5). These two groups showed the same highly significant correlation with mean serum vitamin A levels ($P < .0001$) (Table 5).

Response to Vitamin A

One hundred twenty-one children were followed up for six months after receiving orally at least 200 000 IU of vitamin A. An equal number (14) of patients and controls were unavailable for follow-up evaluation during this period.

Almost all cytologic scores improved following treatment. Fifty-six subjects (42 patients, 14 controls) entered the study with abnormal results of conjunctival impression cytology (stages 2 through 5) and were followed up for the full six months. Fifty-three subjects (95%) (40 patients, 13 controls) returned to normal (stage 0 or 1) following vitamin A therapy. Three subjects had abnormal

Table 1.—Staging of Conjunctival Squamous Metaplasia*

Stage	Criteria
0	Abundant goblet cells and mucin spots, small epithelial cells
1	Fewer goblet cells and mucin spots, small epithelial cells
2	Loss of goblet cells and mucin spots, enlarging epithelial cells
3	Enlarging and separating epithelial cells
4	Large, separate epithelial cells with scattered keratinization and pyknotic nuclei
5	Large keratinized epithelial cells with pyknotic nuclei or loss of nuclei

*Adopted from Tseng.[10]

Table 2.—Comparison of Mean Serum Vitamin A Levels and Results of Conjunctival Impression Cytology in All Subjects

Stage	No. of Subjects	Serum Vitamin A Level, μmol/L (μg/dL)		
		Mean*	SD	Range
0	39	0.83 (23.7)	0.16 (4.6)	0.56-1.19 (16-34)
1	44	0.73 (20.8)	0.21 (5.9)	0.35-1.26 (10-36)
2	21	0.56 (15.9)	0.17 (5.0)	0.10-0.87 (3-25)
3	29	0.54 (15.4)	0.15 (4.2)	0.31-0.80 (9-23)
4	11	0.52 (14.9)	0.14 (4.1)	0.28-0.84 (8-24)
5	4	0.39 (11.2)	0.13 (3.6)	0.28-0.56 (8-16)

*$P < .002$ for monotonically decreasing trend.

Table 3.—Comparison of Mean Serum Vitamin A Levels and Results of Conjunctival Impression Cytology in Patients With Mild Xerophthalmia

Stage	No. of Patients	Serum Vitamin A Level, μmol/L (μg/dL)		
		Mean*	SD	Range
0	11	0.82 (23.6)	0.21 (6.1)	0.56-1.19 (16-34)
1	15	0.66 (18.9)	0.17 (5.0)	0.35-0.91 (10-26)
2	13	0.52 (15.0)	0.19 (5.5)	0.10-0.84 (3-24)
3	21	0.54 (15.4)	0.14 (3.9)	0.31-0.80 (9-23)
4	8	0.49 (13.9)	0.12 (3.3)	0.28-0.70 (8-20)
5	4	0.39 (11.2)	0.12 (3.6)	0.28-0.56 (8-16)

*$P < .002$ for monotonically decreasing trend.

Table 4.—Comparison of Mean Serum Vitamin A Levels and Results of Conjunctival Impression Cytology in Controls

Stage	No. of Controls	Serum Vitamin A Level, μmol/L (μg/dL)		
		Mean*	SD	Range
0	28	0.83 (23.7)	0.14 (4.0)	0.59-1.15 (17-33)
1	29	0.76 (21.9)	0.22 (6.2)	0.35-1.26 (10-36)
2	8	0.61 (17.5)	0.15 (4.2)	0.45-0.87 (13-25)
3	5	0.54 (15.4)	0.21 (5.9)	0.31-0.77 (9-22)
4	3	0.62 (17.7)	0.19 (5.5)	0.49-0.84 (14-24)

*$P < .002$ for monotonically decreasing trend.

Table 5.—Mean Serum Vitamin A Levels of All Subjects With Normal Results vs All Subjects With Abnormal Results of Conjunctival Impression Cytology

Status	No. of Subjects	Mean (± SEM) Serum Vitamin A Level, μmol/L (μg/dL)*
Normal (stage 0 or 1)	83	0.78 ± 0.19 (22.2 ± 5.5)
Abnormal (stages 2-5)	65	0.53 ± 0.16 (15.2 ± 4.5)

*$P < .0001$ for difference between means.

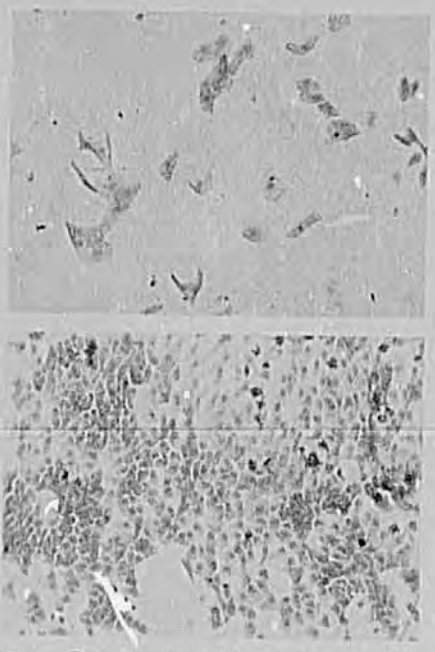


Fig 1.—Top, Specimen from nasal quadrant of right eye is typical of stage 4, exhibiting loss of all goblet cells and enlarged, separated epithelial cells (periodic acid-Schiff and modified Papanicolaou's stain, ×100). Bottom, Specimen from nasal quadrant of left eye of same patient. Specimen is typical of stage 1, exhibiting goblet cells and normal epithelial cells (periodic acid-Schiff and modified Papanicolaou's stain, ×100). Child was therefore graded stage 1 (normal) overall.

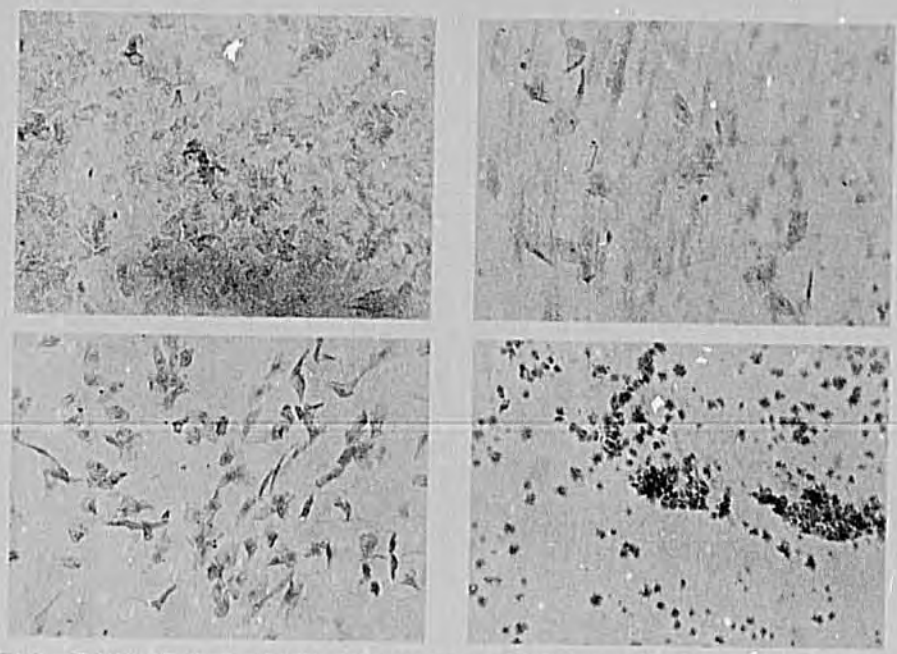
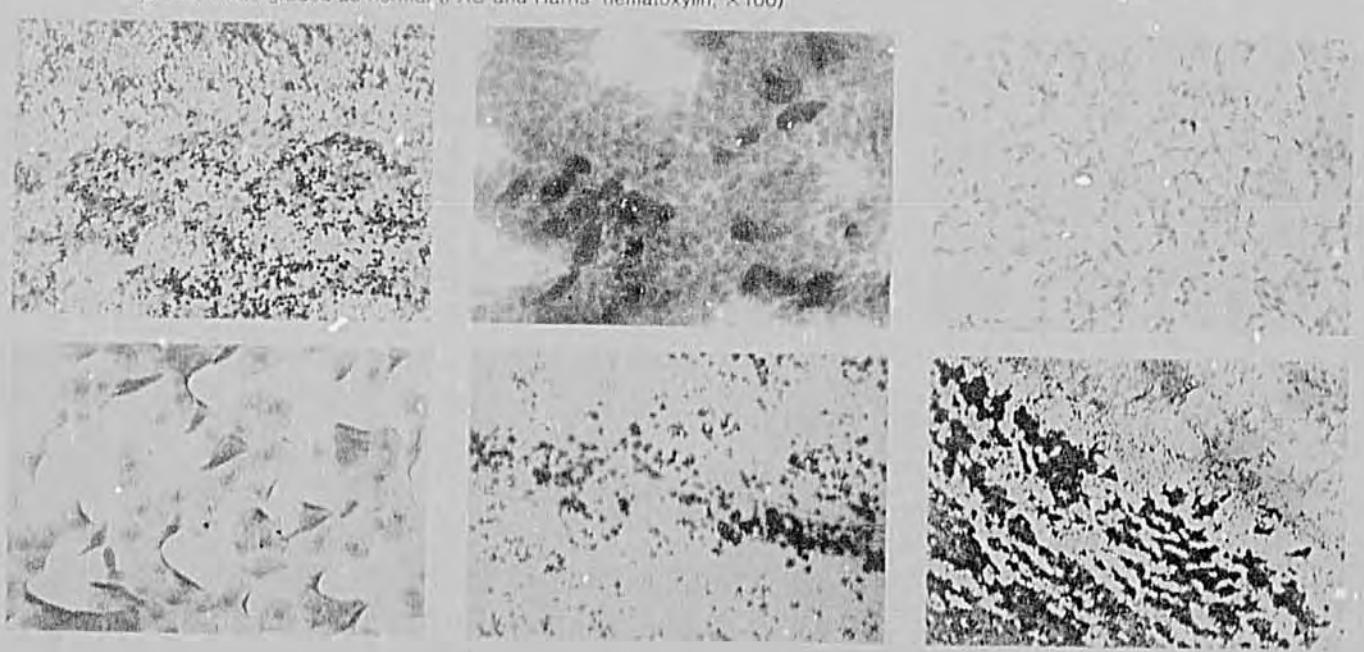


Fig 2.—Top left, 42-month-old child with night blindness and Bitot's spots entered study at stage 3, with marked epithelial cell enlargement, loss of nuclei, and keratinization (periodic acid-Schiff [PAS] and modified Papanicolaou's stain, ×100). Top right, Two weeks after receiving vitamin A therapy, results of impression cytology had improved to stage 4, characterized by enlarged, nucleated epithelial cells and patchy keratinization (PAS and modified Papanicolaou's stain, ×100). Bottom left, Two months after treatment, results of impression cytology continued to improve, showing mixed picture with some persistent, enlarged epithelial cells, some smaller, more normal epithelial cells, and, most importantly, PAS-positive smears representing mucin from returning goblet cells (PAS and modified Papanicolaou's stain, ×100). Bottom right, Six months after treatment, impression cytologic specimen is typical of stage 0, exhibiting small, normal epithelial cells, goblet cells, and abundant mucin spots indicating abundant goblet cells (PAS and modified Papanicolaou's stain, ×100).

Fig 3.—Top left, Normal conjunctival impression with abundant goblet cells, sheets of small epithelial cells, and mucin spots (periodic acid-Schiff [PAS] and Harris' hematoxylin, ×160). Top center, Higher power of normal conjunctiva, showing contrast between PAS-positive goblet cells and epithelial cells (PAS and Harris' hematoxylin, ×400). Top right, Abnormal conjunctival impression with complete loss of goblet cells and mucin spots, along with appearance of enlarged epithelial cells (PAS and Harris' hematoxylin, ×100). Bottom left, Higher power of abnormal, enlarged conjunctival cells (PAS and Harris' hematoxylin, ×400). Bottom center, PAS-positive mucin spots representing "impressions" of goblet cells on conjunctival surface (PAS and Harris' hematoxylin, ×400). Bottom right, Results of impression cytology from normal child showing transition from abundant normal epithelium (lower left) to abnormal epithelium (upper right). Specimen was graded as normal (PAS and Harris' hematoxylin, ×100).



results at all examinations, but two of these subjects improved from stage 5 to stage 2 at two months and from stage 4 to stage 2 at two months, respectively. Both subjects had low baseline serum vitamin A levels (0.52 and 0.56 μmol/L [15 and 16 μg/dL], respectively), and both had dropped to stage 3 by six months. The third subject (control with a serum vitamin A level of 0.80 μmol/L[23 μg/dL] at baseline) was at stage 2 initially, dropping to stage 3 at six months.

The rapidity of response to oral vitamin A treatment varied, with improvement requiring from as little as two weeks to more than two months (Fig 2). Seventeen of the 53 vitamin A–responsive patients were still at stage 2 at the two-month examination. Fourteen of these 17 patients subsequently improved to stage 0 or 1 by six months. Therefore, 95% of the patients who started with abnormal results of conjunctival impression cytology reverted to normal at some point during the six months following large-dose vitamin A treatment. Interestingly, ten of these 53 responsive subjects relapsed and were again abnormal by six months despite having received vitamin A. An additional eight of 83 subjects who entered the study with normal results of impression cytology became abnormal by six months. This finding is consistent with other observations that a single large dose of vitamin A is inadequate to protect all individuals in a deficient population for a full six months.[11] In fact, in this series the serum vitamin A levels had returned to baseline between two and six months regardless of the therapeutic regimen (G.N., J.R.W., K.P.W., Muhilal, A.S., unpublished data, 1987).

COMMENT

Vitamin A deficiency among preschool children in developing countries causes blindness and is associated with increased morbidity and mortality from respiratory and diarrheal diseases.[1-6] Recent reports have also documented significantly improved mortality among nonxerophthalmic children receiving vitamin A supplementation, suggesting the existence of subclinical but physiologically significant vitamin A deficiency.[7]

Initiation of effective intervention programs requires a simple, objective technique for identifying populations in which mild vitamin A deficiency is prevalent. Presently, the ocular changes of xerophthalmia are the most accessible physiologic indicator of vitamin A status. Measurement of serum vitamin A levels requires invasive sampling procedures, sophisticated equipment, highly trained personnel, and methods for preparing, storing, and transporting delicate samples that are impractical for most field surveys in developing regions of the world. Serum vitamin A levels also suffer from poor correlation with body stores, except under conditions of severe depletion, and are not a direct indicator of individual physiologic status.[12] Clinical surveys for xerophthalmia assess physiologic status but require large sample sizes because of the low prevalence of detectable disease. Furthermore, they miss individuals with subclinical deficiency. Impression cytology provides a means for partially overcoming many of these limitations.

Vitamin A is essential for the proper differentiation and maintenance of mucosal epithelium.[13,14] Absence of vitamin A causes loss of goblet cells and keratinizing metaplasia of the epithelium.[13,14] The process occurs on mucosal surfaces of the respiratory, urinary, and gastrointestinal tracts as well as diffusely throughout the bulbar conjunctiva.[15-18] Furthermore, biopsy specimens have already shown that conjunctiva undergoing squamous metaplasia may appear normal clinically.[3,18]

Impression cytology permits atraumatic sampling of superficial conjunctival epithelial cells for histologic examination.[19] Impression cytology detected the early disappearance of goblet cells and the appearance of enlarged epithelial cells in the vitamin A–deficient rabbit model.[20] Preliminary studies on a small number of Indian and Indonesian children suggested that impression cytology might distinguish between children with mild xerophthalmia and seemingly normal controls.[8] This large-scale study confirms that impression cytology is closely correlated with vitamin A status and is more sensitive than a clinical ocular examination.

Three indicators of vitamin A status were used in the present study: mean serum vitamin A level, clinical xerophthalmia, and response to vitamin A treatment. Staging by impression cytology correlated directly with the mean serum vitamin A level of subjects in each stage. The change in mean serum vitamin A level from greater than 0.70 μmol/L (20 μg/dL) to less than 0.70 μmol/L (20 μg/dL) at the transition between stages 1 and 2 suggests that we can collapse our earlier six-stage classification into two stages: normal (0 to 1) and abnormal (2 through 5), based primarily on the presence or absence of goblet cells or evidence of their presence (mucin droplets).

An individual was considered *normal* if any area of any specimen obtained from either eye demonstrated a substantial proportion of normal epithelium with evidence of goblet cells. This criteria is meant to compensate for well-documented variations of goblet cell density across the conjunctival surface.[21] (Fig 3, bottom right, demonstrates one such area of transition from normal to abnormal epithelium in a normal, vitamin A–sufficient child.)

Collapsing the staging into *normal* and *abnormal* based on the presence or absence of goblet cells also facilitates specimen processing and evaluation. The modified Papanicolaou's stain needed for detailed staging of the degree of keratinization is no longer necessary, and personnel need only be trained to recognize the presence or absence of goblet cells. Furthermore, specimens with poor epithelial cell adherence may still reveal the presence of goblet cells by the presence of multiple, discrete mucin droplets staining PAS-positive (Fig 2, bottom left, and Fig 3, bottom center). These droplets correspond to goblet cells on the conjunctival surface.[22]

Following vitamin A treatment, impression cytology detected improvement in vitamin A status in 95% of the subjects who had abnormal results at baseline examination. This response to vitamin A coupled with the significantly lower mean serum vitamin A level of the cytologically abnormal patients confirms their deficient status, especially as clinical signs alone may be misleading.[2,3,18,23] Analysis of individual cases suggests that this combination explains children with night blindness (and the small number with Bitot's spots) presenting with normal imprints.

Importantly, 14 of the 56 subjects with abnormal results of impression cytology who were followed up for the full six months originally entered the study as clinically normal controls. A total of 14 of the 60 seemingly normal controls followed up for six months therefore had evidence of vitamin A deficiency. This finding suggests that up to 23% (14/60) of clinically nonxerophthalmic children in similar Indonesian communities may have physiologically significant vitamin A deficiency detectable by impression cytology. This is the first demonstration that a significant proportion of

seemingly normal children are suffering metabolic consequences of vitamin A deficiency and may be at increased risk of ocular and systemic consequences of vitamin A deficiency. This finding may well explain the marked reduction in mortality among nonxerophthalmic children receiving vitamin A supplementation.[7] It is consistent with earlier observations that neighborhood controls of xerophthalmic patients are likely to be vitamin A deficient.[23]

The rate of response to oral vitamin A, as measured by impression cytology, varied from two weeks to more than two months. This variation is consistent with that noted in previous clinical studies describing patients with conjunctival xerosis or Bitot's spots requiring two weeks to more than two months to return to normal.[24]

Thus, impression cytology detects early, physiologically significant vitamin A deficiency. The technique is well suited for population surveys to determine a community's vitamin A status. Specimens are obtained easily and atraumatically, can remain in fixative indefinitely, and require only an ordinary microscope for interpretation. Prevalence rates of abnormal cytologic findings are likely to be manyfold that of clinical disease, drastically reducing sample size requirements. Simpler staining techniques to determine the presence or absence of goblet cells will facilitate objective determinations of vitamin A status. Staining with PAS and Harris' hematoxylin is simpler to perform and improves recognition of PAS-positive goblet cells and mucin spots (Fig 3).[20] A large-scale field evaluation utilizing this modified staining process is presently in progress.

This investigation was supported in part by the Thrasher Research Fund, Salt Lake City; the Eleanor Naylor Dana Charitable Trust, New York; the Heed Foundation, Chicago (J.R.W.); and Cooperative Agreement AID/DSAN-CA/0267 between the Office of Nutrition of the US Agency for International Development and the International Center for Epidemiologic and Preventive Ophthalmology, Baltimore.

References

1. Sommer A, Tarwotjo I, Hussaini G, et al: Incidence, prevalence, and scale of blinding malnutrition. *Lancet* 1981;1:1407-1408.

2. Sommer A: *Field Guide to the Detection and Control of Xerophthalmia*, ed 2. Geneva, World Health Organization, 1982.

3. Sommer A: *Nutritional Blindness: Xerophthalmia and Keratomalacia*. New York, Oxford University Press Inc, 1982.

4. Sommer A, Katz J, Tarwotjo I: Increased risk of respiratory disease and diarrhea in children with preexisting mild vitamin A deficiency. *Am J Clin Nutr* 1984;40:1090-1095.

5. Sommer A, Tarwotjo I, Hussaini G, et al: Increased mortality in children with mild vitamin A deficiency. *Lancet* 1983;2:585-588.

6. Sommer A: Mortality associated with mild, untreated xerophthalmia. *Trans Am Ophthalmol Soc* 1983;81:825-853.

7. Sommer A, Tarwotjo I, West K, et al: Impact of vitamin A supplementation on childhood mortality: A randomized controlled community trial. *Lancet* 1986;1:1169-1173.

8. Wittpenn J, Tseng S, Sommer A: Detection of early xerophthalmia by impression cytology. *Arch Ophthalmol* 1986;104:237-239.

9. Arroyave G, Chichester CO, Flores H, et al: *Biochemical Methodology for the Assessment of Vitamin A Status: A Report of the International Vitamin A Consultative Group*. Washington, DC, Nutrition Foundation, 1982.

10. Tseng S: Staging of conjunctival squamous metaplasia by impression cytology. *Ophthalmology* 1985;92:728-733.

11. Pereira S, Begum A: Failure of a massive single oral dose of vitamin A to prevent deficiency. *Arch Dis Child* 1971;46:525-527.

12. Suthutvoravoot S, Olson J: Plasma and liver concentrations of vitamin A in a normal population of urban Thai. *Am J Clin Nutr* 1974;27:883-891.

13. Wolbach S, Howe P: Tissue changes following deprivation of fat-soluble A vitamin. *J Exp Med* 1925;42:753-777.

14. Mori S: Primary changes in eyes of rats which result from deficiency of fat-soluble A in diet. *JAMA* 1922;79:197-200.

15. Wilson J, DuBois R: Keratomalacia in infants with postmortem examination. *AJDC* 1923;26:431-436.

16. Blackfan K, Wolbach S: Vitamin A deficiency in infants: A clinical and pathological study. *J Pediatr* 1933;3:679-706.

17. Sweet L, K'ang H: Clinical and anatomic study of avitaminosis A among the Chinese. *AJDC* 1935;50:699-734.

18. Sommer A, Green W, Kenyon K: Bitot's spots responsive and nonresponsive to vitamin A: Clinicopathologic correlations. *Arch Ophthalmol* 1981;99:2019-2027.

19. Egbert P, Lauber S, Maurice D: A simple conjunctival biopsy. *Am J Ophthalmol* 1977;84:798-801.

20. Hatchell D, Sommer A: Detection of ocular surface abnormalities in experimental vitamin A deficiency. *Arch Ophthalmol* 1984;102:1389-1393.

21. Kessing S: Mucous gland system of the conjunctiva: A quantitative normal anatomical study. *Acta Ophthalmol Suppl* 1986;95:9-133.

22. Kenyon K, John T, Hanninen L, et al: Evaluation of conjunctival goblet cells in vitamin A–deficient rats by impression cytology and flat mount preparation. *Invest Ophthalmol Vis Sci* 1986;27(suppl):27.

23. Sommer A, Hussaini G, Muhilal, et al: History of nightblindness: A simple tool for xerophthalmia screening. *Am J Clin Nutr* 1980;33:887-891.

24. Sommer A, Emran N, Tjakrasudjatma S: Clinical characteristics of vitamin A responsive and nonresponsive Bitot's spots. *Am J Ophthalmol* 1980;90:160-171.

Printed and Published in the United States of America

APPENDIX D

Natadisastra G, Wittpenn J, Muhilal, West KP Jr., Mele L, and Sommer A: Impression cytology: a practical index of vitamin A status. **Am J Clin Nutr** 48:695-701 1988.

Impression cytology: a practical index of vitamin A status[1-3]

Gantira Natadisastra, MD; John R Wittpenn, MD; Muhilal, PhD; Keith P West, Jr, DrPH, RD; Lisa Mele, MS; and Alfred Sommer, MD

ABSTRACT Impression cytology was performed on 248 Indonesian preschool children of whom half had mild xerophthalmia and half were age-matched control subjects. Subjects were divided into subgroups that reflected the degree of confidence in their true vitamin A status as determined by serum vitamin A levels, clinical examination, and response to therapy. Impression cytology was considered normal if goblet cells were present and abnormal if they were absent. Thirteen of 14 (93%) children with vitamin A-responsive Bitot's spots and night blindness with base-line serum vitamin A < 20 μg/dl (0.70 μmol/l) (group 1, definite deficiency) had abnormal cytology. In contrast, 17 of 18 (94%) children with normal ocular exam and serum vitamin A > 25 μg/dl (0.87 μmol/l) (group 2, least likely deficient) had normal cytology. Importantly, 12 of 26 (46%) clinically normal children with serum vitamin A levels < 20 μg/dl (0.70 μmol/l) had abnormal impression cytology. *Am J Clin Nutr* 1988;48:695–701.

KEY WORDS Vitamin A deficiency, diagnosis, surveys, xerophthalmia, keratinization, impression cytology

Introduction

Vitamin A deficiency is the major cause of childhood blindness in many developing countries (1, 2). Mild xerophthalmia consisting of night blindness and conjunctival xerosis is associated with increased morbidity and mortality (3–6). Vitamin A supplementation of nonxerophthalmic children reduces mortality, suggesting that subclinical vitamin A deficiency (ie, physiologic deficiency without ocular manifestations of xerophthalmia) is also associated with increased mortality (7). Previous studies demonstrated that conjunctival impression cytology correlated with vitamin A status in a vitamin A-deficient rabbit model (8) and was often abnormal in the presence of xerophthalmia (9) or depleted liver stores (10) in children. We herein report indices of sensitivity and specificity of impression cytology for the detection of early, physiologically significant vitamin A deficiency among young children.

Subjects and methods

The study was performed at the Cicendo Eye Hospital, Bandung, Indonesia. Children aged 36–72 mo with mild xerophthalmia, defined as a history of night blindness or the presence of conjunctival xerosis with Bitot's spots, were identified as cases in surrounding villages by a trained nurse. Whenever a case was identified, an age-matched control from the same village was also identified. All case and control subjects were brought to the hospital where they were examined by one of two ophthalmologists. Seventy-five cases and 73 age-matched controls were identified.

Each child's dietary and disease history was obtained from the parent or guardian. After parental consent was obtained, each child underwent base-line evaluation consisting of an ocular exam, anthropometry, and impression cytology. All ocular findings were drawn and photographed. Venous blood was obtained and promptly separated and the serum was frozen. Serum vitamin A was analyzed by high-performance liquid chromatography (HPLC) (11).

Conjunctival impression cytology was performed on each patient using our previously described technique (9, 12). Topical 0.5% proparacaine was applied to each eye. Precut 5 mm by 5 mm pieces of cellulose acetate filter paper (HAWP 304F0,

[1] From the Cicendo Eye Hospital, Bandung, Indonesia; the International Center for Epidemiologic and Preventive Ophthalmology, Dana Center of the Wilmer Institute and School of Public Health, Johns Hopkins University, Baltimore, MD; the Eye Research Institute of the Retina Foundation, Boston, MA; and the Nutrition Research and Development Center, Bogor, Indonesia.

[2] Supported by the Thrasher Research Fund, the Eleanor Naylor Dana Charitable Trust, Task Force Sight and Life, the Heed Foundation, NIH Grant EY05991, and Cooperative Agreement AID/DSAN-CA/0267 between the Office of Nutrition of the United States Agency for International Development and the International Center for Epidemiologic and Preventive Ophthalmology.

[3] Address reprint requests to A Sommer, Wilmer 120, Johns Hopkins Hospital, Baltimore, MD 21205.

Received June 4, 1987.

Accepted for publication September 29, 1987.

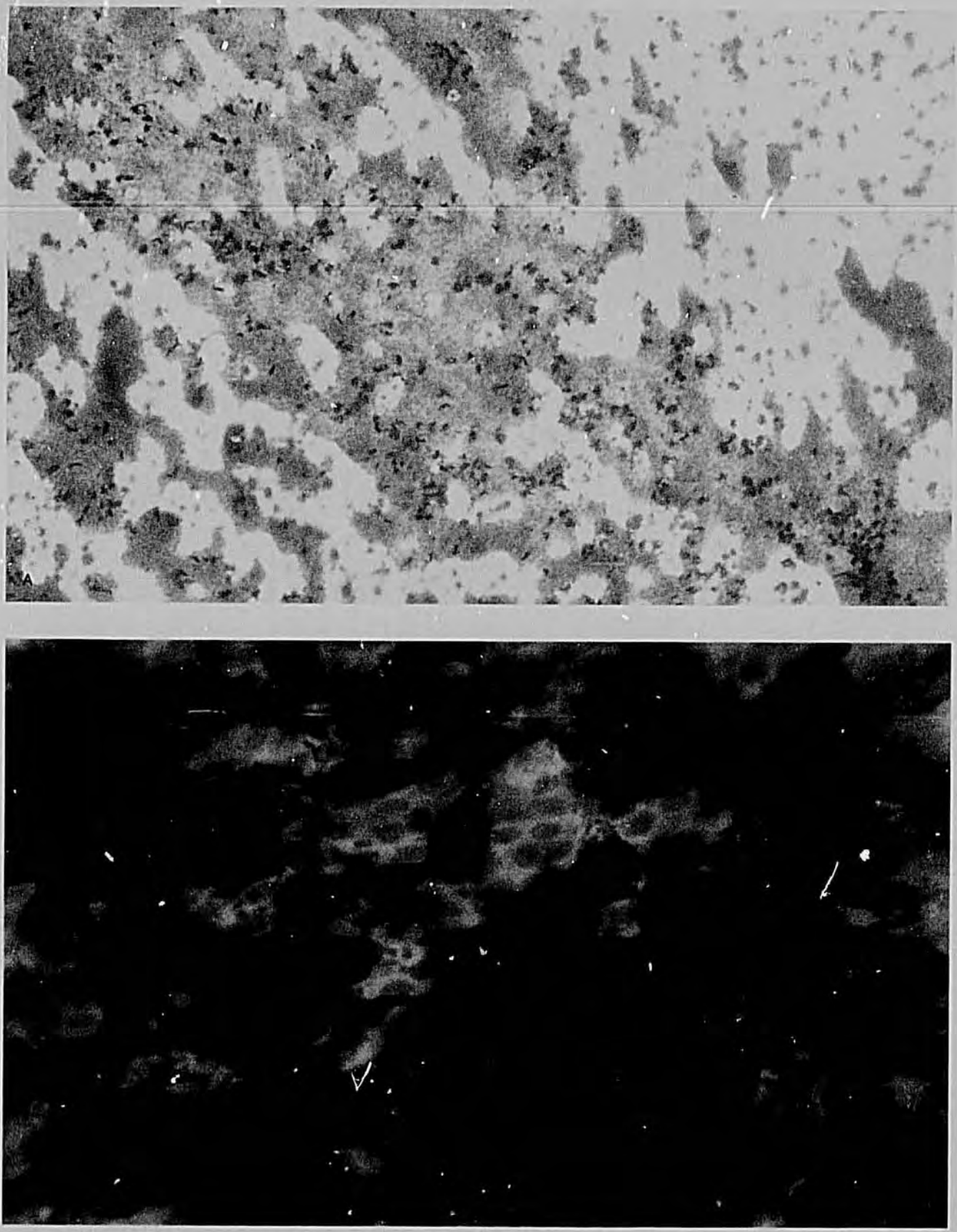


FIG 1. *A*: Low-power view of imprint from normal child. Sheets of small uniform epithelial cells are evident along with PAS positive goblet cells (periodic-acid Schiff and Harris hematoxylin, 100×). *B*: Higher-power view of same specimen showing mucin containing goblet cells densely stained with periodic-acid Schiff (400×).

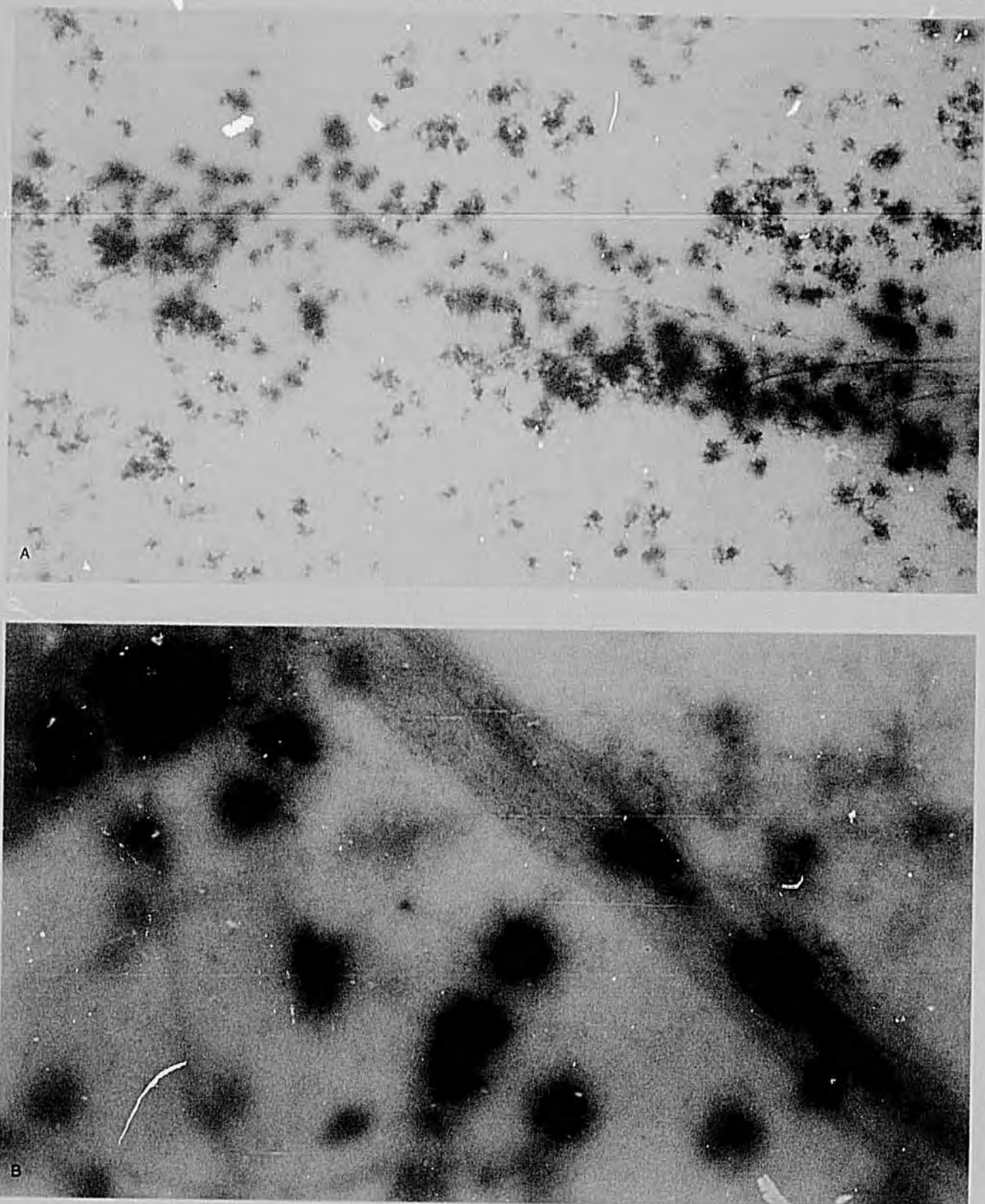


FIG 2. *A*: Low-power view of imprint from normal child. Note absence of epithelial cell sheets but abundant PAS-positive mucin spots, presumably the contents of adherent but broken goblet cells. These are a definite sign of normally differentiated epithelium (periodic-acid Schiff and Harris hematoxylin, 160×). *B*: Higher-power view of imprint from another normal child. The specimen contain few if any intact cells of any type but PAS-positive, smudged, mucin spots particularly in the lower left half of the figure. This specimen is graded as normal (periodic-acid Schiff and Harris hematoxylin, 400×).

Millipore, Bedford, MA) were applied to the bulbar nasal and temporal conjunctiva of each eye. The filter paper was removed with a peeling motion after 3–5 s. The filter paper with the adherent epithelial cells was immediately placed in a fixative solution prepared by mixing 750 mL 70% ethyl alcohol, 50 mL 37% formaldehyde, 50 mL glacial acetic acid, and 150 mL distilled water.

After fixation the specimens were stained with periodic-acid Schiff and modified Papanicolaou's stain as described previously (9, 12). All impression-cytology specimens were examined by one investigator in blinded fashion. Specimens were graded as normal if goblet cells or abundant mucin spots were present (previous stages 0 and 1) or abnormal if enlarged epithelial cells were present and goblet cells and mucin spots were few or absent (previous stages 2–5). Mucin spots are discrete clusters of PAS-positive granules of variable size. Each cluster is slightly larger than an intact goblet cell and represents secretions from a goblet cell that failed to adhere to the filter paper (13). The child was graded normal if any of the specimens taken at that exam was normal and abnormal if all specimens were abnormal. **Figures 1 and 2** show imprints from a normal child and **Figure 3** shows an imprint from a vitamin A-deficient child.

These figures were collected subsequent to this study and were stained by a modification of our earlier technique (8), which we find simpler to carry out and interpret and therefore presently recommend (14). The more complicated modified Papanicolaou's stain (9) used in this study was chosen to further reveal the degree of epithelial keratinization, which did not add materially to our ability to classify the specimens.

All patients received at least 110 mg retinyl palmitate orally within 1 wk of base-line exam. Follow-up ocular examinations with impression cytology were performed 2 wk, 2 mo, and 6 mo after the base-line exam; 121 children remained through the 6-mo follow-up. Examiners were blinded at each exam as to treatment group, previous diagnosis, impression-cytology results, and base-line serum vitamin A level.

Statistical analyses utilized binomially derived confidence limits about proportions and a nonparametric test for monotonic trends (15).

Results

The ability of impression cytology to detect physiologically significant vitamin A deficiency was determined by subdividing case and control subjects into subgroups reflecting our degree of confidence in their true vitamin A status (**Table 1**). At one extreme were children who were certainly deficient with vitamin A-responsive Bitot's spots and night blindness and with serum vitamin A levels < 20 μg/dL (0.70 μmol/L) (group 1). At the other extreme were those children least likely to be deficient having normal ocular examinations, a negative history for night blindness, and serum vitamin A of ≥ 25 μg/dL (0.87 μmol/L) (group 7). (Although clinically significant deficiency has been occasionally reported at a serum level of 25–30 μg/dL [0.87–1.05 μmol/L], few Indonesian children have serum levels above this range.) The remaining children had various clinical signs, symptoms, and serum levels and were of less certain, intermediary status.

TABLE 1
Subdivision of patients by their combined clinical and biochemical vitamin A status

Vitamin A status	Group
Deficient	1. Definite vitamin A deficiency Night blindness (XN) with Bitot's spot (XIB) responding to treatment and serum vitamin A < 20 μg/dL (0.70 μmol/L)
	2. Probable vitamin A deficiency Bilateral X1B responding to treatment
	3. Probable vitamin A deficiency XN responding to treatment with base-line serum vitamin A < 20 μg/dL (0.70 μmol/L)
	4. Possible vitamin A deficiency Unilateral X1B (without XN) responding to treatment
	5. Possible vitamin A deficiency Normal exam with base-line serum vitamin A < 20 μg/dL (0.70 μmol/L)
	6. Borderline vitamin A status XN with base-line serum ≥ 20 μg/dL (0.70 μmol/L) or normal subjects with base-line serum between 20 and 25 μg/dL (0.70–0.87 μmol/L)
Normal	7. Normal vitamin A Normal exam with base-line serum vitamin A > 25 μg/dL (0.87 μmol/L)*

* There were insufficient numbers to include > 30 μg/dL (1.05 μmol/L) as a criterion for normal.

The proportion of subjects with abnormal impression cytology was directly related to the likelihood that they were vitamin A deficient (Table 2, **Fig 4**): 93% of children definitely vitamin A deficient (group 1) had abnormal cytologic impressions whereas 6% of children least likely to be vitamin A deficient (group 7) had abnormal cytology. The single exception in group 7 became normal after receiving vitamin A, suggesting he was also deficient despite a serum vitamin A level > 25 μg/dL (0.87 μmol/L) and the absence of clinical xerophthalmia.

With the extreme groups taken as approximations of true deficiency (group 1) and normality (group 7), the sensitivity for detecting vitamin A deficiency was 93% (95% confidence limit [CL] of 66–100%) and specificity at least 94% (95% CL of 73–100%).

Importantly, 12 of 26 (46%; 95% CL of 27–65%) seemingly normal control subjects whose serum vitamin A was < 20 μg/dL (0.70 μmol/L) (group 5) had abnormal cytology. Follow-up cytology was available on 10 of these 12 abnormal subjects: all became normal by 6 mo.

Discussion

Vitamin A deficiency in developing countries is the major cause of blindness and increases both morbidity and mortality among preschool children (1–6). Recent reports documenting improved mortality among nonxe-

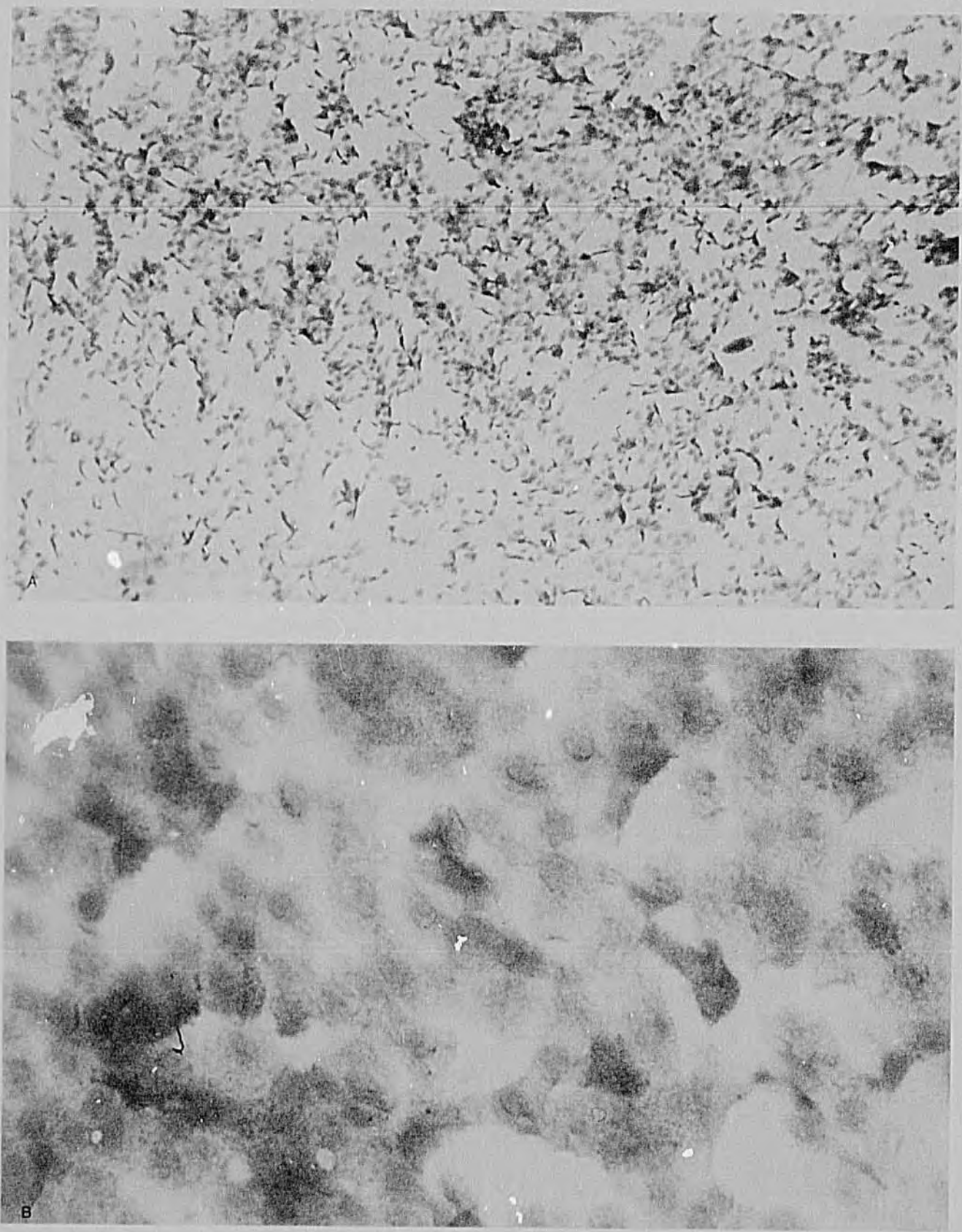


FIG 3. *A*: Low-power view of imprint from vitamin A-deficient child with clinical xerophthalmia (X1B and XN). Note irregularly shaped, separating epithelial cells and lack of goblet cells (periodic-acid Schiff and Harris hematoxylin, 100×). *B*: Higher-power view of same specimen (400×).

TABLE 2
Impression cytology results for each group of subjects

Group	Number of subjects	Impression cytology			
		Normal		Abnormal	
		n	%	*n*	%
1 (Deficient)	14	1	7	13	93
2	22	4	18	18	82
3	15	5	33	10	67
4	8	4	50	4	50
5	26	14	54	12	46
6	43	37	86	6	14
7 (Normal)	18	17	94	1	6
Total	146*	82	56	64	44

* One study child who lacked a serum vitamin A level and one on whom follow-up was inadequate to determine clinical response are omitted from the analysis.

rophthalmic children who received vitamin A supplementation suggest subclinical but physiologically significant vitamin A deficiency may constitute a serious public health problem (7, 16, 17).

A previous report (9) showed that impression cytology is a simple, objective technique for confirming the presence of clinical xerophthalmia. The present study demonstrates that impression cytology is highly sensitive and specific for the detection of physiologically significant vitamin A deficiency and that such deficiency may affect a large proportion of apparently normal children.

The percentage of subjects with abnormal impression cytology corresponded to vitamin A status defined on clinical, biochemical, and therapeutic grounds because no single test defines physiologic truth. Bitot's spots may be sequelae of past deficiency (18), which is the reason we gave higher weighting to bilaterality and reversibility; a history of nightblindness is never 100% specific (19); and both normal and abnormal ocular appearance are consistent with serum levels between 10 and 30 μg/dL (0.32 and 1.05 μmol/L) (2). Thirteen of 14 (93%) patients with definite vitamin A deficiency (group 1) had abnormal impression cytology. The single exception in the present series is probably attributable to variations in the severity of histologic abnormalities across the ocular surface (3, 18) and our operative definition that a subject was normal if even a small area of goblet cell-containing normal conjunctiva was present on any of the four specimens obtained.

The specificity of the technique was an equally impressive 94%. The single exception was a clinically normal child with a serum vitamin A > 25 μg/dL (0.87 μmol/L). Because subtle clinical abnormalities have been noted in this range and the time required for cellular turnover and differentiation would cause cytologic results to lag behind acute changes in biochemical status, this child may indeed have been deficient, either at the time of base-line examination or in the recent past. Indeed, his impression cytology became normal after treatment.

Equally importantly, impression cytology was abnormal in a large proportion of children at risk of physiologically significant deficiency but with normal ocular examinations. Fully 46% of clinically normal children with serum vitamin A levels < 20 μg/dL (0.70 μmol/L) (and 15% of those with vitamin A levels between 20 and 25 μg/dL [0.70 and 0.87 μmol/L]) had abnormal impressions. Almost half of all preschool-age rural Indonesian children have serum vitamin A levels < 20 μg/dL (16). If 46% of these children have abnormal impression cytology (as well as 15% of children with vitamin A levels between 20 and 25 μg/dL) the prevalence of physiologically significant vitamin A deficiency probably approaches or exceeds 25% of the preschool-age population. The prevalence of clinically detectable mild xerophthalmia is only a small fraction of this rate. Field surveys utilizing impression cytology should more accurately reflect the vitamin A status of the population while requiring far fewer subjects to achieve similar degrees of precision. The high prevalence of metabolically detectable deficiency revealed by impression cytology helps explain the large impact on mortality achieved by vitamin A supplementation (7, 20).

Impression cytology differentiates vitamin A status (as defined on clinical and biochemical grounds) with a high degree of sensitivity and specificity. More importantly,

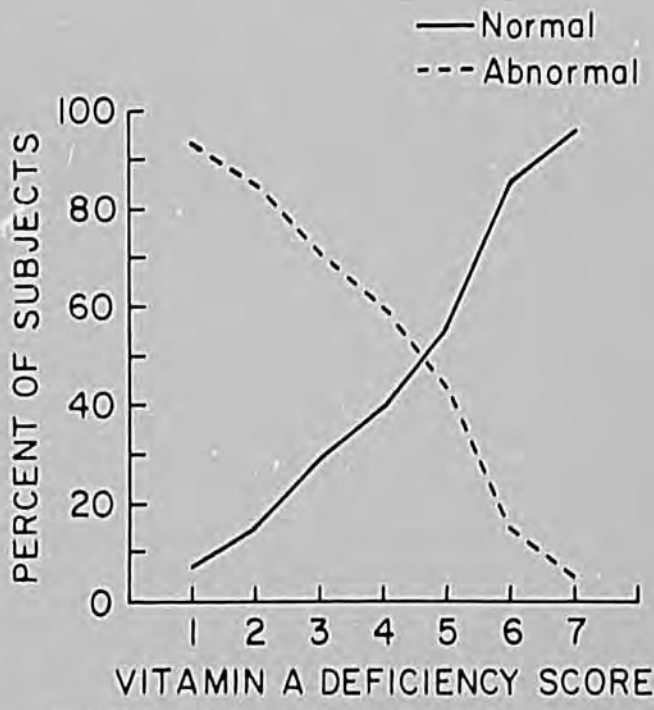


FIG 4. Percent of subjects with normal and abnormal impression cytology by degree of vitamin A deficiency as determined by biochemical and clinical status and therapeutic responsiveness. Group 1 consists of children almost surely deficient and group 7 children least likely deficient.

this technique identifies early, physiologically significant vitamin A deficiency not apparent by standard methods of assessment. Impression cytology is well suited for population surveys to determine the prevalence of vitamin A deficiency or to monitor the impact of supplementation programs. Its great strength is simplicity, logistical practicality, and close association with apparent vitamin A status. Sensitivity and specificity of course are < 100%, especially given the confidence limits in this study. It should prove a useful and more convenient gauge of vitamin A status of the community than other approaches but is not infallible in individual subjects. The more areas sampled per eye, however, the more likely normal conjunctiva will be identified and the higher the specificity will be. Specimens are obtained easily and atraumatically, can remain in fixative indefinitely, and require only an ordinary microscope for interpretation. Simpler staining techniques to determine the presence or absence of goblet cells without needing to delineate keratin (for which the more complicated modified Papanicolaou's stain [9] was adopted in this study) will facilitate objective determinations of vitamin A status. A further, large scale field evaluation utilizing a modification of our original simplified PAS and hematoxylin staining process (8, 9) for goblet cells is presently in progress (Figs 1–3).

Clinical studies suggest reversal of keratinization in the presence of conjunctival inflammation (21). Sensitivity and specificity derived in this study may not, therefore, be valid in the presence of acute or chronic conjunctivitis and other external ocular inflammation. Until more data and experience are available, interpretation of impression cytology, particularly for gauging a community's vitamin A status, should be limited to noninflamed eyes.

References

1. Sommer A, Tarwotjo I, Hussaini G, Susanto D, Soegiharto T. Incidence, prevalence, and scale of blinding malnutrition. Lancet 1981;1:1407–8.
2. Sommer A. Field guide to the detection and control of xerophthalmia. 2nd ed. Geneva: World Health Organization, 1982.
3. Sommer A. Nutritional blindness: xerophthalmia and keratomalacia. New York: Oxford University Press, 1982.
4. Sommer A, Katz J, Tarwotjo I. Increased risk of respiratory disease and diarrhea in children with pre-existing mild vitamin A deficiency. Am J Clin Nutr 1984;40:1090–5.
5. Sommer A, Tarwotjo I, Hussaini G, Susanto D. Increased mortality in children with mild vitamin A deficiency. Lancet 1983;2: 585–8.
6. Sommer A. Mortality associated with mild, untreated xerophthalmia. Trans Am Ophthalmol Soc 1983;81:825–53.
7. Sommer A, Tarwotjo I, West KP, et al. Impact of vitamin A supplementation on childhood mortality. A randomized controlled community trial. Lancet 1986;1:1169–73.
8. Hatchell DL, Sommer A. Detection of ocular surface abnormalities in experimental vitamin A deficiency. Arch Ophthalmol 1984;102: 1389–93.
9. Wittpenn J, Tseng S, Sommer A. Detection of early xerophthalmia by impression cytology. Arch Ophthalmol 1986;104:237–9.
10. Amedee-Manesme O, Luzeau R, Wittpenn JR, Hanek A, Sommer A. Impression cytology detects subclinical vitamin A deficiency. Am J Clin Nutr 1988;47:875–8.
11. Arroyave G, Chichester CO, Flores H, et al. Biochemical methodology for the assessment of vitamin A status. A report of the International Vitamin A Consultative Group. Washington, DC: International Life Sciences Institute-Nutrition Foundation, 1982.
12. Tseng S. Staging of conjunctival squamous metaplasia by impression cytology. Ophthalmology 1985;92:728–33.
13. Kenyon K, John T, Hanninen L, Wolf G. Evaluation of goblet cells in vitamin A-deficient rats by impression cytology and flat mount preparation. Invest Ophthalmol Vis Sci 1986;29(suppl):29 (abstr).
14. Natadisastra G, Wittpenn JR, West KP Jr, Muhilal, Sommer A. Impression cytology for detection of vitamin A deficiency. Arch Ophthalmol (in press).
15. Armitage P. Statistical methods in medical research. Oxford: Blackwell Scientific Publications, 1977.
16. Muhilal, Permeisih, Idjradinata YR, Muherdiyantiningsih, Karyadi D. Impact of vitamin A fortified MSG on health, growth, and survival of children: a controlled field trial. Am J Clin Nutr (in press).
17. Barclay AJG, Foster A, Sommer A. Vitamin A supplementation and measles-related mortality: a randomized clinical trial. Br Med J 1986;294:294–6.
18. Sommer A, Green W, Kenyon K. Bitot's spots responsive and nonresponsive to vitamin A: clinicopathologic correlations. Arch Ophthalmol 1981;99:2019–27.
19. Sommer A, Hussaini G, Muhilal, Tarwotjo I, Susanto D, Saroso J. History of nightblindness: a simple tool for xerophthalmia screening. Am J Clin Nutr 1980;33:887–91.
20. Tarwotjo I, Sommer A, West KP Jr, et al. Influence of participation on mortality in a randomized trial of vitamin A prophylaxis. Am J Clin Nutr 1987;45:1466–71.
21. Sommer A. Conjunctival appearance in corneal xerophthalmia. Arch Ophthalmol 1982;100:951–2.

APPENDIX E

Muhilal, Murdiana A, Azis I, Saidin S, Jahari A, and Karyadi D:
Vitamin A-fortified monosodium glutamate and vitamin status:
A controlled field trial.
Am J Clin Nutr 48:1265-1270 1988.

Vitamin A-fortified monosodium glutamate and vitamin A status: a controlled field trial[1–4]

Muhilal, PhD; Ance Murdiana, BS; Izar Azis, MD; Sukati Saidin, BS; Abas Basuni Jahari, MS; and Darwin Karyadi, MD, PhD

ABSTRACT A controlled trial of fortification of crystalline monosodium glutamate (MSG) with 810 μg RE vitamin A/g was undertaken in an area of endemic vitamin A deficiency in Indonesia. Powdered MSG was used to mask the yellow color of the vitamin A. Fortified MSG was marketed through ordinary channels in five villages in the program area and five nearby villages served as the control area. The product retained 84% of its potency after 4 mo and 57% after 11 mo in the marketplace. Base-line serum and breast-milk vitamin A levels were slightly higher in the control areas. Follow-up serum levels increased dramatically in program villages, 0.67 ± 0.33 at prefortification base line to 0.92 ± 0.33 μmol/L ($p < 0.001$) at 11 mo after introduction of the fortified product. Breast-milk levels also rose, from 0.60 ± 0.29 at base line to 0.67 ± 0.30 μmol/L at 11 mo ($p < 0.05$). Serum and breast-milk levels in control villages did not change. *Am J Clin Nutr* 1988;48:1265–70.

KEY WORDS Monosodium glutamate (MSC), vitamin A, fortification, xerophthalmia

Introduction

Vitamin A deficiency has long been a major nutritional problem in Indonesia. A national xerophthalmia survey completed in 1980 (1, 2) revealed that the mean prevalence of Bitot's spots among preschool children in the rural area as a whole was ~1% while that of active corneal disease related to vitamin A deficiency was 6.4/10 000, both well above WHO criteria for a public health problem (3). It was estimated that 50 000 children were in danger of becoming blind every year. In addition, subsequent studies indicate that Indonesian children with vitamin A deficiency are at increased risk of respiratory disease, diarrhea, and mortality. (4, 5) Mass dosing with vitamin A capsules reduced childhood mortality by 35–70%. (6, 7)

To control the problem three intervention strategies have been considered: nutrition education, supplementation through distribution of a large dose of vitamin A (60 000 μg RE [200 000 IU]) twice a year, and fortification of a commonly consumed item with vitamin A. Dietary modification through nutrition education is underway but is considered a long-term, slowly accepted solution. Biannual distribution of high doses of vitamin A has been carried out through various delivery systems for > 15 y. However it has proven too costly to expand beyond the highest risk areas and coverage has fallen from an initial high of ≥ 80% to 40–50%.

A nationwide program of fortifying sugar in Guatemala (8) and a pilot study of MSG fortification in the Philippines (9) demonstrated the potential feasibility and impact of this approach. Financial and technical problems, however, interfered with expansion and/or continuation of these activities.

The Government of Indonesia has decided that fortification of a commonly consumed dietary item with vitamin A could prove an effective means of controlling most vitamin A deficiency. A national survey (1, 2) revealed that four substances, white sugar, flour, MSG, and salt, reached the high-risk target groups. Of these four potential vehicles, MSG most closely fulfilled the necessary conditions for fortification: production was highly centralized; MSG reached the largest proportion of target

[1] From the Nutrition Research and Development Center, Ministry of Health, Bogor, Indonesia, and the Cicendo Eye Hospital, Bandung, Indonesia.

[2] This report was prepared under Cooperative Agreement #0045 between ICEPO and the Office of Nutrition, United States Agency for International Development. The Indonesian Nutrition Research and Development Center and ICEPO are WHO collaborating centers for the prevention of vitamin A deficiency and xerophthalmia.

[3] Supported by the Ministry of Health, Government of Indonesia; Helen Keller International, New York; the International Development Research Center, Ottawa; the United States Agency for International Development; the Ford Foundation; and Task Force Sight and Life, Hoffman-La Roche, Basle.

[4] Address reprint requests to A Sommer, ICEPO, Wilmer Institute 120, Johns Hopkins Hospital, Baltimore, MD 21205.

Received August 31, 1987.

Accepted for publication December 8, 1987.

children and mothers with relatively little variation in per capita consumption; and the poorest, highest-risk segments of society purchased MSG in small packets whereas wealthier families purchased large packages, permitting fortification to be targeted to small packets thus reducing vitamin A wastage.

MSG is metabolized quickly in the body (10). It is generally recognized as a safe additive (11), WHO considering the maximal permissable daily intake to be 150 mg/kg body wt (12). Maximum recorded daily intakes for children in Indonesia rarely exceed 85 $mg \cdot kg^{-1} \cdot d^{-1}$ (Muhilal, unpublished observation).

This paper reports a pilot MSG-fortification project in Indonesia that utilized a novel method for overcoming technical and organoleptic obstacles to the fortification process and that had a demonstrable and significant impact on serum vitamin A levels of children and breast-milk levels of lactating mothers residing in program villages.

Methods

The level of vitamin A added to MSG was determined from the amount needed to supplement dietary sources to prevent serious deficiency in relation to the quantity of MSG consumed by the target high-risk group. The average amount of MSG consumed by preschool children was calculated from in-depth dietary assessments of rural families by considering the proportion of all family foods prepared with MSG that were consumed by the children. This amounted to an average of 0.23 ± 0.20 g MSG/d. We estimated that the addition of 50% of the preschool Recommended Dietary Allowance (~450 μg RE; Muhilal, T Apunain, D Karyadi, et al, unpublished observations, 1983) would provide children with an adequate total daily intake of vitamin A. Thus, the amount of the vitamin added to MSG was 210 μg RE/0.23 g (~810 μg RE vitamin A/g MSG).

The vitamin A used in this study was type 250-CWS (75 000 μg RE/g, cold-water storage) supplied by Hoffman-La Roche, Basle. To mask the yellow color of the vitamin A, which has negative connotations in Indonesia where MSG is promoted as being a pure white substance, vitamin A was covered with finely ground MSG dust. We first mixed 800 g of vitamin A 250-CWS with 60 g of hydroxypropyl cellulose that had been dissolved in 450 mL ethyl alcohol to serve as the binding agent or glue. This mixture was then combined with 3200 g of 100-mesh MSG powder so that MSG powder stuck to the vitamin A particles. This premix was then dried by fanning and mixed using a Patterson-Kelly blender (East Stroudsburg, PA) with commercial MSG crystals at a 5:95 ratio until it was homogeneous. This MSG-A contained ~810 μg RE of vitamin A/g.

The study was carried out in a rural, traditional rice-eating area in West Java ~20 km from the city of Bogor. Of the three major MSG producers in Indonesia, one (PT Sasa Inti, Surabaya, Indonesia), controlled the highest proportion (80%) of the market in the study area and was willing to cooperate with the project. The Sasa brand was, therefore, selected for fortification. Packets of MSG marketed in the study area varied in size from 0.65 to 13.6 g. All these sizes were included in the fortification scheme. The MSG-A was marketed through normal channels and without promotion. It was produced in the Sasa factory in Surabaya, ~965 km away, then sent to the agent at the nearest city (Bogor) to the program area. From this agent the MSG-A was sold to markets and foodstalls in five villages in the study area; in the control area, composed of five nearby villages, nonfortified MSG was marketed as usual.

The five villages in the program area consisted of 48 subvillages; those in control areas consisted of 44 subvillages. The research team did not participate in the marketing. At regular intervals packets of MSG and MSG-A were purchased from all village foodstalls and vitamin A content was assayed. The samples were obtained at 1, 2, 4, 6, 9, and 11 mo after marketing began. Samples were also obtained at the consumer level from 10 households in each village. The quantitative analysis of vitamin A in MSG was performed by the spectrophotometric method (13). A quick test for vitamin A content of MSG-A in the field was performed semiquantitatively by a modification of the Carr-Price reaction (14) as follows: ~15 g MSG was mixed with ~0.5 mL trichloroacetic acid in chloroform; the blue color that appeared in several seconds was compared with standard blue colors equivalent to 150, 300, 450, 600, and 900 μg RE. This quick test was used for screening whether or not quantitative analysis was necessary and in monitoring the penetration of MSG-A into the two study areas.

Program and control areas contained ~5500 preschool-age children (0–5 y) each. Children were examined three times: at base line and at 5 and 11 mo after MSG-A was introduced (6 and 12 mo after base line). Ages were ascertained directly from parents with the aid of a local events calendar. Field workers visited every household 2 d before the examination to obtain informed consent from the mothers and to ask that they bring their preschool children to a central site where the children would undergo medical, anthropometric, and ophthalmologic examinations. These findings are reported elsewhere (15). Approximately 70% of the mothers brought their children to the examination site at each of the rounds. Samples of blood for vitamin A analysis were collected from an independent, systematic sample of at least 200 program and control children at each round by using a random start and selecting every 16th subject to arrive at the central site. Therefore, children whose blood was obtained at base line were rarely the same children who contributed blood at the subsequent visit. Follow-up blood samples could not be collected on the same children because mothers objected to collection of more than one blood sample. The sample of children donating specimens at each round was taken to be representative of all children examined at that particular round. Samples of breast milk were taken from mothers who, at the time of examination, were still breast-feeding their babies < 6 mo of age. Breast-milk samples of ≥ 25 mL were collected in the middle of a feed between 0900 and 1200 by use of a manual pump. Samples were kept at −20 °C until analysis.

Blood samples were collected from finger tips in four to five capillary tubes. The tubes were sealed with molten candle wax and then placed in an ice thermos. When the samples reached the laboratory several hours later, the serum was separated and kept at −20 °C until analysis.

Vitamin A levels in the serum were determined by HPLC (13). Breast-milk samples were analyzed by the triflouroacetic acid method (16). Before analysis, breast-milk samples were incubated with an equal volume of 1 mol KOH/L in 95% alcohol for 30 min at 60 °C because preliminary analysis indicated optimal results were obtained with this preparation.

Trained nutritionists assessed 24-h dietary intake on two consecutive days from a 4% random subsample of families. An abbreviated method was employed that focused particularly on

TABLE 1
Retention of vitamin A in MSG-A in relation to the duration at market

Length of time marketed	Number of samples	Vitamin A level	Percent retention
mo	*n*	*μg RE/g**	%
0	10	810 ± 390	100.0
1	42	795 ± 395	98.1
2	42	750 ± 308	92.6
4	42	675 ± 418	83.3
6	42	555 ± 418	68.5
9	42	480 ± 355	59.3
11	42	465 ± 318	57.4

* ±SD.

food sources of β-carotene (leafy greens, yellow fruits and fibers, etc). The purpose was to provide estimates of base-line comparability between program and control groups.

Statistical analysis utilized Students *t* test for the difference between means and chi-square for the shift in distributions (17). The primary objective of analysis was the change in each group over time. Midyear and 12-mo measurements were compared with those at base line in the same group to reveal whether the effect of fortification on program children was progressive. Control villages adjacent and similar to the program area were followed in the same fashion to identify changes in vitamin A status that might have been unrelated to fortification (eg, seasonality, annual variation in harvests, etc).

Results

MSG-A marketing commenced in January 1985, 1 mo after base-line data were collected. MSG-A penetrated three control subvillages. The reverse also occurred: six subvillages in the program area did not receive MSG-A because they were closer to markets and foodstalls in the control area. The data from these nine cross-contaminated subvillages were excluded before any comparisons, leaving 5755 children in the program area and 5445 in the control area.

Retention of vitamin A in MSG-A in relation to duration at market is shown in **Table 1**.

There were no significant differences in dietary consumption by preschool program and control children at base-line examination (**Table 2**). As expected, consumption of β-carotene was low, representing only 30% of the RDA for vitamin A (Muhilal, T Apunain, D Karyadi, et al, unpublished observations, 1983) despite the emphasis placed on assessing the intake of this nutrient. Other reported nutrient intakes are low due in part to the shortened design of the dietary questionnaire.

TABLE 2
Daily nutrient consumption of program and control children*

Energy and nutrient	Program group (n = 138)	Control group (n = 137)
Energy (kcal)	496 ± 287	518 ± 309
Protein (g)	13 ± 9	14 ± 9
Fat (g)	12 ± 9	13 ± 9
Carotene (μg)	718 ± 1047	789 ± 1203
Vitamin C (mg)	18 ± 21	22 ± 29
Iron (mg)	3.2 ± 2.7	3.6 ± 3.3

* $\bar{x}$ ± SD.

TABLE 3
Mean serum vitamin A before and after MSG-A marketing

Group	Duration of marketing MSG-A	Number of samples	Serum vitamin A*
	mo	*n*	*μmol/L*
Program	0	205	0.67 ± 0.33
	5	258	0.78 ± 0.32†
	11	217	0.92 ± 0.33†
Control	0	240	0.78 ± 0.35
	5	289	0.71 ± 0.30‡
	11	290	0.72 ± 0.33‡

* $\bar{x}$ ± SD.
† $p < 0.001$ (increase) compared with level at 0 mo in program area.
‡ $p < 0.05$ (decrease) compared to 0 mo in control area.

Base-line serum vitamin A levels were lower in the program villages (**Table 3**). Levels in program villages rose significantly between base line and the 5-mo follow-up and rose still higher by 11 mo. Serum vitamin A levels in the control group fell significantly below base line at 5 and 11 mo.

There was a significant shift in serum vitamin A levels over time in program-village children but not in control-village children (**Table 4**, **Fig 1**). The improved distribution of serum vitamin A levels among program children was statistically significant ($p < 0.05$).

Vitamin A levels in breast milk of lactating mothers in program and control areas were similar at base line (**Table 5**, **Fig 2**). Five months after the marketing of MSG-A, the vitamin A in breast milk in the program area rose significantly. Eleven months after the marketing of MSG-A the vitamin A in the breast milk remained at this higher level. In the control group, breast-milk vitamin A levels at 5 and 11 mo were below those at base line.

Discussion

Just as in many developing countries, vitamin A deficiency is prevalent in Indonesia (1, 2). From previous work (2) and from base-line values in this study, almost half the preschool children have serum vitamin A levels < 0.70 μmol/L.

A nationwide survey revealed that most xerophthalmic children have regular access to β-carotene–rich dark green leafy vegetables (2, 18). Unfortunately these are consumed in small amounts if at all. Nutrition-education campaigns have had little success in raising consumption in Indonesia and more aggressive, comprehensive strategies are planned for the future.

To date, the major approach to combatting vitamin A

TABLE 4
Distribution of serum vitamin A values before and after MSG-A marketing

Group	Duration of marketing MSG-A	Total number of children	Serum vitamin A		
			<0.35 μmol/L	0.35–0.69 μmol/L	≥0.70 μmol/L
	mo	*n*	*n* [%]	*n* [%]	*n* [%]
Program	0	205	21 [10.2]	78 [38.0]	106 [51.8]
	5	258	10 [3.9]	93 [36.0]	155 [60.1]
	11	217	8 [3.7]	56 [25.8]	153 [70.5]
Control	0	240	22 [9.2]	93 [38.8]	125 [52.0]
	5	289	29 [10.0]	121 [41.9]	139 [48.1]
	11	290	30 [10.3]	115 [39.7]	145 [50.0]

deficiency in Indonesia has been periodic distribution, every 6 mo, of UNICEF-supplied capsules of 60 000 μg RE vitamin A to preschool children in high-risk areas either through a special, dedicated system or integrated into established multipurpose programs. Various pilot studies demonstrated the effectiveness of this approach for reducing xerophthalmia and blindness rates (19, 20) and mortality (6). Unfortunately coverage rates fall with time to ~40–50% of the target group (19); those missed are usually in greatest need (7). The cost of distribution can prove prohibitive (19).

Fortification of a commonly consumed dietary item provides a potential mechanism for overcoming many of these limitations. The main problem lies in identifying a suitable vehicle: one that is consumed in substantial amounts by a large proportion of the children with significant vitamin A deficiency; that passes through a small number of central processing plants where fortification can be readily accomplished and supervised; and for which there is relatively little variation in consumption among potential recipients, permitting levels of fortification that ensure adequate amounts of vitamin A to reach the target children without overdosing maximum consumers. In Indonesia MSG, a popular food enhancer, best met these criteria.

Concerns about acceptability were allayed by the marketing and distribution figures from the manufacturer during the intervention period, which indicated that MSG sales were unchanged after fortification. Further, daily MSG consumption levels were the same in the program and control villages for both adults (0.40 and 0.41 g/d, respectively) and preschool children (0.24 and 0.21 g/d, respectively), supporting our earlier, small-scale

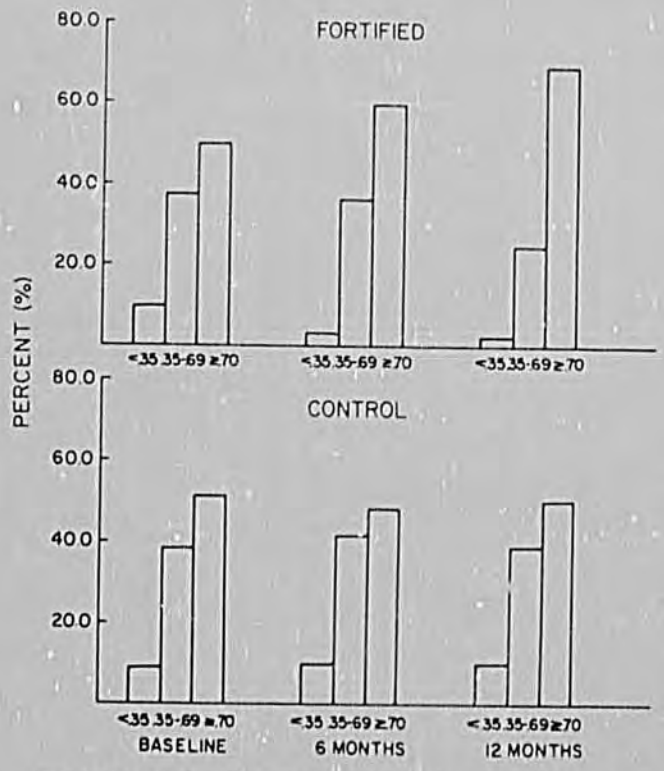


FIG 1. Distribution of serum vitamin A levels among children from program (upper graph) and control (lower graph) villages at base line and at 5 and 11 mo after introduction of fortified MSG in the program area (6 and 12 mo after base line).

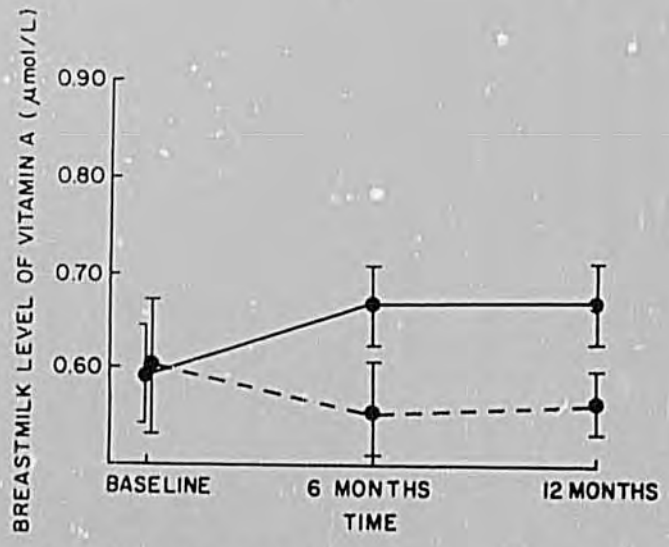


FIG 2. Mean levels and 95% confidence limits of vitamin A in the breast milk of lactating mothers at base line and at 5 and 11 mo after introduction of fortified MSG in the program area (solid line) and continued use of nonfortified MSG in the control area (broken line).

TABLE 5
Vitamin A level in breast milk among lactating mothers before and after MSG-A marketing

Duration of marketing MSG-A	Program area		Control area	
	Number of samples	Breast-milk vitamin A level*	Number of samples	Breast-milk vitamin A level*
mo	*n*	*μmol/L*	*n*	*μmol/L*
0	178	0.60 ± 0.29	200	0.61 ± 0.45
5	218	0.67 ± 0.27†	245	0.58 ± 0.35
11	263	0.67 ± 0.30†	192	0.58 ± 0.20

* $\bar{x} \pm$ SD.
† Increase in value compared with 0 mo $p < 0.05$.

studies on the organoleptic acceptability of the fortified product.

Our approach also overcame one of the technical difficulties encountered in a pilot Philippines trial (R Florentino, personal communication, 1980), where fine powder migrated between the walls of the containers preventing water-tight heat sealing. As a result early samples in the Philippines suffered rapid loss of potency. In contrast our assay of samples purchased from local markets retained > 50% of vitamin A at 11 mo. Although even this level is far from ideal, marketing surveys indicate that most MSG reaches consumers within 2–4 mo after leaving the factory, when retention rates are well in excess of 80%. The large standard deviation of mean vitamin A content at base line indicates some problems with consistancy of the fortified product. Levels were never excessive, however, and given the large number of packets purchased by most families (almost 1–2/d) long-term levels should approach the average.

Comparison of serum and breast-milk vitamin A levels at base line and again 5 and 11 mo after introduction of MSG-A demonstrated significant impact on the vitamin A status of the target population. Not only did mean serum vitamin levels rise but there was a shift in the distribution of these levels with a significant reduction in the proportion of children with deficient and low values. A similar phenomenon was observed in Guatemala (8, 21) and the Philippines (9, 22), indicating the vitamin A supplement reached the neediest segment of society. Values in the control area remained unchanged, supporting the supposition that improvement in vitamin A status was related to introduction of MSG-A and not to other, extraneous factors such as seasonality. Breast-milk levels followed a similar pattern.

The full impact MSG fortification might have on vitamin A status remains unknown. Serum and breast-milk vitamin A levels were still rising at the last follow-up examination 11 mo after introduction of MSG-A. Longer-term consumption by pregnant and lactating women, by all women of child-bearing age, and by young children might raise vitamin A levels further and move a larger group of children (including infants) into a state of adequate vitamin A reserves. The impact should also be greater if all MSG marketed to this population is fortified not just the 80% controlled by one manufacturer.

Unlike the early Philippine trials the MSG-A was not promoted or provided free of charge. The cost of fortification was subsidized to retain parity in price between the fortified and nonfortified product. MSG consumption rates remained unchanged. The manner in which the added cost of fortification is handled is critical especially because the Indonesian government has adopted a policy of nationwide fortification. In the Philippines (9, 23) the cost of fortification was covered by reducing the MSG content of the fortified packets. This led consumers to purchase larger packets of nonfortified MSG that provided them with more MSG for their money. In Guatemala sugar manufacturers were responsible for absorbing the cost of fortification. With a fall in world sugar prices and rise in the cost of vitamin A however, they were forced to suspend fortification.

The government of Indonesia will probably circumvent these potential problems by requiring that all MSG in packages below a certain size be fortified, that the cost of fortification be spread over all MSG produced regardless of package size, and by gradually passing on the cost to the consumer through annual reductions in the level of government subsidization of the process. Such a system would encourage stable market patterns and eventually insulate the fortification process from the vagaries of government budgets. For example, the marginal cost of fortifying MSG with vitamin A in Indonesia is presently estimated to be 13% of the cost of the unfortified product. If only the 35–50% of MSG that reaches rural consumers is fortified (reflecting program targeting) but the cost increment is uniformly spread over all marketed MSG in the country, the marginal increase in cost to individual consumers would be < 7% over a total period of several years.

This pilot study of vitamin A fortification of MSG demonstrates that a national program is feasible and has significant effects on the state of vitamin A nutriture of the community and on the community's health (15). In the next phase towards national fortification, the program will be expanded to a far larger area. In the interim, MSG producers will need time to develop the capacity

to produce and deliver the fortified product on a large scale.

Technical assistance was provided by Drs Alfred Sommer and Keith West and Ms Joanne Katz of the International Center for Epidemiologic and Preventive Ophthalmology (ICEPO), Johns Hopkins University, Baltimore, MD; Mr Rod Crowley of the USDA, Washington, DC; Dr Daniel Kraushaar of Helen Keller International, New York; and Mr Harlan Hall of the Coating Place, Verona, WI. The project could not have taken place without the support and cooperation of PT Sasa Inti, Indonesia.

References

1. Nutritional Blindness Prevention Project. Characterization of vitamin A deficiency and xerophthalmia and the design of effective intervention program. Jakarta, Indonesia: Ministry of Health, 1980.
2. Sommer A. Nutritional blindness: xerophthalmia and keratomalacia. New York: Oxford University Press, 1982.
3. Sommer A. Field guide to the detection and control of xerophthalmia. 2nd ed. Geneva: World Health Organization, 1982.
4. Sommer A, Katz J, Tarwotjo I. Increased risk of respiratory disease and diarrhea in children with pre-existing mild vitamin A deficiency. Am J Clin Nutr 1984;40:1090–5.
5. Sommer A, Tarwotjo I, Hussaini G, Susanto D. Increased mortality in children with mild vitamin A deficiency. Lancet 1983;2: 585–8.
6. Sommer A, Tarwotjo I, Djunaedi E, et al. Impact of vitamin A supplementation on childhood mortality: a randomized controlled community trial. Lancet 1986;1:1169–73.
7. Tarwotjo I, Sommer A, West KP, et al. Influence of participation on mortality in a randomized trial of vitamin A prophylaxis. Am J Clin Nutr 1987;45:1466–71.
8. Arroyave G, Mejia LA, Aguilar JR. The effect of vitamin A fortification of sugar on the serum vitamin A levels of preschool Guatemalan children: a longitudinal evaluation. Am J Clin Nutr 1981;34:41–9.
9. Solon F, Fernandez TL, Latham MC, Popkin BM. An evaluation of strategies to control vitamin A deficiency in the Philippines. Am J Clin Nutr 1979;32:1445–53.
10. Tiler LJ, Gorathim W, Kare MR, Reynolds WA, Wertman RJ. Glutamic acid: advances in biochemistry and physiology. New York: Raven Press, 1979.
11. Code of Federal Regulations. Title 21, part 182.1 (A). Washington, DC: US Government Printing Office, 1987.
12. World Health Organization. Toxicological evaluation of certain food additives with a review of general principle and specification. Geneva: WHO, 1974. (WHO technical report series #538.)
13. Arroyave G, Mejia LA, Chichester CO, et al. Biochemical methodology for the assessment of vitamin A status. Washington, DC: The Nutrition Foundation, 1982. (International Vitamin A Consultative Group report.)
14. Muhilal, Muriana A. Technology of MSG fortification with vitamin A. Penelitian Gizi Makan 1985;8:57–66.
15. Muhilal, Permeisih D, Idjradinata YR, Muherdiyantiningsih, Karyadi D. Vitamin A fortified MSG and health, growth, and survival of children: a controlled field trial. Am J Clin Nutr 1988;48: 1271–6.
16. Neeld JB, Pearson WN. Macro and micro methods for the determination of serum vitamin A using trifluoroacetic acid. J Nutr 1963;79:454–62.
17. Snedecor GW, Cochran WG. Statistical methods. 6th ed. Ames, IA: Iowa State University Press, 1967.
18. Tarwotjo I, Sommer A, Soegiharto T. Dietary practices and xerophthalmia among Indonesian children. Am J Clin Nutr 1982;35: 574–81.
19. West KP, Sommer A. Periodic, large oral doses of vitamin A for the prevention of vitamin A deficiency and xerophthalmia. Washington, DC: Nutrition Foundation, 1984. (International Vitamin A Consultative Group Report.)
20. Vijayaraghavan K, Rameshwar Sarma KV, Prahlad Rao N, Reddy V. Impact of massive doses of vitamin A on incidence of nutritional blindness. Lancet 1984;2:149–51.
21. Arroyave G, Aguilar JR, Flores M, Guzman MA. Evaluation of sugar fortification with vitamin A at the national level. Washington, DC: Pan Am Health Organization, 1979. (PAHO science publication #384.)
22. Latham M, Solon F. Vitamin A deficiency in the Philippines. In: Bauernfiend JC, ed. Vitamin A deficiency and its control. Orlando, FL: Academic Press, 1986:425–43.
23. Solon F, Latham MC, Guirriec R, Florentino R, Williamson DF, Aguilar J. Fortification of MSG with vitamin A: the Philippine experience. Food Technol 1985;39:71–7.

APPENDIX F

Muhilal, Permeisih D, Idjradinata Y, Muherdiyantiningsih, and Karyadi D: Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial. **Am J Clin Nutr** 48:1271-1276 1988.

Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial[1-4]

Muhilal, PhD; Dewi Permeisih, BS; Yanyan R Lajradinata, MD; Muherdiyantiningsih, BS; Darwin Karyadi, MD, PhD

ABSTRACT In a controlled trial, fortification of commercially marketed monosodium glutamate (MSG) with vitamin A improved serum vitamin A levels of young children and the vitamin A content of breast milk of lactating women. These improvements in vitamin A indices were accompanied by dramatic changes in health and anthropometric status. During the course of the study, the prevalence of Bitot's spots among children in program villages fell progressively from 1.2% at base line to 0.2% 11 mo after introduction of the fortified product ($p < 0.001$); xerophthalmia rates in control villages remained essentially unchanged. Linear growth was greater among program than among control children at every age. Hemoglobin levels among program children rose by ~10 g, from 113 ± 16 g/L at base line to 123 ± 16 by 5 mo ($p < 0.001$); they remained essentially unchanged among children of control villages. Preschool children in control villages died at 1.8 times the rate of children in program villages. *Am J Clin Nutr* 1988;48:1271–6.

KEY WORDS Fortification, monosodium glutamate (MSG), vitamin A, xerophthalmia, hemoglobin, mortality, growth

Introduction

Vitamin A deficiency is a major nutritional problem in Indonesia (1) and much of the developing world (2, 3). The three major approaches to the control of vitamin A deficiency are nutrition education, periodic distribution of a large dose of vitamin A (60 000 μg RE [200 000 IU]) two or three times a year, and fortification of a commonly consumed dietary item with vitamin A. We recently completed a controlled field trial in which vitamin A-fortified monosodium glutamate (MSG) was distributed through normal market channels (4). The vitamin A status of children and lactating mothers in villages receiving fortified MSG were significantly improved in contrast with those in control villages as noted by a rise in the levels of vitamin A in serum and breast milk. In the present paper we report the impact this improved vitamin A status had on xerophthalmia rates, growth, hemoglobin levels, and child survival.

Methods

The unique technology for fortifying MSG with vitamin A, choice of concentration to provide an average of one-fourth to one-half the Indonesian Recommended Dietary Allowance to MSG-consuming children, and selection of the study areas were detailed elsewhere (4). The program area consisted of five villages with the five nearby villages serving as a control area. Children were examined three times: at base line and 5 and 11 mo after introduction of vitamin A-fortified MSG (MSG-A). As expected not all children were available for each examination (**Table 1**). The fortified product was substituted for unfortified MSG and distributed without promotion via normal market channels in program villages. Sales figures maintained by the manufacturer indicated little if any change in per capita MSG consumption in either the program or control areas. MSG-A penetrated 3 of 44 subvillages in the control area and unfortified MSG penetrated 6 of 48 subvillages in the program area. These nine subvillages are excluded from the analyses.

Two teams conducted all examinations and were assigned

[1] From the Nutrition Research and Development Centre, Ministry of Health, Bogor, Indonesia, and the Cicendo Eye Hospital, Bandung, Indonesia.

[2] This report was prepared under cooperative agreement #0045 between ICEPO and the Office of Nutrition, United States Agency for International Development. The Indonesian Nutrition Research and Development Center and ICEPO are WHO collaborating centers for the prevention of vitamin A deficiency and xerophthalmia.

[3] Supported by the Ministry of Health, Government of Indonesia; Helen Keller International, New York; the International Development Research Center, Ottawa; the United States Agency for International Development; the Ford Foundation; and Task Force Sight and Life, Hoffman-La Roche, Basle.

[4] Reprint requests to A Sommer, ICEPO, Wilmer Institute 120, Johns Hopkins Hospital, Baltimore, MD 21205.

Received August 31, 1987.

Accepted for publication December 8, 1987.

TABLE 1
Number and percent of children examined in program and control areas

	Month 0	Month 6	Month 12	RT* census at 10 mo
Program				
<1 y				
n	870	791	667	1199
%	73	66	56	100
1–5 y				
n	2903	3254	3386	4556
%	64	71	74	100
Total†				
n	3773	4058	4059	5755
%	66	71	71	100
Control				
<1 y				
n	902	808	710	1134
%	80	71	63	100
1–5 y				
n	3231	3270	3650	4311
%	75	76	85	100
Total†				
n	4133	4115	4396	5445
%	76	76	81	100

* RT, local neighborhood leaders.
† Includes children of unknown ages.

to an equal mixture of program and control areas. All three examinations in a subvillage were conducted by the same team. Each team consisted of an ophthalmologist, a nurse, a nutritionist, an enumerator, a laboratory technologist, and two administrative officers. Advance visits to every household were made by field workers (two field workers in every village) to ask mothers to bring their preschool children to a central examination site located in a nearby building. All available children were examined by an ophthalmologist. The diagnosis of xerophthalmia was based upon standard WHO criteria (5, 6). Children with evidence of active xerophthalmia (XN, X1B, X2, and X3) received vitamin A treatment.

Twenty percent of all children presenting at the examination site were systematically selected (after a random start) for measurement of weight and height. For children > 15 mo of age, weight was measured on an Indonesian-made beam balance (a dacin) to the nearest 0.1 kg. Children ≤ 15 mo were weighed on a Detecto platform scale (Detecto Industrial Scale Co, Long Island City, NY). Standing height (for ages > 15 mo) and recumbent length (for ≤ 15 mo) were measured on a locally constructed wooden board to the nearest 5 mm.

Hemoglobin was determined on 6% of the children (a systematic subsample of one of every three children undergoing anthropometry) using the cyanomethemoglobin method (7).

Because recent data collected elsewhere in Indonesia indicated that vitamin A supplementation might have a favorable impact upon mortality, we devised a method by which we could obtain potentially relevant information even though the study was already underway. The population of preschool children in the two study areas was ascertained 10 mo after the base-line survey by consulting birth and death registrations maintained by the official local neighborhood leaders (RTs) responsible for every 15–20 households. By this method 5755 children aged 0–5 y allegedly resided in program villages and 5445 in control villages after the small number of control subvillages into which MSG-A had penetrated and the program villages into which it had not had been removed.

Infant and child deaths were identified by demographic research teams assisted by local field workers at the 11-mo follow-up. All available families were questioned about infant and preschool (0–5 y) child deaths in the previous year. Marketing of MSG-A commenced in January 1985 and mortality data were collected in December 1985. If at the time of the visit neither the wife nor the husband was at home, the information was sought from the RT.

Statistical analysis utilized the Student's *t* test for the difference between means and McNemar chi-square test for differences in proportions (8).

Results

On the basis of the estimated population of children in the two study areas, a slightly larger proportion were examined in control than in the program areas (Table 1).

Xerophthalmia

Data are presented in two ways: on all children available for examination on that particular round and on the smaller cohort of children who were consistantly available at each of the three examinations. In theory, the former provides a more representative cross-sectional assessment of the entire group of children at that particular time, the latter a more coherent longitudinal assessment of change in a less-representative, more-self-selected group of subjects. The cohort contains 39% of all children said to live in the study areas, about half the total examined at each round. Because cultural proclivities precluded obtaining more than a single blood sample from the same child, change in hemoglobin values within each group are only available on a cross-sectional basis.

Paralleling results of the biochemical data previously reported (4), base-line xerophthalmia rates were higher in program than in control areas (**Table 2, Fig 1**). Rates were 1.5 to 4 times higher among males than among females and higher in older than in younger children (not shown), both common observations in most vitamin A-deficient cultures (2). The prevalence of Bitot's spots in the program area declined 73% between base line and

TABLE 2
Prevalence of Bitot's spots (X1B) in program and control children

Group	Duration of marketing MSG-A	Number examined	Prevalence of X1B
	mo	*n*	%
Program	0	3803	1.24
	5	4059	0.32*
	11	4065	0.15*
Control	0	4135	0.77
	5	4115	0.90
	11	4400	0.80

* $p < 0.001$ compared with 0 mo for program children.

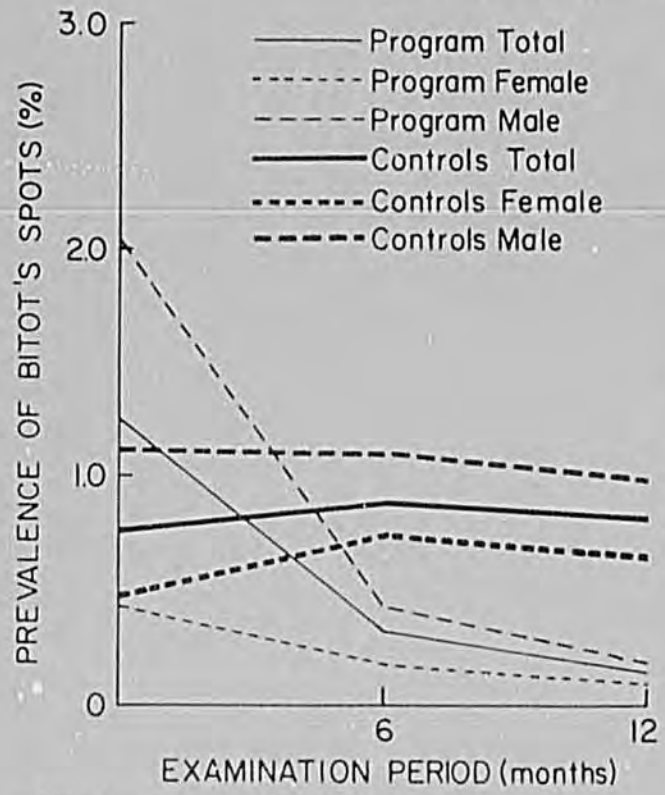


FIG 1. Prevalence of Bitot's spots (X1B) at base line and at follow-up examinations 6 and 12 mo later among children in program and control villages.

first follow-up examination 5 mo after introduction of fortified MSG; by 11 mo it had declined an additional 12% for a total decline of 85%. Declines of similar magnitude were registered in both sexes and all older children. (There were few cases at any time among children < 2 y of age). Prevalence rates among control children remained essentially unchanged throughout the three examinations.

Essentially identical results were observed among the more selective cohort group (**Table 3**).

Anthropometry

At base line, children in program areas were slightly heavier but no taller than children in control areas (**Table 4**). Net weight gain among the cohort of children examined both at base line and again 1 y later were similar in the two study populations for the first 2 y of life (**Fig 2**). Program children appeared to gain more weight during the third and fourth years of life but the differences are not statistically significant. Only a very small proportion of children in the fifth year of life at base line were still eligible to be weighed at follow-up, which may explain the large apparent difference in favor of control children.

In comparison with the small, variable difference in weight gain, there was a strong and consistant advantage in linear growth among program children at every age (**Fig 3**). Individual age-specific differences were statistically significant for the second and third years of life. This differential linear growth but similar weight gain resulted in relatively less weight-for-height gain in program than in control children (for all ages combined, 97.4 ± 0.4–98.2 ± 0.4% vs 94.4 ± 0.4–96.9 ± 0.4% of NCHS standards, respectively).

Hemoglobin

Hemoglobin values for program and control children were virtually identical at base line, 113 and 114 g/L, respectively (**Table 5**). The levels among program subjects rose 10 g within 5 mo of introducing MSG-A to 123 g/L ($p < 0.001$). The level was still significantly elevated although slightly lower at 11 mo. Hemoglobin levels remained unchanged among control subjects.

Mortality

As in most controlled trials of a very morbid or fatal outcome, base-line, prefortification rates were not collected. The analysis therefore compares rates observed in program and control areas. This would appear to be a reasonable approach because the two study areas were nearby one another and comparable in many respects. Base-line anthropometry results were slightly better in the program area but base-line vitamin A status was better in the control group both on biochemical (4) and clinical grounds. Previous studies suggested that vitamin A status may be a stronger predictor than anthropometric status of morbidity and mortality in Javanese children (9, 10).

Mortality rates among children in program villages were consistently below those for control children (**Table 6**). The odds ratio (OR) of dying among control vs program children varied from 1.14 among infants to 1.87 among preschool children, equivalent to a reduction in mortality among program infants of 11% and among program preschoolers of 45%.

Discussion

We demonstrated that fortified MSG distributed through normal marketing channels had a significant

TABLE 3
Prevalence of Bitot's spots (X1B) in the cohort of program and control children

Group	Duration of marketing MSG-A	Number examined	Prevalence of X1B
	mo	*n*	%
Program	0	2102	1.24
	5	2102	0.33*
	11	2102	0.19*
Control	0	2169	0.83
	5	2169	0.92
	11	2169	1.11

* $p < 0.001$ compared with 0 mo for program children.

TABLE 4
Baseline anthropometric status of program and control children*

Age	Program children			Control children		
	Number of children	Weight	Height	Number of children	Weight	Height
y	*n*	*kg*	*mm*	*n*	*kg*	*mm*
<1	178	6.63 ± 1.45	626.3 ± 56.8	184	6.44 ± 1.41	629.8 ± 59.3
1	164	8.80 ± 1.21	731.0 ± 38.1	198	8.58 ± 1.36	732.4 ± 46.6
2	158	10.52 ± 1.54	804.4 ± 51.1	163	10.10 ± 1.45	799.9 ± 49.3
3	138	12.21 ± 1.57	865.5 ± 87.9	145	11.79 ± 1.42	860.0 ± 54.9
4	125	13.63 ± 1.58	922.9 ± 57.2	143	13.25 ± 1.61	929.1 ± 59.0
5	41	14.46 ± 1.48	962.0 ± 51.8	31	14.16 ± 1.71	962.2 ± 67.0

* Weights and heights given as $\bar{X}$ ± SD.

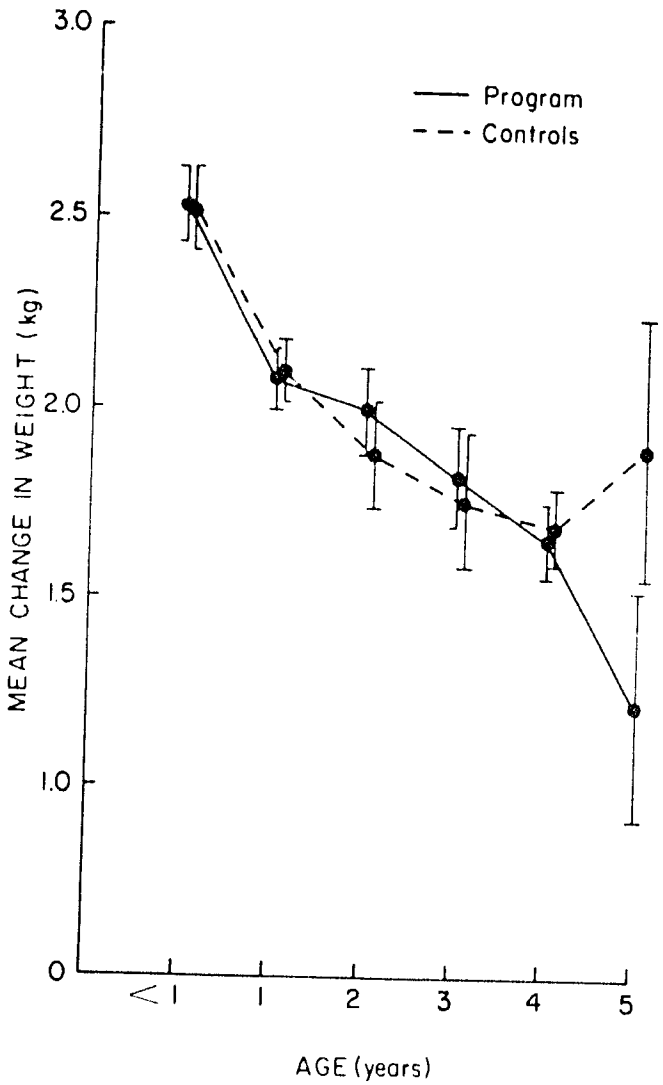


FIG 2. Mean (±SEM) age-specific increment in weight (kg) between base line and final examination among the cohort of children residing in program (n = 419) and control villages (n = 447) who were weighed at both examinations. None of the age-specific differences are statistically significant (by paired t test). The apparent large increase among 5-y-old control children is because of the small number of subjects.

impact on vitamin A status of preschool children as measured by a rise in serum vitamin A level between base line and 5 mo follow-up and a further rise between 5 and 11 mo (4). Vitamin A clearly reached the group needing

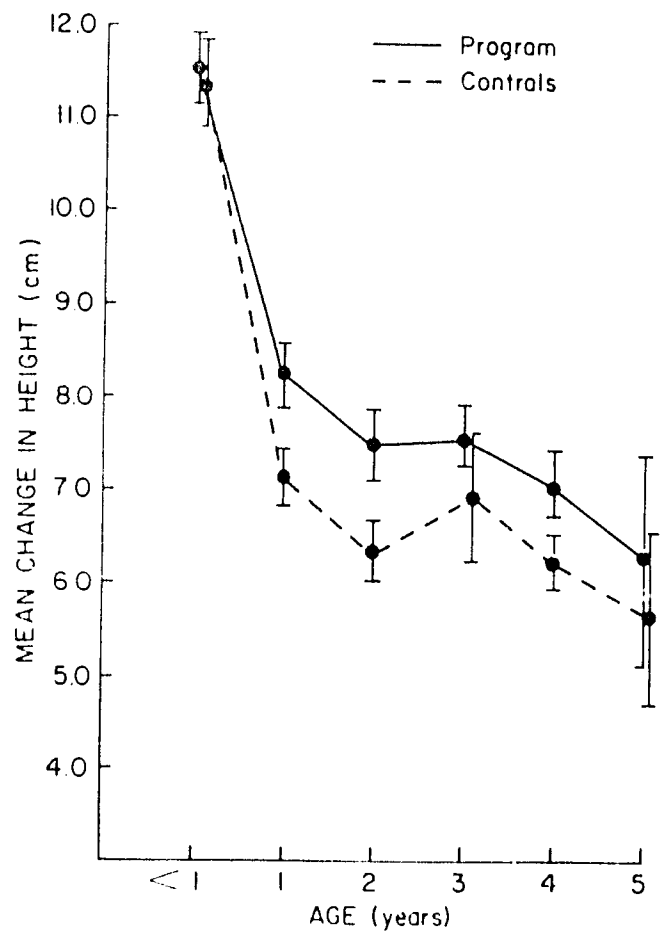


FIG 3. Mean (±SEM) age-specific increment in height between base line and final examination among the cohort of children residing in program (n = 419) and control villages (n = 447) who were measured at both examinations. Statistically significant differences were present at 1 (p = 0.02), 2 (p = 0.02), and (barely) at 4 (p = 0.06) y of age (by t test).

TABLE 5
Mean hemoglobin levels in program and control children

Group	Duration of marketing MSG-A	Number of children	Hemoglobin level*
	mo	*n*	*g/L*
Program	0	205	113 ± 16
	5	258	123 ± 16†
	11	217	121 ± 13†
Control	0	240	114 ± 16
	5	289	112 ± 15
	11	290	114 ± 14

* $\bar{x} \pm$ SD.
† $p < 0.001$ compared with 0 mo for program children.

it most, as demonstrated by a reduction in the proportion of children with low and deficient values. In comparison, levels in the control area, in which nonfortified MSG continued to be marketed, were unchanged.

The present analysis indicates the change in vitamin A status in program villages was associated with improvement in a variety of health variables: xerophthalmia rates declined whereas growth, hemoglobin levels, and child survival all increased. The striking reduction in the prevalence of new cases of xerophthalmia is consistant with the known responsiveness of xerophthalmia in young Indonesian children (2) and the successful delivery of supplemental vitamin A to needy children through MSG fortification. Solon et al (11) found a comparable response to vitamin A fortification in the Philippines.

The impact on other health variables was impressive. The rise in hemoglobin levels averaged 10 g/L within 5 mo of initiating fortification. It appears vitamin A is a limiting factor to hemoglobin formation but only to a point; hemoglobin did not rise further despite continued improvement in vitamin A status between mo 5 and 11 (4). The mechanism responsible remains uncertain though it appears to involve iron mobilization (12). Others reported a similar favorable influence on Fe metabolism during experimental vitamin A-repletion studies (13) and after vitamin A fortification of sugar (14) and salt (Hussaini, unpublished observation, 1982) (15). Anemia is a well-recognized problem among Indonesian children (I Tarwotjo, Muhilal, D Karyadi, Soekirmin, unpublished observations, 1978).

The influence on growth was largely limited to linear growth. Children in supplemented villages appeared to gain more length and/or height than did children in control villages at every age. The greatest differences were among children aged 1- and 2-y. Vitamin A may have been particularly growth limiting in this age group because of a greater degree of vitamin A deficiency. However, clinical and biochemical deficiency was more prevalent in older children, suggesting it is the greater potential for growth ordinarily seen in this age group that accounted for the greater impact.

The strong effect on linear growth in this study contrasts with a recent report from Aceh, Indonesia, where West et al (16) found periodic (once every 6 mo) supplementation with large dose (60 000 μ RE) vitamin A capsules had a greater impact on ponderal than on linear growth. Potential explanations include genetic and cultural factors, general food availability (especially calories and protein), other limiting micronutrients, and study design. Periodic massive dosing improves vitamin A status but does not maintain normal or even improved levels for > 2–3 mo (17, 18). Conceivably the Aceh study failed to sustain vitamin A levels above the threshold needed to promote linear growth for more than a few months thus limiting the potential response. Fortification, on the other hand, should lead to a progressive, sustained improvement in vitamin A status as was reflected in the biochemical variables (4). Experience in the Philippines confirms the advantages of fortification to periodic massive dosing in producing a sustained impact on vitamin A status (9).

It has long been known that vitamin A deficiency in animals increases their susceptibility to infection and drastically reduces survival (19). Only recently, however, has epidemiologic data indicated that mild vitamin A deficiency increases the risk of respiratory disease, diarrhea, and mortality in young children (9, 10). In the recent community-based field trial in Aceh (20, 21), periodic massive dose vitamin A supplementation was associated with a 35–70% lower mortality rate. The present study supports these findings in the absence of potential nonspecific benefits from contact between the child and capsule distributor or from the possible adjuvant effect of a massive dose. Potential weaknesses in our mortality data collection scheme need mentioning. Because the study was not originally intended to address mortality, solid base-line demographic data were not collected from each household at the start of the study. Instead, special teams subsequently reviewed the available records maintained by the local neighborhood leaders (RTs) who are each responsible for 10–15 families. These formed the basis for our denominator. Undoubtedly these records contain inaccuracies; however, there is no reason to suspect the degree of inaccuracy differed in a systematic (ie, biased) way between program and control areas. The only concern in this regard is because a smaller proportion of the children estimated to reside in the program area presented for examination than did control children. If this reflects an inflated estimate of the number of children living in the program area, the overestimate was still

TABLE 6
Death rates in program and control children after MSG had been marketed for 11 mo

Age	Program villages	Control villages	Odds ratio [$CI_{95\%}$]
mo	*n deaths/children [rate per 1000]*		
<12	109/1199 [91]	116/1134 [102]	1.14 [0.87, 1.50]
12–60	77/4556 [17]	134/4311 [31]	1.87 [1.41, 2.48]
Total	186/5775 [32]	250/5445 [46]	1.45 [1.19, 1.76]

< 10%. Assuming there was a 10% overestimate in the denominator used to calculate mortality among program children, the mortality rate among preschoolers in program villages would have been 19 per 1000 and the excess mortality among preschool-age control children 65 instead of 87%, a difference that is still highly significant. It further supports recent evidence from Africa that vitamin A supplementation can reduce short-term case-fatality rates in measles (22).

The multiple benefits that accrued from vitamin A fortification of MSG occurred in the absence of universal coverage. Not all children in the study area consumed MSG and of those that did only 80% received the fortified brand. Mandatory fortification of all MSG marketed to poor rural communities should have an even greater effect.

The magnitude of the impact may also have been limited by the relatively short duration of the present investigation. Serum vitamin A levels continued to climb and xerophthalmia rates continued to fall during the second 6 mo of observation. Regular, almost daily, vitamin A supplementation acts in many ways like dietary intake from natural sources: a large proportion is absorbed and retained, increasing liver stores. The longer the fortification is maintained, the greater the opportunity for children with even modest MSG intake to accumulate adequate vitamin A stores. This is especially true of infants. Increased vitamin A intake by pregnant and lactating women provides more vitamin A for the fetus, which may be born with greater liver stores; as shown in this study (4), infants received increased levels of vitamin A in breast milk during the postnatal period. Little clinical impact was seen among infants in this study, in part because they rarely suffer demonstrable xerophthalmia. It is also conceivable too few were able to benefit from the short course of fortification or that vitamin A status at birth is already relatively adequate in this population.

Importantly, fortification is free of the potential hazards of teratogenicity that might be associated with periodic massive dosing of women of child-bearing age. Given the relative safety and efficacy of MSG fortification with vitamin A and the feasibility of the new production process designed for this purpose (4), the Government of Indonesia has embarked on a massive fortification scheme as the most practical, effective, and rapid solution to a major national health problem. ■

Technical assistance was provided by Drs Alfred Sommer and Keith West and Ms Joanne Katz of the International Center for Epidemiologic and Preventive Ophthalmology (ICEPO), Johns Hopkins University, Baltimore, MD; Mr Rod Crowley of the USDA, Washington, DC; Dr Daniel Kraushaar of Helen Keller International, New York; and Mr Harlan Hall of the Coating Place, Verona, WI. The project could not have taken place without the support and cooperation of PT Sasa Inti, Indonesia.

References

1. Ministry of Health, Indonesia. Nutritional blindness prevention project. Characterization of vitamin A deficiency and xerophthalmia and the design of effective intervention programme. Jakarta, Indonesia: Ministry of Health, 1980.
2. Sommer A. Nutritional blindness: xerophthalmia and keratomalacia. New York: Oxford University Press, 1982.
3. World Health Organization. Prevention and control of vitamin A deficiency, xerophthalmia and nutritional blindness: proposal for a ten-year programme of support to countries. Geneva: WHO, 1985. (Nut/84.5, Rev 1.)
4. Muhilal, Murdiana A, Azis I, Saidin S, Jahari AB, Karyadi D. Vitamin A fortified MSG and vitamin A status: a controlled field trial. Am J Clin Nutr 1988;48:1265–70.
5. World Health Organization. Control of vitamin A deficiency and xerophthalmia. Geneva: WHO, 1982. (WHO technical report series #672.)
6. Sommer A. Field guide to the detection and control of xerophthalmia. 2nd ed. Geneva: WHO, 1982.
7. Lynch MG. Medical laboratory technology and clinical pathology. Philadelphia: WB Saunders, 1969.
8. Snedecor GW, Cochran WG. Statistical methods. 6th ed. Ames, IA: Iowa State University Press, 1967.
9. Sommer A, Katz J, Tarwotjo I. Increased risk of respiratory disease and diarrhea in children with pre-existing mild vitamin A deficiency. Am J Clin Nutr 1984;40:1090–5.
10. Sommer A, Tarwotjo I, Hussaini G, Susanto D. Increased mortality in children with mild vitamin A deficiency. Lancet 1983;2: 585–8.
11. Solon F, Fernandez TL, Latham MC, Popkin PM. An evaluation of strategies to control vitamin A deficiency in the Philippines. Am J Clin Nutr 1979;32:1445–53.
12. Mejia LA, Hodges RE, Rucker RB. Role of vitamin A in the absorption, retention and distribution of iron in the rat. J Nut 1979;109:129–37.
13. Hodges RE, Saurbelich HE, Conham JE, Wallace DL, Rucker RB. Hematopoietic studies in vitamin A deficiency. Am J Clin Nutr 1978;31:876–85.
14. Mejia LA, Arroyave G. The effect of vitamin A fortification of sugar on iron metabolism in preschool children in Guatemala. Am J Clin Nutr 1982;36:87–93.
15. Muhilal, Karyadi D. Highlight of current studies: considerations for program intervention. In: Human nutrition, better nutrition better life. Bangkok, Thailand: Aksornsmai Pres, 1984:191–5.
16. West KP Jr, Djunaedi E, Pandji A, et al. The influence of vitamin A supplementation on growth: a randomized community trial. Am J Clin Nutr 1988;48:1257–64.
17. Pereira SM, Begum A. Failure of a massive single oral dose of vitamin A to prevent deficiency. Arch Dis Child 1971;46:525–7.
18. West KP, Sommer A. Periodic large oral doses of vitamin A for the prevention of vitamin A deficiency and xerophthalmia: a summary of experiences. Washington, DC: Nutrition Foundation, 1984. (IVACG report.)
19. De Luca LM, Glover J, Heller J, Olson JA, Underwood BA. Recent advances in the metabolism and function of vitamin A and their relationship to applied nutrition. Washington, DC: Nutrition Foundation, 1979. (IVACG report.)
20. Sommer A, Tarwotjo I, West KP Jr, Loedin AA, Tilden R, Mele L. Impact of vitamin A supplementation on childhood mortality: a randomized controlled community trial. Lancet 1986;1:1169–73.
21. Tarwotjo I, Sommer A, West KP Jr, et al. Influence of participation on mortality in a randomized trial of vitamin A prophylaxis. Am J Clin Nutr 1987;45:1466–71.
22. Barclay AJG, Foster A, Sommer A. Vitamin A supplementation and measles-related mortality: a randomized clinical trial. Br Med J 1987;294:294–6.

APPENDIX G

Lloyd-Puryear M, Humphrey J, West KP Jr., Aniol K, Mahoney F, Mahoney J, and Keenum D: Vitamin A deficiency and anemia among Micronesian children. (submitted to **Nutrition Research**)

VITAMIN A DEFICIENCY AND ANEMIA AMONG MICRONESIAN CHILDREN

Michelle Lloyd-Puryear, PhD, MD,[1] Jean H Humphrey, MSPH, RD,[2] Keith P West, Jr, DrPH, RD,[2] Kiosi Aniol, MO, MPH,[1] Frank Mahoney, MD,[1] Joan Mahoney, MS, RD,[1] Deborah G Keenum, MA[2]

[1]The Truk State Hospital, Moen, Truk, Federated States of Micronesia

[2]The International Center for Epidemiologic and Preventive Ophthalmology, Wilmer Institute, Johns Hopkins University, Baltimore, MD 21205 USA

ABSTRACT

Vitamin A status was assessed by conjunctival impression cytology (CIC-A) and clinical signs in 60 systematically sampled 36-83 month old children attending a hospital outpatient department on Moen, Truk. Seventeen percent had xerophthalmia (12% with XN, 5% with XN+X1B). More than half (57%) were CIC-A abnormal reflecting mild subclinical vitamin A deficiency. CIC-A abnormal children were more anemic (by heratocrit, $p<0.05$) and were at greater risk of middle ear infection (OR = 3.5, 95% CL: 0.8, 14.5). Vitamin A deficiency appears to be a previously unrecognized nutritional problem among Micronesian children, the causes for which are speculative at present.

KEY WORDS: vitamin A deficiency, impression cytology, anemia, Truk, Micronesia

INTRODUCTION

Vitamin A deficiency, leading to xerophthalmia, is the leading cause of childhood blindness in developing countries throughout the world (1). Children with severe xerophthalmia (corneal xerosis, ulceration, or keratomalacia) are usually very ill, malnourished and carry an extremely high risk of mortality (2). Recent studies suggest that children with even mild xerophthalmia (nightblindness or Bitot's spots) are at an increased risk of infectious morbidity, including respiratory (3-4) and diarrheal (3) diseases, anemia (5),

---

Address correspondence and reprint requests to: Dr. Keith P. West, Jr., ICEPO - Wilmer 120, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21205.

and growth retardation (2,6-7), reflecting the systemic consequences of vitamin A deficiency. Risk of mortality among these children may be several-fold higher than that of children with normal eyes (8). Moreover, community-based vitamin A supplementation of children in areas of endemic deficiency may improve growth (9-10), hematopoiesis (9,11) and reduce mortality by as much as one-third (9,12). With this evidence relating vitamin A status to child health and survival, it is essential to identify communities where vitamin A deficiency may constitute a public health problem.

Vitamin A status among preschool children has not been previously reported from Micronesia. This preliminary study provides a first estimate of the magnitude of xerophthalmia and subclinical vitamin A deficiency in a clnic population of children living in Truk, Micronesia.

METHODS AND MATERIALS

Truk State, with a total landmass of 46 sq km consisting of 207 islands (40 inhabited) and a population of approximately 46,000 people, is the most populous state in the Federated States of Micronesia. Truk is divided into the core "Truk Islands," of volcanic origin (forming what is known as the Truk Lagoon), and the "outer islands," comprising flat, narrow, coral atolls lying up to 140 km from the island capital of Moen. The population growth rate is approximately 3.5% and infant mortality estimated at 25 per 1000 live births.

The present study comprised a vitamin A status and general health assessment survey of the outpatient pediatric population of Truk State Hospital. During a pre-determined three week period of enrollment (October 13 - November 6, 1987) approximately 1 in every 7 children 36-83 months of age presenting to the clinic, and not requiring hospitalization, were systematically selected for study. The sampling interval reflected a feasible schedule which could be adhered to by the investigators (ML-P, FM) amidst other clinical duties. A total of 60 children were successfully enrolled, representing 90% of all sampled children and 14% of the registered outpatient clinic population in that age group during the enrollment period. Seven selected children were not examined due to child noncompliance or parental refusal. Children presented with a wide variety of complaints typical of a general outpatient service. Following parental consent, a trained clinic nurse obtained a current history of nightblindness. There are no local terms which specifically refer to nightblindness in Truk. The condition was, therefore, carefully explained as normal vision and activity for age during the day, but greater difficulty seeing at twilight and later in the evening than their peers. A positive history was recorded if the mother described child's behavior in the evening to be consistent with nightblindness.

Children underwent a physical examination: 54 by a pediatrician (ML-P) and 6 by a family practitioner (FM), both fully familiar with the study protocol. The examination included hand light assessment of the anterior segment of the eye for xerophthalmia following standard diagnostic criteria (13), the middle ear for inflammation (erythemethous, non-mobile tympanic

membrane ± perforation) or discharge (otitis media), the oral cavity, the cardiopulmonary system (respiratory rate, costal retractions, breath sounds, heart rate, murmur), the abdomen for the presence of masses and liver or spleen enlargement, and the skin of the head, face, chest, and limbs for rashes and scabies.

Conjunctival impression cytology (CIC-A) was employed to assess vitamin A status (14-16). Specimens were obtained from the temporal bulbar conjunctiva of each eye using cut strips (4 x 20 mm) of Millipore acetate filter paper (Millipore, Corp., Bedford, Mass.) following standard procedures (16). Specimens were placed into vials of fixative which were securely capped and stored under ambient conditions. One week following completion of work, impression cytology specimens were transported to the Johns Hopkins University in Baltimore (ICEPO) for staining and microscopic evaluation of goblet and epithelial cell profiles. Specimens were classified as normal or abnormal according to a standardized algorithm (16). All specimens were read by one worker (DK) who was masked to all other health data. Impression cytology specimens from vitamin A deficient children lack goblet cells and mucin spots, and exhibit enlarged, separated, and often distorted epithelial cells. Normal specimens show goblet cells and/or mucin spots with sheets of small, tightly packed epithelial cells (14-16). Children were classified as CIC-A normal (vitamin A sufficient) or abnormal (vitamin A deficient) based on the most normal of the 2 specimens. Thus, vitamin A deficiency was diagnosed only when both cytologic specimens were abnormal.

Blood samples from the median cubital vein were drawn from 54 (90%) of the enrolled study children. Alliquots were collected in capillary tubes, sealed, centrifuged and read within 3 hours for hematocrit by the packed cell volume method (17). The remaining blood (1-4 cc) for vitamin A analysis was refrigerated, spun, and frozen at -20°. At the completion of the study serum specimens were packed in ice and handcarried to ICEPO in Baltimore for serum retinol determination by High Pressure Liquid Chromatography (18). Unfortunately, the specimens were not sufficiently light-protected, yielding a large number of extremely low retinol concentrations: (35% <0.35 µmol/L, 53% 0.35 - 0.70 µmol/L) (Figure 1) While consistent with widespread vitamin A deficiency many values were incompatible with the children's clinical (ocular and systemic) status. Assessment was, therefore, based solely on a history of nightblindness, clinical signs of xerophthalmia, and (independently) CIC-A status.

Anthropometric assessment by a nurse included measuring weight to the nearest 0.25 kg and standing height to the nearest0.2 cm using a standing beam balance scale with attached height measurement rod (Healthometer Corp., Bridgeview, IL). Percentsmedian weight for height (%WH) and height for age (%HA) were derived from the National Center for Health Statistics reference population (19) reflecting wasting and stunting malnutrition, respectively. Left mid-upper arm circumference (MUAC) was measured with a Zerfas insertion tape (20).

Usual dietary intake was assessed by a Registered Dietitian (JM) asking mothers how often their child consumed selected foods, including local dietary sources of vitamin A (i.e., dark green leaves, papaya, and eggs). Portion sizes were not assessed.

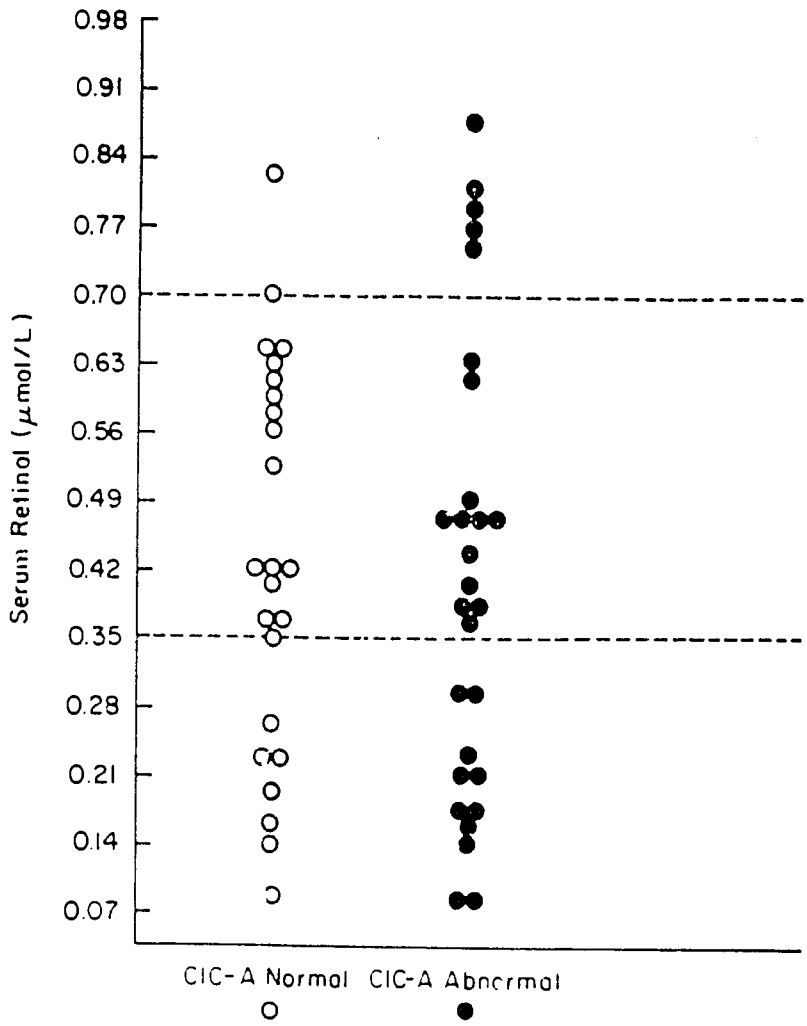


FIG. 1: Serum retinol levels by vitamin A (CIC-A) status. Specimens appeared to be altered during storage and transport from Micronesia to Baltimore resulting in many extremely low values. These data could not be used to evaluate status. CIC-A normal: open circles, n=24, 2 missing; CIC-A abnormal: solid circles, n=28, 6 missing. (0.03491 μmol/L = 1 μg/dL)

Data were entered onto microcomputers using RBase 5000 (Microrim Inc., Bellevue, WA) and analyzed using the SAS (SAS Institute, Cary, NC). Between group differences were tested using the Student's t-test for continuous variables and the chi-squared statistic for discrete variables (21). The odds ratio was computed with 95% confidence limits (95% CL) estimated by Woolf's method (22). Study procedures were approved by the Truk State Department of Health.

RESULTS

A total of 60 children were assessed: 37 males, 23 females, reflecting the general distribution of pediatric patients seen at this clinic.

More than half [57±13% (±2 SD)] of all study children had abnormal CIC-A in both eyes and were classified as vitamin A deficient (Table 1). Among non-xerophthalmic children (n=50), 54±14% had abnormal CIC-A. Of the 26 children (43%) with normal CIC-A status, 7 (12%) had one normal and one abnormal specimen, and in only 19 (31%) were both eyes normal.

TABLE 1
Vitamin A Status (by Impression Cytology and Clinical Signs) by Age (Sexes Combined)

		CIC-A abn		XN		X1B + XN		XN or XB	
Age (mos)	No.	n	%	n	%	n	%	n	%
36-59	28	18	64	2	7	2	7	4	14
60-83	32	16	50	5	16	1	3	6	19
All ages	60	34	57	7	12	3	5	10	17
95% CL		44,60						7,27	

Ten children (17±10%) had xerophthalmia. Seven (12%) had a positive history of nightblindness (XN) of whom 4 had abnormal impression cytology. Three children had nightblindness plus bilateral Bitot's spots (XN + X1B), all of whom had abnormal CIC-A status.

The prevalence of vitamin A deficiency did not vary by sex: 54% of males vs 61% of females had abnormal CIC-A; 17 vs 18% had nightblindness, respectively. Bitot's spots were observed in one male and two females.

Hematologic values were positively associated with CIC-A status (Figure 2). Children with abnormal CIC-A had significantly lower hematocrits ($\bar{x}$ = 33.0 ± 3.8) than children with normal cytology ($\bar{x}$ = 35.7 ± 3.5) ($p<0.05$). Differences in hematocrit distributions were similar by sex.

Children with abnormal CIC-A were at a 3.5 - fold higher risk (95% CL: 0.8, 14.5) of otitis media than children with normal CIC-A status (Table 2). Skin rashes were also slightly more common in children with abnormal CIC-A (Odds Ratio = 1.6). Lower 95% confidence limits for these two risk estimates bracket unity. Five of the ten mildly xerophthalmic children had otitis media; 3 had skin rashes. This population was free of lower respiratory tract infection [based on respiratory rate above 40 per minute (0/60), costal retractions (0/60), and breath sounds (4/60)] and thus could not be evaluated relative to vitamin A status. Other abnormalities

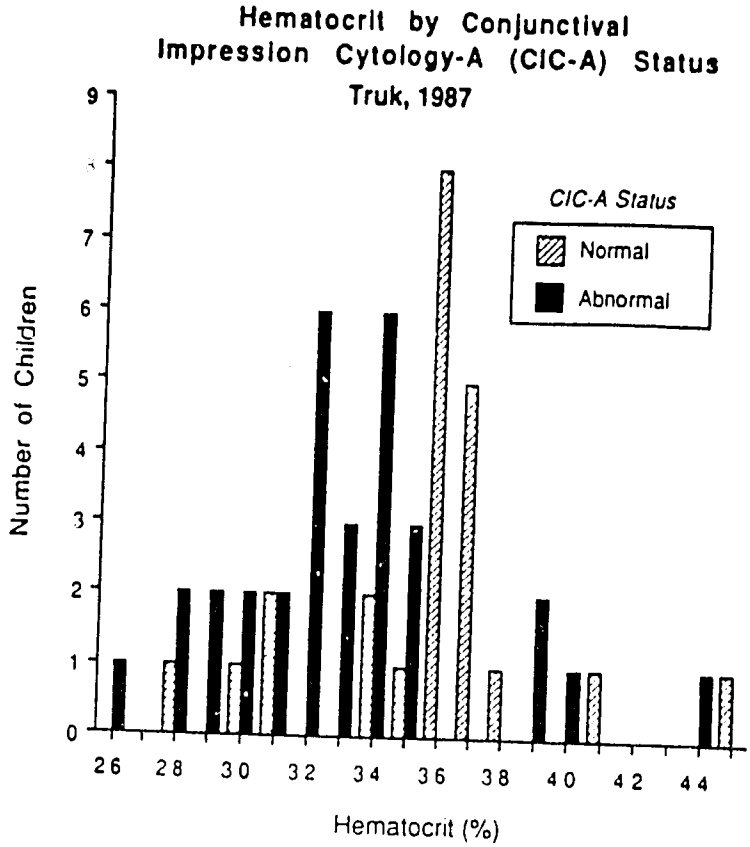


FIG. 2: Hematocrit levels by vitamin A status. Cross-hatched, CIC-A normal (n=31, 3 missing); solid, CIC-A abnormal (n=23, 3 missing).

TABLE 2
Physical Signs of Infection by Conjunctival Impression Cytology-A (CIC-A) Status, Ages and Sexes Combined

Sign/symptom	----CIC-A Status---- Abnormal n	%	Normal n	%	Odds ratio	(95% CL)
Otitis media	10/32	31	3/26	12	3.5	(0.8, 14.5)
Skin rash	12/33	36	7/26	27	1.6	(0.5, 4.9)
Lower RTI	0/23	0	0/26	0	-	- -

on physical exam were also absent or rare [heart rate (range: 72-140/minute), murmur (1/60), abdominal mass (0/60), hepato-splenomegaly (1/60), and scabies (0/60)].

Anthropometric data demonstrate a relatively non-wasted (by either %WH and MUAC) but mildly stunted (by %HA) sample of children (Table 3). There were no statistically significant differences

between groups (p>0.1). Sixty-one percent of all children reportedly consumed local dark green leaves less than once per month. Half (51%) ate papaya with the same low frequency. There were no differences by CIC-A status. Ninety percent of CIC-A normal and 67% CIC-A abnormal children reportedly ate eggs at least once per week (p<0.2 between groups).

TABLE 3
Anthropometry by Conjunctival Impression Cytology-A (CIC-A) Status, Age and Sex Combined, Truk 1987

CIC-A status	%WH*			%HA†			MUAC# (mm)		
	n	$\bar{x}$	SD	n	$\bar{x}$	SD	n	$\bar{x}$	SD
Abnormal	32	96.6	10.1	32	94.2	5.1	31	16.1	16
Normal	25	99.1	8.4	25	95.5	5.4	20	16.3	15

*%WH = percent of NCHS reference median weight for height;
†%HA = percent of NCHS reference median height for age;
#MUAC = left mid-upper arm circumference

DISCUSSION

More than half of these outpatient children in Truk had clinically inapparent but physiologically significant vitamin A deficiency by abnormal conjunctival impression cytology. Seventeen percent of the study children were nightblind, a third of whom had Bitot's spots. While such estimates are not directly applicable to the community at-large, this outpatient survey suggests that vitamin A deficiency may be an important public health problem in this region of Micronesia.

Xerophthalmia (mostly nightblindness) has been recognized in clinical settings in the Truk Islands only during the past two decades, sporadically at first but more regularly in recent years (KA and ML-P, personal observations). During 1986-7 an average of 15-20 children with mild xerophthalmia presented to the Truk Hospital outpatient clinic each month prompting interest to carry out the present study. In 1988 three children were hospitalized for keratomalacia (ML-P, unpublished observation).

Several observations suggest that vitamin A deficiency may be a recent phenomenon in Truk. First, in most areas where xerophthalmia is long-standing there is frequently a local, specific term for the condition. In Truk no such term exists, yet descriptions by the mothers of the ten children with nightblindness in this study were clear and exact: the child plays normally during the day but after sunset holds onto the mother's skirt, he feels the wall when moving about the house, sits quietly and does not play with other chilren, or has difficulty finding things. This lack of a local "diagnostic term" may reflect the culture's unfamiliarity with the condition. Importantly, elder members of

the community generally have no recollection of nightblindness existing when they were young (KA, personal observation).

Second, in endemically vitamin A deficient areas, women may frequently experience transient nightblindness during the third trimester of pregnancy which disappears within a week after childbirth or with vitamin A treatment (23), a likely consequence of a chronic, life-long deficit in dietary vitamin A. In contrast, few mothers in Truk have, to date, reported this condition.

Third, there has been a widely recognized and distinct shift in the Trukese diet during the past 25 years away from locally available fruits (eg. papaya), vegetables (eg, breadfruit, taro, green leaves), and fish for cash-purchased, imported food stuffs (eg, rice, tinned meats, turkey tails) (23). Small scale farming and fishing appear to be decreasing both quantitatively and qualitatively among young adults in the core Truk islands with the stronger attraction to, and dependence on, a market economy.

Finally, a "threshold" of recognition appears to have been crossed in the region during the past two to three years with a markedly increased frequency of cases of xerophthalmia being observed in clinics in Truk and elsewhere in Micronesia, especially in the Marshall Islands (MP Sanchez, and N Palofax, unpublished observations) and in Kiribati (R Galloway, personal communication).

Evidence from this study suggests that mild vitamin A deficiency may pose an increased health risk to young Trukese children. A greater proportion of children with abnormal impression cytology had middle ear infection, often a chronic condition. Other signs of acute morbidity (e.g., respiratory infection) were too infrequent in this sample of children, in part due to the study's exclusion criteria, to evaluate associations with vitamin A status. Early epithelial and immunologic defects appear to accompany mild vitamin A deficiency (25) which may predispose vitamin A deficient children to a greater risk of infection (3,4) and mortality (8,12) as observed in some populations. Trukese children with abnormal impression cytology also had significantly lower hematocrit levels than normal children. Hematocrits for 53% vs 17% of these children, respectively, were below a normal, age-adjusted hematocrit threshold of 34% (26). These findings are consistent with recent studies showing elevated hemoglobin or hematocrit levels following vitamin A supplementation among marginally nourished populations (5,9,11,27), suggesting a role (direct or indirect) for vitamin A in hematopoiesis. While attained growth status of CIC-A abnormal children was not significantly below normal children, their marginal linear growth deficit is consistent with comparisons between more severely vitamin A deficient (with mild xerophthalmia) and clinically normal children reported elsewhere (2,10).

This clinic survey provides a first quantitative estimate of both clinical and subclinical vitamin A deficiency in Micronesia. Certain dietary trends may be implicated in the apparent emergence of this disorder. However, much work needs to be done to quantify the severity, distribution, and likely causes of vitamin A deficiency in the population for planning public health intervention programs in the state and federation. These efforts are currently underway in Truk.

ACKNOWLEDGEMENT

This study was supported by the United States Public Health Service, Task Force Sight and Life, Basle, and Cooperative Agreement No. DAN-0045 between the International Center for Epidemiologic and Preventive Ophthalmology, the Johns Hopkins University, and the Office of Nutrition, Bureau for Science and Technology, United States Agency for International Development (USAID). The authors gratefully acknowledge the assistance of Lisa Mele, Mahmood Farazdaghi, and Drs. Alfred Sommer and David Morraga in carrying out this work.

REFERENCES

1. Sommer A, Tarwotjo I, Hussaini G. Incidence prevalence and scale of blinding malnutrition Lancet 1981; 1:1407-8.

2. Sommer A. Nutritional blindness: Xerophthalmia and Keratomalacia. New York: Oxford University Press, 1982.

3. Sommer A, Katz J, Tarwotjo I. Increased risk of respiratory disease and diarrhea in children with preexisting mild vitamin A deficiency. Am J Clin Nutr 1984; 40:1090-5.

4. Milton R Reddy V, Maidu A. Mild vitamin A deficiency and childhood morbidity: An Indian experience. Am J Clni Nutr 1987; 46:827-9.

5. Mohanram M, Kukarni KA, Reddy V. Hematological studies in vitamin A deficient children. Int J Vit Nutr Res 1977; 47:389-9[illegible].

6. Brink EW, Perera WDA, Broske SP, Cash RA, Smith JL, Sauberlich HE, Basbor MM. Vitamin A states of chilren in Sri Lanka. Am J Clin Nutr 1979; 32:84-91.

7. Santos LMP, Dricot JM, Asciutti LS, Dricot-D'Ans C. Xerophthalmia in the state of Paraiba, northeast of Brazil: Clinical findings. Am J Clin Nutr 1983; 38:139-44.

8. Sommer A, Tarwotjo I, Hussaini G, Susanto D. Increased mortality in children with mild vitamin A deficiency. Lancet 1985; 2:585-8.

9. Muhilal, Permeisih D, Idjradinata YR, Muherdiyantiningsih, Karyadi D. Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: A controlled field trial. Am J Clin Nutr 1988 (in press).

10. West KP, Djunaedi E, Pandji A, Kusdiono, Tarwotjo I, Sommer A, the Aceh Study Group. Vitamin A supplementation and growth: A randomized community trial. Am J Clin Nutr 1988 (in press).

11. Mejia LA, Arroyave G. The effect of vitamin A fortification of sugar on iron metabolism in preschool children in Guatemala. Am J Clin Nutr 1982; 36:87-93.

12. Sommer A, Tarwotjo I, Djunaedi E, West KP Jr, Loedin AA, Tilden R, Mele L, the Aceh Study Group. Impact of vitamin A supplementation on childhood mortality: a randomized controlled community trial. Lancet 1986; 2:1169-73.

13. Sommer A. Field guide to the detection and control of xerophthalmia, ed 2. Geneva: World Health Organization, 1982.

14. Natadisastra G, Wittpenn JR, West KP, Muhilal, Sommer A. Impression cytology for detection of vitamin A deficiency. Arch Ophtalmol 1987; 105:1224-8.

15. Natadisastra G, Wittpenn JR, Muhilal, West KP Jr, Mele L, Sommer A. Impression cytology: A practical index of vitamin A status. Am J Clin Nutr 1988; 48:695-701.

16. Wittpenn JR, Keenum D, West KP, Farazdaghi M, Humphrey J, Howard GR, Sommer A. Impression Cytology Training Manual. Baltimore: International Center for Epidemiologic and Preventive Ophthalmology, Johns Hopkins School of Medicine, 1988.

17. Fishbach F. A manual of laboratory diagnostic tests. Philadelphia: JP Lippincott Company, 1980.

18. Bieri JG, Tolliver TJ, Catignani GL. Simultaneous determination of alpha-tocopherol and retinol in plasma or red cells by high pressure liquid chromotography. Am J Clin Nutr 1979; 32:2143-9.

19. Hamill PVV, Drized TA, Johnson CL, Reed RB, Roche AF, Moore WM. Physical growth: National center for health statistics percentiles. Am J Clin Nutr 1979; 32:607-29.

20. Zerfas AJ. The insertion tape: A new circumference tape for use in nutritional assessment. Am J Clin Nutr 1975; 28:782-87.

21. Snedecor GW, Cochran WG. Statistical methods, ed 7. Ames, IA: The Iowa State University Press, 1980.

22. Fleiss JL. Statistical methods for rates and proportions, ed 2. New York: John Wiley and Sons, 1981.

23. Dixit DT. Nightblindness in third trimester of pregnancy. Indian J Med Res 1966; 54:791-5.

24. Ashby G. Micronesian customs and beliefs, ed 2. Eugene OR: Rainy Day Press, 1985.

25. Nauss KM. Influence of vitamin A status on the immune system. In: Bauernfeind JC, ed. Vitamin a deficiency and its control. Orlando: Academic Press, 1986.

26. Miller DR, Baehner RL, McMillan CW. Blood disorders of infancy and childhood, ed 5. St Louis: Mosby, 1984.

27. Mejia LA, Chew F. Hematological effect of supplementing anemic children with vitamin A alone and in combination with iron. Am J Clin Nutr 1988; 48:595-600.

RUNNING TITLE: Vitamin A Deficiency in Truk

APPENDIX H

Wittpenn J, West KP Jr., Keenum D, Farazdaghi M, Humphrey J, Howard G, and Sommer A: Training manual: assessment of vitamin A status by impression cytology.

TRAINING MANUAL

ASSESSMENT OF VITAMIN A STATUS BY IMPRESSION CYTOLOGY

1988

ICEPO, Dana Center for Preventive Ophthalmology
The Wilmer Institute and School of Hygiene and Public Health of The Johns Hopkins University, Baltimore, Maryland.  A WHO Collaborating Center for the Prevention of Blindness and Vitamin A Deficiency.

Publication of this manual was made possible by a grant from Task Force "Sight and Life," Hoffman-LaRoche and Company, Basle, Switzerland.

Prepared under Cooperative Agreement No. DAN-0045-A-00-5094-00 between the International Center for Epidemiologic and Preventive Ophthalmology, The Johns Hopkins University, and the Office of Nutrition, Bureau for Science and Technology, United States Agency for International Development.

TRAINING MANUAL

ASSESSMENT OF VITAMIN A STATUS BY IMPRESSION CYTOLOGY

Prepared by John R. Wittpenn, M.D., Keith P. West, Jr., Dr.P.H., R.D., Deborah Keenum, M.A., Mahmood Farazdaghi, Jean Humphrey, M.S.P.H., R.D., Gene R. Howard, M.D., and Alfred Sommer, M.D., M.H.Sc. with the collaboration of Gantira Natadisastra, M.D. (Cicendo Eye Hospital, Bandung, Indonesia), Eva Santos, M.D., (Institute of Ophthalmology, Manila, Philippines), Anna Gadomski, M.D. and Chris Kjolhede, M.D. (Johns Hopkins University, Baltimore, USA).

TABLE OF CONTENTS

CHAPTER 1 INTRODUCTION TO IMPRESSION CYTOLOGY

Section I. Vitamin A

Vitamin A (retinol) is a fat-soluble vitamin which is essential for numerous body processes. Its role in the visual cycle is the best understood. In its aldehyde form (retinal), vitamin A is a chromophore in the visual pigment rhodopsin ("visual purple") in the rods of the retina. The rods are sensory cells responsible for vision under low intensity light, as at night.

It is well known that vitamin A is also essential for normal cellular differentiation, particularly of mucous-secreting epithelium (1). While mucous-secreting epithelium of many organs are involved, including the respiratory and genito-urinary tracts, changes are most readily observed in the conjunctiva. In vitamin A deficiency, normal columnar epithelium transform to a stratified squamous type. Goblet cells, responsible for mucous production, disappear. The resulting keratinizing metaplasia produces a xerotic, granular, "skinlike" appearance to the conjunctiva. As deficiency progresses, xerosis extends to the cornea, which may ulcerate and ultimately lead to irreversible blindness.

The same metaplastic process seen in the conjunctiva also occurs in other epithelial tissues, perhaps even earlier. In the tracheobronchial tree, loss of ciliated epithelium and keratinization impair mechanisms for clearing inhaled particles and microbes. Goblet cell density decreases in the gastrointestinal tract. Squamous metaplasia of the genitourinary tract may promote bacterial colonization and infection. Similar processes have been observed in the middle ear and eustatian tubes. These abnormalities may be responsible, at least in part, for the increased risk of infection that appears to accompany vitamin A deficiency.

Beyond vitamin A's role in vision and maintenance of epithelium, it is also required for reproduction, immune function, growth, and hematopoiesis.

Vitamin A deficiency is an important public health problem in many developing regions of the world. It accounts for the majority of childhood blindness, and is likely to play a contributory role in a large proportion of childhood morbidity and mortality. In a longitudinal study of 3000 Indonesian preschool children, the mortality rate among children with mild xerophthalmia was 4 to 12 times higher than among children with normal eyes (2). In an intervention community-based trial in another ethnically distinct population in Indonesia, a vitamin A prophylaxis program reduced preschool child mortality by 34% (3). Similar results were reported in a field trial of vitamin A fortification of monosodium glutamate (4). These studies indicate that children may be suffering physiologically important consequences of vitamin A deficiency even before they reach the stage of exhibiting clinical xerophthalmia.

The mechanism(s) by which vitamin A deficiency increases mortality remain uncertain, though it is well known that vitamin A deficiency is associated with increased rates of infection (5 - 9). This infection may be due in part to disruption of mucosal barriers. Vitamin A also appears to play a role in humoral and cellular immune function (10).

The increasing importance of vitamin A deficiency in even its mild "subclinical" form has pointed to the need for a simple test to identify populations deficient in vitamin A and to monitor the impact of vitamin A intervention programs. Current methods of vitamin A assessment are listed in TABLE 1, with the advantages and disadvantages of each. Interpretive criteria are listed in TABLE 2.

TABLE 1. Current Methods of Vitamin A Assessment

Method	Advantages	Disadvantages
Liver biopsy	Most accurate estimate of vitamin A body stores	–Does not assess amount of vitamin A actually available to peripheral target tissues –Highly invasive, tissue generally available only from autopsy (not representative of population at large) –Potential problem with obtaining a representative sample of liver
Relative Dose Response	Indirect indicator of vitamin A liver stores, far less invasive than biopsy	–Requires two blood drawings 5 hours apart which is difficult to manage in field setting, (a new approach with promise requires a single blood drawing without the 5 hour wait between administration and blood collection) –Storage, handling and analysis of serum sample can be problematic and expensive –Where AIDS is prevalent collection of blood samples may prove difficult
Serum retinol concentration	Estimates circulating vitamin A levels	–Reflects liver stores only after moderate to severe depletion –Invasive –Storage, handling, and analysis can be problematic and expensive –Where AIDS is prevalent collection of blood samples may prove difficult
Immunoassay assay for RBP	Correlates with serum levels at high normal down to mild deficiency	–Fails to distinguish holo from apo-RBP –As a result, does not parallel moderate to severe deficiency when apo-RBP levels may remain normal
Clinical signs of Xerophthalmia	Noninvasive, represents tissue dysfunction	–Requires trained clinical examiners –Requires very large sample size for community assessment
Conjunctival Impression Cytology (new approach described in detail in this manual)	–Minimally invasive, no blood required –Reflects physiologic function/vitamin A status –Minimal equipment/supplies required –Stable sample under routine field conditions	–Epithelial "memory" may cause persistent or recurrent abnormalities despite acutely normal liver and serum levels

TABLE 2. Cut off Criteria that have been Proposed for Interpreting Indicators of Vitamin A Status

Individual Assessment

Relative Dose Response (11,12)

<10%	Normal
≥10, ≤20%	Inconclusive
>20%	Deficient

Hepatic Vitamin A Concentration (μg/g) (13)

≥20	Normal
<20	Deficient

Serum Vitamin A Concentration (μg/dl) (14)

≥20	Adequate
≥10, <20	Low
<10	Deficient

Community Assessment

(Clinical) Prevalence Criteria for a Xerophthalmia Problem of Public Health Significance (15)

	Prevalence
Nightblindness (XN)	≥1.0%
Bitot's spots (X1B)	≥0.5%
Corneal xercsis/corneal ulceration/ keratomalacia (X2/X3A/X3B)	≥0.01%
Corneal scar (XS)	≥0.05%
Plasma Vitamin A <10 μg/dl*	≥5%

*Among preschool-age children

Conjunctival Impression Cytology

Prevalence criteria not yet established. False positive rates among preschool children may vary between 5% - 15%. Further data required before levels can be fixed.

Section II. Impression Cytology

A. Description

Conjunctival impression cytology (CIC) is a method of obtaining surface cells from the bulbar conjunctiva to stain and observe for histologic changes. This manual describes CIC for assessment of vitamin A status (CIC-A).

B. Rationale

1. Vitamin A deficiency results in well-described sequential histopathologic changes of the conjunctival epithelium.
   a. *NORMAL:* Continuous sheets of small epithelial cells with abundant goblet cells and mucin spots, (**0, 1**)
   b. *BORDERLINE:* Very few goblet cells or mucin spots. Enlarged epithelial cells beginning to separate from sheets, (**2, 3**)
   c. *ABNORMAL:* Absence of goblet cells and mucin spots. Markedly enlarged discreet epithelial cells, (**4, 5**).
2. These changes are apparent in areas of the conjunctiva which may appear to be clinically normal.

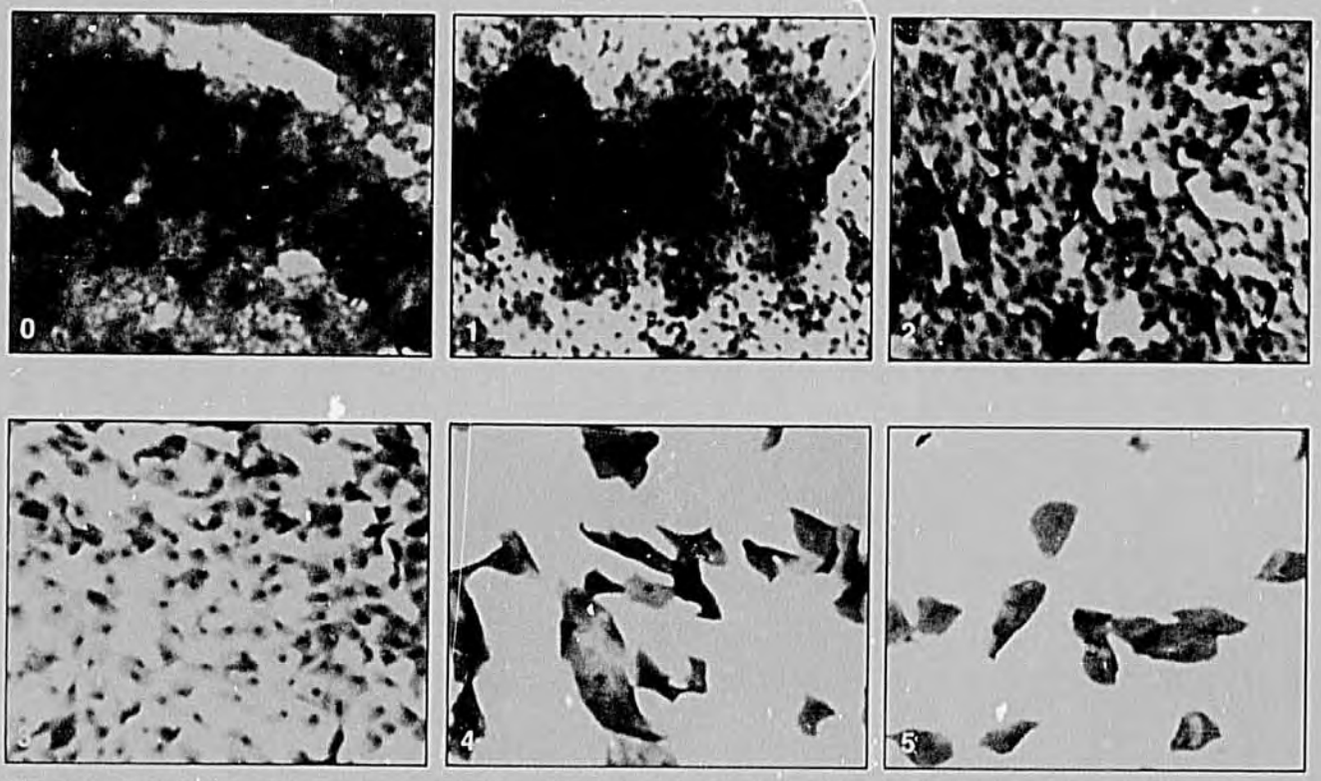


Figure 1. Progression of squamous metaplasia with increasing severity of vitamin A deficiency. (Papanicolaou stain, reprinted from reference 16).

C. Supportive Studies

Several published works provide evidence that impression cytology can be a valid and reliable measure of physiologically significant vitamin A deficiency.

1. Baltimore, Maryland/ Milwaukee, Wisconsin (1984) (17)

   Impression cytology was used to study ocular surface abnormalities in vitamin A deficient rabbits at early stages of xerophthalmia. Goblet cells decreased, and enlarged epithelial cells increased in a linear fashion beginning at least 4 to 6 weeks before clinical changes become apparent. The study concluded that impression cytology may be a useful screening tool for early xerophthalmia.

2. Madurai, India (1986) (18)

   Impression cytology was used to evaluate children with xerophthalmia before and after treatment and to compare them with normal children. Impressions from xerophthalmic children showed complete loss of goblet cells and the appearance of enlarged partially keratinized epithelial cells and sheets of small epithelial cells. The study suggested that impression cytology may be a simple, objective, diagnostic test for the detection of early vitamin A deficiency in the population.

3. Bogor, Indonesia (1987) (19)

   Impression cytology was used to evaluate and follow up 75 preschool children with mild xerophthalmia and 74 age-matched clinically normal controls. Children with normal and abnormal specimens, regardless of their clinical appearance, had mean serum vitamin A levels of 22.2 and 15.2 μg/dl, respectively ($p<0.001$). Twenty-three percent (23%) of the children entering the study as normal controls had baseline abnormal impression cytology which improved to normal after receiving vitamin A. The study concluded that impression cytology appears to detect clinical and physiologically significant preclinical vitamin A deficiency.

4. Paris, France (1988) (20)

   Children with cholestatic and noncholestatic liver disease were evaluated by impression cytology, serum vitamin A analysis, and either liver biopsy or intravenous relative dose response test. Children with normal impression cytology had normal vitamin A status by the other measures. Children with abnormal impression cytology were abnormal by the other techniques. The study concluded that impression cytology is a simple objective test with a high degree of sensitivity and specificity.

CHAPTER 2 SAMPLING TECHNIQUE

Section I. Preparation for Obtaining Specimens

A. Necessary materials (Figure 2)

1. Box of mixed cellulose esters (~85% nitrate, 15% acetate) filter paper, Millipore - Cat. #HAWP 304 FO, Pore size 0.45 µm. Can be ordered from Millipore Corporation; 80 Ashby Rd., Bedford Massachusetts 01730 USA; telephone number 800-225-1380. One box contains 10 sheets measuring 15x15 cm. This is enough paper to sample one thousand children. Other forms of cellulose acetate filter paper may be equally as effective especially if the pore size matches the Millipore filter paper.
2. A papoose board (Figure 3) is good for restraining young children but not essential. A sheet wrapped tightly around the child's body and someone holding the head can be equally effective. Many older children (age 4-6) can be talked through the procedure without using any restraint. In many cases it is effective to restrain the child in the mother's lap.
3. Microsponges, tissue paper, or gauze pads to absorb the inferior tear lake before sampling. If the filter paper gets wet during the sampling process, the cells will not adhere to the paper.
4. Smooth, blunt glass or plastic rods (diameter 0.5-1.0 cm) for flattening the paper on the conjunctiva.
5. A sharp pair of scissors to cut the filter paper into appropriately sized pieces.

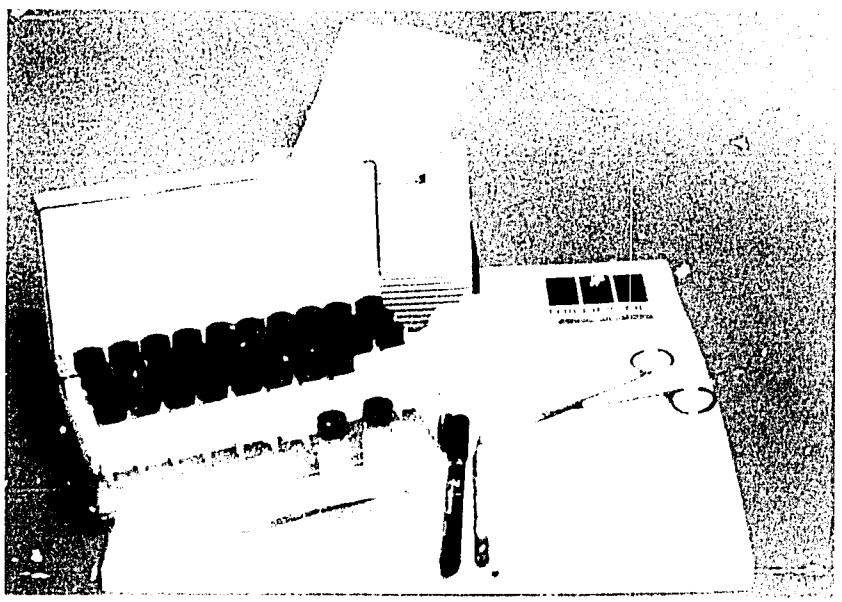


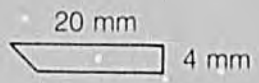
Figure 2. Necessary materials for obtaining specimens: cellulose esters (nitrate/acetate) filter paper, tissue paper, glass rod, scissors, petri dish, labeled specimen bottles, permanent marking pen, forceps.

Figure 3. Papoose board suitable for gently restraining child.

6. 2 or 3 low, wide-mouthed containers such as petri dishes to hold precut filter paper.
7. Small screw-topped wide mouth bottles for holding the specimens, one bottle for each child sampled.
8. Labels, forms for identifying the samples and collecting the desired information on each patient. Permanent marking pens that will not smear when wet.
9. Handlight for examining eyes. Some people also prefer to use loupes while examining and sampling the children.
10. Several small (child-size) lid specula or lid retractors may be helpful. Lid retractors can be more effective than specula as some children can squeeze closed spring action specula. A simple paper clip can be formed into a retractor.
11. Ingredients for fixative:
    Glacial acetic acid
    37% formaldehyde
    95% ethyl alcohol
    distilled water
12. Forceps for transferring specimens.

B. Preparations before going into the field

1. Cut filter paper, being careful to avoid touching the paper with your hands (Figure 4). Use rubber or plastic gloves if available. Place in low, wide-mouthed container. Cut at least 2 per child. Size should be approximately 20×4 mm with a point at one corner.



2. Prepare fixative:
    75 ml 95% ethyl alcohol
    25 ml distilled water
     5 ml glacial acetic acid
     5 ml 37% formaldehyde
3. Fill the sample vials with fixative to the top. If an airspace is left, the filter paper invariably sticks to the top and dries out.
4. Assemble remaining equipment. Field workers have found it advantageous to label the sample vials before going into the field. The well-plate used in the staining procedure is labeled in rows of A-D and columns of 1-6. It is useful to incorporate these numbers (e.g. A1, D6) as part of the sample identification number. The vials are then placed in a carrying rack or box in the order to be used.

Figure 4. Cut filter paper into 20 × 4 mm strips.

FIXATIVE

75 ml	95% ethyl alcohol
25 ml	distilled water
5 ml	glacial acetic acid
5 ml	37% formaldehyde

Figure 5. Composition of fixative solution.

Section II. Obtaining Specimens

A. Before sampling

1. Record all desired information such as name, sex, age, history from parent on appropriate, carefully maintained form.
2. Examine eyes.
3. Complete all other non-invasive studies before taking impression cytology specimen.

B. Sampling

1. Appropriately restrain child. This may require use of a papoose board or a sheet wrapped around child. If the child is cooperative, he can often be held on the mother's lap with her chin holding the top of the child's head and her arms wrapped around the child's arms.
2. Have an assistant hold lids of the right eye apart using fingers, lid speculum, or lid retractor.
3. Use microsponges, tissue paper or gauze pad to dry the inferior tear lake if it is excessive. Dry by touching the lower eyelid. *Avoid touching the eye itself.*
4. Using the fingers of left hand, grasp the filter paper at the point (Figure 6).
5. A child will look away from bright light and toward a squeaky toy (Figure 7). This may help fix the child's gaze and expose the temporal conjunctiva.
6. Apply the filter paper to the infero-temporal (lower outer) portion of the conjunctiva, pointed end toward temples (Figures 7 and 8). The blunt end should be about 3 mm from the limbus. *Do not touch the eyelids* or you will get an erroneous reading; *only* touch the eyeball.
7. Be sure the filter paper flattens down on the conjunctiva. This may require gentle pressure with the plastic or glass rod (Figure 8). If the paper becomes wet with tears, the cells may not adhere to the paper.
8. After 2 seconds, remove the paper with a gentle peeling motion toward the nose.
9. Holding the specimen by the point over the opened fixative vial, cut the portion of the paper nearest the hand at an angle, allowing the specimen end to drop into the vial (Figure 9). The paper containing the specimen should not be more than 15 mm long.
10. Repeat the procedure on the left eye.[1]

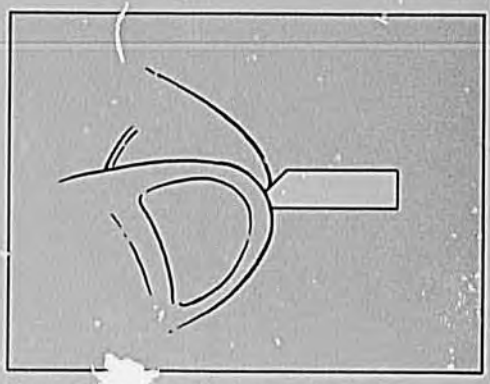


Figure 6. Grasp filter paper strip by pointed end.

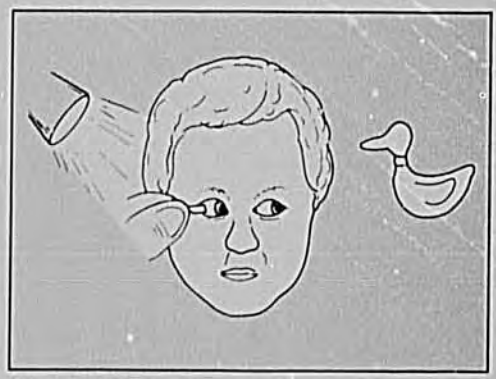


Figure 7. Child's gaze fixed away from bright light and toward toy, baring temporal conjunctival surface.

[1] At the discretion of the clinician, antibiotic solution may be instilled in the child's eye after impression cytology specimen is taken.

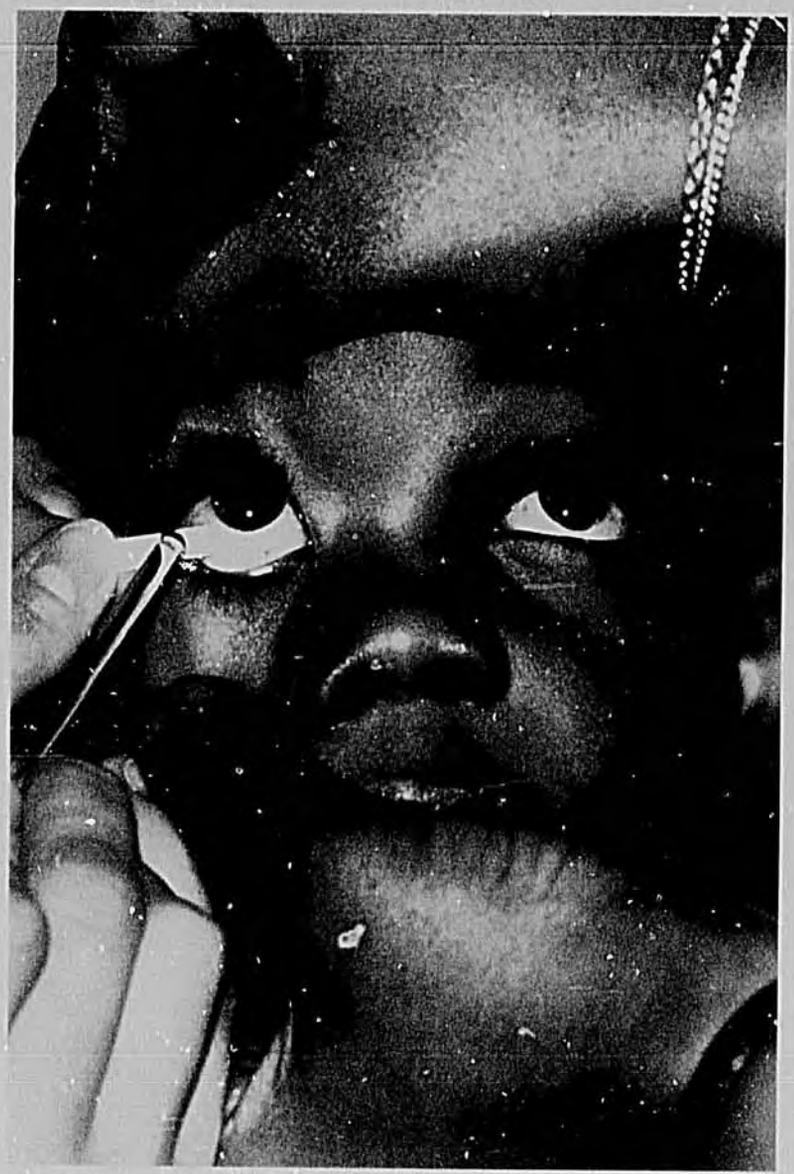


Figure 8. Apply filter paper to inferior-temporal portion of conjunctiva, 3 mm from the limbus. Apply gentle pressure with glass rod to flatten paper on conjunctiva.

Figure 9. Cut paper at an angle, allowing specimen to drop into fixative vial.

C. Storage

1. Keep the vials closed and upright.
2. Check the vials twice per month for evaporation and refill with fixative as needed. The specimens are ready for staining after 20 minutes, or can remain in the fixative at room temperature for several weeks before they are stained.

Section III. Staining Procedure

A. *Principal of Staining Procedure:* Periodic Acid— Schiff (PAS) Reagent stains mucin spots and goblet cells a bright pink. Sodium metabisulfite fixes the PAS stain. Harris hematoxylin counterstains the epithelial nuclei bluish-purple. Ethanol baths are used for drying the samples (21, 22).

B. Preparation of Baths:

Glass or plastic baths may be used. Be sure to label each bath.

Bath #1 Fresh tap water.

Bath #2 0.5% Periodic Acid.

Bath #3 Schiff reagent
Dilute 1:1 with distilled water.

Bath #4 0.5% Sodium metabisulfite.

Bath #5 Harris Hematoxylin.
Filter before each use, and every 3 hours during staining. See Addendum 2 for preparation directions.

Bath #6 95% ethanol.
Replace after ten well-plates have been stained

Bath #7 100% (absolute) ethanol.
Replace after ten well-plates have been stained. Bath #7 can be substituted for Bath #6 after 10 well-plates have been processed.

Bath #8 100% (absolute) ethanol.
Replace after ten well-plates have been stained. Bath #8 can be substituted for Bath #7 after 10 well-plates have been processed.

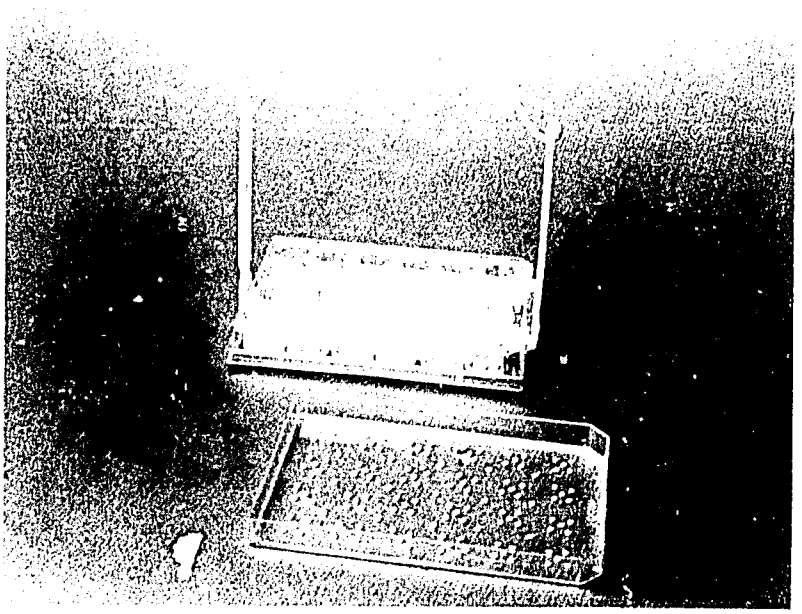


Figure 10. Well-plate.

C. Procedure (see Figure on pp 15-16):

1. A numbered well-plate in which holes have been drilled at the bottom of each well for drainage should be used (Figure 10). Submerge this well-plate into Bath #1 containing tap water (Figure 11). Then, transfer the specimens from storage bottles lifting the pointed end with forceps. Do not touch the blunt end with the forceps or you may damage the specimen. Both specimens from one patient may be placed in one well. Secure the cover on the well-plate.
2. Let water from the tap flood the well-plate for 2 minutes to rinse away all of the preservative. When flooding the bath, it is important that water not fall directly on the well-plate. A small steady flow is all that is necessary.
3. Remove the well-plate from Bath #1 and let excess water drip off. Following each Bath #1, hold the well-plate at an angle and gently blot the well-plate on a towel to be sure that the wells are drained. Place the well-plate into Bath #2 containing 0.5% periodic acid. Gently agitate the well-plate in the periodic acid bath for 2 minutes.
4. Remove the well-plate from Bath #2 and return it to Bath #1 which should now be filled with fresh water. Continue to flood Bath #1 with water from the tap for 2 minutes. Remove the well-plate from Bath #1 and let excess water drain on towel.
5. Place the well-plate in Bath #3 filled with Schiff reagent diluted in a one to one ratio with DISTILLED water. Agitate the well-plate occasionally for 8 minutes.
6. Remove the well-plate from Bath #3 and return to Bath #1. Bath #1 should be filled with clean tap water. Change the tap water immediately, then gently flood Bath #1 from the tap for 2 minutes. Change water again, and flood for 1 more minute or until the wash is clear. Remove the well-plate from Bath #1 and let excess water drain on towel.
7. Place the well-plate into Bath #4 filled with 0.5% sodium metabisulfite for 2 minutes. Agitate gently.
8. Remove the well-plate from Bath #4 and return to Bath #1, filled with fresh tap water. Flood gently under the tap for 2 minutes. Remove the well-plate from Bath #1 and let excess water drain on towel.
9. Place Bath #5 filled with filtered Harris hematoxylin directly next to the sink. This is an important step in the staining procedure. Understaining or overstaining with Harris hematoxylin may make the specimen difficult to read. Completely submerge the well-plate 3 times for 1 second each time. Then, immediately rinse thoroughly in Bath #1 of clean tap water. The bath water will become dark purple. As long as there is a purple color, the staining process is continuing. Therefore, it is important to rapidly change the bath water 3 times. Continue to rinse under running tap water for about 2 minutes, or until no further hematoxylin can be seen in the wash water.

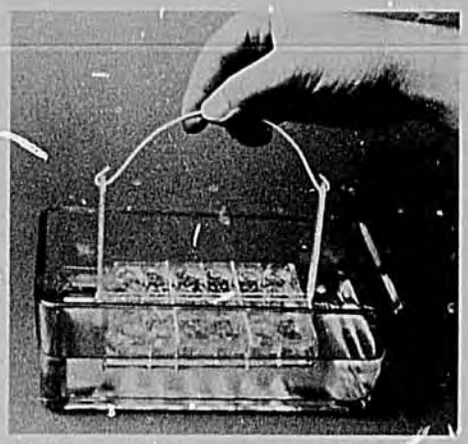


Figure 11. Well-plate in water bath.

10. Remove the well-plate from Bath #1 and let excess water run off. Be sure that excess water is removed from the surface and interior of the well-plate before going on to the next step. This is the final wash with tap water. Steps 11-13 are ethanol baths for drying. DO NOT go back to Bath #1.

11. Place the well-plate in Bath #6 filled with 95% ethanol. Agitate for 2 minutes and remove. Allow the excess 95% ethanol to drip off.

12. Place the well-plate in Bath #7 filled with 100% (absolute) ethanol. Agitate for 2 minutes. Allow the excess ethanol to drip off.

13. Repeat step #12 in a second bath of 100% (absolute) ethanol. Agitate for 2 minutes.

14. Carefully remove the cover of the well-plate leaving well-plate in the alcohol bath. Once the cover is off the samples can easily float out of their wells. Therefore it is critical to avoid moving the well-plate. Using forceps, transfer all specimens from a single patient to an individually labeled glass bottle containing xylene. Be sure to pick up specimen by the pointed end only. Let the specimens remain in xylene for at least 20 minutes to fix before proceeding. This will also turn the paper from opaque to transparent.

D. Storage and Care of Reagents

Periodic Acid (PA)
Pour used reagent into original bottle, cap, and store in a dark place. PA can be reused for about one year.

Schiff Reagent
Discard diluted Schiff reagent after one week's use. Opened, undiluted Schiff reagent must be refrigerated and used within 2-3 months. If Schiff reagent turns blue, it is no longer effective and must be discarded.

Sodium Metabisulfite (SM)
Pour used SM into original bottle. SM may be reused for 1 year.

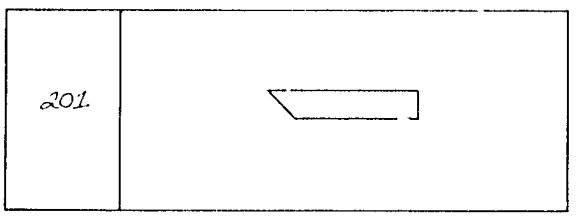
Harris Hematoxylin (HH)
Pour used HH into original bottle. It may be reused for up to 1 year, but must be filtered before each use.

95% Ethanol
Do not pour used 95% ethanol back into original bottle. Discard after ten well-plates have been processed.

100% Ethanol
Do not pour used 100% ethanol back into original bottle. After 10 well-plates have been processed, Bath #7 is no longer pure but may be substituted for Bath #6, and Bath #8 of 100% ethanol can be substituted for Bath #7 of 100% ethanol.

Section IV. Preparation of the Slide.

A. Place one specimen on a slide as seen in the drawing below. The blunt end of the paper will contain the cells. It does not matter which side is up: since the paper is translucent the cells can be read whether they are on top of or underneath the paper.



B. Immediately, add several drops of Permount[2] directly on top of the specimen using a pipette dropper. It is critical to add the Permount before the xylene evaporates. If the specimen dries, it will become opaque again and uninterpretable. Therefore, DO NOT remove more than 2 specimens at a time from the xylene.

C. Gently and slowly place the coverslip over the Permount to avoid creating bubbles under the coverslip.

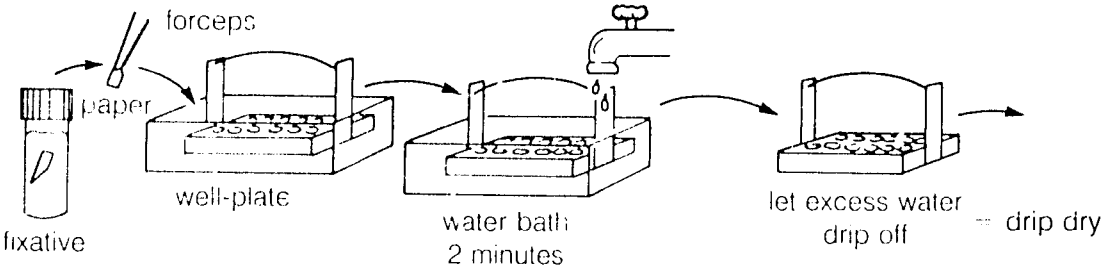
D. It is advisable to wait overnight for the Permount to dry on the slide before viewing. If the slide is viewed sooner, the coverslip may slide, smearing Permount onto the microscope and on top of the coverslip. This would obscure a clear view. Smeared Permount can be cleaned with xylene.

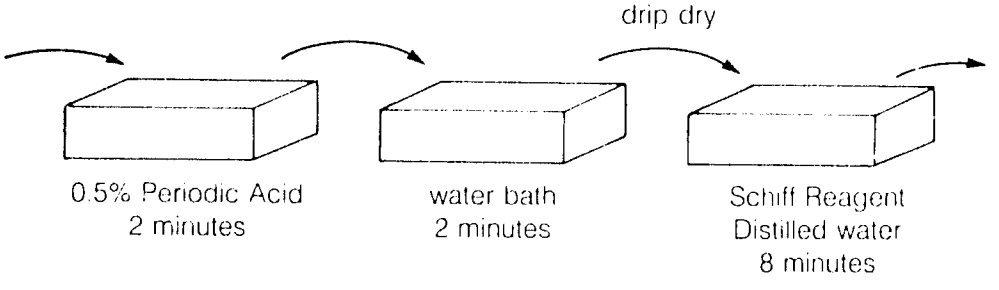
Using two well-plates a single technician can process over 200 specimens per day including all labeling, staining and mounting.

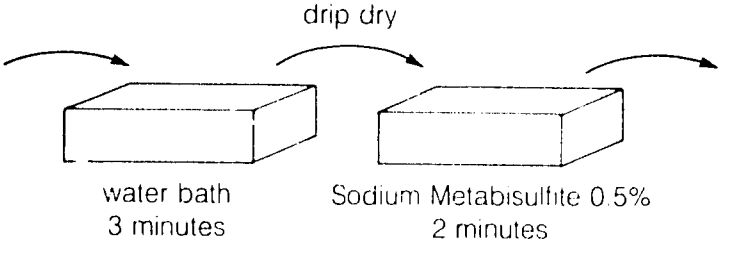
[2] It is essential to use Permount because other mounting agents may result in molds forming on specimens. If Permount thickens with time, thin with xylene.

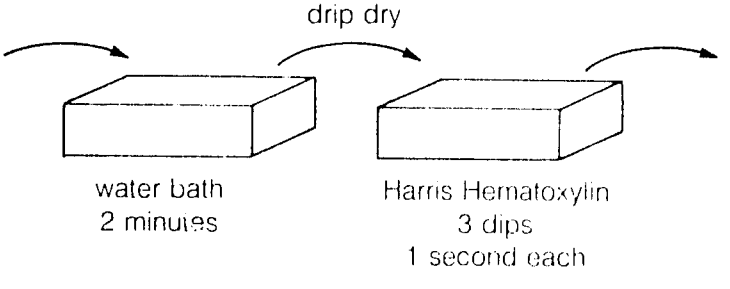
Figure 12
Staining and Mounting Procedure

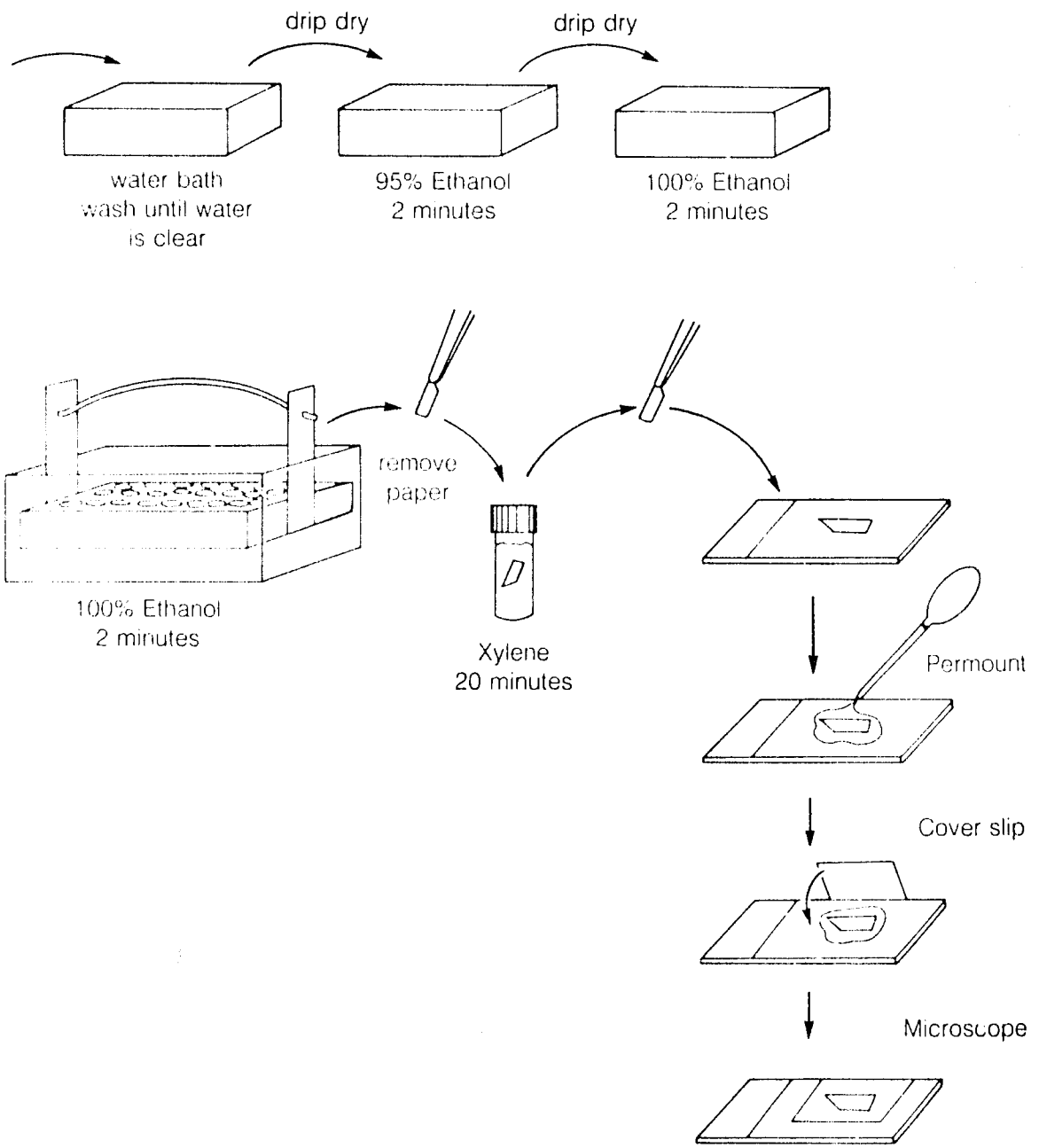
STAINING PROCEDURE










drip dry
drip dry
water bath
wash until water
is clear
95% Ethanol
2 minutes
100% Ethanol
2 minutes
remove
paper
100% Ethanol
2 minutes
Xylene
20 minutes
Permount
Cover slip
Microscope

ADDENDUM 1

Sampling Technique with Prototype Vacuum Pump Applicator

I. Preparation for obtaining specimens

A prototype applicator has been designed based on a vacuum principal (Figure 13). Using a disc of filter paper, it offers several advantages over the strip technique: eliminates contact with fingers, applies a disc of paper of fixed area to the conjunctiva, reduces variation in pressure, improves cellular adhesion, and improves targeting of sample site.

A. Necessary materials

1. Box of mixed cellulose esters (~85% nitrate, 15% acetate) filter paper. Millipore - Cat. #HAWP 304 FO. Pore size 0.45 μm. Can be ordered from Millipore Corporation; 80 Ashby Rd., Bedford Massachusetts 01730 USA; telephone number 800-225-1380. One box contains 10 sheets measuring 15×15 cm. This is enough paper to sample one thousand children. Other forms of cellulose acetate filter paper may be equally as effective especially if the pore size matches the Millipore filter paper.
2. A papoose board is good for restraining young children but not essential. A sheet wrapped tightly around the child's body and someone holding the head can be equally effective. Many older children (age 4-6) can be talked through the procedure without using any restraint. In many cases it is effective to restrain the child in the mother's lap.

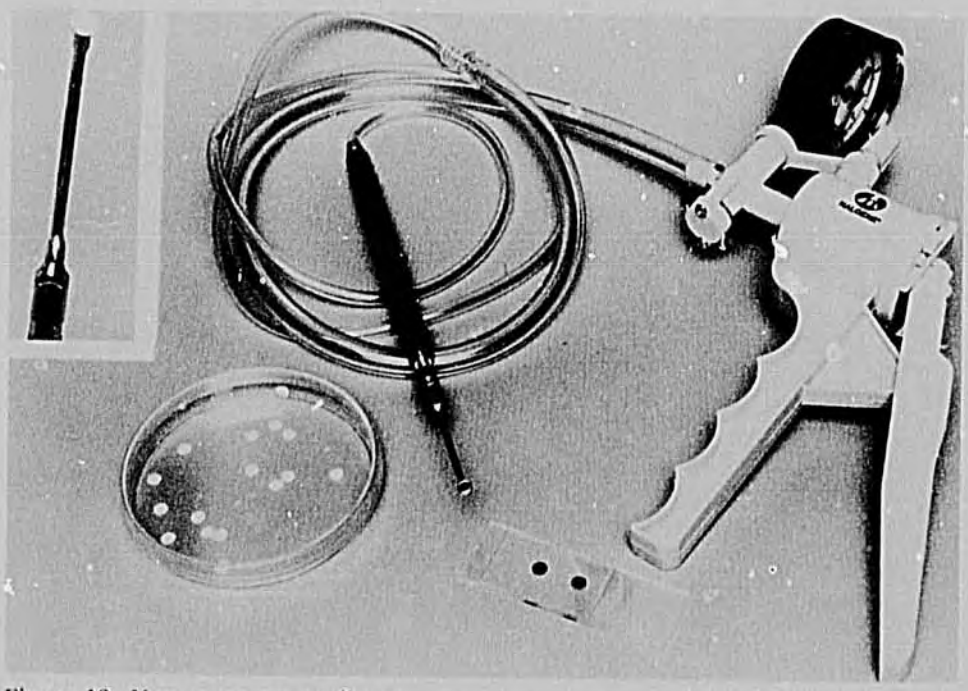


Figure 13. Vacuum pump applicator.

3. Microsponges, tissue paper, or gauze pads to absorb the inferior tear lake before sampling. If the filter paper gets wet during the sampling process, the cells will not adhere to the paper.

4. Vacuum pump applicator, consisting of 4 parts (Figure 13):

   a. Nalgene hand-operated vacuum pump with pressure gauge (to 76 cm mercury).

   b. 5 feet clear tubing.

   c. Vacuum probe with by-pass hole.

   d. 14 gauge needle adapted to fit over the end of the probe. The shaft is 4 cm long. Two and one half cm from the base it is angled at 30°. The tip is flared into a shallow cup of 3/16 inch diameter.

5. A 3/16 inch hole punch to cut filter paper into appropriately sized discs.

6. 2 or 3 low, wide-mouthed containers such as petri dishes to hold precut filter paper.

7. Small screw-topped wide mouth bottles for holding the specimens, one bottle for each child sampled.

8. Labels, forms for identifying the samples and collecting the desired information on each patient. Permanent marking pens that will not smear when wet.

9. Handlight for examining eyes. Some people also prefer to use loupes while examining and sampling the children.

10. Several small (child-size) lid specula or lid retractors may be helpful. Lid retractors can be more effective than specula as some children can squeeze closed spring action specula. A simple paper clip can be formed into a retractor.

11. Ingredients for fixative:

    Glacial acetic acid

    37% formaldehyde

    95% ethyl alcohol

    distilled water

12. Small jar filled with 95% ethanol for sterilizing applicator tips.

B. Preparations before going into the field.

1. Punch filter paper, being careful to avoid touching the paper with your hands. Use rubber or plastic gloves if available. Place in low, wide-mouthed container. Cut at least 2 per child.
2. Prepare fixative:
   75 ml 95% ethyl alcohol
   25 ml distilled water
   5 ml glacial acetic acid
   5 ml 37% formaldehyde
3. Fill the sample vials with fixative to the top. If an airspace is left, the filter paper invariably sticks to the top and dries out.
4. Assemble vacuum pump applicator: attach one end of clear tubing to pump, the other end to probe. Fit adapted needle over probe.
5. Assemble remaining equipment. Field workers have found it advantageous to label the sample vials before going into the field. The well-plate used in the staining procedure is labeled in rows of A-D and columns of 1-6. It is useful to incorporate these numbers (e.g. A1, D6) as part of the sample identification number. The vials are then placed in a carrying rack or box in the order to be used.

II. Obtaining specimens

A. Before sampling

1. Record all desired information such as name, sex, age, history from parent on appropriate, carefully maintained form.
2. Examine eyes.
3. Complete all other non-invasive studies before taking impression cytology specimen.

B. Sampling

1. Appropriately restrain child. This may require use of a papoose board or a sheet wrapped around child. If the child is cooperative, he can often be held on the mother's lap with her chin holding the top of the child's head and her arms wrapped around the child's arms.
2. Open the eyelids of the right eye. Hold lids apart with fingers of nondominant hand, lid speculum or lid retractor.

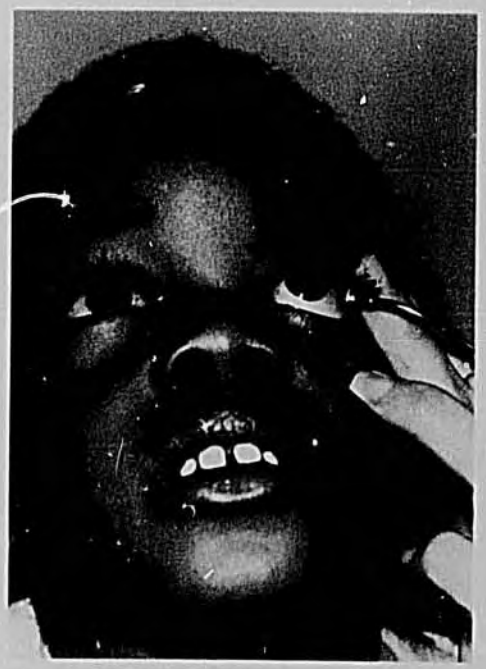


Figure 14. Apply applicator tip with paper disc to the inferior temporal conjunctiva.

3. Use microsponges, tissue paper or gauze pad to dry the inferior tear lake if it is excessive. Dry by touching the lower eyelid. *Avoid touching the eye itself.*

4. Place the tip of the applicator on top of a single paper disc. An assistant should then begin squeezing the hand pump once per second to maintain a steady pressure of 40cm mercury throughout the procedure. When suction is applied, the disc conforms to the inner surface of the tip.

5. A child will look away from bright light and toward a squeaky toy. This may help fix the child's gaze and expose the temporal conjunctiva.

6. Apply the applicator tip with paper disc to the inferior temporal conjunctiva (Figure 14). Press the applicator gently, yet firmly onto the conjunctiva for one second, then remove.

7. *It is critical that the assistant continue pumping throughout the procedure.* If the suction is inadequate, the paper disc cannot be removed from the conjunctiva. In the unlikely event that the paper sticks on the eye, simply place the applicator tip on the disc, increase the pressure to 40cm, and remove.

8. Hold the applicator tip with paper disc over an open vial of fixative. Lift finger from the by-pass hole to remove suction. The disc will drop into the vial (Figure 15). The assistant may then stop pumping.

9. Repeat procedure on the left eye.

C. Storage

1. Keep the vials closed and upright.

2. Check the vials twice per month for evaporation and refill with fixative as needed. The specimens can remain in the fixative at room temperature for several weeks before they are stained.

Figure 15. Holding applicator tip with paper disc over open fixative vial, lift finger from by-pass hole to remove suction, allowing disc to drop into vial.

III. Staining and Mounting Procedure

The staining and mounting procedure is similar to that of the strips (see pgs. 15-16). A needle-nosed forceps is used to transfer the discs to the staining trays, holding the disc at the edge so as not to damage the cells.

ADDENDUM 2

Ordering and Preparing Laboratory Supplies

I. Address for Ordering Material

A. 24-well tissue culture clusters:
Costar
205 Broadway
Cambridge, Massachusetts 02139 USA

B. Filter Paper: Catalog Number HAWP 304 FO, Pore size 0.45 μm
Millipore Corporation
80 Ashby Rd., Bedford Massachusetts 01730 USA

NOTE: Well tissue culture cluster (Cat. #35-24) must be modified for staining process. Drill 5 holes in the bottom and top of each well. Use rubber bands to hold cover on firmly. Fashion a handle from a piece of plastic (not metal) and attach to culture cluster using rubber bands (see Figure 10).

II. List of Staining Materials

A. Fixative
B. Periodic Acid (0.5% solution)
C. Schiff Reagent (PARA Fuscin 4.55g/l, Hydrochoric acid, Normal 86.5g/l, Potassium Metabisulfite 4.55g/l in 1000 cc distilled H_2O)
C. Distilled water
D. Sodium metabisulfite (0.5% solution)
E. Harris Hematoxylin (hematoxylin 5.0 gm; absolute alcohol 50.0 ml; aluminum ammonium sulfate 100.0 gm; mercuric oxide 2.5 gm in 1000 cc distilled H_2O)
F. 95% Ethanol
G. 100% Ethanol
H. Xylene

III. Directions for Preparation of Harris Hematoxylin

5.0 gm Hematoxylin crystals
50.0 ml 100% Alcohol (absolute ethyl)
100.0 gm Aluminum ammonium sulfate (alum)
1000.0 ml Distilled water
2.5 gm Mercuric oxide (red)
32.0 ml Glacial acetic acid

1. Dissolve the hematoxylin in alcohol with aid of gentle heat.
2. Dissolve the alum in distilled water by aid of heat.
3. When each solution is completely dissolved, combine the two solutions together in a large Pyrex Erlenmeyer flask (2000 ml capacity).
4. Bring mixture to boil as rapidly as possible. Turn off flame.
5. While moderate bubbling continues, *slowly* add mercuric oxide. (If mercuric oxide is added too quickly, the solution will boil over). The solution will become dark purple.
6. Cool solution by plunging flask into a tub of cold water. Allow cold water to run continuously from tap into tub. Rotate flask in cold water until solution is evenly cooled.
7. Stopper the flask lightly with a gauze square. Leave flask where it will be exposed to light to encourage ripening for 2-3 days.
8. Add 3ml glacial acetic acid per 100 ml solution to increase nuclear clarity. Filter before each use.

CHAPTER 3 SPECIMEN ANALYSIS

Section I. Histology

A. Cell types

1. Epithelial cells
   a. Normal (A)
      (1) Sheets of small cells or small individual cells.
      (2) Nucleus fills most of cytoplasm.
      (3) Predominant cell in normal individuals.
   b. Abnormal (B)
      (1) Enlarged, separated. (Some enlarged cells are found even in specimens from entirely normal eyes).
      (2) Nucleus may be the same size, shrunken or absent.
      (3) Increased cell size due to increased cytoplasm.
2. Goblet cells (C)
   a. Plump, smooth periodic acid-Schiff positive cells (stains reddish pink with PAS).
   b. Contains mucin.
   c. May be intact or discharging mucin.
3. Mucin spots (D)
   a. Discrete clusters of periodic-acid Schiff positive granules which represent goblet cell secretions.
   b. Represent presence of goblet cells which failed to adhere to the filter paper.
4. Mucin strands (E)

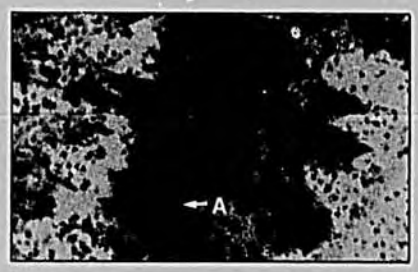
   Large collections of periodic acid-Schiff positive material often containing accumulations of cells and debris which may appear as large irregularly shaped masses.
5. Foreign debris on the ocular surface (dust, dirt).
6. Other cells such as polymorphonuclear leukocytes (F) and mast cells are occasionally seen with special stains.

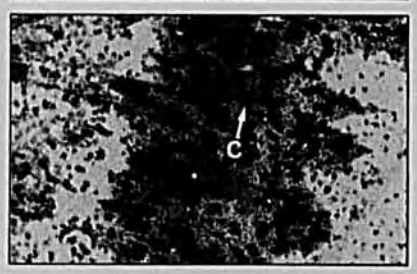
B. Distribution of cells

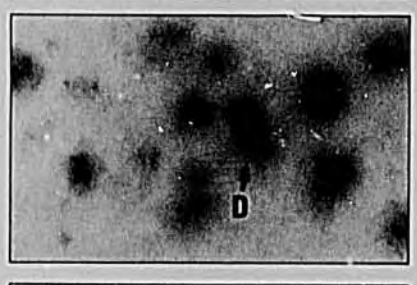
Variations exist across ocular suface even in normal individuals.

1. Goblet cell density is greatest in the lower quadrant near the nose and least in the temporal quadrant.
2. There are no goblet cells in an area about 1-1.5 mm around the limbus. Epithelial cells within this region are enlarged and may look "abnormal".

NOTE: Relation of photos on this page to color plates (pgs 26-27): A = ⑦, B = ⑳, C = ⑦, D = ⑫, F = ⑨, F = ⑥.







Section II. Analysis

A. Normal conjunctiva

1. Sheets of small epithelial cells with goblet cells or corresponding mucin spots. Some individual small epithelial cells.
2. Alternatively, abundant mucin spots in the absence of any adherent cells.

B. Abnormal conjunctiva

1. Enlarged separated or separating epithelial cells throughout the specimen in conjunction with rare or absent goblet cells and focal or absent mucin spots.

C. Artifacts

1. Rolled epithelium
2. Smeared mucin spots.
3. Overstaining
4. Variable staining.

D. Diagnosis

Diagnosis is based on the presence or absence of goblet cells or mucin spots in sufficient quantity.

1. A child is considered normal if either specimen is normal. Vitamin A deficiency is a systemic disease, therefore both eyes will be affected. Lack of concordance between 2 specimens taken from the same child may be due to:
   a. The well-documented variation of goblet cell density across the conjunctival surface.
   b. Poor technique which may result in a false positive reading.

CAUTION: At this time data suggests that once chronic metaplasia has occurred, the epithelium may show persistent or recurrent abnormalities despite acutely normal liver and serum retinol levels. False positive rates among preschool children may vary between 5-15%. This is under investigation.

REFERENCES

1. Wolbach SB and Howe PR: Tissue changes following deprivation of fat-soluble A vitamin. J Exp Med 42:753-777, 1925.
2. Sommer A, Tarwotjo I, Hussaini G, Susanto D: Increased mortality in mild vitamin A deficiency. Lancet ii:585-588, 1983.
3. Sommer A, Tarwotjo I, Djunaedi E, et. al.: Impact of vitamin A supplementation on childhood mortality. Lancet i:1169-1173, 1986.
4. Muhilal, Permeisih D, Idjradinata YR, et. al.: Impact of vitamin A fortified MSG on health, growth, and survival of children. A controlled field trial. Am J Clin Nutr (IN PRESS).
5. Bieri JG, McDaniel EG, and Rogers WE: Survival of germ-free rats without vitamin A. Science 163:574-575, 1969.
6. Sommer A, Katz J, and Tarwotjo I: Increased risk of respiratory disease and diarrhea in children with preexisting mild vitamin A deficiency. Am J Clin Nutr 40:1090-1095, 1984.
7. Milton RC, Reddy V, and Naidu AN: Mild vitamin A deficiency and childhood morbidity- An Indian experience. Am J Clin Nutr 46:827-829, 1987.
8. Barclay AJG, Foster A, and Sommer A: Vitamin A supplements and mortality related to measles: a randomized clinical trial. Br Med J 294:294-296, 1987.
9. Pinnock CB, Douglas RM, and Badcock NR: Vitamin A status in children who are prone to respiratory tract infections. Aust Paediatr J 22:95-99, 1986.
10. Nauss KM: Influence of vitamin A status on the immune system. In: Vitamin A Deficiency and its Control. ed: JC Bauernfeind. Academic Press, Orlando, 1986.
11. Loerch JD, Underwood BA, and Lewis KC: Response of plasma levels of vitamin A to a dose of vitamin a as an indicator of hepatic vitamin A reserves in rats. J Nutr 109:778-786, 1979.
12. Amedee-Manesme, O, Mourey MS, Hanck A, and Therasse J: Vitamin A relative dose and response test: validation by intravenous injection in children with liver disease. Am J Clin Nutr 46:286-289, 1987.
13. Olson JA: New approaches to methods for the assessment of nutritional status of the individual. Am J Clin Nutr 35:1166-1168, 1982.
14. Sommer A: Nutritional Blindness: Xerophthalmia and Keratomalacia. Oxford Press, New York, 1982.
15. Control of vitamin A deficiency and xerophthalmia. Report of a joint WHO/UNICEF/USAID/HKI/IVACG Meeting, Geneva, World Health Organization, 1982 (WHO Technical Report Series, No. 672).
16. Tseng SCG: Staging of conjunctival squamous metaplasia by impression cytology. Ophthal 92:728-733, 1985.
17. Hatchel DL, and Sommer A: Detection of ocular surface abnormalities in experimental vitamin A deficiency. Arch Ophthalmol 102:1389-1393, 1984.
18. Wittpenn JR, Tseng SCG, and Sommer A: Detection of early xerophthalmia by impression cytology. Arch Ophthalmol 104:237-239, 1986.
19. Natadisastra G, Wittpenn JR, West KP, Muhilal, and Sommer A: Impression cytology for detection of vitamin A deficiency. Arch Ophthalmol 105:1224-1228, 1987.
20. Amedee-Manesme O, Luzeau R, Wittpenn JR, Hanck A, Sommer A: Impression cytology detects subclinical vitamin A deficiency. Am J Clin Nutr 47:875-878, 1988.
21. Lund LG, (ed): Manual of histologic staining methods of the Armed Forces Institute of Pathology, ed 3. American Registry of Pathology. New York, McGraw-Hill Book Co., 1968.
22. McManus JFA, Mowry RW: Staining methods. Histologic and histochemical. New York, Hoeber Medical Division, Harper and Row Publisher, 1965.

ADDENDUM 3

Flow Chart to Assist Interpretation of Specimens

On the facing page is a flow chart in which one asks four questions:

1) **Is there adequate conjunctival material covering at least one-quarter of one microscopic field (4x objective)?**

Put slide on microscope stage. View under 4x objective. Scan the entire specimen for conjunctival material: epithelial cells, goblet cells, mucin spots. If after scanning the entire area of the paper, there is no conjunctival material, then the specimen is unreadable. If cells are distributed throughout the zone of contact (area of paper which touched conjunctiva), but are so sparse that interpretation is not possible, the specimen is unreadable (A). If there are cells or mucin spots, but they occupy less than one quarter of one low power field, then it is unreadable (B). If there are cells or mucin spots that occupy less than one quarter of two or more low power fields, the specimen is readable (C).

(Not drawn to scale)

A Unreadable **B** Unreadable **C** Readable

Examples:

(8) Ocular debris with adherent mucin. There are no goblet cells, epithelial cells or mucin spots. (100x) UNREADABLE

(9) Too few cells to grade adequately. Note the polymorphonuclear leukocytes (dull purple cells, smaller than mucin spots). (100x) UNREADABLE

(10) Too few mucin spots, or epithelail cells to grade adequtely. Note that the mucin spots are streaked. (100x) UNREADABLE

(11) Too few cells to grade adequately. (100x) UNREADABLE

(1) Abundant cells; can proceed to next question. (100x) READABLE

2) **If the specimen has adequate cells then the next question is: Are there at least five goblet cells?**

Examples:

(2) Abundant goblet cells; background of normal epithelial cells. (40x) NORMAL

(3) More than 5 goblet cells. (100x) NORMAL

(4) More than 5 goblet cells; note presence of mucin spots as well. (40x) NORMAL

(5) No goblet cells; note mucin spots. (100x) NEXT PAGE

(6) No goblet cells; no mucin spots; note separation of epithelial cells. (100x) NEXT PAGE

(7) No goblet cells: note mucin spots. (100x) NEXT PAGE

3) **If there were less than 5 goblet cells on a specimen, then one proceeds to the next page and the following question: Are there any mucin spots?**

(12) Several large mucin spots. (400x) NEXT QUESTION

(17) No mucin spots; note enlarged epithelial cells with small nuclei. (400x) ABNORMAL

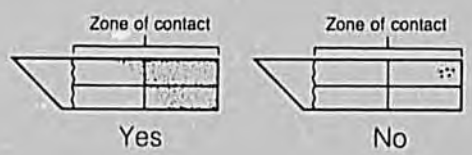
(18) No mucin spots; note epithelial cells are double thickness in places, giving a more intense stain to the cells; do not confuse this with goblet cells. (100x) ABNORMAL

(19) No mucin spots; broken up epithelial cells. (100x) ABNORMAL

(20) No mucin spots; epithelial cells with low nucleus to cytoplasm ratio. (400x) ABNORMAL

4) **If there were mucin spots present, the final question is: Do the mucin spots cover at least 25% of the zone of contact?**

(Not drawn to scale)



(13) Abundant mucin spots covering more than 25% of the zone of contact. (100x) NORMAL

(14) Mucin spots covering more than 25% of the zone of contact. (100x) NORMAL

(15) There are mucin spots in the lower left corner, but they do not cover at least 25% of the zone of contact. (100x) ABNORMAL

(16) Very few mucin spots and streaks in upper center, which do not cover at least 25% of the zone of contact. (40x) ABNORMAL

NOTE: In answering the questions, one must scan the entire "zone of contact" defined above. In other words, one cannot interpret a slide without moving it around. The kodachromes are only one part of a specimen; in specimen (15), if one scanned the entire area and there were no more mucin spots seen, then the slide would be abnormal. If however, upon scanning the entire area, mucin spots covered > 25%, then the slide would be normal.

NOTE: Avoid reading the edge of the paper, since it often contains mucin from the palpebral conjunctiva, if the patient blinked.

APPENDIX I

The updated African Xerophthalmia Recognition Cards published in five languages: **ENGLISH, FRENCH, SWAHILI, CHICHEWA, AND PORTUGUESE** in September, 1988.

Health Workers
Find • Treat • Prevent
Vitamin A Deficiency

Children Go Blind From Lack of Vitamin A

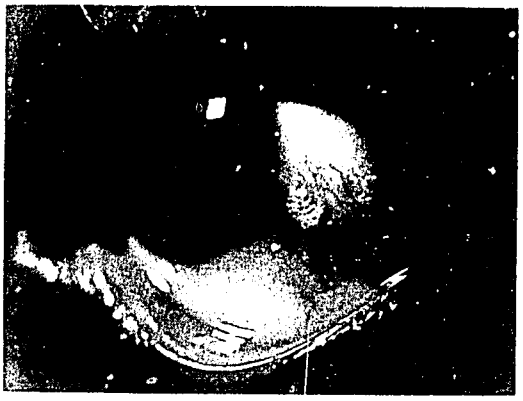
You Can Prevent This Blindness

Find
Children Who Need Vitamin A

Mother says
child is night blind →

or

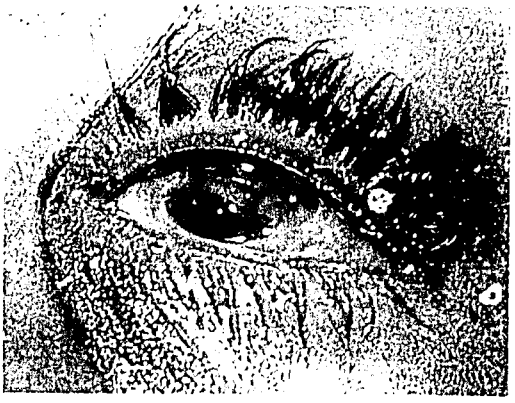
Child's eyes look like this:



White spots

White spots

Bulging



Turning gray

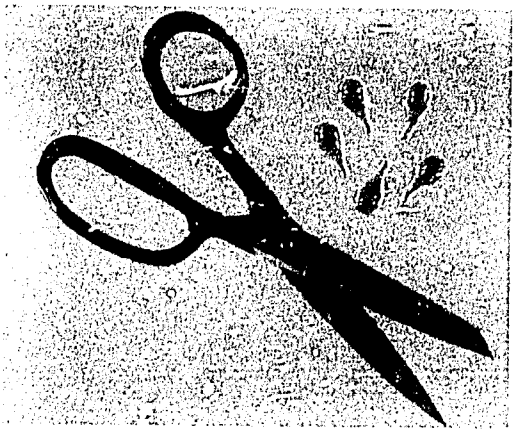
or

Child has measles

Treat
Children Who Need Vitamin A

Now	**Give** 200,000 IU Vitamin A capsule into child's mouth (100,000 IU under 1 year)
Tomorrow	**Give** 200,000 IU Vitamin A capsule into child's mouth (100,000 IU under 1 year)
Again 1 to 4 weeks later	**Give** 200,000 IU Vitamin A capsule into child's mouth (100,000 IU under 1 year)

For young children who cannot chew or swallow capsule, cut capsule and squeeze liquid into child's mouth



Children with frequent **diarrhea** lower **respiratory infection** severe **malnutrition**	**Give** 200,000 IU Vitamin A capsule into child's mouth (100,000 IU under 1 year)

Vitamin A Helps Keep Children Healthy and Prevents Blindness

Sources of Vitamin A

Feed children dark green, leafy vegetables, yellow fruits or red palm oil

Encourage breast feeding

Prevention Dose

Children (1 year or older)	Give 200,000 IU Vitamin A orally every 3 to 6 months
Infants (3-12 months)	Give 100,000 IU Vitamin A orally every 3 to 6 months (give one-half of 200,000 IU capsule)

JOHNS HOPKINS

WORLD HEALTH ORGANIZATION

HELEN KELLER INTERNATIONAL INCORPORATED

With special thanks to U.S. Agency for International Development (USAID), United Nations Children's Fund (UNICEF) and the Task Force Sight and Life

Rev. 1988

Tout Agent de Santé doit savoir

Dépister • Traiter • Prévenir la Carence en Vitamine A

La Carence en Vitamine A peut Provoquer la Cécité chez les Enfants

---

Vous Pouvez Prévenir cette Cécité

Identifiez

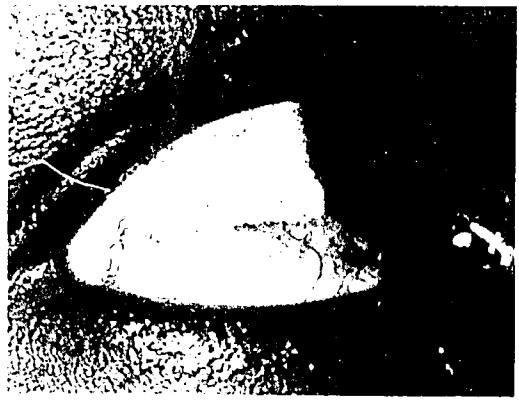
Les Enfants Qui Ont Besoin de Vitamine A

La mère dit que l'enfant ne voit pas dans l'obscurité →

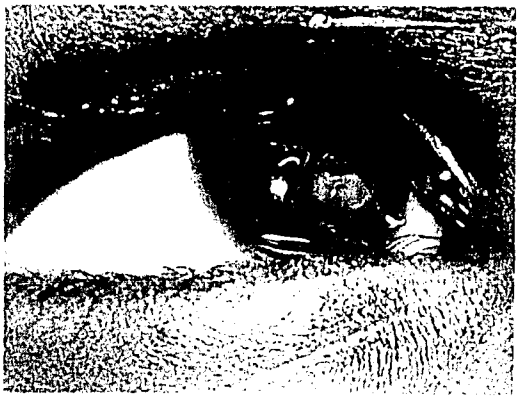
ou

Que les yeux de l'enfant présentent les lésions suivantes:

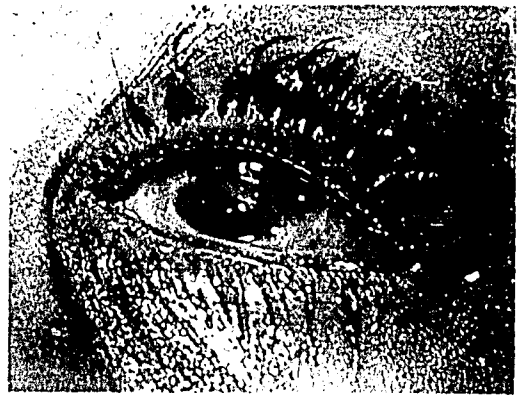
Taches blanches



Taches blanches



Déformation du globe



Aspect laiteux

ou encore

l'enfant a la rougeole

Traitez
Les Enfants Qui Ont Besoin de Vitamine A

Immédiatement

Donnez par voie orale une capsule de 200 000 UI de Vitamine A (100 000 UI si l'enfant a moins d'un an)

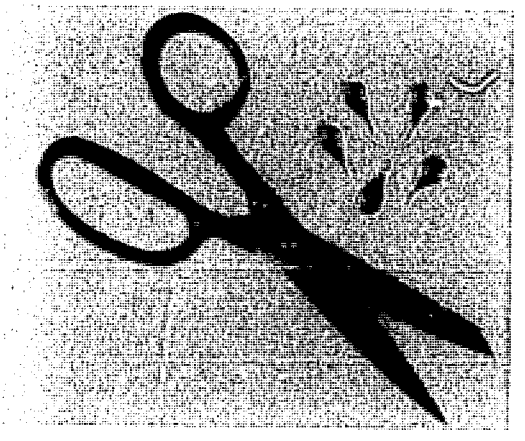
Le lendemain

Donnez par voie orale une capsule de 200 000 UI de Vitamine A (100 000 UI si l'enfant a moins d'un an)

Une à 4 semaines plus tard

Donnez par voie orale une capsule de 200 000 UI de Vitamine A (100 000 UI si l'enfants a moins d'un an)

Pour les enfants qui ne peuvent ni mâcher ni avaler la capsule, coupez le bout de celle-ci et pressez le contenu dans la bouche de l'enfant



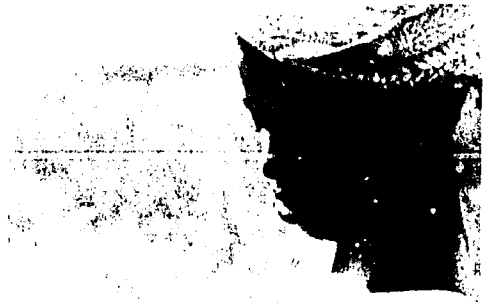
Aux enfants atteints de **diarrhée** fréquente ou **d'infections pulmonaires** ou de **malnutrition** sévère

Donnez par voie orale **200 000 UI de Vitamine A (100 000 UI pour les enfants de moins d'un an)**

La Vitamine A est nécessaire à la bonne Santé des Enfants et elle Permet de Prévenir la Cécité

Sources de Vitamine A

Donnez a manger des légumes à feuilles vert foncé, des fruits jaunes et de l'huile de palme rouge



Encouragez l'allaitement maternel

Prophylaxie

Enfants ages	
-d'un an ou plus	Donnez 200 000 UI de Vitamine A par la bouche tous les 3 a 6 mois
-entre 3 et 12 mois	Donnez 100 000 UI de Vitamine A par la bouch tous les 3 a 6 mois (donnez la moitie d'une capsule de 200 000 UI)

JOHNS HOPKINS

ORGANISATION MONDIALE DE LA SANTÉ

HKI HELEN KELLER INTERNATIONAL

Enfance (UNICEF) et le Groupe de Travail Vue et Vie

Wafanyakazi wa Afya
Tafuta • Tibu • Zuia
Upungufu wa Vitamin A

Watoto Wana kuwa Vipofu Kwa Sababu ya Ukosefu wa Vitamin A

Unaweza Kuzuia Upofu Huu wa Macho

Tafuta Kama

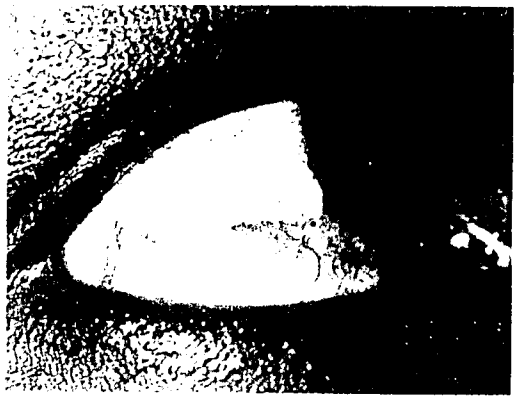
Watoto Waliopungukiwa na Vitamin A

Mama anasema mtoto haoni usiku →

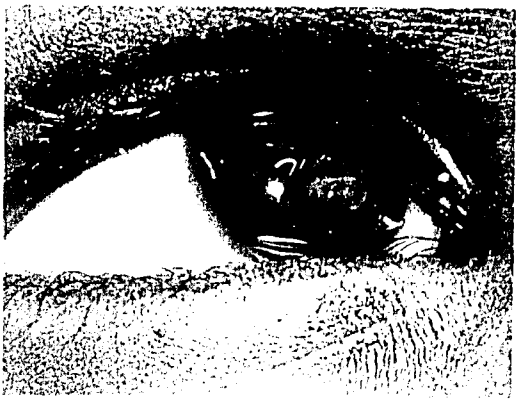
au

Angalia macho ya mtoto

Madowa meupe



Madowa meupe



Kuvimba

Kuwa na rangi ya Kijivu

au

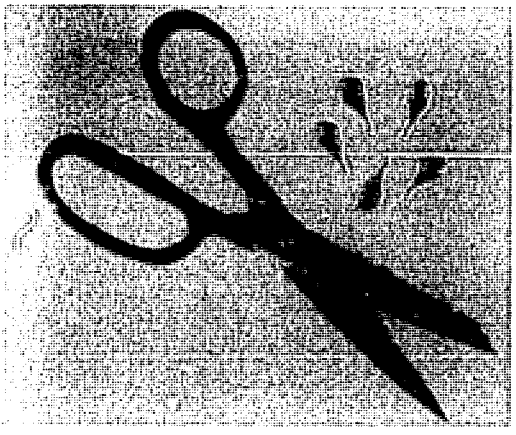
Mtoto ana Surua

Tibu

Watoto Waliopungukiwa na Vitamin A

Sasa hivi	**Mpe** mtoto Kidonge Kimoja cha IU 200,000 Vitamin A (IU 100,000 vitamin A Kama Umri ni chini ya mwaka 1)
Kesho yake	**Mpe** mtoto Kidonge Kimoja cha IU 200,000 Vitamin A (IU 100,000 Vitamin A Kama Umri ni chini ya mwaka 1)
Tena, wiki 1 hadi 4 baadaye	**Mpe** mtoto Kidonge Kimoja cha IU 200,000 Vitamin A (IU 100,000 Vitamin A Kama Umri ni chini ya mwaka 1)

Kwa watoto wadogo, wasioweza kutafuna au
Kumeza Kidonge, pasua Kidonge halafu
Kamulia maji yake mdomoni



Watoto wenye
Kuhara mara Kwa mara
Marathi ya kupumua
Ukosefu wa malisho bora

Mpe mtoto Kidonge Kimoja cha IU 200,000 Vitamin A (IU 100,000 Vitamin A Kama Umri ni chini ya mwaka 1)

Vitamin A Inadumisha Afya ya watoto na Kuzuia Upofu wa macho

Vitamin A inakopatikana

Walishe watoto mboga za majani mabichi, matunda ya manjano, au mafuta ya mawese

Wanyonyeshe maziwa ya mama yao

Dawa ya Kuzuia

Watoto (Mwaka 1 au Zaidi)	Wameze Kidonge Kimoja cha IU 200,000 Vitam · A (Kile miezi 3 mpaka miezi 6).
Watoto Wachanga (Miezi 3 had 12)	Wameze Kidonge Kimoja cha IU 100,000 Vitamin A (kila miezi 3 mpaka 6)

JOHNS HOPKINS

WORLD HEALTH ORGANIZATION
SHIRIKA LA AFYA LA DUNIA

HELEN KELLER INTERNATIONAL INCORPORATED

Shukurani kwa Shirika la Amerika la Maendeleo ya Kimataifaq UNICEF na Task Force Sight and Life

Kimetengenezwa Upya 1988

Azaumoyo

Mupeze • Muchiritse • Muteteze

Kusowa kwa Vitameni A M'thupi

Ŵana Amakhala Akhungu (Osaona) Chifukwa Chosowa Vitameni A M'thupi

---

Mungathe Kuteteza Bvuto la Khungu Limeneri

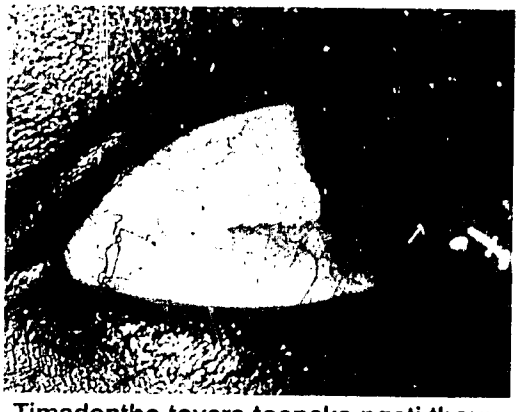
Pezani
Ŵana Omwe Akufunika Kulandira Vitameni A

Mai amanena kuti mwana samaona usiku →

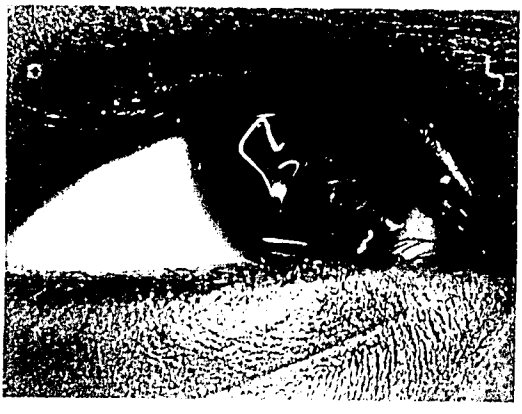
kapena

Maso a mwana amaoneka motere:

Timadontho toyera mu diso



Timadontho toyera tooneka ngati thovu mu diso



Chotupa pa diso

Diso lotumbuluka

kapena

Mwana amene ali ndi chikuku

Muchiritse
Ŵana Amene Akusowa Vitameni A

Tsopano

Alandire m'bulu wa Vitameni A wa 200,000 IU umodzi (ŵana osakwana chaka alandire wa 100,000 IU). Dulani m'bulu ndi kupsyinyira mkamwa mwake

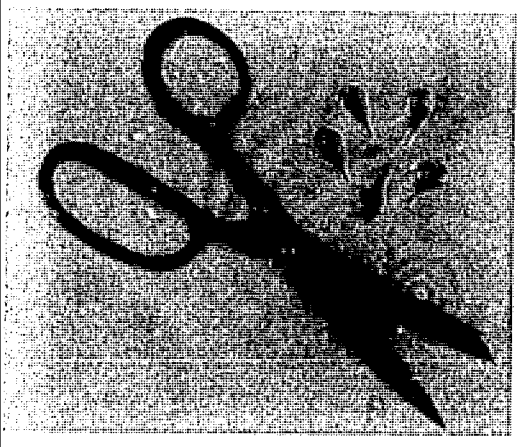
Mawa

Alandire m'bulu wa Vitameni A wa 200,000 IU umodzi (ŵana osakwana chaka alandire wa 100,000 IU). Dulani m'bulu ndi kupsyinyira mkamwa mwake

Patapita Sabata Kapena Masabata Anayi

Alandire m'bulu wa Vitameni A wa 200,000 IU umodzi (ŵana osakwana chaka alandire wa 100,000 IU). Dulani m'bulu ndi kupsyinyira mkamwa mwake

Kwa ŵana omwe sangathe kutafuna kapena kumeza m'bulu, dulani m'bulu ndi kupsyinyira mkamwa mwake madontho. Bulu umodzi wa 200,000 IU tikadula ndikuupsyinya umatulutsa madontho 6. Theka ndi madontho 3 (100,000 IU).



Ŵana **omwe akutsegula m'mimba pafupipafupi**
Ŵana **opelewera zakudya m'thupi**
Ŵana **amene ali ndi zironda za kukhosi**

Alandire m'bulu wa Vitameni A wa 200,000 IU umodzi (Ŵana osakwana chaka alandire wa 100,000 IU). Dulani m'bulu ndi kupsyinyira mkamwa mwake.

Vitameni A Amathandiza Kuti Wana Akhare Athanzi Ndi Kupewa Khungu

Zakudya zomwe ziri ndi Vitameni A

Wana adye ndiwo za masamba, zipatso zakupsya za chikasu kapena mafuta (batala)

Muwalimbikitse amayi kuyamwitsa wana wao

Kuteteza Ndi M'bulu wa Vitameni A

Wana opitilira chaka chimodzi	Mwana amwe m'bulu wa 200,000 IU umodzi pa miyezi 3 kapena 6 iri yonse
Wana a miyezi itatu mpaka chaka chimodzi	Mwana amwe m'bulu wa 100,000 IU pa miyezi 3 kapena 6 iri yonse (perekani theka la m'bulu wa 200,000 IU)

JOHNS HOPKINS

WORLD HEALTH ORGANIZATION

HELEN KELLER INTERNATIONAL INCORPORATED

With special thanks to: U.S. Agency for International Development (USAID), United Nations Children's Fund (UNICEF), the Task Force "Sight and Life", and IBM Europe

Rev. 1988

Trabalhadores de Saúde
Descubra • Trate • Previna
Deficiência de Vitamina A

Crianças Ficam Cegas por Falta de Vitamina A

Você pode prevenir esta cegueira

Descubra

Crianças que necessitam de Vitamina A

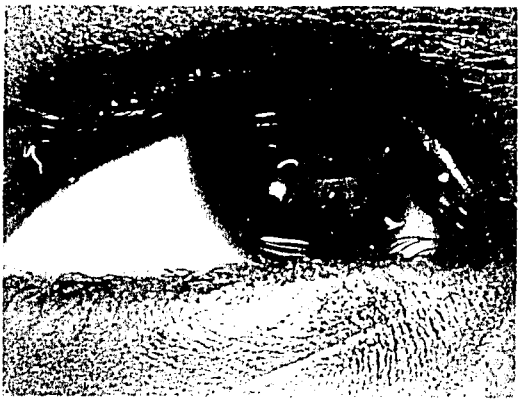
A mãe diz que a criança está com cegueira noturna →

ou

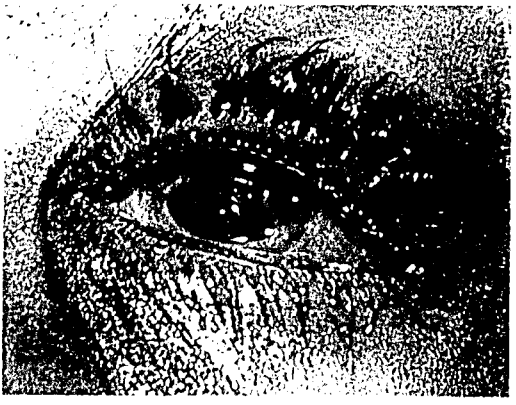
Os olhos da criança estão assim:

Manchas brancas

Manchas brancas



Abaulados



Ficando cinzas

ou

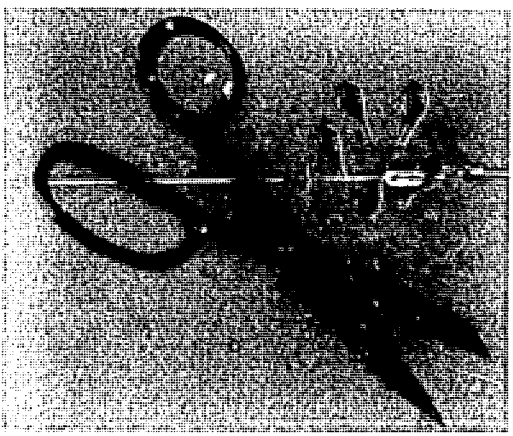
A Criança Tem Sarampo

Trate

Crianças que necessitam de Vitamina A

Agora	**Dê** uma cápsula de Vitamina A de 200.000 UI na boca da criança (100.000 UI para menores de 1 ano)
Amanhã	**Dê** uma cápsula de Vitamina A de 200.000 UI na boca da criança (100.000 UI para menores de 1 ano)
Novamente 1 a 4 semanas depois	**Dê** uma cápsula de Vitamina A de 200.000 UI na boca da criança (100.000 UI para menores de 1 ano)

Para crianças pequenas que não podem mastigar
ou engolir a cápsula, corte a cápsula
e esprema o líquido dentro da boca da criança



Crianças com **diarréia frequente infecção respiratória baixa desnutriçao severa**	**Dê** uma cápsula de Vitamina A de 200.000 UI na boca da criança (100.000 UI para menores de 1 ano)

Vitamina A Ajuda a Manter as Crianças Sadias e Previne a Cegueira

Fontes de Vitamina A

Alimente as crianças com vegetais de folhas verdes escuras, frutas amarelas ou óleo vermelho de palmeira

Recomende a amamentação

Dose Preventiva

Crianças (1 ano ou mais velhas)	Dê Vitamina A de 200.000 UI oralmente cada 3 a 6 meses
Infantes (3-12 meses)	Dê vitamina A de 100.000 UI cada 3 a 6 meses (dê metade da cápsula de 200.000 UI

JOHNS HOPKINS

ORGANIZAÇÃO MUNDIAL DA SAÚDE

HKI HELEN KELLER INTERNATIONAL INCORPORATED

Agradecimento especial a U.S. Agency for International Development (USAID), United Nations Children's Fund (UNICEF) e Task Force Sight and Life

Rev. 1988

APPENDIX J

West KP Jr. and Sommer A: Review of: "Delivery of oral doses of vitamin A to prevent vitamin A deficiency and nutritional blindness." (State-of-the-Art paper). **U.N. Administrative Committee on Coordination - SCN News** March 30, 1988 No. 1: p. 4 and No. 2: p. 11

ingredients of success are at hand – scientific knowledge, inexpensive and effective technology, and accumulated practical experience – the world community were prevented from taking concerted action for want of a modest shift in resources." While discussions go on, vitamin A deficiency continues to kill or blind hundreds of thousands of children each year.

Costs and Benefits of Vitamin A Capsules

A single 200,000 I.U. dose of vitamin A, delivered every four to six months at a cost of less than 50 cents a year, may be enough to protect a young child against vitamin A deficiency and the threat of nutritional blindness and death. That is one conclusion of an SCN policy discussion paper on the prevention of vitamin A deficiency, published in June 1987. "Preliminary cost-benefit analysis shows that the benefits of preventing xerophthalmia calculated in monetary terms can far outweigh programme costs," said the paper. "Delivery of Oral Doses of Vitamin A to prevent Vitamin A Deficiency and Nutritional Blindness." What is more, "given the emerging evidence that vitamin A supplementation may reduce mortality among children with even mild deficiency, the benefit from improving vitamin A nutrition in a population may be even greater than those so far assessed". However, the paper cautioned, while vitamin A supplementation programmes were conceptually simple, ensuring their adequacy and efficiency posed major challenges.

Capsules Containing Doses of Vitamin A are Given Six-Monthly by Mouth

PUBLICATIONS

Nutrition solutions "need not await economic development"

Malnutrition: what can be done? Lessons from World Bank experience, by Alan Berg (John Hopkins University Press, 1987) 120 pp.

Action to eradicate the underlying causes of poverty are important in dealing with the problem of malnutrition. However, as Alan Berg argues in Malnutrition: What can be done?, although nutrition problems are closely linked to a country's level of economic development "nutrition improvements need not await that development". World Bank experience suggests that efficacious and affordable measures for dealing with nutritional deficiencies are at hand. Evidence is provided by analysis of four major Bank-supported projects in Brazil, Colombia, India and Indonesia and 57 nutrition actions in other projects. For example, the Tamil Nadu Integrated Nutrition Project in India used a combination of "sensitive but practical" growth monitoring, highly selective supplementary feeding of nutritionally at-risk mothers and children, a comprehensive communications programme and rigorous management, to reduce malnutrition by an estimated 50 percent in 9,000 villages between 1980 and 1987. The author estimates that the project delivered about twice the benefit for half the cost of comparable programmes in Tamil Nadu. "This finding....suggests," Berg writes, "that a well-managed and targeted programme is able to reduce serious and severe malnutrition more than a less-focussed programme, and at a significantly lower cost".

Malnutrition: what can be done? cites similar World Bank experiences to challenge widely held assumptions about nutrition interventions. Large food programmes, the study found, can be targeted in ways that push costs to much lower levels than earlier programmes. There is also evidence from a large-scale Indonesian project that nutrition education alone can do much to improve nutritional status — women's lack of schooling need not be an insurmountable obstacle. Other World Bank research has shown that vitamin and mineral deficiencies may be caused by a rapid shift from traditional, locally produced grains to polished rice and refined wheat, and that the price low-income families pay for food can be substantially reduced by increasing the efficiency of the food marketing system.

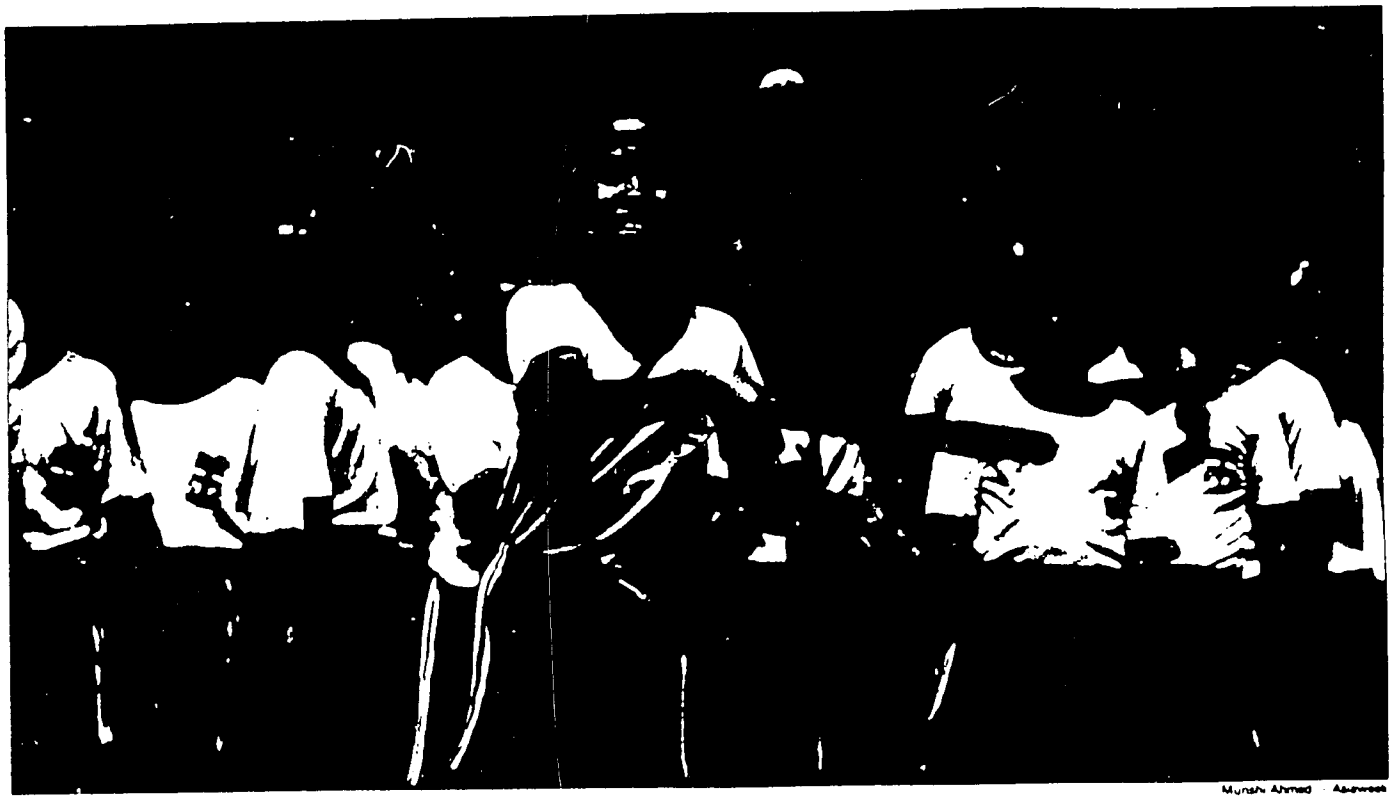
Prevention of Vitamin A Deficiency

Delivery of Oral Doses of Vitamin A to Prevent Vitamin A Deficiency and Nutritional Blindness — A State of the Art Review, Keith P. West Jr. and Alfred Sommer, with Discussion by G. Arroyave, E.M. DeMaeyer, R.P. Devadas, S.J. Eastman, K. Vijayaraghavan and V. Reddy; and an Introduction by J.B. Mason with S.J. Eastman and M. Lotfi. (ACC/SCN, Rome.)

This review, the second in the ACC/SCN's State-of-the-Art Series, is available free of charge from the SCN Secretariat. It reviews the case for vitamin A prevention programmes, focussing on distribution of vitamin A capsules as usually the first intervention for rapid effect. Fortification and dietary modification are introduced in the discussions.

APPENDIX K

A Miracle Vitamin?
ASIAWEEK December 4, 1987



Munshi Ahmad - Asiaweek

Healthy, happy children in Jakarta: An Indonesian-American team tests a new weapon to fight childhood disease

NUTRITION

A Miracle Vitamin?

Fourteen million lives are needlessly lost every year. They are not the aged, nor the unfortunate victims of flood or drought; they are children, caught in the downward spiral of disease and malnutrition. More than half of them were born in Asia. About 5 million perish from diarrhoea, 3 million from respiratory disorders, and 3½ million from measles and other diseases. The deaths occur during the most vulnerable period of life, the first six years.

The means to halt this waste of young lives is readily at hand. Poverty — the root cause of high infant mortality — is not necessarily a block to fighting childhood disease. Hi-tech medicine is not required. Immunisation can guard children against six major diseases. Simple and inexpensive techniques have been developed to help parents protect their young from other debilitating ailments. *see box, p. 56* Clean drinking water and basic sanitation facilities, which require more capital but will pay for themselves in the long run, could help control the breeding and spread of harmful bacteria.

These solutions are already being implemented to some extent in most developing countries. The stumbling block is not so much money (although that, too, is a problem) as education and organisation. What's required is a restructuring of social priorities, and that takes time. Meanwhile, every extra year means more lives lost. But what if a single-shot remedy for childhood illness could be found that would tide over societies until more permanent solutions were in place? Just such a breakthrough is being mooted by scientists in Asia and the United States. An American-Indonesian team has made a remarkable discovery that could add a major new weapon to the health worker's armory. The potential "magic bullet": vitamin A. New evidence suggests it may be the single most important factor in curbing premature deaths.

Doctors have long known that vitamin A — found in carrots and other yellow, orange and dark-green vegetables, and in butterfat, fish oils, liver and egg-yolk — helps the body resist infection. The earliest sign of vitamin A deficiency (VAD) is often an inability to see in dim light. If the diet is not improved, the eyes dry up and lose their lustre. Next, ulcers or lesions develop on the cornea, and may even destroy the eye. If healed, scars may affect vision. The young are the most vulnerable, about half a million are blinded every year.

Vitamin A's broader significance was discovered by Dr. Alfred Sommer of the Johns Hopkins Medical Centre in the U.S. and Ignatius Tarwotjo, head of the Indonesian Health Ministry's directorate of nutrition. They set out on the trail of VAD eleven years ago, in Bandung, West Java, examining children below eight years of age for signs of night blindness. Two years into the study, poring over their records, the scientists noticed a trend: many who had shown symptoms of VAD had stopped turning up for checkups. The men discovered a simple but disturbing explanation: the children were dead.

Further tests were conducted and data re-examined with compensations made for other factors that may have caused the deaths. The figures were plain: the average mortality rate among those

with VAD was four times higher than for others; in some age groups, eight to twelve times higher. To confirm that VAD was indeed responsible for the accelerated death rate, the team conducted an experiment, from 1982 to 1986, involving 450 villages in Aceh, northern Sumatra. The scientists gave 12,991 children between one and five years of age capsules with 200,000 International Units (0.06 grams) of vitamin A at six-month intervals.

The results were remarkable: only 101 of them died, a mortality rate thirteen times lower than children who had not received the capsules, and six times lower compared with other villages. Given to all children, vitamin A could cut child deaths by 34%, concluded the scientists. Last June, Sommer said a new analysis of the data suggested the decline in mortality was more in the range of 70% to 80%, although Tarwotjo questions this estimate. Supportive results from other parts of the world "all point in the same direction," said Sommer.

However, many are sceptical about the findings, at least until more evidence is gathered. "It seems unlikely that childhood mortality [has] a single cause," says a World Health Organisation consultant in Jakarta. "If a child is immunised, VAD will become less important," he adds. Indeed, many childhood afflictions are so closely interrelated that it is difficult to separate out any one of them as primarily responsible for fatalities. Frequent illnesses sap children's energy and appetite, leaving them malnourished. Malnutrition, of which VAD is one aspect, in turn lowers resistance to disease. A simple cold or cough may well deliver the final blow to a weakened system. "It is like the question of the chicken and the egg," says Dr. Ratna Budiarso, an epidemiologist at the Health Ministry's Survey Department. She believes it is difficult to prove through a single study that VAD is the cause of premature death, and says preliminary research must be done on the different VAD levels among children with good and with poor nutrition, before the vitamin's influence can be measured.

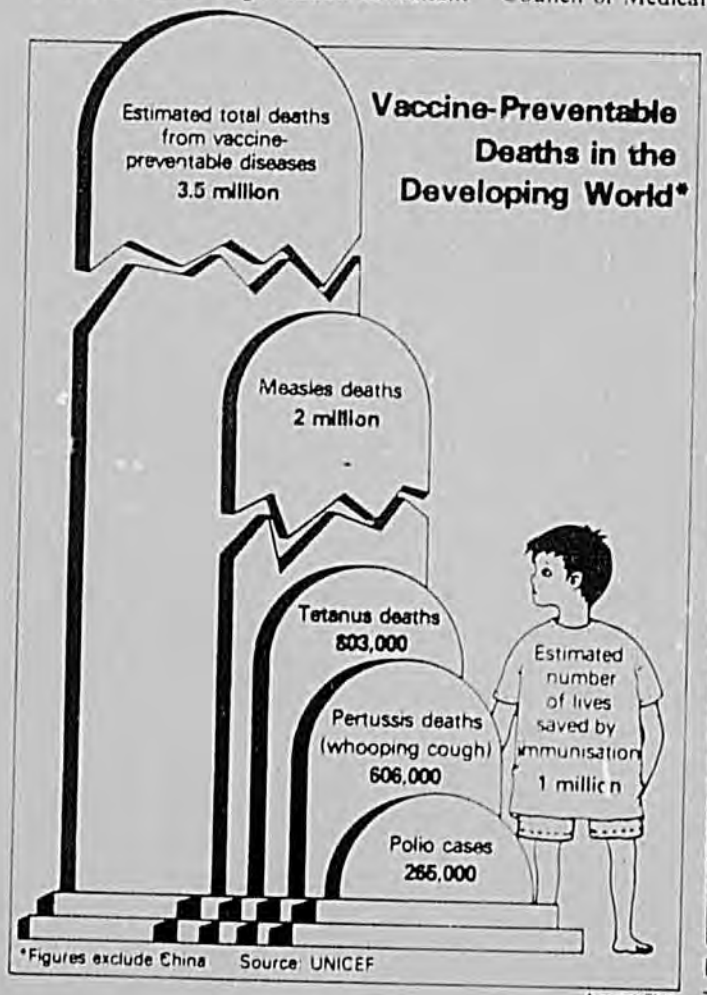
Asiaweek Picture

Tarwotjo: Trend

India, too, is reluctant to take the findings at face value. "We are not convinced," says Dr. B.N. Saxena, senior deputy director-general of the Indian Council of Medical Research. "We'd like to prove it to ourselves," he adds. "It's a bit hard to believe," agrees Dr. Vinodini Reddy, senior deputy director of Hyderabad's National Institute of Nutrition (NIN). "This is not to say that vitamin A doesn't have a role," she cautions, "but protein-energy malnutrition is equally important." Last month, Reddy began a pilot study to investigate the claim.

Even without the rock-solid evidence to prove vitamin A's effectiveness, however, scientists already know a lot about its role in combating infection. The oil-soluble vitamin is stored mainly in the liver and released slowly throughout the body as needed. It is used by the epithelial cells that form skin tissue and the membranes that line the body's internal cavities. In the respiratory tract, for instance, these cells produce mucous and tiny hair-like cilia that sweep out bacteria and foreign particles that get into the lungs, ejecting them with phlegm. When vitamin A is absent in the diet, the cells do not develop properly, leaving the body vulnerable to infection.

The immune system, which fights



Wander Tyap - Asiaweek

Delhi children: Each year, 14 million needless deaths

CAMPAIGNS

An Ounce of Prevention

Sri Lankan shopkeepers sell the packets from street-corner kiosks. Popular actress Karima Mokhtar demonstrates their use six times a day on Egyptian TV. An army of 700,000 villagers in Indonesia fan out regularly to propagate it in their neighbourhoods. The push is on to spread the word: oral rehydration therapy (ORT) can save children's lives. Last year half a million children were rescued from death by dehydration using this remarkably simple do-it-yourself remedy. Children afflicted by acute diarrhoea lose up to 2% of their weight daily through vomiting and purging. Death soon follows. Countering the menace requires a few pennies worth of materials: a glass of water with the correct mix of sugar and table salt binds the stomach and replaces lost energy and fluid. In many countries, commercially prepared mixtures are now sold in local stores. The treatment is at least a decade old. However, only in recent years has it reached people who need it most.

Ravi Vellodi — Asiaweek

Baby-weighing in India: Early warning

Each week some 280,000 children in developing countries die from preventable illnesses; many could be saved using simple techniques like ORT. According to a United Nations Children's Fund (UNICEF) report *The State of The World's Children 1987*, this high death rate can be reduced substantially within a decade. Even poor nations can do it: all it takes is a major communications campaign to empower parents with low-cost ways of protecting their children's health.

About [illegible] million lives could be saved each year through immunisation. More than 40% of the developing world's children are now vaccinated against five of six major diseases: tetanus, whooping-cough, polio, diphtheria and tuberculosis. The exception is measles, against which only about 26% are protected, mainly because the vaccine must be given when the child is about nine months old, no earlier or later. Many children are unprotected not because of a shortage of vaccine or equipment, but because parents are unaware of the need for immunisation. The problem is compounded when vaccinations require three to five visits to a doctor or health clinic. While little effort is required to motivate a mother to seek treatment for a sick child, getting millions to travel long hours and stand in queues to treat children who do not even seem to be sick is a major selling job.

Such campaigns can and have been mounted. In the last two years, Turkey immunised 80% of its unvaccinated children after massive publicity over radio and TV. The drive was personally launched by heads of government at all levels, and promoted by teachers, village heads, police, private corporations and many others. Driving home the message were 54,000 imams who delivered Friday sermons on the Koranic text: "Know the value of life before death comes, and of health before illness strikes."

Malnutrition plays a key role in the vicious cycle of early death: it predisposes children to illness, and if they survive, leaves mental and physical disabilities. These are not necessarily the gaunt and starving portrayed in documentaries: for them, damage to mind and body is irreversible. In most cases, the malnourished are not victims of a food shortage, nor are they hungry. Feeding programs do not necessarily eliminate the cause. Malnutrition results from repeated illnesses, which take appetite away, inhibit the body from absorbing food, and drain nutrients through diarrhoea.

Another major cause of malnutrition is unsatisfactory feeding: not nourishing an infant frequently enough, giving him solids too early or late, not feeding her extra to compensate for weight lost after an illness, or proffering him a bottle instead of breastfeeding. The most vulnerable stage is between 6 months, when the child needs additional food besides milk, and two years. Children become malnourished not because parents are uncaring, but because they lack information to make their care effective.

Malnutrition often results in a slow faltering of growth that is difficult to spot. To a mother's eyes, a child frolicking with equally malnourished playmates may look normal. The only way to be sure is to monitor weight increase every month. Thailand launched such a scheme in 1981. Now, mothers in 37,000 villages track the growth of more than 1.5 million young children. In its early years, the program revealed only 49% were growing normally. Four years later, as worried parents took remedial steps, the figure rose to 70%.

This major improvement in the nation's health was brought about not by doctors in expensive hospitals, but by village mothers assisted by community health workers, often villagers themselves with a few weeks' training. Informal weighing sessions, held in groups in the verandahs of peasant houses, provide early warnings of faltering growth. With such a system, information and responsibility for the child's health is placed where it is most effective — in the hands of parents and the local community.

There is an added benefit to improved health care for children: high birth rates that trap nations in poverty could decline if infant deaths were reduced, says UNICEF. Grieving parents often try to forget their sorrow by having another child too soon. Others, anticipating likely fatalities, raise large families. The inability to ward off sickness and premature death breeds fatalism and reinforces the pattern of runaway population growth. Training parents in simple life-saving techniques can generate a sense of being able to control one's life. A mother who learns how to protect her child also realises she can take steps to avoid having another one. ■

bacterial invasions, may itself be harmed, says Sommer, citing animal studies. Respiratory infections soon develop. Sommer and his colleagues have now come up with a test that can detect VAD at an early stage, even before it affects the eyes. Said to be ten times more sensitive than other techniques, it will allow abnormalities in cell development to be spotted in time for the process to be reversed. The scientists now plan two more studies in West and Central Java to investigate the vitamin's effect on the respiratory, digestive and immune systems, says Tarwotjo.

VAD is a serious problem in many parts of Asia and the world. The deficiency is prevalent in eleven out of 23 provinces in Indonesia, according to a joint survey by the Health Department and Helen Keller International. Between 0.5% and 1% of preschoolers are affected. For the last ten years, vitamin A capsules, supplied by United Nations Children's Fund (UNICEF), have been distributed every six months through some 5,000 community health centres in targeted areas. The government's program has helped to reduce the prevalence of VAD from between 3% and 1% of preschoolers, as estimated in 1950, to the current levels.

Edwin Tuyay

Tan: No progress

SUPPLEMENTS

The MSG Controversy

One way to ensure a vitamin A-rich diet is to have a garden in one's backyard. One such project in the Philippines, supported by UNICEF, distributes seeds of local vitamin-A-rich vegetables to home gardeners. About 6,000 plots in Negros island now supply up to 60% of each family's daily vitamin-A requirement as well as all the vitamin C and iron they need.

Vitamin capsules and syrups can achieve quicker results. However, they require an infrastructure to ensure the full course of doses are administered. To prevent nutritional blindness, for instance, the World Health Organisation (WHO) recommends giving 200,000 International Units of vitamin A every six months to children between 1 and 6 years of age, the most vulnerable group. Those being treated for night blindness must be given three doses of 200,000 IU within a fortnight, and every six months after that, till they reach the age of six. The approach can be effective, but health workers must be able to reach the children at greatest risk. Last year, the Philippines Health Department distributed the vitamin, supplied by U.N. agencies at about 4 cents per capsule, to about 48,000 preschoolers in Antique province. However, its budget does not permit expanding this nationwide. Officials say educating people to eat more nutritious food would be more effective in the long run.

Alan Fajardo

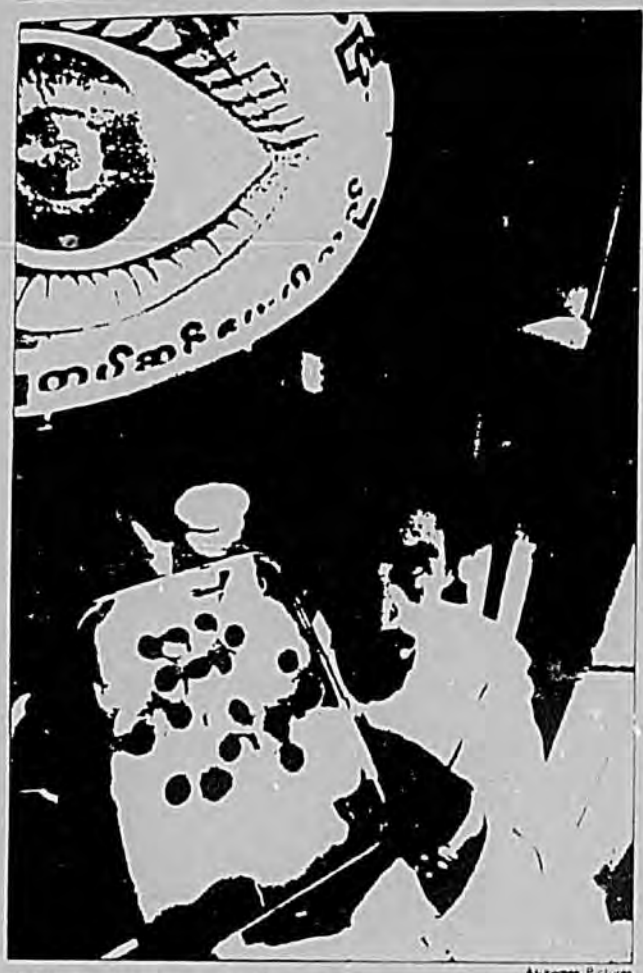
Eating in Negros: Backyard gardens

An easier approach may be to enrich existing diets. In fact, various foods such as margarine, edible oils and sugar are fortified with vitamin A. However, to totally eradicate the vitamin deficiency, food selected for enrichment must be eaten widely, especially by those most likely to have VAD. Only the enriched food item should be released in the market; to ensure this, all supplies must pass through a few factories. Since vitamin A remains in the body for a while, to prevent harmful buildup, consumption of the enriched food must not vary too much from person to person. Finally, to ensure sales, enrichment should not unfavourably affect taste and price.

The Nutrition Centre of the Philippines has identified a likely candidate: monosodium glutamate (MSG). Although critics say it causes unpleasant side-effects, the taste-enhancer is widely used in even the poorest of Asian households. In a 1978 study, Dr. Florentino Solon found 94% of children under 16 years of age in Cebu island consumed soups, stews and other dishes with MSG at least once a week. The seasoning comes in well-sealed two-layered plastic sachets, ideal for protecting vitamin A from exposure. Since only two firms manufacture MSG in the Philippines, fortification can be easily implemented and monitored. A pilot study was conducted in Nueva Vizcaya, Marinduque and Cebu provinces the following year. Packets of MSG mixed with vitamin A granules were given free of charge to target households in two provinces, while the third was supplied with the normal seasoning. Concludes Dr. Michael Latham at Cornell University, who participated in the project: "I think that MSG is the most effective vehicle for the widespread distribution of vitamin A in rural areas of the Philippines and Indonesia."

Indonesia plans to use the idea for combating nutritional blindness in children aged under five. A pilot scheme will begin in December or January in three provinces most affected by VAD. Small sachets containing 3,000 IU of the vitamin per gram of MSG will be sold in local stores. The plan has provoked a bitter debate on the seasoning and its use in young children's food. Although WHO gave MSG a clean bill of health this year, Tini Hadad, executive secretary of the Indonesian Consumer Protection Agency, says its safety is still "a worldwide controversy." The danger of its overuse is "real here," she says, given the local custom of feeding six-month olds with food cooked for adults. "If people are allowed to choose, it's OK," says Dr Waluyo S. Suryodibroto, "but this seems to suggest people should consume MSG." A child nutrition expert at the University of Indonesia, Waluyo says the government should have found a safer alternative.

However, identifying a food that meets all the criteria is not easy. Some countries may not have one. In India, for instance, few factory-processed foods are consumed widely. Reports Dr. Vinodini Reddy from the National Institute of Nutrition about India's attempts at fortification: "With salt, trials haven't been successful, and as for sugar, it's not feasible because of its high price." The vitamin works well with milk, however, and Delhi as well as Calcutta fortify a million litres a day. "This really has little meaning," points out Reddy. "It is not the population of Delhi that requires vitamin A urgently. But why criticise a good thing?" In such countries, till the purchasing power of the needy improves, promoting natural sources of the nutrient and distributing vitamin supplements seem to be the best alternatives. ■



Selling glass eyes in Burma: Grim statistics

Jakarta hopes to eliminate the deficiency entirely by the year 2000.

To achieve this, it plans to go beyond the current selective supplements program to reach the general population by fortifying certain food additives with vitamin A *(see box, p. 57)*. If the plan succeeds, life for many Indonesian children may not have to be the grim fight for survival it is today. About 13% of the country's estimated 168 million people are below five years of age. Compared with a 1.2% annual death rate for the total population, 12.6% of children die before they reach age five, 7.9% before they are a year old, according to 1985 figures from UNICEF. "Infant mortality rate is still the highest among ASEAN countries," confesses Health Minister Suwardjono Surjaningrat. Leading causes: tetanus (13.8%), still-birth or death soon after birth (13.2%), diarrhoea (11.2%) and respiratory infection (10.3%), according to a Health Ministry survey. Nevertheless, conditions are better than they were 25 years ago, when the infant mortality rate was twice as high.

The statistics are just as grim in the Philippines. Five years ago almost 3% of Filipino preschoolers showed symptoms of VAD, and according to health workers the situation has worsened. Although children's nutrition appeared to have improved in the early 1980s, it began to deteriorate in 1984 and 1985 as the country's economy floundered, says Dr. Jaime Golez Tan, officer for nutrition and urban basic services. Some 32,000 children go blind each year. Almost eight out of every hundred children never live to be five years old. Although there is no national anti-VAD effort, pilot programs are being carried out in urban Metro-Manila and adjoining Las Pinas, and Antique province in the Western Visayas. Based on their results, the government hopes to develop an effective community-based VAD prevention program. Besides VAD, many children below four are also deficient in protein-energy and iron, and are anaemic.

India, home to about 15% of humanity, has more than its share of poverty and disease. A child's fight for survival there is a desperate struggle against heavy odds: one out of every ten do not live to be a year old, 15.8% die before age five. The figures would be even more severe if it were not for the country's far-reaching health programs. Within two decades, infant mortality has been cut by 30% and birth rate by 25%, while life expectancy has gone up by 40% to 57 years. Vitamin A distribution, which began in 1972, has been mainly aimed at preventing blindness. "There are 80 million children who need it, but we supply only to 25 million," says NIN's Reddy. This year, 30 million children between one and five will receive the vitamin as part of the government's Mother and Child health program. Says Geeta Athreya, a senior UNICEF staffer in Delhi monitoring the distribution: "We recommend that vitamin A starts at six months. The government is very lukewarm to this and keener to push immunisation. [We would prefer them to] combine vitamin A along with it."

However, some experts consider vitamin A supplements as only a stopgap measure. The underlying problem, they argue, is a deficient diet that may also be denying the body other essential nutrients. Says Dr. M.C. Gupta, professor at the Human Nutrition Unit of the All-India Institute of Medical Sciences: "Unless we are able to remove the cause of VAD, there is no point in giving doses. Even cheap sources of vitamin A are not used by the community due to ignorance."

Agrees Athreya: "Often we run into cultural problems. In the south, for instance, green leafy vegetables are looked down upon. North Arcot district in Tamil Nadu produces the best variety of papayas in India. Yet, many people are suspicious of it, thinking it induces abortion." Their comments highlight the need for comprehensive programs that combine short-term supplements with long-term efforts to get people to improve their diet.

Despite the scepticism generated, Indonesia's research has renewed interest in vitamin A. If studies in India and other places bear out the initial promise, the nutrient may well turn out to be a major weapon in the fight to curb unnecessary child deaths. "[It] looks too good to be true," admits Rolf Carriere, head of nutrition at UNICEF in Delhi, who helped set up the study during his years in Indonesia. "Nevertheless, vitamin A is the most cost-effective thing you can do. For less than $5 a head, you can rule out six diseases per child." By combining vitamin A programs with mass immunisation, basic improvements in sanitation and village-level health care, none of which are beyond the reach of most governments, a revolution in child survival could take place within this century. ■

India's Reddy; Saxena: "Hard to believe"

APPENDIX L

Sommer A: Staying in sight with vitamin A.
UNICEF INTERCOM
October 1987

Staying in sight with Vitamin A

THERE is now hope of avoiding some of the most lethal and disabling effects of measles, a disease that kills two million children in the developing world. Professor ALFRED SOMMER, Director of the International Centre for Epidemiologic and Preventive Ophthamology, comments on a recent WHO/UNICEF joint statement on the blinding combination of measles and Vitamin A deficiency.

IMMUNIZATION

MEASLES remains a scourge of young children throughout the developing world. Case-fatality rates often exceed 40 per cent while blindness associated with the disease fills schools for the blind. The long-term, definitive solution is elimination of all cases of measles through universal immunization. In the meanwhile, is there anything that can be done to reduce the high rates of morbidity, mortality and blindness? The WHO/UNICEF joint statement of May 1987, recommending Vitamin A in the treatment of measles, rests upon the reasonable expectation that there is.

To grasp the significance of the joint statement it is worth recalling that measles is not invariably accompanied by high rates of mortality and blindness. These problems accompany measles in deprived populations of 19th century industrial labourers in Europe, or among landless villagers of Africa and Asia today. Well-nourished, otherwise healthy populations rarely suffer severe consequences of the disease. The WHO/UNICEF recommendation seeks to exploit this dichotomy between measles and its severe complications. While it is unlikely a single factor explains all instances of severe complications, Vitamin A deficiency appears to be an important one. Moreover, it is a factor well within our ability to control.

CORNEAL DESTRUCTION

Careful clinical studies in Asia and Africa indicate that measles is a frequent precipitating event for keratomalacia, a form of corneal destruction and blindness caused by Vitamin A deficiency. In Indonesia, measles accounted for over 50 per cent of the cases of Vitamin A-related corneal destruction and blindness. In Tanzania, over 50 per cent of the cases of bilateral corneal destruction and blindness accompanying measles are caused by Vitamin A deficiency.

The mechanism(s) by which measles results in Vitamin A deficiency and the attendant corneal ulceration are not entirely clear. It is well established however that measles infection markedly increases the body's need for Vitamin A. A child with only border-line reserves may suddenly become deficient, resulting in rapid corneal ulceration.

Perhaps even more commonly, the acute reduction in Vitamin A stores is compounded by continued, chronic depletion resulting from reduced dietary intake and absorption accompanying the dreaded cycle of anorexia-diarrhoea-malnutrition that frequently follows a measles attack. In many instances the situation is exacerbated by protein deficiency that further impairs the ability to mobilize Vitamin A from existing liver stores and deliver it to target tissues. Fortunately, if treated early, Vitamin A deficiency can be reversed and eyes not yet destroyed can be saved, even those with active but localized corneal ulceration.

A recent hospital-based study in Tanzania also suggests that Vitamin A deficiency is at least partially responsible for high case-fatality rates. Half the children admitted to hospital with moderate to severe measles received a large dose of Vitamin A on two successive days. Short-term in-hospital mortality among the Vitamin A recipients was only half that of the non-recipients, and this difference appeared particularly striking among younger children and those suffering from respiratory complications. Again the mechanism is unclear. By causing acute depletion of Vitamin A stores measles may simply exacerbate existing Vitamin A deficiency and further reduce the child's general resistance to infection and death.

Measles virus, however, also invades epithelial structures, including the surface of the eye and respiratory tract; Vitamin A is necessary for maintaining the normal epithelial lining of these and other organs. Hence a contributory influence may be Vitamin A's action on epithelial integrity and the effect this has on measles invasion or its consequences.

While direct measurement of the impact Vitamin A treatment is limited to a single clinical trial, the conclusions rest on a large body of supporting evidence. Literally decades of animal research have repeatedly demonstrated that Vitamin A deficient animals become increasingly susceptible to infection and death, often before developing any eye signs (xerophthalmia). Recent epidemiological studies confirm a similar situation in children.

Mild, even sub-clinical Vitamin A deficiency is associated with increased risk of respiratory disease and diarrhoea; and the greater the deficiency, the greater the mortality. In two large-scale controlled trials in Indonesia, children who received Vitamin A supplements (either as periodic large doses or as fortified MSG) died at only one-third to one-half the rate of non-supplemented children. Other studies suggest the vast majority of children suffering physiological consequences of Vitamin A deficiency look entirely normal on routine clinical examination.

EMINENT SENSE

Given the enormous risks at stake, literally the sight and lives of millions of children, and the ease and safety with which Vitamin A deficiency can be treated, it makes eminent sense to apply the WHO/UNICEF recommendation to all children with measles in communities where Vitamin A deficiency is known to be a problem. Recognizing that many communities with Vitamin A deficiency are unaware of it, the second part of the recommendation is equally important: Even where Vitamin A deficiency is not recognized to be a problem, Vitamin A treatment should be used if measles case-fatality rates are 1 per cent or greater.

Of course, all children with measles should receive appropriate ancillary care, including proper hydration, nutrition, and attention to secondary infections. In particular, both eyes should be carefully examined for ulcers that may not respond to Vitamin A alone and require additional treatment (for fungal, bacterial or viral infection, or the consequences of "folk" remedies.)

MINIMALIST APPROACH

The joint WHO/UNICEF recommendation is a timely, forceful response. However, it still represents a "minimalist" approach. Boosting Vitamin A reserves in children who present with measles is like putting out a raging fire. Some homes will be saved but a substantial proportion will burn down before aid arrives. It would be far more effective to ensure all children adequate Vitamin A reserves at all times. Not only will they already be "protected" should they develop measles, but they will benefit from the protection adequate Vitamin A status provides against non-measles morbidity and mortality, including xerophthalmia and blindness.

Admittedly this requires a more comprehensive and necessarily expensive approach. With development and testing of locally appropriate mechanisms for achieving this goal, usually through some combination of administering periodic large doses of Vitamin A, fortifying a common dietary item with Vitamin A, or encouraging increased consumption of foods naturally rich in Vitamin A, a far greater impact will be made on children's health, vision and survival.

APPENDIX M

Transcript from:
Worldnet United States Information Agency
Television and Film Service
Washington, D.C.
"Child Survival in Africa"
Dr. Keith West, Jr., guest.
June 28, 1988

WORLDNET
UNITED STATES INFORMATION AGENCY
Television and Film Service
Washington, D.C.

GUESTS: Mr. Bradshaw Langmaid, Jr., Deputy Assistant Administrator for Research, Bureau for Science and Technology, Agency of International Development
and
Dr. Keith West, Assistant Professor of Ophthalmology and International Health/Project Director, USAID Cooperative Agreement to Control Vitamin A Deficiency, International Center for Epidemiologic and Preventive Ophthalmology (ICEPO)

TOPIC: Child Survival in Africa

HOST: George Collinet

INTERACTIVE POSTS: Abidjan, Brazzaville, Libreville, Niamey

DATE: June 28, 1988

TIME: 10:00-11:00 a.m. EDT

Diversified Reporting Services, Inc.
1511 K Street, N.W., Suite 547
Washington, D.C. 20005
(202) 628-2121

ANNOUNCER: Worldnet presents Dialogue, an unrehearsed televised exchange of ideas. Now, from our studios in Washington, D.C., here is your host, broadcast journalist George Collinet.

MR. COLLINET: Good afternoon, and welcome to Worldnet's Dialogue. Today for our international audience and participants in Abidjan, Niamey, Libreville, and Brazzaville, we are happy to present a discussion on child survival in Africa.

It is estimated in the developing world one child dies every three seconds, or forty thousand children per day, fourteen to fifteen million children per year. The cause of death may be measles, diarrhea or diseases associated with poverty and malnutrition.

In addition, tens of millions of children in developing countries suffer from vitamin A deficiency. Research shows that this predisposes children to illness and death from a variety of causes. Joining us today to discuss the current problems for child survival in Africa in this matter, two leading authorities on the subject: Dr. Keith West is an Assistant Professor of Ophthalmology and International Health. He is also Project Director for the Vitamin A Control Program at Johns Hopkins University sponsored by AID.

Mr. Bradshaw Langmaid is Deputy Administrator for Research at the Bureau for Science and Technology at the U.S. Agency of International Development, and is Chairman of the Child Survival Task Force.

Welcome to Worldnet, gent'emen. I shall start with Dr. West. It appears that current research shows a relationship between many diseases which are killing young children around the world and vitamin A deficiency.

Could you briefly explain to us this phenomenon?

DR. WEST: Yes, vitamin A is a required nutrient in everyone's diet. The deficiency of vitamin A has long been known to cause blindness in children; for decades, that has been known.

In recent years, we have been looking at the health problems associated with mild vitamin A deficiency, at levels that do not cause the blindness due to xeroph^thalmia.

This research that has been carried out largely in Asia, but also now emerging in Africa, has shown that children with mild vitamin A deficiency appear to be at an increased risk of morbidity, diarrheal disease, respiratory infection, and of course, these are the major causes of child mortality in most developing countries around the world.

This evidence of mild xeroph^thalmia, mild vitamin A deficiency, being related to an increased risk of morbidity and mortality, has been further researched to answer the question, well, if it is related to mild -- if mild deficiency is related to morbidity and mortality -- if you give vitamin A to children, what will it do that risk?

There have been a few trials now carried out in Asia to show that if you supplement children with mild deficiency, that their risk of mortality can be decreased.

MR. COLLINET: Thank you very much, Dr. West. Mr. Langmaid, there are many programs which your agency, AID, is supporting to assist developing countries with health care. What is AID's role in assisting overseas doctors with child survival?

MR. LANGMAID: Thank you, as you indicate, my agency is concerned with helping developing countries improve the lives of their people. A principal focus of our program is the child survival effort. Child survival represents over sixty percent of our health programs. In the child survival area, we really refer to four distinct interventions: immunizations, six specific immunizations of the most preventable childhood diseases; the application of oral rehydration therapy, a simple salt solution that in many of

the typical diarrheal cases can treat the diarrhea effectively, and prevent child death as a result of diarrhea, which is a leading cause of death in the developing world;

nutritional interventions which, along with the application of oral rehydration salts can insure effective recovery from the bouts of diarrhea, and the capacity to withstand other illnesses; & lastly, birth spacing.

We have set as a goal, in conjunction with UNICEF and WHO, achieving eighty percent coverage in these areas by the year 1990. We feel in many countries, we are substantially along the way towards that coverage.

MR. COLLINET: Thank you, Mr. Langmaid. I would like to ask our participants to please identify yourselves and your organizations. We are going to Abidjan first. Over to you, Abidjan.

Dago, Faculty of Pharmacy, U. of Abidjan

DR. Monney: I am Dr. Monney (phonetic), School of Pharmacy. My question is to know about vitamin A in child survival. Is it the best marker, and why not vitamin D, or the beta carotene, or retinal-binding protein, for instance, used concurrently?

DR. WEST: If I understood that question correctly, it deals with the markers for vitamin A status and why vitamin A and not other nutrients? Well, vitamin A is one of those

nutrients that slips the cracks, that becomes deficient in a diet that -- where the variety of foods are restricted -- in particular, in rural diets throughout many regions. Vitamin A has many functions in the body, of course, as you know. Among those are included the multiple reproductive functions. It is essential for growth.

It is essential for maintaining the integrity of epithelial tissues throughout the oral cavity, the respiratory tract, genito urinary tract, the gastrointestinal tract. Of course, these are the sites where bacterial and pathogenic invasion are likely to occur, making vitamin A an important nutrient for maintaining host resistance.

The markers for vitamin A status include those that you mentioned. Retinal binding protein is, of course, the carrier protein in the blood that delivers vitamin A from the liver to the peripheral tissues for use.

Retinal-binding protein levels in the blood are related to vitamin A status as measured by serum vitamin A levels, clinical status and so forth. So it is possible to measure retinal binding protein. However, the most obvious indicator of vitamin A status is clinical status.

The signs of xeroph^thalmia, range from the earliest that are currently accepted, which includes night blindness, through to the dryness that we see on a surface of the eye, conjunctival xerosis leading to corneal xerosis, and ultimately, destruction of the cornea.

These clinical signs are the tell-tale signs of vitamin A deficiency, } they represent the more severe point on the continuum of vitamin A status. There, of course, are children who are deficient in vitamin A that do not have clinical signs.

The question that has been a major question in terms of research in recent years has been what indicators can be derived to identify children or to identify communities of children with early vitamin A deficiency?

There has been work done with looking at serum vitamin A levels, } also, with a new technique that is still under development, using conjunctival impression cytology. This invclves taking a sample of the superficial layer of cells from the conjunctival surface of the eye with a filter paper strip which can remove the goblet cells and epithelial cells that are normally replete in vitamin A status, in normal vitamin A status, and look at the presence or absence of

these cells as a way of looking at early vitamin A deficiency.

So, there are a number of markers that are available, and becoming increasingly -- their limitations and their strengths are becoming increasingly known.

MR. COLLINET: Thank you, Abidjan. Over to Niamey, go ahead.

DR. EDY: Dr. Edy (phonetic) of the Ophthalmology Department of the National Hospital. There is a great correlation between wide vitamin A deficiency and some disease such as measles, malnutrition, serious malnutrition, diarrhea and the respiratory ailments. The question is, for us at least, what is the best therapy to follow faced with these ailments in the presence of these vitamin A deficiency?

DR. WEST : Vitamin A therapy, of course, will not prevent exposure to pathogens that cause respiratory infection, diarrhea. Certainly, it will not prevent exposure to the measles virus.

Therefore, vitamin A is considered to be adjunct therapy for children who have these diseases. It will not stop children from getting protein energy malnutrition. What it does do, though, is address an imbalance in the diet.

Children with severe protein energy malnutrition are likely to be vitamin A deficient.

Children who do not have apparent protein energy malnutrition, however, may also be vitamin A deficient. We should keep that distinction in mind.

Vitamin A, because it is necessary for maintaining epithalamic integrity, and there is also increasing evidence to indicate that it plays a role in the immune response, becomes an important adjunct for treating children at high risk of developing acute vitamin A deficiency, and these are just the children that you mentioned.

The children with acute lower respiratory tract infection; children with measles, in the post-measles state as well since in Africa, in particular, measles appears to be particularly severe, and those children who develop measles are at an increased risk of developing blinding corneal xeroph thalmia.

So, vitamin A becomes an important part of the treatment for children with measles. What is becoming apparent now from a trial in Tanzania that was carried out two years and published in the British Medical Journal a year ago January; January of '87 showed that children who were receiving vitamin A supplements at the time of admission (children with

measles who were admitted to the hospital with measles), those who were given a vitamin A supplement experienced a reduced mortality, in-hospital mortality.

The reduction was fifty percent. It was a small trial. It needs to be corroborated, but it does show that treating children with vitamin A even in the acute phase of illness may have a very beneficial effect on their prognosis, particularly as it relates to mortality due to that infection.

MR. COLLINET: Thank you. Over to Libreville.

QUESTION: From the School of Medicine Libreville, Director of Scientific Programs on Television. In Africa, in most developing countries, child survival is a major problem, not to say a real scourge. There are many cholera infections, parasite diseases and enteritis.

My question is the following: what can we expect from the United States in helping developing countries to try and assist in child survival?

MR. LANGMAID: As I indicated in my opening comments, child survival is one of the major areas of AID attention in Africa as elsewhere in the world. We are spending around $150 million annually on child survival interventions, and in cooperation with UNICEF and WHO are making a substantial

investment in both the financing of vaccines and delivery of vaccines, the procurement and delivery of oral rehydration salts.

We are particularly concerned with the production of those salts in developing countries and their application to the problems of diarrhea.

The real key to child survival is the delivery of these kinds of interventions. The interventions themselves are quite simple. The cost of the full regime of immunizations is less than two dollars. The cost of one package of salt is less than eighteen cents. I believe the cost of a vitamin A application is in the same general area.

The cost of delivering these services which largely depend on the health delivery services of the countries concerned, through both the public sector, and I think increasingly, the private sector, are frequently five, six, seven times the cost of the intervention itself.

So, the real key to successful application of these rather simple tools to saving lives of children is delivery systems which are low cost, effective, and reach the child concerned. That means increasingly we must rely on the private sector and a normal distribution system of marketing the private sector for those interventions that can move in

that area and increasing the services delivery from the public sector.

MR. COLLINET: Thank you, Mr. Langmaid. We are now going to Brazzaville.

DR. MYONDA: Dr. Myonda (phonetic) at Brazzaville. I would like to ask a question for Mr. Langmaid. In your programs for Africa (inaudible) from USAID, child survival and more particularly, infant mortality is a serious problem in Africa, particularly in the Congo. I believe that among measures advocated today, these are measures aimed at the child from twelve months or up to five years of age, but the infant survival problem has been somewhat put in the background. I should like to know, in your programs what do you anticipate for this particular timeframe?

MR. LANGMAID: I am glad you asked that question, because I need to emphasize a particular aspect of the program which is equally important.

Clearly, one of the serious concerns for the high level infant mortality is the closeness of repeated births, and birth spacing to insure adequate spread between births and hence, a more healthy child is terribly important.

Equally important is the use of breast feeding to insure the transfer of maternal antibodies to the child and adequate

start on life for the child. This is also a very part of our program.

Thirdly, neonatal tetanus is a serious concern and frankly, among the immunizations the area where probably the coverage is least and yet, the level of infant mortality as a result of tetanus is quite high.

All three of these are an integral part of our child survival activity and help deal with the problems of the zero to one year old.

Lastly, and this is an item for the future, we are concerned with various aspects of research on immunizations, particularly measles, that can be applied earlier in life. Although we do not have those tools now, we are hopeful in the future we will have such tools to deal with some of the threatening diseases that attack the young child.

MR. COLLINET: Back to Abidjan. Please go ahead.

QUESTION: My name is Dr. Wandji N'gah, African Development Bank. My question has to do with the family, for in the African countries there are several programs, the programs against onchocerciasis, the programs against river blindness. In the cases of vitamin A deficiency struggles, does AID expect to help countries to set up national committees to fight vitamin A deficiency.

How can we integrate this vitamin deficiency program in our current programs in our young nations?

MR. LANGMAID: Let me make a few comments, if I might, and then ask Dr. West to amplify if he wishes. I think AID is one of the major financiers of vitamin A activity in terms of trials in the field, as well as working on development of adequate diets, the use of farm-based vegetable plots to improve the diet.

Last year we financed, I think, eight million dollars in a range of vitamin A activities, some of which were in Africa and other parts of the world. So, in that sense it is an integral part of our child survival effort.

I think the key issue with vitamin A is the cost of delivery and targeting those in most need, & the cost effectiveness of various forms of fortification on a regular basis as well as the application of higher dosage to those who are most at risk and most in need. That becomes very much a cost delivery program.

I do not think at this stage we have thought in terms of national level vitamin A committees in the same context as maybe child survival committees, or in some countries AIDS national committees as an implementation tool. We would see,

I think, vitamin A as becoming part of an integrated child survival service program.

DR. WEST: In addition to that, it is important to bear in mind that the problem needs to, of course, be defined first. In Africa, in particular, a decade ago vitamin A deficiency was not felt to be an important problem. Where it has been looked for, it has been found.

There have been surveys in Mauritania, Niger, Chad, Mali, Zambia, Malawi, Tanzania and other countries which have looked for vitamin A deficiency and indeed found it, either nationally or in regional pockets.

Once there is an interest in defining the problem, however, the first step is not necessarily to launch out and do a survey, but to answer the question, is vitamin A deficiency a problem of public health significance? That question can be answered by certain techniques.

One is to, in a structured way, carry out interviews with those clinicians and treatment facilities that are likely to see children with vitamin A deficiency. Active case ascertainment, looking in a structured way, going to measles wards, infectious disease wards and treatment facilities, and looking for cases xeroph^h^thalmia.

Looking in the community for children with an historic record of a past with xeroph^h^thalmia, that is, children with scars on their corneas, with a history that is compatible with xeroph^h^thalmia. Looking at existing reports on dietary intakes, serum levels of vitamin A that may have been recorded during previous surveys.

To basically answer the question, does the problem exist and where, and what is the magnitude and severity likely to be? Once those questions are answered, then the likely area is defined, and it would be appropriate to carry out a survey to identify and establish the magnitude and the severity and the high risk groups for vitamin A deficiency.

Now you have got the problem defined, and the question that you have raised is, what do we do about it, and how do we improve the vitamin A status of those highest risk populations? We are talking about communities now.

There are three basic strategies. Mr. Langmaid mentioned one about fortification. Fortification requires that a food that is technically fortifiable, and somewhat centrally produced so that it can be fortified, exists. That food is also consumed by those who are most at risk, those who you are trying to target with the program.

Those foods have not been well identified in Africa, although there have been other foods in Asia and Central America that have addressed this problem; sugar, monosodium glutamate and some other foods.

Fortification is something to keep in mind, though, as the problem and resources become better defined. There is also, though, the vitamin A dosing strategy, periodically providing the UNICEF capsule of vitamin A containing two hundred thousand international units every four to six months to children one through five years of age, or older if need be, and half of that dose for young infants.

Then, the question is, well, how do we deliver that, through what system? Of course, the primary health care system infrastructure that exists should be primed to provide vitamin A supplementation to children on a periodic basis through the existing infrastructure, growth monitoring clinics. Wherever the health system comes into contact with children, that system can be exploited to provide routine supplementation with these UNICEF capsules.

They should be part of the -- where the problem exists, the UNICEF vitamin A capsules should be part of the essential drugs program. Other areas, other mechanisms can be explored. The EPI program can be looked at. Mothers in the

first two months after birth can be given a large, single dose of vitamin A, the UNICEF capsule.

Infants who come in for their oral polio and DPT series of vaccinations, can be given once during those early weeks of life, a small dose of vitamin A, fifty thousand units for example. During measles vaccination campaigns, at nine months of age, children can be given one hundred thousand units or a half a dose of vitamin A.

Then, after that, whenever children come into contact with the system, they can be given a large dose of vitamin A. The third part of this strategy that is available is the dietary improvement strategy, improving the local diet through nutrition education where the foods are available, and people know about the foods sources of vitamin A, which are, in most countries, dark green leafy vegetables, mangos, papayas, the yellow fruits and vegetables.

So, nutrition education has a role to play, and there are ways so making nutrition education more effective. There are social marketing techniques that are on the horizon, that are being tested, taking commercial advertising techniques and applying it to creating demand for local foods that contain vitamin A.

There is home gardening activities. A new program has sprung up in Niamey at the Institute for Rural Development to look at how to construct a garden plot that is culturally acceptable and environmentally appropriate for different regions of Africa.

It is a slow process, but it needs to start somewhere in terms of formalizing these kinds of program activities. So, periodic dosing, fortification, and nutrition education/-dietary improvement, are three broad ways to approach the problem.

MR. COLLINET: Thank you, Abidjan, over to Niamey.

DR. GARBA: I am Dr. Yarro Garba (phonetic), Chief of Nutrition at the Ministry of Public Health and Social Welfare. Thank you both, since I speak to both of you, thank you both for shedding some light on the questions I have been asking myself.

I would like to make a point, express a viewpoint which is a controversial point, but it may lead to a question. You cannot speak of child survival without stressing two basic dimensions. The globality of the problem, I mean as my pharmacist colleague said in Abidjan, you cannot simply speak of vitamin A deficiency, it is a global nutritional program that is required.

We should not have sector-by-sector programs, but we should have a fully integrated program, all nutritional aspects accompanying any program to promote child survival. My second point, I would like to speak about the cultural component of the problem.

You stress much more the child; we give an importance to our adults as well. In this particular case, perhaps we should rethink the sociological approach to the problem, so that we can either give aid through an assistance program to adult populations, with, at the back of your mind, the fact that this will be a positive spin off for the child.

Or, another approach would be to carry out a full reconversion of the mindset of the frame of mind, so that the philosophy towards the child would be much better understood in our own countries. Thank you.

DR. WEST : Your points are well taken, sir. There is no question that vitamin A deficiency is a part and parcel of a larger malnutrition problem in many countries throughout the world. What is emerging is that it may have similar consequences, of course.

That is the bottom line. If it had similar consequences, then the global strategy needs to be prevention. Now, the way you go about preventing may take on

different components, depending on the country, on the culture, on the resources that are available, on the political commitment that a country makes to preventing vitamin A deficiency within this milieu, within the context of the many problems that exist, there has to be that political commitment.

I heard an interesting phrase the other day. It was preventive politics. Preventive politics takes on that notion, that of a political institution committed to preventing these diseases in the population.

MR. LANGMAID: I would add and agree with what was said. I think the question is an excellent one. We are all faced in the design of both foreign assistance programs and national health programs with making choices on the allocation of resources and how those resources are spent.

It is a very difficult kind of choice to be made. Obviously, health systems will not be able to deal with all the needs. We at AID have made a rather conscious choice that we will focus on preventive medicine, rather than the curative aspects for the simple reason that we feel we can save more lives in that fashion.

Within that, we came to realize that probably the best way of building effective health delivery systems is to have

them start with the kinds of services whose affect is immediate and demonstrable in the fashion of saving lives.

We have found in our own case in mobilizing public support for our health activities, is that child survival has an identity which all the American people can associate with and can support.

I think it is worth noting in our own context that not more than five years ago, the health program of the agency was at least one fifth of what it is now. We are now talking about a health program which is the second largest development assistance component of our foreign assistance activity, second only to agriculture.

I think we are finding, as is UNICEF is finding in their own programs, that the same effect is occurring in the developing world, that with a leading sector in the sense of child survival, which the population can identify with, resources are brought to bear in the problems of health which were not really available before, and public mobilization for health is growing rapidly.

We clearly have in mind a child survival program that is sustainable, and that can bring with it other health interventions and time to bring the entire health program to bear on the health problems of an individual country.

We felt we have to start somewhere, and we wanted to start with something which works and is demonstrably beneficial. We think child survival meets both those tests.

MR. COLLINET: Thank you, Niamey. Over to Libreville.

QUESTION: I am Deputy Chief Doctor at the Hospital Center, Libreville. My question is for Mr. Langmaid. Among means for the prevention of diarrhea ailments, you spoke of oral rehydration, but we have problems here.

We are running out of supplies, because we are not producing the supplies here in the country. What do you think about local production? What is your view of local production of such supplies?

MR. LANGMAID: We are strongly in favor of local production of oral rehydration salts. There is also very effective, sort of village and family level solutions that can be almost as effective as the commercially prepared.

One does have to be careful to provide adequate oversight of the production facilities. One of the attractiveness of oral rehydration salts is not only its effectiveness, but it is the kind of health care that can be integrated with a national system, and also with the private sector.

The package is simple, they can be packaged easily in the country, and they can be sold. We certainly would be strongly in favor, and are working in a number of countries to develop a local production capability.

QUESTION: To continue along the same lines, what do you think of family education in the struggle to ensure child survival?

MR. LANGMAID: There are a number of studies which would suggest that the amount of funds that an individual family spends on the health care of its family members, is six, seven, eight times the amount per capita which a government spends in its health delivery system,

a fact of the normal health care that goes on within the family. We are very concerned that that family spends those dollars wisely on health care which actually makes a difference in their lives.

In that sense, nothing is more fundamental than both education programs and public information programs that aid the family member in understanding its health situation, improve sanitation, the availability of effective medications in the market place, as well as the availability of effective public health care facilities.

So, clearly an integral part of all aspects of child survival has to be public information, public education, and family education.

DR. WEST : If I may just add one more word in terms of how that relates to vitamin A deficiency prevention, that where the studies have been carried out in a number of places, one finds frequently sources of vitamin A foods in the family pot, that are in the diet, but may not be given to the children.

So, family education about feeding the child foods that are available in the family, can become an important part of a vitamin A deficiency program, literally getting the food from the family pot onto the child's plate, and it does not stop there, but from the plate into the child's mouth can be an important part of a family education process.

QUESTION: Do you take into account climate conditions, lifestyle, kind of food productions, that are so diversified that it is difficult to draw a correlation, or make a comparison with industrialized nations?

Also, comparison between the rural and the urban, what are your main priorities?

MR. LANGMALD: I think at this point in time, our focus of our program has been on the rural areas. But increasingly, it

is evident that major poor populations at severe risk in a health sense, are in the urban areas.

If I was to project into the future, I would see my agency spending considerably more time than it has in the past on the problems in the health care delivery systems of urban populations.

Frequently the urban population is better served in a commercial marketing sense than some of the rural populations. Their problems are somewhat different in a health delivery program.

I must emphasize, because I think the inference has been in a numbe of questions. The cultural specificity of health delivery is essential. Our role is providing some technical resources in a variety of inputs.

But the application of those inputs to the country situation has to be done at the country level by the health delivery systems, and the marketing systems and the officials of your governments, as culturally and politically and socially specific as possible, to deal with the unique characteristics of each society.

QUESTION: What is the place of vaccination programs in the policies that you advocate?

MR. LANGMAID: In the AID program, what we tend to refer to as the twin engines of our child survival program, are vaccinations/ immunizations, and oral rehydration therapy, Approximately sixty percent of our health programs are in child survival, and roughly fifty or sixty million dollars a year are spent both for immunization and for oral rehydration therapy, so it is a twin focus.

We are concerned with the delivery of vaccinations, with the financing of vaccinations, with the procurement of safe needles, with a whole range of services associated with effective vaccination programs as well as with the research of new kinds, of new adaptions of new vaccines to make them more effective, make one shot rather than three, a range of issues that have to do with he effective delivery of vaccination in a rural environment as well as an urban environment.

MR. COLLINET: Thank you, Mr. Langmaid. Over to Brazzaville.

DR. MOCAR: I am Dr. Alain MoKa , Chief Doctor for Neonatal and Materrity Care.

In the Congo, among causes of child mortality, vitamin A deficiency is not there, but it is malnutrition which takes the preponderant place.

What are measures that you advocate to assume the care for these serious malnutrition cases?

DR. WEST : You have brought on obvicusly an extremely problem which has probably no -- certainly no one answer and it needs to be, obviously, answered within the context of your own resources.

Maternal malnutrition is obviously extremely important in terms of increasing the likelihood of an improved birth outcome and infant survival.

Low birth weight predicts a higher risk of mortality, not only during the infant year, as you know, but through the early childhood years, and your overall concern of protein erergy malnutrition obviously needs to be addressed and is extremely important. Infant malnutrition as well.

This deals with the issue of ensuring an adequate food supply for women in the child bearing years and protecting the infant, not only nutritionally, but from early childhood diseases.

How vitamin A deficiency plugs into that. It remains to be elucidated to some degree except that we know that it is probably important, and because it is important, you need to when constructing your nutrition program, to consider balance, to consider dietary balance of foods.

It is not sufficient to just think about calories and protein, the staple diet and essentially the staple food. You need to always consider the accessory foods as they are called.

The vegetable side dishes, the fruits, that can accompany a well-balanced diet at low cost, and by improving the balance of the diet, the imbalanced nutrients, the imbalanced malnutrition, can be taken care of and at least, one of those aspects of poverty and malnutrition can be controlled.

MR. LANGMAID: Another aspect of that issue also -- there is increasing evidence of substantial malnutritions in societies which has substantial food supplies in their country.

What one is finding is frequently nutritional deficiency is as much an incomes problem as it is a food availability problem. The foods are there, but the funds are not spent on the right kinds of foods that a family needs.

I think one has to also look at the incomes issue to ensure that there are funds available to obtain the foods and the right kinds of foods are used in the family. This is a very complex, social, and cultural issue as well as simply a straightforward education on production issue.

QUESTION: My question is for Mr. Langmaid. Does AID contemplate to financing of a project for production of flour in order to help wean babies?

MR. LANGMAID: We have been involved and are involved in weaning foods programs. We are also involved in a range of agricultural activities around the world for production of agricultural crops.

We are very concerned as part of the overall child survival with the availability of appropriate weaning foods when they are applied, as well as have active programs in the whole area of breast feeding prior to weaning. So, it is an integral part of the program.

QUESTION: I am Director for Child Services in the Social Directorate, Minister of Social Welfare.

My question is, we know that vitamin A deficiency in the Congo is not a real issue given our climate, given the vegetation.

We believe that Congolese children should not suffer from malnutrition due to food deficiency. The problem is to know what is the -- to know how to make it available to the families in the rural and urban -- the knowledge that you share with the families.

DR. WEST : One observation that I am always struck by in villages, be it in Africa or in Asia, is that when you walk into a village and sit down with people and ask the more knowledgeable women, the grandmothers, and the mothers in the village about what are the best foods for young children.

Are these green leaves necessary and how do you prepare them? Usually, somebody there knows. Usually there is a knowledgeable and skilled group of women who know the answers, but the process may not be formalized.

So, it seems that the challenge to nutrition education, at the family and at the community level, is to formalize the knowledge that frequently exist right in the village and turn it around so that it is fed to others, that the knowledges and the skills are fed to other women in the village.

Frequently, that knowledge exists, and we should not impose new ideas unless they are absolutely necessary, that there is home gardening that does exist frequently, where it can.

There are proper foods available and where these conditions exist, there is usually people in the village who know the answers, but it needs to be formalized and as nutrition educators, it is incumbent on us to follow that type of process.

That is where nutrition education is likely to succeed, where the people who live in the villages feel that it is their ideas that are being taken seriously and used to prevent malnutrition.

MR. COLLINET: Thank you, Brazzaville. In the time remaining to us, we are going back to Niamey.

DR. GARBA: In the context of a program that nutritions support program, we have conducted nutrition investigation taking into account the incidence of night blindness.

The result of the investigation show that the age groups are particularly from four years -- between three and four years and four and five years age groups. We believe that the symptoms that are obtained and compared with nutrition investigation between one year and two year, this corresponds to the period of weaning, so this is a period that occurs after weaning.

My question for Dr. West is the preventives dose in vitamin A capsule to be administer to children under one year, because there is great controversy surrounding that? At present, can we know exactly what the answer is? Thank you.

DR. WEST: Yes, you have brought up a number of extremely important points. To answer your last question, the current recommendation is to provide infants under twelve

months of age, actually from three to twelve months of age, one hundred thousand international units of vitamin A every three to six months, is the current recommendation.

Below three months, children can be given a 50,000 unit dose is they are available. The 100,000 dose is logistically more feasible because the UNICEF capsule contains 200,000 units. This involves two or three drops out of the capsule before giving it to the young infant as a prophylactic measure.

Then, for children one through five or six through seven years of age, the recommendation is one capsule every three to six months; an entire 200,000 unit dose.

Your point on night blindness among three to five year olds is absolutely correct. It is true in a number of countries that the peak of active, mild xeroph thalmia occurs among three to five year olds in the post-weaning phase, and that where the studies have been done, extended breast feeding appears to protect children even after weaning; after they have been weaned onto the household diet, it seems to protect them for an extended period of time against zeropthalmia.

So, your observations are in complete agreement with investigators from other countries as well.

MR. COLLINET: Thank you, Dr. West. We are now going to Libreville for another question.

QUESTION: My comment concurs with my colleague in Niamey who said that child survival must not be tied exclusively to vitamin deficiency, but must be tied to malnutrition in general and other exogenous causes such as malaria. One must not forget endogenous congenital malformations and the like.

DR. WEST: Yes, that is very true. I will make one comment and then Mr. Langmaid can expand on it if he wishes to.

You are absolutely right. Vitamin A deficiency prevention is not a panacea. It is seen as an emerging component to consider for your existing child survival strategies. Vitamin A deficiency appears to be an underlying problem that increases the risk of children -- increases the risk of morbidity and mortality due to a number of infectious causes.

So, it is a component, it is an underlying factor, and to remove that underlying factor may reduce morbidity and mortality and, therefore, improve the quality of life of children to a certain degree. To what degree that is, is not known for sure. In the studies that were carried out in

Indonesia, the reduction in mortality was twenty-five to thirty-five percent, reduction in childhood mortality.

There are studies being planned in Africa and elsewhere in Asia to corroborate, to see if the same level of reduced mortality can be achieved when you change the constellation of risk factors that exist.

So, it is another component. It may be an extremely important component to add to the existing child survival strategies.

MR. LANGMAID: One brief comment I would add. I could not agree more with what Dr. West said. We have not talked about a number of health interventions which are also crucial in this context. Water and sanitation is probably as important an intervention as a number of the things we have talked about.

It is the kind of intervention, however, that depends heavily on the kinds of resources and policies of the country concerned. You mentioned malaria, and we have a major concern with that very lethal and widespread affliction as well. One of our major research activities is in the development of a malaria vaccine, which has a very high priority within our overall agency. Although it may not be a specific part of

what we are referring to as child survival, it is one of the high priorities of our research activities within AID.

MR. COLLINET: One quick question from Brazzaville.

QUESTION: I am a pediatrician. Based on your experience, what do you think of hospitalization in a pediatric ward of both mother and child?

MR. COLLINET: Could you repeat the question?

QUESTION: I want to know what you think of hospitalization of mother and child both in the pediatric ward in African hospitals?

DR. WEST: It certainly has its advantages. Where treatment of children with malnutrition under basic clinic facility conditions have been done, to include the mother in the treatment protocol, to have the mother actively involved in seeing her child get better using existing simple treatments and technologies and food can greatly strengthen the mother's impression that she can, in fact, take care of her child.

MR. COLLINET: We have run out of time. I should like to thank Bradshaw Langmaid and Dr. Keith West for joining us today. This program is made possible by Worldnet, the television service of the United States Information Agency. In Washington, I am George Collinet for Dialogue.

ACTION OFFICE TVVP-Ø5
INFO ACOC-Ø1 DSO-Ø2 PD-Ø2 AF-Ø5 XWU-Ø1 PDS-Ø3 AC-Ø1 TV-Ø3
DD-Ø1 TVP-Ø4 TVN-Ø4 TSPM-Ø6 TVW-Ø4 TVS-Ø5 O-Ø5
/Ø52 A2 25

R Ø212ØZ JUL 88
FM AMEMBASSY BRAZZAVILLE
TO RUEHIA/USIA WASHDC 5167
INFO RUEHAD/AMEMBASSY ABIDJAN 1448
RUEHKI/AMEMBASSY KINSHASA 5563
RUFHLC/AMEMBASSY LIBREVILLE 1141
RUEHNM/AMEMBASSY NIAMEY 212
BT
UNCLAS SECTION Ø1 OF Ø2 BRAZZAVILLE 1888

USIA

WASH FOR TV/WPI (POULARD); AF (FISCHER/MCMAHON)

E.O. 12356: N/A
TAGS: N/A
SUBJECT: TV/WPI WORLDNET DIALOGUE ON "CHILD SURVIVAL" WITH DR. WEST AND DR. LANGMAID: JUNE 30, 1988- REPORT NO. 1

1. SUMMARY. ALTHOUGH ALL OUR THREE PROGRAMMED INTERLOCUTORS WERE BUSY MARKING EXAM COPIES AT THE MEDICAL SCHOOL, WHICH RESULTED IN A SMALLER AUDIENCE (MOSTLY COMPOSED OF PEOPLE WHO PARTICIPATED FOR THE FIRST TIME IN AN AFNET DIALOGUE), INTEREST WAS HIGH. WHILE MODERATOR GEROGES COLLINET WAS INTRODUCING DR. WEST AND DR. LANGMAID, ALL OUR INVITED GUESTS GOT TOGETHER TO DECIDE WHAT KIND OF QUESTIONS TO ASK. FORTUNATELY MOST OF THEM HAD ALREADY PREPARED THEIR QUESTIONS AS WE HAD REQUESTED IN OUR LETTERS OF INVITATION. CONGRATULATIONS AGAIN TO TV/WPI AND TO DR. WEST AND DR. LANGMAID FOR AN EXCELLENT PROGRAM. END SUMMARY.

2. INTERLOCUTORS WERE:
-MRS. BERTHEFILA, HEAD, INFANT DEPARTMENT, MINISTRY OF HEALTH AND SOCIAL AFFAIRS
-DR. ALAIN MOKA, HEAD, MATERNAL AND INFANT SERVICE
-DR. FORTUNE MAYANDA, SERVICE OF CLINIC PEDIATRY, GENERAL HOSPITAL, BRAZZAVILLE
OTHER GUESTS:
-M. JEAN-CLAUDE MINKALA, MALE NURSE, DIRECTION OF PUBLIC HEALTH
-DR. RAPHAEL ISSOIBEKA, SERVICE OF DIGESTION SURGERY, GENERAL HOSPITAL, BRAZZAVILLE
- DR. BURIOT, W.H.O.
- M. JEAN-GILBERT FOUTOU, HEAD, SPORTS SERVICE, NATIONAL RADIO, A LAST MINUTE GUEST WHO AGREED TO ATTEND AND SAT TAKING NOTES THROUGHOUT.

3. MISSION PERSONNEL: PAO (COORD. LINE)

4. EVALUATION:

A. BECAUSE CHILD MOTALITY IS A CRUCIAL PROBLEM IN THE DEVELOPING COUNTRIES AND THIS BEING POST'S SECOND AFNET DIALOGUE ON A MEDICAL SUBJECT, PROGRAM WAS FOLLOWED WITH GREAT INTEREST. AMONG THE HIGH POINTS WERE USAID ASSISTANCE TO AFRICA, FAMILY PLANNING, BREAST

#1929Ø ICA567

FEEDING, IMMUNIZATION BETWEEN Ø TO 5 YEARS (ESPECIALLY AGAINST SMALLPOX). INTERLOCUTORS AND POST'S OTHER GUESTS LAMENTED THE FACT THAT PARTICIPATING POSTS WERE SO DISPARATE IN CHILD HEALTH PROBLEMS. BECAUSE VITAMIN A DEFICIENCY IS PRACTICALLY NON-EXISTANT IN THE CONGO, THAT PORTION OF THE PROGRAM WAS OF LESS INTEREST, ALTHOUGH A MAJOR PORTION OF THE PROGRAM DEALT WITH IT. ALL, HOWEVER, PRAISED THE CHOICE OF GUESTS WHICH AFFORDED THE MEDICAL AND USG-FUNDING SOLUTIONS TO PROBLEMS OF CHILD MORTALITY. THEY SUGGESTED, AND POST CONCURS, THAT FUTURE PROGRAMS ON MEDICAL ISSUES DEAL WITH SPECIFIC PROBLEM WHICH WILL ALLOW PARTICIPATING POSTS TO JUDGE APPLICABILITY. THEY ALSO REQUESTED MORE INFORMATION ON RELEVANT AFRICAN EXPERIENCE AS BETTER GUAGE OF QUESTIONS TO BE ASKED.

B. UNFORTUNATELY, NO PROGRESS HAS BEEN MADE IN REDUCING NUMBER OF PARTICIPATING POSTS. WE RECOMMEND A LIMIT OF THREE FRANCOPHONE POSTS DUE THE NEED FOR SIMULTANEOUS TRANSLATION. PERHAPS IT WOULD BE EASIER IF PARTICIPATING POSTS TOOK TURNS ON NON-PARTICIPATION.
BT
#1888

190

UNITED STATES
INFORMATION AGENCY

INCOMING
TELEGRAM

015490 ICA049
30/1527Z

ACTION OFFICE TVWP-05
INFO ACOC-01 DSO-02 PD-02 AF-05 XWU-01 PDS-03 AC-01 TV-03
DD-01 TVP-04 TVN-04 TSPM-06 TVW-04 TVS-05 D-05
/052 A4 S

R 301520Z JUN 88
FM AMEMBASSY ABIDJAN
TO RUEHIA/USIA WASHDC 7672
INFO RUEHBZ/AMEMBASSY BRAZZAVILLE 2098
RUFHLC/AMEMBASSY LIBREVILLE 3773
RUEHNM/AMEMBASSY NIAMEY 8814
RUEHOS/AMEMBASSY LAGOS 5595
BT
UNCLAS ABIDJAN 13505

FOR TV/WPI - POULARD, TV/PA - JOHNSON, AF-GRANT, FISHER;
POSTS FOR WORLDNET OFFICERS

E.O. 12356: N/A
SUBJECT: TV/WPI WORLDNET INTERACTIVE ON CHILD SURVIVAL IN AFRICA - WITH LANGMAID AND WEST - JUNE 28, 1988

1. POST AND PARTICIPANTS SATISFIED WITH SUBJECT PROGRAM. PROGRAM WAS ATTENDED MOSTLY BY PHYSICIANS, ALTHOUGH A HEALTH POLICY PLANNER FROM THE AFRICAN DEVELOPMENT BANK AND THE COORDINATOR OF RURAL HEALTH CENTERS IN COTE D'IVOIRE WERE ALSO PRESENT.

2. FOR THE FIRST TIME AT AN ABIDJAN INTERACTIVE, PARTICIPANTS DID NOT HAVE QUESTIONS FOR THE SECOND ROUND BECAUSE THEIR PREPARED QUESTIONS HAD BEEN ASKED BY THE OTHER POSTS. THIS REFLECTED THE MAKE-UP OF OUR AUDIENCE. THE PHYSICIANS WERE MORE INTERESTED IN THE ACTUAL MEDICAL TECHNIQUES OF CHILD SURVIVAL THAN POLICY ISSUES. NONETHELESS, THE AUDIENCE FOLLOWED THE PROGRAM CLOSELY AND TOOK NOTES. POST FOUND THAT LANGMAID AND WEST'S KNOWLEDGE OF THEIR SUBJECT IN THE CONTEXT OF THE THIRD WORLD WAS A GREAT PLUS.

2. THE QUESTIONERS WERE:

DR. MONNEY DAGUI
FACULTY OF PHARMACY, UNIVERSITY OF ABIDJAN

DR. WANDJI NGAH
HEALTH EXPERT
AFRICAN DEVELOPMENT BANK

3. THE AUDIENCE INCLUDED 10 PHYSICIANS AND A USAID OFFICER.

4. POST SENT AUDIO TAPE OF PROGRAM TO IVORIAN RADIO AND VCR TO IVORIAN TELEVISION. DALGLIESH
BT
#3505

UNITED STATES
INFORMATION AGENCY

INCOMING
TELEGRAM

019291 ICA508
02/1403Z

ACTION OFFICE TVWP-05
INFO ACOC-01 DSO-02 PD-02 AF-05 XWU-01 PDS-03 AC-01 TV-03
DD-01 TVP-04 TVN-04 TSPM-06 TVW-04 TVS-05 D-05
/052 A3 25

R 021212Z JUL 88
FM AMEMBASSY BRAZZAVILLE
TO RUEHIA/USIA WASHDC 6170
INFO RUEHAD/AMEMBASSY ABIDJAN 1449
RUEHKI/AMEMBASSY KINSHASA 5568
RUFHLC/AMEMBASSY LIBREVILLE 1142
RUEHNM/AMEMBASSY NIAMEY 213
BT
UNCLAS SECTION 02 OF 02 BRAZZAVILLE 1880

C. RESPONSES FROM GUEST SPEAKERS REMAINED TOO LONG (ESPECIALLY DURING ABIDJAN'S FIRST BLOCK, WHICH UNFORTUNATELY DID NOT GIVE THEM AN OPPORTUNITY TO ASK ANOTHER QUESTION). IF ONLY ONE HOUR IS TO BE ASSIGNED TO FOUR POSTS, GUESTS MUST BE ADVISED TO LIMIT THEIR RESPONSES.

5. MEDIA PLACEMENT:

LOCAL TV BROADCAST THREE MINUTES OF THE PROGRAM THE SAME EVENING ON PRIMETIME EVENING NEWS. THE ANSWER WHICH WAS AIRED DEALT WITH DR. WEST'S RESPONSE TO BRAZZAVILLE PARTICIPANT ON CHILD MALNUTRITION WHICH IS ONE OF THE MAJOR CAUSES OF CHILD MORTALITY IN DEVELOPING COUNTRIES.
ESTIMATED AUDIENCE: 600,000.
TECHNICAL PROBLEMS: OTHER THAN MIX UP IN COORD LINE AND PROGRAM LINES AT THE VERY BEGINNING OF PROGRAM, THERE WERE NO TECHNICAL PROBLEMS.
GUICHARD
BT
#1880

196

APPENDIX N

Transcript from:
Worldnet United States Information Agency
Television and Film Service
Washington, D.C.
"Child Survival in Africa"
Dr. Alfred Sommer, guest
July 14, 1988

WORLDNET
UNITED STATES INFORMATION AGENCY
Television and Film Service
Washington, D.C.

GUESTS: Dr. Alfred Sommer, Professor of Ophthalmology, Epidemiology and International Health, Director of the Dana Center for Preventive Ophthalmology at Johns Hopkins University, Baltimore, Maryland
and
Dr. Nyle Brady
Senior Assistant Administrator of the Bureau for Scienc and Technology, U.S. Agency for International Developmer

TOPIC: Child Survival in Africa

HOST: Judlynne Lilly

INTERACTIVE POSTS: Monrovia, Lagos

DATE: July 14, 1988

TIME: 8:00 a.m. - 9:00 a.m. EDT

TRANSCRIBED BY:
Diversified Reporting Services, Inc.
1511 K Street, N.W., Suite 547
Washington, D.C. 20005
(202) 628-2121

837/62

ANNOUNCER: Worldnet presents Dialogue, an international televised exchange of ideas. Now, live from our studios in Washington, D.C., here is your moderator, Judlynne Lilly. Ms. Lilly is a reporter for the Washington-based all news radio WTOP.

MS. LILLY: Good afternoon and welcome to Worldnet's Dialogue. Today for our international audience and participants in Monrovia and Lagos, we are pleased to present a discussion on child survival in Africa.

It is estimated that in the developing world one child dies every three seconds; forty thousand children per day, fourteen to fifteen million children per year. The cause of death may be measles, diarrhea or diseases associated with poverty and malnutrition.

In addition, tens of millions of children in developing countries suffer from vitamin A deficiency. Research has shown that this predisposes children to illness and death from a variety of causes.

Joining us to discuss the current trends in child survival treatment and U.S. assistance to Africa on this matter are two leading authorities on the subject, Dr. Nyle (phonetic) Brady and Dr. Alfred Sommer.

That may have caused maybe something that needs to be done in the future. Certainly, vitamin A does not have a monopoly on adverse effects.

One of the reasons for pursuing the vitamin A question and one of the reasons it is not surprising that it has been found to have the tremendous impact that it appears to, in fact, elicit because the early work at the turn of the century when it was discovered and the early work on humans demonstrated quite clearly that children who are vitamin A deficient had an increased risk of developing infections of not growing well, of having a problem with anemia and so forth.

The latest studies are simply demonstrating that even within the complex situation and generally deprived environments in which rural children grow up in Africa and other developing areas, that the single nutrient can exercise a profound effect.

It is certainly conceivable that some of the other vitamins, if looked at carefully, might also have major effects, but we tend to recognize them from their more obvious clinical deficiency states and by and large, those have not seemed to be a problem in most areas of the world.

MS. LILLY: Dr. Brady, do you have a response to that?

DR. BRADY: We have, as I have indicated, attempted to focus on those diseases or those problems that are most pervasive and, of course, vitamin A, not only in Africa, but in Latin America, in Asia, and elsewhere, because of its association with blindness has been the area that we have focused on most.

That does not mean to say that we do not recognize that there are the problems, but because of our limited resources, we have to focus in those areas where we feel we can make the biggest difference and bring about the greatest improvement. In supporting the work of Dr. Sommer and others, we have focused on vitamin A.

MS. LILLY: Thank you. Go ahead, Monrovia, with your next question.

QUESTION: A follow-up question to Dr. Sommer. The example that you gave about the research for our purposes was in East Africa. Do you have any figures at all for West African countries, close to Liberia?

DR. SUMMER: Well, I do not have any data on the impact that vitamin A supplementation would have in West Africa. There is no question that there has been a series of surveys done in a number of countries in West Africa which have demonstrated that vitamin A deficiency does exist and at a

level which WHO has indicated represents a public health problem.

That does not mean it is universal throughout a country or region, but if you do look in most countries, you will find at least pockets and often, very large regions in the rural areas, particularly, but sometimes in the urban areas as well, where vitamin A deficiency is prevalent.

So, there is really no reason to suspect that a vitamin A supplementation program in West Africa should not have the same consequences as one in East Africa.

It so turns out, in fact, that there are two studies that are being planned and are in the preliminary stages of implementation in West Africa to begin to directly assess what impact vitamin A supplementation would have on morbidity and mortality.

While it is likely to differ to certain degrees from one country to another, depending upon how severe the vitamin A deficiency is, how prevalent the vitamin A deficiency is, and how compromised the children are by other adverse influences, such as malnutrition and malaria and other parasitic infections and the rate of diarrhea and ARI, etc.,

it is also going to be very surprising if one does not find that it has a positive effect, though the level of effect

may vary to some degree from one environmental situation to another.

MS. COPPELL: My name is Margaret Coppell (phonetic). I am Health Information Officer at the WHO office, Monrovia.

Dr. Sommer, I would like to know to what extent can the ability of vitamin A reverse the condition of blindness once it has set in?

DR. SOMMER: Now, that is an excellent question and, unfortunately, once a child becomes truly blind, that means that the eye has been destroyed, the cornea, the front clear part of the eye is gone forever.

There is nothing that vitamin A can do. There is nothing that anybody or any technology can do to change that. The real challenge before us is recognizing those children who are in earlier stages of vitamin A deficiency.

Even children who have lost one eye, if one acts quickly, and gives vitamin A, and it is very simple and very inexpensive to do, it can be done by any health promoter, it can be done by any teacher, it can be done by any mother,

it is just the equivalent of one UNICEF-type capsule or one teaspoon full of two hundred thousand units of vitamin A, will save that other eye if that other eye is not yet destroyed.

Now, far preferable to all of that, are to find children who have any earlier stages of vitamin A deficiency. Some of those children will be children who come to clinic or are seen by the primary health care worker with milder evidence of eye lesions, children with night blindness, totally reversible, children with Bitot's spots, and dryness of the eye, totally reversible.

Even more important than that is getting vitamin A to children who are at risk of developing severe vitamin A deficiency, but do not yet even demonstrate the earliest eye signs.

These would be children who have measles, and so it is recommended, in fact, especially in Africa where measles is such a devastating disease, it has been recommended by both UNICEF and WHO in a joint statement, that children with measles should receive a large dose of vitamin A.

In fact, in Africa, perhaps, a large dose on two successive days, whenever they have measles. Children with acute respiratory infection are at high risk of developing sudden deficiency and going blind, they should receive a dose of vitamin A.

Children with diarrhea who are also at high risk of developing sudden devastating blindness from vitamin A

deficiency should receive an additional dose of vitamin A, high dose vitamin A, if they had not received any in the last month or so.

Because most of these children are already barely functioning at a low level of vitamin A, they can just sustain normal ocular tissues and any adverse effect; diarrhea, acute respiratory disease and especially measles, can suddenly make that vitamin A deficiency worse.

So suddenly that one can see a perfectly normal looking eye absolutely dissolve and become blind in a matter of hours or days.

Best of all, of course, is ensuring that no children have such poor vitamin A stores that they are at risk of sudden deterioration and then we get into the types of programs that they have already pioneered in many areas of Asia and India and Bangladesh and Indonesia, where they try and provide all the children in the country with an adequate amount of vitamin A so that they do not fall into the trap of having sudden deficiency.

MS. LILLY: Dr. Brady, do you have a response?

DR. BRADY: I think the response that Dr. Sommer has given is not only quite appropriate but much better than I could give. I can simply say that we are supporting a series

of research efforts to try to better establish the relationship between vitamin A deficiency and child mortality.

The preliminary findings are of such significance that if it is true, and holds not only in the countries where these preliminary studies have been made, the implications for child survival are, indeed, great.

We are carrying out these studies in cooperation with Dr. Sommer and others in Asia and preliminary studies in Africa and if this relationship does hold, then there must be mounted a worldwide effort to be certain that vitamin A deficiency is reduced to a minimum.

MS. LILLY: Let's return now to Monrovia for more questions.

QUESTION: I would like to follow-up on my first question. I would like to know if there is any specific U.S. AID programs for nutrition with emphasis on vitamin A deficiencies for West Africa or Liberia.

DR. BRADY: We have a number of projects that are set up, specifically, as I said, to respond to the needs of countries. We have a project that we call PRITECH technologies for primary health care.

We have a project called HEALTHCOM (phonetic) that is set up primarily to help in the educational component of programs. These private voluntary organizations and companies that carry out this kind of activity do respond to the requests from countries.

I have indicated that in the child survival area we have four areas that we feel are terribly important: oral rehydration therapy, diarrhea disease problems, the immunization to the six major diseases that are killing most of the children, and this is in cooperation with other agencies as well, and then, nutrition and child spacing.

The help that these organizations can give can be arranged for through our country program leaders and they can make requests -- you can make requests of those leaders for help, and then these organizations will send individuals in to try to provide some help for you and some advise as to what might be done.

Although there is a greater proportion of our effort going into the oral rehydration therapy and to the immunization program because that is -- those are the two areas where we have found that more children are dying, but we do respond to requests for assistance with regard to both nutrition and to child spacing.

MS. LILLY: Dr. Sommer, I believe you have a response to that.

DR. SOMMER: As one of those agencies that is supported by Dr. Brady and by other organization within U.S. AID, I would just like to echo and support what Dr. Brady has said. Johns Hopkins University, for example, operates under a cooperative agreement in which we provide technical assistance and training and educational materials to countries that are interested in pursuing the potential problem of vitamin A deficiency, whether it is to carry out a survey and determine where and how much vitamin A deficiency they have; whether it is to just discuss where they might begin; or as in a number of countries now increasingly, to carry out studies to demonstrate in their own country, in their own milieu, that vitamin A supplementation will make a big difference not only in preventing child blindness, which is a common complication, not only of obvious and simple vitamin A deficiency, but a vitamin A complication of measles, that we provide that kind of assistance and that kind of visits to them under a program that has already been set up by AID and that pays for that. In fact, I have just returned from East Africa where I was visiting with colleagues in Kenya

where they are just beginning to embark on just such a program, setting up a task force under the Kenyan pediatric association in collaboration with UNICEF and with their ministry of health.

I have also visited Ethiopia, and we have had ongoing programs in Zambia and in Tanzania; all of which have been begun over the recent years by people in the ministries of health, in the universities, in the private sector who have been interested in that. Then there are a number of private voluntary organizations that Dr. Brady has alluded to.

One in particular, Helen Keller International that has been working both in the East but very largely in West Africa carrying out surveys, making vitamin A capsules available in relationship with UNICEF, and trying to begin to wean countries from the necessity to use vitamin A capsules which after all, have to be imported, even if they are often provided at cost or free by UNICEF, to something more appropriate, and that is nutrition education; having people feed their children better vitamin A sources that are often readily available and very inexpensive. It is simply a matter of changing dietary habits.

MS. LILLY: Thank you, Monrovia. We will go back to Lagos. Please go ahead, Lagos.

QUESTION: What efforts are being made to develop vaccines against illness that cannot be prevented such as certain cases of pneumonia, rotavirus diarrhea and malaria.

DR. BRADY: That is a very important question and one to which we are addressing some of our attention. We have, with regard to the immunization programs, we have two general types of effort.

One is to use the tools that are available to us for the six major diseases. There are vaccines available. We know, however, that those vaccines are, as I have indicated, on many occasions, are really in the long run not good enough for the developing countries.

They demand cold chain. They demand a degree of sophistication that frequently the countries are unable to sustain. So, while we are making use of the tools that we now have, we are putting some resources and others are putting resources into developing improved vaccines; petussis, for example, is one we know, has some side affects that are not good.

We are trying to develop a vaccine for this disease.

Malaria is the disease that we have devoted a great deal of attention to and we have -- we are putting about $10

million a year into attempts to develop vaccine candidates that could be tested out not only in Africa but in Asia and Latin America.

We have had some success, but we have also found that the disease organism is quite a difficult one to work with but we are putting a good deal of resources there.

Likewise, in the rotavirus disease, we are working primarily through cooperators in international centers and elsewhere to try to develop viable candidates that could be tested out for these important pathogens.

So, we are trying to put some of our efforts into the creation of new and better vaccines. We are particularly concerned, in the long run, with getting vaccines that are heat stable; that you do not have to have a cold chain to make use of and even vaccines that can be taken orally rather than to have to use the syringe and needle.

This, of course, may be the next generation before those are available to us. Our objective is to try to develop technologies that are not only usable in the developing countries but will permit them to sustain the types of programs that we know and they know should be put into effect.

QUESTION: On environmental issues, you have said at one time that child mortality rates follows a pattern of a nation's economy. Would you like to talk more about this?

DR. BRADY: Yes, we all recognize that one of the primary reasons that the health problems are much more difficult in the developing countries is that there are not the economic and, in some cases, human resources to carry out the programs.

So, we do look upon economic development, sustainable economic development, as a primary objective of the program that we are working with countries on out of USAID.

Because, in the long run the help that we provide may not permit a country to sustain an effort. In the long run, this is going to happen only if they have economic development and this economic development does take place. We are working with countries to try to find out what we can do to accelerate their economic development.

We have found that in many of these countries, this is related to giving opportunity to their people, to increase their income, to carry out their programs, and this does mean in some cases that -- greater freedom on the part of the private enterprise.

When I mean private enterprise I am not talking about big companies, I am talking about individuals. I am talking about micro enterprise out in the villages. I am talking about farmers that have opportunities to make money, quite frankly, by producing food.

To make money and, therefore, make it possible for them to employ people in small cities and large cities and so forth. So, there is no question that what the primary efforts that we are making is to try to increase the economic development, and particularly the economic development of the lower income people, because those are the ones that are largest in number.

If we can help them increase their income, we are going to help these countries truly develop.

DR. SUMMER: There is no question, as Dr. Brady has indicated, that economic development is clearly an importa aspect of health development, and in sustainability of health programs.

I think we should not lose sight of the fact that a number of countries, perhaps the majority of countries in the developing world, have made dramatic gains in the health of the populations, dramatic reductions in infant mortality,

dramatic reductions in preschool mortality rates, with very little overall economic development.

In fact, in some areas with a negative economic development, so that there are many things that can be done with existing resources or with very, very modest gains in economic development that can have a profound impact on the health and lives of children. It is just important to recognize that.

The more things that can be turned over by the government to the community, the better off it is because, when the government gets into a financial bind and can no longer afford to finance particular activities, then it is up to the people to do it.

One example I would like to give that is being tested out, for example, in Indonesia, in Asia, is the fortification of a commonly consumed condiment in the cooking process, monosodium glutamate.

There are two ways one can go about financing putting vitamin A into monosodium glutamate so that all the children in the country end up getting the vitamin A that they need. One would be for the government to keep spending three or four million dollars a year on the process.

A totally alternative way is to pass on the cost to the consumer in a graded fashion. The first year pass on one third the cost, the second year another third, the third year the last third. That marginal cost which comes out to be roughly three or four percent a year is lost within the general inflation rate of ten or twelve percent a year.

So, at the end of three years, the government of Indonesia is out of the vitamin A supplementation business. It no longer matters what happens to the health budget in terms of the delivery of vitamin A, because that burden has been accepted and carried out on the community.

Similarly, one could see similar things happening once you are able to encourage people to eat readily available green leafy vegetables or red palm oil or other readily available, inexpensive materials that are rich in vitamin A. It is not something that requires the government to become wealthier in all cases.

DR. BRADY: Could I just make a couple of comments adding to that, and to reinforce what has been said here. If we do take a look at Asia, we find examples of countries that have been able to increase the length of life and improve their health care much more rapidly than their economic development.

Sri Lanka is, perhaps, the best example in terms of education, in terms of length of life, even though their per capita income is not as high as some of the other countries. I would also like to comment we do not think it is appropriate to wait until economic development has taken place before we try to help countries utilize techniques to improve their health.

The little oral rehydration packets that are very inexpensive that a family can use, make it available to them without going to a clinic, without paying the expenses of a doctor, are examples.

Even going further than this, we have worked -- carried out research work that would indicate that a little salt in rice boiled for appropriate periods of time provides a mixture of the materials that are necessary to keep children alive that are in danger of dehydration.

So that we are doing two things to try to increase their economic development, but at the same time to provide them tools they can use that is in accord with their current economic status.

QUESTION: (inaudible) I am from Nigeria. How have you been able to suppress the vitamin A deficiency from the general

malnutrition as a predisposing factor in infection in children and (inaudible)?

DR. SOMMER : That is a very good question since general malnutrition is certainly a risk factor that predisposes children to infection and increased risk of death. It also is something that tends to correlate with vitamin A deficiency. There are a couple of things to say about that.

The first is that vitamin A deficiency as we now look at it, not just the severity that causes changes to the eye, but we now find that there are, perhaps, five to ten times as many children as have eye lesions, five to ten times that number of children have vitamin A deficiency at a level that is impairing their resistance to infection, but is not severe enough to cause the eye changes.

It really is improving the vitamin A status in these children, which is going to make the greatest impact in reducing overall child mortality and morbidity.

When we have carried out the studies, there are a number of statistical tricks that one can use in purely observational studies to say, "Well, all right, let's only look at what the mortality rate is in children who have vitamin A deficiency and are well nourished, versus those who

do not have vitamin A deficiency and are well nourished. Then let's compare the mortality rate of poorly nourished children with vitamin A deficiency and those without vitamin A deficiency."

What we find in those types of observational studies is that the vitamin A status of the child seems to have a greater impact on the child's life expectancy than does the child's general nutritional status, as long as you are not dealing with children who are grade three severe marasmus and Kwashiorkor, who are likely to die within the next few days.

In fact, what we have found in children who are mildly to moderately malnourished versus those who are well nourished, children who had vitamin A deficiency of a mild to moderate degree, but were normally nourished by the usual anthropometric indices, these children had a higher long-term mortality rate than the children without vitamin A deficiency who were moderately malnourished.

So, in that setting it would appear, in fact, that vitamin A had a greater influence both on their risk of respiratory disease, the risk of diarrhea, and their ultimate risk of dying than did moderate degrees of generalized malnutrition.

The other types of studies that have been carried out to finally prove the difference, so one does not have to use these more complicated statistical analyses which are modeling and one can criticize or be concerned about some of the assumptions that are made, we have carried out studies in large populations, twenty-five, thirty thousand children, in which half the children are randomized to receive periodic high dose vitamin A and the other half are not.

Any child in either group who has evidence of clinical vitamin A deficiency, even the mildest forms of night blindness, are always treated and removed from the study.

Of those children who do not have any evidence of vitamin A deficiency, when you split them into two groups and you give one group supplemental vitamin A, and you do not give it to the other group, the overall mortality rate in the group that received the extra vitamin A was a third or a half lower than the mortality in the group that was not given the vitamin A.

The average baseline anthropometric status, general nutritional status of both groups, are very similar. Indeed, what two studies have now shown, both in Indonesia, is that the group given vitamin A actually gained more weight and

grew on average on centimeter taller than the group that was not given the vitamin A.

In recent studies, both in Indonesia, in Guatemala and in Thailand, and again all of these early studies, as you can see, have been carried out to some degree in Asia and in Latin America, have shown that vitamin A supplementation can have a marked impact on the degree of anemia as well, with hemoglobin values going up an average of one gram without giving any iron.

There is no doubt that iron becomes a limiting factor as well, but in the studies in Indonesia, the children who have just received vitamin A, their hemoglobin values went up by a gram in five months, whereas there was no change whatsoever in the control group.

And in recent studies in Guatemala they found that if they divided the children and gave some of them iron and vitamin A, those who got the iron and vitamin A had a better hemoglobin response than those who just got the iron.

QUESTION: My second question: What is your strategy and approach to combat respiratory infection in children?

MS. LILLY: I think you are going to have to repeat that, sir, please.

QUESTION: What is your strategy and approach to combat respiratory infection in children?

DR. SUMMER : Respiratory infection?

MS. LILLY: I think that is what he is saying. Let's make sure we have that correct.

DR. SOMMER : Was that respiratory infection?

QUESTION: Yes.

DR. SOMMER : Well, there are obviously a number of approaches to attack respiratory infection. The one that we have been concentrating on, again, because of the work on vitamin A, is the role that vitamin A can play in either reducing the incidence, the number of cases that develop respiratory disease, or the severity of respiratory disease.

The result so far in a number of studies have shown that children who are vitamin A deficient, both in India and in Indonesia, are much more likely to develop clinically significant respiratory disease than children who are not deficient.

This has been done in observational studies, and this has been done by supplementing some of the children and not others and seeing what has happened. It has also been seen in children with measles, that if you supplement them with vitamin A, they are much less likely to develop the lower

respiratory problems than children who are not given vitamin A.

Rather surprisingly to me, and I do not understand it, but it seems to work there as well, there was a study carried out in otherwise well nourished Australian children who were at frequent risk, they were a subgroup who had frequent lower respiratory disease, and they divided this group of otherwise healthy and well nourished Australian children into two groups and gave one group supplementary vitamin A and not the other group.

Even in that particular situation, the children who were given vitamin A had a twenty-five percent reduction in the frequency with which they developed lower respiratory disease. So, the story about the relationship between vitamin A and lower respiratory disease is an exciting one and one that is being pursued in several investigational activities.

Of course, there are other ways to combat respiratory infection, and that has to do with crowding with the treatment for tuberculosis and with the development, as was previously suggested, of specific vaccines that might be useful against influenza, pneumococcal pneumonia and the like.

MS. LILLY: Thank you. Let's go now to Monrovia. Please begin, Monrovia.

MR. JOHNSON: Thank you. This is Eric Johnson (phonetic), Assistant Minister for Planning Research and Development in (inaudible).

Mr. Brady, you know that the horn of Africa accounts for a greater percent of malnourished children and mothers. Can you say that this is attributed to the economic situation, or to superpower interference, vis-a-vis the war?

Don't you think by giving assistance to these programs we are only treating the symptoms rather than finding a solution?

DR. BRADY: I will be glad to give you my opinion, but I am sure that you, who are on the spot, are much better qualified to answer that question than I. You have brought our attention to a problem that we, not only the United States, but more importantly the people in the developing nations face.

Very frequently the factors completely unrelated to health or to the programs that we are trying to put forward, are the factors that are major constraints. We do have wars, we do have tribal differences. We do have, I guess in some

cases, even some evidence of discrimination from one group to another.

We recognize that those are factors that have to be taken into consideration. At the same time, we recognize that these are factors that are not -- it is not appropriate for outsiders to try to come in and to settle.

We do our best when called upon to do so, but in general, we try to focus our efforts on those, taking into consideration the difficulties that we have of communications, taking into consideration the difficulties that the country faces economically, to try to help them develop programs that under the circumstances will be most effective.

As a scientist, as a technical person, this is about the best that we can do.

MS. ZIMBE: I am Isabelle Zimbe, a physician from the Ministry of Health, Monrovia.

My question is not too different from his, and it is to Dr. Brady. The question is that there are social and economic variables which have a very strong influence on child survival, and we have seen that most of the child survival programs that are disease oriented.

MS. LILLY: Thank you, Monrovia. With the remaining time, let's return to Lagos.

QUESTION: (inaudible) is my name from that state television (inaudible). What in broad time is U.S. AID's strategy for child survival with particular reference to Nigeria's development of a sustained primary health care program, in relation to neonatal and child health?

MS. LILLY: Dr. Brady?

DR. BRADY: That, too, is a very good question, because of course, Nigeria has by far the largest population of any African country. We recognize the importance of that country and the overall economic and social development of Africa as a whole.

As you know, because of the advance state of your development, we do not have a regular bilateral program with Nigeria, but we do make available the support of the various organizations that are working with us.

So, that our program in Nigeria is carried out primarily through these cooperating organizations. We do provide, for example, in Nigeria, the services of this technologies for primary health care, the PRITECH (phonetic) organization.

We also provide the resources for child health, what we call the REACH project for interaction with you on the immunization programs in cooperation, of course, with UNICEF.

We provide cooperation through what we call our WASH program, Water and Sanitation Program, to come out and try to help design water systems, try to work with you in improving means of preventing the disease rather than to try to cure it.

Of course, we have the communications for health programs that also, again, upon demand. We do not send them out and say, "You go to Nigeria and tell the Nigerians they need help."

We wait until the Nigerians request the help and then we come cut with these programs. Our private, voluntary organizations and contractors do work in Nigeria upon request and are carrying out, I think, a very effective program in working with cooperation with you.

MS. LILLY: We have time for one last quick question and a quick answer from Monrovia.

QUESTION: Our question is: In light of the discoveries about the research in vitamin A deficiencies, do you know of any public health education programs that will assist

countries to prevent vitamin A deficiency problems in a country?

MS. LILLY: Dr. Sammer and you have about fifteen seconds.

DR. SOMMER: The answer is yes, you can contact me at Johns Hopkins University. You can contact your local AID office that is aware of a number of private voluntary organizations as well as us at Johns Hopkins who are happy to help you look at the problem and attempt to do something about it.

MS. LILLY: Thank you. I am afraid we are out of time. I would like to thank Dr. Alfred Sammer and Dr. Nyle Brady for joining us. Credit for this program should be given to Worldnet, the television service of the United States Information Agency.

In Washington, I am Judlynne Lilly for Worldnet's Dialogue.

* * * * *

APPENDIX O

Sommer A:
Imperatives for control of vitamin A deficiency
World Health Organization
May, 1988.

WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTE

NUT/VIT.A/88.1

ORIGINAL: ENGLISH
May 1988

IMPERATIVES FOR CONTROL OF VITAMIN A DEFICIENCY

Alfred Sommer, M.D., M.H.Sc.

Professor of Ophthalmology, Epidemiology and International Health, Wilmer Ophthalmological Institute and School of Public Health, Johns Hopkins Medical Institutions, Director, International Center for Epidemiologic and Preventive Ophthalmology.*

Supported, in part, by the
United States Agency for International Development,
Task Force "Sight and Life", and the World Health Organization

* A WHO Collaborating Centre for the Prevention of Blindness and Vitamin A Deficiency.

229

Renewed interest in combatting the problem stems from evidence accumulated over the past 20 years that xerophthalmia and blinding malnutrition are prevalent throughout the developing world. Even greater impetus derives from recent evidence that vitamin A deficiency may be responsible for many of the complications associated with measles; that physiologically significant vitamin A deficiency is far more prevalent than xerophthalmia rates would suggest; and that such "subclinical" deficiency has a pronounced influence on growth, health and survival of third-world children.

Recently, longitudinal studies on non-institutionalized children indicate vitamin A can play an important role in determining risk of death, even among otherwise well-nourished, previously healthy children. In a study of 6000 preschool children re-examined every three months, those with nightblindness or Bitot's spots died at 3-9 times the rate of their nonxerophthalmic peers. Indeed, mortality among otherwise well-nourished, xerophthalmic children was greater than among more wasted nonxerophthalmic children, suggesting vitamin A status was a more important determinant of mortality than mild to moderate wasting. The risk of death increased directly with the degree of mild xerophthalmia.

Two controlled intervention trials confirm the importance of vitamin A deficiency as a contributory factor in a significant proportion of preschool-age deaths.

Children in villages randomly assigned to the distribution of 200 000 IU vitamin A every six months died at only two-thirds the rate of children in the control villages. One would not expect identical results elsewhere, as nutritional, health, and genetic factors, as well as the severity and prevalence of vitamin A deficiency, are likely to vary. Yet the other mortality intervention trial yielded almost identical results. Monosodium glutamate (MSG) purchased by one group of villages was fortified with vitamin A. MSG marketed in the control area was not. Preschool mortality in the fortified-MSG villages was again only two-thirds that in the control villages.

In a small treatment trial in Tanzania, half the children admitted to hospital with severe measles were randomized to receive 200 000 IU vitamin A on two successive days. The vitamin A recipient-group died at only half the rate of nonrecipients, with most of the reduction occurring among the youngest children.

If vitamin A supplementation has the same impact in other populations where it is known to be deficient, effective intervention might well prevent upwards of 1 million childhood deaths annually.

The common killers of preschool children are measles, respiratory disease and diarrhoea. Presumably vitamin A influences mortality, at least in part, by altering resistance to these infections. In both Indonesia and India mild xerophthalmia doubles the risk of respiratory infection; in Indonesia it triples the risk of diarrhoea.

Somewhat surprisingly, modest vitamin A supplementation of otherwise well nourished Australian children with a history of frequent respiratory disease reduced the recurrence of lower respiratory infections by 25%. In Thailand, supplementation reduced the rate of both respiratory and diarrhoeal disease.

The mechanism(s) by which vitamin A deficiency influences resistance to infection remain uncertain. Recent data, primarily from animal work, suggest widespread alterations in immune-competence. Deranged differentiation of epithelial linings of the respiratory, gastorintestinal and genitourinary tracts, which occurs early in deficiency, probably degrades their barrier function.

The potential importance of vitamin A-dependent cellular differentiation is emphasized by recent evidence that premature infants are vitamin A deficient and that vitamin A supplementation may reduce their risk of bronchopulmonary dysplasia and retinopathy of prematurity.

One of the earliest clinical signs of vitamin A deficiency in young animals is a growth plateau; among young children at the turn of the century it was absence of the "spring growth spurt". In the two population-based supplementation trials in Indonesia, children assigned to receive added vitamin A gained more weight and grew taller (on average, by 1 cm annually).

Animal and human studies have also suggested vitamin A influences iron utilization and quite possibly hematopoiesis. Recent supplementation trials in Indonesia, Central America and Thailand all resulted in a rise in hemoglobin values: in the Indonesian study, by 1 gm per dl.

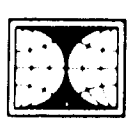
Whether vitamin A's influence on growth and hematopoiesis is direct or secondary to alterations in the frequency and severity of infections (or both) is as yet unclear.

The impact of vitamin A supplementation on mortality, growth and hematopoesis are more extensive than would be expected from the prevalence of clinically detectable xerophthalmia. This would suggest that "subclinical" but physiologically significant deficiency is more pervasive than "clinical" xerophthalmia. Recent studies of cellular differentiation, as monitored by impression cytologic examination of conjunctival epithelium, support this contention.

Despite the vast literature detailing the consequences of vitamin A deficiency, recent epidemiologic studies and clinical trials indicate it remains a threat to the health, sight and lives of millions of children worldwide. Renewed recognition of the pervasive nature and influence of vitamin A deficiency is altering political perceptions and priorities. Previously, many governments had been loath to divert limited health resources from child survival to prevention of nutritional blindness. Increasingly they now view vitamin A intervention as a potentially cost-efficient child survival tool.

- - -

SOCIAL MARKETING OF VITAMIN A



Manoff International Inc.

Social Marketing of Vitamin A

Supported by:

International Center for Epidemiologic and Preventive Ophthalmology
Subcontract to Manoff International Inc.
AID Cooperative Agreement #DAN-0045-A-00-5094-00

SOCIAL MARKETING OF VITAMIN A

Biannual Report

March 15, 1988 - September 30, 1988

CONTENTS

I. INTRODUCTION AND SUMMARY

This report summarizes the activities carried out by Manoff International Inc. (MI) from March to September 1988 under a subcontract with the International Center for Epidemiologic and Preventive Ophthalmology, Johns Hopkins University, funded through ICEPO's cooperative agreement with the Office of Nutrition, U.S. Agency for International Development. MI's basic task is to provide social marketing assistance to alleviate vitamin A deficiencies in developing countries.

The highlights of this reporting period are tne following:

- The educational phase in the West Sumatra social marketing of vitamin A project has continued, and MI consultants worked with HKI field staff to prepare several adjustments to improve the project's effectiveness.

- Based on an MI/HKI/Bangladesh research protocol, field work for the formative research has been completed in Comilla District, and the findings are now being analyzed and used as the basis for the development of intervention strategies that will soon be tested in a sample of households.

- HKI/Philippines' social marketing of vitamin A project has progressed well. During this reporting period, MI helped devise the intervention strategy and provided model question guides for pretesting materials. The project development phase is nearing completion with the pretesting and final production of the materials. The educational phase should be launched soon.

- An MI consultant worked with World Vision staff in Mauritania to plan, pretest, and prepare messages and materials for the child survival/vitamin A project in the Assaba region.

- The Institute of Nutrition, Mahidol University (INMU) recently signed a contract with USAID/Bangkok to fund the local costs for the joint MI/INMU vitamin A study. Through one visit and correspondence, MI has continued to work with INMU during this reporting period to prepare for the formative research.

- The vitamin A public information project has remained active, arranging for two live satellite broadcasts on vitamin A, developing and disseminating written materials, and continuing to play a coordinating role among organizations interested in promoting public information on vitamin A.

- Finally, MI took a number of steps to analyze and disseminate lessons learned from our experience thus far under the project, including actively participating in the development of IVACG communications guidelines and giving several presentations about the field projects.

B. Indonesia

MI is providing ongoing technical assistance to a vitamin A social marketing project in West Sumatra being implemented by Helen Keller International (HKI) and the Ministry of Health. The thrust of this project is a public education campaign aimed at increasing consumption of vitamin A-rich foods and extending awareness and utilization of the government's capsule program. The educational phase of this project was launched at the end of October 1987.

During this reporting period, HKI, with MI assistance, conducted two monitoring studies and has instituted a number of modifications based on the results. In April 1988, MI social marketing consultant Richard Pollard worked with HKI to analyze the first monitoring study and to formulate actions based on the findings. (A list of consultant reports is found in Appendix A.) The study found a good project impact on the first vitamin A capsule (VAC) distribution month (December 1987) but a disappointingly slow implementation of some of the planned communications activities.

- VAC coverage increased from a previous level of some 20 percent to approximately 68 percent during the first VAC distribution month.

- The provincial health office reported that it had trained over 3,600 kaders in VAC distribution and counseling in the fall of 1987. However, by March only an estimated 1,200 kaders remained active. Kaders spent little time talking to mothers about VAC and dark green leafy vegetables (DGLVs), despite being oriented and furnished counseling materials by the project. Kaders blamed time constraints.

- There were serious difficulties in placing media and promotional materials which occurred because of inadequate monitoring by the contracted advertising agency. Billboards were set up late, the radio station broadcast only 30 percent of spots booked, medicine sellers did not broadcast messages as often as expected, and letters to religious leaders and schools either were not sent or did not arrive.

Upon learning of these implementation problems, Pollard left a series of specific recommendations for rectifying them.

In July, Pollard worked briefly with HKI to accelerate the pace of project improvements. During these months of refining project implementation, the Pariaman District Head of Health Services (Dokabu) became very involved in the project. The Dokabu requested a revised VAC action kit (to explain the program and motivate kaders and health center staff) and agreed to motivate the district health staff for VAC distribution through regular monthly mini-workshops. He agreed to promote VAC distribution at monthly intersectoral meetings and through special workshops and mailings for religious leaders and school officials.

- o Scanned all existing research information on topics of relevance to get an orientation for designing protocols for the project's formative research;

- o Met with all potential research organizations that could be entrusted with the focus groups discussions and in-depth interviews and left HKI an assessment of the apparent strengths and weaknesses of each;

- o Prepared a detailed research brief for inviting proposals from research organizations and left a short list of organizations recommended to receive the brief;

- o Visited Comilla District to talk to mothers and local officials to gain insights necessary for planning the formative research.

- o Left a sample draft question guide that the contractors could use as a reference for preparing guides for all of the target audience segments.

After selecting PIACT/PATH and FDSR to carry out the formative research, HKI mailed the draft question guides to Mr. Sethi, who reviewed them thoroughly and suggested many necessary changes. When he returned to Bangladesh in July, Sethi spent substantial time explaining and discussing these changes with the agencies, and visited Comilla for pretesting and to orient research investigators and moderators. The work with PIACT went smoothly, with substantial progress made in improving the question guides and moderators' capabilities. Progress was more difficult with FDSR, which resisted changes due to ostensible time and budget constraints. The issues were substantially resolved, and plans made for extra training for the interviewers.

The field research took place in August and September. Beginning October 1, 1988, Ashok Sethi and Bonani Kakkar have begun working with HKI/Bangladesh to finalize the analysis of the formative research, to begin formulating the intervention strategy, and to begin plans for household trials of the proposed behavior-change messages. It is hoped that Ms. Kakkar can take over major responsibility for technical assistance to this project, given Mr. Sethi's heavy commitments in other countries.

D. Philippines

Mr. Sethi has also provided assistance to HKI's social marketing of vitamin A project in Region VI of the Philippines. In February 1988, he helped HKI and the Nutrition Service redesign the project and to understand the social marketing method and all the steps involved. That assignment also included assisting with a three-day workshop conducted among government nutritionists and health educators, to develop the detailed project plan. He also worked with the Nutrition Service and HKI to design the

II. VITAMIN A STUDY: THAILAND

Since 1986, MI and the Institute of Nutrition, Mahidol University (INMU) have planned a social marketing study in northeastern Thailand, with funding from AID. In the absence of other vitamin A interventions such as capsule distribution and food fortification, this study will evaluate the impact of nutrition education alone on knowledge and attitudes regarding vitamin A-rich foods, consumption of these foods, serum levels, and observable signs of vitamin A deficiency.

Prior to this reporting period, MI staff and consultants had made a few planning trips, and MI had funded INMU to carry out a small feasibility study which confirmed a low dietary intake of beta carotene and fats among preschool children, low blood serum of vitamin A, and market availability, apparently year-round, of vitamin A-rich foods in the proposed study areas.

Final approval of the study itself, however, was delayed due to skepticism in AID's Bureau for Asia and the Near East as well as in the Thailand Ministry of Health that the vitamin A deficiency problem justified a major intervention study. During this reporting period, the MOH carried out a regional survey of vitamin A deficiency that, it can be assumed, confirmed a sufficient problem to proceed with the proposed study. The MOH recently approved the project, and in September 1988 INMU signed an agreement with USAID/Bangkok covering the in-country costs of the study.

Ashok Sethi made a brief visit to Thailand in April, when he helped INMU evaluate three research proposals that potential subcontractors had submitted and did further work on question guides for the formative research. In September he prepared and mailed to INMU complete versions of all of the question guides for the initial formative research.

INMU is proceding with the formative research now that it has signed its contract after more than a year's wait. However, due to the delay in funding in-country implementation and to a misunderstanding about the existence of additional funding for the technical assistance component, at present there is nc money in MI's cooperative agreement to fund the 17 technical assistance visits planned over the three-year duration of the study.

III. VITAMIN A PUBLIC INFORMATION PROJECT

During the past six months, this subproject has continued at an active pace. Most significantly, MI worked with USIA to organize two WORLDNET live satellite press conferences on vitamin A and child survival. The June 28 broadcast featured Dr. Keith West from Johns Hopkins and Bradshaw Langmaid, Deputy Assistant Administrator, Bureau for Science and Technology, AID. The program was broadcast to 22 overseas USIA posts in French. Four posts questioned the guests: Abidjan, Niamey, Brazzaville, and Libreville.

IV. ANALYZING AND DISSEMINATING LESSONS LEARNED

After two and a half years of activities under this project, MI has naturally learned a number of lessons. During this reporting period, we have made a conscious effort to analyze and disseminate these insights for the benefit of all who are working to combat vitamin A deficiency through dietary change and more effective capsule distribution.

MI staff have been very active in the deliberations of IVACG's communications task force. At that group's request, we recently submitted a model description of the communications development process in the HKI West Sumatra project with which we have been working. MI staff continue to play a major role in the preparation of the task force's guidelines for effective vitamin A communications.

We have prepared a "popular" article on the Indonesia project that we intend to disseminate to persons and groups on the vitamin A mailing list.

Marcia Griffiths gave a poster session on our social marketing of vitamin A work at the International Union for Health Education conference in Houston in August.

During the past few weeks, we have held a series of presentations and discussions of our work at Helen Keller International, the Wilmer Eye Institute at Johns Hopkins, and the Office of Nutrition at AID.

In a proposal for a two-year extension of the social marketing of vitamin A project, we proposed several methods of disseminating lessons learned, including preparation of a methodology guidelines and initiation of new field projects in Africa, possibly in direct assistance to host governments rather than through the intermediary of a PVO.

We are a collaborating institution with HKI's new technical assistance project to strengthen U.S. PVOs' vitamin A activities.

Finally, and potentially very significantly, we have been requested by the FAO to prepare a module for national vitamin A communications projects. The FAO would use this module as an outline for planning and attracting donors to fund such projects.

V. WORKPLAN

The workplan for the next year is very much dependent on the availability of new funding. As indicated in the budget report below, funds under the current AID-funded subcontract with ICEPO are quite low and will expire by the end of December. On June 1, 1988, we submitted an extension proposal to the Office of Nutrition, AID, to complete our field assistance with the projects with which we have begun to work, to maintain a similar level of public information activities, and to initiate a modest number of new activities in the field.

VI. BUDGET REPORT

MANOFF INTERNATIONAL INC.
SOCIAL MARKETING OF VITAMIN A
SUMMARY OF EXPENSES BY COUNTRY
FISCAL YEARS 1986 - 1988

	1986	1987	1988	TOTALS
GENERAL	$35,470.39	$51,825.83	$77,989.48	$165,285.70
PUBLIC AWARENESS	0.00	7,636.38	32,596.18	$40,232.57
BANGLADESH	0.00	25,799.83	21,644.85	$47,444.69
INDONESIA	6,305.97	90,099.02	31,250.02	$127,655.02
MAURITANIA	0.00	0.00	23,550.34	$23,550.34
PHILIPPINES	0.00	0.00	12,475.89	$12,475.89
THAILAND	2,915.23	33,376.37	5,735.46	$42,027.05
TOTAL	44,691.59	208,737.44	205,242.22	458,671.26

MANOFF INTERNATIONAL INC.
SOCIAL MARKETING OF VITAMIN A
BUDGET ANALYSIS - SUMMARY
FISCAL YEARS 1986 - 1988

CONTRACT LINE ITEM	BUDGET	BUDGET BALANCE	TOTAL EXPENDITURES	EXPENDITURES FY 86	EXPENDITURES FY 87	EXPENDITURES FY 88
HOME OFFICE SALARIES						
Professional	171,200.00	82,232.27	88,967.73	14,445.55	22,786.07	51,736.11
Non-Professional	19,100.00	4,833.26	14,266.74	1,566.81	5,917.29	6,782.64
Total Salaries	190,300.00	87,065.53	103,234.47	16,012.36	28,703.36	58,518.75
FRINGE	42,100.00	18,589.96	23,510.04	3,548.34	6,430.14	13,531.56
SALARIES AND FRINGE	232,400.00	105,655.49	126,744.51	19,560.70	35,133.50	72,050.31
CONSULTANTS	0.00	-72,948.20	72,948.20	1,525.81	44,405.07	27,017.32
PER DIEM	46,000.00	15,946.11	30,053.89	2,945.43	16,462.55	10,645.91
TRAVEL	38,900.00	-10,051.74	48,951.74	3,565.35	27,578.96	17,807.43
OTHER DIRECT COSTS	14,200.00	-2,032.03	16,232.03	2,017.78	6,192.68	8,021.57
SUBTOTAL	331,500.00	36,569.63	294,930.37	29,615.07	129,772.76	135,542.54
GENERAL & ADMINISTRATIVE	131,700.00	12,788.71	118,911.29	11,766.07	52,648.65	54,496.57
SUBTOTAL	463,200.00	49,358.34	413,841.66	41,381.14	182,421.41	190,039.11
SUBCONTRACTS	0.00	-10,854.05	10,854.05	0.00	10,854.05	0.00
SUBTOTAL	463,200.00	38,504.29	424,695.71	41,381.14	193,275.46	190,039.11
FIXED FEE	37,000.00	3,024.34	33,975.66	3,310.49	15,462.04	15,203.13
TOTAL SALES	500,200.00	41,528.63	458,671.37	44,691.63	208,737.50	205,242.24

TOTAL AMOUNT OBLIGATED	500,200.00
TOTAL EXPENDITURES	458,671.37
1987 DIFFERENTIAL	2,248.04
TOTAL FUNDS REMAINING	39,280.59
WORKING CAPITAL RECEIVED	50,000.00

Appendix A

Social Marketing of Vitamin A Reports
March - September 1988

Indonesia

"Review and Follow-up of the First Monitoring Study: West Sumatra Vitamin A Project," by Richard Pollard, April 1-6, 1988

"Revising Implementation Plans," by Richard Pollard, July 4-8, 1988

"SOMATA Activity Plan, August 1988," by Richard Pollard, Ashok Sethi, and Marcia Griffiths

"Social Marketing of Vitamin A Project, West Sumatra, Indonesia," by Ashok Sethi, Richard Pollard, and Michael Favin, prepared for IVACG communications task force, September 1988

"VITAMIN `A´, Helping Mothers to Help Their Children Grow Healthy and Strong," brochure draft by Richard Pollard, Ashok Sethi, and Michael Favin, September 1988

Bangladesh

"Preparing the Workplan for the Social Marketing of Vitamin A Project," by Richard Pollard, February 28-March 8, 1988

"Planning Formative Research - Social Marketing of Vitamin A," by Ashok Sethi, March 7-14, 1988

"Preparing for Formative Research," by Ashok Sethi, July 8-17, 1988

Philippines

"Completing the Formative Research and Preparing the Communication Strategy," by Ashok Sethi, May 10-27, 1988

Mauritania

"Social Marketing Assessment Visit, World Vision Vitamin A Project: Assaba Region," by Benedict Tisa, May 16-June 2, 1988

Thailand

"Planning the Formative Research," by Ashok Sethi, April 18-26, 1988

Appendix B

Letters from Recipients of Public Information Mailings

Bruxelles, le 2/8/88

MANOFF INTERNATIONAL INC.
2001 S Street N.W.
WASHINGTON D.C. 20009

Messieurs,

Notre organisme, ayant le souci de l'éducation nutritionnelle des populations du Zaïre, du Rwanda et du Burundi, nous vous sommes très reconnaissantes de la documentation concernant la vitamine A que vous nous avez envoyée. Nous souhaitons pouvoir partager ces connaissances avec les personnes sur place, responsables aux centres de santé. Il nous paraît, en effet, particulièrement important que les habitants sachent où ils peuvent puiser ces vitamines dans leur nourriture locale.

Si vous préparez d'autres dossiers d'information, ils nous intéressent et d'avance nous vous en remercions.

Veuillez agréer, Messieurs, l'expression de nos sentiments distingués

A.M De Brabandere

A-M De Brabandere

WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR AFRICA

ORGANISATION MONDIALE DE LA SANTE
BUREAU REGIONAL DE L'AFRIQUE

ORGANIZAÇÃO MUNDIAL DA SAÚDE
SEDE REGIONAL EM ÁFRICA
Tel 81 38 60-65 Telex 5217 KG - 5364 KG

19 September 1988

In reply please refer to N3/27/1
Priere de rappeler la réference :
Queira indicar a referência :

RECEIVED OCT 17 1988

Dear Sir, or Madam,

This refers to your memo of 22 July 1988 addressed to "Vitamin A Public Awareness Group" and the attached reproduction of various posters and pamphlets and other educational materials regarding Vitamin A deficiency.

We found the information on Vitamin A contained in the memo to be well prepared and easy to understand and therefore useful in raising public awareness of institutions and individuals in particular those who do not have a medical training.

The WHO Regional Office for Africa is presently engaged in developing a programme to combat health problems arising from Vitamin A deficiency. To this end, we have started the process of sensitizing national health authorities and the general public by distributing appropriate educational material.

We would therefore be grateful to receive about fifty copies, or less if not available, of both the English and French versions of the above mentioned materials. We feel such publications would be useful in strengthening the education component of this office's programme of control of Vitamin A deficiency

Please also keep us in your mailing list.

Thank you for your cooperation.

Yours sincerely,

K. V. Bailey
Regional Officer
for the Regional Director

MANOFF INTERNATIONAL INC.
2001 S Street, NW, Suite 240,
Washington, D.C. 20009.
U. S. A.

ORGANISME DE RECHERCHES
SUR L'ALIMENTATION
ET LA NUTRITION AFRICAINES
O. R. A. N. A.
39, Avenue Pasteur
Boîte Postale 2089
Tél. : 22.58.92
DAKAR

Dakar, le 22 Septembre 1988

LE DIRECTEUR DE L'O.R.A.N.A

_//_

Manoff International INC

Service d'Information sur la
Vitamine A
2001 S Street, N.W
WASHINGTON.D.C. 20009
(U.S.A.)

N° 88/222/OR

Messieurs,

J'ai l'honneur de vous écrire cette lettre pour vous faire savoir que nous sommes très intéressés par vos dossiers sur la Vitamine A.

Nous vous demandons de bien vouloir nous les faire parvenir.

Dans cette attente, veuillez agréer, Messieurs, l'expression de nos sentiments les meilleurs.

Le Directeur de l'ORANA
Dr.A.M. NDIAYE

Appendix C

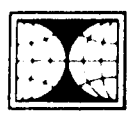
SOCIAL MARKETING OF VITAMIN A
TRIPS CURRENTLY REQUESTED

Country	Approx. date	Main tasks	Weeks/Research Consultant	Weeks/Marketing Consultant
THAILAND	November 1988	Analyze formative research Write research report	2	
	December 1988	Formulate intervention strategies		1
	December 1988	Design household trials Train interviewers	2	
	February 1989	Analyze trials Write research report	2	
	February 1989	Write creative and media brief Appoint ad agency or consultants		2
	March 1989	Design pretesting of messages/materials Train interviewers	2	
	April 1989	Amend materials Finalize program		2
	April 1989	Design baseline survey Train interviewers	2	
	October 1989, April 1990	Design monitoring studies Train interviewers	3	
	November 1989, May 1990	Analyze monitoring studies Recommend project modifications		3
	March 1991	Plan final evaluation	1	
	June 1991	Analyze final evaluation Help write final project report	2	1
	July 1991	Participate in national seminar on project	1	1
			Total = 17 weeks 10 trips	Total = 10 weeks 7 trips

INDONESIA	December 1988	Write baseline report Plan third monitoring study	2	
	January 1989	Analyze monitoring Recommend modifications		2
	April 1989	Plan final evaluation	2	
	July 1989	Analyze final evaluation Help write final report	2	2
			Total = 6 weeks 3 trips	Total = 4 weeks 2 trips
PHILIPPINES	January 1989	Design pretesting of materials Design monitoring protocols	2	
	April 1989	Analyze first monitoring study Recommend modifications	2	
			Total = 4 weeks 2 trips	

SOCIAL MARKETING OF VITAMIN A

[redacted]



Manoff International Inc.

SOCIAL MARKETING OF VITAMIN A

Supported by:

International Center for Epidemiology & Preventive Ophthalmology
Subcontract to Manoff International Inc.
AID Cooperative Agreement #DAN-0045-A-00-5094-00

CONSULTANT TRIP REPORT: INDONESIA
April 1-6, 1988

REVIEW AND FOLLOW-UP OF THE FIRST MONITORING STUDY: WEST SUMATRA VITAMIN A PROJECT

Richard Pollard
Marketing Consultant

TABLE OF CONTENTS

The following scope of work was established for this consultancy:

1. Review the results of the first monitoring study with the project manager.

2. Recommend improvements or changes in strategy that are indicated by the study findings.

3. Review the project budget.

The above tasks were accomplished as follows:

1. The monitoring study findings were reviewed in Pariaman. The final report is to be completed by the project manager by mid-April.

2. This consultant, Dr. Musni (Head, Nutrition Section, Kanwil, Padang) Ibu Asmira (Head, Sub-directorate of Nutrition Deficiency, Jakarta), and the project manager met in Padang to discuss general findings and actions required. These were further detailed during a meeting of the project manager and this consultant with the advertising agency in Jakarta. A summary of the status of the project, the more relevant monitoring findings, and proposed actions is attached.

3. The budget was reviewed. Expenditures to date are well within expenditure targets, and there are adequate reserves to undertake proposed revisions.

Major Findings and Recommendations

1. The project was launched in November 1987 following an extremely successful Bupati (District Head) Proclamation event that was attended by 2,000 guests and widely reported in the mass media.

2. The first vitamin A capsule (VAC) distribution month, which occurred in December, achieved a distribution level of 46% in four villages surveyed. However, kaders did not give VAC to children who had received capsules from posyandu over the previous six months, estimated to be about 20% of target children. Interviews showed that 68% of children had received VAC over the last six months. Therefore, it can be assumed, subject to availability of data from all Pariaman, that coverage increased from about 20% to a maximum of 68% due to this promotion.

3. Kanwil reported that over 3,600 kaders were trained in VAC distribution and counseling. Many dropped out after the VAC month. An estimated 1,200 trained and active kaders remained at the time of monitoring in March.

10. This consultant noted that capsules were distributed to 1-5 year old children. However, government policy is that the target group for semiannual distribution should be children 9 months to 5 years old. This is to be taken up with Kanwil.

11. A discussion was held among the project manager, Ms. Susan Eastman from HKI/NY, and this consultant on a possible time extension of the project. It was agreed that, in principle, the project should be extended by at least six months and, therefore, be evaluated in July 1989 rather than January 1989. The final evaluation report would then be completed by the end of September 1989.

12. This consultant recommended that implementation of the second VAC distribution should be more closely observed and monitored by the project management team to gain first-hand insights into both positive areas and problems.

Next Consultancies

The MI research consultant should come at the end July/early August to assist, if necessary, report on the second monitoring; to prepare for the evaluation study in January; and to complete the baseline study analysis.

The MI social marketing consultant should overlap with the research consultant in early August and review results of the second monitoring and assist in project revisions.

252

APPENDIX A

Persons Contacted

APPENDIX A

Persons Contacted

Government of Indonesia

Ministry of Health

Dr. Rafki Ismail, Head, DEPKES, Kanwil, Padang
Dr. Musni, Head, Nutrition Section, Kanwil, Padang
Ibu Asmira S. MSc., Head, Sub-directorate, Nutrition Deficiency, Jakarta

Helen Keller International

Martin Poland, Interim Country Director
Steve Wilbur, Country Director
Susan Eastman, HKI/New York
Raharjo Suwandi, Project Manager

Fortune

Freida Djoko, Account Executive

APPENDIX B

SUMMARY OF STATUS AT FIRST MONITORING

APPENDIX B

SUMMARY OF STATUS AT FIRST MONITORING

April 1988

Richard Pollard - MI Marketing Consultant

The first monitoring exercise was designed to evaluate the implementation of the first VAC distribution month and the launch phase of the DGLV promotion.

The launch commenced in November 1987 and first VAC month occurred in December. The monitoring fieldwork took place in March 1988, four months after launch.

It was not expected that this first monitoring would unearth significant attitudinal or behavioral change indicators relative to the campaign to increase consumption of DGLVs, although some indicators were looked for. The prime aim was to check the quantity and quality of kader training and its result in the field; to check media and PR placement, billboard and banner erection, poster distribution, and the playing of messages via medicine sellers, and recall of having heard or seen messages via these activities. The results of motivation efforts toward village chiefs/the PKK, schools and religious leaders was also studied. The results, along with agreed program modifications, are summarized below.

IMPLEMENTATION FINDINGS

1. Bupati Proclamation Event

Date:	October 22, 1987
Purpose:	To motivate the effort at the district-puskesmas level.
Attendance:	Well attended by 2,000 invitees.
Success:	Reported to have been extremely successful.
PR Coverage:	Excellent. Widely reported on local and national TV, radio and press.
Spin-off:	Copies of the Proclamation were sent to kaders.

2. Capsule Stocks

HKI provided and delivered VACs.

3. Kader Training

Kader training took place during the last week of November, after the training of puskesmas staff. The training was a simple hands-on

early November. The agency failed to send monitoring reports until January. These stated that broadcasts started on schedule, with full spots broadcast over November, but that progressively fewer spots were broadcast over the following months. Up until March, only 30% of all spots had been broadcast, for which we had been charged fully instead of an agreed 50% discount. The agency had failed to explain or rectify this. They have now promised to do so.

e. Medicine sellers' cassettes

These were delivered by the advertising agency on November 15. Again, the agency failed to monitor and report on this until January. Medicine sellers found the one-minute messages on the tapes too long to fit into their own sales pitches. This was still being rectified at the time of the monitoring.

f. Letters to religious leaders

These were mailed by the advertising agency. There was no evidence of receipt, however.

g. Letters to schools

These were to be mailed by the advertising agency primarily to request announcements on the VAC distribution. The agency failed to mail them on schedule and the order, therefore, was canceled.

5. VAC Distribution

VAC distribution was undertaken during December 1987. It was agreed to change the distribution method from monthly via posyandu for children 1-5 years old, to twice a year, in line with government policy.

Kaders were asked to concentrate on encouraging mothers to come to posyandu in December for VAC, in line with formative research indications of some resistances from kaders (time and motivation constraints) to home distribution. Monitoring showed very low attendance at posyandu and that kaders had delivered most of the capsules to mothers at home.

Tentative data from four monitored villages showed:

a.	Capsule coverage over five months prior to program	17%
b.	Capsule coverage in December	46%
c.	Approximate total coverage over six-month period	63%
d.	Mothers reported receiving over last six months	68%

c. Via medicine sellers in markets - The implementation of this component has been poor. They had rarely used the cassette tapes given to them as they claimed the 60-second spots on it were too long to fit into their own sales pitch. A tape with short, sharp announcement messages was proposed to the agency in January, but has not yet been prepared. Almost 10% of researched mothers claimed to have heard the messages.

d. Via billboards in markets - These were put up only one month before monitoring and are designed as reminders to kader and radio messages. Less than 1% of mothers recalled them.

e. Via posters - Although primarily intended as reminders to providers, a high 40% of mothers recalled seeing them.

f. Via ulama and schools - No ulama or schools reported receiving the direct mail letters asking for announcements on VACs.

7. Analysis of Weaknesses in the Communications Effort

The implementation of the communications effort had been weak.

- o Radio spots were not being broadcast as scheduled.
- o Billboards were put up four months late.
- o Medicine sellers had failed to broadcast messages regularly.
- o Direct mail to ulama and schools was not reaching targets.

These activities, to be implemented by the advertising agency, were not well monitored as had been recommended by this consultant. Also,

- o Puskesmas do not seem to have passed Action Kits to village chiefs, as requested.
- o Kaders has, in general, failed to counsel mothers.

RECOMMENDATIONS

It is clear that without urgent rectification of the weaknesses in the communications effort, it is unlikely that the desired behavioral changes expected of the project will be accomplished.

In addition, should the existing program not be rectifiable, the degree of lost communications in reach and frequency must be replaced by comparable alternative communications to targets. Specific recommendations:

constraints, even though posyandu attendance is very low.

b. Endeavor to influence a change to national policy on counseling at posyandu and at mothers' homes by kaders.

c. Rely on developing other communications channels.

There was absolute unanimity of view that the kader system is best utilized for "product" delivery. To train kaders and operate them as effective purveyors of behavioral change was seen as neither cost effective nor sustainable, at least in the present realities of the situation in Pariaman.

A compromise solution to be considered, however, is utilizing an existing budget for retraining scheduled later this year. This will be further discussed with the MI consultant in June.

6. Second VAC month - This was postponed until to June owing to Ramadhan, which takes place mid-April to mid-May. Dr. Musni felt that sufficient motivation exists among puskesmas and kaders to repeat and, hopefully, improve the first VAC distribution. As a test to this and as an indicator of sustainability, it was agreed not to undertake any major additional activity beyond those established, i.e. erection of banners, special announcements through radio and via ulama and schools. However, some concern was expressed at the high drop-out rate of kaders and the burdens placed on those remaining active. If seen as the cause of any weakness in the second VAC distribution, this will influence decisions on on-going training (see above).

The MI consultant proposed that while being careful to maintain a close working relationship with Kanwil and without appearing to be overseeing the work of the VAC distribution, the HKI project management team should try to be with a number of kaders while they distribute VACs in June to gain first-hand insights on what actually happens in the field and on the kaders' attitudes.

April 7, 1988