

**PAN AMERICAN HEALTH
ORGANIZATION**

**ADVISORY COMMITTEE
ON MEDICAL RESEARCH**

SECOND MEETING

**17-21 June 1963
Washington, D.C.**

RESEARCH ACTIVITIES IN NUTRITION

RESTRICTED

Ref: RES 2/24

22 May 1963

PAN AMERICAN HEALTH ORGANIZATION
Pan American Sanitary Bureau, Regional Office of the
WORLD HEALTH ORGANIZATION

WASHINGTON, D.C.

RESEARCH ACTIVITIES IN NUTRITION*

During the first meeting of the PAHO Advisory Committee on Medical Research, the Committee recommended that research related to nutrition should receive the highest priority. Within this field certain areas were established in terms of priorities. These were: protein-calorie malnutrition in children, anemias, endemic goiter, and nutrition and infection.

It was felt that they represented the most widespread and severe problems of nutrition in Latin America and therefore should receive greatest attention. Since that time, the priorities have remained unchanged. This presentation will review the activities carried out during the past year in relation to these problems.

Protein-calorie malnutrition in children.

The principal work in this field is being carried out at INCAP and the report of that Institute covers it in detail (RES 2/10). Other laboratories in which research is being conducted in conjunction with the PAHO program include the National Institutes of Nutrition in Ecuador (Williams-Waterman Foundation), Dr. George Graham (NIH) in Peru and Dr. Nelson Chaves (US/NRC) in Recife, Brazil.

In Ecuador, research on the protein resources of the country has been principally confined to vegetable sources and in particular to lupin seed and quinoa, two high altitude crops traditionally consumed by the highland populations. A mixture of these two products

*Prepared for the Second Meeting of the PAHO Advisory Committee on Medical Research, 17-21 June 1963, by the Regional Advisor in Nutrition, PASB.

- 2 -

has demonstrated excellent biological value on laboratory analysis and in animal trials. At present the problem of removal of bitter-tasting alkaloids from lupin seed is being studied, both by means of chemical extraction and by the cultivation of alkaloid-free strains. Long-term toxicity studies are also being carried out in animals using high-alkaloid content seeds.

As a complement to this study, work is being carried out in the Children's Hospital (Baca Ortiz), Quito, to define the classical picture of malnutrition in the Andean highlands from the sociological, dietary, biochemical and clinical standpoints. Efforts are being made to find a simple standard treatment of severe malnutrition that can be used at the level of local health centers.

Reference will be made in RES 2/25 to the work carried out by Dr. Graham in Perú in testing fish protein concentrates as food additives on a population basis. In view of the fact that fish protein is the most widely available and cheapest animal protein available in Latin America today, this research is of considerable significance. The fish protein concentrate used in this study has been obtained from the UNICEF-assisted plant in Quintero, Chile.

In Recife, the Institute of Nutrition is currently carrying out work on protein malnutrition in Northeast Brazil. Basically the work aims to identify the cause and contributing factors of malnutrition, to define the clinical pathological picture and to seek simple means that may be generally applicable throughout the area for prevention and treatment of this condition.

With a view to coordinating existing and future research in

protein-calorie malnutrition in Latin America, it has been proposed that a scientific group of principal investigators be convened in order to exchange information, define further fields of research and standardize methodology. The Williams-Waterman Foundation has expressed interest in assisting in the financing of such a meeting. The report of the Committee on Protein Malnutrition of the Food and Nutrition Board of the National Academy of Sciences/National Research Council on Evaluation of Protein Quality may serve as a useful basis for such a meeting.

Endemic Goiter

Following the visit to various countries of Latin America in 1962 by the PAHO Consultant on Endemic Goiter, it was felt that considerable benefit could be derived from a scientific meeting of the principal investigators in this field. The meeting took place in April 1963 at IVIC, Caracas, and was devoted to a review of research in endemic goiter, to identification of areas in need of further inquiry, to discussion of study methods and procedures, and to the possible coordination of present and future research efforts among investigators.

All of the major objectives of the meeting were fulfilled and the participants expressed great satisfaction with the proceedings. A detailed report appears as document RES 2/20.

Apart from the organization and realization of the meeting, three research projects in endemic goiter have been set up as a result of the Consultant's preliminary tour in 1962 (Ecuador, México, Brazil). All of the projects involve applications for funds to NIH

- 4 -

directly from the investigators: one has been approved, the other is pending and the third is in preparation.

Anemias;

In conjunction with the WHO research program on anemias, a special consultant, Dr. Clement Finch, visited six countries in Latin America in order to appraise the situation with regard to further research. Of specific interest were anemias related to iron, folic acid and B-12 deficiencies. A detailed report of this consultancy is attached (Annex A).

In general, it was the opinion of the Consultant that anemia in Latin America is widespread and represents a serious public health problem. There is considerable interest in research on etiology and prophylaxis of anemias and there are some well-trained personnel carrying out programs along these lines. The Consultant felt, however, that there are notable obstacles in the solution of the existing public health problems. The current methods being used to study anemias in many areas do not contribute significantly to present knowledge with regard to etiology; they refer to prevalence, severity and morphology of the disease rather than to identifying etiology. In areas where precise methods are being used to study etiology (serum iron, IBC, folate and B-12) there is considerable need to set up a reference laboratory in order to standardize techniques used and to compare and verify results.

Though there are at present some well-trained hematologists in Latin America, there is need for more trained research workers in

- 5 -

this field, both at the professional level and at the level of qualified laboratory technicians. It was felt that it might be advisable to establish a coordinated training program in relation with specific centers in the U.S.A.

Finally, it was observed that there existed little or no communication between the various investigators of the continent and that it might be advisable, as an initial step in the program to hold a scientific meeting of prominent investigators in the field to obtain their opinion on such matters as the establishment of a reference laboratory and a training program, and to try to coordinate and guide future research efforts. To implement this aspect of the Consultant's report, PAHO has taken preliminary steps to secure the funds needed for convening such a meeting in 1963.

Vitamin A deficiency.

Evidence has accumulated that vitamin A deficiency is fairly widespread in Latin America, at least from studies of dietary intakes and, in certain areas, from clinical studies. Clinical deficiencies of vitamin A are usually not identified as an isolated deficiency but more often as part of the overall picture of severe protein-calorie malnutrition.

A WHO Consultant in ophthalmic diseases with specific reference to vitamin A deficiency (xerophthalmia and keratomalacia) visited 11 countries in Latin America during the period January-March 1963. A written summary of the Consultant's findings can be found in Annex B.

Nutrition and infection.

Details are contained in Document RES 2/10.

NEEDS AND RESOURCES FOR RESEARCH ON NUTRITIONAL
ANEMIAS IN THE AMERICAS^{*}

Site visits were made from December 2nd to 15th, 1962, and from January 20th to February 12th, 1963. Places visited included San Juan, Puerto Rico (regarding research in Trinidad); Caracas, Venezuela; Cali and Bogota, Colombia; INCAP, Guatemala; Buenos Aires, Argentina; and Rio de Janeiro, São Paulo and Recife, Brazil.

The individuals interviewed had been selected by the World Health Organization and included outstanding hematologists and nutritionists in the areas visited. Attention was given to laboratory facilities, techniques, research interests, and to the calibre of established and younger affiliated personnel.

As is perhaps inevitable, key people were often absent, necessitating changes in the schedule of the trip. The latent period involved in the usual communication channels made it impractical to anticipate this. Undoubtedly some of the difficulties could have been obviated had there been more direct contact between the consultant and the people visited by telephone and cable.

In this report, nutrition aspects are not stressed, because information concerning the presence of dietary deficiencies and resultant

^{*}By Dr. Clement A. Finch, University of Washington School of Medicine, acting as consultant to WHO.

megaloblastic anemia was so limited as to be of little value and perhaps even misleading. Rather, emphasis was placed on capabilities and interests of investigators. As background for this report, nutritional surveys by ICNND in Ecuador, Peru, Colombia, Chile and the West Indies should be consulted.

TRINIDAD

Anemia in Trinidad has been the subject of a nutrition survey by the U.S. Interdepartmental Committee on Nutrition for National Defense. This study indicated that the mean hemoglobin level in Trinidad and Tobago is about 2 grams below the accepted normal in all age groups. Iron deficiency anemia and megaloblastic anemia are both known to be present. In San Juan, Puerto Rico, discussions were had with Dr. J.E. Chopra, the Nutrition Advisor for Zone I, PASB, who will conduct a survey-study in Trinidad to determine the nature of the anemias present, under a grant from the NIH/USPHS.

VENEZUELA

A detailed visit was made to the Instituto Venezolano de Investigaciones Cientificas, where a program of investigation on hookworm anemia is under way (1,2). Dr. Marcel Roche and Dr. Miguel Layrisse have a fine laboratory capable of doing accurate work and have access to rural populations with high incidence of hookworm anemia, and to large numbers of pregnant women. They have established relationships between the degree of hookworm infestation and the amount of blood loss. Studies of iron

excretion, liver iron stores, and food tagging with radioiron are in progress in connection with the WHO program on iron deficiency anemia. Further, they have had experience with B₁₂ and folate assays. It is evident that this laboratory is an excellent one and should be a focal point for studies in Venezuela. The hookworm infestation is severe in certain areas of Venezuela, whereas megaloblastic anemia would not be anticipated to be a serious problem. However, studies in pregnant women show that it is not uncommon (3,4).

COLOMBIA

The University Medical School at Cali is a good school and has profited from relationships with Tulane and other U.S. schools. Dr. J. Ghitis, a well-trained clinical hematologist, despite his heavy clinical load, has an interest in research, and has recently been involved in studies of the red cell abnormalities in kwashiorkor (5). He has been interested both in marrow hypo-function, which occurs in the acute phases of the disease, and evidences of megaloblastic change which occur during the recovery phase. Special laboratory procedures are not well developed and the strength of this program rests in the adequate clinical material and the sound clinical experience of Dr. Ghitis. Dr. Escobar, who has recently joined him, has been trained in isotope techniques and is interested in setting up radioactive iron and radioactive chromium procedures, but as yet little progress has been made in this direction. In Bogota Dr. A. Villamil and Dr. Sarasti are both interested in hematology and have obtained special training in this field in the United States. These physicians are heavily burdened with their clinical responsibilities and with part-time practice. At the present time there

is essentially no hematology research going on, although there are plans of limited extent. The National Medical School is overloaded with patients and financial restrictions are severe. Research equipment is very limited, but they do have a great number of patients with severe iron deficiency anemia. It was planned to see Dr. H. Velez, from the Department of Nutrition, University of Antioquia in Medellin. However, this did not prove possible.

Colombia is a country in which there is obviously a high incidence of iron deficiency anemia, and undoubtedly megaloblastic anemia, although this has not been well documented in the adult.

GUATEMALA

Guatemala City was visited, and in particular INCAP, along with Roosevelt Hospital and adjacent villages in which INCAP is working. Unfortunately, a number of people were away, including Dr. Carlos Tejada. Most of the time was spent with Dr. F. Viteri, who had just returned from the United States. Dr. Viteri is certainly a knowledgeable and enthusiastic person, and INCAP is an excellent organization in which to study nutritional problems. It was apparent that as of the moment, however, very little in the way of hematologic research was going on at INCAP, and only simple hematologic procedures are being carried out. Their hematologic interests lie primarily in a study of the anemia associated with hypoproteinemia. It might be hoped that they would take this on as a special problem. As in the preceding countries, hookworm anemia was found in the hospital wards and iron deficiency anemia represents the major problem. Again, there was insufficient data to indicate whether there was any appreciable incidence of megaloblastic anemia.

ARGENTINA

The Instituto de Hematologia in Buenos Aires has the responsibility of investigating problems of anemia throughout the country. Dr. Luís Podestá and his associates have a protocol for the investigation of iron deficiency in Argentina. Initial studies in Buenos Aires indicate an incidence of iron deficiency anemia of about 20 per cent among pregnant women. Regional studies are planned, but may be hampered by financing problems. Plasma iron, folate, and B₁₂ assays are not yet being carried out in the Institute laboratories, and this group is at the present time restricted in financial support. Other groups visited in Buenos Aires included the hematology unit at the Municipal Hospital, Dr. Pavlovski's group at the Academy of Medicine, and the medical division of the Atomic Energy program under Dr. George Varela and his associates. These programs are meritorious, but their interests are directed to other areas than that of the WHO program.

BRAZIL

In Rio de Janeiro, Professor C. Cruz Lima, Dr. E. M. Marinho, head of the Institute of Hematology, Dr. Pedro Borges, of the Comissão Nacional de Alimentação, Professor Lacaz, of the Department of Biochemistry, and Dr. Walter Oswaldo Cruz were among those visited. In São Paulo, the following were visited: Dr. Alvaro Guimarães, Director of the Institute of Hygiene and Maternal Health, Yaro Gandra, a nutritionist who has recently completed a study of anemias at the Head of the Amazon in Peru (the information had not yet been assembled, although preliminary impressions would indicate that there was an appreciable incidence of iron anemia relating to hookworm parasitism), Professor M. A. Jamra at the

University of São Paulo Medical School, Dr. Gastão Rosenfeld at the Butantan Institute, and Professor Paulo da Silva Lacaz, who is Professor of Biochemistry at the University. Dr. Jamra and Dr. Marinho are both very competent clinical hematologists, and both are involved in clinical investigation. There has been some work by Dr. Jamra and his associates on iron metabolism and pernicious anemia (6-8). However, there are no B₁₂ folate or iron binding capacities being done on plasma in any of these laboratories. Although Dr. Gandra had reviewed the pertinent literature concerning studies on anemia in Brazil at Dr. Rao's request, the available publications which he had selected carried very little information concerning the geographic incidence of nutritional anemias in Brazil. Data which was given on dietary iron intake also indicated about 15 mg a day as being an average amount ingested. There are active programs of hematologic research going on at the Instituto Oswaldo Cruz in Rio, and at the Butantan Institute in São Paulo. Drs. Oswaldo Cruz and Gastão Rosenfeld are competent investigators, but at the present time, neither of their interests is closely related to the WHO program.

In Recife, Dr. Nelson Chaves, Professor of Physiology and Head of the Nutrition Institute, Professor Lins of the Biochemistry Department, and Dr. Fernando Figueira were visited. A nutrition study is going on at the present time in this area. While there were no good figures on the incidence of anemia in this locale, it is worth pointing out that Dr. Figueira has in 1960 completed a treatise on hookworm anemia (9) and is very interested in this problem, and also that that part of Brazil might be a very useful area to study in view of its borderline economic state.

REFERENCES

1. Roche, Marcel, Perez-Gimenez, M. E., Layrisse, Miguel and Di Prisco, Estela. Study of Urinary and Fecal Excretion of Radioactive Chromium Cr³¹ in Man. Its Use in the Measurement of Intestinal Blood Loss Associated with Hookworm Infection. J. Clin. Invest. 2: 1183, 1957.
2. Layrisse, Miguel, Paz, Alfredo, Blumenfeld, Norma, and Roche, Marcel. Hookworm Anemia: Iron Metabolism and Erythrokinetics. Blood 18: 61, July, 1961.
3. Aguero, Oscar and Layrisse, Miguel. Megaloblastic Anemia in Pregnancy in Venezuela. Am. J. Obstet. and Gyn. 76: 903-908, October, 1958.
4. Layrisse, Miguel, Aguero, Oscar, Blumenfeld, Norma, Wallis, Henry, Dugarte, Iris, and Ojeda, Adelina. Megaloblastic Anemia of Pregnancy: Characteristics of Pure Megaloblastic Anemia and Megaloblastic Anemia Associated with Iron Deficiency. Blood 15: 724, May, 1960.
5. Velez, H., Ghitis, J., Pradilla, A., and Vitalle, J. J. Cali-Harvard Nutrition Project. I. Megaloblastic Anemia in Kwashiorkor. Am. J. Clin. Nut. 12: 54, January, 1963.
6. Gomes, Zulmira, da Silva, Alberto Carvalho, Jamra, Michel, Niveis de Ferro Sérico, Siderofilina Livre e Siderofilina Total, em Individuos Adultos, Normais, de Ambos os Sexos. Rev. Assoc. Med. Brasil. 5: 38, 1958.
7. Cillo, D. M., Jamra, M.: Hemosiderina, sideroblastos y siderocitos. Su importancia en el estudio de las anemias. Sangre 5: 271-291, 1960.

8. Jamra, Michel Abu. Contribuição para o Estudo do Metabolismo da Hemoglobina na Anemia Perniciosa. Empresa Grafica da "Revista dos Tribunais" Ltda., São Paulo, 1946.
9. Figueira, Fernando. Contribuição ao Tratamento da Ancilostomóse na Criança. Pernambuco, Recife, Brasil, 1960.

REPORT ON THE SURVEY ON XEROPHTHALMIA AND
KERATOMALACIA CAUSED BY HYPOVITAMINOSIS A IN LATIN AMERICA

by

Dr. U. Escapini, WHO Consultant

SUMMARY

The survey was made in 46 days, from 15 January to 1 March. Taking into account holidays and travelling time, 27 working days were used in the survey. During this period I visited 43 institutions in 11 countries and was invited to give 16 lectures in different places.

Clinical examinations were made of 2,532 children in hospitals, health units, schools and orphanages. We found 324 malnourished children, i.e. 12.7% of the total. Of these, 36 presented ocular lesions, i.e. 11% of the malnourished children, a total of 2,241 children were seen in hospitals and 291 in schools. Among the children in hospitals 14.45% were malnourished and 1.6% of the total number of children presented ocular lesions. Among the school children none had clinical ocular signs from the nutrition point of view. Some differences were found in the frequency of malnutrition and ocular lesions in different countries. This was seen in all countries except Venezuela and Bolivia. Children from hospitals and health centers in Brazil, Haiti, Guatemala, Salvador and Nicaragua showed the highest percentage.

There were differences within countries in different geo-

graphical areas, depending mainly on the social and economic conditions. For example, in Mexico City the investigation proved negative, while in Merida the manifestations were frequent. In Venezuela I was unable to see one single case but apparently some cases have been found in Barquisimeto (500 kilometers from Caracas). In Brazil it is more frequent in Recife than in Rio de Janeiro. In this City I found 7 severe cases among 61 malnourished children. Even in the same city differences were found in the frequency according to the level of the population treated in the different institutions. For example, in the free public hospitals where the level of the population is very poor, the frequency was higher than in the social security hospitals.

There are also differences in the frequency among the children in the hospitals and in out-patients clinics. The percentage of malnutrition is higher in the former. However, the ocular lesions were more frequent in the out-patients clinics, although of less severity, while the hospitalized children had more advanced and severe lesions.

Of the 36 children seen with xerophthalmia, 9 were not in a very advanced state and the condition was reversible, and 27 were in a very severe, grave state that was irreversible.

Apart from the clinical lesions due to hypovitaminosis A, many malnourished children also presented infectious conjunctivitis, and some infectious conditions of the cornea.

The personal contacts with pediatricians and ophthalmologists proved that in all of the countries visited ocular lesions have been

seen in the past, although very little attention has been given to the problem. With the malnourished children under the care of the pediatricians, the ophthalmologist has very little opportunity to offer his assistance to study the ocular lesions and the treatment. Differing opinions are held by ophthalmologists in various countries on the frequency of xerophthalmia, but this is due to the fact that the information they have is based on their personal impressions and not on the results of a serious epidemiological study. The Institutes, Departments and Divisions of Nutrition have carried out some clinical studies on the nutritional conditions of the population and also some biochemical determinations. The criteria used in defining the clinical findings are not uniform. In some cases ocular lesions, pigmentation etc. have been described, in which the frequency increases with age. These signs have no specificity and probably there are environmental factors which play an important role. This lack of uniformity in the criteria is due to the fact that the results of the surveys cannot be compared, as they depend upon the personal criteria of the observer.

The food consumption surveys show that the vitamin A intake is very low. The intake varies from 11% to 76% of the requirement. The figures given for Central American countries are the average of the intake of urban and rural populations. In Guatemala and Nicaragua the intake is higher in the rural population; however, in the rest of the countries the intake is higher in the urban population. In some areas the intake is as low as 347 International Units of vitamin A in the rural population (El Salvador). In some

countries it was possible to obtain information about the serum level of vitamin A and carotene, and these were seen to be very low. In Haiti 7% of the population have serum levels below 20 micrograms and 26.5% have levels of carotene below 100 micrograms. In Central America the levels are about 50% of the levels considered normal. There are very few published papers about ocular nutritional lesions. Most of them have been written by pediatricians as part of the general study on malnutrition. In general there is evidence of the lack of interest of these pediatricians in giving the attention needed to the dramatic consequences on the sight of the child.

RECOMMENDATIONS

I - Related to Ophthalmopathy

1. Well defined clinical criteria should be adopted on what could be called nutritional ophthalmopathy and the different phases of its evolution. I would suggest the following classification, which I have used since 1954 with good results:

Grade I	Night blindness
Grade II	Bitot's spot
Grade III	Conjunctival-corneal xerosis
Grade IV	Cloudiness of the cornea
Grade V	Ulcer of the cornea
Grade VI	Keratomalacia
Grade VII	Sequalae (leucomas, estafilomas corneales, phthisis bulbi).

At the present time there is no general term which includes

all the nutritional ocular lesions and I would suggest the term nutriophthalmopathy and for the specific lesions of hypovitaminosis A, I suggest the term nutriophthalmopathia A, which would indicate the nature of the lesions and the localization.

2. I would suggest that a research plan should be set up on nutritional ophthalmopathies, particularly those due to hypovitaminosis A, both from the clinical and epidemiological point of view. This implies the creation of research groups in each country, which would be composed of specialists in nutrition, epidemiology, pediatrics and ophthalmology. During my visits to the countries and through the lectures given, I called attention to the problem and I am sure that a new interest has been created in the problem and in the need for such research in the future.

3. It is advisable to stimulate the interest of the ophthalmologists in the assistance given to the malnourished children. Each malnourished child in the hospitals should be examined by an ophthalmologist.

4. It is desirable to hospitalize all children with ocular lesions, starting at Grade III of the classification, as most of them are reversible. Night blindness and Bitot's spot can be treated in out-patients clinics. The basic treatment should be that of the nutritional deficiency, using only antibiotics locally in the eyes, avoiding the use of corticosteroids.

5. To complement the diets with additional foods rich in vitamin A.

6. To establish the practice of applying simple antibiotic ointment to the eyes of each malnourished child, as a prophylactic against the infections to which it may be exposed.

II - GENERAL RECOMMENDATIONS

The ocular manifestations in malnourished children are a consequence of this malnutrition. Attention to the eyes alone, therefore, is not enough to prevent and to treat the condition. The basis of the prevention should be to combat the serious problems of malnutrition which attack a great number of children.

A - SHORT TERM MEASURES

1. Health and nutrition education
2. To introduce nutrition into teachers training schools as well as into primary and secondary schools.
3. To increase the applied nutrition programs undertaken in collaboration with WHO, FAO and UNICEF.
4. To increase the UNICEF programs of skim milk distribution enriched with vitamin A.
5. To increase and improve the health centers, especially the MCH activities.