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ORGANIZATION**

**ADVISORY COMMITTEE  
ON MEDICAL RESEARCH**

**THIRD MEETING**

**15-19 JUNE 1964**

**Washington, D.C.**

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**REPORT OF THE  
PAHO SCIENTIFIC GROUP ON RESEARCH  
IN PROTEIN-CALORIE MALNUTRITION**

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

WASHINGTON, D.C.

PAHO SCIENTIFIC GROUP ON RESEARCH  
IN PROTEIN-CALORIE MALNUTRITION

Instituto Nacional de Nutrición  
Bogotá, Colombia

16-20 March 1964

Dr. Cecilio ABELA-DEHEZA\*  
Departamento Nacional de Nutrición  
La Paz, Bolivia

Dr. Guillermo ARROYAVE  
Instituto de Nutrición de Centro  
América y Panamá (INCAP)  
Guatemala City, Guatemala

Dr. G. BARRERA-MONCADA\*  
Departamento de Pediatría  
Universidad Central de Venezuela  
Caracas, Venezuela

Dr. M. A. BAYAS-VALLE\*  
Instituto Nacional de Nutrición  
Quito, Ecuador

Dr. Nelson CHAVES\*\*  
Instituto de Nutrição  
Universidade do Recife  
Recife, Brazil

Dr. Joaquín CRAVIOTO  
Instituto de Nutrición de Centro  
América y Panamá (INCAP)  
Guatemala City, Guatemala

Dr. William J. DARBY  
Division of Nutrition  
Vanderbilt University  
Nashville, U.S.A.

Dr. J.E. DUTRA de OLIVEIRA  
Departamento de Clínica Médica  
Faculdade de Medicina de Ribeirão  
Preto  
Universidade de São Paulo  
Ribeirão Preto, S.P., Brazil

Dr. John S. GARROW  
Tropical Metabolism Research Unit  
University College of the West Indies  
Kingston, Jamaica

Dr. George G. GRAHAM  
Clínica Anglo Americana  
Lima, Perú

Dr. Julio MENECHHELLO  
Departamento de Pediatría  
Universidad de Chile  
Santiago, Chile

Dr. Rafael RAMOS-GALVAN  
Departamento de Nutrición  
Hospital Infantil de México  
México, D.F., México

Dr. R. RUEDA-WILLIAMSON (Chairman)  
Instituto Nacional de Nutrición  
Bogotá, Colombia

Dr. W.H. SEBRELL, Jr.  
Institute of Nutrition Sciences  
Columbia University  
New York, U.S.A.

Dr. Leonardo SINISTERRA  
Departamento de Nutrición  
Facultad de Medicina  
Universidad del Valle  
Cali, Colombia

(Continued on the  
next page)

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\* Rapporteur

\*\* Unable to attend

Participants from International Organizations  
and Foundations

Dr. Ivan D. BEGHIN\*  
Nutrition Advisor  
Pan American Health Organization  
Port-au-Prince, Haiti

Dr. E.M. DeMAEYER\*  
Protein Advisory Group  
WHO/FAO/UNICEF  
United Nations  
New York, U.S.A.

Dr. M. EISLER  
Nutrition Advisor  
Pan American Health Organization  
Bogotá, Colombia

Dr. K. S. RAO  
Nutrition Advisor  
Pan American Health Organization  
Rio de Janeiro, Brazil

Dr. Sam C. SMITH  
Williams Waterman Fund for the Combat  
of Dietary Diseases  
405 Lexington Avenue  
New York City, U.S.A.

Dr. Lester J. TEPLY  
Applied Nutrition  
United Nations Children's Fund (UNICEF)  
United Nations  
New York, U.S.A.

Dr. Fernando VITERI\*  
Instituto de Nutrición de Centro  
América y Panamá  
Guatemala City, Guatemala

Dr. Alfred YANKAUER  
Health Promotion Branch  
Pan American Health Organization  
Washington, D.C., U.S.A.

SECRETARIAT

Dr. J.J. KEVANY  
Health Promotion Branch

Pan American Health Organization  
Washington, D.C., U.S.A.

Dr. M. MARTINS da SILVA  
Office of Research Coordination

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\* Rapporteur

PAHO SCIENTIFIC GROUP ON RESEARCH  
IN PROTEIN-CALORIE MALNUTRITION

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PAHO SCIENTIFIC GROUP ON  
RESEARCH IN PROTEIN-CALORIE MALNUTRITION

Instituto Nacional de Nutrición  
Bogotá, Colombia

16-20 March 1964

A g e n d a

Monday, 16 March

Welcome by the Director, Instituto Nacional de Nutrición -  
Dr. R. Rueda-Williamson

Opening of the Meeting - Dr. M. Martins da Silva

Purpose of the Meeting - Drs. J.J. Kevany and W.H. Sebrell, Jr.

Review of Present Knowledge on Protein-Calorie Malnutrition -  
Dr. E.M. DeMaeyer

Discussion

Report of Current Research Activity and Discussion

|                                 |                                    |
|---------------------------------|------------------------------------|
| Dr. Abela-Deheza (Bolivia)      | Dr. Meneghello (Chile)             |
| Dr. Barrera-Moncada (Venezuela) | Dr. Ramos-Galván (Mexico)          |
| Dr. Bayas-Valle (Ecuador)       | Dr. Sebrell (U.S.A.)               |
| Dr. Dutra de Oliveira (Brazil)  | Dr. Sinisterra (Colombia)          |
| Dr. Garrow (Jamaica)            | Dr. Viteri (Central America-INCAP) |
| Dr. Graham (Peru)               |                                    |

PAHO - Drs. Kevany and Martins da Silva

PAG (WHO/FAO/UNICEF) - Dr. DeMaeyer

UNICEF - Dr. Teply

Tuesday, 17 March

Report of Current Research Activity (Cont'd)

Discussion

Tuesday, 17 March (Cont'd)

Clinical Picture of Protein-Calorie Malnutrition -  
Dr. Julio Meneghello

Discussion opened by Dr. Miguel A. Bayas-Valle

Methodology of Feeding Trials - Dr. Leonardo Sinisterra

Discussion opened by Dr. K.S. Rao

Wednesday, 18 March

Biochemical Changes in Protein-Calorie Malnutrition -  
Dr. Guillermo Arroyave

Discussion opened by Dr. John Garrow

Physical Growth and Development in Protein-Calorie Malnutrition -  
Dr. R. Ramos-Galván

Discussion opened by Dr. C. Abela-Deheza

Thursday, 19 March

Mental Development in Protein-Calorie Malnutrition -  
Dr. Joaquín Cravioto

Discussion opened by Dr. G. Barrera-Moncada

Anemias in Protein-Calorie Malnutrition - Dr. William J. Darby

Discussion opened by Dr. F. Viteri

Treatment of Protein-Calorie Malnutrition - Dr. G.G. Graham

Discussion opened by Dr. J.E. Dutra de Oliveira

Friday, 20 March

Presentation and adoption of report

Adjournment

Report of the  
PAHO Scientific Group on  
Research in Protein-Calorie Malnutrition

16-20 March 1964  
Bogotá, Colombia

REPORT OF THE PAHO SCIENTIFIC GROUP ON  
RESEARCH IN PROTEIN-CALORIE MALNUTRITION\*

Protein-calorie malnutrition represents one of the greatest public health problems in this Hemisphere. The Pan American Health Organization Nutrition Advisory Group, which met in Washington, D.C., in January 1962, assigned to this nutritional disease the highest priority for action. Studies on protein-calorie malnutrition, particularly as it affects infants and young children, were deemed to be of the utmost importance by the PAHO Advisory Committee on Medical Research at its June 1962 meeting.

In the past two decades a considerable amount of important research has been carried out in the Americas to define the characteristics of this disease and to seek effective methods for its prevention and cure.

In order to provide a continuing stimulus for these studies, the Pan American Health Organization, under a grant from the Williams-Waterman Fund for the Combat of Dietary Diseases, convened a Scientific Group on Research in Protein-Calorie Malnutrition in Bogota, Colombia, 16-20 March 1964. The Group limited itself to clinical, biochemical and therapeutic considerations of the disease, and to its effect on physical and mental development. Investigators from eleven countries of the Americas participated (see list of participants, page 1). The National Institute of Nutrition of Colombia was host. The meeting was opened by Dr. M. Martins da Silva who outlined the research program of PAHO. Dr. R. Rueda-Williamson was elected Chairman.

Review of Present Knowledge on Protein-Calorie Malnutrition

A comprehensive review of knowledge on protein-calorie malnutrition was published in 1960 by Waterlow, Cravioto and Stephens. The present review deals

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\*Prepared for the Third Meeting of the PAHO Advisory Committee on Medical Research, 15-19 June 1964, by the Drafting Committee (Drs. W.J. Darby, K.S. Rao, R. Rueda-Williamson, J.J. Kevany and W. H. Sebrell) from summaries of the sessions submitted by the Rapporteurs.



mainly with progress made since that date. Although the disease is of great public health importance, very few data concerning its prevalence are available. The literature has recently been reviewed and it is obvious that more information is desirable. The same etiologic factors, which include inadequate food supply, poverty, lack of education and poor sanitation, are found in each developing country. The frequent association between protein-calorie malnutrition and avitaminosis A has been observed in many areas of the world. Studies on mental retardation in relation to protein-calorie malnutrition have shown that language development is the most retarded and motor response the least retarded; as recovery takes place the difference between the chronological and mental ages compared on the basis of psychological behavior diminishes in all except the youngest children. Megaloblastic anemias have been reported in India, Africa, Latin America and other parts of the world. However, the mechanism of the production of anemia in protein-calorie malnutrition is not yet clearly understood and deserves more attention.

Much recent research in protein-calorie malnutrition deals with changes in free aminoacids in plasma, urine and muscle. In the plasma there is a reduction of free essential aminoacids with the exception of lysine. The branched amino acids, leucine, isoleucine, and valine, are especially affected. In the acute phase of the disease, before treatment, there is an increased urinary excretion of taurine and beta-amino-isobutyric acid. After initiation of treatment there is a general hyperaminoaciduria which recedes after 10 to 15 days. In muscle the amino acids are generally decreased with the exception of lysine and taurine; the latter may reach high levels. There is also evidence of impaired metabolism of histidine, phenylalanine and tyrosine. Mental changes observed may possibly be related to these biochemical changes.

Total body water is increased, the extracellular space being most affected. There is also a decrease in intracellular potassium, inorganic phosphorus and possibly magnesium.

Endocrinological changes occur as indicated by urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids. The metabolism of aldosterone in relation to water and sodium retention has been investigated, but no clear causal relationship has been established.

The guidelines for treatment are generally agreed upon and include the following: prevention or treatment of infections and correction of water balance are most important during the first days; simultaneous dietary treatment to provide an ample supply of calories and protein of good quality should be initiated. Around 3.5 gms. of protein (from milk) and 150 Cal/Kg/day should be attained for most children; milk seems to be the best source of protein in the acute phase of treatment. Supplementation with potassium is important.

#### Clinical Picture

The clinical picture of the disease, whose onset is usually at weaning, has been often described. Height and weight are below expected norms for age and a disharmony in the various parameters of body growth is observed. This is manifested by alterations in somatometric indices such as the ratio between the superior and inferior segments of the skeleton and the cranioccephalic ratio, which resemble those of younger children. Psychic changes appear as apathy alternating with irritability. Anorexia and diarrhea are frequently seen. Many patients also harbor infections which generally respond to antibiotics. Dermatologic manifestations include pigmentation, desquamation, exudative lesions and keratosis of varying degrees. At times pellagra-like lesions are seen. Petechiae are rare and of serious import. Intertrigo is frequent. There

may be loss of hair and hair luster and changes in hair color. The extremities are often cold and cyanotic. The cheeks are typically rounded. The conjunctiva are often injected and dry and in many cases the conjunctival keratinization test is positive; keratomalacia is seen more rarely. Cheilosis and papular atrophy of the buccal mucosa are not uncommon. Edema, when it is clinically manifest, is most common in the lower limbs and peripherally in the extremities with occasional severe manifestations of anasarca. Edema may coexist with dehydration, especially in severe cases. There may be hepatomegaly and abdominal distension, the latter produced by hypotonicity of the intestinal and abdominal wall.

#### Discussion

The initial discussion pertained to the definition of the term protein-calorie malnutrition. In some countries, differences in the incidence and mortality rates and in the clinical symptomatology warrant the keeping of a distinction between marasmus and the kwashiorkor-type malnutrition. It appears that both are manifestations of protein-calorie deficiency. The differences, however, are sometimes associated with several variables including different ages of onset. The distinction between kwashiorkor and marasmus is useful for clinical and research purposes but from the public health point of view a unified concept covering the whole symptomatology that the disease may take should be preserved. A useful classification of signs for reporting primary undernutrition was suggested. (See Appendix, page 37).

Emphasis was put on the value of somatometric measurements, on the interest in looking after associated clinical signs, as well as in knowing the dietary history of the child in order to establish a correct diagnosis. The value of a clinical or biometrical sign, however, is not absolute but should be assessed in relation to the objective sought: clinical diagnosis, prognosis, or assessment of nutritional status at the community level. The distinction between mild and

severe forms is, from a practical standpoint, extremely important. The classification of Gómez is also a useful index for determining the prevalence of protein-calorie malnutrition. It is not advisable to rely only on clinical signs and, when available, full use should be made of biochemical techniques in the diagnosis. Further investigation is needed on the pathology of protein-calorie malnutrition to bring more light on the differentiation of the various forms.

### Anemia

Anemia is generally described as a component of the syndrome of kwashiorkor. Despite considerable variation in morphology of the peripheral blood, a hypochromic, macrocytic picture predominates with a biphasic or sometimes triphasic Price-Jones curve. The proportion of normocytic and microcytic anemias varies from location to location.

The spectrum of the bone marrow picture ranges from megaloblastic dysplasia of varying degrees, similar to the bone marrow in fully relapsed pernicious anemia, through intermediate changes of megaloblastic nature, to a normoblastic picture. An erythroid hypoplasia has been described. None of the reports contain sufficient biochemical data and well correlated peripheral and marrow hematology to permit definitive correlations of these several findings,

Reports attribute the response of anemia in protein-calorie malnutrition to the administration of iron, folic acid, vitamin B<sub>12</sub>, protein, riboflavin, tocopherols, coenzyme Q<sub>4</sub>-chromanol, or an adequate diet. Conversely failure of each of these agents to induce a hematologic remission has been observed.

In this severe nutritional syndrome it is not logical to expect the identification of a single type of anemia or of a single effecting agent which will be specific for all instances of anemia. The children with these

syndromes are at an age of great potential growth, and nutrient stores are being subjected to the depleting effects of diarrhea and/or febrile illness or have been depleted through semistarvation. The demonstrable deficits encountered include those of calories, protein, and amino acids, fat, vitamin A, carotene, tocopherols, iron, riboflavin, zinc, copper, potassium, and other electrolytes, water, sometimes folic acid, vitamin B<sub>12</sub>, calcium and pyridoxine.

Infection frequently is present and antibiotics are often employed. Rigidly restricted dietary control excluding all but a single potential hematologic factor is not possible during therapeutic studies. None of the reports include adequate information on the content of diets during development of the syndrome in those fed during the test periods to permit evaluation of the role of the known hemopoietic factors which often are interrelated in metabolism.

Interpretation of therapeutic responses should be made with full understanding of the possible influence of these complex factors. Reliance should be placed on associated biochemical observations of nutrition with respect to the particular nutrient and other relevant nutrients and of metabolic alterations induced by the administered factor. Cognizance should be taken of the influence of parasitism, hepatic damage, infection, etc.

The object of study should be the child who is malnourished and has anemia, not the anemia of the protein-calorie malnutrition syndrome. In such study it must be recognized that anemias in this complex developmental stage are vastly different from the relatively simple anemias which are encountered in adults. Hematologic parameters likewise are different, for example, the frequency with which macrocytosis and hypochromia are encountered.

### Discussion

The occurrence of macrocytic indices in anemia associated with protein-calorie malnutrition was discussed, as was the variable nature of response to

therapy. It was agreed that any of several nutritional anemias may be encountered in severe protein-calorie malnutrition. These same anemias are also seen in ambulatory children of the same age group and, therefore, are not limited in occurrence to the severe protein-calorie malnutrition syndrome. The usual hematopoietic nutrients (iron, folic acid, vitamin B<sub>12</sub>) or even good diet do not always lead to full recovery from the anemia. Recent observations in Peru indicate that copper may evoke a rapid hemopoiesis in some instances of anemia associated with neutropenia. The role of copper deserves further study. The same is true of vitamin E.

Individuals with protein-calorie malnutrition and anemia show wide variations in serum iron, copper, vitamin B<sub>12</sub>, total iron binding capacity and its degree of saturation. There is almost no information on serum folic acid concentration in these anemias. Systematic studies of these biochemical levels coupled with biochemical functional tests, bone marrow examination, including stainable iron, peripheral hematology and critically executed therapeutic observation should allow separation of this mixture of anemias which now are not adequately differentiated for diagnosis or therapy.

The current WHO world-wide program on anemias was noted including the meeting of the Scientific Group on Research in Nutritional Anemias sponsored by WHO in Caracas, Venezuela, in 1963.

#### Biochemical Changes

The clinical picture of protein-calorie malnutrition in children with marasmus and kwashiorkor at the two extremes and with a range of intermediate forms was described. The most important biochemical and physiological features common to both marasmus and kwashiorkor, and those which characterize either of them, were reviewed.

A consistent characteristic of protein-calorie malnutrition is the disturbance in water and electrolyte metabolism. An increase in total body water is always found. The presence of clinical edema in kwashiorkor is a distinguishing sign. Its absence in marasmus, however, does not mean that total body water is not higher than normal.

There is a marked reduction in total body potassium and a retention of sodium. Partial replacement of intracellular potassium by sodium has been demonstrated and is considered a critical metabolic derangement affecting important enzymatic systems which normally depend on potassium.

Although definitive conclusions cannot be reached, the probability was discussed that various factors may be responsible for these disturbances, among which hypoalbuminemia, endocrine dysfunction, and circulatory failure might be mentioned.

A magnesium deficit following the pattern of potassium depletion has been described which may have wide physiological and biochemical implications with regard to enzyme function.

Studies on carbohydrate metabolism, in particular, suggest alterations in cellular energy levels. Evidence for defective oxidative phosphorylation is also available.

Abnormal lipid blood transport has been found, but whether this alteration is characteristic of kwashiorkor or whether it also occurs in "pure" marasmus cannot be established with certainty. Extremely low levels of vitamin A are found and are likely to be explained by the lipid transport abnormalities mentioned. Alterations in lipid synthesis and catabolism are beginning to be documented. Preliminary studies suggest a deficiency of essential fatty acids, but the evidence is very scanty.

Thorough studies on protein metabolism indicate an extreme depletion which reaches different degrees in different organs and tissues. Those tissues with faster protein turnover are the most affected. The concentration of protein moieties which play very important metabolic functions is disturbed. Among them are many enzymes, as well as some electrophoretic blood plasma proteins, such as albumin, beta-globulin, transferrin, ceruloplasmin and beta-lipoprotein. From investigations on plasma albumin turnover rate, it seems that the general phenomenon may be one of reduced anabolism and catabolism with the decrease in anabolic rate being quantitatively larger. The significance of these findings in connection with the abnormalities of other aspects of metabolism was emphasized.

Evidence of marked alterations in protein metabolism is also derived from the extremely decreased plasma free amino acids. These decreases are not harmonious, the branched essential amino acids and tyrosine being, in general, the most affected. The concentration of urea in plasma and its excretion in urine are low. Impairment in the metabolism of individual amino acids is indicated by studies on histidine and phenylalanine.

Low blood levels of vitamins are found; but the metabolic demand for these substances may be so reduced under the conditions of an overall decreased metabolism, that clinical signs of deficiency may not appear. The same seems to be true for iron and copper.

A possible fundamental difference between marasmus and kwashiorkor was discussed. The biochemical picture of marasmus suggests that the child affected with this condition catabolizes muscle proteins, a process which results in an increase in free amino acid supply to the liver and other vital organs thus preserving their protein-anabolic functions. In kwashiorkor this shift of nitrogen does not seem to be operating, and consequently, without



either endogenous amino acids from muscle catabolism or exogenous ones from the diet, the vital organs, including the liver, suffer from an acute and drastic protein deficiency.

In adults, protein-calorie malnutrition is associated specially with calorie deficiency. The condition may show biochemical characteristics similar to those found in kwashiorkor and marasmus in children.

### Discussion

The discussion centered around two aspects: a) biochemical research as applied to the mildly undernourished child, and b) biochemical problems of the severely malnourished child.

For the investigation of the mildly undernourished child it would be useful to have biochemical tests of nutrient intake and body composition. It was suggested that the basal excretion of urea, or the urea/creatinine ratio under fasting conditions, are useful tests for the evaluation of protein nutriture. For muscle mass, the creatinine excretion per unit time per centimeter height may be a useful index. Other biochemical measurements of protein nutriture such as serum albumin or pseudocholinesterase are rather insensitive. It was suggested that the partition of nitrogen in the urine, or the time required to produce changes in water or lipid content of the blood might be more useful tests. It was agreed that an attempt should be made to explore new metabolic load tests as indicators of biochemical function.

In the severely malnourished child, it was agreed that it was very important to find a method for measuring body composition in these children and that it would probably be necessary to do whole body chemical analysis in some cases. Nitrogen balance is not a satisfactory test for protein depletion since it may only reflect recent intake. There is similar disadvantage in using the response to a sodium load.

Some discussion was devoted to the question of the mechanism governing the rate of growth. The effects of malnutrition on the endocrine system were discussed as were the histological changes found in the pancreas, thyroid and the pituitary gland.

#### Physical Growth and Development

A detailed review of the effect of undernutrition on the growth of a large series of Mexican children was presented. It was pointed out that there are four different types of tissue growth (general, neural, lymphatic, genital) and that the effect of malnutrition depends upon the age of the child and upon the duration of the undernutrition.

In the assessment of growth the following should be measured: 1) weight and height; 2) cephalic, thoracic, arm and leg circumferences; 3) biacromial and bicristal diameters; 4) sitting height (for lower and upper segments); 5) skinfolds of the arm, scapula, and thorax; and 6) antero-posterior X-ray films of the hand and of the wrist.

The measurements which are affected by undernutrition depend on the stage of development of the child. During the first or intrauterine stage no measurements can be made. During infancy, the parameter most deeply affected by protein-calorie malnutrition is weight, followed by thoracic circumference and lastly by height and cephalic circumference. No correlation was noted between cephalic circumference and the behavior or intelligence of these children.

In school age children the best index of nutrition is weight and height compared to that of normal children. In the series presented it appeared that, at five years of age the girls had suffered more from malnutrition than boys. It

was useful to measure the annual increments in the circumference of the leg, arm and thorax as well as the increments in weight and height. During the period from 4 to 12 years the parameter which was most markedly reduced by undernutrition in both boys and girls was the arm circumference. The most useful measurements to make at each age for either sex were also discussed.

The age of the menarche was delayed by undernutrition with a resulting modification in the body build of the adolescents.

### Discussion

It was agreed that measurements of weight and height are the most reliable signs of nutritional status.

Other clinical signs such as dyspigmentation of the hair and dryness of the skin can be quite misleading. It was also agreed that it would be most useful to have a common standard against which heights and weights could be compared. In the collection of data for the construction of standard curves, consideration was given to the methods by which healthy children could be sampled. Since in most children suffering from protein-calorie malnutrition there is a period of arrested growth, it is important to know both the consequences of this phenomenon, and whether the damage, once done, is completely reversible. Failure to grow might be due to deficiency of nutrients other than protein and calories and \_\_\_\_\_ deficiency of trace elements and vitamins might also cause stunting of growth.

The use of somatometric measurements was discussed in relation to nutritional status. This can serve three research purposes:

1. It can lead to a better understanding of how nutrition affects the growth process and how the growth process affects nutrition.

2. It can lead to a better understanding of how nutrition affects the incidence, severity and outcome of disease caused by other agents, and how disease affects human nutrition.

3. It can help define nutritional status of the community and plan, execute, and evaluate community health programs.

For the first two aims, the somatometric definition of malnutrition in relation to an arbitrary common standard is often unnecessary and undesirable since patients may be grouped and analyzed in accordance with the data assembled for studies and/or compared with themselves over a period of time. In some cases, reference to a fixed standard may be helpful in analysis, the most useful references being weight and height for age and weight for height.

The third purpose involves community surveys, case finding and preventive and treatment activities. It necessitates a definition of malnutrition based on a somatometric standard. Percentage deviation from fixed reference standards of weight for age as well as growth charts of weight for age are the simplest methods available.

#### Mental Development

In areas where protein-calorie malnutrition is prevalent, preliminary attempts have been made to determine whether the degree of malnutrition sufficient to retard somatic growth and biochemical maturation is also sufficient to produce transient or permanent retardation of mental development. Well-designed, long-term longitudinal field studies should continue these explorations.

The Gesell technique and the André Thomas method have been applied to children from birth to three years in Guatemala, Mexico and Africa. Results show that though their scores of psychomotor development are usually higher at birth than those of their European counterparts and though they seem to grow well during the first months of life, there is soon a decline in the expected weight and height increments; by the 18th to 24th month, when they are weaned, height is lower than in the Europeans. Semilongitudinal studies in which undernourished and well nourished children of low economic groups were matched on the basis of age and sex showed that the mean I.Q. of the undernourished group was well below that of the better-nourished with a mean difference of 22.62 points, which is statistically significant at the 1% level.

Adapted Terman-Merrill tests applied to preschool age children showed that intelligence scores correlated negatively with chronological age; the older the child, the greater his chance of showing a poorer performance relative to his age. In younger children tested with the Gesell technique, weights and heights were found to be positively correlated with intelligence scores. Figures from the standardized Goodenough-Draw-A-Man-Test in school-age children suggest that as weight deficit for age increased, mental performance decreased. In severe protein-calorie malnutrition, children show a marked developmental retardation in language, personal-social and psychomotor development.

In the rehabilitation period of children with severe protein-calorie malnutrition, psychological behavior was explored after correction of any acute infectious and/or electrolytic disturbance and repeatedly at regular intervals during hospitalization. Apparently, rate of recovery of initial deficit

varied in direct relation to chronological age at admission. In children under 6 months of age, a probable loss in intellectual potential was found.

Studies in adult malnutrition suggest that the impact of malnutrition on intellectual capacity is less marked than in children, more transitory or even non-existent.

In conclusion, there is a high probability that at least, the children severely malnourished during the first semester of life will retain permanent mental deficits. These findings demand confirmation, especially if one considers that in certain areas malnourished children constitute a significant segment of the future population.

#### Discussion

It was pointed out that the majority of children suffering from protein-calorie malnutrition do not die. As a consequence the need to establish the degree and permanence of the mental changes observed in the course of the disease assumes great importance.

Studies on children recovering from protein-calorie malnutrition as well as on children from poor and isolated rural areas indicate a retardation in growth. Severe protein-calorie malnutrition in children produces, in addition to retarded growth, psychic changes which appear very early. The question of whether this degree of retardation in somatic growth and in biochemical maturation is accompanied by a transitory or permanent retardation of mental development requires longitudinal field studies.

Studies in early childhood have shown that newborn children from several pre-industrial areas have high scores of psychomotor development. These scores later show a stationary phase which corresponds to the arrest

of somatic growth when nutrition is severely affected. Body weight and height for age correlate with intelligence curves in preschool children. There is a greater proportion of low scorers among underweight children than among children of normal weight.

The psychological changes in severe protein-calorie malnutrition involve marked retardation in language, personal-social and psychomotor behavior. It was stated that children who suffer from severe protein-calorie malnutrition for a longer period of time show greater retardation, and that the potential for psychological development may be permanently affected when that child is younger than six months of age. There appears to be a positive correlation between the educational level and intelligence of the parents and the psychological development of the child. The possible influences of child care, malnutrition and infection and the probable mechanisms by which they affect psychological development were briefly presented. Data recently collected in Mexican schools suggest that moderate protein-calorie malnutrition has little influence on mental development and produces no mental retardation in older children.

In the discussion it was brought out that in comparing psychological performance between different groups of children, careful attention should be paid to the composition of the samples with reference to age and with reference to social, intellectual and cultural environment. Evidence was presented that Mexican school age children of different nutritional status (normal versus second degree malnutrition) but of the same socio-economic level and intellectual background performed equally well on tests. Data were presented indicating that in adolescence there is no difference between the overall intelligence test results of well-nourished and second degree malnourished children but the inventive capacity of the latter is somewhat less than that of the former.

As part of the discussion a motion picture\* was shown illustrating four steps in the psychic rehabilitation of children with severe protein-calorie malnutrition: extreme apathy, passive receptivity, active receptivity and frank recovery. In the series of cases presented none of the children had attained psychological normality two years after hospital discharge. Language and social behavior were more affected than intellectual capacity.

A number of other points were touched upon in the discussion, considerable stress being placed on the possible role played by emotional deprivation and the family environment of the severely malnourished child as factors influencing his psychological development. Possible prior brain damage and the contribution of associated nutrient deficiencies to the picture were also mentioned. It was pointed out that growth retardation associated with malnutrition is seen in children with fibrocystic disease of the pancreas without accompanying mental changes. It was suggested that the inmates of mental institutions could be studied with profit.

The importance of conducting simultaneously psychological, neuro-biochemical and neurophysiological studies in an effort to clarify the mechanisms of the mental alterations in nutritional disease was also discussed.

The group agreed that the area under discussion was an important field for future investigation. It felt, however, that new psychological and psychometric techniques should be explored. Furthermore, the role of emotional deprivation must be clarified and studies to do so undertaken. The application of field epidemiological techniques was recommended. Testing techniques should be carefully standardized and their results interpreted with caution.

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\*" El Psiquismo en el Kwashiorkor", by Dr. G. Barrera-Moncada, 16 mm color sound movie, Spanish language, 17 minutes. Ministerio de Sanidad y Asistencia Social, Caracas, Venezuela.



### Treatment

In all forms of severe malnutrition, prompt recognition of inapparent infection is of life-saving importance. Blood cultures, clean urinalyses, chest X-rays and differential white blood cell counts routinely on admission are useful in diagnosis. Where adequate facilities are not available, the routine use of penicillin and sulfonamides is probably justified; otherwise antibiotics in full dosage, preferably by the intravenous route, should be used promptly at the first indication. Petechiae, jaundice and the presence of many immature neutrophils on the blood smear are usually due to septicemia. The chest X-ray can detect the presence of unsuspected pneumonia or tuberculosis. Routine daily bathing of all patients with a detergent containing 3% hexachlorophene helps prevent or clear up skin infections. Advantage should be taken of convalescence to immunize children against diphtheria, pertussis, tetanus, smallpox, measles and poliomyelitis.

Hypovolemic shock and acidosis should be treated with sodium-containing intravenous fluids, even in the presence of edema. It may be necessary to initiate the treatment of hypokalemia even before urine flow is established. The intravenous route, with close observation for signs of hyperkalemia, is more advisable than the oral one during the initial stages; subsequently, supplemental potassium should be given orally for about 10 days, 5 mEq/kg of body weight daily.

Hypoalbuminemia and edema are best treated by the early administration of milk, occasionally by stomach tube. Only rarely is milk not retained, in which case intravenous plasma might be used. Blood is reserved for life-threatening anemia only. Excessive protein and electrolyte intakes can lead to excessive diuresis and dehydration, and possibly to hyperammonemia and hypoglycemia.

Intakes of milk protein of 2-3 gm/kg/day are quite adequate to produce nitrogen retention and regeneration of serum albumin, independent of caloric intake, in patients with low serum protein, with or without edema.

Prolonged or recurrent diarrhea and malabsorption may be due to lactase deficiency, particularly in patients who have not received milk for many months. Shigella and giardia infections have also been encountered, as well as folic acid deficiency. Poor weight gain and inadequate nitrogen retention may be due to recurrent pyelonephritis, otitis media or other infections. In marasmic infants iron deficiency anemia will develop during recovery if iron is not given routinely, 3-5 mg/kg of body weight daily.

Infants and children with kwashiorkor are rarely seen in Peru without underlying marasmus. Their treatment requires a normal caloric intake and only a moderate intake of milk protein. The more severe the underlying malnutrition, as manifested by height and weight deficits, the greater must the caloric intake be, usually 150 and occasionally 175 Cal/kg/day. In the marasmic or in kwashiorkor after it has responded initially to milk, good vegetable proteins or mixtures of wheat and fish proteins may be used at a level of 2 to 3 gm/kg/day. The younger the patient or his "length age", the higher is this requirement. In these patients, particularly when receiving proteins other than those in milk, nitrogen retention is dependent on caloric intake. Excessive weight gain can adversely affect serum albumin levels in these cases.

Relapses are most likely to occur in the youngest cases, who are nearly impossible to maintain in good health and growing normally without a good intake of milk at home. In other cases, simple education of the mother, with instructions compatible with her means, has been of great value in continuing satisfactory progress after discharge.

Discussion

The administration of good quality protein and sufficient calories was stressed as fundamental in the dietary treatment of "kwashiorkor." There is no advantage to using excessive amounts of protein. In the case of marasmus, the initial dietary treatment is the same, but caloric intake must be increased after a short time with the nutritional requirements for recovery being more related to height than to weight. The administration of high levels of protein and solutes can induce dehydration through osmotic diuresis. The discussion identified various levels of protein intake which are effective in treatment of protein-calorie malnutrition. This ranges from 2.0-3.5 gm/kg/day of protein, in association with a caloric intake of 100-150 cal/kg/day.

Primary attention should be placed first of all in the restoration of water and electrolyte balance and to the energetic and prompt treatment of infections. The rapid but careful correction of the potassium deficit as well as the treatment of shock, when present, is best accomplished by the administration of intravenous solutions. Blood transfusion should be restricted to cases in which severe anemia endangers life. An oral administration of potassium should be started after the initial phase of intravenous therapy.

Comparisons have been made between the effectiveness of several protein sources for treatment. Compared with milk, vegetable proteins produce excellent weight gain and good nitrogen retention, but result in lower plasma albumin levels.

After the initial high retention of nitrogen characteristic of patients with hypoalbumenia, weight gain and nitrogen retention depend on the satisfaction of the caloric requirement. The advisability of a varied diet after initial recovery was stressed.

Infections of all types should be prevented at all cost because of their adverse effect on nutritional recovery. When established these can be difficult to recognize; all possible facilities for good pediatric care should be used in establishing the presence and the type of infection.

Where facilities are not optimal for diagnosis and treatment of infections, it is probably wise to use penicillin and sulfonamides routinely during the initial phases of hospitalization. Advantage should be taken of the hospital stay to immunize the child against the common infectious diseases, and to educate the mother on feeding practices within her means.

### Methodology of Feeding Trials

Feeding trials can be divided into two types: animal and human.

Animal feeding trials study the biological characteristics of a diet or a specific component of a diet. Under biological characteristics one considers digestibility, degree of absorption, and biological parameters as protein efficiency in growth promotion.

The second type of feeding trials involves the human. This latter type can, in turn, be divided into two sub-types. a) The first sub-type does not differ essentially from the animal experiments and consists of feeding trials in hospitalized patients (generally children). The object of these studies is to check the biological impact as to change in the state of health of the child when maintained on a specific diet. b) The second, human feeding trials in volunteers, can be either in children or adults. The criticisms and opinions of the subject are desired; in particular, information as to the taste, consistency, ease of preparation and the reasonableness of its cost. In short, one is testing the market, although on occasions, some critical scientific investigations have been made.

Few feeding trials of consequence have been carried out in which the eating habits of a population have been altered to adopt new dietary practices in breast-fed infants, pre-schoolers, pregnant and lactating mothers and the aged.

The main problems encountered in feeding trials can be divided arbitrarily into intrinsic and extrinsic groups.

Those internal problems facing a scientific group as they develop their project are classified as being intrinsic. Frequently, the competition of commercial enterprises has produced many problems and misunderstandings on the part of the community. At the scientific level, the origin of the failure has

most frequently been the incapacity of the members of the scientific team to understand that the primitive populations have a very limited capacity to assimilate new knowledge.

Extrinsic problems are those arising outside of the scientific group and which originate in the community. They are associated with multiple factors (social, inherited, ecological, etc.) which resist change in feeding habits.

Experience has taught the underprivileged that foods that we call protective such as milk, aside from being expensive, is often dangerous to one's health, producing diarrhea, gastroenteritis, and even death. They, consequently, hesitate to give milk to their children. The unhygienic handling of milk has made it a food which people fear rather than desire.

#### Discussion

Human feeding trials were considered to constitute an essential link in the introduction of new foods to meet existing and potential undernutrition in the community.

Such new foods should be based on raw materials which are readily available locally at a low cost. They should be introduced only after thorough laboratory study of their biological value and testing to insure freedom from toxic substances, both chemical and bacteriological.

Once such a formula is made available, three types of feeding trials are desirable:

1. Metabolic studies in apparently healthy individuals to determine biological effectiveness.
2. Carefully controlled metabolic studies on properly selected cases of undernutrition to determine its therapeutic effectiveness.
3. Field feeding trials to test the acceptability and tolerance of the product, on free distribution as well as on sale basis (marketing tests).

Each of these trials have thus a definite role to play in answering specific questions. Only then can the product be considered ready for general use.

The methodology for these studies covering the type and size of the sample, the actual techniques to be applied, and other precautions to be taken are well described in documents prepared by the Protein Advisory Group.

It was noted, furthermore, that feeding trials in the field have a definite demonstrational and educational value. They are useful in establishing the value of the food product in the improvement or maintenance of the health of the recipient and, in the long run, in bettering the food habits of the population. It is felt, however, that fuller advantage should be taken of feeding trials to establish the true value of the product and to help introduce the same in needy communities.

### RECOMMENDATIONS

1. The object of research attention should be the child who is malnourished and not the protein-calorie malnutrition syndrome per se.

2. A manual of methods and procedures should be developed and published in Spanish and English outlining and describing techniques for obtaining the most useful and practical somatometric measurements including height and weight and for recording observations on sexual maturation. It should specify the method of assembling and analyzing data for presentation.

3. Reference standards for interpretation of weight-height-age data should be developed by a specially convened group of experts familiar with the existing reference standards and the nature of the data upon which these rest. Such standards may not serve as definitions of normality but rather as useful tools for making comparisons among groups.

4. A meeting of active investigators and appropriate specialists from relevant disciplines such as epidemiology, psychology, psychiatry, sociology and statistics should be convened to discuss the design and techniques for study of mental and psychological development of the child in relation to nutrition, psychological stress, and emotional deprivation and to recommend methods for coordinated cross-cultural studies.

5. Investigators should precisely define in published reports the syndromes named, such as "marasmus" or "kwashiorkor", in terms of the clinical, somatometric and biochemical findings.

6. Other major areas of research should be:

- a) The further development of methods for detecting incipient or latent protein deficiency;
- b) The elucidation of the anemias of grossly malnourished infants;



- c) The pathology of malnutrition;
- d) A search for other nutrients which may be deficient in the grossly malnourished child such as vitamin A, B<sub>12</sub>, folic acid, and thiamine, as well as studies of the role and importance of nutrients such as copper, zinc, iron, magnesium, and tocopherol which recently have been found to be low in protein-calorie malnutrition;
- e) Long term follow-up studies on recovered cases of severe protein-calorie malnutrition.

7. Prior to the introduction of foods for infants and children, laboratory and clinical studies should be carried out to determine their nutritive value, usefulness, safety, and acceptance; appropriate quality controls should be established.

APPENDICES

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Current Research

The summaries below reflect the statements made by individuals participating in this meeting which in some cases dealt with national programs and activities and in other with the work of a group of research workers.

Dr. C. Abela-Deheza (Bolivia) The Department of Nutrition, attached since 1960 to the Ministry of Public Health, is currently engaged in dietary and nutritional surveys and in gathering data for future investigations. No report on research activity is submitted.

Dr. Gabriel Barrera-Moncada (Venezuela) The malnutrition mortality and morbidity are high in Venezuela. In long-term studies a relationship is found between growth retardation and bone age which does not change after discharge from the hospital. Electromyographic studies show changes in neuromuscular transmission, probably due to retardation in neuromuscular maturation. Mental retardation and apathy are also common findings, which do not improve for a long time following hospital discharge.

Eight hundred centers administered by the Ministry of Health give a supplementary diet based on milk, cereals, minerals, vitamins, and artificial flavor to about 40,000 children all over the country. As a consequence, infant mortality has considerably dropped. This work makes a significant contribution to the extremely difficult problem of reaching successfully the preschool child.

Dr. Miguel Angel Bayas (Ecuador) Collaborative work between the Baca Ortiz Children's Hospital and the National Institute of Nutrition was presented. The majority of the children presenting protein-calorie malnutrition are admitted to the hospital for acute water-electrolyte

disturbances. Electrolyte adjustment in the acute condition is achieved in three to five days. After this, the children are fed a high protein-calorie diet. Edema is frequent in cases over one year of age while the younger cases very often do not show any clinical signs of water retention. All clinical types show hypoproteinemia with hypoalbuminemia, increased levels of plasma mucoproteins and low levels of cholesterol. The death rate remains high especially in the youngest cases without edema. The majority of the deaths occurred during the first 24 hours or at a later stage due to intercurrent infections.

Dr. Nelson Chaves\* (Brazil) Protein-calorie malnutrition is widespread in Brazil, especially in the Northeast. One of the principal causes for this is the exhaustion of the land and consequent lowered fertility with inadequate food production. The Institute of Nutrition of the University of Recife has been carrying out a research program into the problems of the area during recent years.

Studies have been carried out on human growth and development and an early and permanent retardation of growth is observed in children, commencing at 6 to 9 months of age. Birth weights and growth and development up to six months are comparable with patterns in other better nourished populations.

In 1963 a nutrition survey was carried out in Northeast Brazil by the Interdepartmental Committee on Nutrition in National Development (ICNND) of the U.S. Government, the Institute of Nutrition of the University of Recife and the National Food Commission (CNA). The survey covered 5,538 individuals

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\* Unable to attend. Report arrived too late for presentation at the meeting but is presented here in summary form.

examined, of which 963 were infants and children under five years of age.

Conclusions from the analysis of dietary data included the following:

- 1) there is an overall insufficiency of available proteins and calories to cover the dietary requirements of the existing population. There is extreme variability in the intake;
- 2) the pattern of two meals per day - principally of carbohydrates - using the best protein sources for only one of them may not be the most satisfactory eating pattern. A better distribution of protein and improved meal amino acid patterns might be desirable;
- 3) thiamine and riboflavin intakes may be critical in some families;
- 4) iron intake may be insufficient to meet the needs of some segments of the population.

There is considerable interest in studying methods for increasing food production, especially vegetable protein. Chemical and animal studies have been carried out on locally available sources of cheap protein. The majority of these have centered on the macassarbean (*Vigna sinensis*) and the cashew nut (*Anacardium occidentale* L.) in some of these studies abnormalities of ocular development have been observed in animals fed at the 10% level of protein. The most frequent include microcornea, cataract, persistence of the pupillary membrane, lesions of the eyelid and conjunctiva and of Harder's glands. Further studies are being pursued to determine the etiology of these defects.

Dr. J.E. Dutra de Oliveira (Brazil) Three projects are under way in Ribeirão Preto: 1) a nutritional study of a group of children of low-socio-economic status living in Ribeirão Preto; 2) the nutritive value of soy milk versus cow's milk as determined in rats by the protein efficiency ratio technique. The supplementation of soy milk with methionine increases

the protein efficiency ratio to a level similar to that obtained with cow's milk; 3) the nutritive value of soy milk versus cow's milk is measured by nitrogen balance, fat absorption, and plasma albumin regeneration in children recovering from kwashiorkor. The results show that the preparations of soy milk used in the treatment of protein-calorie malnutrition gave results comparable to those obtained with cow's milk.

In Northeastern Brazil, it was found during the Brazil-Inter-departmental Committee on Nutrition in National Development survey that 12% of the children under 5 years of age had albumin levels below 3.5 gms%. Evaluation of the nutritional value of local vegetable protein is being made by animal studies and these may later serve as guides in the prevention of protein-calorie malnutrition in that part of the country.

Dr. J.S. Garrow (Jamaica) The Tropical Metabolism Research Unit established by the Medical Research Council and directed by Dr. J. Waterlow is dealing mainly with severe infantile malnutrition. After delineating the features of protein-calorie malnutrition and analyzing the factors related to a bad prognosis and their interrelationships, the group is now orienting its efforts towards a better understanding of the disturbances in salt and water balance and in protein metabolism. Research on leaf protein is also under way.

Dr. George G. Graham (Peru) The British-American Hospital group mainly studies severe protein-calorie malnutrition with diarrhea, with special reference to practical treatment under primitive conditions. Current research includes studies on protein and calorie requirements in protein-calorie malnutrition; exhaustion of iron and other reserves in marasmus; neutropenia, anemia, and demineralization of bone after prolonged feeding of an exclusive milk diet with dramatic response to copper administration; and protein quality in the recovering child. After measles vaccination nitrogen balance is not

significantly altered but weight gain stops briefly and serum albumin falls 2 to 3 weeks later. Feeding trials are being performed in two of four almost identical communities, with regular and fish-flour enriched noodles, both supplements showing a favorable effect on the growth of pre-school children and adolescents but not in school children.

Research at the Agrarian University is centered on the production of a cottonseed flour with a low gossypol content. Work on the formulation and introduction of a dietary supplement based on cottonseed flour, quinoa, and skimmed milk is being done at the Institute of Nutrition.

Dr. Julio Meneghello (Chile) The work of the pediatrics department in the school of medicine of the University of Chile in Santiago was presented. A majority of the children who are hospitalized for malnutrition are under one year of age and present a clinical picture of marasmus. The sub-cutaneous fat layer has completely disappeared but the plasma proteins and the blood picture are normal or slightly lower than normal. Recovery is slow and the death rate among these children is high. Evidence of considerable changes in the endocrinological balance (adrenal cortex, thyroid, and pituitary gland) was also presented. Serum iron, iron binding capacity, copper and para-phenylene diamine oxidase activity are low, but these low levels may not represent a true deficiency because requirements are decreased by the diminished body growth.

Dr. Rafael Ramos-Galván (México) In the Children's Hospital in Mexico City, the main emphasis is on the clinical approach to the under-nourished child. A comparison of the utilization of powdered whole milk and of a modified commercial formula was made. A persistent neutropenia was observed in young children fed autoclaved milk for a long time. This condition is not related to significant changes in weight gain, and responds

to thiamine administration. The supplementation of the basic diet of the Mexican highlands utilizing diverse legumes is being approached from three aspects: 1) studies in rats (PER, NPU); 2) balance studies in children during weaning; and 3) long term studies in preschool children.

Other studies include testing of gluten-free wheat flour in malabsorption syndrome and chromatography of plasma fatty acids in protein-calorie malnutrition.

Dr. W.H. Sebrell, Jr. (United States of America) The amount of research currently under way is too broad to be reviewed in detail. The Committee on Protein Malnutrition, created in 1956 to stimulate and to support research on the development of new means of prevention of protein-calorie malnutrition, will modify its activities at the end of 1964. The work sponsored by this Committee was reviewed at an international meeting held in Washington in 1960, the proceedings of which were published in a monograph entitled "Meeting Protein Needs of Infants and Children" published in 1961 by the NAS-NRC. Another international meeting was held under the sponsorship of this Committee in 1963 to review the methodology, techniques, and research needs in relation to protein evaluation. The proceedings of this meeting were published in a monograph entitled "Evaluation of Protein Quality", by the NAS-NRC, in 1964. Many individuals and research teams are presently engaged in research closely related to protein-calorie malnutrition. Among them may be listed the work at Rutgers University on protein reserves, at Vanderbilt University on nutritional anemias, at New York University on free plasma and urinary amino acids in protein-calorie malnutrition, at Washington University on water and electrolyte metabolism, at Harvard and Tulane Universities on nutritional anemias, at the University of Pennsylvania on protein allowances for infants and children and at Columbia University on the



relation between vitamin A and protein metabolism.

The work at Massachusetts Institute of Technology on the influence of various types of stress on nitrogen metabolism may help in the clarification of the relationship between the occurrence of infectious diseases and protein-calorie malnutrition.

Dr. Leonardo Sinisterra (Colombia) A report on the work in Antioquia and Valle was presented:

- a) A clinical survey on a sample representing 15% of the population is being conducted in four villages in the vicinity of Medellín by the University of Antioquia. Dietetic and clinical surveys, some biochemical measurements and bone age determination are performed. Clinical investigation on various aspects of protein-calorie malnutrition include the evaluation of the pancreatic and duodeno-jejunal mucosa and pituitary function, as well as immunological response to vaccination.
- b) In Cali a survey was conducted which covered all children below 6 years of age, living in a rural community with a population of 4,774. The malnourished children found in the survey have been enrolled in a nutritional education and supplementation program based on free distribution of skimmed milk and the sale of Incaparina. The overall incidence of protein-calorie malnutrition (I, II, III, according to Gomez classification) among the 1,099 children surveyed was around 20%. These children are now being followed systematically to evaluate their growth. Other studies on longitudinal growth and its relation to dietary and morbidity background are also being conducted by the Growth and Development Unit of the University of Valle. One hundred and seventeen children have now been followed for a full year.

Dr. Fernando E. Viteri (Central America) Research projects now being conducted at the Instituto de Nutrición de Centro América y Panamá in the biochemical and clinical fields related to this conference include investigations on intestinal absorption, anemia, adreno-hypophyseal changes, the relation between infection and nutrition and muscle pathology during the acute stage of protein-calorie malnutrition, biochemical characterization of moderate to severe protein-calorie malnutrition, and the relationship between nutrition and mental development. Studies now being initiated include acute and chronic malnutrition in adults, body composition and influence of nutrition on work capacity. Special mention was made of the work presently conducted in three villages; in one a feeding and nutrition education program has been set up, in the second general sanitation and good medical care are provided and the third village is kept as a control. Growth rate, incidence of infectious diseases and of malnutrition and death rate in children under five years of age are recorded. Although it is too early to draw definite conclusions, it seems that the incidence of malnutrition and the mortality among children are lower in the village where a feeding and nutrition education program is conducted.

#### International Agencies

Pan American Health Organization. (Drs. M. Martins da Silva and J.J. Kevany)

The PAHO research program has the following objectives: a) stimulation of bio-medical research in the Americas; b) promotion of research training; and c) facilitation of scientific communications.

Within the guidelines of the PAHO Advisory Committee on Medical Research, the Organization implements the above objectives through: a) the identification of research problems with emphasis on those that are best resolved by

multicountry collaborative efforts; and b) the obtaining of financial support for research projects which qualify under the standards required by granting agencies.

Through its Office of Research Coordination, PAHO convenes scientific meetings which bring together active research workers interested in a given field of endeavor for an opportunity to exchange information on each other's research activities and to define more clearly approaches to specific problems.

Protein Advisory Group (Dr. E. DeMaeyer) The joint WHO/FAO/UNICEF Protein Advisory Group which is strictly advisory, concentrates its technical guidance on two main items: on the one hand the promotion of traditional protein-rich foods, such as pulses, and on the other hand the promotion of more sophisticated industrially processed foods such as those derived from fish, soybeans, peanuts, and cottonseed. A world-wide collaborative study on standardizing methods of assessing protein quality is under way.

UNICEF (Dr. Lester J. Teply) It is mainly concerned with the child's health, and thus gives financial support to programs for the development of protein-rich foods and improvement of processing methods. Its present policy is to extend its support even further and to fill the gaps between the activities of other organizations.

Suggested Classification of Clinical Signs of  
Protein-Calorie Malnutrition in Children

1. Subclinical protein-calorie malnutrition

A child who is getting less than an ideal diet, and who may show no clinical signs except a decreased rate of growth. This is usually diagnosed in retrospect.

2. Mild clinical protein-calorie malnutrition

A child who is ambulatory with:

- a) A poor dietary history
- b) Decreased weight or height for age or weight for height

3. Severe protein-calorie malnutrition

A child (ambulatory or otherwise) with:

- a) A more severe weight deficit
- b) Psychomotor changes (usually apathy or irritability)

In addition the following signs may occur:

- c) Edema
- d) Neurological changes
- e) Mucocutaneous and hair changes
- f) Liver enlargement
- g) Muscle wasting
- h) Diarrhea

The presence and severity of these latter signs do not necessarily indicate the degree of undernutrition but they can define two extreme syndromes. In some countries, syndromes with and without edema have a different age incidence and prognosis, but in others they do not.