Project Title: Clinical and Subclinical Malnutrition: Their Influence on the Capacity To Do Work

Contractor: The Medical College of Wisconsin (formerly Marquette School of Medicine)
Milwaukee, Wisconsin 53233

Principal Investigators:
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Duration: 4 years

Total Estimated Cost:
- FY 1971 29,686
- FY 1972 54,458
- FY 1973 59,785
- FY 1974 64,468

Total Estimated Cost: $208,397

Project Manager: Irwin Hornstein TA/N
Project Digest

Developing effective methods of alleviating malnutrition in the Less Developed Countries is a major AID objective. Various approaches are being utilized e.g., fortification of cereal grains, introduction of new low-cost, high-protein foods, agronomic improvements, etc. No single approach is of necessity best and all have a contribution to make. However of prime importance is the creation of an awareness at the highest government levels in the LDC's that malnutrition is a major impediment to development and progress. The proposed research addresses itself to this key problem. How can government be motivated to improve the nutritional status of their populace.

The proposal describes a study designed to measure the increase of productivity that can result from alleviating chronic malnutrition. Basically, the physical work capacity and cardiovascular reactivity in chronically malnourished patients in various stages of malnutrition will be determined. The changes in work capacity will then be quantified and related to the initial severity of malnutrition. Such objective data may provide the ammunition for documenting the economic losses attributable to malnutrition.

The specific aims of the project are as follows:

1. To determine the ability of malnourished subject to respond to a superimposed stress (exercise);
2. To reveal if physical exercise will reveal the subclinical malady (malnutrition);
3. To determine the feasibility of quantifying the reduction in work capacity and/or efficiency and relating this to the nutritional status of an individual; and
4. To develop if possible a simple work test for revealing malnourishment in overtly healthy individuals.

The studies will be done at the Faculty of Medicine, Universidad del Valle in Cali, Columbia, where a well-staffed and well run metabolic ward exists; where chronically malnourished individuals are available, and where an active interest in studying adult malnutrition exists.

Background

Research on the physical work capacity of malnourished human adults has been limited to studies on experimentally induced malnutrition. The classic studies are those of Benedict et al in 1919 and of Keys et al in 1945-6. These studies were performed on basically well nourished
individuals. Thus, in Keys' studies 32 healthy adult males underwent six months of acute starvation and an equal period of rehabilitation as a one-time experience. Studies of work capacity in people whose life is one of chronic struggle for and frequent failure in obtaining sufficient calories and proteins for adequate nutrition have not been carried out.

There are, however, sufficient grounds to expect considerable differences in the functional changes encountered in acute experimentally induced and chronic naturally occurring malnutrition. For example, the basal metabolic rate BMR is depressed in acute starvation whereas it is within normal limits in chronic undernutrition. Studies on renal function in acute malnutrition reveal marked polyuria (2-3 liters of urine per day) and inability to produce a concentrated urine. In chronic malnutrition polyuria is not as marked (1-1.5 liters of urine per day) but there is the diminished urine concentrating ability. Also while the ability to increase renal ammonia production during acidosis is conserved in acutely starved patients, it is markedly depressed in chronic malnutrition. Studies on body composition in chronically malnourished patients also indicate that there are profound differences in the changes in body composition observed in acute starvation and in chronic undernutrition. One might therefore expect differences to be observed in the physical work capacity of chronically malnourished subjects as compared to well nourished individuals. To what extent chronic malnutrition alters the work capacity, physical performance and the work productivity is, however, largely unknown.

Subclinical malnutrition can exist in apparently healthy subjects as evidenced by decreased labile protein stores in some apparently well nourished individuals. Dr. Tripathy has found that in frankly malnourished adults treatment with a high protein diet causes the disappearance within 3-4 weeks of such clinical signs of malnutrition as edema, hepatomegaly and hypoproteinemia. But for another 12 weeks these patients maintain a state of positive nitrogen balance, undergo gradual decreases in the proportion of total body water (TBW) and Extracellular Space (ES) and achieve a steady increment in creatinine output. Thus, the interval between the 4th and 16th week of a repletion regime in a previously frankly malnourished individual resembles in many ways a state of subclinical malnutrition. To what extent work capacity is affected by a state of subclinical malnutrition is also largely unknown. The approach the investigators propose to use in trying to quantitate the limitations in work capacity that might occur at various stages of malnutrition and recovery from malnutrition as well as in subclinically malnourished patients is based on the principle of the "physiological reserve" and its reduction during states of stress. It is expected that malnutrition whether subclinical or overt will reduce the "physiological reserve".
The superimposition then of an additional stress (exercise) may serve to reveal the underlying condition of malnourishment. It may thus be possible to quantitate the reduction in work capacity and efficiency and relate this to what one sees in normals.

Description of the Project and Proposed Work Plan

The purpose of the proposed research is to study the work capacity and cardiovascular reactivity of individuals suffering from chronic subclinical malnutrition in order to answer the following questions:

(1) Do malnourished subjects suffer a reduction in their physiological reserve i.e., in their ability to respond normally to a superimposed stress?

(2) Will physical exercise reveal the subclinical malady (malnutrition)?

(3) Will it be possible with the data obtained in these experiments to quantitate the reduction in work capacity and/or efficiency and to relate this to the nutritional status of the individual? and

(4) If the response to physical exercise is abnormal in these subjects, can a simple work test be designed to be utilized to reveal malnourishment in an otherwise apparently healthy individual?

These studies will be done at the Faculty of Medicine, Universidad del Valle in Cali, Colombia, where there is a well-staffed and well-run metabolic ward in the Department of Medicine and a history of research in adult malnutrition.

Three groups of subjects will be studied (a) clinically malnourished patients, (b) subclinically malnourished patients, and (c) control subjects.

Evaluation of Nutritional Status

Candidates for this study will undergo a physical examination plus a complete medical and nutritional evaluation. The following biochemical analytical data will be obtained (a) complete blood count; (b) serum levels of albumin and total protein, cholesterol, iron, folic acid, vitamin B12, and erythrocyte transketolase activity; and (c) urinary excretions of thiamine, riboflavin, N-methyl nicotinamide and ascorbic acid.
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So complete a survey is necessary for the establishment of a correct diagnosis and a proper repletion regime.

I Primary Clinical Malnutrition will be defined on the bases of the following criteria:

1. Poor dietary intake in the absence of any specific disease;
2. Presence of edema, or in its absence, body weight of less than 75 percent of ideal weight;
3. Serum albumin less than 2.5 g/100 ml;
4. Serum cholesterol less than 150 mg/100 ml and an abnormal pattern of fatty acids in serum cholesterol esters;
5. Urinary creatinine output less than 800 mg/24 hours in males and less than 500 mg/24 hours in females; and
6. Absence of any pathologic process to explain any of the above.

II Subclinical Malnutrition will be defined on the basis of the following criteria:

1. Absence of signs of clinical malnutrition as described above;
2. Total Body Water (TBW) more than 65 percent of the body weight;
3. Extra Cellular Water (ECW) more than 30 percent of the body weight; and
4. Creatinine output less than 25 mg/liter: TBW/24 hours.

III Control Subjects (as well as completely repleted individuals) will be defined as follows:

1. Nitrogen balance zero;
2. TBW less than 65 percent of the body weight;
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(3) ECW less than 30 percent of the body weight;

(4) Intracellular water between 35-40 percent; and

(5) Creatinine output greater than 25 mg/liter TBW/24 hours.

Plan of Work

I - Clinically Malnourished Patients (Group 1)

(1) Basal Study

The subjects will receive "control diets" similar to their natural diets containing adequate calories to maintain body weight, vitamins and minerals in recommended allowances and 25 g of mostly vegetable protein. The "control diet" will be maintained for a period of 2-3 weeks in order to allow for several 4 days pool collections for studies of nitrogen balance and creatinine output. Once stabilization of body weight, creatinine excretion rates and nitrogen balance have occurred body composition studies and skin fold measurements will be carried out.

(2) Experimental Periods

Upon the termination of the control study, the dietary protein will be raised isocalorically to 100 g per day. All the above mentioned measurements will then be repeated at monthly intervals. This protocol will thus allow for the study of clinically malnourished individuals during:

(a) the period of frank clinical malnutrition immediately following their admission;

(b) the period of subclinical malnutrition between approximately the 4th and 16th week of the repletion regime; and

(c) following complete repletion.

At each of the three stages, studies of physical work capacity and cardiovascular reactivity will be carried out on each patient at monthly intervals. The studies to be performed are described on the section on Methodology.
II - Subclinically Malnourished Patients (Group 2)

Colombian male subjects (age 16-59) showing characteristics of subclinical malnutrition and having a poor history of nutrition will be studied.

Each patient will be admitted to the Metabolic Ward for a 4-day period. The studies of body composition will be done on the 3rd Hospital Day, daily creatinine output will be determined during days 2, 3 and 4. On the first Hospital Day the subjects will undergo basal testing, pulmonary function measurements and a training exercise session. On the 2nd Hospital Day, the subject will undergo the FWC 170 test, the maximal VO₂ test and the cardiovascular tolerance test (see section on Methodology). This group of subjects will be subdivided in several subgroups according to:

(a) activity levels;

(b) altitude of residence; and

(c) temperature of place of residence.

III - Control Subjects (Group 3)

(a) Colombian Normals - These will be individuals with a history of good nutrition and whose body composition, creatinine output values and serum proteins correspond to criteria for well nourished individuals. Detailed information concerning their employment will be obtained. It may be necessary to obtain a number of subjects from several different types of employment, e.g., factory workers, construction workers, etc. in order to establish meaningful relationships between work capacity in malnourished patients with normals.

(b) U.S.A. Normals a group of subjects comparable to those in III (a) will also be studied to establish the comparability of results obtained in Colombia with those which can be observed in this country.

It is estimated in the course of 3 years of experimentation at least 24 subjects in Group I, 80 subjects in Group II and 30 subjects in each Control Group (III (a) and III (b)) will be studied.
Significance of Projects to AID Objectives

Developing effective methods of alleviating malnutrition in the LDC's is a prime AID objective. No single approach can be considered uniquely best. But of prime importance is the creation of an awareness at the highest government levels that malnutrition is a major impediment to economic, developmental and social progress. The proposed research addresses itself to this key problem - How to motivate the power structure to improve the nutritional well-being of people.

The development planner is faced with the problem of how best to allocate limited resources. He may be reluctant to fund nutrition programs when other needs appear more pressing, and the cost of malnutrition may be less than obvious. If, however, one can relate improvement in nutrition to increased productivity and economic development, governments may lend a more receptive ear to developing national nutrition policies and to provide funds for nutrition programs.

Efforts have been made to demonstrate that malnutrition is a drain on a nation's economy but the economic cost of malnutrition has never been adequately documented. This proposed project attempts to relate nutritional status to work capacity and vice versa. This information may then be utilized to estimate the economic loss due to this one factor, loss in work capacity, to a society wherein malnutrition is widespread.

Relation of Proposal to Existing Knowledge

There is every indication that malnutrition is a major obstacle to development. However, unequivocal data to support this belief is simply not available. It is therefore essential to develop the data needed to quantitate the economic cost of malnutrition. A key question that must be answered is how much more productive is a well nourished as compared to a poorly nourished man. This proposed research provides an approach to supply the answer.

Further, from a strictly scientific viewpoint, studies of work capacity in people whose life history is dominated by poor nutrition have not been carried out and this proposed research will fill an important gap in our knowledge.

Description and Evaluation of Methodology

(1) Body Composition

Total Body Water (TBW) will be measured by the tritium dilution method and extracellular water (ECW) by thiocyanate space. The difference between TBW and ECW will be taken as intracellular water (ICW). Cell body
mass and degree of adiposity will be determined from ICW values. In addition, several skinfold measurements will be recorded as an independent check on the degree of adiposity. Daily creatinine output as related to body weight, TBW and ICW will be calculated.

(2) Basal Parameters

These will include the determination of body temperature, heart rate and basal metabolic rate. The latter will be determined by the open-circuit, Haldane-Tissot technique so that Respiratory Quotients (RQ) can also be determined.

(3) PWC$_{170}$ Test (Work Capacity at heart rate 170)

Three exercise tests will be performed, each for six minutes, using a motor driven treadmill. The workloads will be designed to elicit heart rates of 130, 150 and 170 beats per minute. The treadmill speed will be held constant at 6 mph. Increases in workload will be achieved by increasing the treadmill grade. The heart rate will be monitored throughout the exercises using a radiotelemetry system. The heart rate between the 5th and 6th minute of each workload will be used to establish the work capacity (PWC$_{170}$).

Expired air will be collected the last minute of each workload. Analysis for oxygen and carbon dioxide will permit calculations of oxygen intake. Other calculations will permit determination of oxygen pulse, percent of oxygen extraction and RQ.

Measurements of heart rate will also permit estimation of maximal aerobic capacity.

The subjects will be thoroughly trained on the treadmill prior to data collection and otherwise made familiar with laboratory procedures in order to reduce anxiety. All experiments will be conducted in an air-conditioned laboratory in order to control temperature and humidity.

The PWC$_{170}$ Test has been applied universally to establish work capacity. Its application has included normal and well-trained subjects. The application of
the test to subjects at various fitness levels will provide adequate data for comparative purposes;

(4) Maximal VO₂ Test (Maximal Aerobic Capacity)

The relationship between heart rate and oxygen uptake or workload with normal subjects is well established. It will be necessary to establish the validity of the relationship for malnourished patients or to develop a new set of correlations. This test will permit comparison of maximal aerobic (work) capacity of the malnourished patient with data from the literature on various groups of subjects and with the control groups.

The test will consist of a 5 minute warm up at about 50 percent of calculated VO₂ max. Following a 5 minute recovery period the subject will commence running at a treadmill grade designed to elicit about 90 percent of VO₂ max. At the end of 2 minutes and each subsequent 2 minute period, the grade will be increased by 2 percent until subjective fatigue. Heart rate will be monitored and expired air collected throughout the exercise period. Minute ventilation and oxygen uptake will be determined. Data will be used to calculate maximal oxygen pulse, percent oxygen extraction and R.Q.

(5) Pulmonary Function

These measurements in Group I subjects will be made so as to determine whether limitations in work capacity during chronic malnutrition may occur as a result of changes in pulmonary function and to exclude possible superimposed pathology.

Measurements to be made will include vital capacity, residual volume, functional residual volume, total lung capacity, one-second forced expiratory volume, maximum voluntary ventilations and pulmonary diffusion capacity at rest and during exercise.

(6) Cardiovascular Responses to an Orthostatic Tolerance Test

The test will consist of a ten minute supine posture followed by a 20 minute period of a 70° upright posture. Heart rate and blood pressure will be monitored periodically - Heart
rate by radiotelemetry, blood pressure from arterial catheters.

Physiological changes of the cardiovascular system have been observed by Keyes during periods of undernutrition. Among the more common observations are bradycardia (slow heart beat), and reduction in venous pressure. Perhaps changes of these parameters under standard conditions can be related to the state of nutrition.

Evaluation of Research Competence of Investigators

The two senior scientists associated with this proposal are well regarded in their respective spheres of expertise and are highly qualified to carry out these studies. Dr. Spurr is professor physiology at the Medical College of Wisconsin and is responsible for the exercise methodology and physiological measurements. His major research interest is in Environmental Physiology. Dr. Tripathy is well known for his work on adult malnutrition his major research interests are in clinical malnutrition. His work is supported in part by a U.S. Public Health program grant through Tulane University. He is currently Professor of Medicine at the Universidad del Valle.

Two major co-investigators are Associate Professor and Director of the Exercise Physiology Laboratory at the University of Wisconsin and Dr. Nieto, Chief, Section of Physiology, Department of Physiological Sciences at the Universidad del Valle whose major interest is in environmental physiology and Renal Physiology.

Internal and External Technical Review of Proposal

Reviews of this proposal have been solicited from our own immediate collaborators including Dr. Altschul and his staff at USDA; Dr. Weisberg of L.I.F.E.; and Dr. Frank W. Lowenstein of L.E.W.; Outside reviewers include Dr. George Graham, Department of International Health, Johns Hopkins University; Dr. David Coursin, Research Institute, St. Joseph Hospital; Dr. Frank C. Consolazio, Bioenergetics Division, Fitzsimons General Hospital; Dr. Thomas Allen, U.S.A.F. School Aerospace Medicine, Brooks Air Force Base; Dr. LeRoy Vorhis, Food and Nutrition Board, NAS; and Dr. Ellsworth Buskirk, Human Performance Laboratory, Pennsylvania State, University.
As a result of reviewers' comments, the original proposal was reoriented to suit AID objectives. The primary objection of the present proposal is that of quantitating the limitations in work capacity and/or efficiency which may occur in the malnourished state; secondary analysis has been placed on the development of a clinical test for revealing subclinical malnutrition. This is a reversal of the original proposal goals.

Relation to AID Current Research Projects

The Office of Nutrition has an ongoing contract with Battelle Memorial Institute AID/cad 2840. The objective of this contract is to delineate the major questions to be answered in trying to assess the Economic Cost of Malnutrition in the LCD's. One of the most important and most difficult questions to answer is how to quantitate the loss of work capacity due to malnutrition and/or subclinical malnutrition.

At a recent meeting with the senior investigators associated with the Battelle study and with Dr. David Call of Cornell, a consultant on this project to Battelle, there was complete agreement that a basic study of the type described in this proposal is sorely needed.

There is also a tie-in to current fortification studies in Tunisia, Thailand and Guatemala in that data collected in this study may make it possible to construct a more practical food supplemental program for obtaining optimal work capacity from malnourished adults.

Anticipated Mission and LLC Participation

By far the major portion of these studies will be done at the Faculty of Medicine, Universidad del Valle in Cali, Colombia. Personnel engaged in this project will be predominately Colombian.

Anticipated Contribution to Institution Building

The major portion of the training of personnel and the setting up of equipment and laboratories will be in Colombia. E.g., during the 2nd year of the program a laboratory to carry out the exercise methodology will be established. This laboratory will add a new dimension to the already excellent facilities at the University.

As a result of this research one can assume that the nutrition program at the Universidad del Valle will continue its growth thus providing a benefit not only to Colombia but also to its neighbors.
Plan for Utilization of Results

The results of the proposed research will provide the type of information and data required to help quantitate the Economic Costs of Malnutrition. The data will be used to substantiate the importance of nutrition to the development of the LDC's.

Appraisal of Research Resources and Budget

(1) Universidad del Valle

A metabolic ward with 8 beds is available for the study. The nutrition chemistry laboratory is adequately equipped to carry out all the procedures indicated in the proposal. Space for the exercise laboratory will be available next to the pulmonary function laboratories. The latter is supplied with all the necessary instrumentation to carry out the required studies. The exercise laboratory will be established during the second year of the project. The equipment is included in the first year's budget.

(2) The Medical College of Wisconsin

The exercise laboratory is located in the Research Service of the Wood Veterans Administration Center. The equipment and instrumentation for measurement of cardiovascular and ventilatory responses to exercise is ample for the needs of the study. A cardiopulmonary laboratory is also available for research purposes.

(3) University of Wisconsin - Milwaukee

While technically this institution is not an official part of the present proposal, the facilities of the Exercise Physiology Laboratory are available to the investigators if needed.

Attachment I is a detailed budget for this proposed project.

Summary Evaluation:

TA/N believes the proposed project deserves favorable consideration. This work is an attempt to explore a relatively unknown area. If a relationship between nutritional status and work capacity can be established the
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data will be of great importance by providing an effective tool for evaluating the economic cost of malnutrition in the LDC's.

It has been agreed by all who have reviewed this project that the project covers a heretofore neglected aspect of malnutrition in adults and is well worth supporting.