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ABSTRACT

This report, one of 10 prepared in 1980 for the Steering Committee for the Five-Year Research Plan of the National Institute of Child Health and Human Development (NICHD), was prepared to address the state of the science of nutrition research and to relate the programs of the NICHD to present and future needs in nutrition research. Specifically, the report defines the NICHD mission and overall objectives in nutrition research; reviews recent significant findings in nutrition and development; surveys the current state of nutrition knowledge, and defines gaps in that knowledge; recommends, within the framework of the NICHD mission, research issues or objectives that need to be addressed during the next 5 years; suggests research priorities among these 5-year objectives; and states the resources needed to accomplish these objectives. (MP)

Child Health and Human Development

An Evaluation and Assessment of the State of the Science

Nutrition

Nutrition

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Foreword

This report is one of ten prepared in 1980 for the Steering Committee for the Five-Year Research Plan of the National Institute of Child Health and Human Development (NICHD). In developing the plan, a Study Group for each of the ten NICHD program areas was asked to evaluate the state of the science, identify areas of promise, and recommend directions for future research. Each Study Group consisted of leading scientists and staff of the NICHD. The Steering Committee conducted an extensive scientific and policy review of the reports, and collected and published them in Child Health and Human Development: An Evaluation and Assessment of the State of the Science (October 1981). The reports reflect specific interests and expertise of the authors and not necessarily NICHD policy. The report on the following pages is reprinted from the collection. The ten program areas are:

I Fertility and Infertility
II Pregnancy, Birth, and the Infant
III Nutrition
IV Sudden Infant Death Syndrome
V Congenital Defects
VI Mental Retardation
VII Child and Adolescent Development
VIII Contraceptive Development
IX Contraceptive Evaluation
X Population Dynamics

Each program area will be reviewed and updated annually as part of the NICHD planning and evaluation process. By this means, areas not emphasized adequately can be addressed, the guidance of other experts can be sought, and changes in the state of the science and changes in health issues can be accommodated.

Single copies of each reprint are available free from NICHD, Office of Research Reporting, NIH, Building 31, Room 2A-32, Bethesda, Maryland 20205. Reprints should be requested by title.

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Nutrition

I. Introduction

The interaction of mankind with food is one of the most intimate, prolonged, and pervasive of environmental exposures. In fact, human nutrition can be viewed as man's ability to adapt to one aspect of his environment--food. Recognized as a field of science only within the last half-century, nutrition has grown to receive, and continues to receive, more public attention than many other disciplines. This visibility results from the fact that advances and developments in nutrition influence the fields of economics, political science, agriculture, medicine, ecology, business, and sociology.

The purpose of this report is to address the state of science in nutrition research and to relate the programs of the National Institute of Child Health and Human Development (NICHD) to present and future needs in nutrition research. Specifically, the report:

- Defines the NICHD mission and overall objectives in nutrition research;
- Reviews recent significant findings in nutrition and development, surveys the current state of nutrition knowledge, and defines gaps in the knowledge of the science;
- Recommends, in the framework of the mission of the NICHD, research issues or objectives that should be addressed in the next 5 years;
- Suggests research priorities among the 5-year objectives; and
- States the resources needed to accomplish this program.

Definitions

Although there are many definitions of nutrition, the term used in this report refers to the "science of food as it relates to optimal health and performance."[1] Nutrition research, therefore, is concerned with the way in which the body uses food from the time it is ingested until it is eventually incorporated into the body and either participates in biological reactions or is excreted.[2] More recently, research on nutrition focuses on an area of study broadly defined as the psychosocial aspects of food, including such concerns as taste predilections, customary cuisines, food aversions, and dietary taboos.

Nutrition is the substance of all life processes, and it is essential for reproduction, growth, and development. Development in this sense means "changes from fertilization to maturity."[3] Insufficient intake of energy and inappropriate nutrients have been shown to cause physical growth retardation, developmental defects or anomalies, and, in extreme cases, death. The number of deaths and the prevalence of health problems attributable to inadequate nutrition during development are unknown. It has been estimated that about 5 percent of all annual live births in the United States (about 114,000 infants) are small at birth because they were nourished inadequately in utero. Another 16,000 to 17,000 infants are stillborn or die early in life because of poor fetal nutrition.[4] Although there are no hard data on the subject, the incidence of growth retardation probably increases during the first year of life when the growth rate is very rapid and nutritional needs are high.

Malnutrition is generally considered to mean "inadequate nutrition" or "undernutrition." The term malnutrition actually denotes faulty or poor nutrition in all of its aspects: under- as well as overnutrition.[1] Another commonly used term is nutrient imbalance; this condition may occur when the level of some dietary component is excessive in concentration while other components are adequate in the same diet, or when some dietary components are below the required level while others are adequate. Fad diets can also cause nutrient imbalance; the deaths associated with liquid protein diets are ominous examples.

In the United States, both over- and undernutrition exist, but their prevalence is unknown. Obesity, or excessive fatness, is the most common form of malnutrition in the United States. Data from the National Center for Health Statistics[5] suggest that its prevalence rises sharply after age 30 and reaches a level of 39 percent of men and 50 percent of women who are 10 percent or more overweight. The prevalence of obesity in children is lower, about 10 percent, and obese children generally remain obese as adults.

Another problem of overnutrition, less prevalent but still potentially harmful to health, is vitamin toxicity. Cases of vitamin A or D toxicity are reported annually. Often they are the result of self-medication with readily available commercial vitamin supplies. Trace elements, such as zinc and selenium, are also available commercially and, when taken in excessive amounts, are potentially toxic. Since health claims have been made for these nutrients, toxicities resulting from overzealous self-medication can become a problem.

In the United States, undernutrition is thought to be less prevalent than overnutrition, but isolated cases of growth retardation due to inadequate food intake probably exist among children in all stages of growth. Undernutrition of specific essential nutrients is also a problem. Iron deficiency is common, for instance, in some groups of children and adolescents. Almost 50 percent of low-income children between 12 and 23 months of age have serum iron levels below 50 µg/dl.[1] The normal level is approximately 100 µg/dl. More than 30 percent of the children of the same age in middle- and upper-income groups show the same signs of iron deficiency. Public health programs, which provide such aid as iron supplementation during pregnancy and iron fortification of infant cereals, have been initiated to reduce the incidence of this nutritional problem in infants and children. Other nutritional deficiencies most likely exist in infants and children, but because of the lack of practical, sensitive detection techniques, their incidence is less well defined.

Objectives in Nutrition Research

The nutrition research program of the NICHD, based on the broad definition of nutrition given above, has the following mission: (a) To advance knowledge on the interrelationships of food, nutrition, and human development, (b) develop new knowledge on nutritional imbalances and interactions in early life that may be antecedents to disease and disability, and (c) understand the role of nutrition in promoting and maintaining health and improving the quality of life.

Specific research objectives have been identified with reference to the Institute's overall mission for nutrition research as follows:

To learn through human metabolic and population studies how nutrients, combinations of nutrients, and other components of foods will best support normal human development.

The developmental process in the human species is among the most complicated of all forms of life, and the pattern differs from that of most other species.[6] The growth rate is slower and growth lasts longer. In accord with slower growth rates, nutritional needs per 1,000 kcal appear to be lower in humans than in other species. Also, nutritional needs vary during the life cycle and depend on physiological changes that occur. The growth rate of the infant is much faster than that of a 7- to 10-year-old. An infant uses about 25 percent of his energy intake for growth; the 7- to 10-year-old only 2 to 3 percent.

Information on the amounts and combinations of nutrients that best support human development must come from studies of humans per se. Longitudinal or semilongitudinal studies are necessary to complement cross-sectional and clinical studies. Meanwhile, investigations of nutrition, growth, and development in experimental animals are extremely useful for identifying biochemical, physical, and functional markers sensitive to nutritional imbalances; specific roles of nutrients during development; the impact of nutrients' interactions and also nutrient/nonnutrient interactions; and the influence of environmental differences on the developmental process.

To determine the specific roles of nutrients in physical and functional development.

Development is a continuum and all of its stages are linked, and the effects of nutritional imbalances during an earlier stage of development on later development and on susceptibility to degenerative or other diseases are important issues. Research on this subject can be divided into two types: those focusing on the effects of general undernutrition in which the quantity of food intake is restricted; and those focusing on deficiencies of specific nutrients.[3] Studies of general undernutrition can be further divided into two kinds: short-term total starvation or fasting studies, and longer term studies in which an animal's food intake is restricted but not totally withheld. To understand how the specific role of a nutrient may vary with level of intake, the scope of such studies should include a range of intakes--from severely deficient, to marginal, to several times that above need, to toxic levels. Development needs to be investigated through hormonal, enzymatic, and functional changes, in addition to the more commonly measured morphologic and physical changes.

To establish nutrient requirements for critical stages of life--for example, in pregnancy and during lactation as well as in infancy, childhood, and adolescence--by improving the methodology for assessing the nutritional status and increasing the understanding of the functions of and needs for individual nutrients.

Nutritional requirements are influenced by physiological changes at all stages of reproduction and development. One of the first steps in advancing knowledge of the requirements for humans is to "map" the normal physiological changes that occur from fertilization of the ovum to maturity. Special attention needs to be paid to the physiological changes that alter nutrient utilization, such as nutrient absorption, accretion, metabolism, and excretion. A second step is to establish criteria for normal function and health. The criteria would provide standards for nutritional requirements.

The difference in nutrient requirements within populations needs to be determined. Nutritional requirements vary among individuals and from time to time for a given individual, according to age, body size, sex, and physiological state.[7] Some nutrient requirements are further influenced by levels of physical activity and by the environment in which an individual lives, including climatic conditions or exposure to atmospheric pollutants. Sociocultural influences on food selection may have a greater impact than natural environmental conditions. The influence of genetic and racial differences on nutrient requirements also needs further study.

To develop nutritional interventions to prevent and treat nutrition-related problems that may occur in utero, at birth, and in early life.

Congenital anomalies, growth retardation, delayed or impaired functional performance, endocrinologic or biochemical defects in nutrient metabolism, and abnormalities in body composition are all possible manifestations of nutrition-related problems in utero, at birth, or in early life.

Nutrition-related health problems need to be defined for various nutritional imbalances, with initial emphasis on the more common imbalances in human dietaries, such as high protein, fat, sodium, or iodine intakes, marginal vitamin B_6 or zinc intakes, and excessive iron intakes due to supplementation programs. The early identification of metabolic, functional, or physical changes may foretell health problems, as do common causal factors in populations at risk. The means of such early identification need to be improved. In addition, appropriate nutrition intervention programs need to be developed for individuals with existing disorders, such as growth retardation, and for individuals with early precursors of a disorder. It is important also to prevent nutrition-related problems in high-risk populations. Methodologies to evaluate the effectiveness of nutrition intervention programs need to be developed.

To determine physiological, psychological, and cultural factors that establish dietary patterns and to assess the impact of these patterns on nutritional status, health, and development.

All animals require nourishment and all have some mechanism that directs them to eat. Their behavioral patterns are diverse, but usually some control is exerted over the kind and the amount of food taken.[1] How this complicated system works to maintain homeostasis within the animal is not well known, nor are the developmental aspects of food intake regulation understood.

Recently, it has been noted that some neurotransmitters alter eating behavior. Norepinephrine injected into the hypothalamus, for example, stimulates food-satiated animals to eat. Acetylcholine triggers drinking, and severe amino acid imbalances in the diet lead to a cessation of eating.[1] Methodology is now available to advance knowledge on the role of neurotransmitters (catecholamines, acetylcholine, serotonin, and amino acids) in the regulation of food intake. Basic mechanisms of food intake regulation should be identified, the regulatory process itself needs to be studied developmentally, and factors associated with abnormalities in regulation should be identified.

Other factors that undoubtedly influence food intake are taste and smell. Research is needed to ascertain the temporal sequence of early development of taste and smell, the effects of variations in nutrient and food intake on taste, and the influence of early infant diets and exposure to various tastes and smells on later food preferences.

A more complex problem is how people maintain their weight in spite of large day-to-day variations in physical activity or food intake. Also, what mechanism triggers the regaining of weight after an illness or food deprivation? It is currently thought that the individual has internal ability to sense the degree of body fatness, a so-called "internal adipose tissue sensor."[1] Investigations are needed on the nature of this sensor, its relationship to circulating metabolites, and whether it can be readjusted so that new levels of energy stores are maintained..

Dietary practices, which consist of food choices and patterns of consumption, vary widely among individuals and within the same individual over time. Research on dietary practices suggests that many factors are involved and that the interaction among them is complex. Studies in experimental animals show that nutrient metabolism is altered by changes in frequency of food consumption. Although the pattern of consumption and how it relates to nutritional status and health have not been studied to any degree in humans, they are likely to experience comparable metabolic

adjustments. Dietary practices may be as important in determining health as is adequacy of nutrient intake, and they may be established by early exposure to foods, tastes, smells, and patterns of food consumption. Such practices may underlie subsequent susceptibility to degeneration and to chronic diseases. A clear understanding of how dietary practices really are established will be helpful in designing nutrition education programs.

II. Current State of Knowledge

Historical Development

The science of nutrition was recognized as a distinct discipline only in 1934 with the organization of the American Institute of Nutrition.[2] Although in early history man knew that food was essential for life, he seldom discriminated the relative value of different foods. An exception can be found in the Book of Daniel, where it is written that the men who ate pulses and drank water thrived better than those who ate the king's food and drank wine.

In 1747, a British physician, James Lind, attempted to find a cure for scurvy by giving 12 sailors 6 different treatments. He learned that lemon juice and lime juice were effective in treating the disorder, but that seawater, vinegar, and oil of vitriol were not. It can be said that the science of nutrition began with this experiment. Also in the eighteenth century, by showing that there was a relationship between heat production and oxygen use in the body, Lavoisier opened up the field of calorimetry in nutrition.

During the nineteenth century, analyses of food for carbon, hydrogen, and nitrogen led to the conclusion that an adequate diet contains plastic foods (protein) and fuel foods (carbohydrate and fat). Between 1880 and 1910, numerous experiments were conducted attempting to nourish animals with purified diets composed of a protein source such as casein, carbohydrate, fat, and inorganic ash. Unless a small amount of natural food was added, the animals all died.[2] This result suggested strongly that something else was required for the maintenance of life. Funk called this dietary component vitamine, after vita, meaning "essential for life," and amine, or "nitrogen containing." It was later learned that not all of these essential components contain nitrogen, and the e was dropped to form the word vitamin, which is still in use today.

By 1940, four fat-soluble and eight water-soluble vitamins had been identified and the chemical structure

established, and many vitamins had been synthesized. After 1940, two more water-soluble vitamins, folacin and vitamin B_{12}, were found to be dietary essentials.[2] During this same period, it was also discovered that the dietary substance, mineral ash, was a complex mixture of elements, and about 20 different elements from this ash have now been found to be dietary essentials for humans.

New instruments and techniques developed within the past 25 years have made it possible to study the metabolism of nutrients in individual cells and even subcellular components, and they have shown that nutrients play a vital role in the growth, development, and maintenance of cells. A link between cellular nutrition and health has also been ascertained. Nourishment of the cell is basic to the nourishment of groups of cells or tissues and in turn is basic to the nourishment of organs, and ultimately, the whole complex body. When nutrients are lacking, a number of metabolic defects can occur at the cellular level. These defects can be a failure to form an enzyme, a failure to form cellular components, or a failure to incorporate cellular components into functional structures. Any one of these defects can lead to loss of cell function and eventually to the death of the cell. This process is the metabolic event of malnutrition and leads to the physical symptoms of ill health associated with a nutritional deficiency.[2]

Investigations of vitamin D illustrate how the science of nutrition has progressed from assessing the relationship between nutrient intake and physical growth, to determining the nutrient's metabolic role, to integrating the association of nutrients with health.[8] Vitamin D nutrition began historically with the recognition of rickets. In 1650, an English physician wrote a treatise on "wrikken," which described the weakened and deformed bones of young children with the disease. The disease seemed to strike in cold foggy regions of the country where children remained mostly indoors, the variety of food was limited, and sanitation was questionable.

In the mid-1800s, histological studies made possible an accurate description of the lesion in rickets. They showed that bone consists of an organic matrix, largely protein, into which mineral subsequently becomes embedded. Extensive examination of ricketic bones showed that synthesis of the organic matrix continues normally but that the deposition of calcium and phosphorus is impaired. The bones, particularly of the limbs and the rib cage, become weak and misshapen from lack of mineralization. The discovery that rickets was due to a failure of calcium and phosphorus to deposit in growing bone, coupled with the common knowledge that animals in captivity grew poorly and had weak bones unless their

diet included either ash or bones, reinforced the idea that rickets might be a disease of nutritional origin.

In the early 1900s, it was found that the addition of calcium phosphate to diets for ricketic puppies was to no avail; the most effective additive was cod liver oil, which was known to contain the recently discovered vitamin A. Even when this nutrient was destroyed by oxidation, however, the oil retained potency to cure rickets. The antiricketic factor was therefore not vitamin A, and a new factor was eventually identified as vitamin D. It was later learned that rickets could also be prevented by exposing either the diet or the experimental animal to sunlight. The puzzling interactions between calcium, phosphorus, vitamin D, and sunlight were gradually resolved into one cogent picture when vitamin D was isolated and synthesized in 1931.

Vitamin D is now known to be a sterol, chemically named cholecalciferol, which can be synthesized by the action of ultraviolet rays upon a related compound, cholesterol. Thus, the exposure of children or experimental animals to sunlight converts the cholesterol naturally present in the skin to vitamin D. Since calcium and phosphorus are essential structural components of bone, the dietary requirement for these minerals is evident, and without sunlight or vitamin D, these minerals alone are not sufficient to prevent rickets because they depend upon vitamin D for intestinal absorption.

This knowledge led to the belief that administration of vitamin D would end rickets once and for all. Instead of a cure, however, the bones in many cases became brittle and less mineralized, and soft tissue calcification occurred. This unexpected result led laboratory investigators to focus on the precise mechanism of the effect of vitamin D on bone, and they found that the principal metabolic role of vitamin D is to maintain a constant level of calcium in the blood. The body's main calcium sources are the intestine and bone; when blood calcium falls, vitamin D increases movement of calcium into blood from both sources. Since blood calcium regulates muscle contraction, its careful monitoring is essential to life. The very high doses of vitamin D administered to ricketic children overrode the usual control mechanism. Unneeded calcium precipitated from the bone and caused mineralization of soft tissues.

With the synthesis of tritiated vitamin D in 1966, information on the metabolism and function of vitamin D has advanced rapidly. Studies show that vitamin D, or cholecalciferol, is chemically modified, by a hydroxylation reaction in the liver, to 25 hydroxycholecalciferol ($25\text{-}OHD_3$), the major circulating form of the vitamin. This compound is converted to 1,25-dihydroxycholecalciferol ($1,25\text{-}(OH)_2D_3$) in the kidney.

Since the active form of vitamin D is synthesized in one organ and transported in the blood to a different action site, $1,25\text{-}(OH)_2D_3$ is considered to be a hormone, and vitamin D is more accurately referred to as a prohormone. The hormone itself, acting in concert with parathyroid hormone (PTH) secreted by the parathyroid glands, plays a major role in the maintenance of the normal level of calcium in blood. When the blood calcium level falls, PTH is secreted and stimulates the kidney to increase formation of $1,25\text{-}(OH)_2D_3$, which in turn stimulates calcium absorption from the intestine. It also stimulates bone demineralization. As the blood calcium level rises, PTH secretion is decreased, as is synthesis of $1,25\text{-}(OH)_2D_3$, and the feedback loop is completed.

With this broader understanding of the role of vitamin D, a number of diseases with the unifying pathological feature of inadequate mineralization of bone matrix can now be understood and treated effectively with vitamin D or one of its metabolites. Hepatic rickets, for instance, is a disease that does not respond to vitamin D itself, but is responsive to $25\text{-}OHD_3$. This disorder is thought to result from a failure of the liver to form normal amounts of $25\text{-}OHD_3$. Supplying the body with an external source of $25\text{-}OHD_3$ is the suggested treatment. Bone changes generally resulting from the kidney's reduced capacity to convert $25\text{-}OHD_3$ to $1,25\text{-}(OH)_2D_3$ often accompany renal disease. These disorders are successfully treated with physiological doses of $1,25\text{-}(OH)_2D_3$. Vitamin D-dependent rickets is thought to result from a genetic inability to hydroxylate $25\text{-}OHD_3$ to $1,25\text{-}(OH)_2D_3$, and is treatable with the latter metabolite.

Comparable basic research of other nutrients integrating metabolic functions with biochemical and functional defects and clinical health is needed. This type of research will help identify nutritional factors associated with cardiovascular disease, hypertension, diabetes, and cancer.

Major Recent Research Advances

Progress in nutrition research has been rapid. The American Institute of Nutrition, whose membership is restricted to scientists who have made significant contributions to the field, has over 1,500 members. In 1978 over 4,000 papers dealing directly or indirectly with the subject were presented at a single scientific meeting.[2] Reviewed below are significant research findings of the past 5 to 10 years, organized under four general concepts. The concepts point to directions for future nutrition research.

- A link exists between cellular nutrition and tissue functional competency such as immune function or cognitive function. Changes in tissue function are linked to health problems associated with malnutrition, such as increased incidence of infection or impaired socialization and learning ability.

If not nourished adequately, infants and children are very susceptible to infection. Cicely Williams first observed this susceptibility in her description of kwashiorkor in African infants and children in 1931-32. In fact, any acute nutritional deficiency caused by excessive nutrient losses, surgical procedures, or a poor diet results in an increased incidence and severity of infectious diseases. Malnutrition appears to affect both immunologic and nonspecific systems of the host defense.

The ability to synthesize new proteins from amino acid precursors is essential for producing either cellular or humoral immunity. Protein synthesis is also required for nonspecific host defensive mechanisms, such as the formation and function of phagocytic cells. In malnutrition, and especially in protein-energy malnutrition, competition exists for amino acids necessary for cellular maintenance, growth, other subcellular activities, and immunogenesis. Even a mild infection can stimulate excessive competition for the limited supply of amino acids, and it appears that immunocompetent cells do not have priority over muscle and liver cells in time of need.[9] These observations have led to investigations on the role of nutrition in immunologic function. Preliminary evidence suggests that malnutrition may have a particularly important influence on cell-mediated immunity, but the humoral response, phagocytosis, and complement system are all affected by nutrition as well.

Recently, there has been increasing concern that the administration of iron, either as supplements or in iron-fortified formulas or cereals, may predispose infants to infection. The basis of this concern is that in vitro studies have shown that the bacteriostatic properties of transferrin and lactoferrin (iron-binding proteins in the serum, human milk, and cow's milk) are diminished or obliterated when these proteins are saturated with iron.[10] Clinical human studies, however, do not show that iron fortification of infant formulas and cereals increases the risk of infection. Conversely, infectious disorders appear to increase with iron deficiency in low-birthweight (LBW) and full-term infants.

Malnutrition can also retard brain maturation. In fact, longitudinal studies in children up to 60 months of age have shown that such effects are exacerbated by a poor socioeconomic environment.[11] Although the mechanism of

the effects has not been elucidated, animal studies have led to two theories. The first involves structural damage to the developing nervous system imposed by nutritional deficits at critical periods. The second theory involves functional isolation resulting from malnutrition. The effects of malnutrition seem to be more of a behavioral nature than an impairment of learning. The behaviors most affected include attention, responsiveness, motivation, and emotionality.[12] Malnourished children are often more apathetic, demonstrate less exploratory behavior, and have a minimal amount of nondirected or incidental learning. Such changes result in less environmental stimulation or socialization, which often leads to further deterioration of mental development. Malnourished children in deprived environments seem to have little hope of substantial improvement. Unfortunately, malnutrition and poor socioeconomic environments often coexist. This fact needs to be remembered when food policy programs are developed. Provision of food without opportunities for improved education, sanitation, and housing is likely to be of little benefit.

Findings on the effects of malnutrition demonstrate a significant link between nutritional status and behavior. Food deprivation studies in humans show a range of physiological, attitudinal, and behavioral adaptations and also indicate that the behavioral changes occur earlier and possibly more rapidly.[13] Unfortunately, behavioral adaptation in man may have the most lasting functional outcomes.

In the past, most studies on nutrition and behavior focused on the behavioral effects of moderate to severe food deprivation. Some studies on the lack of a specific nutrient, iron, have also been undertaken, and a relationship between iron deficiency and behavioral disturbances has been proposed. Iron-deficient rats have definite and remediable behavioral derangements, but the effects of iron deficiency in humans are not as clear. Some studies suggest that iron deficiency imposed during critical periods of central nervous system development causes learning disorders,[14] but most show no significant effect on mental development.[12] A mild iron deficiency in children has been associated with decreased attentiveness, an inability to integrate cumulative experiences, and increased conduct disturbances. These studies are only preliminary, however, and further investigation is needed.

Within the past several years, nutritionists have begun investigating the effect of nonnutritional substances in food on behavior in children. Several studies on hyperkinesis and the intake of food coloring agents in susceptible children have been done, but the results have been inconclusive.

Other functional impairments may be identified as future research focuses on the link between cellular nutrition and functional competency. Basic studies of experimental animals are needed to determine the sensitivity of various functions to nutrient deficits. These studies may identify noninvasive markers of nutritional state that will be very useful in assessing the nutritional health of infants and children.

- Severe nutrient deficits will alter growth and development from fertilization to maturity; the effects, however, vary with the degree of severity, length of deprivation, and stage of development when deprivation occurs.

Prenatal malnutrition can have deleterious effects on both the mother and the developing fetus, ranging from growth retardation, to structural and metabolic anomalies, to death in severe cases. Research has demonstrated a striking reduction in birthweight mediated through maternal undernutrition in species characterized by rapid fetal growth rates.[3] The effect is different in subhuman primates where severe maternal malnutrition caused increased morbidity and mortality but reduced birthweight by only 10 to 15 percent.[15]

Severe famine conditions imposed during World War II provide relevant human data. During the siege of Leningrad, 18 months of near famine were associated with a striking increase in perinatal morbidity and mortality and a 500-600 g reduction in birthweight. A more limited famine in Holland was associated with a 300-350 g reduction in birthweight, but only if the famine conditions were experienced during the last trimester of pregnancy.

If severe lack of food decreases birthweight by only 300-400 g, it is unlikely that supplementation for women with borderline malnutrition would increase birthweight. This was the general experience of food assistance programs in several countries during the past few years.[16] Although methodologic approaches differed, the results were similar. The most promising results of food supplementation programs were reported from rural Guatemala, where consumption of 20,000 extra kilocalories during pregnancy increased mean birthweight by about 200 g and the incidence of LBW infants was reduced from 9.9 to 3.5 percent. The Montreal Diet Dispensary provided food supplements and dietary counseling to pregnant women considered at risk for a variety of reasons, and the program increased birthweight by 50-100 g. Birthweight was increased a comparable amount, 60 g, when pregnant women from disadvantaged areas of Bogota, Colombia, who previously had given birth to a malnourished infant, were given food supplements during the last trimester.

Birthweight was not affected when nutrient supplements were given to low-income black women in New York. Also, an evaluation of the U.S. food supplementation program during pregnancy has disclosed only modest effects on birthweight.[17]

The results of these supplementation studies on birthweight and therefore on intrauterine growth should be interpreted with caution, for the extra food may have been used as a substitute rather than a supplement for foods in the normal diet. Despite this problem, the conclusion can be drawn that nutritional intakes during pregnancy do influence fetal growth and that except in famine conditions the net effect on birthweight is probably in the range of 50-100 g.

Research with experimental animals makes it possible to study the effects of a specific nutrient not only on physical growth but also on tissue development and function. Animal studies help define the specific role of nutrients in growth and development, and they may provide a model for identifying the role of nutrition in human congenital anomalies or growth retardation. The effects on development of severe dietary protein deficits have been studied in experimental animals more extensively than those of any other nutrient. In general, severe lack of protein during gestation leads to a large number of fetal losses, and young carried to term have low birthweights, high mortality, and poor survival. Damage done during fetal development is apparently irreversible.[3]

A large part of the work on prenatal protein deprivation has been undertaken with an experimental model in which pregnant rats throughout the 21-day gestation period are fed either a control diet containing 24 percent protein or a protein-deficient diet containing 4 percent protein. In the control group, approximately half of the total weight gain is due to the combined placental, uterine, and fetal gain, and the other half to maternal gain. In contrast, the protein-deprived dams gain negligible weight and the pregnancy seems to proceed at the expense of maternal tissues.[18]

Although these findings might suggest that these fetuses are successfully parasitic, their development is far from normal. Examination of the skeletal system shows that the beginning of bone growth is significantly delayed. The intestine is shorter, narrower, and has fewer cells. A decreased uptake of lipid and protein has been observed, which interferes with normal postnatal growth. The kidney fails to develop fully. At the functional level, the glomeruli of the kidney, which are the cellular complexes that filter blood, are fewer in number and functionally impaired.

Since rats fed the protein-deficient diet eat less than the controls, they are deprived of energy as well. In an effort to separate the effects of protein deprivation from those of energy deficit, pregnant rats have been fed a diet that was adequate in protein but provided only as much energy intake as the protein-deprived rats consumed. The energy intake of the two groups was equal, but one group was receiving adequate protein. Offspring of the rats fed sufficient protein were smaller than the controls, but they did not show the severe developmental failure of the protein-deprived pups. The finding indicates that the lack of protein was the primary deficit.[18]

Further experimentation has attempted to assess the permanence of the damage to prenatally protein-deprived rats. When pregnant females were fed the 4-percent protein diet for 16 days, then switched to the 24-percent protein diet during the last 4 days of gestation, the fetal weight gain was greater than in the group fed only 4 percent protein for the entire 21 days. Decreases in cell number, size, and function of organs, however, were still evident. In other studies, pups of protein-deprived mothers were allowed to suckle with lactating rats that had been receiving normal diets. Even with long-term adequate feeding, the morphological and functional changes in their organs were not reversed.[3]

This work with rats shows that a lack of protein in the maternal diet delays maturation of the fetus, with the result that newborn pups that survive have low birthweights and fail to grow normally. Most of the organs that have been studied, including the intestine, kidney, liver, and brain, have fewer and smaller cells than do controls. Furthermore, many of the enzyme systems required for normal digestion, absorption, biosynthesis, and excretion are significantly reduced. Neither protein supplementation near the end of gestation nor adequate postnatal nutrition completely corrects these deficits, and catchup growth is generally not possible.

The effects of severe vitamin and mineral deficiencies on fetal growth and development have also been studied in experimental animals.[3] As with protein, the research confirms the indispensable role of these nutrients for fetal development. When maternal diets are severely deficient in a vitamin or one of the minerals, such as calcium, magnesium, zinc, copper, or manganese, the number of fetal deaths and congenital defects is increased and fetal growth is reduced. Often the changes are irreversible despite postnatal refeeding.

Although the mechanism(s) leading to these changes is not known for most of the nutrients, the underlying defects

leading to the changes associated with zinc deficiency have been studied quite extensively. Zinc is a constituent of a number of important metalloenzymes and is a necessary cofactor for many other enzymes. Two enzymes that have lowered activities in embryos of zinc-deficient dams are thymidine kinase and DNA polymerase.[3] Both are critical for cellular division and growth. Cytogenetic studies confirm that zinc deficiency causes aberrations of DNA synthesis. Chromosomal gaps and terminal deletions have been seen in the fetal liver and maternal bone marrow of zinc-deficient animals.[3] These studies suggest that nutritional deficits during gestation may have their primary effect on an aspect of cellular function that leads to a defect in tissue differentiation and growth. Survival depends upon the timing, nature, and severity of the deficiency.

- Physiological adjustments associated with various stages of growth and development have an effect on nutrient absorption, excretion, metabolism, and storage. Some of these adjustments for nutrient utilization in pregnancy have been identified, and changes have been made in criteria for normal blood levels of nutrients and in recommendations for nutrient needs during pregnancy.

Investigations show that the placenta has a critical role in adjusting maternal utilization of nutrients to assure better fetal support. In addition to determining the rate and selection of nutrient transfer, the placenta synthesizes and secretes hormones that modify maternal metabolism. A normal, metabolically active placenta is required for these transport and secretory functions.

One of the placental hormones, human placental lactogen (HPL), appears to have a marked effect on nutrient utilization. HPL is remarkably similar biologically and immunologically to growth hormone and may represent some type of growth factor for the fetus and/or placenta. HPL exerts major effects on maternal carbohydrate, lipid, and protein metabolism. The main role of HPL seems to be to assure a constant supply of maternal glucose to the fetus. To spare glucose for the fetus, maternal fatty acids are mobilized as the predominant oxidative fuel for the mother.[19] The net effect is a rise in the plasma concentration of free fatty acids and a decreased sensitivity to endogenous and exogenous insulin.

HPL may also increase the fetal supply of amino acids by restricting maternal utilization of protein in late gestation. Nitrogen retention data from human studies support the concept of protein storage in early gestation.[20] The process occurs when fetal needs for amino acids are small. Elevated progesterone and insulin levels in early

pregnancy may facilitate protein storage. As pregnancy progresses into the second trimester, fetal amino acid requirements increase as a result of rapid fetal growth. Active placental amino acid transport assures that fetal needs are met. The diet normally provides adequate amino acids for growth, and the previously stored protein serves as a backup system or as a protein source for early lactation. Changing hormonal patterns toward the end of pregnancy are consistent with the concept of withdrawal of protein from storage sites in the form of amino acids.

Iron provides an example of how utilization of a specific nutrient is altered to meet increased needs during pregnancy. Total iron needs for pregnancy are calculated to be about 675 mg, or about 5 mg/day, during the last half of gestation. If the usual 10 percent of dietary iron were absorbed throughout gestation, 50 mg iron would have to be consumed daily--an impossibility. However, iron absorption increases during pregnancy to as much as 30 percent. Thus a dietary supply of only about 17 mg iron daily would provide the needed 5 mg. This level of iron intake is feasible. These calculations are based on the assumption that adjustments in absorption are the only changes occurring in iron utilization. Reduced excretory losses are also working in the mother's favor in that she saves 120 mg or so during gestation when she is not menstruating. Mobilization of maternal iron stores may also be increased.

The story of iron utilization during pregnancy is far from complete. Studies on the relationship between blood volume expansion and fetal growth and efficiency of iron absorption are needed. Also, what is the recovery of iron with reduction in blood volume and uterine involution post partum? Results of iron absorption studies show, however, that the pregnant woman utilizes her dietary iron much more efficiently than nonpregnant women and may not be as dependent on iron supplementation as commonly thought.

Breast-fed infants are another example of how nutrient absorption is altered to meet increased needs. Milk is generally considered to be a poor source of iron. Reported values for iron in breast milk range from 0.2 to 0.8 mg/l. In spite of this low level, iron deficiency anemia is very rare among breast-fed infants. In fact, infants who are breast fed for the first 6 months of life have an iron nutritional status equal to that of infants fed formulas fortified with 8 to 12 mg iron per liter. This suggests that the bioavailability of iron from mother's milk is much higher than from cow's milk, although the mechanism for this difference is not known.[21]

Zinc is another mineral that appears to be better absorbed from mother's milk than from cow's milk. The

difference becomes critical in acrodermatitis enteropathica. This disease is seen in some infants soon after they are weaned to cow's milk and is characterized by widespread skin lesions and severe diarrhea. The symptoms are completely cured by feeding breast milk. The disease is now believed to be a result of a genetic inability to absorb zinc from the intestine, and the therapeutic value of breast milk is attributed to its content of a zinc binding ligand not present in cow's milk, which allows the zinc to be absorbed.[22] Possibly a similar ligand exists for iron.

- The nutritional status of humans is influenced first of all by genetic makeup, but the environmental milieu within which they exist probably has the greatest overall, long-term influence on food choices and, therefore, on nutritional health.

One of the most notable examples of how genetic differences affect food selection and nutrition is the condition of lactase deficiency among specific population groups. Three lines of evidence support the hypothesis that this condition is genetically predetermined: the prevalence of lactase deficiency among apparently healthy populations; the absence of this decline in enzyme activity among specific population groups; and the inevitable fall with age in lactase activity in most mammalian species.[23] Lactase deficiency, or primary lactose intolerance, is particularly common among children of some American ethnic groups, with a prevalence approaching 90 percent among the black, Mexican-American, and American Indian populations studied. The prevalence of lactose malabsorption in white children tends to be much lower, averaging 30 percent.

Of major concern is the relationship of lactose intolerance to nutritional status. Multiple studies have shown that, among children 1 to 9 years of age, no differences in milk consumption are found between the lactose-tolerant and the lactose-intolerant, regardless of ethnic groups. In older children, however, studies have suggested that some children with lactose malabsorption consumed far less milk than other lactose-intolerant children. Findings suggest that, among older children, a continuum of milk intolerance exists within the lactose-intolerant group, and this has been confirmed by studies showing higher intestinal lactase activity among lactose-intolerant children who drink average amounts of milk. Among all lactose-intolerant children, however, very few have symptoms after consuming 240 ml (8 ounces) of milk.

Even though milk intolerance is generally not a major problem, the question of the effects on bioavailability of nutrients in the presence of lactose malabsorption without symptoms of intolerance is important. In general, there are

few data available to address this question, but the data that do exist indicate that this is not a major problem, except perhaps in cases when overall intakes are marginal.

Besides primary lactose intolerance, a number of other genetic defects in nutrient utilization have been identified in the last 20 years. At present, about 270 inborn errors of metabolism have been described for man. Many are disturbances of amino acid metabolism, but carbohydrate, lipid, and vitamin metabolism are also affected. The most common of these, phenylketonuria, has been known for some time. Some of the other amino acid metabolic defects include alterations in the metabolism of branched-chain amino acids, such as maple syrup urine disease, hypervalinemia, homocystinuria, cystathioninuria, and defects of urea cycle metabolites. Recently, defects have been identified for trace element metabolism. These include acrodermatitis enteropathica, a defect in zinc absorption, and Menke syndrome, a genetic defect in copper absorption. By studying these genetic defects in nutrient utilization, investigators can determine nutrient metabolic functions and the effects of the lack of availability of a nutrient on cellular metabolism, growth, and development.

Data from investigations of environmental-nutritional interactions suggest that overall growth and development of children are affected by variations in their social environments and early experience. Like the effect of malnutrition in combination with socioenvironmental deprivation on mental development and function, early disturbances of mother-infant interaction, including feeding disturbances, can retard weight gain, and in more extreme cases, cause "failure to thrive."[12] Furthermore, an infant's or young child's altered nutritional status, which is reflected in physical appearance, general demeanor, and behavior, can affect the manner in which the mother or other primary caregiver responds to and cares for the child. Which comes first is not clear--the disturbance of the mother-infant interaction or poor nutrition. In either case, the end result is potentially devastating. Poor early nutritional-social experiences can significantly affect physical and behavioral development.

The link between early nutritional-social experiences and development needs further investigation. How do early experiences, for example, alter subsequent dietary patterns and nutrient utilization? Chronic early food deprivation in experimental animals has been shown to lead to metabolic changes that affect nutrient utilization for growth and development later. It has also been suggested that early exposure to taste modalities affect later food selection and, potentially, nutritional status. Research relating early food and nutrition experiences and later development

is likely to identify other relationships. Knowledge of these relationships will help define preferred dietary patterns and nutrient intakes during development.

III. Needs and Opportunities for Research

Because of the major technological advances of the past decade, opportunities for resolving basic biological questions and, ultimately, the more applied issues are better now than ever before. New instruments and methods, such as the electron microscope with an analytical microprobe, the ultracentrifuge, and immunoassays, have made it possible to investigate subcellular aspects of metabolism. Improved hormonal assays now allow researchers to evaluate better the effect of nutritional variables on homeostatic mechanisms. Furthermore, stable isotope tracers make it possible for tracer studies to be extended to growing infants, children, and pregnant and lactating women without exposure to radioactive risks. Extensive definition of animal models, particularly the nonhuman primate, will enable scientists to undertake the more invasive metabolic studies that would not be ethical in humans. Answers to fundamental research questions will provide tools and theories for rapid advances in the more applied or clinical questions. Five fundamental areas are described below. In-depth review of high priority, applied issues may suggest additional fundamental research areas.

Growth: Criteria for Evaluation

As pointed out elsewhere, anthropometric measures such as height, weight, and sometimes head circumference are the most common determinants of growth. The underlying assumption in evaluating these data is that "larger is better" or "faster is nicer." Methods of assessment of the composition of tissue gained during growth must be improved and optimal compositional gains must be defined. The capacity to define growth in terms of carbohydrate, fat, or protein content along with improved assessment by biochemical and functional markers (to be considered below) will greatly enhance the ability to evaluate such questions as the relationship of protein intake to growth, the appropriateness of mixtures for total parenteral nutrition, and the impact of chronic disease on growth. Without better criteria and methodology to judge growth, progress on questions in great need of answers will be impeded.

Assessment of Nutritional Status

Clinicians and nutritionists are constantly plagued by their relative inability to discern differences in nutritional status. Many are well aware of the questions on nutritional state that need to be answered, such as the effect of environmental pollutants and of iron supplementation, and breast milk vs. cow's milk, but sensitive methods to characterize either an individual or a population nutritionally just do not exist. Several approaches may provide better tools of evaluation:

- Information is needed on the sensitivity of more rapidly metabolized proteins to nutritional variations. Retinol-binding protein, prealbumin, or enzymatic proteins may be more sensitive to nutritional state than serum total protein or albumin.
- Trace elements and vitamins probably can be evaluated better by measuring a process, such as a metabolic reaction, dependent on the compound in question. Such a test more closely related to biological function should be more sensitive than blood or urinary concentrations, which may not change until stores are depleted or may fluctuate with dietary variations.
- Nonbiochemical functions such as behavior, cognitive ability, or immune function seem to respond to nutritional changes more quickly than circulatory or excretory nutrient levels. The sensitivity of these functions to nutrition needs to be defined. Also, improved methodology for assessing these functions is required.

Nutrition During Growth and Development

The continuous, well-programmed growth process results in metabolic and functional changes occurring in sequence throughout the life cycle. These changes lead to changes in nutrient utilization and thereby alter nutrient requirements and criteria for evaluating status. Until enzymatic, endocrine, metabolic, and functional changes have been "mapped out" for each stage of human growth, studies on questions such as the effect of physical activity or high sucrose diets on development cannot be answered because physiological norms have not been established.

Maternal-Fetal Interactions

It is difficult to associate fetal malnutrition and growth retardation with evidence of poor uterine blood flow,

placental function, or other direct fetal factors. Several questions need to be answered to sort out factors that alter intrauterine growth. Some fundamental issues include:

- Continued elucidation of factors affecting placental blood flow and how those factors affect nutritional supply to the fetus.
- Intensive study of placental metabolism and physiology, and definition of techniques for in vivo assessment of placental function.
- Consideration of mechanisms by which the fetus may exert autocontrol over placental function: Is it true that the fetus is only a passive recipient of nutrients without some mechanism(s) for autocontrol?
- Patterns of substrate utilization by the developing fetus.
- Humoral mechanisms regulating growth and differentiation of specific cells or groups of cells within the fetus.

The basic issue here is the contention that questions regarding altered intrauterine growth, a major "nutritional" problem, can be resolved only by clarifying the biology of maternal-fetal interactions.

Health Education and Nutrition

Although countless biologic, neurophysiologic, and behavioral questions need to be answered in order to understand fully the genesis of obesity, the major push toward public nutrition education creates both problems and opportunities of a fundamental nature. An implicit assumption of this effort is that health education "applied" at an early and appropriate age will be of major importance in modifying the subsequent behavior of children. It seems clear that the methods by which behavior can be changed must, if possible, be defined.

IV. Priorities and Recommendations

Set forth below are recommended 5-year research objectives. The recommendations have been developed in the framework of four broad major questions: Are current

clinical practices, recommendations, and standards in given issues of nutrition and health appropriate? Are the biological or methodological issues that are involved basic to the resolution of other questions? In terms of recent and current research, is the issue now ripe for investigation? Is existing technology such that the issue can probably be resolved in the next 5 years? These questions are predicated on the principle that research should be supported on the basis of scientific excellence.

Priority Category I

(Evaluation of current clinical practices, recommendations, or standards)

To define the effects of different levels of iron supplementation during pregnancy on maternal nutrition and function and on fetal growth and development.

Iron toxicity will occur in humans if a large intake of a highly available iron dose is continued over a long period of time. The result is a generalized increase in the iron content of the body tissues, particularly of the liver and the reticuloendothelial system. Once iron is absorbed, it is not readily eliminated. Eventually, fibrotic changes occur in the affected organs.

Currently, the National Research Council recommends that all pregnant women receive 30 to 60 mg supplemental iron daily.[7] This recommendation was made because of the low iron content of habitual diets of American women and their low existing levels of iron stores. Much of the research underlying this recommendation was done before iron-enriched breakfast cereals, containing 10 mg iron per serving, became commonplace. In addition, because of nutrition education programs, many women are aware of the need routinely to select good sources of iron in their diets. Because of these changes, the question of routine iron supplementation for all pregnant women should be reevaluated.

At greater risk of iron toxicity due to chronic supplementation are those iron-sufficient women who receive as much as 200 mg iron daily. Iron-deficiency anemia is more common during pregnancy because of expansion of blood volume and fetal demands. Pregnant women who develop clinical signs of iron deficiency, such as low percent saturation of transferrin or low hemoglobin levels, should be treated orally with about 200 mg medicinal iron daily. In an attempt to prevent iron deficiency during pregnancy, some

clinics routinely treat all women with as much as 200 mg iron daily whether there is evidence of iron deficiency or not. This practice needs to be evaluated critically.

There is some preliminary evidence that routine iron supplementation of iron-sufficient, healthy pregnant women may be a risk to the mother and the fetus. In a British study, the mean corpuscular volume of red blood cells increased in pregnant women given iron supplements during pregnancy.[24] Does this morphological change alter oxygen transport to the fetus? Do other erythrocyte changes and tissue degeneration occur with the chronic, higher supplementation levels? This very critical question should be pursued immediately because the clinical management of all pregnant women with regard to iron is at issue.

To determine the growth rate that best supports physical and functional development.

Currently, when birthweights, physical size, and growth rates are evaluated, "the bigger, the better" is assumed to be the standard. But are bigger children stronger, smarter, and healthier? Is being the biggest an advantage? Is a faster growth rate the best? These questions have not been adequately answered even though physical size is often used as a standard for assessment of nutritional status and health.

Some early rat studies showed that a lower energy intake in the early post weaning period led to a longer life span than when the animals were liberally fed.[1] This finding suggests that delayed growth and maturation rates brought about by restriction of dietary energy early in life lead to a longer life. Epidemiological studies do not confirm the same longevity effect in humans, for in parts of the world where food intake is chronically low, the average life span is shorter than in richer countries with a more generous food supply. It should be remembered, however, that richer countries usually have better public health practices as well; this evidence really does not rule out a relationship between growth rate, size, and health in humans.

Statistics on infant mortality provide some human evidence that beyond a certain point, bigger is not better. There is an increase in infant mortality for birthweights above a critical point as well as for birthweights below a critical point. This observation needs to be followed up with well-controlled investigations on functional development and morbidity in infants and children who are in the upper percentiles of growth charts and who are experiencing fast growth rates.

To determine the effects of parenteral nutrition during infancy on gastrointestinal development and function.

Low-birthweight infants and those born with congenital defects of the gastrointestinal tract often require total parenteral nutrition (TPN) for survival. In 1977, 7.1 percent of all births in the United States were low-birthweight--i.e., 2,500 g or less. Statistics collected 1 year later showed that 2.3/1,000 births in Metropolitan Atlanta had either atresias or stenosis of some segment of the gastrointestinal tract. Thus, an appreciable percentage of all live births in the United States are in need of parenteral nutrition.

Introducing nutrients solely through the vein means that the gut may not be exposed to nutrients and other food components during the early stages of development. Experimental studies suggest that enzyme maturation in the mucosal cells is responsive to substrate (or nutrient) exposure. Other aspects of gastrointestinal development may also be influenced by exposure to food. What then are the effects of parenteral feeding on development of the gastrointestinal tract? Is long-term function compromised in individuals fed parenterally early in life? Should some combination of enteral and parenteral feeding be used to support normal gastrointestinal tract development? If so, what foods are the best choices for enteral feeding, and is there an advantage in feeding human milk rather than formulas? Although it is important to continue current investigations on parenteral nutritional requirements of infants, the impact of this mode of feeding on gut development needs investigation to assess better the risk and benefits associated with this means of nutritional support.

To determine the nutritional requirements of pregnant women with metabolic disorders, such as obesity, hypertension, diabetes mellitus, or inborn errors of metabolism.

Metabolic disorders in the pregnant woman increase the risk to the fetus and to the mother. Dietary modifications are often used to manage the disorders and lower the rates of complications. The advice often given to obese, hypertensive, or diabetic pregnant women is to eat regularly a "well-balanced" diet. Such a diet is further interpreted as one that emphasizes animal sources of protein, fruits, and vegetables and deemphasizes carbohydrate sources, especially cakes, cookies, sweet rolls, and pies.

The net result is that the percentage of energy provided by protein is increased. Although reduction of simple carbohydrate sources is well justified for the diabetic woman, the merits of the high protein diet that often results have not been determined for her or for the obese and hypertensive woman.

The Food and Nutrition Board of the National Research Council recommends 76 g protein/day during pregnancy.[7] This is 13 percent of the recommended daily energy intake. With emphasis on dietary protein sources, total protein intake may be increased by 50 to 75 percent so that over 20 percent of the energy is provided by protein. Such an increase in high quality protein will induce the formation of hepatic amino acid catabolic enzymes and result in increased urea. The consequences of these metabolic adjustments during pregnancy have not been evaluated. Does the high protein intake jeopardize fetal glucose supply? Is maternal hepatic metabolism stressed? Basic research of the optimal distribution of energy sources from carbohydrate, protein, and fat for healthy and high-risk pregnant women is needed.

Other questions exist regarding the nutritional management of high-risk pregnant women. Are the energy and nutrient requirements of obese pregnant women different from those of nonobese pregnant women? Is the pattern of weight gain and composition of weight gain different in obese pregnant women? Is sodium utilization altered in the pregnant woman with chronic hypertension? What level of dietary sodium best supports normal physiological adjustments of pregnancy in the hypertensive woman? Is the utilization of other nutrients, such as protein or trace elements, altered in the hypertensive pregnant woman? Is nutrient utilization, especially energy, protein, vitamin B_6, and chromium, altered in the diabetic pregnant woman? What is the pattern of weight gain and the composition of weight gain in the diabetic woman? How do inborn errors of metabolism alter the utilization of vitamins and minerals?

<u>To learn if reduced activity precedes or follows obesity in children.</u>

The incidence of obesity varies with locale (urban children tend to be more obese than rural children), but on the average about 10 percent of U.S. children are obese.[25] There is evidence that the incidence is increasing.

The value of exercise in the prevention or treatment of obesity is well established, but the role of energy expenditure in the etiology of the disorder is not well understood. It has been noted that many obese youngsters eat less than average but are incredibly inactive. Is their inactivity a consequence of obesity or does it contribute to the problem? If it precedes obesity, when and how can activity patterns be optimally altered in children?

Priority Category II

(Biological or methodological questions crucial to improving the ability to make appropriate nutritional recommendations)

To advance knowledge on the mechanisms leading to intrauterine growth retardation (IUGR), and to assess the postnatal consequences of this condition.

IUGR is thought to be a result, at least in part, of fetal malnutrition. Two factors critical to fetal nourishment are normal placental function and maternal blood volume expansion. Although research has been done on identification of nutritional predictors of IUGR based on placental nutrient transport and endocrine function, and on the association of maternal blood volume expansion with birthweight, factors that alter normal placental and circulatory function have not been worked out. Presumably, hormonal function is involved in some manner. Can abnormal hormone levels be used therefore to predict IUGR? Also, the postnatal problems of the IUGR infant caused by a lack of nutritional stores deposited during gestation need to be studied. Specific research objectives that should be addressed to accomplish this goal are:

- To ascertain how nutritional factors influence placental development and metabolic function.

Normal placental development and function are essential for support of fetal nutrition and development. Infant birthweight and placental weight are highly correlated. Does fetal demand affect placental size or does placental size determine fetal growth? Do abnormalities in placental development precede reductions in fetal growth rate due to nutritional insufficiency? What are the nutritional requirements for normal placental development? After the placenta reaches its mature size, what are its metabolic requirements for normal functioning? How can reduced placental size be detected during gestation? Can earlier reductions in placental growth rate be corrected later in gestation? How is abnormal placental function correlated with maternal state of nutrition? Answers to these questions may make it possible to improve fetal nutrition and development by modifying placental function.

- To identify the role of the placenta in facilitating maternal physiological adjustments to pregnancy and in modifying nutrient absorption, retention, metabolism, and excretion.

Numerous physiological changes occur during pregnancy, but the timing and degree of change vary. For instance, different patterns of weight gain, fluid retention, and blood volume expansion have been observed in pregnant women. Are these differences due to differences in placental hormone secretion? Do women with abnormalities in placental development have different patterns of physiological changes? How do differences in placental hormone secretion

affect maternal nutrient absorption, accretion, metabolism, and excretion? In brief, what is the impact of the condition of the placenta on the mother, and what are some maternal markers of poor placental development and function?

Of those infants born at term, some are small because they grew slowly throughout gestation; others are small because they grew normally to a point and then growth stopped or slowed appreciably. Why do these different patterns of intrauterine growth retardation occur? Do differences in placental function contribute to these growth abnormalities? Do certain maternal nutritional imbalances alter fetal growth in one way, whereas other imbalances affect it differently? Are there maternal biochemical or functional markers of IUGR? Can different patterns of IUGR be differentiated by these markers?

- To ascertain the relationship between maternal nutrient intake, placental function, blood volume expansion, and fetal growth and development.

A direct correlation between birthweight and blood volume has been observed.[26] Also, there is limited evidence that food or protein restriction during pregnancy is associated with a smaller maternal blood volume.[27] Thus, one of the links between maternal nutrition and fetal growth and development may be blood volume expansion. Studies are needed to extend information in this area. What is the hormonal influence on blood volume during pregnancy? How do nutritional imbalances affect hormonal levels and blood volume? Specifically, what is the effect of sodium and protein restriction on blood volume expansion?

- To determine what penalties the IUGR infant suffers in postnatal life due to lack of stores laid down in pregnancy and to assess how this condition differs for the preterm infant.

Growth-retarded and premature infants are both born with reduced energy, mineral, and fat-soluble vitamin stores. Do these deficits cause any postnatal functional abnormalities? Does the course of postnatal repletion of these stores differ between premature and IUGR infants? What growth rate is conducive to both tissue nutrient repletion and normal development? How do the nutritional needs differ for premature and IUGR infants, and what feeding regimen best supports their tissue repletion, catchup growth, and development?

To identify markers of nutritional status through improved understanding of the physiological adjustments in nutrient utilization that occur during various stages of growth and development.

Data collected on normal physiological adjustments in nutrient utilization during development will provide a basis for the establishment of standards for normal changes in biomedical, physical, and functional parameters. Subsequent research could then be designed to ascertain which of these parameters are sensitive to nutritional imbalances. The parameters would be useful markers of nutritional imbalances. It is especially important to emphasize the need for noninvasive markers for use in field situations with little or no traumatic effects on the child. Such techniques are in demand for evaluations of the nutritional health of the U.S. population and for evaluations of the impact of public nutrition programs within the United States.

Specific research objectives are:

- To determine how nutrient utilization and requirements are modified during the various stages of human pregnancy and lactation, and to find out what physiological adjustments are associated with these modifications.

To date, most of the studies of human nutrient requirements during pregnancy have focused on the last half of pregnancy. It is often assumed that needs are lower in the first half when fetal growth is minimal. This assumption may not be valid because tissue changes and weight gain during pregnancy seem to be biphasic, with maternal accretion occurring primarily in the first half and fetal growth in the last half. What hormonal changes and metabolic adjustments occur when a larger proportion of tissue synthesis occurs in the fetal compartment? How does this switch affect total nutrient absorption, storage, and excretion? Do dietary nutrient requirements differ according to the stage of pregnancy? If so, how?

Some nutrients during pregnancy have been studied inadequately. These include energy, vitamins B_6 and B_{12}, pantothenic acid and biotin, and trace elements. Although other nutrients have received more attention, they still require further investigation with regard to the above questions.

Except for protein and vitamin B_6, the recommended nutrient allowances for lactating women are the same as or greater than those for pregnant women.[22] The energy cost to produce 850 ml/day of milk is about 750 kcal. It is assumed that about one-third of this energy need comes from fat stores deposited in pregnancy and the remainder from the diet. These calorie demands on the mother may also facilitate postpartum weight loss. However, maternal weight changes during lactation have not been carefully studied. What is the usual pattern of weight change? How does this

pattern vary and what are the sources of variation? More precisely, what is the effect of lactation on maternal fat stores? Furthermore, does lactation alter maternal stores of other nutrients in calcium, zinc, vitamin A? Do the effects differ with poor maternal nutrition during gestation and/or lactation?

- To ascertain the time course for postpartum or post lactation physiological adjustments in nutrient utilization and to identify good markers of maternal nutrient depletion in the postpartum or postlactation period.

Studies of the effect of pregnancy on nutrient utilization generally stop with birth. It has not been determined if nutritional stores possibly utilized during pregnancy or lactation are replenished at a later time. Also, it is not even known how quickly the anabolic state of pregnancy or lactation reverts to a state of equilibrium. How soon do nutrient absorption, storage, metabolism, and excretion rates return to nonpregnancy levels? How does the rate of these changes vary with maternal nutritional and physiological condition? If postpartum changes, for instance, are sensitive to maternal nutrient deficits, what are some biochemical or functional markers of maternal depletion? What nutritional intake best supports the postpartum or postlactation adjustments in nutrient utilization? Do nutrient intakes during pregnancy and lactation, or the decision to lactate or not, affect health status in later life?

- To define physiological changes that alter nutrient utilization and requirements during the first year of life and during childhood.

Except for energy and protein, information on the nutritional requirements for infants is very limited. Allowances for the first 6 months of life are often based on human milk composition.[22] With the use of noninvasive techniques, such as stable isotopically labeled nutrients, vitamin and mineral requirements need to be assessed in infants. The effects of variation in growth rate, body size, activity levels, and metabolic or functional differences on nutrient utilization and, therefore, on nutrient requirements need to be studied. Biochemical, physical, or functional markers of nutritional imbalances also should be identified.

- To estimate the nutritional impact and nutritional requirements of the adolescent growth spurt.

The growth spurt during early adolescence is second in intensity only to that in infancy. The peak height change

in males is 10 cm (4 inches) per year, a rate of growth equal to that of a 2-year-old boy.[28] For girls, the peak height change is 8 cm (3 inches) per year. The nutritional impact of this growth spurt is not well defined. How much do the needs for energy and other essential nutrients increase during the prepubertal growth spurt? Does nutrient utilization change at this time? Are nutrients utilized more efficiently during the growth spurt? What is the effect of nutrient deficits on the growth spurt? How is the growth spurt altered by the previous state of nutrition? What are the consequences of inadequate diet during the growth spurt?

- To develop noninvasive indicators of nutritional status and nutrient utilization.

Many tests of nutritional status involve drawing blood. This is a traumatic experience for most children, and it is not appropriate to take from small infants the large quantities of blood required for a thorough evaluation. Also, it is not feasible in a field setting to rely on blood sampling for evaluations of large populations. Some reliable, quick, noninvasive tests are needed to improve our ability to assess nutritional status.

To approach this problem, more attention should be given to functional performance tests, such as cognitive function, muscle performance, work performance, visual function, gastrointestinal function via breath analysis, and taste perception tests. Noninvasive sources of cells include the buccal mucosa and hair bulb. The response of these tissues to nutrient imbalances needs further testing. Breath gas analysis (H_2 and $^{13}CO_2$) has been useful in assessing carbohydrate and lipid digestion and absorption. This method should be developed further and used to assess other aspects of gastrointestinal function, such as protein and lipid digestion and absorption using C^{13} and H_2 labels. Breath analysis is also useful in assessing bacterial overgrowth, ileal dysfunction, and intestinal transit time.

<u>To identify the impact of environmental variables on nutrient requirements</u>.

Cultural and regional influences on food choices, early exposure to food and subsequent taste preferences, and climatic variations are some of the many environmental factors that can influence nutrient utilization and requirements. Definition of their impact on human nutrition or on the capacity of humans to adapt to them will enable nutritionists to ascertain the unique nutritional needs of individuals in various environmental settings.

Research objectives that demand immediate attention in this area are:

- To find out how alternative dietary practices and nutritional abuses affect maternal nutrition and fetal growth and development.

Because of health, economic, ecological, and religious concerns, people are eliminating animal products from their diets. The degree of elimination varies from total exclusion to only red meats. These dietary modifications will alter total nutrient intake, dietary nutrient ratios, total dietary fat and carbohydrate, kinds of dietary fat and carbohydrate, and the intake of nonnutritional components such as fiber. Do these modifications cause any changes in maternal nutrient utilization? Are maternal physiological changes different? Is fetal growth altered? Are there functional, biochemical, or physical differences in the postnatal growth and development of infants due to the diet of vegetarian mothers? In brief, is there any health risk or benefit to the mother or child associated with these dietary practices? What is the effect of megadoses of vitamins and minerals during pregnancy on fetal and neonatal growth and development or on the mother's physiological adjustment to pregnancy?

- To define what anthropological and cultural factors influence dietary practices during gestation and post partum, and to learn how they affect maternal nutrition.

Anthropological and cultural influences on diets during pregnancy and post partum have been identified, but how widely these customs are practiced in the United States is uncertain. Also, the impact of the practices on maternal nutrient intake and status is unknown. Studies are needed on such practices in the United States--how long they last, what their prevalence is, and whether they are detrimental or beneficial to maternal and infant nutrition and health.

- To determine how environmental differences, such as climate variations, alter infant nutrient requirements.

Temperature, humidity, sun exposure, and air pollution vary within the United States. Little attention has been paid to how these climatic differences affect nutrient utilization and needs. How does the climate influence water and electrolyte requirements of infants and children? Are activity and energy needs affected by climate? What is the effect of high temperatures on sweat losses of electrolytes and trace elements? How are vitamin D needs affected by exposure to the sun? Does air pollution affect nutrient absorption, especially of minerals? Are vitamin E and selenium needs in infants increased by air pollution? To what extent does inadequate clothing in low ambient temperatures alter energy requirements and/or growth rate?

- To determine if there are racial differences in nutrient utilization of children.

Although there is evidence that American blacks have different growth patterns, lower hemoglobin levels, and more highly calcified bones, ethnic differences in nutrient utilization and requirements are not now recognized. Are nutrients absorbed, stored, metabolized, and excreted differently because of racial differences? If so, how does this alter biochemical, physical, and functional markers of growth and development? Should different criteria be used for evaluation of nutritional status in various ethnic groups? Are nutrient requirements altered by ethnicity?

- To learn how taste perception develops in infants, whether it differs between breast-fed and formula-fed infants, and how it affects nutritional status.

The details of the developmental process producing taste perception are largely unknown. What is the sequence of timing of development of the four taste sensations--sweetness, saltiness, sourness, and bitterness? What are the sources of variation in this developmental process? Are early flavor preferences or aversions associated with breast feeding? With formula feeding? Are later dietary preferences for sweetness or saltiness influenced by early feeding practices? Is there an association between later disease experience, especially obesity or hypertension, and early taste preferences? Are there familial, racial, or genetic differences in taste preferences?

To determine how growth and development are influenced by repeated, but brief exposure to hunger or malnutrition, physical activity, or chronic disease.

Physical growth and development are a synthetic process requiring a constant, adequate supply of essential nutrients. Two conditions that can alter the availability of nutrients for growth are physical activity and chronic disease. What kind of an impact do these processes have on growth? Also, as expected, chronic mild to severe malnutrition alters anthropometric aspects of growth. In the United States, more children are probably exposed to repeated, brief periods of hunger or poor nutrition, such as skipping breakfast or consuming a high-carbohydrate, high-fat, low-protein diet, than to chronic malnutrition. How do these dietary patterns alter growth? Three specific research objectives should be addressed.

- To ascertain why growth retardation occurs in infants and children with chronic systemic diseases, such as hepatic insufficiency, congenital heart disease, inflammatory bowel disease, or ulcerative colitis.

Growth retardation can occur in infants or children with chronic systemic diseases that apparently do not directly affect nutrient utilization. Is this growth retardation due to poor appetites and, therefore, reduced nutrient intake, or are there metabolic defects in nutrient utilization leading to growth retardation? In these disorders is growth improved with parenteral feeding? Is there an association between activity and growth in these children? Do these chronic systemic disorders alter nutrient requirements? If so, how?

- To ascertain the effect of different activity patterns on energy requirements and growth.

Activity levels vary widely among children and also for the same child. Does the level of activity change during growth spurts? How does activity affect appetite and food intake? What is the impact of different activity levels on dietary energy requirements? If energy is restricted, what is altered first, activity or growth?

- To evaluate the effects of nutritional imbalances and hunger on behavior and cognitive function.

Although little attention has been paid to the effect of nutrient deficiencies and short-term food deprivation on cognitive performance, there is evidence that the state of nutrition and cognitive function are related. Behavioral changes have been noted in malnourished children and iron-deficient children; the impact of deficiencies of other nutrients remains relatively unexplored. Further investigations are needed to define the relationship between cognitive performance and nutrition. What cognitive functions are most susceptible to nutritional imbalance? Are the changes evident with marginal nutrient deficits, such as 70 to 80 percent of standard? Does hunger, such as that caused by skipping breakfast or lunch, alter cognitive performance? How useful is cognitive function in assessing the nutritional state of infants and children?

Lower Priority Research Objectives

Objectives consistent with the mission of the NICHD but falling outside the range of broad major questions for high priority research are:

I. The Preimplantation Stage

- To determine the effect of nutrition on the function of the sperm, ova, and reproductive organs.

- To advance knowledge on the role of nutrition in fertility.

2. The Pregnant Woman

- To ascertain differences that exist in nutrient requirements and utilization by healthy, pregnant women, and what the sources of these differences are.

- To determine how differences in weight gain, such as total gain and pattern of gain, affect fetal or neonatal growth, development, and nutritional status.

- To learn the nutritional impact of pregnancy in adolescent girls.

3. The Lactating Woman

- To determine the effects of the maternal nutritional state during gestation and lactation on the lactation process and infant growth and development; and to determine the nutritional requirements that best support maternal nutrition and lactation.

- To evaluate the effects of differences in infant size, gestational age, and growth rate on the lactation process.

- To learn if there is a relationship between maternal nutrition and the complaint of "milk insufficiency."

4. The Nonlactating, Postpartum Woman

- To assess the nutritional consequences of postpartum contraceptive practices, including the number and spacing of births, on women and their children.

5. The Infant

- To ascertain what nutritional factors affect perinatal mortality and morbidity, and to develop a predictive pattern of outcome.

- To find out how various infant diets (human milk versus different commercial formulas) affect infant nutrient intake, utilization, growth and development, and disease experience.

6. Children

- To define the nutritional requirements of handicapped children.

- To determine the effects of nonnutritional components in food on growth, development, and health of children.

7. The Adolescent

   - To learn how the nutritional state, specifically nutritional stores, influences the onset of puberty.
   - To define the major factors influencing the dietary practices of adolescents.
   - To ascertain the effect of alcohol, tobacco, marihuana, and prescription drugs on nutrient status and requirements, and how the use of these substances influences development.

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