Fifty-Five-Year Personal Experience with Human Nutrition Worldwide

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Annu. Rev. Nutr. 2007. 27:1–18

The *Annual Review of Nutrition* is online at http://nutr.annualreviews.org

This article's doi:
10.1146/annurev.nutr.27.061406.093746

0199-9885/07/0821-0001$20.00

Key Words

protein, amino acids, kwashiorkor, infection, atherosclerosis, single-cell protein, cholesterol, Incaparina, iron deficiency

Abstract

By 1950 the vitamins had been identified, but little was known of their functions. Beriberi, pellagra, and ariboflavinosis were disappearing, but kwashiorkor and/or marasmus were common in most developing countries. Requirements for protein were still uncertain, and those for essential amino acids or essential fatty acids were unknown. The author's contributions in the field of vitamins began in the 1950s and have been reported in more than 650 publications and in 20 books or monographs. These contributions include establishing the Institute of Nutrition of Central America and Panama, the Department of Nutrition and Food Science at the Massachusetts Institute of Technology, the World Hunger Program of the United Nations University, and the International Nutrition Foundation. His scientific contributions include identification of synergistic interactions of nutrition and infection, use of potassium iodate for fortifying crude moist salt, research in the epidemiology of kwashiorkor and marasmus, development of a successful low-cost protein-rich food for infants and young children, establishment of human protein requirements, and investigation of single-cell protein for food use.

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PROLOGUE

The attack on Pearl Harbor on December 7, 1941, found me an instructor for advanced biology courses at Ohio Wesleyan University after obtaining a PhD in Biology at Harvard University the preceding June. I was already admitted to the University of Rochester Medical School with a research assistantship and laboratory in the Department of Vital Economics (Nutrition and Endocrinology).

In June 1942, I arrived in Rochester, New York, to find most departments pioneering in nutrition. Dean G. Whipple (Pathology) was demonstrating the role of amino acids in protein synthesis through plasmaphoresis studies in dogs, K. Mason (Anatomy) was studying vitamin E, W.R. Bloor (Biochemistry) was describing the metabolism of fatty acids, and S. Clausen (Pediatrics) was researching vitamin A in children. In Vital Economics, E. Nasset was exploring the metabolic role of intestinal flora, and R. Sealock was developing microbiological methods for amino acid analysis. The department head, J.R. Murlin, had obtained an army contract to study nitrogen balance and exercise capacity with various diets. My role was to analyze B vitamins in the diets using recently developed microbiological methods.

After I graduated from medical school in 1945, a rotating internship in Gorgas Hospital, Panama Canal Zone, enabled me to review dietary differences among socioeconomic and racial groups in relation to complications of pregnancy in the records of 10,000 patients seen by a single physician. Contrary to expectations, nutrition did not account for the sharp differences in hypertension and pre-eclampsia among groups (47).

Upon my return to the University of Rochester in 1946 as a postdoctoral fellow, I obtained support for studying the effect of nutrition on complications of pregnancy among women in the City of Rochester. Again, no nutritional effect on pre-eclampsia was found. During this period, I interacted closely with I.M. Hoobler, director of the Children's Fund of Michigan, and W.J. Darby, who were conducting studies that yielded similar results.

Stimulating acquaintances in those early years were H. Sebrell, who had worked with J. Goldberger in demonstrating the role of diet in pellagra; C.A. Elvehjem, who described niacin as the cause of "black-tongue" in dogs, triggering recognition of its role in pellagra; P. Gyorgy, who identified pyridoxine and biotin; W.R. Rose, who determined human requirements for individual essential amino acids;

and C.G. King, who identified the structure of ascorbic acid. Other acquaintances included R.R. Williams, who synthesized thiamine; H. VonDam, the discoverer of vitamin K; E.V. McCollum, the discoverer of vitamin A; W. Aykroid, the first director of the Nutrition Division of the Food and Agriculture Organization (FAO); Cicely Williams, who first described kwashiorkor, HAPC Oomens, who crusaded against avitaminosis A and keratomalacia in Indonesia, R.A. McCance and Elsie Widdowson, who investigated starvation in prisoners of the Germans at the end of World II; G. Goldsmith, who did classical clinical studies of pellagra; and A. Keys, who studied human starvation. Later, Keys and my lifelong friend, M. Hegsted, would quantify the influence of lipids on cholesterol levels. The aforementioned as well as many other pioneers in the field strengthened my commitment to nutrition.

INCAP YEARS: 1949–1961

Beginnings

After three years of fellowship and residency at the University of Rochester, I agreed to organize and direct an Institute of Nutrition of Central America and Panama (INCAP), based in Guatemala. My medical school professors felt that I was throwing away a promising academic career. How wrong they were! Although we started in September 1949 in an adobe building with only three laboratories, three offices, and a conference room/library, an operating budget of $37,500, and no PhDs, the discoveries and publications followed rapidly. By 1955, we had a large, new, permanent building, which was provided by Guatemala. In 12 years—with increased country quotas and National Institutes of Health (NIH), foundation, and industry research grants—the annual budget was about $900,000, and the heads of seven divisions had doctorates. By its 25th anniversary, INCAP had published 695 scientific papers in English and as many in Spanish.

Kwashiorkor and Marasmus

Cicely Williams first described kwashiorkor (K) in what is now Ghana in 1933 (73). Her excellent publication was overlooked until J. Brock (World Health Organization; WHO) and M. Autret (FAO) toured Africa and reported to the second FAO/WHO Expert Committee in 1951 that the disease described by Williams was widespread throughout Africa. At the meeting, I recognized it as a condition common in Central America.

We began to study intensively both K and marasmus (M) using one cot and one crib for six children on an overcrowded pediatric ward in the general hospital. With a nutritionist to supervise their food intake, the K children rapidly lost edema, skin lesions, anorexia, and apathy. However, they failed to gain weight for many more weeks (41). After we acquired a research unit of six individual cubicles in a private pediatric hospital, we never again saw a stationary period in the treatment of K. We then realized that it was the adverse nutritional impact of multiple cross-infections in an open ward that prevented these children from gaining weight (42).

We found that the signs and symptoms of K (edema, pigmented skin lesions, pale pluckable hair, profound apathy, and serum biochemical changes) disappeared with skim milk alone administered by gastric tube. Of course, it then became necessary to add vitamins and minerals for further recovery (44). Concurrently, J. Brock and J. Hanson in South Africa achieved initial recovery with an amino acid mixture and energy source. We developed guidelines for treatment of K and M that nearly eliminated deaths in the hospital, which previously had a high rate (4, 5). Since nearly all patients had concurrent diarrhea and pneumonia, we routinely administered penicillin.

As we explored the epidemiology of K, we concluded that in Central America it was always acutely superimposed, mainly as the result of preceding infection(s), on some degrees of chronic undernutrition (41). M usually developed slowly over months or years before death threatened, whereas K could develop in a few weeks and was often fatal soon after the classical symptoms appeared. We conceptualized severe malnutrition in Central America as a triangle; the hypotenuse represented increasing degrees of chronic undernutrition, with K superimposed as an acute episode on any degree of marasmus (38).

M alone was characterized by wasting but did not show the clinical signs and symptoms of K. Nor were the abnormal biochemical changes present characteristic of severe protein deficiency.[1] We concluded that the child with M was wasting from lack of food and living on his or her own tissues. The latter supplied a balance of energy and good-quality protein. At first both body fat and muscle are metabolized, but once all of the fat has been consumed, lean body mass must supply both energy and protein, and the end is near.

The Incaparina Story

The most frustrating aspect of field visits at this time was our inability to help women with severely malnourished children who approached us in the villages we visited. They could not afford the protein sources we could suggest. Milk was too expensive and their diets had almost no meat. An egg could be exchanged for corn to provide a meal for the entire family. We set about to develop a culturally acceptable plant-based complementary food for older infants and young children at the lowest possible cost.

Soy, a potential protein source, was not grown in the American tropics, and peanut meal, another protein source, was too costly. Cottonseed meal was being shipped to Europe in large quantities for feeding ruminants. It was cheap and its protein quality was an excellent complement to the amino acid pattern of maize protein. However, it contained unacceptable amounts of the toxic pigment gossypol. With guidance from A. Altshul, a specialist at the United States Department of Agriculture (USDA) Southern Regional Research Laboratory, we worked with a large mill in Nicaragua to press the seed at a lower temperature and pressure so that the gossypol was expressed with the oil. A mixture containing approximately one-third cottonseed meal and two-thirds maize meal with added vitamins and minerals had essentially the same protein value and more complete micronutrient content in comparison with milk, at one-third the cost. Guatemalan mothers cooked and flavored it as traditional maize gruel (atole) (34).

Although it was intended as a complementary food for infants and young children when breast milk was not sufficient, it is still extremely popular among Guatemalans of all ages and is recognized as nutritious. The concept of Incaparina was patented for free use with the indigenous protein resources of any developing country.

In 1967, India was experiencing famine and was dependent on wheat donated by United States. This provided for older children and adults, but not for infants and young children. I was invited by the government of India to develop an acceptable food for young children, patterned after Incaparina, using the donated wheat and local complementary protein sources.

My first day in India was spent in New Delhi with Venkatachalam, Deputy Director of the Indian Council of Medical Research, working out an agreement on the nutritional composition of the new food based on United Nations (UN) Protein Advisory Group (PAG) recommendations. The second day was spent in Hyderabad, looking at potential sources of oil seed meals. Suitable cottonseed flour was not available, but peanut meal was abundant. The problem was aflatoxin produced by a ubiquitous soil mold under conditions of

[1]So-called classical kwashiorkor without chronic weight loss was not seen in Central America and was exceedingly rare even in Jamaica, where it was first described. The "mehlnahrschaden" or "starch dystrophy" of 19th- and early 20th-century Europe was the development of severe protein deficiency with little or no loss of weight for length because of abundant calories.

high humidity. Although chemical processing to remove it was too costly, a solution was provided through using conveyor belts with workers on each side picking out moldy peanuts. With strict supervision and sampling of each batch before use, meal could be produced that met PAG standards for cottonseed flour in complementary food mixtures for child feeding.

I spent the third and fourth days at the Central Food Technology Laboratory in Mysore, developing various formulas that would meet specifications and testing the formulas with female staff. The name "balahar" was chosen for the new food source because it meant "child food" in most of the Indian languages. At the beginning of the next week, the Ministry of Health in New Delhi approved the proposal, and construction began promptly on factories to produce balahar for relief purposes. Balahar proved valuable in the emergency and continued to be available as a relief food for many decades. An instant form, balamul, is commercially available. Some years later I led a team to assist Thailand with complementary food development (38). The concept of Incaparina and balahar has been the basis for the development of similar low-cost nutritious complementary foods in many other developing countries.

Nutrition and Infection

In the 1950s, no textbook mentioned a relationship between nutrition and infection, except for tuberculosis. My colleagues and I began to document the greater severity of infections in malnourished subjects. We soon concluded that nearly all cases of kwashiorkor were precipitated by preceding infections (64). Measles, chicken pox, whooping cough, rubella, diarrheal disease, and even staphylococcal skin infections were capable of precipitating kwashiorkor in malnourished children (31). It is common for Central American villages to have a composite child growth curve at the third percentile of normal. Growth of a breastfed village child during the first six months of life is usually satisfactory, but when breast milk is no longer sufficient as the sole source of food, infants are more exposed to pathogens, and growth begins to falter in response to multiple infections. As an example of the impact of infections, the time required for poorly nourished children to regain their weight at the onset of whooping cough was 13–24 weeks in 25% of children and 25 weeks or more in another 25% (22).

Our metabolic studies demonstrated a decrease in nitrogen balance during the acute, catabolic phase of an infection, followed by rapid anabolic recovery if the diet has enough protein. Otherwise, children lose nitrogen during the acute phase of the illness and will fail to catch up after the acute illness has passed. We determined through metabolic balance studies that any infection—no matter how mild, or even subclinical—has an adverse effect on nutritional status (12).

A variety of mechanisms contribute to the adverse effect of infections on nutritional status. Decreased food intake due to anorexia plays a role, as do metabolic losses in the urine, internal diversion of protein for synthesis of immune proteins (e.g., antibodies, globulins, cytokines), decreased absorption (if infection affects the gastrointestinal tract), increased metabolic rate (related to altered cytokine profile), and direct nutrient losses in the stool, if diarrhea is present.

The notion that improved nutritional status could reduce the frequency and severity of infections was based, in part, on a previous investigation into the causes of death in children in four Guatemalan Highland villages (3). Kwashiorkor, respiratory infections, and diarrhea were each associated with approximately one-third of the postneonatal deaths. However, kwashiorkor deaths would not have occurred without precipitating infections, and few of the diarrheal and respiratory deaths would have occurred in well-nourished children. Our conclusion was that nearly all of the postneonatal young child deaths were due to the synergistic interaction of malnutrition and infection and not to either alone.

The results stimulated an investigation into hospital deaths in Latin American public hospitals, which found that nutrition was a factor in more than half of all deaths, although most of these were officially attributed to infection (29).

Research in three Guatemalan highland villages from 1959 to 1964 was designed to test whether improved nutrition alone or health care alone was more effective in improving nutritional status, lowering morbidity and mortality, and promoting growth and development in children younger than five years old (53). Children fed Incaparina made with dried skim milk daily to supply 16 g protein and micronutrients had significantly fewer diarrheal and respiratory illnesses than did those in health care and placebo villages. Our funds did not allow us to explore the effects of both interventions in the same village because the NIH study section members said "the results were obvious." This study demonstrated a close relationship between growth and infections. Later studies confirmed a relationship between early growth retardation and lasting cognitive impairment (10, 20).

As evidence from our Central American field studies of the synergistic interactions between nutrition and infection accumulated during the 1950s, it was met with skepticism or indifference. This reaction, along with the encouragement of epidemiologist John Gordon, motivated me to assemble evidence for the concept of synergism between nutrition and infection in the scientific literature (59). With added material, it became the 1968 WHO monograph with the same title (60). The role of infection in worsening nutritional status was documented (37). Important concepts such as "weanling diarrhea" and "second-year death rate" were introduced and became widely accepted. A great deal of information has accumulated since 1968 in support of these relationships, and the subsequent knowledge explosion of cell-mediated immune mechanisms has led to an understanding of how malnutrition lowers resistance. Today, recognition of the synergistic relationship between nutrition and infection is a driving force in public health interventions to reduce the burden of infections and malnutrition.

Early Protein and Amino Acid Requirement Studies

Working with Ricardo Bressani and others, I conducted a long series of metabolic studies in young children that explored the protein quality and limiting amino acids in plant protein sources in the region. With wheat, lysine supplementation alone restored its protein value to that of milk (45). This was replicated later by studies at the Massachusetts Institute of Technology (MIT) (61).

Lysine partially restored the protein utilization of maize, but only with added tryptophan did the nitrogen utilization per gram of protein from maize approach that of milk (6, 8). One variety analyzed had an essential amino acid pattern and protein value similar to that of egg or milk (7). This variety was later developed at CIMMYT in Mexico, and we found it had high protein quality for consumption by children (7) and adults (74).

Other essential amino acids were not significantly limiting in cereal protein. Methionine was observed to be the limiting amino acid in legumes, and the complementarity of the essential amino patterns of an appropriate mix of protein from cereal and legumes was confirmed. Retention was always higher after a period of deficiency of either total nitrogen or of one or more essential amino acids, confirming the importance of the anabolic recovery period after an infection.

Endemic Goiter and Potassium Iodate

As we began to work in the Guatemala villages, we observed that goiters were readily visible in many villagers. Consequently, endemic goiter surveys were conducted in all of the INCAP member countries. It was determined through palpation of the thyroid gland (27) that the prevalence of goiters in Guatemala was 38%, with comparable prevalence levels in the other INCAP member countries surveyed. The United States and Canada had addressed the problem of goiters by adding potassium iodide to salt. However, such a solution was not feasible in Central America because potassium iodide could be used only with refined, dry salt, with an added stabilizer and moisture-proof packaging. Such salt would be unrecognizable and prohibitively expensive in Central America, where crude salt was sold, often from moist open piles in the marketplace.

After consulting a chemical handbook, we identified a compound, potassium iodate, that was not hygroscopic, but there was no information on its bioavailability. We conducted trials in schoolchildren in two villages in Guatemala and El Salvador. Schoolchildren were given identical-looking tablets with no iodine, potassium iodide, or iodate in amounts simulating that provided by iodized salt (46). The fall in goiter prevalence was identical with iodide and iodate. Potassium iodate mixed into salt and stored in burlap bags in the humid, tropical Pacific coast of Guatemala remained well distributed after nine months (1).

With this information, the governments of Central America passed legislation requiring the iodation of salt for human consumption. INCAP helped the governments set up control laboratories and provided manufacturers with technical help. In Guatemala the prevalence of endemic goiter dropped to 7% three years after iodation began (49). Iodation was soon adopted by all of the Central American countries as well as a number of countries in South America. Today it is making possible the campaign of the UN and other agencies and foundations to eliminate goiter as a public health problem in developing countries.

Inter-American Atherosclerosis Study

The growing interest in serum cholesterol and lipoprotein levels in the United States prompted us to explore these levels in Central America. We found that the levels were much lower in local populations (19, 24–26, 62). Virtually no overlap existed among children from rural areas, urban areas, and the privileged children in private schools in Guatemala (37). Deaths from heart disease were rare in the public hospitals of Central America. These observations were sufficient for a large NIH grant to determine the frequency and severity of atherosclerosis in comparisons of autopsies from 13 Latin American (LA) hospitals with those from Charity Hospital in New Orleans. The lead investigators were two pathologists from Louisiana State University, one from the Universidad del Valle, Colombia, and one from INCAP. The statistician, M. Guzman, and I looked for nutritional correlations. The project lasted from 1960 to 1964; during that time, we obtained aortas and coronary and cerebral vessels stained for fat from more than 14,000 male and nearly 8000 female autopsies.

The degree of atherosclerosis was evaluated independently by each of the four pathologists, with samples mixed and blinded. In New Orleans, the severity of lesions increased rapidly after age 20, but in the LA hospitals, it increased only slowly and rarely became significant at any age. The only factor that we could identify as correlating significantly was the total fat in the diet (52). Unfortunately, we did not have sufficient dietary data to relate the findings to the type of fat.

Transition

In 1960, James Killian, the president of MIT and chairman of the trustees of the Nutrition Foundation, was persuaded by Glen King, president of the Nutrition Foundation, to invite me to establish a Department of Nutrition and Food Science at MIT, absorbing a small Department of Food Technology. I agreed, but it was another year before I reluctantly left INCAP. The competence and leadership capabilities of the senior INCAP staff indicated that it was time. This judgment was confirmed by INCAP's continued productivity and growth for the next 30 years. Unfortunately, a civil war, a terrorist kidnapping of the director and administrator, and Pan American Health Organization policies have since caused the loss of key staff and research capacity.

THE MIT YEARS: 1961–1986

Establishing a Department

In July 1961, I arrived at MIT to establish the new graduate Nutrition and Food Science department. The opportunity provided the resources to select and hire an outstanding faculty and the freedom to determine the research mission and graduate training programs of the department. As the first department to combine nutrition, food science and technology, and food toxicology, it became a successful model for other institutions. It soon provided in-depth multidisciplinary graduate degree training in nutritional biochemistry and metabolism, clinical nutrition, food toxicology, food science and technology, industrial and food microbiology, and biochemical engineering.

Within a year, we started an outpatient unit for metabolic balance studies. Within three years, an NIH grant established the only Clinical Research Center (CRC) outside a teaching hospital. An NIH clinical training grant and other support concurrently attracted a long series of exceptionally well-qualified and motivated MDs to obtain PhDs in nutritional biochemistry and metabolism. The CRC facilities provided 24-hour nursing and medical coverage for clinical research, and the MDs in the program had major medical responsibility for the center and the quality of its research.

With faculty of the Nutrition and Food Science Department, clinicians from Harvard and Boston universities, and physicians in the PhD program, the center became extremely productive. MDs in the program pioneered the concept of nutrition support services in hospitals. Everyone in the clinical nutrition training program spent time on nutrition support services established in area teaching hospitals. Graduates of the MD-PhD program are now leaders in nutrition investigation and research administration in the United States and many foreign countries.

In 1971, the International Nutrition Program was established with its own MA and PhD track. After my retirement as department head in 1988, I became its director and obtained support for fellowships from the United Nations University (UNU). The MA and PhD programs were unique for North American students, and most are now leaders in national and international agencies and nongovernmental organizations.

Single-Cell Protein Studies

Talented students and I carried out a long series of studies of protein requirements under various physiological and pathological conditions, including an examination of the value of a variety of protein sources. Using students and staff as subjects, we investigated torula yeast as a dietary protein source and soon learned that despite good biological value, its use for this purpose was limited by its high nucleic acid content, which induced elevated uric acid levels and increased the risk of gout (11).

An N balance study to evaluate the biological value of food yeast shocked at high temperature to reduce its nucleic acid to acceptable limits was favorable in the study's six subjects. However, a large-scale study to evaluate its acceptability and tolerance in a group of 50 students had to be suspended because of both intestinal and cutaneous allergic reactions. We learned that, to reduce the cost, the second batch had been heat shocked at a lower temperature for a longer time. French MD graduate student Jean Claude Dillon developed an in vitro immunological method using leucocytes of sensitized subjects to show that the culprit was a polypeptide of approximately 50,000 molecular weight produced only at the lower temperature (35, 48).

We soon became the world center for the evaluation of single-cell protein and work with yeast and bacteria produced by different companies on a variety of substrates. Processing to reduce the RNA content was necessary and often made the product allergenic. We used the in vitro method to guide processing. However, the development of bacterial and yeast protein was ultimately suspended on economic grounds. The production requirements are now known, and work can be resumed when financial prospects become favorable.

Fungi as a food protein source do not need processing to reduce RNA (57). No problems were encountered with filamentous microfungi produced on sulfite paper waste in Finland or starch in the United Kingdom (69). Unfortunately, the former was doomed when industry discontinued the sulfite process, but the latter is in British and U.S. markets, labeled as Quorn™.

Protein and Amino Acid Requirements

Vernon Young came to MIT in 1965 as a research associate and rapidly rose in the academic ranks to full professor, became a National Academy member, and won prestigious awards. We soon had joint laboratories and research conferences with our graduate students. Although we each had projects of our own, many were shared. I obtained a grant from US AID to explore the extent to which milk protein could be diluted by the less expensive nonessential N sources glycine and diamonium citrate. If the essential amino acid pattern proposed by Rose and accepted by FAO/WHO was valid, the proportion of N from essential amino acids required for optimum utilization was much less than that contained in milk, meat, and eggs. The results of my research were not consistent with the Rose pattern, but an explanation of the discrepancy had to wait until after my retirement, when Vernon Young determined amino acid requirements with a powerful new approach using stable isotopes. He demonstrated that essential amino acid requirements were about double the previous estimates (75).

Following my INCAP work on the effects of infection on nitrogen balance and confirmation at MIT of significant negative effects of even yellow fever vaccine despite the lack of febrile response (12), we explored effects of other causes of stress on N balance. We found that freshmen but not upper-class MIT students had increased nitrogen losses during the final exam period (54). Our N balance studies that had the greatest practical consequences concerned the protein requirements of normal adults.

Prior to 1971, diets of developing country populations were usually found to be limiting in protein relative to calories based on FAO/WHO estimates of protein and energy requirements. In an effort to put protein requirements on a more quantitative basis, MIT professor Hamish Munro proposed a factorial approach at the 1971 committee meeting (17). This assumed that human protein requirements must be the sum of obligatory urinary, fecal, and miscellaneous N losses (hair, nails, skin, etc.) × 6.25 in subjects reaching equilibrium on a free diet. This could not be applied for lack of data. Instead, by rather tortuous reasoning, the committee arrived at an allowance of 0.71 g of egg or milk protein per kg, but then suggested 0.8 to 1.1 for a good mixed diet, as consumed in the United States and Europe.

Soon afterward, we placed 100 MIT students on a nitrogen-free diet for 28 days. Within eight days, they reached a plateau that gave us stable figures for "obligatory" urinary and fecal losses and their variances (55). We later obtained similar data for women and elderly subjects. Our data for men were almost exactly confirmed by Callaway et al. (9), who also measured losses for hair, skin, nails, etc. (9). The 1971 Expert Consultation used these data to arrive at a factorial estimate of 0.57 g protein per kg as sufficient to meet the requirements of almost all normal adults.

Before the report was published, graduate student Cuthbert Garza began a three-month

N balance study with six MIT students at this level. At the end of one month, three were in negative N balance. At the end of the three months, all six had two or more of the following: loss of lean body mass, lower creatinine excretion, and cumulative negative N balance elevated serum transaminase (13). The study was replicated immediately with four subjects, three of whom had had a cumulatively negative N balance at 50 days, and one of whom had had abnormally elevated serum amylase (14). In one subject, N loss was the equivalent of 1.5 kg lean body mass. Losses were corrected by giving 250–500 calories more than the estimated energy requirement, although this resulted in weight gain. The results of these two studies suggested that the 1973 committee had made a serious mistake to which the obligatory N data had contributed. In a third study with six subjects, N balance was negative in five of six subjects until above-requirement N balance was achieved with progressive caloric additions (15).

Getting protein requirements right became a priority of the UNU. A working group was convened in Costa Rica in 1977 (71) to analyze the problem and determine how best to approach it. The recommendation, based on our work at MIT, was to select individuals in many different countries and determine their nitrogen balance at four different levels of protein when consuming their usual diets adjusted to their energy requirement. The zero nitrogen balance intercept of a line through the four points gave the individual protein requirement under these conditions, and the multiple intercepts gave their variance (36). The preliminary findings, which were reviewed during a workshop, indicated that the results from all of the countries were remarkably uniform, and the mean requirement was close to the value recommended by the 1971 committee as sufficient for nearly all normal adults (67).

Longer-term N balance studies were planned at the new mean plus two standard deviations of 0.8 g protein/kg, and additional countries were recruited for the shorter studies. A final workshop of the project was held in 1981 to summarize the data in advance of the next FAO/WHO/UNU Expert Group on Protein and Energy Requirements (30). The combined data for 10 countries indicated a mean requirement of 0.63 g protein/kg, with a standard deviation of 0.20. The next Expert consultation accepted these data as definitive and with some minor adjustment for additional data, proposed an adult protein allowance of 0.75 g/kg body weight (18). This correction returned the estimated protein requirement to previous levels, but economists and nutritionists had already accepted the erroneous low value, recalculated developing country diets, and announced that calories were limiting in developing country diets, not protein. Unfortunately, this error still lingers. The first N balance study in elderly subjects suggested there is a higher protein requirement for this group than for younger adults (68).

Other Activities

A long series of investigations of symptoms from milk consumption in lactose malabsorbers led to a definitive monograph on the subject (56). Among other significant studies was the demonstration that hemoglobin is linearly related to the take-home pay of rubber tappers in Indonesia who are paid by the amount they collect (2). The same was true for women tea pickers. In both cases, iron supplementation increased take-home pay.

In studies in both Indonesia and Egypt, young children who were iron deficient performed more poorly on cognitive tests, and scores improved with iron supplementation (28).

During the MIT period, the convening of major international conferences opened new fields. Two were particularly influential. In 1967, there were almost no interactions between professionals studying behavior in rats and in children, and nutrition and cognition was not a recognized field. After an international conference on malnutrition, learning, and behavior supported by the Nutrition Foundation and publication of the resulting book (51), nutrition and cognition became an increasingly recognized discipline.

A 1967 workshop focused on the possibility of producing edible protein from yeasts, bacteria, and microfungi (23). The term "single cell protein" was used for the first time in its title and was soon universally adopted. Academic and industrial research was stimulated, and a larger conference was held only six years later (66).

INTERNATIONAL UNION OF NUTRITION SCIENCES

In 1972, Glen King asked for my help in developing a system of commissions with specialized committees for the International Union of Nutrition Sciences (IUNS), of which he had become president. Soon three commissions with multiple committees were functioning. Although some did little, others produced valuable recommendations and publishable reports. IUNS was changed from an organization inactive between triennial International Congresses to a continuous international influence. As president of IUNS from 1978 to 1981, I expanded the committee structure. Later, the UNU World Hunger Program was able to support and make use of a number of IUNS committees for specific objectives. IUNS continues to have a network of active committees and task forces and to work closely with the International Nutrition Foundation.

UNITED NATIONS UNIVERSITY

In the mid 1970s, the government of Japan contributed an endowment of 100 million dollars for a United Nations University in Tokyo, plus building space and upkeep. Its mission was to apply instruments of scholarship (research, advanced training, and dissemination of knowledge) to the solution of pressing global problems of human survival and welfare. It was to have no faculty or students but instead to work through existing institutions, with special emphasis on developing countries. In its approval, the General Assembly of the United Nations stipulated that one of its three initial programs should be focused on world hunger.

Fourteen years after I established the Nutrition and Food Science Department at MIT, I was invited to come to Tokyo as one of three program vice rectors, each with an annual budget of one million dollars, plus an equal amount for an overall fellowship program. I felt that I could not leave MIT, but I agreed to help initially. I ended up as de facto vice rector for the program for the next six years, and when it became the UNU's Food and Nutrition Program, I continued to direct it for an additional 12 years.

Initially, an International Advisory Committee for the Hunger Program selected three priorities: "Human Protein Needs Under Conditions of Developing Countries," "Post Harvest Food Conservation," and "Food and Nutrition Policy." A network of 36 associated and cooperating institutions and a larger number of institutional research collaborations was established. In its first six years, more than 500 fellowships were awarded to developing country scientists for advanced training in areas related to food and nutrition wherever in the world seemed most appropriate. Fellowships were limited to two years, but those doing well in doctoral programs found ways to complete them.

THE INTERNATIONAL NUTRITION FOUNDATION

Another institution for which I am responsible is the International Nutrition Foundation (INF). It was organized in 1983 to carry on some of the programs of the UNU/WFP at a time when it was threatened by a change in rectors. Fortunately, the UNU Council valued the program and would not allow its termination. The primary role of INF became facilitating the nutrition programs of UNU. I have served as president since the founding of INF, which has a governing board of distinguished academics. With support from international agencies, bilateral and nongovernmental agencies, and industry, INF now has an extensive fellowship program, edits and publishes the UNU *Food and Nutrition Bulletin*, and supports research.

Over the past few years I have designed INF field studies in Pakistan (16), China (76), and Syria, in which the lysine fortification of wheat flour improved immune status as judged by T-cell increase and enhanced complement C3 response. In Syria, it also reduced indicators of anxiety and stress in family members (65). The impact of lysine supplementation on diarrhea incidence is currently being investigated in Bangladesh, and the stress effect is being researched in Ghana.

OTHER INTERNATIONAL ACTIVITIES

Some of the international activities that I was instrumental in founding deserve mention. In 1966, a report I prepared for the United Nations Economic and Social Council, "International Action to Avert the Impending Protein Crisis," became the basis for a meeting convened by the UN Secretary-General (70). In the same year, I became involved in establishing and guiding the UN PAG to advise on the development of complementary foods for young children in developing countries. It produced much-needed specifications for possible components of weaning foods and their preclinical and clinical evaluation and served its purpose well. When its task of developing guidelines and standards for the development of complementary foods was completed, it was replaced in 1977 by the UN Subcommittee on Nutrition and its Scientific Advisory Committee.

The International Dietary Energy Consultative Group reflected the growing recognition of the consequences of chronic energy deficiency. I served as chair, but Nestle Foundation (NF) Director Beat Schurch, as its technical secretary, was responsible for much of its success. Meetings supported largely by UNU and NF produced a series of valuable monographs widely distributed by NF without charge (21, 32, 33, 58, 63).

Three committees that I chaired from the start had gratifying impact. The first was the International Committee of the U.S. Food and Nutrition Board, which is still active. The second was the Committee on International Centers for Medical Research, which was supported by program grants from NIH. Centers were in Cali, Colombia; San Jose, Costa Rica; Kuala Lumpur, Malaysia; Lahore, Pakistan, and Calcutta, India. The entire committee visited each site annually for several days during the 10 years of the program. The third was the Malnutrition Panel of the U.S. Cooperative Medical Science program. Beginning in 1973, the panel met alternately in Japan and the United States to develop a network of nutrition research projects in Southeast Asia; it still continues.

I chaired two missions for the U.S. Senate Subcommittee on Refugees headed by Senator Ted Kennedy. One was a visit to five countries with food shortages—Egypt, Pakistan, India, Indonesia, and Philippines—to develop recommendations for U.S. policy (70). The other was a mission of five physicians to determine the needs of Vietnam for rebuilding its health and social infrastructure when the peace treaty under negotiation in Paris was concluded. The destruction caused by air raids on the industrial periphery of Hanoi, the largest hospital, and a residential area were recent and painfully evident. To our surprise, however, levels of sanitation were high and unlike all of the rest of Southeast and South Asia, diarrhea was not a health problem even in rural villages. Moreover, sufficient vaccines were being produced for the entire child population (50). We made constructive suggestions for helping Vietnam after the war, but the United States was too bitter to ever implement them.

My most memorable foreign trip was with Senator Ted Kennedy. By September 1971, the number of refugees in India from the war in what is now Bangladesh had escalated to ten million. We visited camps around the entire periphery of Bangladesh in torrential monsoon rains and found the Indian government doing an outstanding job of feeding the refugees from its own grain stores and with dried milk contributed by the United Nations Children's Fund (UNICEF). A team from the All-India Institute of Medical Sciences had observed that infant mortality rates in the camps were extremely high, in part because infants who were severely malnourished and dehydrated with diarrheal or respiratory disease needed a special formula to survive. This recommendation had been agreed upon by UNICEF and the Indian Council of Medical Research but was ignored by authorities in New Delhi, who were overwhelmed by other problems. Kennedy's prestige supported by my recommendation as an international nutrition authority was sufficient to overcome the bureaucratic barrier, and a few weeks later the special food provided by UNICEF began arriving in the camps.

LIFE-SPAN HEALTH OF U.S. CIVIL WAR VETERANS

In 1989, Robert Fogel, the economic historian at the University of Chicago who later received a Nobel Prize and whom I had met at a conference in Bellagio, revealed a grand design for collecting life-span health and social information on 40,000 U.S. Civil War veterans. Data were available from physicians' examinations at induction, when sick or wounded, when reporting for pension examinations, and at death. The problem posed was how to enable student coders in the National Archives to interpret the often illegible handwriting, arcane and inconsistent medical terminology, overly detailed description of wounds, and lack of quantitative measures.

With the help of I. Rosenberg, the coding task was accomplished over a period of years, and the resulting public use tapes have been the bases of dozens of seminal articles. In general, the data reveal a much earlier onset of chronic disease in nineteenth-century males compared with a similar contemporary sample and point to the economic implications. Recently data from 6000 African American Civil War veterans have been added and are available for analysis.

INTERNATIONAL INVOLVEMENT

The foregoing account does not capture the full extent of my international life. After spending nine months in Panama from 1945 to 1946 and two months in 1947, I lived for 12 years in Guatemala. However, during this period, I visited other Central American countries almost monthly, and I was sent by the Pan American Health Organization as a consultant to every Latin American country except Uruguay. I made frequent trips to Geneva and Rome to represent WHO as the Secretariat of Expert Committees and attended joint FAO/WHO nutrition meetings. I have continued to spend much of my time in travel for international nutrition activities.

During the first six years with UNU, I traveled to Tokyo every two months and lived in Tokyo for 12 months. In addition to travel to congresses, workshops, and meetings and work in Latin America, I designed and supervised field studies in Egypt, Indonesia, and Kazakhstan on the effects of iron supplementation in rural communities, of lysine fortification of wheat flour in Pakistan, China, and Syria, and currently of lysine supplementation in Bangladesh and Ghana. Outside of Latin America, countries I have visited for nutrition activities 10 to 30 or more times include China, India, Italy (FAO), Japan, Kazakhstan (ADB/UNICEF), Malaysia, Pakistan, Philippines, Switzerland (WHO), Thailand, and the United Kingdom. I have traveled nearly as many times to Bangladesh, Malaysia, Sri Lanka, and other countries. I have participated in some kind of nutrition-related activity in more than 90 countries and have worked extensively for UN agencies.

EPILOGUE

The most prestigious of the honors I have received was the 1991 World Food Prize Laureate for the development of Incaparina, the demonstration of the feasibility of adding potassium iodate to crude moist salt, and the identification of the synergism between nutrition and infection. My scientific career has been characterized by superb collaborators, outstanding and close friends in a large number of countries, constant participation in a wide range of nutrition-related international activities, and remarkable opportunities for developing human capacity and building institutions. With this, along with the strong personal and professional support of my anthropologist wife of 65 years, five successful children who have been tolerant of their father's travels and overcommitments, as well as eight grandchildren, no one could ask for more.

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