Seven Decades of Nutrition Research

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THE HUNDRED YEARS since the founding of the American Association for the Advancement of Science have been one of the most interesting half-centuries in the history of the world. In most fields of science the advances made during this period far overshadow the developments in any previous century. However, it is always valuable to review the early foundations upon which our modern science is built. Even in the field of nutrition, which is considered a 20th century development, we find many phases of it deeply rooted in the science of previous centuries.

There is no specific reason for starting my survey about 1880, although I was probably influenced by the statement in Richard O. Cumming's book, *The American and his food,* namely, "Few Americans thought about the chemical composition of foods before the last quarter of the Nineteenth Century. The diet reformers of the thirties had stressed the advantages of eating food in a condition approximating its natural state, but they were not analysts and had had little scientific data to substantiate their claims. Their teachings were largely forgotten by the eighties, though the word 'Graham' was still used to designate unbolted wheat flour."

Before proceeding to the laboratory developments of nutrition, I want to mention other factors which had much to do with the improved quality of food for the American people. For example, the availability of fresh foods, especially milk and meat, in cities, greatly increased upon construction of our railroads. Although the work of Koch and Pasteur, which indicated that every disease must have a positive causative agent, tended to retard the recognition of positive nutritional factors, the safeguarding of fresh foods from bacterial contamination, which became possible as a result of the early work in bacteriology, did much to improve nutrition in this country. Improved agricultural production also meant more food, but misguided attempts to purify our food products tended to overcome many of the advantages of increased production. The wheat bran and the meat scraps made better pigs and chickens, but the refined flour and the diversion of liver into animal feeds made poorer human beings.

Organized investigations in nutrition originated largely on the European continent and most of the work was closely allied with physiology. Voit at Munich initiated studies on the value of proteins but soon turned his attention to energy requirements. These studies were continued by Rubner in Berlin. In this country during the decade 1880–1890 Armsby, who had studied in Germany, carried on experimental work in animal nutrition and calorimetry at Yale, Wisconsin, and Pennsylvania. During the same period Chittenden started at Yale his work on digestion and metabolism, which continued until his retirement in 1922. In 1887, when the American Physiological Society was created, Chittenden was the only member who had a true interest in nutrition. Thus the contributions during the first decade were meager, but we must not overlook the fact that many of the Agricultural Experiment Stations were organized during this decade after the Hatch Act of 1887 and that much valuable nutritional work has come from these stations. When Babcock came to Wisconsin in 1887 he was convinced that other nutrients in foods besides carbohydrates, fats, proteins, and minerals were important.

The most important event during the second decade of our story, 1890 to 1900, is undoubtedly the work of Eijkman. On the basis of systematic experiments he was able to refute the theories that beri-beri might be due to the presence of pathogenic organisms in rice, to lack of mechanical stimulation of the intestine, or to insufficiency of total food. He suggested that beriberi is a state of intoxication brought about by the metabolism of excessive quantities of starch and that the silver skin of the rice contains a substance which counteracts the toxic products of the disturbed metabolism. The conception of a positive factor in rice polishings, indispensable to health, did not develop until the following decade.

We are probably safe in concluding that no scientific studies on vitamins were conducted in the United States before the 20th century. However, during this last decade of the 19th century, Congress appropriated $10,000 for the year ending June 30, 1895 and $15,000 the following year to enable the Secretary of Agriculture "to investigate and report upon the nutritive value of the various articles and commodities used for human food." Atwater was placed in charge of nutrition investigations, and in 1896 Atwater and Woods published an extensive compilation on the proximate analysis of American food materials. This bulletin (No. 28) has been a standard reference on food composition, and tables in many text books are based on these early values.

The next decade, or the first period in the new century, can be characterized by a growing interest in biochemistry. The American Society of Biological Chemists was organized in 1906 and both the *Journal of biological Chemistry* and the *Biochemical Journal* were started during the first part of the century. Lusk, an active member in the Society, continued to emphasize the importance of energy metabolism in both health and disease. Levine started his important work on nucleic acids and their breakdown products which are assuming such importance in nutrition at the present time. Folin and Benedict developed methods which could be utilized in studies on protein metabolism. The importance of amino acids, the constituents of proteins, in nutrition was being given consideration by Osborne and Mendel in this country, and Hopkins in England. Sherman, during his connections with the U. S. Department of Agriculture, established the early requirements for calcium, iron, and phosphorus in the human body. All of this work provided a sound foundation for future studies but did not stimulate any great interest in nutrition as such. The original Federal Food and Drug Act was passed during this period but the evolution of the law, which took place over a period of 25 years, was based largely on chemical analysis. Greatest emphasis was placed on adulteration of foods and drugs which could be recognized chemically. A few workers were beginning to recognize that true nutritional value of foods could be determined only by animal experimentation. The work of Eijkman was not too well known in this country, but Babcock and Hart were experimenting with calves on rations compounded according to available feeding standards.

The next decade, 1910–1920, brought an entirely new point of view. It was found that calves failed to grow on rations made entirely from products of the wheat plant but thrived on rations made from the corn plant. Hopkins obtained a very significant growth response in rats fed purified rations when a few cc of milk were added. The work of Osborne and Mendel, and McCollum and Davis showed that rats fed purified rations developed normally when the fats of the diet consisted largely of butter fat but failed when other fats, now known to be low in vitamin A, were used. Chicks grew normally if allowed access to sunlight shortly after hatching but developed severe leg weaknesses when they were hatched early in the spring. It was in 1914 that the Pellagra Commission reported that "Pellagra is in all probability a specific infectious disease communicable from person to person by means at present unknown" and that the Surgeon General of the U. S. Public Health Service ordered Dr. Goldberger to take charge of the pellagra investigations. Shortly thereafter, he produced typical pellagra in prison volunteers in Mississippi by placing them on a restricted diet, and also observed the development of blacktongue in dogs fed similar rations. During the first part of this period, Funk isolated a crystalline compound from concentrates which were active in the prevention of polyneuritis in pigeons. The substance which he actually isolated was nicotinic acid, which was later shown to be the antipellagra factor.

By the end of this decade, at least three separate vitamins were recognized as essential for the growth of young, and evidence was available which indicated that there might be additional vitamins. The real significance of these factors in total metabolism was unknown. With the outbreak of the first World War, attempts were made to utilize the limited knowledge available by advocating greater use of the so-called protective foods. This, together with the dramatic responses obtained upon supplying these foods when deficiencies occurred, led to the popularization of vitamins, which developed tremendously the next decade.

The period between 1920 and 1930 represents a transition stage between the early unstandardized animal studies and the more effective approach as a result of the greater interest which biochemists and organic chemists took in this field. By 1925 many laboratories were undertaking systematic nutrition studies, and fairly quantitative assay procedures were developed for the known vitamins. Even with these improved techniques and the use of more highly purified basal rations, many of the B vitamins were not recognized until the following decade, and apparently we still have some to look for. The relation of vitamin D to ultraviolet light was established in 1924, and this stimulated work on the chemical structure of sterols. The early recognition of the relationship of vitamin A to carotenoids stimulated studies on the structure of the carotenes, but the exact relationship was not established until 1929. Small amounts of crystalline vitamin B_1 were isolated in 1926, and in 1927 Szent-Gyorgi isolated a crystalline compound which King and co-workers later found to have antiscorbutic activity. Before leaving this period, it is important to mention that the American Institute of Nutrition was organized in 1928. This society brought together a group of workers trained in many fields but with one common interest, and it also tended to balance the different phases of nutrition research.

The fourth decade of this century will undoubtedly be recognized as the period in history when greatest progress was made in the chemistry of vitamins and other essential nutrients. Work on the isolation, characterization, and synthesis of vitamins has attracted the attention of many of the outstanding chemists in the world. The decrease in the wholesale price of most of the vitamins during the past 10 to 12 years is well known to all of us. It is needless to mention the significance, not only in nutrition but in all metabolic work, of the availability of sufficient quantities of these interesting chemical compounds to make their use unlimited. We are still looking for some of the new vitamins and as a new one becomes available progress accelerates in all phases of nutrition.

It was also in this decade that we began to study and appreciate the mechanisms through which the vitamins function in the living cell. In 1931 Peters, in England, showed that the brain tissue of thiamine-deficient pigeons was incapable of oxidizing glucose at a normal rate. This observation was soon followed by the demonstration that *in vitro* addition of thiamine to deficient brain tissue resulted in an increased rate of respiration. So today we think of thiamine in relation to the coenzyme decarboxylase, which is necessary in the metabolism of α keto acids, and of nicotinamide and riboflavin as necessary for the formation of enzyme systems which function in the transport of electrons during the oxidation of all types of foodstuffs. We think of the B_6 vitamins in relation to the metabolism of amino acids and pantothenic acid as a constituent of the coenzyme required for acetylations. Very recently it has been shown that one of the functions of biotin relates to the fixation of carbon dioxide with pyruvate to form oxalacetate. This relationship between vitamins and the prosthetic groups in enzymes makes it easy to understand the body's continuous requirement for vitamins, and the reason why vitamin requirement may vary, depending upon composition of the diet.

Furthermore, workers began to recognize the relation of vitamins to the growth factors for bacteria. The importance of riboflavin in the animal was recognized in 1933, and the need of this compound for the growth of lactic acid bacteria was shown in 1936. In 1937, nicotinic acid was shown to be important for both animals and microorganisms. Williams first recognized pantothenic acid as a growth factor for yeast in 1933; in 1939 this compound was shown to be the chick antidermatitis factor. Similar relationships were shown for pyridoxine, biotin, and inositol.

These studies led to the use of bacteria for the quantitative estimation of vitamins, and the first widely used method was that proposed by Snell and Strong in 1939 for riboflavin by means of *Lactobacillus casei*. However, extensive use of this and related methods did not take place until later.

The present decade has been most interesting to many of us. In the first place, we have seen the practical application of scientific knowledge to an extent which surpassed the hopes of the most enthusiastic workers. In November 1940 a committee, which later became the Food and Nutrition Board, was called together by the National Research Council to mobilize available knowledge of nutrition for the guidance of the several agencies of the Government which were facing problems involving food and nutrition. This group recognized immediately that if plans were to be made for securing optimum nutrition for either military or civilian groups, uniform values for human requirements must be established. The Board called upon everyone who had given any thought to this problem; and the dietary allowances, which are now so familiar, were first submitted to the National Nutrition Conference for Defense in May, 1941. These values have undergone several revisions and the new 1948 edition will soon be available.

In the words of Dr. Jeans "The allowances have potentialities for innumerable applications. Throughout the war they served as standards for the diets of our military forces throughout the world. The allowances are useful in making dietary surveys, in assessing the needs of our civilian population and as a guide in feeding population groups. They have been widely used as guides for family buying for welfare administration. They have been used as a basis in determining production goals. They serve as a focal point for guiding research that is to fill those gaps in our knowledge which are evident from a review of the derivation of the allowances."

It was also obvious that figures for dietary requirements were of little value unless the composition of the food products consumed was known with considerable accuracy. The need for such information became very critical during the war and in 1942 the Office of the Quartermaster General requested the Food and Nutrition Board to assemble, coordinate, and appraise the available data on food composition. The extensive tables resulting from these studies were finally published as U.S.D.A. Miscellaneous Publication No. 572. Work on the preparation of such tables did much to stimulate interest in the improvement and simplification of the assays for all the essential nutrients. As chemical and microbiological methods replaced animal assays, more and more evidence accumulated to show that many nutrients may be present in several different forms. For example, vitamin B_6 activity in foods may be due to the presence of pyridoxine, pyridoxal, or pyridoxamine. This merely emphasizes the complexity of biological material and the problems encountered when attempts are made to place nutrition on a truly quantitative basis. The food industries and food processors have recognized this problem and have done much to support and stimulate work on food composition. This is important from their point of view since they must know the possible changes in nutritional value of foods during processing and cooking. Each nutrient and each of its different forms may be affected differently.

From these studies has come the interesting observation that often the availability of certain nutrients in natural foods may be improved by a proper degree of processing. Furthermore, natural foods can be improved by combining two incomplete food products or by adding minerals, synthetic vitamins, and even amino acids.

In an effort to bring national nutrition to the suggested levels of the allowances, the Food and Nutrition Board has recognized the desirability of limited types of food fortification. These include iodized salt; the addition of vitamin D to milk; the enrichment of flour, bread, and certain cereals with B vitamins and minerals; and the fortification of margarine with vitamin A. In applying these new scientific developments great care must be taken to control their use and to prevent the indiscriminate use of synthetic products to the detriment of the public. I believe the Council on Foods and Nutrition of the American Medical Association has made the most acceptable statement regarding fortification.

The Council wishes to encourage efforts to improve as far as possible the nutritive quality of all foods which contribute importantly to the American diet and which thereby constitute the food environment of the people. In spite of all these efforts there exists now and will undoubtedly continue to exist for some time, certain specific deficiencies in large segments of the population which can be remedied best through addition of indicated nutrients to cheap, staple foods that occupy substantial places in the dietary. The Council has favored and encouraged the addition of certain nutrients to selected foods for the purpose of overcoming these deficiencies by replacing as nearly as possible that which has been lost in processing, or by making appropriate foods serve as carriers of dietary essentials which are inadequately supplied by many diets. In any case, the purpose of adding synthetics to natural foods should be to prevent known deficiencies in groups of the population and not to use synthetic products which happen to be available at low cost.

The Council disapproves of unlimited or indiscriminate fortification of general purpose foods with minerals, vitamins, amino acids, or other nutrients.

Although fortification is largely a product of the present decade, it is important to mention that the addition of vitamin D to milk was initiated in 1928, and the program has now been in progress long enough to demonstrate its true value. The incidence of rickets in the children of this country is almost nil. Iodized salt was introduced still earlier but due to the absence of controlled procedures, the program has not been so successful.

The improved methods which have been used for the analysis of food have also been applied in metabolic studies especially in carrying out balance studies and saturation tests. These procedures have done much to improve the diagnosis of early nutritional deficiencies. They have also stimulated direct studies on human subjects. For example, studies at the Elgin State Hospital have been in progress several years to determine possible variations in the thiamine and riboflavin requirements between young and old subjects.

Another great development, which will be given more and more recognition with time, was the establishment of the Food and Agriculture Organization of the United Nations, and the recognition that human nutritional needs can only be satisfied through a sound food policy which is not only national but international. It is most gratifying that these applications of science have not detracted from fundamental studies. For example, much of the work on isolation, characterization, and synthesis of folic acid was done during the war period. The availability of folic acid makes it possible to continue the search for remaining members of the vitamin B complex. Although folic acid may not be directly concerned with pernicious anemia, the work on folic acid led to the final isolation of vitamin B_{12}, which appears to be the true pernicious anemia factor. In other words, these studies clear up problems which were initiated two decades ago, when Minot and Murphy found liver and liver extract to be effective in pernicious anemia.

It is also apparent that some of the newer nutritional factors are active in extremely small quantities. For example two to five micrograms of vitamin B_{12} are sufficient to give a very significant hematopoietic response in pernicious anemia. The daily requirement for the human is probably much less. This brings us to another very interesting development which has taken place largely during the present decade, namely the significance of the intestinal microflora in nutrition. I cannot help but refer to the first experiment conducted in our laboratory back in 1940, when it was shown that the feeding of sulfaguanidine reduced the growth rate of rats and that this retardation could be overcome with liver preparations, because many of my co-workers were skeptical when I explained the results on the basis of retarded intestinal synthesis of unknown B vitamins. Today we recognize the importance of intestinal synthesis of vitamins and possibly other nutrients not only in animal experiments but in human nutrition. Emphasis is being placed on the relation of intestinal flora to conditioned deficiency diseases in man.

It will not be possible for me to give any extensive review of the many important fundamental problems now under investigation, but I shall mention a few.

The studies on amino acids initiated 40 years ago are now being brought to successful conclusion. Rose has made extensive studies with humans to determine the quantitative requirements of adults. Cannon has also shown that the recognized essential amino acids may suffice for the maintenance of nitrogen equilibrium in adult rats. However, recent work in our laboratory with the growing animal indicates that many of the nonessential amino acids also need to be added for optimum growth. Very recently we have secured growth in mice equal to that obtained with intact protein by supplying all the amino acids in free form.

Another problem is the interrelationship between various nutrients—the most interesting of which is the interrelationship between niacin and tryptophan. This has led to the complete understanding of the early work of Goldberger during the second decade of this century. Today we know definitely that pellagra is associated with corn consumption not only because it is low in niacin but also because the protein in corn, zein, is low in the amino acid tryptophan.

One of the most interesting developments during this decade has been the recognition of metabolic antagonists. The availability of many of the nutrients in pure and synthetic form has allowed modification in the structure of these compounds. Out of this work has come the general recognition that slight modifications in the structure of certain vitamins may change them from essential nutrients to detrimental metabolites. Although these observations may not have direct application to nutrition, because few of the antagonists occur in nature, these relationships will give much information regarding metabolism.

All of this work emphasizes the importance of recognizing all the nutrients taken in by living cells, whether they be present in animals, plants, or microorganisms. These nutrients may not always be essential, but they may become important under certain environmental conditions. There is great hope for the future in nutrition, if we recognize this broad principle, and if we continue to develop techniques which will measure some of the nutrients which are active in the minutest quantities. During the past few decades, we have developed from a point where we thought milligram quantities were important to a point where we must recognize microgram and millimicrogram quantities. If we can supply these substances in optimum amounts and in the proper ratios we will have an efficient machine for the utilization of energy for growth and development, or in other words, we will have optimum health. In spite of the tremendous advances in the science of nutrition and in food technology, our world food problem today is still one of total calories. On the other hand, in areas like the United States where caloric undernutrition has been relatively rare for many years, there appears to be some correlation between the increased incidence of degenerative diseases and high caloric intake, and efforts are under way to control food intake at least to a limited extent.

We can therefore look back on seven decades of nutrition research with considerable satisfaction. Enthusiasm over newly discovered nutrients may have given too great emphasis to certain phases of nutrition for short periods of time, but active workers soon reinstituted the proper balance. Workers in nutrition have made use of the scientific advances in many of the related fields, and at the same time have contributed to the advances in allied fields, but in doing so they have not diverged too far from the main goal of optimum health for all.

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