BASIC RESEARCH

and its Application in the Field of

CLINICAL NUTRITION

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As a research scientist, one must, of necessity, live very much in the realm of ideas or imagination; and as normal human beings, we develop our sense of direction for living and working very largely on the basis of ideals. In that ideal yet practical sense, we may define nutrition as the science of food and its relation to life and health. Then the goals toward which nutrition scientists work can be seen more clearly. First, they want to be able to identify and measure the concentration of all the useful ingredients in human and animal foods. Second, they want to know how each nutrient functions in living organisms, and how these functions interlink, one with another. Third, they want to know the quantitative relationships between nutrient intake and health on a life-span basis. And fourth, they sense an obligation to assist in the educational activities that will make their work effective in the community at large.

There are two basic reasons why it is urgent that we develop the science of nutrition. There is an unmistakable demand to produce enough food to protect the health of a rapidly growing world population. In so far as this basic requirement is not met, there will be needless and increasing human misery and social turmoil. If we study and attack the problem with sufficient vigor, there is a reasonable prospect that the peak of the population-versus-food struggle will be passed within two or three generations. The second situation is relatively new. Students of public health agree that medical progress in the years ahead is likely to result chiefly from discovering how to maintain a favorable chemical environment within the human body. The greatest research activity is already heading in the direction of warding off the degenerative diseases such as hardening of the arteries, high blood pressure, cancer, cirrhosis of the liver, diabetes, arthritis, obesity, tooth decay, premature births, glandular imbalance, and many forms of physiologically induced nervous instability.

NEW TERRITORY

One can scarcely miss noting the contributions that biochemists are making in cooperation with the medical profession in developing the science of nutrition. Among other reasons for this trend, clinical nutrition has moved rapidly from the older concept by which physicians were chiefly interested in curing and preventing deficiency diseases, such as scurvy and rickets, into a new zone of interest where the poor health condition cannot be

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identified with an obvious or recent cause. Hence, appraisals of nutriture or nutritional status are increasingly dependent upon microchemical analysis. Three examples will illustrate this point:

(1) Accurate methods are now available whereby a few drops of finger-tip blood taken during school health surveys can be analyzed for vitamin A, carotene, vitamin C, vitamin B_1, vitamin B_2, diphosphonucleotide (niacin index), hemoglobin, iron, serum protein, and the enzyme phosphatase.

(2) Physicists, chemists, and physicians at Harvard University and Massachusetts Institute of Technology are now working out detailed procedures for micro-analyses of blood samples to measure nearly all the trace mineral elements, so that medical research can be directed into this area more rapidly.

(3) Blood tests for specific immune bodies, hormones, complex fats, and specific enzymes furnish to the physician a record of metabolic trends that can be influenced by food intake, long before there are any external evidences of an impending break in health.

The Heart of the Situation

The growing importance of diseases associated with faulty metabolism compared with infectious diseases is emphasized when the principal causes of death are studied. In the United States, currently, only one of the five groups of diseases listed among the greatest causes of death can be classed as infectious (pneumonia and influenza). Heart and cardiovascular diseases are in first place, and cancer is in second position.

There is no room to doubt that a close relationship exists between food practices and this leading group of death-dealing diseases. An understanding of the chemical basis for the relationships, however, is just beginning to unfold.

Unquestionably, one of the most damaging practices is simply eating too much. An excessive intake of calories, alone, constitutes a major hazard to health, especially in the upper age bracket, but the prospect of warding off diseases associated with aging is made doubly hazardous when the high calorie foods are low in vitamins, minerals, and good quality protein.

In research on the degenerative diseases, one is impressed by the frequency with which abnormal fat deposits are characteristic of early lesions, long before there is evidence of a break in health. Hence, we feel confident that advances in knowledge of the manner in which fats are synthesized, distributed, and burned in the body will hasten the prevention and improve the treatment of these related diseases.

Among recent research contributions in this field, the following may be of especial interest.

Dr. C. H. Best and his associates at the University of Toronto found that young growing rats were so sensitive to choline deficiency that a diet from which this one nutrient was omitted, but otherwise complete in all respects, resulted in abnormal fat globules appearing in the livers and kidneys of the animals within twenty-four hours. When the deficiency was continued for three to five days, followed by return to a full diet, although growth and outwardly normal appearances continued, the initial injury was never fully corrected. When the animals reached maturity, instead of continuing as normal adults, they showed progressive degenerative changes in the arteries and heart and a gradual rise in blood pressure. The lesions were characteristic of those seen in human hardening of the arteries, high blood pressure, and enlargement of the heart. These observations were confirmed and extended by Dr. Philip Handler and his associates at Duke University.

This year Dr. Best, Dr. Hartroft, and their associates made a further discovery in noting that specialized cells adjacent to the kidney glomeruli were very sensitive to different levels of salt intake. Either too much or too little salt caused marked disturbances in the cells and they have postulated a new hormone function in the kidney cells that influences the adjustment of the adrenal cortical control of salt metabolism. A new lead is thus developing by which to find why and in what dgree low and high salt diets are so intimately related to the medical aspects of high blood pressure.

Cholesterol—Friend or Enemy

Nearly all investigators dealing with fatty livers, kidney disease, hardening of the arteries, and diabetes have been impressed by the frequency with which they find early and continuing deposits of cholesterol. The purely exploratory work of Rittenberg, Bloch, and others has been increasingly valuable in this area of medical research because they had shown that the animal body normally forms cholesterol in large quantities from acetate groups, which in turn are derived normally from carbohydrates and fatty acids. Hence, if one is attempting to suppress or control cholesterol concentration in the blood and to prevent its being deposited in excessive quantities in the tissues, the amount eaten in the form of meat, milk, and eggs is probably of secondary importance. There has been a tendency, especially since the publication of Dr. John Gofman's papers at the University of California, to attach too much importance to low cholesterol diets. Instead, the primary emphasis should be on low calorie diets of high nutritive quality. The mistaken conception of the origin of cholesterol has caused many physicians and writers to sponsor diets that are actually hazardous because of their poor nutritive quality.

A New Vitamin at Work

The work of Dr. F. Lipmann and others in discovering the role of pantothenic acid in forming co-enzyme A has been of notable value in correlating nutrition with both fatty diseases and the anemias. As outlined in the following scheme presented by Dr. Lipmann, co-enzyme A is a controlling catalyst regulating the metabolism of acetate groups. Studies of pantothenic acid deficiency in experimental animals have consistently shown a pattern of injury to the kidneys, adrenals, liver, and other glandular structures. Thus far, unfortunately, there has been extremely little research on the role of pantothenic acid in human metabolism or disease.

The stimulus to greater interest in this area of nutrition research is heightened by Dr. D. Shemin's recent work at Columbia University in discovering that co-enzyme A also serves as a controlling catalyst in the formation of protoporphyrin as a precursor of hemoglobin.

Cancer

The origin of human cancer is not known with enough certainty to evaluate the possible role of nutrition. Hence, one must be extremely careful not to imply too much from recent exploratory research with animals. In experimental animals, however, there are several instances where nutrition is a deciding factor in carcinogenesis. The Yale, Cornell and Wisconsin University groups, Memorial Hospital, and other highly qualified research laboratories have found that generous intakes of riboflavin (vitamin B_2) can, under specific conditions, play a decisive role in preventing cancer in several strains of rats. Careful experiments in another laboratory have shown that chronic choline deficiency, alone, can induce carcinogenesis in both rats and chickens. The low level of intake required to induce cancer, however, is much lower than one would encounter commonly in human experience. Of greater apparent significance are the many reports, especially those from the Michael Reese Hospital in Chicago, that an excess of calories and fat tends to encourage carcinogenesis. On the whole, despite many interesting leads, there is no convincing evidence, thus far, that dietary factors play an important role in causing human cancer. On the other hand, we have no reason to rule out nutritional imbalances as factors of importance in carcinogenesis. And from a practical point of view, we can be confident that continued advances in understanding the principles of cell function and nutrition will shorten the pathway to finding a solution to even this most complex problem.

Proteins

From the viewpoint of severe limitations in the quality and quantity of food supplies, there is much evidence to support the emphasis that has been placed on animal protein foods, such as milk, meat, eggs, and fish. Because of their relatively high cost, however, the task

of maintaining an adequate intake of these foods represents the most acute limitation in the total food problem. One's imagination is certainly taxed to the limit, for example, in suggesting a practical solution of the problem in India, China, South Africa, and sections of Latin America.

From a nutritional point of view, the animal protein foods can be resolved very largely in terms of essential amino acids and an abundant supply of vitamins in the B-complex. Within the last five years, advances in nutrition research have furnished much of the information that is essential to progress toward solving the protein problem—if it can be solved. Among these advances none is more important than the work of Professor W. C. Rose at the University of Illinois, who established for the first time a relatively complete picture of the adult human requirement for each individual amino acid.

In addition to the basic information supplied by Dr. Rose, perhaps the most significant discoveries regarding animal protein foods have dealt with the newer vitamins, especially folic acid and vitamin B_{12}. These two nutrients and choline are supplied in abundance by the animal protein foods. Their functions, in turn, have been rapidly interlinked with the functions and essential balances of other vitamins, amino acids, mineral elements, sugars, fats, and hormones, so that we have a greatly extended appreciation of what is meant by the old-fashioned terms "a good diet" and "good health." Folic acid was found to cure the tropical disease called sprue, and many cases of anemia found in temperate zones. Vitamin B_{12} furnishes protection against pernicious anemia and serves widely as a valuable growth factor.

In broader ways these discoveries contribute to the solution of practical problems. First, in areas where the need for protein foods is most acute, it is urgent to utilize plant protein foods to the greatest possible degree. Such a practice imposes an immediate hazard of failing to supply adequate sources of vitamin B_{12}. It is only when one can measure the individual amino acids and their associated vitamins in different foods, and then relate these quantities to the human requirement that one can plan production and educational programs with any sense of reliability. Furthermore, when supplied with definite information regarding amino acid and vitamin requirements, the agricultural geneticists can work to advantage in improving the quality of protein in such crops as corn, wheat, and legumes. This state of affairs offers certain obvious advantages over having to plan a series of field crop tests on the basis of life-span observations on the human population. An example is evident in the discovery by Dr. Rose that the human body can synthesize its entire requirement for histidine. In their present efforts to improve the protein quality of corn and beans, the geneticists have enough difficulty attempting to increase the content of three other amino acids, tryptophane, lysine, and methionine, without attempting to tie in a fourth one.

Balancing of Many Points

Dr. C. A. Elvehjem and his associates made a classical contribution in demonstrating a high degree of dietary interchangeability between niacin, the antipellagra vitamin, and tryptophane, one of the essential amino acids. The discovery simplified very greatly the entire problem of providing adequate diets in both human and animal feeding. The extent of known comparable interplay between other amino acids and vitamins has grown rapidly. For tryptophane, a second vitamin balance was discovered in the case of vitamin B_6. A currently used method of identifying vitamin B_6 deficiency in the human body is based upon administering a large amount of tryptophane and then measuring the degree of utilization or loss of the excess tryptophane.

Another example of a marked interdependence between amino acids and vitamins was discovered last year by Dr. W. D. Salmon and his associates in demonstrating that vitamin B_{12} is interchangeable with choline to an appreciable degree. A major quantitative interplay between choline and methionine had been recognized for several years. The need for choline, as commonly measured in standard experimental animals, can be varied as much

as 50 per cent by varying the intake of vitamin B_{12}. One might add that the requirement for vitamin B_{12} is also greatly conditioned by the intake of another vitamin in the B-complex, folic acid. In addition (as shown by Dr. R. R. Sealock, Dr. Paul Day, Dr. W. J. Darby, and others), the folic acid supply has a marked effect upon the requirement for vitamin C.

Findings of this kind give strong support to the view that in the development of practical plans for good nutrition, one must look upon the diet pattern as a whole and not be misled by overemphasis upon the supply of individual nutrients at specific levels. The primary educational measures should be based upon educating the public to consume liberal quantities of reliable protective foods. These generally fall into three critical groups, the animal protein foods, yellow and green leafy vegetables, and citrus fruits or tomatoes. Then caloric provision to maintain an ideal body weight can be furnished along with added supplies of essential nutrients by low-cost cereals and carbohydrates or fatty foods, according to circumstances.

Trace Minerals

Another rapidly moving area of nutrition research is represented by the trace mineral elements. Iodine deficiencies were formerly very widespread in America. The use of iodized salt has solved a large part but not all of the problem. In many sections of the world, however, distribution of iodine has scarcely been attempted. The Food and Agriculture Organization of the United Nations believes that iodine deficiency is one of the major world problems in public health.

Dr. N. S. Scrimshaw and his associates in the Central American countries, for example, have found several areas where the incidence of goiter among the Indians reaches at least as high as 80 per cent. Goiters were still regarded locally as a normal condition. Work on the problem is being initiated, and it appears that a solution is at hand in the use of iodate salts instead of iodides. The iodides are too unstable for use in crude salt supplies.

Tooth Decay Not Necessary

Much closer to the research atmosphere is the attempt to provide sufficient fluoride to the human population to accomplish optimum protection against tooth decay. Approximately 150 cities in the United States have initiated plans to furnish fluoride to the entire community at a level of approximately one-part-per-million in the public water supply. The practice of fluoridation does not seem to have developed as rapidly in other countries, but there is no doubt that extension of fluoridation will continue at a rapid pace in American communities. Fluoridation alone should not be expected to completely solve the dental caries problem, however, because other nutrients make important contributions to caries-resistant teeth. There is still an urgent need to educate the public toward decreasing tooth decay by means of a diet that is adequate in all respects. The clinical observations of Dr. Toverud and his associates in western Europe, Dr. Sognnaes and his associates at Harvard University, together with the studies of Dr. Elvehjem and Dr. Phillips at the University of Wisconsin, have shown that good nutrition can play a dominant role in preventing tooth decay. Their work is essentially new also in pointing toward the importance of good diets during gestation and very early growth, in contrast to earlier emphasis upon dietary effects after the teeth were erupted. Monkeys and rats reared on a composite diet of natural foods until about half-grown, and then placed upon conventional diets comparable to our human food supply showed practically no dental caries even with a large amount of sugar in the diet. On the other hand, the same types of animals reared through the complete reproductive cycle of gestation, lactation, and growth on partly purified diets showed a high incidence of dental caries.

Again, Balance

Another interesting area of trace element research deals with the interrelationships of the heavy metals. It has long been known that copper must be supplied in about one-

tenth the amount of iron to make possible the utilization of iron in forming hemoglobin and the iron-containing enzymes. The manner in which copper functions in animals is almost a complete mystery, although its presence in several plant enzymes has been well established.

In some of the Atlantic seacoast areas, as in Florida, it is a common practice to add molybdenum with other fertilizer ingredients. Cattle grazing in some areas developed a disease characterized by rapid loss of weight, diarrhea, and anemia. It was then discovered that the condition could be cured by administering salts of copper, although the forage crops appeared to have a normal copper content. Later they found that some of the forage plants had accumulated too much molybdenum, and the molybdenum had created an increased demand for copper. Additional copper then served to reëstablish a balance and approximately normal health. More recently they have found that cobalt can serve in a similar way. The chemical basis for these relationships is not at all evident, but at least there exists this quantitative interdependence between iron, copper, molybdenum, and cobalt. Even before worrying about the effect upon animals, the farmer finds that a slight change in acid-base balance of the soil can greatly alter the availability to plants, of iron, copper, molybdenum, manganese, and cobalt.

The soil bacteria use cobalt in a great variety of ways, including the formation of a series of true and pseudo forms of vitamin B_{12}. The relation of these nutrients to antibiotics is scarcely understood at all, except in empirical observations based on feeding to see what happens. Nevertheless, feeding antibiotics, such as penicillin, aureomycin, and terramycin, is an established practice in raising chickens, turkeys, and pigs. Under supervision, the antibiotics are being fed to children, with reasonably favorable results.

Conclusion

Exploratory research in the science of nutrition, followed by diligent efforts to apply the findings in terms of medicine, agriculture, and education of the public, represents one of the most promising areas of graduate, professional study. And in addition to the scientific aspects of such work, the social and economic contributions inherent in each advance offer a reasonable basis for laying foundations under the kind of a civilization that our children may want to build.

Resumen

Estudios básicos y su aplicación en el campo de la nutrición

El autor pasa en revista varios importantes adelantos recientes en el campo de la nutrición que han resultado de investigaciones en les ciencias básicas, particularmente en la bioquimia. El interés, en lugar de concentrarse en las enfermedades deficitarias específicas—tales como la raquitis y el escorbuto—se dirige ahora hacia las enfermedades degenerativas. La producción retardada de la hipertensión consecutivamente a una deficiencia pasajera de colina en ratas no es más que un solo ejemplo. El énfasis se ha trasladado del colesterol exógeno a aquello endógeno como factor en la génesis de la arteriosclerosis.

Otras observaciones se describen, tales como los efectos de las vitaminas en el cáncer experimental, el papel de los oligoelementos, los factores que contribuyen al decaer de los dientes, las relaciones entre la triptofana, la vitamina B_6 y la niacina, o entre la cianocobalamina (B_{12}) y los ácidos fólico y ascórbico. El trabajo de Rose y otros en definir más claramente nuestros requerimientos nutritivos específicos se nota. Este conocimiento permitirá a los pueblos y naciones un mejor planear y ajustar de sus responsabilidades alimenticias. Las investigaciones en las ciencias básicas se aplican prontamente al campo de la nutrición: medicina, agricultura, y educación pública. Este esfuerzo en traducir los hallazgos de la experimentación en términos prácticos constituye uno de los campos más prometedores para el estudio graduado y professional.