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VITAMINS IN THE FUTURE[1]

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AMONG the dusty reprints which I treasure is a yellow-backed one from the *Journal of Physiology* bearing the date of December, 1911, in which Casimir Funk first proposed the name "vitamine." As I had at that time been working with Vedder for more than a year on "the beriberi-preventing substance," I may, in a sense, claim to have been one of the midwives in attendance at that historic birth. Vedder and I were among the first, if not the first, authors to take up the use of the term in our first joint paper, published somewhat belatedly in 1913. In 1916 my testimony in refutation of the claims of the manufacturer of a cure-all was part of the first court record in which the term appeared. As the years have overtaken my plodding feet, the number of scientific papers which employ the word "vitamin" has grown from a paltry two or three to some thousands annually.

I have recently been reading some medical biographies and particularly Clapesattle's story of the Mayos. There one notes that, although Pasteur indicted the atmosphere as a source of infective organisms in 1864, although Lister announced his method of antiseptic surgery in 1867 and had achieved international acclaim for his work by 1879, Will Mayo appears to have graduated in medicine at Michigan in 1883 with only a superficial knowledge of Listerism and scant conviction of its merits. It was not till

[1] Address on the occasion of the presentation of the Charles Frederick Chandler Medal of Columbia University, February 26, 1942.

four years later that he became a thorough convert, as were the majority of new medical graduates from that time onward. It had taken nearly twenty years for Listerism to gather momentum, but it then revolutionized surgery in a decade. It made deep surgery, especially abdominal surgery, possible. We are now in the midst of a like development of what may be called vitaminism, a development which is the more conspicuous because much of its content is appropriate to the use of the layman as well as the physician. The progress of its application has likewise been slow till recently but is now greatly accelerated.

May I ask you to consider with me some of those more immediate applications of vitaminism which we can discern are already beginning but which will require many years for full realization. It will be appropriate if I leave to my fellow medalist the role of longer range prophecy, for he will presumably live longer to enjoy the later triumphs of vitaminism, as well as to regret his prophetic errors if he should make such.

There are six vitamins which have already acquired an importance for the workaday world, for the layman, for the food technologist and for the practicing physician. By their lack ye shall know them. Five of the six are commemorated in the existence of ancient and wide-spread diseases which are known by household names in all the principal tongues of the earth. Perhaps the oldest of these diseases is beriberi, due primarily to a lack of thiamin. The earliest supposed reference to the malady is attributed to Hwangti, who adorned the medical profession about 2700 B.C. Scurvy ranks next in antiquity, for it was recognizably described by Hippocrates, the father of western medicine, about 400 B.C. and was the scourge of medieval armies and of the seamen of the age of exploration. The Englishman, long famed as a sailor, is still called a lime-juicer for his judicious use of this source of vitamin C. Rickets once had an association with England also. It was called the English disease because it was first described in 1650 by the Englishman Glisson, though it probably occurred earlier, as has been inferred from the rachitic appearance of children in German paintings of the fifteenth and sixteenth centuries. The virtue of cod liver oil in its treatment we now ascribe to vitamin D.

Pellagra seems definitely a product of the New World and has had an intimate association with maize, the New World cereal. Pellagra was noted first in American Indians about 1600 and almost simultaneously in Italian peasants who used maize as food. For a year or two now we have known that among the cereals maize is conspicuously low in nicotinic acid, only recently recognized as the anti-pellagra vitamin.

Lack of vitamin A is widely associated with a dryness of the eyes and also with night blindness occurring in many lands. The latter has been recognized in such widely separated areas as India, Japan and Newfoundland. It has occurred among Australian cattle. It has, however, belonged primarily to popular lore rather than to official medicine, which long hesitated to rate it as a definite entity. In Eber's papyrus about 1500 B.C. is the statement, "Because the unknown disease was cured by the roast liver of an ox, the disease was supposed to be night blindness."

Only one of the six vitamins which I have mentioned as important in a workaday sense lacks the monument of a well-defined long-known disease. I refer to riboflavin. The disease due to its absence in the food has no vernacular name and reflects its modernity in the term "ariboflavinosis." Some of its symptoms, notably fissures in the corners of the mouth, have often been noted in association with pellagra with which ariboflavinosis has been confused until within the past three years. Ariboflavinosis causes burning and redness of the eyes and may in extreme cases lead to alterations of the cornea and ultimately blindness. In young rats cataract can readily be induced by this deficiency. In man, however, the symptoms are but rarely severe, though they are frequently encountered among poorly nourished people.

From the fact that five of the six vitamins of present-day practical importance have left their traces in the records of centuries of history, one is tempted to classify the remaining vitamins as lesser ones and even to predict that the vitamins which are yet to be discovered are destined to have a progressively lesser significance for human welfare. At best such a prediction can be true only in the sense that the later vitamins will less frequently be found missing in widely used human dietaries. Even in this sense, exceptions may appear, for there remain well-known but obscure diseases, such as epidemic dropsy and sprue, which seem clearly to have dietary causes. On the whole, however, I think we may say that we have already discovered and produced commercially the vitamins which are required to check the great nutritional plagues of mankind.

Clearly this statement should not be construed to mean that the other vitamins play less essential roles in human physiology. Choline, pyridoxine, pantothenic acid, biotin, inositol, para amino benzoic acid and folic acid may and in most cases probably do perform equally essential functions for the human organism. A gross lack of any one of them might lead to a disturbance as pronounced as that of beriberi or pellagra. But it does seem true that the statistical probability of these lacks in human diets is less, else we should have encountered them historically. The lesser vitamins, if we may call them such

for the sake of brevity, may afford us, however, great revelations regarding physiological and even pathological processes and so must be classified as lesser only in a narrowly defined sense.

My point in distinguishing between the major and the lesser vitamins is not one which primarily concerns the future of research. It is one which concerns present-day technology, present-day economics and present-day sociology. I should like to divert the minds of food processors, teachers of nutrition, practicing physicians and laymen from speculating about the latest surmise of vitamin science and persuade them to devote their major energies to the intelligent application of the vitamins which stand in the front row on the shelf. Since the number of vitamins has multiplied in mystifying confusion, the public taste turns to the newest one as the ladies' eyes turn toward the spring hats. The attraction for the latest novelty hardly surpasses that for gruesome details of symptomatology and pathology. We have popular lectures, even radio programs, on nutrition, which abound in the sordid details of ascites, neuropathies and cirrhoses, all of which is morbid and relatively unprofitable for the layman.

It is high time we should be systematically eradicating the long-known deficiency diseases. What has been done so far in that direction is with few exceptions little and local. Infantile scurvy and rickets have been distinctly diminished among the well-to-do and even the middle classes by increasing use of orange juice and cod liver oil for nursing infants. Happily women increasingly call on the doctor to attend them during confinement and the babies benefit from his advice incidentally at least during their early months. It is socially significant that babies are helpless and can not reject the mother's ministrations. They have accordingly benefited most systematically from nutritional advance. This, however, does not endure long and as the child grows older he is increasingly free to follow the prevalent nutritional abuses of his elders.

There are some aspects of nutrition in which we must continue to rely primarily on the educational process. Good foods must be chosen with reasonable regard to their supplementary relationships. Milk, meats, eggs, green vegetables and fruits need to be used in fair proportion to potatoes, cereals and sugar. Even the careless cookery can seriously mar not only the palatability but also the dietary values of the products. In our present society, care in these particulars must be supplied by the housewife who will continue to need no little instruction, especially if her husband's pocketbook restricts her choices.

We should, however, rely as little as possible upon the uncertain discernment, diligence and discipline of the housewife. Securing good nutrition by volitional choices, especially under economic, geographic and often nationalistic restrictions, often involves an amount of scientific knowledge which can not yet be imparted to the rank and file of working people. When our forebears lived in a state of nature, they got great protection from the fact that they ate things whole, even whole carcasses, and thus got a wide assortment of the chemical substances present in and necessary to all forms of life. Moreover, they had no great staples grown in broad cultivated fields. They pieced out their needs from the intermingled plants of the forest and field and from the animal life that scurried or crawled or swam within the range of their habitat. Diversity was forced upon them. But as husbandry came, there was increasing temptation to subsist largely on that staple food which was produced with the least labor and the greatest assurance. The one-sidedness of these diets was later further aggravated by refining processes applied to the great staples, such as rice, wheat and latterly sugar. Both diversity and wholeness were lost except for the more luxuriously fed segments of mankind.

The first impulsion of our present knowledge of vitamins and their essential roles should be to promote restoration of values lost to the masses by these restrictions. A general removal of economic restraints would largely achieve the result because appetites lead to diversity when income permits. This, however, is a Utopian ideal far beyond our immediate reach. Education, if universal, would largely accomplish the result, for avoidance of refinement is not inherently costly. However, education of the most needy elements is exceedingly slow and difficult. We must, therefore, turn to more effective weapons as soon as education has pervaded the public mind sufficiently to permit their employment.

Legislation is a possible weapon, but considerable public education must precede it. A bill to put a tax on white rice in order to discourage its use was first introduced into the Philippine legislature in 1911. Although it has since been reintroduced several times, it has never succeeded of passage. As a result incapacitation from beriberi is substantially as prevalent as it was thirty years ago, though we have known all that time how it could be prevented. The same condition prevails generally through the rice-eating areas of the Orient. There is apparently nothing prohibitively difficult about handling undermilled rice commercially, for I am told that Cuba prefers its rice in that form and gets nothing else.

Legislation in the United States prohibiting the sale of impoverished white bread and flour is a possibility. Undoubtedly any attempt to prohibit the sale of white wheat products in the United States would meet with insuperable public opposition. However, it is now possible to add artificially the principal

valuable vitamins and minerals of wheat at a cost of something less than twenty-five cents per capita per annum. Increased economic productivity of the bulk of the population would repay the cost perhaps a thousand-fold to say nothing of improved health and sense of well-being. Yet this great reform is being sabotaged or damned with faint praise by half the nutritionists of the country on the ground that it would be still better if we could arrange breakfasts of ham and eggs, whole wheat buns and a glass of milk for everybody. Of course it would, but shall we wait for the millennium to take our first steps to mass repair of our nutritional errors?

Our present pure food legislation does not provide for such regulation of bread and flour. Our food law was aimed at the elimination of poisonous preservatives and the eradication of false statements of quality or identity. It assumed that our traditional and unsophisticated foods were wholesome and does not concern itself directly with their nutritional values. This must presently be changed so that the character of our available staples shall provide automatic protection against gross malnutrition when these staples are consumed in customary proportions and forms.

Pending the day when such legislation can be secured and the necessary scientific methods of control are developed, we must look largely to the food industries for correction of our dietary faults. These industries have been made very conscious of their public obligations, to a great extent through the operation of the pure food laws during recent decades. Within the limits of practicality, they are in general ready to cooperate in such reforms on a voluntary basis. Such an undertaking is the great program for the enrichment of bread and flour which began last May under the auspices of the National Research Council, the Federal Security Agency and particularly its subordinate unit, the Food and Drug Administration. As the addition of vitamins and minerals to bread and flour adds a few per cent. to the cost of production, a considerable public consciousness of the values it provides is essential to the maintenance and extension of the practice in these highly competitive industries. Further public education is necessary, a task which has been rendered difficult by rival advocacies by nutritionists of whole wheat or of other desirable nutritional reforms. It can not be claimed that enriched bread and enriched flour will correct all the nutritional faults of the nation. It is claimed, however, that this reform is incomparably more important than any other which is feasible of accomplishment within a decade.

There are some other staples which deserve analogous treatment. Addition of vitamin A to oleomargarine and of vitamin D to milk are such worthy projects. Iodized salt is another and there is much to be said for the increments of calcium which self-rising flour and baking powder furnish to the South, especially in areas where the milk supply is low. Because of the extensive occurrence of pellagra among maize eaters, addition of nicotinic acid to corn meal is under consideration. There is no sufficient evidence that rectification of staples should go further than this now. Vitamin C is sometimes too meagerly supplied, but there appears to be no other vehicle so effective as the increased use of fresh fruits and vegetables.

Riboflavin presents a rather peculiar problem. A partial deficiency of it is wide-spread, but we can not definitely lay the blame on any recently introduced food process or new alteration of habit. We need more extensive and more reliable assays of the riboflavin contents of foods. Light destroys this vitamin rapidly and this may be significant during manufacturing and distribution of certain foods. Milk is an excellent prophylactic when available. In normal times there is an enormous amount of skim milk, rich in riboflavin, which is never recovered in dry form or which is devoted to poultry feeds. The principal human use of skim milk powder is in bakery breads.

These and kindred problems of the conservation of the outstanding nutrient components of foodstuffs as related to variety, soil, climate, cultivation, transportation, storage, drying and canning of foods will furnish an enormous grist of work for the food industry laboratories for many years. Only recently have rapid assay methods for the principal vitamins begun to be available for the guidance of such studies. So long as the industries were dependent on laborious and sometimes uncertain animal experiments, progress was necessarily slow. Nowadays the food industry laboratories are turning out vitamin assays in great volume and with increasing precision. In general, these laboratories are able to select their samples for analysis with a far better perspective of the origin, classification, processing and destination of the products than is possible for the academic or government laboratory. Every laboratory performing such analyses should feel an obligation to publish its results for the public good or better still to contribute the analyses toward compilations which are almost constantly in progress in government bureaus.

When such nutritional reforms have been in full operation for some years, the physician will have little occasion to treat deficiencies of the major vitamins. Until that happy day, which must be some years hence, he will encounter an abundance of avitaminoses, especially in clinics for the under-privileged. His immediate task is to recognize the symptoms. If they are mild or mixed, this is usually beyond the average physician of to-day. An increasing number of younger men, however, are well schooled in their

recognition and a host of laboratory methods for confirmation of diagnosis are in use or under development. They include principally optical methods for detection of eye lesions, mechanical tests of the fragility of capillaries and chemical analyses of blood, urine, breast milk and occasional biopsy specimens of tissue. Norms are gradually being established for each of these measurements; knowledge of the vitamin contents of each organ of the human body is slowly accumulating. These studies are not only of diagnostic value for guidance of treatment. They are peculiarly valuable for establishing optimal levels of daily intakes of each of the vitamins in food. Our earlier estimates of the desirable levels were often too low because they were based on findings for individuals then supposed to be normal but now recognized as sub-normal, so wide-spread are some of the deficiencies.

Many individual idiosyncrasies are encountered. Sometimes they may be due to the malfunction of a secretory organ, for example, the thyroid or pancreas. Obviously people suffering from organic disfunction are not immune to vitamin deficiencies. Intestinal sluggishness or hyperactivity often profoundly influences a vitamin economy. To judge from the findings in experimental animals, man's vitamin economy may be greatly affected by the organisms he harbors in his intestines. They may synthesize or destroy vitamins in quantity according to the strains present and the character of the milieu in which they live.

Fortunately for the physician in general practice who naturally can not keep pace with the manifold weekly developments of modern medicine, the therapeutic response of vitamin dosage is very often convincing. If it is not favorable, he may rest assured that he has done his patient no harm and proceed to the next indicated therapy. Often physicians resort to polyvitamin preparations. Knowledge of the nature of the deficiency is thus sacrificed, but the practice is at least in part justified by the fact that deficiencies are often multiple.

Six vitamins have been referred to as major ones. The physician, even in general practice, can not wholly afford to neglect some of the lesser ones. Notably pre-administration of vitamin K to prevent excessive bleeding in childbed is becoming routine in many hospitals.

You are doubtless asking what all this vitamin knowledge will get us in terms of health, strength and longevity. No quantitative estimates are possible. Very few long-term experiments with animals have been carried out since all the major vitamins became available in pure form and since several of the lesser ones have been at least recognized. There is much need for patient and thorough work along these lines. The testimony of the clinics, the results of experiments with school lunches or supplementary feeding, as well as the observation of health trends in nutrition-conscious populations, are very reassuring. Since partial deficiencies are often most apparent in middle or later life when the body mechanism is beginning to feel the strain of the years, it seems reasonable to hope that nutritional reform will extend the span of life measurably. Control of infectious diseases has principally affected mortality in infancy and early life. Those who survive to old age tend to be those who have acquired immunity to infectious disease or at least to have undergone a selection for resistance to disease. In nutritional disease, the phenomenon of immunity is absent. We do not grow accustomed to deficiencies with the years. Early damage remains and later damage accumulates till the slowing bloodstream of age leaves our cells grossly undernourished, so it seems.

I have dealt with what I believe we may do within some years in applying our present knowledge of vitamins to the problems of public health. I would not have you suppose, however, that my imaginative sensibilities are wholly dulled to the possibilities which future pioneering research may bring to light.

The chief product of our studies of vitaminism has perhaps been a knowledge of the nature and behavior of those once quite obscure or unknown substances. Major by-products have been techniques and philosophies.

Of techniques, there are many which have been provoked or promoted by the necessities of vitamin research. One may reflect that, had thiamin been isolated at the time its isolation was first seriously attempted, there was no one in all the world who could have made a competent elementary analysis with any available sample. It was the microanalytical techniques of Pregl and his successors which really gave usefulness to the isolation procedure. But to go back a step further, the isolation itself would have been impossible without an appreciation of adsorption and of hydrogen-ion control. Our knowledge and skill in these matters has been drawn from wide fields, from artificial catalysts, from gas mask construction, from the theory of solutions and the arts of the brewmaster. Yet the needs of vitamin chemistry have aided greatly in forcing a refinement of the methods and a sharpening of the tools. To go a step forward, had we succeeded in our isolation and obtained a significant analysis, we might well have been baffled for an explanation of the peculiar acid-base properties of thiamin had we no glass electrode to run a titration curve with precision, a device which depends for its excellence on recent advances in electrical arts. All this range of techniques has been brought to the ser-

vice of biology in no small measure by the demands of the chemistry of minor organic constituents of living things.

And lastly of philosophy. We have long known there are enzymes and we recognized their analogy of function to the inorganic catalysts brought to light in great measure by Sabatier. The idea that a catalyst and its substrate must have a lock and key relationship arose early, based possibly upon Ehrlich's notions of immune reactions. Nobody, however, could prove the case, for the enzymes appeared to be gross and unmanageable molecules of great complexity. Turning to the inorganic catalysts for analogy did not help much because they obviously involved properties of the surface which were not shared by the interior of the particles. Precise chemistry of the surface, aside from the insides, was a poser. Even the electron microscope has its limitations in dealing with the irregular surface of a dense body.

It remained for vitamin chemistry to furnish the first example of an enzyme with a detachable prosthetic group, a key with the bit detachable from the stem. The bit or coenzyme turned out to be simple enough to be dealt with by classic methods of determining molecular structure; in fact it was a relatively simple derivative of a recently isolated vitamin. A similar relationship to enzymes has been proven for some other vitamins, though not all, and we know from the specificity of the coenzymes that the lock and key idea has validity. It is a notable step forward in enzyme chemistry and seems to offer an entering wedge for an attack on the chemistry even of genetics.

Another philosophy brought into relief by vitamin chemistry is the intimate chemical kinships of all forms of life. This permits the use of any convenient living thing to learn something about the probable behavior of more complex, delicate or unmanageable organisms, such as man. Vitaminism has taught us that metabolism is primarily cellular and not systemic.

It is true that these bits of philosophy are implications of vitamin chemistry and not necessarily integral parts of it. Nevertheless, vitamin chemistry will proudly observe their future progress, assured that presently we shall not attempt to distinguish sharply between vitamins and non-vitamins. That is an accident of the distribution of particular synthetic capacities among living things. We already know there is no sharp division along the borders of the animal and vegetable kingdoms.

VITAMINS IN THE FUTURE[1]

By Dr. ROGER J. WILLIAMS

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THERE is an anecdote regarding the president of one of the smaller colleges who was induced to set aside a substantial fund for research. If my hearers can believe the first part of this story, namely, the alleged fact that a president of a smaller college actually found and set aside substantial funds for research, they will find no difficulty in believing the rest of it. It seems that the plea made to this president was that there were *questions* which needed to be answered and research offered the only promise of answers to these questions.

At length the money was spent and more was asked for. But after reading the report the president objected strenuously to an additional appropriation on the basis that while the original purpose of the research was to *answer* questions, the investigators had ended by *asking* more questions than they had answered.

It seems that nowhere has this principle been better exemplified than in the vitamin field. At first the question was asked and answered, "What are vitamins?" Secondly, skeptics challenged the chemist, "Show me *one!*" Parenthetically, I will say I am sure that the first time many people in this country saw a vitamin was when my big brother Bob went traipsing over the country under the auspices of Sigma Xi lecturing and carrying with him a huge bottle of pure crystalline thiamin. People really got an eyeful. I believe he doesn't have his big bottle of thiamin with him this evening. So many people are taking daily doses of it now that it has become unsafe for him to appear with it on the street for fear of being mobbed.

After one or two vitamins had been produced by the chemist, the clamor was "More! More!", and now the chemist is able to show to any skeptical individual about fourteen different, distinct vitamins in crystalline form. In addition, there are interchangeable forms of a number of the fat-soluble vitamins.

On this occasion we want to discuss a few of the questions regarding vitamins which are largely for the future to answer. These questions could never have been *asked* were it not for the knowledge already gained through extensive research. Some are ques-

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