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-

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

tions of purely scientific interest. Many, however, have import from the standpoint of practical value to society.

Aside from the obvious question of what and how many vitamins exist, one of the most fundamental problems for the immediate future is to find out how vitamins act in the body—not what outward manifestations appear when they are lacking in the diet, but exactly how they function and why are they necessary. Each vitamin will present a more or less distinct answer to this question.

It appears that the "B vitamins," those comprising the group in which my brother and I have been primarily interested, are most fundamental to life. Living organisms are known (yeast is an example) which apparently can live and reproduce indefinitely without having in the cells at any time, so far as we know, any vitamin A, vitamin D or vitamin C. But in yeast and in other lower forms of life the "B vitamins" are, so far as we know, all present and functioning.

I was one of those who a few years back privately objected to jumping to the conclusion that since vitamins are present in tissues in small amounts they therefore are catalysts. It is now clear, however, with respect to several of the "B vitamins," that they do act as catalysts or at least are fundamental parts of catalytic systems. It seems not too dangerous now to infer that the other B vitamins probably act catalytically also. This conclusion does not follow necessarily for vitamin A, vitamin C and vitamin D. The functioning of these is very obscure at present.

We chemists have a simple device for representing a chemical reaction. If substance A is transformed into substance B, we write the formula of substance A, then draw an arrow pointing to the formula of the transformation product, substance B. The arrow indicates the transformation. Some one has defined a catalyst as something which "lubricates the arrow."

Vitamins of the "B group," we may conclude, probably act essentially as highly specialized lubricants for biochemical processes. In keeping with this idea they do not furnish energy but make possible its utilization. They do not function contrary to thermodynamics but make possible the flow of energy through the unbelievably intricate channels of living matter.

But we need a more intimate picture of how each of these vitamins act, what particular processes they lubricate and how they function. In the case of several of the B vitamins an excellent start has already been made; nicotinamide and riboflavin enter into indispensable "lubricants" for oxidative processes; thiamin is a part of a "lubricant" which is essential for decarboxylation mechanisms. However, our picture of why exactly these substances serve as "lubricants" is very hazy.

The case of pantothenic acid will illustrate our need for further knowledge. So far as we are able to tell, it is present in every type of living cell and we are led to assume that it catalyzes certain processes which are essential to life. There are facts which hint that it may be a lubricant for some step in the process of carbohydrate utilization. However, the subject of carbohydrate utilization has been studied extensively; many of the special "lubricants" have been identified and their action studied. Pantothenic acid, as yet, doesn't fit in anywhere in the scheme. So far as we can tell from its structure and chemical behavior it does not possess the properties necessary for an oxidation "lubricant." It doesn't appear to be adapted to receiving or donating hydrogen or electrons, and in this respect it is different from several of the other "B vitamins."

For a long time nutritionists have had some information regarding the functioning of vitamins. When a particular vitamin is lacking from the diet of an animal, it is usually possible to see that something is wrong. Often it is possible to identify the lack by the appearance or behavior of the animal, or the lesions which may appear on its body. When, for example, chicks are kept for a time on a diet relatively free from pantothenic acid, they develop what has become known as "chick dermatitis." But dermatitis, dermatosis or dermapathosis, if you like a more high-sounding word, simply means a diseased skin, and the trouble is much more deep-seated than this. Dermapathosis of one sort or another in one experimental animal or another may be caused by the lack of almost any member of the "B family" of vitamins. The symptoms may involve roughness or cracking of the skin in various areas, development of sores and loss of hair. Closely related is an unhealthy appearance of the hair or actual graying, since hair is a modified epidermal tissue. But in all cases the real trouble is probably not in the skin alone but in every tissue of the body. Naturally when we look at an animal we see the outside covering—the skin and fur. If there is something wrong with every tissue in the body of an animal, including the skin, we notice the skin and diagnose with a grunt of satisfaction—"dermatosis."

Studies made in our laboratory at Texas have showed that both in pantothenic acid deficiency and biotin deficiency not only the skin but every tissue and internal organ is lacking in the essential substance and shows its lack by failure to develop normally. If we were better pathologists we might be able to describe the changed morphology of the various internal tissues induced by the vitamin lack. I suspect, however, that the approach open to the pathologist would not always be a very fruitful one. A house infested with termites and about to fall down because of the weakness of the timbers could not be distinguished from a building having strong timbers, merely by photographic studies of its exterior. Just so it might not be feasible to distinguish morphologically between healthy cells from those which are deficient in some essential principle.

Physicians have coined the term avitaminosis to designate a diseased condition brought about by the lack of a vitamin. The various "avitaminoses" are poorly characterized indeed when we consider how many tissues may be affected. Superficial appearances and symptoms are wholly inadequate.

A question closely related to the one we have been discussing has to do with how the vitamins are interrelated. Each vitamin in general has been considered to have its individual independent function, and to be required as a separate entity for this reason.

There are some suggestive facts, particularly with regard to the "B vitamins," however, which cause one to be cautious and not too dogmatic. Several years ago we were studying the nutritional requirements of certain mold, and found much to our surprise that whereas it would not grow on a medium containing nothing more "special" than amino acids it would grow when to the medium was added thiamin, pantothenic acid, riboflavin *or* inositol. Growth would initiate when only one (not all four) was added. This observation should not be considered as a very valuable one so far as possible application to animals is concerned, because the mold in question was probably actually capable of synthesizing all four of the vitamins and required one of them only as an initial stimulus. In animals thiamin, pantothenic acid and riboflavin can not be synthesized (the case of inositol is uncertain) and one certainly can not replace another.

Another interesting and suggestive fact is that the various B vitamins are definitely associated together. Our recent studies of the vitamin content of tissues show a definite and often high positive correlation between the vitamin contents of different tissues. Those that are relatively rich in some of the "B vitamins," notably liver and kidney, have a tendency to be rich in all. Tissues such as skeletal muscle have a tendency to be low in all. Heart muscle, incidentally, is almost invariably richer in all B vitamins than skeletal muscle.

We have found also, for example, that feeding hens a diet enriched with respect to pantothenic acid causes the other "B vitamins" to be somewhat changed in their distribution in the chicks hatched from the eggs. This indicates that the different "B vitamins" are not working entirely independently.

The probability that one known vitamin can actually replace another can be pretty well ruled out on the basis of available evidence. We can not be sure, however, that our need for one is not influenced by our supply of another. It is well recognized, of course, that thiamin is essential for carbohydrate metabolism and that on a high fat diet less thiamin is required. If there are vitamins which are peculiarly essential to fat metabolism, it is easy to imagine that the amount of these in the diet might affect the thiamin requirement and *vice versa,* yet neither of the two vitamins would be capable of actually replacing the other.

With regard to amino acids, it had become customary to think of them as being in two groups—essential and non-essential—until Rose and his coworkers showed that arginine is not essential for growth but is essential for *rapid* growth in rats. It is one amino acid which can be built up in the bodies of rats but not with sufficient readiness to allow rapid growth. Is there any parallel in the field of vitamins? Are there vitamins which are not absolutely essential, but which are necessary if good performance is to be induced? One reason for thinking that this may be is the fact that in yeasts, for example, the phenomenon is observed again and again. Biotin, the remarkably potent yeast growth substance discovered by Kögl, is so far as I know not required for the growth of any of the yeasts which it stimulates. These yeasts will grow without biotin, and as they grow it is produced in abundance. But biotin is a powerful stimulant of yeast growth; it can not be produced by yeast readily enough to allow the most rapid multiplication. The most rapid multiplication takes place only when it is furnished in the culture medium.

Whether "non-essential" or "optional" vitamins occur which are effective in animal nutrition is a question for the future. It is entirely possible that some of the lesser known members of the "B family," the status of which is still in doubt, may belong in this category.

Another question arises naturally as a result of our work with microorganisms. Are there such things as "anti-vitamins" or inhibitory principles in foods which affect health and well-being? Of course the existence of a special protein "avidin" in raw egg white, which is capable of inactivating biotin, has been demonstrated, but I am thinking more particularly of low molecular weight compounds. In laboratory studies with microorganisms (yeasts particularly) we are constantly confronted with the presence in extracts of inhibitory substances which profoundly influence growth. We have long suspected that the same or similar substances may have an influence on mammalian nutrition, but very little is known about the existence or functioning of such substances.

A field of study which should be pointed out while we are mentioning microorganisms is that of the bacterial production of vitamins in the intestines of animals. Of course we must know to what extent this is being accomplished before we can have an adequate idea of how much of the vitamins are required in the food under different conditions. Elvehjem at Wisconsin and Mitchell at Texas have made recent studies of this problem, but I must not tarry on this particular phase of the subject.

I must turn now to a discussion of some of the possible applications of the new knowledge which I believe will be forthcoming. One of the subjects which has been of particular interest to me is that of individual differences. Vitamin study has not in general been concerned with this at all. Every attempt has been made in dealing with experimental animals to have them as uniform as possible so they will give the same responses. By careful inbreeding and use of litter mates for controls much has been accomplished in this direction, but even so it is still necessary to use a number of animals if one is to perform a conclusive experiment. This merely means that irregularities of response are to be expected.

How great a contrast is there, biologically speaking, between an inbred colony of experimental animals and, say, the population of New York City, where even within each of the numerous racial groups there are tremendous genetic differences. But our nutritional knowledge when applied must be used in precisely such diverse groups. It may be that some day the medical profession will be able to concentrate its attention upon the very thing that the nutritionist likes to eliminate as completely as possible, namely, the variation in the needs of individuals. There are two convincing arguments in favor of the therapeutic use of vitamins: one is that they *work* and the other is that their use is rational in view of the existence of individual differences and exaggerated requirements which may not be met by ordinary foods. Not only the heritage of an individual but his case history may conceivably make for altered and probably increased vitamin requirements.

We know that the chemistry of our individual bodies is not all exactly the same, otherwise a bloodhound could not use his nose to distinguish between individuals. It is a well-known fact, though not always recognized in practice, that individuals do not all respond alike to common drugs. I once had a student who had his tonsils removed almost without an anesthetic, because the operating physician could not believe that he was unaffected by novocaine, even though the fact had been demonstrated previous to this occasion. Curious individual peculiarities sometimes show themselves. I have an acquaintance who, though his sense of smell is normal in all other known respects, is unable to detect the odor of a skunk. For him, the pure substance n-butyl mercaptan, the active principle of "skunk perfume," has no striking or obnoxious odor. When such remarkable differences exist with respect to other chemical substances it would not be surprising if the vitamin requirements of some individuals deviated sharply from the mean. Virtually nothing is known at present regarding this possibility.

Another field where vitamin study will doubtless find fundamental applications is in chemotherapy. Not many years ago chemotherapy was considered almost a dead issue, with salvarsan and its relatives as the outstanding achievement. In recent years with the advent of sulfanilamide and its relatives chemotherapy is riding the crest of the wave and is more important than ever before.

While the action of drugs is never simple, there can be no reasonable question but that sulfanilamide and related drugs owe their action at least in part to their structural similarity to a vitamin, *p*-amino benzoic acid. It has been demonstrated that sulfanilamide inhibits bacterial growth *in vitro* by blocking out *p*-amino benzoic acid, and that its effects can be neutralized by the presence of an excess of *p*-amino benzoic acid.

Snell at the University of Texas has shown that the sulfonic acid analog of pantothenic acid inhibits the growth of bacteria which require it, and that its effect can be neutralized by additional amounts of pantothenic acid in an exactly analogous fashion.

These facts appear to be the basis for an entirely new approach to chemotherapy. It seems a reasonable working hypothesis to assume that chemical substances which have striking physiological effects have these effects because of their resemblance to naturally occurring tissue constituents, and that many substances of potential therapeutic value will be found which bear chemical resemblances to the various vitamins, of which we now have a considerable variety. If these remarks are valid, chemotherapy can now develop, not in a hit-and-miss and entirely empirical fashion, but by making use of at least one definite guiding principle.

One of the most important applications of vitamin knowledge will be, I believe, to the study of cancer. About a year and a half ago we were enabled, by a generous grant from the Clayton Foundation of Houston, Texas, to start a study along this line.

We felt, and have had no occasion to alter our opinion, that any study of the interrelations between vitamins and cancer must be a thorough one, so that our work in this field is not narrowly confined to cancer as such but also to a better understanding of how vitamins act in normal tissues. We are cognizant of the fact that vitamins which are as yet undiscovered may play a role, so we are interested in these also.

Aside from the development of methods and the study of the vitamin content of tissues, my associates, Drs. Pollack and Taylor, are carrying forward a more systematic study than has ever yet been attempted of the effect of vitamins in the diet on the incidence and development of various types of malignant growth.

In a book from the Bar Harbor Laboratories, published late in 1941, appears the following statement:

> Various experimental, unbalanced and defective diets have been reported as influencing the number of ''takes'' and the rates of growth of transplanted tumors. There is no doubt that diet may play a part in determining the reaction of the animal. On the other hand, the fact that the investigators have not used inbred strains to reduce and control the genetic variables, leaves it uncertain as to the cause and effect relationship between diet and changes in percentage of growth. This fact, coupled with an almost complete disregard of criteria of mathematical significance between the groups that are being compared, seems to have left the problem of diet in a most unsatisfactory condition. For this reason no attempt is made in this volume to cover the extensive but non-critical bibliography. The whole problem will have to be approached ''from the ground up'' by investigators who understand and utilize genetics, biochemistry and mathematics.

We were pleased when we read this because it coincided with our ideas and we had in fact just planned extensive experiments along exactly the lines suggested. These experiments are now under way and the results will be reported in due time. There are various groups of workers interested in essentially the same problem. It has been demonstrated many times that diet and specific vitamins affect the incidence and development of cancers induced by feeding butter-yellow. Our work as well as that of others indicates that the vitamins in the diet make a difference in cancers other than those induced by butter-yellow. We can not say yet just what the total results of our rather comprehensive experiments will be, but we can already be sure of one thing. They will be interesting.

A pet thought of mine which it seems appropriate to mention on this occasion is that one of the most important borderline fields in the future will be that existing between biochemistry and psychology. In this particular field vitamins will probably play an interesting role.

We have noted in our laboratories "personality differences" developed in experimental animals apparently as a result of diet. I presume similar observations have been made elsewhere. It is well recognized that good health and good dispositions tend to go together, and in so far as an abundant supply of vitamins may foster good health it will also promote good psychological adjustments. The current view with regard to psychological disturbances is that they are essentially pathological and amenable to treatment just as other ills are. It is a truism that mental health is based upon bodily health, and there are some good reasons for thinking that vitamins may in the future contribute materially to mental health and to satisfactory psychological adjustments. It is recognized already that one vitamin can and does cure mental derangements. One of the most distressing symptoms of pellagra are the hallucinations, dreams and other mental symptoms. These are tremendously helped by nicotinic acid administration. People who were so "crazy" as to be totally incapacitated have been brought back to the point where they can perform the functions of a useful member of society. What other vitamins may do for mental ills is yet to be demonstrated.

It should be pointed out that good diets, which mean an abundant supply of vitamins, among other things, promote intellectual keenness as measured by psychological tests both on animals and human beings. There can be no doubt that much dullness on the part of school children, particularly among the lower income groups, can be traced in part to a lack of the proper kind of food and specifically to the lack of enough vitamins.

We may as well end this part of the discussion on as lofty a plane as possible. Recent studies, several of them in New York City, have shown without question that intelligence and morality go together. The more intelligent a child is the less is his tendency to cheat, lie, steal or become delinquent. This high correlation between intelligence and morality can lead us to one conclusion. Since an ample supply of vitamins can foster a higher intelligence in human subjects it has also the capability of fostering morality. Vitamins in the future will not only give people better health both bodily and mentally but will increase their intelligence and their morality. It remains for the future to show to what extent these ends can be accomplished and how useful vitamins will be as tools for their accomplishment.

OBITUARY

JACOB ELLSWORTH REIGHARD

AFTER an illness of some weeks, Professor Jacob Ellsworth Reighard died on the 13th of February, 1942, in his eighty-first year. Thus passed a leader in the field of ichthyology, fresh-water biology, animal behavior and evolution—a man whose biography