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THE OUTLOOK IN THE SCIENCE OF NUTRITION[1]

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THERE can be little doubt, I think, that the world war exerted a profound influence upon the status of science. The stress of that period developed among all the civilized nations a realization of the enormous part that the contributions of science really played in the pressing affairs of the day. Only a few years earlier one might have been content to say, with Michael Pupin: "Science in its abstract side is poetry; it is Divine Philosophy, as Milton calls it." "Science," he added, "is the food which feeds not only the material but also the spiritual body of man." Then, quite suddenly, in times of national need, there was awakened a conviction that everything is possible to science; and it was promptly called upon to solve some of the most perplexing practical problems that had ever confronted the world.

In 1919 the late Professor W. D. Halliburton stressed the usefulness of physiologists during the war.

> It has been a war [he wrote] in which science has played a leading rôle. It has been so for mechanicians of every sort, on the land, on the sea and in the air. It has been so for the chemists who devised new explosives and new methods of attack, for instance, the poison gases. Many other examples of the chemical side of warfare might be adduced, but let us see what physiologists and physiological chemists have done. They stepped in not to add to the horrors of the battlefield, but to alleviate distress, and the very agent, chlorine, used for destructive purposes became in their hands the basis of the new antiseptics which have done so much to cure the wounds of war.[2]

The science of nutrition, in particular, was subjected to the influences of that turbulent period. The familiar wartime slogan, "Food will win the war," became the expression of research aspirations as well as practical endeavors. Permit me to quote some of the vigorous propaganda of the day.

[1] A paper presented at the meeting of the Federation of Biological Societies, Cincinnati, April, 1933.

[2] W. D. Halliburton, "Physiology and National Needs." E. P. Dutton and Company, New York, 1919.

Patriotism and food! Winning a world war by eating corn and chicken instead of wheat and beef! It will take much education to get this point of view. An army of food-savers does not appeal to the imagination at first consideration. But remember the large words of M. Bloch: "That is the future of war—not fighting but famine." . . . It is a time of rare and glorious opportunity; a time in which prosaic business and industry may be lifted up to the high plane of national service. And it is being so conceived in many quarters. . . . It is not a sordid association, patriotism and food. It can be as fine as the spirit of democracy and as ennobling as the struggle for democracy. For it is, in truth, in these days an essential part of each.

These are the words of Vernon Kellogg and Alonzo Taylor.[3]

The older members of the Federation will readily recall the general public indifference to the discoveries in the science of nutrition at the beginning of the century. When the need for food control became acute as a war-time measure there was, as Halliburton[4] has recorded for Great Britain, "a tendency to pooh-pooh the scientific aspect of the question: these were the days when mistakes occurred, for example, the use of rhubarb leaves. Things did not run smoothly until the Ministry made the remarkable discovery that people who have made a lifelong study of a subject are those who really know something about it, and are the only people in the position to give trustworthy advice." Referring to one of the meetings of the Interallied Food Commission at Rome, Halliburton[5] remarked:

My friend, Professor Chittenden, the apostle of moderation in food in the United States, and one of the representatives of that country at the Interallied Conference, put it very happily when he said, "In the ancient days the edict went forth from Rome that all the world should be taxed; to-day it is from Rome that the world will hear how it is to be fed." But the work of such conferences has not been final: one thing became very clear as time went on, and that is, the imperfection of our present knowledge, and therefore the machinery has been set in action for the future; various topics about which at present we know very little still are to be investigated.

It was inevitable that, amid an environment in which practical needs daily obtruded, attention should be directed to the energy aspects of nutrition. The word "calorie," in reference to food fuel, attained a long-deserved popularity. Our lamented colleague, Graham Lusk,[6] wrote in 1914:

The workshops of life require fuel to maintain them, and a necessary function of nutrition is to furnish fuel to the organism that the motions of life continue. Furthermore, the workshops of life are in a constant state of partial breaking down and materials must be furnished to repair the worn-out parts. In the fuel factor and the repair factor lie the essence of the science of nutrition.

In harmony with such views the study of animal and clinical calorimetry flourished. The investigation of basal metabolism and of related domains was prosecuted with outstanding success.

Thus there are times, as we have already noted, when special conditions tend to motivate the efforts of physiologists so that they are directed into certain experimental channels. There are also periods in the history of most branches of scientific endeavor when the conventional methods of study in certain fields seem to reach the limit of their profitable applicability. Progress becomes slowed; and investigators tend to abandon what seem to be sterile fields. This appears to have been true of that branch of the science of nutrition which I shall designate as alimentation. The expression is intended to include the sum total of the several processes that occur in the different regions of the digestive tract. Here ingested food materials are subjected to the varied environments furnished by the alimentary secretions—the saliva, gastric, pancreatic and intestinal juices and bile. In the contents of the gastro-intestinal canal a diversity of enzymes promotes a succession of chemical changes of outstanding importance for the nutritive functions of the body. The so-called "building stones" for the rest of the organism are liberated. Microbiotic changes also enter into the picture. At the same time absorptive processes take place, to a variable extent, in the different regions of the bowel.

Some of us can recall the days when these highly important functions—secretion, digestion, absorption, to which may be added the alimentary movements—were among the dominant topics of physiological and biochemical investigation. In recent years, however, this research interest has waned. Shall we conclude that the details of the fate of our foods in alimentation have been fully discovered and that the physiological problems presented thereby are adequately solved? Professor Abderhalden, of Halle, once wrote: "The cells of our body never know the food that we eat." This statement was a protest against the older assumptions that our foodstuffs are only slightly changed—perhaps only rendered more soluble and diffusible—prior to their absorption and transport from the digestive tract to the other tissues. Presently newer theories of alimentary function were propounded, in which simple sugars, amino acids, fatty acids, glycerol, sterols, inorganic ions, and the

[3] V. Kellogg and A. E. Taylor, "The Food Problem." Macmillan Company, New York, 1917.
[4] *Op. cit.*
[5] *Op. cit.*
[6] G. Lusk, "The Fundamental Basis of Nutrition." Yale University Press, New Haven, 1914.

as yet unidentified vitamins, became the true nutrients in the minds of physiologists.

The current teachings are familiar to all of you. Are we satisfied that they tell the correct story in its entirety? Let us select a few items for the purpose of illustrative discussion. Consider first, if you will, the fate of ingested fats and related substances. A prominent text-book writer[7] of my own student days summarized the knowledge of 1891 as follows:

> Since fat is the only alimentary substance that can be detected after its absorption from the contents of the intestine, attention has been chiefly directed towards the investigation of the path taken by the absorbed fat-particles, but it is highly probable that the amoeboid cells are actively concerned in promoting the absorption of alimentary substances of all kinds. . . . Many observations have been accumulating recently, which show the importance of the part played by leucocytes in the promotion of various absorption processes.

Obviously such an indefinite explanation could at best serve only to stimulate further investigation. The assumption that fats are absorbed, presumably with only slight chemical change, in the form of a fine emulsion was presently attacked by Pflüger. He championed the digestive hydrolysis of fats whereby they are absorbed in the form of water-soluble compounds—soaps and glycerol. This hypothesis was later supplemented by the claim that certain bile constituents favor the solution and absorption of free fatty acids. The demonstrated occurrence of neutral fats in large amounts in the lacteals necessitated the postulation of a resynthesis of fats within the absorbing cells.

The digestive aspects of this explanation are in complete accord with the current assumptions about the changes undergone in alimentation by proteins and carbohydrates. In a review of our knowledge of the absorption of fats in one of the newest issues of *Nutrition Abstracts and Reviews,* Verzár[8] presents some of the difficulties entailed by the conventional teachings. I venture to quote a few:

> The work of Henriques and Hansen has long been quoted as convincing evidence in support of Pflüger's theory. They found that when emulsions of fat and paraffin were fed to animals it was only the fat that was absorbed. This result is obviously not so conclusive as at one time believed. . . .
>
> Recent investigations of the reaction of the intestinal contents have cast considerable doubt as to the veracity of the contention that the fatty acids, as soon as they are liberated, combine with the alkali present there to form soaps. It has indeed been shown that an alkaline reaction is rarely, if ever, found in the small intestine, but that the contents are generally frankly acid in the higher levels, and less so in the lower levels. Even in the ileum the pH rarely rises above neutrality. . . .
>
> We have no basis for the assumption that lecithin is a factor in the absorption of fats, nor do we consider this assumption necessary. The question why less bile acid is required for fat absorption in the intestine than is necessary *in vitro* still remains to be answered. One can only come to the conclusion that the bile acids must act locally upon the permeability of the mucous membrane. Therefore we have suggested the hypothesis that it is unnecessary for the bile acids to dissolve all the fatty acid at the same time, but that the former are adsorbed on the surface of the epithelial cells of the intestinal mucous membrane, and in that position can repeatedly conduct new quantities of fatty acids in water-soluble form through the surface of the epithelium. This seems probable, because of the well-known fact that the fat present in the interior of the epithelial cell is neutral fat; so that the choleic acid complex must have been split there. The bile acid when set free could, as a strongly surface-active substance, easily be adsorbed on the cell surface, especially on to the outer finely striated border of the cells. There it could repeatedly dissolve fatty acids and transport them through the membrane. Conclusive evidence of the accuracy of the above view is very difficult to obtain.

Verzär points out that the alleged effect of bile acids in absorption is concerned not only with the fatty acids but also with a principle of much more general significance.

> These extraordinarily active hydrotropic substances are constantly secreted by the liver. They influence not only the absorption of fats, but also that of many other substances, exerting their effect directly on the substances and partly on the surface of the mucous membrane.

Again we are reminded that

> The subsequent fate of the fat is almost a complete mystery. Neutral fat is found in the lymph stream, but how it gets there from the interior of the epithelial cells or into the fat depots from the blood stream, and back again when it is being mobilized, is almost entirely unknown. It may be that besides bile acids other hydrotropically active substances are formed in the body with the aid of which water-insoluble substances can be taken up into the cells. If such is the case, it is probable that these (hypothetical) substances are called into activity during the laying down of fat in the depots and also when there is a demand for fat from other regions of the body. It is well known that during starvation as well as during fat absorption, the blood is laden with fat, and it is obvious that this lipemia can only be brought about in the starving animal by the transference of fat from the depots into the blood stream. It is indeed probable that the lipoids of the cell membrane

[7] W. D. Halliburton, "A Text-book of Chemical Physiology and Pathology." Longmans, Green and Company, London, 1891.

[8] F. Verzär, "The Absorption of Fats." *Nutrition Abstracts and Reviews,* 2: 441, 1933.

play some part in the passage of fat across cell boundaries.

It has recently been claimed by Tangl and Berend that the fatty acids set free in the intestine by lipase are then converted into unsaturated and water-soluble fatty acids, in which form they can readily pass into the epithelium without the aid of the bile salts. The existence of such unsaturated acids in the fat depots of the organism had been previously pointed out. Analyses of intestinal contents that have been made in regard to this point suggest that these unsaturated acids are formed in such small amounts that they can not be considered to play any rôle other than a very subordinate one in fat absorption.

It must be frankly admitted that no adequate "balance sheet" has ever been submitted for the disposal of digested and absorbed fat. Part of the fat found in the feces is asserted to be of intestinal origin. Much of the fats absorbed can be recovered in the thoracic lymph; but what becomes of the missing fraction? Have our experimental procedures proved to be inadequate?

In connection with the behavior of fats reference may appropriately be made to the possible indispensability of certain types of fatty acid for adequate nutrition. Until quite recently the dietary fats were regarded to be useful merely as fuel for the expenditure of energy. Studies reported during the past six years, notably by Burr and by Evans working with diets rendered rigidly fat-free, raise the question as to the need of small amounts of unsaturated fatty acids such as lineoleic acid to avert nutritive disaster. This discovery, if confirmed, would place such fat components in a class with the known indispensable amino acids, notably cystine, lysine, histidine and tryptophane. Hitherto unsuspected but highly important physiological distinctions may exist between different ingredients of the numerous dietary fats and the little considered fatty components of other foods. The implications of the specific rôles of highly unsaturated fatty acids in the body are manifold. Such substances present abundant opportunities for the investigation of their intermediary behavior in the body.

Far from having a satisfactory story of the fate of fat, a foodstuff that commonly constitutes about one third of our daily food fuel intake, we must frankly admit a record of incompleteness, if not actual confusion. There are added problems of enzymatic (lipase) functions, the influence of the alimentary reactions, the possible rôle of bile constituents, and of vitamin factors. Histology and biochemistry have not yet furnished concordant and conclusive evidences about the behavior of fats. The entire record presents an illustration of what Sir Michael Foster, speaking of an analogous situation in regard to the intermediary metabolism of proteins, once termed "a chapter of gaps and guesses."

The most optimistic conclusion that Verzär has marshaled intimates that

> We are justified in saying that the mechanism of absorption of fat is now understood, at least to some extent. The process is a complicated one, and depends on the reaction of the intestinal contents, on the formation of hydrotropic substances and on the action of these in bringing the insoluble fatty acids into solution and in altering the permeability of the epithelial cells. On the other hand, the precise way in which the fat is transferred from the intestinal mucosa into the depots and from there to other tissues in accordance with metabolic requirements is almost unknown.

Surely this is a vigorous challenge to renewed research.

A somewhat similar, though perhaps less confused situation prevails with respect to the nitrogenous foods. We prefer at present to believe that proteins are completely disintegrated into amino acids prior to the absorption of the nutrient components. This is a postulate of the current theories of nutrition. It obviously represents a profound change from the earlier inadequate views of protein digestion; but is it entirely tenable? Are we justified in concluding dogmatically that none of the ingested protein is absorbed in the form of polypeptide fragments? I recall that only a few years ago Abel raised the question as to whether or not proteoses penetrate the gastrointestinal barrier to some extent. Prolonged nutrition and growth have not yet been secured on rations in which amino acids alone supply the nitrogenous food. The splendid experiments of W. C. Rose represent the nearest approach to success. However, even success with such a dietary regimen is not proof that in ordinary nutrition polypeptides are not absorbed and that they do not participate in metabolism.

With respect to the nucleoproteins also, the student of to-day is taught the theory of complete alimentary disintegration of these compounds to the stage of purines, pyrimidines and the other end products of enzymatic hydrolysis. Nevertheless, the possibility of the absorption of intermediate nucleosides and nucleotides is by no means conclusively excluded. Indeed, these may represent in no small measure the physiologically preferred form in which purine compounds are distributed in metabolism.

Several writers have recently pointed out that the time is now at hand to appraise more clearly the relation of the "minerals" in the diet to such factors as vitamins, internal secretions and especially to intermediary metabolism. If this is true, one of the important steps is to learn more about the manner and the form in which the important inorganic elements are made available in the alimentary canal during the customary dietary régimes. Despite the enormous amount of study that has been devoted to the most prominent inorganic elements, calcium and phosphorus, the details of their ingress and egress are far from satisfactorily explained. The possible rôles of the so-called "trace" elements continue to present an engaging opportunity for research. The newer findings regarding the behavior of magnesium, the claims regarding manganese, the action of copper and the revelations of mottled enamel in human teeth afford illustrations of some of the popular research trends in the laboratories of to-day.

In the past the study of alimentation in relation to nutrition has been concerned primarily, if not almost exclusively, with the familiar predominant "proximate principles." In every-day life, however, diet consists of something more than simple mixtures of the commonly recognized foodstuffs, such as milk conspicuously represents. Vegetable products in the form of leaves, roots, tubers, buds and fruits enter abundantly into the rations of man and of animals. Unique nutrient advantages are being ascribed to these foods; while our knowledge of what actually happens to them chemically in the long reaches of the alimentary tract is woefully limited. The investigation of the "roughage" problem, for instance, is still being prosecuted, if not greatly promoted, by the questionnaire method of study.

The discovery of the remarkable relationship between carotene and vitamin A may serve to remind us of our ignorance regarding the possible biological value of a number of pigmentary substances, not excluding the ubiquitous chlorophyll. The student of nutrition has frankly neglected them. Now that the biochemist is developing new methods of approach we may perhaps look forward to interesting new contributions.

The dietary function of the organic acids of vegetables is almost entirely unknown. Man and animals must ingest considerable quantities of compounds like citric, malic, tartaric and oxalic acids. How do they function in alimentation? Do they find their way into the systemic circulation or are they disposed of in the liver? Again, the edible glandular foods, such as liver, kidney and thymus, were formerly thought of, aside from their protein content, primarily as potential sources of uric acid-forming purines. Now they are regarded as sources of other dietary factors including hemopoietic agents; thus they present additional complex problems for the physiological chemist engaged in the study of digestion and intermediary metabolism.

In order to convince myself that my thesis regarding the present-day indifference to some of the unsolved problems of digestion is not utterly untenable I have examined some of the representative sources of information. The indexes of *Physiological Reviews,* which now cover more than a decade, fail to reveal any comprehensive essay devoted primarily to the debated chemical aspects of alimentary digestion. These years have, of course, witnessed a renewed interest in the biochemistry of enzymes. The work of Willstätter, Waldschmidt-Leitz, Northrup, Sumner, Sherman and many others has brought outstanding new contributions to our knowledge of the isolation, structure, specificity and dynamics of the organic catalysts. But the direct application of these contributions to the alimenary functions has rarely been attempted. Alimentary digestion, *per se,* is not discussed in the "Annual Review of Biochemistry"; and it is referred to only sporadically in the recent very comprehensive volume on "Nutrition" issued by the White House Conference on Child Welfare and Development. These omissions are, in my opinion, an indication of the difficulty experienced by reviewers in presenting new or novel information about alimentation. There is need of additional facts secured through new methods of attack upon the problems involved.

It is fortunate that attention is being directed anew to the absorbing force of the intestine in studies such as those of Drinker, H. S. Wells and their coworkers. Their investigations involve, among other features, the relative participation of the lymph and blood systems. The provision for the transport of the digestion products is a physiological feature of nutrition in its broadest aspects. It deserves further scientific consideration destined to eliminate the hazy hypotheses of indefinable "vital" forces. When we attempt to peer beyond the alimentary barrier into the blood stream the newer conceptions of the relation of the circulating proteins to nutritional edema present novel features of practical medical importance as well as of purely scientific interest. The existence of "war dropsy" and of endemic edema of nutritional origin in this country calls for serious consideration; the investigation of plasma proteins has aroused new enthusiasms.

If in these hurried and admittedly superficial comments I have appeared to overlook or disregard some of the obviously pressing problems of research in nutrition, it is not because of indifference to their importance. No one could have followed closely the progress of vitamin research during the past two decades without appreciating the imperative need of a chemical identification of the vitamins, and a clear explanation of their individual physiological rôles. This audience needs no such reminders, nor is it unaware of the pressing and complex problems of the intermediary metabolism of the foodstuffs, their interconvertibility and the chemical reactions concerned in the exchange of energy. Soon the question whether alcohol is a food will be heard again. I have ventured rather to direct attention to less popular and partly neglected opportunities for intensive study.

Sir William Osler, describing a special part of medical literature, once remarked: "What a desolate sea of theory and speculation!" Most of us are familiar with such areas in our own domains of science. They call for initiative and forethought to explore and chart them more satisfactorily.

THE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

THE SEVENTEENTH ANNUAL MEETING OF THE PACIFIC DIVISION

By Dr. J. MURRAY LUCK

SECRETARY, STANFORD UNIVERSITY

THE seventeenth annual meeting of the Pacific Division of the American Association for the Advancement of Science, together with its associated societies, was held from June 12 to 15 in Salt Lake City, Utah, eleven years having elapsed since the association last met in this region. Generous hospitality was provided by the University of Utah.

Two hundred eighty-seven members and guests registered for the meeting and twelve of the associated societies participated. Though ranking as one of the smaller meetings of the Division, the sessions were of singular interest by virtue of the large proportion of excellent papers and the lively discussions which followed.

The sessions commenced on the afternoon of June 12 with reviews of the scientific contributions of the past year in four fields of science. Dr. H. H. Kimball, president of the American Meteorological Society, presented the report on recent advances in meteorological research. Studies of the Bjerknes polar front theory of the development of cyclonic storms and investigations on the vertical temperature distribution in the atmosphere were reviewed in some detail. The researches at Point Barrow, Alaska, proceeding under the program of the International Polar Year were outlined. Professor R. G. Aitken, director of the Lick Observatory, presented the review on "Astronomy and Astrophysics." Attention was given to some of the major problems of stellar research, such as the distribution of stars, their spectral peculiarities and distances, their apparent and absolute magnitudes and radial velocities. The bearing of these investigations on current theories of the nature of the universe was discussed. Several recent observations of general interest were referred to: the meteoric shower of last November, night sky radiation, bands identified in the spectra of Venus and Jupiter, the total eclipse of August 31, and observation of the corona without eclipse. Professor Eliot Blackwelder, of Stanford University, reviewed the recent contributions in geology and seismology, selecting five or six problems of major interest which are being actively investigated in the west. Among these might be mentioned the nature and origin of batholiths, the origin of the characteristic plains of deserts and certain problems of mountain growth. The final review on "Chemistry in Relation to Medicine" was presented by Dr. Chauncey D. Leake, professor of pharmacology in the University of California.

In the evening Professor W. F. Durand, of Stanford University, retiring president of the Pacific Division, presented an address on "The Development of our Knowledge of the Laws of Fluid Mechanics." This will be published *in extenso* in SCIENCE. Prior to President Durand's address, Dr. George Thomas, president of the University of Utah, formally welcomed the association and its guests.

The morning of Tuesday, June 13, was devoted to a symposium on "Scientific Problems of the Great Salt Lake," in which five papers of considerable interest were presented by members of the faculty of the University of Utah whose studies have been largely centered upon the problems under discussion. The titles are "The Ancestry of Great Salt Lake," Dr. Hyrum Schneider; "Climatological and Hydrological Problems," T. C. Adams; "Chemical Deposits and Problems," Dr. Thomas B. Brighton; "Animal Life and Relations," Dr. A. M. Woodbury, and "Plant Life and Relations," Dr. Walter P. Cottam.

At 4 P. M. President and Mrs. Thomas received the members and guests of the Division and associated societies. In the evening, Dr. H. H. Kimball addressed the association on "Meteorology—Ancient and Modern; its Development and Applications." The address was largely devoted to the growth of observational and experimental work in meteorology as conducted under the auspices of various government departments from 1812 on.