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ANNUAL REVIEW OF NUTRITION

PREFACE

The *Annual Review of Nutrition*, in conformity with the goals of Annual Reviews Inc., provides a systematic, periodic examination of scholarly advances in nutrition through "critical, authoritative surveys of the recent original literature describing the current developments in the science of nutrition."

The purpose of a critical review is not only to summarize a topic, but to root out errors of fact or concept and to provoke discussion that will lead to vigorous new research activity. The critical review is as essential a part of the overall scientific method as the original experiments and is part of a continuing peer-review process. The experimenter creates a hypothesis, plans an experiment, records his data, and evaluates his hypothesis. In due time he publishes a paper that is reviewed by peers in the field for adequacy of materials and methods, originality, and soundness of its conclusions. As other papers accumulate, however, it is necessary to take a second look at the published record to see what new scientific discoveries have been made and corroborated, what new areas have been opened, and which research should be encouraged. Fallacies and questionable hypotheses must also be combatted in these reviews in order to limit research in less promising directions. No human judgment, of course, is infallible, but the overall scientific effort depends upon a critical review at each stage in the development of a scientific report, from the experimental plan to the integration of the results into a broader field of science. This is particularly important for nutrition science at this time because of two major threats to the integrity, stability, and funding of the nutritional sciences. These factors apply to all science to an extent but it appears to me at the moment that nutrition science is particularly vulnerable.

The first factor is the turf battle between nutrition scientists and nutrition politicians for control of the data base that underlies food and health policy. Nutrition scientists depend upon the scientific method for their data base. Nutrition politicians, on the other hand, lean on descriptive epidemiology and anecdotal evidence, influenced by their particular beliefs about foods and by those of their constituents (consumerists, corporate interests, the media, and the public). It is regrettable that some scientists have joined these politicians in supporting unsound programs in nutrition education. Critical reviews play an important role in separating nutrition fact from fancy.

In addition, the tightening of the Federal Budget under such political phenomena as the Gramm-Rudman-Hollings Anti-deficit Act creates a gloomy financial future for the NIH and the NSF, particularly in the biological sciences. Such constraints in Federal funding make it extremely important that the most imaginative ideas in the hands of the most productive scientists be supported. Again, the critical review can be of value in guiding the assessment of grant

(continued)

applications, so that the scientific study of nutrition can grow. Such study is crucial, not only in clarifying the function of nutrients but also in elucidating the interactions of genetics, metabolism, and nutrition in the pathogenesis and prevention of the chronic degenerative diseases.

The *Annual Review of Nutrition* strives to cover the wide range of subjects that constitute the field of nutrition. Nutrition is not a single discipline; it draws from a variety of disciplines in both the basic and clinical areas. In the first six volumes, 50% of the pages deal with basic and experimental nutrition, 33% are devoted to clinical nutrition, and the remainder are related to epidemiology, anthropology, and public health nutrition.

The present issue, Volume 6, begins with a prefatory chapter by Dr. Hamish Munro of the Massachusetts Institute of Technology. He pleads for application of the modern disciplines of molecular and cell biology to problems in nutrition science. Nutrition science is not in any sense limited by its past or present technologies but must demand the application of new technologies and concepts to the study of nutrient requirements, metabolism, function, and the relationship of nutritional status to health.

This issue also includes reviews on the energetics of ethanol, the role of sugars in nutrition, the regulation of cholesterol biosynthesis, the metabolism of sulfur-containing amino acids, and the function of inositol phospholipids. The biochemical function of vitamins C and D, metabolism of carotenoids, and the function of carnitine in humans are also reviewed.

In clinical nutrition, Volume 6 includes reviews of the physiological adaptation to lower intakes of energy and protein; nutrition and infection; calcium and hypertension; mutagens and carcinogens in foods; labile methyl groups in the promotion of cancer; and inheritable disorders of biotin metabolism. In comparative nutrition we have essays on the nutrition of fish and of ruminants and an article on the role of gastrointestinal microflora in mammals. In the field of nutritional anthropology we present chapters on the impact of culture on food habits; diet and human behavior; and food likes and dislikes.

I would like to thank my associates on the Editorial Committee, the consultants who aided us in assembling the reviews, and the authors who have provided such excellent reviews for Volume 6. Our work has been ably complemented by that of Ms. Margot Platt, the Production Editor of the *Annual Review of Nutrition* in Palo Alto.

ROBERT E. OLSON, EDITOR

SOME RELATED ARTICLES IN OTHER *ANNUAL REVIEWS*

From the *Annual Review of Biochemistry*, Volume 55 (1986):

Beta-Amino Acids: Mammalian Metabolism and Utility as Alpha-Amino Acid Analogues, *O. Griffith*

Metallothionein, *D. H. Hamer*

Arachidonic Acid Metabolism, *P. Needleman, J. Turk, B. A. Jakschik, A. R. Morrison, and J. B. Lefkowith*

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Taurine: Biological Update, *C. E. Wright, H. H. Tallan, Y. Y. Lin, and G. E. Gaull*

From the *Annual Review of Physiology*, Volume 48 (1986):

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Hamish N. Munro

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BACK TO BASICS: An Evolutionary Odyssey With Reflections on the Nutrition Research of Tomorrow[1]

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PRELUDE

The *Annual Review of Nutrition* provides the rare opportunity and challenge of reflecting on the status of nutrition research within the family of Life Sciences. I shall argue that, like other applied biological sciences, nutrition research needs to be continuously enriched by concepts and techniques developed in the course of basic biological research. This implies that some in the community of nutrition scientists must maintain lively contact with the rapidly moving front in basic biological sciences. Hence the phrase "back to basics" in my title. Not only will this have a beneficial effect on nutrition research, but it will also improve credibility for nutritionists among their basic science colleagues.

The mature scientist always appears to be a more or less autonomous individualist. Yet there are encounters along the way that determine our career patterns. Looking back on my own progress, I can identify several such factors that, without my seeking them out, have conspired to steer my own progress into basic directions. In its own way, each displays an aspect of evolution, whether it be the evolution of a species or of a scientific discipline.

First, I have always had an interest in history, an interest I share with other prefatory essayists in this *Annual Review* series. In editing the first volume in a series on protein metabolism in the 1960s (21, 22), I decided to explore the history of this area for an introductory chapter, and found that I and the people I had worked with early in my career came from a scientific lineage going back two hundred years to the beginning of modern chemistry, like a family tree that progressively evolves in sophistication.

Second, in continuation of the same series on protein metabolism, I concluded that it needed a section on the role of nutrition as a central factor in the evolution of *animals*, which, I was able to show, share a distinctive common pattern of nutrient needs not found in other life forms, a pattern that can only be satisfied by a supply of food. This need distinguishes unicellular animals from unicellular plants or molds, while multicellular animals can be shown to have made evolutionary adaptations to accommodate their needs for nutrients. In particular, mammals, the class we most often deal with experimentally, show an inverse relationship between body weight and daily intake of nutrients per unit of body weight.

Third, during the past decade it has become possible to explore these evolutionary changes at the level of the genome and this has provided me and others with the exciting possibility of observing both conservation of functional components of proteins along with new adaptations as evolution progresses.

The final molding effect on my career has been my good fortune in being associated with the development of the USDA Human Nutrition Research Center on Aging at Tufts University. It offers the possibility of determining how nutritional and other environmental factors cooperate to allow the human to optimize his or her genomic potential throughout the life span and to ameliorate the gradual aging process.

THE HISTORICAL BACKGROUND OF NUTRITIONAL SCIENCE

Scientific research is an evolutionary process in which the present builds on the past, often without recognition of the latter. In the words of Carl Voit in 1865 [cited in translation by Lusk (17)]: "The man of science ought to realise the factors which have given him the vantage which he holds. But there are textbooks on the animal mechanism which do not even mention the name of Liebig. This anomaly is possible only for those who do not understand history and hold only the new to be worthy of consideration." Here, I want to illustrate how my early association with the nutritional sciences was predestined from the succession of previous investigators ~~whose~~ work pointed in that direction.

I have written elsewhere (23) about the development of protein metabolism and nutrition. Modern chemical science began with the discovery of carbon dioxide by the Edinburgh physician Joseph Black in 1756 (4). That discovery was rapidly followed by the identification of oxygen and nitrogen in the atmosphere. The biological importance of these gases was appreciated from the beginning. Nitrogen was first recognized by its inability to sustain the life of a mouse (35), a property commemorated in the French word for nitrogen, *azote* (Greek "without life"). In France, Black's contemporary Lavoisier developed the first systematic modern chemistry that included gasometric volume determinations for many compounds. In 1790, he wrote to Black to tell him that his gasometric measurements showed that respiration is accompanied by the disappearance of some oxygen and its replacement by carbon dioxide in the expired air, and that this exchange is accelerated some 50% after meals and several-fold by exercise (23). Thus modern chemistry was born in an atmosphere of physiological function, including measurement of the energy needs of different states. It may be noted that energy needs is as good a place as any to start nutritional research. It remains a major field of nutritional research.

Although Lavoisier did not survive the French Revolution, his school of chemistry flourished and provided fertile ground in which the biological sciences could develop. In 1817, the French physiologist Magendie issued his *Elementary Compendium of Physiology* (18), the first modern text on this discipline. In the preceding century, Haller had published an eight-volume text on physiology written in turgid Latin, and without benefit of the new chemistry. With Magendie, we step from the primeval forests of mystery and speculation created by Haller's *Elementa Physiologiae* (12) into the bright sunshine of scientific observation and deductive reasoning displayed in Magendie's book. Because of his Parisian contemporaries, who had been trained in chemistry in the school of Lavoisier, Magendie was able to state that "the proximate principles of animals are divided into nitrogenous and non-nitrogenous. The nitrogenous principles of animals are: albumen, fibrin, gelatin, mucus, casein, urea, uric acid, red-colouring matter of blood. The non-nitrogenous principles are: olein, stearin, fatty matter of the brain, acetic, benzoic, lactic, formic, oxalic acids, as well as sugar of milk, sugar of diabetic urine, colouring matter of bile." Magendie went on to demonstrate that essential dietary constituents included nitrogenous organic compounds, later to receive the unifying name of "protein" by Mulder (20) in 1839.

Another scientist who benefited from the Lavoisier school of chemistry was Liebig, a German scientist who spent the years 1823–1824 in Paris. He carried the new chemistry to Giessen in Germany, where he applied organic chemistry to the study of animal metabolism. From this emerged his book *Animal*

Chemistry or Organic Chemistry in its Applications to Physiology and Pathology (15) in 1840, which laid the foundations of metabolic principles. In 1852, Liebig transferred from Giessen to Munich, where he established a vigorous school of metabolic studies from which emerged Carl Voit, later to be Liebig's successor in Munich. Although balance studies of carbon, hydrogen, oxygen, and nitrogen had been carried out on cattle by Boussingault (5) in 1844, it was Voit who raised the technique of nitrogen balance to fine precision (3). He taught these skills to various foreign workers who went back to their own countries to perpetuate the science of nutrition: Atwater and Lusk to the US, Rubner to Germany, and Cathcart to Britain, the last-named to be the teacher of the present author.

Voit may be regarded for other reasons as the father of modern nutritional experimentation. In 1853 and again in 1865, Playfair (33), professor of chemistry at Edinburgh University, had surveyed the diets of different classes in the British population and had concluded that the daily diet of the average man contained 119 g protein, 51 g fat, and 530 g carbohydrate. In 1881, Voit (38) summarized these surveys and others, including his own, and assessed the needs of the average working man to be 118 g protein, 56 g fat, and 500 g of carbohydrate. At the time, these intakes were also regarded as desirable quantities of each nutrient class needed to maintain health, but were challenged at the turn of the century by Sivén (37), Chittenden (8), and Hindhede (14). The low intakes of protein advocated by these investigators were later rejected by many who had observed impaired resistance to disease on diets low in protein. Thus Voit and his immediate successors had begun to ask the questions with which we still struggle in the field of nutrition, and which are reflected in another chapter in the present volume (39). It may be noted that, through his long-term role as editor of the *Zeitschrift für Biologie,* Carl Voit identified himself as a generalist in biology.

From this brief history, it will not have escaped the reader that science is made up of a series of successive small steps in which skills in laboratory techniques, and practice in both deductive and inductive reasoning that lead to new concepts, are passed on from the older to the younger investigator. In my own case, I first studied protein metabolism in 1934 with D. P. Cuthbertson (later Sir David Cuthbertson, Director of the Rowett Institute, Aberdeen), who at that time was in the Department of Physiology at Glasgow University headed by Cathcart. Cathcart had also acted as a preceptor for Boyd Orr, the founder of the Rowett Institute and later of the Food and Agricultural Organization in post–World War II Rome. Thus, through Cuthbertson and Cathcart, I learned the concepts developed by Voit, who in turn was influenced by the teachings of Liebig, based on the organic chemistry he had learned from the French school of Lavoisier in Paris. Thus the mature investigator is not an island unto himself, but is part of an ongoing process in the evolution of scientific knowledge!

INTERMISSION

The period of my life from the mid-1930s until the mid-1950s was punctuated by a teaching position in clinical medicine, a war, and other changing events. However, the basic allure of studying nutritional and other factors in protein metabolism persisted. Under the guidance of Dr. Cuthbertson, the relationship of energy intake to protein utilization was extensively explored between the years 1936 and 1952 and it still provides basic data. Indeed, my most recent publication (11) on this topic was in 1979 with John Kinney's surgical metabolism group in Columbia College of Medicine and deals with the influence of energy intake on nitrogen balance in surgical cases. But slowly the desire to delve deeper became irresistible. There was a perceived need to integrate the metabolic events that make protein metabolism the wild ballet that it is, with whirling metabolites answering to the orchestration of the endocrine system as they shuttle among the tissues. To reduce this to order, there followed a period of examining the principles on which protein metabolism is accomplished in different mammals. This was consolidated by an in-depth survey of the evolution of animals, seen from the viewpoint of their nutritional needs and their metabolic responses.

NUTRITION AND THE EVOLUTION OF ANIMALS

A defensible case can be made for the view that the main driving force in the evolution of animals from the most primitive forms onward has been the supply of nutrients in the environment (24). It can be presumed that primitive unicellular organisms evolved from non-nucleated (prokaryotic) forms into nucleated (eukaryotic) unicellular forms, such as molds, which still retain the general prokaryotic property of synthesizing all organic compounds required for metabolism. However, it seems likely that, in the early history of the Earth as the fluid surrounding the colonies of such organisms became enriched with their metabolites, it was possible for some mutant cells that had lost the capacity to make certain metabolic pathways to find enough of the missing metabolites to survive. In this way, cells that had eliminated metabolic pathways could multiply even faster than their better-endowed neighbors who had to divert energy to the synthesis of these metabolites. Zamenhof & Eichhorn (40) showed with a histidine-deficient mutant of *B. subtilis* that, in the presence of histidine, this mutant grows faster than the wild type, which continues to make this amino acid and thus has to divert energy to its synthesis.

Eventually, cell populations must have emerged with a stable inheritance of DNA lacking the synthetic pathways for eight to ten amino acids, the B vitamins, and some other essential cell components. These were the first animal cells. Thus the animal kingdom became distinguishable because such cells