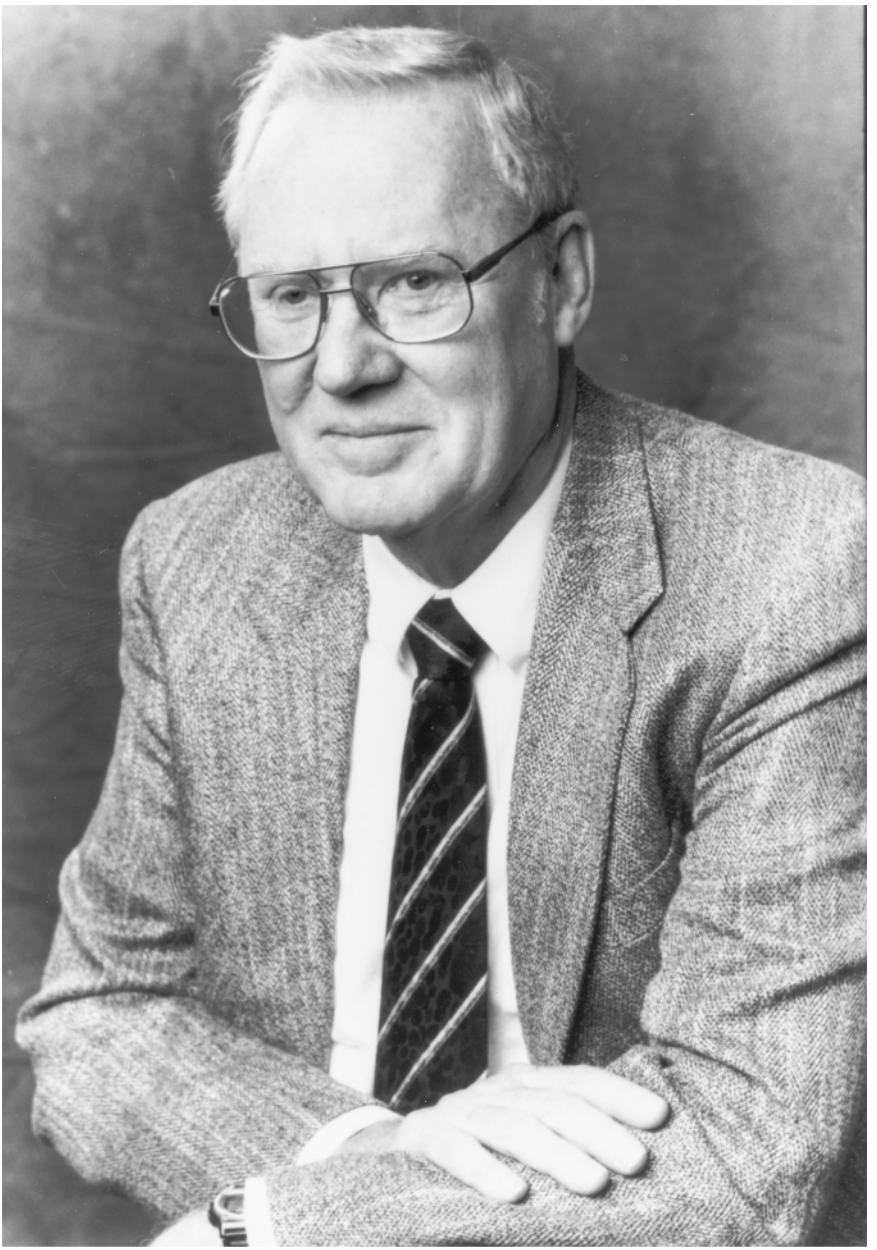

Donald B. McCormick

Annu. Rev. Nutr. 2004. 24:1–11
doi: 10.1146/annurev.nutr.24.120203.113511

First published online as a Review in Advance on January 16, 2004

ON BECOMING A NUTRITIONAL BIOCHEMIST

Donald B. McCormick
Department of Biochemistry, Emory University, Atlanta, Georgia 30322-3050; email: biocdbm@emory.edu

Key Words cofactors, water-soluble vitamins, coenzymes, metal ions, enzymes, metabolism

■ **Abstract** Much of the science underlying nutrition has come from biochemical studies. This certainly is true in our understanding of the metabolism and function of such micronutrient cofactors as vitamins and metal ions. My own interest stems from an early desire to understand the molecular events in an organism and ultimately to know the fate of those nutrients that are needed to maintain life. My training in chemistry, biochemistry, and nutrition was helpful in gaining knowledge about the interface among these disciplines. My interests followed an understandable trail, beginning with those factors that cause plant galls and continuing through carbohydrate metabolism to vitamins. After all, from studying such pentitols as ribitol with Professor Touster at Vanderbilt University through indoctrination with enzymes, vitamins, and coenzymes with Professor Snell at the University of California-Berkeley, it was rational to begin my independent academic life investigating the enzymes that convert a ribityl-containing vitamin, namely riboflavin, to its operational flavocoenzymes. While at Cornell University, I encountered Professor Wright, who shared an interest in biotin. My realization that there was a similar need to determine the metabolism of lipoate followed logically. Interactions with inorganic chemists such as Professor Sigel at Basel University, as well as inorganic chemists at Cornell, led to an interest in metal ions. As summarized in this article, my colleagues and I are pleased to have contributed to both basic knowledge about cofactors and to have utilized much of this information in extensions to applications. Along the way, I have served by teaching, researching, and administrating at the universities that provided my positions in academe, and I have worked to share the load of numerous public and professional duties that are summarized herein. Altogether it has been an enjoyable career to be a nutritional biochemist. I recommend it for those who follow.

CONTENTS

PROLOGUE

Those familiar with the Annual Reviews, which are published yearly to encapsulate significant progress in the sciences, medicine, and their extensions, know that most volumes have prefatory chapters that feature senior professionals in the area covered by that particular series. It is an honor for me to have been asked to write the prefatory chapter for this volume of *Annual Review of Nutrition*, a series I am proud to have served as an editorial committee member (1985–1990), then as an associate editor (1990–1995), and finally as the editor (1995–2004).

Previous prefatory chapters in the *Annual Review of Nutrition* have covered the scope of nutrition from science to policy, and almost all are cast in the autobiographical mode. Among those who have preceded me as authors are Bill Darby (1), who was the founding editor of this series and a former chairman of Biochemistry at Vanderbilt while I was a graduate student there; Esmond Snell (5), my postdoctoral mentor at the University of California-Berkeley and the person who helped to focus my attention on vitamins and coenzymes; and Bob Olson (4), who was the preceding editor of this series and who shared my belief that science is the foundation upon which nutrition should stand.

Thanks to some of my students and postdoctoral associates who honored me with a symposium on the "Mechanistic Aspects of Vitamin and Coenzyme Utilization and Function," I have had the opportunity to summarize many of my research contributions and acknowledge most of my coworkers in "Trail of Research on Cofactors: An Odyssey with Friends" (2). In the more recent "Micronutrient Cofactor Research with Extensions to Applications" (3), there was an opportunity additionally to indicate where much of our research has led in applied directions to utilitarian purposes. Hence, I can point to these publications, which contain numerous citations as documentation of my laboratory-derived work, and frame the present article along more historical and autobiographic lines. In attempting to do so, I shall describe my evolution from a student of natural science to one ultimately more satisfied by an understanding at the molecular level, particularly as concerns enzymes, many of which require a micronutrient cofactor, either a

coenzyme derived from a water-soluble vitamin or a metal ion, to enable their catalyses.

EDUCATIONAL AND EARLY RESEARCH EXPERIENCES

It was my good fortune to have parents who appreciated the value of a formal education (both had been teachers) and a "walking" knowledge of things about us. My father had taught biology and chemistry in high school and had become somewhat of an expert in explosives. He had been involved with the production of nitrate for gunpowder, TNT, and finally the atomic bomb. I had opportunity to acquire knowledge from walks in the fields and woods of Virginia and Tennessee with my father and to read further on the wide range of natural science that spanned from biology to geology and even astronomy.

Growing up in Oak Ridge, Tennessee, 1943–1949

Following my birth in Front Royal, Virginia, in 1932 and the start of my elementary education in that state and in Lookout Mountain, Tennessee, I moved with my family to Oak Ridge where the Manhattan Project was initiated with the purpose of producing enough material for the atomic bombs used to end World War II. Though the area was cloaked in secrecy during much of my time there, I managed to sneak through the fenced area that circumscribed both town and factories to augment my knowledge of nature in the surrounding wooded countryside. I raised frogs, snakes, opossums, raccoons, and other critters not fast enough to escape a curious kid.

The best aspect of this government-built city, however, was its school system. To attract and hold the numerous scientists involved in the A-bomb project, generally excellent teachers who were trained in subject matter (and not just the theory of how to teach) were available to those of us who were schooled there. I attended junior and senior high schools in Oak Ridge and was even allowed to take courses at the Oak Ridge Institute for Nuclear Studies, the purpose of which was to teach isotope procedures to professionals with doctorate degrees. Such educational experiences were a real incentive for me to be a serious student and continue in science. My parents had given a Chemcraft chemistry set to me when I was eight. With my meager allowance and the help of an older brother who worked in a drugstore, I added to the stock of chemicals and glassware. Collections of rocks, bird nests, pickled reptiles, and insects augmented my home laboratory, where many a happy hour was spent. For extensions of my observations into the outside world, I had built a three-inch reflector telescope for starry nights and used a monocular microscope to examine the wonders in pond scum and the like.

In 1947 I received first prize from the Tennessee Junior Academy of Science for my project on plant galls. This was expanded along more biochemical lines by my extraction of terpenoids and glycosides from the ball gall on Canadian goldenrod

(*Solidago canadensis*) caused by a fly (*Eurosta solidaginous* Fitch); the uptake of ^{32}P-labeled phosphate into the developing excrescence was also recorded by autoradiography. This expanded project plus high scores on a national test, good grades, teachers' recommendations, and eventually interviews by psychologists led to my being named a winner of the Westinghouse Science Talent Search in 1950. Other science honors in my high school years included the Bausch & Lomb Award and becoming an honorary member of the American Association for the Advancement of Science.

Studies at Vanderbilt University, 1950–1958

Thanks to the money from the Westinghouse award, I could afford to further my education at Vanderbilt, where I majored in chemistry and minored in math for the baccalaureate degree in 1953. With the intent of undertaking my Ph.D. studies in the chemistry of life, I joined the Department of Biochemistry, which was in the School of Medicine at Vanderbilt. My dissertation on pentoses and pentitols (the xylulose/xylitol pathway) was guided by Professor Oscar Touster, himself an essential pentosuric; the doctorate was awarded in 1958. As chairman of the department, Professor Darby helped me secure a National Institutes of Health (NIH) postdoctoral fellowship in Professor Snell's laboratory at the University of California-Berkeley, but before reporting for duty, I had the summer to learn some nutritional biochemistry in Spain.

Interdepartmental Committee for Nutrition for National Defense Survey in Spain, Summer 1958

An extension of the Marshall Plan to help Europe recover after WW II was the Interdepartmental Committee for Nutrition for National Defense (ICNND), which was directed by Dr. Arnold Schaefer. Bill Darby was very much involved in the nutrition surveys organized by the ICNND with overseership from our Departments of State and of Health and with cooperation from governments of countries hosting the surveys. In the case of Spain during the summer of 1958, a survey was taken of the Armed Services, which were then under the control of Francisco Franco. We established our laboratory in the Faculty of Pharmacy of the University of Madrid, where we ran assays for vitamins and their metabolites in blood and urine collected in the military bases around the country. These collection junkets permitted some respite from lab chores, as did periodic visits to the Prado Art Museum near our hotel in Madrid. Among things learned in the lab was a fluorometric procedure for red cell riboflavin that Bill Pearson, the leader of our lab group, helped develop. I was also responsible for determining levels of vitamins A and C, β-carotene, thiamin, and niacin (as its N^1-methylnicotinamide). Such activities planted my interest in vitamins, which was to be enlarged upon during my forthcoming postdoctoral stint in California.

Postdoctoral Research at the University of California-Berkeley, 1959–1960

The focus of my attention became the purification and characterization of enzymes that catalyzed the adenosine triphosphate (ATP)-dependent phosphorylation of the three vitaminic forms of B_6, namely pyridoxine, pyridoxamine, and pyridoxal. Upon examining the nature of the phosphokinases that were obtained from diverse sources and could act varyingly on all three vitaminic forms, it became evident that for most, Zn^{2+} rather than Mg^{2+} is the preferred divalent cation that forms a cosubstrate chelate with ATP, and K^+ is an activating monovalent cation. An interesting and medically relevant finding was that carbonyl reagents react with pyridoxal to form Schiff bases that are potent inhibitors of the kinases. The ability of carbonyl reagents to impair the action of Vitamin B6 necessitates care in the use of some as chelators for metals that accumulate in toxic amounts, e.g., copper in Wilson's disease.

ACADEMIC POSITIONS AND SABBATICS

Given the rather varied nature of my activities, ranging from chemistry through biochemistry to nutrition, it seems simplest to synopsize in this section the tale of where I have been in the academic world and then to collate my research contributions and service in following sections.

Cornell University, 1960–1979

In July of 1960, I moved with my family to Ithaca, New York, to join the faculty in the Graduate School of Nutrition of Cornell University, where Dick Barnes was dean. At that time the Department of Biochemistry, with Harold Williams as chairman, was housed in Savage Hall with those of us who eventually became the core faculty of the Division of Nutritional Sciences. My years at Cornell were busy and productive. I derived real pleasure in teaching biochemistry and nutrition courses and in providing my course "Vitamins and Coenzymes" that was attended by graduate students from various disciplines. Several honors came my way as a result of research activities. I was elected a Fellow of the American Association for the Advancement of Science in 1966, and received both the Mead Johnson (1970) and Osborne & Mendel (1978) awards from the American Institute of Nutrition (now the American Society for Nutritional Sciences). By 1978 I was named the Liberty Hyde Bailey Professor of Nutritional Biochemistry; my faculty membership was in both the Division of Nutritional Sciences, with Mal Nesheim as director, and in the Section of Biochemistry and Molecular Biology of the Division of Biological Sciences.

During my appointment to Cornell, there were three occasions to spend some time at other institutions. The first of these stemmed from a three-way friendship

among Esmond Snell (my postdoc mentor), Lemuel Wright (an avuncular colleague at Cornell), and I.C. Gunsalus, better known as Gunny (a former Cornellian then at the University of Illinois). Gunny came to give a seminar visit at Cornell, where I first met him. As Gunny was an expert on the bacterial genus *Pseudomonas*, he and I discussed some of the work on biotin catabolism that my students were doing using a pseudomonad that Lem Wright and his student had obtained through culture enrichment from local soil. I also mentioned that my interest in flavins and flavoproteins was now at a point where I intended to investigate the quenching of fluorescence due to the intramolecular interaction between the isoalloxazine and adenosyl moieties of the coenzyme flavin-adenine dinucleotide (FAD). Gunny immediately pointed out that an expert on flavin fluorescence, Gregorio Weber, was in the Department of Biochemistry at Illinois, and by the way, the department offered a graduate biochemistry course during the summer and usually brought in an outsider to teach it. Gunny could be rather persuasive.

University of Illinois-Urbana, Summer 1963

The summer in an unair-conditioned dormitory in Urbana was nothing to take lightly for one used to the cooler climes of the Finger Lakes of New York; however, I managed to prepare my lectures in the evenings, give them in the mornings, and spend the afternoons synthesizing FAD analogues in which I replaced the adenine with other purines and pyrimidines. Though Weber was around, he was getting over the reattachment of a retina, so we never used his fluorometry equipment. I finished the project when I returned to Cornell; however, I did enjoy the colleagueship of some of the students and such summer-hardy faculty as were in Urbana during my stay there.

Universities of Basel, Switzerland and Wageningen, Netherlands, 1966–1967

My first official sabbatic leave from Cornell was as a Guggenheim Fellow, first in the Department of Chemistry at Basel University in Switzerland, then in the Department of Biochemistry at Wageningen University in the Netherlands. The first part was in association with Peter Hemmerich in the Institute for Inorganic Chemistry, where I helped guide the PhD work of a student synthesizing the 5′-phosphates of riboflavin analogues that I would later test in enzyme systems dependent on riboflavin 5′-phosphate (flavin mononucleotide). I also synthesized a heavy atom (Br)-labeled flavin for X-ray crystallographic determination of structure.

The second part of the sabbatic, in Wageningen, was in association with Cees Veeger, another flavinologist. There we managed to test the properties of some of our flavins and study their photoreductive properties. One of my Basel colleagues, Helmut Sigel, joined me in a project to study the electron paramagnetic resonance characteristics of some copper chelates of potential interest to biochemists.

University of Arizona, Winter and Spring 1975

A second half-year sabbatic was spent in the Chemistry Department of the University of Arizona in Tucson, where I provided some senior leadership in Gordon Tollin's laboratory while he took his sabbatic at the research laboratories of DuPont. I used Tollin's flash photolysis equipment to study some aspects of flavin photochemistry, especially as it involves the ability of flavins to photooxidize amino acid residues. This work was usefully extrapolated when I returned to Cornell by using flavocoenzymes to identify the neighboring oxidizable amino acid residues at the catalytic site of flavoproteins to which the coenzymes are bound. I might also add that my family and I enjoyed the different flora and fauna of the Sonoran Desert during our weekend excursions around Tucson.

Emory University, 1979–Present

In spite of my good friendships and the support of colleagues at Cornell, the itch to be an "academic missionary" and help another place with potential to become first-rate in such areas as biochemistry and nutrition pulled me to Emory University in Atlanta in August of 1979. I served for 15 years as the F.E. Callaway Professor and Chairman of the Department of Biochemistry, and for four of those years as the Executive Associate Dean for Science in the School of Medicine. The excellent faculty we brought to Emory did much to raise recognition of the university to one of the two-dozen best research universities in our country. While doing numerous duties of an administrative nature for the university, I shared in the teaching of graduate students in biochemistry and nutrition programs and gave lectures to the professional school students. Thanks to an occasional technician and a few dedicated postdoctoral associates, I continued my research in the area of vitamins and coenzymes. Again I was fortunate to receive such honors as the Wellcome Visiting Professor in Basic Medical Sciences (University of Florida, 1986; Medical College of Pennsylvania, 1989), Lucille S. Hurley Lecturer at the University of California-Davis (1992), Boyd O'Dell Lecturer at the University of Missouri (1993), the Award for Excellence from the Georgia Nutrition Council (1989), the Bristol-Myers Squibb/Mead Johnson Award for Distinguished Achievement in Nutrition Research (1999), and election to the Fellows of the American Society for Nutritional Sciences (2000). The list of these honors is more to acknowledge the generosity of those who have thought well of me rather than to brag. After all, Ambrose Bierce wrote that "Prizes and awards are the merit badges of mediocrity."

RESEARCH FINDINGS

A compilation of what may be considered highlights of the knowledge generated by my research efforts, largely supported by the National Institutes of Health, is given in Table 1. Again I refer readers to my summaries of this work (2, 3) if they

TABLE 1 Research contributions to nutritional sciences

Basic findings
Metabolic pathways and metabolites: pentose/pentitol (xylulose/xylitol) interconversions, conversions of B_6 vitamin forms to pyridoxal 5′-phosphate, interconversions of riboflavin with flavin mononucleotide and FAD, metabolism of biotin and its precursor dethiobiotin, catabolism of lipoate
Enzyme isolations and characterizations: D-ribulokinase, pyridoxal phosphokinases, pyridoxine (pyridoxamine) 5′-phosphate oxidase, flavokinase, FAD synthetase, riboflavin 5′-hydroxymethyl oxidase
Metal ion requirements and functions: K^+ activation of pyridoxal kinases, Zn^{2+} required in dihydroorotase and chelated with ATP as a cosubstrate for pyridoxal phosphokinases and flavokinase, Mg^{2+} as the preferred ATP chelate for FAD synthetase, liganding of divalent cations with biochemicals
Derived applications
Biochemically specific (“affinity”) absorbents developed for: B_6-binding proteins, pyridoxal phosphokinases, pyridoxine (pyridoxamine) 5′-phosphate oxidase, riboflavin-binding proteins, flavokinase, FAD synthetase, riboflavin 5′-hydroxymethyloxidase, avidin, and polyA
Drug delivery based on transporter-enhanced delivery of bioactive compounds with metabolic release inside cells: example with N-(4′-phosphopyridoxal)amines
Biopolymer modifications where bases for determining the number of residues modified was determined: examples with chemical modifications of specific amino acid residues within pyridoxine (pyridoxamine) 5′-phosphate oxidase
Pathogen photoinactivation: example using riboflavin to photooxidize the nucleic acid (especially guanine bases) of pathogenic microorganisms within blood components that lack cellular nucleic acid, e.g., erythrocytes, platelets, and plasma
Dietary recommendations based on quantitation of vitamins and metabolites in milk and urine: examples include riboflavin and biotin

Abbreviations: ATP, adenosine triphosphate; FAD, flavin-adenine dinucleotide.

are interested in the original, documenting literature, and especially to note the names of coworkers who helped along the way.

PUBLIC AND PROFESSIONAL SERVICE

It has been my privilege to serve science, especially nutrition, in numerous capacities at national and international levels. Most of such activities are summarized in Table 2. Over the span of my academic career, particularly since joining the faculty at Emory, I have done such duty as requested by my peers whenever possible. Typically academic chairmen ask young faculty to teach, participate in professional activities to demonstrate citizenship, and garner grant support to allow publication of sufficient scholarship (research) to warrant promotion. Yet many such chairmen

TABLE 2 Service activities in support of nutrition

Organization	Duty	Year
National Institutes of Health		
Nutrition Study Section	Member and chairman	1977–1981
Aging Small Grants Program	Member	1983–1984
Chemical (Metabolic) Pathology Study Section	Member	1985–1987
National Cancer Institute Division of Cancer Prevention and Control (Board of Scientific Counselors)	Member	1988–1992
United States Department of Agriculture Science Grants Program for Human Nutrition	Member	1982
National Aeronautics and Space Administration Space and Life Sciences Nutrition Advisory Committee	Member	1990–1999
Civilian Research and Defense Foundation (grants program for former USSR/USA)	Member and chairman	1996–present
Pew Foundation National Nutrition Program	Scientific evaluator	1988–1991
Heinz Endowment Fund (Nutrition Awards Committee)	Member	1991
American Society for Nutritional Sciences (formerly the American Institute of Nutrition)	Member and president	1963–present
Life Science Research Office Scientific Advisory Committee	Member and chairman	1980–1985
Journal of Nutrition	Biographical editor	2000–present
Committees, e.g., Nomenclature, Abstract Review, Awards		
Federation of American Societies for Experimental Biology	Member of four societies	1963–present
FASEB Board	Member	1992–1995
Food and Nutrition Board of the Institute of Medicine/National Academy of Sciences	Member and vice chairman	1987–1991
Diet and Health Committee	Vice chairman	1989
Panel on Folate and Other B Vitamins	Member	1996–1997
Food and Agriculture Organization/World Health Organization (Expert Consultant Committee for Micronutrients)	Chairman	1998–1999

(*Continued*)

TABLE 2 (*Continued*)

Organization	Duty	Year
Pan American Health Organization (Technical Consult on Fortification)	Member	2001
Publishers		
Academic Press		
Vitamins and Coenzymes	Editor (with others)	1970–1997
Vitamins and Hormones	Editor (with others)	1983–1993
Nutrition Foundation/International Life Sciences Institute		
Nutrition Reviews	Contributing editor	1970–1988
Marcel Dekker		
Handbook of Vitamins	Author and editor	2001
Other journals		
Anal. Biochem., *Arch. Biochem. Biophys.*, *Cancer Prev.*, *Enzyme Commun.*, *J. Natl. Cancer Inst.*, *J. Nutr. Growth and Cancer*, *Monatshefte fur Chemie*, *Proc. Soc. Exp. Biol. Med.*, etc.	Editorial committee member	

feel that they do not need to carry all of the same activities in addition to their "directing" roles. In my role as an administrator, I have attempted to practice a dictum that I preached; namely, don't tell others to do something unless you are participating yourself.

EPILOGUE

When I officially retired from Emory in 1999, I had already helped "stir the pot" for the university to begin an Emeritus College to help maintain the scholarship of those who are still active and able. The university gains from the *pro bono* activities of such faculty who represent a pool of expertise that augments at little or no cost the activities of the salaried faculty. As a member of the Advisory Council of our Emeritus College, and with only a few duties left to complete in the outside world, I find myself again drawn to the byways of nature where I hope to encourage conservation of our diminished wildlife and perhaps inspire another youngster who will lead from the fundaments of natural science to the exciting arena of tomorrow's discovery.

As a final statement, I would again like to acknowledge the professors who were part of my training and sabbatic enrichments, to express appreciation and

continued encouragement to the many students, postdocs, and sabbatic professors who came to my laboratories at Cornell and Emory, and to say thanks to the colleagues who have been kind in their benefactions in my behalf.

The *Annual Review of Nutrition* is online at http://nutr.annualreviews.org

LITERATURE CITED

1. Darby WJ. 1985. Some personal reflections on a half century of nutrition science: 1930s–1990s. *Annu. Rev. Nutr.* 5:1–24
2. McCormick DB. 2000. A trail of research on cofactors: an odyssey with friends. *J. Nutr.* 130:323–30S
3. McCormick DB. 2002. Micronutrient cofactor research with extensions to applications. *Nutr. Res. Rev.* 15:245–62
4. Olson RE. 1996. On the making of a clinical nutritionist. *Annu. Rev. Nutr.* 16:1–32
5. Snell EE. 1989. Nutrition research with lactic bacteria: a retrospective view. *Annu. Rev. Nutr.* 9:1–19

Annual Review of Nutrition
Volume 24, 2004

CONTENTS