



ANNUAL REVIEW OF NUTRITION

VOLUME 2, 1982

CONTRIBUTING AUTHORS

David H. Alpers
Thomas A. Anderson
B. Andersson
J. P. Baker
William B. Bean
Plinio Bernardini
J. P. Blass
Joseph G. Brand
Robert H. Cagan
Darla Erhard Danford
P. B. Dewis
Gabriel Fernandes
Josef E. Fischer
Robert A. Good
P. D. Greig
Peter Hahn
Mary Ann Hansen

K. N. Jeejeebhoy
H. R. Kissileff
Arthur L. Klatsky
David H. Lawson
L. G. Leksell
Kauko K. Mäkinen
Esteban Mezey
Michael Naim
Daniel W. Nixon
Ann Richmond
Daniel Rudman
M. Rundgren
Arje Scheinin
Bellur Seetharam
T. B. Van Itallie
C. Wagner
R. C. Young

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WILLIAM J. DARBY, *Editor*

Nutrition Foundation

HARRY P. BROQUIST, *Associate Editor*

Vanderbilt University

ROBERT E. OLSON, *Associate Editor*

St. Louis University



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PREFACE

In planning the second volume of the *Annual Review of Nutrition* the Editorial Committee has adhered to the intention that guided selection of topics for the initial volume—to display the wide scope of the subject through “critical, authoritative surveys of the original literature describing the current developments in the science of nutrition.” As the complexity and breadth of nutrition cannot be explored fully in a single volume, we plan to concentrate on the major aspects of the field in turn, cycling at multi-year intervals to reassess topics reviewed in the past. Matters of immediate interest, or in which rapid advance is currently taking place, will be reviewed promptly.

Since the production process at Annual Reviews does not enable us to co-position related chapters within each volume, our dual Table of Contents displays both the usual sequence of chapters by page number, and related chapters grouped by category of interest. For the convenience of the reader, the categorical Table of Contents for the current volume also lists the chapters of Volume 1.

The continued excitement of discovery in the science of nutrition is evident to the reader of these reviews. Equally clear is the satisfying evidence of the vast improvement in health care, preventive medicine, and therapy that is occurring through assimilation into practice of the basic scientific understanding generated by research—experimental, observational, chemical, and genetic, whether in vivo, in vitro, clinical, or epidemiologic.

The opening chapter of this second volume is timely because its publication coincides with that of several recent accounts of the long evolution of the understanding of pellagra. Dr. William Bean's essay brings the reader a series of fascinating personal reflections concerning the elucidation of this clinical syndrome. It is written by a scholar who was associated with two prolific centers of study (Birmingham and Cincinnati) from which came notes, papers, and observations that contributed to definition of the role(s) of B-vitamins in clinical nutrition. Dr. Bean's recollections of and reflections on human experimentation provide much ethical wisdom for today's investigator of newly recognized syndromes of nutritional origin. Readers who enjoy perusing this essay will also want to reread Dr. Bean's 1952

Presidential Address to the American Society of Clinical Nutrition (The Clinician Interrogates Nutrition. *Am. J. Clin. Nutr.* 13:263-74), including its text of the Pellagra Song.

The Editors are grateful both to the authors who have so generously contributed to this second volume and to the staff of Annual Reviews Inc. for their painstaking efforts throughout the planning and production of Volume 2.

William J. Darby
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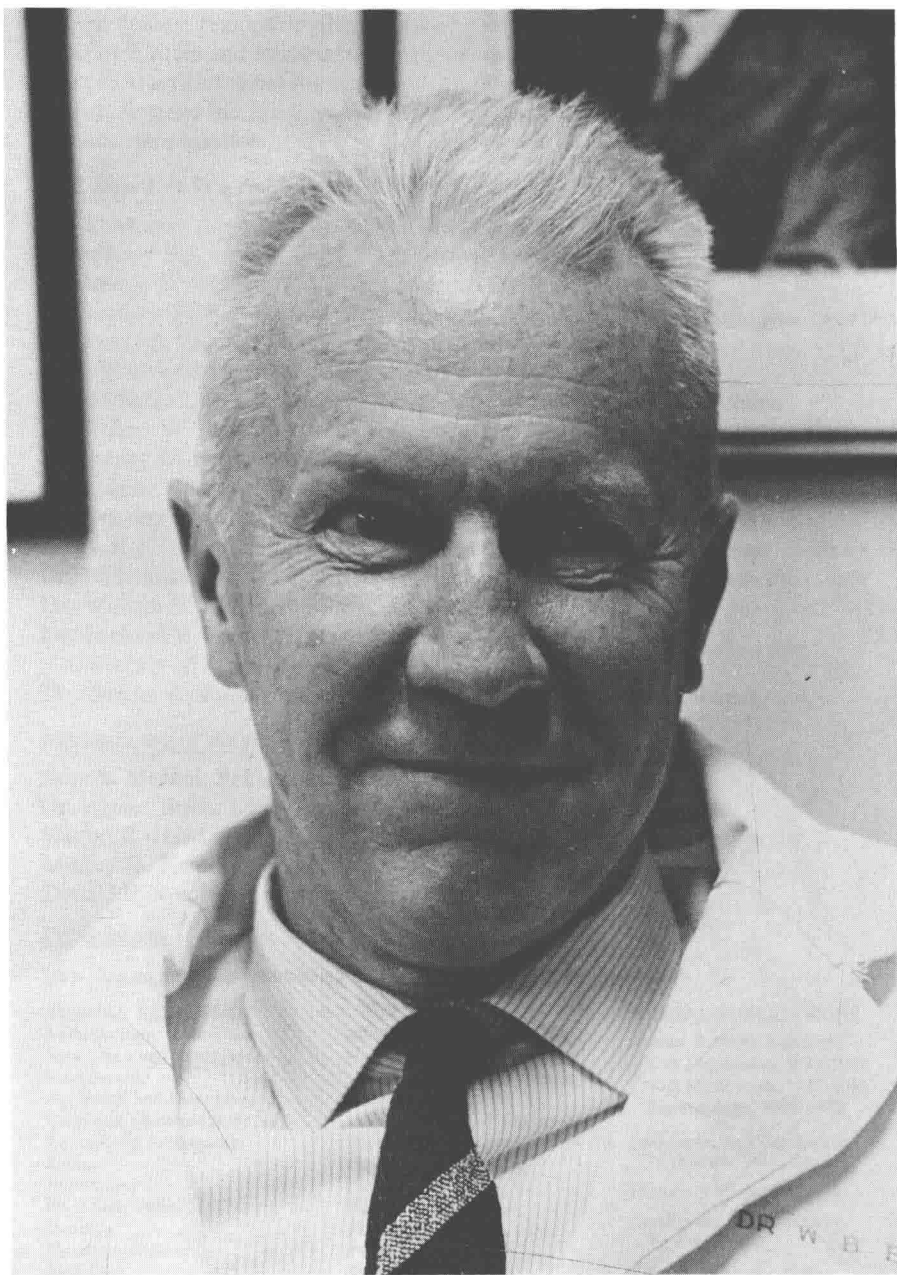
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PERSONAL REFLECTIONS ON CLINICAL INVESTIGATIONS

*William B. Bean*¹

Department of Internal Medicine, University of Iowa, Iowa City, IA 52240

Introduction

I was fortunate to participate in one of the explosive phases of clinical nutrition more than 40 years ago, just before World War II began. At that time water-soluble vitamin B was becoming the vitamin-B complex, budding off many separate new vitamins. These were being discovered by students of animal nutrition and biochemistry, and by those interested in the nutritional growth requirements of such lowly organisms as bacteria, yeasts, and fungi.

As an undergraduate medical student at the University of Virginia, I saw pellagra. We were told about malnutrition and Goldberger's work. I saw one pellagra patient on the Osler Service at Johns Hopkins in 1935–1936. The next year, when I went to the Thorndike Laboratory, Soma Weiss and Robert Wilkins were in the midst of their exciting studies demonstrating that vitamin B₁, thiamin, quieted the alarming and precarious hyperdynamic state of the circulation in beri-beri, then so prevalent among the alcoholic gentry who crowded into the Boston City Hospital.

In 1937 I went to work in Marion Blankenhorn's Department of Medicine in Cincinnati. It was an exciting place to be. Gene Stead, Gene Ferris, Johnson McGuire, Leon Schiff, Lee Foshay, and others there were stimulating young investigators and teachers. Tom Spies had done excellent clinical studies on pellagra at the Lakeside Hospital in Cleveland and the Cincinnati General Hospital. Near the end of my year as a senior medical resident an

¹William B. Bean, medical scholar—physician, clinical investigator, editor, teacher, writer, and medical philosopher—was intimately involved in clinical nutrition research during the exciting era of discoveries of the 1930s–1950s. His reflections on clinical research in and knowledge of nutrition during that period of more direct, relatively uncomplicated, less restrictive investigations provide much wisdom for consideration by investigative-minded physicians today.

opportunity arose to work as a Fellow in nutrition. I had no special competence in the field of human nutrition but had helped Soma Weiss and Bob Wilkins in some of their clinical experiments. A good friend of Blankenhorn, Dr. James McLester of Birmingham, Alabama, still skeptical of the ideas introduced by Goldberger, welcomed Tom Spies to Birmingham to see if he could get the same good results in treating desperately ill pellagrins there that he had obtained in Ohio. The mobility of the staff, which shifted to Birmingham for the spring and summer months and then returned to Cincinnati for the fall and winter months, was remarkable. Richard and Sue Vilter and I had the main clinical and laboratory responsibilities. In the considerable outpouring of papers from the nutrition clinic, Spies's name led all the rest. Charles Aring, Cincinnati neurologist, essayist, and scholar, made prominent contributions to the thiamin and beri-beri studies. Many physicians, biochemists, nurses, dentists, and others from various medical schools in the country were eager participants. In addition to A. B. Chinn and Blankenhorn, the following co-workers are listed alphabetically: W. F. Ashe, A. E. Axelrod, W. Beckh, C. E. Bills, Hugh Butt, C. Cogswell, Clark Cooper, Zola K. Cooper, G. Delfs, R. Eakin, Conrad Elvehjem, Joe P. Evans, E. Gross, Morton Hamburger, Harold E. Himwich, M. P. Hudson, T. H. Jukes, Walter F. Lever, J. B. McLester, A. W. Mann, V. Minnick, Carl V. Moore, Robert A. Moore, Gordon R. Morey, Milton Rosenbaum, J. M. Ruegsegger, E. E. Snell, S. R. Stanbury, R. E. Stone, E. P. Swain, Emory D. Warner, R. J. Williams. After I had left Carl Vilter and Wally Frommeyer were important contributors.

A Note on the History of Pellagra

Three recently published books (25a, 27a, 40a) afford detailed accounts of the history of pellagra. These and the earlier compilation of selected reprints of Joseph Goldberger and an evaluation of his classical studies of the disease, *Goldberger on Pellagra* by Milton Terris (62a), make it redundant to detail here an account of the evolution of understanding of this fascinating deficiency syndrome. Rather, I recall here but a few especially poignant personal recollections pertinent to my own early involvement with clinical evidence concerning pellagra.

For more than two hundred years the nature of pellagra had been a subject of great debate and confusion (32). Many drugs had been tested on severely ill pellagrins brought into a hospital, put to bed, and given fluids and good nursing care. For a brief time many experienced clinical improvement. Spies had shown that this might occur even while they were eating a pellagra-producing diet or given nothing but salt solution and dextrose. Such a program, however, could not be continued long or the patients would suddenly get sicker and might die if the elements missing from the diet were not restored in ample quantities.

Perhaps the first controlled study in human nutrition after Lind's observation on scurvy was Cerri's study of pellagra carried out in Milan, Italy in 1795 and 1796 (32). Cerri was convinced that a diet made up largely of corn and corn products somehow explained the very high incidence of pellagra among the country folk. He selected ten of them, who for two years moved to town and ate the diet common to those in the city. On this regimen no signs of pellagra developed, while in the peasant controls in the country the incidence remained high. The following year the subjects were allowed to revert to their polenta (corn meal) diet, and pellagra returned as usual. One, however, was so much impressed that he got work in the city and never had pellagra again. These observations have been largely neglected by those who have written on pellagra.

A good example of the pre-Goldberger confusion is found in a 1912 book entitled *Report of the Pellagra Commission of the State of Illinois* (40). It describes the distressing outbreak of pellagra in Illinois mental hospitals from 1909–1911. Of the 258 patients with pellagra in Peoria, 128 died. In Kankakee, with fewer patients, 40% died, and about a third died at the Elgin State Hospital [subsequently the site of a long series of remarkable studies by Horwitt et al, in which deficiencies of niacin, thiamine, riboflavin, or tocopherol were induced by feeding diets deficient in the nutrients. These studies were made in collaboration between the Food and Nutrition Board of the National Research Council and the Elgin State Hospital over a 23-year period (33a)]. At that time all the Commission could think of were infections. Study of fecal bacteria occupied 105 pages of the special report, which then proceeded to complement fixation tests, cutaneous tests with corn extracts in pellagrins, and a learned discourse on black flies and buffalo gnats, including beautiful drawings of the various larval phases of the *Simulium* in Illinois. An essay on the protozoan infections was followed by dietary studies from the hospital concerned only with the food as issued, not the food as eaten. A corn-free diet was compared with a mainly-corn diet without definite conclusions. The experiment is a good example of how not to do a study comparing one food with another. In the summary the authors wrote that “the lack of definite information regarding the food requirements and metabolism in the class of subjects experimented upon has made it difficult to interpret the results obtained in these studies.” A rather wistful comment added that “the experimental work here reported is in itself brief and is not extensive enough to allow any broad interpretation.”

Joseph Goldberger Solves the Problem

The spectacular prevalence of pellagra in the Southern states seemed related to poverty. Of course, infection was known to follow poverty fairly closely. In 1914, Joseph Goldberger of the US Public Health Service, the old Marine Hospital Service, was sent to Georgia to see if the peculiar epidemiology of