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The Paths to the Discovery of Vitamins A and D

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Editor's Note: *In this 1967paper, McCollum reminisces about his establishment in 1907 of the first albino rat colony in America, at the University of Wisconsin. Using these small experimental animals and purified diets, McCollum and Davis discovered that butter and egg yolk, but not lard, contained a lipid-soluble factor required for growth of rats (*J Biol Chem *11: 167-175, 1913) which was later christened vitamin* A. *As his discoveries multiplied, McCollum confided to a friend that his decision to use the rat in nutritional studies was the keystone of his career.*

In 1907, on completing my studies at Yale I was, by the standards of the period prepared to undertake investigations in organic and biological chemistry. 1 wanted an academic position. The only opportunity I found was an instructorship in Agricultural Chemistry in the College of Agriculture at the University of Wisconsin. I was to work principally in the Experiment Station under the direction of Professor E. B. Hart. The project was to find the cause or causes of the malnutrition manifested by cows which had been restricted through most of their period of growth to rations derived solely from single plant sources, viz, the wheat, oat, and corn (maize) plant. Malnutrition was severe in the wheat-fed cows. They were inferior in appearance, had become blind, and delivered very premature, undersized dead calves. The oat-fed cows looked better, their eyes appeared normal, and though they carried their calves to term, none survived longer than a few hours. In marked contrast the corn-fed cows were in fine

condition and produced vigorous calves. Chemical analysis had shown that the rations were of equivalent nutritive value. Obviously the chemical method of analysis was unreliable as a guide to nutritive values.

At Dorpat, Lunin restricted mice to a diet of isolated, purified protein (casein), carbohydrates, fats and an inorganic salt mixture made in imitation of the ash of milk. The mice failed rapidly and all were dead within 21 days. Mice, to which he gave only milk, were in good condition and were lively at 60 days. He concluded that milk contained unidentified nutrients not hitherto suspected. In other volumes I found descriptions of similar experiments with "purified" foodstuffs described by 13 other investigators. All reported that their animals, mostly mice, failed rapidly and died when confined to such diets. I took notes on these studies, and concluded that the most important problem in nutrition was to discover what was lacking in diets containing only "purified" constituents.

Another result of this study of the experiments of earlier biochemists was the discovery that no one had attempted to investigate the degree of completeness of individual natural food substances such as leaf, seed, tuber, root or fruit, as sole source of essential nutrients for an animal. Such an inquiry would be the simplest possible type of nutrition investigation. If in any case the animals failed nutritionally it should be possible to systematically study the problem of what was lacking by supplementing the food with single or multiple known substances . . . If this approach was not successful the addition of very small amounts of one or another natural food, should reveal where the missing unidentified nutrient was to be found. From this reasoning the thought occurred that animal feeding studies with two-source diets, one constituent small, the other large, should reveal which foods made good the deficiencies of each other. Similar studies, I concluded, should be made using single type animal derivatives—muscle, liver, kidney, etc. Nothing of this type of study had ever been attempted. Reflecting on these ideas, I saw a vista of great promise for revealing new knowledge of the biochemistry of nutrition.

It also occurred to me that experiments should be made with small animals. They grew to maturity in a short time, reproduced, reared young, and had a short life-span. They ate little, so one could afford to the necessary chemical work on the diets. The life history of the animals could be observed.

While engaged in these speculations I became convinced that the project we were engaged in with cows, fed highly complex chemical rations could not lead to the discovery of anything of importance and that I was wasting my time.

Two days later I told about my speculations to Emeritus Professor Steven M. Babcock. He responded enthusiastically, saying that mine was the best suggestion he had ever heard of for study of foods.

Dr. Babcock was the most honored man in the College of Agriculture, and because he insisted that he wanted to know what could be learned by my plan, I

was meekly permitted to set up my rat colony. No formal project was made of my enterprise, and no funds were allocated for its support.

I made cages out of boxes in which supplies came to the laboratory. I needed quarter-inch wire netting for one side, and placed on Professor Hart's desk a requisition for two dollars' worth. He declined to sign it and I bought it out of my $1,200 annual salary. I caught wild rats and tried to use them, but they were so frightened and ferocious that I discarded them and bought, at my own cost, a dozen albino rats from which I built up my colony.

The ingredients of my diets were prepared incidentally while doing analytical work on the cows, but I cared for my rats outside of regular work hours. Starting with enthusiasm I soon realized that although most of my projected experiments would be terminated in a short time because of failure of the little rats to survive on my "purified" diets, much time would be required to complete the several hundred tests on formulas I had devised. It would take several years to accumulate sufficient data to enable me to make any important conclusions. I doubted I should be permitted to continue so long without justifying myself by results.

In July 1909,1 had the good fortune to have Miss Marguerite Davis ask me to take her as a student in biochemistry. She had just graduated at the University of California at Berkeley, and had come to Madison to live with her father. I gave her a place in the laboratory and assigned some exercises; and from time to time stopped to talk with her. Before long I told her what I was trying to do with my rat colony. She was enthusiastic about the project and volunteered to take care of the rats, I at once began to teach her rat housekeeping, and began the construction of more cages. Before long we were carrying on ten or more times as many experiments as I alone could manage. It was due to her interest and loyalty to the enterprise that we made important discoveries.

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