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This Week's Citation Classic

Williams R J, Lyman C M, Goodyear G H, Truesdail J H & Holaday D.
"Pantothenic acid," a growth determinant of universal biological occurrence.
J. Amer. Chem. Soc. 55:2912-27, 1933.
[Chemical Laboratories, University of Oregon, Eugene, and Oregon State College, Corvallis, OR]

Using the "Gebrüder Mayer" strain of *Saccharomyces cerevisiae* as the experimental subject, this report indicated that a single acid substance stimulates yeast's growth in a remarkable way and that this acid substance is a widespread if not universal constituent of living matter. This substance was tentatively designated as pantothenic acid, the name coming from Greek and meaning "from everywhere." [The *SCI*® indicates that this paper has been cited in over 25 publications, 1945-1990.]

The Discovery of a Universal Growth Factor

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Although the classic paper was published in 1933, its beginnings came about 14 years earlier. In 1918 I was a graduate student in chemistry at the University of Chicago and was awarded a fellowship given by the Fleischmann Company to study yeast nutrition. The outcome of that work was my PhD dissertation, which was published in 1919 in the *Journal of Biological Chemistry* under the heading of "The vitamine requirements of yeasts. A simple biological test for vitamine."[1] In the conclusions segment of that paper, I stated: "A substance of unknown nature, which is a constituent of yeast, is necessary in addition to the ordinary nutrients for the nutrition of yeast cells."

That statement, and a strong intuitive "hunch" that the unknown substance would also have something to do with the growth of human babies and other mammals, started me on a 22-year-long detective trail. That trail culminated in the synthesis of pantothenic acid in 1940 and in its acceptance as an essential "vitamin" needed by numerous species. Subsequent branches of that trail continue to uncover interesting metabolic functions of this "substance of unknown nature."[2,3]

Just in passing, I would like to point out that during those years in which my research work was being done, I had so many commitments that the *real* problem, I suppose, was that there were only 24 hours in any given day and that, being thoroughly human, I had to have some sleep every once in awhile. However, in regard to problems that had to do with the pantothenic acid research, there are a few that stand out in my mind.

One was to find a strain of yeast from which we could obtain consistent results from our experiments. The common baker's and brewer's yeasts available were *all* called *Saccharomyces cerevisiae*, but in actuality they were genetically different from each other. Fortunately, after some hunting around, I was able to

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procure two useful pure cultures of yeast—one was the "Gebrüder Mayer." We decided to concentrate on using the Gebrüder Mayer strain because we found that it seemed to respond to a single nutrient better than other pure strains.

Of course, as we went along there were always basic questions in our minds regarding the overall problem, such as, what *kind* of a substance are we dealing with? How best can we demonstrate its universality? Will we be able to synthesize it? Is it an essential nutrient for human beings?

Each of these questions—and many more—posed unique problems, many of which required us to develop new tests, to design new equipment and new techniques, and to carry out hundreds of trials.

As an example of the intricacy of the scientific riddle that we had set out to solve, we found that our unknown substance was an acid at least 10 years before the substance was obtained even at a level of 1 percent purity.

Our use of yeast to explore vitamin research problems was not greeted with unanimous approval by other scientists. Early in our work we were criticized for not using strict bacteriological techniques. I also remember a very friendly but fatherly letter from an editor of the *Journal of Biological Chemistry*, who advised me to forget about my yeast work and attack the subject of vitamins in a more realistic, practical way, using laboratory animals. If I had followed his well-meant advice, many of the vitamins we have known for 30 years or more might still be undiscovered, and the vast information that we have learned from the use of microorganisms in vitamin research—particularly how the B vitamins function—would be largely unknown. It is a source of personal satisfaction that, in addition to other test species,[4] research on pantothenic acid using microorganisms continues.

[Editor's note: Professor Roger J. Williams died on February 20, 1988, before we were able to publish his *Citation Classic* commentary first sent to us in 1986. We have made slight revisions to his last draft, with the assistance of Professors L.J. Reed, W. Shive, and D. Davis of the Clayton Foundation Biochemical Institute, University of Texas, Austin.

Dr. Williams discovered the universal growth factor pantothenic acid, now known as one of the B vitamins, in 1919 and synthesized it in 1940. His work on pantothenic acid was incorporated into the texts and classrooms of biochemistry long before the beginning of the *SCI* database (1945-1990).

Dr. Williams was chiefly known in his later career as a spokesman for biochemical individuality, the name of his book[5] in several editions, and for the advancement of nutrition in medicine and preventive medicine.]

1. **Williams R J.** The vitamine requirements of yeasts. A simple biological test for vitamine. *J. Biol. Chem.* 55:2912-7, 1919.
2. **Plesofsky-Vig N & Brambl R.** Three subunit proteins of membrane enzymes in mitochondria of *Neurospora crassa* contain a pantothenate derivative. *J. Biol. Chem.* 259:10660-3, 1984. (Cited 5 times.)
3. **Brambl R & Plesofsky-Vig N.** Pantothenate is required in *Neurospora crassa* for assembly of subunit peptides of cytochrome *c* oxidase and ATPase/ATP synthase. *Proc. Nat. Acad. Sci. USA* 83:3644-8, 1986. (Cited 5 times.)
4. **Nutritional and Chemical Division, Syntex Agribusiness, Inc.** *Pantothenic acid: its applications in medicine and nutrition.* Springfield, MO: Syntex Agribusiness, Inc., 1979.
5. **Williams R J.** *Biochemical individuality: the basis for the genetotrophic concept.* Austin, TX: University of Texas Press, (1956) 1969. 228 p. (Cited 490 times.)

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