

## Classics

A PAPER IN A SERIES REPRINTED TO CELEBRATE THE CENTENARY OF THE JBC IN 2005

### JBC Centennial 1905–2005

100 Years of Biochemistry and Molecular Biology

#### A Short Career in Baseball and a Long Career in Vitamin B<sub>12</sub>: the Work of Herbert Weissbach

**Studies on Methionine Biosynthesis. Effect of Alkylcobamide Derivatives on the Formation of Holoenzyme**

(Weissbach, H., Redfield, B. G., Dickerman, H., and Brot, N. (1965) *J. Biol. Chem.* 240, 856–862)

**N<sup>5</sup>-Methyltetrahydrofolate-Homocysteine Transmethylase. Role of S-Adenosylmethionine in Vitamin B<sub>12</sub>-dependent Methionine Synthesis**

(Taylor, R. T., and Weissbach, H. (1967) *J. Biol. Chem.* 242, 1517–1521)



Herbert Weissbach

Herbert Weissbach was born in 1932, in New York City. As a child, he became very interested in baseball, and by the time he was 13 and thinking of going to high school, he wanted to become a professional baseball player. He applied to the Bronx High School of Science, not because of its national reputation for excellence, but because he would have a better chance at making the baseball team at a school that bred scientists not athletes. He passed the entrance exam, and in 1946 he entered high school and began what would be an abbreviated baseball career and lifelong love of science.

After graduating from Bronx Science in 1949, Weissbach entered the City College of New York where he played baseball during his freshman year but then realized his future in competitive sports was limited. Being unsure what to major in, he chose organic chemistry because he was bored with math and biology courses, did not care for analytical, inorganic, or physical chemistry, and did not want to follow in his older brother Arthur's footsteps and become a biochemist. However, in the fall of 1952 he took a biochemistry course and became smitten with the subject. He recalls, "For the first time I saw how biology and chemistry could come together, and how biochemistry could provide the answers to some of the most basic problems in biology. By the end of that semester I knew I was going to sign up for the advanced biochemistry course (1)."

In 1953, Weissbach graduated from City College and joined Sidney Udenfriend's laboratory in the National Heart Institute at the National Institutes of Health and began graduate studies in the Department of Biochemistry at George Washington University. Shortly before he arrived, Udenfriend had become interested in serotonin, and Weissbach was given a project involving research on the biosynthesis and metabolism of serotonin. He received his Ph.D. in 1957, and eager to learn how to work with bacteria, he decided to pursue postdoctoral studies with Horace Barker at the University of California, Berkeley. Barker, who was the subject of a previous *Journal of Biological Chemistry* (JBC) Classic (2), was recognized at that time as one of the finest microbial biochemists.

In Barker's laboratory, Weissbach was assigned to study glutamate metabolism in *Clostridium tetanomorphum*. The first step in the metabolic pathway was the conversion of glutamate to  $\beta$ -methylaspartic acid. Weissbach initially worked on identifying the product of the reaction

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and also looked unsuccessfully for intermediates in the reaction. After this, he began studies on a cofactor that was required for the reaction. He was able to purify the cofactor, which turned out to be the first coenzyme form of vitamin B<sub>12</sub> or 5'-deoxyadenosyl-B<sub>12</sub>.

Weissbach returned to the National Heart Institute in 1959 and continued to work on vitamin B<sub>12</sub>. His isolation of the B<sub>12</sub> coenzyme had revitalized the vitamin B<sub>12</sub> field, and it had been discovered that the vitamin was involved in methionine biosynthesis. Intrigued by this finding, Weissbach initiated studies on methionine synthesis in *Escherichia coli* hoping to learn how the vitamin functioned in this pathway. He was particularly interested in the terminal reaction of the pathway in which a methyl group from a folate derivative was added to homocysteine to generate methionine.

In the first JBC Classic reprinted here, Weissbach and his colleagues investigated the effects of cobamide derivatives on the formation of the holoenzyme that catalyzed the terminal reaction. It was known that the holoenzyme was formed in the presence of the vitamin and that the vitamin or a derivative of B<sub>12</sub> needed to be added to the apoenzyme to fulfill the cobamide requirement for the enzymatic reaction. Weissbach showed that certain alkylcobamides reacted with the apoenzyme forming an inactive enzyme, which was readily converted to active holoenzyme by exposure to visible light. From these experiments, he deduced that a methyl B<sub>12</sub> intermediate was likely involved in the mechanism.

In the second JBC Classic, Weissbach and his colleagues studied the role of *S*-adenosyl-L-methionine, a cofactor that is necessary for the conversion of homocysteine to methionine. From the cofactor activities of various related compounds, they suggested that *S*-adenosyl-L-methionine activates the vitamin B<sub>12</sub> enzyme by methylation. Within the next several years, Weissbach managed to work out the full mechanism for methyl group transfer in the terminal reaction (3, 4).

In 1967 Udenfriend asked Weissbach to help establish the Roche Institute of Molecular Biology, and in 1969 he moved to Nutley, New Jersey as Associate Director of the newly formed Institute. In 1983 he became Director of the Roche Institute and a vice-president of Hoffmann-La Roche. The Roche Institute closed in 1997, and Weissbach accepted a position as Distinguished Research Professor in the Department of Biological Sciences and Head of the Center for Molecular Biology and Biotechnology at Florida Atlantic University. He remains there today.

Included among Weissbach's honors and awards are the Department of Health, Education, and Welfare Superior Service Award, the American Chemical Society Enzyme Award, the City College of New York Townsend Harris Medal, and the George Washington University Distinguished Alumni Award. He is a member of the National Academy of Sciences and Fellow of the American Academy of Microbiology.<sup>1</sup>

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<sup>1</sup> Biographical information on Herbert Weissbach was taken from Refs. 1 and 5.