A Trail of Research in Sulfur Chemistry and Metabolism: the Work of Vincent du Vigneaud

The Utilization of the Methyl Group of Methionine in the Biological Synthesis of Choline and Creatine

The Structure of Biotin: a Study of Desthiobiotin

The Sequence of Amino Acids in Oxytocin, with a Proposal for the Structure of Oxytocin

Arginine-Vasotocin, a Synthetic Analogue of the Posterior Pituitary Hormones Containing the Ring of Oxytocin and the Side Chain of Vasopressin

Vincent du Vigneaud (1901–1978) was born in Chicago in 1901. His first exposure to chemistry came in high school, when he and his friends would obtain chemicals from a pharmacist and conduct experiments involving the fabrication of sulfur-containing explosives. Although he did not know it at the time, sulfur would figure prominently later in his life.

When he finished high school, du Vigneaud went to the University of Illinois at Urbana-Champaign to study chemistry. While at Illinois, he was particularly impressed by a lecture given by W. C. Rose on the discovery of insulin by Frederick Banting and Charles Best. After earning his Masters degree in 1924, du Vigneaud received an invitation from John R. Murlin at the University of Rochester to do graduate work on the chemistry of insulin. “The chance to work on the chemistry of insulin transcended all other interests for me, and I accepted Professor Murlin’s invitation,” said du Vigneaud (1). During his graduate studies, du Vigneaud became intrigued with the fact that insulin contained sulfur and spent the next 2 years studying this phenomenon, coming to the conclusion that sulfur was present in insulin as disulfide linkages.

He finished his degree in 1927 and then began postdoctoral studies on insulin at Johns Hopkins with J. J. Abel, who was a co-founder of the Journal of Biological Chemistry (JBC) and author of a previous JBC Classic (2). In Abel’s laboratory he collaborated with Oskar Wintersteiner on work that allowed him to conclude that insulin was a protein rather than a small organic molecule bound to a protein carrier, thereby establishing that proteins could be hormones. He then carried out further postdoctoral studies with Max Bergmann (author of a previous JBC Classic (3)) in Germany, where his interest in peptide synthesis began.

In 1929, du Vigneaud was offered a position at the University of Illinois. He stayed there until 1932 when he became Professor and Chairman of Biochemistry at George Washington University Medical School. In 1938, he left George Washington to head the Department of Biochemistry at Cornell Medical College in New York City where he remained until 1967 when he joined the Chemistry Department at Cornell University in Ithaca. du Vigneaud’s scientific

1 All biographical information on Vincent du Vigneaud was taken from Refs. 1 and 11.
research encompassed a wide focus, from insulin to cysteine, methionine, biotin, oxytocin, and vasopressin, but it was united by what he called “a trail of research in sulfur chemistry and metabolism.”

The first JBC Classic reprinted here is from du Vigneaud’s metabolism research trail. Previously, he had discovered that homocystine could support rats on a methionine-free diet only if choline or a related substance was included in the diet (4). On the basis of these findings, he speculated that choline acted as a methyl donor for the conversion of homocysteine to methionine and that animals were incapable of generating methyl groups themselves. He also suspected that methionine could serve as a source of methyl for choline synthesis and set out to prove this by following the migration of deuterium-labeled methyl groups from methionine to choline and creatine. du Vigneaud synthesized deuteriomethionine and fed it to rats on a diet free of methionine and choline. He then analyzed the deuterium content of choline and creatine from the tissues of these animals and found that both compounds contained approximately the same amount of deuterium, proving his hypothesis.

Sometime later, Paul Gyorgy asked du Vigneaud to aid in establishing the chemical nature of a sulfur-containing compound: the anti-egg-white injury factor known as biotin. In the second JBC Classic reprinted here, du Vigneaud reports on his elucidation of the structure of biotin on the basis of several degradation reactions. In prior studies, he had come up with two possible structures for biotin (5).

\[\text{du Vigneaud hypothesized that if he performed a sulfide cleavage reaction on biotin and then hydrolyzed the product, he would obtain desthiodiaminocarboxylic acid with either one carbon methyl group, in the case of structure I, or two carbon methyl groups, in the case of structure II. He could then use a carbon-methyl group determination to differentiate between the two structures. Using these and other methods, du Vigneaud proved that structure I is the structure of biotin.} \]

In 1932, du Vigneaud started working on the sulfur-containing posterior pituitary hormones, oxytocin and vasopressin, focusing on the metabolic aspects of the two peptides. His studies were briefly interrupted by World War II, when he was invited by the war time Committee on Medical Research to join the effort to work on the chemistry of another sulfur-containing compound, penicillin. After the war, du Vigneaud resumed his study of the peptides and determined the primary sequence of oxytocin, which is the subject of the third JBC Classic reprinted here.
du Vigneaud knew from previous studies that oxytocin contained equal amounts of leucine, isoleucine, tyrosine, proline, glutamic acid, aspartic acid, glycine, and cystine (6, 7). In this paper, he uses partial hydrolysis of oxytocin, desulfurized oxytocin, and a heptapeptide fragment of oxytocin along with ion exchange and paper chromatography to determine the amino acid sequence of the peptide. He also proposed a tentative cyclic structure for oxytocin based on his data. However, displaying characteristic caution, du Vigneaud stated, “It is obvious that, in spite of the fact that this was the only structure we could arrive at through the realization of the results from our degradative work, synthetic proof of structure was mandatory.” Following up on this statement, du Vigneaud published the first oxytocin synthesis in 1953, which was also the first synthesis of a polypeptide hormone (8).

du Vigneaud also determined the structure of vasopressin and realized that its structure was very similar to that of oxytocin (9). Vasopressin has the same ring structure as oxytocin but differs in two amino acids. However, the two compounds have different physiological activities, oxytocin stimulates uterine contractions and lactation while vasopressin regulates the function of the kidneys. These findings were of great importance because they demonstrated, for the first time, that replacing certain amino acids in a physiologically active peptide can cause significant changes in biological action.

The final JBC Classic reprinted here focuses on the synthesis of an oxytocin-vasopressin peptide. Over the years, du Vigneaud had synthesized several oxytocin and vasopressin analogues in hopes of understanding correlations between the structures and properties of the two compounds. One of the structures, oxypressin IV, had a cyclic pentapeptide amide portion identical to that found in vasopressin, linked to a tripeptide amide side chain from oxytocin (10). du Vigneaud found that oxypressin had very low pressor activity, even though it contained the ring structure present in the vasopressin, possibly due to the lack of a strongly basic amino acid in the oxytocin side chain. In order to test this hypothesis, du Vigneaud synthesized arginine-vasotocin, a “cyclic octapeptide amide that contains a cyclic pentapeptide amide portion identical with the one existing in oxytocin I, linked to the tripeptide amide side chain that is present in arginine-vasopressin II.” When du Vigneaud assayed his peptide for activity, he found that it possessed high levels of oxytocic, avian depressor, and pressor activities, confirming his hypothesis.

du Vigneaud had a large number of students and postdoctoral fellows during his career and collaborated with many more senior biochemists. Among this group many went on to distinguished research careers of their own; 3 won Nobel prizes and 15 became members of the National Academy of Sciences, whereas many more held prominent academic and industrial positions in the U.S. Thus, he had a remarkable influence on biochemical research in the U. S. du Vigneaud received many awards and distinctions for his research, including the Nobel Prize in Chemistry in 1955, “for his work on biochemically important sulfur compounds, especially for the first synthesis of a polypeptide hormone.” However, he had definite opinions about awarding prizes for scientific achievement and once said to a
reporter, “I am expecting to stay in the research field, in the academic world, but I want to
tell you I will never work for any prize. I refuse to let my rewards rest in the hands of any
committee.”

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