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Historical Essay

The Nobel trail of Vincent du Vigneaud

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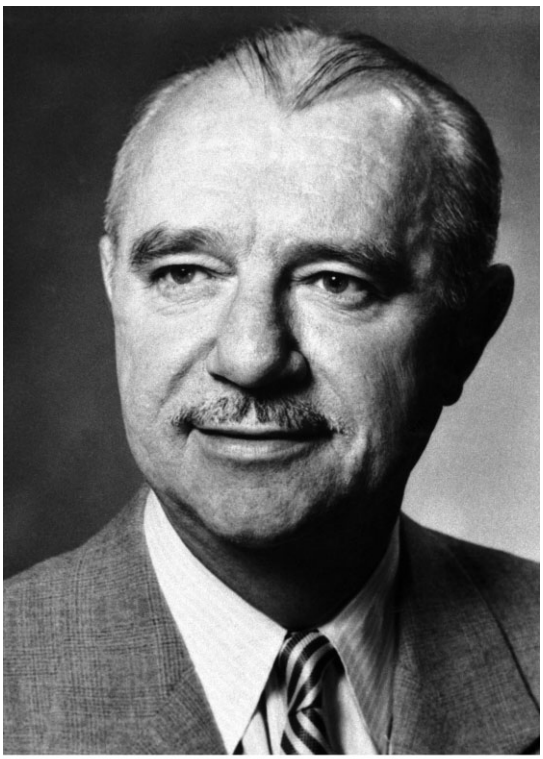
Abstract: The Nobel Prize for chemistry of 1955 was awarded to Vincent du Vigneaud. After a brief outline of his career and accomplishments, some archive material related to this decision of the Royal Swedish Academy of Sciences is presented. Other archive studies have shown that du Vigneaud was also considered for the corresponding prize in physiology or medicine. Copyright © 2007 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: biotin; insulin; oxytocin; peptide science; history of; transmethylation; trans-sulfuration; vasopressin; Vincent du Vigneaud



du VIGNEAUD, Vincent
Nobel Laureate CHEMISTRY 1955
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INTRODUCTION

The 1955 Nobel Prize for chemistry was awarded to Professor Vincent du Vigneaud [1] of the Cornell University Medical College in New York City 'for his work on biochemically important sulfur compounds, especially for the first synthesis of a polypeptide hormone' [2,3]. His formal Nobel Lecture bore the title *A trail of sulfur research: from insulin to oxytocin.* After initial improvement of insulin purification and analytical work on this hormone [4], his chemical and biological interests led him into the field of peptides, and as a result of several groundbreaking accomplishments in this area he established a reputation as a pioneer in peptide research. With the steadily increasing number of biologically active peptides isolated during the second half of the last century, this branch of science soon turned out to be of wide medical, technical and commercial interest. In this article, the material related to his Prize in the archive of the awarding body, the Royal Swedish Academy of Sciences, is reviewed as well as some in that of the Karolinska Institute Nobel Assembly, supplementing those already on record [5].

BACKGROUND

Vincent du Vigneaud was born in Chicago in 1901. He attended the University of Illinois (M.S. 1924) and while there, learnt about the insulin work recently initiated and led by Banting (Nobel laureate in medicine 1923) [3]. His own research career in the insulin field began in Rochester (Ph.D. 1927) and continued for several years in different places. Although at that time peptide and protein chemistry was in its infancy, he provided essential chemical information on insulin with respect to its sulfur content, presence of cystine and absence of methionine, behaviour on reduction and reoxidation, etc., and concluded that insulin was a protein. In this connection he also undertook the synthesis of small peptides and sulfur-containing amino acids requiring novel methodologies, some of which are still in use. In the early 1930s he initiated biosynthetic studies aiming at finding the relation between methionine and cysteine/cystine, and by feeding rats on a diet

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low in these amino acids with various analogues and derivatives, he was able to postulate a mechanism for their inter-conversion. This was named trans-sulfuration and afterwards rigorously proved by the application of isotopically labelled sulfur, also in other species. In further, related original work, he was able to demonstrate the significance of methionine as a methyl donor in the biosynthesis of many physiologically important compounds, which led to the concept of transmethylation. Isotopic labelling played a decisive role in many of these experiments.

Crude pituitary extracts were already in clinical use, when in 1928, a paper appeared describing the isolation of two physiologically active compounds of this origin, nowadays known as oxytocin and vasopressin [6]. They were characterized as 'basic bodies, presumably amines' and therefore at this stage called α- and β-hypophamine. A few years later, du Vigneaud began investigating them chemically and determined their sulfur and cystine content, and demonstrated that, unlike insulin, they did not lose their activities on reduction and reoxidation. Vasopressin was shown to move faster than oxytocin towards the cathode on electrophoresis, and that could be exploited for partial purification. The major efforts were initially spent on securing enough material for subsequent structural investigations. Between 1940 and 1942, research was also undertaken on the yeast growth factor biotin, leading to its identification with the anti-egg-white injury factor and final structure determination. These results appear to have drawn the attention of a wide scientific audience.

During the Second World War, du Vigneaud played a key role in the transatlantic penicillin project. This work finally resulted in the isolation of a small amount of synthetic penicillin after application of Craig's recently developed purification method based on counter-current distribution.

After the War, du Vigneaud resumed his work on oxytocin and vasopressin, improved their purification by counter-current distribution and determined their amino-acid composition by chromatography on starch columns after hydrolysis. Free amino groups were identified with Sanger's reagent, whereupon the hormones were cleaved under different conditions and the fragments purified and characterized by the same procedures, from which work the structures of both oxytocin and vasopressin could be derived in 1953. Parallel synthetic work, in part based on procedures previously worked out in his laboratories, demonstrated that these structures were correct by providing material with all chemical and biological properties identical to those of the native hormones.

As all major aspects of du Vigneaud's work have been reviewed in detail by himself [2,3,7–9] or discussed by others [10–13], to avoid repetition only a brief list of his accomplishments with particular relevance to the nominations for the Prize is given. References 4 and 6 illustrate the state of the art of hormone research in the mid-1920s, when his work was initiated, before chemistry made its entry around the time of the Second World War with him as the key practitioner.

THE NOBEL PRIZE IN CHEMISTRY 1955

Nobel Prizes in chemistry have been awarded by the Nobel Foundation essentially every year since 1901, except in times of war. The responsibility for the selection of Laureates resides with the Nobel Committee for chemistry of the Royal Swedish Academy of Sciences [3,5]. Information about the nominations, investigations and opinions concerning the awards is kept secret for 50 years.

In 1944, du Vigneaud received two nominations for the Nobel Prize in chemistry [5], both emphasizing his investigations on biotin, which was characterized as 'trustworthy experimental data on the role of sulfur in metabolism' by the evaluating committee. Also, in 1945, two proposals in his favour were based on this work and in the archive documents he is mentioned together with Fritz Kögl, who had figured as a candidate nearly every year since 1934. It was followed by three more nominations in 1947, three in 1948 and one in 1949, five of which were from previous laureates [5]. In some of them, transmethylation and penicillin were cited in addition to biotin.

Already in 1948, after four committee evaluations in five years, it seems du Vigneaud's work had established him as a serious candidate for a future Prize as he was then declared 'well deserving the attention of the committee'. Further nominations, one each year, followed in 1950–1952, by which time he had already published several preliminary but chemically groundbreaking papers on the structure of oxytocin and vasopressin. After completing the determinations of their amino-acid sequences in 1953 and reporting active synthetic preparations of oxytocin as well as both lysine- and arginine-vasopressin within a year, du Vigneaud received six nominations in 1954 and eight the following year, especially stressing this work. The 1954 prize, however, was awarded to Linus Pauling, 'for his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances'. In 1955, the Committee originally proposed Hugo Theorell, first nominated in 1937 for the Prize, 'for his discoveries concerning the chemical nature and mechanism of action of the oxidation ferments', but it seems du Vigneaud was a strong competitor. When Theorell received the award that year in physiology or medicine, the one in chemistry was given to du Vigneaud with the citation mentioned in the introduction above.

It is not surprising that du Vigneaud's work made him a strong contender also for the Prize for physiology

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or medicine. According to the nomination database covering the period 1901–1951 [3], his name was put forward the first time already in 1943, and he subsequently received eight nominations during the years 1948–1951. Also, in these early nominations, his work on transmethylation and biotin and in a few cases penicillin was cited. It should be mentioned that the Prize in 1945 was awarded 'for the discovery of penicillin and its curative effect in various infectious diseases' to Alexander Fleming, Ernst Chain and Howard Florey.

The breakthrough on oxytocin and vasopressin seems to have had a dramatic effect within the medical circles and consequently in 1954 du Vigneaud doubled the total number of nominations he had received to 18. The Committee also expressed its esteem for his work and its majority recommended him for the award in physiology and medicine in 1954 'for his discovery of the structures of vasopressin and oxytocin and their confirmation by synthesis'. A minority instead favoured John F. Enders, Thomas H. Weller and Frederick C. Robbins and in the final decision they were given the Prize 'for their discovery of the ability of poliomyelitis viruses to grow in cultures of various types of tissue'. As already mentioned, in the following year Theorell became the medical laureate 'for his discoveries concerning the nature and mode of action of oxidation enzymes', although the external support for du Vigneaud had now reached its peak as judged from the available documents.

After 1955, du Vigneaud continued with his original research trail for many years and prepared a large number of synthetic oxytocin and vasopressin analogues, thereby pioneering structure–activity studies on these hormones [14,15]. Many others have subsequently adopted similar approaches in their explorations of a multitude of biologically active peptides. Viewed from a different perspective, du Vigneaud's award also represented a breakthrough for the emerging branch of chemistry dealing with peptides and proteins. Already three years later the structure determination of insulin was also rewarded and more recently work dealing with more complex proteins.

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