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This Week's Citation Classic

Bodanszky M & du Vigneaud V. A method of synthesis of long peptide chains using a synthesis of oxytocin as an example. *J. Amer. Chem. Soc.* **81**:5688-91, 1959.
[Dept. of Biochemistry, Cornell Univ., Ithaca, NY]

The previously generally accepted method for the construction of peptides, combination of shorter segments of their chain, is replaced by a new approach to chain building, the addition of single amino acids. Unequivocal incorporation of the (protected) amino acids was achieved by the application of nitrophenyl esters. [The *SCI*® indicates that this paper has been cited over 615 times since 1961.]

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"Early in 1957 my wife, our five-year old daughter, and I arrived as refugees in New York City. I came to join du Vigneaud in his studies (recognized a year earlier by the Nobel Prize) on the chemistry of the peptide hormones oxytocin and vasopressin. Our newly acquired freedom, together with the absence of material possessions such as home, car, or television set, allowed me to concentrate on the task at hand: a new synthesis of oxytocin. At the same time, I was still somewhat obsessed by thoughts about my new procedure for the coupling of amino acids to each other, developed before I left Hungary: the nitrophenyl ester method.[1] Thus, the idea to incorporate only protected-activated amino acids in the synthesis of oxytocin, rather than to follow the classical approach of combining segments of the peptide chain, presented itself quite naturally. The stepwise addition of single residues allowed systematic lengthening of the chain, without endangering the optical purity of the amino acid constituents Du Vigneaud enthusiastically approved the project and supported it with his tremendous knowledge of the problems surrounding oxytocin, his baby protein.' The progress of the synthesis appeared breathtakingly fast. Within a short time we had a fairly large sample of oxytocin in our hand in a yield far exceeding the yields of previous syntheses. The purity of the intermediates, all isolated in crystalline form, was also encouraging. The simplicity of the handling of the prefabricated reactive intermediates, *p*-nitrophenyl esters of benzyloxycarbonyl amino acids, suggested that this could be a general method for the synthesis of any long peptide chain. This view was expressed also in the title of our paper The repetitiveness of the operation seemed to lend itself to mechanization and automation,[2] and the stepwise strategy indeed acted as a stimulus in the invention of techniques for the facilitation of peptide synthesis.

"It remains to be seen whether or not all peptides and proteins can be synthesized by a single process. The specificity of the biological activities of individual peptides is directly related to differences in their chemistry. Therefore, an entirely universal approach could be near to impossible. Yet, stepwise synthesis is often practical and we could successfully apply it for the first synthesis of the gastrointestinal hormone secretin and, most recently, for the avian vasoactive intestinal peptide. Several laboratories adopted the stepwise strategy. Some of the publications referred to this much cited paper, but gave credit for the details of the reactive intermediates (which we described years earlier[1]) rather than for the general idea proposed in it. Thus, we read these references with mixed feelings. Nevertheless, it is very gratifying to write these comments. They bring back the memory of our first years in the United States, the excitement of New York City, the congenial atmosphere of the du Vigneaud laboratory, the colleagues (many distinguished peptide chemists by now. J. Meienhofer, J. Stouffer, R. Studer, A. Light, W. Cash, P. Katsoyannis, C Ressler, V.V.S. Murti, P. Fitt, to mention a few), a time of great expectations, and a time when we all were very much alive That a *'Citation Classic'* resulted from this period, shows that some of the expectations were fulfilled: it is not easy to make even a small dent on the surface of chemistry. Our time was not spent in vain."

1. **Bodanszky M**. Synthesis of peptides by aminolysis of nitrophenyl esters. *Nature* (London) **175**:685, 1955.
2. **Bodanszky M**. Stepwise synthesis of peptides by the nitrophenyl ester method. *Ann. NY Acad. Sci.* **88**:655-64, 1960.