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This Week's Citation Classic®

Bergink E W, Wallace R A, van de Berg J A, Bos E S, Gruber M & AB G.
Estrogen-induced synthesis of yolk proteins in roosters.
Amer. Zool. 14:1177-93, 1974.
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In the avian liver oestrogens regulate the synthesis of vitellogenin, which is the serum precursor of the yolk proteins phosvitin and lipovitellin. This paper describes the characterization of chicken vitellogenin, its relationship to the yolk proteins, and the kinetics of its induction by oestrogen in roosters. [The *SCI*® indicates that this paper has been cited in over 130 publications.]

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During my stay as a postdoctoral fellow in the laboratory of Robin Wallace at the Biology Division of the Oak Ridge National Laboratory (1973-1974), I received an invitation to present a paper on avian yolk protein synthesis at the meeting of the American Society of Zoologists in Houston. The proceedings of this meeting were to be published in the *American Zoologist*. This invitation offered me the opportunity to present unpublished parts of predoctoral studies performed from 1970 to 1973 in the Biochemical Laboratory of the University of Groningen in The Netherlands. I intended to combine my own data with those of my fellow students, Ebo Bos and Johan van de Berg, which dealt with different aspects of oestradiol-induced yolk protein synthesis. This work was performed under the direction of Max Gruber and Geert AB. Gruber, who had become interested in regulation of yolk protein synthesis as early as 1965, was head of the institute until his retirement in 1986. AB, who is now in charge of the group, was our supervisor.

I believe the paper has been cited frequently because it showed for the first time that the yolk precursor present in the serum of chickens consists of a continuous polypeptide chain synthesized in the liver from a high-molecular-weight RNA, secreted into the blood, and subsequently cleaved proteolytically to yield the ultimate yolk proteins. Previously, the nature of the serum precursor for these yolk proteins was not clear since the precursor is very easily degraded and a mixture of degradation products was found in serum. It had even been suggested that the synthesis of the yolk proteins phosvitin and lipovitellin may be regulated independently.

Immediately after finishing my thesis in 1973, I went to Oak Ridge to start working with Wallace, who had a reputation in the field of maturation of amphibian oocytes. We rapidly established the precursor product relationship between amphibian vitellogenin and amphibian yolk proteins; the resulting paper, which appeared in the *Journal of Biological Chemistry* in 1974,[1] was the first in the English literature to describe such a relationship for a vertebrate vitellogenin. Shortly afterwards, in the same journal, M.J. Clemens and coworkers confirmed the observation.[2] At that time, the original findings on the avian system had not yet been published. It was therefore a great pleasure that the work from Groningen, which threatened to fall into oblivion, was published as a paper in 1974 and has since been cited very frequently. Recently, these studies have culminated in the elucidation of the 1,850-amino acid long sequence of the chicken yolk precursor protein through nucleotide sequence analysis of the cloned vitellogenin gene.[3]

Finally, I may add, the initial conclusion that these studies on oestrogen-induced protein synthesis were probably not relevant for the human system is no longer valid. Recently, it was shown that one aspect of the manuscript—namely, the description of the "memory effect" or "priming effect," which is a long-lasting alteration in liver cells after a transient stimulation with oestrogens—is not only relevant for toads and chickens but can be observed in human hepatocytes as well.[4]

1. Bergink E W & Wallace R A. Precursor product relationship between amphibian vitellogenin and the yolk proteins lipovitellin and phosvitin. *J. Biol. Chem.* 249:2897-903, 1974. (Cited 130 times.)
2. Clemens M J, Lofthouse R & Tata J R. Sequential changes in the protein synthetic activity of male *Xenopus laevis* liver following induction of egg-yolk proteins by estradiol-17β. *J. Biol. Chem.* 250:2213-8, 1975. (Cited 50 times.)
3. van het Schip F D, Samallo J, Broos J, Ophuis J, Mojet M, Gruber M & AB G. Nucleotide sequence of a chicken vitellogenin gene and derived amino acid sequence of the encoded yolk precursor protein. *J. Biol. Chem.* (In press.)
4. Tam S-P, Haché R J G & Deeley R G. Estrogen memory effect in human hepatocytes during repeated cell division without hormone. *Science* 234:1234-7, 1986.

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