

# This Week's Citation Classic

Chance B & Williams G R. The respiratory chain and oxidative phosphorylation. *Advan. Enzymol. Relat. Areas Mol. Biol.* 17:65-134, 1956. [University of Pennsylvania, Philadelphia, PA]

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On the occasion of Dr. Chance's 70th birthday, we asked him to write a *Citation Classic* commentary. He graciously accepted with the following.

The identification of metabolic states of isolated mitochondria appears to have laid the foundation for quantitation of metabolic function in host cells and organelles. The mitochondria themselves provide consumer reports on oxygen and substrate metabolism. [The SC/® indicates that this paper has been cited in over 1,705 publications since 1961.]

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"The postwar period was especially important to those biological scientists who had either willingly or perforce given up their chosen disciplines to contribute to their nations' efforts in World War II. This was especially true of myself, having volunteered before the US was engaged in the war to devote my maximal scientific effort over a period of six years to pursuing the war and to consolidating the scientific gains made in radar and circuitry developments. Thus, it was a breath of fresh air to resume my prewar research on enzyme-substrate compounds and visit in the laboratories of the 'giants' of the postwar years, Theorell and Keilin, who had continued their work during World War II. Shortly thereafter, I returned to Philadelphia to find a challenging position at the Johnson Research Foundation, University of Pennsylvania, available to me which I've held ever since.

"Given the security of tenure at a young age (36), a chair and an endowment, and satisfied that the work on enzyme-substrate compounds of peroxidases had established an experimental basis for the Michaelis-Menten theory, I decided to venture into the field of 'insoluble enzymes' and to develop rapid and sensitive spectrophotometric methods in order to understand the mechanism of their action.

"After some abortive attempts with Gene Kennedy, it became apparent that the quali-

ty of the mitochondrial preparations and the exhibiting respiratory control were critical to a successful experiment. The work of Lardy and Wellman showed the way and Lardy, G.R. Williams, and I prepared mitochondria which would respond to ADP, phosphate, or calcium addition with tenfold or even more increase of respiration (respiratory control). Williams and I worked together feverishly to obtain spectroscopic responses corresponding to various states of metabolic activity. Soon Joe Higgins joined us and was able to make a mathematical formulation explaining these responses, known as the crossover theorem. Verification of mitochondrial metabolic states in frog skeletal tissue was obtained with C.N. Connelly to extend the crossover theorem and gave me the necessary feeling of confidence to write up our work in detail in the *Journal of Biological Chemistry*<sup>1,2</sup> and to write the comprehensive review as well.

"The responses to the ideas were definitely 'not great'; the initial presentation before the American Society of Biological Chemists at San Francisco as a ten-minute presentation was disaster-ridden. The chairman, my good friend A. Lehninger, apparently misread the clock and told me that I was to sit down after four of the ten minutes allotted for the talk. However, confirmation of the work in other laboratories through use of the dual wavelength spectrophotometer and its extension to living tissues provided validation and extension of the basic principles. A significant influx of postdoctorals to my laboratory was especially helpful as was the publication of this comprehensive review. All these events gave the work a general acceptance and a large part of the work seems useful today, as applied not only to the respiratory chain but as applied to metabolic control in general.

"Perhaps the moral of this communication is that it really does pay to work at a new idea until it is fully developed, and, as this case, not only published in the

in original literature, but also pulled together as a comprehensive review article. Obviously, I'm pleased that this article fared so well, apparently better than the full paper in the *Journal of Biological Chemistry*<sup>1,2</sup>

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1. Chance B & Williams G R. Respiratory enzymes in oxidative phosphorylation. I-IV. *J. Biol. Chem.* 217:383-93; 395-407; 409-27; 429-38, 1955.

[These papers have been cited over 1,445 times in 1,317 publications since 1961.]

2. Chance B, Williams G R, Holmes W F & Higgins J. Respiratory enzymes in oxidative phosphorylation. V. *J. Biol. Chem.* 217:439-51, 1955.