

# This Week's Citation Classic

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Majno G & Palade G E. Studies on inflammation. I. The effect of histamine and serotonin on vascular permeability: an electron microscopic study. *J. Biophys. Biochem. Cytol.* **11**:571-605, 1961.  
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It was well known that histamine increased the permeability of small blood vessels; we found the mechanism: the cells that line the smallest veins become partially disconnected, so that fluid can escape between them. This is one of the key events in acute inflammation. [The *SCI*<sup>®</sup> indicates that this paper has been cited over 625 times since 1961.]

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"Citation Classic? Would ISI<sup>®</sup> care to open a new category of *Refusal Classics*? Of all the scientific papers on which I was the senior author, only one was turned down: you know which one. This paper had been a labor of love. I had joined G.E. Palade's laboratory at the Rockefeller Institute in 1958, to be initiated in the new art of electron microscopy. We had carefully chosen a topic of common interest: Palade was an authority on blood vessels, and I was interested in any tissue as long as it was sick, so we settled for leaking blood vessels. Histamine was supposed to make capillaries leak, but nobody knew by what mechanism; so we injected histamine into rats and began to look for leaking capillaries. I remember spending days of frustration looking at capillaries that remained stubbornly normal —until we found out that the exciting events happened a little further downstream, in the venules, which had become riddled with tiny leaks. In the process we also stumbled upon an

extremely cheap and beautiful biological trick: a drop of India ink injected into the bloodstream causes leaking vessels to become elegantly 'tattooed' in black; an experimental technique now known as vascular labeling (the phenomenon itself had been published at least 12 times before, but with the wrong explanation).

"When I was advised that the resulting paper would be turned down by the *Journal of Experimental Medicine*, I was half shocked, half amused, but completely sure that the reason could not be scientific. Sure enough, the startling reason given by that grand old gentleman, Peyton Rous, was that the paper contained *too much history*! Was I really supposed to chop out the historical roots of our work? 'Stick to your guns,' said Palade, lapsing into vernacular English (we used to speak French at that time). So we sent the paper to a new, competing journal, now called the *Journal of Cell Biology*. (It took me another eight years to go one step further, and find that the leaks were caused by endothelial contraction.)<sup>1</sup>

"Looking back upon that work, produced under the wing of a great master, I can say with a touch of nostalgia that we were bound to produce a paper of more than passing value because we found out — just in time —that we had merely confirmed, with more refined methods, a paper that had appeared in *Virchows Archiv* in 1875.<sup>2</sup> Since 1961, a mountain of literature has been appearing on the endothelium. A review of this field was recently published in *The Thrombotic Process in Atherogenesis*\*

"I believe that our work attracted attention because it solved a long-standing functional riddle by very simple (and very aesthetic) morphologic observations."

1. Majno G, Shea S M & Leventhal M. Endothelial contraction induced by histamine-type mediators. *J. Cell Biol.* **42**:647-72. 1969.
2. Arnold J. Ueber das Verhalten der Wandungen der Blutgefäße bei der Emigration weisser Blutkörper. *Virchows Arch.* **62**:487-503. 1875.
3. Majno G & Joris I. Endothelium 1977: a review (Chandler A B, Eurenus K, McMilan G C, Nelson C B, Schwartz C J & Wessler S, eds.) *The thrombotic process in atherogenesis*. New York: Plenum. 1978. p. 169-225: 481-526.