

This Week's Citation Classic

Bourne H R, Lichtenstein L M, Melmon K L, Henney C S, Weinstein Y & Shearer G M. Modulation of inflammation and immunity by cyclic AMP. *Science* **184**:19-28. 1974.

[Depts. Med. and Pharmacol., Div. Clin. Pharmacol., Univ. Calif. Med. Ctr., San Francisco, CA; Div. Immunol., Good Samaritan Hosp., Johns Hopkins Univ., Baltimore; and Immunol. Branch, Natl. Cancer Inst., Bethesda, MD]

Drawing on experimental studies of basophils, mast cells, neutrophils, and lymphocytes, this review proposes the hypothesis that certain hormones and mediators of inflammation utilize cyclic AMP as an inhibitory second messenger to regulate the character and intensity of inflammatory and immune responses. [The *SC*[®] indicates that this paper has been cited in over 570 publications since 1974.]

Henry R. Bourne
Departments of Pharmacology
and Medicine
and
Cardiovascular Research Institute
University of California San
Francisco, CA 94143

June 1, 1984

"By 1970, the discovery of cyclic AMP as an intracellular second messenger for hormones had been extended to embrace the actions of a multitude of first messengers acting on many types of mammalian cells. As a postdoc, I wanted to join the bandwagon by finding a hormone-responsive cell that had not yet been tested. I chose the human leukocyte after Ken Melmon, my adviser, showed me a paper¹ that suggested cyclic AMP might regulate at least one leukocyte function. β -adrenergic amines, prostaglandin- E_1 , histamine, and cholera toxin turned out to stimulate leukocyte adenylate cyclase. A transcontinental collaboration with Larry Lichtenstein and Chris Henney at Johns Hopkins University then showed that the same agents, as well as a cyclic AMP analogue, inhibited allergic (IgE-mediated) release of histamine from baso-philic leukocytes and killing of allogeneic cells by sensitized T lymphocytes. Melmon, in collaboration with Yacov Weinstein and Gene Shearer at the Weizmann Institute in Israel, found selective binding of functionally distinct lymphocyte subpopulations to histamine immobilized on Sepharose beads.

"The 1974 review summarized these experiments as the basis of a grand hypothesis regarding the inhibitory role of leukocyte cyclic AMP in regulation of inflammation and immunity. The hypothesis has held up remarkably well as a predictor of pharmacological effects *in vitro*, in that agents that elevate cyclic AMP in leukocyte subpopulations and mast cells do inhibit each cell's characteristic inflammatory or immune response.

"Our review emphasized a much broader prediction: that catecholamines, histamine, and prostaglandins — and probably other first messengers as well — would prove to play physiologically important roles in inhibiting inflammatory and immune responses *in vivo*. We proposed, for example, that histamine's ability to inhibit its own release might constitute the basis of an inhibitory feedback loop that would serve to inhibit the extent or intensity of allergic responses. Subsequent experiments (summarized in reference 2) provided suggestive evidence in favor of this broader implication, with respect to an inhibitory role of histamine in delayed hypersensitivity.

"My guess is that the review has been frequently cited because it highlighted the intersection of one extremely active area of investigation, cyclic AMP, with the even more rapidly expanding research fronts of inflammation and immunity, and did so in a journal that is widely read. In addition, investigators over the years may have continued to cite an attractive hypothesis that survived in part because it was so difficult to test *in vivo*.

"Now immunologists can clone and propagate functionally specific leukocytes and lymphocytes in tissue culture and study their responses to a large number of recently discovered chemical signals. Investigators of such responses must now consider a panoply of second messengers in addition to cyclic nucleotides. The results of their investigations will be much more complex and more interesting than we envisioned in 1974.

"Two recent reviews^{2,3} cover more recent research in this area."

1. Lichtenstein L. M & Margolis S. Histamine release in vitro: inhibition by catecholamines and methylxanthines. *Science* **161**:902-3. 1968. (Cited 415 times.)
2. Melmon K L, Rocklin R E & Rosenkranz R P. Autacoids as modulators of the inflammatory and immune response *Amer J. Med.* **71**:100 1981.
3. Rocklin R E & Beer D J. *Histamine and immune modulation. Advan. Internal Med.* **28**:225-51. 1983.