

This Week's Citation Classic®

Zurier R B, Weissmann G, Hoffstein S, Kammerman S & Tai H H. Mechanisms of lysosomal enzyme release from human leukocytes. II. Effects of cAMP and cGMP, autonomic agonists, and agents which affect microtubule function. *J. Clin. Invest.* 53:297-309, 1974.
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The studies reported in this paper demonstrated that selective release of inflammatory materials from lysosomes of human peripheral blood polymorphonuclear leukocytes is reduced by compounds that increase cyclic AMP and is augmented by agents that increase cyclic GMP concentrations in the cells. In addition, the results indicate that impairment of microtubule integrity reduces selective release of lysosomal enzymes whereas compounds that favor microtubule assembly enhance enzyme release. [The SCJ® indicates that this paper has been cited in over 515 publications.]

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I arrived in Gerald Weissmann's laboratory at Bellevue Hospital, New York, in January 1970, fresh from a country practice of general medicine. Having witnessed in my own practice the remission of rheumatoid arthritis (RA) in pregnant patients (the clinical observation that led P.S. Hench¹ to treat RA patients with corticosteroids), I was persuaded that the high concentrations of phospholipids in serum from pregnant women and the substantial amounts of prostaglandins in amniotic fluid pointed to prostaglandins as the agents responsible for suppression of inflammation in pregnant RA patients. It seemed clear from Weissmann's work that the concept of lysosomal stability related to more than the isolated organelle and that release of lysosomal enzymes from polymorphonuclear leukocytes (PMN) was probably central among events leading to inflammation and tissue injury in joints of patients with RA.² Most investigators interested in lysosomal enzyme release had studied isolated lysosomes or fabricated liposomes. Primitive as it seems now, use of intact human cells for such experiments was a fairly new enterprise.

I initially worked with PMN from pregnant patients. That fruitless endeavor was shelved after three months by gentle but firm suggestions from Weissmann that a better controlled system might be easier to interpret. He had postulated² that microtubules influence intracellular traffic of organelles and that they are regulated by cyclic nucleotides. In addition, it was known that prostaglandins could influence cyclic nucleotide concentrations in several cell types, including human leukocytes. Thus, the stage was set for our studies. The data presented in the paper suggested that granule movement and acid hydrolase release from human PMN lysosomes requires intact microtubules and may be modulated by adrenergic and cholinergic agents that provoke changes in cellular concentrations of cyclic nucleotides.

The paper may be cited frequently because the results helped secure the biochemical basis for the contention^{3,4} that certain prostaglandins that increase cellular cyclic AMP can exhibit anti-inflammatory properties by suppressing leukocyte effector function and that they do not function solely as mediators of inflammation. Recently, there has been a greater appreciation of a role for prostaglandins as regulators of immune/inflammatory responses,⁵ as cytoprotective agents,⁶ and as potentially useful agents for suppression of inflammation and tissue injury.⁷

Also, the paper was among the first to correlate cyclic nucleotide action with microtubule-dependent secretory events. Although controversy still exists about the precise relationship between cyclic nucleotides and microtubules, these events have now assumed an important role in cell biology, and investigators continue to dissect the mechanisms whereby cyclic AMP-dependent effects—including those induced by β -adrenergic agents—modulate PMN activation.⁸

I consider myself fortunate to have been in Weissmann's laboratory at that particular time. Colleagues included Philip Davies, Peter Dukor, Ira M. Goldstein, Rochelle Hirschhorn, and Sylvia Hoffstein. The enthusiasm and energy of the investigators in the laboratory was fueled in large part by Weissmann's imagination, excitement about and love for biological puzzles, and his support and encouragement.

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