This Week's Citation Classic®

Black J W, Duncan W A M, Durant G J, Ganellin C R & Parsons M E. Definition and antagonism of histamine H_2-receptors. *Nature* 236:385-90, 1972.
[The Research Institute, Smith Kline and French Laboratories Ltd., Welwyn Garden City, Hertfordshire, England]

Evidence for two receptor populations was obtained by quantitative analysis of agonist activity of histamine analogues on five tissue systems. The pharmacological characterization of histamine H_2 receptors was achieved by means of burimamide, a novel thiourea derivative, which competitively antagonized the action of histamine on isolated guinea pig atrium and rat uterus. Burimamide inhibited histamine- and pentagastrin-stimulated gastric acid secretion in several animal species and man. [The *SCI*® indicates that this paper has been cited in more than 1,860 publications.]

The Reemergence of Histamine

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It is nearly two decades since publication of the *Nature* article which described the characterization and antagonism of histamine H_2 receptors. This proved to be a milestone publication for many reasons and dramatic advances have occurred. It seems highly appropriate for this *Citation Classic* to be published in the same year as the first publication of the cloning of the histamine H_2 receptor.[1]

Many of us recall the excitement of meeting Jim W. Black for the first time in 1964, when he visited Smith Kline and French Laboratories at Welwyn, England, soon after the discovery of beta blockers at ICI Pharmaceuticals, in which he was deeply involved.[2] Greater excitement followed when Black set up a new research program at SmithKline aimed at the discovery of a novel histamine antagonist. In fact, the excitement was to last for more than a decade with many highs and lows, up to and beyond the launch of cimetidine (Tagamet) in 1976. Publication of the *Nature* article in 1972 was certainly one of the high points. The great interest generated was predictive of the numerous and significant developments that followed.

First, the histamine H_2-receptor antagonist led to a major advance in gastroenterology and to an increased understanding of the physiological processes involved in the secretion of gastric acid. They proved to be an extremely effective means of controlling gastric acid secretion, and cimetidine (Tagamet), which was a direct development from burimamide, demonstrated great clinical utility. Most gastroenterologists consider that cimetidine and subsequent H_2-receptor antagonists have revolutionized the treatment of peptic ulcer disease. A previous *Citation Classic* cited the paper[3] that described the definitive pharmacology and clinical efficacy of cimetidine.

The 1972 *Nature* article also caused a resurgence of interest in histamine that persists until the present day. Histamine research had been in the doldrums for many years following the initial interest created by I. Bovet's original discovery[4] of antihistamines for treating allergies in the 1930s. However, the appearance of the *Nature* article gave rise to a plethora of publications on the chemistry and biology of histamine and H_2 receptors. Greater interest developed in the pharmacology and biochemistry of histamine and its physiological role throughout the body. Large numbers of H_2-receptor antagonists have been described, several of proven clinical utility. Histamine has been shown to fulfill all the criteria for a neurotransmitter in the CNS, and a third histamine receptor, the H_3-receptor, has been shown to modulate the synthesis and release of histamine in the brain and some peripheral tissues.[5]

The *Nature* article is perhaps especially noteworthy, since the criteria used to analyze the pharmacological actions of histamine and its analogues in terms of receptor subtypes set a valuable precedent and standard for subsequent investigators. Additionally, the development of a selective antagonist, by structural modification of an agonist, and avoiding general screening, provided a much-quoted case history in drug design.

The authors of the *Nature* article have been awarded many honors, crowned by the Nobel Prize for physiology or medicine in 1988, to Sir James Black for his momentous drug discoveries that include adrenergic beta blockers in addition to histamine H_2-receptor antagonists. His coworkers are privileged to have had the experience of working with one of the greatest intellects to have been applied to the drug discovery process.

1. Ganz I, Schafer M, Delvelle J, Logsdon C, Campbell V, Uhler M & Yamada T. Molecular cloning of a gene encoding the histamine H_2 receptor. *Proc. Nat. Acad. Sci. USA* 88:429-33, 1991.
2. Black J W & Stephenson J S. Pharmacology of a new adrenergic beta-receptor-blocking compound (nethalide). *Lancet* 2:311-4, 1962. (Cited 610 times.) [See also: Garfield E. The 1988 Nobel Prize in medicine: Sir James Black, Gertrude B. Elion, and George H. Hitchings ennobel pharmaceutical research. *Essays of an information scientist*. Philadelphia: ISI Press, 1991. Vol. 12. p. 201-11.]
3. Brimblecombe R W, Duncan W A M, Durant G J, Emmett J C, Ganellin C R & Parsons M E. Cimetidine—a non-thiourea H_2-receptor antagonist. *J. Int. Med. Res.* 3:86-92, 1975. (Cited 465 times.) [See also: Brimblecombe R W. Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 1: cell biology*. Philadelphia: ISI Press, 1986. p. 210.]
4. Bovet I & Staub A M. Action protectrice des éthers phénoliques au cours de l' intoxication histaminique. *C.R. Soc. Biol.* 124:547-9, 1937. (Cited 175 times since 1945.)
5. Arrang J M, Garbarg M, Lancelot J M, Lecomte J M, Pollard H, Robba M, Schunack W & Schwartz J C. Highly potent and selective ligands for histamine H_3 receptors. *Nature* 327:117-23, 1987.

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