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This Week's Citation Classic

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.
[Research Inst., Smith Kline & French Labs. Ltd., Welwyn Garden City, Hertfordshire, England]

Data are presented on the chemistry, pharmacology, toxicology, and biochemistry of cimetidine, a histamine H_2-receptor antagonist. Pharmacologically, e.g., as an inhibitor of gastric acid secretion, cimetidine is similar to the previously described metiamide, but in toxicity studies with cimetidine, no haematological changes or renal damage were observed. [The *SCI*® indicates that this paper has been cited over 260 times since 1975.]

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"The main pharmacological actions of histamine have been recognised since the first two decades of this century.[1] That these actions implied involvement of histamine in inflammatory and allergic reactions led to the search for drugs to antagonise the effects of histamine. Such drugs have been available and widely used clinically for about 40 years, but it soon became apparent that they were not capable of antagonising all the actions of histamine. This led to an idea, promulgated in the 1960s, that histamine exerted its effects through more than one set of pharmacological receptors.[2] This is now an accepted concept—the actions of histamine which can be antagonised by classical antihistamines are mediated through H_1 receptors, and other effects, including stimulation of gastric acid secretion, are mediated through H_2 receptors. The proof of the existence of H_2 receptors resulted from the discovery, in the UK laboratories of Smith Kline & French, of specific antagonists of histamine at these receptors.

"The first of these drugs, burimamide, was tested in human subjects, but was not sufficiently active by the oral route to be developed as a medicine. Its successor, metiamide, was also tested in healthy human subjects and, additionally, in extensive clinical trials in which it proved an effective agent in promoting the healing of duodenal ulcers. However, a reversible granulocytopenia, seen occasionally in dogs in toxicity studies, eventually manifested itself in a very low proportion of the treated subjects.

"This led to the search for a compound with essentially the same pharmacological profile as metiamide, but lacking the propensity for producing this undesirable effect. In cimetidine, the thiourea group of metiamide was replaced by a cyanoguanidine group with consequent elimination of the haematological side effect. Cimetidine has now been marketed in over 100 countries, has been used in over 11,000,000 patients, and is a highly effective agent in the treatment of peptic ulcer disease and other diseases associated with gastric hypersecretion.

"As well as proving to be a revolutionary new therapeutic agent in terms of clinical efficacy and marketing success, cimetidine has also proved to be a major new tool for studying the physiology, pharmacology, and pathology of histamine. These are the reasons for the high number of citations to the publication.

"The work to search for histamine H_2-receptor antagonists began at Smith Kline & French in 1964. The first publication, on burimamide, appeared in 1972,[3] and cimetidine was first marketed in 1976. Thus, 12 years elapsed during which hundreds of compounds were synthesized and tested, many scientists were involved in various aspects of research and development, and much money was spent.

"Individual authors of this paper and others connected with the research program have received a variety of awards for their work and in 1978 the Smith Kline & French research laboratories in the UK were granted the Queen's Award for Technological Achievement in recognition of this discovery. A book reporting recent work in this field has been published."[4]

1. **Douglas W W.** Histamine and antihistamines; 5-hydroxytryptamine and antagonists. (Goodman L S & Gilman A. eds.) *The pharmacological basis of therapeutics.* New York: Macmillan, 1975. p. 590-629.
2. **Ash A S F & Schild H O.** Receptors mediating some actions of histamine. *Brit. J. Pharmacol.* 27:427-39, 1966.
3. **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.
4. **Torsoli A, Lucchelli P E & Brimblecombe R W, eds.** *Further experience with H_2-receptor antagonists in peptic ulcer disease and progress in histamine research.* Amsterdam: Excerpta Medica, 1980. 370 p.