Tagamet: The Discovery of Histamine H_2 -receptor Antagonists

International Historic Chemical Landmark

Dedicated November 24, 1997, in Harlow, UK, and February 27, 1998, in King of Prussia, Pennsylvania, USA, at Smith Kline & French's research facilities (now GlaxoSmithKline).

Commemorative Booklet (PDF)

It's hard to believe that, just 20 years ago, a peptic ulcer could be a life-threatening condition. The discovery of the compound cimetidine (sold under the trademark Tagamet) by researchers at Smith Kline & French in 1970 had a revolutionary impact on the treatment of this common disorder.

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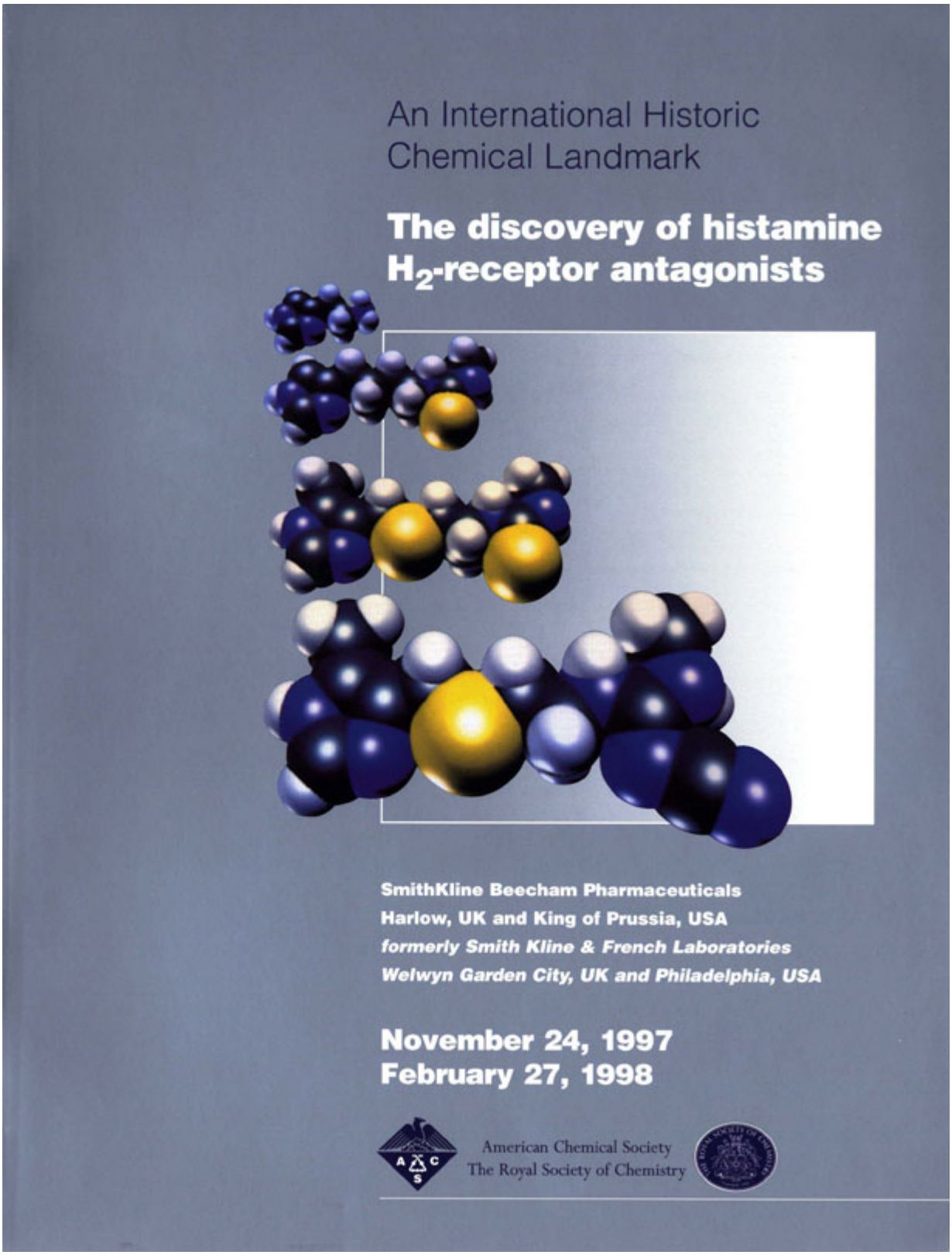

"The discovery of histamine H_2-receptor antagonists" commemorative booklet produced by the National Historic Chemical Landmarks program of the American Chemical Society in 1997.

Tagamet®: A Revolutionary Ulcer Treatment

As late as the 1970s, a peptic ulcer could be a life-threatening condition. Sufferers often endured periods of intense pain over many years, especially at mealtimes and at night, with social and economic repercussions for

A major cause of ulcers is the release of excess stomach acid, which leads to breaches in the lining of the intestinal tract. Continuing acid secretion prevents healing. The main treatment used to be the administration of alkalis, which provided only temporary relief. Patients were told to rest and follow a bland diet. Surgery to remove part of the stomach was a last resort.

The discovery of the compound cimetidine by researchers at the UK laboratories of Smith Kline & French in the 1970s, transformed the lives of millions of people. Sold under the trademark Tagamet®, it was the first effective anti-ulcer drug and had a revolutionary impact on treatment. Tagamet® profoundly decreases acid secretion, thus promoting healing and avoiding the need for surgery.

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New Era of Logical Drug Design

The research program leading to cimetidine also represented a revolution in the way pharmaceuticals are developed. Traditionally, the development of a new drug would often depend on the fortuitous discovery of a plant or microbial extract that showed some of the required biological activity. Using that first extract as a lead, many similar compounds would be made and tested for pharmacological effectiveness. In many cases, the researchers did not know how the drug worked, so finding an optimal compound was difficult.

The development of cimetidine was radically different: It was one of the first drugs to be designed logically from first principles. Smith Kline & French's multidisciplinary research team first looked at the physiological cause of acid secretion. They confirmed that a molecule found in the body called histamine triggers the release of acid when it binds to a specific receptor (now called the H_2-receptor) in the stomach lining. Their aim was to find a molecule that successfully competed with histamine in combining with the receptor, but then blocked, rather than stimulated, acid release. Such a molecule was called a histamine H_2-receptor antagonist and represented a new class of drugs.

Using a step by step analysis of structural and physical properties, the team made a series of histamine-based molecules, which were then tested for antagonist activity using carefully designed pharmacological assays. Today, this approach of rational drug design underpins the discovery programs of many major pharmaceutical companies.

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Discovery of Histamine H_2-receptor Antagonists

The discovery of histamine H_2-antagonists is a story of single-minded commitment by a group of creative scientists working in close collaboration in the United Kingdom. The process of research and development for economical production of the resulting drug, cimetidine, was the work of equally creative scientists working in the United States.

Discovery of H_2-receptor Antagonists

In 1963 George Paget, a pathologist from ICI (Imperial Chemical Industries), joined Smith Kline & French to head its R&D laboratories at Welwyn Garden City in the United Kingdom. He soon recruited two colleagues: James Black as head of pharmacology and William Duncan as head of biochemistry.

Black had been instrumental in developing beta-blocker drugs for the treatment of heart disease. They were based on his notion of blocking the stimulating action of a molecule (agonist) at a receptor site implicated in the

disease with a similar but inactive chemical (antagonist). He was keen to start a new research program looking at histamine receptors and antagonists.

Histamine is found throughout body tissues and is released during allergic reactions such as hay fever. It also stimulates acid secretion in the stomach and increases the heart rate. However, tests with antihistamines had indicated there were possibly two types of histamine (H) receptor, one of which did not respond to antihistamines. Black wanted to establish the existence of the latter receptor and to find histamine antagonists that selectively inhibited acid secretion. Since this work promised to lead to an effective anti-ulcer medicine, the company started an acid secretion program in 1964.

Chemists Graham Durant, Robin Ganellin, and John Emmett joined Black on the project together with Mike Parsons, a pharmacologist. Their aim was to make chemical variants of histamine and test them for antagonism using a combination of in vitro and in vivo assays.

A New Receptor

The histamine molecule has a ringlike structure with a short side chain attached. Black's first idea was to alter the ring by tacking on chemical groups. Although no antagonists were found, it did produce an agonist called 4-methylhistamine, which stimulated acid secretion without any of the other histamine responses. This proved the existence of a second receptor, thus establishing a clear target for drug research. The project was then renamed the H_2-receptor program.

However, finding and synthesizing potential histamine antagonists turned out to be more difficult than expected. By 1968, of the 200-odd compounds made, none had shown any activity in the assays. Fortunately, Parsons recognized that modifying the assays would increase their sensitivity. The team then retested a compound Durant had made earlier and found that it showed partial antagonism.

Tagamet®: A Revolutionary Treatment

Durant's compound became the lead, and after two years of hard work, an active antagonist called burimamide was produced. Burimamide was not orally active and so a new analogue, metiamide, which was orally active and ten times more potent, replaced it. The results of clinical trials with metiamide begun in 1973 were impressive: ulcers were healed within three weeks. Unfortunately, metiamide gave rise to a blood disorder called agranulocytosis as a side effect of treatment. This had been anticipated as a possibility, so as an insurance policy, the team prepared a similar compound replacing the thiourea group with a cyanoguanidine moiety.

The new lead compound, cimetidine, passed every test with flying colors and in November 1976 was launched as Tagamet® (derived from the anTAGonist and ciMETidine). Tagamet® was greeted with great enthusiasm by doctors and patients alike. Ten years after its introduction, it had achieved sales of one billion dollars and had become the world's number one prescription drug.

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Producing Tagamet®

With the spectacular success of Tagamet®, it became very important to discover an economic process to make cimetidine. The production volume was expected to reach 1,000 tons a year - a large amount by pharmaceutical standards.

Process Patent Protection for Tagamet®

The initial process used to prepare cimetidine, while adequate for initial supplies, involved a bottleneck step which required the reduction of an imidazole ester intermediate using lithium aluminum hydride (LAH). The LAH process was difficult and expensive to operate and was threatened by a shortage of LAH supplies. Because of the high dose of cimetidine, cost reductions were essential to make the revolutionary new drug successful in the market. Since cimetidine was anticipated to be a worldwide success, it also would require patent protection around the world, including countries that offered process patent protection only.

To address these issues, Charles Berkoff and Elvin Anderson established a process research effort at the Smith Kline & French research and development facilities in Philadelphia aimed at finding cost-effective, practical, and patentable routes for synthesizing cimetidine. Groups headed by George Wellman and Lee Webb were among the first in the industry to emphasize the search for new synthetic methods instead of optimization of existing processes.

The initial objective was to find alternative routes to an alcohol intermediate. A number of alternate methods of preparing the alcohol were devised and patented, and the most cost-effective method, using sodium in liquid ammonia for the reduction of the ester, was finally implemented. This cleaner, less expensive pathway helped cut tens of millions of dollars per year from the manufacturing cost. Many of the other innovative methods of preparing cimetidine also provided process patent protection and therefore enhanced exclusivity in countries around the globe. This process patent strategy was especially important in Japan, where it was not possible to protect the product any other way.

A Better Manufacturing Process

Manufacturing of cimetidine was begun at Cork, Ireland, where production increased from approximately 18 metric tons in 1976 to about 1,000 metric tons by 1982. This dramatic increase in production demand led to further streamlining and perfection of the process. Low-cost cysteamine equivalents were implemented, and the alcohol was eventually acquired from a company that had developed a new manufacturing method employing a hydroxymethylation reaction. The number of operational steps was reduced and the throughput was dramatically improved so that the hundreds of tons of drug substance could be manufactured economically and in an environmentally friendly manner.

Just as the discovery of cimetidine is a landmark in logical drug design, so the discovery and development of efficient synthetic routes to cimetidine is a landmark in process research and development.

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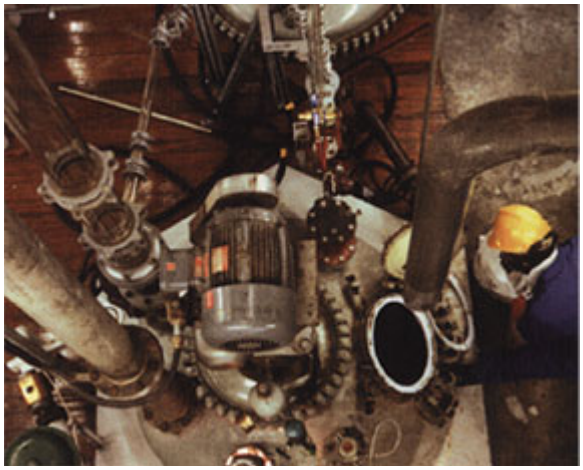

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