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The Development of Cimetidine: 1964–1976

A Human Story

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There was still controversy regarding the physiology of acid secretion in 1964 when a team at Smith Kline & French Laboratories in England started a project to prove the existence of more than one receptor for histamine and to find a substance capable of blocking the effects not blocked by the commonly used antihistamines. The team was convinced that histamine was the final mediator of acid secretion. After 8 years, James Black and his coworkers published evidence of the first histamine$_2$-receptor antagonist, burimamide. As this substance was not suitable for oral therapy, the research continued. Metiamide was synthesized with promising clinical effects but questionable safety. The final answer was cimetidine (Tagamet), approved in England in November 1976. Cimetidine was a breakthrough in the treatment of peptic ulcers. In this article I focus on the human factors lying behind many of the decisions made during the years of research. Without personal courage under stressful conditions, the H_2-receptor antagonists might never have reached the market.

Key Words: H_2-receptor antagonist—Cimetidine—Acid secretion—Research and development—Human factors—Decision-making.

Significant breakthroughs in medical treatment were scarce when the research for an H_2-receptor antagonist started in 1964. At that time, important advances in drug treatment occurred not more than once a decade; antibiotics, antihistamines, and β blockers were introduced at different periods. During the 1980s, cimetidine (Tagamet) transformed the therapy of peptic ulcer.

Numerous articles have described the chemical and pharmacological development of cimetidine. A story of human thinking and decision-making also exists. I will try to tell this story from a personal angle. Decisions were not always made during meetings with management, but often in haste or involving disagreements between directors. What happened inside the company during the research phase? What decisions and what findings became crucial?

Smith Kline & French (SK&F), an American drug company with its head office in Philadelphia, had expanded and opened a new research institute in Welwyn Garden City north of London in 1959. However, no new drugs were discovered during the following 4 years, and it was evident that the institute needed new management and new ideas. In 1963, George Paget, a pathologist and then Head of the Toxicology Department at Imperial Chemical Industries Pharmaceuticals (ICI), became Head of the Department for Research and Development in Welwyn. Two of Paget's former colleagues at ICI joined SK&F: William Duncan as Head of the Biochemistry Division and James Black as Head of Pharmacology. Black and Paget had worked very closely together at ICI when Black's discovery of the β-adrenergic receptor agents was made. The first drug, propranolol (Inderal), had been introduced and Black was eager to start a new project on receptor pharmacology. Analysis of the action of propranolol in a number of tissues highlighted a parallel case: that of histamine and its various effects. Black wanted to investigate the existence of a second histamine receptor and to find a histamine analog blocking only this receptor. Black never doubted that he would eventually succeed; in the end, he was right.

I was employed at SK&F when the company was established in Scandinavia in 1977. From 1979 on, medical information became my main duty until I retired in 1991. During those years I had the opportunity to liaise with people inside the company as well as with internationally known gastroenterologists. My observations are based on careful studies of published literature, on personal interviews,

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and on my access to internal reports, which made it possible to present material previously not published.

HISTAMINE AND ACID SECRETION

> Histamine has done a lot for a lot of people, including me.—Charles Code (1)

When the histamine project started there was no consensus regarding the physiological role of histamine in acid secretion. No one had yet proven the existence of receptors for histamine on the parietal cells. In 1938 MacIntosh (2) had discovered that small amounts of histamine were present in the gastric juice of dogs after stimulation of the vagus nerve and proposed that histamine was produced by cells in the gastric mucosa. Almost 20 years later, Code (3) referred to the MacIntosh and other studies when he wrote that "Stimulation of gastric secretion is a function of histamine. No other chemostimulator is interposed between histamine and the parietal cell. Histamine is the final common local chemostimulator of the parietal cell of the gastric mucosa." Some 10 years later, Code (4) ended a review paper with the following: "Conclusion 1965: Stimulation of gastric secretion is a physiologic function of histamine."

THE FIRST HISTAMINE H_2-RECEPTOR ANTAGONIST, BURIMAMIDE

In 1948 Folkow and co-workers (5) investigated the vasodilating effect of histamine in the hind leg of cats and dogs and showed that the increasing effect of higher doses was only partially inhibited by the antihistamines used to treat allergic conditions. This finding could be explained by the presence of at least two types of histamine receptors. In 1966 Ash and Schild (6) investigated the agonistic effect of different histamine analogs on rat stomach and uterus and guinea pig ileum and attempted to block these effects. They concluded that "The relative activities of several histamine analogues support the differentiation of histamine into at least two classes."

At SK&F, Black worked closely with chemists Robin Ganellin and Graham Durant. They established test procedures for the effects of histamine on the "non-H_1" receptors, including isolated pieces of rat uterine horn and guinea pig right atrium and gastric acid secretion in the anesthetized rat (7).

Great optimism prevailed at the outset of the program. The researchers said, "It won't take long and it won't need too many chemists involved." However, it soon became evident that the project was very complex and a new specialist, pharmacologist Mike Parsons, was added to the team. There was a stimulating cooperation among experts in chemistry, biology and pharmacology.

The team's objectives were to prove that histamine acted by different receptors, that it was possible to inhibit the stimulation of acid secretion of histamine by antagonizing selected receptors, that blocking these would lead to decreased gastric acid secretion, and that the decrease of acid secretion would be a tool in the medical treatment of hypersecretory states such as peptic ulcer.

The search for an antagonist was based on the same thought process that had led to the first β-adrenergic blocking compound: modification of the agonist to produce a substance that was chemically similar but lacked the stimulating effect. Attempting to change the ring structure of histamine yet leaving the side chain intact did not give rise to any significant antagonists (8–10). Many hundreds of substances with altered side chains were then synthesized, but none acted as a competitive non-H_1 antagonist.

At the head office of SK&F in Philadelphia, management faced considerable financial problems. Despite large investments since 1959, no products of significance had come out of either Welwyn or Philadelphia. By 1967, enormous pressure was placed on all departments. At that time gastrointestinal research programs were being conducted both in Philadelphia and Welwyn. In Philadelphia acid secretion inhibition and antispasmodic compounds were studied. Naturally, competition arose between the two centers. As nothing useful emerged from Welwyn after more than 4 years after the reorganization, Philadelphia put the pressure on to show results. Since the Philadelphia program was considered more advanced, with a better margin for success, Duncan, now Director of Research and Development in Welwyn, was told to stop the acid secretion program in Welwyn. Duncan acted as a shield between the head office in Philadelphia and the Research Department in Welwyn and instead of stopping the program, he changed the name of the Welwyn effort to "H_2-receptor program." The main goal in Welwyn was not only to find a new drug for treatment of peptic ulcer, but also to describe the different effects of histamine and the blockade of H_2 receptors in other conditions. At a joint meeting between task forces of the United States and England in Welwyn in 1969, Leon Greene, who later became Vice President of Worldwide Development, was impressed by the work going on in Welwyn, and the antispasmodic project in Philadelphia was terminated. Greene and Duncan worked

together with great mutual respect, not always agreeing but never forgetting their ultimate objective of an new product.

Peptic ulcer disease was mentioned for the first time in SK&F's annual report in 1969, which said that SK&F was planning to market a new long-acting antacid and was also screening for "a unique oral drug that would prevent the secretion of excess acid without affecting the autonomic nervous system."

A contrary opinion about the role of histamine in gastric acid secretion was expressed by Johnson (11) in 1971 when he stated that histamine had nothing to do with the direct stimulation of acid secretion. This created concern in the SK&F head office in Philadelphia among those who still had doubts about the ongoing project in Welwyn. However, an increasing number of publications supported Black's theory on the role of histamine in the stimulation of gastric acid secretion, encouraging the team in Welwyn to go on with their research.

Durant was on the right track by 1964 when he investigated compound SK&F 71448 (Fig. 1), which acted as an agonist, stimulating acid secretion. However, the compound, a guanidine analog, was put on the shelf together with hundreds of other substances. Subsequently, Parsons discovered in 1966 (unpublished observation) that because of submaximal histamine stimulation, the partial antagonistic effect of SK&F 71448 had not been detected (12–14). The antagonistic activity was finally seen when the gastric secretion assay was changed to near maximal stimulation with histamine. Chemical work restarted with SK&F 71448, the "lead" compound. Extension of the side chain increased the antagonistic activity, and further work finally produced a compound, burimamide, that lacked the agonistic effect (8–10,12,14) (Fig. 1). Black et al. (7) published "Definition and Antagonism of Histamine H_2-Receptors" in *Nature* in 1972. Even if direct cholinergic stimulation was unaffected, burimamide inhibited acid secretion in dogs after stimulation with histamine, pentagastrin, or food. "This relationship must tip the balance of opinion towards the idea that the actions of gastrin are somehow coupled to those of histamine."

The article generated enormous interest all over the world but was challenged by Johnson (15), who suggested that the actions of gastrin were somehow coupled at the level of the histamine H_2 receptor. Black and Parsons (16) replied, "Since gastrin does not appear to interact with H_2-receptors in heart and uterus, this conclusion does not seem (on present evidence) to be particularly helpful."

New budgetary constraints were proposed, but

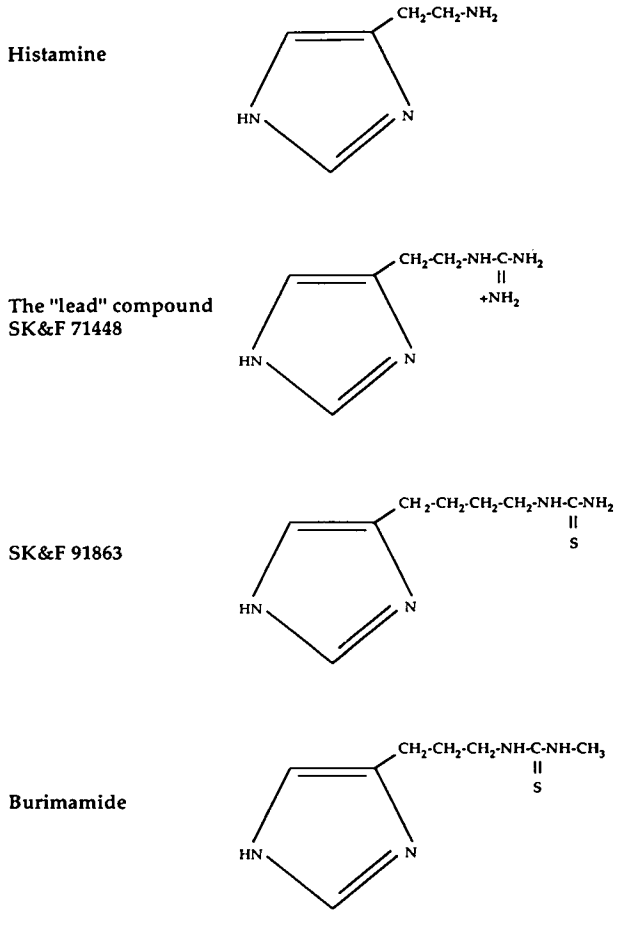

FIG. 1. The molecular structure of histamine and its chemical modifications into burimamide.

Duncan, convinced that they were on the right track, terminated as many of the other programs as possible to continue support for the H_2 project. The annual report of SK&F in 1972 mentioned a new drug showing early promise that "blocks the effect of histamine not antagonised by traditional antihistamines and is called an H_2-receptor antagonist . . . this discovery may provide a new step forward in the control of gastric hypersecretion." A patent for burimamide, the first H_2 blocker, was applied for in June 1971; for its successor metiamide, application was made in March 1972.

METIAMIDE

> A new compound, metiamide, has now been developed which has properties suitable for evaluation of the therapeutic potential of histamine H_2 receptor blockade in man, namely, high specific activity, low toxicity and good oral bioavailability.
> Black et al. (17)

Because of lack of absorption, burimamide was unsuitable for oral administration. Structural changes to the compound were tested, and metiamide was

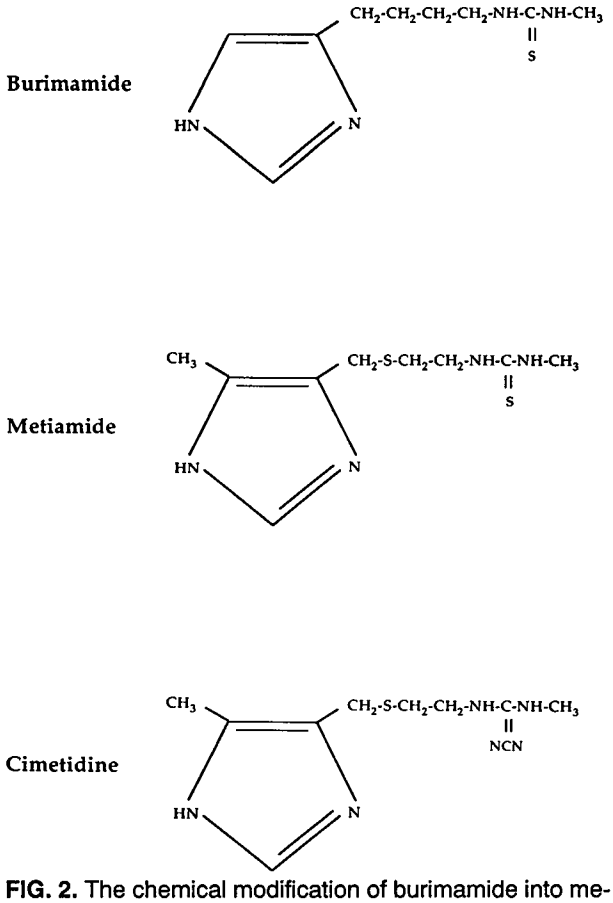

FIG. 2. The chemical modification of burimamide into metiamide and cimetidine.

developed (8–10,14) (Fig. 2). This substance had good oral bioavailability and was 10 times more active than burimamide in vitro in antagonizing histamine H_2 receptors (17). Grossman and Konturek (18) found that metiamide inhibited gastric acid secretion in dogs after stimulation with histamine, pentagastrin 2-deoxyglucose, or food, and they speculated on an interaction between the receptors for gastrin, histamine, and acetylcholine. Parsons (19) showed that metiamide acted as a competitive antagonist of H_2 receptors in the gastric mucosa. Metiamide was five times more active than burimamide in inhibiting histamine or pentagastrin-stimulated acid secretion in humans (17,20,21).

The safety profile seemed initially encouraging (18). An extensive evaluation of the toxicity of metiamide in animals was reported by Roger Brimblecombe et al. (22) at the first symposium on H_2-receptor antagonists in 1973. Very high doses (60–100 times ED_{50}) given for up to 3 months caused kidney damage in rats and dogs and a depression of the white blood cells and neutrophil counts in some dogs. However, doses of up to 20 times ED_{50} were unlikely to produce any unacceptable toxic effect in rats and dogs. Early efficacy data looked good as well. Milton-Thompson and coworkers (23) showed that metiamide inhibited nocturnal acid secretion in duodenal ulcer patients. The clinical effect in healing and in relief of pain in duodenal ulcer patients was demonstrated in controlled trials (24,25). No severe adverse reactions were reported in healthy volunteers or in patients (21,23–25).

INTERNATIONAL SYMPOSIUM ON HISTAMINE H_2-RECEPTOR ANTAGONISTS

> Although we have only scratched the surface of investigating the potential clinical utility of the compounds we are going to discuss, it is my hope that all of us—academic scientists, regulatory authorities, clinicians and we in Smith Kline & French—will benefit from an early discussion of these compounds.
>
> Duncan (26)

The research team at SK&F considered an open discussion among scientists and clinicians to be of great importance for the further development of the H_2-receptor antagonist project. Therefore, an international symposium was arranged in 1973 during an early stage of the research program. Metiamide was presented as the first compound of an entirely new group of drugs. The pharmacological and chemical properties were thoroughly discussed as were findings from numerous studies in animals (9,19,21,22,26,27). The first results showing inhibition of gastric secretion in humans were demonstrated (21), but no information was presented from the limited experience of metiamide in patients. On the second day, Dr. Grossman (27) put this question in his opening remarks: "Regardless of what the mechanism of inhibition is ultimately shown to be, the practical question is: can this class of drugs produce sufficient inhibition of acid secretion to treat ulcers without producing unacceptable side effects?"

Black gave a lecture at the symposium, but he was no longer one of the team in Welwyn. He had accepted an offer from the University of London to become Professor of Pharmacology. Black felt that his main objective, to show different receptors for histamine and the possibility of inhibiting the effect at the H_2 receptors, had been achieved. The final work, to produce a drug, was not his main interest; he preferred continuing research on the physiology of histamine and gastrin, as clearly stated in the subtitle of his 1972 article (7): "A New Group of Drugs That May Help to Unravel the Physiology of Histamine and Gastrin." Dr. Roger Brimblecombe became Black's successor.

In the symposium, SK&F received strong sup-

port from all the participants to continue work with metiamide. However, soon after, a case of agranulocytosis with metiamide use was reported by physicians in Edinburgh and 6 months later a second case occurred (28). All metiamide trials were stopped in England. After careful consideration, top management at SK&F decided to continue with the clinical trials in the United States and South America but with extraordinarily close hematological monitoring. It was of great importance to prove that an H_2-receptor antagonist could not only control acid secretion in patients with peptic ulcers but also increase the healing rate of these ulcers versus placebo.

In the 1973 annual report from SK&F, the H_2-receptor antagonists were described in an extended text as a new class of pharmacological agents, therapeutically important to treat peptic ulcer and other conditions associated with increased acid production.

CIMETIDINE

> Cimetidine is a non-thiourea analog of metiamide.
> Brimblecombe et al. (29)

Since both burimamide and metiamide were thiourea derivates, reports of agranulocytosis were not a complete surprise to the team in Welwyn. Some concern had been intimated in 1971 when a new objective for the Research Institute was established: "to find replacement for metiamide, which does not have the potential disadvantage of containing a thiourea group" (30). The chemists' first step was to substitute the sulfur in the thiourea group with an NH moiety, resulting in a guanidine. Guanidines occur naturally in the human body and should therefore be well-tolerated. To improve the pharmacokinetic properties, new analogs were tested which changed the basicity of the compound (8–10,29,30). The final product, cimetidine, had a cyanoguanidine group instead of a sulfur atom in the side chain (Fig. 2).

The Committee on Safety of Medicines regranted a clinical trial certificate for metiamide in 1974 but only for seriously ill patients. However, Duncan decided to concentrate all efforts on cimetidine and to terminate the metiamide program. The risk that metiamide might be associated with agranulocytosis was too serious. It is an understatement to say that there was not total agreement on this decision! Some of Duncan's colleagues believed that he overreacted (13). A patent application for cimetidine was filed in September of 1973.

Cimetidine was a competitive H_2-receptor antagonist, with 10 times more activity than burimamide in vitro and twice the activity of metiamide in vivo in inhibiting gastric acid secretion (29). Preliminary results showed that in humans cimetidine was at least as effective as metiamide in reducing gastric acid output after stimulation with histamine or pentagastrin (32), insulin (33), or food (34).

Was metiamide's effect on the blood count a consequence of the H_2 blockade or was it an effect of the compound itself? Although no case of decreased granulocytes had been reported with cimetidine in humans, the opportunity to prove that metiamide's effect was not an H_2-receptor effect came in 1975. (The following is a summary of patient record data, kindly supplied by Dr. Duncan Colin-Jones.)

A 40-year-old man had a 7-year history of severe duodenal ulcer disease that led to vomiting and hematemesis in July 1975. In spite of a truncal vagotomy and later emergency surgery, he continued to bleed and vomit and needed several transfusions. On August 20, he collapsed and his condition was critical. A gastrectomy was performed. Histology showed a malignant carcinoid-like tumor under the duodenal mucosa. Postoperatively, he improved but he continued to vomit and aspirate huge amounts of acid fluid; a large gastric ulcer was diagnosed during gastroscopy. A note in his record card says, "We are now trying to acquire a supply of metiamide. Metiamide is cited to reduce acid secretion to allow healing before further surgery."

William Burland, then heading the cimetidine program at SK&F, arranged for a supply of metiamide "to be used as directed." The drug was accompanied by a letter explaining that two patients had earlier developed agranulocytosis on metiamide and that therefore a full blood test was advisable weekly. It was also suggested that hepatic and thyroid function be controlled. On September 5, the treatment started with 250 mg metiamide given at noon. By the next day, a short note in the patient record read, "Condition much improved. I am delighted with the progress." A week later, another note said, "The metiamide is tremendous." The gastric aspirates decreased and his gastric ulcer healed, "a remarkable result." The patient was discharged from the hospital on October 9. Two days earlier, his treatment was discussed and the question of continuing with metiamide was raised. Would it be possible to change to cimetidine? But cimetidine was not easily available yet and he "evidently had no marrow problems."

On November 3, the patient was readmitted to the hospital, very ill. He had been vomiting for 1 week and showed multiple signs of infection (eye, skin, and nose) with complete neutropenia (Table

TABLE 1. *White blood count and hemoglobin values for the patient*

Date	WBC	Hemoglobin	Treatment
November 2	1.8	11.3	Metiamide
November 3	0.7	8.9	Metiamide stopped
November 4	1.5	13.0	Cimetidine i.v.
November 5	2.5	13.7	Cimetidine i.v.
November 6	3.4	13.1	Cimetidine i.v.
November 7	3.7	13.5	Cimetidine i.v.
November 8	5.5	14.4	Cimetidine i.v.
November 9	5.8	15.7	Cimetidine i.v.
November 10	5.0	14.8	Cimetidine i.v.
November 11	10.0	16.0	Oral cimetidine
November 12	9.0	15.1	Oral cimetidine
November 14	10.0	14.7	Patient discharged home

Table based on data from Duncan Colin-Jones (personal communication).

1). Metiamide was stopped. Transfusions were given and a request for cimetidine was made. The next day, treatment with cimetidine, 250 mg i.v., was begun. His condition improved; after 1 week, oral treatment with standard-dose cimetidine, 1 g/day, was initiated. White blood count and hemoglobin normalized (Table 1). On November 14, he was discharged on continuous treatment with cimetidine, 400 mg q.i.d. Seventeen years later, he is still alive and in good health.

The decision to give this patient cimetidine had to be made very quickly and at great risk to all concerned, including SK&F. At this time cimetidine had only recently been administered to patients for the first time. Burland at Welwyn needed okays from Greene and Duncan, who at that time were in the United States to give a lecture on H_2-receptor antagonists. Their agreement came via a telephone call from New Orleans, but it was a tough decision. If the patient had died, it would have been difficult to prove that he died of his underlying disease, and his death would have seriously delayed the development of cimetidine. The idea that blocking H_2 receptors could be toxic to the bone marrow could have lingered on for several years. However, the fact that the agranulocytosis that had developed during treatment with metiamide resolved during treatment with another H_2-receptor antagonist, cimetidine, was good evidence that the agranulocytosis induced by metiamide was not an H_2-receptor effect. The decision to supply the patient with cimetidine was a turning point in the development of the H_2-receptor antagonists.

Whether or not to publish this case was the next difficult decision. Clearly, it was the only positive evidence that the metiamide-induced agranulocytosis was not an H_2-receptor effect. But it also emphasized that a severe reaction could be caused by an H_2-receptor antagonist. The case was published by Burland et al. (35), and it provided great support for the safety of cimetidine. In July 1974, cimetidine was administered for the first time to healthy volunteers. In July 1976, the first controlled trial with positive results in treating patients with severe duodenal ulcer disease was published (36).

The SK&F annual report in 1975 was very positive. The company told of measurable progress both in generating new compounds and in undertaking new programs that might lead to improved therapies in the future. Cimetidine and its brandname Tagamet were mentioned for the first time and a worldwide clinical evaluation program was under way.

THE SECOND INTERNATIONAL SYMPOSIUM ON HISTAMINE H_2-RECEPTOR ANTAGONISTS

> Fortunately my colleagues discovered a successor to metiamide which while sharing the essential pharmacological action of metiamide was without its toxic effects and this compound, cimetidine, is of course the H_2-receptor antagonist which has now been the object of considerable clinical investigation so that a symposium to discuss the clinical properties of an H_2-antagonist is now possible.
>
> Duncan (37)

The first symposium on histamine H_2-receptor antagonists in 1973 dealt exclusively with preclinical work, but the second symposium, which presented cimetidine, was different. Through a series of 18 lectures, the positive effects of cimetidine in various indications were reported. Significantly superior efficacy to placebo in duodenal ulcer patients in four trials and a review of clinical safety in more than 800 patients were presented (38).

The year 1976 became a turning point for SK&F. Tagamet was approved in the United Kingdom on November 8, 1976, and launched later that month. Within 2 years, Tagamet was introduced in the United States and Europe, and gastroenterologists gained access to a new treatment for peptic ulcer disease. The scientific work and the personal spirit that had been necessary to bring the program to a successful conclusion were recognized in many ways and in many countries and were finally honored with the presentation of the Nobel Prize to James Black in 1988.

With the benefit of hindsight, one can see how great the risk of early project termination really was. The scientific research went on for many years without evidence of success. Without the long-standing cooperation between people from different departments in Welwyn and Philadelphia, along with personal belief of the researchers in the hypothesis of different histamine receptors, a successful con-

clusion would never have been reached. Without the personal courage of various people to make decisions in critical situations, the final H_2-receptor antagonist, cimetidine, would never have been synthesized.

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