The Influence of the Pharmaceutical Industry on Medicine, as Exemplified by Proton Pump Inhibitors

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By

Helge L. Waldum

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During my career, I spent 8 years in the far north, Tromsø, where Professor Per Burhol immediately guided me into the field of gastroenterology because, on my very first day, he told me that I should start research on gastrin (January 2, 1974). Since then, I have devoted all of my energy to this field, and I am very grateful because, as I see it, the stomach and gastrin are ideal research areas which may make important contributions to physiology and diseases, particularly with regard to tumorigenesis. Since 1981, I have worked at the University Hospital in Trondheim where Professor Hermod Petersen helped me to establish my research; he also provided excellent clinical facilities. I also spent a year in Paris at the Hôpital Bichat, which was headed by Professor Serge Bonfils, who inspired me to focus on basic science and devote my research to trophic regulation, which later led to my interest in tumorigenesis. I would also like to express my gratitude to the head of my institute, Torstein Baade Rø, for letting me continue as a professor even though I was over 72 years old.

I am grateful to my first wife Christin for teaching me how to behave. Finally, I would like to express my gratitude to my wife, Wilma, for her support, patience and, particularly, her technical help.

My 20 PhD Candidates


Per Martin Kleveland


Arne Sandvik


Eiliv Brenna


Unni Syversen


Anders Angelsen


Ronald Mårvik


Gunnar Qvigstad


Guanglin Cui


Ingunn Bakke


Tom Chr. Martinsen


Reidar Fossmark


Björn Gustafsson


Sveinung Sørhaug


Øyvind Hauso


Karin E. Bakkelund


Constantin S. Jianu


Øystein F. Sørdal


Fatemeh Zeinali


Liv Sagatun


Patricia Mjønes

PREFACE

During my long clinical and scientific career, I have met with a lot of obstruction, which has not appeared to be scientifically based. During my younger years, I was surprised to see how doctors and scientists took the side of the pharmaceutical industry, but over time I have learnt that this is, unfortunately, the usual way.

I have also realized that the pharmaceutical industry is not interested in long-term side effects. This attitude has gained traction by relying solely on "evidence-based medicine", which does not say anything about long-term side effects. Using statements such as "a man is not a rat" suppresses the importance of animal toxicology studies, despite the fact that long-term animal studies are the only way to detect late occurring side effects before they occur in patients.

My experience is based on gastric physiology and gastroenterology, but I feel certain that similar experiences may be gained in other parts of medicine. I hope that this short book will show that the pharmaceutical industry suppresses any discussion on long-term side effects, and that most doctors and scientists within the area are willing to adjust their work to please industrial interests.

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Norwegian University of Science and Technology,
Trondheim, Norway

CHAPTER 1

BACKGROUND

Abstract

My family background, education, and career are described. I also mention the people who have guided me and who I have collaborated with in the field of gastric physiology and pathology. Professor Per G. Burhol in Tromsø guided me into clinical gastroenterology and research. On my first day at work at Tromsø Hospital, he told me that I should study gastrin and I have continued to pursue this area for 45 years. I am very happy with my decision to do so because the stomach is an ideal organ to study because the gastric juice is useful for both animal and human biological studies. Moreover, due to the fact that gastric juice primarily kills microorganisms, apart from Helicobacter pylori, the results are not influenced by infections. Later, I was inspired by Professor Hermod Petersen in Trondheim, and then, in Paris, Professor Serge Bonfils made me consider how gastrin's trophic effects could pave my way into tumor research. Professor Jens Rehfeld helped me establish radioimmunoassays for gastrointestinal hormones, and Professor Rolf Håkanson assisted me in the creation of new methods for studying the regulation of gastric acid secretion. Finally, Sir James Black was a friend and an inspiration. My friendship with him allowed me early access to the gastrin antagonist, netazepide. Black believed that this compound could be his third most important drug following the first β-blocker and the first histamine-2 blocker.

Keywords: animal studies; gastric acid; gastric physiology; gastric pathology; gastrin; inhibitors of gastric acid secretion; isolated rat stomach; long-term side effects; pharmaceutical companies.

I was born in rural Norway one year after the Second World War ended. My father was a worker and my mother, the daughter of a farmer, was a housewife. I have a brother who is six years older than me, who was born at the start of the war in Norway. I was the result of peace and optimism. My parents built a new house on my mother's father's land. We moved into the new house shortly before I was born. I grew up close to my grandparents and their three sons and daughter, who were all unmarried at that time. Moreover, my grandfather's brother and his wife lived at the same farm. They had no children. The small farm where my father grew up was run by my father's brother and sister. I was the only young child among a lot of relatives who adored me.

My grandfather and his brother taught me that a man should be tough and strong and do heavy manual work. Office work was not regarded as real work for a man. At the same time, my parents and relatives were interested in politics, and in the late evenings I remember sitting on my father's lap listening to parliamentary debates on the radio. I was cared for by all my relatives as I was the youngest child. For instance, my grandfather's childless brother would not wake me up if I fell asleep on his lap. He would wait until I woke up before he started his work on the farm. This meant that I had a lot of self-confidence during my early childhood. However, I was not spoiled, and I knew that I needed to excel to reach my goals. Fortunately, I was good at both sport and schoolwork. My elder brother let me play sport with him and his friends. I had a talent for soccer and cross-country skiing, which are the most important sports in Norway. Now I joke that if I was still young then I would play soccer instead of being a doctor. Mathematics was my favorite subject at school, along with history and related subjects. My interests were helped by the discussions I was having at home.

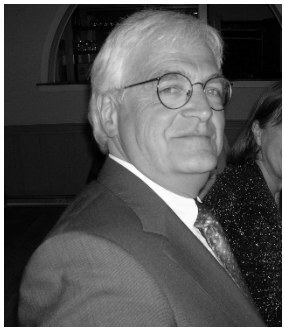
At school, I was always among the best pupils at each level. I moved to the small town of Steinkjer at sixteen years old. Moving away from home was perhaps good for my professional career, but harmful for my sporting activities. After three years, I passed my exams, but I did not get top marks in my favorite subjects, mathematics and physics, despite having the correct answers. However, I received top marks in English, which was never one of my best subjects. I received the marks required to study medicine at the University of Oslo. During my six years in Oslo, I met my first wife and had my first child. Every time I moved to another school, I thought that I would meet students who were brighter than me. However, I continued to excel and when I was in Oslo passed a degree with such good marks that it was reported to the King. This was based on hard work and the fact that I never left anything without understanding it. If there was something I did not

understand, I would attempt to make my own hypothesis. I enjoyed working as a young doctor at the hospital in Molde and as general practitioner in the community. However, I wanted to work in a hospital, preferably performing a combination of clinical work and research.

Professor Per G. Burhol
(Photo: private)

After a short stay in Oslo, I moved to Tromsø where a new university had just been established, which had plenty of money but needed devoted people. Some months before my arrival in Tromsø, Professor Per G. Burhol had become the head of gastroenterology (Burhol et al. 1982) He had seen my good marks at the University of Oslo and immediately offered me a position in gastroenterology, which combined clinical work and research. He said that I should start researching gastrin, and so I went to Copenhagen to learn about gastrin radioimmunoassay from Professor Jens F. Rehfeld (Rehfeld 1973).

This went well and after six years I was a specialist in internal medicine with a subspecialty in gastroenterology and had made research sufficient to become a professor. I then became the Head of the Department during my last year in Tromsø. Here, I learned the value of frank discussions and openness, particularly from Professor Arne Nordøy (von Houwelingen et al. 1987).



Professor Jens F. Rehfeld
(Photo: private)

Coming from a farming family, I felt that the soil in Tromsø was too barren, and so I moved Trondheim in the middle of Norway, which is close to the valley where I grew up. Since then, I have lived in Trondheim, apart from one sabbatical year in Paris in 1987–88. I chose France because I had been Francophile since my childhood when I listened to the dramatic events that took place during the fifties on

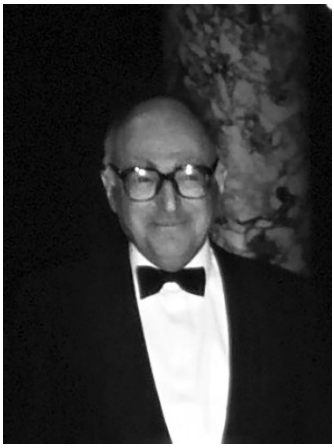
the radio. I enjoyed the warm and long summer in Paris but felt that the winter was a little dull compared with the snow in Norway.

In Paris, I worked at Hôpital Bichat, which was led by the "King" of French gastroenterology, Professor Serge Bonfils (Bonfils, Mignon, and Accary 1975). While I was there, I fulfilled a course in basic science with a focus on the gastrointestinal tract. It included two written and two oral examinations and, once you had passed these tests, you could start your thesis. This course not only benefitted me scientifically, but it also enabled me to learn the language. I also realized during a discussion in one of the oral examinations that I had to study not only the physiological role of gastrin with respect to gastric acid secretion, but also gastrin's role in the regulation of the growth and development of tumors. These subjects became my main interests, and the quarrel I had with Bonfils during my examination was later a great help.

Professor Hermod Petersen
(Photo: private)

When I came from Tromsø to Trondheim, I immediately received support from Professor Hermod Petersen (Petersen 1969), who made me a senior consultant and then later a professor. I was given my professorship by the King, which made me an officer of the Crown. However, not long after this, professors lost that title. Together with my first candidate, Professor Per M. Kleveland; an eminent pediatric surgeon, Stein Haugen; and Arne Sandvik we established the completely isolated rat stomach model, and made it produce acid (Kleveland et al. 1986). This breakthrough in gastric physiology was partly due to a membrane oxygenator, which was produced by the Department of Technology at our university. Soon afterwards, we came across the first reliable method to determine histamine concentrations. We applied this method on blood from the stomach and, in doing so, we were able to study the effects of substances added to the arterial side on gastric acid secretion, as well as the release of signal substances to the blood.

Our manuscripts based upon these new methods were turned down, and even met with hostility, which of course was a great disappointment. However, I have come to learn that the most popular manuscripts are the ones that support the view of certain influential "gurus" within the field. New findings, even if they are supported experimentally, tend to be discarded. It has been especially problematic to have studies accepted within pathology that cast doubt upon current tumor classifications. I went into pathology after my stay in France, as I was interested in the tumors that occur in rodents after the long-term inhibition of gastric acid secretion.



Dr. Kenneth Wormsley
(Photo: private)

It seemed curious to me that animal studies should have no impact on the clinical use of these types of drugs considering that humans and rats are more than 90% genetically identical.

The British doctor, Kenneth Wormsley, stated that omeprazole (the first proton pump inhibitor) is the first compound that has been accepted for clinical use after inducing cancer in its target organ in animal studies (Penston and Wormsley 1992). Therefore, the acceptance of omeprazole for clinical use broke a taboo.

Omeprazole was initially only used for severe ulcer disease, but gradually PPIs are now among the most frequently used drugs, and they are even regarded to be so harmless that they are able to be sold over the counter.

Despite the limited financial support locally, nationally, and from the European Union, we have been able to continue our research based on our knowledge of physiology and pathology using our patients and the local infrastructure. My collaborators' dedication has made it possible to perform research of a high standard with little money. It has been satisfying to see how many of our results, which were heavily disputed when first presented, are now gradually becoming accepted.

During all of these years of research within the same field, I have met a lot of resistance but I have also lived a good life. Medicine and science have taken me all over the world, and I have met some very interesting people. I got to know Nobel Laureate Sir James Black (Black et al. 1972), who even at his late age came to my 60th birthday party. He was a very nice man, and we liked each other. We often sat together sipping whiskey. He was the first to understand how to make new drugs by slightly changing the natural ligand so that it binds to, but does not elicit a response from, the actual receptor. This idea enabled him to make the first β-blocker propranolol and then, 7 years later, the first histamine-2 blocker, cimetidine.

Nobel Laureate Sir James Black (Photo: private)

I would also like to mention Professor Irvin Modlin from Yale (Modlin, Bloom, and Mitchell 1979). I have known him for at least 20 years. He has sometimes supported me and sometimes turned me down, but he is the only American that has included me.

Professor Irvin Modlin with my wife (Photo: private)

When I started in medicine and science, I thought that colleagues supported each other. I was sad to realize that most people choose money over their colleagues. Over time I have learned to accept this. However,

I have often noticed rich but sad scientists because joy in science depends on freedom. Throughout my long career, I have seen how pharmaceutical companies control my field of medicine, and I suppose that it is similar in other areas. Few have had the opportunity to work and stay

at the top of a very competitive area and I am very grateful that I was able to experience this.

I hope that the reader finds this book interesting. My experience is that evidence-based medicine, which is now so popular that it has become a mantra, is only studied for a short time, despite the fact that long-term side effects are possible. Animal toxicity studies should be given much more consideration than they are currently granted. Also, when toxic changes occur, the onus should be on the drug producer to convincingly demonstrate that there are qualitative differences between animals and man, which make animal experiments irrelevant.

It is a sad fact that directors and shareholders have received payments long before late but foreseen side effects are recognized. Throughout my career, the pharmaceutical industry has tried to stop me in different ways on various occasions. My experience is in gastroenterology, but I suppose it is the same in other areas of medicine. I hope that my experiences will be of general interest to the medical community, administrators, patients, and the general population.

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CHAPTER 2

GASTRIC JUICE AND ITS FUNCTION

Abstract

Gastric juice is a unique combination of a strong acid and active enzymes for the degradation of proteins (pepsin) and fat (lipase). This allows it to perform its main function of killing swallowed microorganisms. The production of acid in the upper part of the gastrointestinal tract was developed in primitive fish and this process has been preserved during evolution. Gastric acidity is tightly regulated by nerves (vagal nerves) and hormones (gastrin). Symptoms from the upper gastrointestinal tract are often accompanied by gastric acidic reflux. Therefore, patients, as well as doctors, have been interested in the regulation of gastric acid secretion. This process was among the first to be studied by Pavlov, who was famous for using experimental animal physiology (Pavlov 1902), demonstrating the importance of the vagal nerves. In the same period the hormonal concept was introduced (Bayliss & Starling, 1903). Shortly afterwards, Edkins (1906) postulated the presence of gastrin, which is produced by the G cell in the antral mucosa and released by proteins and the reduction of gastric acidity, reaches the acid production oxyntic mucosa via the blood. In 1920, Popielski showed that histamine was an efficient stimulator of acid secretion, which led to the discovery of the three principal gastric acid secretagogues: acetylcholine, gastrin, and histamine. However, their interaction, as well as the histamine-producing cell's part in the regulation, was disputed for decades. Gregory and Tracy purified and sequenced gastrin, while Berglindh and Öbrink developed the radioactive aminopyrine method to assess gastric acid secretion in isolated oxyntic glands and parietal cells. They showed that in contrast to histamine or a cholinergic agent, gastrin had no direct effect on rabbit glands or parietal cells. However, Soll's demonstration of gastrin's faint and inconsistent effect on similar canine preparations was given more credibility. We were able to unequivocally show that the gastrin receptor was on the histamine producing ECL cell and not on the parietal cell using an isolated rat's stomach.

In the middle of the eighties, Marshall and Warren showed that Helicobacter pylori caused chronic gastritis and peptic ulcer disease, which changed the focus on upper gastrointestinal diseases.

Keywords: acetylcholine; acid; ECL cell; function of gastrin; gastrin receptor; gastritis; Helicobacter pylori; histamine; parietal cell; peptic ulcer disease; regulation of gastric acid secretion.

The regulation of gastric acid secretion

In many ways, modern physiology began by studying the regulation of acid secretion, which reflects the significant interest that both clinicians and the general public have in gastric acidity.

Beaumont studied the regulation of gastric acid secretion in detail in a patient, who suffered from a gastric fistula, which was secondary to a shot accident, in the first half of the nineteenth century (Beaumont 1833). This single patient allowed him to perform studies and obtain results, which were later confirmed.

At the turn of the century, Bayliss and Starling (Bayliss and Starling 1903) created the hormone concept based upon studies centred on the secretion of water and bicarbonate from a denervated pancreas (secretin) and, a few years later, Edkins (1906) postulated the presence of a hormone which regulates gastric acidity produced in the stomach's antral mucosa (gastrin) (Edkins 1906). During the same period, in St. Petersburg, Pavlov started to use live animals (dogs) in his physiological research, which showed the importance of the vagal nerves in the stimulation of gastric acid secretion (Pavlov 1902).

More than a decade later, Popielski stated that histamine, a signal substance present in primitive animals as well as plants, also stimulated gastric acid secretion (Popielski 1920). Therefore, the three principal stimulators (secretagogues) of gastric acid secretion have been known for nearly a century. Their interactions were, however, disputed for more than fifty years.

Another disputed topic was the histamine-producing cell, which takes part in the regulation of gastric acid secretion. For a long time, the mast cell was the only cell in the acid producing gastric mucosa shown to produce histamine; this means it was thought to be the histamine source for the regulation of acid secretion. However, the mast cell has no fixed position

with respect to the acid producing parietal cell, which would usually be expected for a regulatory cell.

In the late sixties in Lund, Håkanson described that a neuroendocrine rodent cell in gastric acid secreting mucosa also produced histamine. Due to the fact that it resembled the serotonin producing cell in the small intestine (the enterochromaffin cell) he named it the enterochromaffin-like cell (ECL) (Hakanson and Owman 1967).

During the same period in Lund, Kahlsson showed that meals and gastrin, which had recently been purified, sequenced, and synthesized by Gregory and Tracy (Gregory and Tracy 1961), released histamine and stimulated histamine synthesis in rodents (Kahlson et al. 1964). Nevertheless, American researchers believed that the mast cell produced the histamine and thus had a central role in the regulation of acid secretion in man.

Professor Rolf Håkansson
(Photo: private)

Even after the Swedes, Berglindh et al. (Berglindh, Helander, and Obrink 1976) developed their method to study acid secretion in isolated glands and parietal cells via the accumulation of radioactively-labelled aminopyrine in the acid compartment and found no effect from gastrin, most scientists still believed that it had a direct stimulatory effect on the parietal cell. In fact, as late as 1997, the scientific community had not realized the physiological, and therefore the clinical, consequences of this new understanding of the regulation of gastric acid secretion.

Based upon our experiments on isolated rat stomach it was evident that gastrin works by releasing histamine from the ECL cell (Sandvik and Waldum 1991), and that the magnitude of the histamine release was a restrictive factor in gastrin stimulated acid secretion (Waldum, Lehy, et al. 1991). However, cholinergic stimulation was due to a direct effect on the parietal cell (Kleveland, Waldum, and Larsson 1987). Therefore, gastrin stimulated acid secretion does not give the maximum acid secretion. We explored this by combining gastrin stimulation with controlled (glucose clamp) hypoglycaemia through the stimulus of the vagal nerves, and we

found, as expected, that the combined stimulation exceeded the effect from pentagastrin stimulation (Qvigstad et al. 1999). This study was also met with negativity and its findings were denied despite their accuracy.

Acid related diseases

It is well-known that gastric acid plays a central role in the pathogenesis of peptic ulcer disease. Therefore, before drugs became available, surgical methods were used to reduce acid secretion. These procedures could be debilitating and even lethal. Acid secretion could be reduced by removing the antrum of the stomach, which is where most of the gastrin producing G cells are located, or by removing the vagal nerves of the oxyntic mucosa (which is also called the parietal cell vagotomy). These operations are now rare because we have efficient drugs that are able to reduce gastric acid secretion. In addition, Marshall and Warren have proved that peptic ulcers are caused by Helicobacter pylori (Marshall and Warren 1984), which can be treated with antibiotics.

Besides peptic ulcer disease, gastric acid has a dominating role in the pathogenesis of gastro-oesophageal reflux disease (GERD). The oesophagus mucosa cannot withstand exposure to acidic gastric juice for a long time. Reflux does not only cause pain, but it also leads to inflammation with ulceration, which may cause fibrosis and stricture when it heals and, in the long-term, even predispose the sufferer to the risk of cancer. There has been a peculiar increase in GERD (Richter and Rubenstein 2018), which may be due to a reduction in the occurrence of Helicobacter pylori gastritis with reduced acid secretory capacity, or due to rebound acid hypersecretion secondary to the use of potent acid secretion inhibitors (Waldum et al. 1996). Furthermore, the increased numbers of overweight people have also probably contributed to the increased occurrence of GERD. The frequent

Nobel Prize Laureates Warren and Marshall
(Photo: By permission of the University of Western Australia)

occurrence of GERD has contributed to an increased usage of acid secretion inhibitors. The most efficient are proton pump inhibitors (PPIs), which are available over the counter. Therefore, many people have to live without normal functioning gastric juices, which may have long-term consequences.

Gastric juice is a unique combination of a strong acid and active enzymes, which degrade proteins (pepsin) and fat (lipase); however, its main function is killing swallowed microorganisms (Martinsen, Bergh, and Waldum 2005). The production of acid in the upper part of the gastrointestinal tract was first developed in primitive fish and this process has been preserved during evolution. Individually, gastric acidity is tightly regulated by the nerves (vagal nerves) and hormones (gastrin). Symptoms from the upper gastrointestinal tract are often accompanied by gastric acidic reflux. Therefore, patients as well as doctors have been interested in the regulation of gastric acid secretion. This process was among the first to be studied by Pavlov, who was famous for using experimental animal physiology (Pavlov 1902).demonstrating the important role of the vagal nerves. At the same time period Bayliss and Starling established the hormonal concept (Bayliss and Starling 1903), and Edkins postulated the presence of gastrin (Edkins 1906). Gastrin is produced by the G cell in the antral mucosa and released by proteins and the reduction of gastric acidity, reaches the acid production oxyntic mucosa via the blood. In 1920, Popielski showed that histamine was an efficient stimulator of acid secretion (Popielski 1920), which lead to the discovery of the three principal gastric acid secretagogues: acetylcholine, gastrin, and histamine. However, this interaction, as well as the histamine-producing cell's part in the regulation, was disputed for decades. Using the radioactive aminopyrine method to assess gastric acid secretion in isolated oxyntic glands and parietal cells, it was shown that gastrin, in contrast to histamine or a cholinergic agent, had no direct effect on rabbit glands/parietal cells (Berglindh, Helander, and Obrink 1976). However, Soll created a faint and inconsistent effect using gastrin on similar canine preparations (Soll 1982), which was considered to be more credible. It was possible to unequivocally show that the gastrin receptor was on the histamine producing ECL cell and not on the parietal cell using an isolated rat stomach (Waldum, Sandvik, et al. 1991; Bakke et al. 2001).

In the middle of the eighties, Marshall and Warren showed that Helicobacter pylori caused chronic gastritis and peptic ulcer disease (Marshall and Warren 1984). This changed the focus on upper gastrointestinal diseases.

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CHAPTER 3

PERSONAL CONTRIBUTIONS

Abstract

I began my work in Tromsø in the middle of the seventies with radioimmunoassays of gastrointestinal hormones and enzymes (pepsinogen I). I concentrated on gastric physiology. When I moved to Trondheim in 1981, the interaction between the three major gastric acid secretagogues—acetylcholine, gastrin, and histamine—was disputed. The available methods for studying the interaction were either too complex (studies in man and living animals) or too artificial, such as research on key enzymes (histidine decarboxylase). An isolated stomach model seemed ideal, but curiously it did not produce acid. However, the arterial perfusate used did not contain red blood cells, and the production of gastric acid lead to a concentration gradient of 1 million, which requires a lot of energy. Therefore, we added red blood cells to the perfusate and, when we applied a membrane oxygenator, the isolated rat stomach produced acid. This model allows us to have complete control over what goes into the stomach via both the vascular and luminal sides. It also allows us to collect both luminal and vascular effluents. Shortly afterwards we came across a sensitive and specific commercial immunoassay for histamine. By histamine determination in the vascular and acid titration in the luminal effluent we could show that the functional gastrin receptor was localized to the ECL cell. The idea that pentagastrin stimulated the maximal acid secretion was challenged, and it was shown that maximal acid secretion depended on both the ECL cell and parietal cell masses, which explains why profound acid inhibition with proton pump inhibitors (PPIs) induced rebound acid inhibition. Combining vagal stimulation by controlled hypoglycemia using a glucose-clamp and the maximum effect dose of pentagastrin also increased acid secretion beyond the amount produced by pentagastrin alone. In rat studies, we showed that a positive trophic of gastrin on the ECL cell followed the same concentration dependence as the functional one and reached the maximum at a lower level than previously realized. Consequently, we began to study the ECL cell's role in gastric carcinomas and eventually proved that ECL cell differentiation in cancer cells occurred in a portion of the carcinomas,

particularly in the diffuse type and the signet ring subtype. All of these studies were difficult to get published and were generally negatively received. Moreover, most "experts" in the field never mentioned them.

Keywords: acid; classification of carcinomas; ECL cell; gastric cancer; gastrin; gastrin receptor; histamine; interactions between secretagogues; maximal gastric acid secretion; parietal cell; rebound acid hypersecretion; regulation of gastric acid secretion.

The acid producing isolated rat's stomach

When we started to study the role of gastrin in gastric carcinogenesis in the early eighties in Trondheim, it became apparent that there was a need for a new method of assessing biological gastrin activity. Studying the regulation of acid secretion in humans or in awake or anesthetized animals requires complex models, whereas studies on isolated parietal cells or oxyntic glands could give false results due to the risk of damage to receptors or other key molecules during preparation.

An isolated stomach artificially perfused through the lumen and the vascular bed without recirculation looked like a promising compromise. However, at that time, nobody had succeeded in making an isolated stomach produce acid. Previous attempts at establishing a model to perform this function used oxygenated buffers to perfuse the vascular bed.

Taking into consideration that stomach acid production probably requires the most energy in the body, which creates a concentration gradient of more than one million H+, it appeared that the lack of acid secretion could be due to O_2 deficiency. We started to first add human red cells to the buffer and then O_2 by bubbling; however, this was not successful. Then we contacted engineers who were working with membrane oxygenators at our university's technology faculty. At the same time, Short et al. reported success when using ovine red cells in this procedure (Short, Wolfe, and McGuigan 1984). We then succeeded in creating a stable reproducible model to study the regulation of acid secretion, which allowed a comparison between the release of mediators to the blood and the secretion of acid to the lumen (Kleveland, Haugen, and Waldum 1986). This model was in use over a fifteen years period in our laboratory. Previously, it had been an accepted fact that maximal gastric acid secretion could be induced by stimulation with either histamine or gastrin.

Due to histamine's general toxicity, it has to be given with a histamine-1-antagonist (Kay 1953) or alternatively use a selective histamine-2 agonist (Durant et al. 1978). However, even when histamine was given with a histamine-1 antagonist, there was some toxicity preventing a further increase to the histamine dose. Furthermore, it was not proven that the histamine agonists, such as impromidine, were complete histamine-2 agonists. Therefore, maximal gastric acid secretion during histamine stimulation in humans and living animals has not yet been completely explored; this means that the belief that maximal gastrin and histamine stimulated acid secretions are similar has not been experimentally proven.

With the isolated rat stomach, we could soon show that the maximal histamine stimulated acid secretion exceeded that of gastrin (Kleveland, Waldum, and Larsson 1987). Furthermore, gastrin did not have any additive stimulatory effect on maximal histamine stimulated acid secretion, which is in contrast to a cholinergic agent. These findings clearly showed that gastrin stimulated acid secretion through the stimulation of histamine, which obviously was a restrictive factor in terms of gastrin stimulated, and therefore meal stimulated, acid secretion.

Maximal gastric acid secretion in man

This new physiological insight has great clinical implications, as exemplified by rebound acid hypersecretion after the long-term inhibition of acid secretion (Waldum, Arnestad, et al. 1996). Moreover, we were also able to show that vagal stimulation augmented maximal gastrin stimulated acid secretion in humans (Qvigstad, Bjorgaas, et al. 1999). Therefore, gastrin stimulated acid secretion is an imperfect parameter for maximal gastric acid secretion (Waldum, Brenna, and Sandvik 1998).

This new concept was met with negative attitudes, as shown in the following correspondence with *Gastroenterology*.

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RE: Manuscript No. 97-7576-00

Dear Dr. Waldum:

We regret to inform you that your manuscript entitled "Maximal Gastric Acid Secretion In Man - A Concept That Needs Precision" was not accepted for publication in *Gastroenterology*. The manuscript was assessed by two reviewers, the Associate Editor, and the Board of Editors. Both reviewers acknowledged the interest of this study but also pointed out several shortcomings, as can be seen in the copies attached. Important criticism related to the need for a test and the lack of convincing proof in favor of the test proposed. Because of these limitations, we were unable to assign a publishable priority to this manuscript.

We regret that these concerns preclude publication in *Gastroenterology*, but we hope you find the enclosed comments of the reviewer(s) useful when submitting your paper to another journal. We look forward to future submissions of other manuscripts.

Sincerely,

Guido N.J. Tytgat, M.D.
Associate Editor

Daniel K. Podolsky, M.D.
Editor