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# From the “hungry acid” to pepsinogen: a journey through time in quest for the stomach’s secretion

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## Abstract

The stomach’s secretion has been a mystery for centuries. Even after the first indications of its function and role appeared, every formulated idea on the nature of the gastric liquid remained open to controversy. After the ancient Greek perceptions which identified acids as bitter-sour liquids, the physicians of the Iatrochemical School, under the influence of Paracelsus and the alchemists, were the first to point out the physiologic chemistry of secretion. Experiments on animals and humans during the 17<sup>th</sup>-18<sup>th</sup> centuries, which mainly included swallowing various substances and observing the process, enhanced knowledge, with Stevens and Spallanzani playing the leading part. Any existing objections ceased in 1823, when Prout clearly identified hydrochloric acid as the acid agent of the stomach. Later on, the role of pepsin and pepsinogen was also judged to be important in digestion. In addition, the tremendous contribution of French scientists, experienced in the science of nutrition, must not be underestimated. It took centuries of research, and the involvement of many notable figures from many nations and countries, to form modern concepts of gastric secretion.

**Keywords** stomach, hydrochloric acid, William Prout, Paracelsus, Lazzaro Spallanzani

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## Introduction

The stomach’s secretion has been a mystery for centuries. Even after the first indications of its function and role appeared, every formulated idea on the nature of the gastric liquid remained open to controversy. Human concern about the stomach, from the ancient Greek perception to the French contribution, reflects the dim and dubious origins of rational medicine itself. A journey through the history of stomach secretion research reveals not only notable figures of medicine, but also interesting debates.

## The Ancient Greeks

The concept of the stomach as an organ actively secreting acid and pepsin, and responsible for digestion, was not appreciated by the early medical references. The ancient Greeks were not aware of acids in the modern sense of chemistry but

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identified them only as bitter-sour liquids [1]. Thus, Diocles of Carystos (ca. 350 BC) specified sour eruptions, watery spitting, gas, heartburn and epigastric hunger pains radiating to the back as symptoms of melancholic gassy illness originating in the stomach [2]. Approximately 300 years later, Celsus (30 BC-25 AD) recognized that certain foods were acidic and recommended light and gelatinous food when the stomach is infested with an ulcer [3].

## From the alchemists to the Iatrochemical and Iatromathematical Schools

There appears to have been little further development in understanding the function of the stomach and the nature of digestive processes until the 16<sup>th</sup> century [4]. The eminent alchemist and physician Paracelsus (1493-1541) believed that there is acid in the stomach, necessary for digestion. He reckoned that the acid in the stomach of humans came from the drinking of acidic spa water (*acetosum ensurinum*, “hungry acid”) and that its action was part of a catalytic process necessary to prevent the formation of precipitations and concretions within the body. The observations of Paracelsus were far advanced for his time, and although many of his assertions appear as successful guesses or evidence of remarkable intuition, he clearly recognized the importance of chemistry and its relation to disease [5].

Alchemists and chemiatrists had made progress in the



Figure 1 Jean Baptiste van Helmont (1759-1644)

identification of many substances. Johan Thölde (1565-1614) is reported to have identified hydrochloric acid. By the middle of the 17<sup>th</sup> century, Jean Baptiste van Helmont (1579-1644) (Fig. 1), the founder of the Iatrochemical School, was able to write of an acid ferment in the stomach responsible for digestion. The Iatrochemical School based its way of thinking on the belief that each material process of the body was presided over by a special *archeus*, or spirit, named *Blas*. According to van Helmont's doctrine, physiologic processes are of themselves purely chemical, being attributed, in each case, to the agency of specific ferment and, therefore, he proposed the existence of an acid *ensurinum* as a normal component of the human stomach, although he thought that it was derived from the spleen. The physiologic chemistry of van Helmont was divested of much of its mystic and spiritual overtones by the physician-priest Sylvius (1614-1672) who was in charge of the first chemical laboratory of Leiden, from 1658 to 1672 [5,6].

The opposing school of thought of the era, the Iatomathematical School, maintained that all physiologic happenings should be treated as fixed consequences of the laws of physics and included individuals like René Descartes (1596-1650), Giovanni Alphonso Borelli (1608-1679) and Herman Boerhaave (1668-1738). In this context they suggested that digestion should be an act of trituration. They cared little for the new science of chemistry and their postulates occasionally faded into sterile eccentricities basing the whole of medical practice on mechanical principles [7].

### The first experiments

Therefore, in late 17<sup>th</sup> century the first attempts at obtaining gastric secretion appeared. Viridet, experimenting with

animals, noted that, in humans, acid could be recognized in the esophagus, but this was because of regurgitation of the contents of the stomach [8]. René Antoine Ferchault de Réaumur (1683-1757), experimenting with a tame buzzard which he fed small hollow metal tubes containing a variety of food and sponges, added that gastric juice required constant renewal [9]. Reus and Goss induced emesis at specific times after eating and suggested that secretion occurred by a mechanical process [10]. Edward Stevens was the first to perform an experiment of *in vitro* digestion successfully and proved that the gastric juice itself contained the active principle necessary for the assimilation of food [11].

In 1780, Lazzaro Spallanzani (1729-1799) (Fig. 2), who was the Professor of Natural History in Pavia, published his extensive observations in this area. He had used the method of Réaumur upon animals and himself. He initially swallowed linen bags containing food and bread and collected them for examination after they had been passed through the rectum. Later, he substituted small metal tubes to avoid any possibility of trituration. Finding no evidence of fermentation, as was then believed, or putrefaction, he postulated that digestion was by an acid and, in 1783, he finally concluded that digestion *in vitro* as well as *in vivo* was a chemical process. However, being still somewhat uncertain, in 1784, he collaborated with Giovanni Antoni Scopoli (1723-1788), a Professor of Chemistry in Pavia. The latter reported that the gastric juice from the crows that Spallanzani was studying contained pure water, some soapy and gelatinous animal substances, sal ammoniac and earthy matter similar to that found in all animal liquids. Spallanzani, therefore, was uncertain about his findings regarding the acidity of gastric juice [12]. In 1785, he corresponded his work to Carminati, who was the first to detect the acidity of the contents of a meal and advised Spallanzani to test birds on a meat-free diet. He found marine acid in the juice squeezed from sponges in five ravens that were fed on vegetables for 15 days [13].

Later, Brugnatelli in 1786 and Werner in 1800, found the contents of the stomachs of sheep, cats, fish, and birds to be acid [7].

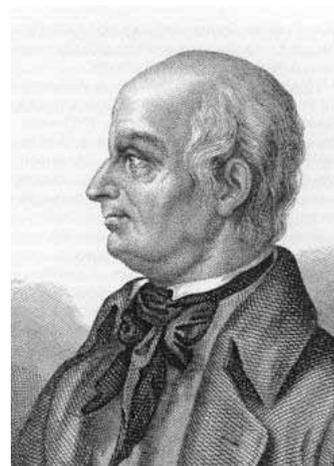


Figure 2 Lazzaro Spallanzani (1729-1799)

Despite the relatively clear evidence produced by Spallanzani and his colleagues that there was acid in the stomach and that it was hydrochloric acid, considerable controversy persisted. Indeed, many of the investigators of this area reversed their thoughts a number of times during the study of the subject. While objections insisted (mainly supporting the presence of phosphoric acid in the stomach, with famous supporters, like Young and Berzelius), the final resolution to the question of the exact nature of acid produced by the stomach was provided in 1823 by Prout, an erudite and diverse physician [11].

### William Prout's work

William Prout (1785-1850) (Fig. 3), at an earlier stage of his studies supported phosphoric acid as the acid agent of the stomach. However, on December 11, 1823, at the Royal Society of London, he presented his landmark paper, *On the Nature of Acid and Saline Matters usually existing in the Stomach of Animals*. This presentation was unique in two ways: First, Prout had specifically identified hydrochloric acid in the gastric juice of many species, and second, he was able to quantify the free and total hydrochloric acid and chloride present [14]. The acid was measured by neutralization with a potash solution of known strength and the chloride by titration with silver nitrate. More than 100 years were to elapse before his subsequent proposal was confirmed [15].

### Completing the puzzle

A little time later, Tiedemann and Gmelin confirmed Prout's earlier observations that the exact nature of acid in the stomach was hydrochloric [16,17].

Meanwhile, in June 1822, in Connecticut, the pioneer researcher William Beaumont (1785-1853) recorded the healing process of the stomach after treating a victim of a gunshot wound of the upper left abdomen and chest. Given the opportunity to study the gastric fistula of his patient,

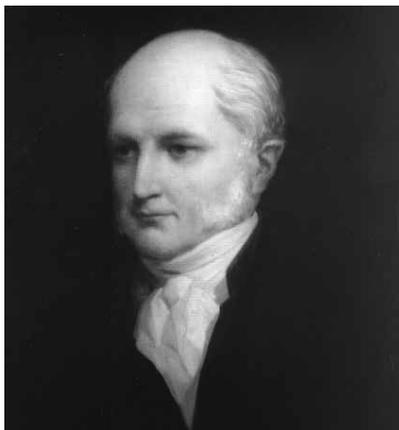


Figure 3 William Prout (1785-1850)

Beaumont began his investigation into gastric function and digestion. For years, he studied the physiologic manifestation of digestion and produced a classic text on the subject in 1833 [18]. Despite his lack of training as a physiologist and his relatively unsophisticated medical background, Beaumont's work remained a model on the subject. He outlined the basic principles of digestion and established the presence of hydrochloric acid in gastric juice [19].

The puzzle of gastric secretion was completed in 1836 when Theodor Schwann (1810-1882) described a water-soluble factor in gastric juice which digested egg white. He called it "pepsin", after the Greek word for digestion [20]. Although Schwann deserves the credit for initially postulating the existence of the digestive enzyme, it was Langley (1852-1925) of Trinity College, Cambridge, who formalized the study of pepsinogen and the mechanisms of its secretion from the gastric mucosa [21,22]. However, to date, despite extensive study and epidemiological correlation of pepsinogen to the gastric ulcer and carcinoma, no specific pathogenetic role exists for this potent and prolific enzyme [7].

### The French contribution

In order to make the next step, and reach from research (quest for the gastric acid) to practice (surgical intervention to the stomach diseases) it took a tremendous overall French contribution. The subject of digestion and the role of the stomach have been of considerable importance in France for many years. Rarely has a nation been so closely associated with food and the sciences relating to its digestion. Notable physiologist, Claude Bernard (1813-1878) spoke with philosophical conviction of "le milieu intérieur" [23]. Apart from the aforementioned experiments by Réaumur, Jean Anthelme Brillat-Savarin (1755-1826) with his chemistry of food [24], Claude Bernard with his physiological observations, and Jean Cruveilhier (1791-1874) with his descriptions of stomach ulcers [25,26], also contributed to answering the questions concerning acid in the stomach. It was them who laid the foundation for Guillaume Dupuytren (1777-1835), who described ulceration in detail [27], Jules Emile Péan (1830-1898), who resected a pyloric gastric cancer [28] and André Raphael Latarjet (1877-1947), who introduced the concept of vagotomy [29-31]. All these French scientists, more or less, set the stage for modern knowledge and practice.

### Conclusion

It took centuries of research, and the involvement of many notable figures from many nations and countries, to form the modern knowledge of gastric secretion. This intriguing journey through time ends in justifying the words of the ancient Roman poet Persius (34-62 AD): "Magister artis ingenique largitor venter" (That master of arts, that dispenser of genius, the belly) [32].

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