REVIEW

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A History of the Discovery of *Helicobacter Pylori*, with Special Reference to Giulio Bizzozero

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ABSTRACT

Helicobacter pylori (*H. pylori*) is a microorganism that is highly prevalent in mankind and closely linked to several gastroduodenal disorders. Though *Helicobacter pylori* was introduced to the scientific community in 1983 by Robin Warren and Barry Marshall, a closely related *Helicobacter* species had been described one hundred years earlier by the Italian pathologist Giulio Bizzozero in the canine stomach. In this review we analyze the different steps involved in the discovery of *Helicobacter* species and provide a biography of the pioneer Giulio Bizzozero.

Key words: *Helicobacter pylori* – gastritis- peptic ulcer – gastric cancer – microscopy – microbiology – Bizzozero.

Abbreviations: *H. felis: Helicobacter felis; H. heilamnnii: Helicobacter heilmannii; H. pylori: Helicobacter pylori*; MALT: mucosa-associated lymphoid tissue lymphoma.

INTRODUCTION

Helicobacter pylori (H. pylori) is an organism that has coexisted with mankind for many generations [1]. Recent studies suggest that *H. pylori* could have spread from East Africa with human migration as long as 58,000 years ago [2]. In South America, *H. pylori* was identified using ELISA in feces from pre-Inca mummies [3, 4].

Another study, using PCR, found strains of *H. pylori* featuring an East Asian genotype in a native Amazonian indigenous population of South America. However, these strains were not present in a mestizo population in another city of the same country [5-7]. Collectively, these findings provide evidence of the presence of *H. pylori* in the ancestors of indigenous Americans who migrated from Asia 11,000 years ago [5-7].

Helicobacter pylori belongs to a group of bacteria adapted to live in the digestive tract mucus of vertebrates. It has specific characteristics including morphology (spiral shape, presence of flagella) and metabolism (microaerobic, not saccharolytic) adapted to this environment. Gastric *Helicobacter* probably evolved from an ancestral intestinal bacterium when stomachs appeared in vertebrates, and *H. pylori* is specific to humans [1]. Prior to its isolation, the stomach was presumed to be a sterile environment due to its high levels of acid, which precluded the survival of any living organism in the stomach [8].

Since its discovery *H. pylori*, a spiral-shaped (hence its name) gram-negative bacterium, has been associated with certain pathologies of the upper digestive tract in humans [8]. It is now recognized that *H. pylori* plays a crucial role in the pathogenesis of chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma (MALT) and gastric adenocarcinoma [9]. Universal prevalence is high as approximately half the world's population is infected [8]. *Helicobacter pylori* was designated as a type 1 carcinogen agent by WHO in 1994 [9].

This microorganism gained global recognition in 1983 [10] based on the report by Robin Warren and Barry Marshall on their study describing a bacterium similar to *Campylobacter* (*Campylobacter-like* bacterium) that they observed in large numbers in the gastric mucosa of patients with chronic gastritis and duodenal ulcers [10]. This discovery would eventually lead to their being awarded the Nobel Prize in Physiology

and Medicine in 2005. It soon became clear, however, that prior work had at the very least, hinted at the presence of microorganisms in the human stomach. Indeed, in 2002 Barry Marshall published a book called "*Helicobacter* Pioneers", a compilation of studies by many researchers who had seen or suspected the presence of a bacterium in the stomach, but whose work had faded from scientific memory [11].

THE PATH TO DISCOVERY

In the approximate 100 years before the first publication by Warren and Marshall there were many reports by researchers of bacteria in the gastric mucosa [2-17] and cures of peptic ulcer disease using antibiotics, either alone or in combination with other medications, had been described [17].

The work of these researchers from Italy [13], Ireland [18], Belgium [19], Germany [4], United Kingdom [20], United States [15], Greece [17], China [21], Soviet Union [16] and others, was largely forgotten and, occasionally, even discredited.

For the late Dr. Robin Warren, the history of Helicobacter began on his birthday, 11 June 1979. On examination of a gastric biopsy showing chronic gastritis, he observed a blue line on the gastric mucosal surface. Under high power magnification he was able to see several small bacilli, firmly attached to the epithelium [22].

In February 1983 Warren and Marshall prepared an abstract titled "Spiral Bacteria in gastritis and associated disease" for presentation at the Australian Gastroenterology Congress; but it was not presented [23]. Shortly thereafter, they sent a letter to the editor of the Lancet, titled "Unidentified curved bacilli on gastric epithelium in active chronic gastritis". The paper was published in June 1983 and contained excellent electron micrograph photographs. Without these illustrations they would probably not have made news nor would the findings have been so convincing [11, 23].

Marshall later tested Koch's third postulate by ingesting a *H. pylori* culture, which led to gastritis [24]. The same process was repeated and confirmed by Morris [25]. Skirrow, a microbiologist studying *Campylobacter*, suggested these organisms were members of the *Campylobacter* genus, and the name *Campylobacter pyloridis* (derived from the Greek *pylorus* meaning "gate guardian") was applied on account of its specific location in the pyloric or antral region [26]. Successful culture of the bacterium resulted in acceptance of the name, later changed to *Campylobacter pylori* [26].

Later studies of this organism and, especially, on its genome, concluded the bacterium belonged to a new genus, *Helicobacter* (helical: curved; bacter: rod) [5, 27]. In 1997 the complete genomic sequence of *H. pylori* strain 26695 was published [28]. Why had it taken so long for an organism so ubiquitous in humans to be fully identified? The Nobel Prize Committee answered this question succinctly in their press release.

In underlining the importance of *H. pylori* they recognized that the "tenacity" and "prepared mind" of the new prize-winners were keys to their success, agreeing with Louis Pasteur, who in his celebrated phrase, said *Dans les champs de l´observation le hasard ne favorise que les esprits préparés* (chance favors only the prepared mind). However, the Committee failed to mention the many other factors that conspired in their favor [14]. Warren specifically acknowledges the key role of the advent and widespread availability of fiber optic endoscopy. Before the advent of modern endoscopy, gastric tissue was only obtainable from specimens obtained at autopsy or surgery. By the 1970s, endoscopic biopsies were being performed on a routine basis, permitting the delineation of fine details of the gastric mucosa in living patients [14].

Several other technological developments were critical. Indeed, years earlier, the development of the microscope, one of the most important breakthroughs in medicine and science [29], anticipated these discoveries. Though lenses had been in use for many centuries and monocles were made in the Middle Ages, Zacharias Janssen, a Dutch eyeglass manufacturer, and his son were the first to introduce a combination of more than two lenses to increase magnifying capacity; these microscopes were very rudimentary and incapable of more than a 10x magnification [29].

The word microscope was first used by members of the Accademia dei Lincei, a scientific society to which Galileo belonged. They published a study on the microscopic observation of bees. In the mid-17th century, Anton Van Leuwenhoek, a textile merchant from Delft (Holland), in his own time and using a simple home-made microscope, described, for the first time, protozoa, bacteria, spermatozoids, and red blood cells. Self-taught and a non-Latin speaker, he, therefore, struggled to access the current scientific literature. By the time of his death, he had a collection of some 400 microscopes, part of which he donated to the Royal Society of London, where he had sent his research reports [29].

In 1660, Marcello Malpighi, widely regarded as the creator of biological microscopy, noted his observations in the form of brief abstracts sent to the Royal Society of London. His contributions in the field of botany and biology had a decisive influence on the development of microscopy. He was the first to confirm, through microscopic examination of the lung, the presence of the capillaries proposed by Harvey [29].

Robert Hooke reported on his microscopic examination of a cork and observed compartments which he called cells; an observation that in the 19th century led to the development of cell theory, the cell being the basic unit of life [30]. These experiments and others were published in his book "Micrographia" [30] together with drawings of his observations.

In the latter half of 19th century, the German bacteriologist Robert Koch, proposed his scientific theory that bacteria caused certain diseases.

These developments set the stage for the first investigations of the gastric microbiome. In 1881, the German pathologist Klebs noted the presence of organisms resembling bacilli in the lumen of the gastric glands, with an associated inflammatory cell infiltration of the gastric mucosa [31].

Then, in Italy (1892), bacterial colonization was observed in the stomach of six dogs, in a report describing the presence of "spirochetes" or "spiral shaped" organisms in the pyloric and fundic mucosa and distributed in the superficial epithelial cells and in the base of the gastric glands [13]. „...*Ancora piu curiosi sono degli spirilli che ho trovato costanti nello stomaco del cane e che, oltre all'essere numerosi nello strato di muco che*

riveste la mucosa, pene- trano nel lume delle ghiandole tanto del píloro quanto del fondo" (…Even more curious is that I have constantly observed spirochetes in the dog stomach and besides being present in great numbers on the mucus layer that covers the mucosa, they penetrate deep into the lumen of the pylorus glands.") [12, 13].

So, with these words, over 100 years ago, Italian pathologist Giulio Bizzozero described for the first time the presence of a species *Helicobacter* in the stomach of a mammal (a dog) [13].

These observations were published as an appendix to a manuscript "on the tubular glands of the gastroenteric tract and its relations with the epithelial mucosa". Bizzozero reported his discovery at a meeting of the Turin Medical Academy on March 18, 1892. The description of spirochetes was accompanied by many illustrations that were included in the publication (Fig. 1) [12, 13]. The author described them as follows: "Such spirochetes are thin, 3-8 microns long and have 3-7 spiral shaped flagella. They stain intensely with fuchsin or safranin dissolved in aniline solution, followed by an alcohol wash. They are Gram-negative. Usually present in small numbers in the deepest part of the gland; they are, in contrast, more abundant at the superficial level and are, sometimes, found in a line one after the other, forming a group on the axis of the gland lumen" [12, 13].

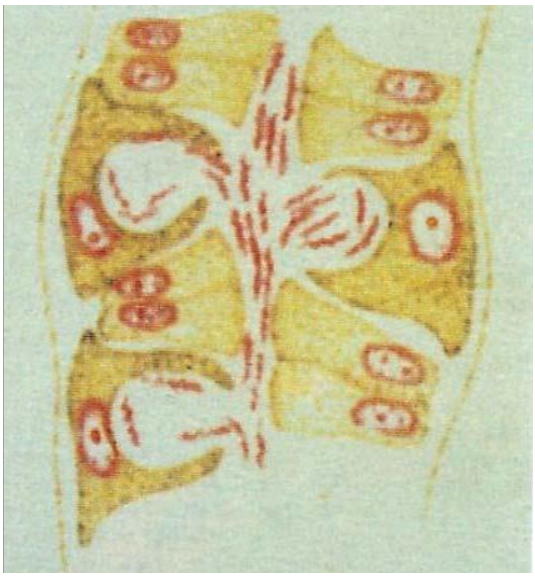

Fig. 1. Detailed drawing by Bizzozero, showing free "spirochetes" in the lumen of the canine gastric gland and accumulating in vacuoles (x 3) [12, 13].

This discovery was not accidental; it was the result of a series of factors: a rare spirit of observation (considering limited technology), unique skill in histological techniques and the advent of a new discipline, pathophysiology. Indeed, he had emphasized these attributes in his Clinical Microscopy Manual, published in 1879 and translated into French, English, and Russian [12, 32]. With this book, Bizzozero sought to promote the use of microscopes as a diagnostic tool among the medical profession, and included a description of the microscope with several chapters dedicated to pathogenic bacteria and the examination of human body fluids [13, 32]. Discovering that the canine stomach could be colonized by spiral-shaped organisms was a consequence of Bizzozero's interest in this organ. His profound knowledge of histological and microscopic techniques allowed him not only to differentiate between parietal and chief cells, but also to establish that cells in the neck of the gland generated both chief cells as well as superficial epithelial cells. His favorite disciple, Camilo Golgi, better known for his discovery of the intracellular body which carries his name, was intimately involved in this research [13]. This research ultimately led to our current understanding of the acid secretory function of the parietal gastric cell [13].

There were several milestones along the road to the discovery of *H. pylori*; the main milestones are shown in Table I which also places Bizzozero in his rightful place in this path to discovery.

Table I. History of the discovery of Helicobacter pylori, adapted from Fukuda Y, Marshall B et al. [33]

Year	Scientist(s)	Discovery
1875	Bottchet/Letulle	Bacteria detected at ulcer margins
1881	Klebs	Bacterial colonization and inflammation
1881	Letulle	Staphylococcus aureus induces gastritis in guinea pigs
1888	Jaworski	Vibrio Rugula in the stomach
1893	Bizzozzero	Spirochetes in dog stomach
1906	Krienitz	Spirochetes in stomachs with gastric cancer
1917	Dragstedt	Bacteria does not induce gastric ulcer
1924	Luck	Urease activity in the stomach
1940	Feegberg/Barron	Gastric Spirochetes induce gastric ulcers
1966	Aoyagi	Very high urease activity in the stomach
1979	Warren	Spiral shaped bacteria in the human stomach
1983	Warren	Gastric spiral shaped bacteria associated with gastritis in humans
1984	Inoue	First successful *H. pylori* culture in Japan
1985-1987	Marshall/Morris	*H. pylori* inoculation fulfilling Koch's third postulate
1989	Goodwin	Spiral shaped bacteria called *H. pylor*i
1994	WHO (World Health Organization)	WHO declares *H. Pylori* as carcinogenic agent in gastric cancer [10]
1997	Tomb	Full genome sequence of *H. pylori* is published [28]

The genus *Helicobacter* comprises 18 well-described species and 10 other potentially new ones. Of the first group, 7 are of gastric origin and the remaining species have been found in the intestinal tract in a wide variety of animal species (Table II) [8].

The spirochete described by Bizzozero was presumably *Helicobacter heilmannii* (*H. heilmannii*) or *Helicobacter felis (H. felis)* [13, 33, 34]. The *in vivo* morphology of these two bacteria is similar, although they differ in their rolling pattern (more subtle or less frequent in *H. felis*: and more consistent in *H. heilmannii*) and by the presence of periplasmic fibers [34] in *H. felis*, which certainly could not be have been detected with the rudimentary instruments that Bizzozero used in the late 19th

Table II. Natural host and usual site of isolation of Helicobacter species [8]

Helicobacter species	Natural host	Origin
H. pylori	Human	Gastric
H. mustalae	Ferret	Gastric
H. nemestrinae	Macaque Monkey	Gastric
H. felis	Dog, Cat	Gastric
H. acinonychis	Cheetah	Gastric
H. bizzozzeroni	Dog	Gastric
H. salomonis	Dog	Gastric
H. heilmannii	Human, cat, dog, pig	Gastric
H. cinaedi	Human, hamster	Intestinal
H. fennelliae	Human, hamster	Intestinal
H. muridarum	Rat, mouse	Intestinal
H. canis	Dog	Intestinal
H. pullorum	Poultry	Intestinal
H. pamentesis	Calf	Intestinal
H. hepaticus	Mouse	Intestinal
H. bilis	Mouse	Intestinal
H. cholecystitis	Hamster	Intestinal
H. trogontum	Rat	Intestinal
H. rodentium	Mouse	Intestinal

century. Both species, especially *H. heilmannii*, can temporarily colonize the human stomach. The canine stomach can be colonized by another *Helicobacter* species, morphologically similar to *H. heilmannii*: *Helicobacter bizzozeronii* [13, 34, 35]. Named for the Italian scientist, it is now known that this species can be transmitted to humans [13, 34, 35].

It should be noted that Figura and Biancardi [13] point out that the species of *Helicobacter* colonizing the dog stomach should instead be referred to as *H. bizzozeri* and not *H. bizzozeroni*; the former being grammatically correct [13, 34].

GUILIO BIZZOZERO: A BIOGRAPHY

Giulio Cesare Bizzozero was born in Varese on March 20th, 1846 [13, 14, 36]. Son of Felice Bizzozero, an industrialist, and Carolina Veratti [36], his last name probably derives from "Bizzozzero", a district near Varese [13]. This middle-class family was deeply involved in the Unification and Risorgimento movements (social activities and politics directly related to the liberation of Italy from Austrian rule) [36]. He grew up in a stimulating cultural environment, and in 1861, after completing his classical schooling in Milan, he enrolled as a student in medicine at the University of Pavia [36, 37]. During the 19th century, this university was the main cultural center of La Lombardia, and hosted major researchers such as Cardano, Scarpa, Volta, and Tissot, among others. In the 19th and 20th centuries its faculty included Golgi, Bassi, Corti, Sertoli, Negri, Grassi, and Carini [36]. In 1862, at the age of 16, he studied for one year at the Experimental Physiology Institute of Eusebio Oehl in Pavia [36, 37], where he made his first microscopic study of the distribution of blood vessels [13]. As a student at the General Pathology Institute he published many experimental research studies on normal histology and pathology. At 20 years of age, in 1866, he graduated in medicine and was awarded the Matteucci prize for his excellent grades and research [13, 36].

Bizzozero then served as a military medic in the war of independence against Austria. Subsequently, he travelled to broaden his scientific knowledge, visiting the laboratories of the histologist Heinrich Frey in Zurich [36], and Rudolf Virchow, the founder of cellular pathology, in Berlin, who referred to him as "Bizzozero, my best pupil" [36, 37].

Back in Pavia in 1867 he embarked on his career as a professor of general pathology and histology, returning as an Italian "prophet" of the new theories proposed by Virchow on cell structure and pathology [36].

Fig. 2: Giulio Bizzozero (1846-1901). Clendening History of Medicine Library, University of Kansas Medical Center.

Bizzozero was interested in many fields of medicine. The study of blood cells and the clotting mechanism were two contributions which gained him a place in the history of medicine. His seminal observations on bone marrow date back to his student days in the laboratory of Mantegazza, at the General Pathology Institute at the University of Pavia. From 1868 to 1869 he published a series of observations on the hematopoietic function of bone marrow: "*Sulla funzione ematopoietica del midollo delle ossa. Due comunicazioni preventive*", ratifying the concept that the bone marrow plays a major role in hematopoiesis [39]. He went on to describe the various cellular different elements of the bone marrow. He also began a systematic study of bone marrow disorders [13, 36, 39, 40].

At the age of 27, in 1873, he was elected as Head of General Pathology at the University of Turin, where he founded the General Pathology Institute [36, 39]. His laboratory fostered the careers of several great scientists, including some of the greatest Italian medical researchers (i.e. 1906 Nobel Prize winner for Physiology and Medicine, Camilo Golgi) [13]. At the same time, he initiated a new interpretation of general pathology, and inspired a new course of study based on a biological approach.

He actively supported scientific publications through the "Giornale di Scienze Fisiche e Naturali" (Natural and Physical Science Magazine) and the "Archivio Italiano per le Scienze Mediche" (Italian Archive for Medical Science) with two sections: Italian Bibliographic Journal and "Nuove Pubblicazioni". For all of this he was recognized as an Italian authority in Experimental Medicine. He also implemented many civic activities in Turin, such as the establishment of the Hygiene Laboratory and the "Amedeo d'Aosta" Hospital and also modernized the water distribution and drainage systems [13, 14, 36, 39].

Bizzozero's experience and skills were essential to the completion of his "Mannuale di Microscopia Clinica" (Clinical Microscopy Manual) [32] published in 1879 and translated into French, English and Russian. Through this pocketbook he promoted the use of the microscope as a diagnostic tool among physicians.

For his studies on the infectious origins of tuberculosis (proven by Koch in 1882), certain aspects of inflammatory reactions, and a description of the phagocytosis (proven later by Ilya Ilyich Metchnikoff; who in 1908 shared, with Paul Erlich, the Nobel prize for Physiology and Medicine for their work on phagocytosis and immunity) [41] Bizzozero was endowed with the title "Father of Italian Histology"; he was also recognized as a hero of preventive medicine [36, 37] .

Max Schultze´s work published in 1865 was the first accurate and convincing description of platelets as a normal constituent of blood [42]. In 1881 Bizzozero achieved another scientific milestone with his discovery of a "constant blood particle, different to red and white blood cells", whose existence had been suspected by many authors for some time [37, 43-45, 46].

Furthermore, he went on to show that platelets were the first component to adhere to the walls of damaged blood vessels *in vitro* and *in vivo*, subsequently being covered by fibrin. Therefore, one of the first names for platelets was "Bizzozero's corpuscle". He called this third blood morphological element "*piastrine*" (1883-1884) (in Italian: "small plates", *Bulnchplätten* in German, and "*petites plaques*" in French) later called platelets [36, 44-46].

From 1884, Bizzozero was Director of the Veterinary School of Turin. At the age of 40, in 1886 he was appointed Chancellor of the University of Turin [13, 36]. In 1887, he became a member of the Italian Superior Health Council, in 1888 was welcomed as a member of the Science Academy of Berlin, and in 1890 became Senator for the Kingdom of Italy [13, 14, 36].

Bizzozero wrote about the advantages of vaccination and the practical application of the principles of hygiene to improve public health. He linked cancer to smoking [36].

Bizzozero also left his footprint in the field of nephrology. Another of his disciples, Sacerdotti, in Turin (1896) published his hypothesis on compensatory renal hypertrophy following unilateral nephrectomy. Based on his observation of several mitoses in the renal epithelium (an expression of kidney hypertrophy), when the kidneys of a normal dog received a blood transfusion from nephrectomized dogs, he proposed the existence of mediators released by the kidney. Sacerdotti's observations were confirmed years later with the discovery of proliferative peptides [13, 14, 36, 37].

Towards the end of his life, he suffered a serious bout of choroiditis, which forced him to withdraw from his research with the microscope. However, this did not prevent him from taking part in public debate, in 1879 contributing his work on "Sui Provvedimenti Contro la Trichina" (Measures against Trichinosis). A colleague Piemonte commented: "just like Beethoven composed even when deaf, Bizzozero, with eyes too weak for laboratory work, never stopped enriching the healing arts with his masterful contributions" [37].

Bizzozero died of bronchopneumonia [13, 37] at the age of 55, on April 8th, 1901, and was given an exceptionally large and solemn public funeral attended by his colleagues and fellow countrymen [37]. The Lancet of April the 20th 1901 paid tribute to Bizzozero in an obituary, listing all his achievements throughout a life dedicated to research [37]. One hundred years later, John Heillbron and William Bynun, in the April 4th, 2001, issue of Nature, recognized Bizzozero for his work [47]. Likewise, Paolo Mazzarello et al. in Nature Reviews (2001) revisited the history of this pioneer in cellular biology [36]. Also, R. Vigliani in Pathologica (2002) reviewed his work to commemorate the centenary of his death [39].

A dynamic, even-tempered, graceful, and sociable young man, Bizzozero was a hero to many students and young physicians, as many began their careers under his leadership. Never imposing, Bizzozero's authority was generally accepted as being a reflection of his magnetic personality, the true sign of a natural leader [36].

CONCLUSIONS

Marshall and Warren will forever be linked with bringing the pathogenic potential of *H. pylori* to the attention of the scientific community at the end of the 20th century. However, many others had alluded to the presence and potential pathogenicity of gastric bacteria prior to this. Here we recognize the pioneering work of Guilio Bizzozero in the study of microbiology and gastric pathology in the 19th century. He made the initial discovery of microorganisms, most likely a species of *Helicobacter,* in the canine stomach. He also made multiple contributions in the areas of public health, hematology (he discovered platelets), nephrology, and histopathology.

Conflicts of interest: None to declare.

Authors' contributions: R.J.L.C. conceived the idea, researched the topic and prepared the first draft. E.M.M.Q. performed further research on the topic, reviewed and revised several drafts of the manuscript, added references and checked all references. Both authors reviewed and approved of the final submitted version. Both authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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