Received: 27 June 2020 | Revised: 5 August 2020 | Accepted: 21 August 2020

DOI: 10.1111/nmo.13995

REVIEW

Neurogastroenterology & Motility NGM WILEY

Translating the seminal findings of Carl Lüderitz: A description in English of his extraordinary studies of gastrointestinal motility accompanied by a historical view of peristalsis

Michael Schemann[1] | Gunther Mai[2] | Marcello Costa[3] | Paul Enck[4]

[1]Human Biology, Technical University of Munich, Munich, Germany

[2]Modern and Contemporary History, University Erfurt, Erfurt, Germany

[3]Human Physiology, College of Medicine and Public Health, Flinders University, Adelaide, South Australia, Australia

[4]Department of Internal Medicine VI, Psychosomatic Medicine and Psychotherapy, University Hospital Tübingen, Tübingen, Germany

Correspondence
Michael Schemann, Human Biology, Technical University Munich, Liesel-Beckmann Strasse 4, 85354 Freising, Germany.
Email: schemann@wzw.tum.de

Abstract

Background: Carl Lüderitz provided the first comprehensive description of peristalsis in vivo in his publication from 1889 before Bayliss and Starling described the peristaltic reflex in isolated intestinal segments ex vivo 10 years later. At that time, the peristaltic reflex, responsible for progression of intestinal content, was referred to as the Lüderitz-Bayliss-Starling reflex. This shows that his peers around 1900 were very well aware of the significant impact of Lüderitz´s papers.

Purpose: A major intention in this review is to bring the significant contributions by Dr. Carl Lüderitz (1854–1930) to the attention of our colleagues working in the field of Gastroenterology, in particular those interested in Neurogastroenterology and Gastrointestinal Motility. Until 1891, Carl Lüderitz published five more papers on the sensory and motor components of peristalsis including one seminal paper on stimulus-evoked muscle responses in the stomach in vivo. For most of his life, Carl Lüderitz was a practicing physician and doctor for the poor in Berlin. He spent a rather short time in academia, mostly during his studies in Jena under supervision of his cousin, the famous internist Hermann Nothnagel, and later in Berlin, where he volunteered for short periods at various university institutes but without any formal appointment. This paper is to honor Carl Lüderitz. We divided it into four chapters: a short biography, a summary and evaluation of his contributions, a translation of his seminal paper on peristalsis, and finally a historical view on peristalsis.

KEYWORDS
lüderitz, peristalsis, polarized reflex, propagation, transit of content

1 | INTRODUCTION

The idea for this project started in the summer of 2018 initiated by the search of one of us (MS) for a picture of Carl Lüderitz. Such a picture should honor him during state-of-the-art lectures at meetings for the first detailed description of reflex-induced intestinal motility published in 1889 in German.[1] Our common search for a picture of him turned into an academic research of his life and work, information that was at that time not available at all.

Michael Schemann, Gunther Mai, Marcello Costa and Paul Enck are equal contribution to this work.

Within the last 2 years, we were able to reconstruct the life of Carl Lüderitz to an extent not imaginable at the beginning, and we finally found a painting from his sister showing him, his siblings and his mother (Figure 1).

Part of this issue of Neurogastroenterology & Motility is dedicated to Carl Lüderitz, and we are grateful to the Editors who gave us the opportunity to raise the awareness of the significant contributions of Carl Lüderitz to our field by publishing a translation of his seminal paper and a historical perspective on intestinal peristalsis. An article in Wikipedia will "immortalize" Carl Lüderitz for the generations to come.

We intend to bring the significant contributions by Carl Lüderitz to the attention of our colleagues hoping that his work will never again disappear in oblivion. We have to admit that we became increasingly impressed with him the more we learned about his life, his attitude toward life, and his science.

Our paper is divided into four chapters: first a biography of Carl Lüderitz followed by a summary of his scientific contributions. The third chapter is the translation of his seminal paper on peristalsis from 1889.[1] In the fourth chapter, we discuss some historical aspects related to the description of peristalsis.

Key points

- Dr. Carl Lüderitz provided the first comprehensive description of peristalsis 10 years before Bayliss and Starling described the peristaltic reflex.
- In textbooks at that time, the peristaltic reflex was called Lüderitz–Bayliss–Starling reflex.
- This review provides a short biography of Dr. Carl Lüderitz, a translation of his 1889 paper, honors his contributions, and reviews the history of peristalsis.

2 | CHAPTER I: CARL FERDINAND LÜDERITZ (1854–1930), A SHORT BIOGRAPHY

Carl Ferdinand Lüderitz was born in Berlin on February 2, 1854, as the second son of a merchant family, in the center of Berlin, at a time when the capital of Prussia had some 420,000 inhabitants. Carl Lüderitz´ grandmother, Dorothea Doussin, was of Huguenot origin, and the Lüderitz family belonged to the French Colony in Berlin. His father Carl Adolph died of a furuncle in 1866 before he turned 50 and left his wife with four young kids. The firstborn Albert Carl Siegfried (1850–1928) took over the merchant´s shop and became a bank clerk later in life. His younger sister Kathinka Dorothea Elisabeth (1858–1930) was a well-perceived painter, and the youngest brother, Hermann Guillaume Theobald (1864–1909), was appointed to diplomatic service in Morocco after studying law and the Arabic language. We found considerable evidence for a very close relationship between all of them.

FIGURE 1 This 1888 painting from Elisabeth Lüderitz shows the Lüderitz family. Standing to the left is the painter herself (30 y) next to her mother (63 y). In addition, sitting on the coach is the firstborn Albert (38 y). Sitting in the front chair to the left is the youngest Hermann (24 y). The man standing to the right reading in a book is Dr. Carl Lüderitz (34 y). The painting was stored for decades in a roof storage. We are grateful to Renate Ehrlich, neé Lüderitz (great-niece of Carl Lüderitz), for making us aware of the existence of this painting and Matthias Lüderitz for recovering it. Matthias Lüderitz is the Great-grandnephew of Carl Lüderitz

Carl Lüderitz´ idol and role model was his cousin Hermann Nothnagel (1841–1905), who was one of the most profiled and influential internists at the time. Carl Lüderitz had a great affection for literature and art, and he enjoyed drawing and playing the piano. It was Nothnagel who convinced him to study Medicine instead of Art. Carl Lüderitz began as a medical student at the Friedrich-Wilhelm University (today Humboldt University) in Berlin and enrolled as student No 852 of the year 1872. Two years later, he moved to the University of Jena when Nothnagel became Chairman of Physiology and Director of the Medical Clinic there. Carl Lüderitz was among the best students, so that Nothnagel appointed him one of his four personal assistants for teaching and patient care.

Carl Lüderitz did his final medical examinations during the winter semester 1876/77. He received his diploma as Dr. med. et chir., doctor in medicine and surgery, with a thesis on the theory of progressive muscle atrophy.[2] In 1880, he successfully finished Habilitation, which was (and still is) obligatory in order to enter the academic career pathway in Germany. His Habilitation thesis dealt with experiments on the effects of pressure on motor and sensory nerves.[3] A bit later he was appointed *Privatdozent* (Assistant Professor) and became the only assistant physician in the "Nothnagel clinic" in Jena. The physician Carl Lüderitz certainly impressed Nothnagel as he recommended him to run the private practice of his father Albert Nothnagel while he was on vacation. Shortly before his time in Jena ended, he published a remarkable and highly regarded paper on the morphology and histology of the spinal cord.[4]

With the move of Nothnagel to Vienna in 1882, Carl Lüderitz returned to Berlin. It remains unknown why he did not proceed with a career in academia or why he did not move with Nothnagel. We can rule out any personal discrepancies as both remained very close throughout their lifes. This also applies to the relation between Carl Lüderitz´ siblings and Nothnagel.

After returning to Berlin, Carl Lüderitz shared for a short period home with his family before settling a medical practice in Berlin Kreuzberg, an area with many lower-class apartment buildings. His practice was opposite to one of the largest hospitals at this time, run by protestant nurses (Bethanien Hospital).

Besides running his private practice, he served as a doctor for the poor (*Armenarzt*) from 1883 to 1905, which probably took most of his time. For this, he was paid by the city administration. We cannot really imagine his workload, but assume it was quite high as he served as *Armenarzt* in up to five city districts in various functions, including service as a pediatrician and advising and supervising the poor on hygiene issues. In recognition of his 20 years, community service and the impact of his publications Carl Lüderitz were promoted in 1899 to *Sanitätsrath* (Chief Medical Officer) by the state health administration. This was a very honorable title at the time which filled every physician with great pride.

During his first 10 years in Berlin (until 1890), Carl Lüderitz volunteered for short periods at the Institute of Hygiene headed by Robert Koch and the Institute of Physiology chaired by Johannes Gad. This was one possibility for physicians to use laboratory space and equipment to run experiments without being formerly appointed by the University. He was extremely productive for about 3 years and published 7 papers in the field of gastrointestinal physiology[1,5–11], 2 in microbiology[12,13], and 1 in cardiology[14]. He was a member of the Berlin Medical Society until 1902, attended scientific conferences and local board meetings and medical grand rounds. It remains unclear whether the data in his papers on intestinal and gastric motility were initially generated during his time in Jena under Nothnagel´s supervision or whether the studies were completed or even entirely conducted in Berlin.

According to today's standards, Carl Lüderitz retired early at the age of 53 in 1907. He bought property in the rural colony of Waldsieversdorf, some 50 km east of Berlin. Ida Kreutzfeld, who Carl Lüderitz accommodated in his household at the age of 10 in 1888, took care of him until his death. Carl Lüderitz kept practicing in Waldsieversdorf on an irregular basis. Not much is known what else he did during these years, except finishing a booklet in which he published his thoughts about the general energetics of organisms[15], that received mixed receptions by the medical and scientific community. The ideas presented in this book clearly revealed his affection for the monistic philosophy but not disclosing at how early or how late he developed these thoughts. Although he was not a strict follower, Carl Lüderitz was supportive of the ideas put forward by Herbert Spencer (1820–1903) and Ernst Mach (1838–1916).

On November 16, 1930, Carl Lüderitz died unmarried and childless in his house in Waldsieversdorf from renal insufficiency.

3 | CHAPTER II. SUMMARY AND EVALUATION OF THE SCIENTIFIC CONTRIBUTIONS BY CARL LÜDERITZ

Carl Lüderitz published seminal papers on gastrointestinal motility. He provided the first detailed description of muscle responses after distension of the intestinal lumen by a balloon or by fluid instillation.[1] It is important to note that he confirmed results from his in vivo studies on ether- or chloroform-anesthetized animals. Before his time, many experiments were exclusively based on vivisection research with questionable functional relevance. His study design allowed him to observe not only the contractile state of the muscle but also the consequences of contractile patterns for intraluminal transit of the balloon or the fluid. By the observation of both, he was the first to reveal the relevance of peristaltic and non-peristaltic motility patterns on transit. It is fascinating to read in the two companion papers his detailed observations of muscle movements and his honesty to describe the variations in the response in great detail.[1,8] He never actually recorded motility but his skills to describe muscle movements and transit down to the smallest detail is so impressive that one actually imagines seeing the real tracing. He was the first to realize that the aboral movement of a bolus triggers consecutive reflexes, which result in propagating contractions as part of a peristaltic wave. Although he did not perform pharmacological studies, he was convinced that the reflexes triggered by distension of the gut were to a great extent mediated by intrinsic nerves. Already in the earlier paper, however, he suggested that muscle reflexes are not solely triggered by mechanosensitive intrinsic neurons but also by mucosal elements and the muscle itself.[1] In the companion paper, he observed in anesthetized rabbits and cats the consequence of spontaneous motility for the transit of an intestine still filled with regular content.[8] He verified that the same muscle responses induced by balloon distensions were also responsible for peristalsis in the normally filled intestine. Moreover, he reported that crushing a defined region by tweezer caused a substantial impairment of the peristaltic contraction.[8] The rational for applying the damage was to disrupt the signal conductance without producing a constricted area; the size of the crushed region was not specified but based on the description it must have been around 1 cm. Frequently, the propagating contractions became smaller and smaller as they approached the crushed region and stopped about 1 cm proximal to it. In case, the content was pushed through the crushed area the contraction was restored distal to that region, provided the distension was sufficiently strong. However, the contraction amplitude immediately distal to the crushed region was much smaller and regained its normal strength only a few centimeters further distally. In the same study, he found out that ligation of the mesenteries had no negative effects on propagating contraction and peristalsis, but rather increased the excitability such that already a weak mechanical stimulation with tweezers evoked peristalsis even in an empty segment. Most important, he concluded that exogenous influences are not necessary to evoke propagating contraction and stressed

again the importance of intrinsic nerves and other structures in the gut wall for the reflexes.

Although he was aware of the muscle quiescence distal to the distension, he believed that the contraction proximal to it is more important and viewed peristalsis as propagating contractions without the necessity for active muscle relaxation ahead of the bolus. He carefully distinguished between peristaltic movements of the muscle, meaning propagating contractions, and proximal to distal transit of luminal content. He reported that peristaltic movements of the muscle only empty the segment if the contractions are strong enough. Moreover, he emphasized that distension at one region or fluid instillation does not per se evoke propagating contractions. It is rather the amount of distally propelled content and the resulting degree of distension that decided whether the muscle will be sequentially activated.

His observations go beyond the mere description of muscle activation proximal and muscle inhibition distal to the site of stimulation. He revealed the relevance of local muscle excitation at the site of distension.[1,7] This local muscle contraction is an important part of the reflex as it helps to sensitize mechanosensitive enteric neurons to compressive forces. We suggest that the failure of the muscle to contract at the site where it is distended may explain the lack of peristalsis in an atonic intestine. He later found that this local muscle contraction is the most reliable muscle response in the stomach after mechanical stimulation by serosal probing.[9] To the best of our knowledge, he was the first to appreciate the role of the longitudinal muscle during and in preparation of peristalsis.[9] He observed that during peristalsis the longitudinal muscle contracted shortly before the circular muscle, and the longitudinal contraction involved a much larger region (up to 5 centimeters proximal and distal to site of stimulation). In addition, he reported that the longitudinal shortening and elongation sometimes occurred way before the circular muscle induced the narrowing of the lumen which then pushed the content distally. From his findings, Lüderitz concluded that propagating contractions and peristalsis in vivo is not triggered by a single stimulus modality but rather a result of several stimuli of different modalities that sum up to initiate peristalsis. Thus, he was probably the first to realize that the peristaltic reflex is not an "all or none" response but highly variable due to modulatory influence.

In 1891, Lüderitz published his finding on motor reflexes in the rabbit, cat, and dog stomach.[10] Here, we only summarize the consistent, species-independent findings. The muscle response to mechanical (probing the serosa) or chemical (serosal application of a sodium crystal for 5 seconds) stimulation was different from those observed in the small and large intestine and by far more variable. In the corpus and fundus area, there was a reproducible contraction at the site of stimulation, less often a proximal contraction whereas propagating contractions were rarely evoked. In the antrum, serosal application of a sodium crystal evoked not only a contraction at the stimulus site but also a muscle excitation proximal and distal. In this study, he also reported that the muscle reflexes were similar in an isolated stomach preparation and therefore independent of extrinsic nerve supply. Contrary to what he observed in the small and large intestine, neither serosal probing, chemical stimulation with the sodium crystal, nor electrical stimulation evoked a contraction covering the entire circumference.[10] In most cases, the contractions did not even span the entire half stomach (ventral or dorsal part) but was generated more or less around the stimulated area. He was also among the first to describe region-specific motor patterns in that spontaneously occurring peristaltic waves (phasic contractions) occurred in the distal but never in the proximal stomach (isolated whole stomach preparation). Although Hofmeister and Schütz described spontaneous motility in an isolated stomach preparation already in 1886,[16] they could not make the functional distinction as their preparation revealed phasic contractions in all areas. Using more sophisticated techniques, we confirmed more than 100 years later the observations of Lüderitz by showing that the muscle reflexes in the stomach are mainly excitatory.[17] Stretching a flat sheet stomach preparation evoked muscle contractions at the site of stimulation as well as above and below. A small inhibitory response at the distal site is only elicited when the muscle excitation is blocked by atropine. The achievement of Lüderitz is even more amazing considering that years of recordings, refinement of techniques, and gigabytes of data were needed to come up with basically the same conclusion as he did, by carefully observing the muscle contract.

As long as the vast majority of scientific papers were mostly published in German, the contributions of Carl Lüderitz were very well received among his peers. The highest honor was probably the recognition of his achievements by Paul Trendelenburg who termed the muscle responses evoked by distension of the gut as the Lüderitz-Bayliss-Starling reflex.[18] It is not known whether the two ever met or whether Lüderitz was aware of the studies by the late Trendelenburg as he retired well before.

Bayliss and Starling and the investigators thereafter ignored the discoveries by Lüderitz (see section on the history of peristalsis further below).[19] Once introduced, the term “Bayliss & Starling reflex” kept penetrating the literature. In contrast to most of his peers publishing in English, Lüderitz was multilingual; he spoke Latin (that is why he could read the original description of motility by Albrecht von Haller), ancient Greek, French, and presumably also English.

Carl Lüderitz published two papers in the field of microbiology which arose from his time at the Institute of Hygiene in Berlin[12,13]. He discovered some anaerobic bacteria that were named after him. We know from one source that he sent out those bacterial cultures. Marcel Nencki (1847–1901), a well-known chemist, thanked Lüderitz for the generous supply of his bacterial strains to study protein digestion by anaerobic microorganisms.[20]

Lüderitz´s study at the Institute of Physiology in Berlin led to a groundbreaking paper in the field of heart physiology.[14] According to Schaefer and Kuhtz-Buschbeck,[21] Carl Lüderitz provided the earliest observations on mechanotransduction in the rabbit heart with this 1892 paper.[14] He recorded irregularities in cardiac rhythm after

increasing the outflow resistance (aortic stenosis) and concluded that increase in pressure in the left ventricle was responsible for this intrinsic reflex of the heart. Three years later, Otto Frank reported the same phenomenon in the frog heart.[22] Although Frank referred to the Lüderitz paper, he received all the credits resulting in the "Frank-Starling-law of the heart," which is taught in every physiology course. This is another example of a forgotten discovery by Lüderitz.

It seems that at this time, discoveries were credited to Professors rather than to practicing physicians doing science. Carl Lüderitz had his most productive years around 1890 when almost all his papers were published.

4 | CHAPTER III. TRANSLATION OF EXPERIMENTELLE UNTERSUCHUNGEN ÜBER DIE ENTSTEHUNG DER DARMPERISTALTIK. [EXPERIMENTAL STUDIES ON THE GENERATION OF INTESTINAL PERISTALSIS]. *ARCHIV FÜR PATHOLOGISCHE ANATOMIE UND PHYSIOLOGIE UND FÜR KLINISCHE MEDICIN* 1889; 118(1): 19–36

Dr. Carl Lüderitz from Berlin

Even though numerous observations show that intestinal movements depend on the nature of luminal contents and on the excitability state of the intestine, a detailed description of these movements, and how peristalsis is evoked under physiological conditions is unclear. In particular, the question how luminal content is transported under normal circumstances from proximal to distal, from stomach to anus, awaits to be answered.

Having said that, it needs to be emphasized that the concepts about the cause of the peculiar direction of luminal movements became more and more plausible and comprehensible over the last few years. As *Nothagel's* animal research showed, the peristaltic movements in a normal intestine filled with regular content only occurred from stomach to anus. In contrast, the presence of irritating substances within the intestine caused antiperistaltic movements. As *Nothnagel* correctly stated: Preformed features must exist, which only allow movements down the gut in the living intestine in which normal content leads to intestinal filling in a normal way. Related to the above, *Nothnagel* discovered peculiar movements after chemical or electrical stimulation of a circumscript area of the normal intestine. This was opposite to previous assumptions that motility extends evenly in proximal and distal directions. Nothnagel described a contraction of the circular muscle which starts at the site of stimulation and extends for varying distances in the direction of the pylorus upon touching the outer surface of the intestine with a Natron crystal (most robustly in the rabbit, as here the occurrence is most pronounced). Electrical stimulation of the intestine evokes a similar contraction which moves in the direction of the pylorus, whereas the distally moving contraction spans far less, or even generates a more complex response due to the development of an invagination.

Nothnagel H. Zeitschrift für klinische Medicin. Experimentelle Untersuchungen über die Bewegungen des Darmes Band IV. Heft 4. 534. 1882.

Nothnagel H. Zur chemischen Reizung der glatten Muskeln; zugleich als Beitrag zur Physiologie des Darmes. Archiv für pathologische Anatomie und Physiologie und für klinische Medicin. 1882;88:1–11.

Nothnagel H. Beiträge zur Physiologie und Pathologie des Darmes. Berlin: Hirschwald Verlag; 1884:43.

What is the relevance of these events, especially of the sodium crystal-induced contraction? Is this contraction related to those mechanisms supposed to be responsible for normal peristalsis? And what are the underlying mechanisms?

I believe my herein described observations provide some important answers to these questions. This was possible by using a rather simple method which allowed me to observe intestinal motility in living rabbits with opened abdomen kept in a 38°C warm 0.6% saline solution. The experiments were conducted in 19 medium to large size rabbits. However, I confirm that the observed intestinal wall movements occurred in the same way in a total of 75 animals. Some animals were anesthetized by subcutaneous ether injection, and in others, no anesthesia was used; the reported motility events were in both cases the same.

Careful observation of the intestinal behavior of living healthy animals in the lukewarm saline bath—I omit a more detailed description but rather refer to the reports by *van Braam-Houckgeest* and *Nothnagel*—reveals, aside of the many movements whose origin are completely obscure, some motor events with explainable origin. Thus, one can observe quite frequently the following event. The quiet, almost empty duodenum generates upon gradual filling (with bile as more detailed experiments revealed) some weak contractions of the longitudinal muscle which create a pendular movement. Filling and movements become stronger and light ring-like constrictions accompany here and there the longitudinal muscle contractions. Those ring-like constrictions become stronger, more frequent, and longer lasting with increased filling. Finally, more or less rapid, sometimes all of a sudden, the gradually increasing contractions of the circular muscle empty the content of the constricted region distally. After that, the intestinal segment is relaxed and returns to its previous resting state. This sequence often occurs repetitively and was clearly evoked by the liquid content in the duodenum. The final trigger for this activity remains unclear, but it may be the chemical composition of the content or, as it appears, the mechanical deformation alone or in combination with the chemical stimulation. Another motility pattern, called by *van Braam-Houckgeest* in its strongest form "rolling movement" (editorial note: The equivalent today would be giant or power contractions) would suggest that the mechanical stimulus is the main trigger because distally propagating constrictions of the circular muscle push large quantities of liquid content rapidly down the gut. The less vigorous forms of this type of peristalsis

reveal that the region immediately distal to the constriction ring is strongly filled with content, and it seems that this is the starting point where peristalsis is initiated or maintained. There is hardly any doubt left about the activating role of distension when we look at the propagation of a fecal pellet. I observed this movement quite often in the hyperemic, excited intestine or shortly after the death of the animal, when the entire intestine is hyperexcited but less often in an intact not yet excited gut shortly after it has been immersed in saline. The gut segments, locally distended by the fecal pellet, are initially relaxed and quiescent, but all of a sudden, a small region narrows immediately above the pellet and the constriction ring moves the pellet aborally; for no obvious reasons, this movement suddenly stops again.

van Braam-Houckgeest JP. Untersuchungen über die Peristaltik des Magens und Darmkanals. Pflügers Arch. d. ges. Physiol. 1872;6:266–302.

Nothnagel H. Beiträge zur Physiologie und Pathologie des Darmes. Berlin: Hirschwald Verlag; 1884:43.

These observations suggest to study the initiation and sequence of peristalsis after distension of a circumscript region of the gut. Before doing so, I thought it may be advisable to conduct some initial experiments looking at motility after injecting larger amounts of non-irritating liquid into the lumen at various sites. The studies revealed that increased filling of the intestine, irrespective of other properties of the content, is significant for the generation of bowel movements; the daily experience with enemas proves this notion. However, systemic studies are not available, at least not such that visual inspection of the bowel movement verified the response to the stimulus. The observation by Falck that larger water volumes, applied as enemas in dogs, is eliminated faster and more reliable when applied at once instead of in smaller portions only means that a rapid load represents a stronger stimulus for peristalsis than an equally strong but slower distension; in this study (editorial note: Falck study), the underlying bowel wall movements were not observed.

Falck FA. Zweiter Beitrag zur Physiologie des Wassers. Zeitschrift für Biologie, 1873;9:171–242.

To first learn about the effects of rapid filling on motility in longer gut segments, the 38°C warm bathing solution was applied into the lumen by either an enema-like procedure or by puncturing the wall with a fine cannula. This method allowed infusion at different locations, in particular at active or quiescent segments of the small or large intestine. Before infusion, the respective gut segment was tied up orally by a fine thread and lightly clamped 6–10 cm distal by a tweezer. As already known, both the incision (editorial note: evoked by the cannula) and the small pressure applied by the tweezer only generate a very local contraction. Likewise, the thread-induced obstruction did not cause any changes in basal motility above or below the constriction. Of course, these manipulations have to be performed very carefully. The solution was injected rather fast, meaning within 30–60 s, into the small or large intestine at volumes of 5–8 or 10–20 ccm, respectively (editorial note: 1 ccm =1 ml). This resulted in a rather strong distension in the longitudinal and circular direction, which, however, was still below the maximum. Motility ceases of course if the maximal capacity is reached and neither natron nor potassium salt crystals nor strong crushing with the tweezer will cause the muscle to contract. Quite differently are the effects with distension below maximum which gives the muscle enough room to develop its forces.

The results (from 34 experiments) for the different regions were as follows. One observes in the rectum that immediately after infusion the liquid first moved upwards for a few centimeters apparently due to elastic forces of the distal, strongly distended segment. Immediately thereafter, movements occurred at several sites along the distended segment, which consisted of short or long spreading ring-like constrictions that transported the fecal pellets, which had been in part moved orally with the infusion of the liquid, aborally again. After some minutes, these (editorial note: aboral) movements became weaker and the liquid content disappeared gradually. In the proximal colon, delicate, weak movements of the longitudinal muscle at individual haustra occurred either along the entire distended segment or locally at single spots. The distended segment of the small intestine remained quite often quiescent. Orally directed contractions occurred upon touching the serosal surface with a sodium nitrate crystal. In most cases, the distended segment exhibited waxing and waning contractions of the longitudinal muscle or existing contractions got stronger, which was sometimes associated with weak contractions of the circular muscle. The duodenum was particularly sensitive. Most frequently, strong contractions of the circular muscle covering a broader area started at the most oral side (editorial note: side of obstruction by the thread) and propagated all the way down to where the tweezer blocked further movement of the content. The content accumulated there and is completely emptied after releasing the obstruction induced by the tweezers.

As expected, these experiments illustrate, that rapid (editorial note: remember that it lasts 30–60 s), strong filling in the small and large intestine with a neutral solution functions as a motor stimulus: In most cases, muscle movements occur that may increase until forceful evacuation of the content. However, a closer insight into the process which generates peristalsis was not possible with this experimental design. For this to achieve, it is necessary to perform a very local confined mechanical stimulus with a freely moving stimulus device.

I achieved this by the use of a small caoutchouc (soft rubber) balloon which is introduced into the intestinal lumen and inflated only after it was in position. This method is not new for the study of gut motility. *Legros and Onimus* introduced a small rubber balloon attached to a rubber catheter into the gut lumen via a gastric or intestinal fistula, and measured by a manometer attached to the catheter the intraballoon volume changes induced by the muscle contractions. However, they did not measure distension-induced motility but rather recorded "spontaneously" occurring peristalsis. Furthermore, *Hess* introduced a balloon into the dog duodenum via a gastric fistula, filled it through the attached catheter, and concluded from the movement of the catheter which was drawn into the lumen by the aborally moving balloon that the time course of movements

showed strong variations. Both approaches did not allow to observe the movements of the muscle and the balloon at the same time, and hence, the mechanisms generating the movements remain obscure.

Legros C, Onimus ENJ. Recherches experimental sur les mouvements de l'intestine. Journaux d'Anatomie et Physiologie Normale et Pathologie des Hommes et Animaux, 1869;6:37–66.

Hess J. Versuche über die peristaltische Bewegung und die Wirkung der Abführmittel. Deutsches Archiv für klinische Medizin 1887;40:93–116.

The self-made device, which had to be appropriate for the small and thin rabbit intestine, consisted of a 2.5-cm-long hard rubber tube with a diameter of 2 mm. On one end, a thin membrane covered several side ports and the membrane was tied 1 cm away from the tip of the tube. On the other end, I fixed a 0.5-m-long elastic rubber tube with 2.5 mm diameter. The elastic membrane could be strongly inflated with air through a syringe connected to the elastic rubber tube. In collapsed condition, the little balloon had a maximum width of 5 mm and thus could easily be positioned in any part of the gut. After inflation, it could reach a diameter of 2.5–3 cm. The balloon was inserted into the various regions of the small or large intestine by an antimesenteric, longitudinal incision. The incision was performed very carefully to avoid bleeding as much as possible. The non-inflated balloon was pushed for a few centimeters through this incision either in the oral or anal direction. The incision did not cause a particular stimulation of the intestine, except local contractions causing inversions of the mucosa. Carefully performed incisions did not cause any stimulation. Insertion of the tube caused no movements in the usually moderately excitable intestine.

The effect of rapid distension, approximately within a second or even faster, was very variable. The gut could remain completely silent, or more or less vivid movements occur, which eventually lead to nice peristalsis, which is described in more detail below. The reason for the variable responses to distension was due to the degree of distension, and even more importantly to the excitability state of the distended gut segment. The excitability state differed between the various gut regions and varied over time in a particular region. The duodenum was quite sensitive, less the remaining small intestine. The proximal part of the large intestine showed weak responses, whereas the rectum showed again stronger response.

According to the strength of the distension-induced motility, three response types can be distinguished, notwithstanding that there existed transitional variants.

1. The intestine remains silent after weak but also very strong balloon distensions which eventually cause rupture of the gut. The strongest distension evokes pain responses in the animal together with a reflex-evoked decrease in the blood supply of the intestine. The absence of motility responses even after strong balloon distension is a quite frequent phenomenon in the proximal large intestine, the lower half of the small intestine, and in regions that were without spontaneous motility before distension. Under these conditions, the reaction to application of a sodium crystal ranges from poor to prominent.
2. The intestine contracts immediately above the distension, and often the contraction moves further orally, sometimes for several centimeters, while the balloon itself does not move (editorial note: What Lüderitz describes here is that the ring-like constriction above the distension propagates orally. This compares to the sequence during milking by hand where the teat is constricted by a rolling movement of the fingers and is similar to the description later by Bayliss & Starling 1899). No motility occurs below the distension. The length of the region that contracts is very variable. Often, there is a small indentation just above the balloon. In other, rarer cases, but most pronounced in the small bowel, the contraction extends for variable lengths, from 1 to 3 and up to 6 cm orally. With strong contractions, the gut elongates and becomes a narrow, solid tube. At the upper end, the constriction either gradually extends to the adjacent relaxed region (editorial note: still above the distension), or the relaxed segment invaginates and thereby covers the contracted segment. Occasionally, the oral contractions do not cover the entire segment but leave a few millimeters of quiescent muscle in between, which then contracts a bit later.

The pattern does not start immediately after the distension but it usually takes 2 or 3, sometimes even 5–8 seconds to develop. The constriction oral to the distension peaks within 1–2 s and then gradually declines starting from the most oral site of the contracted segment (editorial note: that means that the gut relaxes first where it contracts last). Close to the balloon, however, the constriction remains. The sequence of a waxing and waning oral contraction may occur again (editorial note: under maintained distension). The contraction which develops oral to the balloon may stay for minutes, provided the distension remains.

The above-described phenomena have been basically observed before and are very similar to the motor events induced by touching the outside of the gut wall with a natron crystal. The fact that the contraction after distension lasts longer is due to the fact that the distension is maintained whereas the crystal is only briefly applied. In addition, the contractile response at the site of the chemical stimulus is masked in the case of balloon distension because the balloon acts as a resistance to contractions. If the balloon is deflated, it is obvious that the previously distended area narrows as a result of circular muscle contraction. There is only one quantitative difference between distension and chemically induced responses. While a prominent 1 cm wide contraction may occur after touching the gut wall with the sodium nitrate crystal, this particular spot showed in most cases a smaller response to distension and sometimes no response at all. This was true for all regions (the cecum and appendix were not studied). A forceful 2 cm wide contraction in response to distension was only seen if the region exhibited a high excitability, something that actually happened quite often.

To round off the picture, it has to be noted that the degree of distension, of course within certain limits, has significant influence on the response. Usually, the balloon was distended only up to 15 mm diameter so that the intestine was only moderately dilated, by far not to its maximum. If a response is lacking or only very weak, it can

be evoked or prominently enhanced by increasing the distension. In addition, the speed of distension affects the response. While a moderate but rapid distention evokes the typical oral contraction, a strong but rather slow distension which develops within 1 to 2 minutes may not induce a contractile response at all. Although the degree and the speed of distension influence the response, the state of excitability of the segment is of utmost importance and much more relevant for the strength of the response. The reasons for the variability in excitability along the gut and at different times of the experiment remain unknown.

1. The balloon moves down the gut because the ring contraction immediately at the oral edge of the balloon propagates in a peristaltic fashion distally and pushes the balloon ahead of it. The distal movement may only span 1 cm, and then, the balloon rests or the propagating contractions occur at even smaller distances in between. By far most often, the balloon moves distally for 10 cm and more. The speed is quite impressive and reached many times 8 cm in 30 seconds.

It is evident that the oral contraction causes the movement down the gut. If propagation in the distal direction happens the contraction starts at the very oral edge of the balloon, immediately above the distended area, as soon as the elastic membrane starts stiffen. The contraction then extends a short distance orally before it propagates aborally to push the balloon distally ahead of the contraction. Unfortunately, the exact origin of the oral contraction remains unknown as it is masked by the distension. It may start where the maximal distension is or a bit further orally. In particular, I am not able to report whether the oral contraction, once generated, only extends orally or also anally. The latter is very unlikely because the intestine distal to the distension is wide and relaxed even when the oral contraction covers 6–8 cm of the intestine. Direct evidence that the oral contraction causes movement down the gut came from two types of experiments. I applied a natron crystal onto the intestinal surface either at a region where one fecal pellet was isolated from other pellets or whenever the moderately inflated balloon rest quietly. If one touches the surface above the pellet or above the balloon, an oral contraction is induced but neither of the two objects (editorial note: pellet or balloon) moves. Stimulation a few millimeters distal to the objects induced an oral contraction that pushes the object in the oral direction. Application of the salt crystal in the middle of the distended region, where the state of excitability of the distended region is the highest, causes an oral contraction that constricts the gut just above the objects and pushes them down the gut; the movement usually stops at the site of stimulation or a bit further distally.

As described above, it may happen that distension-induced oral contraction that involves a large constricted area of 4 to 6 or even 8 cm (in the duodenum) in length does not induce any movements. This is simply due to the fact that the strength of the contraction cannot overcome the resistance generated by a strongly distended balloon which works against the propulsive force of the contraction, in particular, when it is compared to the relatively low resistance generated by liquids or gas at amounts which distend the gut to a degree similar to that induced by the balloon distension. Although there is ongoing stimulation of the gut with maintained distension, the force of the oral contraction is then not strong enough to push the balloon distally.

The further transport of the balloon is possible because the balloon keeps distending more distal regions and the distension sequentially activates contractions just above the balloon. If one deflates the balloon during its propagation, there is still a contraction at the previously distended area but the peristalsis ceases.

In the normal intestine, the distension-induced peristalsis over long distances is a rather rare phenomenon. It is also rare to see spontaneous strong contractions. I mostly observed that the balloon was sitting there without or more often with weak oral contractions. However, I observed the distal movement of the balloon also under apparently normal conditions in the small and in the large bowel. At the same time, these regions exhibited a higher excitability as revealed by the strong reaction to the application of the natron crystal onto the gut wall. In one large and strong rabbit, I observed shortly after exposing the viscera very vivid, wheel-shaped rolling movements that pushed plenty of liquid content down the small intestine followed by a period of quiescence. The large bowel was completely quiet, but the rest of the intestines appeared more filled than usual. In this animal, the balloon, when positioned in the small and various regions of the large intestine, was transported distally much smoother and faster than in all other animals. For this to happen, it was not necessary to apply a lot of distension, as a rather small inflation of the balloon was sufficient. In the duodenum, the following events were seen in several animals. First, the balloon was introduced through an opening 16 cm below the pylorus and pushed a few centimeters toward the pylorus into the resting, only slightly filled duodenum. After inflation, which caused only a very small distension of the gut wall, the segment gradually filled with liquid content and started to show increasingly more movements, while below the balloon the gut stayed completely quiet. Shortening and elongation, in particular ring-like contractions, covering a broad area occurred. The latter contracted the distended area just above the balloon and rapidly pushed the liquid content and the balloon distally and finally through the incision out of the intestine. In case, the segment above the balloon did not fill-up, the moderately inflated balloon mostly remained at one place. However, under those conditions irregular contractions just above the balloon occurred pushing the balloon distally. Such fluctuations in the excitability of the intestine were not rare as also stated above. Thus, it happens that no activity is observed after careful introduction of the collapsed balloon into the resting duodenum. However, a second introduction shortly thereafter caused a spasmodic constriction pushing the non-inflated balloon distally and through the incision out of the gut. I cannot provide an explanation for such a variation in the local excitability.

Once the intestine becomes irritated due to the manipulation, it is more often than normally seen that individual gut segments are so excited that the distension stimulus induces peristalsis. This occurred primarily in the rectum where it is difficult to avoid insults by the incision

and the introduction of the balloon and the tube. As a result, a delicate peristalsis was evoked which pushes the balloon and a fecal pellet toward the anus. Enhanced excitability of the entire gastrointestinal tract developed shortly after the death of the animal. Much more frequent than in the normal intestine of the living animal, of course not all the time and not everywhere, very nice distension-induced peristalsis could be observed, in particular in the rectum.

The above findings must be complemented in future studies and extended to other species. I summarize the most important results realizing that this cannot provide a detailed discussion or explanation of the phenomena.

Rapid filling of the intestine is in every region an appropriate stimulus to evoke peristaltic movements in the filled segment. The local distension with the rubber balloon provided further insights into this process. Under certain conditions, which depend on the degree of distension and the state of excitability, the distension evokes an oral contraction spreading over various short distances which narrows the lumen above the balloon while there is no activity below the distended segment. This contraction is similar in all aspects to the one that occurs by touching the outer surface of the intestine with sodium salt crystal. When there is enhanced excitability, the balloon is forced downwards and keeps stimulating more distal areas which eventually results in a peristaltic wave.

These results confirm at first the assumption that preformed structures exist by which the downward movement of the content is initiated. The fact—not described in detail above—that distention still evoked an oral contraction even after ablation of the nerves that enter the gut via the mesentery proves that such structures must reside within the gut wall.

The way the peristalsis pushes the gut-distending object distally is interesting: not, as one may assume, is it the result of a single local stimulation of a highly excitable segment but it is the result of many triggers originating in always new (editorial note: he means more distal) gut locations. The single contraction as part of the peristaltic wave and as a result of the local distension has no tendency at all to propagate further down. Just to the contrary, it moves upwards. This also explains the rather peculiar contraction that occurs after stimulation of the gut surface by a natron salt crystal, which is in every aspect similar to the distension-induced oral contraction. Now the relevance of these peculiar contractions becomes obvious and it is now readily understandable that this contractile response may be used to reveal the excitability state of the intestine. After all, the fact that the ascending contraction tends to extend orally is striking. It is conceivable that such a contraction, provided it generates enough force, causes downward movement of an object (fecal pellet or rubber balloon) that locally distends the gut. The contraction starts at the site where the distension is the strongest and narrows the lumen in an ascending direction, thereby pushing the object distally. Peristalsis which is induced by other stimuli than distension seems to require more. However, it has to be considered that the exact starting point of the ascending contraction, which is masked by the distending object, always occurs slightly oral to the application site of the natron salt crystal. I suggest that exactly this phenomenon is crucial for the downward movement.

The oral contraction clearly involves the nervous apparatus and is not a consequence of direct muscle stimulation. For the natron salt-induced contraction, the nervous origin has been proven. For distension-induced contractions, a similar origin may be assumed without doubt. In the first place, the nerves of the myenteric plexus, which is located between the two muscle layers, come into question. Whether the excitation is directly mediated through distension of the ganglionic network, or rather indirect through stimulation of the mucosa or both awaits a final answer. Even dedicated experiments, that attempted to restrict the mechanical stimulation to the mucosa, were inconclusive. Besides the neurally generated muscle excitation, an additional direct excitation of the muscle at the site of distension seems likely. This direct muscle excitation is revealed by narrowing of the distended area after deflation of the balloon.

The ascending spread of the oral contraction cannot be sufficiently answered by histological and physiological means. A possible yet to be substantiated explanation for the ascending spread of the oral contraction may lie in the particular properties of the ganglionic plexus in the gut wall. After local activation (through distension or adequate chemical stimulation), the resistance to the spread of excitation in the oral direction may be smaller than in the anal direction. Upon chemical stimulation of a moderately excitable segment, the contraction starts slightly above the site of stimulus and only moves upwards. However, if the segment is in a highly excitable state, contraction also moves a little bit downwards. This may be due to projection-specific nerve conduction properties within the nervous apparatus. I suggest this with reservations as there is no sufficient evidence for this assumption. I like to point out that my findings refer to the activity of the circular muscle. The role of the longitudinal muscle still needs to be studied. Recently, *Biedermann* observed that electrical stimulation caused contraction of the circular muscle beneath the anode whereas the longitudinal muscle contracts beneath the cathode; this may eventually help but is at the moment not really useable. In the normal intestine, the activity of the longitudinal muscle is often very pronounced and more frequent than the contractions of the circular muscle. If a segment starts to be active, it is frequently the case that there is initially a longitudinal shortening and elongation, often in a peristaltic way. Only if this reaches a certain strength, there is an additional circular narrowing of this segment. I cannot say how the longitudinal muscle behaves during the distension-induced oral contraction. Sometimes it seemed that the longitudinal muscle contracted a little bit before the circular narrowing occurred. I refrain from discussing the various hypotheses about the role of the two muscle layers for peristalsis.

Biedermann W. Zur Physiologie der glatten Muskeln. Pflüger's Archiv für die gesamte Physiologie des Menschen und der Tiere 1889;45:369–389.

5 | CHAPTER IV: HISTORICAL PERSPECTIVE OF INTESTINAL PERISTALSIS

In order to fully appreciate the work of Lüderitz in its historical perspective, we briefly revise the history of investigations on intestinal

peristalsis. We do not cover studies using current methodologies. We also turn our attention to the confusing terminology used, over the centuries, and in different languages, to describe not just peristalsis, but also the direction in which it progresses.

Contrasted with studies of other organs, studies of intestinal motility are relatively recent. Because the digestive tract is mostly hidden from direct view, it has been hard to properly describe its complex behavior, except at its oral and anal ends. Whereas sophisticated anatomical descriptions have been available since the Renaissance, this has not been the case for movement with its changes of size, position over time (kinematics), or forces (kinetics). The history of these studies is intertwined with the history of the available methodologies and instruments.

Most of the early observers must have surmised that since ingested food usually comes out through defaecation, it must progress by a process of aboral propulsion toward the anus.

The earliest descriptions of this polarized movement are lost in the mists of time, as Cannon commented in 1911, “for centuries, the priests and the butchers, who watched the entrails of their sacrifice victims, knew as much as the physicians about the mechanical factors of digestion” and that “the food must be moved always onward”.[23]

5.1 | The 1600 s

During early vivisection studies on blood circulation, movements of the intestines would have been noticed, but were not described in detail. In 1679, however, the Swiss physician and anatomist, Johann Jakob Wepfer, published a remarkable work (quoted in ref. 24). He mentions the inhibitory effect of an ancient poison, *cicuta* (hemlock) on the movements of dogs’ and wolves’ digestive systems.

The detailed drawing of Johannes Walaeus (from ref. 25) of a loop of intestine, with the chylic vessels ligated, would leave little doubt that movement of the intestine during vivisection would have been noticed.

The main observation, since ancient times, was a ring of intestinal constriction traveling aborally—named "peristalsis," a generic term from the Greek roots, *peri*, "around," and *stalsis*, "constriction."

The term was already well-defined in the *Dictionaire Raisonne’ d’Anatomie et de Physiologie* 1766 (Paris; Chez Vincent imprimeur) where the word "*peristaltique"* was defined as “to contract, to tighten. We give this name to the vermicular movement of the intestines, which tends to push out the excrement outside, and to facilitate the entry of the chyle into the milky vessels (“‘peristalticus’, ‘contracter’, ‘resserrer’." “On donne ce nom au mouvement vermiculaire des intestins, qui fert à pouffer les excrémens dehors, & à faciliter l'entrée du chyle dans les vaisseaux laiteux”).”

Early scientists’ descriptions of peristaltic movements showed superb scientific insight. However, much faster or much slower events were bound to escape even the most attentive observers. Not surprisingly, more complex behaviors went unnoticed until recently, when some kind of recording apparatus was used.

5.2 | The 1700 s

Since the 1700 s, there have been many explicit mentions of intestinal movements, and even of the possible presence of nerves in the gut. Albrecht von Haller, in his classic dissertation, was one of the first to ask about the nature, in living organisms, of the mechanisms behind the bowel's responses to different stimuli.[26] "The main issue was the nature of ‘irritability,’ that is, the responses of different parts of the bodies of dogs, goats, rats, rabbits, and other animals to some irritation—blowing, heat, spirit of wine, the scalpel, *lapis infinalis* (silver nitrate), oil of vitriol (sulfuric acid), and butter of antimony (antimony trichloride). I examined attentively whether or not—upon touching, cutting, burning, or lacerating the part—the animal seemed disquieted, made a noise, struggled, or pulled back the wounded limb." He concluded, “In the human body, the nerves only are capable of sensation.” He distinguished between irritability and sensibility. "If you irritate the nerve which has been cut, the muscles of the leg are seized with a trembling motion; therefore, at that time, it is irritable, though quite insensible”. He "irritated" the isolated intestine and described its movements. “I have tried experiments of the same kind upon parts separated from the body. The intestines in this state, after being deprived of all communication with the brain, preserve their peristaltic motion; and if you touch them with a knife or corrosives, they put on the same appearances as if they were in their natural situation, and still preserved their connection with the nerves and the brain”. He adds, “I have frequently repeated the experiment just now mentioned: *viz*, I pulled out the intestines as quickly as I could, and cut them into four or eight pieces, all of which moved separately, still preserving their peristaltic motion and contracting, however manner they were irritated." Albrecht von Haller also gave what is probably the first explanation of how peristalsis might operate. “I never saw the peristaltic motion more plain than in a cat which had swallowed corrosive sublimate, but it is so difficult to observe the peristaltic motion that it is very hard to reduce it to any certain rule. In general, however, the intestines are evidently constricted where that motion obtains, while the part below the constriction is dilated, and receives the contents which the constricted part sends to it”—clearly a first description of functional polarity. He also described the effect of opium on intestinal movements “This medicine destroys so effectually the peristaltic motion of the intestines and stomach that it cannot be revived again by any irritation.” The effect of opium on peristalsis had already been reported in 1745 by Kaau-Boerhaave, who administered 3 grains of opium to a small dog and noted, among its effects, the cessation of peristalsis.[27]

Similar observations were made by von Haller, with another of his students, Johann Adrian Sproegel, when in 1750 and 1751, they were experimenting on the effects of poisonous substances (quoted in ref. 28).

5.3 | The 1800 s

In his textbook of "Morbid Anatomy" in the early 1800 s, Monro briefly mentions propulsive movements: “the food is carried

though this long circuitous route by a series of powerful muscular fibres, which constitute one of the coats of the alimentary canal; and these coats perform their offices so accurately, as to propel their contents contrary to their gravity, and even to push forward air or quicksilver. The muscular coats also produce the peristaltic and anti-peristaltic motion, which is kept up by the stimulus of the food."[29]

Reports by surgeons began to include observations on intestinal motor disorder. Interestingly, "peristalsis" was commonly used to describe apparent movements of the gut seen by palpation or by observing ripples over the surface of the abdomen and attributed to the intestine.

In general, books of medicine relating to intestinal diseases mostly described acute diseases, such as obstructions, wounds, ulcerations, strictures, internal strangulations, volvulus, intussusceptions, perforations, poisoning, inflammation, and infestation. They gave only cursory mention to the movements of the intestine.[30]

The discipline of physiology was to be developed, notably by Claude Bernard, in the second half of the century.[31] It included some pioneering work, not directly on intestinal motility, for example, on vagus-mediated gastric secretion by Brodie.[32]

The major obstacle to the advancement of physiology was the lack of suitable methods for recording movements of bodily organs. William Harvey, while studying the heartbeat and associated arterial pulse in the late 1600 s, concluded that their relation to breathing was impossible "without a more exact method of simultaneous measurements of heartbeat and respiration". He wrote "…I found the task so truly arduous… that I was almost tempted to think… that the movement of the heart was only to be comprehended by God. For I could neither rightly perceive at first when the systole and when the diastole took place by reason of the rapidity of the movement…" (quoted in ref. [33]).

By the 1840 s, physiologists, mostly in Germany, aimed increasingly at a more quantitative, physically oriented physiology.[34,35] The need to develop apparatuses to record physiological parameters was well expressed in several laboratories. Carl Ludwig, a professor of physiology, originally in Marburg and later in Leipzig, developed the "kymograph," a revolving cylinder coated with smoked paper.[36] This recorded graphically the motions of the heart. Its development has been recognized as a crucial advance in physiology. The main advantage was objective quantification—and therefore the sharing of experience. It allowed "precise measurements and mathematical analysis of curves. Recording become crucial to reveal subtle motor patterns and to investigate quantitatively hidden mechanisms".[34] Ludwig's kymograph enabled the study and analysis of a wide range of physiological events which had previously been inaccessible. The ability to graphically record physical events, and thus share and repeat experiments marked not only the birth of modern physiology but, in general, the birth of modern biological science. Ludwig initially applied the graphic method to measure blood pressure[36] and was used to measure other movements such as striated muscle contractions.[37,38] von Helmholtz used preparations of striated muscle to measure the speed of propagation of previously mysterious nerve signals.[37]

Paradoxically perhaps, after the German invention of the kymograph, two French investigators, Legros and Onimus, were the first to use it to record, in 1869, spontaneous contractions of the small intestine in animals.[39] Using rubber balloons, they recorded intraluminal rhythmic pressure changes in stomach and intestine in a rabbit, a dog, and a guinea pig. They also used a simple "differential manometer" consisting of a U-shaped glass tube partially filled with fluid. The oral end of an isolated segment of rabbit small intestine was attached to one end of the differential manometer and the anal end of the segment to the other end. They drew a realistic diagram showing the results, with the meniscus at the anal end at a higher level than the oral, revealing, probably for the first time, a clear polarity of the propulsive forces. They stated "…in a living animal, if by chance there are movements, it is impossible to determine exactly their frequency and, above all, their direction, and the observer believes that he is seeing undulations as much in one direction as in the other. Because we experienced these illusions when we started our investigations, we immediately realized the need to use more rigorous methods". They also developed an ingenious method, using a rubber balloon and electrodes for stimulation. The rationale was impeccable: The graphic recordings "give the advantage of rendering indisputable the results of the observations and place beyond doubt the sincerity or the illusions of the observer."

Other methods of recording other physiological parameters were developed in the 1800 s, for example, regarding the auscultation of bodily sounds. Auscultation was known to Hippocrates and practiced in ancient Greece in respect of the lungs, but probably also applied to stomach and intestines. In 1702, Hooke had written "it is common to hear the Motion of Wind to and fro in the Guts…".[40] The practice of direct or proximate auscultation (listening to the chest sounds and heartbeat by pressing the ear to the chest wall) was used by doctors in the 1800 s (as was percussion). Direct auscultation was hardly an ideal way to examine obese or unclean and often infected patients; modesty was an issue with females. This led Parisian René Laënnec to invent the stethoscope in 1816 to listen for sounds from the lungs and heart. His invention revolutionized Medicine.[41] Hooker was probably the first to use a stethoscope to auscultate intestinal sounds—or what he thought were the sounds associated with peristalsis.[42] Much later, Cannon recorded stomach sounds by a telephone system which triggered an electrical stimulus of a neuromuscular preparation, graphically recording the contractions with a kymograph.[23]

5.4 | The origin of the idea that peristalsis is a neurally mediated phenomenon

Peristalsis has been described either as single waves of contraction which push the contents slowly or quickly, or as advancing fronts of strong rhythmic activity. It was also described as a sudden, fast wave of contraction which can sweep through the entire

small intestine. These fast peristaltic movements were described as *Rollbewegung* or worm-like waves [23,43,44] and were later described as "peristaltic rushes" in asphyxiated rabbits[45] and in the rabbit small intestine subjected to intraluminal irritants.[46] Movements of the longitudinal muscle were well described as *Pendelwegungen* (pendulum movements).[23,43,44]

One of the first to explicitly postulate the existence of an intrinsic nervous system responsible for peristalsis was Lister.[47] "The fact that the movements continue in a portion of gut deprived of its mesentery proves that the nervous apparatus by which the muscular contractions are induced and coordinated in post-mortem peristaltic action, is contained within the intestine... it appears that the intestines possess an intrinsic ganglionic apparatus which is, in all cases, essential to the peristaltic movements, and, while capable of independent action, is liable to be stimulated or checked by other parts of the nervous system...".

The presence of enteric neurones was to be revealed later, with the first descriptions of the submucosal plexus by Meissner in 1857[48] and of the myenteric plexus by Auerbach in 1862.[49] Both publications appeared long after the first microscopic description of the multiple layers of the human intestine had been made by van Leeuwenhoek in 1706.[50] In his original description of the myenteric plexus, Auerbach hinted at a neural influence on motility, although he did not mention peristalsis.[49]

Also Legros and Onimus concluded in 1869 that "without nerve cells peristaltic movements are impossible".[39] An ever more convincing view of intrinsic neural mechanisms responsible for peristalsis was provided by Thom and Crieff in 1879[51] "The vagi and splanchnics unite in forming the solar plexus, from which nerve fibers pass to all parts of the small intestines, breaking up in their walls into smaller gangliated plexuses, called Auerbach's and Meissner's plexuses. These plexuses, containing nucleated nerve cells, are analogous to the intracardiac ganglia, but the muscular action over which they preside is not automatic."

"Each cell possesses an afferent or sensory nerve fiber from the inner surface of the gut, and an efferent one which may be either motor (i.e., to a muscle fiber) or secretory (i.e., to a gland). Stimulation of the afferent fiber by means of food causes the evolution of nerve energy by the nerve cell, and consequent muscular contraction or glandular secretion or both. To these cells, then, is primarily due the peristaltic action of the intestines, and as that is produced by the combined action of the circular and longitudinal muscular fibers, probably separate groups of nerve cells preside over each."

"In the ordinary course of digestion, the presence of food in the small intestine gives rise to stimulation of the afferent nerves proceeding to Auerbach's and Meissner's plexuses, whereby nervous energy is there evolved, and peristaltic action takes place. Thus, the food is passed."

Gowers in 1887 using balloon distension in the human rectum suspected that there was a polarity of neural pathways responsible for peristalsis, with relaxation of the muscle anally and contraction orally to advance the contents.[52] Clear evidence of functional polarity of intestinal responses to irritants was provided in 1882 by Nothnagel.[53]

Cash recorded in 1887 propulsion of artificial boluses and mentioned peristalsis, but without defining the term.[54] He used exteriorized loops and a graphic method *via* a glass cannula [in the] oral end of a loop connected via a membrane. This constituted the "sound" and was connected by means of a system of thick-walled India-rubber tubes with a mercurial manometer or a Marey's recipient tambour. He called boluses "sounds," because they were recorded with a transducer of mechanical vibrations "...the travelling sounds were oblong bodies having rounded ends, and measuring in breadth from 5 to 9 mm, in length 12 to 14 mm, and were made of metal, cork hollowed out, or glass, and in several experiments a solid sound was replaced by a small piece of lean meat." "The registering apparatus consisted merely of a thin wedge of cork bearing a glass pen and traveling vertically by means of two glass eyes passed through its substance upon parallel steel guides. The weight of this falling pen was 2 grams. A fine silk thread from the sound to the pen passed over two pulleys, one placed opposite and in the same plane as the fistulous opening, the second vertically above the steel guides of the traveling pen. When traction was made by the sound, the pen was drawn upwards, its elevation being directly proportional to the extent of withdrawal of the sound from the lower pulley". "Even when peristalsis is occurring, it is slow, and has much of a forward and backward character, complete relaxation behind the sound succeeding an active local contraction. Peristaltic progression in the fistulous intestine is always in the physiological direction. If the sound be placed well within the lower mouth, it is invariably rejected from this mouth."

This detailed description described the main features of the strong polarity of propulsive mechanisms. Later (in 1896), Mall explained propulsion as a process whereby, as a result of the advance of a bolus,[55] "a new portion of mucous membrane is now irritated, which causes renewed contractions."

5.5 | The 1900 s

There is little doubt that the most influential work on the mechanisms of peristalsis was the work of Bayliss and Starling at the turn of the 20th century.[19] They developed the "enterograph," to record contractions and relaxations of the circular and longitudinal muscles elicited by balloon distention and also during the propulsion of a bolus of cotton wool covered with Vaseline.

They revealed a clear polarity of these "peristaltic contractions" with "augmentation of contractions above and inhibition below the advancing bolus". They suggested "for the onward progress of the bolus two factors are equally necessary, namely a condition of excitation and increased contraction above the bolus, and a condition of inhibition and relaxation of the intestine below." They concluded "The facts we have brought forward however show beyond doubt that the local nervous structures in the gut have this power of coordination, of directing one kind of influence along one path, and

another kind of influence along another path, the result being a 'purposive' response directed to the propulsion of the food down along the alimentary canal."

Bayliss and Starling were quite clear in attributing the location of these reflex pathways to the myenteric plexus. "Auerbach's plexus is in fact a local nervous system with two reflexes, inhibition and augmentation, and one function, propulsion of food. The different time relations of the two reflexes would lead one to guess that the system is composed of long paths which conduct inhibitory impulses downwards, and short paths which carry augmentatory impulses from one cell station to another in an upward direction." They warned "A histological testing of this hypothesis presents however considerable difficulties." It would take almost another century before the histological bases of the enteric reflex pathways underlying peristalsis could be revealed by Furness and Costa in 1987.[56]

Bayliss and Starling had already drawn a clear distinction between myogenic and neurogenic movements based on the effect of nicotine, when they wrote "the rhythmic pendular movements produced by simultaneous contractions of circular and longitudinal coats, are entirely myogenic in origin." "The peristaltic contraction, on the other band, is a [true] coordinated reflex excited by the distension of the gut."[19]

Their main conclusion was "The production of the true peristaltic wave is dependent on the unvarying response of the intestinal nervous mechanism to local stimulation, the law of the intestine. This law is as follows: 'local stimulation of the gut produces excitation above and inhibition below the excited spot'. These effects are dependent on the activity of the local nervous mechanism." This suggestion generated subsequent ongoing debate about the wisdom of using such "lawyer-like" terminology.[57,58]

5.6 | What was the role of Lüderitz in the early history of peristalsis studies?

The dual methodological approaches, namely visual description and graphic recording of intestinal movements, raise the question of why Lüderitz chose verbal description of his observations instead of using graphic methods. Was this due to lack of knowledge of the available graphic methods or was it a deliberate choice?

Lüderitz must have been aware of the kymograph, because he quoted the paper by Legros and Onimus. Lüderitz must also have known of Ludwig as an authority since the mid-1800 s and of his invention of the kymograph. So Lüderitz did not lack this knowledge, and he used a manometer in his studies on blood pressure regulation.[14] He must have made a deliberate choice of restricting his description to the verbal. There are clear advantages in using sophisticated verbal descriptions of complex intestinal movements compared with the spatial limitations of a few points of some graphically recorded parameters.

Visual descriptions of intestinal movements gained a significant advance with the discovery of the X-rays by Röngten in 1895. Only a few years later, Cannon applied this novel method to investigate movements in human intestine.[23] The images were either described verbally or as silhouettes of the intestine drawn from the X-rays. These descriptions of human intestinal movements were the beginning of extensive X-ray studies. This technique lasted until the mid-20th century when they were deemed too dangerous for health.

Even in publications quoting graphic recordings, an appropriate verbal description was needed to provide a clearer interpretation of the results. Even Cannon's 1911 classic book, which summarizes an enormous number of observations using X-rays, is fundamentally the result of live visual observations of gut silhouettes filled by radiopaque medium.[23] This need for an appropriate verbal description explains why the insightful observations of an attentive investigator like Lüderitz remain a valid contribution to the history of the study of peristalsis.

Why then has the Lüderitz's work been underestimated? A partial answer might be found in the history of the way in which scientific findings are published, and the prevailing dominance of different languages. From the 1800 s through the 1900 s, a clear shift took place from German to English, with French and Italian remaining marginal. The language barrier played a significant role in the history of these studies and might explain why Lüderitz's work has been little acknowledged.

German was the prominent language of physiology at the turn of the 20th century. Even Luciani's comprehensive Italian textbook on physiology was translated into German in 1890 [59] and only 23 years later into English.[60] Not surprisingly, in an extensive review by Magnus in 1908 the vast majority of papers quoted were in German.[61]

The first comprehensive book by Cannon from 1911 quoted 228 articles in German, 133 articles in English, several in French, and very few in Italian.[23] Thus, 63% of the quoted papers were in German and 37% in English, French, or Italian. By the late 1940 s, however, the extensive book by Alvarez, reviewing his own work in the 20 s and 30 s, and summarizing the full history, quoted a staggering number of articles (2682), of which nearly 64% were in English and just 30% in German.[57] With increasing numbers of investigators publishing in English, papers in German become less acknowledged.

5.7 | How was Lüderitz's work quoted?

Mall, while quoting some German-language papers, did not quote Lüderitz's work. Surprisingly, Bayliss and Starling, although widely quoting several other German and French authors—including Openchowski, Mislawski, Bunch, Courtade, and Guyon—failed to acknowledge either Lüderitz's work or the work of Legros and Onimus. Starling, having quoted Ludwig in his chapter for the Textbook of Physiology (1900),[62] was well aware of German physiology. Even Magnus in his 1908 review failed to quote Lüderitz.[61]

Cannon's 1911 comprehensive book on the motility of the gut (Cannon 1911) quotes two papers by Lüderitz out of the 228 papers quoted.[23] Alvarez, in his monumental 1948 book, quotes Lüderitz's three major papers.[57] Davenport quoted Lüderitz's

papers in his comprehensive historical review.[44] Despite some of these important authors quoting Lüderitz, the majority of researchers have tended to ignore his work. Furness and Costa in a first monograph on the enteric nervous system gave a succinct early history of enteric reflexes in peristalsis but failed to quote the Lüderitz's contribution.[56]

By the early 1900 s, the idea that peristalsis is a neurally mediated phenomenon was well established with the two very different methodological approaches available for studying it. The visual approach offered an unsurpassed finesse in describing fine features of movements, but had poor ability for quantitative analysis. The second method gave precise graphic measurements of one or other physical parameter, objectively recorded, and easily shared. However, such graphic recordings were usually limited to a single or a few points along the intestine and therefore missed the more complete features of the complex movements. It was only much later in the 20th century that a combination of methods permitted better integration.

5.8 | Advances of recording methods and combinations in the 20th century

It was only with the combination of graphic recording of visual and functional physical parameters that the complexity of intestinal movements begun to be unraveled.

In the 1920 s, Welch and Plant, placing a single fluid-filled balloon in the sigmoid colon, demonstrated that the distal colon was rarely inactive, showing regular pressure waves at approximately 2–3/min.[63] They recorded contractions with a rubber balloon introduced *via* a fistula; this was connected though a pear-shaped flask to a Brodie bellows recorder. With this method, and using a kymograph, they also studied in more detail the rhythmic changes in volume of the dog intestine. Welch and Plant had also used X-rays and a transparent abdominal window in dogs to visualize intestinal movements, but complained that both methods failed "to show the finer graduations in activity and furnish no graphic record."[63] The use of transparent windows of the abdomen was used by several investigators to observe intestinal movement in conscious animals.[64,65]

In 1931, Templeton and Lawson used multiple intraluminal balloons showing simultaneous motor activity across several adjacent balloons, and motor activity which appeared to pass continuously from the proximal to distal colon.[66] In 1941, Adler and colleagues conducted similar experiments in the human descending colon, collating over 150 hours of contractile activity from one or two fluid-filled balloons passed through a colostomy.[67]

Following the most promising introduction of X-rays by Cannon, intestinal motility in humans took off with colonic mass movements first described by Holtzknecht [68] and confirmed by Barclay[69] and by Hertz and Newton[70]. The method was abandoned in the 1980 s because of the radiation. Intraluminal manometry, together with other new techniques, has become the golden tools for modern gastroenterologists. Several extensive reviews are available.[71]

A further advance on methods for graphic representation of intestinal movements was the 1921 development of the polygraph, eventually replacing the kymograph. John A. Larson, a California-based policeman and physiologist, devised an apparatus to aid in the detection of verbal deception. It measured, simultaneously, changes in blood pressure, heart rate, and respiratory rate.[72]

Computer programs have today taken the place of both kymographs and polygraphs in such data acquisition. The advent of movie, and eventually video, recordings of either exposed intestinal preparations or X-ray fluoroscopy has provided more objective information and enabled visual observations to be available to others. A most significant advance in detecting the complexity of intestinal movements and the underlying physical processes was made by in the classic work of Ehrlein and colleagues by combining fluoroscopy and intraluminal pressure recordings on a variety of experimental animals.[73] Similar methods have been described as "X-ray cinematography, Röntgen-cinematography-cineradiography, and Röntgen kymography."

5.9 | Changing concepts of peristalsis and of the complexity of intestinal movements

In the 20th century, the description of peristalsis has been subject to major controversies regarding terminology. We briefly discuss three major issues.

1. "Is peristalsis a reflex?"

In 1899, Bayliss and Starling used the term "peristaltic contractions" and suggested that they are due to coordinated reflexes.[19] "The peristaltic contractions are true coordinated reflexes, started by mechanical stimulation of the intestine, and carried out by the local nervous mechanism (Auerbach's plexus). They are independent of the connections of the gut with the central nervous system. They travel only in one direction, from above downwards, and are abolished on paralyzing the local nervous apparatus by means of nicotine or cocaine".

Cannon coined 1912 the term "myenteric reflex" [74]—a local reflex to describe the polarized responses previously observed by Nothnagel,[53] Lüderitz,[1,8] Mall,[55] and Bayliss & Starling[19]. Cannon made the important distinction between reflex and peristalsis "but the reflex, and the progression of the reflex, is not the same phenomenon. Peristalsis implies an advancing wave. Food containing cellulose seems to be carried though the gut rapidly because of the mechanical effect induced by it".[23] In addition, he discussed in his 1912 paper, the relation between the local reflex(es) and peristalsis, stating that while there is plenty of "evidence that the myenteric reflex is present throughout the gastrointestinal tract," this might not be active all the time and thus might not subserve continuous propulsion.[74]

One of the best-known methods of studying peristalsis was developed by Trendelenburg and tested on some experimental

animals.[18,75] It was particularly effective in the guinea pig intestine. He perfectioned a method invented by Gayda, a Turin physiologist who wrote in German.[76]

Cognizant of the work of Lüderitz, Trendelenburg used the term "peristaltic reflex." In referring to the Bayliss and Starling reflexes, he added, appropriately, Lüderitz's name, calling it "the Lüderitz-Bayliss-Starling reflex." He wrote "Lüderitz observed this (reflex) in the small intestine of the rabbit, immersed in a bath of kitchen salt solution.[1,8] According to him, inflating the intestine by inserting a rubber balloon, or touching the intestinal serosa with a kitchen salt crystal led to excitation of the circular muscle of increasing intensity towards the pylorus", and added "we can conclude that the orally located circular muscles in the distended intestine have a higher tone than the aboral ones. Hence it could not be an endogenous tone of the intestine that determined the difference between the aboral and oral diameter, and the distension must have induced an orally directed gradient of tone." Trendelenburg continues "the Lüderitz-Bayliss-Starling reflex" explains the drifting of a local distending object in the aboral direction, as demonstrated by the movement of a cotton wool ball or a fecal pellet.[1] The contraction of the tonic ring muscle will push the solid contents anally. The propulsion is facilitated by the inhibition of the muscular system at the aboral side: So, the phenomenon is similar to the reflex sliding of a segment of a leech out of a thread loop by the force of an increased muscle tone at one side with a reflex reduction in tone on the opposite side." The "Trendelenburg technique" for studying peristalsis in the guinea pig ileum has since become the most extensively used method to investigate the pharmacology of peristalsis.

A search in Google Scholar identified some 70 papers published subsequent to Trendelenburg's 1917 work, with the term "peristaltic reflex" in the title. 102 had "peristalsis" or other terms—including "peristaltic contractions," "peristaltic activity," "peristaltic waves," "peristaltic response," or "peristaltic transport."

Tonini and colleagues provided compelling experimental evidence that, even in the classic Trendelenburg preparation for peristalsis, it was possible to record "standing enteric reflexes" as propulsive behavior separate from the actual peristalsis.[77] Interestingly, Cannon had said, "…but the reflex, and its progression of the reflex along the intestine, are not the same phenomenon."

The very nature of the enteric reflexes underlying peristalsis has been the subject of intense research since the prediction by Bayliss and Starling in 1899 that the histological analysis of such reflexes was complex.[19] This is not the place to review the vast literature which combines and integrates histochemical, electrophysiological, and physiological investigations leading to the identification of the main polarized reflex pathways in the intestine of most mammalian species studied.[56,78–80] Perhaps the first proposal that the then newly discovered non-adrenergic non-cholinergic (NANC) enteric inhibitory neurons are an intrinsic part of the polarity of enteric pathways involved in peristalsis was made back in 1973.[81]

Experiments on the isolated rabbit colon, in which the functional state of the smooth muscle during propulsion of boluses could be established by a combination of recording methods, demonstrated that peristalsis was due to excitation of the circular muscle orally and relaxation anally.[82] Peristalsis can thus be seen as a neuromechanical loop.[82] These finding confirmed early ideas put forward by Lüderitz[1,8] and later by Bayliss & Starling[19] that peristalsis can be viewed as a loop being activated by the bolus itself, sustaining its own propulsion.

A predictable consequence of the neuromechanical loop hypothesis is that peristalsis should adapt the speed of propulsion to the consistency and size of boluses. While studies show many examples of differences in the speed of peristaltic propulsion, depending on gas, fluid or solid content, the hypothesis was experimentally confirmed in the isolated guinea pig colon by showing that the speed of propulsion was a function of the viscosity and size of the contents.[83] This work generated the idea that peristalsis might resemble more a form of "intestinal locomotion" than a reflex, with a similarity to real locomotion.

When the intestinal contents act as an "irritating" stimulus, full blown peristalsis might act as a defense mechanism—an "escape response" to quickly empty the content. A more solid content would generate peristaltic contractions which travel more slowly. At low stimuli, such contractions would consist in clusters of rhythmic contractions generated by each slow wave. By contrast, greater stimuli would produce single prolonged contractions, generated by the synthesis of individual slow wave-mediated contractions. An excellent example of such shapes of these propulsive contractions was provided by Ehrlein and colleagues.[73]

2. "Is the 'law of the intestine' valid?"

We must first make allowance for the literature abounding with confusing functional and anatomical terminology. "Proximal," "behind," "above," "backwards," "ascending," and "upwards" refer to *orally* directed events or pathways; "distal," "ahead," "below," "forward," "descending," and "downwards" refer to *anally* directed events or pathways.

As mentioned earlier, Bayliss and Starling proposed the idea that peristalsis involved polarized reflex pathways—the "law of the intestine." Doubt about the universal validity of this law was expressed by Cannon, who noted "…the absence of inhibition below the bolus"[74] and quoted earlier observations by Langley and Magnus.[84] Lüderitz, in his two paper 1889 and 1890,[1,8] already noted peristalsis without visually detectable inhibition below the distension and stressed the enormous variability of movements which cause peristalsis. He emphasized at the same time the dominant role of the contraction oral to a mechanical or chemical stimulus for the forward movement of the content.

This issue was raised forcefully by Alvarez, who pointed to the numerous exceptions provided by several investigators, including himself and even by Bayliss and Starling themselves—all reporting failure to observe anal inhibition in different species, particularly during peristaltic rushes.[57]

Evidence against a "law of the intestine" was also provided by Spencer and colleagues, who, using a preparation of guinea pig small

intestine to study standing enteric reflexes, recorded excitation on the anal side of localized mechanical stimuli.[58] There is ample evidence of descending excitatory pathways in the guinea pig small intestine.[85] However, in that paper Spencer and colleagues argued that enteric inhibitory transmission is involved in the actual neural peristalsis.

The arguments against specific "laws" in biology resonate well with much earlier arguments by Stuart Mills (originally published 1843) about the natural laws applied to physics and biology.[86] He was one of the first to suggest that the properties of more complex systems were emerging properties based on simpler fundamental laws. Philosopher Arthur Koestler considered such complexity as individual systems ("holons") becoming incorporated into larger, integrated and therefore more complex, systems.[87]

3. "Does myogenic peristalsis exist and what is the relationship between neural peristalsis and myogenic movements?"

In his book of 1948, Alvarez raised the question as to whether or not peristalsis is really a neural phenomenon.[57] He stated "downward peristalsis can take place without the help of the myenteric reflex," and suggested that peristaltic movements could occur independently of propulsion of content. It is perhaps mediated by propagating "action currents" in the muscles, similar to the conduction of signals in the heart. The idea of myogenic peristalsis in the intestine would be revived by Bortoff[88] and even more recently by Huizinga and Lammers[89]. The conditions for some kind of "myogenic" peristalsis would occur if the circular muscle of an extended section of the intestine (small intestine) was constantly excited. The result would be that every slow wave, generated by the ongoing activity of the pacemaker net of the interstitial cells of Cajal (ICCs), would reach the threshold for contraction. The contractions would occur at the frequency of the slow wave and their propagation at the propagation speed of the slow wave. Such conditions can be produced experimentally, for example, by adding a muscarinic agonist to isolated segments of cat ileum.

Such conditions also occur during phase III of the small intestine interdigestive migrating motor complexes (interdigestive MMCs).[90] During this phase, in which every slow wave is driven beyond its threshold for contraction, repeated propagating waves of contractions sweep the segment of intestine occupied by phase III.[91] The frequency, direction, and speed of the contractions within phase III are determined by the properties of the slow waves. The migrating neural excitation independently of the slow waves simply provides a continuous depolarization of the entire segment of intestine occupied by phase III.

Probably the most convincing case of myogenic peristalsis with a clear physiological function is gastric peristalsis, where the net of pacemaker cells (ICCs) provides frequency, direction, and speed of propagation of the circumferential contractions which start in the corpus and push the content toward the pylorus. It is noteworthy that Lüderitz reported in his 1891 paper on gastric contractility that the reflex, while easily evoked in the intestine, does not seem to be operative in the stomach.[10] Whether or not slow myogenic contractions observed in the colon of some experimental animal species do play a physiological role in propulsion remains to be established.

Unification of the two fundamental methodological approaches, that is, verbal description of visual images and graphic recording of mechanical and electrophysiological parameters has occurred more recently. Complex motor patterns, recorded by video and spatiotemporal maps of changes in dimensions of the intestinal wall, could be constructed and digitized for quantitation.[92] Combining these spatiotemporal maps with corresponding forces with electrophysiological recording of the smooth muscle and enteric neural activity gives a promising methodology to reach a better consensus on the complexity of intestinal motor patterns.[93]

6 | CONCLUSIONS

In 1899, Bayliss and Starling stated "On no subject in physiology do we meet with so many discrepancies of fact and opinion as in that of the physiology of the small intestine."[19] Alvarez, in 1948, stated "The mode of progress of solid and liquids through the small bowel can probably never be summed up by any short phrase as that devised by Bayliss and Starling; there are too many mechanisms at work."[57]

The existence of specific polarized enteric pathways appears to be a general feature along the entire gastrointestinal tract in all mammalian species studied. The complex relation between neural peristalsis and myogenic mechanisms—based on strong polarity of the enteric pathways, superimposed on ongoing myogenic activity generated by the specific pacemaker cells network—can easily be reconciled with the control of intestinal movements by neurogenic mechanisms. These interactions appear to generate much more than simply peristalsis. They comprise a variety of motor patterns, such as clustered contractions, migrating motor complexes, minute rhythms, and colonic motor complexes. Yet the correlation between measured intraluminal pressures, wall movements, and actual luminal flows remains a challenge despite some promising findings.[94-97]

Today's neuro-gastroenterologists need a critical analysis of the actual physical relations between the mechanical events described as propagation of contractions, propulsion of contents, traveling of waves, migration of motor activity, segmental contractions, rushed movement etc. A clear call to give significant attention to questions of terminology come from Ehrlein and colleagues,[73] who wrote "the conventional terms 'peristalsis' and 'segmentation' are inadequate to describe the complexity of luminal transit. Some of the difficulties in understanding transit through the alimentary canal center around problems of terminology" as proposed in a recent consensus article.[98]

Much remains to be done to clarify both terminology and actual motility patterns.

ACKNOWLEDGMENT

We would like to thank Dr. Peter Arnold, Editor in Chief, Friends of Science in Medicine, for his thorough corrections of language and Nick Spencer for pointing to von Haller's historical publication. Open access funding enabled and organized by ProjektDEAL.

DISCLOSURES

The authors declare no conflict of interest.

ORCID

Michael Schemann https://orcid.org/0000-0003-1007-9843
Paul Enck https://orcid.org/0000-0001-8873-0486

REFERENCES

1. Lüderitz C. Experimentelle Untersuchungen über die Entstehung der Darmperistaltik. *Archiv für Pathologische Anatomie und Physiologie und für Klinische Medicin*. 1889;118(1):19-36.
2. Lüderitz C. Beitrag zur Lehre der progressiven Muskelatrophie. Inauguraldissertation Jena, 1876.
3. Lüderitz C.Versuche über die Einwirkung des Druckes auf die motorischen und sensiblen Nerven. Zeitschrift für klinische Medicin 1880; Band II, Heft 1, separater Abdruck, 1-29.
4. Lüderitz C. Ueber das Rückenmarkssegment. Ein Beitrag zur Morphologie und Histologie des Rückenmarks. *Arch. Anat. Phys*. 1881;8:405-495.
5. Lüderitz C. Ein fall von magengeschwür mit in heilung begriffener perforationsperitonitis. *Berliner Klinische Wochenschrift*. 1879;16(33):493-496.
6. Lüderitz C. Über Glycerinklistiere. *Berliner klinische Wochenschrift*. 1889;26(13):283-285.
7. Lüderitz C. Experimentelle Untersuchungen über das Verhalten der Darmbewegungen bei herabgesetzter Körpertemperatur. *Archiv für pathologische Anatomie und Physiologie und für klinische Medicin*. 1889;116(1):49-64.
8. Lüderitz C. Experimentelle untersuchungen über die Entstehung der darmperistaltik. *Archiv für Pathologische Anatomie und Physiologie und für Klinische Medicin* 1890;122(1):1-28.
9. Lüderitz C. Zur elektrischen Reizung des Darmes. *Archiv für Pathologische Anatomie und Physiologie und für Klinische Medicin*. 1890;119(1):168-174.
10. Lüderitz C. Das motorische Verhalten des Magens bei Reizung seiner äusseren Fläche. *Archiv für die gesamte Physiologie des Menschen und der Tiere*. 1891;49(3-4):158-174.
11. Lüderitz C. Ueber die Wirkung des constanten Stromes auf die Darmmusculatur. *Pflüger, Archiv für die Gesammte Physiologie des Menschen und der Thiere*. 1891;48(1):1-16.
12. Lüderitz C. Einige untersuchungen über die einwirkung des kaffeeinfuses auf die bacterien. *Zeitschrift für Hygiene*. 1889;7(1):241-258. https://doi.org/10.1007/BF02188339
13. Lüderitz C. Zur Kenntniss der anaëroben Bacterien. *Zeitschrift für Hygiene*. 1889;5(1):141-160.
14. Lüderitz C. Versuche über den ablauf des blutdruckes bei aortenstenose. *Zeitschrift für klinische Medicin*. 1892;20:374-396.
15. Lüderitz C. *Gedanken zur allgemeinen Energetik der Organismen*. Berlin: Verlag Hirschwald; 1910.
16. Hofmeister F, Schütz E. Über die automatischen Bewegungen des Magens. *Arch Exp Path und Pharmak*. 1886;20:1-33.
17. Schemann M, Rohn M, Michel K. Motor control of the stomach. *Eur Rev Med Pharmacol Sci*. 2008;12(Suppl 1):41-51.
18. Trendelenburg P. Physiologische und pharmakologische Versuche über die Dünndarmperistaltik. *Arch Exp Pathol Pharmakol*. 1917;81:55-129.
19. Bayliss WM, Starling EH. The movements and innervation of the small intestine. *J Physiol*. 1899;24:99-143.
20. Nencki M. Untersuchungen über die Zersetzung des Eiweißes durch anaerobe Spaltpilze. *Monatshefte für Chemie und verwandte Teile anderer Wissenschaften*. 1889;10:506-525.
21. Schaefer J, Kuhtz-Buschbeck JP.Earliest (?) observation of mechano-transduction in publications of Otto Frank (1895) and Carl Lüderitz (1892). In: *Proceedings of the 7th International Workshop Freiburg 2016*, 09, 21–24 on Cardiac Mechano-Electric Coupling and Arrhythmias, Freiburg 2016, poster 39.
22. Frank O. Zur Dynamik des Herzmuskels. *Zeitschrift für Biologie*. 1895;32:370-437.
23. Cannon WB. *The mechanical factors of digestion, Longmans*. London, UK: Green & Company; 1911.
24. Meli DB. Early modern experimentation on live animals. *J Hist Biol*. 2013;46:199-226.
25. Bartholin T. *Institutiones anatomicae*, 2nd edn, Leiden, NL: Franciscum Hackium; 1645.
26. Von Haller A. Elementa Phisiologiae corporis humani -Tomus Septimus. Apud Vicentium ursinum. Neapoli, 1776.
27. Kaau-Boerhaave H.Impetum Faciens Dictum Hippocrati Per Corpus Consentiens Philologicae Et Physiologice Illustratum Observationibus Et Experimentis Passim Firmatum. Samuelem Luchtmans, & fil., bibliopolam & Typographum Academiae, Lugduni Batavorum, 1745.
28. Earles MP. *Studies in the Development of Experimental Pharmacology. In the Eighteenth and Early Nineteenth Centuries*. University College London; 1961.
29. Monro A. *The Morbid Anatomy of the Human Gullet, Stomach, and Intestines*. Edinburgh: George Ramsay and Company; 1812.
30. Franks K. *Intussusception of the small intestine Transactions of the Academy of Medicine in Ireland*. 1885;3:271-276.
31. Bernard C. *Introduction à l'étude de la médecine expérimentale*. Paris: JB Baillière et fils; 1865.
32. Brodie BC. Experiments and observations on the influence of the nerves of the eighth pair on the secretions of the stomach. *Philos Trans R Soc Lond*. 1814;104:102-106.
33. D'Arcy P. *William Harvey: Masters of Medicine*. pp. 193. London: T. Fisher Unwin; 1897.
34. Borell M. Extending the senses: the graphic method. *Med Herit*. 1986;2:114-121.
35. Olesko M.The meaning of precision: the exact sensibility in early nineteenth-century Germany. In: Norton Wise M, ed. *The Values of Precision*. Princeton, NJ: Princeton University Press; 1995: 105-134.
36. Ludwig C. Beitrage zur Kenntniss des Einflusses der Respirationbewegungen auf den Blutlauf in Aortensysteme. *Arch Anat Physiol wiss Med*. 1847;13:242-307.
37. Von Helmholtz H. Vorläufiger bericht über die fortpflanzungs-geschwindigkeit der nervenreizung. *Arch Anat Physiol wiss Med*. 1850;17:71-73.
38. Volkmann AW. Ueber das Zustandekommen der Muskelcontractionen im Verlaufe der Zeit. *Berichte über die Verhandlungen der Königlich Sächsischen Gesellschaft der Wissenschaften zu Leipzig*. 1851;3:1-5.
39. Legros C, Onimus ENJ. Mouvements de l'intestine. *J Anat Physiol (Paris)*. 1869;6:37-66.
40. Waller R. *The Posthumous Works of Robert Hooke*. In: Samuel Smith and Benjamin Walford eds; 1705. London.
41. Laennec RTH. eds. *De l'auscultation médiate: ou traité du diagnostic des maladies des poumons et du cœur*. Paris: J.-A. BROSSON and J.-S. CHAUDE; 1819.
42. Hooker C. An essay on intestinal auscultation. *The Boston Medical and Surgical Journal* 1849;40:409-439.
43. Ludwig C. *Lehrbuch der Physiologie des Menschen*. Heidelberg: Leipzig/Heidelberg Winter'sche Verlagsbuchhandlung; 1861.
44. Davenport HW. Gastrointestinal physiology, 1895-1975: Motility. In: *Comprehensive Physiology. Supplement 16 Handbook of Physiology, The Gastrointestinal System, Motility and Circulation*, 2011.
45. Braam-Houckeest V. Untersuchungen über Peristaltik des Magen und Darmkanal. *Pflügers Archiv f d ges Phys*. 1872;6:266-302.

46. Meltzer SJ, Auer J. Peristaltic rush. *Am J Physiol*. 1907;20:259-281.
47. Lister J. Preliminary account of an inquiry into the functions of the visceral nerves, with special reference to the so-called 'Inhibitory System'. *Proceedings of the Royal Society of London*. 1857– 1859;9:367-380.
48. Meissner G. Uber die Nerven der Darmwand. *Zeitschrift für rationelle Medicin*. 1857;8:364-366.
49. Auerbach L. *Über einen Plexus myentericus, einen bisher unbekannten ganglio-nervösen Apparat im Darmkanal der Wirbelthiere*. Breslau: Morgenstern E (ed); 1862.
50. van Leeuwenhoek A. Microscopical observations on the blood vessels and membranes of the intestines. *Philos Trans*. 1706;26:53-58.
51. Thom A, Crieff CM. The therapeutics of belladonna in intestinal obstruction; notes of a case; faecal vomiting. *Recovery. Edinb Med J*. 1879;25:538-543.
52. Gowers WR. The automatic action of the sphincter ani. *Proc R Soc Lond*. 1877;26:77-84.
53. Nothnagel H. Zur chemischen Reizung der glatten Muskeln; zugleich als Beitrag zur Physiologie des Darmes. *Archiv für pathologische Anatomie und Physiologie und für klinische Medicin*. 1882;88:1-11.
54. Cash JT. Contribution to the study of intestinal rest and movement. *Proceedings of the Royal Society of London*. 1887;41:212-231.
55. Mall FP. A study of intestinal contractions. *John Hopkins Hosp Rep*. 1896;1:37-75.
56. Furness JB, Costa M. *The Enteric Nervous System*. Edinburgh: Churchill Livingstone; 1987.
57. Alvarez WC. *An Introduction to Gastroenterology*, 4th edn. Revised and enlarged. New York: Paul Hoeber Inc; 1948.
58. Spencer N, Walsh M, Smith TK. Does the guinea-pig ileum obey the 'law of the intestine'? *J Physiol*. 1999;517:889-898.
59. Luciani L. *Das Hungern; Studien Und Experimente Am Menschen*. Verlag von Leopold Voss; Hamburg and Leipzig, 1890.
60. Luciani L. *Human physiology*. London: MacMillan; 1913.
61. Magnus R. Die Bewegungen des Verdauungskanals. *Ergebnisse der Physiologie*. 1908;7:27-64.
62. Starling EH.The Muscular and nervous mechanism of the digestive tract. In Schäfer EA, ed. *Textbook of Physiology*. Edinburgh London: Young J Pentland; 1900;313–337.
63. Welch PB, Plant OH. A graphic study of the muscular activity of the colon, with special reference to its response to feeding. *Am J Med Sci*. 1926;172:261-268.
64. Hukuhara T. Die Bewegung und Innervation des Dünndarmes. *Pflügers Arch*. 1932;229:311-335.
65. Der ZB. Einfluß des Hypophysenextraktes auf die Peristaltik. *Pflügers Arch*. 1920;180:68-74.
66. Templeton R, Lawson H. Studies in the motor activity of the large intestine. I. Normal motility in the dog, recorded by the tandem balloon method. *Am J Physiol*. 1931;9:667-676.
67. Adler HF, Atkinson AJ, Ivy AC. A study of the motility of the human colon: an explanation of dysynergia of the colon, or of the "unstable colon". *Am J Dig Dis*. 1941;8:197-202.
68. Holzknecht G. Die normale Peristaltik des Kolon. *Münch med Woch*. 1909;47:2401-2403.
69. Barclay AE. Note on the movements of the large intestine. *Arch Roentgen Ray*. 1912;16:422-424.
70. Hertz AF, Newton A. The normal movements of the colon in man. *J Physiol*. 1913;47:57-65.
71. Dinning PG, O'Grady G.Colonic manometry. In Kuipers EJ, ed. *Encyclopedia of Gastroenterology*, 2nd edn, vol. 1. Oxford: Academic Press; 618-626.
72. Larson JA. *Lying and its detection: A study of deception and deception tests*. Chicago, IL: University of Chicago Press; 1932:99.
73. Ehrlein HJ, Schemann M, Siegle ML. Motor patterns of small intestine determined by closely spaced extraluminal transducers and videofluoroscopy. *Am J Physiol*. 1987;253:G259-G267.
74. Cannon WB. Peristalsis, segmentation, and the myenteric reflex. *Am J Physiol*. 1912;30:114-127.
75. Lammers WJEP, Lammers-van den Berg AM, Morrison JFB, Petroianu GA. Translating Trendelenburg; Back to the Future. *Naunyn-Schmiedeberg's Arch Pharmacol*. 2006;373(2):134-138.
76. Gayda T. Beiträge zur Physiologie des überlebenden Dünndarms von Säugetieren. *Pflüger's Arch*. 1913;151:407-455.
77. Tonini M, Costa M, Brookes SJH, Humphreys CM. Dissociation of the ascending excitatory reflex from peristalsis in the guinea-pig small intestine. *Neuroscience*. 1996;73:287-297.
78. Gershon MD. (2005) Nerves, reflexes, and the enteric nervous system. *J Clin Gastroenterol*. 2005;38:S184-S193.
79. Furness JB. *The Enteric Nervous System*. Oxford: Blackwell; 2006.
80. Brookes SJH, Costa M. Functional Histoanatomy of the Enteric Nervous System. Johnson LR, In *Physiology of the Gastrointestinal Tract*, 4th edn. Amsterdam, NL: Elsevier; 2006:577-602.
81. Furness JB, Costa M. The nervous release and the action of substances which affect intestinal muscle through neither adrenoreceptors nor cholinoreceptors. *Phil Trans R Soc Lond B*. 1972;265:123-133.
82. Dinning PG, Wiklendt L, Omari T, et al. Neural mechanisms of peristalsis in the isolated rabbit distal colon: a neuromechanical loop hypothesis. *Frontiers in Neuroscience*. 2014;8:75.
83. Costa M, Wiklendt L, Simpson P, Spencer NJ, Brookes SJ, Dinning PG. Neuromechanical factors involved in the formation and propulsion of fecal pellets in the guinea-pig colon. *Neurogastroenterol Motil*. 2015;2015(27):1466-1477.
84. Langley JN, Magnus R. Some observations of the movements of the intestine before and after degenerative section of the mesenteric nerves. *J Physiol*. 1905;33:34-51.
85. Hirst GDS, Holman ME, McKirdy HC. Two descending nerve pathways activated by distension of guinea pig small intestine. *J Physiol*. 1975;244:113-127.
86. Mills JS. *A System of Logic, Ratiocinative and Inductive: Being a Connected View of the Principles of Evidence, and the Methods of Scientific Investigation*. London: Parker, Son, and Bourn; 1862.
87. Koestler A. *The Ghost in the Machine*. New York: Macmillan; 1967.
88. Bortoff A. Myogenic control of intestinal motility. *Physiol Rev*. 1976;56:418-434.
89. Huizinga JD, Lammers WJ. Gut peristalsis is governed by a multitude of cooperating mechanisms. *Am J Physiol*. 2009;296:G1-G8.
90. Code CF. The interdigestive housekeeper of the gastrointestinal tract. *Perspect Biol Med*. 1979;22:S49-S55.
91. Schemann M, Ehrlein HJ. Mechanical characteristics of phase II and phase III of the interdigestive migrating motor complex in dogs. *Gastroenterology*. 1986;91:117-123.
92. Hennig GW, Costa M, Chen BN, Brookes SJH. Quantitative analysis of peristalsis in the guinea-pig small intestine using spatio-temporal maps. *J Physiol*. 1999;517:575-590.
93. Costa M, Keightley LJ, Wiklendt L, et al. Roles of three distinct neurogenic motor patterns during pellet propulsion in guinea pig distal colon. *J Physiol*. 2019;597:5125-5140.
94. Schemann M, Erhlein HJ. Postprandial patterns of canine jejunal motility and transit of luminal content. *Gastroenterology*. 1986;90:991-1000.
95. Schemann M, Ehrlein HJ, Sahyoun H. Computerised method for pattern recognition of intestinal motility: functional

significance of the spread of contractions. *Med Biol Eng Comput*. 1985;23:143-149.

96. Schulze-Delrieu K. Clearance patterns of the isolated guinea pig duodenum. *Gastroenterology*. 1992;102:849-856.
97. Tasaka K, Farrar JT. Intraluminal pressure of the small intestine of the unanesthetized dog. *Pflugers Arch*. 1976;364:35-44.
98. Corsetti M, Costa M, Bassotti G, et al. First translational consensus on terminology and definitions of colonic motility in animals and humans studied by manometric and other techniques. *Nat Rev Gastroenterol Hepatol*. 2019;16:559-579.

How to cite this article: Schemann M, Mai G, Costa M, Enck P. Translating the seminal findings of Carl Lüderitz: A description in English of his extraordinary studies of gastrointestinal motility accompanied by a historical view of peristalsis. *Neurogastroenterology & Motility*. 2020;00:e13995. https://doi.org/10.1111/nmo.13995