Ludwig: The Bioengineer

By Max E. Valentinuzzi, Klaus Beneke, and Germán E. González

On the basis of the strict exclusion of the vis vitalis, the demand was raised by Carl Ludwig, Helmholtz, Du Bois-Reymond, and Brücke for a physiology which was causal-analytical and physically and chemically experimental. If, out of these four investigators, we pick Ludwig as the actual founder of modern physiology, the grounds for this must be justified specifically. That modern physiology is not to be contemplated without the works of the three great students of Johannes Müller is explicitly emphasized. However, Carl Ludwig occupies a special position for physiology. [1]

Physiology truly entered into the scientific quantitative phase when its many events began to be systematically measured and recorded, and Carl Ludwig and his school became the epitome of such a developmental stage. Much has been written about Carl Friedrich Wilhelm Ludwig's outstanding life (29 December 1816–23 April 1895), so there is no need to repeat his biographical details here except mentioning, when necessary, a few specific aspects [1], [2]. In 1916, on the 100th anniversary of his birth, Prof. Warren P. Lombard honored him in *Science* [3] and now, with what will be his 200th birthday looming in 2016, this series of three short articles appears as a good opportunity for a somewhat early and renewed academic celebration, looking at him from three different frames of reference:

- Luwig as bioengineer
- Ludwig as physiologist
- Ludwig as teacher par excellence.

The subject herein deals with the first facet of his particular personality as a de facto early and pioneering modern bioengineer. Briefly said, Carl Friedrich Wilhelm Ludwig was born in 1816 in Witzenhausen, within the present German territory, three years after Claude Bernard and five years before Hermann Ludwig Ferdinand von Helmholtz. His secondary schooling (gymnasium and abitur) was done in Hanau, while his medical schooling was in Marburg (1834–1840). However, there was one compulsory year exclusion, apparently for political reasons, which restricted him to the surgical hospital in Bamberg and one semester in Erlangen, ending with the medical state examination back in Marburg. It was there when, in 1839, he met the already accomplished chemist Robert Bunsen (1811–1899), from Erlangen, and collaborated with him in gas analysis studies. This gave him the first time opportunity to conduct precise and well-carried out scientific research [4], [5]. Ludwig was appointed, in 1841, as a second prosector in anatomy at Marburg [with Ludwig Fick (1813–1858)]. In 1842, he received formal admission to the faculty, where he became an assistant professor of comparative anatomy in 1846, again in Marburg. In 1849, he became a professor of anatomy and physiology in Zürich, and in 1855, he was appointed as a professor of zoology and physiology at the medical military academy (Josephinum) in Vienna (Figure 1), until 1865, when he succeeded Ernst Heinrich Weber (1795–1878), a professor of physiology in Leipzig. After 30 years of continuous activity, Ludwig died in 1895 [1]–[4]. There is an abundant amount of literature regarding Ludwig's academic and scientific life, which is easily available on the Internet for those more interested in the biographical data, although not much is known about his personal and family life.

Ludwig was appointed, in 1841, as a second prosector in anatomy at Marburg.

At age 30, when he was a prosector at the University of Marburg, Ludwig invented the kymograph in 1846 and reported it in a paper published in the following year [6]. He recognized that good measurements were essential for physiology in the search of explanations and understanding of the different phenomena,


(a)


(b)

FIGURE 1 (a) Ludwig in 1859 when he was 43 years old and (b) the Josephinum in Vienna. (Images used with permission from [4].)

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and thereby became known to the scientific world as the inventor of the kymograph, which is the first-known continuous blood pressure (BP) recorder. During a visit to Johannes Müller (1801–1858) in Berlin in 1847, Ludwig met Müller's disciples Emil du Bois-Reymond (1818–1896), Ernst Wilhelm Ritter von Brücke (1819–1892), and Hermann Ludwig Ferdinand von Helmholtz (1821–1894). All three men were in their late 20s (29, 28, and 26 years old, respectively). In 1845, they cofounded the Physikalische Gesellschaft zu Berlin, now Deutsche Physikalische Gesellschaft (the Physics Society of Berlin, now the German Physics Society). They soon became close friends and shared the same general research philosophy, turning to the idea that physiological phenomena were based on physicochemical laws—their ultimate objective was to describe nature in mathematical terms. Thus, the four young men openly challenged and disposed of the old vital force concept (vitalism) sustained by Johannes Müller, a former grand in the field who died relatively young.

They called themselves "organic physicists," however, looking back at this philosophical position today, we should say that they already were within the biomedical engineering track. The biomathematics path took longer and is steadily progressing. Measurements, mathematical definition of variables, technological design and development along, when possible, with the establishment of models, even simple models, constitute the essence of an engineering attitude that leads to the quantification of a discipline. These young and enthusiastic men wanted to quantify physiology more than 150 years ago—and one objective of bioengineering is precisely the quantification of biological and medical sciences [7].

The Kymograph—The First-Known Continuous Pressure Recorder

Even though BP had long been measured before experiments in mammals first by Stephen Hales (1677–1761) [8] and then by Jean Louis Marie Poiseuille (1797–1869) [9], Ludwig recognized that such a physiological variable changed with time and graphic records showing those probably periodic changes were a must. Indeed, the design was ingenious (Figure 2). The artery was connected to *d* and, through a valve, to an open U-tube mercury manometer, obviously taken from Poiseuille [9], as he clearly acknowledged in his 1847 paper. A light vertical metallic rod (*ecf*) floated on the left arm upper mercury meniscus (the rod was probably provided with a lower small surface, described by Ludwig as *Schwimmer*, in German (or *swimmer* in English) articulated at *f* and attached to a moving stylus (*gf*). Blood pulsations moved up and down the two mercury arms so that the stylus end point *g* followed them. The stylus length *gf* (a lever) acted as a mechanical amplifier of the tiny vertical mercury movements. Figure 2 does not seem to have an identified origin because, even though it is didactic, it does not coincide with the original figure published in Ludwig's paper. It has been repeatedly reproduced in literature [10]–[14], with the version found in [13] being slightly different. We believe that Ludwig also used it in his textbook of physiology [15]–[17], which, unfortunately, could not be located in print. However, Klaus Beneke found a digitalized version of its second volume revised edition, where the kymograph is not shown. Ludwig dedicated the book to E. Brücke, E. du Bois-Reymond, and H. Helmholtz, in Wien, Berlin, and Bonn, respectively. Further details are provided in [17].

The biomathematics path took longer and is steadily progressing.

Beneke, in a comprehensive and superb article, displayed several versions of the recorder [4], as its inventor improved it over the years. The bibliography in [4] shows old antecedents of graphic registration, including the Greek etymology of the words *kymos* (wave) and *graph* (record). Ludwig's original image can be found in his 1847 paper [6], where there are two views; in one he displays the pulley–clock mechanism to impart the drum's rotation, obviously nonlinearly influenced by gravity because it depended on a falling weight. These figures are not given in this article because of their poor quality, but they can be accessed easily with the link from [6].

Ludwig's paper [6] is mainly concerned with the influence of the respiratory movements on blood circulation, as its title indicates (Figure 3). The journal in which it appeared was founded by Johannes Müller in 1834 and was often called *Müller's Archive* (Figure 4). Since 1866, papers from Ludwig's group appeared in his own journal named *Arbeiten aus der physiologischen Anstalt zu Leipzig* (*Works of the Physiological Institute of Leipzig*); however, when Du Bois-Reymond took over editorship of the older and better-known *Archiv für Anatomie, Physiologie und wissenschaftliche Medizin*, (or *Müller's Archiv*), the Leipzig Institute's intellectual products shifted to the latter and the other journal, *Arbeiten*, which lasted 11 years, ceased publication.

Ludwig recorded arterial BPs and intrapleural pressures (IPs) in dogs and horses (quite a task with the latter species, as anyone with that experience will

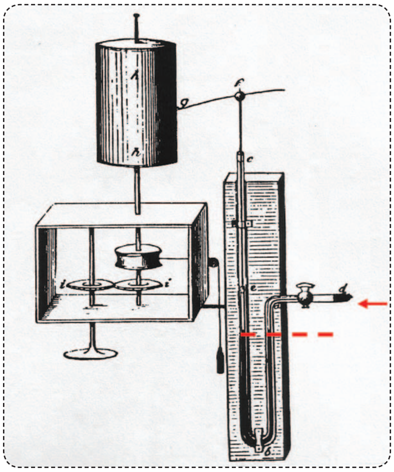
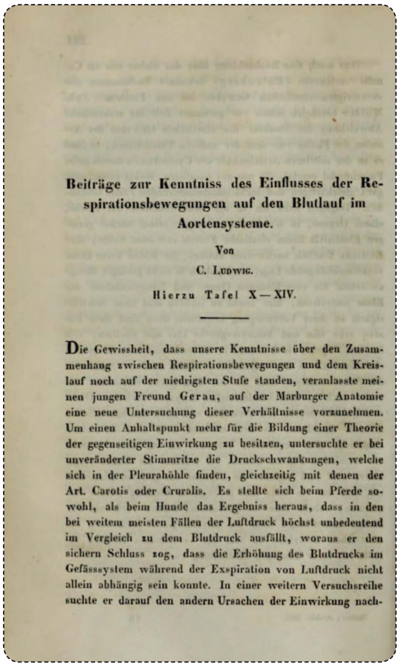


IMAGE IN PUBLIC DOMAIN.

FIGURE 2 Ludwig's kymograph. The black portion of the U-tube shown depicts mercury, with the two menisci at the same level (dashed red horizontal line) because no pressure is applied from the right at the input *d* (horizontal red arrow), where an animal's artery had to be connected. The whole mercury-filled U-tube and the moving stylus *gf* is what we would now call a hydraulic-mechanical transducer (including some amplification given by the stylus length), for it transformed BP (hydraulic side or input) into a vertical displacement (or output) by mechanical coupling. This figure has been reproduced in several publications, including some with minor changes that suggest doubts in its origin. The sketch, though conceptually similar, differs from the original one published in two figures in Ludwig's paper.



Beiträge zur Kenntniss des Einflusses der Respirationsbewegungen auf den Blutlauf im Aortensysteme.

Von

C. Ludwig.

Hierzu Tafel X—XIV.

Die Gewissheit, dass unsere Kenntnisse über den Zusammenhang zwischen Respirationsbewegungen und dem Kreislauf noch auf der niedrigsten Stufe standen, veranlasste meinen jungen Freund Gerau, auf der Marburger Anatomie eine neue Untersuchung dieser Verhältnisse vorzunehmen. Um einen Anhaltspunkt mehr für die Bildung einer Theorie der gegenseitigen Einwirkung zu besitzen, untersuchte er bei unveränderter Stimmritze die Druckschwankungen, welche sich in der Pleurahöhle finden, gleichzeitig mit denen der Art. Carotis oder Cruralis. Es stellte sich beim Pferde sowohl, als beim Hunde das Ergebniss heraus, dass in den bei weitem meisten Fällen der Luftdruck höchst unbedeutend im Vergleich zu dem Blutdruck ausfällt, woraus er den sichern Schluss zog, dass die Erhöhung des Blutdrucks im Gefässsystem während der Exspiration von Luftdruck nicht allein abhängig sein konnte. In einer weitern Versuchsreihe suchte er darauf den andern Ursachen der Einwirkung nach-

FIGURE 3 The first page (p. 242) of Ludwig's paper, where he described the kymograph for the first time. The first sentence says that Ludwig's friend Gerau, from Marburg, was "sure that our knowledge of the link between respiratory movements and circulation was at a very low level, which led him to undertake a new investigation for this relationship." [Image courtesy of Prof. Günther Rau, Aachen, Germany, member of the International Academy of Biomedical Engineering (IABME). See http://www.biodiversitylibrary.org/item/50159#page/464/mode/1upU for free access. The original copy of this photograph is at the British Museum of National History and was digitalized by the latter.]

know). A long appendix in his 1847 paper describes the procedures for both measurements, including calibrations in the vertical (in mm Hg for BP and mm H_2O for IP) and horizontal time axes (in seconds). However, two aspects are not clear: 1) whether both pressures were simultaneously recorded and 2) whether some kind of anesthesia was used.

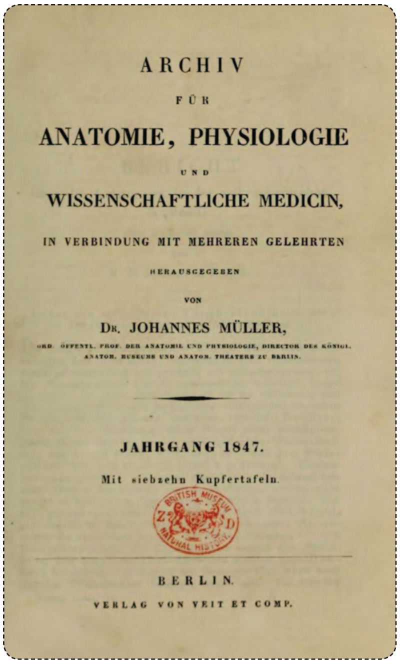
Regarding the first aspect, the figures do not suggest simultaneous traces while the technical description of the kymograph does not mention a two-channel design. There is one record that, perhaps, was a two-channel set (designated as no. 7) showing BP and IP. Besides, the time seems to run from right to left because of the position of the dicrotic wave while the frequency ratio is approximately 3:1, which may be realistic considering the animal was probably in pain. Furthermore, the numbers given in the text when referring to the figures do not coincide with the numbers in figures, thus making it rather difficult to follow the descriptions. The paper abounds in numerically long tables, which were often seen in the scientific literature of those days.

As for the second point, no anesthetic is mentioned in the paper. We should recall that ether was used for the first time in October 1846, in Boston at Massachusetts General Hospital, and the experiments reported by Ludwig were carried out during the same year. It is doubtful that he applied that substance, which incidentally does not work well in canines and equines. Moreover, he also refers to pain manifestations during the experiments [6, p. 258]. It is known for certain that anesthesia was first used in Leipzig much later [18]. Ludwig's writing style, (in the opinion of this column's coauthor, Max E. Valentinuzzi, who poorly translates German), does not help make its readability easy. Overall, the paper [6] is difficult to read, and it is hard to clearly grasp its entire meaning. However, the latter comment is lateral and inconsequential, for the paper's content was far reaching.

It is also of interest to note that Ludwig obtained his first BP and respiratory movement records on 12 December 1846. Many years later, on 15 August 1874, he dedicated the piece of printed paper to his friend, Italian physiologist Angelo Mosso (1846–1910), who spent a year with him in Leipzig (in 1874), and who was a great and gifted experimentalist. The original copy is currently in Torino, and a digitalized version can be accessed through the Virtual Laboratory of Berlin [19]. The same record can be found in [4].

Other Technological Contributions by Ludwig

There is no doubt that the kymograph was the most significant contribution classified within the area of biomedical instrumentation, and in turn, part of current biomedical engineering (and obviously the ancestor of modern recorders). But Ludwig's vision also led him to the development of the blood flow meter (*stromuhr*), the mercury blood gas pump, the concept of viability of isolated perfused organs (like heart, liver, or



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IN VERBINDUNG MIT MEHREREN GELEHRTEN

HERAUSGEGEBEN

VON

DR. JOHANNES MÜLLER,

ORD. ÖFFENTL. PROF. DER ANATOMIE UND PHYSIOLOGIE, DIRECTOR DES KÖNIGL. ANATOM. MUSEUMS UND ANATOM. THEATERS ZU BERLIN.

JAHRGANG 1847.

Mit siebzehn Kupfertafeln.

BRITISH MUSEUM Z D NATURAL HISTORY

BERLIN.

VERLAG VON VEIT ET COMP.

FIGURE 4 The front page of the *Müller's Archives* volume, in which Ludwig's paper describing the kymograph was published. (Image digitalized by the British Museum of Natural History and freely available at http://www.biodiversitylibrary.org/item/50159#page/464/mode/1up. Image courtesy of Prof. Günther Rau, Aachen, Germany.)

kidneys), and the injection method for vessel visualization [20].

Stromuhr

This is a compound German word, literally meaning "current," "stream," and "clock," because volume rate was obtained after timing the capsules that were filling with blood when the arterial inflow was opened. Obviously, the capsules' volume had to be previously known while the whole system was inserted in series, just like an electric ammeter (Figure 5). The concept appears quite advanced and shows a clear engineering view [21].

Mercury Blood Gas Pump

During his ten years in Vienna, Carl Ludwig, in 1858, invented the blood gas pump and elucidated the principal processes involved in gas exchange. His pupil, J. Setschenow (1829–1905), was in charge of the project and perhaps can be considered the beginning of biochemistry [22], [23].

Isolated Perfused Organs

Carl Ludwig introduced the isolated organ preparation (Figure 6), a technique

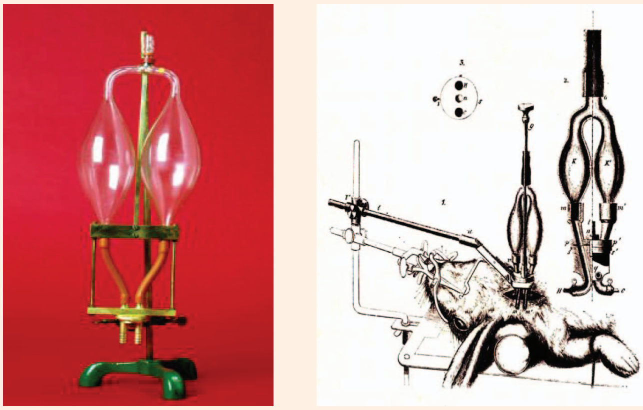

FIGURE 5 Ludwig's *stromuhr* (or flow meter). Two glass capsules with known volume were inserted in series between an artery and a vein. When blood started filling up the capsules, time was measured in seconds; hence, the volume rate was measured. (a) A plastic model currently in the collection of Johannes-Müller-Institut für Physiologie; see http://www.sammlungen.hu-berlin.de/dokumente/6903/. (b) The stromuhr connected to a rabbit's circulation, as set up by Ludwig himself. (Images used with permission from Christoph Knoch, Humboldt-Universität zu Berlin, Historische Instrumentensammlung—Inventer no. 0/52.)

that has projected to our current times. At the Leipzig Institute, the isolated perfused frog heart preparation was first established in 1866, by Elias Cyon (1843–1912). This technique was modified several times and improved upon by many outstanding physiologists who spent their training and research periods in Leipzig. It was a basic technique that led to significant discoveries and was also widely used as a teaching and research model for different organs.Furthermore, as Prof. Heinz-Gerd Zimmer said in 2000 [24], the isolated perfused frog heart was the starting point for the development of the isolated mammalian heart in the retrogradely perfused, nonworking mode in the heart–lung modification and in the working heart preparation. It was perhaps Oscar Langendorff, in 1897, who gave it a decisive forward push and made it well known [25], [26].

Injection Method for Vessel Visualization

Theodor Leber (1840–1917) grew up in Heidelberg, Germany. Taking Bunsen's advice, he went to medical school and later went to Vienna with Carl Ludwig. Around 1863–1864, at the age of 24, Leber had the capacity to demonstrate blood circulation of the eye by color injections into the arteries and veins. Drawings of his results can be found in many ophthalmology textbooks. Theodor Leber is often referred to as the father of experimental ophthalmology.

Discussion

The enlightening and new quantitative approach of physiology initiated by Ludwig is clearly shown in this article, standing on serious and well-developed experimental methodology and the measurement of events. During (or for) some years (it is difficult to determine how many), animal research was probably carried out without anesthesia or even analgesia. Little information is unequivocally offered but, it is certain that perhaps in the 1870s, this aspect of research was taken care of, since Ludwig respected life in general, especially life of animals. He is remembered for advising his students to not to make an incision longer than actually needed. Angelo Mosso, a prolific Italian physiologist, probably played an important role in the enterprise of reducing the suffering of animals. It must be noted that in Ludwig's institute, several species were routinely used, including horses.

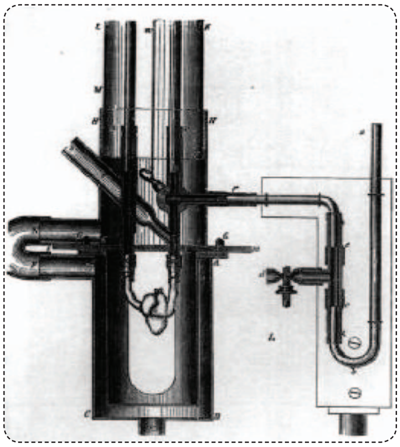

FIGURE 6 Ludwig's isolated frog heart apparatus. (Figure used with permission from Klaus Beneke [4].)

Instruments are required to measure, and this means technology. Ludwig himself often referred to mechanics, for in those days that was essentially the kind of engineering at hand. The kymograph was his masterpiece, and it was developed in several models. One unit was still kept and operable until 2004 at Ludwig's Institute in Leipzig, where Germán E. González worked under the direction of Prof. Heinz-Gerd Zimmer; it is probably still there. If he or any of his students ever had a two-channel model and produced simultaneous two-channel records. We think they did. The original kymograph is not in Leipzig, but there is a later model. The *Physiologische Anstalt* (building) that Carl Ludwig had designed and built in 1865 was destroyed in World War II, together with all the equipment and the library. Very few items were saved. Where the old Physiological Institute once stood, now stands the University Clinic of Internal Medicine. We cannot refrain from sadly exclaiming how many irreparable losses occur due to violence and human intolerance. However, the situation has not changed much in that respect, despite outstanding technological advances.

The influence produced by the kymograph in physiology was outstanding, long lasting, and quickly spread throughout the world. In France, for example, the veterinarian Jean Baptiste Auguste Chauveau (1827–1917) and physician Etienne Jules Marey (1830–1904) developed several models, including a three-channel projecting unit (Figure 7) that was revived and updated in 1967–1968 at the Department of Physiology of Baylor College of Medicine, in Houston, Texas [27]; even commercial equipment was produced by E&M Instruments, which is a company no longer in business. For decades, the kymograph

(in any of its different versions) was the instrument in any well-behaved physiology laboratory around the world. Germán E. González took the photograph shown in Figure 8. The instrument was used for years by medical students in Buenos Aires and, in all likelihood, was also used by Dr. Bernardo Houssay (1887–1971) and his collaborators. Houssay shared, in 1947, the Nobel Prize of medicine and physiology for his contribution to the understanding of the pituitary functions. Otto Frank (1865–1944), another outstanding German physiologist, first obtained a ventricular pressure–volume diagram from a frog's heart and, in 1911, came up with a technical chapter where several kymograph models were described [28]. A more recent special publication rendering homage to a few Leipzig scientists briefly updated Ludwig contributions [29]. The two latter references constitute remarkable pieces for science historians. There is no doubt that Ludwig's technical development went a long way.

Other devices and procedures stem from Ludwig's ideas, as described earlier, where the isolated preparation and vessel visualization stand out, perhaps, as the most relevant. Surely, all of his technological contributions have been deeply projected into the 20th and 21st centuries and should be classified as biomedical instruments. Ludwig and his colleagues and lifelong friends Helmholtz, Brücke, and Du Bois-Reymond, who shared his scientific philosophy, called themselves organic physicists; with today's knowledge, there is no doubt that this is bioengineering or biomedical engineering.

Conclusions

Carl Ludwig acted as a de facto bioengineer, both for his thinking and technological production and development. Young 21st century professionals of this interdiscipline must be proud of having such a great-great-grandfather (*Ururgroßvater* or, more affectionately, *Ururgroßpapa*). He certainly won such an honorable degree.

FIGURE 7 Jean Baptiste Auguste Chauveau's projecting kymograph used during the 1860s. Presented by Max E. Valentinuzzi and the IEEE/EMBS History Group, in Lyon, France, September 2007. (Photo courtesy of Prof. Andrè Dittmar.)

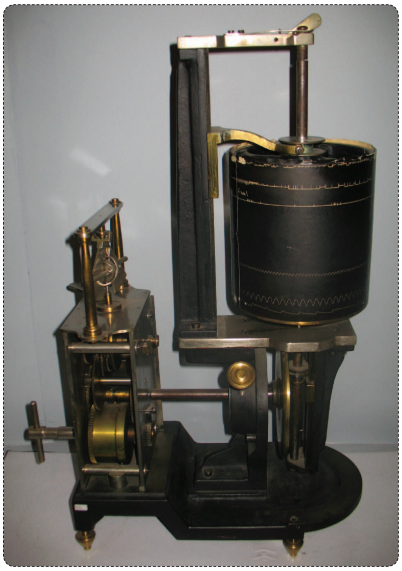

FIGURE 8 An early 20th century kymograph, currently in the Museum of the Medical School of the University of Buenos Aires. (Photo courtesy of Germán E. González with permission from the Museum of the Medical School of the University of Buenos Aires.)

Acknowledgments

We thank Prof. Günther Rau, Aachen, for kindly supplying the link to Ludwig's original paper and Klaus Beneke, from Kiel, who generously brought up significant information and comments, including help translating the German language that obviously called for coauthorship. Thanks to Germán González, from the Medical School of the University of Buenos Aires, who spent a fellowship period at the Leipzig's Carl-Ludwig-Institute in 2003–2004, when the director was Prof. H.G. Zimmer. He provided considerable first-hand information (e.g., he provided the photo of an old kymograph that was kept functioning mechanically). Max E. Valentinuzzi expresses his sincere thanks and deep recognition to all. There is no doubt that all of these contributions enhanced this column about Ludwig, the bioengineer.

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