CARL LUDWIG AND HENRY PICKERING BROWDITCH: THE LEGACY THAT LED TO W. B. CANNON

RAMÓN ORTEGA LOZANO

ABSTRACT. This article analyzes the influences that Walter Bradford Cannon, one of the most important physiologists of the 20th century, received from two main figures from such discipline: Carl Friedrich Wilhelm Ludwig and Henry Pickering Bowditch. The first run the most important laboratory of physiology of the 19th century, the Leipzig Institute of Physiology. Bowditch, who spent some time working in the Leipzig Institute under the former, founded the first American laboratory of physiology at Harvard University. The Harvard Laboratory of Physiology is where Walter Cannon acquired his methodology and his passion for researching, being its director at the end. This article narrates the life and work of Ludwig and Bowditch in order to understand their legacy and their influence in Walter Cannon.

The epistemological and methodological perspective of Bowditch and Ludwig is described. Their mechanistic stance in physiology passed from one to the other thanks to the institutionalization of physiology, that is, the creation, development and spread of physiological laboratories. These practices reached Cannon trough Bowditch. However, Cannon assumed the mechanistic physiology perspective as a method only, changing its epistemology into a holistic one. The innovative approach of this paper is focus on the roll that the institutionalization of physiology had in the legacy that led to Cannon. This is important if we want to understand that Cannon, one of the main figures of holistic physiology, first worked influenced by the mechanistic method and epistemology.

KEY WORDS. Walter Bradford Cannon, Henry Pickering Bowditch, Carl Ludwig, Harvard laboratory of physiology, Leipzig Institute of Physiology.

1. INTRODUCTION

> [...] I am a son of Bowditch, who led me into physiological investigation. Dr. Bowditch in turn was the son of Karl Ludwig, to whose laboratory in Leipzig in the last century he resorted together with other young men from many lands.
>
> Walter Cannon[1]

Walter Bradford Cannon is one of the most important figures in physiology of the first part of the twentieth century. The term "homeostasis",

Centro de Ciencias de la Salud San Rafael, Universidad Antonio de Nebrija, Madrid, España.
ortega.lozano.ramon@gmail.com

which he coined, constitutes one of the most important concepts in biology in the last two centuries. Cannon can also be seen as the main representative of holistic physiology, along with others such as Lawrence Joseph Henderson, Charles Scott Sherrington and John Scott Haldane. His contributions led to the living organism being studied as a whole, that is, in order to find the true nature of the particular elements of an organism, one has to pay attention to different levels, i.e., organs, systems, and the organism as a whole.

Many science historians such as Fleming [2] or García Barreno [3] have remarked the influence of Claude Bernard's term *milieu intérieur* in the conception of Cannon's homeostasis theory. That is why, when looking for other authors' influences on Cannon, Claude Bernard is the main figure who emerges first. Nonetheless, there is a principal and major influence that Cannon himself accepted. The quote that opens this article, written by him in his autobiography (*The Way of an Investigator*), can summarize in a simple way, yet exceptional, the chain of influences in which each master led to his disciple until it reached Cannon. Not only gratitude and admiration can be appreciated in each link of this chain, but also an example of solid friendship as a benefit of scientific collaboration.

Bowditch decided to leave the United States when he realized that his studies at Harvard University would not give him the opportunity to achieve a complete training and that his best option was to continue his formation in Europe, where some of the most important physiology investigations were taking place at that time. He did not know that this adventure would lead him to meet Carl Ludwig, and even less did he know the remarkable impact this relationship would have on him. A similar situation happened to Cannon when he began his work at the Harvard Laboratory—an institute under Bowditch's direction. Thanks to those first investigations, under Bowditch's guidance, on the peristaltic movements of the digestive tract using the newly discovered *Röntgen rays*, Cannon got in contact with experimental research. He never would have imagined that he was discovering a different way from the one he had in mind when he first started his medical studies: "[If it wasn't for Bowditch] I would have become a neurologist [4]." Actually, he was following the way of an investigator.

The following article will detail the life and work of Carl Ludwig and Henry Pickering Bowditch in order to understand their legacy and contributions to the chain that led to Walter Cannon. The main objective of this work is to show some of their characteristics as professors, as well as the theoretical aspects they established in their methods of researching, to better describe how the mechanistic physiology yielded to the holistic one. The following exposition is chronological; it is not possible to understand

Cannon's advances without Bowditch's training, nor Bowditch's progress without Ludwig's education.

2. THE ORGANIC PHYSICISTS AS LABORATORY

Carl Friedrich Wilhelm Ludwig was born in Witzenhausen, a small village in the south of Gottingen in Germany, on December 29 of 1816. After living in Hanau (near Frankfurt), he moved to Marburg to start his medical studies at the University of Marburg. Due to his political activities, he was expelled from this university, so he continued his education in Erlangen and later in the School of Surgery of Bamberg. Nevertheless, he went back to the University of Marburg in 1839 and obtained his M.D. degree in 1840.

After a short period in the laboratory with Robert Bunsen (1811-1899), two years later, when obtained his medical degree, Ludwig got the *venia legendi* (Latin "for permission to read", i.e., lecture) with his habilitation thesis on blood vessels in the kidney. He presented a description of the function of the glomeruli similar as we understand it nowadays. From that time, he was already a mechanistic physiologist, because his main objective was to finish with the teleological conception of the kidney activity. At that time, it was thought that the complexity of these kinds of organs could not be reduced to a mechanistic explanation (a substance is just transformed into another, due to the vital forces of the living being). Even so, Ludwig was able to explain the function of the kidney as a complex machine that works under physical laws. With his habilitation he was able to be a medical professor in a university. He started to work as "second prosector at the Department of Anatomy of the University of Marburg [5]" and later promoted as the first prosector in 1846.

Mechanistic physiology is also related to the creation and development of many physiological apparatus of measure, in order to analyze the body processes within the laws of physics and chemistry. It was in his years at the University of Marburg that Ludwig developed one of his more famous inventions: the kymograph, a device used to record over time physiological processes, such as blood pressure or respiratory movements (and as it is going to be seen, thanks to Bowditch, to enable a graphical representation of the processes). With his invention, he attracted the attention of the scientific world. This could be the reason which explains the warm welcome he received in one of the most important places for physiology research at that time, the Humboldt University in Berlin, where Johannes Müller had a chair in anatomy and physiology. This was a great opportunity for him to learn from Müller's lectures, and even more, Ludwig could meet one of his main allies and later friends. In the spring of 1847, he visited Johannes Müller in Berlin and met his disciples Herman Helmholtz, Ernst Brücke, Emil du Bois-Reymond and Rudolf Virchow [6]. Later, these researches would be known as the *organic physicists* or *the German reductionists*, with Ludwig as the head of the group. The group postulated that all physiological processes of the organism are governed under physico-chemical laws.

Some years later, in 1849, Ludwig got a position as professor and chairman of the Anatomy and Physiology Department at the University of Zürich. During that time he worked on his textbook on physiology, a project he had already started at the University of Marburg. At the time, his mechanist perspective was so well established that he focused all his efforts to achieve one goal: to systematize the physiological knowledge that had been discovered until that time, free from any vitalist or *Naturphilosophie* influences. The result was the publication of the first volume of his textbook of physiology (*Lehrbuch der Physiologie des Menschen*) in 1852, and (the second one in 1856), which became the summary of the program that joined all the reductionist ideas of the organic physicists.

Later he was appointed as physiology and zoology professor at the Medical-Surgical Military Academy, where he worked for ten years. He was able to strengthen his relationship with Ernst Brüke who was professor at the Physiology Department of the University of Vienna. By this time, Ludwig has become popular as a professor and researcher in physiology. Then he received his most interesting professional opportunity as a chairman of the Physiology Department of the University of Leipzig. Ludwig "gladly and immediately accepted [7]."

This proposal came at an unbeatable moment. By that time, scientific and medical education received special attention in Saxony. The new Minister of Culture and Science, Johann Paul Freiherr von Falkenstein (1801-1882), implemented a series of measures as soon as he occupied his post. One of his objectives was to reform medical education at the University of Leipzig, as it was the main university in Saxony. To achieve this goal, one of his objectives was to build a new institute of physiology, and he found in Carl Ludwig the perfect man to develop and run such project. In 1865, Ludwig took over the chair of physiology and four years later he became the director of the Leipzig Institute of Physiology (as the new laboratory of experimental physiology research was called). "The institute which was erected under Ludwig's supervision was however based on his broad conception of physiology [8]." Ludwig remained in such positions until he died in 1895.

2.1. THE INSTITUTE OF PHYSIOLOGY

The nineteenth century bears witness to great progress in the knowledge of physics and chemistry. This progress had an impact on the study and interpretation of living beings. Nevertheless, at the beginning of the century, medical research faced some problems in the implementation of the new methods: "The fast progress in physics and chemistry allowed new forms of accurate observation and more precise measurable methods for the usage of the physiologist. Anyhow, the application of these methods encountered major difficulties. There were no physiology laboratories, nor instruments, nor technicians that the researcher could resort to [9]." Indeed, this was the time when Germany began, gradually, to promote the establishment of physiology chairs and to design and construct some laboratories:

> The history of institutes for experimental pursuit of physiology and other medical sciences is little more than a century old. Gruithuisen in 1812 had published an article advocating physiological institutes. Twelve years later, in 1824, Purkinje established the first physiological institute in Breslau [10].

Initially, progress started slowly, but a remarkable change was noticed with the breakthrough and spread of scientific institutionalization. France and England were the leaders in scientific advancement by the beginning of the nineteenth century, and as the century moved forward, German scientific advancement grew widely, especially in the decades of 1870 to 1900. When the twentieth century started, the German contribution to scientific advancement decreased as the American started to increase (figure 1):

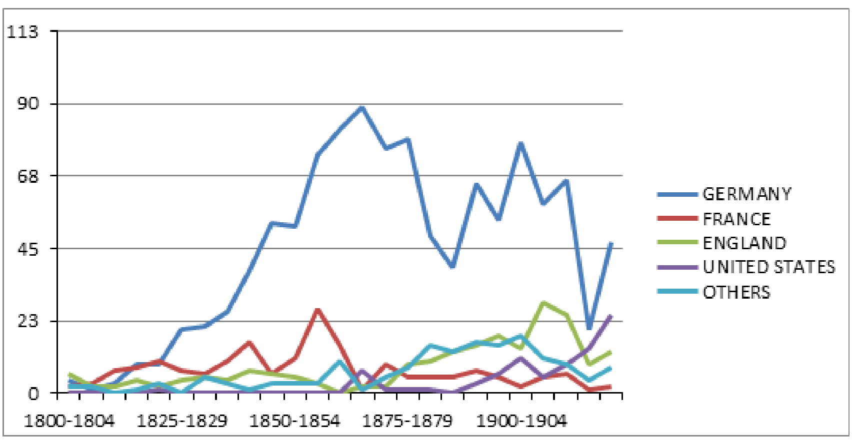

FIGURE 1. Number of original contributions to physiology in Germany, France, England and United States of America[11].

Many of the physiologists of Ludwig's generation confront the concepts of natural philosophy and Vitalism, consolidating mechanistic physiology. Even so, this new approach to the biological world needed a methodological shift based in direct experimentation (far from the theoretical speculation and the passive observation characteristic of the vitalist), and the instauration of physico-chemical techniques that were quantitative and demonstrable. As a consequence, the phenomenon of institutionalization [12], linked to the creation and development of experimental laboratories, gathered strength. Not only the researchers, but also the political and state powers, understood that without these institutions of experimentation, the development of medical investigation based on the new mechanistic approach was not going to be possible. These can be observed in the increase of the laboratories and the establishment of independent physiology chairs in the German universities. The first physiological research unit, with an experimental physiology course, was founded by Carl August Sigmund Schultze (1795-1877), in 1821, at the University of Baden: "Schultze was a harsh critic of *Naturphilosophische* speculation and believed that his course, which was based upon direct experience with the experimental animal itself, provided the necessary antidote to this not uncommon mental poison [13]." On the other hand, the first chair in physiology was created at the University of Breslau, in 1823, run by Jan Evangelista Purkynê (1787-1869). He also founded a small laboratory in 1824 and some years later, in 1839, he built a proper institution of physiology. More or less at the same time, Justus von Liebig (1803-1973) inaugurated a chemistry laboratory at the University of Giessen and Rudolf Virchow established the first pathology laboratory in Berlin, in 1856.

Additionally, this phenomenon of institutionalization changed the way the new medical generations were educated. The main idea was that it was not possible to have a real medical education without direct hands-on experience by the students of the concepts seen in class. The reform that started with the French physiologist François Magendie (1783-1855) and followed in Germany by Johannes Müller, was a constant battle to dismiss speculation. They tried to show that in the organism no other forces are active but the ones that rule inorganic matter. This was so, despite Müller, who did a lot to achieve this goal, but still believed in the existence of a vital force. That is why not until the next generation of physiologists that this goal was achieved: "No one however was more instrumental in the modern development of physiology than Carl Ludwig [14]."

Probably the chemistry laboratory of Liebig in Giessen and the physiological laboratory of Bunsen in Marburg served as models to Ludwig for the design and construction of his own institution. There is no better way to enter into this impressive building than to be being driven by one of Ludwig's outstanding disciples: Henry Pickering Bowditch. During his visit to the Leipzig Institute, Bowditch wrote a review in the journal *Nature* expressing what the work was like and the daily activity of the laboratory:

> The physiological laboratory, where I am at present working, owes its existence to the energy of Prof. Carl Ludwig, and to the liberality of the Government of Saxony. As it is universally acknowledged to be the most complete establishment of the kind in Europe, it seems to me to merit a somewhat detailed description [15].

The building had the shape of a capital "E". In the middle of the structure was a conference room, with a capacity for a hundred students. In the right side was the microscopy department, and in the left the chemistry department. In the central section was placed the area for experimental one. The main idea in Ludwig's design of the building was to solve physiological problems by combining anatomy studies and the physico-chemical knowledge of the organism. For him, all physiological problems had to be researched starting from the anatomy of a functioning organ analyzing the mechanisms and changes that happen inside it. All the organic functions could be reduced to physico-chemical laws. To achieve this goal he divided the building in different sections for the study of physics, chemistry and anatomy (which included histology).

Before this time, physiology was only studied inside the anatomy chairs, and it was only theoretical. For Ludwig, the new methodology consisted in a complex artifact that had to be studied, dividing its parts until its physical and chemical natures could be discovered. The institution allowed each speciality to study the mechanisms in a separate way, in order to bring light to the physiological processes. It is interesting that in the twentieth century, when the mechanical perspective was called into question by researchers such as Walter B. Cannon, John S. Haldane, Joseph L. Henderson, Charles S. Sherrington and others, they did not criticize the methodological approach but its epistemological perspective. In other words, the twentieth century physiologists attacked the mechanisists arguing that the physiological knowledge cannot be obtained just by analyzing the isolated parts of the organism. They proposed, on the contrary, that the physiological processes had to be understood as part of a whole, and it is important to pay attention to the interrelations within this whole.

Probably, the origin of the success of Ludwig's laboratory was the enthusiastic spirit of teamwork that he transmitted in the investigations he addressed. As soon as his students started to work with him, they were able to feel this enthusiasm. He had a great capacity to judge the learning capacity and capabilities of his students, and was able to assign something to do for each of them. Warren P. Lombard describes the work done at the Leipzig Institute:

> Every morning he visited the tables of different men and discussed with them the next steps to be taken [...] or he would take them into his private room and critically discuss the methods employed, making suggestions as to the direction in which more effective methods could be sought [...] This was not done offhand, for each night when he left the laboratory he carried to his room above, records and protocols of investigations in progress, for careful study [16].

Institutionalization introduced a new practical education and this was important for Ludwig. He tried to balance theory and practice in order to get a unity for the best instruction for their colleagues. "Ludwig attended his lectures with the same thorough and enthusiastic manner which characterizes all his work [17]." His lectures were interesting and concern practical aspects such as the daily experiments. He had a positive attitude and was an accessible person, so it is not surprising that his colleagues saw him as a "director of vast and deep culture that was beloved by his disciples as an ideal guide [18]."

For many years, the laboratories constructed first in Germany, later in the rest of Europe, and finally on other continents, had as a model the Leipzig institute. This fact has two reasons: the success of the mechanical theories, and the fame that this institute had, thanks to its pedagogic program that attracted several physiologists from around the world. "It's been estimated that there were 200-300 students and collaborators from Germany and abroad [19]" during Ludwig's leadership. Hugo Kronecker, one of his disciples, said that "it was not strange to find one German student among a group of nine or ten foreigner investigators [20]."·Many of them, when they return from their visit to Leipzig, brought with them the new knowledge to their own countries, spreading the mechanistic methodology in other parts of the world.

As this article is following the intellectual genealogy that leads to Cannon, it is important to remark the opinion that Henry P. Bowditch had about his mentor. Bowditch always saw in Ludwig a generous and humble person; these characteristics could be found at the time when an article was published with the results of an experiment addressed by him, and for which Ludwig declined to be included in the credits: "The results arrived at are published at the end of the year, sometimes under the name of the Professor and the pupil together, and sometimes under that of the pupil alone [21]." This attitude might be a motivation strategy for his collaborators; when they saw their names in a scientific publication, they would like to keep on the way of an investigator. Bowditch, himself, applied the same method with his collaborators some years later, when he became the director of the Harvard Laboratory, and it became a tradition as Cannon also followed this way in motivating his students.

The Leipzig Institute kept on working after Ludwig's death in 1895. His successor, with a remarkable career and age (61 years old) was Ewald Hering. As has been said, the institute served as a model for many laboratories in Germany and abroad. In the following century "the building was destroyed in World War II [22]."

2.2. CARL LUDWIG'S PROPOSAL

Ludwig's life as a professor acquired an important dimension thanks to his physiology textbook, *Lehrbuch der Physiologie des Menschen*, where he defended that physiology has to be based on analysis. In the introduction of his book he mentions: "Scientific physiology has the task of determining the functions of the animal body and of deriving them consequentially from its elementary conditions [23]." His textbook was addressed to medical students and had a didactic goal. He posited that all the explanations of the processes of the organism could be reduced to physics and chemistry.

Ludwig's textbook is considered "the first modern text book of physiology and anyone comparing Ludwig's work with recent texts will be struck by the similarity of arrangement and presentation [24]." It is the material proof of the epistemological shift in physiology that took place during the second half of the nineteenth century. It worked as a model for the new perspective in understanding and investigating the function of the organisms based on a reductionist program. Ludwig's aim was very ambitious because he wanted to demonstrate that the whole physiology could be reduced to physics and chemistry, even though, to his regret, "he conceded that he did not attain his high goal [25]." Anyway, he left at the disposal of his students and colleagues a new perspective in physiology research based in quantitative and verifiable experimentation. "There is not comparative anatomy, not a single sentence concerning embryology, and only those aspects of the cell theory relating to function are to be found in Ludwig's text. [...] Ludwig responded that it was not a matter of preference whether one emphasized physics over anatomy in a textbook of physiology [26]."

Many of the physiological advances proposed by Ludwig, some nowadays accepted, would not be possible without the experimental and quantitative isolation of the studied organs. In other words, all that progress would not be possible without mechanistic physiology. If there is a later criticism of Ludwig's proposal, it is that of John Scott Haldane [27]. This author showed that the systematic isolation of organs and physiological functions only gets incomplete results compared to the real complexity of bodily functions that actually work in the service of a higher hierarchy of organization. Cannon did not criticize Ludwig's epistemology in a direct way [28], but agreed with Haldane's idea that the answers to any function of the body have to be found in thinking the organism as a complete and integrated whole, and not as a host of isolated parts. Nevertheless, Haldane and Cannon also agreed in the acknowledgement that without the mechanistic progress of scientists such as Ludwig, the holistic perspective would not have been possible.

Another factor that help developed medical knowledge during the nineteenth century, also due to of the mechanistic perspective, was the series of new artifacts and techniques adopted in experimental physiological research. Ludwig is remembered as a great physiologist, as well a resourceful inventor. He constructed the kymograph with which it was possible to record physiological processes over time. In collaboration with one of his students, Ivan M. Sechenov—mentor of Ivan P. Pavlov—he invented the *mercury blood gas pump*. "It is one of the first devices to do a quantitative analysis of the arterial gases [29]." He also contributed to the task of isolating organs of the body and keeping them alive (among them the heart). Many of his techniques and apparatus were rapidly adopted by the scientific community of his time and soon his contributions could be seen in other laboratories of Germany and then abroad; the Harvard laboratory can be mentioned among them.

It has been said that Carl Ludwig is related to a group of scientists that developed this new physiology: "The historians had recently recognized a small group of physiologists exceptionally clever and active in Berlin during the 1840 decade, as decisive figures of all this progress [30]." This group defended the reductionism of biology to physics and chemistry. That is why his methods required a quantitative accuracy, based on apparatus to measure physico-chemical data. In addition to the instruments of Ludwig, it can be mentioned the ophthalmoscope of Hermann von Helmholtz or the galvanometer of Emil du Bois-Reymond. Every reductionist developed a research program similar to the one followed in the Leipzig Institute to dispute the concepts of Vitalism.

3. THE GREAT ADVENTURE OF HENRY P. BOWDITCH AND THE FIRST PHYSIOLOGY LABORATORY IN AMERICA

Henry P. Bowditch was born in Boston in 1840. He belonged to a significant scientific family in New England. "His youth was uneventful and was typical of that of the youth of his class in Boston during the middle of the nineteenth century [31]." In 1857, he entered Harvard College and already showed his interest in anatomy "[...] to clean the bones of one of his father's horses which had died, and later to set up the skeleton, properly articulated [32]." When he finished college, he studied a special term on chemistry, natural history and comparative anatomy at Lawrence Scientific School.

He entered Harvard Medical School after a period of service in the American Civil War. In 1868, he received his M.D. degree with a thesis on the physiological action of potassium bromide.

At that time, Europe was the best place for physiological research, so when Bowditch finished college education, his professor of comparative anatomy, Jeffries Wyman, suggested that he go abroad. Bowditch took such advice and he became one of the first pioneers (without knowing it) that acknowledged the limitations of continuing his studies at Harvard. He went to Paris the same year of his graduation. In the beginning, he continued his studies in the clinics of Jean-Martin Charcot (1825-1893) and Paul Pierre Broca (1824-1880), but he wanted to work under the direction of Charles-Édouard Brown-Séquard (1817-1894), a French physiologist and neurologist who lectured at Harvard. Unfortunately, "when Brown-Séquard failed to establish a laboratory where he could work in Paris, Bowditch turned to study with Claude Bernard and Louis Ranvier [33]." During this time, he was spending three days a week in physiology and another three in microscopy. Despite studying with two remarkable figures of medicine, he decided to leave, on account that none of these laboratories providing accommodations to visiting students. After a long tour— where he studied with Wilhelm Kühne (1837-1900) in Paris, later with Virchow in Berlin, then with the histologist Max Johann Sigismund Schultze (1825-1874) in Bonn, later with Helmholtz—finally he reached his last stop, the one that changed his life and introduced him to physiological experimentation: a term in Ludwig's Leipzig Institute.

Once Bowditch started to work in this laboratory, the scientific environment and the enthusiasm of his colleagues seduced him. By that time, Ludwig had already invented the kymograph. However, the measures of time and period of electrical stimulation were still written by hand. Bowditch called this to Ludwig's attention, so the latter gave him the duty of inventing a mechanism that allowed the registration automatically. Bowditch described this experience to his parents in a letter:

> Prof. Ludwig is a very amiable and agreeable man. He must be between fifty and sixty years old, but he retains his youthful enthusiasm and a remarkable faculty of finding pleasure and amusement in trifling matters. I arranged a little apparatus yesterday attached to a metronome for the purpose of marking time on a revolving cylinder covered with smoked paper (an instrument much used in various physiological experiments), and it was real fun to see how delighted the professor was with it [34].

The impression that Ludwig caused in Bowditch was extraordinary. From Ludwig, he learned not only the use of physiological devices, a methodology based in experimentation, and the physico-chemical analysis in physiology; he also learned a passion for research, an enthusiasm that Ludwig knew how to transmit.

In 1869, Charles William Eliot (1834-1926) was elected president of Harvard University, and in December of the same year he proposed Bowditch to return to the United States to deliver some lectures on physiology in the spring semester of the academic year 1870-1871. This was a good opportunity to start a career at this prestigious university. However, Bowditch kindly declined Eliot's proposal. It was not a strange decision, since accepting would mean leaving Germany six months before his visiting program ended. Actually, this last term was the most valuable for him.

During this last period, Bowditch assimilated the mechanistic methodology that was typical of the work done in the Leipzig laboratory, already shown above. Some of the research in which he collaborated was on the heart, focused on the cardiac muscle and the heart proper. In the same way as Ludwig posit the renal function reduced to the physical forces involved, Bowditch described the muscular process of the heart. This investigation had two parts: "One group of experiments was concerned with the neural control of cardiac action [...] The second line of investigation was devoted to an examination of myocardial irritability [35]."

Other investigations of Bowditch led to the development of two important physiological concepts: the "*treppe* (staircase) effect" stimulation and the "all-or-none" law of contraction. These results were very helpful in the study of the passage of impulses along nerve trunks. This last study was later continued by Sechenov and Pavlov. The work of a year was presented in a paper, and in the words of Bowditch himself: "[Ludwig] seemed quite well pleased with it [36]." With this essay, Bowditch ended direct collaboration with his German mentor. Nevertheless, the communication between both scientists remained fluid, as Cannon wrote in Bowditch biography.

After this period, Bowditch returned to Boston concluding his studies abroad. From his visit to Leipzig Institute, Bowditch obtained great benefits: he learned the experimental method using the most advanced techniques of his time; he appreciated the role of invention in order to solve the technical difficulties that obstructed physiological research; he became familiar with the use of physiological apparatus, and, finally, he assimilate the passion for researching. He also acquired the pedagogic method implanted by Ludwig, as these institutes were constructed for medical education and students' practice. This was well assimilated by Bowditch and transmitted later to his disciple Walter B. Cannon.

3.1. THE HARVARD LABORATORY

The United States of America, after some years of delay, showed a similar concern on the medical condition as Europe during the nineteenth century. There were not physiology chairs, the little research in this field was based on passive observation, and there were no physiological laboratories, so no experimental methodology was done. During this period, the American medical schools did not have the quality as those in Europe (especially in Germany). This situation might be one of the reasons that Bowditch himself decided to decline Eliot's first offer to be part of Harvard University. Medical education in the United States was deficient and Harvard Medical School was not different. Indeed, there were increasing calls to attention from the medical community in Boston that demanded the academic authorities to develop and improve medical education. Nevertheless, "nothing changed until Charles W. Eliot became president of Harvard in 1869 [37]." As its new president, he realized that the university needed reform. Eliot was shocked by the quality of the students and the poor standards of instruction. He decided to reorganize the medical school: "[...] the young president recognized that his ultimate goals for the School depended largely on the quality of the teachers he could attract. One of the first new faculty members he tried to recruit was Henry Pickering Bowditch [38]."

In 1871, once Bowditch had returned to Boston, Eliot made a new offer. He invited Bowditch to be part of the medical school as an assistant professor of physiology. Later he was promoted to full professor (1876), becoming the first one in this field at the Harvard Medical School (before, physiology was part of the anatomy course). Bowditch used the same pedagogic method as Ludwig, with well-organized lectures and detailed demonstrations. "Putting all of his enthusiasm, vigor and interest into his exposition, Bowditch stimulated some medical students to research out the original literature mentioned in their textbook... [39]." Nevertheless, he knew that the students' education would be incomplete until they received practical instruction. This situation led him to an important decision for the medical education.

Before leaving Leipzig, Bowditch bought some apparatus to use for his own research in the United States; he did not know that such equipment would serve for a major project. Once he was working at the Harvard Medical School, he realized there was no experimental laboratory where the students can put into practice the knowledge learnt in class. This became one of his first goals, to find a place for practical instruction. As almost all rooms were in use, he asked permission to install his German apparatus in two small rooms at the attic of the building. This modest attic [40] became "the first physiological laboratory for the use of students in the United States [41]." This small institute, as Ludwig's laboratory, was characterized by a mechanistic methodology and for physiological research based on direct experimentation. In spite of its modest size, research was practiced in a variety of medical disciplines: the absence of resonance on percussion as diagnostic of pericardial effusion, the effects of electrical stimulation of the cerebral cortex, the nature of digestion to pharyngeal respiration in lower animals, among others [42]. What is common in all the investigations was their reductionist perspective.

The Harvard Laboratory, directed by Bowditch, can be used as an example of the phenomenon of institutionalization of physiology. This American laboratory was "imported" from Germany and had all the elements (in a small-scale) of Ludwig's Institute. The epistemological perspective was the same as Ludwig's model; in order to know the functions of an organism it is necessary to analyze separately its elements and to use a methodology based in the use of physico-chemical apparatus and techniques. This case helps to understand better the role that these laboratories had in the spread of the mechanism theories and the abandonment of vitalists concepts [43]. In the specific case of the Harvard Medical School, it allowed the students to approach the experimental method and to know the importance of physico-chemical techniques and the mechanistic perspective in order to solve physiological problems. For the students, scientific physiology became a synonym for a reductionist study of organic functions and their nature based in physics and chemistry. Later, this model of experimental laboratory was implemented by other universities all over the nation until it was an inseparable part of medical instruction.

Moreover, the development of these laboratories is also linked to their pedagogic function. Bowditch, as Ludwig did, allowed his students to propose freely their experiments. He wanted them to acquire a passion for researching by choosing those subjects they were more interested in, without imposing any issues that did not call their attention. It was an attitude without hierarchy: "beginning students as well as advanced workers were encouraged to pursue their own interests and problems [44]." Soon, Bowditch got the admiration not only of the students, but from the academic community in general, and his fame was extended outside Harvard:

> By 1893, Bowditch had become a major force in the Boston medical and scientific community. Everyone who came in close contact with him was impressed by his stately appearance, sure judgment, and earnest devotion to his profession. In the faculty room of the Medical School, his counsel had become recognized as indispensable, and from first to last, when he rose to speak, he was listened to with respectful attention [45].

In essence, Bowditch's aim was to transmit the curiosity for experimental research in physiology, as he learned from Ludwig. It would be imprecise to compare the impressive Leipzig Institute with those two attic rooms in the medical school. Anyway, at Harvard different kinds of experiments took place in almost all fields of medicine: physiology, general biology, pharmacology, pathology, surgery and even psychology. The resources were limited, but Bowditch's goal was very clear: to set an American laboratory as a mirror of the one his tutor had in Germany. The work done in the Harvard Laboratory became significant to the medical progress of the United States. A good example is Walter Cannon's labor; still a student, he started to work in the research of digestive movements under Bowditch's direction. In such way Cannon started his career as an investigator.

In 1883, the Medical School of Harvard opened its doors at a new building. The physiology department, from its two rooms in an attic, was now allocated on more than a quarter of the surface on the second floor of the new building. Bowditch became the new dean of the medical school and supervised the transit to the new building. Thanks to Bowditch and his collaborators, the medical school improved its quality: "Under Bowditch's guidance, Harvard was the first American medical school to give normal instruction of pathology and the new science of bacteriology, and the subject of histology was expanded to include embryology [46]." The Harvard Laboratory became the most important physiological laboratory for academic research in the United States. A fact that can show its quality level is the number of publications of that time: "From 1883 to 1889 investigators in the physiological laboratories published twenty-three papers [47]."

Also related to mechanistic methodology is the invention of apparatus. Bowditch, who already had shown his skills in Leipzig, continued to design and produce a number of instruments useful to physiology research. Bowditch knew the importance of these kinds of devices and published an article in *The Journal of Physiology* where he described the physiological equipment that was used in the Harvard laboratory, so anyone could benefit from its use:

> Pieces of apparatus constructed in a physiological laboratory to meet special wants are frequently found to possess a general usefulness sufficient to justify their description in a journal devoted to physiological science. For this reason the following brief account of a few forms of apparatus in use at Harvard Medical School is presented to the readers of the journal in the hope that the instruments described will be found as useful elsewhere as in the laboratory where they originated [48].

The article describes some of the instruments he invented, from the more complex—apparatus of artificial respiration, practical cannula for observations on the vocal cords—to the most simple, as a dog-holder that also prevented the mouth from being opened.

To summarize, the methods used in the Harvard Laboratory are the ones inherited from the German reductionists. It is not only the use of apparatus to measure physico-chemical data, typical of the mechanism, but also the epistemological perspective of inquiry into physiological processes, isolating the components of the organism to understand their functions. Cannon himself started his research under such perspective. When he was still a medicine student he analyze the phenomenon of swallowing. With an X-ray apparatus, he observe the motion of the esophagus, then the stomach, then the intestines, as well as the conditions affecting their activities. He studied the digestive canal as if it were a machine that could be divided into different parts that work independently. Cannon was "the last, but maybe the most important collaborator of Bowditch [49]." Indeed, he succeeded Bowditch as director of the Physiology Department and the Harvard Laboratory from 1906 to 1942, when he retired.

4. THE LEGACY INHERITED BY CANNON

Probably never in the history of medicine had technique such a major influence on the basis of scientific knowledge as it did during the nineteenth century (and continuing today). The main progress in physiology during the nineteenth century was in part due to the phenomenon of institutionalization, with the construction and development of experimental laboratories linked to public universities (before the nineteenth, scientific research was a private affair that took place in private houses and academies). At the beginning of the century they were almost nonexistent, and then slowly multiplied, showing their utility. Some important figures were fundamental for the establishment of these laboratories. Bernard, Müller, Liebig, Purkynê, Ludwig, Bowditch, and their collaborators, were conscious of the importance of these institutions and the implementation of a new experimental methodology. As has been shown in this article, some of these investigators assumed the mechanistic perspective. Anyhow, all of them thought that direct experimentation was a fundamental part of the daily work of a researcher, and a first step in the standardization of a real scientific method and its techniques. The boundary between the development of this new methodology and the creation of experimental institutions is so thin that it is difficult to realize which of them was the cause of the other.

When someone thinks about the fast spread of experimental physiology during the nineteenth century, and understands that it was within experimental institutions where the mechanistic methodology was developed, it is easy to realize how fast the vitalist concepts were expelled from physiological research. The German reductionists could explain some of the mechanisms that were involved in the organ's activity and their methodology had produced outstanding progress in comprehending physiological and pathological processes. However, they were not able to give a satisfactory answer to the complexity of living beings. Ludwig, Bowditch and other mechanism physiologists promoted the implementation of techniques, apparatus and procedures to analyze body functions by the isolation of their simple elements. All the same, it is the next generation of physiologists—Cannon, Henderson, Haldane, among others—who realized that to understand the nature of the integrated process a new perspective would be needed: a holistic physiology.

The legacy that Cannon received from his predecessor is related directly to the Harvard Laboratory and before, and indirectly, to the foundation of the Leipzig Institute and the experimental practices that took place in both of them. Ludwig was a mechanistic physiologist, who established that the only possible approach to organic functions is by a quantitative reduction to their physico-chemical nature. For him, organisms are dynamic material that follow the laws of physics and chemistry. This perspective is what he taught to all of his collaborators who came to his institute. From Ludwig, Bowditch inherited a methodology based in physico-chemical techniques. As it was shown, to do adequate experimentation it was necessary to use a series of instruments and apparatus for quantitative registration. Moreover, those devices, in cases where they did not exist would have to be designed and constructed as demanded by research. Ludwig and Bowditch were two good examples of this kind of inventor. With this information, it is recognized that Bowditch's point of view on physiology is a reflection of Ludwig's own perspective: "Bowditch's work exhibited very little speculation and dealt almost exclusively with facts [50]."

Even more important is the pedagogic influence that Ludwig had over Bowditch, one that could be appreciated in the daily work at the Leipzig Institute. In that same way Bowditch tried to educate his students at the Harvard Laboratory. From the beginning he motivated his collaborators to design their own experiments and to pursuit the subjects they were more interested in. Sometimes, he was the one who gave tasks to his collaborators, and some of them concluded in new discoveries. The results were published under the students' names, even though they were supervised by Bowditch. This was a motivational strategy followed by Ludwig, and that Cannon also adopted when he became the laboratory's director. Cannon is one of Bowditch's best biographers, to whom he showed a lot of admiration: "It seems to me that we have in this [Harvard] laboratory a very rich inheritance in valuable traditions and influences which have come to us from these two great sources [Ludwig and Bowditch] [51]."

It is unavoidable to acknowledge the enormous similarity between the influence that Bowditch had over Cannon, and the one Ludwig had over Bowditch. Cannon directed the Harvard Laboratory with the same didactic bases founded in experimental instructions, as did his predecessors. Cannon's collaborators remembered him as an enthusiastic professor, with a great passion for research. By Cannon's times, the use of physiological apparatus and physico-chemical techniques were completely accepted, and kept improving. Communication and technology also advanced so the standardization of artifacts and techniques was extended to all laboratories. In the same way, the scientific literature grew with a major production of articles that showed the results of a growing research. However, not everything was done; the researchers had to face new challenges. One of them was the complexity of the organism's functions and its interrelations, which was difficult to explain from the mechanistic perspective. Cannon worked on this, and when he realized that the mechanistic approach did not show the real nature of the physiological problems, he started to change his perspective, attending first to the relation of some processes with others, and then studying the organism as a whole.

It is important to say that none of the holistic physiologists would neglect certain facts set by the mechanistic: "One of these is that the matter of which the bodies of organism are found by analysis to be composed consists of the same chemical elements as are found outside the body, and that no new matter is formed in the body, or disappears from it [52]." Neither would they doubt the necessity of direct experimentation and the use of physico-chemical techniques. It is true that without the mechanism, it would have not been possible to understand the later integrated processes of the organism by the holistic approach. A good way to understand this assumption is by the chain of biographies exposed in this article. Without a model of a physiological institute, it is probable that Bowditch would not have established the Harvard Laboratory. Without Ludwig's instruction on experimental methodology and mechanistic perspective, Bowditch would not have had such a successful research institution. The same happened with Cannon, who learned the methodology and epistemology he later applied when the Harvard Laboratory was under his direction.

A programmatic and epistemology shift was necessary, yet it did not completely nullify the previous tradition. A good example is the physiological work of Walter Cannon. His first work on digestive movements shows a mechanistic perspective. He analyzed, as if they were independent parts of a machine, the esophagus, the stomach and the intestines. The title of the book where he showed all his results is informative in this respect: *The Mechanical Factors of Digestion* [53]. He would probably have continued his research in a mechanistic way, until some enigmas appeared. The peristaltic movements suddenly stopped without an apparent reason. Thanks to his ingenuity, he realized that emotional excitement was the cause (when the experimental animals suffered from pain, anger or fear) why the peristaltic movements cease. Therefore, he started to research the relation of the digestive system with the adrenal glands and the nervous system. The results of this new research were published in his book *Bodily Changes in Pain, Hunger, Fear and Rage* [54], which started a new perspective he would continue using in later investigations, one that was based on the interrelation of different organs and systems. In this phase Cannon was already holistic; he described his “emergency theory” that settled that the organism is prepared for a prompt and extreme effort in order to “fight or flee” in case of emergency. Cannon understood that the best way to research physiological phenomena is studying the body as a whole. With this holistic perspective, he finally coined the concept “homeostasis”, which is the property of organisms in which variables are regulated so that internal conditions remain stable and relatively constant. Cannon himself showed the steps that physiology took from the mechanistic physiology to the holistic one. In the preface of his book *The Wisdom of the Body*, Cannon summarized his scientific career and how he reached the homeostasis concept:

> In the main [volume] it pertains to the relation of autonomic systems to the self-regulation of physiological processes. That relation was only slowly disclosed.
>
> [...]Only by understanding the wisdom of the body, he [Prof. E. H. Starling] declared, shall we attain that “mystery of disease and pain which will enable us to relieve the burden of mankind.” Because my own convictions coincide with those of Professor Starling, and because the facts and interpretations which I shall offer illustrate his point of view, I have chosen to give the title of his oration to the present volume [55].

NOTES

1 Cannon, Walter B. *The Way of an Investigator*. New York and London: Hafner Publishing Company; 1965, p. 89.
2 Fleming, Donald. "Walter B. Cannon and Homeostasis". *Social Research. Modern Masters of Science.* 1984; vol. 51, num. 3, pp. 609-640.
3 García Barreno, Pedro. "Prólogo". In: Bernard, Claude. *Introducción al estudio de la medicina experimental*. Barcelona: Crítica; 2005.
4 Cannon, n. 1, p. 21.
5 Zimmer, German. Carl Ludwig: "The man, his time, his influence". *European Journal of Physiology*. 1996; supp. 3, vol. 432, p. R.10.
6 Zimmer, n. 5, pp. R10-R11
7 Zimmer, n. 5, pp. R10-R11
8 Rosen, George. "Carl Ludwig and his American students". *Bulletin of the Institute of the History of Medicine.* The Johns Hopkins University Press. 1936; vol. 4, n. 8, p. 616.
9 Singer, Charles, Underwood, E. Ashwort. *Breve historia de la medicina*. Madrid: Ediciones Guadarrama; 1966, p. 297·
10 Rosen, n. 8, p. 619.
11 Ortega, R. (2013): "Carl Ludwig y el fenómeno de la institucionalización como triunfo del mecanicismo fisiológico", *Ludus Vitalis*, No. 39, p. 77. The data of the graphic is obtained from Sánchez Ron, J. M. (2007), *El poder de la ciencia*, Crítica, Barcelona, pp. 229-230.
12 *The phenomenon of institutionalization* can be also found as "laboratory revolution" in Cunningham, Andrew, Williams, Perry. *The Laboratory Revolution in Medicine*. New York: Cambridge University Press; 1992.
13 Coleman, William. "The Prussian Pedagody: Purkyne at Breslau, 1823-1839". In: Coleman, William, Holmes, Frederic, eds. *The Investigative Enterprise: Experimental Physiology in the Nineteenth Century Medicine*. London: University of California Press; 1988, p. 39.
14 Rosen, n. 8, pp. 610-611.
15 Bowditch, Henry P. "The physiological laboratory at Leipzig". *Nature*. 1870; n. 3, p. 142.
16 Lombard, Warren. P. "The life and work of Carl Ludwig". *Science*, 1916; p. 366. In: Rosen, n. 8, p. 617.
17 Rosen, n. 8, p. 618.
18 Castiglioni, Arturo. *Historia de la medicina*. Barcelona: Salvat Editores [Hispano-Americana]; 1941, p. 722
19 Zimmer, n. 5, p. R20.
20 Kronecker, Hugo. *Carl Friedrich Wilhelm Ludwig. 1816-1895.* Berlin Klinische Wochenschrift. 1895; 32, n. 2, pp. 466-467.
21 Bowditch, n. 14, p. 143.
22 Zimmer, n. 5, p. R13.
23 Ludwig, C. (1858): *Lehrbuch der Physiologie des Menschen*, Ester Band, Zweite neu bearbeitete Auflage, C.F. Winter Verlansbuchhandlung, Leipzig und Heidelberg, p. 12, translated by Frank, M., Weiss, J. "The introduction to Carl Ludwig's textbook of human physiology", p. 77.
24 Rosen, G. (1936), p. 615.
25 Zimmer, G.H. (1996), p. R20.
26 Lenoir, T. (1988), "Science for clinic: science policy and the formation of Carl Ludwig's Institute in Leipzig" in Coleman, William & Holmes Frederic L.

(ed.): *The Investigative Enterprise: Experimental Physiology in the Nineteenth Century Medicine*, University of California Press, London p. 157.

27 Haldane, John Scott (1913): *Mechanism, Life and Personality; an Examination of the Mechanistic Theory of Life and Mind*, John Murray, London; Haldane, John Scott (1935): *The Philosophy of a Biologist*, Oxford University Press, Oxford.

28 Cannon felt admiration for Ludwig's, because as it will be seen, he was Henry Pickering Bowditch's mentor.

29 Puigbo, J. J. (2002): *La fragua de la medicina clínica y de la cardiología*, Consejo de Desarrollo Científico y Humanístico, Universidad Central de Venezuela Caracas, p. 683.

30 Coleman, William (1983)*: La biología en el siglo xx. Problema de forma, función y transformación*, Fondo de Cultura Económica, México, p. 205.

31 Rosen, n. 8, p. 620.

32 Cannon, Walter B. "Henry Pickering Bowditch". Academy of the Annual Meeting; 1922, p. 183.

33 Beninson, Saul; Barger, A. Clifford; Wolfe, Elin: Walter B. Cannon: *The Life and Times of a Young Scientist*. USA: The Belknap Press of Harvard University Press; 1987, p. 36.

34 Cannon, n. 24, p. 184.

35 Rosen, n. 8, p. 622.

36 Cannon, n. 24, p. 186.

37 Beninson, et al. n. 25, p. 34.

38 Beninson, et al. n. 25, p. 35.

39 Beninson, et al. n. 25, p. 38.

40 It is probable that its modest size was the origin of a controversy about which was the first physiological laboratory in the United States. Cannon complained that the issue of *Science* for September 22, 1933, mentioned that the first physiological laboratory of the country was constructed at Johns Hopkins University: "In the notice it was stated that in 1876 'there was but one laboratory of experimental physiology in the United States, that of the late professor H. Newell Martin, which had recently been established at the Johns Hopkins University'. May I call attention to the fact that when Dr. Henry P. Bowditch returned from Ludwig's laboratory in 1871 he established a laboratory of experimental physiology in Harvard Medical School" Cannon, Walter B. "The first American laboratory of Physiology". *Science*; 1933, 78 (Oct), p. 365.

41 Cannon, n. 24, p. 186.

42 Beninson, et al. n, 25, p. 39.

43 To learn more: Ortega, Ramon. "Carl Ludwig y el fenómeno de la institucionalización como triunfo del mecanicismo fisiológico". *Ludus Vitalis*; 2013, n. 39, pp. 67-85.

44 Beninson, et al., n. 25, p. 40.

45 Beninson, et al. n. 25, p. 41.

46 Beninson, et al. n. 25, p. 41.

47 Beninson, et al. n. 25, p. 42.

48 Bowditch Henry P. "Physiological Apparatus in use at Harvard Medical School". *The Journal of Physiology*; 1879, 2(3), p. 202.

Rothschuh, Karl. "La fisiología". In Entralgo, Pedro Laín (ed.). *Historia universal de la medicina.* Barcelona: Salvat Ediciones, 1974, Tomo IV, p. 89.

50 Rosen, n. 8, p. 625.

51 Cannon, Walter B. "The story of the Physiology Department of the Harvard Medical School". Harvard Medical Alumni Bulletin; 1927, 1, p. 18.
52 Haldane, John Scott. Mechanism, *Life and Personality; an Examination of the Mechanistic Theory of Life and Mind*, London: John Murray, 1913, pp. 1-2.
53 Cannon, Walter B. *The Mechanical Factors of Digestion*, New York & London: Edward Arnold Longmans & Co., 1911.
54 Cannon, Walter B. *Bodily Changes in Pain, Hunger, Fear and Rage*. Boston: Charles T. Brandford Company, 1929.
55 Cannon, Walter B. *The Wisdom of the Body*. New York: The North Library, 1932, pp. xiii-xiv.

BIBLIOGRAPHY

Ackerknecht, Erwin H. (1982), *A Short History of Medicine,* Baltimore: The Johns Hopkins University Press.

Ayala, Francisco J.: Dobzhansky, Theodosius (ed.) (1983), *Estudios sobre la filosofía de la biología,* Barcelona: Ariel.

Beninson, Saul; Barger, A. Clifford; Wolfe, Elin (1987), *Walter B. Cannon: The Life and Times of a Young Scientist*, Harvard: The Belknap Press of Harvard University Press.

Bernard, Claude (2005), *Introducción al estudio de la medicina experimental*, Barcelona: Crítica.

Bowditch H.P. (1879), "Physiological apparatus in use at Harvard Medical School", *The Journal of Physiology* 2 (3): 202-205.

Bowditch, H.P. (1870), "The physiological laboratory at Leipzig", *Nature* 3: 142-143.

Cannon, Walter B. (1911), *The Mechanical Factors of Digestion*, New York & London: Edward. Arnold Longmans & Co.

Cannon, Walter B. (1922), "Henry Pickering Bowditch", presentado en la *Academy of the Annual Meeting*, p. 184.

Cannon, W. B. (1929), *Bodily Changes in Pain, Hunger, Fear and Rage*, Boston: Charles T. Brandford Company.

Cannon, Walter B. (1927), "The story of the Physiology Department of the Harvard Medical School", *Harvard Medical Alumni Bulletin* 1: 12-19.

Cannon, Walter B. (1932), *The Wisdom of the Body*, NY: The North Library.

Cannon, Walter B. (1933), "The first American laboratory of physiology", *Science* 78 (Oct): 365-366.

Cannon, W. B. (1965), *The Way of an Investigator: a Scientist's Experiences in Medical Research*, New York and London: Hafner Publishing Company.

Castiglioni, A. (1941), *Historia de la medicina*, Barcelona: Salvat Editores [Hispano-Americana].

Coleman, William & Holmes Frederic L. (ed.), *The Investigative Enterprise: Experimental Physiology in the Nineteenth Century Medicine*, LA: University of California Press.

Coleman, William (1983), *La biología en el siglo xx. Problema de forma, función y transformación*, México: Fondo de Cultura Económica.

Cunningham, A., Williams, P. (eds.) (1992), *The Laboratory Revolution in Medicine*, NY: Cambridge University Press.

Fleming, Donald (1984), "Walter B. Cannon and homeostasis", *Social Research* 51 (3): 609-614, *Modern Masters of Science*.

Haldane, John Scott (1913), *Mechanism, Life and Personality; an Examination of the Mechanistic Theory of Life and Mind*, London: John Murray.

Haldane, John Scott (1935), *The Philosophy of a Biologist*, Oxford: Oxford University Press.

Hull, David (1974), *Philosophy of Biological Science*, Englewood Cliffs, Nueva Jersey: Prentice-Hall Inc.

Kronecker, H. (1895), "Carl Friedrich Wilhelm Ludwig. 1816-1895", *Berliner Klinische Wochenschrift* 32 (2): 466-467.

Laín Entralgo, P. (1986), *Ciencia, técnica y medicina*, Madrid: Alianza Editorial.

Laín Entralgo, P. (ed.), *Historia universal de la medicina*, Barcelona: Salvat Ediciones, Tomo IV.

Ludwig, C. (1858-61), *Lehrbuch der Physiologie des Menschen*, Ester Band, Zweite neu bearbeitete Auflage, 2 vols., Leipzig und Heidelberg: C.F. Winter Verlagsbuchhandlung.

Ortega, R. (2013), "Carl Ludwig y el fenómeno de la institucionalización como triunfo del mecanicismo fisiológico", *Ludus Vitalis* XVI (39): 67-85.

Puigbo, J. J. (2002), *La fragua de la medicina clínica y de la cardiología*, Caracas: Consejo de Desarrollo Científico y Humanístico, Universidad Central de Venezuela.

Rosen, G. (1936), "Carl Ludwig and his American Students", *Bulletin of the Institute of the History of Medicine,* The Johns Hopkins University Press 4 (8): 609-650.

Sánchez Ron, J. M. (2007), *El poder de la ciencia*, Barcelona: Crítica.

Singer, Ch. & Underwood, E. A. (1966), *Breve historia de la medicina*. Madrid: Ediciones Guadarrama.

Zimmer, German H. (1996), "Carl Ludwig: The man, his time, his influence", *European Journal of Physiology supp. 3, vol. 432: R9-R22.*