Claude Bernard

"Mais la méthode expérimentale a pour objet de transformer cette conception a priori fondée sur une intuition..., en une interprétation a posteriori établie sur l'étude expérimentale des phénomènes..." Claude Bernard: Introduction à l'étude de la médecine expérimentale.
["But the experimental method aims at transforming this a priori conception based on a vague intuition...into an a posteriori interpretation established on the experimental study of phenomena..."]

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The name Claude Bernard (1813-1878) is known across the world to medical students for the Claude Bernard-Horner's syndrome; but more important are his ground-breaking works in physiology, particularly homeostasis. Peter Wise provides an excellent, detailed account of his life and bibliography.[1]

Claude Bernard was one of the epoch-making giants of experimental medicine, who dominated the nineteenth century. His ideas, researches and scientific principles are enshrined in his *Cahier Rouge*[2] (compiled, 1850 -1860), his *Pensées – Notes Détachées*, and the now-famous *Introduction to the Study of Experimental Medicine*[3] that remain undiminished by time as inspiring works of reference for students of physiology and the natural sciences.

Claude Bernard (Figure 1) was born in 1813 in the village of Saint-Julien-en-Beaujolais. He attended the Jesuit school, and then the college at Lyon, which he soon left to become assistant at the Millet pharmacy in Lyon-Vaise. With a flare for the theatrical he wrote a comedy, and a play titled: 'Arthur de Bretagne' which in 1834 he presented to Saint-Marc Girardin a famous Parisian drama critic, who unimpressed, discouraged him from a career in theatre but urged him to study Medicine. He soon enrolled at the Faculty of Medicine of Paris, sharing lodgings with Charles Lasègue. He studied under François Magendie (1783-1855) in the Hotel Dieu. Magendie, impressed by Bernard's dissecting skills appointed him in 1841 as laboratory assistant.

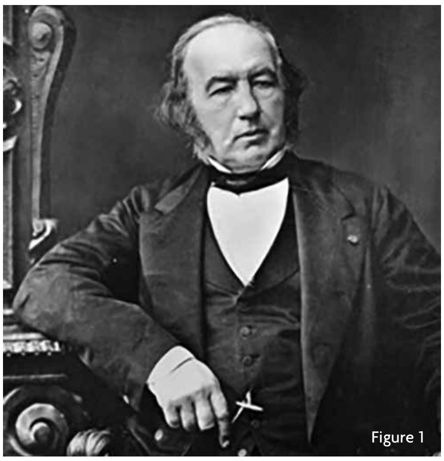
Figure 1

Figure 2

An 'arranged marriage' with the prosperous Marie Françoise Martin was engineered in 1845 by his mentors, Pierre Rayer and Théophile-Jules Pelouze to allow their protégé to develop his research potential under Magendie. Marie Françoise, an ardent anti-vivisectionist, chastised him for his animal experiments; their long marriage was unhappy and ended in separation in 1870. They had two daughters, and a son who died in infancy. After separation he formed a close friendship with Marie Raffalovich, a Jewish intellectual from Odessa, who later nursed him in his final illness.

Before receiving a galaxy of awards and distinctions,[1] in 1847 he was elected Magendie's deputy at the Collège de France, and in 1855, when Magendie died, Bernard was appointed to his Chair of Medicine at the Collège and succeeded to his Chair of Physiology at Sorbonne University. His crucial scientific principles flourished: an idea or observation led to a hypothesis, and then to either support or disprove it, he embarked on systematic experimentation making many scientific contributions, sketched below. His reputation spread and at Louis Napoleon's instigation he moved to the Muséum National d'Histoire Naturelle in 1868. He was later elected to the Academy of Sciences, the Academy of Medicine, and to the Imperial Senate — at the behest of the Emperor.

A memorial plaque in Paris (Figure 2) displays the site of Claude Bernard's laboratory from 1847 until his death in 1878. The Claude Bernard Lyon University commemorates his name. When he died he was accorded a public funeral – an honour never before bestowed by France on a man of science. He was interred in Le Père Lachaise Cemetery in Paris. A stone statue (Figure 3) graces the entrance to the Collège de France, replacing the original bronze barbarically destroyed by the Nazis.

Some scientific contributions

Glycogenesis

He began by studying pancreatic juices which he was able to show were vital in the process of digestion.[4] For this he was awarded the prize for experimental physiology from the French Academy of Sciences. He next studied the workings of the liver and showed that not only did it secrete bile but was, like the pancreas, an 'organ of internal secretions' (enzymes) that converted glycogen into glucose (glycogenolysis), and could store glucose in the form of glycogen (glycogenesis).[5]

To see whether the release of glucose from liver glycogen depended on a neural stimulus via the vagus, in a classical experiment in 1849 Bernard used a needle to stimulate the vagus in the floor of the fourth ventricle, and noted that the urinary and blood glucose increased. Bernard called this *piqûre* [puncture] *diabetes*. He later cut the spinal cord above the splanchnic sympathetic nerves; this blocked the *piqûre* phenomenon. He concluded that the sympathetic nerves directly released liver glucose. Subsequently, it was shown it was adrenaline released from sympathetic nerve endings that was the main cause of glucose discharge from the liver.

Sympathetic paralysis

Assisting Magendie he began his neurological researches.[6] His first in 1843, concerned the chorda tympani which when cut in the dog, was followed by a slow continuous secretion of saliva from the sub-maxillary gland. This secretion was called the 'paralytic' secretion.[7] From several experiments he established the existence both of vasodilator thermal and secretory, and the sympathetic vasoconstrictor nervous mechanisms.[8] He differentiated their functions:

> 'The sympathetic nerve is the constrictor of the blood vessels; the tympanicolingual nerve [chorda tympani] is their dilator'[3] (p.158)

In his several experiments he also established the concept of the physiological equilibrium of these two components of the autonomic nerves.[9]

Figure 3

Claude Bernard-Horner syndrome

In 1727, Pourfour de Petit (1664-1741) had described dilatation of the pupil (mydriasis) owing to stimulation of sympathetic nerves in a man whose neck had been injured by a gunshot wound. When he cut the sympathetic nerve on one side of the neck Petit showed the opposite phenomenon (miosis). In 1851 Claude Bernard repeated Petit's experiment; and gave a more precise description:

> "After the section of the cephalic branch of the great sympathetic, it is possible to observe a contraction of the pupil of the corresponding eye, accompanied by a narrowing of the palpebral opening, a retraction of the ocular globe, and an increase of the circulation, as well as of the temperature, in all parts of the corresponding face. If the upper extremity of the sectioned sympathetic is galvanized, all the phenomena observed after the removal of the influence of the great sympathetic changes at once, appearing an opposite presentation. The pupil enlarges, the palpebral opening augments, the eye protrude out the orbit. The former active circulation becomes weak, the conjunctiva, the nose, the ears previously red become pale. If the galvanism is stopped, all phenomena originally produced by the section of the sympathetic gradually reappear, disappearing again after a second galvanic stimulation."[9,10]

Edward Selleck Hare, House Surgeon to Stafford County General Infirmary, had described the physical signs in a letter to the Medical Gazette on 11 September 1838.[11] Weir Mitchell also gave an account five years before Horner, describing a 24 year old soldier with a gunshot wound of his neck:

> The pupil of the right eye is very small... slight but very distinct ptosis...The ball of the right eye looks smaller than that on the left...

Johann Friedrich Horner (1831-1886) was a Swiss ophthalmologist, who in 1869 observed similar signs and impaired facial sweating in a woman with a tumour invading the cervical sympathetic nerves.[12] These clinical signs are called the Claude Bernard-Horner syndrome.

Curare

Walter Raleigh discovered the paralysing effect of curare applied to poisoned arrow tips in Guyana in 1595. By experiments with curare Bernard initiated the modern distinction between neural and muscular paralysis.[13,14] In the curarised frog, he found that the muscle when directly stimulated retained its contractility; but when its nerve was stimulated no muscular contraction ensued. But, in the frog in which one leg was protected from the curare by a vascular ligature, the sensory nerves were not affected by curare.

> 'I finally reached this general proposition, that curare causes death by destroying all the motor nerves, without affecting the sensory nerves.'

This was the first demonstration of the selective action of curare on nerves. If the animal survived, the paralysing effects of curare would fully recover. This led to its use as a muscle relaxant. However, he failed to implicate the neuromuscular junction; Alfred Vulpian (1826-1887) showed that curare acted on the motor endplate that had been described by Kühne. These studies led Bernard to study asphyxia and anaesthetics. He also showed that spinal reflexes were initiated by excitation of sensory nerves without involving consciousness, but acted on motor nerves through the spinal cord. Vulpian confirmed this in experiments on decapitated salamanders and frogs.[13]

Milieu intérieur

Bernard's numerous experiments caused him to recognise a *Milieu intérieur*, a phrase that he coined to refer to the extra-cellular fluid environment, and its physiological capacity to buffer changes, to ensure protective stability for the tissues and organs of living organisms. He wrote:

> ...The blood constitutes an actual organic environment, an intermediary between the external environment and the (internal) living molecules, which cannot safely be brought into contact with their external environment...

He believed that all organs liberate into the tissue fluids special substances that maintain a physiological equilibrium of the "milieu intérieur." It established his concept of a stable balance of blood components, akin to his sympathetic- parasympathetic neural equilibrium. This notion opposed the old theory of "vitalism".[14] He said:

> "La fixité du milieu intérieur est la condition d'une vie libre et indépendante".[15]

This remains the underlying principle of homeostasis. Walter Bradford Cannon (1871-1945) coined the word homeostasis in 1926:[16] a self-regulating process by which biological systems tend to maintain stability while adjusting to conditions that are optimal for survival.

Scientific concepts in Experimental Medicine

Claude Bernard's historic role was to demonstrate the experimenter's need for a hypothesis to be either confirmed or refuted by the results of experiments.

Failing health after 1860 enforced time for leisure and reflection, out of which would come his masterpiece, *Introduction à la médecine expérimentale* (1865).[3] In this philosophical exposition he describes what makes a scientific theory good and what makes a scientist important: a true discoverer. Unlike many scientists, Claude Bernard, averse to flimsy conjecture, wrote about his own experiments and ideas.[2] He had developed and established the principles and practice of what is now accepted as the scientific method in medical research. In this fundamental approach he towered both over both his ancestors and contemporaries. Like Sherlock Holmes his method was of scrupulous observation and logical deduction. Amongst many memorable quotations his writings disclose:

- What makes a scientist important, he states, is how well he or she has penetrated into the unknown.
- Observable reality is our only authority.
- Experimental science is a constant interchange between theory and fact, induction and deduction. Induction, reasoning from the particular to the general, and deduction, or reasoning from the general to the particular, are never truly separate.
- The "philosophic spirit" is always active in its desire for truth. It stimulates a "kind of thirst for the unknown" which ennobles and enlivens science.

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