

Claude Bernard and the Constancy of the Internal Environment

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Claude Bernard (1813–1878) was the founder of modern experimental physiology and one of the most famous French scientists of all time. Although he is particularly remembered today for his concept of the constancy of the internal environment, this idea had no impact in his lifetime. This article considers his achievements and some possible reasons for the delay in understanding his ideas about the internal environment. *NEUROSCIENTIST* 4:380–385, 1998

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Today, the fame of Claude Bernard (Fig. 1; ref. 1) rests primarily (if not entirely) on his idea that the maintenance of the stability of the internal environment (*milieu interieur*) is a prerequisite for the development of a complex nervous system. In Bernard's time, his many experimental discoveries in physiology were widely recognized and he received virtually every honor possible for a scientist in France. Yet, his conception of the internal environment had no impact for more than 50 years after its formulation. In this essay, after his life and major work are summarized, some reasons both for the delay in the recognition of this idea and for its subsequent importance to the physiology of the first quarter of this century will be examined.

Life and Major Work

Claude Bernard came from poor peasant stock in the Rhône Valley. At the age of 19, after some nonscientific education, he was apprenticed to a local pharmacist. Bernard was more interested in writing plays, however, and set out for Paris in 1834 to seek his fortune in the theater. He showed his play *Arthur de Bretagne* to an illustrious critic of the day. The critic, learning of Bernard's previous job and, apparently more impressed by his energy than by the play, suggested he try medicine instead of literature. (The critic and Bernard were later to be fellow "Im-

mortals" in the French Academy.) Bernard was an indifferent medical student; nonetheless, he somehow fell into the hands and laboratory of François Magendie (1783–1855), Professor of Medicine at the College de France and head of one of the first laboratories devoted to experimental physiology (2–4).

Magendie's father had been an active Republican in the French Revolution and, following Rousseau, had brought up his son as a free spirit. Magendie became a thoroughgoing materialist, and was heavily influenced by the Ideologues, a group of revolutionary philosophers led by Pierre Cabanis (1757–1808) and A. L. C. Destutt de Tracy (1754–1836). They rejected Cartesian dualism, vigorously asserting that the mind was a "mere" function of the body and that "the brain was a bodily organ that . . . digests impressions and . . . secretes thought" (5–7).

Magendie had contempt for social convention and utter contempt for contemporary theories of medicine—indeed for the very idea of "theory" in science. For him, science meant only experiments and the facts that could be unambiguously and directly derived from them. He raised empiricism to a faith and denied that he was guided by hypotheses (as he obviously often was) (5–7).

Before Magendie, much of physiology had been speculation and inference from anatomy and clinical medicine. Magendie established the importance of direct experiments on living mammals, usually cats, dogs and rabbits (5–7). Even after their discovery in the 1840s, anesthetic agents were often not used in animal experiments, perhaps because of their de-

pressing effect on nervous function; in this period experiments on the neural control of physiological function or on the nervous system itself were of central concern. In Magendie's (and Bernard's) time there was much less popular opposition to vivisection in France than in Great Britain; with the rise of a strong British antivivisection movement toward the end of the 19th century, this difference became even more pronounced (8–12).

Perhaps Magendie's most famous discovery was of the Law of Spinal Roots, also known as the Bell-Magendie Law (i.e., that ventral spinal roots are motor and dorsal ones sensory). There was a long and bitter priority controversy with Charles Bell (1774–1842) over its discovery. In fact, Bell had originally proposed only the sensory functions of the dorsal roots; there is no reason to believe that Magendie knew of Bell's claims before he carried out and published his own experiments. Both halves of the law were physiologically demonstrated by Magendie, whereas the Englishman Bell (not a vivisectionist) had inferred the functions of the dorsal roots solely from anatomical observation (13).

From Magendie, Bernard acquired a profound skepticism of established dogma and learned the techniques of vivisection that were the basis of the new animal physiology. He never practiced medicine and instead concentrated on research, eventually taking over Magendie's laboratory and chair. Bernard made a number of major experimental discoveries and theoretical advances that established him as the founder of modern physiology. Among his most important discoveries were the glycogenic function of the liver, the role of the pancreas in digestion, the regulation of temperature by vasomotor nerves (see Box 1), the action of curare and carbon monoxide, and the vagal control of cardiac function. Most of this work was done early in his career, between 1843 and 1858, in a small damp cellar and with little funding (2–4, 14, 15).

Although he continued some laboratory work for the rest of his life, Bernard became increasingly involved in two other concerns. The first was the political goal of establishing physiology, "experimental medicine," as an independent discipline. He was particularly concerned about separating it from clinical medicine, with its emphasis on intuition and

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Fig. 1. Portrait of Claude Bernard (1).

“touch,” and from chemistry, with its claims that the inorganic and organic could be treated equivalently. His second major interest was in broad theoretical issues such as the role of determinism in biology, the relation of theory and experimentation in biology, and the existence of phenomena common to both plants and animals and absent in the inorganic world. Among his new and important theoretical concepts were those of internal secretions, reciprocal innervation, and, as we discuss in detail below, the internal milieu (4, 16, 17).

Bernard was a consistent opponent of vitalism, arguing that biology never violated the laws of physics and chemistry. However, he did stress the emergent properties of complex biological systems much more than his German physiological contemporaries such as Helmholtz and Du Bois Reymond, who strove to reduce biological phenomena to physics and chemistry (18–20).

The high point of Bernard’s theoretical endeavors was the publication in 1865 of his *Introduction to the Experimental Study of Medicine* (18). It was an immediate success among scientists and physicians as well as philosophers and writers. Indeed, it remains in print to this day, even in English, and is still heralded as required reading for any prospective experimental biologist. One of its most timeless and attractive aspects is its autobiographical character; Bernard illustrates various principles and practices of experimentation almost exclusively from his own work. He does clean up the sto-

ries of some of his discoveries, however, omitting errors, blind alleys, and failed experiments (4, 21). Thus the book makes science seem easier than it really is.

Mme. Bernard and Mme. Raffalovich

In 1845, near the beginning of his career, financial difficulties led Bernard into an arranged marriage with Fanny Martin, the daughter of a relatively well-off physician. Her dowry enabled him to avoid a rural practice and stay in research. The marriage was a disaster. Mme. Bernard bitterly resented her husband’s low paying research career and became an ardent antivivisectionist. Bernard’s propensity to bring home opened up and dying animals with various tubes stuck in them did not help matters. Finally, in 1869, when Bernard reached the peak of his career, they separated. Subsequently, she and her daughters founded a home for stray dogs and cats (2, 3).

After the separation, Claude Bernard became close to Marie Raffalovich, a Jewish intellectual from Odessa interested in science and philosophy. She attended his lectures, he visited her twice a week and they often went to galleries and museums together. Unlike Bernard, she was an accomplished linguist and helped him with the foreign literature. Over the course of 9 years he wrote over 500 letters to her, often when she was away on holiday with her family. Many of them have been published in two collections and they yield a fine-grained account of his daily life and thoughts (See Box 2). In 1876 she published a novel and he claimed that she was deserting him for the literary crowd. Then, in 1878, when she received news he was very ill, she and her daughter went to nurse him in his final days. Mme. Raffalovich had her letters to Bernard destroyed after his death (2, 3, 22–24).

Honors and Fame

Claude Bernard collected more honors and, arguably, became more famous than any French scientist before or after. He was elected to the Academy of Science, then the Academy of Medicine and finally, most prestigious of all, he became one of the 40 “immortals” of the French Academy and eventually its president. He was commander of the Légion d’Honneur and a member of the Senate (a powerless front for the autocracy of Napoleon III). Bernard dutifully attended every Senate

Box 1. From Bernard’s letters to Mme. Raffalovich

[1870, After a discussion of science, intuition and superstition] The scientist, if he is to have great ability, must have imagination but he must master this imagination and coldly probe the unknown. However, if he lets himself be carried away by his imagination, he will be overcome by vertigo and, like Faust and others, fall into the chasm of magic and succumb to phantoms of the mind.

[1873, After a description of the history of the College de France.]

... I follow in the tradition of my predecessors, who have all been men in the avant-garde of science, men of fighting spirit. I am fighting for physiology because it is the future of medicine.

meeting but did not speak, even on such issues as academic freedom and rural medicine. When he died he was given the first State funeral ever afforded a scientist in France. Flaubert called it more beautiful and more stirring than the then-recent funeral of Pope Pius IX (2–4).

From the height of his career until well after his death, Bernard was so famous that he became identified in the public mind as the stereotypical scientist, much like Albert Einstein in the 20th century (2, 3, 22). He appears in poetry, memoirs, and novels of the time, both in France and abroad (e.g., “The Brothers Karamazov”). Zola considered writing a novel in which a scientist is persecuted by his antivivisectionist wife, writing:

I will make a scientist married to a backward bigoted women, who will destroy his researches as he works . . . I am tempted to model him after Claude Bernard, getting access to his papers and letters. It will be amusing . . . (22).

In the completed novel *Le docteur Pascal*, Zola moved away from Bernard as a model; the plot complications required a heredity researcher rather than a physiologist, but some similarities to Bernard remain. In his essay “The Experimental Novel,” originally published as a preface to *Nana*, Zola suggests that his naturalistic novels were “experimental novels” modeled after Bernard’s ex-

Box 2 and Figure 2. Claude Bernard in his laboratory

This is an anonymous copy of a painting by L. A. L'Hermitte made 10 years after Bernard's death (53). Bernard is the central figure, wearing an apron, and is surrounded by some of his most famous French students (Paul Bert, mentioned in the text, is standing third from the left). The setting is Bernard's laboratory at the College de France, which still can be visited today. The experiment illustrated is one in which the vasomotor functions of sympathetic nerves were demonstrated for the first time. Bernard is studying the effect of unilaterally cutting and stimulating the cut end of the cervical sympathetic nerve on the temperature of each side of the head of a rabbit. He discusses this experiment in *An Introduction to the Experimental Study of Medicine* (18) to illustrate two principles of experimentation. The first was the importance of the choice of species, the rabbit being ideal here because the cervical sympathetic vascular nerves, unlike in other common laboratory animals, run separately from sensory and motor nerves.

The second was the value of hypotheses, even when wrong, as in this case.

On the basis of a prevailing theory and of earlier observations I had been led . . . to make the hypothesis that the temperature should be reduced . . . after severing the cervical sympathetic nerve in the neck . . . The result was . . . precisely the reverse of what my hypothesis, deduced from theory, had led me to expect; thereupon I did as I always do, that is to say, I at once abandoned theories and hypothesis, to observe and study the fact itself . . . Today my experiments on the vascular and thermo-regulatory nerves have opened a new path for investigation and are the subject of numerous studies which, I hope, may some day yield really important results in physiology and pathology. This example . . . proves that in experiments we may meet with results different from what

theories and hypothesis lead us to expect . . . This . . . example . . . gives us an important lesson, to wit: without the original guiding hypothesis, the experimental fact which contradicted it would never have been perceived . . . Indeed I was not the first experimenter to cut this part of the cervical sympathetic in living animals . . . But none of them noticed the local temperature phenomenon . . . though this phenomenon must necessarily have occurred . . . The hypothesis . . . had prepared my mind [and my predecessors'] for seeing things in a certain direction . . . We had the fact under our eyes and did not see it because it conveyed nothing to our mind. However, it could not be simpler to perceive, and since I described it, every physiologist without exception has noted and verified it with the greatest ease" (18).

See also Fig. 3.





Fig. 3. An unlabeled sketch from Bernard's *Cahier Rouge*,

a diary in which he wrote [1850–1860] about not only things he had seen in the laboratory that day and the experiments or hypothesis that these had suggested, but also his constant search to express the experimental method in physiology, and to show how it related to other sciences (54).

The sketch seems to be a device for measuring the temperature in the two ears of a rabbit, presumably for an experiment like the one shown in Figure 2.

perimental medicine. Supposedly, Zola manipulated plots and observed the behavior of his human characters just as Bernard manipulated physiological variables and observed their effects. "I have

but one desire," Zola wrote. "Given a powerful man and an unsated woman, to cast them into a violent drama and scrupulously note down the sensation of these creatures." In fact this was hyperbole if not outright hype: Zola had begun his novel cycle before he was familiar with Bernard's writings (and before Bernard was famous) (22).

A bronze statue of Bernard engaged in vivisection was set up in front of the College de France after his death. The Germans melted it down in World War II and it was replaced by a new statue in stone after the war (3). This was destroyed during the student uprising of '68, but has subsequently been replaced.

As Bernard had desired, his early play *Arthur de Bretagne* was published after his death. However, his widow and daughters claimed its preface defamed them and they successfully sued to have all copies destroyed. It had a radio production in 1936 and a second edition appeared in 1943 (3).

The Constancy of the Internal Environment

Bernard's ideas about the internal environment evolved from its first mention in 1854 until his death in 1878. He probably took the term from Charles Robin, a contemporary histologist who used *milieu de l'intérieur* as a synonym for "the humors." Initially, for Bernard, the internal environment was simply the blood. But even at this stage, he understood that the temperature of the blood is actively regulated and that its constancy is particularly critical in higher animals. It was only later that he recognized that this constancy might be achieved through the vasomotor mechanisms he had discovered. At about the same time he realized that the glycogenic mechanism he had found controlled the constancy of blood sugar level. It was primarily on these two (limited) lines of evidence that he built his brilliant generalizations that unify the fundamental physiologies of the body (25–27):

The fixity of the milieu supposes a perfection of the organism such that the external variations are at each instant compensated for and equilibrated . . . All of the vital mechanisms, however varied they may be, have always one goal, to maintain the uniformity of the conditions of life in the internal environment . . . The stability of the internal environ-

ment is the condition for the free and independent life (19).

These generalizations both summarized many of Claude Bernard's experimental achievements and provided a program for the next 100 years of general physiology. Although Bernard made these ideas central to his well-attended lectures and his widely disseminated writings, they were ignored in his lifetime and they had no impact at all until about 50 years later. Indeed, Bernard's ideas on the internal environment are hardly mentioned in the extensive 1899 biography by Michael Foster, the distinguished Cambridge physiologist; they are not mentioned at all in the 12-page obituary in the American journal that had published much of Bernard's research or in a 1931 biographical essay by the eminent historian of science Henry Sigerist. Whereas the 1911 *Encyclopedia Britannica* is totally silent on the constancy of the internal environment, the 1975 edition calls it Bernard's "most seminal contribution" (28–31).

An exception to the 19th century silence on Bernard's internal milieu was George Henry Lewes, the Darwinian publicist (and life partner to George Eliot, in which capacity he made the inside back cover of the *New Yorker* in 1998). In his *The Physical Basis of Mind*, Lewis used the concept of the internal environment to answer an objection to evolution by the American anti-Darwinian Alexander Aggasiz (32). The latter had claimed that the diversity of animals in the same environment argued against the possibility of natural selection. Lewis countered by stressing the similarities in their internal environment. Bernard himself varied between skepticism and dismissal of Darwinism, reflecting his view that if biological phenomena were not experimentally demonstrable they were of little validity (18, 19, 22, 33). Yet, it was only when the profound evolutionary significance of the constitution of the internal environment was realized that Bernard's idea finally had a major impact on physiology.

The development that catalyzed the understanding of Bernard's milieu intérieur was the comparison of the ionic concentrations of body fluids with those of sea water (31). In 1882, Leon Fredericq observed that the body fluids of ocean crabs, lobsters and octopuses were about as salty as sea water, whereas marine fish, like fresh water ones, were much less salty. (He made these observations

initially by taste.) He realized that this was the first evidence for Bernard's idea that the internal milieu becomes increasingly independent of the external environment as one ascends the "living scale," thereby providing the basis for the "free life" of higher organisms (31, 34). Fredericq had studied in Paris with Paul Bert, a major student, collaborator, and biographer of Bernard (see Fig. 2). In marked contrast to Bernard, however, Fredericq interpreted his comparative observations as evidence for the evolution of the independence of the internal environment from the external one. By the end of the century, evolutionary thinking had finally made the constituents of the internal environment a meaningful subject. Independently, Rene Quinon and Archibald Macallum took the next step, arguing that life arose in the sea and that body fluids represented the original sea water that had been enclosed within the skin. More generally, it became clear that a major trend in evolution was the development of increasingly sophisticated mechanisms whereby the internal environment is protected from the external world (31, 35).

In the first decades of the 20th century, Bernard's ideas about the importance of the internal environment entered the mainstream of mammalian physiology both as a central explanatory concept and a program for research. Among the major British figures explicitly relating their work closely to Bernard's idea were William Bayliss and E. H. Starling, co-discoverers of secretin, the first hormone identified; J. S. Haldane (J. B. S. Haldane's father) and Joseph Barcroft, pioneers in the regulatory functions of breathing; and C. S. Sherrington, a founder of modern neurophysiology. Starling seconded Macallum and Quinon's ideas on the evolution of the internal environment and later coined the term "the wisdom of the body" for the maintenance of the internal constancies that Bernard had postulated (36). Barcroft claimed that the "principles . . . of the fixity of the internal environment have been as thoroughly established as any" (37). Haldane noted that Bernard's conception "sums up and predicts" his own work on the regulation of blood composition by respiration (38). Sherrington suggested that "the nervous system is the highest expression of . . . the milieu intérieur" (39).

In the United States, the chief advocates of Bernard's constancy ideas were L. J. Henderson and Walter B. Cannon, long-time members of the Harvard Med-

ical School faculty. Henderson related his work on the maintenance of blood pH directly to Macallum's marine biology as well as to Bernard. He helped bring Bernard to a wider American audience both in his introduction to the American translation of Bernard's *Introduction* and in his own influential book, *The Fitness of the Environment* (40-42).

Walter B. Cannon was particularly instrumental in making Bernard's ideas central to the neurophysiology and psychology of the time. He coined the term "homeostasis" for the tendency of the mammalian organism to maintain a constant internal environment (43). His own major discoveries were in elucidating the role of the sympathetic nervous system in maintaining homeostasis; he brought these to the educated public in the classic *The Wisdom of the Body* (44). Cannon viewed behavior as a homeostatic mechanism: shivering, seeking shelter, and putting on a coat were all examples of homeostatic mechanisms of temperature regulation. Writing at the height of the Depression, he suggested that some institutional arrangements for social homeostasis were sorely needed:

The main service of social homeostasis would be to support bodily homeostasis. It would therefore release the highest activities of the nervous system for adventure and achievement. With essential needs assured, the priceless unessentials could be freely sought (44).

J. B. Watson and other early behaviorists such as Curt Richter rejected the myriad of previously postulated central drives as explanations for motivation. They turned instead to the experiments of Cannon for alternative and peripheral mechanisms of motivation and considered "motivated" behavior as a homeostatic mechanism. Thus, following him, they viewed thirst as a result of dryness in the mouth, which, when signaled to the brain, elicited drinking. Similarly, hunger was caused by stomach contractions ("pangs") which signaled the brain to elicit eating. Extrapolating beyond Cannon, they interpreted sexual motivation to be due to tension in the gonads (45-47).

Both Cannon and Henderson had extended Bernard's ideas of self regulation from the realm of bodily fluids to the wider social environment (44, 48). The idea of self-regulation was extended even further to include the nonbiological

world by Arturo Rosenblueth (one of Cannon's collaborators), Norbert Wiener, and J. Bigelow (49). In the context of World War II control and communication systems, they pointed out that negative feedback covered self-regulation both in the nervous system and in nonliving machines. Soon after, Wiener coined the term "cybernetics" for "the entire field of control and communication theory, whether in the machine or in the animal" (50). Today, cybernetics, a formalization of Bernard's constancy hypothesis, is viewed as one of critical antecedents of contemporary cognitive science (51).

Some Reasons for the Renaissance

Despite the emphasis with which he repeatedly promulgated it, Claude Bernard's insight that the "constancy of the internal environment is the condition for the free life" had no significance (indeed, no meaning) for biologists for more than 50 years. There seem to have been several reasons for this inability to process his idea. One was that Pasteur's new bacteriology and its omnipresent, omnipotent germs were dominating the biomedical Zeitgeist. Another, as discussed above, was the gap between evolutionary thought and general physiology. When this gap began to be closed through the comparison of the constituents of sea water and the bodily fluids at different phylogenetic stages, the constancy of the internal environment suddenly took on new and accessible meaning. Finally, the tools, techniques, and concepts for adequately measuring the internal environment were simply not available in Bernard's time and for the rest of the century. For example, the work of Haldane, Henderson, and Barcroft required the development of organic and especially physical chemistry, as well as techniques for measuring ions, gases, and other components of the internal environment; the work of Sherrington and Cannon required the replacement of the reticular doctrine by the neuron doctrine, and the development of the cathode-ray tube oscilloscope and electrical stimulating devices (22, 28, 31).

In the history of biology, there have been those, such as Gregor Mendel and Emmanuel Swedenborg (52), who were so far ahead of their time that they died unrecognized for their scientific work. Claude Bernard, by contrast, received every possible recognition as a scientist, yet what is today considered his most salient contribution had to wait half a cen-

ture for advances in theory and practice to make it meaningful.

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