August Krogh and Claude Bernard on Basic Principles in Experimental Physiology

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The so-called August Krogh principle—"For many problems there is an animal on which it can be most conveniently studied"—has attained great popularity in the biological literature since it was formulated by Hans Krebs in 1975. Sometimes the reference to Krogh (1929) and his use of the "principle" is, however, misleading or incorrect. Thus, Feder and Watt (1992) cite Krogh for having articulated the principle that "for every biological question is an organism best suited to its solution," and a recent textbook on animal physiology states that "one of the reasons for Krogh's extraordinary success as a physiologist was his uncanny ability to choose just the right experimental animal with which to test his hypotheses. His view was that for every defined physiological problem, there was an optimally suited animal that would most efficiently yield an answer" (Randall et al. 1997). Participants in a roundtable on the application of the Krogh principle to plants introduced a corollary: "No single organism...exists that can provide easy access to the diversity of hidden mechanisms that underlie all interesting and important physiological and biochemical problems" (Wayne and Staves 1996). This corollary is, however, not a consequence of the principle as formulated by Krogh (1929).

The animals chosen for the study of specific physiological problems are often considered as models, ignoring the qualification Krebs and Krebs (1980) added to the August Krogh principle. They pointed out that although the principle was valid at the molecular level of biological organization, uncritical application of the principle may lead to fallacious generalizations, especially if used in generalizations at higher and more complex levels of biological organization where specialized functional adaptations have evolved. More recently, Bolker (1995) warned against uncritical generalizations from model systems in developmental biology, and Gest (1995) pointed out that, even at the molecular level, the use of "model species" may lead to fallacious generalizations. Furthermore, he finds it "curious that some molecular biologists seem to be surprised, or somewhat taken aback, when they find that their organism models are in fact not universal models and that obviously different kinds of organisms differ from each other." Similar warnings against generalizations were implicit in Krogh's (1929) and Bernard's (1865) views on the study of physiology.

After Krebs' (1975) formulation of the Krogh principle, the strong focus on Krogh's (1929) reference to the importance of choosing the right animal to the solutions of physiological problems that followed Krebs' (1975) formulation of the August Krogh principle has diverted the attention from Krogh's other important thoughts "to the general progress of physiology and the problems raised by its growth," all thoughts he brought up in his opening address before the International Physiology Congress at Harvard University in 1929. Claude Bernard (1865) had expressed similar thoughts, but there is nothing to indicate that Krogh knew Bernard's philosophy of physiology, reflecting the often noticed lack of interest among biologists in the philosophical basis of their work (e.g., Hinshelwood 1960, Eccles 1970, Macfadyen 1975, Gjertsen 1989). I therefore found it desirable to revive Krogh's and Bernard's thoughts on basic principles in physiology.

August Krogh

In his address to the International Physiology Congress, Krogh (1929) confesses to have no sympathy for "general" physiology. He finds that "a general physiology which can describe the essential characteristics of matter in the living state is an ideal to which we may hope that our successors may attain" and that "the route by which we can strive toward the ideal is by the study of the vital functions in all their aspects throughout the myriads of organisms." He was confident that "we will find out before very long the essential mechanisms of mammalian kidney function, but the general problem of excretion can be solved only when excretory organs are

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studied wherever we find them and in all their essential modifications."

Krogh thus endorsed the study of comparative physiology as a means in establishing a general physiology. However, he also wanted "to say a word for the study of comparative physiology for its own sake. You will find in the lower animals mechanisms and adaptations of exquisite beauty and the most surprising character, and I think that nothing is more fascinating than the senses and instincts of insects as revealed by the modern investigations." Krogh was very fascinated by Karl von Frisch's studies of the language of the bees.

Krogh's emphasis on the importance of the study of comparative physiology and his own numerous contributions to the field thus had nothing to do with "his uncanny ability to choose just the right experimental animal" (Randall et al. 1997). After all, standard laboratory animals—frogs—were the first subjects of the experiments Krogh conducted in his study of the structure and function of capillaries, for which he was awarded the Nobel Prize in Physiology and Medicine in 1920. The section in Krogh's address that inspired Hans Krebs to the formulation of the August Krogh principle, however, was actually based not so much on Krogh's recent work as on some of his memories of his time as an assistant to Christian Bohr. Krogh recollected that when Bohr was interested in the respiratory mechanism of the lung and in the gas exchange through each lung separately, he found a certain kind of tortoise especially suited for such experiments because it possessed a trachea dividing into the main bronchi high up in the neck. They used to say as a laboratory joke that this animal had been created expressly for the purpose of respiration studies. Krogh (1929) had "no doubt there is quite a number of animals which are similarly 'created' for special physiological purposes...unknown to the men for whom they were 'created.'" In his own lecture, Krebs (1975) provided a number of examples to illustrate the August Krogh principle.

A fourth theme in Krogh's thoughts on physiology was the place of facts and their relations to ideas, a subject that has been a central theme in the theories of scientific methods from Aristotle to present (Laudan 1968, Harré 1972, Gjertsen 1989). Krogh said: "When I attempt to pass in review the physiological literature of today I notice certain defects which are too common and which could no doubt be remedied to a certain extent. In a recent small book of instructions for medical writers I find the statement that what is needed in scientific papers is facts and again facts and still more facts. I venture to disagree emphatically with this statement. Facts are necessary, of course, but unless fertilized by ideas, correlated with other facts, illuminated by thought, I consider them as material only for science. I am prepared to submit the thesis, revolting as it may seem, that too many experiments and observations are being made and published and too little thought is bestowed upon them" (Krogh 1929).

Claude Bernard

Claude Bernard, the founder of modern experimental physiology, is one of the very few biologists who was also a philosopher of his science, according to Gjertsen (1989) perhaps the first since Aristotle. Bernard's philosophy of physiology is contained in his book, *Introduction a l'étude de la Médecine Expérimentale* (1865). The book has become a classic, but it seems uncertain how much it has been read, let alone used, by practicing physiologists. It was not translated into English until 1927. Bernard seems to have been the first to discuss the proper use of animals in experiments, pointing out the importance of choosing the right animal for the solution of certain physiological problems. He returned to the question of the choice of animals several times in the book, and a whole section deals with the subject. He wrote:

> Among the objections that physicians have offered to experimentation is one which must be seriously considered because it throws doubt on the usefulness of animal experiments to human physiology and medicine. It has been said, indeed, that experiments performed on a dog or a frog may be conclusive in their application to dogs and frogs, but never to man, because man has a physiological and pathological nature proper to himself and different from all other animals. It has been further stated that to be really conclusive for man, experiments would have to be made on man or animals as near to him as possible. It was surely with this idea that Galen chose a monkey for his experiments, and Vesalius a pig, as subjects more closely resembling man in his omnivorous capacity. Even today, many people choose dogs for experiments, not only because it is easier to procure this animal, but also because they think that experiments performed on dogs can more properly be applied to man than those performed on frogs. How well founded are these opinions? How much importance should we ascribe to the choice of animals in relation to the usefulness of the experiment to physicians? (Bernard 1927, pp. 122–123)

In answering these questions, Bernard points out the indispensability of all sorts of animals in experimentation. But among all animals on which physiologists may experiment, some are better suited than others, depending on the problems to be studied, and the solution of a physiological problem often depended on "the happy choice of an animal" for experiment.

One of the examples of animals that offered a favorable anatomical arrangement was the cervical sympathetic nerve in rabbits, which allowed Bernard to sever only the vascular nerves and to spare the others, experiments that led to the discovery of the vasomotor control mechanism (Bernard 1927).

The relationship between ideas, experimental facts, and thinking is the central theme in Bernard's philosophy of scientific physiology. His in-depth analysis of experimental physiology opened with some general reflections on the nature of observation and of experiment:

> Observation is investigation of a natural phenomenon, and experiment is investigation of a phenomenon altered by the investigator.... It is impossible to devise an experiment without a preconceived idea.... As for noting the results of the experiment, which is itself only an induced observation, I posit it similarly as a principle that we must here, as always, observe without a preconceived idea.
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> People who condemn the use of hypotheses and of preconceived ideas in the experimental method make the mistake of confusing invention of an experiment with noting its results.... The true scientist is one whose work includes both experimental theory and experimental practice. (1) He notes a fact; (2) *à propos* of this fact, an idea is born in his mind; (3) in the light of this idea, he reasons, devises an experiment, imagines and brings to pass its material conditions; (4) from this experiment, new phenomena result which must be observed, and so on and so forth. The mind of a scientist is always placed, as it were, between two observations: one which serves as starting point for reasoning and the other which serves as conclusion.
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> We see, then, that the elements of the scientific method are interrelated. Facts are necessary materials; but their working up by experimental reasoning, i.e., by theory, is what establishes and really builds up science. (Bernard 1927, pp. 15, 23–26)

The subsequent chapters of the book develop these reflections on facts, ideas and reasoning and their interrelations into a method of experimental physiology, illuminated by examples from Bernard's own research.

Connections between Bernard and Krogh?

The striking similarities between Krogh's and Bernard's views on the philosophy of physiology raise the question whether any connections might lead from Bernard to Krogh. In an attempt to answer this question, it may be significant that PL Panum (1820–1885), the first Danish professor in physiology, spent a year in Bernard's laboratory (Petersen 1885), eventually establishing a close friendship with Bernard. In 1865, Panum (1865–1869) began publishing his lectures on human physiology for medical students. The introduction to the lectures included a section on the study of experimental physiology that expressed views remarkably similar to those expressed by Bernard. Panum thus stressed the importance of comparative physiology and anatomy in the study of human physiology. He contended that comparative anatomy is indispensable for choosing the correct animals, both with regard to the organ to be studied and with regard to proper anatomical features for operation. This view was in contrast to that of Carl Ludwig, a founder of modern experimental physiology in Germany, who had stated, incorrectly according to Panum, that comparative anatomy was an entirely unimportant discipline for human physiology. Panum also stressed the importance of the premeditated experiment, of observation without a preconceived idea, of accepting objective observations even when they were inconsistent with expectations, and of distinguishing between observations ("naked facts") and the testable hypotheses that these observations can give rise to.

Christian Bohr (1855–1911) was a student of Panum who early realized Bohr's great talents. Bohr became Panum's assistant, and he performed his first scientific work under Panum's guidance (Bohr 1876). Bohr succeeded Panum at his early death in 1885, and some 10 years later Krogh (1874–1949) became Bohr's student and collaborator. It seems quite conceivable that Krogh's laboratory joke, remembered from his time with Bohr and which gave rise to the August Krogh principle, had its roots in Bernard's influence on Panum's views on the study of experimental physiology.

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