© 2014. Published by The Company of Biologists Ltd | The Journal of Experimental Biology (2014) 217, 1640-1641 doi:10.1242/jeb.095505

Krogh 1929 or 'The Krogh Principle'

Comparative approach

Stan Lindstedt discusses August Krogh's classic paper 'The progress of physiology', published in the *American Journal of Physiology* in 1929.

August Krogh wrote an essay that appeared in the *American Journal of Physiology* in 1929. In this essay he introduces an experimental approach that would later be identified as 'The Krogh Principle'. Simply stated, among the diversity of animal species there will be one ideally suited as an experimental model for any biological problem. An example most familiar might be the 'giant' axon of the squid, which was crucial in unraveling the nature of neurotransmission two decades after this essay was written.

In the 1920s, physiology was still in its formative stages. As is true for all sciences, a significant 'descriptive' phase is the essential foundation required prior to 'experimental' testing of hypotheses. Most of the descriptive contemporary understanding of physiology understandably consisted of cataloging numerous pathologies. Hence, in the 1920s, the majority of workers in physiology were physicians. Krogh observes, 'A large and increasing proportion of physiological research is carried on in hospital laboratories by men and women [interesting choice of words as in 1914, Marie Krogh had become only the fourth Danish woman ever to earn a doctorate in medicine] who are at the same time practicing the art of healing.'

The transition to experimental physiology was fueled in part by Jacques Loeb, an American physiologist who championed a new concept that he called 'the mechanistic conception of life' (Allen, 1978). Thus began the integration of physiology into a broad context of first principles of chemistry, physics and math. Truly, this was a time of exponential growth in the physiological sciences, as demonstrated by Krogh, who must have taken considerable time to compile the following data: in 1907 there were 3500 physiology papers and 18,000 by 1926: a growth of >500% in less than two decades!

It was in this context that Banting and Best's discovery of insulin, using beagle dogs as their model system, rocked medicine, resulting in a Nobel Prize in 1923, a mere year following the discovery. Because Marie Krogh was diabetic, this story of discovery hit very close to home. In fact, in 1922, immediately after news of the Banting and Best experiments broke, August and Marie made the difficult journey to Toronto to bring the technology necessary to produce insulin back to Norway, in the process founding what is now Novo Nordisk.

It was in this interesting, sometimes personal and very dynamic context that Krogh wrote this paper, 'The Progress of Physiology' (Krogh, 1929), which is much more a philosophical essay than a scientific paper as it contains neither references nor experimental results. Rather, he exploits his prominent position as recent Nobel Laureate (1920) to outline both directions and goals for this newly experimental field of physiology.

He thus makes several key points in this forward-looking essay. The first is that as the discipline of physiology expands, it must do so in a context that embraces contributions and collaborations with allied sciences, in particular mathematical analysis, as well as biochemistry and pharmacology. What may have been the most prophetic statement is his observation that biophysics will become a necessary academic partner of physiology in the future.

As mentioned above, he discusses in some detail the role that clinical medicine played in the development of physiology. He not only acknowledges the important historical influence of this contribution, but he flatly states that physiology must nurture its clinical roots. He saw 'the physiology of disease' or 'pathological physiology' as an essential continuing contributor to inform physiology.

However, it is the next of the key points of this essay, which (ironically) he viewed as 'not perhaps such a pressing need' as physiology's continued clinical association, for which this paper has become a true classic in our field. He introduces, perhaps for the first time, the term 'comparative physiology' as the desirable consequence of an unprecedented partnership between physiology and zoology. He uses as an example the respiratory insights of his mentor, the famous physiologist Christian Bohr, which were made possible because of his use of a tortoise as a model system. As Krogh delightfully explains, 'We used to say as a laboratory joke that this animal had been created expressly for the purposes of respiratory physiology.' It seems clear that experience provided the evidence he needed for the most quoted line from this paper, and the one that is the grounds for this Classics discussion, what is now recognizable as 'The Krogh Principle': 'For a large number of problems there will be some animal of choice or a few such animals on which it can be most conveniently studied.' This principle has since become a cornerstone of comparative physiology. By selecting the right experimental animal, one maximizes the ratio of signal to noise, making interpretation of results much simpler. We now recognize this as a, if not the, critical step in any experimental design: 'Is this the most suitable organism on which this problem is best studied?'

Lest it be thought that the only contribution of comparative physiology is to investigate broad physiological questions, Krogh makes a final point that comparative physiology should also be studied 'for its own sake'. He states specifically, 'You will find in lower animals mechanisms and adaptations of exquisite beauty and the most surprising character….' It should come as no surprise that Krogh, the acknowledged

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'father of comparative physiology', should also find an inherent beauty and fascination in unique physiological adaptations, what Somero (Somero, 2000) refers to as 'exploratory physiology'. It may have been Krogh's best known student, Knut Schmidt-Nielsen, whose career most exemplified this approach (e.g. Schmidt-Nielsen, 1998).

This paper, though written 85 years ago, is replete with surprising insights into physiology and some enduring lessons as well. One of those lessons appears toward the end of this engaging essay. Krogh draws the analogy between the evolution of physiological discoveries and the evolution of life itself. 'Ideas are conceived, facts are elaborated with immense joy and with infinite labour. A large number die without ever coming to the light of publication and of those which are published an appalling proportion sink to the bottom and can only be dug out as fossils… a minority only survive in the sense that they beget new ideas and give rise to the discovery of new facts.' Thus, Krogh seems to be advocating sufficient risk-taking such that failed ideas become an expected and necessary part of scientific innovation and advancement. It is interesting that funding agencies only recently recognize this link between innovation (e.g. risk) and discovery.

On a personal note, August Krogh was my academic 'great grandfather'. As I read this essay I often had the experience of 'hearing' the words of my academic mentor (William Calder). Thus, one very pleasant insight from reviewing this paper is the realization that while ideas, as Krogh points out, always have a finite lifespan, there is also a scientific culture that is transmitted across academic generations. While I didn't know it, lessons from Krogh had made their way through Schmidt-Nielsen to Calder and eventually to me. I hope I have been a faithful purveyor of these principles to my students as well.

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