

More on Physiology Without Borders

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Physiology 28:2-3, 2013. ;

doi: 10.1152/physiol.00044.2012

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More on Physiology Without Borders

Two previous editorials have referred to the international nature of physiology, the first from Presidents of the American Physiological Society (1) and the second from the Executive Committee of IUPS (10). The larger societies within the IUPS family hold meetings that are attended by scientists from many countries. This is not restricted to the US and UK societies. I recently lectured to the annual meeting of the Scandinavian Physiological Society in Helsinki and saw for myself how strongly international the meetings of that society have now become. The second editorial on “physiology without borders” acknowledged and welcomed these developments on behalf of IUPS and outlined the ways in which IUPS and those societies could cooperate in protecting the universality of science as enshrined in *statute 8* of the International Council of Science (ICSU). Physiological societies around the world connect with ICSU through membership of IUPS.

The full extent of this absence of borders will be evident at the IUPS World Congress in Birmingham in July, 2013. Over 50 nations will be represented, and some of them will be sending delegates for the first time, hopefully including Myanmar (Burma) and North Korea, where we have secured funding for travel fellowships. The Congress will be hosted by a society, that of the UK and Ireland, that has encouraged international cooperation ever since its foundation in 1876. The first minute books show how the young society welcomed guests from around the world even in the 19th century when travel was so much more difficult (8). No borders indeed.

There is, however, another border that needs to be eliminated: that of the discipline itself. Physiology needs to reconnect with the mainstreams of biological thought and practice. Such reconnection would return us to our roots. Charles Darwin and Thomas Henry Huxley were both members of The Physiological Society. So were polymaths like George Henry Lewes. It was another 19th century physiologist, George Romanes, who coined the term neodarwinism.

Yet, the 20th century witnessed a great fragmentation, as more specialist societies peeled off from physiology. Some of this specialization was benign. It recognized the need for biochemists, pharmacologists, pathologists, evolutionary biologists, neuroscientists, and many others to develop their own forums. But there was also a major development that was far from benign. A pincer movement, spearheaded by molecular biology on the one hand and evolutionary biology on the other, effectively squeezed physiology out from the mainstream.

Of course, this is only a broad-brush description of what happened. There were always notable exceptions, including Jared Diamond and Knut Schmidt-Nielsen, both of whom spanned brilliantly between physiology and mainstream biology. It is worth recalling that Schmidt-Nielsen was President of IUPS and a founding editor of *Physiology* when it was called *News in Physiological Sciences*. IUPS has always reached out toward the other biological sciences and is now collaborating with other biological scientific unions within ICSU in organizing an inter-union satellite at the 2013 Congress.

Both aspects of the pincer movement were, of course, unintended. But they were problematic nonetheless. Molecular biology created the undoubtedly exciting prospect of being able to work out all the molecular structures and mechanisms in physiological systems. To those with a mechanical frame of mind, this held out the prospect of completely understanding organisms from a bottom-up perspective. That view was reinforced by two developments in molecular biology: the coining of the term “genetic program” (by Ref. 6), later to be described as the “book of life” when the human genome project was launched, and the statement of the “central dogma of molecular biology” by Francis Crick (3). Both of these ideas and metaphors strongly reinforced the trend within evolutionary biology to relegate the phenotype to the role of a transient carrier of the “real” holders of the “secret of life,” the genes. The version of neo-darwinism that became the modern synthesis (4) went

further. Genes became the real object of natural selection. Moreover, the source of variation was attributed to chance events, random mutations. But, if the source of change was entirely random, physiology would have no role whatever in understanding the process. It would become important only at the stage of selection among the random variations. Any influence of the environment on the genome, other than retrospectively through the selection process, was also excluded.

No wonder that a central focus of biology became genes and their evolution. Within physiology itself, molecular biology and molecular genetics became dominant. In many cases, whole departments became devoted to these areas at the expense of more integrative approaches, whereas any contribution physiology might have to evolutionary biology was ignored. The wheels of evolution grind slowly, on time scales that are way beyond those of the great majority of physiological research.

But two problems were waiting in the wings to upset this consensus.

The first was subtle. It is more a philosophical problem than a scientific one. What precisely is meant when we talk about a gene (2)? When the term was introduced by Johanssen (7), it referred to a discrete inheritable phenotype: the gene for eye color, wrinkly peas, and all the other characteristics that could be identified as following Mendelian rules of inheritance. Notice that, although the assumption was that something inside the organism and transmitted through the gametes was the cause of this inheritance, they were defined in terms of function at the level of the phenotype. They were, therefore, hypothetical entities: the postulated causes of the observed phenotype.

The modern molecular biological definition of a gene is very different. It is no longer hypothetical since it refers to a specific sequence or sequences of DNA. It has to be shown that it is the cause of particular phenotypes. This is problematic because organisms are robust and can buffer themselves against many forms of DNA variation, such as knock-outs and mutations. Defining genes in terms of phenotypes so as to be equivalent to the original definition is difficult

¹Denis Noble is writing in his role as President of IUPS.

since many genes are involved in each function, and biological functions depend on many gene products in cooperation. Furthermore, as we come to understand the structure of the genome better, even the concept of a gene as a DNA sequence is changing. Surely, 80% of the former “junk” DNA that has now been shown to be transcribed (<http://genome.ucsc.edu/ENCODE/>) also has a right to be called genes, even if it doesn't form templates for proteins.

The reason that this change is subtle is that the *language* of the old phenotype-oriented definition has been retained. We continue to talk of the gene for this and the gene for that. This linguistic confusion is also the reason why people continue to debate whether genes are or are not selfish. An organism can be selfish as an expression of its phenotype, but a DNA sequence cannot be. The idea is a non-provable and empty circularity. This is not a matter of whether the idea is or is not metaphorical. On both interpretations, metaphorical or literal, the idea is empty from a physiological point of view (9). We would do better to drop the concept entirely when using the modern definition of a gene.

The second problem is that there is accumulating experimental evidence that the modern synthesis is far from complete as a theory of evolution (11). The evidence concerns all aspects of the modern synthesis (13). Mutations are far from random. Genome variations in evolution are also far from gradual. Whole domains of genomes have moved around within and between species. In some cases, notably genes involved in immunity, the

mutation rate can be influenced by environmental challenges and the physiological response to them. Inheritance by mechanisms other than the orthodox view has been shown in a whole variety of cases, many of them mediated by epigenetic processes (5).

We are therefore at the threshold of a phenomenal development. At the least, the modern synthesis needs extending to take account of the new experimental data. The remarkable fact is that much of the deconstruction of the central dogma and of the modern synthesis has come from molecular biology itself.

It is far too early to know where exactly all this is leading. The experiments are difficult and involve multi-level work ranging all the way from molecular mechanisms to ethology and animal behavior, including observation over many generations. Examples include behavior-induced marking of genes (14) and RNA-dependent inheritance of viral immunity in *C. elegans* (12). The progress in this area may therefore be slow and accumulative rather than sudden and immediately convincing. But what is certain is that the relevance of physiology and the investigation of function at the level of the phenotype and its interaction with the environment is back in contention as one of the possible influences on evolutionary variation.

If you want to keep abreast of these and many other new developments in physiological science, then come to the 2013 IUPS World Congress. The border between physiology and mainstream biology is also disappearing with major implications both for physiology and for biology in general. The full consequences

of understanding all those DNA sequences are still to be realized. At that meeting of the Scandinavian Society, after my lecture that “physiology is back in action,” someone commented, “You bet it is.” ■

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