nature genetics



# Krogh's principle for a new era

It's August, and our thoughts turn to the Danish physiologist August Krogh, a remarkable figure in twentieth-century science. His legacy of discoveries, including the Nobel-winning work on the anatomy and physiology of capillaries, is unparalleled in the history of his field. Krogh is also well known for an approach to science that he offered in 1929: "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." 'Krogh's principle,' as it was later dubbed by Hans Krebs, is a motto for today's scientists whose animal of choice may not attract thousands (or hundreds) of participants to an annual meeting.

Geneticists have been less comfortable exploring a wide range of experimental organisms, for a number of reasons, including the need for short generation times and a set of tools that enable sophisticated genetic analyses. The necessity of a critical mass of techniques and reagents has limited interest to a handful of currently favored models. The communities studying *Drosophila melanogaster*, *Caenorhabditis elegans*, *Danio rerio* and *Mus musculus* have unsurprisingly attracted large numbers of younger scientists who are eager to exploit these hard-won resources in the company of an established pool of potential collaborators. If this group of organisms (and a few others) isn't necessarily the ideal in which to address all possible problems in physiology, there's no arguing with their obvious successes in advancing the study of heredity.

In a recent review (*Annu. Rev. Physiol.* **65**, 231–259; 2003), Andrew Gracey and Andrew Cossens suggested a modified version of Krogh's principle for environmental and comparative physiologists. Acknowledging the importance of genetic tractability, Gracey and Cossens suggest that physiologists might study an organism that is less than perfectly suited to the problem in question, secure in the knowledge that evolutionary conservation makes discoveries likely to be broadly applicable. In genetics, one unmistakable trend is the ease with which investigators leap from one model organism to the next in the same line of work, particularly when it comes to studying complex traits and diseases. In such cases, the difficulty and uncertainty of approaches like QTL mapping and population-based association studies cries out for new findings to be supported by several converging lines of evidence—the more the better. As a result, this particular revision of Krogh's principle may be a useful guidepost for post-mendelian genetics.

A few examples drawn from this issue underscore the point. On page 403, Amanda Ewart-Toland *et al.* identify the gene encoding Aurora2 as a candidate low-penetrance tumor-susceptibility factor in mice and humans. As William Dove outlines in his accompanying News and Views article on page 353, the task of finding such subtle modifiers of cancer risk is an immense one, which in this case required a team of human and mouse geneticists in several different laboratories. Linkage analysis, haplotype mapping and expression analysis in mice narrowed the region to a single gene (although the causative polymorphism remains elusive), followed by functional analysis of the human locus. Each piece of evidence by itself is only suggestive, but taken together, they make a strong case that the Ile31 variant of Aurora2 has a role in cancer susceptibility.

On page 383, Diether Lambrechts and colleagues show that *VEGF* is a modifier of susceptibility to sporadic amyotrophic lateral sclerosis (SALS), a multi-factorial disease. Previous work had indicated that *VEGF* expression in response to hypoxia is essential to prevent adult-onset motoneuron degeneration in mice. The probable relevance of this finding to human disease is now clear, as Lambrechts *et al.* have found distinct *VEGF* haplotypes that are associated with lower *VEGF* expression and increased incidence of SALS in two populations. Although the association was not found in a third subset, the subsequent finding that administration of Vegf can protect motoneurons from ischemia-induced death in mice further strengthens the result.

Sometimes three organisms come into play, as in the work on nephronophthisis (NPHP) on page 413 by Edgar Otto and colleagues. One of the NPHP loci, *NPHP2*, had been mapped to human chromosome 9q21–q22, containing *INVS*, which suggested the *inv*/*inv* (*situs inversus*) mouse as a possible model, given that its phenotype is characterized by large cystic kidneys. Candidate gene sequencing of *INVS* made it immediately clear that *NPHP2* and *INVS* are allelic. A subsequent knockdown of *invs* in zebrafish recapitulated the key features of NPHP in yet another model, confirming

the evolutionarily conserved role of INVS. In a companion paper on page 455, Heike Olbrich *et al*. implicate yet another gene in the disease, *NPHP3*. A mutation in the mouse ortholog is probably responsible for the phenotype of the *pcy*/*pcy* mouse model. As progression of the disease in these mice was previously shown to be slowed by modified diet and steroids, these findings raise hope for a treatment that can be applied to humans.

Although limited to a single organism, one final example from this issue is worth noting. The work by Maria De Luca and colleagues on page 429 shows that quantitative genetic approaches in *Drosophila* can be extended all the way to the analysis of a complex trait in a natural population. The identification of dopa decarboxylase as a factor contributing to variation in lifespan echoes previous studies on tyrosine hydroxylase and its potential role in extreme longevity in humans. And if James Curtsinger is correct in saying on page 358 that this approach should be broadly applicable, then *Drosophila* may serve as an essential model for the analysis of natural variation.

These are relatively early days in the analysis of complex traits, but it is clear that a degree of uncertainty is inevitable, even in the face of heroic efforts. There is no entirely 'convenient' organism in which to study them, least of all humans. Each of these examples illustrates the increasing relevance of model organisms in dispelling some of this uncertainty. What's more, they make clear the increasing facility with which two or more can be incorporated into ongoing lines of work by nimble labs that are eager to collaborate or dare to study more than one model at a time. Such 'cross-species' research programs will no doubt be increasingly evident as we attempt to bridge the gap between genotype and phenotype. ■