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Can You Teach an Old Dogma New Tricks?

When people are least sure, they are often most dogmatic.
—John Kenneth Galbraith

In *The Structure of Scientific Revolutions*, Thomas S. Kuhn (1) discussed the resistance of science to embrace new concepts. He described how fields of scientific research are guided by dominant paradigms. He used the term "paradigm" to mean "normal science" or "accepted examples of actual scientific practice." As Kuhn noted, the benefits of a paradigm in defining and directing research in a particular field are inevitably coupled with a tendency to disregard those ideas that fall outside its purview. He wrote:

"No part of the aim of normal science is to call forth new sorts of phenomena; indeed those that will not fit in the box are often not seen at all. Nor do scientists normally aim to invent new theories, and they are often intolerant of those invented by others. Instead, normal-scientific research is directed to the articulation of those phenomena and theories that the paradigm already supplies."

In this issue of *Endocrinology*, you will find five minireviews, each covering a different topic but with a common purpose. Each author has written about an issue that does not receive as much attention as it deserves within the field of neuroendocrinology. In most cases, this is because the dominant paradigm or prevailing dogma encourages a particular kind of thinking, which then may constrain us from thinking beyond it.

For example, most neuroendocrinologists don't question the dogma that testicular secretions are solely responsible for the sexual differentiation of the brain. Perhaps they are, but a few findings now allow us to look at the issue again, and ask whether testicular secretions can account for all of brain sexual differentiation. In their minireview, Arnold *et al.* (2) persuasively make the case that in addition to determining the presence of the gonads, genes encoded on the sex chromosomes might act within the brain to make XX and XY cells different. They discuss a number of recently developed models that will enable us to thoroughly reconsider previous assumptions and test new ideas about the sexual differentiation of the brain. Will these testable ideas be embraced by a scientific community entrenched in a particular way of thinking, or are we relegated to constrain our thinking that only androgens and the genes that determine the presence or absence of the testes have relevance?

Another strongly held view is that sex differences in brain structures should relate in a direct way to sex differences in behavior. De Vries (3), however, elaborates the idea that some sex differences in brain structure may not support sex differences in behavior; on the contrary, he argues, they may exist to allow the two sexes to perform the same behavior with different neural equipment. He provides data to support this idea and provides a road map for further studies in this novel area, which violates traditional thinking on the role of a sex difference in the brain, and its relationship to sex differences in behaviors.

When life was simpler, there was only one estrogen receptor (ER), and it was thought to act as a transcription factor. This originally described ER was renamed ERα when another ER gene, ERβ, was discovered in 1996. In her review, Toran-Allerand (4) takes on the thorny question of how many ERs there are in the brain. It appears that these two transcription factor ERs, ERα and ERβ, may just be the tip of the iceberg. Now we know of a variety of other receptors, including other nuclear receptors, cytoplasmic receptors, and membrane receptors, some perhaps coded by the same genes that direct the expression of the transcription factor receptors, and the story is probably not yet complete. The challenge now will be to consider each of these receptors in developing our hypotheses, to test the existence of each, to determine the physiological function of each, and then make sense of how signaling of estradiol is integrated within cells by the mix of receptors. And we will have to continue to keep an open mind that some of these receptors may be activated by other second messenger pathways, in addition to being activated by estrogens, a topic discussed in the next minireview.

Steroid hormone receptors were originally named for the fact that activation was believed to require binding to cognate ligand. In my minireview (5), I ask that we stop thinking of transcription factor steroid hormone receptors only as ligand-dependent transcription factors. I stop short of asking for a renaming of these transcription factors that are activated by a wide variety of intracellular signaling pathways, as well as by steroid hormones. Although the idea that these transcription factors can be activated by multiple routes has taken hold in some fields, this does not seem to be the case within neuroendocrinology. Few papers within this field test this idea that originates with *in vitro* work. In many studies, the assumption is still made that steroid hormone receptors are activated only by steroid hormones and that steroid hormone level should vary with response. Clearly this need not be the case if the receptors can be activated by alternate routes.

We tend to think of hormone-sensitive circuits as networks of interconnected neurons that express hormone receptors. In their minireview, Garcia-Segura and McCarthy (6) demonstrate that glia may play a much more important role in these networks than we generally assumed. The name glia itself, German for glue, implies that these cells are merely the supporting matrix for the all-important neurons. These authors, however, give numerous examples of the interaction between glia and neurons playing an important and essential part in neuroendocrine regulation. How can we overlook these cells that have such an intimate relationship with neu-

Abbreviation: ER, Estrogen receptor.

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rons and that synthesize steroid hormones or metabolize them into active forms?

In his classic book, Kuhn went on to write, "Discovery commences with the awareness of anomaly, *i.e.* with the recognition that nature has somehow violated the paradigm-induced expectations that govern normal science. It then continues with a more or less extended exploration of the area of anomaly."

Each of the papers in this issue presents anomalies that challenge dogma in one way or another. All we need do for now is keep an open mind that what is discovered, studied, or decided first is seldom the final word.

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