A Possible Paradigm Shift

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This month, guest editors Laura N. Antar, MD, PhD, and Eric Hollander, MD, and colleagues examine hypotheses about the relationship between inflammation and psychiatric illness. Their articles focus on a possible mechanism of psychiatric disorders that could constitute a major paradigm shift.

As a psychiatry resident in the 1960s, I was taught that depression was caused by “anger turned inward,” rather than the humoral theories based on early Greek and Chinese medicine. About the same time, the effectiveness of antipsychotics was becoming realized with the use of chlorpromazine. This, taken together with the antidepressant effects of imipramine and iproniazid, led to the psychopharmacologic revolution and a marked increase in neurobiologic research.

Following my residency, I was a fellow at the National Institute of Mental Health (NIMH), also in the mid-1960s, where I was focused on the norepinephrine depletion theory of depression. Also at that time, the NIMH was investigating the role of serotonin.

We discovered changes in MHPG (a metabolite of norepinephrine) in patients with depression and our excitement grew. Had we established a biochemical basis for depression? My excitement was immense.

The development of fluoxetine in the mid- to late-1980s shifted the attention to selective serotonin reuptake inhibitors (SSRIs). It was a new twist on the neurotransmitter theme, ultimately becoming the dominant truth.

For a while, norepinephrine was nearly forgotten, as was dopamine, despite the fact that it is key in hedonic functions (one of the primary dysfunctions in depression). Maybe the avoidance of developing more potent dopaminergic medications was due to the fear of developing addictive substances.

As the therapeutic limitations of the new-generation antidepressants that were more specific in their effect became evident, the field started to realize that the “dirtier” the drug (meaning it affected more neurotransmitters), the more effective it might be for treatment-resistant patients. (Tricyclic antidepressants and monoamine oxidase inhibitors are in this category.)

NEUROGENESIS REVOLUTION

Meanwhile, evidence that the brain, particularly the hippocampus, routinely makes new cells became clear (I had been taught in medical school that the brain cells did not regenerate), suggesting the possibility that one of the most important effects of antidepressants might be the restoration of normal neurogenesis in the brain.

There is also evidence that elevated cytokines and oxidative stress may play a major role in the brain dysfunctions associated with a range of mental disorders. They may not be specifically implicated but perhaps their effect is to a quantitative degree, implying that antioxidants and substances that tend to lower cytokines may have therapeutic value.

ROLE OF INFLAMMATION

This brings us to the work in this issue. Is it possible that we’re at the beginning of another paradigm shift? Hollander and colleagues argue that there are subtypes of depressive illness precipitated exogenously by cytokines (interferon-alpha), or even possible forms of endogenous inflammatory cytokine-associated depression that will respond to specific cytokine-lowering treatments. If so, this could mean we are approaching a new, general pathophysiologic mechanism for depression as well as other psychiatric disorders.

Director of the NIMH, Thomas R. Insel, MD, was gracious enough to share his thoughts with us about this, along with other hot topics in our field (see page 350).

What a wonderful journey – stay tuned!

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