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Toward an Emerging Paradigm for Understanding Attention-Deficit/Hyperactivity Disorder and Other Neurodevelopmental, Mental, and Behavioral Disorders:

Environmental Risks and Epigenetic Associations

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Are psychiatric and neurodevelopmental conditions fundamentally epigenetic disorders? The answer to this question may shape the next generation of clinical science related to psychopathology.[1] The genetic metaphor for developmental psychopathology has long been considered inadequate for the complex dynamics of human development.[2] However, the rise of behavioral epigenetics[3] has amplified the possibility of an actionable paradigm that effectively integrates genetic liability and an environmental modulation of developmental trajectories. If the epigenetic perspective proves to be productive, it would open up not only new treatments but also new preventive approaches that reach the earliest days and months of life.

Attention-deficit/hyperactivity disorder (ADHD) is an interesting case study for this potential shift in perspective. Three major misconceptions have adversely affected research in ADHD. The first is that the disorder is readily treated. That fantasy has been dismantled by the results of long-term follow-up studies that show that, although good treatment certainly can contain symptoms and improve a child's chances, even the best treatment for ADHD does not significantly alter its poor long-term life outcomes.[4] The second is that ADHD is not very serious anyway. To overcome this misunderstanding requires putting together the reality that mental illness and addiction together are the first or second leading cause of disability both worldwide and in the United States[5] with the realization of how much of that burden involves ADHD as a precursive or amplifying condition. For example, in addition to its strong association with future antisocial behavior, school failure, incarceration, occupational failure, and other life outcomes, ADHD also triples the risk of schizophrenia; doubles the risk of depression (and when ADHD co-occurs with depression and conduct disorder, multiplies the chances of suicide); nearly doubles the risk of addiction to alcohol, drugs, or nicotine; nearly triples the risk of skull fracture; and doubles the risk of other serious injuries.[6] Finally, just as hypertension shortens life through secondary complications, through these various risks ADHD increases mortality and shortens life

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spans, too.[7] It is deadly serious, and understanding its roots is a justifiable public health priority.

This brings the third confusion—what are its roots? In twin studies, ADHD—whether viewed as a normally distributed trait or as a discrete disorder—has among the highest heritability of any complex trait or disorder. However, statistical heritability is commonly misunderstood as inheritance. It does not mean that ADHD is simply inherited like a mendelian disorder and it does not describe the biological process through which a disorder emerges. Quantitative geneticists have known for decades that heritability estimates of complex traits and diseases using twin studies do not capture the heritability of the disease but rather the heritability of the liability for the disease. The estimates include certain gene-by-environment interactions and correlations.[8] This can be conveyed intuitively by recognizing the substantial twin heritability of infectious diseases like tuberculosis or malaria (even after taking into account the unique challenges in twin studies of infectious diseases).[9] Thus, the actual potential to prevent or cure disease by environmental manipulation cannot be directly inferred from statistical heritability estimates alone. Attention-deficit/hyperactivity disorder is like other complex diseases: its multifactorial etiology is likely a mix of rare gene mutations and common genetic liability, with environmental modulation.

While the magnitude of gene-by-environment effects in ADHD remains unclear, it is possible, perhaps even likely, that genotype (liability)-environment (modulation) interplay is fundamental. Indeed, the role of environment in ADHD is increasingly recognized; a growing literature has documented important environmental modulators of ADHD incidence and severity.

How can the mechanism behind those associations be clarified? Ideally, we would test the epigenetic hypothesis by directly examining epigenetic effects. However, because (1) the brain is central to mental and behavioral disorders, (2) epigenetic markings on DNA are substantially tissue specific (and in the brain, to some degree, location and cell type specific), and (3) the living brain cannot be assayed for epigenetic status, the study of this problem relies on indirect methods, all with their own important limitations (eg, animal models, human postmortem brain studies, and peripheral tissue studies). These studies have nonetheless yielded provocative findings in multiple psychiatric disorders[10] as well as in ADHD.[11] Wilmot et al[12] conducted what was, to our knowledge, the first methylome-wide study of ADHD (using salivary DNA, in preadolescent boys who had never received medication with ADHD and non-ADHD controls; n = 92 in a discovery group and n = 20 in a confirmation group). The findings included altered methylation in 2 important genes that were not previously associated with ADHD: *myelin transcription factor 1 like* (*MYT1L*) and *vasoactive intestinal peptide receptor 2* (*VIPR2*). Whether associations will hold outside of boys who have not received medication remains a key question. Other studies are emerging.

In this issue of *JAMA Pediatrics*, Kioumourtzoglou et al[13] use an approach that is as important as it is underused: an examination of multigenerational transmission of environmental associations. That approach may be the most important from an epidemiological perspective. They report that pollutant exposure to grandparents conveys a

30% increase in risk of ADHD in grandchildren. The findings are novel and contribute to this emerging shift in the understanding of mental and behavioral disorders such as ADHD. The size of the association, similar to many other concurrent risk factors for ADHD, is striking. Although, as the authors note,[13] the dosages of everyday individual environmental pollutants are generally lower (in developed countries at least) than the dosages of diethylstilbestrol they studied, today's population is exposed to hundreds of poorly studied, neurodevelopmentally or hormonally active compounds, the interactions among which are unknown. Thus, the actual associations today are difficult to quantify.

The limitations in this study should not be overlooked—genetic associations were not able to be examined (so a genotype-environment correlation might partially account for findings), causality could not be evaluated because of the absence of F1 siblings, and ADHD assessment is limited in population studies. Their finding of a first trimester bias in the association, in particular, should be interpreted very cautiously; the incidence of ADHD in the second, third, and first trimester exposures were all higher than the unexposed group, and the statistical power to detect between-trimester associations was low. As the authors appropriately noted, further work on trimester-specific associations will be of interest. Finally, an epigenetic transmission is not the only possibility (because of third-generation oocyte exposure, as the authors noted), although epigenetic transmission by neuroactive chemicals to the third generation is demonstrated in nonhuman animals.[14,15]

While these limitations mandate some caution, they do not undermine the importance of this type of work. Indeed, it remains striking that results are just what one would expect if an epigenetic influence on ADHD was real. The results add converging evidence to a growing body of literature on not only the public health costs of ill-considered use of neuroactive chemicals in our society, but also to a growing revision of our understanding of the etiology of mental disorders, and ADHD in particular, as potentially being epigenetic conditions.

If disorders like ADHD are epigenetic conditions (that is, dependent on or heavily modulated by discoverable epigenetic changes that are traceable to preventable environmental exposures), it would have powerful implications for where national research dollars should focus to find ways to reduce the incidence of ADHD and other mental disorders. Discoveries about epigenetic associations as potential biomarkers of both illness and etiology that are related to common environmental exposures could hold promise to lead directly to renewed and targeted intervention to prevent ADHD and other illnesses from occurring.[1] This may be the most exciting direction open to the field.

Yet, the goal of individual identification (personalizing) of vulnerability and treatment is an important consideration. It is almost certain that inputs, such as environmental pollutants (or diet, emotional stress, or other systemic stressors), do not affect all children equally. Rather, the response is likely moderated by genotype and mediated by epigenetic change. For example, lead is known in animals to increase hyperactivity via epigenetic mechanisms,[15] and lead associations with ADHD appear to be moderated by genotype in humans.[16]

When it comes to psychiatric illness, we are overdue for a "decade of the environment" or perhaps a "decade of epigenetics" in which truly integrative science takes center stage. Such

integrative work includes genetically informed environmental studies and epigenetically informed genetic studies. What has become clear is that environmental moderators or mediators of psychopathology and neurodevelopmental disorders should be high-priority. An investment in understanding the epigenetic aspects of ADHD and other neurodevelopmental and mental disorders appears to be essential as part of a prudent strategy for addressing neurodevelopmental disorder in our society.

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