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Environment, Developmental Origins, and Attention-Deficit/ Hyperactivity Disorder

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In the current issue of the *archives*, we see additional evidence, in a retrospective design, that early developmental events are related to subsequent attention-deficit/hyperactivity disorder (ADHD) in children.[1] Attention-deficit/ hyperactivity disorder is a costly health condition rivaling traditional medical diseases in its effect on social, financial, and quality-of-life issues. Clinicians held a conviction in the early and mid-20th century that children with ADHD had minimal brain damage or minimal brain dysfunction.[2] However, a vague phenotype characterization, the failure to identify the nature of the brain dysfunction in the mid-20th century, and demonstrations of substantial heritability for hyperactivity, inattention, and ADHD in the late-20th century rendered the terminology obsolete and also seemed to discourage investigations of environmental inputs to the condition. Did we discard the concept of brain damage too soon?

Subtle brain abnormalities are now accepted as a common feature of the condition,[3] albeit still not usable diagnostically, and persistent correlations with early environmental events and on going environmental exposures continue to demand an explanation. Most of the relevant environmental risks are presumed to occur very early in development. For example, low birth weight (a proxy for numerous early risks) has a somewhat specific association with symptoms of ADHD,[4] perhaps via microstructural damage or micro-vascular events.[5] As another example, consistent results now confirm that, even at the reduced levels of exposure achieved by regulation of lead in paint and gasoline, lead exposure remains near universal in the US population, and variation in blood lead levels is related to symptoms of ADHD.[6,7] Population studies suggest an association between chlorinated pesticides and ADHD.[8] A surprising lack of crosstalk between environmental epidemiologists and child psychiatric researchers hinders there solution of the meaning of such effects. Epidemiological studies typically fail to confirm that children have the full psychiatric syndrome, where as psychiatric studies typically fail to consider these potentially important environmental inputs.

If causal, and if able to be understood pathophysiologically, such environmental effects on ADHD are of “game-changing” importance because they open the door to eventually

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preventing that portion of cases of ADHD caused by early insult to the nervous system. What, then, do we make of these developments? Three fundamental considerations bear reflection.

First, new genetic insights into epigenetic markings and gene × environment interactions profoundly complicate any simple linear interpretation of heritability figures as the main effects of genes. To what extent these environmental associations are causal remains largely unknown, but with the exploration of epigenetic effects on behavior only beginning, the importance of environmental influences in our theoretical and clinical understanding of the psychopathology of ADHD is likely to increase. Indeed, behavioral epigenetics is a new field that has only emerged in recent years.[9] We still know very little about the importance of developmental timing or other sensitivities of the epigenome or of epigenetic influences on behavioral tendencies and cognition. Direct studies of epigenetic change in the human brain remain impossible during a person's lifetime, and it remains unclear to what extent epigenetic effects in the brain will eventually be able to be detected in peripheral tissues. However, studies of epigenetic effects in the placenta can be a powerful tool for understanding influences during fetal development[1] that predict later changes in brain or behavior. Overall, both animal and human studies will be needed to explore the epigenetic consequences of the key exposures associated with ADHD, as well as other mental disorders, and to seek convergence of effects.

Second, the fetal period is ripe for renewed focus in child psychiatric conditions. The field of developmental origins has come into its own in much of medicine, with strong programs of research investigating fetal and placental effects related to subsequent heart disease, diabetes mellitus, and cancer.[10,11] The brain is an organ that is exquisitely sensitive to environmental exposures and should be susceptible to the same lines of research. This line of thinking proposes that programming occurs in prenatal development, by which the organism adjusts its physiology for the anticipated postnatal environment. Such adaptive effects have been demonstrated in altered placental blood flow and venous shunting. The role of fat intake in psychological and mental health development can be investigated in the same way as medical diseases are investigated. That is, the brain, like other organs, is vulnerable to structural change secondary to the prenatal environment.[12] This opens the door to the study of dietary and toxicant effects. For example, we know that long-chain fatty acids are crucial to placental health and fetal growth. Pregnancy studies[13,14] of the intake of n-3 fatty acids indicate the effects on an offspring's attention at 6 to 12 months and on the hyperactivity of the offspring at 9 years.

The modern fetal environment differs in numerous ways from evolutionary times. For example, take diet; modern pregnancies are typically characterized by more total fat intake and by reduced intake of n-3 fatty acids (particularly relative to n-6 fatty acids) compared with pregnancies during the Paleolithic period,[15] with numerous hypothesized health effects. This reduction in n-3 fatty acids compared with the fetal "expectable environment" presumably leads to alterations in fetal physiology, via changes in placental function, as the organism adapts. However, these adaptations are theorized to impose costs to brain development and thus to behavioral adjustment. The same logic would apply, with different

specific mechanisms, to fetal exposure to toxicants. Mechanisms can be elucidated by considering, for example, epigenetic changes in placental tissue.

However, a major challenge in this research context is to sort out the myriad, correlated environmental influences that may be influencing neural and behavioral development, probably with larger effects in genetically or otherwise susceptible individuals.[16,17] The environmental confounders looked at here are important but obviously not exhaustive, and assessment of gene-environment correlation effects in a singleton population study is hazardous.

A third fundamental consideration, then, is that the conclusion of causal effects for such findings is limited by a shortage of causally informative human studies. Although prospective studies can use statistical means to partially disentangle prenatal smoking, low birth weight, nutrition, toxicants, stress, and other factors, they can do so only partially. Twin and sibling designs, combined with newer mathematical models, can provide important causal evidence, provided that there is sufficient variation in the environmental measure of interest.[18,19] Experimental studies in humans are possible with potential preventive interventions (eg, using vitamins to counteract prenatal smoke exposure and using long-chain fatty acids to counteract dietary or toxicant effects), but these studies will still need to face the challenges of identifying the likely modest-sized effects of any one particular agent against the background of other agents and within-child genetic variation.

With regard to causality, we can take the example of pre-natal smoking exposure. Correlational studies have demonstrated consistent associations between prenatal smoking exposure and ADHD that hold up in population and meta-analytic studies.[20] Yet, only recently have causally informative human studies been conducted. In one novel study, Thapar et al[21] used surrogate pregnancies and found no causal effect. In another study,[22] a sibling analysis using newer propensity models and sibling data also showed no causal effect with oppositional behavior but a small effect for ADHD. In short, if there is a causal effect of smoking on ADHD, it is much smaller than was thought from prospective correlational studies.

Renewed efforts at environmental studies will be of great interest, particularly those that consider the pre-natal environment, have the capacity to examine biological pathways, and are designed to be causally informative in some manner (or else complemented by relevant animal studies). If a specific environmental causal influence can be demonstrated, even if effective in a subset of children, and its biological mechanisms elucidated, then a powerful model will be created for how ADHD can develop. That discovery will be a crucial stepping-stone toward parsing multiple causal routes to what may be a final common pathway of the ADHD phenotype.

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