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Editor-in-Chief

Therapeutic
orchestration
of gene expression
will one day prevent
mental illness

Harnessing epigenetics for psychiatry

It sounds like science fiction, but it may soon become a reality. The young science of epigenetics is revolutionizing the traditional principles of genetics and weaving them into countless environmental factors, from biologic to behavioral, that can modify and direct gene expression toward health or disease. When nature and nurture collide, epigenetic events occur. The most exciting implications of gene-environment interactions are the endless possibilities to exploit and manipulate epigenetics to prevent or ameliorate psychiatric disorders.

Lamarckism, the discredited “inheritance of acquired characteristics,” was a primitive version of epigenetics proposed by Jean-Baptiste Lamarck (1744-1829), to build on Charles Darwin’s theory of evolution and explain adaptation to the environment. Lamarck’s ideas preceded the discovery of “heredity” introduced by the Austrian monk Gregor Johann Mendel in 1865. The terms “gene” and “genetics” were coined by William Bateson in 1902 and the location of genes within the chromosomes was discovered in 1910 by Thomas Morgan. The term “epigenetics” was coined in 1940 by Conrad Hal Waddington, and this science has accelerated dramatically over the past decade when it was discovered that:

1. Certain biologic substances such as histones and methyl groups can attach to the “promoter” region (ie, the switch) of a gene and either silence the gene or turn it on to increase its expression. This explains how >200 distinctly different tissues develop in a fetus although every single cell of those tissues contains the *same* 23 chromosomes, with a total of approximately 20,000 genes.
2. Behaviors or activities by adults may, unbeknownst to them, lead to disease in their yet-to-be-born offspring by switching certain genes on or off, without any change in the structure or sequence of DNA. For example, one study found that men who began to smoke before puberty (when sperm production begins) had offspring with significantly higher body weight than men who did not smoke before puberty.¹ Animal studies show that organisms subjected to caloric restriction will live 30% longer than those with normal caloric intake, and their offspring have 20% longer longevity without being subjected to caloric restriction!² That’s Lamarckism, but a much more sophisticated version than the original.

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How does this link to psychiatry? We already have a large body of evidence that the environment can have a substantial deleterious or salutary impact on the development of psychiatric brain disorders. One set of evidence comes from studying that most important environment, the womb. Prenatal, neonatal (obstetric), and postnatal adverse events can disrupt brain development and lead to serious psychopathology, such as schizophrenia. Another type of evidence is seen in childhood abuse (physical, sexual, or verbal), which can lead to sensitization of the HPA axis and result in serious mood and anxiety disorders in adulthood. On the positive side, an enriched environment during infancy can stimulate neuroplasticity, connectivity, and enhanced brain growth.

Imagine what we will be able to do once research elucidates more than the epigenetic changes caused by *adverse* intrauterine events for a fetus or unhealthy pre-conception behaviors in future parents. Imagine, too, if psychiatric scientists discover parental behaviors that may improve offspring temperament, bolster resilience under stress, blunt impulsivity, suppress antisocial behavior, reduce the susceptibility to addiction(s), enhance cognitive ability, inhibit emergence of psychiatric symptoms, increase motivation, and, importantly, extinguish inherited suicidal or homicidal urges.

Of all medical disciplines, I believe psychiatry stands to benefit the most from advances in what may be designated as the field of "therapeutic epigenetics." Two reasons justify this assertion:

1. A very high proportion (50%) of our 20,000 genes are expressed *only* in the brain, creating huge opportunities for "interventional epigenetics" to prevent, modify, modulate, or ameliorate psychiatric diseases by silencing abnormal genes (once we identify them) or turbocharging the expression of adaptive genes (once they are identified).

2. The brain is the most plastic organ in the body, changing on an ongoing basis by interacting with the environment (ie, the human experiences of everyday life). The unique ongoing neuroplasticity of the brain is driven by gene expression stimulated by environmental stimuli, which can be targeted for therapeutic purposes. In fact, it is likely that psychotherapy and pharmacotherapy exert their efficacy and certain adverse effects via selective gene expression.

Yes, it does sound like science fiction that some day we will be able to capitalize on gene-environment interactions to heal the body, the brain, and the mind, thus circumventing the use of medications. Psychiatric destiny is not in the DNA but in how targeted environmental influences can bring out the best in DNA, that magically malleable matter of life.



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