EDITORIAL

Genetics and Brain Function: Implications for the Treatment of Anxiety

In March 2000, the Anxiety Disorders Association of America (ADAA), jointly with the National Institute of Mental Health (NIMH), sponsored a conference entitled “Genetics and Brain Function: Implications for the Treatment of Anxiety.” With a focus on genetic implications for the understanding of anxiety and development of new treatments for the anxiety disorders, leading researchers presented advances on a spectrum of topics, with perspectives from basic science and clinical research.

This meeting, as reflected in the compendium of articles in this issue (Bakshi and Kalin 2000; Caldji et al 2000; Goldsmith and Lemery 2000; Gross et al 2000; Rosenberg and Hanna 2000; Watson et al 2000), underscored two compelling realities regarding the field of anxiety (i.e., behavioral neuroscience) research. On the one hand, the human genome project, combined with emerging tools such as DNA microarrays (Watson et al 2000), opens heretofore incomprehensible pathways of discovery into the role of genes in the important biological functions of anxiety, startle, fearful temperament, alarm, and arousal. On the other hand, the notion that the pathophysiology of any DSM-IV anxiety disorder might be exclusively linked to a single gene seems implausible. Nonetheless, the intellectual attractiveness of single gene hypotheses underlying pathologic anxiety is reminiscent of earlier single-neurotransmitter or single-receptor or receptor subtype theories of the anxiety disorders (Uhde et al 1990). With the advent of any new research tool (e.g., the “chip” [Watson et al 2000]; functional magnetic resonance imaging [fMRI] [Rosenberg and Hanna 2000]; gene targeting and tissue specific receptor manipulations [Bakshi and Kalin 2000; Gross et al 2000]), the evolution of scientific inquiry predictably moves from reductionist to integrative models of pathophysiology. Thus, though the biological targets of our research have become more discreet (organ to neurotransmitter, to receptor, to cellular, to molecular, etc.), the discovery of a final common pathway has so far eluded detection.

It is probable that fear and anxiety are inevitably mediated by an interplay of factors. Using different terminology, the age-old question of “nature versus nurture” in the mediation of the anxiety disorders may not be elucidated by candidate gene or related methodologies. In fact, asking the nature versus nurture question itself may have delayed more relevant investigations into the relationships among mind, brain, and behavior.

Several lines of evidence, as collectively represented in this issue (Bakshi and Kalin 2000; Caldji et al 2000; Goldsmith and Lemery 2000; Moldin 2000) and elsewhere, highlight that it is increasingly difficult to separate “Chicken–egg” types of causation when it comes to gene–environment interactions, perhaps especially in relation to complex emotions such as anxiety and behavioral inhibition. Genes present at birth shape later life experiences (e.g., trauma), behavioral traits (e.g., risk taking), environmental context (e.g., socioeconomic status, food consumption), and interpersonal dynamics (e.g., maternal bonding), factors that themselves collectively and separately affect gene expression. That genes and environment determine who we are as individuals is self-evident; more interestingly, perhaps, is how these same forces at one point in time may affect individuals across generations. A provocative and emerging area of study might be coined genomic sociology (i.e., how the impact of gene–environmental factors influences emotions and behavior across generations). This has a familiar ring, albeit using a distinctly different construct, similar to Carl Jung’s notions of archetypes and the collective unconscious (Jung 1968). How do genetic–environmental interactions influence human behavior at a single time point and over time (within individuals) as well as across generations and divergent cultures? How do both genomic and non-genomic factors influence the risks for the emergence of anxiety disorders across generations (Francis et al 1999; Yehuda et al 1998)? It appears that we have the tools to begin to unravel such mysteries.

Although the data presented at the ADAA/NIMH meeting do not exclude the importance of single genes in regulating some “seminal” feature(s) of any anxiety disorder, there is striking evidence to suggest that the functions of alarm, stress, and arousal in humans and animals are the result of multiple genes working in concert with environmental factors. Nonetheless, even a single susceptibility gene, which influences a key feature of a “polygenetic” anxiety disorder, may serve as a useful target for drug discovery and the development of therapeutic agents that improve a subset of symptoms and/or course of illness (Anderson and Cook 2000; Gray et al 2000; Kola 1999).

The major reason for investigating the etiology of the anxiety disorders is to improve treatment. Tomorrow’s physician theoretically will have knowledge about anxiety susceptibility genes and, together with other infor-
information (e.g., endocrine status, fMRI and magnetic resonance spectroscopy), will be able to individualize and monitor drug and psychosocial treatments, both acute and prophylactic. I challenged Drs. Rosenberg and Hanna to “wildly” speculate about the future role of pharmacogenetics and imaging genomics to diagnose and treat patients with obsessive–compulsive disorder, which offers the best body of scientific data (in terms of our understanding of anatomic structures, molecular biology, neuronal pathways, specificity of drug response, and biochemical correlates underlying core features of the syndrome [Greenberg et al 2000; Martin et al 1998]) to form such speculations. Rosenberg and Hanna (2000) provide an elegant peek into the future, although their approach was conservative and risk adverse in quality.

There is a major deficiency in the scope of topics covered in this issue of Biological Psychiatry. As chair of the ADAA/NIMH satellite conference I failed to elicit presentations on the political, scientific, and sociologic impact of genetic testing. The role of genetic testing in the diagnosis and treatment of neurologic disorders is already a highly contentious issue. Mental health professionals and genetic counselors can anticipate more poignant questions about the merits and morality of identifying people at risk for anxiety disorders once such technology becomes available. The lay public, and even practicing physicians, express apprehension about the use of information made possible by medical research. Recently, there have been increased efforts to regulate the conduct of both basic and clinical research. Beyond the inherent value of conducting research and providing clinical care in an ethical manner, these external forces demand that the scientific community “take up the challenge” and engage the lay, religious, consumer, and advocacy public, government agencies, and individuals involved in diagnosis and treatment of mental disorders in an ongoing dialogue about the nature and limits of, and realistic implications for, genetic testing.

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References