Commentary: Etiological Hypotheses of Mental Disorders at the Molecular Level may not Help Psychiatry

Jonathan Benjamin, MD, MHA

"Clalit" Sick Fund, Israel, Professor Emeritus, Ben-Gurion University, Beersheba, Israel

This issue of the "Israel Journal of Psychiatry" is devoted to etiological hypotheses of mental disorders at the molecular level. I appreciate the invitation to write a brief commentary in support of my view that as of 2008 such hypotheses seem less likely to be helpful than they were expected to be 50 years ago.

The short explanation for this is that they have not been helpful yet, so why should we expect a change? We in fact know no more about the etiology of schizophrenia, depression or borderline personality disorder today than we did in 1958. We knew then, as now, that all the disorders we study and treat have a genetic component, and that psychoses and neuroses are helped but not cured by drugs affecting dopamine in the first instance, and noradrenaline and/or serotonin in the second. The success of drugs initially discovered by chance, and the demonstration of some of their actions (but this is not the same as the demonstration of *the mechanism of action that treats the disorder*), led to a series of molecular hypotheses which began at the level of messenger (neurotransmitter) and receptor, and then progressed to the level of second-messenger and onward into the interior of the cell (growth factors, response elements, nuclear receptors). This is a logical path to follow for a biochemist or cell biologist attempting to elucidate the working of the signal that begins at the synapse with a single quantum of messenger, and then devolves inward as an increasingly complex cascade of molecular events and adaptations (e.g., 1). But the quest for scientific knowledge has not yet helped the doctor understand the disease, let alone treat the patient. Virtually every piece of knowledge painstakingly learned in this way has been offered as a tentative explanation for an aspect of mental illness; none has survived. The oldest and most famous hypothesis, that every medical student and practitioner still instinctively feels is "right," the mono-amine hypothesis of depression (2, 3), suggests that depression is a disease of too little serotonin and/or noradrenaline. But tianeptine, an effective antidepressant available in Europe, is a selective serotonin reuptake *enhancer*, i.e., *lowers* the levels of synaptic serotonin (4).

The last five decades have seen a partial retreat from dynamic psychotherapy, and growing enthusiasm for cognitive-behavioral therapy, as cost-effective treatments for some mild but common mental disorders (and for some other problems not really considered "disorders"). There has been no parallel development in biological psychiatry, only the discovery of "me-too" drugs with arguably fewer side effects than those that were known in 1958. None of these new drugs were developed using new etiological hypotheses, nor indeed *any* etiological hypotheses; all were extensions of drugs previously discovered by chance. Deliberate attempts to treat schizophrenia by glycine agonists (5), and depression with corticotropin-releasing factor (CRF) receptor antagonists (6), both based on etiological hypotheses, have not led to breakthroughs.

The success of the genetic study of a few single-gene diseases in other areas of medicine prompted the search for linkages and then genes for mental illnesses. This is a logical path to follow for a geneticist; given the demonstration that a phenotype is heritable, scan every chromosome for linkage (impossible in 1958 but possible now), and then focus on the areas of linkage until you

E-mail: zola@netvision.net.il

find (a) mutation(s) or polymorphism(s) responsible for the phenotype. Virtually every chromosome has been implicated in the etiology of serious mental disorders like schizophrenia, no linkage has been *consistently* replicated (7), and no genes that can reliably be said to cause (or account for a major part of) a mental disorder have been found. A report in "Science" described a linkage to schizophrenia on chromosome 1 with chances of less than one in a million of a false positive (8); this too did not replicate (e.g., 9).

The situation is similar in bipolar disorder. Here too promising genes continue to be reported (10), but we do not have a genetic understanding of the illness.

Researchers tell us that this is partly because many genes are responsible for major mental disorders, each gene of very small effect. But this claim does not accord with mathematical models of the genetics of schizophrenia (11), for example, nor with our acquaintance with the risk of schizophrenia in identical twins, other sibs, and second-degree relatives (around 45%, 10% and 3% respectively). Three or four genes for schizophrenia are more compatible with the evidence. Depression, which seems to have a far bigger environmental component in its etiology (12), looks like an even less promising candidate for a molecular-genetic explanation.

The "British Journal of Psychiatry" recently convened a debate with the chilling title "Research into putative biological mechanisms of mental disorders has been of no value to psychiatry." In a paragraph addressing etiology, even the scholar chosen to refute the thesis made no attempt to offer examples of insights from molecular science, and wrote instead, "Biology of course does not just mean drugs or genes: Freud … considered himself a biologist" (13). One of the guest editors of the current issue of the "Israel Journal of Psychiatry," reviewing major depression for the "New England Journal of Medicine," recently wrote, "Depression is a … disorder … with … no established mechanism" (12). This is as good a summary of the current situation as we are likely to get.

I said above that the failure of molecular hypotheses in psychiatry thus far is the "short" explanation for my concern that they may also fail in the future. There is also an explanation of another kind. Mental disorders are extremely complex sets of phenomena, and the path from molecules, which undoubtedly play an important role, to mental disorders must be long and tortuous. A single example can suffice: alcohol is a simple molecule, with familiar effects on subjective states and behavior. Yet these vary tremendously across time and individuals. Nevertheless, inhibition of social restraint and of fine motor control and of wakefulness may all be plausibly explained by alcohol's effects on the benzodiazepine-GABA receptor complex. When we come to the mental disorders associated with alcohol use, which range from withdrawal delirium to persistent dementia to paranoid jealousy, a plausible molecular hypothesis to account for these seems more remote, even though the "responsible" molecule is already known.

Of course, nothing in this brief commentary can convince us that a true breakthrough is not just around the corner. Too much pessimism can paralyze science, and it then fulfills its own prophecy. Society owes it to itself to continue to fund the study of promising hypotheses, and to reward fruitful research. Nevertheless, the experience of the last 50 years in psychiatry suggests that hopeful prognostications on grant applications, in scientific journals, and in the popular media, should be swallowed in small doses, and washed down with a large measure of thoughtful reflection.

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