Homocysteine and Epigenetic DNA Methylation: A Biological Model for Depression?

TO THE EDITOR: In the article by Marshal Folstein, M.D., et al. (1), published in the June 2007 issue of the *Journal*, the authors described the homocysteine hypothesis of depression. This study provides a fundamental overview of the current knowledge regarding involvement of the homocysteine metabolism in the pathogenesis of depressive disorders.

Dr. Folstein et al. hypothesized that hyperhomocysteinemia may lead to an elevated risk of depression, mainly via acting as a cerebrovascular risk factor and by causing neurotransmitter deficiency. However, another important pathophysiological mechanism should be taken into account when discussing the homocysteine hypothesis of depression. Homocysteine is metabolized to methionine after activation to *S*-adenosyl-methionine, which is known to act as a methyldonator. Furthermore, homocysteine itself influences global and gene promoter-specific deoxyribonucleic acid (DNA) methylation (2). Acute homocysteine treatment has been shown to cause misregulation of different gene-specific promoters and changes of corresponding messenger ribonucleic acid (mRNA) levels (3). There is growing evidence that altered promoter-DNA methylation permits genome plasticity and adaption to a variety of environmental factors. This may provide the molecular base for a dynamic interaction between the environment and gene expression, regulated by modified promoter methylation. It has been suggested that these molecular mechanisms play a substantial role in the pathogenesis of different psychiatric disorders associated with hyperhomocysteinemia (4), including schizophrenia, eating disorders, and addiction (2, 5, 6). These epigenetic alterations may directly influence monoaminergic neurotransmission by modifying promoter methylation of candidate genes such as COMT and 5-HTTLPR (6, 7). Dysregulation of epigenetic-DNA methylation may therefore be one important element when discussing the homocysteine hypothesis of depression.

References

1. Folstein M, Liu T, Peter I, Buel J, Arsenault L, Scott T, Qiu WW: The homocysteine hypothesis of depression. Am J Psychiatry 2007; 164:861–867
2. Bleich S, Lenz B, Ziegenbein M, Beutler S, Frieling H, Kornhuber J, Bönsch D: Epigenetic DNA hypermethylation of the HERP gene promoter induces down-regulation of its mRNA expression in patients with alcohol dependence. Alcohol Clin Exp Res 2006; 30:587–591
3. Lenz B, Bleich S, Beutler S, Schlierf B, Schwager K, Reulbach U, Kornhuber J, Bönsch D: Homocysteine regulates expression of HERP by DNA methylation involving the AARE and CREB binding sites. Exp Cell Res 2006; 312:4049–4055
4. Tsankova N, Renthal W, Kumar A, Nestler EJ: Epigenetic regulation in psychiatric disorders. Nat Rev Neurosci 2007; 8:355–367
5. Frieling H, Gozner A, Römer KD, Lenz B, Bönsch D, Wilhelm J, Hillemacher T, de Zwaan M, Kornhuber J, Bleich S: Global DNA hypomethylation and DNA hypermethylation of the alpha synuclein promoter in females with anorexia nervosa. Mol Psychiatry 2007; 12:229–230
6. Abdolmaleky HM, Cheng KH, Faraone SV, Wilcox M, Glatt SJ, Gao F, Smith CL, Shafa R, Aeali B, Carnevale J, Pan H, Papageorgis P, Ponte JF, Sivaraman V, Tsuang MT, Thiagalingam S: Hypomethylation of MB-COMT promoter is a major risk factor for schizophrenia and bipolar disorder. Hum Mol Genet 2006; 15: 3132–3145
7. Mill J, Petronis A: Molecular studies of major depressive disorder: the epigenetic perspective. Mol Psychiatry 2007; 12:799–814

THOMAS HILLEMACHER, M.D.
HELGE FRIELING, M.D.
MARC A.N. MUSCHLER
STEFAN BLEICH, M.D.
Erlangen, Germany

The authors report no competing interests.

This letter (doi: 10.1176/appi.ajp.2007.07060881) was accepted for publication in July 2007.

Treating Trichotillomania in Children and Adolescents: CBT Versus Medication

TO THE EDITOR: As a pediatric psychologist who works at Massachusetts General Hospital, I read with interest the treatment in psychiatry article by Samuel R. Chamberlain, M.A., et al., in the April 2007 issue of the *Journal*, entitled "Lifting the Veil on Trichotillomania" (1). The report by Dr. Chamberlain et al. supports my observations from my extensive clinical experience working with children and teenagers suffering from trichotillomania. Cognitive behavior therapy (CBT) consistently shows positive results, and medication often does not demonstrate significant benefits.

If there is an underlying mood or anxiety disorder that contributes to hair pulling, or if CBT alone has failed, then medication—usually a selective serotonin reuptake inhibitor (SSRI)—in addition to CBT, is often most successful. However, most of the patients in my practice have not presented with an underlying mood or anxiety disorder. Certainly, individuals with trichotillomania may pull their hair when they are anxious, but they usually pull more often when they are in a state of relaxation. Hair pulling for them is a self-soothing behavior, not unlike thumb sucking, which becomes habitual. It can be very difficult to target with medication, and, if there is even a minor side effect of activation, medication could make the hair pulling worse. When CBT is initiated and patients begin to experience a decline in their hair pulling, they will often choose to taper off their medication. They frequently report that medication has no effect, positive or negative.

For children and teens with trichotillomania, an initial comprehensive evaluation is warranted in order to rule out any comorbid conditions that may contribute to the hair pulling. If there is an underlying mood or anxiety disorder, then these patients may indeed represent a subgroup in which hair pulling responds to medication. Intensive CBT of habit reversal training, with parental involvement, is very hard work for the patient, and both motivation and mood stability are crucial in providing an optimal opportunity for CBT to be effective. If the trichotillomania is severe and there is no significant response to CBT, then medication may be indicated to strengthen the patient's ability to apply CBT.

The first line of treatment, however, should be comprehensive, CBT, habit-reversal treatment, not medication, in order

to work toward extinguishing the pulling behavior. Medication should be used cautiously, and if there are no signs of improvement or a worsening of symptoms, consideration should be given to the discontinuation of medication and strengthening of CBT.

Trichotillomania causes tremendous pain for those who sufferer from the disorder as well as their families. Certainly, more research in this area is needed given the complexity, comorbidity, and range in severity of the disorder. A multimodal approach should be emphasized.

Reference

1. Chamberlain SR, Menzies L, Sahakian BJ, Fineberg NA: Lifting the veil on trichotillomania. Am J Psychiatry 2007; 164:568–574

KATHLEEN TRAINOR, Psy.D.
Boston, Mass.

The author reports no competing interests.

This letter (doi: 10.1176/appi.ajp.2007.07040664) was accepted for publication in June 2007.

Samuel R. Chamberlain and Isobel Heyman Reply

TO THE EDITOR: We thank Dr. Trainor for her thoughtful letter regarding the treatment of trichotillomania in children and adolescents. Dr. Trainor suggests that CBT incorporating habit-reversal therapy rather than medication should be used as a first-line treatment for young people.

To our knowledge, there have been no controlled treatment trials (psychological or pharmacological) in childhood or adolescent trichotillomania (1). Our review of available treatment trials in adults with trichotillomania revealed a superiority of CBT relative to waiting-list comparison or pill-placebo. However, treatment studies were typically conducted in academic research settings not representative of most outpatient clinics and did not control for nonspecific therapeutic factors such as time spent with the practitioner. Pharmacological studies we identified were few, with small sample sizes and limited power to detect treatment effects. There was some evidence to support treatment with the serotonin reuptake inhibitors (SRIs) clomipramine or citalopram. As noted in our review, it is difficult to generate treatment algorithms on the basis of such a limited evidence base.

We concur with Dr. Trainor regarding the need for careful screening. Comorbid depression in trichotillomania is likely to interfere with habit reversal, since it requires substantial patient motivation. Consideration of pharmacotherapy in the presence of comorbid depression in young people requires caution. In children with depression, SSRIs have been linked to increased suicidality and suicidal thoughts. There is ongoing debate regarding the risk/benefit ratio in this group, with some studies suggesting an unfavorable balance and others suggesting that these drugs should retain a treatment role (2, 3). SSRIs appear to be effective and well-tolerated in the treatment of childhood obsessive-compulsive disorder (OCD), and several (sertraline and fluvoxamine [4, 5]) are licensed for this purpose in the United Kingdom.

In addition to efficacy and safety, patient preference, treatment availability, and the deleterious consequences of *not* intervening in a timely fashion need to be taken into consideration (6). For adults with trichotillomania, pharmacotherapy may be preferred over CBT incorporating habit reversal. SRIs are widely available and are relatively inexpensive to administer, while tailored CBT (especially incorporating habit reversal) is not widely available. In adults, concurrent OCD or depression would further favor intervention with an SRI (e.g., clomipramine or citalopram) (7). For children and adolescents with trichotillomania, greater caution over the use of pharmacotherapy is required. SRI treatment in youth should be carried out in close consultation with the patient and his or her parents or guardians, with regular monitoring and screening for suicidal ideas or behaviors.

Dr. Trainor raises important diagnostic issues, since many patients do not endorse the strict DSM-IV criteria related to growing tension before hair pulling and subsequent relief. Rather, hair pulling is often undertaken during relaxation or in a habitual and dissociative fashion. A broader conceptualization of trichotillomania, recognizing the role of affect dysregulation, behavioral addiction/compulsivity, and impaired top-down cognitive control has been suggested (8). Such a conceptualization may inform amendment of the diagnostic criteria for trichotillomania in any forthcoming classificatory revision.

References

1. Woods DW, Flessner C, Franklin ME, Wetterneck CT, Walther MR, Anderson ER, Cardona D: Understanding and treating trichotillomania: what we know and what we don't know. Psychiatr Clin North Am 2006; 29:487–501
2. Medicines and Healthcare Products Regulatory Agency (MHRA) UK: Selective Serotonin Reuptake Inhibitors (SSRIs): Overview of Regulatory Status and CSM Advice Relating to Major Depressive Disorder (MDD) in Children and Adolescents Including a Summary of Available Safety and Efficacy Data. London, MHRA, 2005
3. Rogers RD, Tunbridge EM, Bhagwagar Z, Drevets WC, Sahakian BJ, Carter CS: Tryptophan depletion alters the decision-making of healthy volunteers through altered processing of reward cues. Neuropsychopharmacology 2003; 28:153–162
4. Cook EH, Wagner KD, March JS, Biederman J, Landau P, Wolkow R, Messig M: Long-term sertraline treatment of children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry 2001; 40:1175–1181
5. Riddle MA, Reeve EA, Yaryura-Tobias JA, Yang HM, Claghorn JL, Gaffney G, Greist JH, Holland D, McConville BJ, Pigott T, Walkup JT: Fluvoxamine for children and adolescents with obsessive-compulsive disorder: a randomized, controlled, multicenter trial. J Am Acad Child Adolesc Psychiatry 2001; 40:222–229
6. National Institute for Health and Clinical Excellence (NICE): Obsessive-Compulsive Disorder: Core Interventions in the Treatment of Obsessive-Compulsive Disorder and Body Dysmorphic Disorder. London, NICE, 2005
7. Fineberg NA, Gale TM: Evidence-based pharmacotherapy of obsessive compulsive disorder. Int J Neuropsychopharmacol 2005; 8:107–129
8. Stein DJ, Chamberlain SR, Fineberg N: An A-B-C model of habit disorders: hair-pulling, skin-picking, and other stereotypic conditions. CNS Spectr 2006; 11:824–827

SAMUEL R. CHAMBERLAIN, M.A.
Cambridge, United Kingdom
ISOBEL HEYMAN, M.D.
London, United Kingdom