far from unanimous, and the issue of psychological factors as the single cause for these syndromes has not been settled, as asserted by Dr. Berger.

Perhaps the need to simplify these complex and multifactorial conditions stems from a dualistic world view in which the biomedical and psychosocial models of illness are separate. However, a broader perspective would acknowledge the interdependence of mind and body and offer empirical explanations for chronic fatigue syndrome and related conditions. A psychodynamic perspective may provide interesting and potentially credible explanations; unfortunately, little empirical work has been done to move these explanations from the level of opinion to the level of data or evidence-based medicine. Alternately, understanding the heritability (i.e., genetic and environmental influences) of a trait or condition—be it breast cancer, major depression, personality, or pain and fatigue—can have practical implications for the early detection of cases, risk assessment, and delivery of preventative interventions.

Finally, Dr. Berger takes issue with our description of patient advocacy and self-help groups. It is undeniable that patient support groups play an important role in providing information as well as offering support to patients and family members. The aim of most support groups is eventual recovery and not supporting the "sick victim" role, yet support is not always unbiased. This may be especially true in the case of chronic fatigue syndrome, where groups have generally formed against the backdrop of a historically negative patient-doctor relationship. Indeed, it is an artful and well-informed physician who can work with the patient as an active member of the treatment team, teach patients about evidence-based medicine, and provide empowering explanations about the symptoms and illness (4). In sum, advances in the treatment and management of chronic fatigue syndrome must be based on careful and interdisciplinary research as well as providers and patients working together as a team.

References

1. Wessely S: Chronic fatigue syndrome: summary of a report of a joint committee of the Royal Colleges of Physicians, Psychiatrists and General Practitioners. J R Coll Physicians Lond 1996; 30:497–504
2. Wessely S, Nimnuan C, Sharpe M: Functional somatic syndromes: one or many? Lancet 1999; 354:936–939
3. Clauw DJ, Crofford LJ: Chronic widespread pain and fibromyalgia: what we know, and what we need to know. Best Pract Res Clin Rheumatol 2003; 17:685–701
4. Salmon P, Peters S, Stanley I: Patients' perceptions of medical explanations for somatization disorders: qualitative analysis. BMJ 1999; 318:372–376

NILOOFAR AFARI, PH.D.
DEDRA BUCHWALD, M.D.
Seattle, Wash.

Genetic Linkage for Schizophrenia?

TO THE EDITOR: I would like to comment on the article by Stephen J. Glatt, Ph.D., et al. (1), which used meta-analysis in an attempt to demonstrate a genetic linkage for schizophrenia on the catechol *O*-methyltransferase (COMT) gene. I find this trend of using meta-analysis to resurrect largely negative genetic linkage studies disturbing. It appears to be nothing more than a manipulation of data to obtain a desired result.

Of the 18 studies looked at in this meta-analysis, only four originally had positive linkage results. Two of these showed a positive linkage between schizophrenia and the Met allele of the COMT gene, while the other two showed a positive linkage to the Val allele. These are contradictory results. Common sense should dictate that these contradictory positive studies might be nothing more than random false positives. Surprisingly, Dr. Glatt and colleagues never even considered this possibility.

Instead, they parsed the data in an effort to find positive results by first dividing the studies into those that used a case-control method versus those that were family based, then they further divided the family-based studies by the ethnicity of the subjects. When looking at study data after the fact, one can always find subgroups that give the appearance of a positive result. It is hard to imagine a reason that one would expect opposite results for case-controlled studies versus family-based studies. Moreover, the authors' suggestion that the Val allele confers some risk factor for schizophrenia in those of European descent but not in those of Asian descent has no scientific basis whatsoever and, in my opinion, enters the realm of eugenics.

I understand that the search for genetic linkages to schizophrenia has been frustrating. As Dr. Glatt et al. pointed out, "Genetic linkage studies have failed to endorse schizophrenia linkage universally with any chromosomal region" (p. 469). The same could be said for genetic linkage studies of any mental disorder. I suggest that it is the genetic linkage studies themselves that are the problem, by giving frequent false positive results without successfully identifying any genetic linkages to date. Meta-analyses of false positive results will not garner any more merit for the original studies.

Reference

1. Glatt SJ, Faraone SV, Tsuang MT: Association between a functional catechol *O*-methyltransferase gene polymorphism and schizophrenia: meta-analysis of case-control and family-based studies. Am J Psychiatry 2003; 160:469–476

STEPHEN J. PITTELLI, M.D.
Atascadero, Calif.

TO THE EDITOR: We read with interest the meta-analysis of the association between the COMT gene Val158/Met108 polymorphism and schizophrenia. Dr. Glatt et al. concluded that the Val allele of this COMT polymorphism may increase susceptibility to schizophrenia. This association was perhaps more evident in the European sample than in the Asian sample; the patients' ancestry thus contributed to the considerable variance in the results of the studies. We would like to suggest that there are at least two other factors contributing to the variance of the results of such studies: patients' gender and the severity of their illness.

The effects of the COMT gene disruption in mice show clear sexual dimorphism (1). The two family-based studies (one European, one Asian) providing the most persuasive support for the Val association with schizophrenia (2, 3) used preponderantly male subjects. However, a large Asian case-control study providing support for the association of schizophrenia with the Met allele contained only 43% men (4). More recently, a large case-control study demonstrated a significant association of the Val allele with schizophrenia in men