Testosterone Replacement Therapy for Anxiety

TO THE EDITOR: We report the case of a patient with previously undiagnosed hypogonadism whose anxiety symptoms improved after he received testosterone injections.

Mr. A, a 34-year-old man, was diagnosed with generalized anxiety disorder. His symptoms included mental exhaustion, irritability, insomnia, poor concentration, and decreased libido. He unsuccessfully tried relaxation techniques and biofeedback before beginning treatment with buspirone, 30 mg/day. After noticing improvement, he discontinued the medication after 2 months but resumed taking it 6 months later, when his anxiety returned.

A review of his medical record indicated that Mr. A had undergone a right orchiectomy several years earlier for an undescended testicle. Blood samples were taken for laboratory analysis. His testosterone level was 185 ng/dl (normal=241–827), and his free testosterone level was 8.9 pg/ml (normal=18–39). His luteinizing hormone level was 18.7 mIU/ml (normal=2–12), and his level of follicle-stimulating hormone was 31.4 mIU/ml (normal=1–8). The results of a physical examination and laboratory tests were within normal limits. Mr. A tapered his buspirone treatment and elected not to begin treatment with paroxetine.

Mr. A was referred to an endocrinologist, who ruled out occult malignancy and prescribed testosterone enanthate, 200 mg i.m. every 2 weeks. He reported resolution of his anxiety symptoms after 1 month. His concentration and libido increased, and he reported better orgasms. He tried to decrease the frequency of his injections but remained on the bimonthly schedule after feeling his anxiety symptoms returning. He has been on the regimen for more than 18 months and has experienced no side effects. This treatment plan may be continued indefinitely.

Contraindications to androgen replacement therapy include androgen-dependent cancers, such as prostate and male breast cancer, and benign prostatic hypertrophy when obstructive symptoms are present (1). A patient's hematocrit and low-density/high-density lipoprotein ratio should be monitored, since testosterone can elevate these as well (1).

The literature supports a connection between hypogonadism and depression, as evidenced by untreated hypogonadal men scoring significantly higher in ratings of depression, anger, fatigue, and confusion than infertile and normal comparison men (2) and by the improvement of depressive symptoms after the administration of testosterone to hypogonadal men with depression refractory to selective serotonin reuptake inhibitors (3). Another study (4) has shown that testosterone replacement therapy decreases anger, nervousness, and irritability in hypogonadal men. The temporal connection between the improvement of Mr. A's anxiety symptoms and replacement testosterone suggests an association between anxiety and hypogonadism. With this case report, we suggest including anxiety in the list of psychiatric manifestations of hypogonadism that improve with testosterone replacement therapy.

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Amnesia After Carbon Monoxide Poisoning

TO THE EDITOR: Bilateral hippocampal lesions are commonly taught as a model for amnestic syndrome. To be confronted with an acute case of this condition was a profoundly moving clinical experience (1).

Mr. A, a 22-year-old man, was seen after a suicide attempt. A breakup with a girlfriend led to depression. He routed the exhaust from his vehicle into the passenger compartment. After he was discovered, he was sent for emergency hyperbaric oxygen treatment and then transferred to the medical ward.

I was initially relieved to observe Mr. A's pleasant affect. He returned my greeting readily and cooperated fully. He was able to relate his history through age 18, with salient facts verified by family members. But then his story stopped completely. He had no memory of any events after his 18th year. During formal testing, he was able to repeat words accurately but could not recall any new material once his attention was diverted to other tasks. He had no knowledge of his current surroundings and no memory of his lost relationship, his recent depression, or his suicide attempt. When I asked him about any current suicidal intent, he smilingly denied such thoughts and asked why I would need to ask such a question. Mr. A was locked in the present. He could not learn new facts about his environment or himself.

This unfortunate young man was suffering from anterograde and retrograde amnesia. It was notable that the balance of his examination was normal, including his euthymic affect. Magnetic resonance imaging revealed bilateral hippocampal infarcts. Other than his profound memory deficits, the results of his mental status examination were normal.

When I returned the next day, Mr. A again greeted me pleasantly and did not appear depressed, nor did he remember me. During formal testing, his deficits were found to be unchanged. It was striking to me how Mr. A did not appear depressed, despite evidence that he had been significantly depressed before his suicide attempt. Barring an unanticipated recovery, I suspected he would feel himself forever to be 18.

His family members, initially relieved by his having survived, were devastated by the explanation of amnesia and his poor prognosis. They understood the need for a transfer to a rehabilitation facility after discharge.

One may speculate about the existence of a neural circuit that involves the hippocampus and controls mood; perhaps infarction interrupted the neural pathway of Mr. A's depressed

mood. Or perhaps his 4 years of retrograde amnesia swept away his memory of the lost relationship that had driven his suicide attempt. This man's case is a tragic example of the survival of the body but a completed suicide of the mind.

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The Dopamine D_4 Receptor Gene and Novelty Seeking

TO THE EDITOR: Jesper Ekelund, M.D., and colleagues (1) recently reported an association between the dopamine D_4 receptor 48-base-pair-repeat polymorphism (DRD4) and the personality trait of novelty seeking in Finnish subjects. They observed a significant (p=0.007) difference in DRD4 allele frequencies between subjects with high novelty-seeking scores and those with low scores and concluded that "these results confirm the original findings of an association between the DRD4 gene and novelty seeking."

Several caveats should be considered, however, in the interpretation of these data. First, for the purpose of statistical analysis, the authors grouped the DRD4 7-repeat allele with the 8-repeat allele (because of the low frequency of the 8-repeat allele in this population). As we have commented elsewhere (2), this kind of arbitrary grouping reduces the degrees of freedom in the analysis and increases the potential for false positive results. An analysis of these data without the collapsing of these two alleles resulted in a marginally significant result (p=0.012). Moreover, the authors also conducted a "presence or absence" analysis despite the lack of data implicating a codominant mode of action for these alleles but did not correct for the other potential groupings—again inflating the potential for a false positive result.

It is also striking that this study yielded a result that is in opposition to that of the original studies, which showed a relation between DRD4 and novelty seeking. Benjamin et al. (3) and Ebstein et al. (4) found that the DRD4 7-repeat allele was associated with higher levels of novelty seeking. Dr. Ekelund and colleagues reported the reverse; in their cohort, the 7-repeat allele was overrepresented in individuals with low novelty-seeking scores. To explain this discrepancy, the authors proposed that another variant in linkage disequilibrium with the DRD4 48-base-pair-repeat polymorphism influences behavior. It is somewhat surprising, therefore, that these investigators did not genotype any additional DRD4 variants to test this hypothesis.

Although the findings of the article by Dr. Ekelund et al. did not replicate the results of the original reports of Benjamin et al. and Ebstein et al., they were consistent with the results of the only previous study of this subject in Finnish subjects (5). In a study of 138 alcoholic Finns, we also observed an association between the 7-repeat allele and scores for low novelty seeking. At the time, we interpreted these data as a failure to replicate the previous reports of an association of the DRD4 gene and novelty seeking (because the association was in the opposite direction). However, since then another group (6) has also reported an association between the 7-repeat allele and low novelty-seeking scores in substance abusers.

In the study by Dr. Ekelund et al., subjects were selected for extreme novelty seeking (more than one standard deviation from the mean). Because there are considerable data that suggest that substance abusers have higher levels of novelty seeking (5), it is possible that the sample of Dr. Ekelund et al. contained a higher proportion of substance abusers than the general population. If so, the study by Dr. Ekelund et al. may be the third study indicating an association between the 7-repeat allele and levels of low novelty seeking in substance abusers, and two of these associations have been observed in Finns.

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Dr. Ekelund and Colleagues Reply

TO THE EDITOR: Drs. Malhotra and Goldman point out some caveats that should be considered in the interpretation of our data. We appreciate these constructive comments and would like to make some additions to the discussion.

It has been shown that the number of repeats in the DRD4 gene influences clozapine and spiperone binding (1). Therefore, it is was natural to collapse the 8-repeat allele with the allele closest to it in size (i.e., the 7-repeat allele), since these alleles can be assumed to have the most similar binding properties. Drs. Malhotra and Goldman call this an "arbitrary grouping," but we think that the grouping is actually based on prior information about the properties of different alleles of the DRD4 gene.

Drs. Malhotra and Goldman also point out that we conducted a "presence or absence" analysis, despite the lack of data implicating a codominant mode of action for these alleles. As discussed in our article, the strength of our sample was that it was drawn from the population-wide, nonselected epidemiological group of the genetically isolated Finnish

population. Everyone in the original sample was scored for novelty-seeking parameters (2), which enabled us to select extreme scorers for monitoring differences in allele frequencies between high and low scorers, regardless of the mode of action of the alleles. We also performed an additional analysis of the presence or absence of the different alleles. To group the individuals according to all possible genotypes would have required a significantly larger sample.

Given the original findings (Ebstein et al., 1996, and Benjamin et al., 1996), our observed association between novelty seeking and the shorter alleles of DRD4 does replicate the finding of an association, but not to the same allele as in the original reports. Therefore, we proposed that some other polymorphism in linkage disequilibrium with DRD4 might be responsible for the variation in novelty-seeking scores. We agree with Drs. Malhotra and Goldman that it would be interesting and important to study any such polymorphism.

Drs. Malhotra and Goldman interpret our finding as possible support for their finding of an association between the 7-repeat allele and low novelty-seeking scores in Finnish alcoholics. This is on the basis of the assumption that we included a higher proportion of substance abusers in our study group because of our sampling strategy. As we discussed in our article, it is certainly possible that we included in the sample a high proportion of subjects with any given behavioral trait to which extreme novelty seeking might contribute either as a constituent or a risk factor (e.g., some personality disorders and substance abuse). Therefore, the studied polymorphism might be primarily associated with any such trait and only secondarily with novelty seeking. However, since the study sample was collected from the normal population, we are reluctant to draw any conclusion regarding the results concerning alcoholism or any other specific trait. Only further studies of both normal populations and individuals with different personality disorders can reveal the influence of different DRD4 alleles on behavior.

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Patients Requesting Psychiatric Hospitalization

TO THE EDITOR: The study by William Gardner, Ph.D., et al. of changes in patients' beliefs regarding their need for psychiatric hospitalization (1) provided interesting data on an understudied subject. The authors studied voluntary and involuntary psychiatric admissions in Virginia and Pennsylvania. The authors noted that for a patient to be committed, both states require individuals to be mentally ill and either dangerous to themselves or to others or unable to care for themselves. I am puzzled, however, by the authors' statement that "Virginia permits commitment of individuals who are mentally ill if they are at risk of substantial deterioration" (p. 1386). I cannot find any such language in the statutes governing involuntary psychiatric hospitalization of adults in Virginia, nor could our hospital's general counsel (Jean Reed, personal communication, Oct. 19, 1999). The closest language I could find is in the law pertaining to psychiatric admission by a parent of an objecting minor over the age of 14. Here the law allows admission either for danger to self or others or if the minor "is experiencing a serious deterioration of his ability to care for himself in a developmentally age-appropriate manner, as evidenced by delusionary thinking or by a significant impairment of functioning in hydration, nutrition, self-protection, or self-control" (Virginia Code §161.339). This only applies to minors over age 14 and does not seem substantially different from the adult criterion of "unable to care for themselves." Can Dr. Gardner and colleagues clarify this point and provide a citation for their statement?

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Dr. Gardner Replies

TO THE EDITOR: The statement in our article is wrong. The relevant statute (Virginia Code §37.1-67.3) says that someone who is "substantially unable to care for himself" (as the sentence in our article, p. 1386, mentions) can be committed. The statute does not mention "risk of substantial deterioration." We regret the error and thank Dr. Levenson for bringing it to our attention.

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Some Ado About a Polymorphism

TO THE EDITOR: An article by Francesco Benedetti, M.D., et al. (1) reported mood improvement through total sleep deprivation in depressed carriers of the long/long genotype at the serotonin-transporter-linked polymorphic region. Although the authors hypothesized enhancement of serotonergic (5-HT) transmission by total sleep deprivation (1), no direct evidence was provided of a relationship between different genotypes at the 5-HT-transporter-linked polymorphic region and differential 5-HT transporter activity during depression.

We suggest that these results can be connected to a dysfunction of the 5-HT transporter that may be specific to the homozygote carriers of the long variant of the genotype when they become depressed, whereas heterozygotes and short/short homozygotes may have only marginally altered, or normal, 5-HT transporter function during depression. We (2) have reported a group effect, almost entirely sustained by long/long homozygotes, of significantly lower platelet 5-HT uptake (V_{max}) in depressed drug-naive children and adolescents than in their nondepressed peers. Depressed heterozygote and short/short homozygote children had V_{max} rates similar to those of their healthy homologues. None of several

previous studies of altered V_{max} in depression had controlled for the possible effect of 5-HT transporter polymorphisms.

Thus, although 5-HT transporter function differs among individuals in the population in a fashion that can be predicted on the basis of their 5-HT-transporter-linked polymorphic region genotype (2, 3), appreciable intra-individual variation in the course of a depressive episode may be limited to the subgroup of individuals with long/long homozygotes. Since the latter constitute about 30% of the population, their presence among depressed individuals may explain a sizable proportion of the group effect in the V_{max} rate that was found in several studies. The appreciable differences in the effectiveness of selective serotonin reuptake inhibitors in depressed patients according to their genetic setup at the 5-HT-transporter-linked polymorphic region (cited in reference 1) closely parallel our own findings with the three subgroups of the 5-HT-transporter-linked polymorphic region (2). As far as the extent to which total sleep deprivation exerts its action through activation of serotonergic transmission, we suggest that the data by Dr. Benedetti et al. (1) offer a further hint for considering differences at the 5-HT-transporter-linked polymorphic region as a tool for discriminating among individuals with potentially different degrees of 5-HT transporter dysfunction during depressive episodes.

These findings taken together encourage studies of the epigenetic and epistatic factors that may affect 5-HT uptake specifically in patients with long/long homozygotes when they become depressed, follow-up studies of 5-HT transporter function in euthymia, and careful consideration of differences at the 5-HT-transporter-linked polymorphic region when groups of depressed patients are compared to unaffected subjects in clinical studies.

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Dr. Benedetti and Colleagues Reply

TO THE EDITOR: We thank Dr. Nobile and her colleagues for commenting on our data and raising issues for further research. The possibility that a different pattern of 5-HT activity may condition different responses to both pharmacological and chronobiological antidepressant treatments links with current research on 5-HT and the regulation of circadian rhythmicity (1) and on the dimension of cyclicity in mood disorders. Given the heterogeneity of mood disorders, the possibility of defining a kind of "serotonergic depression" (i.e., due to some kind of serotonergic malfunction and thus responding to serotonergic treatment) is of theoretical and clinical relevance.

A caveat is necessary, however. Given the interplay between neurotransmitter systems, clinical response to a treatment acting on one system does not imply a dysfunction of that system. In these respects, the data cited by Dr. Nobile et al. in depressed adolescents are the only findings available to support a 5-HT dysfunction in patients homozygotic for the long/long variant of the promoter of the 5-HT transporter. This new research area is still highly controversial; seasonal fluctuations in 5-HT blood levels have been described in subjects with the long/long variant (2), whereas seasonal affective disorder has shown a higher prevalence in subjects homozygotic for the short/short variant (3). A study of delusional depression showed different responses depending on genotype when patients were treated with fluvoxamine alone but not when fluvoxamine was combined with pindolol (4). These data support a role for self-inhibitory autoreceptors (and not only for the carrier) in determining response differences among genotypes and show that patients with the short/short variant can actually respond to combined therapies acting on 5-HT pathways. Finally, the short allele has been associated with higher anxiety levels in normal subjects and depressed patients (5), and anxious depression is known to show a less favorable response to treatment than melancholic depression. This suggests the presence of complex relationships among the 5-HT carrier genotype, treatment response, and psychopathology that are not limited to patients with the long/long genotype.

Notwithstanding the pioneering importance of every study in the field, additional research seems necessary before we can draw firm conclusions about the relationship between the 5-HT-transporter promoter genotype and the characteristics of mood disorders.

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New DSM-IV Diagnosis of Acute Stress Disorder

TO THE EDITOR: In their recent article, Randall D. Marshall, M.D., et al. (1) raised important considerations regarding the diagnosis of acute stress disorder. This was a much-needed analysis; however, I have reached different conclusions with respect to the importance of including dissociative symptoms in the acute stress disorder diagnosis. Dr. Marshall et al. interpreted their inconsistent findings regarding the ability of peritraumatic dissociative symptoms to predict later posttraumatic stress disorder (PTSD) to indicate that dissociative symptoms should not be required in the diagnosis of acute stress reactions to a traumatic life event. I have two major concerns with this argument, although there may be a common ground, suggested by the analysis by Dr. Marshall et al., on which to resolve this debate.

First, dissociative symptoms do seem to be of clinical relevance in the immediate as well as long-term aftermath of traumatic life events. For example, individuals exposed to a firestorm who reported more dissociative symptoms, compared to those who reported fewer dissociative symptoms, were significantly less likely to engage in active coping strategies in response to the fire (2), were more likely to engage in dangerous coping strategies such as crossing police barricades to get closer to the fire (under conditions of high traumatic exposure) (2), and were more likely to experience major illness or injury and other stressful life events in the next 7–10 months (3).

Second, if there is a form of PTSD in which dissociative symptoms play a major role, and this is not recognized in the PTSD diagnostic criteria, then this weakens the relationship that researchers find between acute dissociative symptoms and subsequent PTSD. Given the dilemmas inherent in determining the acute stress disorder diagnosis on the basis of its empirical links to a controversial PTSD diagnosis, it is important to develop stronger conceptual models of acute stress disorder and PTSD on the basis of empirical data to determine the diagnostic criteria. My colleagues and I have described a diathesis-stress model (4) grounded in considerable empirical research in which dissociative symptoms play a major role in immediate and long-term stress responses to traumatic life events.

The evidence thus far is consistent with the possibility suggested by Dr. Marshall et al. that alternative pathways of symptoms may most accurately characterize traumatic stress responses in the immediate aftermath of trauma, perhaps differing in whether dissociative symptoms are a core feature. We should also consider the possibility that the diagnosis of PTSD may need to be similarly redefined as well.

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TO THE EDITOR: We read with interest the timely article by Dr. Marshall et al. on the newly proposed diagnosis of acute stress disorder and were dismayed by the conclusion that dissociation should be eliminated as a core symptom of acute stress disorder. The usefulness of acute dissociation in predicting PTSD is a complex topic containing several possible roles for dissociation: as a sole predictor, as the most important predictor, as a valuable additional predictor that adds prognostic information, or as an associated feature of limited specific value. Prediction in itself is complicated and encompasses sensitivity, specificity, and positive and negative predictive values. Reports on the topic typically address only aspects of these questions, and the authors do not systematically flush these out, as if set on disproving the importance of many positive findings regarding dissociation.

A good number of well-designed studies, reviewed in this article and others (1), have shown that acute dissociation predicts not only a higher likelihood of PTSD but also greater severity and chronicity. A recent study (2) teased out the contribution of the various acute stress disorder symptoms and clusters to the prediction of developing PTSD. The four clusters (dissociation, reexperiencing, avoidance, and arousal) are comparable in accuracy in predicting PTSD; avoidance leads to the most accurate classification, followed by dissociation. The study concluded that there may be two independent factors increasing the risk of PTSD: one captured by high levels of reexperiencing and arousal and one captured by the acute stress disorder diagnosis itself.

Furthermore, how well it predicts PTSD should not be the sole criterion for keeping dissociation in the acute stress disorder diagnosis. We need to know how the "pathological" acute response to trauma looks, irrespective of what it predicts. If the acute response to trauma has more dissociative features than the later response, that is interesting and needs to be understood. Many PTSD studies unfortunately continue not to measure dissociation, so the temporal evolution of dissociative symptoms is poorly known. In addition, acute dissociation may predict other future psychopathology—dissociative (3) and general. This subject also needs more study.

In conclusion, the reduction of dissociation to an associated feature of acute traumatic reactions is premature and possibly erroneous. The number of required dissociative symptoms in acute stress disorder could be decreased if the current criterion is too stringent. Better still, a diagnostic

broadening that more realistically captures the richness and diversity of trauma-related syndromes (4) should be considered. One possibility is two subtypes of acute and chronic stress disorders: with or without prominent dissociation, or predominantly dissociative versus predominantly PTSD-like (1). PTSD as currently defined is not all that happens after exposure to trauma.

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TO THE EDITOR: I applaud Dr. Marshall et al. for their analysis of the validity and utility of the acute stress disorder symptom criteria and diagnosis; however, I do not draw the same conclusions from the findings reported to date. The fact that acute stress disorder falls short in predicting PTSD does not necessarily undermine its validity; many trauma victims show natural recovery over time (1), and some sufferers experience a delayed onset of symptoms. Moreover, the difficulty in differentiating normative and pathological posttraumatic reactions in the immediate aftermath of an event highlights the failure to identify the elements of the process that underlie the pathology, elements that apparently are not fully captured by the symptoms of either acute stress disorder or PTSD. In addition, findings regarding the predictive power of a variety of peritraumatic reactions (2), including dissociation, and reports of the ubiquity of dissociative symptoms in posttraumatic conditions (Butler et al., 1996) indicate that broadening our conceptions, rather than limiting them, may be most useful. Indeed, subtyping reactions (into, for example, types that principally involve dissociative versus hyperarousal or anxiety symptoms) may have utility. Individual differences, event characteristics, and features of the recovery environment (3) may also differentiate symptom profiles and courses. For example, individual differences in the facility or propensity to dissociate may represent a diathesis for the development of longer-term dissociative conditions, including PTSD, under conditions of extreme stress (Butler et al., 1996). The authors' assertion that the two diagnoses cleave essentially continuous clinical phenomena actually begs the question.

Consequently, I believe that the findings suggest that the time has come for an extensive empirical investigation into the constituents of peritraumatic, acute, and longer-term posttraumatic reactions, including predictors of chronicity. By thoroughly documenting the elements of these reactions—without the Procrustean constraints of the current acute stress disorder and PTSD diagnoses—we will be able to construct empirically defensible diagnoses that truly fit the clinical phenomena.

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TO THE EDITOR: In criticizing the acute stress disorder diagnosis, Dr. Marshall et al. justifiably echoed previously expressed concerns (1). We question the evidence on which some of their conclusions are based. The retrospective studies of acute trauma reactions that they cite are flawed because mood-related memory bias renders questionable the accuracy of retrospective reports. Moreover, only one of the three prospective studies referred to employed a validated diagnostic measure of acute stress disorder (2). The authors did not cite four key prospective studies that found that between 78% and 83% of individuals with acute stress disorder subsequently developed PTSD (3–5; Brewin et al., 1999). The evidence indicates that the acute stress disorder diagnosis can identify a significant proportion of acutely traumatized individuals who develop PTSD. This is a useful development because early intervention with those diagnosed as having acute stress disorder can prevent the development of PTSD (6).

We agree that the current emphasis placed on acute dissociative responses is flawed. Recent studies (although not cited by Dr. Marshall et al.) have demonstrated that there are multiple pathways to PTSD and that most trauma survivors who display severe acute stress reactions without dissociation can develop PTSD (3, 4). The assertion by Dr. Marshall et al. that the diagnosis of PTSD should apply immediately after a trauma is problematic because it potentially "pathologizes" transient stress reactions. Discarding the acute stress disorder diagnosis now may also be an overreaction that "throws the baby out with the bath water." Although the available evidence does not support the current criteria for acute stress disorder, prospective studies are beginning to identify constellations of acute symptoms that can predict PTSD with greater accuracy. Rather than prematurely deciding the worth of the acute stress disorder diagnosis at this time, it is important to conduct prospective studies that employ standardized measures that will define the optimal criteria for acute stress disorder and determine whether it deserves to survive in DSM-V.

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TO THE EDITOR: The introduction of acute stress disorder into DSM-IV has already spawned much useful research about a disorder that can be both hidden and overlooked, providing promise for earlier identification and more effective intervention. We therefore agree with Dr. Marshall et al. that there is a need for a diagnostic entity that defines acute reactions to traumatic stressors as something more than an adjustment disorder. That indeed was the motivation for our recommendation to the DSM-IV task force that acute stress disorder be included in the nosology. However, we disagree with the authors' interpretation of the literature and recommendations for the following reasons.

First, it appears that the pattern of symptoms is different in the acute versus chronic phase of trauma response and that dissociation features more prominently early on (1–5; Harvey and Bryant, 1998). The authors confounded evidence used for the construct (predictive) validity of dissociative symptoms in acute stress disorder with their importance as symptoms per se. Dissociative symptoms are not included in acute stress disorder simply as risk factors for the development of PTSD; also, it would not make sense to include other risk factors, such as neuroticism or history of prior trauma or psychiatric illness.

Second, the authors suggested that dissociative symptoms be "an associated, but not required, feature of acute PTSD" (p. 1683). Yet their argument that dissociative symptoms are a less than perfect predictor of PTSD and therefore should be dropped from acute stress disorder is tautological. Dissociative symptoms are only a minor component of the current DSM-IV PTSD criteria, as are amnesia and numbness. It is axiomatic that predictive power is greatest when one is assessing the same symptom at baseline and follow-up. Thus, it is remarkable that dissociation in the acute phase predicts later PTSD as well as it does (Brewin et al., 1999). If anything, the problem may be that PTSD needs redefinition. In fact, some studies have shown that dissociative symptoms (1, 4, 6) and acute stress disorder (Brewin et al., 1999) are better predictors of long-term PTSD than are acute intrusion and hyperarousal symptoms themselves.

Third, Dr. Marshall et al. are troubled by the overlap between normal aspects of human experience and dissociative psychopathology but are unconcerned that a low symptom threshold for acute stress disorder could "pathologize" normal reactions.

Fourth, the authors concluded that "dissociation is not a core feature of acute PTSD" (p. 1681). However, the review on which this conclusion is based is incomplete. For instance, one of the studies the authors highlighted (7) is a retrospective study that purported to investigate the consequences of acute stress disorder and yet had no systematic evaluation of acute stress disorder. The authors failed to cite a recent prospective study that found clear and strong predictive power for dissociation: "The criteria of three or more dissociative symptoms and one or more avoidance symptoms specified in DSM-IV produce a realistic balance of sensitivity, specificity, and positive and negative predictive power" (Brewin et al., 1999, p. 364).

There is an arbitrariness in any diagnostic scheme, and acute stress disorder is no exception. The differences between the criteria for acute stress disorder and PTSD should be addressed through further research, but the current evidence supports the utility of acute stress disorder and suggests that the criteria for PTSD, as well as acute stress disorder, should include dissociation.

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Dr. Marshall and Colleagues Reply

TO THE EDITOR: Since our overall conclusion was that the DSM-IV approach to posttraumatic syndromes should be reevaluated in its entirety (in agreement with most authors), we welcome the opportunity of constructive dialogue; it is unfortunate that there is not space for a more detailed response. A number of disorders have been extensively revised or eliminated throughout the evolution of DSM. We proposed eliminating the new diagnosis of acute stress disorder on the basis of a review of all studies available at the time of writing that suggested it makes little conceptual or clinical sense to regard the first month of a posttraumatic syndrome as a separate dis-

order. Instead, a single posttraumatic stress syndrome could be created with acute and chronic designations, incorporating dissociative symptoms in a way that recognizes but does not require their presence to make a diagnosis. Our empirical reviews clearly demonstrated that the acute stress disorder diagnosis fails to recognize a significant proportion of patients with symptoms and disability in the first month after trauma who do not have dissociative symptoms and therefore does not accomplish its original intention.

All five of the preceding letters came from authors who have a particular interest in dissociative phenomenology and who have made important contributions in this area of research. Most emphasize the role of dissociative symptoms as a predictor of clinical severity and longitudinal course. Since these findings are well established and were cited in our article, we find no point of disagreement. Unfortunately, none addresses our primary argument, which was that predictor status is not sufficient to identify a core feature of a syndrome. Once examined empirically, our review showed that dissociative symptoms have high specificity but unacceptably low sensitivity to function as a core feature. In addition, most of the letters' authors confound the study of acute predictors of chronicity with the necessity of having two separate diagnoses.

The more recent studies cited by several authors support our primary conclusions. For example, the recent study of Brewin et al. (1999) was cited as a refutation of our proposal. In fact, a careful reading of this excellent article supports our interpretation of the literature: when dissociative symptoms were required diagnostically, sensitivity was lowered while specificity was increased. Brewin et al. also concluded that they had "failed to find a unique role for dissociative symptoms." The fact that this complex study was presented as unequivocal suggests that much discussion is needed for the field to reach agreement on the interpretation of empirical findings in this area.

Dr. Spiegel and colleagues apparently misunderstood several aspects of our review. We will respond to each point separately.

1. We agree that peritraumatic dissociative symptoms often differ from the dissociation observed in chronic PTSD. This is why we called attention to the ICD-10 nosology, which distinguishes between these kinds of symptoms by recognizing an acute stress reaction as well as a posttraumatic stress syndrome.

2. After acknowledging the limitations of predictor analyses for syndrome identification in their first point, Dr. Spiegel and colleagues then cite predictor analyses as a major justification for acute stress disorder. Our article never argued that dissociative symptoms should be dropped from the diagnosis of acute stress disorder because of their limitations as predictors. Rather, we called attention to the subgroup of individuals who do not experience dissociative symptoms. The point that using the same symptom assessment methodology would increase predictive power is certainly true but has no bearing on any of our lines of reasoning, as noted previously.

3. Even a casual reader of our article would have probably taken note of our several discussions of the issue of stigmatization, which was designated specifically as one of three major points of contention in trauma research (p. 1678). We also refer the reader to our discussions on pp. 1679, 1682, and 1683 because this is too important and complex an issue to recapitulate in a limited amount of space.

4. The statement that we "highlight" the retrospective studies is simply wrong (a point also made in other letters). Prospective studies were the primary basis for our conclusions, and in any case, the prospective and retrospective studies were largely consistent with respect to our several major points.

These letters give the impression of some kind of power struggle over the importance of dissociation. After months of consideration and discussion with others in the field, we believe our recommendation was actually a more balanced, nosologically valid, empirically based perspective. The fact that one trauma diagnosis (acute stress disorder) requires dissociative symptoms, whereas the second (PTSD) does not even recognize them, may be symptomatic of this unfortunate polarization within the field. We appreciate the positive feedback we have received on this central point from clinicians and investigators working with trauma patients.

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