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Replication

TO THE EDITOR: Replication in psychiatric research is rare yet important for solidifying the knowledge base; thus, I would like to point out a replication that has been published in two separate studies in the *Journal*. Unfortunately, the more recently published study by Lawrence B. Inderbitzin, M.D., and colleagues (1) on successful dose reduction of neuroleptics in patients with schizophrenia failed to cite an earlier study that also used a gradual dose decremental procedure (2). Both studies documented expected reductions in extrapyramidal symptoms with dose reduction; in addition, Liberman et al. found modest improvements in psychopathology with dose reduction, perhaps because the patients in that study were more severely symptomatic at baseline.

It is likely that publication latencies prevent investigators from being fully aware of their replications. Perhaps editorial boards should be more alert to such replications that otherwise would be lost in the inevitable overlap that occurs in processing and publishing of manuscripts.

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Drs. Inderbitzin and Lewine Reply

TO THE EDITOR: We are pleased that Dr. Liberman considers the findings of our study of sufficient importance to clarify priority of publication.

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Psychotropic Drug Action

TO THE EDITOR: Steven E. Hyman, M.D., and Eric J. Nestler, M.D., Ph.D. (1), discussed the effects of both therapeutic agents and drugs of abuse within a paradigm of initiation and adaptation. They stated that "Many adaptations can be viewed as compensatory homeostatic responses to return the system toward baseline function . . . . Such negative feedback changes could play an important role in drug addiction . . . . It is less clear how compensatory adaptations to a drug would result in a therapeutic response."

A primary distinction between major therapeutic agents such as the antidepressants, mood stabilizers, or antipsychotics and drugs of abuse is that therapeutic agents do remarkably little to a normal subject's thinking or mood. Their spectacular effects are due to the normalization of pathological states, but antidepressants do not make normal subjects happy and, therefore, cannot be sold on the street. Drugs of abuse, on the other hand, profoundly affect normal mood and activation level and have a ready illicit market. (That is not to say that there may not be abnormalities that predispose an individual toward the use of drugs of abuse and pursuing their use, even after withdrawal has been complete.)

I have presented a cybernetic model of the normalizing effect of the major psychotherapeutic drugs (2). If one understands their benefits as being due to repair of pathology, perhaps through reversing pathological positive feedback loops into stabilizing negative feedback loops, then the various perturbations and adaptations produced in normal animals by these drugs are actually unlikely to be central to their therapeutic effects. Hyman and Nestler stated, "In the case of antidepressants and antipsychotic drugs, the resulting states likely produce therapeutic responses by altering the functional activity of critical neural circuits in the brain." I would emphasize that these "critical circuits" are already pathologically deranged. It may be that only after one has worked out the pathophysiology of the deranged circuitry that the physiological basis for the benefits of psychotherapeutic agents will be understood.

Another major piece of psychiatric knowledge, not alluded to in the article, is the growing consensus that there is a large genetic component in many psychiatric illnesses. This makes a persuasive case for an investment in the selective breeding of genetic animal models of psychopathology.

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Drs. Hyman and Nestler Reply

TO THE EDITOR: Dr. Klein's letter highlights an important point that was not discussed in our article: pharmacotherapeutic agents produce their clinically beneficial effects in an abnormal nervous system. As a result, it is likely, as Dr. Klein states, that a full understanding of the mechanisms of action of these treatments will require a greater appreciation of the pathological derangements involved.

Beyond that, we cannot agree with much of Dr. Klein's let-