

## The Authors Reply

*To the Editors:*

Klein and Ross raise objections to various aspects of the data analysis and conclusions of our article, "Lactate Infusions and Panic Attacks: Do Patients and Controls Respond Differently?" We think their comments are misleading as we shall explain.

They begin by quoting our statement, "Our data did not support the hypothesis that response to lactate is a biological marker of a person's proneness to panic attacks." The statement is straightforward and correct in itself, but it does raise questions as to why we failed to find more differences in lactate reactivity between patients and controls. Was it a Type II error resulting from too small a sample, was our analysis or methodology incorrect, or is reality different from what Klein and Ross and we expected? We cannot answer these questions with certainty, but we suspect that the answer to the last of these questions is yes.

Our sample was small, but was it too small? With respect to power, our sample size of 10 patients and 10 controls seemed reasonable since most of the literature claims differences in reactivity so large as to be almost qualitative. It would be surprising for Klein and Ross to take the position that large sample sizes are needed to obtain statistical significance. In a recent article on which Klein was a coauthor (Gorman et al., 1985), it was concluded "that obsessive-compulsive patients are not sensitive to lactate infusion" (p. 866) after studying seven patients with that disorder. The authors show no embarrassment in claiming an affirmation of the null hypothesis from this small sample.

Whatever the size of the differential lactate effect is, the estimate of 29% power for our study as presented by Klein and Ross is misleading, since it is apparently based on a  $2 \times 2$   $\chi^2$  test, which is much weaker than the repeated-measures analysis of variance (ANOVA) we used. Even a *t* test for independent samples would have a power of

nearly 60% (two-tailed) to detect group differences of one standard deviation for our sample size.

One of the difficulties in estimating a proper sample size is that existing studies are methodologically unsound. First, subgroup analyses like the one used by Liebowitz et al. (1985b) are circular for conclusions about differential reactivity of patients and controls. The patient group is split post hoc into responders and nonresponders, and it is then demonstrated that responders among the patients react stronger or faster than the controls as a whole. It is justified, of course, to create subgroups for purposes such as looking for predictors of responsiveness in which case it is logical to form subgroups among both controls and patients.

Second, it is inappropriate to dichotomize subjects' complex responses simply into panic or not panic. One of the major issues raised by our article is that there is no single objective criterion for panic attacks. Different criteria give widely different percentages. Klein's group admitted in Liebowitz et al. (1984, p. 768) that there is "a lack of objective criteria to define lactate-induced panic attacks." From a scientific point of view, neither the consensus of expert clinicians nor patient reports about panic can be taken at face value. In our study, patients and controls differed systematically in their response styles to questions about somatic symptoms. A demand to stop the infusion is the least useful criterion of panic, since it is determined by a combination of baseline levels, reactivity, response bias, and avoidance behavior. All four of our patients who asked to stop had clinical diagnoses of avoidance and high baseline levels, but average reactivities.

Third, most studies neglect mediating factors such as demand characteristics and expectancies created by instructions (Margraf et al., 1986). The impact of these varia-

bles is obvious from Klein's own data. When nonblind observers rated panic attacks, they found rates of 72% (31 of 43; Liebowitz et al., 1984) or 62.2% (21 of 34; Gorman et al., 1985). When they changed their protocol and blinded the observers, these rates dropped to 36% (5 of 14; Gorman et al., 1985) or 48% (14 of 29; Liebowitz et al., 1985a). Pooling results for the two methods results in a significant difference ( $\chi^2 = 5.30, p < 0.05$ , two-tailed). In our study, we tried to avoid these biases by creating identical experimental conditions for the two groups and selecting controls who were not professional subjects or medical staff.

With regard to specific criticisms of our methods, we used an anxiety scale of a standard type that has been widely applied in psychiatric and psychological research. It is especially suited for frequently repeated assessments needed to monitor closely the time of changes. By criticizing this measure, Klein and Ross seem to imply that panic is not a form of anxiety. Scales based on lists of symptoms would serve as an alternative; however, such scales capitalize on the patients' bias toward overreporting somatic symptoms.

Klein and Ross complain about our statistical procedures. They seem to advocate multiple comparisons, which would inflate Type I errors, or at least they tell us not to begin with tests including all time points. We chose to look at a broader range of questions—the responses to fast and slow saline, reactivity, and recovery—in the initial analyses, and then move down the hierarchy of effects with subanalyses, a standard way to analyze data with ANOVAs. Our data analysis was not overly conservative. We did not use multivariate ANOVAs or post hoc tests more restrictive than *t* tests. Our statistics succeeded in showing many effects: differences between groups, changes over time, and, for blood pressure, interactions between group and time.

Furthermore, our methods of dealing with missing data included an analysis with linear

trend extrapolations for patients stopping the infusion early. The results of this analysis were consistent with our other analyses, although it is biased toward finding greater reactivity in the patients. The *F* ratios of time  $\times$  group interactions for anxiety variables ranged from 0.86 to 1.28. Even with an infinite number of subjects, *F* ratios  $< 1$  would not become significant. Moreover, on two of three anxiety measures, the *controls* had larger increases than patients.

If anything, it could be a greater reactivity of controls that distinguishes our study from others. Anxiety ratings, heart rate, and blood pressure rises in our patients were approximately the same as or larger than those found in other studies (Margraf et al., 1986). Two studies using appropriate methodology gave the same results as ours (Kelly et al., 1971; Freedman et al., 1984). We think that our emphasis on the responses of control subjects is important since recent data indicate that a substantial proportion of the general population has occasional panic attacks, including spontaneous ones (Norton et al., 1985; Wittchen, 1986). Panic attacks do not seem to be an either-or phenomenon characteristic of only a small and circumscribed part of the population.

In summary, we do not think that we have proved the null hypothesis and do not make that claim in our article. We do think, however, that our results have implications as to whether there are differences in response to lactate infusions between panic patients and controls. Our data suggest that differences in reactivity between panic patients as a group and controls, if present, are much smaller than many previous studies have implied and less than we expected. There may be reactivity differences in some systems—we found them in demand to stop the infusion with two-tailed tests. For the reasons we have outlined, our methodology was appropriate and our statistical analysis unbiased. We think our results are probably typical when subjects are not artificially dichotomized into panickers and nonpanickers.

Finally, if Klein and Ross attack our conclusions to defend a biological marker hypothesis, their attack is beside the point. Higher reactivity to internal stimuli triggered by lactate would be consistent with a psychophysiological model of panic attacks that does not assume innate biological differences as a sufficient explanation (Clark, in press; Margraf et al., in press). Conversely, biological differences could give rise to panic attacks by means of a mechanism that is not particularly sensitive to lactate infusions.

## References

- Clark, D. A cognitive model of panic. *Behaviour Research and Therapy* (in press).
- Freedman, R.R., Ianni, P., Ettedgui, E., Pohl, R.B., and Rainey, J.M. Psychophysiological factors in panic disorder. *Psychopathology* (Suppl. 1), **17**, 74 (1984).
- Gorman, J.M., Liebowitz, M.R., Fyer, A.J., Dillon, D., Davies, S.O., Stein, J., and Klein, D.F. Lactate infusion in obsessive-compulsive disorder. *American Journal of Psychiatry*, **142**, 864 (1985).
- Kelly, D., Mitchell-Heggs, N., and Sherman, D. Anxiety and the effects of sodium lactate assessed clinically and physiologically. *British Journal of Psychiatry*, **119**, 129 (1971).
- Liebowitz, M.R., Fyer, A.J., Gorman, J.M., Dillon, D., Davies, S.O., Stein, J.M., Cohen, B.S., and Klein, D.F. Specificity of lactate infusions in social phobia versus panic disorders. *American Journal of Psychiatry*, **142**, 947 (1985a).
- Liebowitz, M.R., Fyer, A.J., Gorman, J.M., Dillon, D., Levy, G., Anderson, S., Levitt, M., Palij, M., Davies, S.O., and Klein, D.F. Lactate provocation of panic attacks: I. Clinical and behavioral findings. *Archives of General Psychiatry*, **41**, 764 (1984).
- Liebowitz, M.R., Gorman, J.M., Fyer, A.J., Levitt, M., Dillon, D., Levy, G., Appleby, I.L., Anderson, S., Palij, M., Davies, S.O., and Klein, D.F. Lactate provocation of panic attacks: II. Biochemical and physiological findings. *Archives of General Psychiatry*, **42**, 709 (1985b).
- Margraf, J., Ehlers, A., and Roth, W.T. Sodium lactate infusions and panic attacks: A review and critique. *Psychosomatic Medicine*, **48**, 23 (1986).
- Margraf, J., Ehlers, A., and Roth, W.T. Biological models of panic attacks: A review. *Behaviour Research and Therapy* (in press).
- Norton, G.R., Harrison, B., Hauch, J., and Rhoads, L. Characteristics of people with infrequent panic attacks. *Journal of Abnormal Psychology*, **94**, 216 (1985).
- Wittchen, H.U. Epidemiology of panic attacks and panic disorders. In: Hand, I., and Wittchen, H.U., eds. *Panic and Phobias*. Springer, Berlin, 1986.
- Anke Ehlers, Ph.D.  
Jürgen Margraf, Ph.D.  
Walton T. Roth, M.D.*
- Department of Psychiatry and  
Behavioral Sciences  
Stanford University School of  
Medicine, and  
Psychiatry (116A3)  
Palo Alto VA Medical Center  
3801 Miranda Ave.  
Palo Alto, CA 94304, USA
- July 28, 1986*