Clearly eq (5) is analytically equivalent to eq (4). When implemented on computers of adequate precision, the relationships used by Shell and our group also lead to numerically equivalent results.

Shell states that the correlation (r) between histologic and enzymatic estimates can be improved from .2 to .5 by adjusting for control enzyme levels (regression between columns 1 and 2 in Shell's letter). Table 10, in fact, demonstrates that the correlation can be improved to .84 (r² = 0.71) by limiting analysis to the small infaracts and adjusting for control enzyme levels. This table was apparently overlooked by Shell.

Also overlooked was the analysis of the influence of estimates from defibrillated animals on the correlation with histologic infarct size. Our approach to such problems involves assessment of correlation with and without that data rather than elimination from the study on the basis of pre-conceptions.

Concerning the suggested methodological difference, it is important to note that even with Shell’s recalculation (column 3 of his letter), one cannot distinguish large from small infarcts.

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References

Digitalis after AMI

To the Editor:

With regard to the article in the May issue entitled “Augmentation of serum CKP activity by digitalis in patients with acute myocardial infarction” by Varonkov et al., I am surprised that the editorial staff has failed to see the serious ethical and moral infractions represented by this study.

One of the major parameters for determining infarct size is accumulated CKP activity. That inotropic agents may result in an extension of infarct size (as manifested by a rise in CKP) has been established. While it may well be that the “definitive randomized study” in humans had not been performed, at least one of the authors (William Shell) has published much about determinants of infarct size, and must have suspected before the study was begun that digitalis in this clinical setting would be deleterious to patients. It is clear that the authors set about to prove that a specific intervention, namely the administration of a digitalis preparation in the early stages of an acute myocardial infarction, in the absence of congestive heart failure or arrhythmia, may be harmful. This it appears they have done. The experimental subjects neatly proved the authors’ thesis by appropriately extending their infarcts in response to the therapy. However, nowhere in their article is there any discussion of the method by which informed consent was obtained from these patients who were “predictably” harmed by the experiment. Nor is it easy to imagine obtaining informed consent from patients within the first few hours following an acute myocardial infarction for an intervention which the authors themselves must have suspected was harmful. The fact that digitalis is not infrequently administered by practicing physicians in just this setting is no justification for the design of this study.

The ethical basis of human experimentation demands that no intervention be undertaken with the expressed purpose of harming the subjects being studied. The health and well-being of the individuals involved in a human experiment are more important than the health and well-being of other hypothetical patients to be treated in the future. I cannot help but wonder whether the fact that this study was performed in Moscow explains the lack of concern for the ethical issues involved. The American participants and the American journal in which it was published, however, should have known better.

The scientific data accumulated are numerically of interest, but even there criticism can be made of the nonrandom nature of this study, inasmuch as all of the treated patients were at two hospitals, whereas all of the control patients were at two other hospitals where laboratory facilities and technique of enzyme determinations may have varied according to the institution.

I think that editorial review should include more than an analysis of numbers and tables and that some thought should be given to the ethical and moral qualities of any piece of research, especially those dealing with human subjects.

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The author replies:

To the Editor:

Dr. Shander has perceptively defined three of the multiplicity of problems inherent in performance of complex clinical trials: 1) defining study protocols which examine relevant clinical problems, 2) obtaining ethical advised consent and 3) eliminating bias in data collection. Moreover, he has particularly illuminated the difficulty of cooperative studies between societies with major cultural differences.

First, the effect and utility of digitalis in both uncomplicated and complicated myocardial infarction remains an important clinical problem despite the large number of available studies in both experimental animals and man.1,4 It has been observed that both digitalis and isoproterenol increase epicardial and precordial ST-segment elevation in dogs without heart failure.6,7 Isoproterenol increases CK release in conscious dogs; the effect of digitalis on CK release in animals has not been studied. Moreover, neither of these markers is universally accepted as a measure of infarct size either in dogs or in man;6 also, the applicability of animal data directly to man is questionable. Thus, the effects of inotropic agents on “infarct size” in laboratory animals is incompletely defined and there are few data available in man.

Moreover, digitalis therapy has been recommended as therapy for early myocardial infarction in man since the initial description of the disease by Herrick because myocardial infarction resembles acute heart failure.14 Its use is still widely advocated by thoughtful, sincere investigators because of the inherent hemodynamic effects of the agent.15 Also, “infarct size” as an end point of therapy is new and the role of “infarct size” reduction in clinical practice is not yet established despite the theoretic attractiveness. Accordingly, the influence of digitalis on CK release in relationship to hemodynamic responses, patient mortality and morbidity were unknown at the initiation of the study even though the drug was being routinely used worldwide as therapy for these patients. Thus, a study of digitalis in early myocardial infarction was a relevant clinical problem.

It has been effectively argued recently that when the effects of a “proven” therapy are unknown the only ethical course is a controlled clinical trial comparing that therapy with either no therapy or alternate therapy.19 This is especially true when a drug as potent as digitalis is used in a disease where it could have either beneficial or deleterious effects. Thus, we thought a controlled trial of digitalis was an ethical approach to assess its effects.

Secondly, the problems associated with obtaining advised consent illustrate the cultural differences between the USA and USSR that the joint exchange program is attempting to reconcile. In the USSR, digitalis therapy for definite early myocardial infarction is
Digitalis after AMI.
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