To the Editor:

We wish to provide some additional information not covered in the review of granulocyte transfusions by Dr. Higby and Dr. Burnett. First, we and other investigators of granulocyte transfusions are still very preoccupied in research attempting to demonstrate whether granulocyte transfusions work. Most of our efforts have been stimulated by the vulnerability of previously published studies of granulocyte transfusion therapy to critical analysis and (3) the application of different criteria for evaluating response to therapy. Moreover, none of these studies included more than 20 patients in either the transfused or control group. The analysis of relatively few patients with very complex underlying illnesses and infections may only allow slight differences in prognostic factors between the transfused and control groups to bias the results. In most of these studies, the positive effect of transfused granulocytes was frequently short-lived, and a significant number of transfused patients died shortly after they were released from the study. For all of the above persons, a multicentered, controlled trial both therapeutic and prophylactic granulocyte transfusions sponsored by the National Heart, Lung and Blood Institute is now being carried out in order to accumulate the large number of patients needed to assure better comparability of transfused and control patients in terms of important prognostic factors and to provide data indicating which patients, if any, might benefit from granulocyte transfusions. This ongoing study should be completed soon.

Second, the data on granulocyte procurement provided by Dr. Higby and Dr. Burnett may not be representative of most transfusion centers. Indeed, in a survey of 10 centers located in Southern California, we found that the mean cost of a granulocyte transfusion to the patient or his medical insurer is $468.00 (range, $280.00-$600.00). The Haemonetics Model 30 blood processor is used almost exclusively by all the centers for collection of granulocytes. The mean granulocyte yield per procedure of 1.3 x 10^9 (range, 0.6-3.0 x 10^9) is obtained. The other 4 centers are reluctant to use corticosteroids in their donors and thus obtain a mean granulocyte yield per procedure of only 0.55 x 10^9 (range, 0.1-2.0 x 10^9).

Third, serious side effects of granulocyte transfusions may not be relatively rare. In a recently completed study of prophylactic granulocyte transfusions in bone marrow transplant recipients, oral non-absorbable antibiotics alone were as effective as oral non-absorbable antibiotics plus granulocyte transfusions in preventing serious infections. However, recipients of prophylactic granulocyte transfusions experienced a significantly greater number of cytomegalovirus (CMV) infections, including fatal interstitial pneumonia. Wright and colleagues have reported lethal pulmonary reactions associated with the combined use of amphotericin B and leukocyte transfusions. We have also observed a higher incidence of interstitial pneumonias in acute leukemic patients undergoing initial induction chemotherapy and receiving prophylactic granulocyte transfusions. This higher incidence was independent of amphotericin B administration.

Finally, while transfused granulocytes appear to maintain their functional integrity after collection, neutropenic patients may lack the serum opsonic activity necessary for their optimal function. Three separate studies have found deficient serum opsonic activity in infected neutropenic patients, and in two of the studies the opsonic deficiency correlated with an impaired response to transfused granulocytes. Animal experiments have also demonstrated an improved response to granulocyte transfusions when they are combined with passive immunization against the infecting organism.

In summary, we believe that several critically important questions about the effectiveness and safety of granulocyte transfusions need to be answered before they can be accepted as standard or routine therapy. We support Dr. Higby's and Dr. Burnett's plea for continued research in this area.

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11. Keusch GT, Ambinder EP, Kovaes I: Opsonin deficiency: A
12. Winston DJ, Huang S, Young LS: Decreased serum opsonization and impaired response to transfused granulocytes during gram-negative septicemia. Presented at the 18th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, Ga, October 1978 (abstr 302)

Reply:
We appreciate the comments of Drs. Winston, Ho, and Gale. Our article was based on the premise that the wide availability and increasing use of granulocyte transfusions is evidence that most physicians are convinced from the published literature and personal experience (as we are) that granulocyte transfusions are of benefit to at least a subgroup of patients with neutropenia and infection. The debate as to whether or not they work was deliberately not addressed.

Winston et al. point out many of the defects in the prospective studies so far performed. We dealt with these problems in some depth in the article cited by them1 and are not in disagreement. We would simply maintain that the bulk of evidence, not to mention simple logic, would seem to be in favor of the efficacy of granulocyte transfusions. As for the short-lived character of the responses noted, this is not an issue. One would not expect a long duration of action from a single granulocyte transfusion based on cell kinetics and survival. Responses lasting several weeks from a series of continuing granulocyte transfusions would also not be expected because of the development of antigenic antibodies, resistant organisms, host-defense failure in other areas, etc. Granulocyte transfusions are only worthwhile in the short term, when marrow recovery can be expected in the near future; this is of course the indication stressed in our article.

As for the current multicenter trial, I am pessimistic regarding what it can add to the field. If it reports that granulocyte transfusions are ineffective, the hoary arguments will again be raised—ineffective doses of granulocytes, inappropriate patient selection, inappropriate duration of therapy, and so on—to show why the study was not properly done and why its conclusions are in error. If it reports that granulocyte transfusions are effective in some patients with neutropenia but not others, we will hear arguments that at least they cannot hurt those in the nonbenefited groups, and that it is better to be safe than sorry. If the study clearly indicates benefit in all patients who receive granulocyte transfusions, those of us who know they work already will be standing ready to ask why all those patients had to be subjected to less than the "best" available therapy to again prove something already known.

Furthermore, I personally believe, as do Winston et al., that there are myriad factors that can inhibit the behavior of granulocytes, and the type of organism, locus of infection, and degree of infection all bear on whether a favorable outcome will be noted. Thus, a study such as that currently being performed is premature since most of these factors are only beginning to come to light.

I cannot dispute the cost figures and the granulocyte yields for Southern California. These could be compared with Buchholz's much larger study3 and the fact that the cost-estimates in our article were based on daily operations, not taking into account amortization and the other factors that influence the cost to patient determined by medical insurers.

We, and indeed many other investigators, see serious side effects rarely.4 However, it may be that these surface clinically in prophylactically treated patients more often than in patients who are already infected and seriously ill. We do not advocate routine prophylactic granulocyte transfusions and took pains to indicate our reasons in our article. Drs. Winston, Ho, and Gale, we are sure, do not mean to compare side effects in bone marrow transplant patients receiving prophylactic granulocyte transfusions with those seen in acute leukemia patients receiving therapeutic granulocyte transfusions.

Wright and his colleagues suggested an alarming possibility—that there may be a lethal effect related to combining amphotericin B with leukocyte transfusions.5 While this possibility certainly deserves further investigation, the authors of the original report stressed the preliminary nature of their data, and it is certainly clear that a patient for whom amphotericin B has been prescribed cannot be directly compared with an age, sex, disease, or otherwise matched control in whom amphotericin B has not been prescribed. Thus, to attribute synergism between amphotericin B and leukocytes is premature.

We have evidence that not only opsonic activity, but indeed, serum chemotactic activity correlates with the outcome of infection in patients with neutropenia, whether or not they receive granulocyte transfusions.6 Again, these data and those cited by Winston et al.5-7 simply indicate that a large-scale randomized study of granulocyte transfusion therapy is not appropriate at this time because we do not know enough about other factors influencing outcome.

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Granulocyte transfusions [letter]

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