Anergy in Active Pulmonary Tuberculosis

To the Editor:

We would like to make a few remarks concerning the article entitled "Anergy in Active Pulmonary Tuberculosis; A Comparison between Positive and Negative Reactors and An Evaluation of 5 TU and 250 TU Skin Test Doses" by D. R. Nash and J. E. Douglass (Chest, January, 1980).

Reference to the second strength (0.005-mg) dose of PPD tuberculin as containing 250 TU had been clearly pointed out to be erroneous by Professor D. T. Smith of the Duke University School of Medicine, since 1969.1 Following the same reasoning for biological-reacting units, we maintain labelling of 5 TU and 10 TU to be nonequivalent to the 0.001- and 0.0002-mg doses respectively.2 Nevertheless, there appears to be some unknown influence that favors the unsound use.

Apparently, the authors intended to follow the guidelines of the American Lung Association for skin testing techniques,3 but then, for unspecified reasons, they adopted different ranges of the size of the skin reactions (≤ 5 mm, > 5 < 10 mm and ≥ 10 mm) in the method of study. Furthermore, it is obvious that the division of tuberculous subjects into two arbitrary groups: the positive reactors who exhibited induration of 10 mm or more, and the negative reactors whose skin reactions measured less than 10 mm, had unfortunately led to the inadvertent inclusion of reactors with indurations of 5 through 9 mm (the so-called "doubtful" reaction that can result from infection either with M. tuberculosis or other mycobacteria4) which might ultimately result from tuberculosis, into the latter group. Therefore, it would be untenable that the comparison between data obtained from a positive-reactor group and those from a heterogeneous group comprising negative reactors mixed with low-grade but really positive reactors could ever furnish accurate discriminative results.

Another flaw in the report is the lack of information on the time-intervals between the three consecutive tuberculin tests and also the exact time of blood collection to obtain lymphocytes for study. The provision is imperative in regard to the possibility of the "booster phenomenon" to subsequent tests and the "immunological modification" to circulating lymphocytes by specific antigen which may be incidentally introduced via intracutaneous testing.

As regards the serum protein study, difficulty in interpretation of findings in the present report is due to the inadequate description of subject data such as severity and extent of the disease and the control data for comparison. The authors, however, hinted that states of malnutrition and alcoholism might attribute to the significant difference for the total serum protein values between the two study groups. Our studies5-7 indicated that changes in serum protein patterns occur concurrently with hypersensitivity reactions which closely vary with constitutional disturbances as well as severity and progress of the disease, but on the other hand have no relation to the hypersensitivity state per se of the subjects.

It is interesting to note that their findings of the depressed response of peripheral blood lymphocytes to in vitro stimulation by PHA and less conspicuously by PIA in the <10 mm skin test group confirm to the results of our study.8 Available data in the present report, however, do not warrant the conclusion made by the authors that PPD anergy resulted from the presence of inhibitors in the patients' circulation. In the light of our present understanding regarding the various subpopulations of T lymphocytes and their diverse functions, eg. responsiveness to mitogens, specific antigens, helper and suppressor functions in regard to B cell response, one can no longer depend on a lack of change in the total number of T cells as an evidence to suggest the role of soluble factors. Indeed, a shift in the subpopulations of T cells, eg. an increase in suppressor T lymphocytes, could easily account for the observed depression of in vitro and in vivo reactivity. Although it has been difficult to assess suppressor T cell function in humans, recently available techniques9-10 make it possible now. We are currently studying the role of suppressor T cells (Tγ for a start) in anergy among our patients.

Ultimately, if and when the various mechanisms11 that could lead to depression of immune reactivities in anergy to PPD are fully investigated, it may turn out that more than one mechanism operates among the anergic subjects. At present, we should keep our minds open and should not commit ourselves to any single mechanism. In fact, the significant difference in age reported by the authors should remind us all of the role of immunosenescence in hypo-reactivity. In addition, nutritional status and alcoholism should also be kept in mind. However, the exact cellular and molecular mechanisms by which these factors affect immune responsiveness remain quite obscure.

Somchit Bovornkitti, M.D., F.C.C.P.
Professor of Medicine,
Faculty of Medicine, Siriraj Hospital,
Mahidol University; and
Porochat Matangkasombut, M.D.
Professor and Chairman,
Department of Microbiology,
Faculty of Science, Mahidol University,
Bangkok, Thailand

Reprint requests: Dr. Bovornkitti, Siriraj Hospital, Bangkok 7, Thailand

REFERENCES
1 Smith DT. The tuberculin unit. Am Rev Respir Dis 1969; 99:820-31
To the Editor:

Drs. Bovornkitti and Matangkasombut have raised some questions regarding one or two features of the experimental protocol and the interpretation of results which we reported in Chest.

We generally agree with these investigators, but wish to point out that the study being of a clinical nature, was designed to identify some of the problems encountered by the physician using the PPD skin test reaction as an adjunct for the diagnosis of tuberculosis. We take this opportunity to clarify the experimental design and comment on those features of the results, and their interpretation, that have been questioned.

The accepted use of PPD as a diagnostic aid for tuberculosis has resulted in the commercial distribution of standardized preparations. Generally, these clinical reagents are prepared in large quantity and the 5TU dose standardized against PPD-S. The 250TU dose is made from dilutions of the stock material and represent calculated potencies determined from the standardized 5TU preparation. The preparations we used (Connaught Laboratories) were further standardized in well-controlled studies using human subjects.1,2 Although we used a 5TU dose as an intermediate strength, we have not referred to the 250TU as second strength and furthermore feel that the practical usefulness of bioequivalent PPD preparations eliminates the need to quantitate, in mg, the concentrations of PPD.

Both the American Thoracic Society3 and American Lung Association4 have indicated that a positive skin test to 5TU PPD given intracutaneously is represented by induration equal to or greater than 10 mm. Both published guidelines also suggest that induration from 5-9 mm should be considered doubtful. Although we chose to call a skin test reaction negative when induration was less than 10 mm, we felt it necessary, for completeness, to identify the number of doubtful reactors. Furthermore, when assessing reactivity to 250TU in patients not responding to 5TU, any response suggests that the patient is not generally anergic, but his responsiveness to PPD remains "questionable" since a minimal reaction could represent sensitivity to cross reacting contaminating antigens.

Lymphocytes for in vitro studies were obtained from all subjects prior to skin testing. Repeat skin tests were usually done within 10-15 days. This was the case for both the 5TU and 250TU tests done on negative responders. We did not note any "booster" effect following the second STU tests. It is possible, however, that some of those patients responding to 250TU, but not 5TU might be responding to a prior but heretofore latent sensitivity to PPD. Thus, any conversion following the 250TU dose could represent a booster phenomenon. Other possibilities are discussed.

Differences observed for total serum protein levels could very well reflect a difference in disease state, a variable which was not considered in our study. Other differences in serum protein values, obtained when the positive and negative PPD responders were compared, demonstrated statistical significance, but it is doubtful that these differences are clinically significant and as such have little, if any, practical value. Nevertheless, a more complete analysis taking into account the disease state, age, malnutrition, alcoholism, coexistent diseases and any other variable known to influence serum protein levels should probably be pursued in order to resolve the possibility that some serum protein values might correlate with PPD skin test reactivity in patients with pulmonary tuberculosis.

We agree with Drs. Bovornkitti and Matangkasombut when they suggest that suppressor cells could be influential in abrogating cellular responsiveness. We wish, however, to point out once again that soluble serum factors, inhibiting both in vitro and in vivo responsiveness, have been described. In our discussion, we identify several known inhibitors, both cellular and humoral, present in the systemic circulation of tuberculosis patients.

Donald R. Nash, Ph.D,
Research Associate Professor,
Immunology/Microbiology;
and Jesse Douglass, M.D.,
Assistant Professor Clinical Medicine,
Tuberculosis Service, University of Texas
Health Center at Tyler

REFERENCES
2 Connaught Laboratories. Product information sheet accompanying STU and 250TU skin test antigen

Severity of Aortic Stenosis

To the Editor:

We would like to thank Dr. Spodick for his remarks and comments on our paper on the severity of aortic stenosis. (See page 122, January, 1981 Chest).

We agree completely with his comments on our use of the Bazett formula. Our goal was really not to establish rate-related normal values for T time, U time, etc, but rather to evaluate them by one recommended technique. For an extremely short interval such as the T time, different methods of rate correction are unlikely to yield a practical difference in evaluating disease states.

We were very surprised that our Q-MP data correlated better than other measurements (although still poorly) with the severity of aortic stenosis. Noninvasive records were indeed read without definitive knowledge of catheterization results. We were interested in investigating this because Bonner et al had reported these results. Before commencing our study, we felt we would be unlikely to reproduce these data because of the variability that is commonly encountered in phonocardiograms. Hence, we also were surprised by our findings.

A. Gene Voelkel, M.D., and
Alfred F. Parisi, M.D.,
West Roxbury, Mass.

REFERENCE