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DISCUSSION

DR. LLOYD D. MACLEAN (Montreal, Quebec): This is a remarkable paper, I think, about a naturally-occurring immune regulatory molecule. It's remarkable for several reasons.

First of all, they have showed a stimulatory effect, whereas most of us working in this field have been able to detect only inhibitors.

They have two quantitative assays, and one of those requires that they purify the opsonic protein, which they have done. Any one of these things, I think, would be enough for a complete discussion.

They have also found a concentrated source for the material, in the form of cryoprecipitate. Finally, they have applied it clinically.

I'd like to show two or three slides, just to put it in perspective, maybe, for some who aren't as familiar with these things.

(Slide) The inflammatory response, the component that they're studying, is over on this side. Opsonic activity is buttering up bacteria, or other particles, so they become attractive to the phagocytes. The Kupffer cell is the particular phagocyte that they're studying.

Several people are working on this side, in chemotaxis. There's a good quantitative assay for intracellular killing. This activity can be quantitated. There isn't too much work going on in here. I'd like to show you two or three slides of activity on this side of the scale.

(Slide) Using this quantitative assay, neutrophils can be taken from trauma patients, put in this grid with this attractant below it and the degree of migration can be accurately quantitated of the neutrophils across this grid.

(Slide) Patients who have been traumatized fall into three groups, generally: a group with minor injuries, who have normal skin tests and don't migrate from the normal range; patients with multiple injuries, two body cavity injuries, with, again, a normal skin test, and finally, people with severe multiple injuries, who have abnormal skin testing, and take about a month to get back to normal.

It looks like this measurement, chemotaxis, (slide) might be a more sensitive index of decreased host resistance than is skin testing.

Finally, as was done here in 14 anergic patients, if one follows them long enough, until they do return, as the skin test returns to normal, so does the chemotaxis. Furthermore, if one takes cells from a normal person and adds the abnormal serum from these anergic patients, those cells will also fail to migrate normally.

I have two or three questions that they might like to speculate on. I'd like to know if they did skin testing on these patients, or others, and if they found this to be helpful. What is the normal response to infection with the opsonic protein? Does a normal person with a controlled infection get a jump in that protein?

I think you did tell us some of the hemodynamic effects, but I'd be interested to know whether in the normal setting, this opsonic protein has a hemodynamic effect.

DR. BEN EISEMAN (Denver, Colorado): I was privileged to review this manuscript in advance. This work is important not because following administration of some plasma fraction several sick septic patients got better. Indeed each had good surgical care and some probably would have otherwise recovered. What is important is the authors' evidence that the glycoprotein fraction, which happily can be isolated relatively easily in the cold precipitated fraction of normal serum, increases opsonization. This is a modern return to a bacteriologic principle whose time, I judge, now has returned.

(Slide) Let me put this in context with our own studies, which for several years have emphasized the etiologic role of remote bacterial sepsis to liver, lung, kidney failure and stress ulcer.

(Slide) Our hypothesis is that such infection produces circulating immune complexes of antigen, antibody and complement and that these particles, if sufficiently large, are caught in the reticular endothelial cells of the liver. If they are smaller than 11S or if the RE cells are saturated or damaged, the complexes slip by the Kupffer cells and land in the lung, kidney or other organs where they cause cellular damage (slide).

This was our hypothesis, and we have evidence that we are correct. In four patients in multiple organ failure and in over 25 rabbits made septic by experimental intraperitoneal abscesses, the immune complexes visualized by immunofluorescent antibodies coating the vasculature of the liver, lungs and kidney in a pattern so far recognized only in glomerular basement membrane disease support the concept presented today that an immune mechanism contributes to organ damage during remote sepsis. The unanswered question remains: How does the opsonin described by the Albany group work?

DR. WILLIAM SCOVILL (Closing discussion): Dr. MacLean, we have not done skin testing in any of these patients, and I think the results of skin testing would have a lot of complex interpretations, which may have very important bearings on future lines of investigation. I think that would be an ideal thing to do.

The questions about opsonic protein levels—that is, the opsonin required for normal Kupffer cell phagocytic function and the influence of infection on these opsonic protein levels—is an important one. There is a suggestion that early infection may result in heightened levels of this opsonic protein, whereas the data I presented in severely traumatized man with documented septicemia, indicated that there was a severe undermining of this opsonic system.

The hemodynamic effects, as I presented in a preliminary fashion in these two patients, are probably not due to the volume of cryoprecipitate infused, since it was so small. It would be appealing to hypothesize an improvement in peripheral microcirculation as a means of improving overall dynamics by the phagocytic ingestion of potentially noxious particulates that are circulating during septic periods.

Dr. Eiseman, we have looked at the question of complement early on, in cruder isolated protein fractions, and have not found complement activity in the crude fractions; and you're quite right, the structure of this protein is not compatible with this being complement.

The further question of what happens to liver blood flow, hepatic sinusoidal blood flow, following the ingestion of a large particulate load is a very interesting one, and one that we have not yet confronted. I think the former model of reticuloendothelial blockade, that induced by large volume colloid injections, was thought at one time to be due to a saturation of the capacity of the Kupffer cell to ingest these particles. Actually, it was shown almost ten years ago by Dr. Saba, one of the coauthors, to be due to a depletion of this humoral component.

I would like to add just one additional comment. We have carefully selected patients for study by first assessing them for the prevailing level of opsonic protein. There are some *in vitro* data available in our laboratory that demonstrate that superheightened levels of opsonic protein may, indeed, be deleterious due to rapid agglutination of particles *in vitro* in excess of R.E. activity and thus the potential of pulmonary localization. Therefore, we have carefully limited cryoprecipitate infusion to patients with documented hypopopsonemia, and in this setting an effective response is observed.