concentrations in addition to inhibiting PGE_2 production, and thus ibuprofen may have abrogated any increased sensitivity of T cells to PGE_2 caused by cortisol.

Our *in vitro* data would tend to support the use of nonsteroidal anti-inflammatory drugs in burn victims and would argue for the addition of such agents to therapeutic trials of biologic agents directed at improving immune responses in seriously injured patients. Others have reached similar conclusions. Hansbrough and colleagues[22] have shown in a burned mouse model that the cyclooxygenase inhibitor, ibuprofen, was capable of restoring a contact sensitivity response to previously anergic animals as well as restoring decreased T helper/T suppressor ratios to normal in the spleens of these animals.[23] Furthermore they demonstrated that ibuprofen was capable of preventing the death of these burned mice following a septic challenge by cecal ligation and puncture.[24] Faist et al.[25] have demonstrated improved cellular immunity in patients receiving indomethacin after major surgery. Results from our laboratory[11] have demonstrated the involvement of PGE_2 in suppressing the production of IL-2 in thermally injured mice and that decreases in IL-2 production are associated with increased deaths following a septic challenge.[26] Furthermore we recently demonstrated that a combination of low-dose IL-2 plus low-dose indomethacin *in vivo* can increase significantly survival in this burn model.[27]

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Discussion

DR. JONATHAN L. MEAKINS (Montreal, Quebec, Canada): From this excellent study, there are several questions that present themselves, and in the manuscript of over 20 pages I cannot cover all of the issues that come to mind, and so I will address basically three things.

In light of the fact that we have often thought that all patients had defects or at least some degree of the expression of these defects, it seems to me that one of the forward steps taken here is the identification that really only some patients have the full expression of the defect in host defenses. So that although we see that all peripheral blood monocytes

in burn patients have some increased sensitivity to PGE_2, it is really only a smaller number of patients studied at specific times that seem to express this, and it is measured in a very strict manner; that is, the definition of abnormality is more than 2 standard deviations below the mean for controls.

Now I believe this must be a sequential study in the sense that I could not tell what the exact dates for inclusion of all the patients were, so that I would ask if the set of eight patients who had the 14 abnormalities in phenylalanine (PHA) responsiveness are a subset of the 10 patients with the changes in interleukin-2 (IL-2) synthesis. That is, do both defects occur concurrently or are they sometimes occurring in separate patients at different times?

The endotoxin data, a second point that I would like to discuss, demonstrates a second route to the production of a very similar, if not identical, form of immunosuppression.

In the manuscript, for which I thank Dr. Mannick, infection is able—that is, infection separate from trauma—to produce these same changes; that is, an increased sensitivity to PGE_2, decreased PHA responsiveness, and a decreased production of IL-2. Therefore we have infection; we have burn injury itself, sometimes; burn plus infection, and then fourthly, endotoxin; all producing similar changes.

Do they create these defects all by the same mechanism, not specifically the PGE_2 component; but is the cell production of PGE_2 the same, or are there different mechanisms of activation of this immunosuppression?

The last point comes back to the beginning, and that is that not all defects appear to be present in all patients all the time. Therapy therefore must be integrated with the presence of defects. Do you think we can identify these defects at the bedside? That is, can we tailor therapy at the time when the patients really need support of their immune system and can we tailor therapy on the principle that we should not mess with Mother Nature, or, as Osler would have told us, *primum non nocere?* So that in the use of indomethacin or the adjuvant use of IL-2 or other molecules or products that are or will be available to us soon, how do we identify the key time at which these molecules should be presented to the patient and when we should give them specifically, rather than use indomethacin as a global form of therapy for post-traumatic immunosuppression?

DR. C. JAMES CARRICO (Dallas, Texas): What we have seen is that PGE_2 decreases the response of lymphocytes to a known mitogen, and we have seen it decreased by IL-2 production. We have heard the conclusion that this is suppression of the immune response system, and that suppression needs to be treated by cyclooxygenase or by some other mechanism of decreasing the PGE_2 production.

How do we know whether this is pathologic suppression of the immune system or physiologic down-regulation of the immune system? We think of the immune system appropriately as our defense against invaders and bacteria. Lewis Thomas warned us some time ago that it is so powerful that sometimes we may be in more danger from our immune system than from the invaders. And there is growing evidence that the multiple organ failure syndrome is really the immune system out of control.

Dr. Mannick, can you assure us that maybe you are not beginning to outline the mechanisms of down-regulation and that we ought to be pursuing this as a potentially beneficial effect, rather than corrected as a detriment?

DR. LEWIS M. FLINT, JR. (New Orleans, Lousiana): I have three questions for Dr. Mannick. Some of them stem from questions that have been asked by other discussants and others come from the fact that, at least as of my telephone call home yesterday afternoon, there were six patients with florid multiple systems organ failure in our Charity Hospital intensive care unit, and I would like some clinical guidance.

The first question is: Were there any clinical issues that could be identified that help to separate the patients whose cells were suppressed as opposed to those patients whose cells were not suppressed?

The second question has to do with potential methods for generic cyclooxygenase inhibition in these patients. In a limited clinical trial in patients with adult respiratory distress syndrome (ARDS) in our unit, we found that it was necessary to use a continuous infusion of the cyclooxygenase inhibitor over a relatively long period to get any effect. And I wonder if this is necessary, particularly in light of the fact that cyclooxygenase inhibition can cause some adverse effects, most notably renal vasoconstriction and redistribution of renal blood flow.

And finally if cyclooxygenase inhibition is going to be used as a therapeutic tool, how will we know when to use it and how will we know when to stop?

DR. BASIL PRUITT (Fort Sam Houston, Texas): Dr. Mannick, I enjoyed your paper very much and found a most interesting observation that the maximum immunosuppression was between the 8th and the 14th post-injury day, the most common time to diagnose infection. That emphasizes Dr. Meakins' question whether these changes were the cause or the effect of infection because of the difficulty in relating the diagnosis or onset to the manifestations temporally.

We also know that lymphocyte and white cell function can be changed by antibiotics and by hormones, so were these changes correlated with any antibiotic therapy in particular, or any significant changes in hormone level, such as the catacalls, in particular?

DR. JOHN DALY (Philadelphia, Pennsylvania): I have two questions. There are pathways that other investigators have looked at, one of them being that of nitrous oxide production by suppressor macrophages. I wonder if you have looked at all at any inhibitors *in vitro* of nitrous oxide production in your patients and whether there is any effect on lymphocyte function?

The second question is, can you determine why some patients have this excessive PGE_2 production, and others, presumably with the same degree of injury, do not?

DR. HAILE T. DEBAS (San Francisco, California): Just recently I heard a very elegant piece of work presented in which a naturally occurring receptor, specific receptor antagonist to IL-1, for example, has been cloned, and it specifically suppresses all the effects of endotoxin. It seems to me—and this comes from Dr. Mannick's neck of the woods—that the use of these specific receptor blockers may be a more direct way to deal with the problem than the use of cyclooxygenase inhibitors.

DR. JOHN A. MANNICK (Closing discussion): The point brought out by several discussants is why did some of these patients get suppressed and others did not? I honestly do not know. I think that to some degree we can show that suppression is more likely to take place if the burn is big and if the patient gets infected. And that, I think, covers several of the questions that were asked.

The lesser burn patients, however, sometimes are suppressed, and patients are also sometimes suppressed even though they have no clinical evidence of being infected at that time. Obviously we have to rely to some degree in our thinking here on animal models, and it is very clear that in animal models of injury, improved survival can be obtained if one combines a cyclooxygenase inhibitor, apparently damping down the excessive production of prostaglandins by macrophages or monocytes, coupled with something that will stimulate T lymphocytes.

I think that the key to therapy here, and it probably can be done in a number of ways, is going to be modulating rather than eliminating the excessive mediator production by monocytes/macrophages. I quite agree with Dr. Carrico that Mother Nature is still pretty smart, but I think we also know that after serious injury, Mother Nature can kill you with cytokine poisoning, and we have to try to do something to reduce things back to a normal state of equilibrium.

There are probably a number of approaches to this, and Dr. Debas brings up the idea of the newly characterized interlukin-1 receptor antagonist that shows great promise in reducing some of the effects of endotoxin, for example, and also has been shown to be beneficial in septic shock in some animal preparations. I think that clinical trials are going to be the important way of solving these issues. We have animal models that point the way toward appropriate clinical trials, but we need prospective, randomized trials in our intensive care units, and in our burn units, to define what is safe and what is not, what is beneficial and what is not. We should now try to select first what appears to be both safe and beneficial for use in these clinical trials.

I am not convinced that cyclooxygenase inhibition if it is not pushed to ridiculous extremes is all that unsafe, so I still come down on the side of recommending clinical trials of the use of this kind of modulation of hyperactivity of macrophages.