La Niña "should have been an obvious question," concedes Livezey, "but we just didn't notice. We were so wrapped up in analyzing the signal itself that we didn't consider what would happen."

Barnston and Livezey have now sorted out the roles of QBO winds, the sun, and the El Niño cycle. It turns out that part of the strength of the west-phase correlation was actually El Niño at work.

The sun-weather relation "is shaky in the lower atmosphere," Barnston says. But there is still a detectable solar effect during the west phase of the QBO that may be "worthwhile" in long-range forecasting, he says. It can explain perhaps 15% of the variability of winter temperatures and pressure patterns from year to year even after including the disastrous 1989 case. That's far less than the 50% that it seemed to explain before; forecasters might do better to ignore the sun-weather connection when they think it will be swamped by the El Niño effect.

Barnston sees other causes for guarded optimism about the utility of sun-weather relations in forecasting. The other half of the proposed sun-QBO-weather relation, the one that applies to the QBO's east phase, held up nicely during the winter of 1990. And in the stratosphere, the relation has held during both phases, even in 1989.

Meanwhile, the skeptics are as skeptical as ever, if not more so. When new rules are made up in this sort of game, such as bringing in El Niño, "the statistical rules in the textbooks don't work and can be very misleading," says meteorologist John Wallace of the University of Washington. He wants to wait until all the rules that determine the apparent strength of the correlation are fixed before he starts crediting new observations as supporting it.

The skeptics may be right, but proving them wrong could take a generation or longer. Unless defenders of the theory suddenly discover a mechanism by which the sun affects the weather, which doesn't seem to be in the cards just now, they would need to gather data for another 20 years—for a total of six solar cycles—to meet the traditional standards of verification. Alternatively, researchers are attempting to push the record of QBO winds and sun-related weather variations back before 1950.

For now, Labitzke remains confident. "We are still convinced that we have something here," she says. The next test of that confidence comes this winter when the sun and, if it actually makes an appearance, El Niño should work together, not in opposite directions as in 1989. "If we don't get the expected pattern," notes Livezey, "we're going to have to do a serious reconsideration of all this." ■ RICHARD A. KERR

"Superantigens" May Shed Light on Immune Puzzle

Bacterial toxins may illuminate why the immune system responds to some antigens but not others

THE BACTERIA AND VIRUSES that cause disease can sometimes be extremely creative in finding ways to escape the defenses of the hosts they infect. In fact, they can be so creative that sometimes they stump not only the immune system but also the researchers who attempt to figure how their escape mechanisms operate. That was the case for decades with the toxins produced by some of humanity's most serious pathogens, the staphylococcal and streptococcal bacteria that cause toxic and septic shock, food poisoning, and autoimmune diseases such as rheumatic fever.

The picture was puzzling partly because immunologists knew that the toxins trigger a paradoxical response in the infected organism: a gross overstimulation of the immune system and, at the same time, a profound immunosuppression. That is, the immune system operates in overdrive, but fails to respond to the invaders.

What the immunologists didn't understand was how this paradox was accomplished at the molecular level. But in the past year or so, they have finally begun solving the problem—at least on the overstimulation side. In so doing they have also come up with some deep evolutionary speculations about the functions of the bacterial toxins and about one of the fundamental mysteries of immunology: why the immune system responds to some antigens and ignores others.

On page 705 of this issue, Philippa Marrack and John Kappler, both of the Howard Hughes Medical Institute and the National Jewish Center for Immunology and Respiratory Medicine in Denver, outline the developments that have led up to this new understanding. At the heart of the matter are surprising observations, made over the past few years in their lab and others, that the bacterial toxins act very much like mysterious immune molecules discovered nearly 20 years ago by Hilliard Festenstein of London Hospital Medical College.

Festenstein discovered those molecules—known as minor lymphocyte stimulating (Mls) antigens—when he mixed lymphocytes from two different mouse strains. Both sets carried the same major histocompatibility complex (MHC) proteins: cell surface proteins that play a key role in triggering immune cell activation. Hence, the cells should have been immunologically compatible and not reacted with one another. But they did: the mixture stimulated the proliferation of one type of lymphocyte, the T cell. Festenstein therefore inferred the existence of a second kind of antigen, which he called "minor" to distinguish it from the MHC proteins.

Superspeculation. *Philippa Marrack and John Kappler theorize about the role of superantigens in evolution.*

But what class of molecule might the Mls antigens be? And what might their function be? To this day, neither question has been answered definitively. Most immunologists, however, think the antigens are proteins, and the recent toxin work may provide clues to their function.

As early as the 1970s some similarities had been noted between Mls antigens and the bacterial toxins. Immunologists knew that both types of molecule stimulate massive T cell proliferation against a broad range of antigens. Each group of T cells responds only to specific antigens, a specificity that is mediated by the T cell receptor. Ordinary immune reactions are very specific, stimulating the proliferation of only a fraction of 1% of all T cells. In contrast, the bacterial toxins and Mls antigens can activate as many as 10% of the mouse's T cell repertoire. The range of the response prompted Marrack and Kappler to suggest the name "superantigens" for molecules like the toxins.

The explanation for this very broad range lies in the fact that, on the molecular level, the Mls antigens and bacterial toxins do not work the way conventional antigens do. But before these interactions could be seen as extraordinary, immunologists had to understand how conventional antigens work—which they have done only in the last few years.

What they learned is that some white blood cells, including B cells and macrophages, have the ability to present antigens to the immune system. These antigen-presenting cells first the antigen into fragments and display the fragments on their surfaces in combination with an MHC protein. The antigen presenter then offers this complex to T cells. When it encounters the rare T cell able to recognize the antigen, that T cell is activated.

For its part, a T cell recognizes the antigen-MHC combination by means of the T cell receptor, which consists of two protein chains designated α and β. In a conventional T cell activation, the antigen fragment is essentially sandwiched between the MHC protein on the presenting cell and segments termed the variable, or V, regions of both chains of the T cell receptor.

But, as work by Marrack and Kappler and others has shown, that's not what happens with Mls antigens. Although the Mls antigens do associate with MHC proteins, this complex interacts with the variable region of only one chain—the β chain of the T cell receptor. As a result, a greater number of T cells are activated. Spurred on by this finding, the Denver workers and others wanted to see whether the bacterial toxins also interact only with the V_β region, and, sure enough, that's what they found.

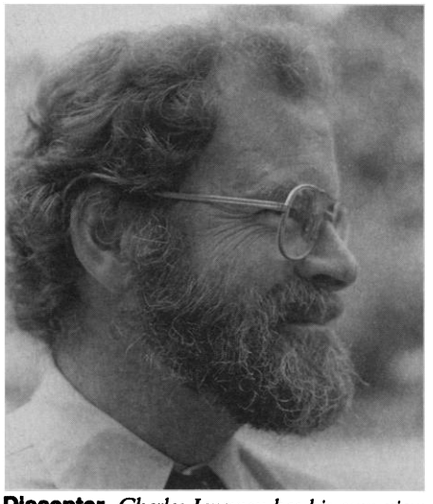
And that's not the only unconventional thing about how these antigens interact with the immune system. They also appear to bind in an unusual way to the MHC proteins. The MHC proteins are arranged on the cell surface as a flat surface scored by a deep groove. Fragments of ordinary antigens bind in that groove. Preliminary evidence from the Marrack-Kappler group and work done by Charles Janeway, Jr., of the Howard Hughes Medical Institute and Yale University School of Medicine, however, suggests that the toxins bind on the outer edges of the MHC molecule instead.

This geometry suggests to Janeway, as well as to Kappler and Marrack, that the bacterial toxins (and presumably the Mls antigens) do not act as an ordinary antigen does, wedged in the groove of the MHC protein. Instead, the toxins and Mls antigens may act like a vice, clamping antigen-presenting cells to T cells and resulting in T cell activation.

But if these molecular interactions are becoming clear, their biological significance is still a matter for debate. What's in it for bacteria? Why do mice have Mls antigens? And why are those antigens so similar in behavior to the bacterial toxins?

Marrack and Kappler have now offered a theory to answer these questions. They propose that bacteria evolved the toxins for the express purpose of activating more T cells than would be activated by any ordinary antigen. "The goal of the bacterium is to stimulate a whole lot of T cells at once," Marrack says. And how does overstimulation lead to immune suppression? That's still a matter for debate. But Marrack says, "this huge response so overwhelms the host that most antigens slip by unnoticed."

Whether or not the chaos created by the toxins makes it easier for the bacteria to escape detection by the immune system, the toxins do seem to stimulate the release of substances that can cause some of the symptoms of toxic shock and food poisoning. Interleukin-1, for example, secreted from macrophages can cause fever, and tumor-necrosis factor, in the high concentrations produced by an overstimulated immune system, can lead to muscle wasting and fatigue.



Dissenter. *Charles Janeway has his own view of how Mls antigens work.*

How these things help the bacteria isn't clear, but, say Marrack and Kappler, the toxins' threat to the host is so great that mice had to evolve a means of countering them—which is where Mls antigens come in.

The Denver workers find that the toxins and Mls antigens do not bind to all T cells. On the contrary, each type binds only to certain V_β regions. Moreover, they have the same range of specificities.

In addition, Marrack and Kappler showed recently that some strains of mice lack T cells expressing particular V_β regions. And, remarkably, the lost T cell subsets were the same ones most likely to react with Mls antigens in other animals. (Festenstein, Robson MacDonald of the Ludwig Institute for Cancer Research in Lausanne, Switzerland, and Hans Hengartner at the University Hospital of Zurich have made similar observations.) The loss is not trivial: as many as 20% of the total potential T cell repertoire can be eliminated.

Now, what does all this mean? "Why would mice bother to have deleting elements?" asks Marrack. "Why don't they just use all of the T cells available to them?" The answer, she and Kappler propose, is that the T cells eliminated are the ones that would be vulnerable to toxin binding—thereby saving the mice from the immunological chaos the toxins cause. Some experimental evidence supports that view.

But though the Mls antigens may have evolved initially to eliminate the T cells that react to toxins, Marrack and Kappler propose that these antigens may have taken on quite a different role in the course of evolution: helping T cells distinguish between self and non-self antigens.

Each individual has a unique set of histocompatibility proteins which serve as immunologic identification tags. The proper functioning of the immune system depends on the ability of T cells to discriminate self tags from foreign ones. T cell precursors that demonstrate this ability in the thymus are allowed to mature and go to the periphery of the immune system. Marrack proposes that Mls-like antigens might help select for T cells with a low intrinsic affinity for self MHC but a high affinity for self MHC when it is combined with foreign antigen.

Janeway has a different view. He suggests that Mls antigens are essential in all T cell receptor interactions at all stages of development, even after T cells mature and are functioning in the periphery. In his model, Mls antigens operate to align the T cell receptor and the histocompatibility proteins on antigen-presenting cells during conventional T cell activation.

It may take some time for these views to be sorted out and tested. In the meantime, one question is whether Mls antigens exist in human beings. The evidence so far is less clear-cut than in mice, and humans certainly do not seem to have deletions of large numbers of T cells, as mice do. The Denver investigators are working on this question now. And both groups express confidence that Mls antigens are there in people. Says Janeway: "It would be difficult to imagine that something would evolve and disappear in the time between the evolution of mice and man." ■ MICHELLE HOFFMAN

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