IMMUNOLOGY

Tracing the Immune System's Evolutionary History

If you asked a group of immunologists what their favorite experimental subjects are, chances are that most would cite mammals—mice, say, or rats. When you want to probe the mysteries of the intricate human immune system, it makes sense to study animals close to us genetically and physiologically.

Yet there have always been a few scientists who have wandered off this well-traveled path of mammalian inquiry to study the immune systems of less evolutionarily advanced species. Take Elie Metchnikoff, who in 1892 made his Nobel Prize–winning discovery of phagocytosis, the process by which certain white blood cells engulf and destroy foreign matter such as bacteria, while studying related cells in starfish larvae. Today a small band of researchers still practice what is sometimes called comparative immunology—examining how nonmammalian species such as insects, earthworms, and sharks protect themselves against pathogens.

Considering the progress mammalian immunologists have made in the past few decades, researchers studying invertebrates and primitive vertebrates may be hard-pressed to produce another Metchnikoff-like observation from their work. But their primary goal is not so much to unearth new immune mechanisms that humans might also share as it is to document how evolution built up the immune system's complex mechanisms piece by piece. At a recent meeting devoted to the study of primitive immune systems,* one of these researchers, immunologist Gail Habicht of the State University of New York at Stony Brook explained the motivation behind the work: "We're united by a common desire to understand the origins of host defenses. Once we comprehend the strategies used by primitive animals, we hope to apply our understanding to mammalian host defenses." As a bonus, the researchers are learning that the lower organisms have novel defense tactics in addition to those that resemble known mammalian immune responses. Besides illuminating evolutionary byways, these findings may have practical payoffs; they have already pointed the way, for example, toward novel agents that fight off bacteria and other pathogens.

What has reawakened the field of comparative immunology, as presentations at the meeting made clear, is the advent of molecular biology, which opens the way to sophisticated analyses of immune systems. "We can finally make direct and meaningful comparisons," explains molecular immunologist John Marchalonis of the University of Arizona College of Medicine. Using genetic and molecular probes, researchers pore over different species to see when evolution first produced crucial parts of the mammalian immune system, including pathogen-destroying proteins like antibodies and complement, as well as molecules such as cytokines and the major histocompatibility proteins needed for immune cell communications.

By looking for DNA sequences that match those which code for parts of mammalian antibody proteins, for example, researchers have traced significant portions of the highly complex antibody-producing system all the way back to sharks, creatures more ancient than dinosaurs and among the most primitive of vertebrates. Some cytokines, key hormone-like molecules of our immune system, go even further back in evolutionary time, report Habicht and her co-worker Gregory Beck. They have found interleukin-1-like molecules in marine invertebrates such as starfish and tunicates, and this starfish interleukin seems to live up to its cytokine label by stimulating various immune actions such as phagocytosis.

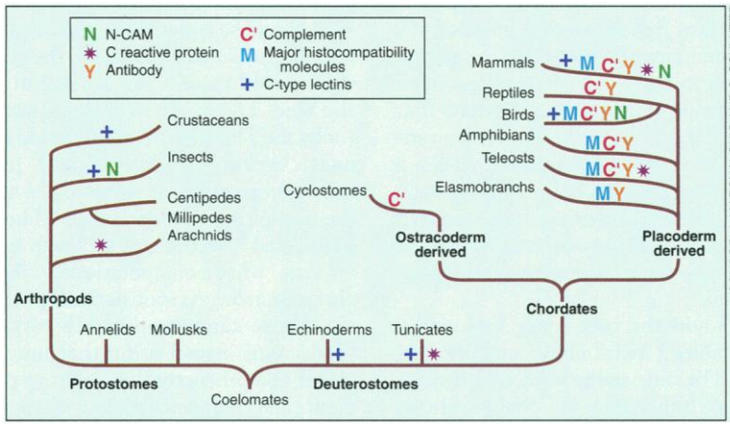
Since providing evolutionary histories for cytokines, antibodies, and other immune-related molecules is a slow process, investigators cannot yet draw an accurate picture of when parts of immune systems originated. For instance, some suggest that sharks may be the birthplace of vertebrate antibodies. But only further analysis of creatures like the hagfish and lamprey, which reside one rung down from shark in the ladder of evolution, will confirm that. "Enough pieces have to fit into the jigsaw puzzle, before we will ever see any patterns," says Marchalonis.

Moreover, the immune system in simpler organisms isn't just a less sophisticated version of our own, as scientists taking a different approach to the subject have found. Instead of focusing on the evolution of immune system molecules, these researchers often begin by injecting an organism with bacteria or other foreign substances and analyzing what proteins, peptides, or other molecules are induced as it mounts an immune response. "I say let's simply look for what techniques animals use to kill [pathogens]. You then start with very few assumptions," explains molecular biologist Michael Zasloff.

This approach is paying off with the discovery of novel immune weapons. In 1987 came the magainins, antimicrobial peptides that Zasloff isolated from the skin of frogs. And just this year, he and graduate student Karen Moore identified squalamine, a novel antimicrobial steroid found in sharks (*Science*, 19 February, p. 1125). So far, no one has found mammalian counterparts to these substance. Whether that happens or not, magainins and squalamine may one day lead to new antibiotic drugs, say Zasloff, who has backed that belief by becoming executive vice president for research at Magainin Pharmaceutical in Plymouth Meeting, Pennsylvania.

Other glimpses of alternate immune systems are also coming from the incredibly diverse world of insects. Because of their short lifespans and prolific reproduction, insects had been thought to have little evolutionary need for a vigorous immune system. Yet even from surveying just a limited number of species, researchers have learned that insects can rise to their own defense even though they do not have the cellular and antibody immune mechanism of mammals. Traditional transplantation experiments show that insects, as do vertebrates and creatures as far down the evolutionary ladder as sponges, can recognize tissue from other species, and even from other individuals of their own, as foreign and reject it. How this rejection actually happens, and which cells are involved, remains unclear.

Challenging insects with bac-



SOURCE: J. MARCHALONIS AND S. SCHLUTER

Spreading defenses. By studying which organisms produce proteins similar to our own immune molecules, investigators hope to construct an evolutionary history of how the immune system developed.

*"Primordial Immunity: Foundations for the Vertebrate Immune System," Woods Hole, Massachusetts, from 2 to 5 May.

teria can also provoke an immune response in which, among other things, they release lectins, sugar-binding antibody-like molecules found in many other creatures including crustaceans and starfish. As lectins circulate in the hemolymph, an insect's version of blood, they presumably aid the immune response by attaching to foreign substances and marking them for phagocytosis. Cockroaches, giant silkmoths, tobacco hornworms, and other insects also rely on at least one other mechanism to combat infection: a variety of defensive peptides such as the antibacterial agents known as cecropins.

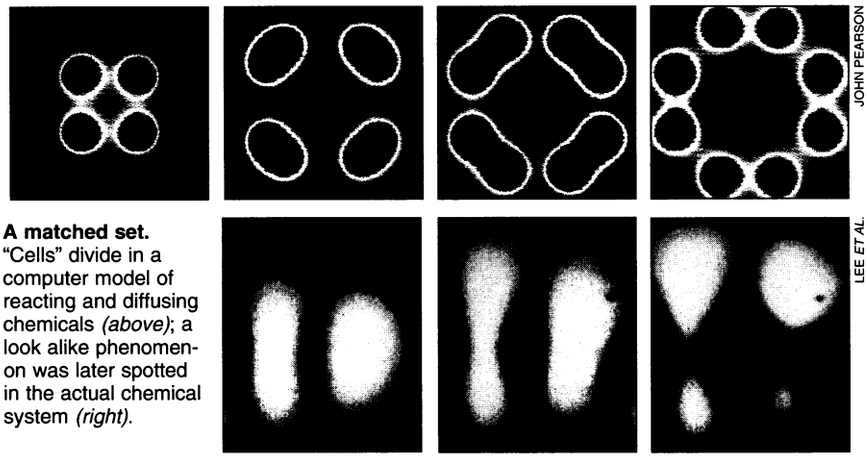
The panoply of immune strategies found in simpler organisms adds to the intellectual appeal of comparative immunology—but may also impede its progress. Compared to mammalian immunology, we have advanced "a bit slower because we have fewer people and almost everyone of us is working on different models," notes comparative immunologist Edwin Cooper of the University of California, Los Angeles. And those involved in moving the subject forward face a constant battle to attract new students and funding at a time when "relevant" research is prized. "Why study a worm, when you can study a mouse? That's what people are fighting," says Zasloff. But as Metchnikoff showed more than a century ago, the fight is worthwhile.

–John Travis

CHEMISTRY

A Chemical Loom Weaves New Patterns

A universe without patterns would be about as intellectually stimulating as a vat of mashed potatoes. There would be no spiral galaxies, no crystal lattices, no zebra stripes, no organized structures of any kind and no scientists trying to explain the whys and wherefores of such patterns. Which is why systems of reacting chemicals that spawn vivid patterns catch the eyes of more than just the researchers studying the reaction. Something very basic about the pattern-populated universe might be showing itself; on the other hand, the patterns might be nothing more than pretty pictures painted by chemistry. Which are they? This week's *Science* raises that question with two reports on pattern-forming systems that exhibit a combination of stability and change reminiscent of pattern formation in living things.



JOHN PEARSON

LEE *ET AL.*

A matched set. "Cells" divide in a computer model of reacting and diffusing chemicals *(above)*; a look alike phenomenon was later spotted in the actual chemical system *(right)*.

In one paper (p. 192), experimentalists at the University of Texas, Austin, report that a homogeneous, well-mixed solution of reacting chemicals (an iodate-ferrocyanide-sulfite system) evolves over several hours into an irregular pattern of curvy, interdigitating light and dark regions. In the other (p. 189), a theorist at the Los Alamos National Laboratory describes a model chemical system that, in a computer, behaves much like the real chemistry seen in Austin. But just what the match may reveal about the actual chemical system—or about pattern formation in nature—is still anybody's guess.

Pattern-forming chemical reactions have been studied since the late 1960s. Even before then, in 1952, the British mathematician Alan Turing speculated about their existence and suggested that the reactions could underlie biological patterns such as creaturely architecture and hide coloring. But both the real and the simulated reactions reported here seem to display a new kind of pattern-forming behavior, says Ken Showalter, a chemist studying pattern-forming chemical reactions at West Virginia University, Morgantown.

Some earlier systems never freeze into a final stable pattern. Instead they may oscillate between different states until they peter out, or their spiraling arms may meet and annihilate each other. Others, reported in 1990 by Patrick De Kepper and colleagues at the University of Bordeaux and later by others, yield the fixed patterns of dots or stripes Turing had predicted. The Turing patterns emerge everywhere at once in the reaction medium, like a slowly developing negative. But in the new experiments, patterns spread out like an avalanche from a site of initial activity—and then reach a stable state.

To create these patterns, the Austin group, led by physicist Harry Swinney, allows the solution of reactants to permeate a thin slab of polyacrylamide gel, which suppresses convective motions. They then expose one edge of the gel to ultraviolet light. The light triggers a complex nexus of reactions that drives up the pH of the illuminated area, causing a pH-sensitive indicator to darken. The disturbance propagates as a traveling wave front with a snaky leading edge, from which projections grow outward like fingers and approach each other without touching, as though a thin demilitarized zone were keeping them at bay. After several hours, the result is a stable, maze-like pattern of dark and light regions.

As in all pattern-forming reactions, some interplay between the rate at which specific chemical reactions take place and the rate at which reactants diffuse through the medium must be at work. But Richard Noyes of the University of Oregon, who has studied pattern-forming reactions since the late 1960s, thinks the details of the process must be new. "I'm used to seeing these waves come together and annihilate," he says.

Finding clues to what underlies the novelty is what John Pearson of the Los Alamos National Laboratory aims to do in the second paper. Pearson adapted a well-known model based on equations that describe how chemicals react and diffuse to resemble the two-dimensional gel system of the Austin group. He then "disturbed" the simulation by adding an extra shot of one reactant to the central region. "I give it a hard kick and then find out what happens," he says. A variety of patterns unfurled, some looking very much like the patterns observed by Swinney's group.

The model also predicted new patterns: sets of self-replicating dots that roughly resemble dividing cells. That prediction inspired the Austin group to run additional experiments after their paper went to press. The result: "We now have found replicating spots," Swinney told *Science* (see photo). In spite of that validation, Noyes recommends caution. A model's success is never a guarantee that it has much basis in reality, he says; conceivably, "the two papers may have nothing to do with each other." Still, many observers agree that the striking visual similarity between dividing cells and the replicating dots in the chemical and computerized systems is breathing new life into Alan Turing's 40-year-old conjecture.

–Ivan Amato