It's hard to name a thinker more important to shaping modern immunology than former Pitt professor Niels Jerne. Shown here, Jerne with the Queen of Sweden at the Nobel prize ceremony in 1984.

AN IMMUNOLOGIST RIDES INTO THE SUNSET | BY ERICA LLOYD

# CHALLENGING COWBOYS

Sometime during the Eisenhower era, somewhere in the Rocky Mountains, a traveling European scientist stood at a cowboy bar with a couple of colleagues and did the unthinkable. Niels Jerne turned to a few locals standing next to him and, uninvited, said something like this: *You probably think that your Colorado countryside is pretty wonderful. Actually, all these mountains and forests are very boring compared to the Champs Elysées.*

His buddies managed to rush him out of the tavern before he was clobbered. Jerne escaped unscathed and went on to serve as the chair of what was then the University of Pittsburgh School of Medicine's Department of Microbiology. In 1984, while director of the Basel Institute, he received the Nobel prize for his theories that jump-started the modern understanding of the immune response. An assay he developed at Pitt went a long way toward refining that understanding. This same man who displayed startling hubris over a beer was considered a nobleman, in the finest sense of the word, among scientists. His nobility has little to do with social circles—although the London-born Dane spent the last years of his life in a French castle near Avignon, where one can see the

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ancient Pont du Gard aqueduct from the library. (For years after he died in 1994, his widow kept his room there as he left it.)

He may have acted like a punk in that bar, yet the late Niels Jerne is remembered for elevating the behavior and pursuits of those around him. The University of California at Berkeley's Gunther Stent, who also survived the cowboy incident, was moved to write the following about him:

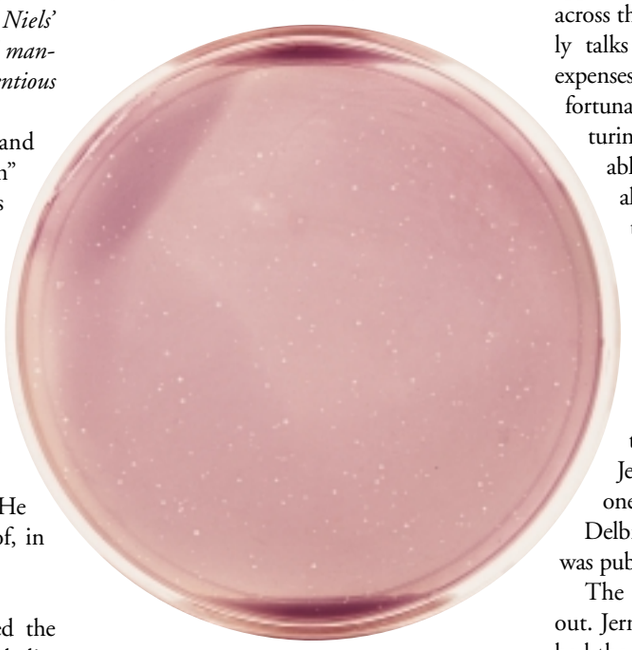
*He brought order to immunology by becoming its conscience. "What will Niels think of it?" had become the Gretchenfrage of the immunological psyche, and to receive his praise counted more for his colleagues' self esteem than prizes, promotions and election to academies. The immunologists' ambition to receive Niels' approval kept order, and especially good manners, in a discipline that had been contentious and disorderly.*

Though his ideas were prolific and prophetic—"too numerous to mention" wrote one journal editor—Jerne put his name on few papers. This was, in part, because he was largely a theorist. But also because honorary authorships were not to his liking—not during his days at Pitt in the '60s, nor when he led the Paul Ehrlich Institute in Frankfurt, Germany, nor later when he directed the Basel Institute for Immunology in Switzerland for two decades.

Jerne also knew how to pick a fight. He certainly upset an order, or lack thereof, in the field of immunology.

By 1950, Jerne probably suspected the status quo wouldn't do. He had discovered something that no one could explain: An antibody response becomes more effective the longer an animal is exposed to an antigen. Each antibody seemed to evolve so that it "fit" the antigen better. Jerne had seen it happen in rabbits when he was doing his MD dissertation work in Copenhagen in a lab shared with Stent and James Watson (the same James Watson who later found the "secret of life" with Francis Crick). In this group, which had been handpicked by the revered Max Delbrück and was inventing the field of molecular biology, Jerne was a bit of an outsider. As he studied the immune response of rabbits, the others were investigating bacteriophages (viruses that infect bacteria). As Jerne put it: "The air was filled with the phage particles that Delbrück had picked out as one of the weakest spots in the armour behind which Nature guards her secrets."

Jerne couldn't see how what he'd found in Copenhagen fit into the reigning explanation for antibody formation espoused by Linus Pauling. Pauling and other "instructionists" believed that when an antigen was introduced, it somehow taught proteins in the body to transform themselves into antibodies; these new structures would fold around the antigen, like an enzyme might, to destroy it. What else could explain the immune system's capacity to fight off an infinitely wide range of antigens? When news eventually spread of Jerne's finding that antibodies grew in effectiveness, it caught people off guard. Some thought: *Well, maybe the proteins learn to fold better—or something.*



**Jerne's plaque assay, developed at Pitt, gave science a new window into the immune system. ABOVE: Lymphocytes secreting antibodies are singled out by Jerne's technique. The clear spots are the plaques in this photograph of an agar plate.**

This line of thinking didn't sit well with Jerne. He didn't know why antibodies got better at their jobs in the course of the immune response, as he'd seen, though this goodness-to-fit phenomenon seemed to have Darwinian overtones. He began to develop a new theory of the whole system. Looking back years later, he compared how he saw the immune system to a glove shop—to be a successful proprietor, one would need a wide variety of sizes and styles in stock to fit the preferences of anyone who walked through the door. A proprietor didn't just magically produce whatever a shopper needed. Jerne believed the body was preprogrammed to have the appropriate antibodies; further, those antibodies existed before the antigen was even introduced. The antigen, in effect, selected the glove that fit it best.

When Jerne was a postdoc at the California Institute of Technology, he managed to secure a personal audience with Pauling to describe his idea, what would come to be known as the "natural selection theory." Pauling took it in, understanding it completely within minutes. Then he dismissed it entirely. When Jerne met up with James Watson at one of Pasadena's all-night eateries, he asked him what he thought of the theory. Watson was succinct: "It stinks!"

Jerne was anxious to get people to take his approach seriously. He and a colleague traveled across the States in a Studebaker, giving scholarly talks along the way (which covered their expenses). The men were not paid especially well; fortunately Jerne's traveling companion was lecturing on the eyes of beetles and claimed to be able to tell if a motel had bed bugs by smell alone. Six dollars a night appeared to be the rate the bugs couldn't afford. Along the way, Jerne got enough encouragement to write a paper on his theory—longhand, he never typed—which Delbrück had offered to submit to the *Proceedings of the National Academy of Sciences*. "Do not make any changes in the text, but please leave it as it stands," Jerne the postdoc requested on a note to one of the fathers of molecular biology. Delbrück added a comma and sent it off; it was published in 1955.

The instructionists were wrong, as it turns out. Jerne wasn't precisely correct either, but he had the right idea. Antibodies were not molded by an antigen directive as the instructionists believed. Instead humans have billions of precommitted antibody-forming cells (lymphocytes) in their systems waiting to be selected and employed. In 1957, the Australian scientist Sir Macfarlane Burnet and others described how each of these billions of antibody-forming cells spawned antibody clones that put down certain antigens. This made sense to Jerne. He delighted in nature's elegant organization—not its apparent randomness, which he'd felt he had witnessed in the Rockies.

Conferring order on the messy field of immunology took up much of Jerne's efforts. As a director at the World Health Organization (WHO), he became known for adding precision to its muddied terminology. He felt the WHO work was important; however, he was eager to see the early immune response

COURTESY CLAUDIA HENRY

**Science had its own Classical period, notes Gunther Stent, and Niels Jerne was one of its last great masters.** TOP FROM LEFT: **Jerne with his wife, Alexandra Jerne, Stent, and Claudia Henry**

in action. He loved writing in train stations; so it may have been in Geneva's Cornavin where he'd taken out his journal and jotted down an idea for an assay that he believed would offer him a close-up view of the primary immune response. The plan was modeled on the methods used by his friends in Copenhagen. Soon he would put it to the test: Pitt recruited him in 1962 to lead its Department of Microbiology.

Claudia Henry hadn't heard much about Jerne when the new microbiology chair arrived. She, a virologist, was working with Julius Youngner, who had developed the polio vaccine with Jonas Salk. When Henry had a little extra time, she would pop down the hall to see what the new crowd was doing and quickly became engaged in their work, especially the mathematical lure of Jerne's effort. The wavy-haired Dane convinced her that compelling mysteries lay in the immune system; she eventually joined his lab.

There was no technique for quantifying smaller bands of antibodies or letting one see what was happening in the early immune response in detail. Generally, one could only measure the end result of a full-blown antigen response in animals. To try to use those methods to figure out what the body was doing cell by cell was pointless—you might as well be asking a gorilla to put away the china. The job required a delicacy that no existing technique offered.

Jerne's idea was to take a diluted set of antibody forming cells, poised in a "lawn" of red blood cells, and entreat them to release antibodies. The antibody would then puncture and explode those red blood cells. You would end up with antibody-forming cells highlighted because the blood cells once surrounding them would be gone—leaving a clear ring of nothingness, called a "plaque." Then you would finally have cells that you could actually count and study.

Albert Nordin, a promising Pitt postdoc, was charged with making this dream plaque a reality. Ole Rostock, a superb technician from the Copenhagen lab, had been recruited as well to help his friend Jerne set up shop. Rostock consented to do this though he had never been further than 80 kilometers outside Copenhagen. One day, after a little jaunt through the western Pennsylvania mountains, Rostock dined with the other hikers at a Chinese restaurant near the med school. All this newness was too much for the homesick Rostock. Looking at a huge, exotic mushroom on his plate he began to weep. He left soon after.

Jerne, Henry, and Nordin were sad to see Rostock go, but the work proceeded. The seventh floor of Scaife soon became a venue for spontaneous colloquia—usually in Jerne's office, with him at a blackboard sketching out an idea with Henry, Nordin, Hiroshi Fuji, Stewart Sell, MD '60 (see p. 18), Aurelia Koros, and anyone else able to contribute.

In Pittsburgh, Jerne was still stirring things up, though now more successfully than he had in that cowboy bar. At local gallery exhibit openings, he was likely to look at a piece and ask the gallery owners, "Could you turn that upside down so we can see how we like it that way?"

They would always do it, for some reason. They were happy to. One had the sense that something interesting was about to happen around Niels Jerne. That was usually the case. By 1963, the Pittsburgh group was watching the primary immune response unfold before them. As Burnet would have predicted, there was a tremendous increase in the number of cells making antibodies—an expansion of clones. Aaron Stock, a bacteriologist, suggested staining the plaques with benzidine. Jerne proclaimed that the view was like taking in the stars in the heavens.

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The group was rewarded with intriguing findings: In a control group, mice were producing antibodies *without* being injected with antigens. (Jerne had seen something similar in horses in Copenhagen.) And the instructionist notion that the antibody destroyed the antigens was finally put to rest altogether. They found antigens still floating around the bloodstream after antibodies had done their jobs.

The plaque was soon adapted in labs everywhere pursuing problems of cellular immunology. It begot exciting new techniques and expositions on the biology of the immune system. Jerne, of course, found much more to say.

His plaque window underlined how dramatically the immune response typically shuts down. He went on to develop his network theory, which pointed out how the immune system imbeds "internal images" of the outside world via antigens. The recognition pattern is like a series of ripples in a lake, he noted: Antigens are recognized by antibodies that are recognized by antiantibodies and so on. And those antiantibodies must then look a bit like—or have characteristics of—the original antigen. Jerne suggested that these internal images help healthy individuals build powerful and self-regulating immune systems that are uniquely appropriate for their environments.

The idea was enticing and important to further thinking in clinical and experimental immunology. It was maddening to model mathematically though. By the '80s, immunologists seemed less interested in describing biology and more interested in genetics. "I feel that the immense crowd in that field are suffering from the universal DNA disease," Jerne wrote his old friend Henry in 1993. "If you ask them what happens to an antigen when it enters into your tissues, they look like rabbits that don't know what way to flee."

Some are still captivated by the hypothesis. Leonore Herzenberg of Stanford University is, though she thinks Jerne was wrong, and said so in a paper she submitted to the *European Journal of Immunology.* She postulated that such a network would work more like a circuit board than interacting ripples. Through the grapevine she heard that Jerne, who was on the journal's editorial board, had been arguing with the other board members—he thought it was important to publish her paper. Herzenberg didn't see it appear, and began to think it wasn't going to run. Finally, it came out: volume 10 (1980), issue 1, page 1—the exact same page that one of Jerne's landmark papers appeared nine years earlier. She likes to think Jerne was behind that.

"This," she says, "I would consider a singular honor." ■