**Dennis Kasper, MD**

# Developing a Vaccine for a Deadly Bacteria

Of the approximately four million babies born in the U.S. annually, 8,000 develop group B streptococcal infection within the first three months of life. The consequences for these infants, as well as their families and society, are often catastrophic: group B strep kills between 10 and 15 percent of stricken newborns and devastates another 30 percent with bacterial meningitis that results in permanent neurological deficits including epilepsy, mental retardation, and deafness.

What turns this common bacteria that often resides symbiotically in its human host into such a devastating pathogen in newborns has been the research focus of Dennis Kasper, MD, for the last 18 years. Along the way, Kasper, co-director of the Channing Laboratory, has made a number of important discoveries. "We've totally defined the fine chemical structure of the cell surface of this bacteria," Kasper says. "We've also explored its role in disease and the mechanisms by which it causes disease, looked at how it is recognized by the immune system, and finally, have developed two very promising vaccines."

Kasper's initial interest in the bacteria came on the heels of a dramatic increase in the incidence of group B strep in newborns in the late 1960s. Born without antibodies passed on by the mother, newborns exposed to group B strep – which are part of the normal flora of the vaginal tract of many women – are at risk from birth through the first three months of life.

"Babies whose mothers lack antibody to the bacteria are more susceptible to infection, and babies who get infected lack antibody," says Kasper, who was the first to demonstrate that antibody production is spurred by the polysaccharide (a molecule made up of a chain of sugars) capsules that coat the bacteria's surface. His discovery of the specific antigenic trigger arose from a series of experiments in which he pulled the polysaccharide coat from the bacteria's surface and defined the molecule's fine chemical structure.

With the antigenic surface molecule separated from the infection-causing bacteria, Kasper proceeded in the mid-1980s to make a vaccine. "It occurred to me that if we could immunize women of childbearing age or even younger, and if that immunity lasted long enough, their babies wouldn't be susceptible to disease," Kasper says. However, the first vaccine he developed, which consisted of the group B strep polysaccharide alone, induced antibody in only 60 percent of antibody-negative women. "We had to go back to the drawing-board and make a better vaccine."

Kasper knew that he could enhance antibody production by chemically linking the polysaccharide to a protein. "The immune system has two basic types of cells: B-cells and T-cells, and B-cells are the ones that make antibodies, but they need T-cells to help. It turns out that polysaccharides by themselves don't induce T-cell help very well, but by coupling them to proteins, the T-cells get turned on."

Although his approach looked good on paper, accomplishing the chemical coupling of the polysaccharide and protein, tetanus toxoid, proved extremely difficult. "The polysaccharides are very labile," Kasper says. "It took us nearly three years to develop methods to achieve this coupling." Kasper and colleagues including Michael Wessels, MD, and Lawrence Paoletti, PhD, recently developed two versions of the vaccine that in animal models produce antibody 100 percent of the time. Clinical trials with his long-time collaborator and former Channing Lab colleague Carol Baker, MD, now at the University of Houston, are scheduled to begin in 1992.

Another promising approach to preventing group B strep infection is giving antibodies directly to high-risk newborns. "When you give the vaccine to people who have antibody, it substantially boosts their antibody production. We can harvest those antibodies from a pool of antibody-positive volunteers," says Kasper, who is

now working with a company to develop this therapy. "Our hope is that if you give a baby antibodies from a bottle, you might achieve the same effect as by immunizing the mother. I see the vaccine to immunize mothers and the antibody therapy for newborns as complementary. Babies at high risk for infection are often those who are so premature that their mothers' antibodies have not been passed on to them yet."

Although he stands on the verge of giving the public a group B strep vaccine and treatment that could save thousands of lives and millions of dollars, Kasper does not regard it as an endpoint for his research. "We've had 18 years of promising results." he says. "We've totally defined the cell surface structure of this bacteria at a level that no one else has been able to do, and we've learned a lot about what makes polysaccharides important in causing disease and their recognition by the immune system."

A tenacious problem-solver, Kasper has already set his sights on a new horizon. "I'm very interested in understanding more about the application of molecular biology to polysaccharides. DNA makes proteins, but it does not make sugars. The biosynthesis of sugars is one of the most sophisticated functions a bacteria can do. I want to understand the genetic regulation responsible for this biosynthesis."