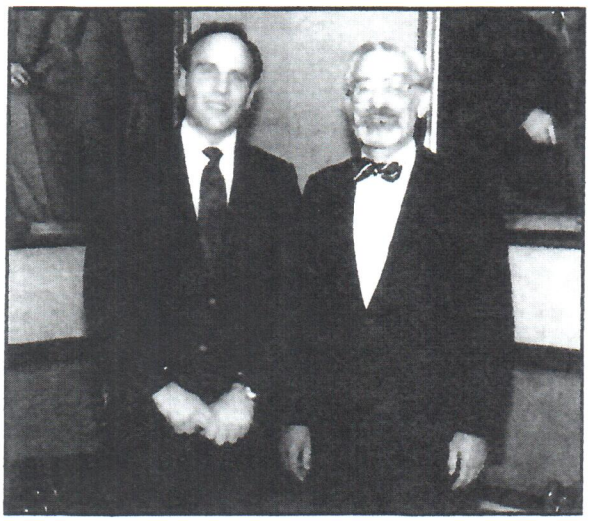
Harvard Medical Area
FOCUS
January 7, 1988

Dr. Dennis Kasper Named Edward Kass Professor

First Incumbent of Newly Created Chair



Drs. Edward Kass (r) and Dennis Kasper celebrate the new Edward Kass Professorship in Medicine.

When the Infectious Disease Society of America chose him to receive the annual Squibb Award for the outstanding researcher under the age of 45, Dr. Dennis Kasper was asked by whom he would like the award presented. "I could think of only one person," says Dr. Kasper, "and that was Ed Kass." Dr. Kasper's choice reflected the intellectual bond shared by him and his mentor at Harvard Medical School, Dr. Edward Kass (see related story on page 7), the William Ellery Channing Professor of Medicine and Director of the Channing Laboratory. With the establishment of the Edward Kass Professorship in Medicine, it seems especially fitting that Dr. Kasper, HMS Professor of Medicine, Associate Director of the Channing Laboratory at Brigham and Women's Hospital (see related story on page 6), and Director of the Division of Infectious Diseases

Continued on page 4

Dr. Dennis Kasper

Continued from page 1

at Beth Israel Hospital, should be selected as the first incumbent.

With vaccine development as a long-range goal, Dr. Kasper has studied the molecular composition of the coats of a variety of bacteria and has evaluated the human immune response to these molecules. Not only do these studies hold promise for antibacterial vaccine development, they have turned up some unexpected facts about the interaction between microbes and the immune system. In the particular case of *Streptococcus hemolyticus group B* such analysis has revealed a case of evolutionary trickery; and with *Bacteroides fragilis* Dr. Kasper observed an unanticipated immune response.

Group B Strep

Before coming to Harvard in 1972, Dr. Kasper had studied the polysaccharide coats of a class of bacteria responsible for meningitis, with the intent of developing a vaccine for bacterial meningitis. With long-time collaborator Dr. Carol Baker, now Professor of Pediatrics at Baylor Medical College in Texas, Dr. Kasper exploited techniques he developed in those earlier studies to analyze the chemistry of the bacterial coats of the group B streptococci. Dr. Baker had been a Research Fellow in the Channing Laboratory. In fact, a presentation given by Dr. Baker at the Channing Laboratory's annual "Proc Soc" meeting about a dozen years ago, describing group B streptococci as an important pathogen of neonates, spurred Dr. Kasper's interest in developing a vaccine for it.

The major infectious cause of morbidity and mortality in newborns, Strep B is part of the normal vaginal flora, and therefore can potentially infect any baby not born by Cesarean section. Annually 12,000 to 15,000 babies become infected. Strep B infection proves fatal in 35 to 40 percent of the cases, and of the survivors, 25 percent experience serious neurological disorders. Early onset Strep B infection manifests itself within the first week of life, usually as respiratory distress syndrome, and half of these cases result in death. In late onset Strep B, symptoms of infection are evident anywhere from one week to three months after birth. Often, late onset infection leads to meningitis, with a mortality rate of 20 percent.

Most babies are protected from infection by maternal antibodies that cross the placenta before birth. Babies born to mothers who do not have these antibodies have a greater risk for infection. Dr. Kasper was therefore interested in developing a vaccine safe enough to administer to pregnant women and effective enough to prevent Strep B infection in newborns.

Normal antibody production arises because the chemical constituents of bacteria often differ from the chemical constituents of host cells. The body, recognizing the presence of an entity that is 'non-self,' will produce antibodies that react specifically with the foreign chemical, or antigen, on the bacterial coat. Antibody-antigen binding will then activate a chemical 'cascade,' which will ultimately result in the destruction of the invading microbe, assuming that the antigen is sufficiently distinct from the host's cell-surface components to activate the antibody-producing response.

An Evolutionary Trick

Dr. Kasper found that in the case of Strep B, one cannot make this assumption. Upon analyzing the Strep B bacterial coats, he found that the polysaccharide -- a polymer of sugar molecules -- in Strep B was nearly identical with the polysaccharides found on mammalian cells. Specifically, he discovered that the bacterial coat had an attached chemical group, sialic acid, which, according to Dr. Kasper, "is ubiquitous on mammalian structures. This shows us how these bacteria take advantage of the host to escape detection by the immune system. Maternal antibodies may therefore not be produced, since the body will not recognize the bacteria as foreign."

Even though the chemical composition of the polysaccharides in Strep B bacteria and humans is similar, Dr. Kasper found that the length of the polysaccharide chains differs in the two species. In collaboration with Dr. Michael Wessels, Dr. Kasper showed that a vaccine containing purified bacterial polysaccharides could generate antibodies that would distinguish the differences in length between Strep B and mammalian polysaccharide chains. Furthermore, the antibodies thus generated were of a higher affinity and were more efficient in clearing bacteria than are endogenously produced antibodies.

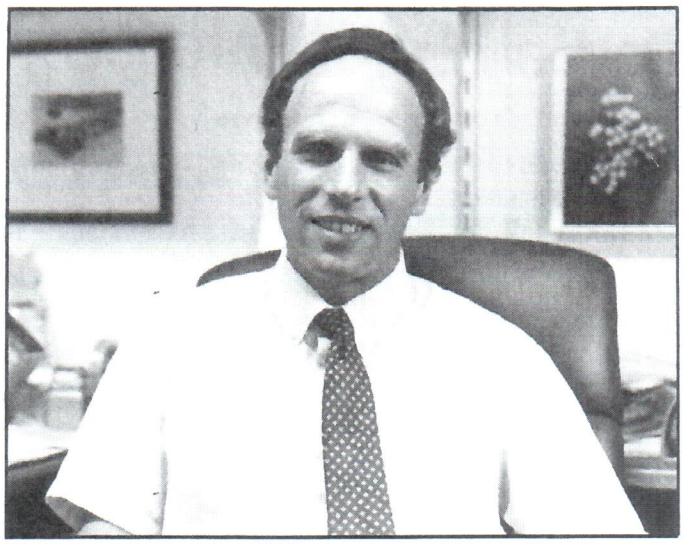
Studies in which Dr. Kasper injected bacterial polysaccharide into subjects who had no immunity to Strep B yielded a 60 percent response rate; that is, 60 percent of the subjects were able to produce protective antibodies to Strep B. According to Dr. Kasper, "these studies have shown that pregnant women can safely be immunized in their second or third trimester, and confirm that the maternal antibodies cross the placenta and protect the newborns. Ideally, we would like to see 100 percent success with this vaccine, but even at 60 percent, use of the vaccine can prevent over half the deaths due to Strep B infection." Currently, Dr. Kasper is exploring ways in which to improve the efficacy of the vaccine, before it is made generally available.

Bacteria in Space

During the early phases of the U.S. space program, NASA scientists were concerned that astronauts in space could become infected by anaerobic bacteria -- bacteria that survive in an oxygen-free environment, such as that found in outer space. NASA's fears proved to be unfounded, but research since has revealed that anaerobic bacteria inhabit more local environs. Omnipresent in the mouth, as well as in the genital and intestinal tracts, anaerobic bacteria become harmful when they are released from the mucosal barriers that contain them. Dr. Kasper's work has focused on one of these anaerobes, a bacterium called *Bacteroides fragilis*.

"In the event of a gunshot wound, military accident, surgery, or any other trauma to the gastrointestinal tract that would release *B. fragilis* from its usual environment into the general circulation, a vaccine would be useful to prevent abscess formation and bowel sepsis, the major clinical manifestations of *B. fragilis* infection," notes Dr. Kasper. Abscesses can lead to prolonged fever and illness, and they require surgical drainage to remove them. In cases where the abscesses remain untreated, they can be fatal. *B. fragilis* is also interesting because it is resistant to penicillin, and "an antibacterial agent effective against this bacterium may be effective against other penicillin-resistant bacteria, both anaerobic and aerobic."

Dr. Kasper's study of *B. fragilis* began with an analysis of the bacteria's structure. As in other bacterial studies, Dr. Kasper's approach would be to determine



Dr. Dennis Kasper

the molecular composition of the bacterial capsule. However, the very presence of a capsule on *B. fragilis* had been a source of much debate in the scientific literature. With his colleagues, Dr. Kasper provided the first demonstration that this bacterium had a capsule and that the capsule was responsible for abscess formation. "We showed that bacteria without capsules could not form abscesses in a mouse model. Capsule-less bacteria required cooperation from other bacteria with capsules for abscesses to form."

Immunological Anomaly

"We believed that since the bacterium was encapsulated, we could use the capsular constituents to induce antibody formation," he recalls. "As in the case of Strep B, we undertook to purify the capsular polysaccharides in an attempt to develop a vaccine." But the antibodies produced in response to polysaccharides in the *B. fragilis* capsule failed to prevent abscess formation in mice.

Surprisingly, protective immunity could be derived when T-cells from immune animals were transferred to non-immune animals. The finding was unexpected, as T-cells were thought to intervene only when an infectious agent enters a host cell, which *B. fragilis* does not. According to Dr. Kasper, this is the "first known case where an encapsulated extracellular bacterium induced T-cell intervention." Since *B. fragilis* does not cause infection by penetrating host cells, classical immunology to polysaccharide antigens

Continued on next page

Dr. Dennis Kasper

Continued from preceding page

would predict only an antibody-producing response, which is under the control of B-cells. T-cell-mediated immunity to *B. fragilis*, says Dr. Kasper, "astounded us. It flew in the face of classical immunology." Instead of boosting the antibody response to *B. fragilis*, vaccine studies will focus on boosting the T-cell-mediated response. This series of studies has been conducted in collaboration with Drs. Robert Finberg, Dori Zaleznik, Joseph Crabb, and Andrew Onderdonk.

Throughout his career, Dr. Kasper credits Dr. Edward Kass with guiding him. "Dr. Kass is a brilliant man whose advice has been invaluable to me. He is a major figure in infectious disease, not only at HMS, but internationally, so it is a great professional honor to hold a chair named for him. Because he has been my mentor, my appointment as the Edward Kass professor has great personal significance as well."

Founding of the Channing Lab

The Channing Laboratory at Harvard Medical School is a relatively young facility, with a relatively old name. It commemorates William Ellery Channing, Boston clergyman and a founder of Unitarianism in the United States, who died in 1842. The Laboratory that now occupies most of 180 Longwood Avenue adjacent to the Medical School began in a single room at Boston City Hospital, in 1957. The story of the link between the Boston cleric and the HMS laboratory for infectious disease research and epidemiological studies is first the story of Harriet Ryan Albee, and then of Edward Kass.

Harriet Ryan was a poor seamstress and hairdresser who lived in Boston from 1829 until her death in 1873. Her mother had cared for women dying of tuberculosis, and Harriet was encouraged to do the same. Although consumptive herself, Harriet spent her days attending her clients, and her nights caring for sick women, sometimes taking them to her own lodgings. Her customers began to help, contributing money for the expenses of the patients. By 1857 Harriet began to look for space to care for more than one at a time.

She lived on Channing Street, named for the late minister whose church was nearby. Harriet Ryan persuaded the current minister to rent out the rectory basement at $100 annually, and with some help from her Beacon Hill customers, the Channing Street Home was opened, with seven beds. When the home had to relocate, it kept the Channing name.

Charitable support increased the home's size and finances, and in time it incorporated. In 1907 it moved to Pilgrim Road opposite the New England Deaconess Hospital, but by the mid-1950s and the coming of isoniazide, its beds were virtually emptied. Dr. Edward Kass, then an HMS researcher at the Thorndike Laboratory at Boston City Hospital, was a member of the committee formed by the Channing Home's board of trustees to decide the future of the Home and its assets. Dr. Kass proposed supporting research in chronic infectious diseases, and the trustees agreed to fund it, thereby creating the Channing Laboratory, which Dr. Kass subsequently headed.

Dr. Kass' own investigations of hypertension and bacteriuria had involved studying large populations, and it was logical that as the lab grew, in addition to microbiology and infectious diseases, it developed expertise in epidemiology. Although most of the Harvard services left Boston City Hospital in 1973, the Channing Lab remained two more years, before moving to Longwood Avenue. The Channing Home assets (matched by funds raised by Dr. Kass) were turned over to HMS in the early 1970s and used to endow the William Ellery Channing chair, and the Harriet Ryan Albee Fellowship in Infectious Diseases, a fellowship once held by Dr. Dennis Kasper.