

# PASTEUR PERSPECTIVES

THE NEWSLETTER OF THE PASTEUR FOUNDATION DEVOTED TO THE WORLD OF THE INSTITUT PASTEUR

## THE CUTTING EDGE

by Caitlin Hawke

### FOCUS ON ANTHRAX THEN AND NOW

**H**AZMAT. Cipro. Strange terms we will never forget, now linked indelibly to the most frightening word of all: anthrax. From the Greek word for coal, the disease got its name from the black, ulcerative skin lesions that occur in humans and livestock infected with the bacterium *Bacillus anthracis*. People can be infected in three ways: via inhalation, ingestion or cutaneous exposure to anthrax spores. Symptoms of



inhalational anthrax include fever, nausea and other flu-like conditions. Difficulty breathing results from pressure on the lungs from swelling in the area behind them, and anthrax infection can therefore be confused with pneumonia.

Until its malevolent appearance in the United States last fall, human cases had been so rare (236 cases were reported here between 1955 and 1999) that the U.S. medical system was ill-equipped to diagnose the telltale symptoms. Since it is not contagious, when anthrax recently appeared in two co-workers, bioterrorism was immediately suspected.

Over a century ago, Louis Pasteur was no stranger to anthrax. Ever mindful of the symbiotic relationship between research and its practical applications, Pasteur studied this disease, a plague that was decimating sheep flocks and causing great economic loss. As did others such as Robert Koch, who discovered the role of *B. anthracis* in anthrax in 1877, Pasteur recognized its infectious nature and, as a result of several elegant experiments using dilution, filtration and attenuation, he demonstrated beyond question that the bacillus caused the disease. Thanks in large part to these two great scientists, the germ theory of disease was beginning to take hold against prevailing dogma.

But there were still many disbelievers. How could they be convinced? Anthrax, or *charbon* (the French word for coal), would become the subject of perhaps Pasteur's most public and

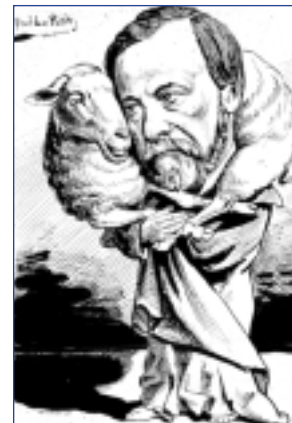
convincing demonstration of the prevention of infectious diseases by vaccination with attenuated or weakened pathogens.

In May 1881, a public demonstration—one that caught the attention of the international scientific community—took place before many skeptics at Pouilly le Fort, a farm owned by the veterinarian Rossignol. On May 5, 24 sheep, six cows and one goat were inoculated with Pasteur's live but weakened *B. anthracis* culture. Twelve days later, the same animals were revaccinated with a slightly more virulent culture. Finally, on May 31, each of these animals, in addition to a control group of 29 new animals, was given a deadly, unattenuated culture. The result: three days later, all of the inoculated animals were alive and well, while 25 of the control animals were dead or dying. Vaccination was soon to become a widely used method, first applied by veterinarians, with immeasurable economic benefits.

Fast-forward to the present, with its oppressive climate created by the threat—and recently the unfortunate reality—of bioterrorism. Pasteur's words resonate with new meaning:

*"I beseech you to take interest in these sacred domains so expressively called 'laboratories.' Ask that there be more and that they be adorned, for these are the temples of the future, wealth and well-being. It is here that humanity will grow, strengthen and improve. Here humanity will learn to read progress and individual harmony in the works of nature, while humanity's own works are all too often those of barbarism, fanaticism and destruction."*

*L. Pasteur*



Louis Pasteur portrayed as the savior of sheep circa 1881



A full 120 years after Pasteur applied what was then cutting-edge technology to fight anthrax, the Institut Pasteur continues to pursue improved tools against the disease. Unfortunately, vaccination of the public at large was not a viable alternative during the recent crisis. In fact, the current human vaccine, different from the live veterinary one, is not completely satisfactory. Treatment with antibiotics has proven effective—but only if anthrax is diagnosed rapidly. Therefore, a goal of Pasteur's Toxins and Bacterial Pathogenesis Unit is to develop an improved vaccine for eventual human use.

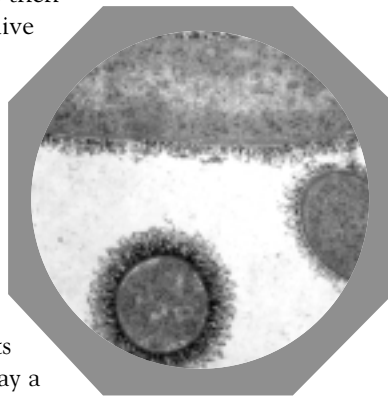
Michèle Mock and her colleagues in the Toxins lab published their work on an experimental anthrax vaccine in the February 2002 issue of *Infection and Immunity*.



Michèle Mock

According to their paper, “after entry into the host, the spores germinate and yield toxin-producing, capsulated bacilli. Toxemia and septicemia rapidly lead to death. The bacilli secrete three proteins, protective antigen (PA), lethal factor (LF) and edema (PA plus EF) which compose the two toxins.” The team’s vaccine makes use of the PA protein and anthrax spores that have been inactivated by formaldehyde. The concept is that protection induced by spores will limit the germination of the spores at the onset of infection. First mice and guinea pigs are inoculated. Once these animals have been protected by the vaccine, scientists then challenge them with live virulent *B. anthracis* spores. These animals do not become infected, showing that a non-living vaccine is able to induce a protection similar to the live veterinary vaccine.

The study suggests that spore antigens play a role in protecting against infection. It is expected that a new, efficient human anthrax vaccine—one that is non-toxic to humans—will result from this promising work.



Anthrax spore

To read more about this work, please refer to: "Anthrax spores make an essential contribution to vaccine efficacy," Fabien Brossier, Martine Levy and Michèle Mock, *Infection and Immunity*, February 2002, pp. 661-664; or visit the website of the Institut Pasteur: [www.pasteur.fr/actu/presse/press/index.html](http://www.pasteur.fr/actu/presse/press/index.html)

#### DR. MOCK RESPONDS TO A FEW QUESTIONS ABOUT HER TEAM'S WORK:

- Q:** *What led you to study the mechanisms of anthrax, given that it is so rare in humans?*
- A:** Anthrax is still endemic in many developing countries, causing both physical illness and secondary effects with economic consequences, such as the loss of cattle. The development of molecular biology and discovery of plasmids reawakened our interest in anthrax, which had been neglected for many years at the Institut Pasteur. The disease, which provokes both toxemia and septicemia, is a fascinating model in the study of the pathogenic virulence mechanism, and our efforts have been supported over the years by the institute.
- Q:** *How does the recent work fit into the context of the mission of your laboratory?*
- A:** Our lab has focused for many years on the virulence mechanisms of *B. anthracis*, the interaction between the pathogen and the host, the physiopathology of anthrax, development of genetics, and so on. The results of this basic research have brought us to an innovative concept for the improvement of the human vaccine.
- Q:** *In your opinion, what is the ultimate application that could result from this work?*
- A:** A new human vaccine. However, years of study and tests are still required. The live vaccine used successfully in animals cannot be used safely in humans, so we must continue to work toward the development of an efficient non-living vaccine.
- Q:** *What makes the currently available anthrax vaccine inadequate for humans? And how can you increase its efficacy?*
- A:** The vaccine based on the protective antigen [PA] does not safeguard against some highly virulent strains. We have found that the addition of inactivated spores can help during the early stages of infection, and this method may also be crucial if, in the future, antibiotic-resistant strains are developed. Secondly, the currently licensed PA vaccine is prepared from a crude supernatant of the Sterne strain containing low amounts of active lethal and edema factors, which could account for the reported reactogenicity. The PA included in our vaccine is prepared from a recombinant strain which does not produce LF and EF, making it much safer.
- Q:** *Where do you see the field moving – if at all – following the events of this past fall, specifically the threat of bioterrorism?*
- A:** It is still too early to see where we are going. However, I can say that, as a researcher, I am troubled by the fact that we are working to fight illnesses—some, such as smallpox, already under control—manufactured by man with the sole purpose of annihilation. Although this paradox is not new to science, we have again forgotten that the knowledge we develop should be used to improve the lot of humanity. We must remain vigilant in our pursuit of that goal.

*We would like to thank Dr. Mock for her participation in this issue.*

## AMERICAN UNDERGRADUATES STUDY AT THE INSTITUT PASTEUR

Last summer, the Institut Pasteur hosted a group of undergraduate biology students from Chicago's Loyola University. The goal was to train these students in the fundamental principles of the biological sciences in preparation for their graduate studies. According to Jeffrey Doering, professor and chairman of Loyola's Biology Department, "Enhancing students' critical thinking skills is the main objective."

Organized by Loyola's Anthony Nappi, Ph.D., and Pasteur laboratory head Paul Brey, who is himself an American, the program attracted immediate attention. Dr. Nappi commented that it "generated so much interest that the limit of students who could participate was reached before it was advertised." Dr. Brey says, "This was a wonderful way to open the campus to young Americans who might consider future work here."

Students devoted three weeks—one in preparation at Loyola and two at the Institut Pasteur—to learn about transmissible diseases such as AIDS, Ebola, malaria and dengue fever. The program addressed disciplines as diverse as molecular epidemiology, molecular biology and immunology, supplemented by discussion sessions. The primary objectives were to develop and expand students' interest in biological research, to teach them to read and analyze primary research, to help them think critically and, finally, to instill in them the importance of international collaboration in scientific disciplines. Dr. Doering comments, "Very rarely does a student pursue a career abroad, but the outstanding scientific community in France would make it a good place to do so."

Among the results of the course: several students who came into the program considering careers as physicians were struck by the synergy that could result from a joint M.D./Ph.D. degree. At the conclusion, one student remarked, "I realized that research is interesting and useful in the realm of public health, and it is definitely something that one can be passionate about."

## INSTITUT PASTEUR JOINS GAVI

This past summer, the Global Alliance for Vaccines and Immunization (GAVI) welcomed the Institut Pasteur to its board. As Director General of the Institut Pasteur, Dr. Philippe Kourilsky will hold the seat representing the international research community



Philippe Kourilsky

for two years, replacing the outgoing U.S. National Institutes of Health.

GAVI, an international partnership formed in 1999 to address the worldwide issue of immunization, pairs public and private sectors in an effort to ensure that all children, regardless of socioeconomic standing, have access to vaccination.

Partners include the Bill and Melinda Gates Children's Vaccine Program, the Rockefeller Foundation, UNICEF, the World Health Organization and the International Federation of Pharmaceutical Manufacturers Association.

GAVI partners have pledged more than \$600 million over the next five years to vaccinate children in 36 of the world's poorest countries where, according to *The New York Times*, only 56% of children (probably an inflated estimate) receive the most basic immunizations.

Carol Bellamy, GAVI Board Chairperson, remarked recently, "The power of GAVI is in the collaboration among partners. When you have UN agencies, industrialized-country donors, vaccine manufacturers and developing-country health officials all sitting around the same table, public health programs can be much more effective."

With regard to this appointment, Dr. Kourilsky noted that "the Institut Pasteur is proud to be involved in this crucial initiative that dovetails beautifully with the mission of our institute: the worldwide improvement of public health."

## THE LAUNCH OF THE PASTEUR FOUNDATION POST-DOCTORAL FELLOWSHIP PROGRAM

The Pasteur Foundation has created a new program to bring U.S. post-doctoral researchers to work in Institut Pasteur laboratories in Paris. Guided by the institute's administration, which seeks to develop international scientific exchanges to ensure the vitality and quality of the Institut Pasteur labs, this program is uniquely for American citizens. Special attention will be given to the Pasteur Foundation Fellows so that their time on the Parisian campus of the Institut Pasteur will be an enriching experience not only scientifically, but also personally and culturally.

Thanks to the generosity of U.S. donors and in particular that of the Florence J. Gould Foundation in New York, eight Pasteur Foundation fellowships have already been established. For those American researchers who may be interested in applying, please contact Isabelle Saint Girons ([isgirons@pasteur.fr](mailto:isgirons@pasteur.fr)) or the Pasteur Foundation ([PasteurUS@aol.com](mailto:PasteurUS@aol.com)) for information on future application deadlines and procedure.

More news to come in a future issue of *Pasteur Perspectives*.

## MORE TO THE POINT: BRIEF NEWS FROM PASTEUR

**AIDS—A CANDIDATE VACCINE:** Scientists in Pasteur's Antiviral Cellular Immunity Unit have used mice with partially "humanized" immune systems to select applicable peptides for an HIV vaccine. This study provides promising data on the possibility of a candidate vaccine, underscoring the relevance of an animal model for evaluation of strategies against AIDS and other pathologies.

**CANCER GENE THERAPY:** Pasteur's start-up company Collectis has signed an agreement with Zentaris for use of its cancer gene therapy using sLTR (single long terminal repeats). This cutting-edge technology permits the elimination of tumor cells without affecting healthy tissue. Zentaris will apply sLTR to treatment of various cancers, including colorectal, brain and throat tumors.

**FOOD POISONING:** Last fall, a comparison of the genome sequences of *Listeria monocytogenes*, a bacterium responsible for potentially lethal food poisoning (particularly toxic in pregnant women and immunocompromised individuals), and its benign cousin *Listeria innocua* was published in *Science*. The work, coordinated by Pasteur's Pascale Cossart and Philippe Glaser, opens the door to a better understanding of the virulence of *L. monocytogenes* and should lead to improved methods of detection and prevention.

**PASTEUR IN SOUTH AMERICA:** In fall 2001, the Institut Pasteur signed an accord with the countries of MERCOSUR (the South American regional economic market that links Argentina, Bolivia, Brazil, Chile, Paraguay and Uruguay). The intent is to foster cooperation in scientific research and exchanges in the domain of human health, with emphasis on infectious diseases of specific concern to the region. A graduate-level educational component and the facilitation of technology transfer are also covered by the agreement.

**MEDICAL TELECOMMUTING MADE EASY:** LEDA, a nonprofit organization for liaison, education, diagnostics and assistance, has been established by a group in France that includes the Institut Pasteur and Médecins du Monde. The purpose is to allow doctors and other health professionals isolated in remote areas in the field to connect via satellite to a center on the Pasteur campus and tap into its resources and the expertise of staff personnel. Future LEDA programs will include coursework and training for medical professionals in developing countries.

### INVEST IN A HEALTHY FUTURE

One of the world's premier centers of fundamental research, the Institut Pasteur is entirely dedicated to life sciences and human health. We need your help to continue this work.

Please consider making a tax-deductible contribution or a bequest to the Pasteur Foundation, a 501(c)(3) corporation.

For further information, contact Caitlin Hawke  
at the Pasteur Foundation, 212.599.2050.

## HELPING THIRD WORLD COUNTRIES FIGHT AIDS

In 1988, the Institut Pasteur and the U.S. Department of Health and Human Services created the World AIDS Foundation to help developing countries fight the epidemic. The primary goal of the foundation remains the prevention of AIDS through research programs as well as the education and training of health personnel. This year the foundation has voted to support 32 programs, including, among others:

- Niger: education program
- South Africa: AIDS prevention program for women who are victims of abuse
- Venezuela: education programs for children and adolescents

Since its inception, the foundation has devoted \$20 million to 250 programs, with an allocation of \$2.3 million for this year's agenda.

### PASTEUR PERSPECTIVES

A 501(c)(3) organization, the Pasteur Foundation is the U.S. nonprofit affiliate of the Institut Pasteur. Located in New York City, the foundation works to introduce the research conducted at the Institut Pasteur to the American public, to develop exchanges between Pasteurian and U.S. scientists, and to raise funds for Pasteurian research. For more information, please contact the Pasteur Foundation.

*A copy of the latest annual report may be obtained, upon written request, from the Office of the Attorney General, Charities Bureau, 120 Broadway, New York, New York 10271.*

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SAVE THE DATE: THURSDAY, MAY 23, 2002

## Pasteur Foundation Spring Benefit

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