Number 5/Fall 1998

PASTEUR FOUNDATION

PASTEUR PERSPECTIVES

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

THE CUTTING EDGE

by Caitlin Hawke

FOCUS ON TUBERCULOSIS

One of every three people is infected with *Mycobacterium tuberculosis*, the organism responsible for one of the world's leading infectious diseases. Tuberculosis causes three million deaths annually, with over 25,000 new cases reported in the United States alone.

Exacerbating this global problem is the fact that antibiotic-resistant strains of tuberculosis have been found in 35 countries, making traditional treatment more difficult at best and futile at worst, and causing the incidence of this lethal respiratory disease to soar.

Discovered in 1882 by the great German bacteriologist Robert Koch, the tubercle bacillus spreads through the air when an infected person sneezes or coughs. Millions of people harbor tuberculosis in its inactive state and many will never develop the disease. However, with age or suppression of the immune system in diseases such as AIDS, the microbe becomes active and begins to cause severe damage to the lungs and often elsewhere in the body. Signs of tuberculosis infection include a persistent cough, loss of weight, diminished appetite, fatigue and fever. Blood in the phlegm is also an indication of infection.

At present, the only effective strategies against TB are childhood vaccination and a disciplined regime of antibiotics, both of which demand a well-organized and coordinated combination of medical and social care to ensure that patients not only receive adequate attention but also diligently follow the prescribed course of treatment.

Having consistently focused on the study of infectious diseases, the Institut Pasteur is investigating tuberculosis on many levels — from its global epidemiology to its genetic composition — in the quest for improved treatment.

The BCG Laboratory

In 1921, two Pasteur scientists, Albert Calmette and Camille Guérin, devised the first tuberculosis vaccine, which consists of live attenuated

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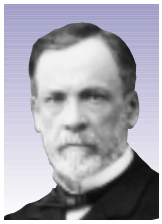


A Message from the Chairman of the Board of the Institut Pasteur

Dear Readers:

As the new Chairman of the Institut Pasteur, I take great pleasure in greeting you, our American friends, who bring moral and financial support to the Pasteur Foundation. Your generous gifts acknowledge and aid the institute's research endeavors to help advance public health throughout the world.

Philippe Rouvillois

Since the time of Louis Pasteur, excellence in research has been our primary goal, and today, in the face of new and pressing public health issues, our scientists continue to work toward fulfillment of that tradition. Our heritage has also directed us resolutely to the future and its new technologies. With this in mind, the Institut Pasteur recently undertook the task of redesigning its long-standing logo to embrace both its rich history and its commitment to an innovative future.

The new logo is built around the initials "I" and "P," which flow together to form "phi," the first Greek letter in the word "philosophy." Indeed, we wish to emphasize the Pasteurian philosophy: a quest for truth rooted in scientific rigor, humanism and concern for public health.

INSTITUT PASTEUR

A new look for the Institut Pasteur

The phi is inscribed within a circle that represents the globe, symbolizing the universal scope of Pasteurian research. The modern lettering is taken directly from the facade of the original building on the Pasteur campus, a perfect confluence of old and new.

For a firsthand experience of our rich past and our dedication to a healthier future, I invite you to visit our campus and the Pasteur Museums (see page 5) the next time you are in Paris.

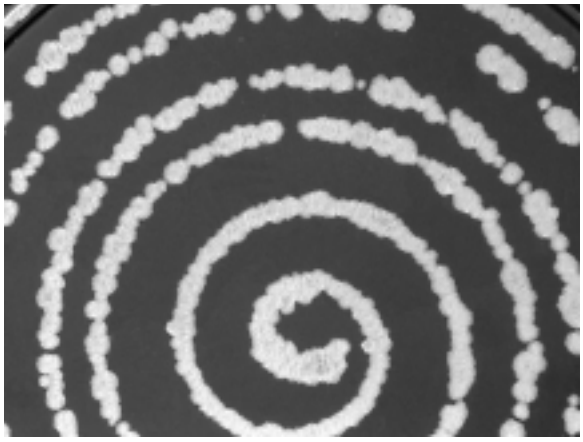
Sincerely,

Philippe Rouvillois
Chairman of the Board, Institut Pasteur

Mr. Rouvillois is a graduate of the École nationale d'administration. Inspecteur Général des Finances, he has been President of the SNCF (French Railways) and the Commissariat à l'Energie Atomique (French Atomic Energy Commission). He is currently the head of CEA-Industrie.

tubercle bacilli. Known as BCG (Bacillus Calmette Guérin vaccine), it has been in use ever since. To date, some three billion doses of BCG have been administered. Though it is the most frequently used vaccine in the world, BCG is not foolproof; it is up to 80% effective in children and only 50% effective in adults. Hence, a primary aim of Pasteur scientists working on TB is the development of an improved vaccine, which may soon be a reality given the latest Pasteur breakthrough in decoding the tuberculosis genome and the progress in mycobacterial genetics.

The BCG Lab, directed by Brigitte Gicquel and Gilles Marchal, studies the various existing strains of BCG used in vaccines available worldwide. These strains differ both morphologically and in their capacity to immunize. Therefore, a comparison of their genomes should yield interesting information about gene function. Pasteur scientists are also working to improve the current preparation and use of the BCG vaccine to ensure a more reliable treatment.



A culture of *Mycobacterium tuberculosis*

TB and the Pasteur International Network

Consisting of 22 institutions scattered throughout the world, the Pasteur network carefully monitors the appearance of different strains of TB. The organization has established a common system with which to track drug-resistant tuberculosis in five African countries.

Pasteur scientists recognized an immediate and pressing challenge: the need to develop a quick means to detect tuberculosis strains resistant to isoniazide and rifampicine, the two most effective drugs to date in the arsenal against the disease. Their work demonstrated that certain of the isoniazide-resistant strains are missing the katG gene, which codes for catarase-peroxydase. This enzyme seems to activate the antibiotic against the bacteria; when the gene is absent the TB strain is resistant to the drug. In 1993, a Pasteur team developed a test to identify the absence or mutation of this gene. Now, in two days rather than eight weeks, drug resistance can be identified and an alternative course of treatment quickly put into place.

The National Reference Center for Mycobacteria

Headed by Véronique Vincent, researchers in this lab are seeking new genetic markers to permit better comprehension of mycobacteria and their modes of infection. Formally known as France's National Reference Center for Mycobacteria, this lab monitors TB cases in France and elsewhere, as requested by the French Ministry of Health and the World Health Organization. It receives close to 2,000 samples for analysis each year. In addition to following the epidemiology of the disease, the reference center also keeps track of antibiotic-resistant strains.

The Mycobacterial Genetics Laboratory

This lab examines the interactions of mycobacteria with their hosts on a genetic level, with efforts directed toward increasing the efficacy of treatment and prevention strategies. For example, pinpointing the genes of the bacillus that code for its pathogenicity may allow them to be inactivated, yielding a more efficient vaccine against tuberculosis.

A few years ago, Brigitte Gicquel, who heads this lab, collaborated with other laboratories in the development of a rapid test to detect different strains of *M. tuberculosis*. Used by the Specialized Diagnostic Center of the Institut Pasteur, this rapid-detection test relies on the polymerase chain reaction (PCR) technique to identify DNA sequences characteristic of the tuberculosis bacillus.

Physiopathology of Infection Laboratory

The techniques of genetic recombination and biochemistry should allow the live attenuated BCG vaccine, which carries an inherent risk especially in immunocompromised (e.g., AIDS) patients, to be replaced by a perfectly safe sub-unit vaccine made of TB antigens. This requires identification of the molecule or molecules of the bacterium that would induce a strong, protective immune response. Gilles Marchal and his team in the Physiopathology of Infection Lab are working to identify these immunodominant antigens, which lie among the thousands of proteins secreted by this bacterium.

The Bacterial Molecular Genetics Unit

Genetic sequencing is the process by which an organism's genome is deciphered; it consists of mapping the precise order of the millions of nucleotides that together make up an organism's DNA molecules. The primary goal of genome sequencing is to obtain a fuller understanding of an organism's biology and to apply this knowledge in the form of new treatments and vaccines.

In the June 11, 1998, issue of *Nature*, a team of 42 French and British scientists, led by Stewart Cole, head of the Institut Pasteur's Bacterial Molecular Genetics Unit, and Bart Barrell of the Sanger Centre in England, announced the complete sequencing of the tuberculosis genome, with its 4,000 genes consisting of 4,411,633 nucleotides. Their work uncovered two new protein families — PE and PPE — the role of which could be to interfere with the host's immune response, a discovery that may prove useful in the development of a vaccine. Their work also revealed that many of the bacterium's

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A Magnificent Bequest for Science

On May 27th, 1998, 120 people attended a reception at Christie's New York to benefit the Pasteur Foundation. The reception had a dual purpose: to celebrate the publication of *Champagne…and Real Pain: Celebrities in Paris in the Fifties*, by Maggi Nolan, and to announce the June auction of the collection of the late Henry Clarke, a renowned American fashion photographer of the 1950s. Mr. Clarke, who died in 1996, bequeathed his entire estate to the Institut Pasteur. In an article appearing on June 23rd, the *International Herald Tribune* reported that the Clarke collection "sparked frenzied bidding and raised twice the amount expected." The spectacular sale, which took place in Monaco on June 20th, raised $2.7 million for cancer research at the Institut Pasteur. Henry Clarke joins the ranks of many other notable Americans who have remembered the institute in their wills and to whom the Institut Pasteur is deeply grateful.

The Pasteur Foundation thanks all of its new friends and faithful donors for their generous support of the May 27th event.

Photos: Susan B. Glattstein

The Consul General of France in New York, Richard Duqué, toasts author Maggi Nolan at Christie's. (*Champagne courtesy of Vranken America.*)

Marie-Hélène Marchand of the Institut Pasteur, Mrs. David Granger, Bobby Short and Mrs. Anastassios Fondaras at the *Champagne…and Real Pain* book party.

You Too Can Help

Planned wisely with your attorney, a specific, percentage, contingent or residual bequest to the Pasteur Foundation could save your estate (and thereby your heirs) substantial tax payments while benefiting scientific research and enabling you to leave your personal impression on the Institut Pasteur. Many of our friends have found this the simplest way to support the Institut Pasteur. Please consult your estate advisor and/or attorney for advice on how best to achieve your goals.

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

Focus on Tuberculosis

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genes play a role in the synthesis of lipids which may enable it to change the makeup of its exterior membrane. This capacity would protect the microbe — sometimes for years — from the onslaught of the host's immune system, which would be unable to launch an effective attack because of failure to keep pace with the ever-changing composition of the bacterium's protective wall.

Sequencing of the tuberculosis genome also provides the key to the bacterium's adaptive resistance to antibiotics and, as a consequence, can identify potential chinks in the microbe's armor that can eventually be targeted by new therapies and vaccines.

More to the Point: Brief News from Pasteur

Deafness Gene:
A mutation of the connexin 26 gene, which codes for the production of a cell junction protein, has been identified as one of the most frequent alterations in cases of hereditary deafness. In addition to permitting early diagnosis, the identification of this mutation may lead to new therapies for this form of deafness. This work has been conducted by internationally recognized Pasteur scientist Christine Petit, head of the Genetics of Sensory Deficiencies Lab.

Viral Surveillance Group:
In keeping with the universal effort to control the spread of infectious diseases, in June the Institut Pasteur announced the creation of a new group to monitor and study viruses. Consisting of eight members of the International Network of the Institut Pasteur, the group will work to quickly identify the first appearance of a virus in order to short-circuit development of an epidemic.

Recent Awards:
The Helena Rubinstein Foundation and UNESCO recognized **Pascale Cossart** with their Women in Science Award for her work on *Listeria monocytogenes*. *(See* Pasteur Perspectives*, Number 3, Fall 1997.)* She is also the 1998 recipient of the National Academy of Sciences' Richard Lounsbery Award.

Patrice Courvalin won the prestigious unrestricted biomedical research grant for $500,000 from Bristol-Myers Squibb last year for his work on antibiotic-resistant bacteria.

Philippe Sansonetti received the 1997 Grand Prize of the Robert Koch Foundation for his research on shigellosis.

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 year-end, tax-deductible contribution to the Pasteur Foundation.

Pasteur Perspectives

A 501(c)(3) corporation, 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.

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☐ I want to help support the research conducted at the Institut Pasteur to improve worldwide public health. I am enclosing a tax-deductible gift to the Pasteur Foundation in the amount of:

☐ $1,000 ☐ $500 ☐ $100 ☐ $50 ☐ $25 ☐ Other $_____

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☐ Please add my name to your mailing list.

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Discover the Pasteur Museums

If you are planning a trip to Paris, you may be interested to learn that there are two Pasteur Museums: the Pasteur Museum in Paris and the Pasteur Museum of Research Applications near Versailles. Both have charming, evocative rooms devoted to the legacy of Louis Pasteur.

The Pasteur Museum in Paris

Located at the heart of the Parisian campus of the Institut Pasteur, this suite of carefully restored rooms was Louis Pasteur's actual residence for the last seven years of his life and remains exactly as it was in his time. A perfect example of the atmosphere of a French residence at the end of the 19th century, Pasteur's home is filled with furniture, art, books, photographs and honors, which combine to yield a rich portrait of the man. The scientific gallery contains almost 1,000 objects used in his experiments in areas including crystallography, spontaneous generation and pasteurization. At the end of the tour, one can visit Pasteur's tomb in the crypt. This extraordinary Byzantine chapel, in the Ravenna style, is decorated with colorful mosaics that represent his most significant discoveries.

Both museums are essential stops for anyone interested in the history of science. Come discover the history of the Institut Pasteur.

The Pasteur Museum of Research Applications in Marnes

This museum is situated in the Pavillon des Cent-Gardes, which originally housed the personal guard corps of Napoleon III. In 1884, the French Government made this property available to Louis Pasteur for his rabies research. The Marnes site became the summer annex of the Institut Pasteur. In fact, it was here that Pasteur died on September 28th, 1895, in a room that has been preserved as it was at the time of his death.

The Museum of Research Applications retraces Pasteur's fight against infectious diseases through photographs, original documents and scientific equipment. In addition, it illustrates the history of serum therapy, vaccination and chemical therapy, and the role of vectors in tropical diseases as illustrated by the work of such Pasteurians as Roux, Yersin, Ramon, Calmette, Nicolle, Laveran and others. The museum also presents the state of current research conducted at the Institut Pasteur.

Visitors to the estate can also view the Lafayette Memorial, erected in memory of volunteer American aviators who sacrificed their lives for France during World War I.

The Pasteur Foundation
cordially invites you to visit

The Pasteur Museum in Paris
and
The Pasteur Museum of Research Applications in Marnes

Free admission for *Pasteur Perspectives* readers with a copy of this invitation.

For more information, please call the Pasteur Foundation at 212.599.2050.

Museum Information:

Pasteur Museum
Phone: 01.45.68.82.83
25, rue du Docteur Roux, 75015 Paris
Métro: Pasteur
Open daily, 2:00 pm to 5:30 pm.
Closed in August and on holidays.

Pasteur Museum of Research Applications
Phone: 01.47.01.15.97
3, avenue Pasteur, 92430 Marnes La Coquette
Car entrance: 3, avenue Poincaré
Trains leave the Gare St.-Lazare (toward St. Nom la Breteche).
Exit at the Garches/Marnes station, about 15 minutes outside of Paris.
Open weekdays, 2:00 pm to 5:30 pm.
Closed in August and on holidays.

Louis Pasteur's room in Marnes

The scientific room of the Pasteur Museum

PASTEUR FOUNDATION

A New Tool for French Teachers

Bring Science to the French Classroom

"À la Découverte de l'Institut Pasteur," a set of 44 flashcards (8¼ x 11½), is the perfect way to bring scientific concepts and vocabulary into the advanced French-language classroom. The cards trace the institute's creation, discoveries and contributions to the worldwide improvement of health. Scientific subjects such as influenza, AIDS, antibiotic resistance and vaccination provide students with timely and relevant departure points in conversation classes.

In clear French, the cards synthesize the main concepts behind microbiology, immunology and molecular biology, providing French and science teachers with an opportunity for cross-curricular collaboration and familiarizing the students with the work of the Institut Pasteur, one of the leading French research institutions.

In recognition of a contribution of $25 or more, the Pasteur Foundation will be happy to send you these cards as our gift. Please return the coupon below with your contribution. For more information, please contact the Pasteur Foundation at 212.599.2050.

PASTEUR FOUNDATION 420 Lexington Avenue, NY, NY 10170

Please find enclosed my gift of $_____ payable to the Pasteur Foundation. I understand that with a gift of $25 or more, I will receive a set of 44 French flashcards about the Institut Pasteur.
(NB: Cards will ship in early 1999.)

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Please note: Gifts to the Pasteur Foundation are tax-deductible to the extent provided by law.

Look for the exposition "**À la Découverte de l'Institut Pasteur**" at the Alliance Française of Chicago in December. For more information, please call 312.337.1070.