Number 7/Winter 1999

PASTEUR FOUNDATION

PASTEUR PERSPECTIVES

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

THE CUTTING EDGE

FOCUS ON CANCER AND HUMAN PAPILLOMAVIRUSES

Several research groups at the Institut Pasteur are investigating oncogenic viruses such as hepatitis B virus, Epstein Barr virus, HTLVI, and—the focus of this article—human papillomaviruses (HPVs). These organisms cause healthy cells to become malignant over the course of several stages from precancerous lesions to invasive tumors. It is highly probable that cancers associated with these viruses result from the concurrence of multiple factors such as exposure to environmental and nutritional carcinogens and genetic predisposition. While the development of vaccines is a primary aim of the teams investigating these cancer-causing viruses, the study of genetic predisposition is also a research priority.

Named for the papillomas more commonly known as warts, HPVs usually cause benign growths on the skin and mucous membranes. In 1977, two teams, from Pasteur and Germany, established the existence of multiple types of HPVs; today, over 100 have been identified. Many are sexually transmitted. Some of them are known to cause genital warts and benign lesions of the cervix. Others are associated with lesions that may convert to genital or cervical cancer in a minority of infected patients. Cervical cancer is the second most fatal cancer in women worldwide. The Pap test is a crucial screening method used by gynecologists to detect precancerous cells.

This spring, using patients with the rare skin disease epidermodysplasia verruciformis (EV) as a model study group, the Papillomavirus Unit at the Institut Pasteur, headed by Gérard Orth, located the first gene (EV1) that predisposes humans to HPV infection. Dr. Orth's team had demonstrated previously that these individuals are abnormally

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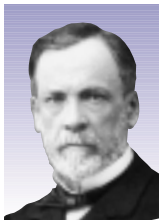
The Institut Pasteur in Numbers

1999 budget: 950 million francs ($153 million)
2,700+ people work on the Parisian campus
9 research departments
110+ research units and laboratories
17 graduate basic science courses offered
241 students of 27 nationalities
949 fellows of 62 nationalities
11 World Health Organization Collaborating Centers
22 National Reference Centers for Communicable Diseases
23 institutes in Pasteur's International Network



WHY YOUR GIFTS ARE VITAL

A Message from the Deputy Director General of the Institut Pasteur

Dear Readers:

Jean Castex

Because of its national image, the Institut Pasteur is often erroneously considered a publicly financed research organization. It is, however, a private, not-for-profit institution that relies heavily on charitable contributions and bequests to balance its budget. In fact, the institute was founded in 1887 with private contributions that poured in from all over the world in support of Louis Pasteur's work. And Pasteur himself wished it to remain private to ensure its philosophical autonomy. Its not-for-profit status means that all earnings are directly reinvested in research.

Because scientific research is costly, maintaining a healthy financial balance presents a great challenge. One way to ensure stability is through diversification of resources. Today, the institute's financing is derived from three sources: government subsidies (33.5%); income from the institute's own activities, such as royalties, consulting fees and the sale of its goods and services (41%); and private support from individuals, corporations and endowment income (25.5%). Over the last

Your help is needed more than ever. Please consider making a charitable contribution to the Pasteur Foundation. Gifts and bequests to the Pasteur Foundation may take many forms and are fully tax-deductible given its 501(c)(3) status.

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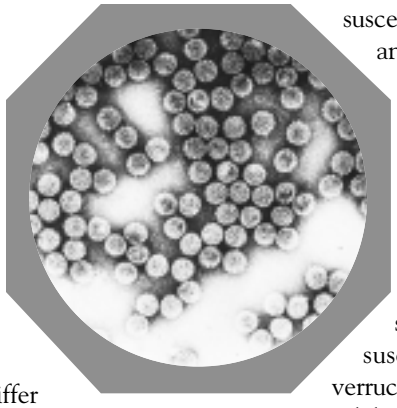
predisposed to infection by HPVs which are harmless to others, including one (HPV5) associated with the skin cancers observed in EV.

These promising results are the subject of the following interview between Dr. Orth and Dr. Judith P. Sulzberger, American Advisory Board Member of the Pasteur Foundation.

Dr. Judith Sulzberger: What type of viruses are HPVs? Are they retroviruses like HIV?

Dr. Gérard Orth: HPVs are very different from retroviruses like HIV. They are small, non-enveloped viruses, with a genome constituted by a circular double-stranded DNA molecule of about 8,000 base pairs. In contrast to HIV, the genomes of HPVs are very stable.



Human Papillomavirus (HPV)

J.S.: How do the cancer-causing HPVs differ from those that are not associated with malignancies?

G.O.: The genome of cancer-associated HPVs encodes two proteins (E6 and E7) that have the capacity to inactivate certain cellular proteins that play a central role in cell cycle control and in maintaining normal cell division. This results in uncontrolled cell growth and genetic instability and leads to the development of clones of abnormal cells.

J.S.: What percentage of patients with cancer of the cervix have a history of prior HPV infection?

G.O.: It is now known that at least 90% of carcinomas of the cervix are linked to HPV infection.

J.S.: Last year, you established a link between psoriasis and the HPV implicated in epidermodysplasia verruciformis. Is there an increased incidence of verrucae in individuals with psoriasis or is psoriasis another manifestation of HPV?

G.O.: There is no evidence of increased incidence of verrucae in individuals with psoriasis. We found that patients with psoriasis harbor low amounts of HPV5 and therefore constitute the long-sought-for reservoir of this virus known to infect patients suffering from epidermodysplasia verruciformis, a very rare disease. This is not sufficient to conclude that psoriasis is another manifestation of HPV. The present aim of our investigations is to ascertain the significance of this unexpected observation.

J.S.: Please briefly describe in simple terms your study of predisposed individuals and the potential applications of your discovery of genetic predisposition to HPV infection.

G.O.: Epidermodysplasia verruciformis is a rare recessive disease. We studied families with patients whose parents were first cousins. In such families, two copies of the same allelic form of polymorphic genetic markers (homozygosity) encompassing the disease gene should be found in the affected individuals. The approach is to screen the genomes of the members of the family for markers spanning all the chromosomes and to further analyze additional markers encompassing the homozygous regions restricted to the patients. This progressive narrowing of regions on the chromosome will lead to the identification of the gene and the mutations involved. This would help us to understand the mechanisms underlying susceptibility or resistance to HPV disease and would constitute a means to identify patients at risk of developing HPV-associated cancer.

J.S.: So this study led you to identify EV1, a chromosomal locus associated with susceptibility to HPV infection. Is this the only one?

G.O.: EV1 is the first identified HPV susceptibility locus. Evidence for a second susceptibility locus for epidermodysplasia verruciformis has recently been discovered in my laboratory, pointing to the genetic heterogeneity of the disease and to multiple mechanisms controlling HPV infections.

Gérard Orth

J.S.: Finally, what are the prospects on the horizon for vaccines or therapeutics to treat HPV infection?

G.O.: There is at present no vaccine available to prevent HPV infections. Phase I/II trials of prophylactic HPV vaccines are currently ongoing or planned. They are based on recombinant virus-like particles of the most common genital HPV genotypes. Clinical trials are also currently underway to test therapeutic vaccines aimed at inducing cell-killing T lymphocytes specific for the viral E6 and E7 nonstructural viral proteins. Progress is also expected in the design of therapeutic agents that would specifically interfere with various steps of HPV infection. All these strategies should contribute to the control of cervical cancer.

DNA, which is the substance of all chromosomes, is a double-stranded molecule made up of only four molecules of deoxyribonucleotides known as A, C, G and T. Every chromosome is one of a pair, one from the father and one from the mother. Any gene on a chromosome is called an **allele**, and any allele has a complementary site on the other chromosome of the pair. When the sequence of DNA molecules is the same on both, the site is **homozygous**, as opposed to **heterozygous**, when the alleles are not alike. If a disease occurs when the alleles are heterozygous, it is a dominant trait. If it occurs only when the alleles are homozygous, it is a recessive trait.

CHROMOSOMES

Mother's	Father's
G-C	G-C
C-G	C-G
T-A	T-A
A-T	A-T
A-T	A-T
T-A	T-A

homozygous

Mother's	Father's
G-C	G-C
C-G	T-A
T-A	C-G
A-T	C-G
A-T	A-T
T-A	G-C

heterozygous

Honoring Pasteur: The United States Pays Tribute

Avenue Louis Pasteur, Boston

by Caitlin Hawke

There is almost certainly a street named for Louis Pasteur in every city in France, and none is more grand than the Boulevard Pasteur, which runs through the heart of the 15th arrondissement between Montparnasse and the Institut Pasteur.

In the United States, from California to Virginia and from Texas to Massachusetts, Pasteur's name has been given to avenues, roads, courts and drives.

Laid out on January 17th, 1907, shortly after Harvard opened its new medical school campus, the beautiful Avenue Louis Pasteur in Boston runs from Longwood Avenue to the Fenway just east of Brookline Avenue.

During lengthy community discussions, Charles William Eliot, Harvard's president from 1869 to 1909, emerged as one of the most ardent advocates of naming the new avenue for Louis Pasteur. President Eliot said:

"Pasteur is the name of a man who, more than anyone else, did the most for medicine in the nineteenth century. Of humble beginnings, Pasteur became a worldwide force in medical science…. It seems that giving the boulevard his name would best indicate this to future generations…. I am in favor of this name for sentimental reasons. Americans have a debt of gratitude to France, and here we have the opportunity to show that we remember what France did for us during the Revolution—not only its king but also its citizens…. I think we will find no more appropriate name; Louis Pasteur's name will teach the children of future generations that which we wish them to know."

Photo: Delphine Lévy

Harvard Medical School and the Avenue Louis Pasteur

Our thanks to the Boston and Massachusetts Historical Societies, Simmons College Archives, Harvard Medical Library, Elizabeth Pezaris and Delphine Lévy for their kind assistance.

In Memoriam

It is with great sadness that we report the loss of two members of the Pasteur community this past summer.

Anastassios Fondaras A cherished friend and patron and the beloved husband of the chairman of our American Advisory Board, Mr. Fondaras was an abiding presence in our circle of American benefactors. Born in Greece, he loved the sea and attended the Greek Royal Navy Academy. He was a Commander in World War II, and several years after he resigned from the Navy he was given the rank of Rear Admiral. After World War II, Mr. Fondaras worked for the Niarchos Group, where he became managing director. In 1958, after attending Harvard Law School, he joined Kidder Peabody in New York. He subsequently moved to France and became a manager in the Paris office of the investment bankers White Weld. After his retirement, he and his wife Elizabeth divided their time between New York, Paris and Greece.

Ludwik Gross An internationally recognized pioneer in the field of oncogenic virology, Dr. Gross began his distinguished scientific career in Europe where, from 1932 to 1939, he worked as a guest investigator at the Institut Pasteur. He wrote two articles about his time at the institute that were published in the *Proceedings of the National Academy of Sciences* (*PNAS* 92:7609-7611, 1995, and *PNAS* 93:10539-10540, 1996). In 1946, he was appointed chief of cancer research at the Bronx Veterans Administration Medical Center, where he remained affiliated for the rest of his career. A member of the National Academy of Sciences, Dr. Gross was the recipient of the Pasteur Silver Medal (1962), the French Legion of Honor (1977) and the highly acclaimed Lasker Award (1974), among many other distinctions.

The Institut Pasteur and the Pasteur Foundation wish to thank those who have made gifts in memory of these two individuals and express deepest sympathies to the Fondaras and Gross families.

MORE TO THE POINT: BRIEF NEWS FROM PASTEUR

DYSENTERY VACCINE: A Pasteur team led by Philippe Sansonetti has developed a live-attenuated oral vaccine against shigellosis, a diarrheal disease that claims between 600,000 and 1 million victims a year, primarily children in Third World countries. Successful phase I clinical trials were held in collaboration with the U.S. Army in Fort Detrick, Maryland; further trials are underway in Bangladesh, where the disease is endemic.

HEREDITARY DEAFNESS: Christine Petit received the prestigious French Academy of Sciences' Charles Leopold Mayer Award for her team's work in clarifying the molecular bases and pathogenic mechanisms of human hereditary deafness. Most recently, team members demonstrated that the DFNB1 gene is responsible for half of the cases of deafness that are recessive, i.e., those in which the parents hear normally while one or more children are born with hearing deficits. This discovery will facilitate early detection of this disability.

HYGIENE AND THE HOME: In July, the Institut Pasteur and Procter & Gamble signed a five-year agreement to develop global products aimed at improving hygiene in the home. The goal is to use new microbiological technologies to research, develop and test new household hygiene products. Pioneered by Louis Pasteur, the field of hygiene remains crucial today in the prevention of infectious diseases.

CANADIAN PASTEUR FOUNDATION: Based in Montreal, the Fondation Canadienne Louis Pasteur was created in 1998 to support and foster collaborative infectious disease research programs between the Institut Pasteur and Canadian laboratories. Last fall the foundation organized a series of inaugural events, including a gala evening with the Grands Ballets Canadiens and the exposition "À la découverte de l'Institut Pasteur."

PASTEUR HOSPITAL: As a result of a citywide reorganization of Parisian hospitals, a new Pasteur-Necker infectious disease center has been created at the Necker Hospital. While all inpatient services of the Institut Pasteur will now be handled at the new center, international vaccination and outpatient consultation services for allergies and infectious and tropical diseases will remain on campus at the institute's Medical Center.

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, a 501(c)(3) corporation.

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.

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.

420 Lexington Avenue, Suite 1654
New York, NY 10170
Phone: 212.599.2050
Fax: 212.599.2047
E-mail: PasteurUS@aol.com

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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 $_____

☐ I would like more information on how to make a bequest in support of Pasteurian research.

☐ I am interested in learning how to make a charitable gift of an insurance policy. Please contact me with more information.

☐ Please add my name to your mailing list.

☐ Please send me more information about the Institut Pasteur.

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Pasteur on Broadway

In May, the Pasteur Foundation benefited from a Broadway performance of *Ring Round the Moon* by Jean Anouilh. The evening raised over $113,000 for Pasteurian research. We wish to acknowledge The Honorable Anne Cox Chambers, Mr. and Mrs. Guy Wildenstein, Mrs. Anastassios Fondaras, Mr. and Mrs. Arthur Ross, CDC North America, Mr. Michel David-Weill, Pasteur Mérieux Connaught, and Schering-Plough Research Institute for their major contributions to the event.

We also extend deepest thanks to each and every individual who supported this event. We are very grateful for your participation and regret that a lack of space precludes us from listing every name.

Philippe Rouvillois

Judith Sulzberger and Budd Levinson

Valerie Zilkha and Barry Cohen

Photos: Susan B. Glatstein

Edward Perlberg and Isabelle Sixtus

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.

Why Your Gifts Are Vital

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decade, as the French economy has sought more solid footing through budget cuts, the percentage of government support has declined significantly. Government cutbacks coincide with a decrease in revenues from royalties, since several of the institute's patents will soon enter the public domain. Therefore, about two-thirds of the institute's budget must be raised from private sources.

To fill this gap, the institute turns for help to its faithful core of international donors and to new friends who wish to make contributions in support of Pasteurian research – research undertaken to improve public health throughout the world.

— Jean Castex, Deputy Director General
Institut Pasteur

Gifts and bequests to the Pasteur Foundation can take many forms and are fully tax-deductible, as the Pasteur Foundation is organized under §501(c)(3) of the Internal Revenue Code. Please consult your tax advisor to obtain the maximum benefit from your gift.

A New Tool for French Teachers

Bring Science to the French Classroom

"À la Découverte de l'Institut Pasteur," a set of 44 flashcards, is the perfect way to bring scientific concepts and vocabulary into the advanced French-language classroom. Covering the history, discoveries and scientific contributions of the institute, these cards provide timely, relevant departure points for conversation. In recognition of a contribution of $25 or more, the Pasteur Foundation will send you the flashcards as our gift.

PASTEUR FOUNDATION
420 Lexington Avenue, Suite 1654, New York, 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 late 1999.)

NAME

ADDRESS

CITY/STATE/ZIP

TELEPHONE *(IMPORTANT)*

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

PASTEUR FOUNDATION

EURΩCONFERENCES

By B. Boris Vargaftig
Program Director

Tailored to address state-of-the-art techniques and advances in biology and medicine, the Institut Pasteur's EURΩCONFERENCES series unites scientists working in the pharmaceutical industry, hospitals, universities and public health laboratories and agencies. Begun in 1994 with the goal of strengthening industrial ties, these meetings are up-to-the-minute forums for the exchange of ideas between theoretical and applied scientists. Past themes have included "New Trends in Research and Treatment of Atherosclerosis," "Anxiety," "Alzheimer's Disease," Chemokines," "Vaccines," "Antibiotics" and "Airways Allergy." This past June, academic and pharmaceutical scientists gathered to discuss opportunities for collaboration in the new and promising field of genomics–the comprehensive physical and genetic mapping of the human genome–which will lead to novel diagnostics, prognostics and therapeutics. This fall, the genetics, physiopathology and therapeutics of obesity will be addressed.

All conferences are held on the Parisian campus of the Institut Pasteur. For more information, visit our website (www.pasteur.fr/applications/euroconf/) or e-mail us at euroconf@pasteur.fr.