PASTEUR PERSPECTIVES

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

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THE CUTTING EDGE

Director General's Note: In light of the recent and potentially devastating outbreak of food poisoning from E. Coli*–contaminated ground beef supplied to the Burger King chain, among others, this column is devoted to another bacterium responsible for foodborne illness—*Listeria monocytogenes. *According to* The New York Times, *in the United States alone, food poisoning causes millions of illnesses and more than 9,000 fatalities annually. Moreover, it is projected that the occurrence of foodborne diseases will rise anywhere from 10 to 15 percent in the next decade. The need is clear for a combination of basic research on how these pathogens contaminate food and invade the human body as well as for vigilant study and surveillance of listeria epidemics. The findings will allow scientists to pinpoint and contain outbreaks and, ultimately, defeat these diseases.*

—Maxime Schwartz

FOCUS ON LISTERIA: A FOODBORNE BACTERIUM

by Caitlin Hawke

Reports of Listeriosis Increase

On June 12, 1997, after learning of several reports of serious illness, the Food and Drug Administration issued a national warning "against the purchase and consumption of hummus and other foods produced by Cedar's Mediterranean Foods" due to possible contamination with *Listeria monocytogenes*. A week later, the FDA recalled all foods produced by Cedar, citing the manufacturer's inadequate response to the possible listeria contamination and its failure to ensure the removal of these foods from store shelves. In August, Orval Kent Food Company announced a voluntary recall of some lots of its potato salad (sold in the New York area as a Pathmark brand), saying they were potentially contaminated with *Listeria monocytogenes*.

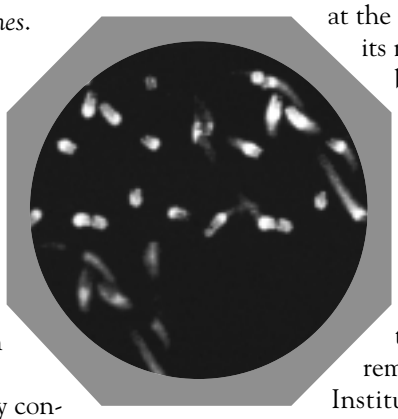
Known for over 50 years to be a bacterial pathogen, *Listeria monocytogenes* was only discovered to cause foodborne illness in the early 1980s. Since that time there have been constant outbreaks such as the ones noted above, and they seem to be on the rise.

Because the *Listeria* bacterium lives in soil and water, it enters the food chain through vegetables and livestock and is therefore found in raw meats and unpasteurized dairy products. It can also invade processed foods, as in the recent hummus and potato salad cases and in earlier cases involving soft cheeses.

According to official FDA statistics, of the 1,850 people who contract listeriosis each year, approximately 425 die. While healthy individuals rarely experience severe symptoms of infection, pregnant woman, newborns, the elderly and people with compromised immune systems are at significantly greater risk. Initial signs of listeria infection include flulike symptoms associated with other foodborne bacterial infections caused by *Escherichia coli* and *Salmonella*: aches, diarrhea, vomiting, and fever. The onset of these symptoms begins approximately twelve hours following initial infection. In the most severe cases, results may include listeric meningitis and septicemia and, in pregnant women, miscarriages, premature births or stillbirths.

Listeria infection is treated with antibiotics such as ampicillin. Infection may be prevented by avoiding unpasteurized foodstuffs and employing safe kitchen practices.

The Bacteriology and Mycology Department at the Institut Pasteur devotes much of its research efforts to the study of bacteria and fungi—pathogens that are major causes of new, emerging and drug-resistant diseases. Bacteriology was pioneered by Louis Pasteur himself, who, for the first time, was able to demonstrate the fundamental role played by bacteria in infectious diseases. Today, this field remains one of the strongest at the Institut Pasteur, and much of its research in this domain leads to applications in the epidemiology, identification, detection and treatment of bacteriological and mycological pathogens. Scientists are now also studying an increasingly alarming problem: the emergence of drug-resistant strains of these organisms. Housing both World Health Organization Collaborating Labs and National Reference Centers for the detection and monitoring of bacterial outbreaks, this department also



Listeria bacteria with their comet tails of actin

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represents a vital component of the Public Health Service in France.

In particular, two laboratories in this department are devoted to listeria research: Pascale Cossart's Bacteria–Cell Interactions Lab and Jocelyne Rocourt's Listeria Lab.

The Bacteria–Cell Interactions Lab

This lab investigates the methods employed by *Listeria monocytogenes* to infect cells by studying bacterial and cellular interactions and the molecular signals these cause. Like all living cells, each bacterium is surrounded by a membrane; this membrane envelopes a cytoplasm which contains both the enzymes the bacterium requires to grow and to reproduce and the bacterial chromosome with its genetic information.

In 1991, Dr. Cossart's team showed that once the *Listeria* bacterium is ingested, a protein on its membrane called "internalin" is necessary for the pathogen to invade the epithelial cells that line the digestive tract. Last year, her team demonstrated how *Listeria monocytogenes* interacts with a protein on the surface of the epithelial cells: internalin locks onto a receptor on the cell membrane called "E-cadherin" in much the same way as a key fits into a lock. This interaction sets off a progressive interlocking of the cell membrane to the bacterium's surface by way of a zipperlike mechanism. This method of invasion is totally different from that of *Salmonella* or *Shigella* bacteria, which send molecular signals to the host cells co-opting them to engulf the pathogen.

Dr. Pascale Cossart

Once inside the cell, *Listeria* is able to travel from cell to cell by an ingenious technique that exploits the cell's actin, a protein that can rapidly polymerize into filaments or depolymerize, giving the cell its plasticity. Actin is also essential for muscle contraction. One of the pathogen's genes – actA – convinces the cell to polymerize its own actin at one end of its rod-shaped body. Thus actin filaments accumulate like a comet's tail behind the bacterium which is propelled within the cell toward the infected cell's membrane and eventually into an uninfected neighbor. This resourceful propulsion mechanism enables the pathogen to infect an increasing number of cells, completely bypassing the blood and lymph systems and thereby preventing any alert to the host's immune system.

Thanks to its discoveries, this team has already helped develop a serodiagnostic for listeriosis and a probe to detect the bacterium in food. In addition to its exploration of the potential use of attenuated *Listeria* in a vaccine, future applications of the basic research conducted here may prove promising; for example, inactivating the pathogen's actA gene could stop *Listeria* in its tracks because without these comet tails infection cannot progress. In a larger sense, the basic research of Dr. Cossart's team has provided a model for the study of intracellular parasitism by deciphering this particular pathogen's mechanisms of cell invasion and intracellular multiplication.

Dr. Jocelyne Rocourt

The Listeria Lab

Following the first foodborne epidemics traced to *Listeria* in the early 1980s, many countries set up surveillance networks to keep track of the incidence of this disease, to identify populations at risk, to detect listeriosis epidemics as they emerge and to participate in studies of foodborne transmission. The Pasteur Listeria Lab serves as a National Reference Center for surveillance of this disease in France and a World Health Organization Collaborating Center of Foodborne Listeriosis. As such, its activity is based primarily on characterizing samples forwarded by biologists for identification.

Because *Listeria monocytogenes* infection can only be positively diagnosed through culturing bacteria from blood or cerebrospinal fluid, surveillance requires the characterization of several thousand strains each year. To best handle this volume, the scientists on Dr. Rocourt's team need simple, rapid, reasonable and discriminating methods, such as serotyping and phage-typing, to analyze the bacteria. While phenotyping remains the simplest way to identify a large number of samples, the recently introduced and rapidly improving molecular typing methods (e.g., ribotyping, DNA macrorestriction patterns analysis) have become the preferred tool in epidemic situations. Here it is necessary to determine if certain strains are related in order to trace the source of the listeria infection and the pathogen's evolution.

These two laboratories—one devoted to basic research and the other to epidemiology—collaborate to respond to disease outbreaks through a better molecular understanding of the pathogen, which leads to improved techniques of identification and diagnosis and ultimately to the containment and prevention of listeria epidemics.

To report a suspected foodborne illness, call the Food and Drug Administration's emergency number: (301) 443-1240.

Science, Ignorance and the Future

by François Jacob

It has been approximately 300 years since science was born in the West. Since its beginnings, it has been characterized by experimentation in many and varied disciplines, leading to advances that have become the basis for what we call our modern civilization. Scientific technology has given us resources we use with appreciation — airplanes, television, penicillin, contraception — as well as those we think of as evil, such as thermonuclear bombs, pesticides and innumerable other harmful products.

Three hundred years is not a very long time, but it is long enough for us to try to evaluate the results of the growth of science and to decide if it has been of service to humanity. Indeed, several objections have been voiced. For example, both the beginning of the Industrial Revolution and the discovery of nuclear energy increased opposition to scientific advancement. The naysayers shouted, "Enough! Stop everything! Let us not endanger mankind! Let us return to the good old days!"

Obviously, scientists themselves have a different perspective. They believe that scientific enterprise has led to mankind's greatest achievements. Science, along with the arts, has truly allowed humanity to pursue its most splendid visions. But what has been accomplished so far is only a beginning. Although science had its start 300 years ago, systematic scientific developments really began only a century ago, and it is just within the past 50 years that science has hit its stride as a group of disciplines flourishing throughout the world, without the artificial borders of geography, nationality or religion.

However, the more science advances the more it becomes clear that vast areas remain to be discovered. For example, biology has just begun to blossom, bringing in its wake the creation of new areas of medicine. If fundamental research continues, not only will we conquer many diseases and improve agricultural technology; we will also acquire a deeper knowledge of the fundamental processes of nature and thus learn more about ourselves. Scientists, along with the rest of mankind, are desperately attempting to discover who we are, where we came from and why we are here. Certainly, science will not provide answers to all our questions. However, it can yield some clues and exclude some answers as nonviable. The pursuit of scientific research will help us make fewer mistakes — and there is a lot at stake for us. Today there are approximately five billion people on Earth, and tomorrow we shall be ten billion and the day after tomorrow twenty billion. This staggering population growth poses a terrifying threat to the survival of humanity. The pursuit of scientific research seems indispensable if we are to find solutions to this and other problems.

Undoubtedly, the principal revelation of this century of scientific research is our awareness of the depth of our ignorance about nature. The more we learn, the more we realize the extent of what is unknown to us. That understanding is in itself of the utmost importance; it is a realization that would have astonished our forebears in the 18th and 19th centuries. For the first time we can openly contemplate and accept our fundamental ignorance. For so long we claimed to understand how the world around us functioned, filling in the gaps with myths and lore to mask our ignorance. Now that we have begun the serious study of nature, we comprehend the breadth of questions and the distance we must cover before we can answer them. We have learned that the greatest danger for humanity is not the expansion of scientific knowledge — it is ignorance.

Nobel Prize winners André Lwoff, Jacques Monod and François Jacob in 1965

This is an excerpt from François Jacob's latest book, La Souris, la Mouche et l'Homme, *published last spring in France.*

Professor Jacob began his brilliant career at the Institut Pasteur in 1950 under André Lwoff. In perhaps the ultimate homage a mentor can bestow upon a student, Professor Lwoff would later remark that "my most beautiful discovery was François Jacob." Since then, Professor Jacob has held positions within the institute ranging from Head of the Unit of Cell Genetics to Chairman of the Board.

Professor Jacob's distinguished body of research has dealt mainly with the genetic mechanisms existing in bacteria and bacteriophages and with the biochemical effects of mutation. His collaboration with Jacques Monod led to an important new series of findings: messenger RNA, regulator genes, operons and allosteric proteins.

In 1965, Professor Jacob, jointly with Professors Lwoff and Monod, was awarded the Nobel Prize in Medicine for "discoveries concerning genetic control of enzyme and virus synthesis." Last year he was elected to the prestigious Académie Française. *Professor Jacob has been recognized internationally; in the United States, he is a member of the National Academy of Sciences, the Academy of Arts and Sciences and the American Philosophical Society.*

We are honored to publish this excerpt from La Souris, la Mouche et l'Homme *to give you a glimpse of this beautifully written book — one that will appeal to laymen and scientists alike.*

—Mrs. Anastassios Fondaras

Honoring Pasteur: The United States Pays Tribute

Louis Pasteur Elementary School, Detroit

Located in the northwest section of Detroit, this public school was built in 1931 and named for Louis Pasteur "in recognition of his dedication to science." The school has a current total enrollment of 650 students, in classes ranging from Head Start early education to sixth grade.

Pasteur Elementary is a member of the Detroit Urban Systemic Initiative, which is funded by the National Science Foundation; as such, it has recently initiated an integrated approach to science education to prepare students for the scientific and technological challenges of the next century. According to Principal June C. Green-Rivers, "The goal is for every classroom to be a science room."

Photo credit: courtesy Pasteur Elementary School

On May 18, 1997, in the presence of 250 alumni, Pasteur Elementary unveiled a mural by local artist Curtis Lewis entitled "The Wall of Pasteur Heroes." It features a portrait of Louis Pasteur surrounded by members of the school's community who have been supportive of its mission.

Our thanks to Dr. Green-Rivers for providing background information for this article.

If you know of U.S. tributes to Louis Pasteur that you would like to see featured here, please contact the Pasteur Foundation.

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The Pasteur–Curie Connection

by Hugues Fleury and Caitlin Hawke

Marie Curie

A truly remarkable figure in the history of science, Marie Curie discovered "radioactivity" – a term she devised – a century ago, thereby laying the groundwork for cancer treatment and nuclear physics. Born Marja Sklodowska in Poland in 1867, she moved to Paris to begin what would prove to be her exceptional studies in mathematics, chemistry and physics; it was there that she met her husband and closest collaborator, Pierre Curie. Together, they received the Nobel Prize in physics for their discovery of radioactivity. In 1911, Marie Curie became the only person ever to win two Nobel Prizes; her second was in chemistry for the discovery of radium.

Many of her dreams were fulfilled when, in 1909, the University of Paris and the Institut Pasteur agreed to establish the Institut du Radium, where she would direct the research laboratory for many years. Twenty years later, Marie Curie succumbed to leukemia, thought to have been caused by her years of exposure to radiation. Recognizing her with perhaps its highest posthumous honor in 1995, the French Government transferred her ashes, together with those of Pierre, to the Panthéon, making her the only woman to be recognized in this way for her own achievements.

Claudius Regaud and the Institut du Radium

Born in Lyon on June 30, 1870, Claudius Regaud was to become a pioneer in the fields of radiobiology and cancer treatment. After attending medical school in Lyon, he took Émile Roux's course on microbiology at the Institut Pasteur, where he soon joined the senior staff. Radiobiology was his focal area of interest and in 1906 he published a study on the general effects caused by Roentgen's rays on living cells.

In 1909, the Institut Pasteur and the University of Paris united to create the Institut du Radium, to be erected a stone's throw from Louis Pasteur's original attic laboratory on the rue d'Ulm. The Institut du Radium was comprised of two parts, a general physics and radioactivity laboratory directed by Marie Curie, as well as the Pasteur Laboratory, a radiophysiology laboratory for the medical and biological

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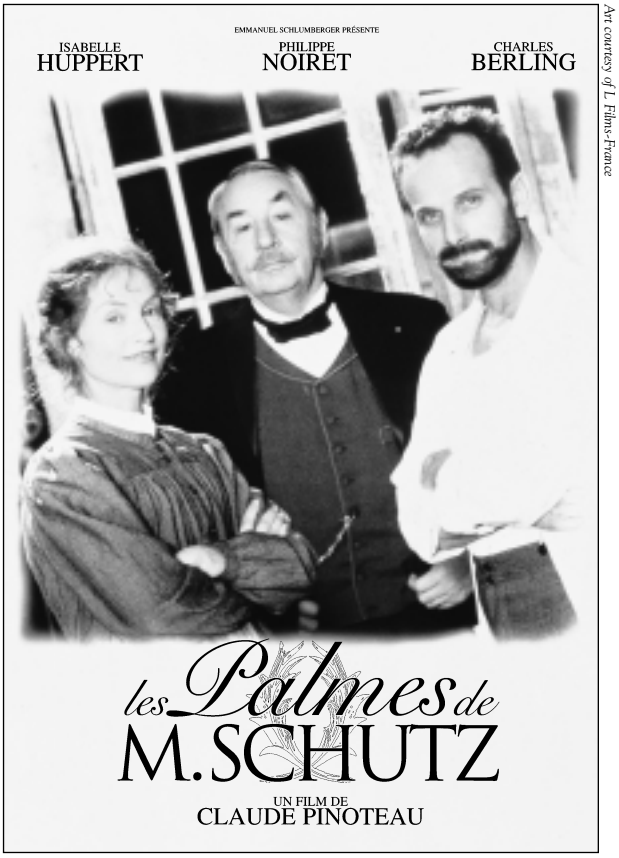

Art courtesy of L Films-France

A Film Première to Benefit Science

Whether you are interested in the history of science or a lover of French films, attending this special première benefit is an excellent way to support the basic and applied biomedical research that continues today at the Institut Pasteur.

The United States première of the film *Les Palmes de M. Schutz* will be held to benefit the Pasteur Foundation on Tuesday, December 9th. Inspired by the lives of Marie and Pierre Curie, the film is an adaptation of Jean-Noël Fenwick's incredibly successful play which attracted over a million theatergoers in 20 different countries and won four of France's coveted Molière Awards in 1990. While Claude Pinoteau's lively and amusing film version, starring Philippe Noiret, Isabelle Huppert and Charles Berling, is not intended to be an exact historical account, it carefully recreates the turn-of-the-century ambiance of the Curies' laboratory while fleshing out the personal lives of these passionate scientists. Isabelle Huppert, best known for films like *Madame Bovary*, *Amateur*, *La Cérémonie* and *Coup de Torchon*, gives a wonderful performance as the brilliant Polish Marie, and Charles Berling (*Petits Arrangements avec les Morts*, *Nelly et M. Arnaud*, and *Ridicule*) plays the charming introverted Pierre. As the title's M. Schutz, the much-adored Philippe Noiret (*Il Postino*, *Cinema Paradiso*) plays the Curies' recognition-starved taskmaster who dreams of receiving France's esteemed academic distinction—*les palmes académiques*. Of course, Pierre and Marie do not disappoint him. This film is an illuminating account of the Curies' lives, rich in drama, humor and suspense.

The benefit première of *Les Palmes de M. Schutz* will be held on Tuesday, December 9, 1997. Benefit tickets are $1,000 (Patrons) and $500 (Sponsors) and include a pre-film champagne reception and screening at Lincoln Center's Walter Reade Theater and a post-film supper at the French Consulate. Tickets to the champagne reception and film only are $75. All tickets are tax-deductible to the extent allowed by law. For further details, please contact the Pasteur Foundation at (212) 599-2050.

The Pasteur–Curie Connection

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applications of radium. Émile Roux, then director of the Institut Pasteur, had the foresight to envision the important effect that ionizing radiation would come to have on the domain of biology, so he summoned Claudius Regaud to direct the Pasteur lab, which would be devoted to this evolving field. An effective collaboration developed between the two great minds of Marie Curie and Claudius Regaud. For decades to follow, Pasteurian scientists continued to staff the biology section of this radium institute.

Upon his return to the Institut Pasteur, Regaud decided to gear his work toward radiobiology and therapeutics. He wrote: "Regretfully abandoning my research in microscopic anatomy and histophysiology, I must focus my greatest efforts upon the study of the effects of X-rays and radium rays on tissues and on the development of a radiation treatment center for malignant tumors."

In 1912, Claudius Regaud was named to head a national program to fight cancer. In 1919, he established the principles of future cancer centers that heralded a distinctly modern approach considered brilliant in oncology circles: "There could be no serious anticancer treatment centers where only either radium and X-ray treatment or surgical treatment would be administered. As in war, cancer treatment requires a team of therapeutic treatments."

Save the Date:
Tuesday, December 9th

See page 5 for details