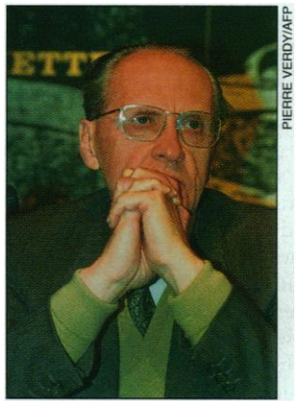
INSTITUTIONAL PROFILE

New French Biomedical Center Breaks the Mold

PARIS—If you were asked to draw up a list of the hottest biomedical research centers in Paris, how many names could you come up with? It's a safe bet that the Pasteur Institute would be on the list. More than likely you'd add the CEPH-Généthon genome research complex, and—especially if you're a cancer researcher—the Gustave Roussy Institute in the suburb of Villejuif. But if you don't live in France, there's one up-and-coming institute you're probably going to miss, at least for now: The Cochin Institute for Molecular Genetics.



PIERRE VERDY/AFP

Founding father. Retrovirologist Jean Paul Lévy.

The Cochin center is too new to have made a splash abroad, but it has become one of the most talked about institutes in French biomedical circles since its formation in 1990. The reason? It's been set up on the assumption that there is something wrong with the typical French way of doing medical research, and that a new model is sorely needed. Ironically—in a country where concessions to the American way of life are often seen as a slap at French culture—the model that's been chosen bears a striking resemblance to a U.S. medical school. And although the Cochin Institute is only 2 years old, the head of INSERM, the French government's biomedical research agency, is already encouraging other researchers to build imitators.

At Cochin, scientists from different labs gather in communal coffee rooms, visit the same library, and share expensive items of equipment like scintillation counters and centrifuges. That may not sound like a big deal to a typical U.S. medical researcher, but in France, says Cochin molecular pharmacologist Françoise Russo-Marie, it's practically unheard of. Although many university teaching hospitals host a handful of research units run by INSERM, groups sharing the same building often might as well be at opposite ends of the country. The usual pattern, says Russo-Marie, is for the heads of research units to concentrate on building their own "little kingdoms....They do not share equipment. They do not share libraries. They do not go to one another's seminars."

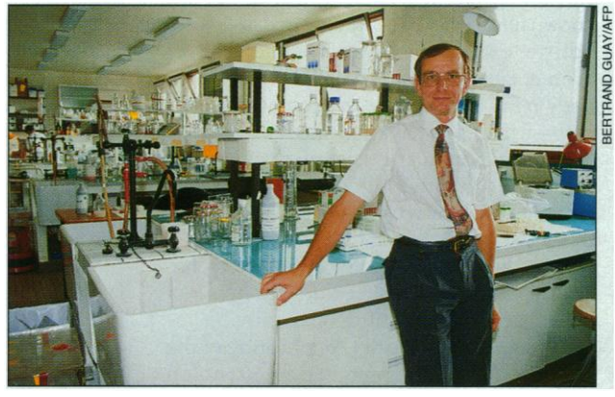
It was to break that mold that Cochin's two founding fathers—retrovirologist Jean Paul Lévy and molecular geneticist Axel Kahn—originally came up with the idea of creating a new institute at the Cochin Hospital, just south of the city center. The institute was designed not only to break down barriers between the institute's constituent labs, but also to get clinicians and basic researchers working together—still a major problem in France where M.D.s and Ph.D.s have traditionally followed different tracks throughout their careers.

Lévy and Kahn were already trying to build links between their separate research groups at the Cochin Hospital when, in 1988, INSERM's plan to move a unit headed by inflammation biologist Jacques Benveniste into a new 3-story building at Cochin was quietly dropped following the furor that surrounded publication of Benveniste's infamous "memory of water" paper in *Nature*. Lévy and Kahn seized on this opportunity, convincing INSERM to make the suddenly vacant building the centerpiece of a new institute focused on mammalian molecular genetics. The institute now consists of eight government agency research units, six of which are run by INSERM. From the start, says Lévy, who is now the institute's director, collaboration was the central theme. Choosing scientists who were free from the typical "fortress mentality" was enough to ensure cooperation among basic researchers, he says, but an innovative structure was needed to break down the barriers between basic biologists and M.D.s. The solution was to encourage clinicians at the Cochin Hospital to band together to form their own research "club," formulating research proposals that they could bring to the biologists on an equal footing. Lévy and Kahn were concerned that, without such a structure, individual Cochin clinicians would feel that they were being steamrollered into collaborations with Cochin Institute researchers.

Thierry Lacaze, an M.D. who specializes in respiratory problems of premature babies, jumped at the chance to become more deeply involved in research. He's now working toward a Ph.D. in Kahn's lab, looking for ways to boost the expression of genes in lung epithelial cells that produce surfactant proteins that stop newborn infants' lungs from collapsing. Lacaze says that his heavy clinical load meant that he couldn't have found time for this research, if he hadn't temporarily given up his hospital job to join the Cochin Institute—and he says that it will be difficult to continue his research when he returns to the wards. "It's not like America, where [clinicians] can make time to do fundamental research," he says. Lacaze is just one of more than 10 physicians working alongside the 45 bench researchers in Kahn's lab, alone—an unusually high proportion for a French lab in basic molecular biology.

Ask Kahn why he and Lévy based the Cochin Institute on labs in the United States, where different groups and different disciplines work together, and he neatly sidesteps the question—he's been around long enough to know that the ideas that go down best in France are those that are perceived to be French. But several of Kahn's younger colleagues say that their major influence when they joined the institute was the collaborative spirit that they'd encountered in U.S. biomedical centers. Russo-Marie, for instance, spent a sabbatical in Paul Berg's biochemistry department at Stanford University in 1989 and was struck by the easy cooperation between research groups. "I decided to try to develop the same spirit [at Cochin]," she says.

In 1990, when Russo-Marie and molecular pharmacologist Donny Strosberg moved their research units to Cochin from the Pasteur Institute, teaming up with molecular pathologist Pascale Briand, who came to Cochin from the nearby Necker Hospital, the first thing they did was to pool their equipment budgets and install a single computer network for all of their laboratories. The collaboration has already begun to pay off: Briand and Strosberg, for instance, have produced transgenic mice that express the human β-adrenergic receptor—the first time a human receptor coupled to a GTP-binding protein has been expressed in a transgenic animal. They intend to use these mice as a model to test candidate heart disease drugs.



BERTRAND GUAY/AFP

Bridge builder. In Axel Kahn's lab, an unusually high proportion of physicians work alongside basic researchers.

Achievements like this have caught the attention of the head of INSERM. In an editorial in the June issue of the French biomedical agency's in-house magazine, Philippe Lazar, the agency's director-general, asked the heads of INSERM units with common research interests to come up with plans to work together as "federations." Cochin researchers were amused to see that he didn't mention their institute by name: "It's his idea now," says Strosberg, with a wry smile, "but it doesn't matter, as long as he supports us." When asked, however, Lazar happily admits that he regards the Cochin Institute as the pilot project for his new scheme. "The Cochin-type organization is something we wish to develop in the future," he says.

Lazar is not just looking for scientific benefits from improved collaboration, however. He's also hoping for "economies of scale." Indeed, Russo-Marie says that the savings Cochin researchers have made by pooling resources have already attracted envious glances from other institute directors. "They think we are very rich," she says. "We are not richer at all. We just have a better way of spending money."

So taken is he with the Cochin model that Lazar says he'd like to create up to 30 such centers throughout France in the next 2 years. If that happens, you can bet that no one will remember that the Cochin Institute was built on an American model—and the new collaborative institutes will be as French as "le weekend."

–Peter Aldhous

FOLIC ACID

Agencies Split on Nutrition Advice

The announcement from the Public Health Service (PHS) last week hardly seemed controversial. The PHS urged women of childbearing age to make sure they consume 400 milligrams—the U.S. recommended daily allowance—of folic acid, a B vitamin. The move was prompted by a new study suggesting that small amounts of folic acid can lower the risk of spina bifida and anencephaly, birth defects caused by a failure of the neural tube to close in the first weeks of pregnancy. But, though it may seem innocuous, the recommendation has touched off a scientific flap among federal agencies whose job is to protect public health.

Consider the different spins put on the announcement by two PHS agencies, the Centers for Disease Control (CDC) and the Food and Drug Administration (FDA). On Monday, 14 September, CDC director William Roper, speaking at a meeting of the Metropolitan Atlanta Congenital Defects Program, called the recommendation "a landmark in public health efforts." But on the very same day, David Kessler, commissioner of the FDA, told an audience at Tufts University in Boston that the recommendation "does *not* say that FDA is ready to permit a health claim for folic acid." At a third agency, the National Institutes of Health, William Harlan, associate director for the office of disease prevention, told *Science*, "I'd hoped they wouldn't bring out the recommendation just now."

What is causing this interagency angst? First, the study that convinced many federal health officials of folic acid's value in reducing neural tube defects, which was conducted in Hungary, has not yet been published in the scientific literature. (A paper describing it has reportedly been submitted to *The New England Journal of Medicine*.) Then there is the potential for folic acid to cause, rather than prevent, health problems. While it is apparently not toxic by itself, folic acid can mask the symptoms of vitamin B 12 deficiency, which if untreated can lead to brain damage. And finally there is the difficulty of ensuring that pregnant women get adequate amounts of the vitamin in the early weeks of pregnancy—the critical time for neural tube defects.

The case for folic acid has been championed by CDC, and in particular pediatrician Godfrey Oakley, head of the division of birth defects and developmental disabilities in the center for environmental health and injury control. Oakley says he has been convinced of folic acid's value for more than a year. In fact, he remembers the very day—24 June 1991—when he received a telephone call from colleagues at the Medical Research Council (MRC) in England describing the results of a randomized clinical trial of high doses of folic acid—4000 mg per day—in preventing neural tube defects in women who had already had one pregnancy that resulted in such a defect. But it was the as yet unpublished study from Hungary conducted by Andrew Czeizel and his colleagues showing a beneficial effect from just 800 mg of folic acid that convinced most federal health officials that the time was right to urge all women to make sure that they were getting enough of the vitamin. CDC estimates that approximately 2500 children are born with neural tube defects in the United States each year, and an unknown number of fetuses with these defects are aborted. Oakley believes that half to three-quarters of all neural tube defects can be prevented with folic acid: "You work all your professional career for something like this," he says.

"The line between benefit and risk with folic acid is apparently quite narrow."
–David Kessler

But FDA officials see problems in implementing the recommendation, even though they did not oppose it. Although folic acid is present in certain foods, notably leafy, dark green vegetables and citrus fruit, even a well-balanced diet may not contain 400 mg per day. And since neural tube defects usually occur before a woman realizes she is pregnant, taking folic acid supplements only after pregnancy has been confirmed would not be sufficient. The obvious solution would be to fortify food such as bread with the vitamin. But FDA is not yet convinced that the benefits sufficiently outweigh the risks to allow companies to add folic acid to their products and then claim that the products reduce birth defects.

Helping to temper enthusiasm at the FDA was Irwin Rosenberg, professor of medicine and nutrition at Tufts University and director of the U.S. Department of Agriculture's Human Research Nutrition Center on Aging. On 26 August, he wrote to FDA commissioner Kessler to point out that the MRC study showed that folic acid could prevent the recurrence of neural tube defects, not the occurrence. Moreover, he argued that the scientific and nutrition community should have a chance to review the Hungarian study before it is used as a basis to recommend that nearly half the U.S. public should increase folic acid consumption. Rosenberg also told Kessler that his own research suggests that in certain elderly populations, one person in four may have low or borderline B 12 levels, indicating the need for caution before making broad recommendations about folic acid.

Evidently taking Rosenberg's concerns to heart, Kessler told his Tufts audience that "the line between benefit and risk with folic acid is apparently quite narrow." NIH's Harlan also urges caution. He says he is organizing an interagency working group to address the issues raised by the recommendation.

Walter Glinsmann, who heads the nutrition policy staff in the PHS office of disease prevention and health promotion, admits there were grumblings about going forward with the statement at this time. "Each agency has its own view of the world," says Glinsmann. But now that the recommendation has been made, Glinsmann says he's sure that an acceptable way can be found to implement it.

–Joseph Palca