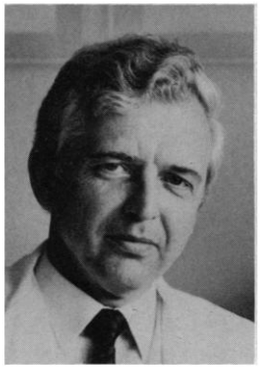
Three Europeans Find Their Own Road to Fame

Even in this era of international science, every country has its own individual research climate. Here three prominent cancer researchers, one each from England, France, and Germany, describe how their home countries have influenced the very different approaches they've taken in their work.

Life at the Front

Strasbourg—For Pierre Chambon, the road to fame has followed one direction: straight up. An international star of molecular biology, Chambon has racked up an imposing score card of achievements, and in an extremely hot area of research—the study of gene regulation. But while building his worldwide reputation, he has maintained a distinctly French temperament—impetuous, demanding, and sometimes contradictory. Still ruggedly handsome at age 60, he is a cancer researcher who smokes Cuban cigarillos. "There are no statistics proving that smoking cigars is bad for your health," he says, adding, "I don't smoke at cancer meetings in the States—people look as me as though I am crazy."



"I've spent my life dropping projects to start new ones."
—Chambon

Chambon's strong personality and willingness to leap into new areas of research are the secrets of his success. "I've spent my life dropping projects to start new ones," he says. But as his army of co-workers has grown into an empire, Chambon has always kept plenty of troops stationed on the projects he himself has left behind.

Chambon first made his mark in 1963, with the discovery of the polynucleotide polyADPribose. From that time on he's been present for the unveiling of many of the central mysteries of gene expression. In 1977 his group, along with several others in Europe and the United States, discovered that the genes of higher organisms could be split, with noncoding introns inserted into their amino acid coding sequences. After that, he switched to an exhaustive study of gene expression in simian virus 40 and was among the first to elucidate the role of the enhancer element, crucial to the control of gene expression in higher organisms.

It was Chambon's work on gene expression that led him to cancer research. In 1982 he and his co-workers begun studying a human cell line derived from an estrogen-dependent breast tumor. "We thought we could perhaps clone some genes whose expression was triggered by the hormone," he says. The result was the identification of the pS2 protein, a possible growth factor that has become a key marker for this type of tumor. More recently, Paul Basset, a leading member of Chambon's fast growing cancer team, has identified an enzyme in the tissues surrounding breast tumors that appears to break down the extracellular matrix, and may play an important role in metastasis.

Chambon's accomplishments have made him one of the most powerful scientists in France. He is director of the Laboratory of Molecular Genetics of Eukaryotes in Strasbourg, a conglomerate of independent research groups totaling more than 180 scientists and taking up most of a 10-story building. But like Paul Nurse (see this page), Chambon recognizes the dominance of U.S. biomedical research and the extra difficulties that presents for European scientists. "You have to realize that 85% to 90% of bioscience in the world today is American," he says. "It takes more time for Europeans to be recognized. Average French science is not going to be recognized in the United States, whereas average American science has a chance."

Chambon is not, however, planning on doing average science himself. Now that he has established a strong beachhead in the study of breast cancer, he has already begun striking out in a new direction. "I see the future of this laboratory as being interested in several aspects of developmental biology," he says. "I have realized from talking to pathologists that cancer is more than just a bunch of cells in a Petri dish. People don't die from the primary tumor, they die from invasion and metastasis. These exist, in fact, in the embryo. Remodeling and cell migration are invasions, but it is a controlled process."

Over the past 5 years, one of his research squads has done important advance scouting in this general area by identifying several receptors for the vitamin A derivative retinoic acid. This compound, which is known to play an important role in the developing embryo, also inhibits the growth of some animal tumors as well as cancer cells in culture.

Chambon is gratified at the thought that his more than three decades of research might actually make a difference in the fight against cancer. "For almost all of my scientific career, I never cared about applications," he says. "It was only when I first began working with breast cancer that I realized that it is my duty, if it can be done, to help people by studying the molecular biology of these tumors." ■ **M.B.**

A Pressure to Think

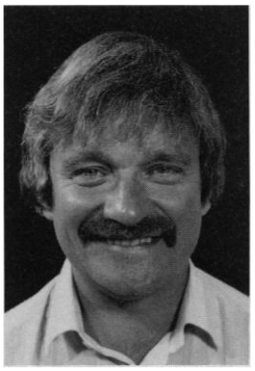
Oxford—At 42 years of age, Oxford University's Paul Nurse has already won a major international reputation for his work on the control of the cell division cycle. Some material rewards have come along too: his own research group, funded by the Imperial Cancer Research Fund (ICRF), a prestigious professorship from the Royal Society, and (coming soon), the directorship of Britain's biggest cancer research laboratory—the Lincoln's Inn Field laboratory of ICRF.

Nurse's rise to stardom is not, however, a conventional story of late nights in the laboratory trying to beat the opposition in the hottest area of the day: rather, it's a peculiarly British tale. "Lots of my American friends tell me I would never have been allowed even to start this research over there," says Nurse. The reason: In the early 1970s he chose to work on fission yeast—an organism that at the time was so totally out of fashion that U.S. granting agencies wouldn't have funded his work—and spent a decade, first at Edinburgh University and then at Sussex University, quietly collecting mutations affecting the control of its cell division cycle.

But even in England, Nurse, who worked in small groups, attracted no huge grants, and once, he says, an early application for cancer research money came back describing his work as "irrelevant." But in the early 1980s, he added molecular biological techniques to his repertoire, enabling him to clone the genes that he was interested in. Then, Nurse says, "we had a goldmine."

The key paper came in 1987: with co-

worker Melanie Lee, he showed that it was possible to replace a key gene, known as *cdc2*, that controls part of the cell cycle in yeast with its mammalian equivalent. All of a sudden, the world woke up to the fact that fission yeast provided an excellent model system for studying control of the eukaryotic cell division cycle, with all its potential implications for understanding cancer. The topic boomed, a spate of big papers from Nurse and several U.S. labs followed, and by 1990 Nurse could confidently talk about "a universal control mechanism common to all eukaryotic cells" for the onset of mitosis, the phase of the cell cycle in which cells divide.



"I have to rely on people in my lab having imaginative ideas."
—Nurse

"The field has changed out of all recognition in the past 10 years," says Jacky Hayles, a senior member of Nurse's team who has worked with him since the early '80s. "We used to get just a couple of letters each week asking for mutant strains of yeast. Now dealing with requests from around the world keeps one technician busy almost full time."

The rapid rise in his fortunes leads Nurse to muse on the sociology of science and how he came to be in the right place at the right time. He points out that back in 1974, Morton Bradbury's group at Portsmouth Polytechnic published evidence that a kinase, which is the type of enzyme encoded by the fission yeast *cdc2* gene, played a key role in the control of cell division. But for a combination of reasons—not least that Bradbury worked on a slime mold—the work just never sparked major international interest.

Nurse was luckier. The "key point" in his career came in 1986 when ICRF offered him a job in London. The move put him in close contact with mammalian cell workers. "We were forced to make our work relevant to other systems," Nurse says. "Then it all began to split open."

Having hit it big, Nurse also muses on what it will take to keep his work going. At the back of his mind is the same demon that haunts many European researchers—the vast, well-funded, and extremely competitive U.S. biomedical research system. "We can't compete in the UK in terms of numbers of people or money with the Howard Hughes Foundation," he says. Competition is not, anyway, Nurse's style. "I don't like putting graduate students and postdocs under competitive pressure," he says. "I prefer a slightly more relaxed atmosphere where you have time to think."

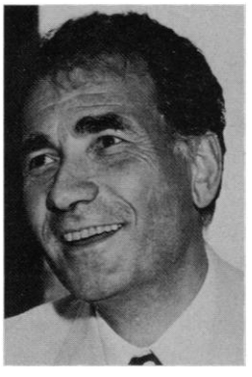
Relaxation is, however, a relative term. "We're under consistent pressure to innovate and be one step ahead," says Christopher Norbury, a postdoc who has been with Nurse for 4 years. As Nurse concedes, the pressure to think can be quite stressful. To keep ahead without gigantic resources, "I have to rely on people in my lab having imaginative ideas," he says. ■ **A.A.**

The Virtues of Patience

Heidelberg—For virologist Harald zur Hausen the path to success lay not in fighting to be the biggest fish in a crowded pond, but by a long swim in sometimes lonely waters. As cancer researchers have thrilled to the discovery of each new oncogene and tumor suppressor gene, zur Hausen has continued to work tirelessly on viruses—a key factor in human cancer that often gets left behind in the excitement.

Viral theories have had their ups and downs over the past 100 years, and at times have come close to landing in the dustbin of scientific history. When zur Hausen first began working in this area in the early 1970s, the field was in just such a downspin. "At that time there was a backlash," he says, "because a number of reports came up with viruses in leukemias and lymphomas that turned out not to be reproducible, and some of them were obviously wrong. That hurt the field."

"Approximately 15% of all cancers are linked to viruses."
—zur Hausen



An irony of the current situation is that when oncogenes were first discovered in the 1970s, they were identified in animal cancer viruses. When researchers later found that these oncogenes were in fact cellular genes that the viruses had picked up from animal cells in the course of infection, most researchers—but not all—shifted their attention away from viruses. "The enthusiasms created by the discovery of cellular oncogenes and suppressors directed attention mainly onto intracellular mechanisms of cancer development," zur Hausen says. "I feel they are extremely important, but it led also to some ignoring of exogenous factors."

Despite that shift in scientific fashion, zur Hausen kept his attention firmly focused on human cancer viruses. The result has been an impressive portfolio of discoveries: Over the past two decades his lab has been a consistent leader in showing that human papilloma viruses play an important role in cancer of the cervix, penis, and vulva, and possibly at a number of other tumor sites as well.

Zur Hausen's willingness to blaze his own trail is also reflected in his strongly held opinions of the German research system. One of the main problems, he says, is the stagnation produced by granting very long-term appointments. This is a custom that he has tried to change as scientific director of the German Cancer Research Center in Heidelberg, and which he broke with in his own career. In a pattern more typical of his American counterparts, he changed institutions several times before settling into his current position in 1983.

The German government's current freeze on spending in the national laboratory system, to which the Cancer Research Center belongs, is also making the difficulties faced by scientists worse, zur Hausen says. "We hope the freeze will be lifted by 1993, and we are trying hard to increase the budget for 1992. But it doesn't look very promising at the moment."

Despite the money worries, zur Hausen, a dapper, white-haired man with intense blue-gray eyes, makes sure that his own research group of 30 scientists remains disciplined and motivated. Toward 9 o'clock each morning, zur Hausen makes the rounds, asking each of his collaborators what they have done since the day before.

If zur Hausen keeps the pressure on his scientists, it's because he knows that viruses play a major role in human cancer, particularly in the developing countries. The current excitement over oncogenes and tumor suppressor genes is not going to change his estimate that after smoking, and perhaps exposure to UV-light, viruses such as human papilloma, hepatitis B, and Epstein-Barr are the second or third most important cause of cancer. "Approximately 15% of all cancers are linked to viruses," zur Hausen says. ■ **M.B.**