not presently subscribe to international patent conventions, there is no legal roadblock to their doing so.

RU 486's future. If Roussel can be persuaded to begin selling RU 486 outside France—and some believe that despite the company's public reticence, that is exactly what it plans to do—marketing it in the United States will still be a problem. A spokeswoman for Roussel's U.S. affiliate, Hoechst-Roussel Pharmaceuticals, Inc., says that the company has no plans to sell the drug. Product liability and the adverse political climate may scare off other large, established pharmaceutical companies. Kamp thinks a more likely scenario is a small company backed by venture capital that would market only RU 486. Boycotts of such a company would be fruitless, since there would be no other products to boycott, and liability suits would find little reward since the company would be designed to have few assets. Another possibility for marketing would be a nonprofit organization, such as the Planned Parenthood Federation.

RU 486 may also have a role as a drug not for abortion but for contraception. That raises the issue of what exactly RU 486 is. Although widely thought of as an abortion pill, its discoverer Baulieu questions that terminology. He calls it a contragestive, derived from contra-gestation just as contraceptives are contra-conception. Baulieu's neologism goes beyond newspeak. It is a genuine attempt to point out that popular attitudes about when life begins were formed at a time when not much was known about the process. He sees gestation as a continuum, from the meiosis that generates the eggs and sperm, to the birth of a baby. All steps are essential, and none is sufficient by itself. But "for society's sake" it has become vitally necessary to find better ways to control gestation. "My aim is to get rid of the word abortion," Baulieu says, because the word "is almost as traumatic as the fact itself." As far as he is concerned his research is not aimed at gaining women abortions. It is aimed at helping them control gestation.

However it may ultimately be used, RU 486 has forced participants in the debate over the moral issues of human reproduction to reconsider their points of view. But it seems likely that legal prohibitions will not be able to stop a drug with the promise of RU 486.

Jose Barzelatto, formerly at WHO and now at the Ford Foundation, puts it succinctly: "The antiprogestins will come into the market one way or another. There's no question about it. They're too important to be stopped." ■ JOSEPH PALCA

With reporting by Jeremy Cherfas in Paris.

Etienne-Emile Baulieu: In the Eye of the Storm

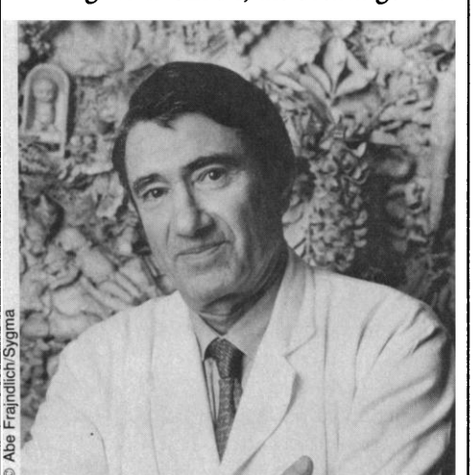
Paris

FOR THE PAST FEW YEARS, Etienne-Emile Baulieu has been on a crusade. Ever since the drug he helped create, popularly known as RU 486, was shown to be highly effective in putting an end to pregnancy without surgery, he has been arguing in every forum he can for its widespread medical use. In the process, he has drawn the wrath of opponents of abortion, heard his discovery condemned by the cardinal of Paris, and even seen the company that manufactures the drug, Roussel-Uclaf, temporarily abandon the first large-scale trials in France in the face of protests.

It is an unusual position for a world-class medical researcher, and Baulieu, an authority on steroid hormones, is certainly that.

RU 486 was only one of Baulieu's important breakthroughs. In the 1950s, he was the first to discover that the adrenal glands secrete a steroid that is soluble in water—a feature that was entirely unexpected and had implications for the hormone's transport in the blood. He followed that discovery with pioneering work on the estrogen and progesterone receptors, the molecules within the cell that are responsible for detecting and passing on the hormonal message. He built on his knowledge of these receptors to create RU 486. And recently he has shown that there are cells in the brain that make steroids, though as yet he has no idea what the hormones are doing there.

Baulieu, 62, made these discoveries while working for INSERM, the French government's medical research organization, which has funded his research for nearly three decades. He currently works at INSERM labs within the Kremlin-Bicêtre hospital in the south of Paris. Baulieu has also been a consultant to Roussel—"independent and exclusive," as he puts it—for more than 25 years.



Practical physician. *Baulieu says he is "a medical doctor who does science."*

The attempt to marry pure science to practical medicine is characteristic of all Baulieu's work. "I am a medical doctor who does science," is how he always describes himself. Indeed, he explains his campaign for RU 486 as strictly a medical matter. "I want to help women. I have not dedicated my life to abortion. I am not anti-children. I have three children and seven grandchildren. But women die in botched abortions. Two hundred thousand every year. RU 486 can save them." Baulieu is quick to point out that he has no personal financial stake in the drug.

Baulieu's father too was a doctor, one of the first in Europe to examine the effects of insulin on diabetics, but he died when Baulieu was only four. For a time Baulieu and his mother disagreed over his career. She did not want him to study medicine, preferring something more like engineering for her son. "To please her, while I was studying medicine, I also studied biochemistry." The M.D. came just before the Ph.D., but although almost all of his subsequent career has been in research, Baulieu insists that "I am a real doctor. I don't have just a diploma. I had patients and everything, and I could have been a professor of internal medicine if I had wished."

Instead he became, at 29, France's youngest professor of biochemistry, at the new university in Reims. He was what the French call a "turboprof," commuting once a week on the fast turbotrains between his laboratories in Paris and a single day of 6 or 7 hours teaching in Reims, 85 miles to the east.

It was his medical training, and practice, that led him to patients with adrenal cancer, which in turn provided his 1959 discovery of soluble steroids. This work came to the attention of Seymour Lieberman, a famous steroid biochemist at Columbia. Lieberman invited the then 35-year-old Frenchman to spend a year in his lab, but at first Baulieu could not go.

"When I was young I was militant in leftist organizations," he told *Science*, "and I

didn't want to go to America." Then came 1956 and the Soviet invasion of Hungary. Like so many other people, Baulieu broke his connections with the left. But now that he had the desire, and the opportunity, to go to the United States, the Americans didn't want him. "I couldn't get a visa," he recalled. Despite interventions from leading scientists such as Lieberman, Baulieu was persona non grata.

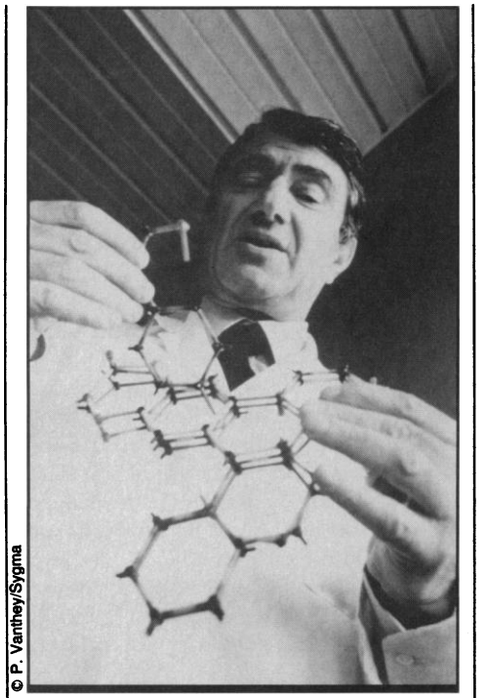
As soon as John Kennedy got into the White House, though, Baulieu got his visa. Shortly after his arrival in New York, Lieberman introduced Baulieu to Gregory Pincus, a Boston University biochemist who had played a key role in the development of the contraceptive pill. It was Pincus who interested Baulieu in contraception and the regulation of pregnancy.

According to Baulieu, Pincus fixed it for him to detour on one of his flights between Paris and New York to Puerto Rico to visit a clinic in San Juan where the pill was being tested. And he arranged for Baulieu to join a World Health Organization committee on contraception, which kept Baulieu shuttling between his Paris laboratories and Geneva. Then, when Baulieu worked on the estrogen and progesterone receptors back in his labs at INSERM in the 1960s, he says Pincus was influential in securing plenty of research support from the Ford Foundation for his research. So when Baulieu isolated the progesterone receptor, his long association with research on contraception quickly led him to wonder how he might make practical use of this discovery to control pregnancy.

Baulieu could see three obvious approaches. One would be to prevent the body from making progesterone. He didn't like that because progesterone is on the direct path to other hormones; if you stop the synthesis of progesterone, you stop the synthesis of those other hormones too, with who knows what consequences. Another was somehow to remove all the progesterone from the body. At the time that seemed impossible, as it still does today. The third was to ignore the hormone and concentrate on the receptor, and that is exactly what Baulieu chose to do.

He already knew that compounds such as Tamoxifen, an antiestrogen drug made by Britain's Imperial Chemical Industries, occupied the receptor and substituted its own weak message for the more powerful signal from estrogen, thus preventing any estrogen present from having a major effect on the cell. All Baulieu had to do was find a similar compound that would block progesterone. "But it was all very vague," he recalls today. "We had no chemical idea how to devise a progesterone analogue."

Two lines of work converged on the solution. Robert Sutherland, an Australian postdoc working in Baulieu's lab, discovered that a derivative of Tamoxifen with an extra hydroxyl group was a much more potent antiestrogen than Tamoxifen itself. And George Teutsch, the chief chemist at Roussel, a company that had a reputation for fine steroid biochemistry, discovered an efficient way to tack appendages onto the progesterone molecule at a position equivalent to the point at which the hydroxyl group had been added to Tamoxifen. So they could produce a series of derivatives of progesterone and screen them to see whether they would block the receptor.



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"We had no chemical idea how to devise a progesterone analogue."

Despite this, the Roussel chemists nearly missed their target. All the compounds capable of blocking steroid receptors discovered at that time had low affinity for the receptor. That is, they bound weakly to the receptor and, it was believed, had a chemical effect on the cell that counteracted the action of the hormone proper. Baulieu discovered that hydroxy-Tamoxifen had a high affinity. It bound tightly to the receptor, but beyond that it did nothing. It worked by occupying the receptor entirely, thereby shutting off the estrogen molecule's access to the cell.

Screening takes time and money. So pharmacologists concentrate first on the most promising classes of compounds, and on the basis of their understanding at that time, they thought all antisteroids would bind weakly to the receptors. When Baulieu realized that hydroxy-Tamoxifen worked so well precisely because it had high affinity, he put the Roussel pharmacologists through a U-turn. "I said, 'Aha. Check all the high-affinity compounds.' " The result was RU 486.

Tests in the laboratory in 1978 showed that the new substance had a very high affinity for the progesterone receptor, completely blocking the effect of progesterone. At much higher doses, RU 486 blocked glucocorticoid receptors too. (Glucocorticoids are hormones responsible for the regulation of carbohydrates and proteins and many other important aspects of metabolism.) "As soon as we had it," Baulieu recalled, "I said the best way to test it is in vivo, to see if it blocks progesterone in pregnant women." This despite the fact that, although progesterone was known to be vital for pregnancy in a whole zoo of laboratory animals, its role had not yet been proven in women.

After tests had shown that RU 486 was not toxic to monkeys, Baulieu took it to Walter Herrmann, professor of obstetrics and gynecology at the University Hospital of Geneva and a long-time friend and collaborator of Baulieu's. Herrmann enlisted the help of 11 pregnant women who wanted an early abortion. Each received RU 486 for 4 days; nine aborted, eight of them within 5 days. Two did not abort and had to undergo suction to remove the fetus. This test proved that Baulieu's concept worked; RU 486 could put an end to pregnancy by blocking the progesterone receptor.

The drug has now been tested on thousands of women around the world, and although the dosage has been somewhat refined, the results have not changed all that much since that first Swiss trial.

Asked to sum up his view of his own career, Baulieu says: "If you have one adjective to attribute to me, I would say that I am full of curiosity." It is a curiosity often spurred by competition. "I like being in a race," Baulieu says. "Competition is amusing, and it certainly helps" to get results. And with competition come prizes, which he also relishes. "It's part of competition. If you are in a competition, you have to keep the score." Baulieu has had his share of awards, but "I would welcome a prize" for RU 486, he says, "because it helps the message to be spread."

Baulieu acknowledges that, as a scientist, he has been luckier than most, at least as far as the quantity and quality of his discoveries are concerned. But he is quick to quote Pasteur's remark: "Le hasard ne favorise que les esprits préparés"—chance favors only the prepared mind. ■ JEREMY CHERFAS