The Pill of Choice?

RU 486 is sweeping France, replacing surgery for abortion. But protests are restricting its use, a particular hardship for developing countries where the drug could save lives

FOR A DRUG not yet a decade old that most people have never heard of, RU 486 is causing quite a ruckus. In scores of research laboratories, molecular biologists are arguing about how it binds to steroid receptors; in government health ministries, bureaucrats are debating whether to license it for use; in the boardrooms of a number of powerful corporations, executives are arguing over whether to risk marketing it. But there is one thing no one argues about: RU 486 taken in conjunction with prostaglandins is an extremely effective method of terminating pregnancy within the first 9 weeks of gestation. And that means that RU 486 could change the context of the debate over abortion and birth control.

The development of RU 486 is a case study in how the forces of biomedical research and public policy occasionally collide. From the start, groups opposed to abortion under any circumstances were calling RU 486 the "death pill," and they have been largely responsible not only for keeping the drug out of this country, but also for intimidating researchers interested in exploring the myriad potential medical uses for the drug.

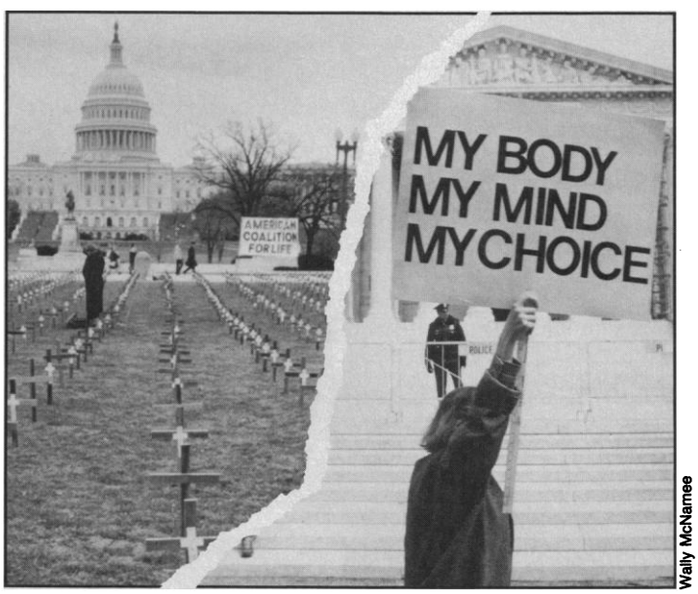
Why should anyone care about an abortion pill, at least in industrialized nations where abortions have become quick, safe, and relatively inexpensive procedures?

The significance of RU 486 for developed countries is not that it is measurably safer or more effective than up-to-date surgical methods but that it can be used in relative privacy. Women seeking early abortions could be treated by their regular doctors and not be forced to visit abortion clinics where protestors may be demonstrating outside.

It is not surprising, then, that RU 486 is viewed with alarm by antiabortion groups. They have good reason to worry: In France, approximately 25,000 have chosen RU 486 over surgery for abortion in the past 11 months since the government decreed that it be made available on an experimental basis.

So far, however, France is the only country in which RU 486 is widely available. The company that manufactures it has been unwilling to permit the drug to be sold anywhere else. And this is threatening to touch off a counterattack from "pro-choice" advocates frustrated at being denied what they see as a prizewinning breakthrough in the technology of reproductive medicine.

The sluggishness with which RU 486 is being brought to the market around the world is also a source of immense frustration to its chief developer, Etienne-Emile Baulieu, one of France's leading scientists (see p. 1323). Baulieu developed RU 486 in the late 1970s while retained as a consultant by the French pharmaceutical company Roussel-Uclaf, a subsidiary of the giant German company Hoechst AG. He has been one of the most outspoken crusaders for the drug, pointing out at every opportunity that it could save thousands of lives. He's not just hyping his own work: Mahmoud Fathalla of the World Health Organization (WHO) says, "the figures are alarming. Possibly 200,000 die every year. In some countries almost 50% of the maternal mortality is due to unsafe abortion."



Wally McNamee

RU 486 and the abortion debate: "It creates a whole new playing field."

The French experience. Although the French government has agreed with Baulieu that women should have access to his drug, RU 486's road to market has been anything but smooth. Health officials gave Roussel permission to begin sending RU 486 out to registered abortion clinics on 23 September 1988. But just 1 month later Roussel decided to suspend distribution of the drug for reasons that even today are not completely clear. In France the abortion debate has not been as vociferous as in the United States, but it has not been without passion. Roussel executives say that the company had received threats of bomb attacks for its plans to market the drug. But Roussel medical director André Ulmann says threats weren't the main reason Roussel withdrew the drug: "At the maximum we received 400 letters, which is nothing."

Profits may have been more important than personal intimidation in Roussel's decision. Some within the company have suggested that boycott threats were influential. Antiabortionists and Catholic hospitals served notice that they would stop buying any product made by Hoechst or its international subsidiaries if the company continued

The Story of RU 486

The article that begins on this page describes clinical experience with RU 486 in France and the debate over its use.

- How the drug works: page 1320.
- Research on medical uses other than abortion: page 1322.
- How it was discovered: page 1323.
- The scientific issues—an article by Etienne-Emile Baulieu: page 1351.

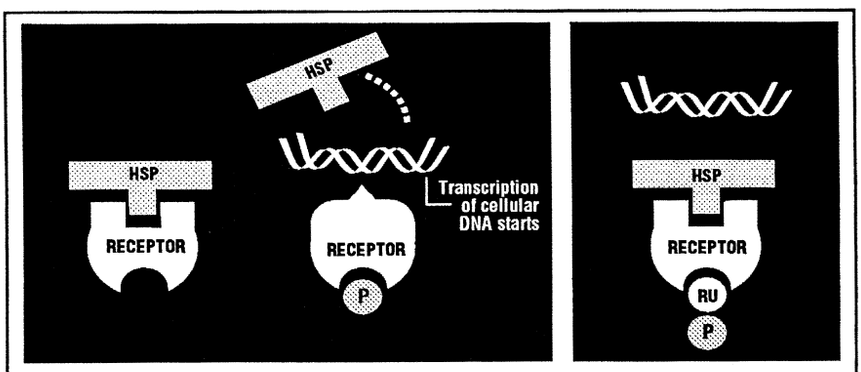
Stopping the Process of Pregnancy

RU 486 works by blocking the normal action of the hormone progesterone during pregnancy. In the first half of a woman's ovulatory cycle, estrogens secreted by the ripening egg follicle (prompted by hormones from the brain) cause the wall of the uterus to start thickening. Near the middle of the cycle, when estrogens are at their peak, a surge of the hormone called luteinizing hormone cues the follicle to release its egg. The cells left behind form the corpus luteum, which secretes progesterone. Progesterone prepares the womb for pregnancy.

In the preparation process, known as decidualization, the lining of the womb becomes thicker and the blood supply to it increases. An embryo will typically attach to the uterine wall about 2 weeks after the egg has been fertilized. After 14 days, unless a fertilized egg implants in the womb, the corpus luteum disintegrates, the level of progesterone drops, and the lining of the womb is expelled.

If there is an embryo, cells around it secrete a hormone called human chorionic gonadotropin, which rescues the corpus luteum, keeping it active and secreting progesterone. As a result the cells lining the uterus, called the endometrium, stay in place and accept the implantation of the embryo. After about 9 weeks the placenta takes over the manufacture of progesterone from the corpus luteum and keeps the level of the hormone high. High levels of progesterone, among other effects, suppress the brain hormones responsible for triggering a new cycle of ovulation, one reason why no further eggs are produced during pregnancy.

Progesterone causes decidualization of the endometrium by directly affecting the transcription of specific genes in the nucleus. Etienne-Emile Baulieu has investigated two of the most important links in the chain of communications between the hormone and the genes. One is the receptor itself. The other is a so-called heat shock protein. (Cells react to being heated to 40° or 41°C, instead of the normal 37°C, by shutting down protein synthesis. A few anomalous proteins, the heat shock proteins, increase instead of decrease when the cell is stressed, and one of these heat shock proteins is an essential component of the progesterone receptor system.)



In normal activation, progesterone (P) changes shape of receptor, releases heat shock protein (HSP), begins DNA transcription.

RU 486 blocks entry of progesterone; heat shock protein remains in place.

According to the presently accepted model, the heat shock protein binds to the receptor and blocks off a region of the receptor that would otherwise connect with areas on a cell's DNA called hormone response elements. When progesterone enters the cell, it also binds to the receptor and, in the process, it changes the shape of the receptor in a way that frees the heat shock protein. This allows the receptor-hormone complex to bind to the hormone response elements on the DNA. That step, in turn, alters the DNA so that the genes controlled by progesterone can be transcribed.

RU 486, like progesterone, binds to the receptor but does not release the heat shock protein. Indeed, the heat shock protein may become even more tightly bound to the receptor. As a result, the receptor is unable to bind to the hormone response elements, and no transcription of the DNA takes place. RU 486 occupies the receptors, preventing progesterone from binding to them, and any processes that depend on progesterone, such as the maintenance of pregnancy, fail. ■ **J.C.**

to market RU 486. But others say the company was anxious to appear as the unwilling debutante, being forced by its government to go forward with a controversial product.

In any case, forces favoring the drug mounted an economic threat of their own. Doctors at the World Congress of Obstetrics and Gynecology meeting that month in Rio de Janiero also threatened to boycott Hoechst products if the company did not make the drug available. Baulieu himself harshly condemned Roussel's decision at the congress and in numerous press interviews.

In the end, it fell to French health minister Claude Evin to change Roussel's corporate mind. Using the French government's 36% stake in Roussel-Uclaf as leverage, Evin threatened to transfer Roussel's patent to another company, something French law allows. He told Roussel that he "could not permit the abortion debate to deprive women of a product that represents medical progress. From the moment government approval for the drug was granted, RU 486 became the moral property of women, not just the property of the drug company."

On 28 October Evin announced that the company had agreed to start supplying the drug once again. The results have been impressive. Roussel has distributed about 150 to 200 treatments per day. RU 486 is being used for between a quarter and a third of all pregnancy terminations in France.

The treatment consists of three 200-milligram pills of RU 486, followed 48 hours later by a small amount of prostaglandin, either as an injection or a pessary. RU 486 blocks the normal action of progesterone on the cells lining the uterus to accept and sustain an embryo through development (see box, left) and the prostaglandin helps encourage the womb to contract and expel its contents. Approximately 96% of women receiving the two drugs within the first 9 weeks of conception have a complete abortion within a day of receiving the prostaglandin. In about one case in a thousand bleeding is sufficient to require a transfusion. Minor pain, cramps, and nausea are the reported side effects, but these are indistinguishable from heavy menstruation.

These results are mirrored in numerous small trials around the world. Other countries have completed the tests necessary for licensing RU 486, but Roussel's parent Hoechst has been unwilling to market the drug outside France. In Britain David Baird, professor of reproductive endocrinology at Edinburgh University, coordinated a multicenter trial involving more than 1000 women at 13 hospitals and clinics and handed the results to Roussel in November 1988. He says Roussel has been dragging its heels

over applying for a product safety license in the United Kingdom. Roussel has also withdrawn an application for a license in Holland.

Illegal markets? Will the success of RU 486 in France prompt a black market in countries where the drug isn't available? Clearly Roussel is concerned about this possibility.

"If the drug becomes available for England," says Ulmann, "and not for the U.S., it is clear that one way or another there will be a black market." Illegally obtained pills used improperly—but nevertheless bearing Roussel's trademark—could become a corporate nightmare if they caused injury or death.

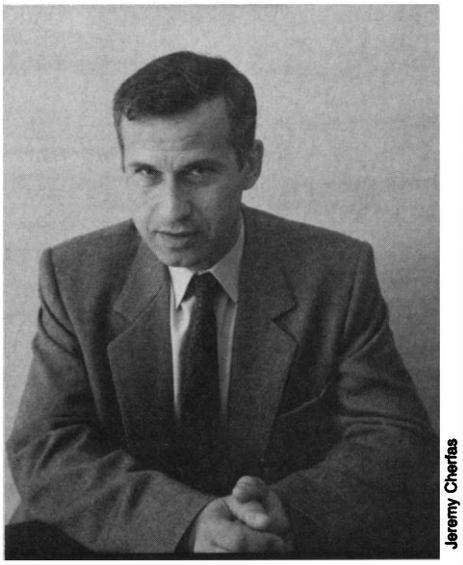
But can Roussel keep control of the drug's destinations to prevent a black market developing? At present RU 486 goes directly from Roussel to the clinics where it is made available to physicians free of charge. But in a matter of weeks Roussel plans simply to make RU 486 available through its normal wholesalers. The company is currently negotiating with health officials in France over the price.

A black market might be supplied by doctors receiving the treatment from Roussel. Or it could come from other sources. "You can find Korean or Hungarian chemists who can synthesize [RU 486] very well and put it on the market," Ulmann points out.

"There will be a black market eventually," agrees Marie Bass, a Washington lobbyist on reproductive rights issues. "I can't imagine that there wouldn't be. And then we have to worry that [RU 486] will be misused."

The potential for misuse will not be limited just to pills obtained on the black market, however. If the drug does become legally available by prescription from pharmacies it is probably inevitable that it will be improperly used. "The problem that I foresee with . . . home use is the adolescent who is, in her own mind, still a virgin until she is 4 months [pregnant] and can no longer fit into her blue jeans," says Sharon Kamp of the Population Crisis Committee. "If [adolescents] were to get their hands on this and try to use it at 4 months' pregnant, it might have some serious consequences."

The U.S. debate. But for the present, there is no chance that RU 486 will be available legally in the United States. Both RU 486 and the prostaglandin that must be taken with it lack approval from the Food and Drug Administration. "A U.S. protocol in my estimate would take 3 years to complete if it started today," says Sheldon J. Segal, director for population sciences at the Rockefeller Foundation.



Jeremy Cherfas

"If the drug becomes available for England and not for the U.S., it is clear that one way or another there will be a black market."

—André Ulmann

There have, however, been clinical trials of RU 486 as an abortifacient in the United States. The University of Southern California (USC) has given the drug to some 400 women in a variety of doses at different stages of pregnancy. But Segal says drug registration trials would require testing a particular dose at a particular regimen, so the USC experience may not be directly applicable to licensing the drug in this country.

Because surgical abortion has been legal and widely available in the United States, there has been little grass-roots pressure to get RU 486 approved here. But this year's Supreme Court decision in the case of *Webster* v. *Reproductive Health Services* may dramatically increase interest in the drug. By signaling that it was prepared to place legal limits on the rights to an abortion granted in the landmark *Roe* v. *Wade* case, many "pro-choice" groups fear the Supreme Court may go further in subsequent cases.

"There was fairly strong support for the drug as a technological advance even before *Webster*, and I think that people are seeing it as even more important now," says David J. Andrews, executive vice president of the Planned Parenthood Federation of America. If states start to restrict abortion services—as some of them are likely to do in the aftermath of *Webster*—that would enhance the need for easy alternatives to surgical abortion, according to Andrews.

Pro-choice supporters feel RU 486 will change the very nature of the abortion debate. "I think it creates a whole new playing field and it is likely to undermine to a very great degree the strength of the antiabortion movement," says Kamp. "If you were able to make abortion something that is entirely private . . . the tactics of the antiabortion movement would have to change. Who are they going to picket?"

To stop what they call "chemical war against babies," organizations like the American Life League and the National Right to Life Coalition have enlisted the support of sympathetic congressmen in making access to the drug as difficult as possible. It is currently illegal for the National Institutes of Health to support any research on abortifacients such as RU 486, although NIH has studied the drug for other medical uses. But normally voluble scientists at NIH are uncharacteristically cautious when talking about research on RU 486. "They've suffered a kind of chilling effect," says Rockefeller's Segal. "They're scared to death of the threats against anybody who does anything with this drug."

NIH isn't the only institution that's nervous. Marcia Lacarra, a nurse and family planning counselor at USC's Women's Hospital where RU 486 is being tested, absolutely refuses to discuss what USC is doing with the drug. "We're tired of getting threatening letters," says Lacarra.

The Bush Administration, like the Reagan Administration before it, has gone along with the restrictions on the drug sought by conservative legislators. As recently as 9 June this year, FDA Commissioner Frank E. Young wrote to Representative Robert K. Dornan (R–CA) assuring him that FDA would not permit RU 486 to be imported into the United States for personal use, something the FDA has allowed for certain other unapproved drugs.

The developing world's needs. The United States has also used its political clout to try to slow testing of the drug by the WHO. The United States does not give financial support to WHO's special program on human reproduction, and observers say the WHO's Director General Hiroshi Nakajima fears that they will stop supporting other WHO programs if WHO continues its research on RU 486.

But WHO is continuing its research program, expanding it to include ZK98734, a drug that acts in the same way as RU 486, made by Schering AG. WHO program officer Paul Van Look says the agency's goal is to find abortion protocols that would not require a second visit to the clinic. RU 486

Hormone Antagonist with Broad Potential

Although medical research has focused primarily on RU 486's usefulness as an abortifacient, researchers at scores of labs around the world are quietly investigating other potential applications of the drug.

At the U.S. National Institutes of Health, George Chrousos has been using RU 486 to treat patients with Cushing's syndrome, a condition resulting from excess production of cortisone. Since RU 486 blocks not only the progesterone receptor but also glucocorticoid receptors, it counteracts the effects of the excess cortisone. Chrousos says that Cushing's syndrome, which effects about 500 people each year, can be caused by a tumor in the adrenal cortex that can't be detected when it first arises. RU 486 can be used to keep patients alive until the tumor becomes large enough to be isolated and surgically removed.

RU 486 also has a role in basic research on how the glucocorticoid receptor works because it binds to the receptor with such high affinity. Using RU 486, researchers can block receptor activation at different stages: from when it first binds to the hormone to when it turns on genes in the cell nucleus.

At Tufts University Health Sciences Center in Boston, ophthalmology chairman Bernard Schwartz has experimented with RU 486 in eyedrops as a treatment for glaucoma, a condition characterized by increased pressure within the eyeball that can cause blindness. Schwartz says glaucoma patients have increased levels of cortisone in their blood which seem to cause the increased pressure. The idea was to use RU 486 locally to block its effect on the eye. But results on rabbits so far have been disappointing, and it has proven difficult to limit the effect of the drug only to receptors in the eye.

Further in the future, RU 486's antiglucocorticoid activity may find a use in the local treatment of skin wounds such as burns and abrasions. Corticosteroids delay healing, so RU 486's developer Etienne-Emile Baulieu believes that anticorticosteroids will accelerate healing.

Other potential medical applications derive from RU 486's effects on the progesterone receptor. Meningiomas, for example, are primary tumors of the membranes that surround the brain. For unknown reasons the cells of the tumor have an abundance of progesterone receptors and few, if any, estrogen receptors. Generally these tumors are benign, but they can become large enough to cause neurological disorders and can be difficult to remove surgically. Teams in Holland, France, and the United States are looking at the effect of RU 486 on these tumors, but no clear-cut results are in yet.

In breast cancer, too, there may be a role for RU 486. Some tumors require a combination of estrogen and progesterone to keep growing. Antiestrogens such as Tamoxifen can halt these tumors, but studies in Montpellier in the south of France indicate that RU 486 can make the antiestrogens more effective. A group at the Lombardi Center of Georgetown University in Washington, D.C., is examining the value of RU 486 in breast cancers that have become resistant to antiestrogens.

RU 486 should also find uses in the management of pregnancy beyond contraception and abortion. Because it effectively removes progesterone, it can mimic the onset of labor, including changes such as the softening and dilation of the cervix that accompany a normal delivery. At present a complex cocktail of drugs is needed to induce labor, but the hope is that RU 486 will be able to do the job more simply in the future. This will be enormously helpful in cases where the fetus has died in utero, and it may also reduce the number of cesarean sections performed.

Baulieu is also enthusiastic about RU 486 as a potential birth control method. He sees three different ways in which the drug could be used for this purpose.

First is what Baulieu calls a "menses inducer." If a woman takes RU 486 in the second half of her cycle, there is an 80% chance that she will begin to bleed. Although a 20% failure rate may seem high, even women with active sex lives conceive on only one in five cycles, so the actual failure rate is 4%.

A second approach is to use very small amounts of RU 486 during the second, luteal, phase of the cycle. This can be tricky, because although the luteal phase always lasts 14 days, the first part of the cycle is variable, making it difficult to know when to start taking RU 486. The idea is not to provoke bleeding but to act solely on the endometrium, preventing the implantation of the embryo. The woman would have to take small doses of RU 486 every day for 10 to 12 days.

The final, and perhaps most promising, potential use of RU 486 is as a contraceptive in the conventional sense. In the first, follicular phase of the cycle there is a small amount of progesterone that seems to be very important for ovulation. Blocking that could block release of the egg. A Finnish team has shown in a small-scale trial that RU 486 can prevent ovulation without the need for estrogens. ■ J.C. AND J.P.

and the Schering drug have an unacceptably low success rate—in some studies as low as 60%—when taken without prostaglandins. The ideal situation would be a combination drug where the prostaglandin wouldn't go to work until after the RU 486 had done its job of starting the shedding of the uterine wall and sensitizing the womb to the prostaglandin.

Opponents of RU 486 worry that the drug will be used indiscriminately in developing countries. Bob Marshall of the American Life League says that, in their rush to terminate pregnancy, supporters of RU 486 are ignoring the health of the mother. "What that tells me is 'get them unpregnant at any cost,' and if a few die in the process, or a number die, the hell with it," he says. "If you start hemorrhaging out in the bush in Kenya, well, goodbye."

But Van Look says that's just not how the drug will be used. "Any medical approach to termination of early pregnancy—like an approach involving one of these antiprogestins—will always require backup from surgical facilities," he says. "What it could offer developing countries is that where existing facilities are overstretched you can now have an outpatient treatment which will be successful in 95% of cases, so you only need facilities and skilled personnel for the remaining 5%."

WHO says Roussel has promised to deliver the drug to any WHO member country that requests it for the purpose of further study, but according to Van Look no other country has made a formal request. The Peoples Republic of China, a participant in WHO-sponsored trials of RU 486, is the only country besides France to approve the drug for use as an abortifacient. It is currently Roussel's policy not to supply the drug outside France, but many believe the Chinese have the capability to manufacture the drug on their own. And since China does

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.

© Abe Frajndlich/Sygma

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