

RU 486

This controversial drug is now used widely in France to terminate unwanted pregnancies. Yet the compound was not invented for that purpose and actually has many possible applications

by André Ulmann, Georges Teutsch and Daniel Philibert

In 1980 one of our colleagues synthesized a molecule with an unexpected property. Chemically it resembled the hormone progesterone, and like progesterone, it bound tightly to the progesterone receptor in cells. Yet instead of evoking the hormone's usual effects, this chemical blocked them. Because progesterone is crucial to the maintenance of pregnancy, the emergence of this unusual property raised the possibility that the new chemical might serve as a means of interrupting pregnancy.

The substance, designated RU 486 (after the maker, Roussel-Uclaf), is now on the market in France and the subject of worldwide controversy. International attention—both favorable and, in the case of antiabortion activists, unfavorable—has focused on the drug's role in the voluntary termination of early pregnancy.

Under the name mifepristone, RU 486 is administered as a tablet in conjunction with a small dose of a prosta-

glandin, which increases the frequency and strength of the uterine contractions needed to expel an embryo. In France the drug combination is approved for ending pregnancies of up to 49 days' duration (counting from the first day of the last menstrual period). There, between a quarter and a third of women who decide to interrupt an early pregnancy now choose this chemical approach over standard surgical procedures.

In the next few years RU 486 may also become available elsewhere for the same purpose. The manufacturer is considering distributing it in such countries as Great Britain, the Netherlands and Sweden, where the data required for licensing have already been amassed. The drug may also ultimately serve other functions as well; it has a number of possible therapeutic applications that are not limited to birth control and that include the treatment of certain cancers.

RU 486 was not invented with the goal of pregnancy interruption in mind. Nevertheless, by the time it was synthesized, social concerns and scientific events had already helped set the stage for that use. International agencies were calling for the introduction of a variety of new birth-control technologies. It was hoped that simplified or otherwise improved methods would help stem global population growth, which is accounted for by overwhelming growth in developing nations. The world's population expansion threatens the future availability of food, water and other resources and thus threatens the well-being

and the survival of the human species.

Among the desired technologies were new approaches to the termination of pregnancy. Many women in developing nations and, to a lesser extent, in industrialized countries rely on pregnancy interruption for birth control. Although legal surgical methods are safe and effective, they have well-known drawbacks. In the first three months of pregnancy, vacuum aspiration (sometimes preceded by dilation of the cervix) is the usual method of choice. In this approach, suction is applied to remove the embryo and the endometrial tissue in which it is embedded. After about three months of pregnancy, the required procedures generally become more complex. As pregnancy progresses, the risks of infection, hemorrhage, scarring and impaired fertility increase. In developing nations, where surgical facilities are often inadequate, the danger is greater. What is worse, where legally operated facilities are not readily accessible, many women die from having unsafe abortions, typically because of uncontrolled bleeding or infection.

Analyses of steroid hormones (of which progesterone is one) pointed to the possibility of a noninvasive and potentially safer means of interrupting pregnancy. Research suggested that if an agent with RU 486's particular anti-progesterone action could be identified and delivered as a tablet or by injection, it might offer a medical alternative to surgery.

This suggestion was informed by independent work done in the late 1960's and the 1970's by Elwood V. Jensen of the University of Chicago,

ANDRÉ ULMANN, GEORGES TEUTSCH and DANIEL PHILIBERT are colleagues at Roussel-Uclaf in Romainville, France. Ulmann, a nephrologist and endocrinologist, is medical director; he headed the clinical testing of RU 486 by the company. Teutsch, a chemist who is director of endocrine research, focuses on the synthesis of steroids and peptides and on the production of new antibiotics. Philibert, a physicist and pharmacologist, supervised the research into how RU 486 acts in cells and in animals and is responsible for similar analyses of other steroid analogues synthesized at Roussel-Uclaf.

Etienne-Emile Baulieu of INSERM (the French institute for medical research) and Bert W. O'Malley of the Baylor College of Medicine in Houston, Tex. These investigators uncovered the basic mechanism by which steroid hormones induce cells to synthesize proteins. The steroids, which are derived from cholesterol, include not only progestins (progesterone and similar molecules) but also estrogens (such as estradiol), androgens (such as testosterone), glucocorticoids (such as cortisone) and mineralocorticoids (such as aldosterone).

The investigators showed that steroids, unlike polypeptide hormones, actually enter target cells. Inside a cell, they bind to receptors in the nucleus. The resulting unit—consisting of the bound steroid (the ligand) and its ac-

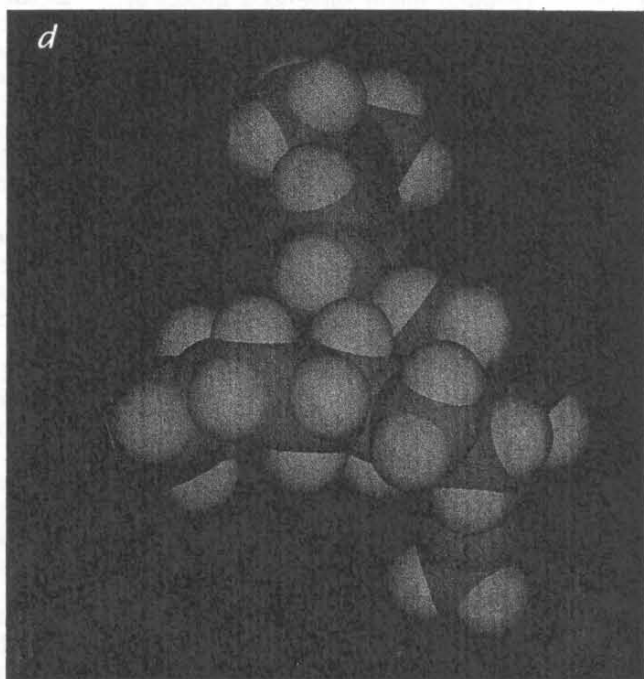
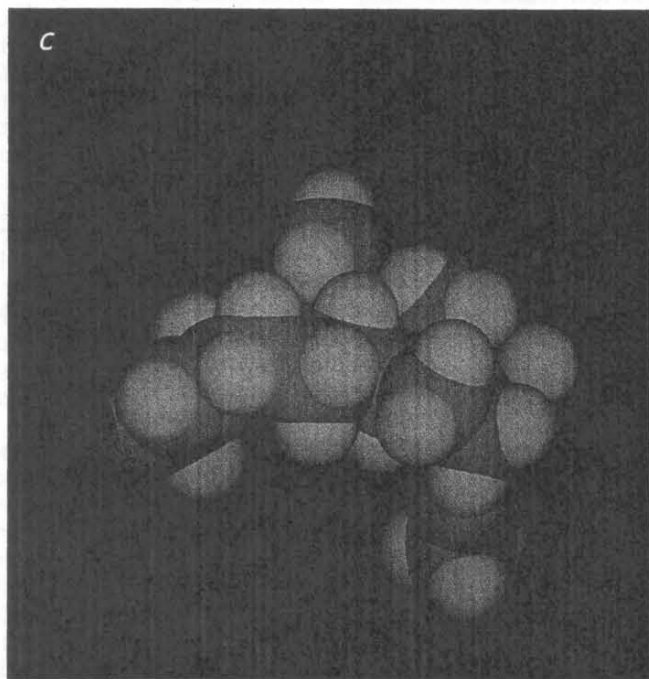
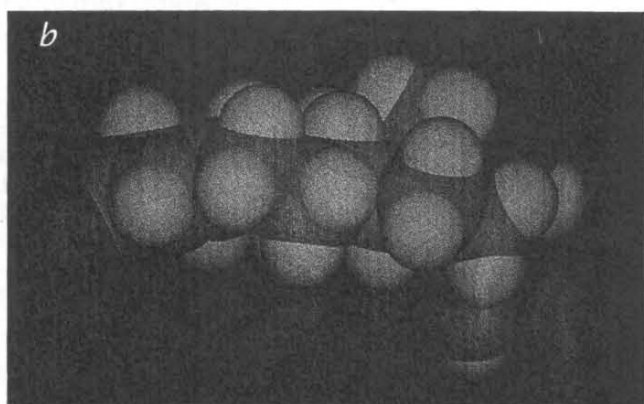
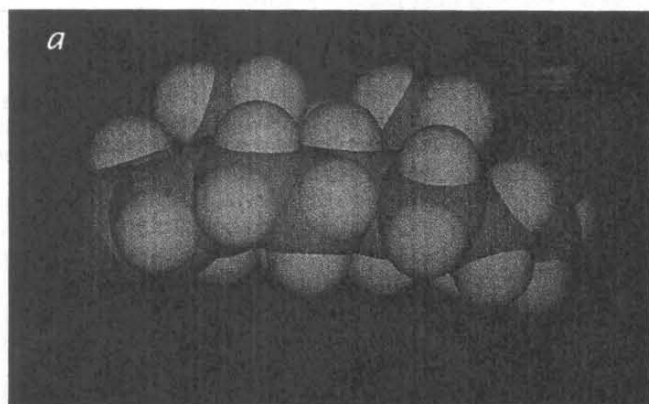
tivated receptor—then binds to the chromatin in the nucleus (the complex of DNA and its associated proteins). That event then triggers the transcription of a selected gene from DNA into messenger RNA. Because the progesterone-stimulated synthesis of proteins in the uterus is essential to the maintenance of pregnancy, it was evident that the day scientists discovered a compound able to occupy progesterone receptors without inducing progesterone's effects, they would have an efficient and selective method for interrupting pregnancy.

It was expected that a progesterone antagonist would, depending on when it was administered, either prevent implantation of a fertilized egg or cause a more developed em-

bryo to detach from the uterine wall. The details of how such effects might be induced were inferred from a long-held understanding of the menstrual cycle and pregnancy in mammals.

In the first half of the menstrual cycle—the follicular phase—estrogen and other hormones direct the development of a single ovarian follicle (an ovum and the cells that envelop it) and also induce the cells of the endometrium to proliferate. After the mid-cycle release of the egg at ovulation, the remnant of the follicle in the ovary becomes the corpus luteum, a transitory gland that secretes a continuous stream of progesterone.

The progesterone converts the proliferating endometrium into a tissue capable of accepting and nourishing a developing embryo. In particular, the



SHAPE of progesterone molecule (a) and three of its synthetic relatives was deduced by computer. Two of the molecules, norethindrone (b) and RU 42764 (c), mimic the hormone's activities, which are crucial to the maintenance of pregnancy. RU

486 (d) counteracts progesterone's effects, an antagonism that seems to stem from the bulky projection rising above the plane of the molecule. The green, blue, red and purple spheres represent carbon, hydrogen, oxygen and nitrogen, respectively.

hormone causes the endometrial cells to synthesize and store the sugar glycogen, promotes the growth of blood vessels in the expanded endometrium and increases the secretory activity of that tissue. Progesterone also relaxes the uterine muscle to forestall the contractions that might expel an embryo, and it further prevents expulsion by firming the cervix and inhibiting its dilation. These last effects derive in

part from the ability of progesterone to inhibit the uterine secretion of prostaglandins.

If the egg is fertilized, it will begin to implant by about the sixth day after fertilization. Soon after, the trophoblast, or developing placenta, signals the corpus luteum to continue secreting progesterone until the placenta becomes fully functional in about the eighth week of pregnancy. If the egg is

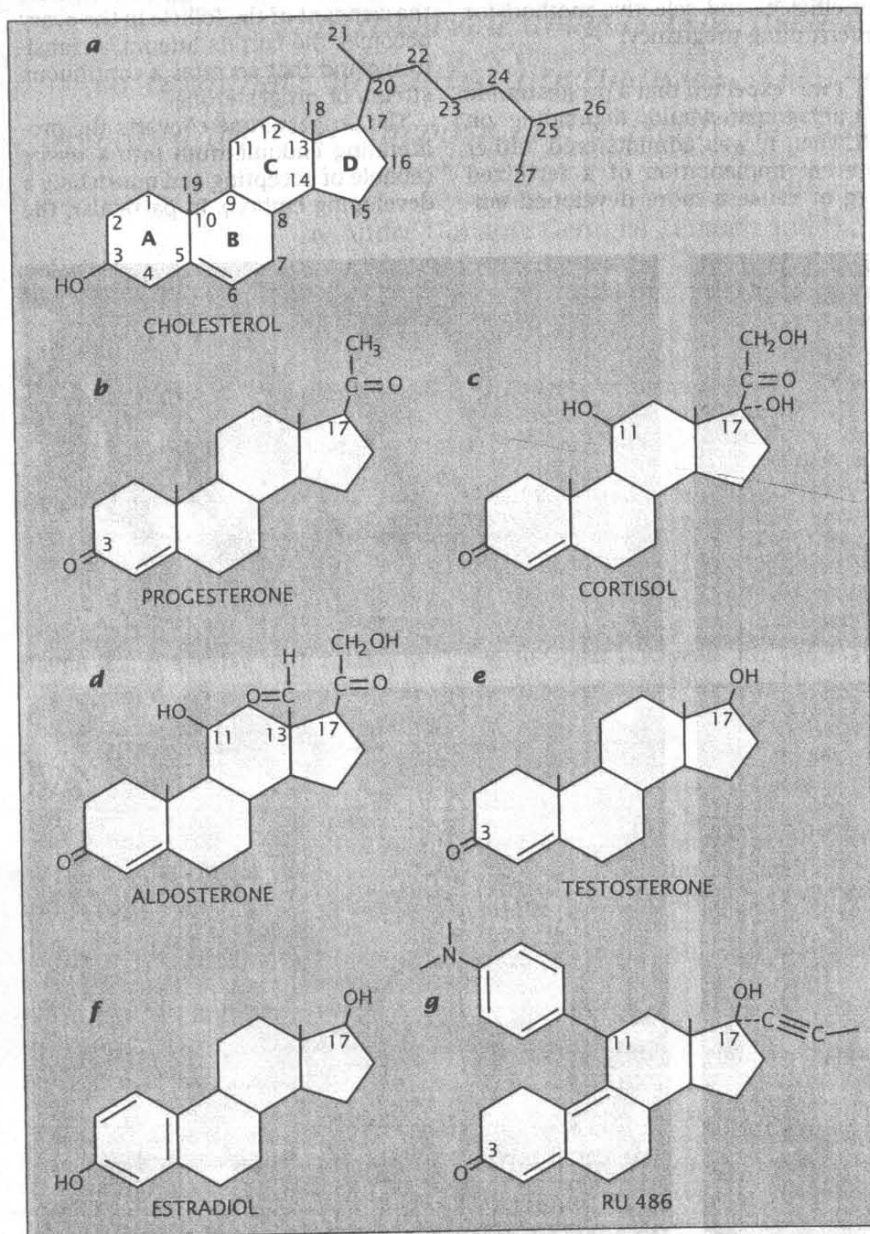
not fertilized, the corpus luteum begins to degrade after some 12 days, so that by about the 28th day of the cycle, the decline in progesterone results in the shedding of all but the basal (permanent) layer of the endometrium. Uterine bleeding follows, and the cycle begins anew.

The delivery of a progesterone antagonist before implantation, then, was expected to prevent the endometrium from undergoing the changes required for it to accept a new embryo. Given after implantation, the drug was expected to initiate a chain of events leading to the expulsion of the embryo. Blocking the secretory activity of the uterine lining would initiate endometrial erosion. That erosion would cause the developing placenta and the embryo to detach from the uterine lining. Then the corpus luteum would decay, resulting in a sharp decline in progesterone secretion. This decline would further erode the endometrium. At the same time, the decline in progesterone would lead to increased contractility of the uterine muscle and would facilitate the softening and dilation of the cervix, leading finally to the expulsion of the embryo.

In spite of such insight—and years of research, conducted primarily by the U.S. National Institutes of Health—no reasonable candidate for an antiprogesterone agent emerged until RU 486 was synthesized in 1980. It is ironic that, at the time, no one at Roussel-Uclaf was actively seeking a progesterone antagonist.

The story of the compound's discovery actually begins a few years earlier, in 1975. One of us (Teutsch) was studying how small chemical alterations affect the ability of steroids to bind and activate their receptors. As part of his work, he developed a method of synthesizing versions of steroids that do not exist in nature. A young postdoctoral fellow, Alain Belanger, then produced the novel molecules.

As a matter of routine, each new steroidlike molecule made at Roussel-Uclaf is screened by the company's pharmacologists as a first step toward determining its possible effects in the body. On the assumption that a molecule capable of binding to a receptor might activate the receptor or block its activities, the pharmacologists determine the affinity of each new synthetic molecule for receptors representative of each of the five classes of steroids. The pharmacologists, led by Roger Deraedt, found that certain of the molecules made by Teutsch!



STEROIDS are derived from cholesterol (a), in which carbons are numbered according to a standard scheme. There is a structural similarity between representatives of each class: the progestins (b), glucocorticoids (c), mineralocorticoids (d), androgens (e) and estrogens (f). Because of this resemblance, synthetic steroids can sometimes bind to more than one kind of steroid receptor. For instance, RU 486 (g), which is a derivative of progesterone, binds strongly to both progestin and glucocorticoid receptors. RU 486 is known as an 11-substituted 19-norsteroid because an atomic grouping not found in progesterone is bound to the 11th carbon and because the methyl group (CH_3) that normally accounts for the 19th carbon has been removed.

method bound extremely strongly to the progesterone receptor, some bound tightly to the glucocorticoid receptor and some bound well to both.

In many cases a molecule that binds tightly to a receptor is an agonist: it will produce the same effects as the natural ligand. Teutsch therefore decided to see if the same were true for the new creations. Because his responsibilities included research into glucocorticoids, he asked the pharmacologists to examine the activity of a molecule called RU 25055, which had a very high affinity for the glucocorticoid receptor.

RU 25055 did not behave as expected. When the molecule was mixed with cells that normally respond to glucocorticoids, it induced no detectable glucocorticoid activity, such as the shrinkage of thymic cells. That finding suggested the compound was actually a glucocorticoid antagonist. By binding strongly to the glucocorticoid receptor but failing to induce the usual effects, the molecule could presumably prevent such effects from occurring or from occurring with their usual intensity.

After this discovery was made, Teutsch and his colleagues gradually reversed their previous thinking about the relation between binding affinity and activity in this molecular series. They suspected that the molecules having the greatest affinity for the glucocorticoid receptor would actually have the strongest antagonistic, not agonistic, effect. This was an exciting notion because interesting therapeutic applications could be envisioned for an antagonist. For instance, a topically applied glucocorticoid antagonist might hasten the closure of burns or other skin lesions by counteracting the tendency of glucocorticoids to impair wound healing.

Toward the end of 1979 Edouard Sakiz, a company executive, created a formal research project for the development of glucocorticoid antagonists. Two of us (Teutsch and Philibert) participated in the project, as did other company employees and two scientific advisers from the outside: Sir Derek H. R. Barton, a 1969 winner of the Nobel prize for chemistry, and Baulieu, who by then was an established authority on steroid activity. One of us (Philibert) coordinated the project and supervised the studies of biological activity.

In April of 1980 three molecules synthesized as part of the new project were produced in succession and handed over to Philibert: RU 38140, RU 38473 and RU 38486—later shortened

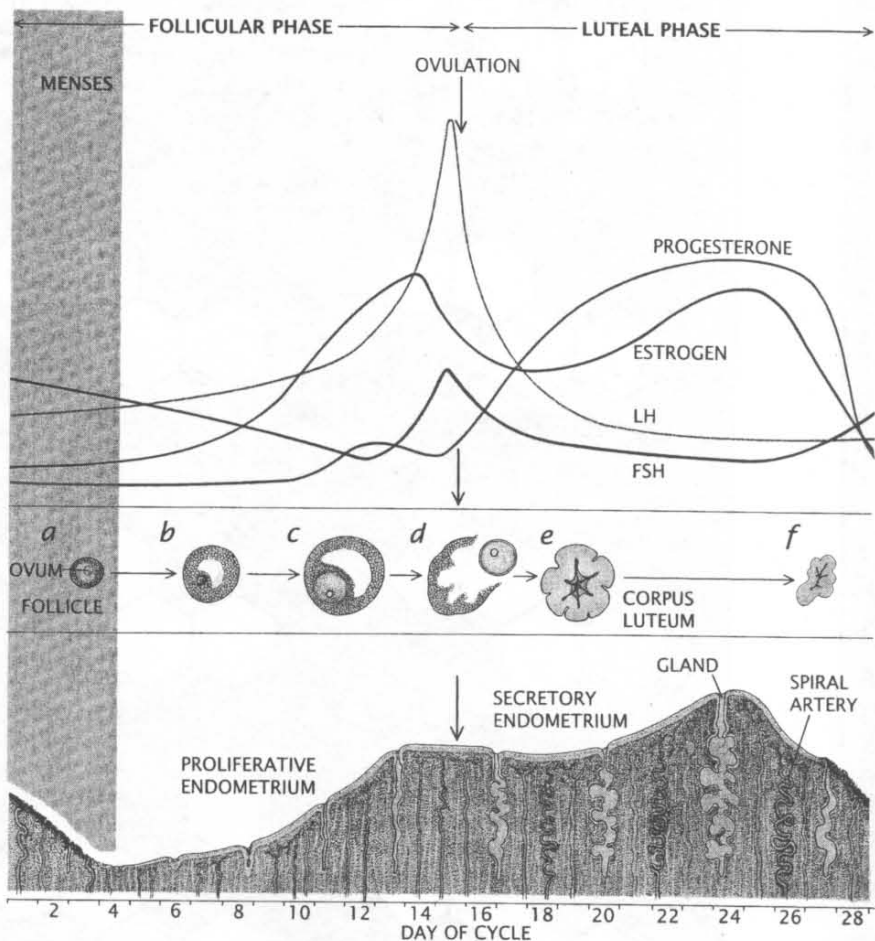
to RU 486. All bound strongly to the glucocorticoid receptor, and all interfered with certain activities of glucocorticoids in cell cultures. Of the three molecules, the last was the most potent; it was best able to block the actions of a powerful synthetic glucocorticoid (dexamethasone).

Yet the antiglucocorticoid activity of RU 486 was not the compound's only outstanding feature. Philibert's studies of its affinity for the five classes of steroid receptors indicated that the molecule also bound very strongly to the progesterone receptor. Initial tests in several

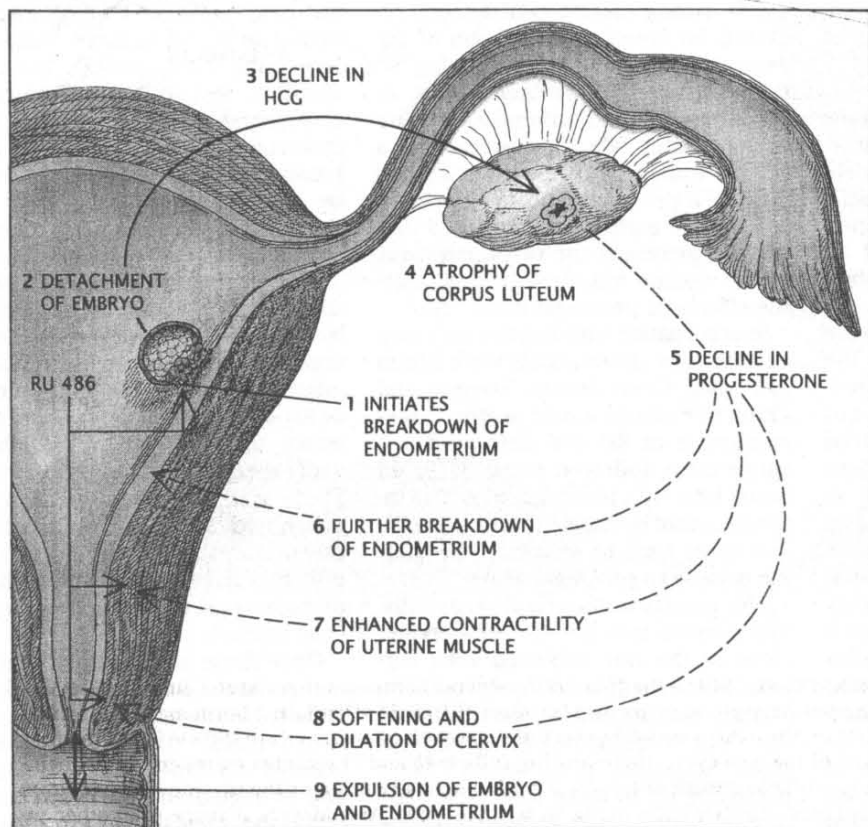
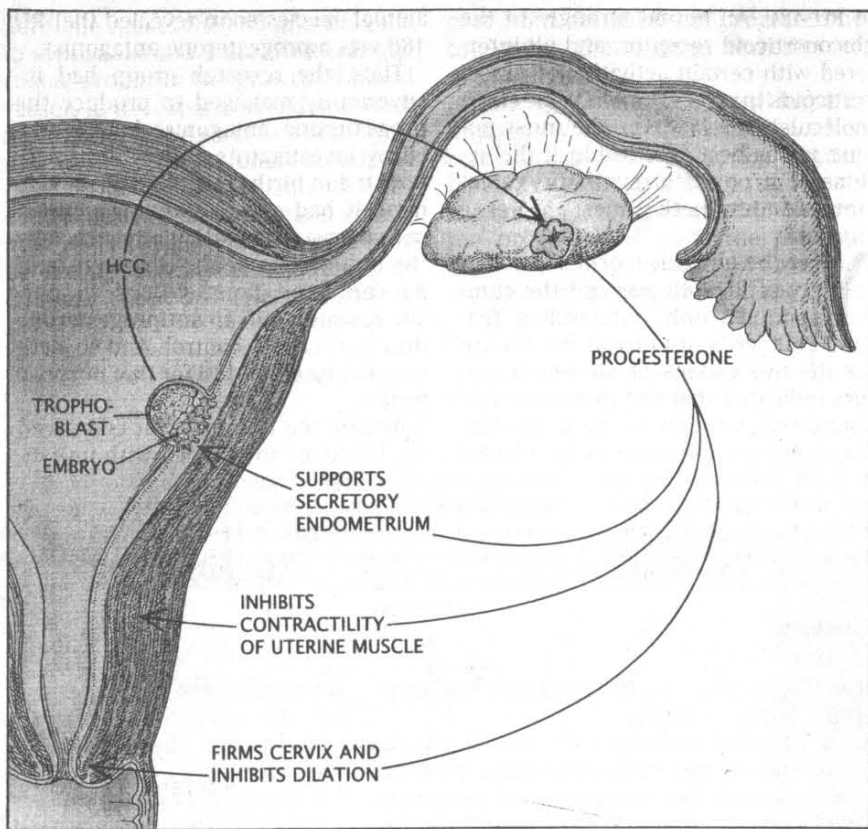
animal species soon revealed that RU 486 was a progesterone antagonist.

Thus, the research group had inadvertently managed to produce the progesterone antagonist long awaited by investigators and clinicians interested in birth control. Baulieu, who himself had a long-standing interest in that area, was particularly struck by the importance of the discovery, and he convinced Roussel-Uclaf to pursue research into an antiprogesterone drug for fertility control. And so, serious testing of RU 486 for that purpose began.

Among the findings that convinced the company to proceed with investi-



MENSTRUAL CYCLE is regulated by several hormones (*top*). At the end of one cycle, the pituitary gland steps up secretion of follicle-stimulating hormone (FSH), which acts on the ovary (*middle*) to stimulate growth of an immature follicle (*a*). In the first half of the new cycle, the maturing follicle (*b* and *c*) secretes estrogen, which maintains follicle growth and both stimulates proliferation of the uterine lining (*bottom left*) and sensitizes the lining to progesterone. At midcycle, a surge of another pituitary factor, luteinizing hormone (LH), triggers ovulation (*d*). In the second half of the cycle, the remnant of the follicle in the ovary becomes the corpus luteum (*e*), which secretes progesterone and estrogen. The progesterone causes the endometrium to develop into a secretory, highly vascularized tissue (*bottom right*) that can receive and nourish a fertilized egg. If the egg is not fertilized, the corpus luteum eventually decays (*f*), and the resulting loss of progesterone leads to erosion of the endometrial lining. Bleeding then ensues, and the cycle begins once more.



RU 486 interrupts pregnancy by opposing the action of progesterone at several sites in the uterus. In a normal pregnancy (*top*), the trophoblast (the future placenta) secretes human chorionic gonadotropin (HCG), which maintains the corpus luteum. Progesterone secreted by the corpus luteum has several effects that support the pregnancy. When that progesterone is blocked by RU 486 (*bottom*), the endometrium erodes and the embryo is detached and expelled along with the endometrial tissue.

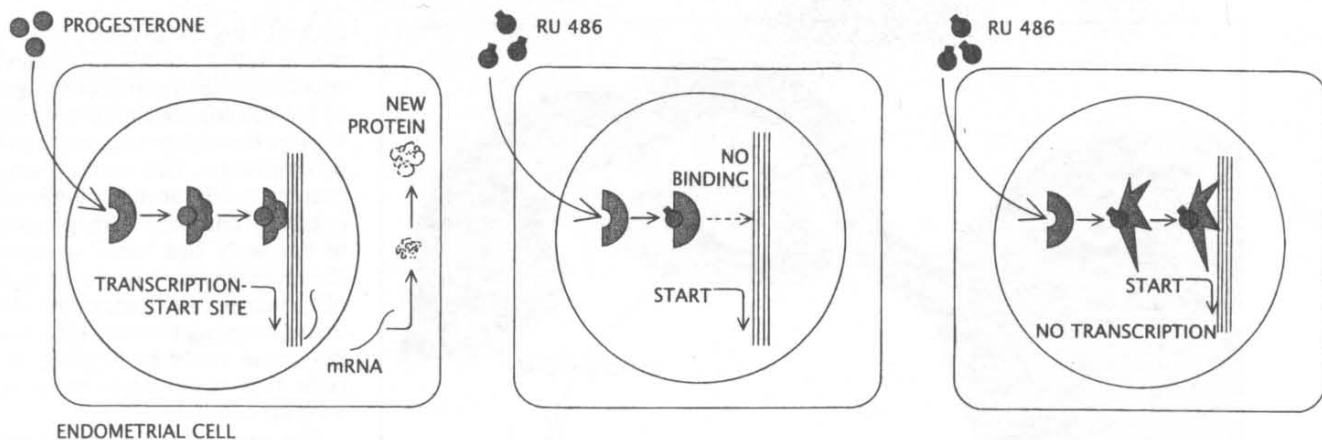
gations into the progesterone-antagonizing activity of RU 486 was the discovery that the *in vitro* binding affinity of RU 486 for the progesterone receptor was three times higher than that of progesterone. This activity suggested that the synthetic molecule would successfully compete with progesterone in the body and "win" occupancy of the receptor much of the time. Studies of cultured cells supported the idea, demonstrating that the effects of progesterone could be blocked in target cells that were exposed to a small amount of RU 486.

The true test of a compound's potential as a drug is its activity *in vivo*, and the results of the early animal studies had been encouraging as well. Some of these examined the effects of the compound on the endometrium of immature female rabbits. The rabbits were first injected with estradiol, an estrogen that both stimulates the growth of the endometrium and induces the cells to produce progesterone receptors. Next some of the animals were exposed to progesterone, which transformed the proliferating endometrium into a secretory tissue. Other rabbits were given RU 486 orally. The exposure to RU 486 alone did not induce the same transformation. Furthermore, when RU 486 was administered together with progesterone, the new compound actually blocked progesterone's ability to induce the change from a proliferative to a secretory state—as would be expected of a progesterone antagonist.

The findings of antagonism *in vivo* were important, but a crucial question still remained unanswered at the time Roussel-Uclaf decided to examine the potential of RU 486 to serve as an antiprogesterone drug: Could the antagonism that had been demonstrated thus far translate into the interruption of pregnancy? Studies of female rats, which do not have a menstrual cycle, confirmed that it could, and experiments with female monkeys (*Macaca fascicularis*), which do have such a cycle, offered further proof.

The first studies of monkeys were done with nonpregnant animals and revealed that a single oral or injected dose of RU 486 given in the second half of the cycle induced a premature menstrual period 48 hours after administration. Subsequently, Gary D. Hodgen and his colleagues at the Eastern Virginia University Medical School showed that the drug could also terminate pregnancy in monkeys. Other animal work established that RU 486, even at high doses, was nontoxic.

Such studies justified the initia-



PROGESTERONE acts within the cell (left). By occupying the progesterone receptor in the nucleus, the hormone modifies the receptor's shape, enabling it to bind to chromatin (DNA and associated proteins). Such binding leads to gene transcription and protein synthesis. RU 486 antagonizes these effects

by occupying the receptor without stimulating gene transcription. It may block transcription by failing to induce the change in receptor shape required for chromatin binding (center). Or it may induce a change in shape that permits such binding but then prevents binding by critical transcription factors (right).

tion of clinical trials, and in October, 1981, Baulieu suggested to one of his colleagues, Walter Herrmann of the University Hospital of Geneva, that RU 486 be tested on human volunteers. The results were promising: RU 486 triggered expulsion of the embryo from the uterus in nine out of 11 women.

As soon followed under the auspices of Roussel-Uclaf, the World Health Organization and the Population Council, a nonprofit organization based in New York City. One of us (Ulmann) directed the clinical testing undertaken by Roussel-Uclaf.

The first large-scale studies were conducted in 1985 to determine the most effective administration schedule. It turned out that a single dose of 600 milligrams of RU 486 produced the best results. In the course of these studies, a consensus was reached as to exactly what constituted successful use of the drug. In short, RU 486 succeeded if no surgery was needed, that is, if the embryo and all but the deepest layer of the endometrium were expelled. (Incomplete expulsion calls for surgical removal, usually by vacuum aspiration, because the retained material can cause infection.)

By that standard, administration of RU 486 alone at best yielded an 80 percent success rate. The studies also found that the method worked only in early pregnancy, up to a week after menstruation would have been expected to begin. Considering that many women have a pregnancy test done only after that time, it became all

too clear that RU 486 alone had limited applicability.

What accounted for the 20 percent failure rate? One reasonable hypothesis was that antagonism of progesterone could not by itself induce the frequent, strong uterine contractions required for complete expulsion of the embryo and the endometrial lining. To help correct that problem, Mark A. Bygdeman of the Karolinska Institute in Stockholm, who was overseeing a clinical trial, proposed adding a small dose of a prostaglandin to the protocol. He had earlier demonstrated that RU 486 increases the responsiveness of the uterine muscle to the contractile effects of prostaglandins.

In accordance with Bygdeman's suggestion, new clinical trials were begun in France, Great Britain, Sweden and China to evaluate a new protocol: 600 milligrams of RU 486 delivered in a single dose, followed some 36 to 48 hours later by a prostaglandin. The interval cannot be shortened, because RU 486 takes time to sensitize the uterine muscle to prostaglandins.

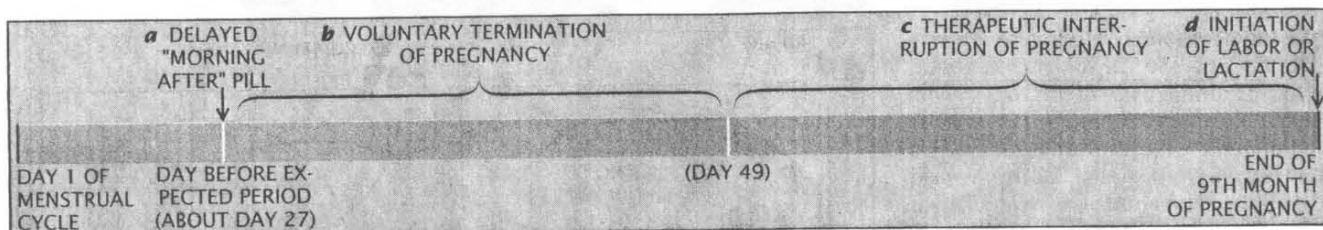
The results improved dramatically. The success rate became 96 percent, close to the rate achieved with surgery, which itself is not foolproof. The studies also looked at the effects of the drug combination on somewhat more advanced pregnancies—those persisting up to three weeks past the missed period—and showed that the same 96 percent success rate could be achieved. In most cases the embryo and all endometrial fragments were expelled within 24 hours after the prostaglandin was administered.

As is true of miscarriages, in which

a pregnancy is spontaneously arrested, the expulsion of the developing embryo and the endometrial lining was inevitably accompanied by uterine bleeding. In 4 to 5 percent of participants in these studies, the bleeding was heavy, as it can be during a normal miscarriage. Sometimes surgical intervention was needed to stop the bleeding, and in exceptional cases, a transfusion was needed. The results indicated that because of the risk of hemorrhage, the prostaglandin must be given in a medical facility where women can be monitored for several hours and, if necessary, treated.

The clinical studies further showed that abdominal pain, caused primarily by the contractile effects of the prostaglandin, is common. They also demonstrated that the 600-milligram dose of RU 486 needed to terminate a pregnancy did not cause clinically relevant antagonism of glucocorticoids. There was therefore no need to be concerned that RU 486 might produce undesirable antiglucocorticoid effects, such as profound fatigue and disturbances of electrolyte and glucose levels in the blood.

Once these studies were completed and reviewed, Roussel-Uclaf asked the French health authorities for permission to market the drug. This was duly granted on September 23, 1988. RU 486 is regulated by French law covering the termination of pregnancy, which stipulates that such terminations be performed only in authorized centers. There is one added restriction in the case of RU 486. Although the law permits voluntary termination of pregnancy through the 12th week, use of



APPLICATIONS OF RU 486 in fertility control and obstetrics are broad. The drug could serve as a delayed "morning after" pill (a) to be taken the day before menstruation is expected, for instance, in cases of rape. In France the compound is given along with another drug, a prostaglandin, to terminate pregnancies of up to 49 days' duration (b). The combination of

drugs is also able to interrupt pregnancy later and might be used when the mother's life is in danger or when the fetus is severely deformed or has died in utero (c). Studies of monkeys show that RU 486 can facilitate labor at term by sensitizing the uterus to the labor-inducing agent oxytocin; they also indicate that the compound can stimulate lactation (d).

RU 486 is limited to the seventh week of pregnancy because that is the outer limit examined in formal studies.

Since the autumn of 1988 more than 40,000 voluntary terminations have been performed with the combination of RU 486 and a prostaglandin. A recent study, published in March, of 2,115 of the women has confirmed the 96 percent success rate and the 4 to 5 percent rate of heavy bleeding. The study also showed that in 86 percent of the successful terminations, expulsion occurred within 24 hours of prostaglandin administration.

The average duration of bleeding in the subjects was nine days. Nevertheless, the time to expulsion, the duration of bleeding and the intensity of pain varied, depending on the dose of prostaglandin. A high dose was associated with faster expulsion but also with more prolonged bleeding and more intense pain.

Outside the study, physicians in the field have reported that two out of all the French women who received RU 486 have had severe disturbances in heart function after receiving the prostaglandin. The occurrence is rare and both women survived, but their difficulties suggest that prostaglandins should be administered cautiously in a woman who has heart disease or is at high risk for it, as in the case of heavy smokers.

It is now a decade since RU 486 was synthesized. The compound has begun to fulfill its potential as a nonsurgical method for interrupting early pregnancies, but that is only one of its many applications related to fertility control and obstetrics.

In theory, RU 486 might be taken as a delayed "morning after" pill, say, on the 27th day of a typical 28-day menstrual cycle. Because the drug is not always effective in this role, the woman must be tested some 10 to 15 days later to confirm she is not pregnant. For the same reason, the drug is not

suitable as a routine postcoital birth-control agent.

The drug may have a place when a woman decides to end an early pregnancy by vacuum aspiration. Several clinical studies have found that the procedure is facilitated by taking RU 486 some 36 to 48 hours before the surgery. The compound helps by softening and dilating the cervix.

Still later in pregnancy, up through the third trimester, the combination of RU 486 and a prostaglandin might offer an alternative to surgery when a pregnancy must be ended because the fetus is seriously malformed or the health of the mother is endangered. Investigators have found that the approach can be effective in late pregnancy and is, in fact, less risky than the kinds of surgery usually required after the first trimester. The drug combination may also be helpful when the fetus dies in utero. In such cases the fetus is usually delivered vaginally, and so contractions are induced, often with much difficulty. Administration of RU 486 followed by a prostaglandin seems to facilitate expulsion of the fetus.

Studies of monkeys indicate that RU 486 may also help to induce labor at term. In the animals the drug has been shown to augment the labor-promoting effect of oxytocin, a pituitary hormone often infused in high doses in cases of stalled labor to stimulate uterine contractions. Hodgen has found that after RU 486 is administered, the frequency of uterine contractions can be increased with just a small amount of oxytocin. Thus, RU 486 may well help to avoid some cesarean deliveries. Hodgen's experiments also suggest yet another role for RU 486: in monkeys, at least, it triggers lactation and increases the volume of milk that is produced in the breasts.

Outside the realm of pregnancy, RU 486 may one day help to treat cancers that bear progesterone receptors, in-

cluding certain breast cancers. In test-tube studies, RU 486 has slowed the growth of tumors displaying such receptors. Certain noncancerous tumors that synthesize progesterone receptors might also be controlled or reduced with RU 486, among them meningiomas (tumors of the meninges, the membranes surrounding the brain). Clinical trials examining applications in cancerous and noncancerous tumors are now in progress.

Finally, RU 486 may yet find application as a glucocorticoid antagonist. For instance, it is being studied as a treatment of Cushing's syndrome, a disorder that results from the overproduction of cortisone and leads to such symptoms as hypertension, rapid fat storage in the upper body and osteoporosis.

Clearly, RU 486, the first progesterone antagonist ever brought to market, has potential beyond its value in terminating pregnancy. Its application in that area is but the first stage in the history of the compound.

FURTHER READING

- ANTI-PROGESTIN STEROID RU 486 AND HUMAN FERTILITY CONTROL. Edited by Etienne-Emile Baulieu and Sheldon J. Segal. Plenum Press, 1985.
- ANTI-PROGESTERONES IN OBSTETRICS, ECTOPIC PREGNANCIES AND GYNAECOLOGICAL MALIGNANCY. André Ulmann and Catherine Dubois in *Antihormones in Clinical Gynaecology*. Edited by D. Healy. Baillière Tindall, 1988.
- MOLECULAR MECHANISM OF ANTISTEROID HORMONES AT THE RECEPTOR LEVEL. Etienne-Emile Baulieu in *Kidney International*, Vol. 34, Supplement 26, pages S2-S7; October, 1988.
- VOLUNTARY INTERRUPTION OF PREGNANCY WITH MIFEPRISTONE (RU 486) AND A PROSTAGLANDIN ANALOGUE: A LARGE-SCALE FRENCH EXPERIENCE. Louise Silvestre, Catherine Dubois, Maguy Renault, Yvonne Rezvani, Etienne-Emile Baulieu and André Ulmann in *New England Journal of Medicine*, Vol. 322, No. 10, pages 645-648; March 8, 1990.