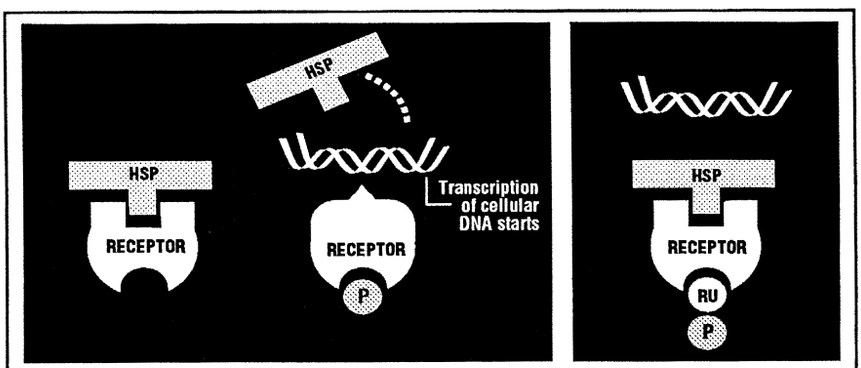
Stopping the Process of Pregnancy

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,



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.

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.)

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