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