

ALASKA LEGISLATURE COMMITTEE FILES 1991-1992 8672

6877 HOUSE HEALTH EDUCATION & SOCIAL SERVICES



Alaska State Legislature

Please enter into the record my testimony to the H. H. E. S. S.
committee name

committee on HJR 58 , dated 3-11-92
bill/subject

I strongly oppose legislation that would allow testing of the Abortion Pill under HJR 58. I feel this is more detrimental to the mother ~~and~~ than abortion. I am also strongly opposed to federal ^{state} sanction of abortion in any way.

Signed: Beverly J. Kokke
Testifier

~~_____~~

Representing (Optional)

631 DeGroot Sitka, AK 99835

Address

907-966-2570

Phone No.



Alaska State Legislature

Please enter into the record my testimony to the House HESS
 committee name
 committee on HJR 58, dated 3/11/92
 bill/subject

House Health, Education & Social Services
 Juneau, Alaska

Greetings:

Sitkans for Choice strongly supports passage of House Joint Resolution No. 58, relating to the drug mifepristone (RU 486). The goals of Sitkans for Choice are to keep abortion safe, legal and accessible to all women regardless of age, marital status, or ability to pay. RU 486 would not only make terminations more accessible to all women but would be safer, less expensive, and certainly more confidential than aspiration abortions.

Sitkans for Choice would like to take this opportunity to thank Representatives Boyer, Brown, Finkelstein, and Ulmer for sponsoring this resolution.

Sincerely,

Ruth McKenzie
 Sitkans for Choice
 Box 2966
 Sitka, Alaska 99835

Signed: _____

Testifier

Representing (Optional)

Address

Phone No.



Alaska State Legislature

Please enter into the record my testimony to the HES
committee name

committee on HJR 58, dated March 11, 1992
bill/subject

I am writing in support of HJR No 58 which supports the use of RU 486. I reject the opposition of this drug based on religious and political grounds. The decision as to the use of this drug to abort pregnancy is the decision of the woman involved, regardless of age when administered by trained physicians.

Signed: William J. Brooks *William J. Brooks*
Testifier

Representing (Optional)
1805 Sawmill Creek Road, Sitka, Alaska 99835
Address
(907) 947-3956
Phone No.



Alaska State Legislature

Please enter into the record my testimony to the Hess
committee name

committee on HJR-58, dated March 11, 1992
bill/subject

I support Resolution No. 58 and the testing of RU 486 in the U.S. The issuance of an import alert/ban against any drug due to political and or moral rationale is inappropriate and should not be part of our political process.

Signed: Jeanine Brooks (Jeanine Brooks)
Testifier

Representing (Optional)

1805 Sawmill Creek Rd. Sitka 99835
Address

907 - 747-3956
Phone No.



Alaska State Legislature

Please enter into the record my testimony to the _____

Hess
committee name

committee on _____

HJR-58

, dated _____

March 11, 1992

bill/subject

I support Resolution No. 58 and the testing of RU 486 in the U.S. I feel that it is a medically safe procedure for those women who need to use it to protect their lives and that this is useful medically for other medical purposes. If this ban is against the moral issue of abortion, then it is inappropriate.

Signed: _____

Shirley Brooks
Testifier

Representing (Optional)

605 Sawmill Creek Road, Sitka 99835

Address

907-747-3956

Phone No.



Alaska State Legislature

Please enter into the record my testimony to the H. H. E. S. S.
 committee name
 committee on HJR 58, dated 3-11-92
 bill/subject

*Please See Attached
 Testimony.*

Signed: *Carl Whisbey*
 Testifier

Representing (Optional)
220 Lakeview Dr. Sitka AK 99835
 Address
907-747-5923.
 Phone No.

To: House and Health Social Services Committee Members.
RE: House Joint Resolution, No. 58.

I am strongly opposed to the legalization of the drug RU 486. There has been no long term testing for short and long term biological consequences for woman or future children. The FDA has not endorsed this drug. It is imperative that this dangerous drug is not introduced to the American public in order to safeguard our nations health.

Sincerely,

Carol A. Hughey

Carol A. Hughey.



Alaska State Legislature

Please enter into the record my testimony to the House HCSS
committee name

committee on HJR 58, dated March 11, 1992.
bill/subject

*I do not support the use of the RU 486 drug.
I do not agree with those who support
abortion and especially through a dangerous drug
like RU 486. I hope you will see others
do not support this bill.*

Signed: John T. Monnin
Testifier

Representing (Optional)
114 B Darrin Sitka AK 99835
Address
347 - 5433
Phone No.

TO: House H.E.S.S. Committee
FROM: Robin Smith
Abortion Rights Project

We need to have RU 486 available in the United States. This drug has multiple health potentials, but what impedes this drug is its link to abortion.


As a society, we in America are sexually distressed. This can be seen in how we either obsess or ignore sexuality. As a result, we are sexually irresponsible. RU 486 offers a birth control option less wrenching than surgical abortion.

Until men as well as women become sexually responsible and until we can offer all children and their mothers social and economic security, we must offer alternatives. RU 486 is an option.

Just as men would not like government telling them to have vasectomies or compulsory castrations, we women do not want the government telling us what we can or cannot do to our bodies. Banning RU 486 is another way of restricting our freedom of choice and privacy.

Supporting the introduction of RU 486 is a progressive decision. We should join other world communities and make this promising drug available to the people of America. Don't deny this drug to those who can modically benefit from its many uses.

Thank you for considering my opinion.


14100 Jarvi
ANCHORAGE, AK 99515

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THE ORIGINAL



Alaska State Legislature

Please enter into the record my testimony to the House HESS
committee name

committee on HTR58, dated March 11, 1992
bill/subject

*Please attached
Testimony*

Signed: Cathy Hazel
Testifier

Representing (Optional)
Box 1876, Sitka 99835
Address

Phone No.

3-11-92

To: House New Committee

From: Cathy A. Hazel
Box 1856
Sitka, AK 99835

Re: RU486 1992 bill

Committee:

This is to inform you of my opposition of any bill that would allow the 72 hour pill to be legally available in the United States.

There are several reasons why this drug should not be legalized in the U.S.

1. With the current controversy regarding abortion and the acknowledged fact that this pill takes approximately 72 hours after ingestion, this pill will be used as a contraceptive. Even though it is being advocated for victims of incest and rape, it is fairly certain to ascertain that the average female can and will use it as a means of birth control.

C. Hazel

2. This drug should be subject to the standard testing and regulations before it is even considered for release to the American public. The FDA has the formal responsibility to do this. Would this step be eliminated? If so, why? It's availability should not be based on political pressure or special interest groups that want to keep the established system.

3. Morally, our constitution and government are founded and based on Godly principles. In the past our government has violated and ignored many of these principles. But not acknowledging them does not change these principles. Abortion is morally wrong and goes against the central intent of our laws that govern the U.S. I am proud that men & women of integrity won't stand for what's morally right.

I appreciate your consideration of my request.
I sincerely challenge you to not allow this drug to

become legalized in the United States of America

Sincerely,

Edith D. Hoel



Alaska State Legislature

Please enter into the record my testimony to the House Health & Social Service committee name
 committee on House Joint Resolution #58 , dated 3-11-92
 bill/subject

To: House Health + Social Service Committee Members
 House Joint Resolution # 58

I Am Strongly opposed to legalizing the drug RU 486 in the U.S. There have been no long term testing to determine the biological consequences on women. Evidence is showing that this is a very dangerous drug. "It's not nice to fool with Mother Nature."

Signed: Stephanie A. Vieira
 Testifier

Representing (Optional)
60 Baker St
 Address
7473698
 Phone No.



Alaska State Legislature

Please enter into the record my testimony to the House HESS
 committee name
 committee on HJR 58, dated March 11, 1992
 bill/subject

LIO OFFICE TO: House Health & Social Services Committee Members

OPPOSE - HOUSE JOINT RESOLUTION No. 58

I understand the drug RU486 would cause an abortion at the woman's home. There has been no long-term testing for short and long term biological consequences for the woman or future children. Our Federal Food and Drug Administration opposes it. Evidence is accumulating that it is a dangerous drug.

Thank you.
Alene Henning
 Alene Henning
 Box 993
 Sitka, AK
 99835

Signed: _____
 Testifier

 Representing (Optional)

 Address

 Phone No.



Alaska State Legislature

Please enter into the record my testimony to the H&S (House)
 committee name
 committee on HJR 58, dated 3/11/92
 bill/subject

My name is Glennette Chavez. I strongly support House Joint Resolution #58, supporting the introduction of RU 486 into the United States.

The safety and effectiveness of RU 486 in terminating early pregnancy has been well documented, and the medical community has recognized its value and supports further research for other medical applications as well.

In the interest of public health, it is important that the medical and scientific communities be allowed to research the benefits of RU 486, free of political pressures from special interest groups.

Signed: Glennette Chavez
 Testifier

Representing (Optional)
Box 2722, Sitka, AK 99835
 Address
747 6127
 Phone No.



Alaska State Legislature

Please enter into the record my testimony to the House HESS
committee name

committee on House Resolution No. 58 dated March 11, 1992
bill/subject

I oppose the use of the drug RU486 due to the fact that I feel the full effects of this drug is unknown. I object to the American women being used for experimentation. I also oppose abortion and would ask that you ban the use of this drug.

Signed: Christine Horan
Testifier

Representing (Optional)
P.O. Box 2003 Sitka Alaska 99835
Address
747-6471

Phone No.



Alaska State Legislature

Please enter into the record my testimony to the House HESS
committee name

committee on HJR 58, HB28, dated 3/11/92
bill/subject

I speak as a woman & registered nurse
RU486 is a pandoras box to a womans body. It blocks
the action of progesterone, but it is not limited to
the womb. It also acts on the hypothalamic-pituitary-
adrenal system, the respiratory system, & has unknown
long range effects ^{on metabolism}. Death has occurred where the drug
is legal.

Infants have been born with teratogenic anomalies in-
compatible with life. Should these infants survive,
the "cost" to the state would be enormous. I men-
tion "cost" not because it is an issue to me, but be-
cause it is the "main" issue to many pro abortionists.

Do you want AK women and children to be-
come guinea pigs? Pro abortion women have
strongly criticized RU486. FDA has not approved
this drug. Please. Take no part in victimizing
innocent women and children with a deadly
poison, by telling us its safe, or legal, or effective!

Many of us did not get to testify today. Most
of the speakers time was pro RU486. Many of us
against RU486 were not heard. Please let us speak.

Signed: Mary S. Soltis
Testifier

Representing (Optional)

615 DeGroff

Address

747-5624

Phone No.

1.51



Alaska State Legislature

Please enter into the record my testimony to the House HESS
committee name

committee on HJR 58 - RU486, dated 3/11/92
bill/subject

The use of RU486 is dangerous, not only for the unborn child but also for the women taking the drug. The absence of long-term data on the effects of this drug are alarming. Documentation of serious side effects such as nausea, vomiting, extensive bleeding, and life-threatening heart attacks are also alarming. Legislators who are truly concerned with the emotional, mental & physical health of the women of Alaska will not support the introduction of this dangerous drug into our country.

Signed: Shelley Demorett
Testifier

Representing (Optional)

316 Workman Loop Sitka, Ak
Address

907-747-3196

Phone No.



Alaska State Legislature

Please enter into the record my testimony to the H. H. & S. S.
committee name

committee on HJR 58, dated 3-11-92
bill/subject

*Please See Attached
Testimony*

Signed: *Charles Jordan*

Testifier *CHARLES JORDAN*

Representing (Optional)

BOX 2003, SITKA, AK

Address

747-6666

Phone No.

March 11, 1992

Testimony of Charles Horan
PO Box 2003
Sitka, Ak 99835
747-6666 or 747-6471

Abortion Pill Hearing HESS Committee

House Joint Resolution No.58 resolves that the Alaska State Legislature supports introduction of RU 486 into the United States. This drug is promoted as an easy safe alternative to surgical abortion. The Food and Drug Administration has not allowed it in the U. S. because it is not. Their are two important factual reasons this pill should not be supported by our legislature.

The pill causes the destruction of a unique human life. This child within the womb has the same right to live a happy prosperous life just like you and I. The legislative endorsement of this destruction of human life devalues all human life. It lulls people involved in crises pregnancies into considering this life taking choice. The government's primary function is to preserve liberty and freedom. Without life there is no liberty no choice for this most innocent helpless member of society.

If the legislature chooses to abdicate its responsibility to preserve the child's life it should not endorse this method of abortion for the sake of the mother's health. The pill is not a simple procedure. It is usually administered by a doctor, it causes premature birth and it occasionally fails. If the child survives she or he has a high risk of sever deformities. Complications to the mother include nausea, vomiting, extensive bleeding, and life threatening heart attacks. To increase the effectiveness of the drug to abort the child the drug prostaglandin is often taken later. This drug causes further complications. The book RU 486: Misconceptions, Myths and Morals by three self proclaimed abortion advocates has criticized the "cocktail drug" for its harmful effects on women urging that it be removed from the market immediately.

If you are concerned about the safety of our smallest Alaskans and the welfare of their mothers please withdraw your support for this resolution.



Alaska State Legislature

Please enter into the record my testimony to the House HFSS
committee name

committee on HJR 58/ RU 468, dated 3/11/92
bill/subject

As a medical professional and a woman I urge this committee and the legislature to pass HJR 58. RU 468 is a drug of significant medical value as attested to by its use in France as well as the U.S medical professionals and scientists supporting its use in this country. The FDA is not a scientific body but a bureaucratic body that is swayed by the current President's views as well as those of a small minority of the population. I thank the sponsors for having the foresight to introduce this legislation

Signed: Luth & McKie
Testifier

Representing (Optional)
Box 1922, Sitka, Alaska 99835
Address
747-6819
Phone No.



Alaska State Legislature

Please enter into the record my testimony to the House H.F.S.S
 committee name
 committee on HJR 53 / RU486, dated March 11, 1992
 bill/subject

I wish to testify in favor of HJR 53, concerning RU 486.

Most discussion I have heard at this teleconference has focused on the polemics regarding the abortion issue. Some support a woman's right to choose, and others oppose it.

Although related to the abortion issue, the research on and approval of RU486 is really a medical issue. Abortion is still legal in Alaska and the US, and women therefore have the right to medical alternatives to the current abortion technology. In addition, RU486 has potential medical benefits beyond its abortifacient use which merit research. Please pass HJR 53.

Signed: Kathleen M. Shaw
 Testifier

Representing (Optional)
Box 8910, Sitka, AK 99835
 Address
747-3671
 Phone No.



Alaska State Legislature

Please enter into the record my testimony to the Health & Social Services
committee name

committee on House Joint Resolution #58 dated March 11, 1992
bill/subject

I am testifying not from my own expertise but from the report, "RU 486: Misconceptions, Myths and Morals," by Janice G. Raymond, Renate Klein and Lynette J. Dumble published by the Institute on Women and Technology at the Massachusetts Institute of Technology.

This report is too extensive for me to quote completely but it is noteworthy that #1 they consider themselves feminists and are actively pro-abortion and #2 it offers documentation that there is clear evidence of severe adverse complications upon using RU 486 - specifically - its action is not limited to the womb but also acts on the hypothalamic-pituitary-adrenal system and the respiratory system.

If the position that RU 486 is not acceptable in the State of Alaska for the sake of unborn children then I hope you'd seriously consider the liability and ramifications on the women of our state, many who are already in tenuous health care situations

Signed: Coralynn Ormerod
Testifier

Representing (Optional)

2414 HPR, Sitka, AK 99835

Address

747-6732

Phone No.



TELECOPY COVER SHEET
Ketchikan Legislative Information Office
Office - (907) 225-9675 Fax - (907) 225-8546

TO: (H) HESS

ATTN: _____ FAX: _____ PHONE: _____

FROM: Susan GASS R.N. - 719 Grant St. Ketchikan PHONE: _____

INSTRUCTIONS: testimony & magazine article on HJR 58 (T/c 92-03-042)

SENT: Date 3/11/92 Time 10:25 am

DISPOSAL OF ORIGINAL: Discard _____ Hold for Pickup _____

NUMBER OF PAGES: 3 (NOT counting cover sheet)

TRANSMITTED BY: Rae

HEALTH

I would underline in important + it is. But this whole article is important + it is.

the trouble with RU 486

Please do not pass this prescription Susan Ince reports 7/19 agent

a way to end the wrangling over abortion once and for all and make abortion more accessible. "How could a state control swallowing?" asked syndicated columnist Ellen Goodman. Eleanor Smeal, past president of the National Organization for Women and founder and president of the Feminist Majority Foundation, says that RU 486 profoundly changes the nature of the abortion debate. The drug would make picketing abortion clinics "meaningless," she says. "RU 486 works so early that it is much closer to a contraceptive than to traditional abortion. And the American people overwhelmingly support contraception."

The new French pill is supposed to make abortion easier and safer, cure a host of diseases, and make protesters shut up and go home. But as SUSAN INCE reports, there's a lot wrong with this picture

To be pro-choice, it seems, means embracing RU 486. But not every pro-choice advocate is buying it. This month the Institute on Women and Technology, based at the Massachusetts Institute of Technology, will issue a one-hundred-page review of the scientific literature on RU 486. The report suggests that much of what is commonly believed about the French pill is simply wishful thinking.

THE NEW REPUBLIC HEADLINED ITS STORY "DRUG OF Choice." The National NOW Times's read "RU 486 Spurs Global Feminist Solidarity." The Boston Globe's was "A Pill Whose Time Has Come."

"Claims that RU 486 abortion is private and demedicalized are belied by the number of medical visits and the whole drug cocktail a woman may be exposed to," says Janice Raymond, associate director of the Institute on Women and Technology and the report's coauthor.

The headlines are typical of the yearlong media blitz on RU 486. Abortion in France, we're told, has become as easy as taking a pill—safe, quick, and private. American women would have this option, too, if only the drug's French manufacturer and the U.S. Food and Drug Administration could be persuaded to ignore this country's vehement antiabortion protesters.

In France, abortion with RU 486 is neither easy nor private. It's a tightly structured four-step regimen, and the pill's maker says it won't export the drug to countries that do not control the drug's use in a similar way. Here's how it works:

Thousands have rallied to bring RU 486 to the United States. Teuting the drug for a dizzying range of possible uses—as a treatment for everything from breast cancer to AIDS—the American Association for the Advancement of Science adopted a pro-RU 486 resolution at its February meeting. The Feminist Majority Foundation has dumped hundreds of pounds of petitions on the pharmaceutical company, Roussel Uclaf. New York City's mayor, David Dinkins, has appealed directly to President Bush. People magazine and Vanity Fair have profiled RU 486's beleaguered inventor, Etienne-Emile Baulieu.

Visit 1: After a pregnancy test and dating of conception (the cutoff for use of the drug is forty-nine days after the last menstrual period), the woman undergoes a blood test, a pelvic exam, and often an ultrasound exam via a probe inserted into the vagina.

Visit 2: After a one-week waiting period required by French law, three RU 486 tablets are registered under the woman's name; she takes them in the specially licensed clinic and then leaves. The drug begins to block the action of progesterone, a hormone essential to the maintenance of the uterine lining.

Visit 3: Thirty-six to forty-eight hours later, a second drug, a synthetic prostaglandin, is injected to induce uterine contractions and shedding of the uterine lining. The woman stays in the clinic for about four hours so that doctors can monitor and treat any side effects (most commonly pain, nausea, vomiting, and diarrhea). Pain medications are often required, as are antibiotics to fend off possible infections. Three out of four women abort while still in the clinic; others return home to wait.

Visit 4: Seven days later, the woman visits the clinic again to be certain that the abortion is complete and to have her bleeding monitored (bleeding can last from three to forty-four days). If the drugs have failed, a surgical abortion is scheduled; this happens about once every twenty times. (In vacuum aspiration abortion in the

United States, fewer than one in two hundred women require a repeat procedure.)

Total cost? With all the clinic visits added to pill costs, slightly *higher* than surgical abortion—although in France, both methods are largely subsidized through the national health service.

Roussel Laboratories' own data support the view that RU 486 abortion isn't as simple as most people think. Last September the company applied for drug approval in the United Kingdom, submitting a dossier that included these findings: out of 950 women followed, 907 had complete abortions, most of them in the clinic in the three to four hours after prostaglandin was administered. Two hundred seventy suffered pain so intense that narcotics were required; another 280 used less-powerful painkillers. Two hundred seventy-six women suffered vomiting; 106 had diarrhea. Forty-three failed to abort and had to start over with a traditional abortion. Seven lost so much blood a transfusion was needed.

In March the post-RU-486 prostaglandin injection sent a thirty-one-year-old French woman, a one-pack-a-day smoker, into cardiovascular shock. She was dead within an hour.

"That death was tragic," says MIT report coauthor Lynette Dumble, "but it shouldn't have come as a surprise. Prostaglandins were at one time used alone to induce abortion, but the pain and the number of deaths were considered intolerable. They've just added a new drug to a failed drug and told us how lucky we are."

Prostaglandin plus RU 486 had already caused life-threatening heart trouble in two other women in France, and after the recent death, the health ministry barred smokers and women over thirty-four from taking the drug. Women with circulation problems, bronchial asthma, high blood pressure, fibroids, glaucoma, ulcers, colitis, anemia, or gynecologic infections, and women who have had a recent cesarean section, are also advised to avoid RU 486. "That's a hell of a long list, and some of these conditions are fairly common, even in young women," says Meredith Turshen, associate professor of public health at Rutgers University in New Brunswick, New Jersey. "What's certain is that this is not a benign pill that can be taken in the privacy of your own home."

The same week that the RU 486/prostaglandin death made the international news, Baulieu told the French Academy of Science that he was already testing an alternative prostaglandin. In early studies, a prostaglandin pill called misoprostol (sold under the commercial name Cytotec) seemed just as effective as the original combination and less likely to cause side effects.

But Dumble, director of transplantation research at the University of Melbourne, Australia, isn't comforted. She has used Cytotec to suppress the immune system in transplant patients. The abortion dosage is many times higher, and she worries that even one-time use could result in long-lasting immune-system and fertility problems that may not be obvious in short-term studies.

RU 486 itself may have a greater impact throughout the body than has been discussed. Besides blocking action of the hormone progesterone, it blocks receptors for cortisone—a hormone produced by the adrenal glands that regulates sugar and protein metabolism, helps maintain blood pressure, and protects the body from physical stress. Raymond suspects that some of the quirkiest RU 486 side effects that show up in the medical literature—extreme thirst, fainting, mood changes, fatigue—may be related to RU 486's effect on the adrenal and pituitary glands.

Using RU 486 in France is neither easy nor private. And it costs more than surgical abortion

The drug would certainly have to work far beyond the uterus in order to deliver on even a fraction of the potential uses that proponents are talking about. When RU 486 promoters testified before a House subcommittee last November, the list of potential uses was as long as that for Lydia Pinkham's tonic: the drug, it was claimed, could save lives by halting the growth of hormone-dependent tumors in the breast and the brain; treat AIDS, Cushing's disease, diabetes, glaucoma, hypertension, and prostate problems. Don't want pregnancy? RU 486 could be more than an early abortion pill: it could be a contraceptive or an adjunct to traditional suction abortion. Want to have a baby? It might reverse infertility and endometriosis, induce or hasten stalled labor, prevent the need for cesarean sections, and boost milk production after delivery. Not concerned about pregnancy? How about relief from irregular periods, PMS, or postmenopausal complaints? Or stress-related illness, obesity—even the symptoms of aging? Chances are good that RU 486, like other hormone blockers, will prove to have significant medical value. Roussel Uclaf is now finishing designs for large studies to test RU 486 as a breast cancer or brain cancer treatment. But we're a long way from knowing much about the drug's other effects.

"To anyone familiar with the history of DES and estrogen replacement therapy," says MIT's Janice Raymond, "the claims have the all-too-wondrous ring of promise later turned peril. How many times have we been told that this or that drug will save us?"

Until supplies ran out in February 1990, David Grimes, a professor of obstetrics and gynecology

gy and preventive medicine at the University of Southern California, conducted trials on RU 486 (unlike most other researchers, without using prostaglandin). He looks forward to the day when abortion drugs will be available over the counter—perhaps even packaged along with early-pregnancy tests. Grimes loves old movies, and he likes to recount an old Groucho Marx exchange whenever doubts are raised about RU 486:

"Say, Groucho, how's your wife?"

"Compared to what?"

Says Grimes, "Sure, I'd love to have a medication with no side effects, but we never will. Let's assume that you're in remote Bangladesh. If RU 486 carries a 1 percent incidence of serious bleeding, I'm concerned about that—but the incidence might be 20 or 30 percent for women trying to abort using a stick. You have to look at the alternatives."

How realistic an alternative is RU 486 in underdeveloped areas? The safest current method in Bangladesh, to use Grimes's example, is menstrual regulation, a suction technique performed by local paramedics. "If a woman hasn't been able to get to these existing local services, will RU 486 really be able to reach her?" asks Joan Dunlop, president of the International Women's Health Coalition, a group involved with eighty third-world reproductive health programs. "It's a fantasy to think that a woman will be able to make four trips to a clinic, walking five or ten miles each trip."

And RU 486 can't make abortion legal. According to Paul Van Look of the World Health Organization, most deaths from abortion occur in countries where it is illegal. He thinks RU 486 holds promise in only a handful of developing countries (notably the two largest, China and India) where surgical abortion facilities do exist but suffer from overcrowding. RU 486 could be used to handle the demand; when the drug failed, abortion clinics could provide the necessary backup.

Applying the "compared to what" test may help explain the allure of RU 486 in Western Europe. In France, for instance, *contraception* has only been legal since the seventies, and abortions are done under very different circumstances than in the United States. "French women are comparing RU 486 with the experience of undergoing general anesthesia and surgery," says Judy Norsigian, codirector of the Boston Women's Health Book Collective. "They talk about the benefits of being conscious, which don't really apply in the United States."

In the United Kingdom, bureaucratic gridlock at the National Health Service means that it's not unusual for women to wait five weeks for an abortion. As in France, abortions are usually performed in hos-

pital operating rooms, using general anesthesia; more than 40 percent of women spend at least one night in the hospital. RU 486 would not only save the NHS an estimated ten to fifteen million pounds a year, it could prod it into giving better service to everyone. Jane Roe, coordinator of Britain's Pro-Choice Alliance, also hopes that RU 486 will make a big difference in the campaign for abortion on request. British law now requires two doctors to certify that an abortion is needed for health reasons.

Abortion with RU 486 is a tightly structured four-step regimen

In the United States, RU 486 has come on the scene at the same time that political pressures are threatening all kinds of scientific research. The government has already halted fetal tissue research. In 1989 the FDA issued an RU 486 import alert, which doesn't prohibit research but is said to have stalled many U.S. scientists. This spring Congressman Robert K. Dornan of California introduced legis-

lation that would ban the drug outright.

"Where will it stop?" asks Eleanor Smeal. "If we can't do research on any medication that could damage a fetus, that's the end of research on cancer in women."

The promise of RU 486 has also emerged just as abortions have become harder to obtain in this country—because of Medicaid restrictions, the Supreme Court's *Webster* decision, and state laws demanding that women notify their parents or spouses before having an abortion. Since 1977 the number of physicians performing abortions in rural areas has dropped by half.

But would RU 486 really improve access to abortion for women in the United States? "Let's face it—how many women don't get a Pap smear every year?" asks Naima Major, acting executive director of the National Black Women's Health Project in Atlanta. "Could they really see a doctor just after they miss a period, and arrange work and child care to make four clinic visits? Women who would have the least access would be women of color, women who rely on public funding, and women in rural areas."

Janice Raymond has this recommendation for people who want to ensure safe and accessible abortions for every woman who needs one: "Don't focus on an unproven drug," she says. "Push for less medical control over the whole abortion procedure." Vermont and Montana, she points out, allow physician's assistants to perform first-trimester suction abortions. In Vermont these practitioners are already performing one-third of the state's abortions.

How does this compare with the alternatives? Very well indeed. A study in Vermont showed that the practitioners' safety records beat not only that of RU 486—they beat the national standard for abortion performed by doctors. ●

10 March 1992

House HESS Committee
Georgiana Lincoln, Chair
Alaska State Legislature

Re: House Joint Resolution 58 - RU 486

I strongly support this resolution to bring RU 486 into the United States. Then it can be tested and treated as any other drug. I believe the issue is: will we have the drug tested and administered under FDA regulations and with the full participation of the medical and scientific community, or will we have women self-dosing with questionable drugs obtained on the streets?

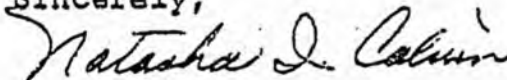
Enclosed is a copy of an article on RU 486 from the journal SCIENCE, the journal of the American Association for the Advancement of Science.

Stating that RU 486 is the moral property of women, the French Health Minister told Roussel, the pharmaceutical company that developed RU 486, that he "could not permit the abortion debate to deprive women of a product that represents medical progress".

We must let women make the choice. We must let doctors and pharmaceutical companies use their resources and skills to help them. We must NOT allow a strident minority of zealots to prevent the testing and possible use of a drug that has promise not only as an inducer of early abortion without surgery, but also for the treatment of a number of other human medical problems, including Cushing's Syndrome, glaucoma, breast cancer, meningiomas, inducing labor, and a contraceptive which prevents ovulation.

Thank you for your attention. Please move HJR 58 with a DO PASS recommendation.

Sincerely,



Natasha I. Calvin
P.O. Box 2966
Sitka, Alaska 99835
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encl.

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 any-

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."

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 Uimann 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



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

where 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

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,



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 Janeiro 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.



"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 antiprogesterins—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 parent 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 contraceptiv, derived from contra-gestation just as contraceptives are contra-conception. Baulieu's neologism goes beyond newswpeak. 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 1980s, 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 govern-



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

ment'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.

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



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

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.

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 antiestrogens 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

THE PRECEDING PAGES WERE TREATED
AS A UNIT IN THE ORIGINAL FILE

THE FOLLOWING PAGES WERE TREATED
AS A UNIT IN THE ORIGINAL FILE

TO: Representative Lincoln, members of House HESS Committee

Please accept this statement in lieu of testimony at today's hearing:

The Coalition of Alaskans for Choice wholeheartedly supports passage of HJR58. The French drug RU 486 offers the possibility of early, safe, effective termination of unwanted pregnancy without the need for surgical intervention. The drug may also offer other medical benefits to women, including the treatment of breast cancer and other types of cancer. The benefits of this drug were well documented at today's hearing by the Resolution's sponsor and other witnesses.

The Federal Food and Drug Administration has not only refused to allow importation of RU 486 into the United States, it has taken the further step of specifically banning the drug. This move is motivated by politics, not by concern for the health and safety of women.

The FDA does have the authority to allow, at its discretion, importation of drugs which have not yet been approved for use in the United States but which are thought to have efficacy in serious or life-threatening circumstances. An example of this would be controversial drugs for treating AIDS and certain types of cancer. Individuals are allowed to obtain these drugs in the countries where they are produced and to bring limited quantities to the U.S. for their own treatment.

In a letter from an FDA official to Alaska Senator Ted Stevens, the FDA's position is stated as follows: "the intended use of RU 486 makes it likely that it could be used without supervision by a physician, and that indiscriminate or unsupervised use could be hazardous to health."

In other words, the FDA has us in a closed loop: The FDA will not allow RU 486 to be safely prescribed by U.S. doctors, at the same time arguing that the drug must be banned because it is not safe unless its use is supervised by a doctor.

This situation reminds me of a bumper sticker I saw once which read: "Go To Health, FDA!"

Respectfully Submitted:

Ileen Self - March 11, 1992
Chair, Coalition of Alaskans
for Choice

ROBERT C. BYRD, WEST VIRGINIA, CHAIRMAN

DANIEL K. INOUE, HAWAII
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JAMES H. ENGLISH, STAFF DIRECTOR
J. KEITH KENNEDY, MINORITY STAFF DIRECTOR

United States Senate

COMMITTEE ON APPROPRIATIONS

WASHINGTON, DC 20510-8025

June 14, 1991

Ileen Self
8209 Nadine Street, #2
Anchorage, Alaska 99507

Dear Ileen:

Enclosed is a copy of a letter I received from the Department of Health & Human Services in response to the inquiry I made on your behalf. I hope the information they provided is useful.

With best wishes,

Cordially,


TED STEVENS

Enclosure

1991 MAY -9 PM 1: MAY 8 1991

The Honorable Ted Stevens
United States Senata
Washington, D.C. 20510

Dear Senator Stevens:

This is in response to your letter of April 12, 1991, on behalf of Silla, Alaska, concerning the unapproved new drug, RU-486.

As you may know, RU-486 is a drug that is approved in France for early abortion through a limited distribution system when used with one of two prostaglandins also approved in France. In addition, studies have been conducted on the treatment uses of this drug for diseases such as breast cancer, Cushing's syndrome, and other types of cancer.

To provide you background information, the Federal Food, Drug, and Cosmetic Act (FDC), which the Food and Drug Administration (FDA) administers, defines a new drug as one not generally recognized by qualified experts as safe and effective for the recommended uses. A new drug may not be distributed interstate (except for clinical study) until we have approved a new drug application (NDA) containing substantial scientific evidence of safety and effectiveness for use of the drug as labeled.

An investigational new drug (IND) application acceptable to the FDA is required of a sponsor (e.g., a drug manufacturer or a clinical investigator) to study the safety and effectiveness of an unapproved new drug. When the sponsor determines that adequate and well-controlled studies have been performed, which reflect favorably on a new drug's safety and effectiveness, the sponsor then submits that information, together with adequate information on manufacturing procedures and controls, in a new drug application to FDA. After a comprehensive review by the FDA the NDA is either approved or not approved; upon approval the drug may be marketed.

We are enclosing a publication, "New Drug Development in the United States," that describes in more detail the requirements for new drug clearance in the United States.

Strictly interpreted, the FDC Act prohibits the import and distribution in interstate commerce of drugs that have not been approved by the FDA. However, out of compassion for individual

Page 2 - The Honorable Ted Stevens

patients, many of whom suffer from serious or life-threatening diseases, FDA has, as a matter of enforcement discretion, long permitted individuals to bring into the United States for personal use limited quantities of drugs sold abroad but not approved in the United States. In exercising this discretion, however, it is incumbent upon the Agency, in its charge to protect the public health, to allow the importation of unapproved drugs only if there is no unreasonable safety risk and only if the other criteria are met.

With regard to RU-486, a conclusion was reached that use of the drug posed unacceptable safety risks to the American public. This is because the intended use of RU-486 makes it likely that it could be used without supervision by a physician, and that indiscriminate or unsupervised use could be hazardous to health. In addition, to be optimally effective, RU-486 must be used in conjunction with another drug, a prostaglandin, also not approved in the United States, further complicating the safety issue.

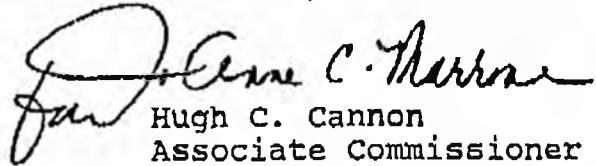
Also, because RU-486 is not proposed for treatment of a serious condition for which no alternative treatment exists (one of the criteria set forth in the Pilot Guidance document), yet poses safety risks, we do not believe that our import policy can be appropriately applied to permit the importation of RU-486. Moreover, the publicity in this country regarding the availability of the drug overseas raised for FDA the possibility that a demand would be created in this country which in turn would foster importation of the drug for commercial use. Thus, we believe that our decision to restrict the importation of RU-486 is sound public health policy and is consistent with our policy guidance and the importation of unapproved drugs.

It is extremely important to point out that this import alert does in no way restrict the importation of this drug for research purposes to determine its usefulness for diseases such as Cushing's syndrome and some forms of cancer.

Page 3 - The Honorable Ted Stevens

We hope the information provided will be helpful. If we can be of any further assistance, please let us know.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Hugh C. Cannon".

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

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*oppose HB 28 - just trying
to not raise ... I don't want to
get on the 486 ...*

HJR # 58--- RU-486

March 11, 1992

House HESS

Madame Chairman, Members of the House HESS
I am Joan Heidersdorf and I'm here to testify in opposition to
HJR 58 which supports bringing the drug RU 486 into the US.

nburn The basic reason I am opposed to RU 486 is that it kills
babies. This should be sufficient reason for ~~for~~ all of us to
oppose it's use. However, for those who are not concerned about
its effects on the child, there are a number of other disturbing
aspects of this drug that should noted.

* RU 486 is a synthetic female hormone. DES is also a
synthetic female hormone which had limited testing
before being prescribed. We have seen its tragic
results in the children of the women who used it. Other
examples of medical procedures which have had women as
their victims are breast implants, the Dalcon shield,
~~contraceptives~~ and fertility drugs. Therefore, as noted
in a recent article in the magazine Vogue, pro-choice
feminist Janice Raymond, an associate director of the
Institute on Women and Technology at MIT, perceives RU
486 "as another assault on women's bodies by the medical
profession." Really, RU 486 is just another example of
experimentation on women which we don't need.

* The use of Ru 486 is open to widespread abuse because it
is not a simple at-home do it yourself abortion method.
It requires 4 visits to a doctor. The initial doctor's
visit to receive the pill must have three follow-up

visits to the clinic or hospital for careful medical supervision. Because of this difficulty, especially for poor women, the Sixth International Women and Health Meeting passed a resolution opposing the use of RU 486.

* But even with careful medical supervision complications associated with the use of RU 486 are hemorrhaging, infection, permanent sterilization, heart attacks and even death. Thus, the French government has banned its use for heavy smokers and women over 35.

* Further, claims that RU 486 can cure a myriad of diseases is unfounded. There has been no proof that it will affect such ailments as brain tumors, depression, hypertension, Alzheimer's, obesity, glaucoma, breast cancer, severe wounds and burns, AIDS, diabetes etc. This magical miracle drug cannot possibly deliver and as Dr. Bernard Nathanson says "It begins to sound a little like Dr. Potter's Snake Oil."

* Ru 486 acts by blocking the babies use of the hormone Progesterone without which the baby starves to death.

> RU486 is effective in approximately 80 - 95% of the instances of its use. For the remaining cases the unborn babies may be injured and born with defects. Several days after taking RU 486 a prostaglandin must be administered to assure that the abortion is complete. We already know that prostaglandins affect the immune

systems but we don't know what a single dose might do.
Really what is so wonderful about this drug that we must
request the Food and Drug Administration to let it into
our country?

We Alaskans should not be on record as supporting a drug that to
be effective kills babies and puts the life and health of the
mother in jeopardy.

Joan Heidersday
PO Box 020658
Juneau, AK - 99802
789-9858

TESTIMONY ON HOUSE JOINT RESOLUTION NO. 58

From: Ida Barnack, Representing Alaskan For Line Inc. -Juneau
8292 Garnet St.
Juneau Ak. 99801

The sole purpose of our organization is to support and advocate the right to life for the unborn members of society. All "born" members of our society (including you committee members) are first unborn members of our society.

The main purpose of RU 486 is to terminate pregnancy (end someone's life). Therefore, our organization is strongly opposed to this resolution.

The proponents of this drug indicate it can be used as a contraceptive, it is safe and it has other medical value.

This drug is not a contraceptive. A contraceptive does not terminate a pregnancy. How can it be safe since it induces a miscarriage. With a miscarriage heavy bleeding occurs and it is always a concern whether or not the uterus will automatically "clamp down" or whether medical intervention is required. I am sure you have all known women who have had to be rushed to the emergency room due to heavy bleeding from a spontaneous miscarriage. Inducing a miscarriage through RU 486 will be no different. Often times a "D" & "C" is required after a miscarriage also.

This always ends the life of at least one person and could potentially end the life of another, the woman. In fact there are reported deaths of woman who have taken this drug.

Representative Boyer stated that this drug can be used to induce delivery thereby reducing the number of caesareans. This is all abortion-speak. If a caesarean is required, I sincerely doubt that there is any drug a woman could take to prevent it. It is common place to induce labor now only to have it end in a caesarean.

If there are other medical uses for the drug other than ending someone's life, we have no objections to it being tested.

Think about the reason Roussel will not bring it into a country where there is opposition. They themselves must be concerned that the pill will cause the death of some women or have bad side effects and they do not want to take the liability.

Our organization is pro-choice. We choose to protect the life of the innocent.

Thank you for accepting this testimony.



Alaska State Legislature

Please enter into the record my testimony to the HESS
committee name

committee on Resolution # 58, dated March 10, 1992
bill/subject

I want to first Thank all of you for being gutsy enough to represent us on very difficult moral issues. I have never written testimony before.

The drug "RU486" will not only make it convenient for the individual, but society as a whole.

The value of life and its consequences, are the perspective we need in order to support each other.

Please note no...

Signed: Levi Pajkar
Testifier

SELF
Representing (Optional)

820 CHARLES ST SITKA, AK 99835
Address

(907) 797-3641
Phone No.

TELECOPY COVER SHEET

Kodiak Legislative Information Office

Office - (907) 486-8118

Fax - (907) 486-5264

TO: ~~XXXXXXXXXX~~ SS Comm. FAX: _____ PHONE: _____

FROM: Kodiak LIO PHONE: _____

INSTRUCTIONS: Testimony for T/d held
on 3/11/92 - 8:30 AM

RECEIVED: Date 3-16-92 Time _____

SENT: Date _____ Time _____

DISPOSAL OF ORIGINAL: Discard _____ Hold for Pickup _____

NUMBER OF PAGES: 2 (Not counting cover sheet)

SENT BY: Tina

CORRECTION

**THIS DOCUMENT
HAS BEEN REPHOTOGRAPHED
TO ASSURE LEGIBILITY**



Alaska State Legislature

Please enter into the record my testimony to the FHESS
committee name

committee on Resolution # 58, dated March 10, 1992
bill/subject

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The drug "RU486" will not only make it convenient for the individual, but society as a whole.

The value of life and its consequences, are the perspective we need in order to support each other.

Please note no...

Signed: [Signature]
Testifier

SELF
Representing (Optional)

820 CHARLES ST SITKA, AK 99835
Address

(907) 747-3641
Phone No.



Alaska State Legislature

Please enter into the record my testimony to the House HESS
committee name

committee on HJR 58, dated 3/10/92
bill/subject

I would like to get on record before this committee stating that I am not in favor of abortion. The only exception to that would be in a case where the mother's life is threatened.

Signed: M.W. Laboure
Michael W. Laboure
Testifier

Representing (Optional)
Box 6369 Sitka, AK 99835
Address
(907) 747-4880
Phone No.

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FROM: Kodiak LIO PHONE: _____

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on 3/11/92 - 8:30 AM

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SENT BY: Tina

ALASKA WOMEN'S LOBBY

P.O. BOX 22156, JUNEAU, ALASKA 99802

March 11, 1992

RU486-HJR 58

RU 486 is a pharmaceutical which, among other uses, provides a means to medically terminate unwanted pregnancies.

American women should be allowed to benefit from this new advance in fertility control.

Use of the RU 486 requires no invasive procedure. There is no risk of any infection, nor need for anesthesia. It is 96% effective in the early stages of pregnancy.

Its use would put most early abortions into a very private realm, and would reduce the need for a majority of all surgical abortions in America.

In addition, it would end the open harassment and violence at abortion clinics that have characterized the bitter battle over reproductive rights.

Researchers believe that the drug has enormous promise in treating: breast cancer which affects one in nine women, endometriosis, a leading cause of infertility, ovarian cancer, glaucoma and ulcers.

RU 486 may be used to induce labor in a difficult delivery reducing the number of cesarean births.

It has been *proven* to effectively treat some forms of Cushing's Syndrome, a rare adrenal tumor which mostly affects women in their 30's to 40's.

The side effects that have been discovered have been minimal. No long term side effects have been observed

The current FDA ban on importation means that our doctors can't use RU 486 in therapy and our scientists can't use it for research even when their work has nothing to do with abortion.

Rep. Ron Wyden of Oregon who chairs the House Small Business subcommittee investigated the import ban for a year and concluded, "The Agency's decision was motivated by politics rather than by science or a desire to protect the public health from a clear and present danger." He charged the FDA with ignoring overwhelming evidence of the drug's safety.

ALASKA WOMEN'S LOBBY
RU 486 Position Paper

When the distributor of the drug in France caved in to anti-abortion pressure and took the product from the French market, they were ordered to resume distribution two days later by France's Minister of Health who declared that RU 486 was "the moral property of women."

The Drug has been available in France since 1988 and it is licensed for use in Britain and Sweden.

The continued testing and availability of RU 486 is advocated by :

The American Medical Association (AMA),
The World Health Organization,
The American Public Health Association,
The World Congress of Obstetrics and Gynecology.

59% of all American adults think RU 486 should be made available in the U.S. (Harris poll).

RU 486 will come to America The chemistry for RU 486 is known. If it does not enter legally it will enter illegally within 2-5 years.

We must not have it enter the U.S. illegally. We want it properly tested and used with medical supervision to ensure its safety for women.

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THE ORIGINAL

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House HESS. Kodiak Legislative Information Office

Office - (907) 486-8116

Fax - (907) 486-8284

TO: Rep. Lincoln - chairman FAX: _____ PHONE: 465-3759

FROM: Kodiak L.I.O. PHONE: 486-8116

INSTRUCTIONS: Written Testimony for T/C 92-03-042
3-11-92 / Wednesday 8:30Am

RECEIVED: Date 3-12-92 Time _____

SENT: Date _____ Time _____

DISPOSAL OF ORIGINAL: Discard _____ Hold for Pickup _____

NUMBER OF PAGES: 2 (Not counting cover sheet)

SENT BY: LS



Alaska State Legislature

Please enter into the record my testimony to the House - HESS
committee name

committee on HJR 58, dated March 11, 1992
bill/subject

Page ①

As I await a turn to publicly testify against the passage of HJR 58, I wonder how many others with my viewpoint have been denied equal access to public and privatized (Channel 9) testimony. I suppose my faxed comments will not appear on Channel 9 news as did the "pro-abortion" voice of this morning.

At the outset, I would like to object to Rep. Boyer and the female from the Feminist Majority Foundation being introduced as "experts" on this subject. They are politicians, nothing more, nothing less. I would hope in the future Reps. Boyer and Kaponen would leave testimony during teleconferences to the public, their constituents, and who they are elected to represent.

I also wonder if there is any ~~reason~~^{room} for the truth in all that is being said. A few facts may help.

1. RU 486 is not opposed by pro-lifers for legitimate research directed at saving lives.
2. To date, RU 486's only proven use is to destroy lives.
3. Already one woman has died from use of RU 486, in addition to the as yet unmentioned side

Signed: Marjorie R. Alenkey (over)
Testifier

Representing (Optional)
3584 Woodland Drive, Kodiak AK
Address
(907) 486-3973

effects as excessive bleeding, requiring transfusions, intense pain and a 10-30% "failure rate" requiring use of a subsequent surgical abortion procedure, provided the woman does not change her mind.

4. RU 486 is touted as safer and easier than surgical abortion. In fact, it requires 4 trips to an abortionist, and if unsuccessful alone, is sometimes used in conjunction with prostaglandin a substance which at one time was also used to induce abortions but the pain and number of deaths resulting were considered intolerable.

5. Pro-abortion advocates want the public to think that RU 486 has many proven beneficial uses - yet none have been safely proven so far. They never mention the Institute on Women and Technology, a pro-abortion group, which came out against the import of RU 486 at this time, because of their concern about the side effects for women. They, despite their viewpoint, could foresee the potential harm to women. The political lobby will probably never forgive them.

How many times does a society need to have a similar experience in order to see the truth? Women were told IUD's were safe, and thousands of women can no longer have children. Thalidomide was used for nausea in pregnancy by women, touted as perfectly safe, only to result in severely deformed human beings. What about the child that survives RU 486? What about Anna Rodriguez, a child who lost her arm to an abortionist during an 'incomplete' procedure and now lives? How will her mother answer her questions?

This bill has nothing to do with curing diseases or saving lives. The pro-abortion groups will stop at nothing to have abortion on demand, for any reason at any point in a pregnancy. They are not concerned with the health of women or those with wishak syndrome who are interested in the continued



Alaska State Legislature

Please enter into the record my testimony to the House HES
 committee name
 committee on HJR 58, dated 3/16/92
 bill/subject

I wish to voice my strong opposition to the legalization of the medication RU468 on the ~~group~~ (error) grounds that there is considerable evidence of its negative health effects for women and as well as evidence of fetal defects in children born for whom the drug was not effective (i.e. fatal).

I am concerned about a continuing birth control / abortion movement which does not fully take into account the health + psychological effects on women, and places on them the burden of responsibility, subjecting their bodies to such "cures" as drugs and abortion which have considerable undesirable complications

Signed: Paul Ruff Testifier

Representing (Optional)
PO 2648 Kodiak AK 99615
 Address
(907) 486-3506
 Phone No.



Alaska State Legislature

Please enter into the record my testimony to the House - HCSS
 committee name
 committee on HJR-50, dated 3-15-92
 bill/subject

As a concerned U.S. citizen I do not support this bill. It disregards potential dangers to women.

Signed: Janice VanRosen JANICE VANROSSEN
 Testifier

The General Public
 Representing (Optional)

Star Pl 3530 Kodiak AK 99615
 Address

486-6050
 Phone No

STATE OF ALASKA
1992 LEGISLATIVE SESSION

BILL NO. HJR 58

Revision Date: _____ Department Affected: LEGISLATURE
 Title: AVAILABILITY OF RU 486 DRUG BRU: _____
 Component: _____
 Sponsor: REP. BOYER
 Requestor: _____ COMPONENT SERIAL NO.

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EXPENDITURES/REVENUES: (Thousands of Dollars)

OPERATING	FY 93	FY 94	FY 95	FY 96	FY 97	FY 98
PERSONAL SERVICES	-0-					
TRAVEL	-0-					
CONTRACTUAL	-0-					
SUPPLIES	-0-					
EQUIPMENT	-0-					
LAND & STRUCTURES	-0-					
GRANTS, CLAIMS	-0-					
MISCELLANEOUS	-0-					
TOTAL OPERATING	-0-					

CAPITAL	-0-					
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REVENUE FUND SOURCE:	-0-					
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FUNDING: (Thousands of Dollars)

GENERAL FUND	-0-					
FEDERAL FUNDS	-0-					
OTHER FUND SOURCE:	-0-					
TOTAL	-0-					

POSITIONS:

FULL-TIME	-0-					
PART-TIME	-0-					
TEMPORARY	-0-					

Estimate of current year impact: _____

ANALYSIS: (Attach a separate page if necessary.)

Prepared By: [Signature] Phone: 465-3732
 Division: HOUSE HEALTH EDUCATION & SOCIAL SVCS CMT Date: 3/10/92
 Approved by Commissioner: _____
 Agency: _____ Date: _____

Statement of the American Medical Association

to the

Subcommittee on Regulation, Business Opportunities, and Energy

Committee on Small Business

U.S. House of Representatives

Presented by

P. John Seward, M.D.

RE: RU 486

November 19, 1990



American Medical Association
515 N. State Street
Chicago, Illinois 60610

Department of Federal Legislation
Division of Legislative Activities
(312) 464-4775

STATEMENT
of the
AMERICAN MEDICAL ASSOCIATION
to the
Subcommittee on Regulation, Business Opportunities, and Energy
Committee on Small Business
U.S. House of Representatives

Presented by
P. John Seward, M.D.

RE: RU 486

November 19, 1990

Mr. Chairman and Members of the Subcommittee:

My name is P. John Seward, M.D., and I am a physician in family practice in Rockford, Illinois. I also am a member of the Board of Trustees of the American Medical Association. Accompanying me is David L. Heidorn of the Association's Division of Legislative Activities. The AMA appreciates this opportunity to appear today to discuss the issue of RU 486 availability in the United States.

In the Subcommittee's letter of invitation to appear, you asked that the AMA respond to a number of special questions regarding the drug. In addressing those inquiries, I want there to be a clear understanding of the AMA's policy regarding RU 486 and what we believe to be the current legal status of that drug within the United States.

At its June 1990 meeting, the AMA's House of Delegates adopted the

following resolution:

RESOLVED, That the American Medical Association support the legal availability of RU 486 for appropriate research and, if indicated, clinical practice.

The reason that the Association took this position was our very real concern that politics or ideology could interfere with a well established, legal decision-making process that is and must always be based on good science and proper medical practice, nothing more.

As you well know, RU 486, or mifepristone, which is a steroidal agent being used as an early abortifacient in some countries, has raised deep feelings among both the proponents and opponents of abortion and the prospective use of RU 486 in the United States. It is the AMA's position that any governmental decision regarding this drug, as with all other drugs, must not be influenced by political debates or social issues such as this one. This must not be taken to mean that the AMA supports the widespread availability of RU 486. We do not believe that there has been adequate research to establish that this drug is a safe and effective therapeutic modality. In fact, the central difficulty in evaluating this drug is that no research is being conducted in the United States to determine whether RU 486 has a role in medical practice, and the reason no research is going forward is its manufacturer's decision not to pursue clinical testing of the drug here.

As we understand the current situation, no Investigational New Drug (IND) applications (the legal precondition for a drug to be transported in interstate commerce for the purpose of clinical research) either are pending or have been approved by the Food and Drug Administration (FDA)

for RU 486. Since the Federal Food, Drug and Cosmetic Act requires that a drug be proven safe and effective for its intended purpose through well controlled clinical investigations, there is no basis for approval of a New Drug Application to allow the drug to be marketed. Therefore, no legal basis exists for this drug to be used in the United States for research or in marketing.

The only other basis for allowing importation of RU 486 would be for individual compassionate use. However, it is the AMA's understanding that RU 486 poses a severe risk to patients unless the drug is administered as part of a complete treatment plan under the supervision of a physician. During an appropriate course of treatment with the drug, it is common that three or four visits to a physician are necessary to avoid hemorrhaging and to ensure that a complete abortion has taken place. It also must be taken with a prostaglandin to increase the probability that a complete abortion occurs. Clearly, the importation of RU 486 for personal compassionate use would not be medically desirable given alternative available care methodologies.

These difficulties do not mean that research on RU 486 should not be conducted. On the contrary, we believe that if this drug can be shown to be a safe and effective medical treatment, it should be available for the appropriate care and treatment of patients. There has been some published conjecture that RU 486 may be an effective treatment for other indications besides its use as a contraceptive or abortifacient, including treatment of breast cancer, gynecological malignancies, glaucoma, infertility, and labor induction. While we do not believe this conjecture to be based on any substantiated tests of the drug, RU 486's

application to these conditions is certainly possible, although adequate drugs for these conditions already exist. It may even be possible that this drug is useful in treatments about which we have no current knowledge. No one, at this time, can say.

The only way to make these determinations and to establish the safety and efficacy of RU 486, as all other drugs, is to conduct the necessary research and clinical trials required by the FDA to market drugs in the United States. This is a highly effective process established to protect the health, safety, and welfare of the American people. For the same reasons drugs proven to be safe and effective should not be kept out of the United States for political reasons, so also should the high standards we have for drugs not be contravened for political purposes.

Rumors exist that the FDA, due to political pressure, is standing in the way of research on RU 486. We do not believe this to be true. On the contrary, it is the FDA's responsibility to ban a drug that has not met legal and regulatory requirements for importation into the United States. Because RU 486 has not met these requirements, the FDA complied with its charge and acted well within its authority in issuing its June 9, 1989, automatic detention import alert concerning the drug.

As we understand the situation, the actual impediment to research on RU 486 is the manufacturer's unwillingness to make the drug available in the United States. Without the drug, it is impossible to apply for an IND. The manufacturer is reportedly unwilling to allow clinical testing in the United States because of its concerns over the political controversy that has followed this drug and is sure to intensify if

research begins in this country. While the French government compelled the French manufacturer to make the drug available in that country, we do not believe that this is a problem that can be easily addressed under our current law.

Conclusion

The AMA stands by the FDA's appropriate application of its legal responsibilities in protecting the health and well being of the American people from unsafe drugs. From our understanding of the current situation, the FDA has acted responsibly in issuing import restrictions for RU 486. At the same time, we would expect that, if an acceptable IND is submitted, the IND would be approved and importation allowed. We hope that the drug can be made available and research eventually can be conducted in this country to determine if the drug is safe and effective for its known uses and whether its use may be appropriate for other medical treatments. It is our primary concern that patients have every opportunity to receive the best possible medical treatment. When possible research into drug therapies does not occur, for whatever reason, the likelihood that the best possible care will not someday be available is greatly increased.

Frankly, we have no answer for this Subcommittee on how to ensure that all appropriate research occurs. Under our current system, which is the world's standard for the development of drugs, the manufacturer is well within its rights to hold the drug from distribution. We can only hope that the political climate will somehow not influence any future consideration of the introduction of RU 486 into the United States.

AMERICAN MEDICAL ASSOCIATION HOUSE OF DELEGATES

Resolution: 100
(A-90)

Introduced by: California Delegation

Subject: RU-486 Availability

Referred to: Reference Committee E
(Charles D. Sherman, Jr., M. D., Chairman)

1 Whereas, An antiprogesterone steroid, known as RU-486, has been developed and tested
2 in Europe, and has been shown to be an efficacious and safe means of terminating early
3 pregnancy when administered orally early in pregnancy by an appropriately trained physi-
4 cian; and

5
6 Whereas, The use of such a medication for terminating early pregnancy constitutes a
7 potentially significant medical and public health gain in terms of efficacy, safety, ease of use,
8 cost and privacy of the physician-patient relationship; and

9
10 Whereas, RU-486 may also be an important treatment for other indications, including
11 treatment of breast cancer, gynecological malignancies and labor induction; and

12
13 Whereas, Existing AMA policy holds that the early termination of pregnancy is a private
14 medical matter to be decided between the patient and her physician, and AMA policy also
15 does not prohibit abortion wherever legal and performed in accordance with good medical
16 practice; and

17
18 Whereas, It is in keeping with basic medical standards to avoid surgical procedures when-
19 ever an equally effective non-invasive alternative is available; and

20
21 Whereas, The potential for a "black market" in RU 486 in this country is very real, with
22 women's health activists already vowing to import the drug for use by American women, thus
23 exposing them to the dangers of non-physician supervised use of the drug; therefore be it

24
25 RESOLVED, That the American Medical Association support the legal availability of
26 RU-486 for appropriate research and, if indicated, clinical practice.

Fiscal Note: No significant fiscal impact

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Editorials

Don't let U.S. politics thwart RU486

The French use it. So far 44,000 Frenchwomen have responded so favorably to RU486 — the pill used to terminate very early pregnancies — that the treatment has become the method of choice among one-third of Frenchwomen opting for abortion. The British and Swedes are enthusiastic about it, too: Next year RU486 will likely be available for marketing in those countries.

Even in the 'abortion-wary' United States, there is a demand for RU486. A Harris poll conducted in 1988 found that 59 percent of Americans think the medication should be available here. And the American Medical Association — hardly a bastion of avant-garde thinking — endorses testing of RU486.

Evaluating the impact of RU486 from a scientific standpoint has been exciting. According to researchers, administered in conjunction with the steroid prostaglandin, the drug has proved to be 96 percent effective in terminating early pregnancies, with few side effects. Risks associated with chemical abortions are less than with surgical abortions. And RU486 shows promise in treating or preventing meningioma (a benign brain tumor), breast cancer, endometriosis, glaucoma and other diseases.

So why isn't it available in the United States?
It's a question of politics.

Although women indicate they prefer the option of monitoring their own abortions, anti-abortion activists in this country have effectively blocked the marketing of RU486 by any pharmaceutical company through the threat of boycotts and harassment. Roussel-Uclaf, the French manufacturer of RU486, has for now stayed out of the fray by keeping the drug from distribution until the political climate becomes more accepting.

But times may be changing. This summer, Eleanor Smeal, president of the non-profit Fund for the Feminist Majority, and a delegation of U.S. scientists delivered 115,000 petitions upholding RU486 and contraceptive research in America to the chief executive officers of Roussel and its German parent company, Hoechst. The manufacturers were impressed by the degree of support demonstrated by the U.S. public.

That support could be magnified in pharmaceutical board rooms if it were backed up by U.S. politicians lobbying in Europe to bring this medical advancement to the United States.

JUDY MANN

Facing the Abortion Issue

One of the reasons women feel so strongly about the abortion issue is that many of them have had to confront the question personally, and if they haven't, they have friends who have, and they know that they might have to. For women, abortion is not an abstract.

Women, as Harvard professor Carol Gilligan wrote in her book, "In a Different Voice," arrive at a decision about abortion in the context of their human connections and values about what is the right thing for them to do under their particular set of circumstances. Men, she wrote, tend to arrive at moral decisions in terms of absolutes of right and wrong.

When the decision about abortion is remote—as it has been for most men since the 1973 Supreme Court decision legalizing it—it is easier to take an absolute stand on it. This may account for the difference in the way men and women are voting in state legislatures that have recently considered abortion laws. The majority of men in most of the legislatures have voted to restrict access to abortion while the majority of women have voted against restricting access, according to a study done by the Feminist Majority.

Now, however, more and more politicians and organizations are having to take positions on abortion and are having to think through the consequences of that question in a far more personal way.

The American Bar Association is the latest to find itself embroiled in internal conflict over its stand on abortion. On Wednesday, its House of Delegates voted 200 to 188 to rescind its position that a woman's right to an abortion was guaranteed by the Constitution. That position, taken as recently as February, led to the resignation of more than 1,400 lawyers and a loss of about \$300,000 in dues. The current ABA president backed the repeal while his successor opposes it, which suggests that the ABA hasn't seen the last of this.

The same day, the National Conference of State Legislatures met, and lawmakers on both sides of the abortion issue were clearly unhappy that they had to deal with it. According to a story in The Washington Post, Rep. Kelly Shackman, a Democrat from North Dakota who opposes abortion, got a round of applause from 200 of his colleagues after he said he resented "the fact that the Supreme Court dumped this whole issue back on the states."

President George Bush, anxious to avoid a firestorm over abortion, nominated to the Supreme Court an obscure federal judge who has been on the appellate bench so briefly that has no paper trail on abortion. What might have been called inexperience (particularly in a woman) was swiftly turned into a plus: "a clean slate," as Sen. Howard Metzenbaum (D-Ohio) called it.

It is clear that in the present political climate, no Supreme Court nominee with a record on abortion will get confirmed without the kind of bloodletting that will leave both sides of the battle exhausted. U.S. senators appear no more eager for these battles than are state legislators.

As the complexities—moral, personal and political—of the abortion debate reach beyond women and begin to embroil men in a direct way, with personal and political costs, they will realize that it is not only the most divisive issue of our time, it is the most personal one.

Each legislator who realizes how difficult the issue is to deal with will have made a giant step in understanding the ordeal that women go through. Politicians and members of professional organizations who have to vote on this will think twice before they parrot terms like "abortion on demand."

And they may find that it is in their best interests to lend their weight to efforts to import the French abortion pill, RU-486. The Feminist Majority recently led a delegation of 10 scientists, feminists and health-care professionals who met with the top officials of the companies that manufacture RU-486. They delivered 115,000 petitions and a list of 250 scientists and medical researchers who support importing the pill, which terminates pregnancies in the embryonic stage.

Myron Allukian, president of the American Public Health Association, who was a member of the delegation, said that RU-486, because it is non-surgical, produces less bleeding and less chance of infection and requires no anesthetic. He warned of a potential black market if it is not imported legally, which could lead to abuses in its use.

The French abortion pill has the potential of defusing much of the abortion controversy. It is cheaper and safer, and it puts a decision about abortion back where it belongs: Between women and their doctors. As more and more political organizations are discovering when they become embroiled in this fight, this is the only place for that decision to be made that makes any sense.

THE FOLLOWING DOCUMENT MAY NOT FILM
LEGIBLY BECAUSE OF THE POOR QUALITY OF
THE ORIGINAL

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 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 Howard S. Jones 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-

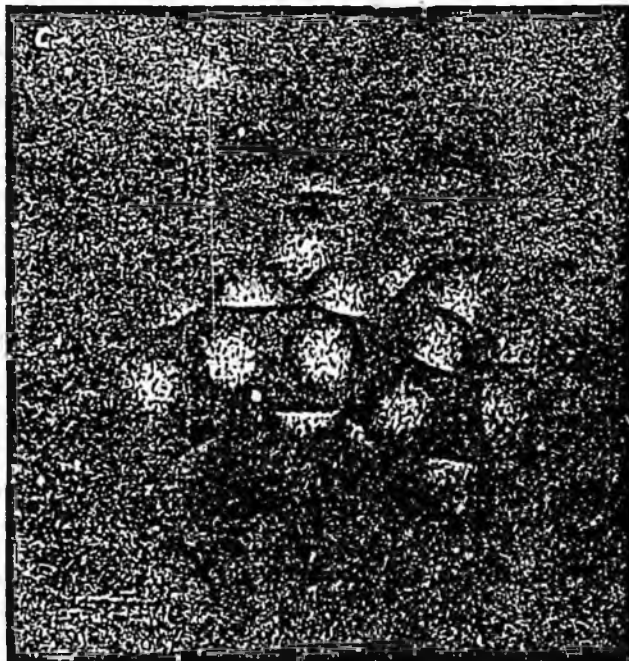
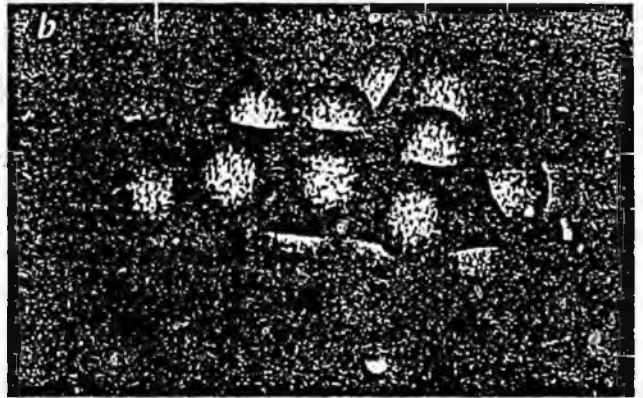
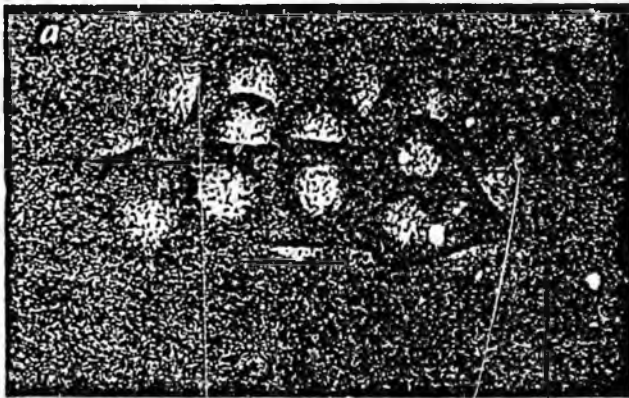
tivated receptor—then binds to the chromatin in the nucleus (the complex of DNA and its associated proteins). That event then triggers the transcription of a selected gene from DNA into messenger RNA. Because the progesterone-stimulated synthesis of proteins in the uterus is essential to the maintenance 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 ovulation 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

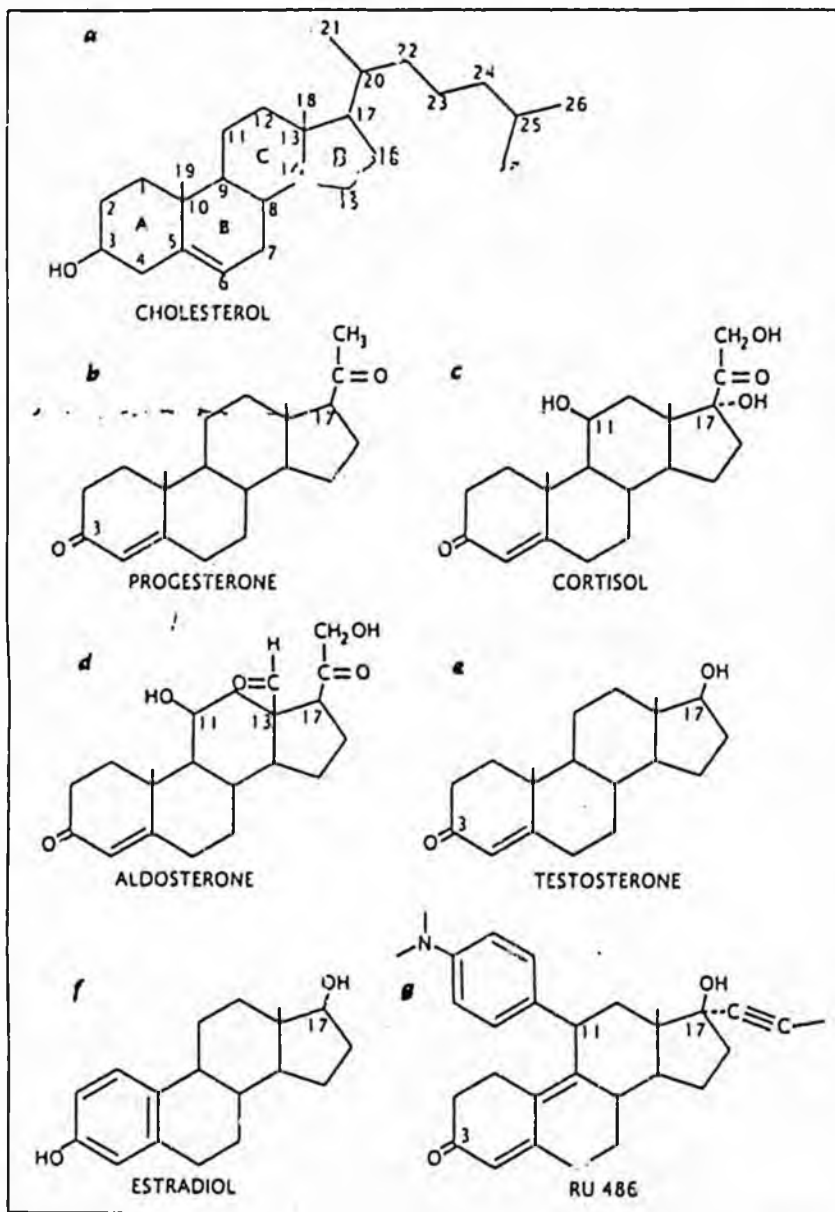
not fertilized, the corpus luteum begins to degrade after some 12 days, so that by about the 28th day of the cycle, the decline in progesterone results in the shedding of all but the basal (permanent) layer of the endometrium. Uterine bleeding follows, and the cycle begins anew.

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 anti-progesterone 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 Deraedi, found that certain of the molecules made by Teutsch's



STERIODS 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 considerable 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

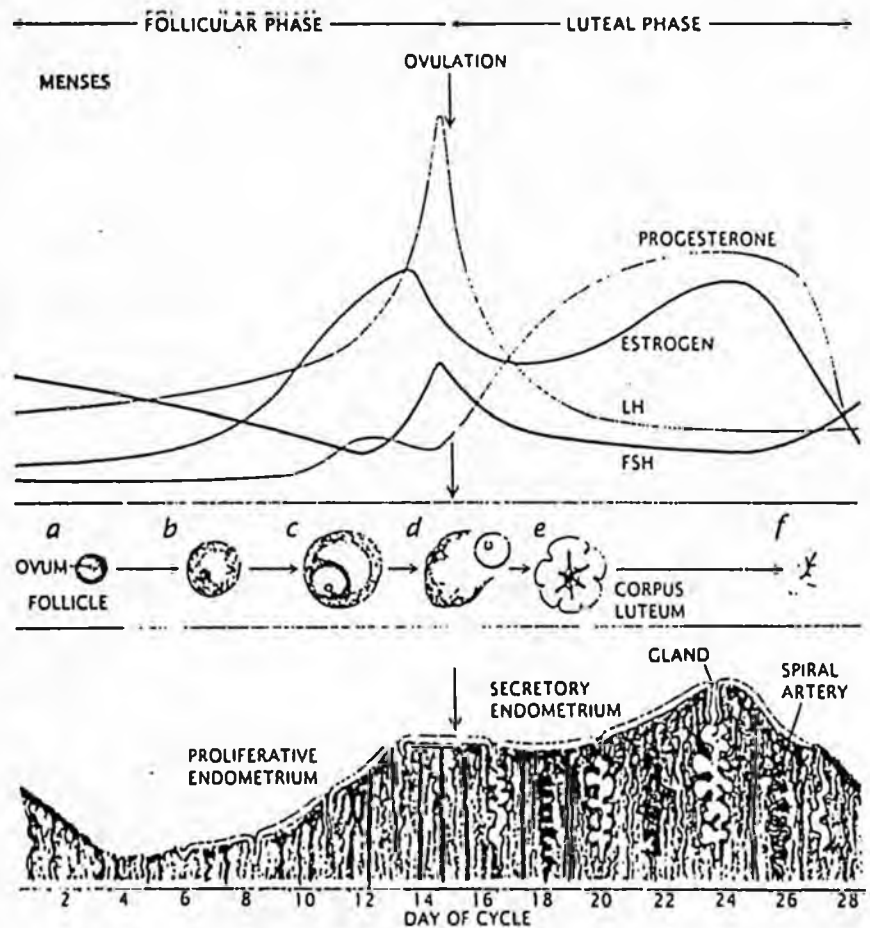
to RU 486. All bound strongly to the glucocorticoid receptor, and all interfered with certain activities of glucocorticoids in cell cultures. Of the three molecules, the last was the most potent; it was best able to block the actions of a powerful synthetic glucocorticoid (dexamethasone).

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.

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