

PN-ABF-032

AGENCY FOR INTERNATIONAL DEVELOPMENT PPC/CDIE/DI REPORT PROCESSING FORM 67207

ENTER INFORMATION ONLY IF NOT INCLUDED ON COVER OR TITLE PAGE OF DOCUMENT

1. Project/Subproject Number

9363041

2. Contract/Grant Number

DPE-CA-4047-00

3. Publication Date

October 1989

4. Document Title/Translated Title

Ru-486
Termination of a pregnancy in the privacy of one's home

5. Author(s)

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2.
3.

6. Contributing Organization(s)

Family Health International

7. Pagination

5 p.

8. Report Number

89-41

9. Sponsoring A.I.D. Office

10. Abstract (optional - 250 word limit)

11. Subject Keywords (optional)

1. RU-486
2. review
3. policy
4.
5.
6.

12. Supplementary Notes

13. Submitting Official

Deborah Wade

14. Telephone Number

919-544-7040

15. Today's Date

3-20-90

DO NOT write below this line

16. DOCID

17. Document Disposition

DOCRD INV DUPLICATE

SCIENTIFIC ARTICLE

RU-486

Termination of a Pregnancy in the Privacy of One's Home

Malcolm Potts, MB, BChir,* Ph.D.

RU-486 is the first in a new class of drugs with considerable promise in a number of therapeutic areas, from fertility regulation to cancer control. It is a computer-designed molecule that blocks the action of progesterone. The implications of its use, however, are broader than those of practically any other drug.

RU-486 offers the potential of a self-administered abortifacient and therefore raises important and insistent ethical issues. It would be wrong to review RU-486 in the same way that one might review a new hypertensive agent, and misleading not to consider the political, ethical and theological aspects of this new drug.

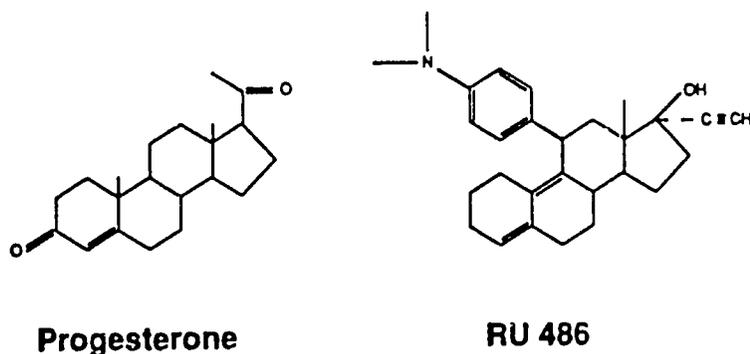
Therapeutics

The development of RU-486 has been a prototypical example of late twentieth century pharmacology and cell biology at its best. RU-38486 (RU-486, Mifepristone), developed and manufactured by the French pharmaceutical firm Roussel-Uclaf, is one of a series of 19-nor steroids substituted with a phenol ring in 11 B position (figure 1). Its action is highly specific; for example, RU-486 has virtually no

effect whatever on uterine estrogen or kidney mineralocorticoid receptors. Depending on the model studied, it has no, or a weak, agonist activity.^{1,2} RU-486 binds one-fourth as strongly as testosterone to testosterone receptors. Even in high doses it seems to be without side effects other than those which a normal reproductive endocrinology would predict.³

To date, the following actions have been studied:

- 1 Given in the luteal phase of the human cycle (from days 19 to 25), RU-486 brings forward the time of menstruation and induces uterine bleeding, primarily as the result of a direct action on the endometrium, and secondly as the result of a luteolytic effect on the corpus luteum.³ It appears to inhibit gonadotrophin secretion by speeding the rate of LH pulses. RU-486 has been considered as a possible contraceptive for monthly use, but when given this way it causes unpredictable timing of the next period and the idea has not been followed up intensively. It has been tried as a post-coital contraceptive agent.⁴
- 2 Used alone (200 mg x 3 per day for 4 full days), RU-486 will terminate an early pregnancy (up to 41 days amenorrhea).⁵ It is 90% successful if used before five weeks amenorrhea, but success declines markedly with duration of pregnancy.^{6,7} The majority of women bleed for about one week, comparable to a heavy period, but a few have a prolonged loss for up to 14 days. In a clinical trial of 350 volunteers, 10 required surgical uterine evacuation and three needed blood transfusions.
- 3 RU-486 will provoke an abortion in cases of spontaneous fetal death, possibly with fewer side effects than conventional oxytocin.⁸ The induction of labor late in pregnancy is associated with an increase in gap junctions between the myometrial cells, converting the uterus to a "functional syncytium." This change in cellular architecture and function appears to be inhibited by progesterone (Csapo's concept of a progesterone block of myometrial activity) and is therefore facilitated by RU-486.⁹



Dr. Potts is a British physician and a laboratory embryologist who has lived in North Carolina for ten years. *'MB, BChir' are the Cambridge University degrees which in the U.S. would be an M.D.

- 4 RU-486 has also been given before the surgical treatment of an ectopic pregnancy, and the medical treatment of ectopics under carefully controlled conditions is an intriguing new research initiative.¹⁰
- 5 In non-human primates, RU-486 has been used to induce labor at term.¹¹ However, RU-486 does cross the placenta and more toxicology data are needed before this indication can be responsibly explored in human therapeutics. In mechanical abortion, the greatest danger is not uterine evacuation, but the passage of instruments through the cervix that can cause damage to the cervix or the uterus. It is interesting, therefore, that RU-486 can also be used to soften the cervix prior to vacuum aspiration abortion, and although not as effective as prostaglandins (PGs), it is associated with fewer side effects.¹²
- 6 RU-486 has been used experimentally in the treatment of Cushing's syndrome in an attempt to exploit the overlap between blocking progesterone and glucocorticoid receptors. It has no acute effect, but may have a chronic therapeutic use, although once again more research is needed.¹³
- 7 As some breast, ovarian and endometrial cancers carry progesterone receptors,¹⁴ RU-486 has been tested as a therapeutic agent in a limited Phase I trial.¹⁵ A transient improvement was noted in six out of 27 women with advanced breast cancer, and more research is needed in this area. RU-486 may also have a role in treating certain types of meningioma.¹⁶
- 8 RU-486 is likely to have the potential to inhibit lactation in cases such as stillbirth, where there are genuine indications for the suppression of breast-feeding.

The Contraceptational Pill

RU-486 can be used to terminate pregnancy after the fertilized egg implants. By some, it has been dubbed an "abortion pill," but use after a missed menstrual period raises both semantic and therapeutic problems. Etienne Baulieu, who was the leader in developing Mifepristone, has coined the term "contragestational" to describe the anti-fertility action of the drug¹⁷ and to distinguish it from a strictly abortifacient drug which kills a fully formed embryo. We will return to this terminology shortly.

Pharmacologically, as noted above (item 2), RU-486 is not fully predictable in inducing menstruation that is delayed. Its effectiveness, however, increased when its use was combined with PGs. Baird in Edinburgh,^{18,19} Bygdeman in Stockholm,²⁰ and Ulmann in France²¹ have all experimented with combinations of RU-486 and PGs.

PGs themselves were touted as possible "abortion pills" in the late 1970s, and like RU-486 alone, worked often enough to excite medical interest yet failed often enough to undermine safe and responsible use. In addition, PGs were often associated with unacceptable levels of pain, diarrhea and vomiting. Together, RU-486 and PGs, each acting in a

different way, induce abortion in over 95% of cases without unacceptable side effects. In the Edinburgh comparison, for example, PGs administered alone required opiates for the relief of pain in half of all cases; but when used in combination with RU-486, PGs could be given at one-fifth the dose with a marked reduction in side effects.

Currently in France, over 100 women a day use the RU-486/PG combination (600 mg RU-486 plus two days' later injection or suppositories of PGs) to terminate pregnancies, or about 15% of all abortions in that country. Uterine bleeding usually lasts 10 to 12 days, and in 95% of cases no other treatment is needed. In 10% of cases the conceptus is expelled but a surgical D&C is still needed for heavy bleeding.²¹ In the few cases where the RU-486/PG combination fails, it is essential to proceed to a surgical abortion.

Theology

The decision to terminate a pregnancy, by whatever means, like the decision to have a child, is a profoundly important one. The British theologian Gordon Dunstan has written of the need to color all discussion of early human development with a "presumption in favor of life"²² and to keep the tension in any discussion wound up. A great deal of suffering follows for the parents, and for the children, when decisions about abortion or having children are taken with little or no thought.²³

Since the 16th century religious wars, western civilization has considered religious beliefs about life after death as matters of individual conscience, and it can be reasonably argued that beliefs about life before birth are also encompassed by the western tradition of religious toleration. The second Vatican Council stated that the "right to religious freedom has its foundation in the very dignity of the human person, as this dignity is known through the revealed Word of God and by reason itself."²⁴ The U.S. Supreme Court in *Roe v. Wade* (1973) expressed this same tradition unambiguously: "We need not resolve the difficult question of when life begins. When those trained in the respective disciplines of medicine, philosophy and theology are unable to arrive at any consensus, the judiciary, at this point in the development of man's knowledge, is not in a position to speculate as to the answer."²⁵

For those who accept that they live in a pluralistic society that separates church from state, it should be no more surprising to find an abortion clinic in a city where many people sincerely believe the embryo has a "right to life" than it is to find a Mosque, a synagogue and a Christian church in the same city block—each of which symbolizes a profoundly different interpretation of spiritual life after death.

For practically the whole of the past 3,000 to 4,000 years of the Judeo-Christian tradition, societies have associated the gradual development of the human embryo with a moral and legal code that placed less value on the embryo early in pregnancy than later. In Exodus 21:22-23—which is the only reference to abortion in a legalistic sense in the whole of the

Bible—an abortion associated with violence to the woman's body is regarded as a crime but explicitly not as murder, although the subsequent verses deal explicitly with giving an eye for an eye and a life for a life. Hebrew law, reflecting Babylonian law, reckoned a wife as the property of her husband, and an abortion was punished by a fine according to the social standing of the wife. Hippocratic medicine adopted the Hittite principle of grading the penalty according to the gestational age of the fetus.²⁶

Father Norman Ford, a Salesian priest and master of the Catholic Theological College, Melbourne, Australia, has followed the Christian interpretation of early human pregnancy in careful detail in his book *When Did I Begin?*²⁷ Ford points out that the early Fathers of the Church based their thinking on the writing of Aristotle (died 322 BC), who distinguished between material and formal causes of development. Aristotle visualized a nutritive or vegetable soul and a sensitive, rational soul. He stated, "The soul is the cause and first principle of the living body," and suggested that the sensitive soul entered the human embryo at 40 days in the male and at 90 days in the female (this difference was not an early example of crude sexual discrimination, but probably reflected the fact that Aristotle, who was a meticulous observer, mistook the tailfold—which is recognizable at about the 50th day of human pregnancy—for the male genitalia). St. Thomas Aquinas (died 1274 AD) used Aristotle to argue that the intellectual or rational soul was created by God only after "the completion of man's coming-into-being." St. Augustine (died 430 AD), whose writings remain central to the Catholic interpretation of fertility regulation, condemned contraception more forcefully than abortion.²⁸ The Council of Vienna (1311-1312) declared that it was heretical to "hold that the rational, intellectual soul is not in itself in essentially the form of the human body"; that is, they considered it heresy to say the soul entered at what today we would call fertilization.

Human spermatozoa were first seen by the Dutch microscopist, van Leeuwenhoek, in 1678, although it was not until the 19th century that the mammalian egg was discovered and fertilization observed. van Leeuwenhoek used a single lens microscope of unusual design, but subsequent microscopists used non-color corrected lenses which could barely resolve sperm. Some observers falsely believed they could see a tiny human figure or homunculus in the head of each sperm (figure 2). This mistaken observation had an important effect on both biologists and theologians.²⁹ In 1620, Flemish physician Thomas Fienus (Feyens) suggested that human ensoulment began only three days after the semen was deposited, and an increasing number of biologists adopted the idea of preformation, the view that the embryo was fully formed and perfect in all its parts from an early stage in development—rather like a baby without its diapers seen through the wrong end of the telescope. The alternative theory of epigenesis, which Aristotle had espoused, was temporarily eclipsed. Since then, modern embryology has thoroughly confirmed epigenetic theories at the expense of

preformation; but for a short while, the aberration of the homunculus "seen" through imperfect microscopes supported the preformation theory, and theologians became increasingly divided over their interpretation of the timing of ensoulment.

Paradoxically, just as modern embryological study was beginning, Pope Pius IX asserted (1869) the idea of immediate ensoulment coinciding with fertilization, overruling the more gradualist approach which had characterized the previous thinking. The second Vatican Council confirmed this judgment, writing, "Life must be protected with the utmost care from conception: abortion and infanticide are abominable crimes." Yet, the Church always stopped short of "categorically asserting that the fertilized egg itself is already a human being or a person." The remainder of contemporary theologians continue to be divided between those who ascribe a "right to life" from the "moment" of fertilization and those who believe, based on a modern embryologic observation, that the embryo and fetus become increasingly complex and therefore increasingly worthy of legal and ethical protection, as pregnancy proceeds. Ford asserts, "The fact of the matter is the Catholic Church has never officially taught when the individual human being, endowed with a rational soul, begins in the mother's womb."²⁷

In 1987, the Holy Office for the Doctrine of the Faith of the Catholic Church issued an Instruction in Respect for Human Life in its Origin and the Dignity of Procreation.²⁹ Although it condemns in vitro fertilization and abortion, this carefully worded document also points out, "The Magisterium has not expressly committed itself to an affirmation of a philosophical nature, but it constantly reaffirms the moral condemnation of any kind of procured abortion." This seems to leave the door sufficiently ajar for Ford and others who have pointed out that human personhood cannot begin until at or after the primitive streak stage of human development (18 to 21 days after fertilization). The reason is that some identical twins, and all conjoined twins, only develop at the

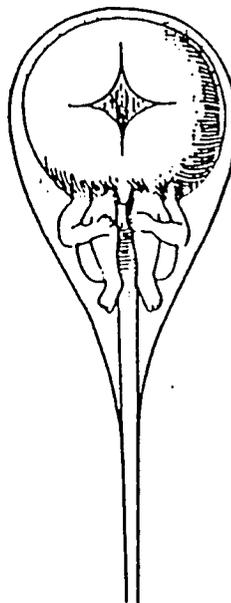


Figure 2.
The homunculus
as drawn by the
seventeenth century
microscopist, Hartsoeker.
From K. Moore,
*The Developing Human:
Clinically Oriented
Embryology*, 3rd ed.
Philadelphia: W.B.
Saunders, 1982.

primitive streak stage; and for human personhood (or ensoulment) to be recognized there must be a physical correlate of human individuality which is truly indivisible. Ford writes, "some are satisfied that the human person is present once a human zygote is constituted with the potential to develop into one or more adult human individuals. Others, myself included, draw the line two weeks later when a living individual human body is actually formed with the active potential to develop further without change in ontological identity. Instead of viewing development in the first two weeks after fertilization as development of the human individual, I have argued the process ought to be seen as a development into a human individual."²⁷

Islam also holds that ensoulment occurs at the end of the first 120 days of pregnancy.³⁰ The Holy Koran (23:12-14) has a poetic description of embryological development—from "a drop of seed" to bones clouded with flesh to "another creature."

Used appropriately, RU-486 (and PGs) will act before the primitive streak stage, that is, before the first time when human individuality can be ascribed to the conceptus. Baulieu's term "contragestational" does indeed seem apt.

The Law

The UK Ministry of Health has stated that the 1967 Abortion Act is not applicable to such drugs as RU-486. In New Zealand and West Germany, the abortion law does not cover actions taken prior to implantation of the embryo.³¹

From the point of view of physicians, any effort to define life as beginning at fertilization will create some clinical and legal problems. Setting aside the issue of whether fertilization is the penetration of the sperm through the zona pellucida or the cell membrane of the ovum, or the union of the chromosomes of the two gametes, such a definition, if accepted by the courts, would raise serious questions about the use of certain contraceptives, such as the pill and IUD which in some cases may act after fertilization but prior to implantation.

In the arguments recently presented to the Supreme Court in the Missouri case (*Webster v. Reproductive Health Services*, U.S. Supreme Court, April 26, 1989), Justice Scalia agreed, "It is impossible to distinguish between abortion and contraception when [abortion is defined] as the destruction of the first joinder of the ovum and the sperm." The court in *Webster* refused to rule on the preamble of the 1986 Missouri law which gave rise to the case and which states, "The life of each human being begins at conception." Justice Stevens, however, in his dissenting opinion, pointed out the preamble implies regulation not only of previability abortions but also of common forms of contraception, such as the IUD and the morning-after pill.

Any legal effort to define human life as beginning at or around the time of fertilization would also raise serious problems concerning operations for ectopic pregnancy, as

some ectopic pregnancies, if untreated, have the potential to survive to term and produce a viable infant, although the overwhelming majority hazard the life of the woman. Obstetricians would be caught between threats of charges of manslaughter for removing the embryo and the certainty of malpractice suits if they failed to operate.

I have reviewed these theological and legal arguments at some length because what we call RU-486 and how we define its action will, in large part, determine its availability and usefulness.

Politics

It is clear that RU-486 represents the first of a new generation of interesting and important therapeutic agents with a variety of possible applications. The fact that the drug, although relatively new, is well understood and highly specific in its actions has led to rapid marketing approval in the country of manufacture, France (September 1988), and in China, where extensive clinical work has also been completed. (Although the drug also received the trade name Mifegyne, it had already become so famous under its research categorization RU-486 that the earlier designation commonly continues to be used.) Prescription in France is limited to specific abortion clinics and to use within seven weeks of the last menstrual period—five weeks of embryonic development. The price was set at approximately \$100, or slightly less than a surgical abortion. Produced in bulk, and when the development costs have been recovered, it could be sold much more cheaply. To date, work that has been done on the possible teratological effects of the drug have not demonstrated any adverse effects, although more research is needed in this field.

In view of the effect of RU-486 on early pregnancies, the manufacturer, Roussel-Uclaf, made an explicit decision to seek drug approval for the abortifacient indication before exploring other possible therapeutic uses. They argued that the motivation to terminate pregnancies is often extremely strong, even driving women to break laws; therefore, they decided to undertake the necessary clinical work to market the drug for early pregnancy termination, before seeking approval of other possible indications.

However, the day after the French marketing license was given for Mifepristone (in combination with the PGs) to terminate early pregnancy, Roussel-Uclaf suspended sales. The largest holder of Roussel-Uclaf stock is the French government, but 36.25% is held by Hoechst AG of West Germany, and it is thought that the Hoechst management brought particular pressure on Dr. E. Sakiz, the President of Roussel-Uclaf, to suspend sales. Hoechst (formerly IG Farben) had been accused of manufacturing the poison gas used for the Nazi concentration camps and, even though they denied this, they were afraid abortion opponents would raise this canard again. (In a paradoxical footnote to 20th century history, which has been overlooked in contemporary polemics, Adolf Hitler explicitly condemned abortion as immoral

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