with the rest of the physics and engineering world. Another critic faults the course for providing little sense of the importance of experiments in science. Yet another critic complains that the PT course material spoon-feeds mathematics to the students. But defenders of PT say the course has different goals than a college physics course because its students have different needs. PT's mission, they say, is to instil the concepts essential in the technological workplace—not to stimulate the abstract thinking needed in academic science.

RU 486 and the abortion debate

Debate and arguments are raging over whether or not to license RU 486 for use. 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.

The way the pill works

In women, the steroid hormone progesterone plays a central role in the establishment and the maintenance of pregnancy. In the preparation process known as decidualization, the womb lining becomes thicker and blood supply to it increases. Progesterone acts on target cells by way of the progesterone receptor, a hormone-binding protein, obligatorily involved in the target cells response. RU 486 is also a steroid with a high affinity for the progesterone receptor. It is the first available active antiprogesterone. When RU 486 enters the target cells, it blocks the binding of progesterone to its receptor by itself binding to the receptor. The sequence of events that follow normal activation by progesterone are prevented and maintenance of pregnancy fails.

The debate

According to Joseph Palca in *Science*, the development of RU 486 is a case study in how biomedical research and public policy occasionally collide. Groups opposed to abortion called RU 486 the 'death pill' and they have been largely responsible not only for keeping the drug out of the US, but also for intimidating researchers interested in exploring the myriad potential medical uses for the drug.

The significance of RU 486 for developed countries is not that it is measurably safer or more effective but that it can be used in relative privacy. It is therefore not surprising that RU 486 is viewed with alarm by antiabortion groups. In France, approximately 25,000 have chosen RU 486 over surgery for abortion in 11 months since the government decreed that it be made available on an experimental basis.

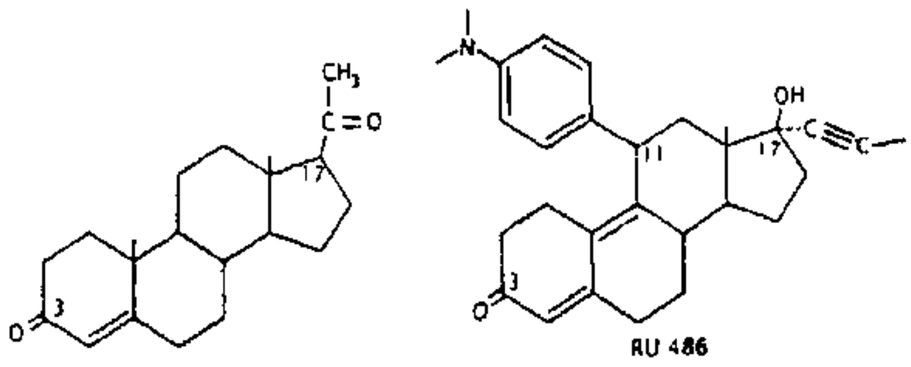
So far, France is the only country in which RU 486 is widely available, due to the reluctance of the manufacturer to permit sale of the drug anywhere else. The sluggishness with which RU 486 is being brought to the market around the world is also a source of immense frustration to its chief developer, Etienne-Emile Baulieu, one of France's leading scientists. Baulieu developed RU 486 in the late seventies while he was consultant to the French pharmaceutical company Roussel-Uclaf, a subsidiary of the giant German company Hoechst AG. 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. In France the abortion debate has not been without passion. Antiabortionists and Catholic hospitals served notice that they would stop buying any product made by Hoechst or its international subsidiaries if the company continued to market RU 486. On the other hand, doctors at the World Congress of Obstetrics and Gynecology meeting two years ago also threatened to boycott Hoechst products if the company did not make the drug available. Many countries have completed the tests necessary for licensing RU 486, but Roussel's parent Hoechst has been unwilling to market the drug outside France.

The treatment consists of three 200-mg 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 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.

One cannot ignore the potential for misuse. This will not be limited just to pills obtained on the black market. If the drug does become legally available by prescription from pharmacies it is probably inevitable that it will be improperly used. Opponents of RU 486 worry that the drug will be used indiscriminately in developing countries. Some say that in their rush to terminate pregnancy, supporters of RU 486 are ignoring the health of the mother. But a supporter says, 'Any medical approach to termination of early pregnancy, like an approach involving one of these antiprogestins, will always require backup from surgical facilities.'

RU 486 future and potential

Potential applications of RU 486 are in the treatment of patients with Cushing's syndrome, a condition caused by excess production of cortisone; in basic research



PROGESTERONE (PROGESTERONE ANTAGONIST)

on how the glucocorticoid receptor works; in eyedrops in treatment of glaucoma; possibly in the local treatment of skin wounds; and as a potential birth-control method. Baulieu, RU 486's developer, sees three different ways in which the drug could be used as a birth-control method. First is as 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. A second approach is to use very small amounts of RU 486 during the second, luteal phase of the cycle. The final and perhaps most promising potential use of RU 486 is as a contraceptive in the conventional sense.

WHO says Roussel has promised to deliver the drug to any WHO member country that requests it for the purpose of further study. The People's 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. In India, an ICMR-funded study has been conducted at the Central Drug Research Institute in Lucknow on the embryotoxicity of RU 486 in rabbits (see *Current Science*, 1990, **59**, 56).

Joseph Palca says in *Science*: '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.'

Protein disulphides: More than just bonds

Utpal Tatu

The compactly folded three-dimensional structure of globular proteins is stabilized by a complex interplay of different intramolecular interactions. Unique among these are disulphide bonds, which are the only commonly observed covalent cross-links. A major attribute of disulphide bonds appears to be their ability to impart conformational stability to proteins [1]. At first sight these cross-links would seem to stabilize proteins in a mechanical fashion by imposing physical constraints to chain unfolding. However, it is now widely accepted that disulphide bonds stabilize the conformation of proteins by their effect on the unfolded state and not on the folded state; by decreasing the degrees of freedom available to the unfolded state, disulphides shift the unfolding equilibrium towards the native state of the protein. Thus their contribution is subtle, influencing the entropy of the unfolded chain. X-ray crystallography and NMR studies indicate that in some globular proteins disulphide bridges may allow a large amount of internal motion, without disturbing the correct folded state of the protein. According to Williams [2]: 'Within a framework, disulphide bonds give an elastic quality to the protein, which allows it to deform somewhat with change in condition but ensures that it returns to its original state on removal of the stress. The protein behaves like a small piece of rubber.' Such molecular fluctuations are known to be linked to biological functions in many proteins.

Disulphide bonds are not merely a kind of structural glue but also influence function. In some cases disulphide bonds participate directly in catalytic mechanisms involving redox reactions, e.g. the small disulphide loops in thioredoxin and glutathione reductase located at the active site. In other cases they play an indirect role, e.g. the disulphide bridge located adjacent to the active site of serine proteases is essential for maintaining the proper orientation of catalytically important amino-acid side-chains. A recent finding [3] points to new ways by which nature harnesses disulphide bonds for regulatory purposes. A search of the Protein Identification Resource (PIR) data base for sequences homologous to the active site of thioredoxin (–Trp–Cys–Gly–Pro–Cys–Lys–) identified sequences from the β-subunits of the gonadotropic hormones luteinizing hormone (–His–Cys–Gly–Pro–Cys–Arg–) and follicle-stimulating hormone (–His–Cys–Gly–Lys–Cys–Asp–). Encouraged by the sequence homology and also a close similarity in the hydropathy profiles and predicted secondary structure in this region, the authors [3] examined these hormones for 'thioredoxin-like' functional activity also. Indeed, LH and FSH exhibited thioredoxin-like activity, catalysing disulphide isomerization in other proteins. The authors invoke a role for disulphide isomerization or reshuffling in the mechanism of signal transduction resulting from hormone–receptor interaction. The binding of the hormone to the receptor might then induce disulphide isomerization in the receptor, resulting in structural alteration required for signal transduction.

The understanding of protein folding

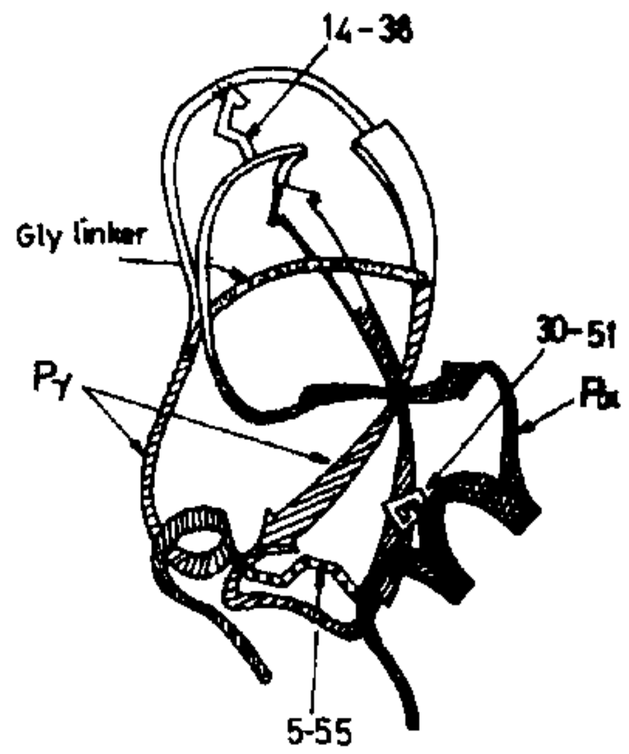


Figure 1. Ribbon diagram of native BPTI (from ref. 6). The hatched, crossed and dotted regions together form the $P_{\alpha\text{-}\gamma}$ subdomain linked by the 5–55 disulphide bond (closed circles). The dotted region indicates the glycine linker which is used to covalently join the N-terminal segment (residues 1–9) to the central β-sheet (residues 20–33). A peptide model lacking the central β-sheet and the glycine linker sequences fails to adopt a 'native-like' conformation.