Journal of Steroid Biochemistry, 1975, Vol. 6, p. 883. Pergamon Press. Printed in Great Britain.

CONTRACEPTION BY INTRAUTERINE RELEASE OF STEROIDS

ALEJANDRO ZAFFARONI

ALZA Corporation, 950 Page Mill Road, Palo Alto, California 94304, U.S.A.

The most important breakthrough in fertility control came about 20 years ago, with the idea that progesterone, one of the female steroid hormones, could be used to prevent pregnancy. This led to the development of the highly effective combination steroid contraceptives. Hormonal contraception developed along the well-established practice in pharmaceutical development of using the oral route, the tablet or pill as the method of delivery, and the dosage schedule of one a day. Using the oral pill as the method of delivery requires the administration of two highly potent synthetic steroids, since the natural hormones are rapidly metabolized and lack effectiveness when given orally. The steroids are absorbed into the bloodstream and distribute themselves throughout the entire body. Incidentally they reach and act on the target organs. In their multiple tissue interactions undesirable side effects occur. There is an inherent and inevitable risk of toxicity associated with this approach. In addition, the schedule of administration requiring the intake of one pill a day carries with it a significant incidence of missed dosages and is responsible for a decrease in use-effectiveness. A recent report in the incidence of contraceptive failures, derived from reproductive histories collected in the 1970 National Fertility Study shows a failure rate of 4–7% for oral contraceptives, depending on the populations studied. This is a direct expression of the real rate of use-effectiveness of the combination oral contraceptives in the hands of a large population and differs markedly from the failure rate of below 1% obtained with women populations in clinical controlled studies.

These problems show the need for new technical approaches to fertility control.

In 1968, in the research laboratories of ALZA Corporation, we began to develop a systems engineering approach to the solution of problems in therapeutics. The underlying philosophy was to achieve effective therapeutic response with what we call "minimal intervention". This means: (a) selection of the most appropriate drug; (b) releasing it at the lowest possible concentration; (c) minimizing the total amount of drug administered to the body; and (d) minimizing patient intervention by building extended duration of delivery in the dosage form. This work culminated with the development of a new generation of pharmaceutical products, which we have named Therapeutic Systems, capable of delivering precision dosages throughout extended time periods. A logical application for the Therapeutic Systems concept was in the field of fertility control, bringing the highly effective pharmacological approach of hormonal contraception right to the target organ, the uterus. Five years ago we commenced development of such a system that we named Progestasert®. It is best described as hormonal fertility control, on target. The system is a small T-shaped bicompatible platform, soft and flexible for uterine placement, carrying a precisely engineered drug delivery capsule. The female hormone progesterone, selected as the most appropriate agent, is contained in a membrane reservoir within the capsule and released continuously at the extremely small rate of 65 μg a day for a period of 1 yr.

To achieve this breakthrough the technology of polymer membranes had to be brought to medicine. The key component of the delivery system is the polymer membrane control element, built by Alza engineers to rigorous specifications to achieve the precision and constancy of drug delivery throughout the intended life of the unit.

Extensive clinical studies with the Progestasert® System in 20 countries with 4,200 women for 36,000 women months of experience have given a failure rate of 1% and a continuation rate of 85% after 1 yr of use. This shows a high order of effectiveness for the Progestasert® System. Hormonal contraception at the uterine level offers a number of advantages over the combination oral contraceptives:

(1) Eliminates the use of the potent synthetic steroids.
(2) Eliminates the need of estrogen.
(3) Avoids hormonal systemic effects since it utilizes a micro amount of the natural hormone progesterone which is rapidly and locally metabolized.
(4) The 1 yr duration of contraceptive coverage would permit significant increase in use-effectiveness.

The total dose of progesterone released by the Progestasert® to achieve 1 yr of fertility control is less than the amount normally produced by the ovaries in a single day during the high point of the menstrual cycle. It constitutes the first once-a-year hormonal fertility control agent and the first hormonal system which is target specific.