SPECIAL REQUIREMENTS FOR HORMONE RELEASING INTRAUTERINE DEVICES

By

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ABSTRACT

In order to understand the special requirements for the assessment of human toxicity for hormone releasing intrauterine devices it is necessary first to describe the constitution of one such system. The uterine progesterone system developed in our laboratories is the hormonal intrauterine system which has been most extensively tested clinically. It releases 50 µg per day of progesterone in continuous form. It has been designed to have a one-year period of functional life and it constitutes the first once a year hormonal fertility control agent and the first hormonal system which is target specific.

A number of unique features in the design and construction of this new and intrinsically safe hormonal system are described.

The assessment of human toxicity for each of the hormonal contraceptive agents that have been developed and brought to human use is a continuing process, since even after 12 years from their introduction to medical practice new toxic effects continue to be recorded as the number of women-years of use have increased and statistical and epidemiological evaluations have been employed.

My presentation will be directed not to the description of toxicity procedures but rather to the guiding principles followed in the design and construction of a new and intrinsically safer hormonal fertility control system.
Development of this new system which we have named the "Uterine Progesterone System" (UPS) commenced in 1969. It has the shape of a T and was designed to be placed and to function in the uterine cavity. The UPS releases 50 micrograms per day of the natural hormone progesterone in a continuous uninterrupted stream throughout its one-year operational life. The UPS constitutes the first once-a-year hormonal fertility control agent, and the first hormonal system which is target specific. Among all of the hormonal fertility control agents that have undergone extensive clinical testing, or are in current medical use, the UPS is the one that utilizes a single hormone and achieves its fertility control at the lowest level of release of hormonal activity. The design and development of the UPS was a natural goal within the basic directives of ALZA Corporation. These directives were initiated in 1968 with the sole aim to improve therapeutics through the strategy of systems engineering. Significant decreases in toxicity and improvements in the effectiveness of drugs were expected by designing new dosage forms, named by us Therapeutic Systems, capable of precision dosing over the entire length of the desired treatment. Our analysis of the current dosage forms and schedules pointed out a number of defects in current therapy which are likely to produce toxic effects (Zaffaroni 1971).

I) Initial "Pulse" and Sustained Drug Overdose

The great majority of oral and injectable dosage forms liberate their drug content very rapidly after administration, resulting in an initial burst or "pulse" due to the rapid buildup of drug concentration in the systemic circulation. In order to achieve increased patient compliance to the drug regimen it is desirable to minimize the number of patient-drug interactions but this requires a large increment in the amount of drug per unit dosage since for most drugs the processes of inactivation and excretion follow first order kinetics. The larger the amount of drug per unit dosage the larger the initial burst in drug concentration. Two possible risks of immediate or deferred toxicity can be perceived as due to this undesirable pattern of drug administration. The first, associated with the initial burst, is due to the transient increase in the drug concentration in the body and augmenting the chance of reaching acutely toxic drug levels. The other relates to the long-term effect produced by the sustained drug overdose. In addition, it is important to realize that when following this approach the therapist is surreptitiously borrowing body space as a reservoir to hold the drug overdose.

II) Patient Failure to Comply with Drug Regimen

Most drug treatments need multiple dosaging at frequencies of drug administration every 6, 12, 18 or 24 hours, which happens to be the incredibly
narrow spectrum of patterns of drug presentation under which our entire pharmacopoeia has been developed. This recurrent high frequency dosaging is a major cause of patient failure to fully comply with dosage schedules. Such failures reflect themselves not only in lack of treatment effectiveness but also in toxic effects in such occasions when patients double or triple their dosage to compensate for their prior omissions.

III) **Lack of Specificity in Drug Delivery to Target Organs**

Most drug therapy in current use is achieved through the systemic route. The most widely used form is that involving oral administration. Since Ehrlich’s goal of constructing drug molecules as “magic bullets” with unique specificity to impact solely on a target organ has not been achieved, it is obvious that multiple drug-tissue interactions take place in the process of drug absorption and distribution, as the drug front indiscriminately advances through the body. Uncertainties as to the effectiveness of the treatment are created by the fluctuations in drug concentration over the treatment period at the target site. These problems are due to: a) the intrinsic lack of controls of the dosage form; b) the rate and concentration changes that occur at multiple membrane crossing points and c) the enzyme-drug interactions that take place during the invasive sojourn of the drug molecule in the body. The compensating mechanism used by the therapist is to increase the amount of drug in the unit dosage, and thus to incur in overdosing.

**Therapeutic Systems**

These major limitations of existing dosage forms brought us to develop the concept of Therapeutic Systems that would permit precision dosaging of drugs with exact control of drug delivery rate and with extended operational delivery time for either target oriented or systemic treatment. It was recognized at the outset that this approach required something beyond the drug itself – since the precise drug concentration behaviour that was desired was unachievable by operating solely through the chemical structure of the drug. It required the construction of a multicomponent physical device or instrument, the Therapeutic System, in which the drug was just one component. The conception and development of specific Therapeutic Systems requires the selection and assembly of the following components:

1) **The Drug.** For any one system the drug component becomes the active centre responsible for ultimate pharmacological action. In our laboratories, we have purposely ruled out any activity directed to the synthesis of new drug entities to insure the unique degree of freedom of being able to select, in each instance, the most appropriate drug from the entire pharmacopoeia.
2) *The Drug Program.* The uncovering of an optimal drug program calls for animal and human pharmacological studies leading to the minimal amount and lowest concentration of drug able to achieve the desired therapeutic benefits with the minimum incidence of toxic effects.

3) *The Drug Delivery Module.* The drug delivery system is bioengineered to contain and protect the drug in a reservoir from which the drug is allowed to escape at a rate precisely determined by a control mechanism. This sensitive and precise component is built to insure the drug delivery rate called for by the therapeutic program and to maintain its functionality *in vivo* over the operational time designed for the unit.

4) *The Platform.* The drug delivery module is firmly embodied into a deployment platform whose mission is to insure the correct positioning and safe coupling of the system to the selected organ or tissue site. It must insure effective transfer of the drug stream from the delivery module to the designated target cells. Materials selection, shape, flex modules, and other variables included in platform construction must be such to insure optimal interface with the biological site.

The goal that was set for the design of ALZA’s UPS was to have a higher order of intrinsic safety than the oral combination hormonal agents, maintaining a similar high order of effectiveness while achieving a higher use continuation rate.

**Uterine Progesterone System**

The goals pursued in the design of ALZA’s UPS were:

a) To achieve a higher order of intrinsic safety while maintaining the high level of effectiveness of the oral combination hormonal agents.

b) To reach for a higher use continuation rate than either the oral contraceptives or the IUDs.

To accomplish these goals, it was clearly the need to eliminate in the design of the new hormonal fertility control system the following elements:

1 – The initial “pulse” and sustained drug overdose.
2 – The distribution of the drug through the whole body.
3 – The oral systemic administration.
4 – The once-a-day dosage schedule.
5 – The use of two hormonal components, leaving out the potent synthetic oestrogen.
6 – The long-acting synthetic progestogen in favour of the rapidly metabolized progesterone.
The approach selected in the UPS is best described as \textit{hormonal fertility control on target}. The uterus was selected as the body site for the deployment of the system in view of the significant role it plays in reproduction and because it is readily accessible for the placement and retrieval of the unit. In fact, the uterine cavity is a pivotal point for drug interventions leading to fertility control, since it is the common ground for the most important cells which are directly involved in the process of fertilization. Our UPS thus inaugurated a new avenue in the development of hormonal fertility control agents, that of \textit{uterine hormonal contraception}. The active hormonal agent for our system was most carefully selected. The criteria were to have a single agent and to contain it within the uterine cavity to insure against systemic effects. Progesterone was selected as the candidate of choice for its extremely short metabolic half-life and because it is the natural ovarian hormone. Progesterone was expected to interfere with fertility processes involving one or more of the key reproductive cells such as the endometrial cells, the egg, and the sperm.

One of the most attractive features of our approach can now be readily seen, the fact that the target for our system is in fact a "moving target", composed of transient cell elements with well-defined cycles of renewal of reappearance.

The effect exerted by the UPS can be interpreted as a cyclic biological hormonal intervention. Although progesterone is continuously released into the uterine cavity, it impacts only on cell events which are themselves cyclic. No permanent organ effect is obtained and no permanent grip on any one cell function is exercised over extended time periods, such as with the protracted inhibition of the ovarian function responsible for ovulation brought about by the oral combination contraceptives. The use of the natural hormone progesterone permits the desired effect at an extremely low concentration in relation to its normal concentration in the female systemic circulation.

Progesterone is the progestational agent in medical practice with the lowest activity per unit weight. To achieve progestational response in the human, an oral dose of the order of 500 milligrams per day is needed. On the other hand, 0.1 to 1 milligram per day is the active dose range for some of the most common synthetic progestogens used in the oral contraceptives. The progesterone activity needed for one day of oral treatment would supply 20 to 25 years of fertility control when released by the UPS. This is due to the extremely rapid rate of inactivation of the natural hormone in the human body by numerous tissues including the endometrial cells. The selection of progesterone as the active agent becomes of paramount importance in providing a unique degree of intrinsic safety to the UPS. Whatever minute fraction of the already insignificant daily dose might escape into the systemic circulation, would go undetected in the body. The fact that the UPS has essentially no effect on the occurrence and duration of the menstrual cycle clearly indicates that its biological effect is not even felt in the deep layers of the endometrium, which
remains under the control of the cycling ovarian hormones. The inherent toxicity risk for a hormonal uterine system releasing a progestogen other than progesterone would necessarily be higher, since all the synthetic progestogens have been conceived and synthetized for the sole purpose of having increased and sustained activity. They have a longer half-life than progesterone and very likely they would be capable of penetrating many tissue interfaces, be immune to the metabolic enzymes responsible for progesterone inactivation thereby allowing their appearance intact in the systemic circulation.

The platform configuration selected was that shaped as a T, following the well-documented work of Tatum (1972). It has excellent retention with the lowest incidence of expulsion and removal of any of the device configurations for uterine placement that had received extensive testing. Such high retention is obtained with a minimal level of pain and bleeding, affording a high order of patient continuation. The intrinsic low order of effect of the T configuration as an IUD made it a logical choice for the platform of our system. Polymer materials were selected for the construction of the platform and delivery module on the basis of inertness toward biological tissue and safety for human use. They also possess the ability to maintain their structural integrity throughout the operational life of the system. Particularly important was to establish definite proof of in vivo functionality of the drug delivery system and the capability of sustaining the established release rates of progesterone throughout the 12 months of active life in residence in the uterine cavity.

The duration of operational life of the system, selecting a period of one year, relates to the maximum space available within the dimensions of the platform and the amount of progesterone needed to achieve fertility control. The selection of one-year duration was based also on what should be best medical practice in requiring a woman user to have a complete gynaecological checkup every 12 months. The oral contraceptives have not achieved a significant impact in fertility control of populations in developing countries because of the lack of motivation – patient compliance – in following the once-a-day dosage schedule. The year duration of the UPS, on the other hand, makes possible that this contraceptive system might be established in such geographical areas, utilizing public health approaches successfully employed in the prophylaxis of infectious diseases through mass vaccinations.

The drug program of 50 micrograms of progesterone per day released as a continuous stream, was arrived at after extensive pharmacological studies in primates and humans. The biological indicator employed was the response of the endometrial cells, monitored through serial biopsies (Pharriss et al. 1974).

Final proof for the fertility control effectiveness of the system was established through a multiple human trial program (Pharriss et al. 1974).

Taking into consideration the safety engineering principles followed in the design and construction of the Uterine Progesterone System it is expected that
it will prove, in large scale human use, as a fertility control method with a level of safety and effectiveness higher than any of the agents in current medical practice.

REFERENCES


DISCUSSION

Diczfalusy: I would like to ask Dr. Zaffaroni what the efficacy of the progesterone system is, and secondly, whether he would like to comment on the problems of assessment of toxicity of devices of this sort.

Zaffaroni: The effectiveness of the uterine progesterone system is indicated in Table A.

Table A.

Uterine progesterone system; results of multiple clinical trial programme.
Life table analysis (Tietze) of first events with ALZA UPS rated 50 \( \mu \)g/day.

<table>
<thead>
<tr>
<th>Period covered</th>
<th>Nulliparous</th>
<th>Parous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First inserter</td>
<td>Second inserter</td>
</tr>
<tr>
<td></td>
<td>1 year</td>
<td>1 year</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Expulsion</td>
<td>16.9</td>
<td>5.5</td>
</tr>
<tr>
<td>Removals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain and bleeding</td>
<td>14.2</td>
<td>5.7</td>
</tr>
<tr>
<td>Other medical</td>
<td>2.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Planning pregnancy</td>
<td>1.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Other personal</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Total events</td>
<td>36.2</td>
<td>15.8</td>
</tr>
<tr>
<td>Continuation</td>
<td>63.8</td>
<td>84.2</td>
</tr>
<tr>
<td>Insertions</td>
<td>247</td>
<td>613</td>
</tr>
<tr>
<td>Woman months</td>
<td>2114</td>
<td>2900</td>
</tr>
</tbody>
</table>

* PROGESTASERT™
** Improved inserter
As to the second question, it is more important to keep in mind that the assessment of toxicity of agents releasing hormones in the uterine cavity will vary according to the nature of the agent released. For instance, for an agent with a very short half life in the uterine cavity, its possible toxicity would be established at the uterine level, since it is expected to be metabolized within that biological space. On the other hand, an agent with a long half life, in spite of being released in the uterine cavity, will appear in the systemic circulation. The assessment of toxicity for such an agent requires not only a review of biological effects at the uterine level, but a complete study of systemic effects. This immediately shows the advantage of using the natural hormone progesterone, because in addition to having a very short half life, and being practically metabolized in its totality at the uterine level, the insignificant amount that might escape into the systemic circulation is totally undetected in the context of the much higher circulating levels for the same hormone.

I would like to comment on the question of pattern of drug administration. The drug industry has made and explored a large number of different chemical structures for their fertility control activities. On the other hand, practically no work has been done with any of these agents in determining the optimal pattern of target presentation or release into the systemic circulation. For instance, for an oral combination contraceptive we have no knowledge as to what would be the effective dose when a) released continuously or b) "pulsed" once every 24 hours (current mode of administration), nor do we know what type and intensity of side effects will be present when the pattern of release is changed from pulsing to continuous delivery. These are but two of many possible patterns of drug presentation. I feel strongly that there is a wealth of potential therapeutic value awaiting to be discovered in current agents. Such values would open up on careful investigation of the relationship between biological activity and pattern of drug presentation.

Prasad: What we have heard from Dr. Zaffaroni is the most heartening breakthrough in drug delivery systems which everyone has been looking forward to. The presently available silastic capsules provide for erratic release which is not uniform over a period of time. Most basic research workers and clinicians would welcome the availability of a device which can release micro-quantities of compounds uniformly for long periods of time, particularly for local delivery of compounds at the site where the action is desired. We have heard that a number of agencies are working on a variety of biopolymers which can be used for such purposes. Dr. Zaffaroni, what is the nature of the biopolymers which are being developed, and are they available for general use by scientists?

Zaffaroni: The problem is that for each drug or hormone to be released and for each release rate there is the need to construct a particular polymer membrane. In our drug delivery systems it is not only the membrane that counts but also the core composition, where the drug is dispersed in an appropriate phase. In addition to the diffusional membrane systems, we are also working with delivery devices built around an erodable biopolymer matrix. The drug is molecularly dispersed in the polymer matrix and is released as the polymer undergoes surface erosion in an aqueous medium. We have been working for several years in a family of materials that we call "Chronomers", polymers that erode in a reproducible fashion in time. This system could accommodate a far larger range of agents and be more universal than the diffusional system.

Prasad: Dr. Zaffaroni has anticipated some of my questions. What is the relation between the nature of the biopolymer, the molecular configuration and the molecular
weight of the compound and the release rate? I think you partly answered this point. Next question: is it possible to have an adsorbable or biodegradable polymer which can be used for preparing drug-impregnated devices which will then free us from the necessity of replacing the device at periodic intervals? Third, we find that if one uses these capsules as implants subcutaneously, as we have experienced in the rhesus monkey, they become walled off by a capsule and the release rate is very seriously impaired. Is this walling off reaction and capsule formation dependent on the nature of the polymer and its response in a particular species, or is it a species characteristic?

Zaffaroni: As to the question of release rate and the molecular structures of the compound and the nature of the biopolymer, again we have to look at two possible systems, the diffusional system in which definitely there is a relationship between molecular weight and constitution and release rate for any given polymer membrane. The higher the molecular weight and the larger the polarity of the compound, the more slowly it will diffuse through any polymer membrane. On the other hand, in the erodible polymer matrix approach, release rates are far less dependent on the molecular structure of the drug. The erosion kinetics of the polymer matrix and drug release will vary somewhat depending on the size and polarity of the drug. There are problems with very low molecular weight and highly water soluble materials, since they tend to escape from the matrix into the aqueous biological medium.

In the design of implants, to avoid tissue encapsulation, we believe in following a system's engineering viewpoint which indicates that an erodible matrix, whose surface is continuously being renewed, offers a far better system to avoid encapsulation than a fixed diffusional-membrane type device.

Bryson: Was there an attempt to re-weigh the entire device to see if more than the weight of the charge and its polymer, or chronomer, had been dissipated? Unexpected decreases might indicate possible degradation of the platform vehicle, an increase might indicate a take-up of polymer-soluble local uterine constituents.

Zaffaroni: We have done studies of this type and found that the uptake of materials is minimal and the integrity of the drug delivery module and platform is maintained throughout the one year of use.

Lei: I think Dr. Zaffaroni’s idea of administering progesterone locally through an intrauterine device is a rational way of drug administration. Concerning the UPS, how do you manage to maintain the balance between consistency of the device and the drop-out rate and side effects? We all know that if a device is smaller and softer you have more expulsions; if it is larger and harder you have more side effects. As I understand it, the UPS is of a softer consistency. Wouldn’t that increase the rate of expulsion? I understand from your Table A that it worked fairly well. I just do not understand how the balance is maintained so as to minimize the side effects and also minimize the rate of expulsion.

Zaffaroni: When we began this work there were many questions among the members of our team as to how soft or how stiff should the unit be. I personally maintained the view that until proven wrong we ought to go in the direction of having the softest possible system to minimize tissue trauma. The harder the surface, the stiffer the platform, the higher the possibility of inflammation. A device like the UPS made of a polymer that is able to adapt itself to the changing modality of the uterine cavity will be far less injurious to the endometrial tissue. In testing our soft UPS we have
proven our assumption to be right in the sense that we have minimized the inflammatory reaction, while maintaining a very high order of retention. This has been an empirical exercise requiring the testing of various flex modes, sizes, and shapes to come to the selection of our current and best tolerated configuration. I think Dr. Mishell might be able to answer the question as to how effective the UPS is without the progesterone.

Mishell: We did a study of comparing the platform for the uterine progesterone system and the system containing progesterone. It was a double blind study so that we did not know which devices contained the active progesterone and which were just the platform. The devices containing progesterone had a significantly lower pregnancy rate than those containing no progesterone, but there was no significant difference in expulsion rates and removal rates for bleeding and pain.

Zaffaroni: I think this is an important piece of information, because those who want to follow the configurations in terms of platforms should take into consideration that platforms can be soft and flexible and still be maintained in the uterine cavity.

Lerner: How much progesterone does the device you employ contain at the time of insertion and how much is left at the end of 52 weeks in utero? You stated that the T device released 50 μg of steroid per day at a steady rate for one year. Will the amount of progesterone left in the T continue to be released at a 50 μg daily rate after the 52 weeks and for how long?

Zaffaroni: The amount of progesterone in the T is 36 mg; so theoretically there is enough to keep the system going for 18 months. However, the release rates begin to drop significantly after 13 months and for these reasons we consider the ALZA system to be effective for one year.

Galal: I would like to ask whether such a system could be a feasible approach in connection with vaginal spermicides; perhaps a system could be developed with no hormones and thus with less physiological interference.

Zaffaroni: Certainly the possibility exists for the development of such systems since the technology is available. Some decisions need to be made in terms of the duration of the system and the point of placement; should it be a vaginal insert, a cervical ring, or a patch attached to the vaginal interior? Should this last for a month or for a year? The question of duration brings up the problem of drug selection. For systems with durations of the order of a year or more there is the need to select extremely active agents in unit weight, since there would not be much reservoir space available to accommodate the drug.

Goldzieher: I am concerned that there has been no mention of bioavailability as an important aspect of pharmacological models. Certainly, there is clinical evidence already at hand that small differences in manufacturing have produced significant differences in pregnancy rates. This would be most important in designing pharmacological studies which might use a different formulation of the drug than would ultimately be used in clinical investigation.

Zaffaroni: There are two considerations here. One is bioavailability and the other is pharmacokinetics. To design a rational dosage schedule and pattern of administration of any contraceptive there is an absolute need to know the half-life of the agent when given through the selected route of administration. It is incredible that we do not
have fundamental information as to the half-life of practically any of the oral contraceptives that are in use. Bioavailability clearly is important and one of the advantages of our system is that the steroid comes out molecularly dispersed because it comes through the control releasing membrane which acts as a molecular sieve.

Shearman: I want to come back to the problem of toxicity screening for this particular contraceptive device, specifically to the assessment of potential teratogenicity. How do you screen for this with this local release system in animals? Furthermore, have you any data on the outcome of those pregnancies that occurred in humans, either on the product of conception, if it was aborted, or on the infant, if it was live born at term?

Zaffaroni: At the animal level studies are in progress to define this question of teratogenicity. They have been pursued by similar approaches as those described by Dr. McConnell. At the human level, in those situations where there has been a pregnancy, no malformation has been observed, but there are very few such pregnancies. There have been a number of cases where women have asked to have the system removed. The five cases that I know of became pregnant within the next menstrual cycle, so there was a rapid resumption of fertility. However, these women had not been on a very protracted period of fertility control, only for periods of 6 to probably 8 or 10 months.

Hertz: In view of the similarity of expulsion rate of the new device versus the one lacking progesterone, I am wondering whether another biological effect of progesterone at a higher dosage level might be capitalized on, namely its capacity to reduce the motility of the uterus. This, of course, would be at a dosage level far beyond what is now proposed for contraception, but enough may be gained by reducing the expulsion rate to compensate. The other question I wanted to raise was the question of crystal versus molecular state. Is there any evidence, as there is to some extent from the implant work with synthetic progestogens, that after the release into the body fluids in the local area there is any tendency to return to the crystal state? This, I think, is important both from the standpoint of tolerance and as a biological effect, in that if there were such a return, the bioavailability would be very much reduced. Secondly, in the early days when we did not have all the progestogens and we administered progesterone parenterally, it was found that the crystal size, the formation of the crystal, and the distribution of crystals in suspensions played a very critical role in the degree of irritation produced locally. Some of the earlier preparations with large crystals were highly irritative. Then, as they were reduced, the local tolerance became much improved. But under the skin, crystalline progesterone still remains, even under optimum conditions, a highly irritating substance. I was wondering what your thinking is about this in relation to the uterine situation.

Zaffaroni: Obviously, when you give progesterone systematically, you need large doses and the solubility of progesterone is limited, so you do have the problem of solid state. In our system we are releasing about 50 micrograms a day. This is a very small amount in comparison to the solubility of progesterone in biological fluids. Second, progesterone has a unique characteristic of having the capacity to distribute itself between lipoidal and water systems in a fashion that allows it to transverse biological membranes with greater ease than most progestogens. In fact, the microbiological synthesis of cortisone developed by Upjohn began with progesterone and still remains with progesterone, because progesterone is the steroid that passes more readily into the microorganism. It is possible to get progesterone to pass through the skin and through

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mucosal membranes quite readily. I believe that the progesterone released by the UPS is picked up rather rapidly by the membranes of the various cell elements in the uterine cavity. For any other steroid, however, the problem of crystallization in biological fluids will need to be investigated.

The first point you raised, concerning the possibility of using a high rate of progesterone release to try to control uterine motility, has been tested by Dr. Scommegna. In fact, we should give credit to Dr. Scommegna who has been the first to explore progesterone in the uterus as a way of controlling fertility. He has used a silastic capsule containing progesterone attached to a regular IUD releasing as much as 900 micrograms a day in a rapidly decaying fashion. I think he has not seen any appreciable effect of this progesterone on uterine motility.