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<th>2. SUBJECT CLASSIFICATION</th>
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5. TITLE AND SUBTITLE (240)

Study of side effects and mechanism of action of prostaglandins, report for 1977-1980

4. PERSONAL AUTHORS (100)

Csapo, A. I.

5. CORPORATE AUTHORS (101)

Washington Univ., St. Louis. School of Medicine

6. DOCUMENT DATE (110)

1980

7. NUMBER OF PAGES (120)

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10. SUPPLEMENTARY NOTES (500)

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13. PROJECT NUMBER (150)

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AID/pha-C-1193

15. CONTRACT TYPE (140)

16. TYPE OF DOCUMENT (160)
REPORT ON

STUDY OF SIDE EFFECTS AND MECHANISM OF ACTION OF PROSTAGLANDINS

AID/pha-C-1193

TO: AGENCY FOR INTERNATIONAL DEVELOPMENT

DECEMBER 20, 1980

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

DEPT. OF OBSTETRICS AND GYNECOLOGY

FROM: ARPAD CSAPU, MD, PhD (H.C.)

PROFESSOR, OBSTETRICS AND GYNECOLOGY

PRINCIPAL INVESTIGATOR
(1) REPORT SUMMARY

(1) Project Title and Contract Number:
STUDY OF SIDE EFFECTS AND MECHANISM OF ACTION OF PROSTAGLANDINS, AID/pha-C-1193

(2) Contract Period: 9/30/77 - 11/30/80

(3) Total AID Funding: $757,139.00

(4) Total Expenditures: $729,650.62*

(5) Narrative Summary of Accomplishments:

In 1977 a 59-pages long Final Progress Report was submitted to AID, describing our achievements between 1971 and 1977 in clarifying the side effects and mechanism of action of prostaglandins. This report resulted in AID approval of a new contract for the period of September 30, 1977 to November 30, 1980 (retaining the earlier title). This present report describes the achievements of these last 3 contract years.

Regarding the central theme of the contract (mechanism of action of PGs), the studies definitively established that in both animal models and patients, prostaglandins (PGs) do not terminate pregnancy by an OXYTOCIC action (as was generally believed) but by COMPROMISING the endocrine function of the CONCEPTUS and thus creating a REGULATORY IMBALANCE in the pregnant uterus.

From this BASIC finding originated experiments in animal models which further clarified mechanism of action; and clinical trials which achieved the therapeutic endpoint of the contract: the development of a simple, safe and acceptable method for the termination of early pregnancy in human patients. As a result we now have for MENSTRUAL INDUCTION two effective treatments: (1) the i.m. Sulproston and (2) the Vaginal Double Suppository of 15M PGF2α methods.

Very considerable progress has been made also in developing an animal, the GUINEA-PIG, into a therapeutically predictive model in PRECLINICAL trials. Several additional studies have been performed both in animals and patients which, while not specified in the contract, were highly informative regarding the basic controlling mechanism of the pregnant and non-pregnant uterus. Also, some of our clinical trials might be considered therapeutic breakthroughs, for example the use of anti-PGs for the treatment of primary dysmenorrhea.

*This figure represents expenditures one month before termination of the contract.
(2) SUBSTANTIVE RESEARCH REPORT

(A) PROJECT OBJECTIVES

(a) The Clarification of the Mechanism of Action On the Pregnant Uterus of the Natural Prostaglandins (PGs) and Some of Their Synthetic Analogues.

(b) The Development of a Simple, Safe, Effective and Acceptable PG-Method for Pregnancy Termination.

(c) The Identification of Agents Other Than PGs for Pregnancy Termination and The Development of an Animal into a Preclinical Model for Predicting the Therapeutic Efficacy and Acceptability of Compounds in Fertility Management.

(B) ACCOMPLISHMENTS

(a) Mechanism of Action.

By measuring simultaneously and sequentially the peripheral blood levels of 15M PGF2α or Sulproston, βHCG, Progesterone (P) and Estradiol 17β(E2) and by monitoring the tonic and cyclic intrauterine pressures (IUP) of the PG-induced pregnant patients, the clarification of the mechanism of action of PGs on the pregnant human uterus has been finalized. These studies are described in enclosed Reprints (1-4 in Appendix). They show that, regardless of gestational age and the chemical character of the PG, an effective "PG-Impact" provokes immediate uterine contracture (a "tonic" response resulting from anoxia) and decrease in βHCG, P and E2 levels, before inducing maximum cyclic IUP (oxytocic response), cervical dilatation and abortion. The published results are complemented and confirmed by the outcome of recent trials with SULPROSTON (a PGE2-analogue) and with a DOUBLE 15M PGF2α SUPPOSITORY (1 mg in a fast and 3 mg in a slow melting base, to provoke an "Impact" and a sustained action). To indicate how other investigators and Ob & Gyn leaders think about these findings and the guiding concept of this program (the "See-Saw" Theory), Schulman's address of the 1978 Annual Meeting of the American Association of Obstetricians and Gynecologists and the subsequent discussions (see Niswander and King) is enclosed(5). Also is enclosed the copy of page 535 from the recent "Obstetrics & Gynecology" Textbook of Danforth(6), showing that the "see-saw" theory is now adopted in teaching.

Thus, the Mechanism of PG-Action on the pregnant human uterus can be summarized, to guide future research in fertility management.

TABLE I

Another report illustrates that our concepts of the mechanism of PG-action and "PG-Impact" are considered by industry in the design of PG delivery systems (Upjohn 15M PGF2α double suppository) first tested by Lauersen and Wilson(7). Also enclosed are three relevant Reviews of our own, published during 1977-1978(8-10).

(b) The Development of a Simple, Safe, Effective and Acceptable PG-Method for Pregnancy Termination.

This objective of the Program has been realized. Having studied the
mechanism and therapeutic action of the natural PGs: PGF2α and PGF2 during several hundred clinical trials (see Progress Report 1977) and having found both highly effective when administered by the extraovular route, we studied the efficacy of PG-analogues in vaginal and i.m. delivery systems.

TABLE II

The effect of 3 mg 15M PGF2α suppository (single dose!) has been examined in 20 1st trimester patients (2). In 10 cases this treatment was supplemented with 250 μg 15M PGF2α i.m. every 2 hours and in 10 additional 1st trimester gravidas 1 mg 15M PGF2α was administered extraovularly (unpublished), to directly compare the efficacies of extraovular and vaginal administrations. This study showed that extraovular delivery of PGs is over 3 times more effective than vaginal, but that even vaginal delivery is successful in about 80% of the cases.

TABLE III

In 40 cases of Menstrual Induction the single dose 3 mg 15M PGF2α suppository has been examined (3). In 20 additional patients Menstrual Induction with the "double suppository" (1 + 3 mg 15M PGF2α) has been achieved with 90% success. However, in all instances the frequency of side effects of 15M PGF2α has been a serious drawback. Apparently, the vaginal delivery system is a relatively ineffective method of PG-treatment when intact pregnancy is to be interrupted. The analogue 15M PGF2α is only efficacious vaginally at high dose levels at which its side effects are not controllable at present. However, in cases of fetal death in utero and mere cervical dilatation (in preparation for suction), when the dose requirement is low, 15M PGF2α in a vaginal delivery system might be both effective and acceptable.

It is of very considerable interest, therefore, that we developed SULPROSTON (PGE2-analogue) into an i.m. method for Menstrual Induction in early pregnant women. While we were waiting for clearance by FDA of this (Pfizer) compound, our Finnish collaborator Dr. Pulkkinen conducted 54 pilot studies (11) with Sulproston, promoting the design of our trials in the US.

Our first study with this compound in 90 early pregnant volunteers has been highly successful (12). At 17.2 ± 0.5 days after the missed menstrual period the 90 gravidas received two i.m. injections of 500 μg Sulproston 4 hours apart. Only 17 patients required less or more injections. Clinical success in pregnancy termination was 96% and we recorded only 26% vomiting, 10% diarrhea and 2% mild endometritis. Most importantly, interviews with 42 (of the 90) women revealed that 90% were satisfied with this Sulproston method and 89% preferred it to previously experienced surgical interruption (12).

TABLE IV

Presently we have completed 200 cases of Menstrual Induction with the i.m. Sulproston technique. After 17.3 ± 0.4 days of menstrual delay, these 200 women received a total average dose of 1.2 ± 0.04mg Sulproston (500 μg, 4 hours apart). Uterine bleeding occurred 4.2 ± 0.2 hours after and discharge of tissue 2.6 ± 0.2 days after the 1st Sulproston injection. Induced menstrual bleeding lasted 9.5 ± 0.4 days. The success rate was 94% (no curettage needed) and normal menstruation occurred spontaneously 35.9 ± 0.9 days after treatment. Vomiting
was recorded in 40% of the cases, diarrhea 7%, blood pressure change (more than 20 mm Hg) 2%, mild endometritis 2%, chills 1%, fever 0.5% and adnexitis 0.5%.

Apparently, the Sulproston regimen is a desired method (simple, safe, effective and acceptable) for Menstrual Induction, as well as for the termination of more advanced pregnancy. High efficacy can be expected in the therapeutic resolutions e.g. fetal death in utero and slow cervical dilatation (not surgical!) before suction. Every legally available avenue should be explored, therefore, for the further improvement as well as the broad therapeutic exploration of this method in developing countries. However, if clinical trials are conducted, the patients' hygienic conditions should be scrutinized between Sulproston treatment and the 1st spontaneous menstrual period (no intercourse!, general cleanliness, etc.).

Regarding the importance of SLOW (rather than rapid surgical) CERVICAL DILATATION, we now have our own evidence showing the correlation between surgical pregnancy termination and increased prematurity rates in subsequent pregnancies(13). At the start of our Program we obtained (from Hungary) massive statistical evidence, documenting that surgical termination markedly increases prematurity rates (Csapo, A.I.: IN: The Prospects of PGs in Postconceptional Therapy, Prostaglandins, 3: 245, 1973). Our own follow-up of 536 cases of Menstrual Inductions with extra-ovular PGF2α revealed that in subsequent pregnancies 8% of the patients had premature delivery if they were only exposed to PG for Menstrual Induction, whereas prematurity was 16% if before PG termination previous pregnancies were interrupted surgically(13).

The broad applicability of this correlation has been debated recently, on the ground that it only exists in Eastern European countries, where sharp curettage rather than suction is used for the evacuation of the uterus, as it is in the U.S. This contention based on the statistical manipulation of very limited data has been definitively contradicted by the recent Harvard Study (ASCHENGRAU et al, JAMA, 243, 2495, 1980) in which SUCTION, rather than sharp curettage was used for pregnancy termination. Thus, when the technique of pregnancy termination is decided upon in the future, the correlation between surgical pregnancy termination and miscarriage or prematurity has to be seriously considered.

(c) The Identification of Agents Other Than PGs for Pregnancy Termination and the Development of an Animal Into a Preclinical Model for Predicting the Therapeutic Efficacy and Acceptability of Compounds in Fertility Management.

A step in these studies has been the confirmation of Csapo's earlier work that the link between excitation and contraction, i.e., the messenger in "excitation-contraction coupling" is the ACTIVATOR-Ca (Csapo, A.I.: Studies on Excitation-Contraction Coupling, Ann. N.Y. Acad. Sci. 81, 453, 1959). This has been achieved by studying the effect on Ca-transport of inhibitors of myometrial excitability(14). A critical step in these experiments was the demonstration that PGF2α is an intrinsic myometrial stimulant because it increases the influx of the activator-Ca(15). Apparently, only the activator-Ca can directly induce uterine contractions and myometrial "stimulants" are actually regulators of Ca-influx.
An important step in clarifying the RELATIONSHIP between the actions of PROSTAGLANDINS (PGs) and PROGESTERONE (P) and the consequences of the changing balance between these two regulators, resulted from those controlled experiments in which the PG and P levels have been altered and the degree of change measured by RIA's(16). These studies provided strong support for the predictive value of the "see-saw" theory.

Two articles address the basic question: THE BIOLOGICAL MEANING OF PG AND P LEVELS. The study of P-levels shows that near term the activation of the pregnant uterus is preventable by P (despite the sharp fall in endogenous P) if treatment begins ~24 hours before parturition. However, if treatment is delayed till 6 hours before parturition, labor is normal despite the restoration of P-levels by exogenous P. Apparently, not only the P-levels (and other hormones) are changing in preparation for labor but also the myometrium itself and as a result of this change the uterus can no longer 'decode' the P-signal. Thus, low P-levels suggest that pregnancy will be interrupted, but high P-levels do not necessarily guarantee pregnancy maintenance(17). The other study in which P and PG-levels and uterine function were simultaneously measured revealed that at term the release of endogenous PGF or intrauterine PG-treatment does not guarantee parturition, unless P decreases to a critical value(18). The message of these 2 crucial studies (supporting the 'see-saw' theory) was internationally received with such interest that (for the first time in our experience) we had to order a 2nd set of 500 reprints of these articles. Of further relevance is the demonstration that P can only suppress myometrial function if previously the uterus is exposed to estradiol (E2) for at least 3 days. Most probably E2 action is required for the manufacturing of P-receptors(19).

As predicted, ANTI-PROGESTERONE antiserum (A-P) reduced free P-levels to a critical value and interrupted pregnancy. Progesterone-treatment prevented this action of A-P as long as the P-levels were restored within 6 hours after A-P treatment(20). The studies with anti-estradiol (A-E2) revealed that, as expected, the reduction of free E2 by A-E2 delayed and prolonged labor(21). Apparently (in the rat at least) E2 is essential for the activation of the term pregnant uterus (Csapo, A.I.: "The Four Direct Regulatory Factors of Myometrial Function" IN: Ciba Foundation Study Group, No. 34, on "Progesterone: Its Regulatory Effect on the Myometrium," G.E.W. Wolstenholme & J. Knight, eds., J. & A. Churchill, London, p.13, 1969).

The A-P and pregnancy terminating actions of the androstano (2,3-d) isoxasoles: CYANOKE TONE(22) and ISOXAZOL(23-25) have been examined throughout pregnancy in the rat. Isoxazol not only provoked abortion at midterm(24) but prevented implantation(23) and induced preterm labor(25). These results were most promising and challenging regarding the development of a new therapeutic agent for fertility control. However, while isoxazol has been effective in the rabbit at greatly increased dose levels(26), it has been ineffective in the guinea-pig. This has been a major disappointment. However, since we have seen earlier the predictive value of the guinea-pig in preclinical trials with PGs, this disappointment was turned into a program, an effort to develop the guinea-pig into a predictive preclinical model.
To develop the GUINEA-PIG into a PREDICTIVE PRECLINICAL MODEL, we had to clarify the gestational changes in PG and P-levels not only in peripheral plasma but also in uterine vein plasma and uterine and intrauterine tissues. This had been a massive effort but hopefully of great benefits. The studies showed that from a climax at around midterm, circulating P-levels decrease as term advances and that PG-release precedes the onset of labor. However, while the circulating P-levels are high throughout pregnancy including term, the uterine tissue levels do not usually exceed 10% of the plasma levels. The studies also showed that the main source of PGF is not the uterus but the placenta.

Using the 43 days pregnant guinea-pig we identified the PGE₁-ANALOGUE: CP 48,630 (Pfizer) as an ORALLY ACTIVE PG. We found that plasma and tissue P-levels are reduced and endogenous PGF is released before the IUP is elevated and the animal aborts (about 6-12 hours after CP 48,630-treatment) (28). These results are currently followed up with the support of PARPR.

On the request of our Program Officer we examined the possible abortifacient effect of the LHRH-AGONIST: [D-Trp⁶,Pro⁹-NEt] - LRF (Salk I). Regardless of the negative outcome, this study has been justified since it serves as a warning that major efforts in further studies with this compound in monkeys and man may not be productive. On the other hand, if the guinea-pig studies would have been positive, this knowledge could have been promotive in designing extensive studies in additional species.

TABLE V

Table V illustrates that between days 1 and 16 of pregnancy this LHRH-agonist has no predictable action on pregnancy if repeatedly administered during 5-8 days in doses totalling 500-2650 μg, in saline or oil (Table V). Apparently, this compound does not terminate pregnancy in the guinea-pig model, not even at high (300 μg) and repeated daily doses, indicating that during tubal migration and after implantation it has little therapeutic promise. When the control and experimental animals are autopsied at day 21, to determine whether or not they are normal pregnant, the circulating P-levels of the control (71 ± 9) and experimental (74 ± 13) guinea-pigs is nearly identical.

Our interest in DEVELOPING THE GUINEA-PIG INTO A PREDICTIVE PRECLINICAL MODEL began when we realized that the therapeutically most successful PG: Sulproston has been identified as an abortifacient by the guinea-pig (for references see (28)). We also learned, at about the same time, (from the researchers of Imperial Chemical Industry) that the PGF₂α-analogue: ICI-81008 which has been highly effective in the rat, but only slightly effective in the human, was also relatively ineffective in the guinea-pig. This knowledge two years earlier could have saved us one year of clinical work. Our first study of the predictive value of the guinea-pig involved experiments with the P-synthesis inhibitor: isoaxazol. This compound, which was highly effective in the rat and effective in the rabbit as a luteolytic agent, was ineffective in the guinea-pig. We learned later (from Dr. A. Beyler of Sterling and Winthrop) that isoaxazol does not provoke luteolysis in the human. All these experiences indicate that the guinea-pig is predictive in preclinical studies. It would be of interest to know whether or not the Salk LHRH-agonist, which has been ineffective in the guinea-pig, will be effective in the human and also whether or not the PGE₁-analogue: CP 48,630, which has been effective in the guinea-pig, will remain effective in the human.
(C) STUDIES NOT SPECIFIED AS PROGRAM OBJECTIVES

Since the clarification of the mechanism of PG-action has been the major objective of the Program, every experiment (animal or clinical) we conducted is relevant which adds to our knowledge of the control of myometrial function. It was in this vein that we studied the controlling action of PG-SYNTHESIS INHIBITORS. We learned that these compounds markedly reduce the levels of both PGF and PGE in the uterus and completely suspend excitability and tension development in vitro (in a dose dependent manner). They also reduce uterine PGF and PGE levels in situ and in so doing delay the onset of labor (29, 30).

From these and other basic experiments of similar kind developed a RATIONAL THERAPY for DYSMENORRHEA. We have shown that these anti-PGs suppress the high "tonic" pressure of the dysmenorrheic uterus and the pain and discomfort of the patients (31, 32) by reducing the PG-excess of the menstrual blood (33, 34). Our rationale for and success with PG-synthesis inhibitors in the treatment of dysmenorrhea has been reviewed (35, 36). The value of these studies is evaluated in a recent editorial in Science, which treats the subject as a break-through in Reproductive Medicine. (Jean I. Marx: Dysmenorrhea: Basic Research Leads to a Rational Therapy IN: Science 205: p. 175, July 1979)

Our studies and reports on PREMATURE LABOR (37), MONITORED INDUCED LABOR (38), DYSFUNCTIONAL LABOR (39), CONTROL OF HUMAN PARTURITION (40), and FORCE OF LABOR (41) are all related to the basic mechanism in control of the pregnant human uterus and thus to the mechanism of PG-action. One of our most challenging concepts and findings is that the pregnant human uterus has a regulatory and functional asymmetry, due to a LOCAL ACTION OF PLACENTAL PROGESTERONE (42). After some 15 years latency this concept is now being considered by other investigators. When better understood, this concept can be expected to resolve some major and persistent puzzles in regulatory biology.

(D) DISSEMINATION AND UTILIZATION OF RESEARCH RESULTS

See Bibliography and Appendix.

(E) STATEMENT OF EXPENDITURES

A detailed statement will be submitted by Washington University in January, when all late bills are paid for.
BIBLIOGRAPHY


-10-
| MECHANISM OF ACTION OF PROSTAGLANDINS  
ON THE PREGNANT HUMAN UTERUS |
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<td>Maximal Cyclic IUP, Progress in Cervical Dilatation</td>
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<td>Discharge of Uterine Contents</td>
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### TABLE II

#### 1. TRIMESTER ABORTION

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<th>Number of Patients</th>
<th>Weeks of Pregnancy</th>
<th>Total Dose, mg</th>
<th>Onset Uterine Contraction, min.</th>
<th>Onset Bleeding, hrs.</th>
<th>Installation Abortion Time, hrs.</th>
<th>Vomiting</th>
<th>Diarrhea</th>
<th>Pregnant at Follow-Up</th>
<th>Success Rate</th>
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**Single 3 mg 15M PGF2α Suppository**

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<td>20</td>
<td>12.6</td>
<td>3000</td>
<td>153.7</td>
<td>6.5</td>
<td>14.2</td>
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<td>80</td>
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<td>±0.7</td>
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<td>±1.2</td>
<td>±1.7</td>
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</table>

Patients were 24.5±1.5 years of age, gravida 2.1±0.3, para 0.7±0.2. Six patients required curettage, all needed sedation.

**Single 3 mg 15M PGF2α Suppository + 250 μg i.m./2 hours**

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Patients were 21.9±1.7 years of age, gravida 2.1±0.5, para 0.5±0.3. All needed sedation.

**Single Extraovular Dose of 1 mg 15M PGF2α**

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<td>10</td>
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<td>1000</td>
<td>7.5</td>
<td>3.1</td>
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<tr>
<td>±0.2</td>
<td>±2.1</td>
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</table>

Patients were 22.8±1.4 years of age, gravida 1.7±0.3, para 0.3±0.2. Nine patients needed sedation. In Table II and in all other Tables, all values are Means ± S.E.
<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Menstrual Delay, Days</th>
<th>Total Dose, µg</th>
<th>Onset Uterine Contraction, min.</th>
<th>Unset Bleeding, hrs.</th>
<th>Discharge Tissue, Days</th>
<th>Duration Bleeding, Days</th>
<th>Vomiting</th>
<th>Diarrhea</th>
<th>Endometritis</th>
<th>Pregnant at Follow-Up</th>
<th>Success Rate</th>
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<tr>
<td>Single 3 mg 15M PGF2α Suppository</td>
<td>40</td>
<td>17.1</td>
<td>3000</td>
<td>150.8</td>
<td>6.4</td>
<td>3.4</td>
<td>11.4</td>
<td>All values %</td>
<td>±0.5</td>
<td>±14.8</td>
<td>±0.7</td>
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Patients were 27.2±1.1 years of age, gravida 2.8±0.3, para 1.1±0.2. Five cases required curettage, 23% needed sedation.

Double 1 + 3 mg 15M PGF2α Suppository

| 20 | 18.0 | 4000 | 75.0 | 3.8 | 2.2 | 9.9 | All values % | ±0.6 | ±12.6 | ±0.3 | ±0.6 | ±0.8 | 35 | 53 | 25 | 10 | 90 |

Patients were 27.4±1.2 years of age, gravida 2.7±0.3, para 1.2±0.2. Two cases required curettage, 55% needed sedation.
### TABLE IV

**MENSTRUAL INDUCTION**

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Menstrual Delay, Days</th>
<th>Total Dose, µg</th>
<th>Onset Uterine Constructions, min.</th>
<th>Onset Bleeding, hrs.</th>
<th>Discharge Tissue, Days</th>
<th>Duration Bleeding, Days</th>
<th>Vomiting</th>
<th>Diarrhea</th>
<th>Endometritis</th>
<th>Pregnant at Follow-Up</th>
<th>Success Rate</th>
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<td>200</td>
<td>17.3 ±0.4</td>
<td>1219.0 ±35.0</td>
<td>101.4 ±8.0</td>
<td>4.2 ±0.2</td>
<td>2.6 ±0.2</td>
<td>9.5 ±0.4</td>
<td>40 ±0.4</td>
<td>7 ±0.2</td>
<td>2 ±0.2</td>
<td>6 ±0.2</td>
<td>94 ±0.2</td>
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</table>

500 µg Sulproston Every 4 Hours Till Bleeding

Patients were 26.9±0.5 years of age, gravida 2.5±0.1, para 1.0±0.1. Twelve patients required curettage for residues, 51% needed sedation.
TABLE V
THE EFFECT OF [D-Trp⁶, Pro⁹-NEt] LRF IN PREGNANT GUINEA-PIGS

<table>
<thead>
<tr>
<th>Grouping Of Animals</th>
<th>Number Of Animals</th>
<th>Maternal Weight g</th>
<th>Litter Size</th>
<th>Treatment</th>
<th>Gest. Length Total µg</th>
<th>Gest. Day At Autopsy</th>
<th>Normal Pregnancy %</th>
<th>Fetal Weight g</th>
<th>Placental Weight g</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Controls</td>
<td>730 ±34 ±0.6</td>
<td>16 Vehicle</td>
<td>21</td>
<td>100 0.111 ±0.008 ±0.04</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Experim.</td>
<td>710 ±27 ±0.7</td>
<td>16 5 500</td>
<td>21</td>
<td>100 0.087 ±0.008 ±0.03</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Controls</td>
<td>730 ±34 ±0.6</td>
<td>10 Vehicle</td>
<td>21</td>
<td>100 0.112 ±0.008 ±0.04</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Experim.</td>
<td>724 ±23 ±0.5</td>
<td>10 5 750</td>
<td>21</td>
<td>92 0.158 ±0.020 ±0.06</td>
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</tr>
<tr>
<td>3</td>
<td>Controls</td>
<td>689 ±12 ±0.3</td>
<td>10 5 700</td>
<td>21</td>
<td>100 0.123 ±0.026 ±0.11</td>
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</tr>
<tr>
<td></td>
<td>Experim.</td>
<td>679 ±33 ±0.4</td>
<td>10 Vehicle</td>
<td>21</td>
<td>100 0.091 ±0.047 ±0.08</td>
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</tr>
<tr>
<td>4</td>
<td>Controls</td>
<td>800 ±27 ±0.2</td>
<td>10 7 2100</td>
<td>21</td>
<td>100 0.108 ±0.020 ±0.02</td>
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</tr>
<tr>
<td></td>
<td>Experim.</td>
<td>788 ±23 ±0.5</td>
<td>1 Vehicle</td>
<td>21</td>
<td>58 0.167 ±0.016 ±0.04</td>
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</tr>
<tr>
<td></td>
<td>Experim.</td>
<td>814 ±27 ±0.4</td>
<td>1 8 2650</td>
<td>21</td>
<td>67 0.164 ±0.024 ±0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Salk II [imB₂ 1-D-His⁶, Pro⁹-NEt]-LRF. All other experiments were conducted with Salk I [D-Trp⁶, Pro⁹-NEt] LRF.