

# CLINICAL EXPERIMENTAL CONSIDERATIONS ON THE PRESENCE OF SET UTERINE PACEMAKERS

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**Summary:** The Authors studied the physiology of human uterine muscle contraction. Clinical experimental results obtained from elementary electrophysiological, electrohysterographic and pharmacological studies using PGs suggested that uterine muscle contraction does not originate in "pacemaker" areas. These data also showed that the electric phenomenon is not propagated along preferential "rails".

## INTRODUCTION

The physiology of uterine contraction is a key point in understanding labour. Even if various Authors have studied the topic from different angles and using different methods, the results concerning uterine contraction in labour are scant and discordant. In the past most "in situ" studies carried out in women concerned the mechanic aspect of myometrial contraction. In fact, Caldeyro-Barcia and Alvarez introduced "microballs" into the myometrium at the superior, medial and inferior segments transcutaneously. This method surpassed the previous tocodynamometric techniques such as external tocometry (started in 1913 by Fabrè) and internal tocometry. The latter recorded intramyometrial pressure by means of manometric tubes passing through the cervical orifice either transabdominally.

These Authors believed that "contractile harmony" of "double coordination" from the right to the left hemiuterus (transversal coordination) provoked uterine contraction. This activity passed downwards from the superior to the medial segment and then to the inferior one (longitudinal coordination), following a triple gradient of intensity, length and propagation. This mechanical activity seems to start up in the tube-uterine area which acts as a "pacemaker" as seen in the cardiac

sino-atrial node. This hypothesis is still widely accepted even if results from up to date electrophysiologic studies and pharmacological development have questioned its validity.

## ASPECTS OF UTERINE ELECTROPHYSIOLOGY

### 1) *Segmental electrohysterography.*

The improvement in the techniques and methods used have transformed studies of the electric aspects of uterine contraction (uterine electrophysiology). Electrohysterography is a valid topographic examination especially for the posterior wall of the uterus which was hitherto ignored. After a review of past papers by Bozler, Jung, Daniel and Kuriyama concerning a dual electric phenomenon together with a smooth muscle contraction (uterine fibre), Sureau described two types of activity: one is formed by a succession of rapid spikes, while the other is represented by slow and wide basal variations. The rapid activity was termed sinusoidal by Steer and later on seen by Lévy-Solal and Morin. It is formed by a succession of ten or so regular spikes (from 1/2 to 2 cycles/sec., from 50 to 1000  $\mu$ V).

Results from studies by Wolfs (1972), Boemi and Reitano (1979) and other AA. deny the presence of a slow widespread ac-

tivity which the spikes stem from. It must be kept in mind that Bozler, Jung, Daniel, Kuriyama and other Authors derived the electric activity by applying cutaneous electrodes to the abdominal projection of the uterus, so exposing the results to technical errors (mechanograms, psychogalvanic reflex, etc.). Recently filiform electrodes have been inserted through the abdominal wall (Reitano-Sureau and Le Houezec) and placed into the myometrial structure. Cylindrical or sucker electrodes have also been inserted between the internal wall and membrane of the uterus (Sureau, Wolfs, Germain and other Authors) (fig. 1). These new techniques have revealed the distinct and regular morphology of the electric activity which is grouped into "trains" followed by intervals of electric silence. Reitano and Cianci demonstrated a close correlation between the intensity of electric activity and labour. It has also been seen that some propagation characteristics of the rapid electric

activity depend on the speed and variability of the propagation. This speed varies from 2 to 100 cm/sec depending on the experimental animal and the positioning of the electrodes (Goto, Kuriyama, Abe, Caldeyro-Barcia). This confirms the results obtained by Jung on studies of female rats and cats. Most Authors agree on the variability of propagation and believe that there is no fixed, predetermined conduction within the uterus.

## 2) Elementary electrophysiology

Evidence from recent studies has shown that smooth muscle activity can be spontaneous or stimulated. In both cases it comes about through an ionic phenomenon and triggering mechanism followed by propagation of the impulse to various parts of the fibre, spreading from fibre to fibre. In other words a series of chemical processes activate mechanical contraction. West, Landa, Kuriyama, Csapo demonstrated that the uterine fibre contains a factor similar to the "stretch receptor" in the striated muscle (Bozler) which renders it sensitive to stretching. Moreover, Sureau believes that unlike cardiac and ureterial fibres, uterine ones (as in the "taenia coli" of the hamster) can act as inductor cells. This hypothesis is confirmed by human clinical data; in fact Bozler underlined that "automation is based on metabolic variations". Recent recordings by means of microelectrodes or "sucrose gap" technique on muscle cells have revealed two types of low amplitude oscillations of the spikes. The first with a periodicity of ten or so seconds is associated with a series of spike discharges, while the second is of much shorter periodicity and associated with prepotentials, which are spontaneous depolarizations preceding spikes generation. These prepotentials are found in cells with pacemaker activity but they can not be seen if the cell is activated by an impulse propagated from one cell to another. In studies on rat uterus under estro-

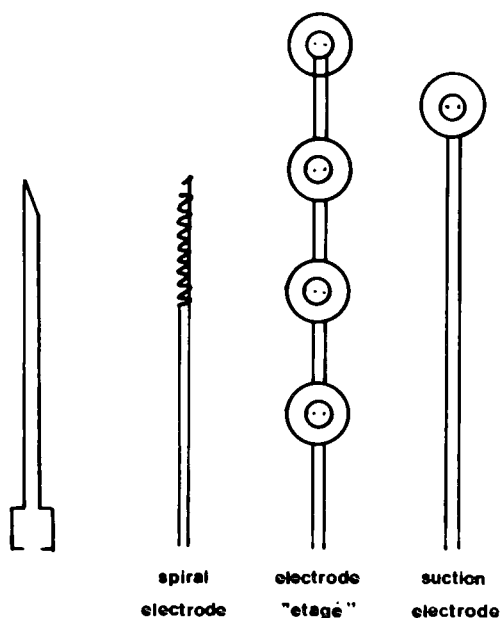


Fig. 1. — Filiform electrodes mounted on 'peridural' needle; sucker electrodes.

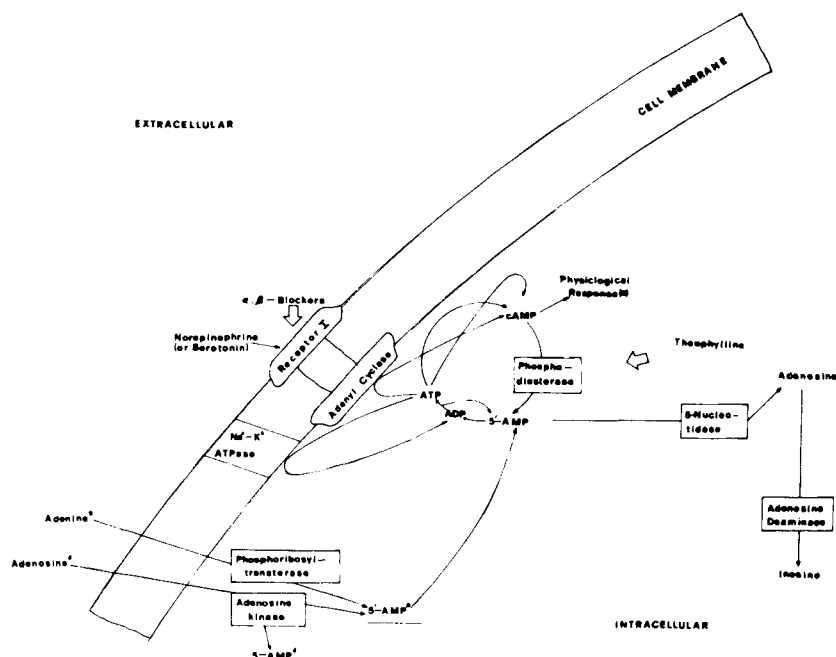


Fig. 2. — c-AMP activation synthesis from ATP through various receptors placed on the cell surface. The PGs can slow down or amplify the response of the stimulation.

genic dominance, Marshall saw in fieri pacemakers formed by prepotentials. This pacemaker activity depended on estrogenic impregnation of the muscle fibres. In fact, abortive pacemakers were present in the myometria not stimulated by estrogen. These myometrial cells show spontaneous depolarizations like the spikes, but do not have enough discharge to generate spikes. In these animals coordinated contractions spread from any area. In recordings using three pairs of bipolar electrodes placed in the superior, medial and inferior areas of the uterus, Marshall did not localize a set point where the impulse generated from.

#### PHARMACOLOGICAL AND EXPERIMENTAL ASPECTS

Studies using PGs have been carried out in the 2nd Department of Obstetrics

and Gynaecology and the Institute of Obstetric and Gynaecologic Pathology (1st) of Catania University since 1973. Boemi, Reitano and co-workers have evaluated data obtained after intravenous, extra-amniotic intrauterine, intramuscular and intracavitary perfusion of PGs. They analyzed the action of possible inhibitors, therapeutic ratio (quotient), the expedience and effectiveness of an intravenous infusion of an added dose of exogenous prostaglandin. With reference to the studies by Dill, Maiden, Niu and Fisch on the regional electrophysiology of the uterus and their hypothesis that electric activity stems from the neck upwards, the Authors induced uterine activity by local perfusion of prostaglandins. In these studies 144 patients (age range 18 to 41 years) of whom 46 were primigravidae and 98 mul-

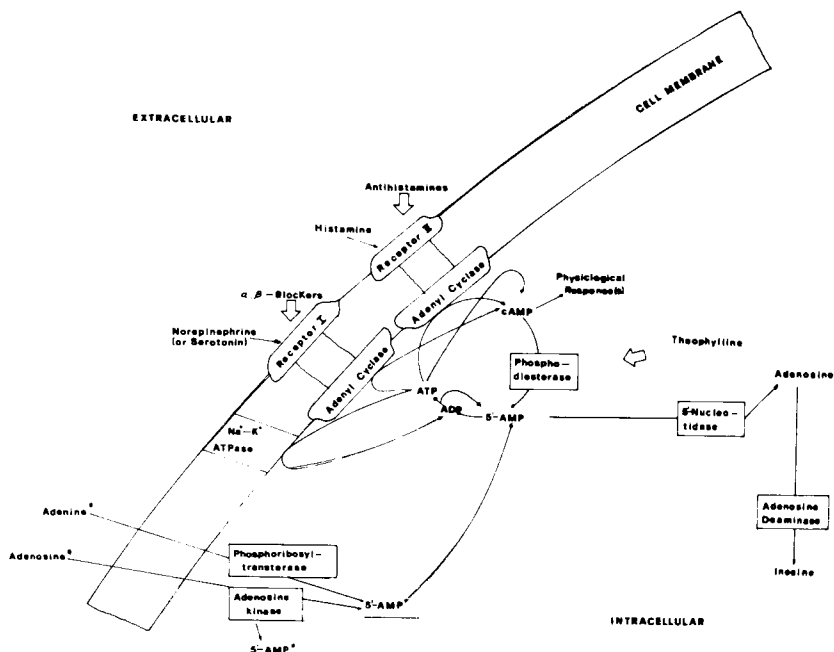


Fig. 3. — c-AMP activation synthesis from ATP through various receptors placed on the cell surface. The PGs can slow down or amplify the response of the stimulation.

tigravidae (86 with pregnancy in course and 58 with missed abortion) were examined. They received a single local perfusion of prostaglandin solution (PGF2  $\alpha$ ) through the anterior lip of the neck of the uterus. In order to do so a butterfly needle was stitched in place (cervical-intramural perfusion). Internal tocography revealed an extremely short time lapse (about 30 to 40 sec.) in the mechanical activity. In women with pregnancy in course, an exponential curve showing the ratio amplitude/time registered a slight increase up to 90 min. after the onset of labour, followed by a maximum slope lasting three hours. On the contrary maximum slope was seen two hours after the onset of labour in the cases with missed abortion. In the latter there was a slight increase in basal tone at the onset of labour.

The PGs attack two points of the periferic agent (muscle, etc.). The first is the cell surface which regulates the quantitative response of the second messenger (c-AMP, c-GMP, etc.), and here the PGs can either slow down or amplify the system (figs. 2-3). The second point is within the cell where  $Ca^{++}$  ions are liberated. In fact, the responses of the second messenger are modulated by the number of free  $Ca^{++}$  ions available (fig. 4). In vivo and in vitro studies have shown that added PGF2  $\alpha$  frees more  $Ca^{++}$  ions from the sarcoplasmatic reticulum and that these PGs probably have chemical characteristics which make them receivers or carriers of the  $Ca^{++}$  ions (Carsten) (fig. 5). It must be remembered that the interaction between myosin, actin and ATP is the fundamental process of myocellular

## KEYPOINTS OF ATTACK IN THE cAMP-SYSTEM

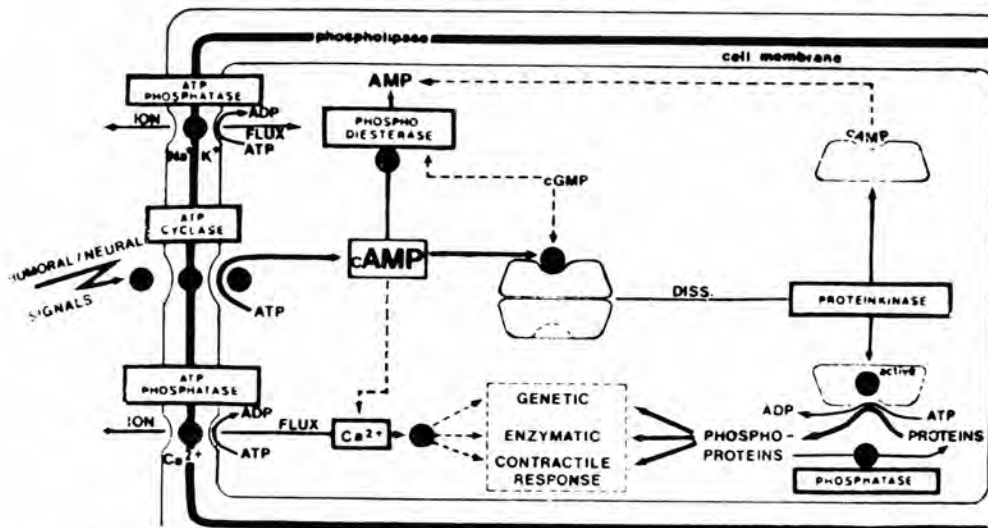


Fig. 4. — The PGs can regulate the quantitative response of the second messenger (c-AMP, c-GMP) with opposed effects on the cell metabolism.

contraction in the electrical-mechanical junction. The  $\text{Ca}^{++}$  ions play an important role in triggering off contraction. They migrate from the extracellular space during electric stimulation and activate myofibril ATP-ases, forming a "fundamental biologic function" (Fleckenstein). In the myometrium there is a similar  $\text{Ca}^{++}$  channel open only to bivalent ions. In fact, administration of Ca-antagonists inhibit the flow, so determining a cellular electric-mechanical disjunction.

Therefore, it seems that the action of PGs on  $\text{Ca}^{++}$  ions that provoke ATP-ase can generate an energetic pool. It is this pool which is the starting point for the biochemical-humoral sequences that culminate in the mechanic process.

Results obtained from studies carried out in the Baudelouque Department in Paris and in Catania by Sureau and Reitano aided our researches. Collaboration between the two Departments allowed the recording of human pregnant uterus at

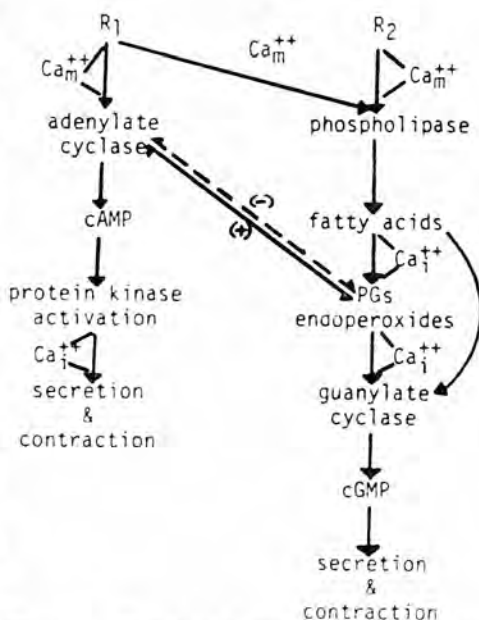


Fig. 5. — Hypothetical scheme of possible sites of interaction between  $\text{Ca}^{++}$ , prostaglandins and the cyclic nucleotides.

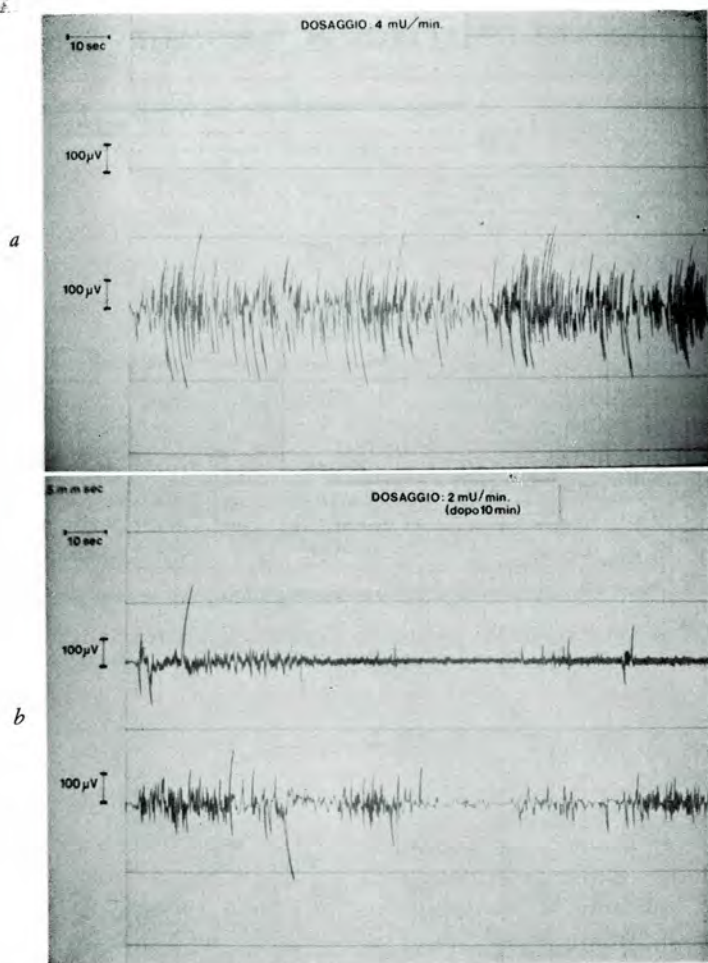


Fig. 6. — *a*: A.F. 31-year-old primigravida at the 41st. Oxytocin infusion rate. Dosage: 4 mU/min. Channel A: silent. Channel B: recording. *b*: Same patient.

term using equipment with input circuits, preamplifiers and postamplifiers<sup>(1)</sup>.

On of patients studied was a 31-years-old primigravida at the 41st week

(1) Characteristics of the equipment were: input impedance 200 ohm; input sensitivity 10 μV, equal to 10 mm of pen movement, strip passing of 2000 Khz; output impedance 200 ohm, blocking time 1 sec after passing stop position; gain on six positions permitting a geometrical progression of 2; filters of 15-35-50 Hz and Khz; time constant of 0.3-0.1-0.3-0.7 and 3 sec, speed paper 1.5 mm/sec.

of gestation. Labour was induced by an intravenous infusion of oxytocin (figs. 6a - 6b; 7a - 7f). Two spiral electrodes were placed transabdominally 10 cm apart in the anterior wall of the uterus. An open-end catheter was inserted inside the uterus between the internal uterine wall and membrane and then connected up to a pressure transducer. The initial perfusion concentration (4mU/min) corresponded to exaggerated electric activity, disappearance of electric silence and unification of



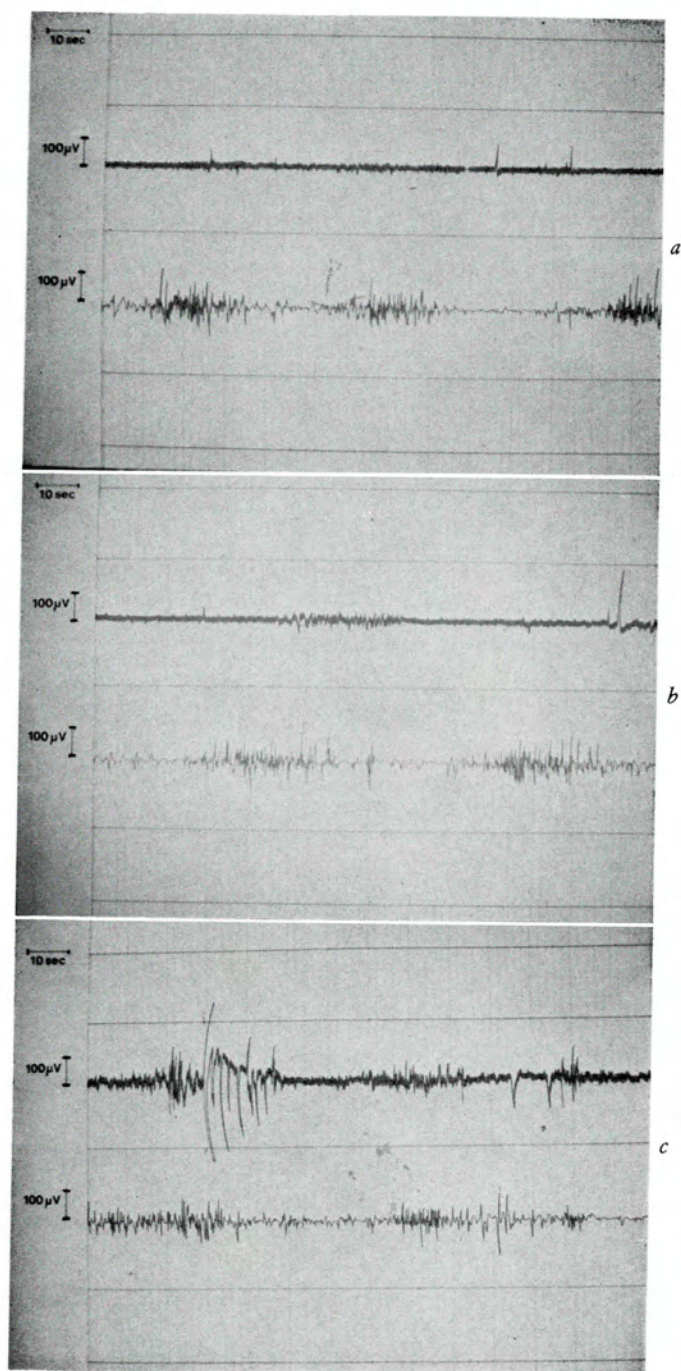


Fig. 7. — *a*, *b*, *c*, *d*, *e*, *f*: Oxytocin infusion rate. Dosage: 2 mU/min (after 10 min). Channel A and B: recording in succession.

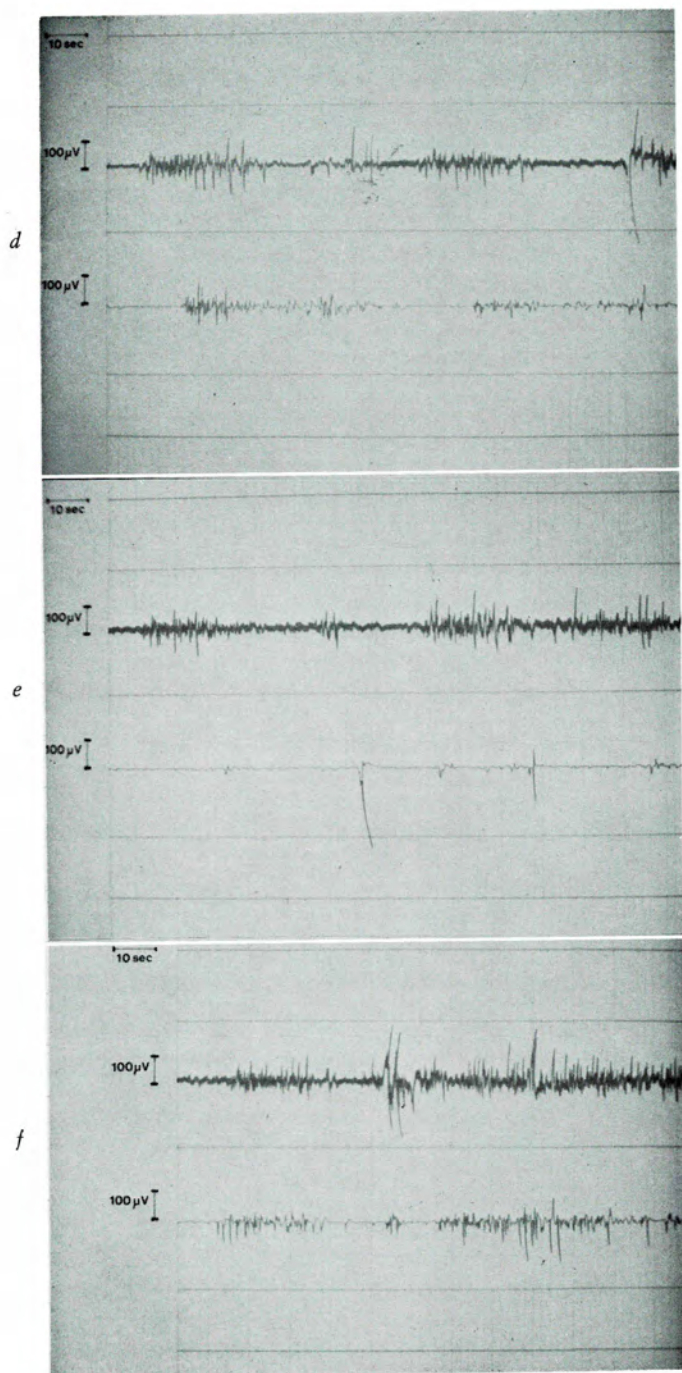


Fig. 7.



the spike trains mean amplitude of the spikes was about 500  $\mu$ V). In other words there was an electric addition effect. When the perfusion concentration was reduced (2mU/min), 10 min after it was initiated, the activity in the two channels recorded was almost normal but presented peculiar characteristics. The mean amplitude of the spikes in each train in channel B was between 100-150  $\mu$ V with regular periods of electric silence; in channel A there was a progressive increase in these periods of electric silence, and progressive reduction of the amplitude of the spikes until they disappeared completely. This resulted in a flat recording with isolated mono and biphasic spikes. Later on there was a progressive increase of the electric activity (appearance of trains with low voltage spikes of 20-30  $\mu$ V) in the silent channel (channel A), and a decrease of this activity (reduction of amplitude of the spikes and increase in electric silence) up to disappearance in channel B. The alternating electric activity recorded in the two channels lasted for about 50 minutes.

## DISCUSSION

The data obtained from the above mentioned studies demonstrate that there are no set uterine tube areas with pacemakers-like tissues.

They induce us to draw the following conclusions:

1) In segmental electrohysterography carried out in women and experimental animals, the analysis of the rapid activity shows that both the propagation of electric activity within the uterus and the origin of each contraction are variable. Elementary electrophysiological studies show that in the smooth muscle, especially the uterus, in the absence of specialized histological structures, hormonal impregnation can provoke spontaneous depolarizations. These depolarization are characterized by prepotentials which trigger off a process

of electric activity which in turn gives rise to mechanical contraction.

2) Administration of PGs determines a receptor-transporter  $\text{Ca}^{++}$  ion phenomenon within the cell. This interacts with the fundamental process of contraction (myosin, actin, ATP) and supplies energy for the contractions. Therefore, a local quota of PGs sets up an energetic pool which promotes area pacemaker activity stimulating-propagating upwards or downwards.

3) Findings from electrohysterographic studies carried out in pregnant women during labour suggest that the electric circuit follows a changing ellipsoidal pattern moving from right to left and viceversa. Therefore, electric activation in the uterine muscle can be produced everywhere in the myometrium depending on the presence of favourable factors. These are: hormone secretion (maternal and foetal oxytocin, adrenal hormones arising from the foetus. ACTH, uterine stretching, mediators action, PGs,), hormone interaction, and the interaction between mediators and hormones in the myometrium. In the uterus electric activation does not follow standard pathways and can modify itself depending on the favourable or unfavourable conditions in the "environment".

## ACKNOWLEDGMENTS

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## OUR EXPERIENCE ABOUT THE ROLE OF URODYNAMIC TESTS IN FEMALE URINARY INCONTINENCE

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**Summary:** The author reports his own experience upon urodynamic evaluation of vesico-urethral function in patients suffering from urinary incontinence. The analysis of the results confirms the high significance of urodynamic investigation in cases of urinary incontinence either preoperatively, in order to define the conditions which lead to the pathology and to decide the most suitable therapeutic approach, or postoperatively, in order to confirm the realisation of therapeutic success.

**Key words:** female stress incontinence; urodynamics.

The importance of urodynamic investigations in gynecology is today universally

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recognised, as witnessed by the numerous researches reported by various Authors in literature. It is notable that a correct differential diagnostic approach is presupposed essential for all forms of urinary patho-