Effects of progesterone on the central nervous system

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D. Central Effects of Endogenous Progesterone and Synthetic Progestational Agents

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Effects of Progesterone on the Central Nervous System

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I. Introduction

A lot of evidence indicates that progesterone and its synthesis derivatives may modify processes controlled by the Central Nervous System (CNS). This evidence includes: a) the demonstration that progesterone plays a fundamental role in the neuroendocrine events leading to ovulation (Everett, 1948, 1961, 1964); b) the observation that progesterone is essential, in several animal species, for a complete expression of female sexual behavior (Lisk, 1967; Zucker, 1968); c) the fact that progesterone and several of its derivatives induce general anesthesia (Gyermek, 1967; Meyerson, 1967), exert hyperthermic effects (Diczfalusy, 1968) and modify food intake (Swanson, 1968; Hervey and Hervey, 1969); d) the finding that progesterone and several progestational agents induce significant changes in the electrical activity of the brain, as evaluated both by electroencephalographic and by "unit" recording techniques (Arai et al., 1967; Komisaruk et al., 1967; Beyer and Sawyer, 1969); e) the data showing that progesterone influences the level and the turnover of brain catecholamines (Fuxe and Hökfelt, 1969).

It is possible that some of these CNS effects are due not to progesterone as such, but to some of its metabolic derivatives; recent data prove that progesterone crosses easily the blood-brain barrier and is actively metabolized in the CNS (Conney et al., 1966; Bidder 1968; Raisinghani et al., 1968; Seiki et al., 1968, 1969).

It is interesting that the CNS effects of progesterone and of its derivatives are not necessarily correlated with the ability to maintain pregnancy in castrated animals. In addition, the presence, in a progestational steroid, of one of the CNS effects mentioned above does not automatically imply that the compound will simultaneously have all the others. On the contrary, progestational agents very often possess one CNS effect but lack of several others. For instance, progesterone is able to maintain pregnancy, to influence estrous behavior and to induce general anesthesia; medroxypro-

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gesterone has exactly the same spectrum of activity; norethisterone is able, like the two steroids previously mentioned, to induce estrous behavior and general anesthesia, but is very poor in maintaining pregnancy; norethinodrel is able to induce general anesthesia, but is devoid of behavioral and of pregnancy-maintaining activities (MEYERSON, 1967).

II. Role of progesterone in ovulation

A. General remarks

The following parts of this paper will consider in detail the role of progesterone in the process of ovulation. The data available indicate that this hormone may intervene in two different phases of the ovulatory cycle: a) at midcycle, when it is secreted in low amounts, it apparently synergises with estrogen and facilitates the release of ovulating amounts of Luteinizing Hormone (LH); b) during the luteal phase, when it is secreted at a higher rate, it inhibits the synthesis of the hypothalamic factor which controls the secretion of FSH (Follicle Stimulating Hormone-Releasing Factor or FSH-RF) and consequently prevents the release of FSH.

A brief description of the neuroendocrine events which take place during an ovulatory cycle will be provided here, in order to facilitate the understanding of these apparently contradictory and conflicting effects of progesterone. This description, which represents an attempt to consider the ovulatory process as a highly automated phenomenon, is taken from a paper by MARTINI et al. (1970); it is based on the evidence recently obtained in women using the sensitive analytical procedures now available for measuring plasma levels of pituitary gonadotropins and of sex steroids, as well as on the animal experiments performed in the authors' laboratory. For more detailed information the reader is referred to the original publication (MARTINI et al., 1970).

B. Description of the ovulatory cycle

MARTINI et al. (1970) have postulated that one rhythmic center ("biological clock"), existing in some extrahypothalamic region of the brain, is responsible for activating the release of FSH-RF into the pituitary portal vessels. This is believed to represent the primary stimulus for the whole process of ovulation. The release of increased amounts of FSH-RF activates FSH secretion; this is the reason why plasma levels of FSH have been found consistently elevated during the first part of the cycle (FAIMAN and RYAN, 1967; MIDGLEY and JAFFE, 1968; TAYMOR et al., 1968; SWERDLOFF and ODELL, 1969). The presence of FSH in the circulation permits the maturation of the ovarian follicle. At a certain stage of its maturation the follicle becomes competent to respond to the small quantities of LH which are secreted in basal amounts throughout the whole cycle (BARRACLOUGH, 1967); consequently the secretion of estrogen can begin. When estrogen reaches a threshold amount in the general circulation two important phenomena

occur: a) the production of FSH-RF starts being inhibited, so that FSH is not secreted any longer ("negative" feedback effect of estrogen) (MARTINI et al., 1968a); b) the release of the Luteinizing Hormone-Releasing Factor (LH-RF) is increased ("positive" feedback effect of estrogen) (RAMIREZ and SAWYER, 1965; BURGER et al., 1968; MOTTA et al., 1968; HOPPER and TULLNER, 1969; YOSHINAGA et al., 1969; KORENMAN et al., 1969); a peak of LH secretion is then achieved, and ovulation (which, in most mammals, is an LH-dependent phenomenon) occurs. As it will be shown in detail in a next section of this paper, the effect of estrogen on the release of ovulatory amounts of LH is facilitated by the presence of progesterone in the general circulation. After ovulation, the corpus luteum develops; this temporary endocrine gland is responsible for the secretion of large amounts of progesterone. Because of the effect this hormone exerts on the FSH-RF-FSH component ("negative" feedback effect of progesterone) (MARTINI et al., 1968a), FSH secretion is very low during the second phase of the cycle (FAIMAN and RYAN, 1967; IGARASHI et al., 1967; TAYMOR et al., 1968; SWERDLOFF and ODELL, 1969). After a certain time (which is characteristic for each species) the process of luteolysis begins; up to now, this must be considered a mysterious phenomenon, in which apparently intervene pituitary as well as uterine factors (CLEGG and DOYLE, 1967). The disappearance of progesterone from the circulation eliminates the "negative" effect of this steroid on the synthesis of FSH-RF; this permits to the primary neural stimulus originating in the "biological clock" to start a new ovulatory cycle.

C. Facilitatory effect of progesterone on LH secretion

A lot of data obtained both in women and in experimental animals support the hypothesis that progesterone might synergise with estrogen and facilitate the release of ovulatory amounts of LH. The information available suggests that this facilitatory effect of progesterone takes place in the CNS.

1. Indirect evidence. It has long been known that progesterone, when given at a proper time of the estrous cycle, is able to advance ovulation in rats normally running a five-day cycle (EVERETT, 1948, 1961, 1964; BROWN-GRANT, 1967; HALLER and BARRACLOUGH, 1968; KAASJAGER, 1969). Progesterone is effective in certain days and not in others, probably because it necessitates the presence of well defined amounts of circulating estrogen; these fluctuate during the estrous cycle, as shown by the data of SCHWARTZ (1964), HORI et al. (1968) and YOSHINAGA et al. (1969).

FSH and Pregnant Mare Serum gonadotropin (PMS) induce ovulation in prepuberal animals, through a very complex mechanism which involves the liberation of estrogen from the ovary and the consequent stimulation of LH secretion (MARTINI et al., 1968b). Progesterone, when injected into immature female rats and mice following the administration of PMS, will permit to non-ovulatory doses of this gonadotropin to become fully effective. In addition, it will increase the number of animals ovulating and the number of ova per animal, when ovulatory doses of PMS are given (MEYER

Table I

Induction of ovulation with progesterone and Ro 4-8347 in immature rats given a non-ovulatory dose of PMS; blockage of ovulation with phenobarbitone

	Number of rats	Number of rats ovulating	Number of ova/ovulating rat (means $\pm$ SE)
Control (PMS[1] only)	12	0	0
PMS + progesterone[2]	10	5	21.0 ± 5.1
PMS + Ro 4-8347[2]	10	8	18.1 ± 2.6
PMS + progesterone + phenobarbitone[3]	5	0	0
PMS + Ro 4-8347 + phenobarbitone ..	5	0	0

[1] 22-day old rats administered 15 IU PMS at 10.00 a.m.

[2] 0.5 mg/rat injected on day 24 at 12.30 p.m.

[3] 7.5 mg/rat injected on day 24 at 13.30 p.m.

and McCORMACK, 1967; ZARROW and GALLO, 1969). It is believed that exogenous progesterone synergises in this test with endogenous estrogen released under the influence of the gonadotropic treatment. The data recently reported by GRAYBURN and BROWN-GRANT (1968) seem to provide a more direct proof of this fact. They have shown that immature animals treated with very low amounts of FSH will ovulate only if treated with a combination of estrogen and progesterone, but not with either steroid alone. The facilitatory effect of progesterone on PMS-induced ovulation takes certainly place at the level of the CNS: the effect of progesterone will disappear if lesions are placed in the hypothalamus or if CNS-blocking drugs (e.g. phenobarbitone) are administered concurrently with the steroid (EVERETT, 1961, 1964; YING and MEYER, 1969).

The ability to potentiate the ovulatory effect of PMS in immature animals is shared by other progestational agents. Table I offers an example of this fact. The progestational compound Ro 4-8347 has recently been shown in our laboratory (SETH and MARTINI, 1970) to be more active than progesterone in this test; also the activity of this steroid appears to be a central one, since it will be obliterated by treatment with phenobarbitone.

The exposure to constant light transforms normally ovulating rats into anovulatory animals (MEYER and McCORMACK, 1967; WURTMAN, 1967). These anovulatory animals will ovulate following treatment with progesterone. Here again, a synergic effect between estrogen and progesterone can be postulated, since animals exposed to constant light exhibit a constant estrus situation and have rather high levels of estrogen in the circulation.

Additional evidence, for the facilitatory activity of progesterone on estrogen-induced LH secretion may be derived from studies performed on the so-called "reflex ovulators". A typical example of these animals is represented by the rabbit. Rabbits normally ovulate only after exposure to

sexual stimulations; however, they may be induced to ovulate "spontaneously" after a treatment with a combination of progesterone plus estrogen (SAWYER et al., 1950). As in the experiments previously quoted, a central site for this effect of progesterone is suggested by the fact that lesions in the basal hypothalamus or treatment with drugs depressing the CNS will eliminate it (EVERETT, 1964).

Immature rats may ovulate following the administration of small doses of estrogen (HOHLWEG, 1934; RAMIREZ and SAWYER, 1965; MOTTA et al., 1968). DÖCKE and DÖRNER (1966, 1969) have recently reported that also this type of experimentally induced ovulation can be facilitated by progesterone. It is interesting that both the systemic administration of the steroid (DÖCKE and DÖRNER, 1966) and its stereotaxic implantation into the ventromedial-arcuate region of the hypothalamus are effective (DÖCKE and DÖRNER, 1969). This last result obviously provides clear-cut evidence in favor of the fact that the facilitatory effect of progesterone takes place in the CNS.

DÖCKE and DÖRNER (1969) have also observed that systemic injections of progesterone increase the efficiency of electric stimulation of the hypothalamic ventromedial-arcuate complex in inducing ovulation in animals bearing electrolytic lesions in the medial preoptic area of the hypothalamus. Also in this very ingenious experiment a synergic effect between progesterone and estrogen may be postulated: animals with lesions in the preoptic area like those used by the German authors are usually in constant estrus (SZENTÁGOTHAI et al., 1968) and consequently have increased levels of estrogen in their blood.

2. Direct evidence. CALIGARIS et al. (1968) have recently shown that castrated female rats in which plasma levels of LH have been lowered by the chronic administration of low doses of estrogen, exhibit an abrupt increase in plasma LH titers following the administration of one single dose of progesterone (Fig. 1). Similar data have been reported by ODELL and SWERDLOFF (1968) in post-menopausal women (Fig. 2). In these subjects, a chronic treatment with estrogen results in a conspicuous reduction of plasma levels of LH; the administration of a single dose of progesterone or of medroxyprogesterone after LH has reached its lowest levels, induces an artificial peak of LH secretion which is perfectly similar in shape and magnitude to that physiologically appearing at midcycle in normally ovulating women.

3. Conclusions. The data discussed in the preceding two sections of this paper have provided evidence in support of the view that a synergistic effect of estrogen and progesterone may induce LH release and ovulation in different animal species and in women. The question may be asked whether this is also the mechanism which operates in normal, physiological conditions. In order to answer this question it would be essential to establish whether estrogen and progesterone are present in the general circulation before the midcycle release of LH occurs. Probably it would also be important
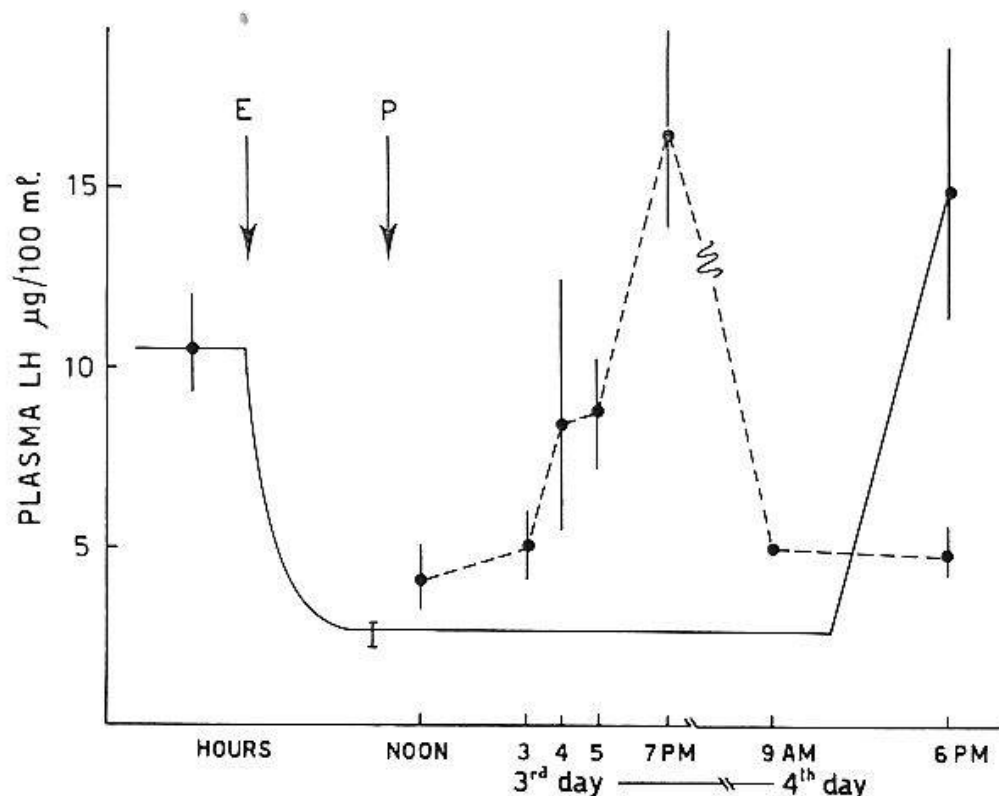
412

Fig. 1. Effect of progesterone on plasma LH activity in ovariectomized rats treated with estrogen. Solid line = plasma LH in ovariectomized rats. Dashed line = plasma LH in ovariectomized estrogen treated rats injected with progesterone. E = injection of 20 μg of estradiol benzoate. P = injection of 2 mg of progesterone 3 days after estrogen administration. – From CALIGARIS et al., 1968.
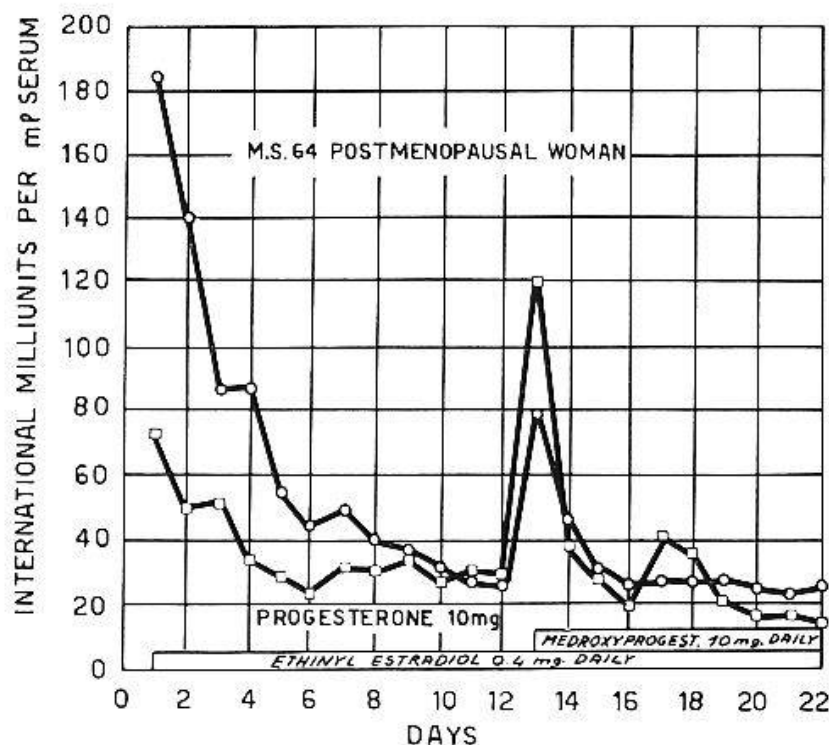

Fig. 2. FSH (o) and LH (□) concentrations in a postmenopausal woman treated with sequential estrogen plus progestogen. Medroxyprogesterone was administered orally starting on day 13. – From ODELL and SWERDLOFF, 1968.

413

to know whether their plasma levels increase before LH is hypersecreted. With regard to estrogen there is now ample evidence indicating that they show a significant rise before the LH peak (BURGER et al., 1968; BAIRD and GUEVARA, 1969; HOPPER and TULLNER, 1969; YOSHINAGA et al., 1969; KORENMAN et al., 1969). With regard to progesterone all the data available indicate that low amounts of this steroid are present in all animal species before LH release and ovulation (ETO et al., 1962; TELEGDY and ENDRÖCZI, 1963; LINDNER and ZMIGROD, 1967). There is also some evidence that progesterone titers start rising before the midcycle LH peak (VAN DER MOLEN and GROEN, 1965; SAXENA et al., 1968; NEILL et al., 1969); however, this evidence has not been confirmed (NEILL et al., 1967; YOSHIMI and LIPSETT, 1968; CARGILLE et al., 1969; FEDER et al., 1969; GOLDMAN and DANHOF, 1969; JOHANSSON and WIDE, 1969).

In the authors' view it is not essential to show that progesterone starts increasing before the LH peak occurs, in order to postulate a physiological role for this steroid in the processes leading to ovulation. It appears from the data discussed in the preceding paragraphs, that also the basal levels of progesterone which are certainly circulating before ovulation, may potentiate the effect of estrogen on the release of LH.

An additional consideration is that progesterone might not be the only progestational agent secreted by the ovary having the facilitatory activity on ovulation. Data indicating that 20α-hydroxypregn-4-en-3-one is able to induce LH release in rabbits have already appeared (HILLIARD et al., 1967). However, this steroid seems to be completely ineffective in rats (McCORMACK and MEYER, 1965; BROWN-GRANT, 1967; HALLER and BARRACLOUGH, 1968). The possible role of 17-hydroxyprogesterone as a facilitatory agent has not been studied so far. Data are highly needed in this area.

D. Inhibitory effect of progesterone on FSH secretion

The other major effect progesterone exerts during the ovulatory cycle is that of eliminating FSH-RF stores from the hypothalamus; probably progesterone does so by blocking the re-synthesis of this principle after it has been secreted into the pituitary portal vessels to initiate the process of ovulation (MARTINI et al., 1968a, 1970). The consequence of the disappearance of FSH-RF from the hypothalamus is that the transmission of the primary neural stimulus for ovulation from the extrahypothalamic "biological clock" to the anterior pituitary is completely prevented.

The idea that progesterone might inhibit FSH secretion has recently gained a lot of support. Plasma FSH levels have been found particularly low during the second phase of the ovulatory cycle when progesterone is secreted in high amounts; in addition, a rapid and significant increase of plasma FSH levels has been observed after cessation of corpus luteum function (FAIMAN and RYAN, 1967; IGARASHI et al., 1967; TAYMOR et al., 1968; SWERDLOFF and ODELL, 1969). The chronic administration of progesterone has been shown to result in the inhibition of ovarian compensatory hyper-

414

trophy in the rat; this is a typical FSH-dependent phenomenon (JELINEK et al., 1968; LABHSETWAR, 1968a, b; SHORT et al., 1968). In addition, DAVIDSON (1969) has reported that implants of progesterone performed in the median eminence region of the hypothalamus induce ovarian atrophy in prepuberal and adult female rats. It is well known that ovarian weight is largely dependent on plasma FSH levels. Implants performed in the pituitary gland were completely ineffective. These data seem to suggest that also the receptors for the "negative" feedback effect of progesterone on FSH secretion are located in the brain and particularly in the hypothalamus.

More recent studies indicate that also several progestational agents used for antifertility purposes are able to reduce the secretion of the FSH-RF-FSH component. MINAGUCHI and MEITES (1967) have reported that the chronic administration of the progestational agent norethinodrel decreases hypothalamic stores of FSH-RF both in normal and in castrated rats. LABHSETWAR (1968a, b) has shown that chlormadinone, administered to intact or unilaterally spayed rats results in ovarian atrophy and in the inhibition of ovarian compensatory hypertrophy respectively. Several clinical findings have given comparable results. Subjects receiving non-sequential contraceptive preparations do not exhibit the elevation of plasma and urinary FSH levels which are typical for the early phase of the cycle (STEVENS et al., 1965; CARGILLE and ROSS, 1968; CARGILLE et al., 1969; SWERDLOFF and ODELL, 1969); several long-acting progestational preparations suppress plasma FSH levels not only in normal women but also in castrated or postmenopausal subjects (FRANCHIMONT, 1970).

In the authors' view these data represent a support for the thesis that ovulation is suppressed in the second phase of the cycle because progesterone renders the hypothalamus refractory by eliminating FSH-RF. In addition, the question may also be asked whether the effect on the FSH-RF-FSH component here described might not represent one of the major mechanisms through which antifertility preparations inhibit ovulation.

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Discussion

P. LEBECH: I wonder whether I understood this correctly. You said that the hyperthermic effect of progestagens is not yet well understood, whether it is a central effect or a peripheral one. I think my chief ALOT in 1956 showed that with barbiturates you can inhibit the thermogenetic effect of progesterone in humans. The second point is: you pointed out the mode of action of ovulation and you said that the start of follicle ripening or the beginning of ovulation is induced by FSH or the FSH releasing factor. In fact, I have never seen any publication where you can see only FSH during the follicular phase. You usually find LH as well. So, I wonder why we could nevertheless state that it is only FSH in the follicular phase.

L. MARTINI: As far as the first point is concerned I agree with you that there are a few indirect data indicating that the thermogenic effect of progesterone is a central one. However, as a neuroendocrinologist, I would like to see somebody placing pro-

gesterone in the areas of the brain which control body temperature and studying whether the steroid itself induces the hyperthermic effect or not; this because when you use the approach of systemic injections you cannot exclude that the effects you observe are due to some metabolites of progesterone rather than to progesterone itself. As far as your second point is concerned, the radioimmunological procedures have clearly indicated that during the first phase of the cycle there is a significant secretion of FSH; LH is also present but in small, basal amounts.

B. LUNENFELD: I was very interested in one big and important message which you gave us today, i.e. that even in a clean colony of animals – we cannot say that our human colonies are clean – you need to give progesterone at a very precise moment. More than this you need in some cases estrogen priming. You need a very specific dose of progesterone and all this linked to a very specific time. Does this not explain the big difficulties and differences in information we get from all kinds of clinical trials where you have a completely heterogeneous population and where all these things cannot be controlled by the same measures as you can control a clean colony of mice or rabbits or rats? I think this should explain to us that we cannot expect to get better results and we must get this different kind of information from different clinicians.

L. MARTINI: I perfectly agree with you.

A. DARRAGH: 1. How is it possible to reconcile the increased appetite and the increased food intake with the normal catabolic action of progesterone? 2. Are we narrowing our field of research completely by looking for the trigger mechanism for ovulation by simply considering the FSH and LH when the alteration in the internal environment created by the estrogen upsurge must also bring into play at least the posterior pituitary factors which could indeed have some effect also in the production of ovulation?

L. MARTINI: As far as your first question is concerned I think that there is now ample evidence indicating that progesterone reduces the basal metabolic rate and increases food intake. I am not aware of data proving a real catabolic effect of progesterone. As far as your second question is concerned, we have shown years ago that both oxytocin and vasopressin may increase the secretion of gonadotropins in the rabbit. Whether this is of physiological significance is still uncertain.

J. FERIN: As a clinician I have treated a great number of patients with lynestrenol – with a high dose of 5 mg daily continuously – in order to suppress menstruation and ovulation. In this kind of patients I have very frequently seen an increase in weight and increase in food intake but also an increase in aggressiveness. I wonder if there is a correlation between the increased food intake and the increased aggressiveness.

L. MARTINI: I do not know if any experimental result was obtained with the particular steroid you mentioned. However, there are several papers suggesting that hypothalamic lesions which increase food intake also increase motor activity and other types of behaviour.