

Zeitschrift: Bulletin der Schweizerischen Akademie der Medizinischen Wissenschaften = Bulletin de l'Académie suisse des sciences médicales = Bollettino dell' Accademia svizzera delle scienze mediche

Herausgeber: Schweizerische Akademie der Medizinischen Wissenschaften

Band: 25 (1969)

Artikel: New aspects of the physiology of progestational agents

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DOI: <https://doi.org/10.5169/seals-307768>

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A. New Aspects of the Physiology of Progestational Agents

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New Aspects of the Physiology of Progestational Agents

E. ODEBLAD

Introduction

When looking over the literature on gestagenic agents one finds that a very extensive amount of experimental information is available. Numerous biological effects in animals have been described as progestational actions and several bio-assay methods for gestagenic effects have been developed. In order to bring about some kind of order in the large amount of data accumulated, one has to select a few effects which, from the biological point of view, are to be considered as very similar to the basic progestational effects in the human (i.e. the immediate preparation of the female organism for gestation). From the medical standpoint the final aim of research in this field is the prophylactic or therapeutic application of the gestagenic agents to the human. The most basic progestational effects in the woman should therefore be considered as the important ones and form the basis for the judgement of gestagenic properties. Unfortunately, the information on human effects is considerably less than the information on common laboratory animals.

Some medical properties of gestagenic hormones

By definition, a gestagen is a hormone which acts with the purpose to prepare the female organism for pregnancy, i.e. to allow the implantation and development of the fertilized ovum. In accordance with the introductory remarks we shall now consider the most important gestagenic effects on the human female. The effects, which are a logical consequence of the definition of a gestagen, are the following:

1. To inhibit the functions of the hypothalamic-hypophyseal-ovarian relationships so that there occur no further maturation of ova and no ovulation as long as the progestational state or pregnancy persists.
2. To prepare the estrogen-primed endometrium for the implantation of the young embryo.
3. To prepare the myometrium and the vascular supply of the uterine corpus for gestation.

4. To bring about a closure of the uterine cavity by a functional constriction of the uterine cervix.
5. To assign to the cervical mucus rheological properties so that it can act as an effective barrier within the cervical canal.
6. To aid in the development of the mammary glandular tissues.
7. To initiate the adaptation of the vagina for the delivery.

Besides these very *basic* or *fundamental effects* there may also be present many effects which are not directly related to the primary purposes of gestagenic action. These *secondary* or *side effects* of gestagens may for example be thermogenic effects or the development of jaundice or other complications in the treatment with gestagens.

A comprehensive review of gestagens, to which I shall refer, is given by ROLAND (1965).

Basic gestagenic effects

We shall now consider the basic or fundamental effects of gestagenic hormones in some more detail.

The primary effect on the hypothalamic-hypophyseal-ovarian system may be the inhibition of the secretion or release of hypophyseal FSH and LH and/or their releasing factors. Because FSH and LH stimulate the ovary, an inhibition of their secretion is accompanied by an inhibition of the maturation of follicles and ovulation. This gives rise morphologically and functionally to a more or less complete resting state of the ovary which can be detected by culdoscopy, measurement of ovarian size or determination of the hormones or metabolites in the blood and urine.

The preparation of the endometrium for nidation is brought about by the transformation of the estrogen-primed endometrium into the so-called secretory state. This means an increased storage of glycogen and other substances of importance for implantation and an appropriate vascularization of the mucus membrane in the "corpus uteri". The effect can be studied in the human by means of biopsies. In animals the Clauberg test or the McGinty test can be used as a fairly good equivalent to the effects in the human. In human the delay-of-menstruation-test can be used, for animals the equivalents being the pregnancy maintenance test and delayed parturition test.

The preparation of the muscular wall of the uterine corpus for the carrying of fetuses is due to growth promoting effects on the uterine tissues. The myometrium is stimulated to grow, both in regard to the number and size of the myometrial cells. There is also a muscular relaxation of the myometrium. In addition, the vascular supply to the whole uterus is increased. For animals, tests based on metrotophy have been developed, but it is uncertain if the effects in the human are comparable.

The closure of the uterine cavity is brought about in two ways. 1. The mechanical closure of the uterine cervix is very important. Therefore, an important primary action of gestagens is to reduce the diameter of the

cervical canal. 2. Another primary action of gestagens is to transform the mucus secreted by the cervical glands so that the mucus does not allow sperm or bacteria from the vagina to penetrate the inside of the uterine cavity. The mucus is made rheologically harder and more stable. Tests for these two effects can be developed for human application, as the cervix is easily accessible for clinical examination. It seems to be somewhat more difficult to develop reliable animal tests for the cervical effects.

The development of the breast is controlled by processes involving an increase of the mammary glandular tissue, the fibrous tissue, the fatty tissue and also the associated vascularization. Also here, tests in the human can certainly be developed, but are presently not available.

The last effect, the preparation of the vagina for delivery, implies an increased diameter of the vagina and also qualitative alterations, especially mucification of the epithelial lining of the vagina. Cytologic or biochemical studies may be an important approach to a quantitative test in the human, but up to now no reliable test is available, apart from the counting of folded cells which may give an approximate indication of gestagenic action.

Secondary effects of gestagenic hormones

As mentioned, there also are a number of secondary effects of gestagenic hormones, for example thermogenic effects, alteration in the personality, alteration of the physical stature of the patient, and retention of body water. There may for example be an increased production of saliva, the thyroid gland may alter its function, there occur changes in the blood, there may occur changes in the liver structure and liver function of unknown significance. The blood vessels in general may undergo alterations, and there may be an increased tendency for the development of varicosities and also alteration of the blood coagulation processes. Some of the gestagens, especially the newer synthetic gestagens may also have some androgenic, estrogenic or antiestrogenic effects. There may also occur effects similar to those of the adrenal corticosteroids.

Action spectra

A useful description of the primary effects is obtained by constructing a kind of action spectrum of the steroid. Action spectra of a large number of gestagens, using animal tests have been compiled by JUNKMAN (1963). A classification based on biological properties has also been discussed by EDGREN et al. (1967). By definition, the normal endogenous gestagen, progesteron, is then considered to have an even spectrum with a relatively equal degree of effect on all primary functions. A synthetic gestagen, on the other hand, may have another action spectrum. There may for example be excessively great hypothalamic-hypophyseal effects, or there may be an excessive action at the level of the cervix and on the vagina. Examples of some action spectra are shown in Fig. 1. Information pertinent

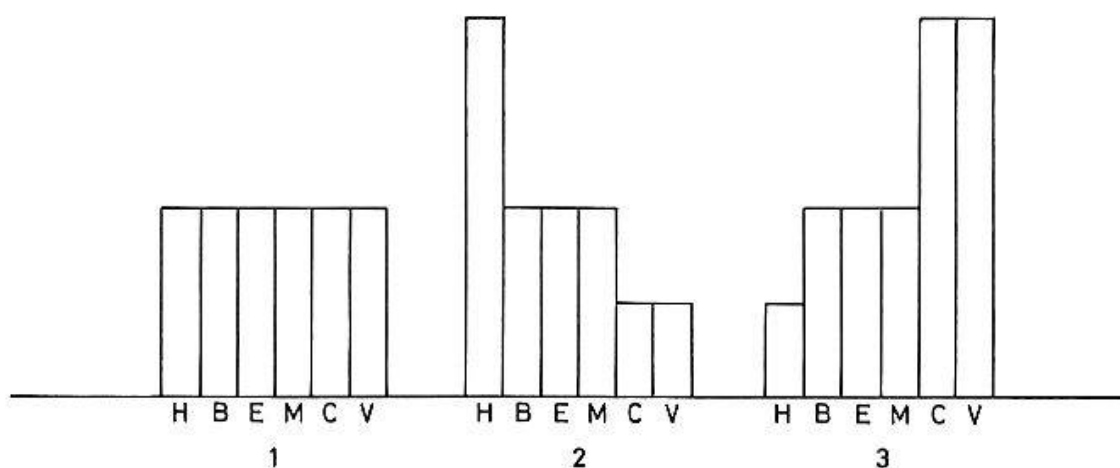


Fig. 1. Action spectra of progesterone (1), a steroid with high hypophyseal inhibition and small cervico-vaginal effects (2), and a steroid with small hypophyseal inhibition and pronounced cervico-vaginal effects (3). H denotes hypothalamic-hypophyseal-ovarian effects, B = breast effects, E = endometrial effects, M = myometrial effects, C = cervical effects, and V = vaginal effects. Basis for normalization = endometrial effects.

to the action spectra in human has been obtained o.a. from the references given by EDGREN et al. (1967).

Molecular chemistry and biophysics

From the chemical point of view the gestagens are steroids. There seem to be several structural requirements for gestagenic action, for example 1. a non-phenolic A ring, 2. a double bond in or associated with the A ring, 3. one or two non-keto radicals at the 17-carbon, and 4. absence of a radical in the 11-position.

There are however great chemical differences among the various gestagens, and some kind of chemical classification of the progestational agents is necessary. A useful first-order classification is based on the configuration at carbon 10. There are three main groups:

- I. *Progesterone derivatives* with the 19-C attached to the 10-C in β -position (19β -steroids).
- II. *Retrosteroids* with the 19-C attached to the 10-C in α -position (19α -steroids).
- III. *19-nor-steroids*, without a carbon in 19-position.

The basic configurations around the 10-19 carbons of these three groups of steroids are shown in Fig. 2. In group III it is not always clearly stated whether the hydrogen at position 10 is behind or in front of the ring planes. It seems usually to be present in the β -position.

All clinically used gestagens fall within these three main groups. It is nowadays fairly well established that the retrosteroids differ biologically from the 19β - and 19-nor-steroids in several respects. The action of the hypothalamic-hypophyseal-ovarian axis is considerably reduced, i.e. the action spectra are of the kind shown in Fig. 1.

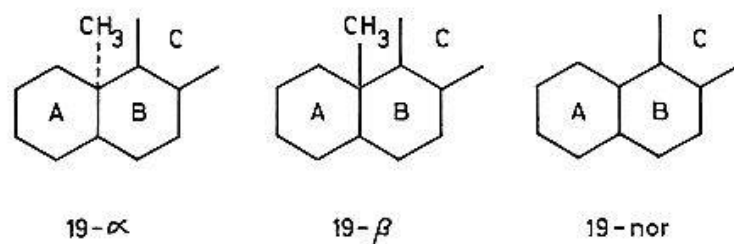


Fig. 2. Basic configurations of 19α -, 19β - and 19-nor -gestagenic steroids.

One important aspect is the molecular shape. As pointed out by SHOPPEE 1952, there is a definite shape to the molecules of steroid nature possessing different functions (for example adrenocorticosteroids, heart glycosides, gestagens and androgens). The retrosteroids differ in molecular shape in comparison to a 19β - and 19-nor -steroids, and this may be an explanation for their different action spectrum.

Another very important aspect of the gestagens is their metabolism. It is now wellknown that an ethinyl group is not, or only slowly, metabolized in the body. For example, if norethisterone is given, part of this is recovered as ethinyl-estradiol in the urine. The ethinyl group thus follows the steroid nucleus during the metabolic processes. It is well possible that unknown metabolites or perhaps unknown stereochemical configurations may be associated with biological action which may contribute in part to the effects recorded in the human organism. Presently, a lot of work is being done on the metabolism of gestagens, and certainly much information will be available within the next few years.

Biophysical studies on gestagenic actions

In recent years biophysics has contributed to the understanding of the actions of gestagens by facilitating studies of the molecular structure of cervical mucus, sperm penetration, and uterine contractility.

Another biophysical method which may contribute to the knowledge of gestagenic effects is the technique for measuring of the ovarian size (ODEBLAD, 1968a). Using a transmitter and receiver coil system, a method has been developed for the measurement of ovarian size in the living intact organism during the bimanual examination of the ovary. The method is based upon the transformer action between a transmitter and a receiver coil, attached to the inner and outer index finger during a gynecologic examination (Fig. 3). In a methodological study, the ovarian size was followed during 14 normal cycles, during 8 cycles of spontaneous anovulation, and during 12 cycles of anovulation induced by oral contraceptives. The three types of cycles were found to have characteristic properties using this type of investigation, and can be reliably distinguished (Fig. 4). Thus, during normal cycles with ovulation there are differences in ovarian sizes between the left and right side during the corpus luteum phase. During anovulation there

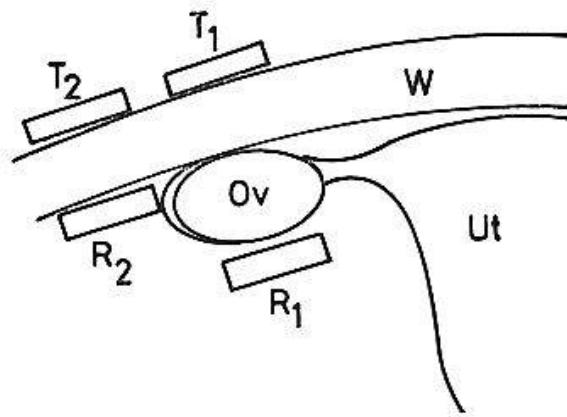


Fig. 3. Principle of electromagnetic determination of ovarian size. W = abdominal wall, Ov = ovary, Ut = uterus. T₁ and R₁ = positions of transmitter and receiver coils for measurement over ovary + abdominal wall. T₂ and R₂ = positions of coils for measurement over abdominal wall only.

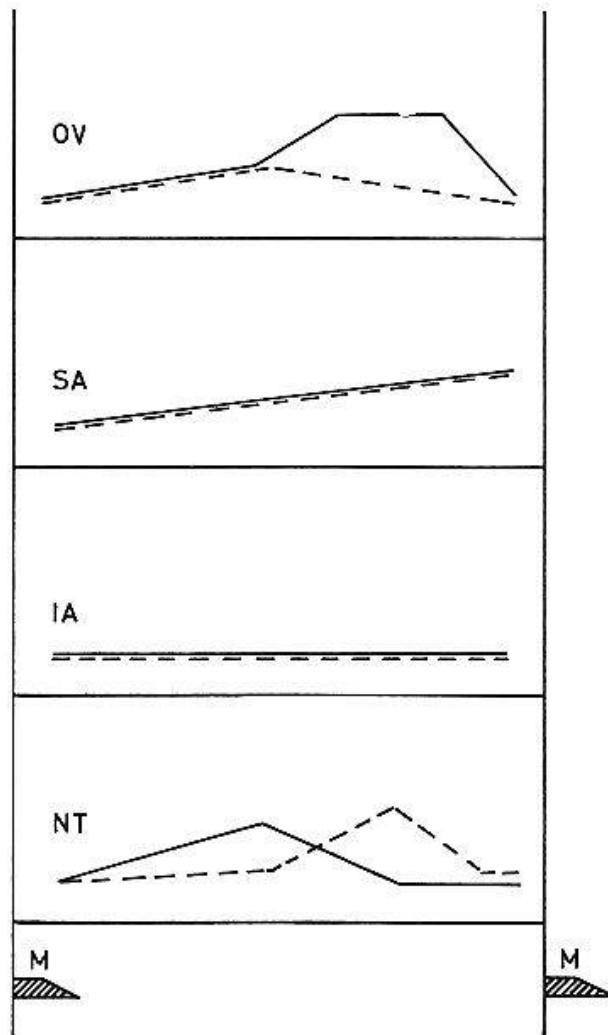


Fig. 4. Types of ovarian size curves. OV = normal ovulatory cycle, SA = spontaneous anovulation, IA = induced anovulation, NT = non-typical cycle at low-dosage gestagen treatment. Full line = right ovary. Dotted line = left ovary. M = menstruation.

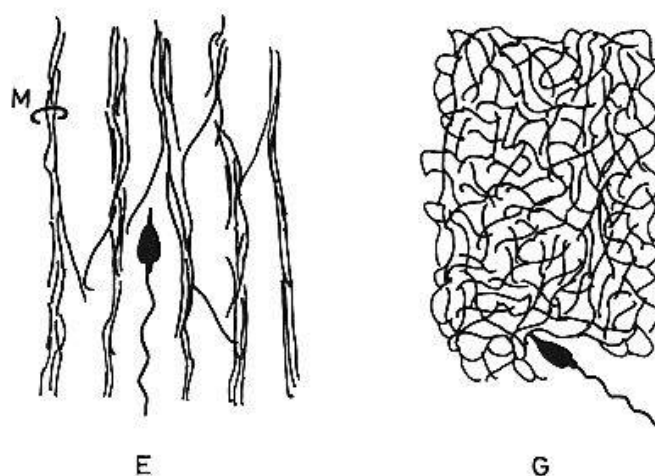


Fig. 5. Schematic diagrams of molecular structure of cervical mucus. E = estrogenic type, G = gestagenic type of mucus. M = micelle in E-type mucus.

is no such difference. The two types of anovulatory cycles can be distinguished due to the fact that in spontaneous anovulation both ovaries increase slowly in size during the course of the cycle, but in cases of induced anovulation both ovaries remain morphologically inactive. Atypical size variation curves due to delayed or multiple ovulations or luteinizations can also be picked up.

Effect of gestagens on cervical secretions

One aspect which has been specially investigated in our department is the effect of gestagenic hormones on the human cervical secretion. As mentioned previously, gestagens tend to make the cervical mucus harder and more viscous and impermeable to sperm cells. We have studied this effect in detail with special regard to the molecular structure of the cervical mucus using nuclear magnetic resonance and other biophysical methods (ODEBLAD, 1968b). It has been found that gestagenic hormones tend to split up the molecular micelles which are normally present in the estrogenic type of mucus (Fig. 5). This leads to a dense and compact network of macromolecules which does not permit the head of the sperm cell to penetrate into the meshes. This is believed to be the basic action of gestagens on the molecular level. The situation is, however, more complicated because it has been shown that the cervical glands possess different reactivity. Some of the glands respond in this normal manner to gestagenic hormones. Other glands do not possess this normal response but continue to secrete a thin estrogenic type of mucus even when there is a heavy gestagenic stimulus. This leads to a heterogeneity of the cervical mucus which is especially pronounced if the cervical mucosa is morphologically altered by the ingrowth of a large transformation zone (Fig. 6). For details, see the monography by ODEBLAD (1966).

The heterogeneity of the cervical mucus is important in several aspects. One aspect is that the analytical results may show a greater variability. Another complication to the heterogeneity is that sperm penetration may

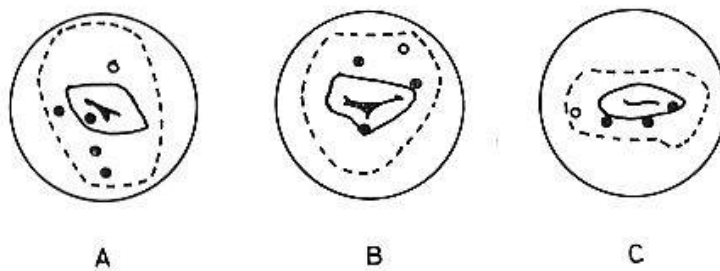


Fig. 6. Three examples of a portio with cervical glands with different reactivity. The glands described by filled circles produce normal G-type of mucus on gestagenic stimulus. The glands with open circles produce E-type of mucus on gestagenic stimulus due to some kind of pathologic alterations in the gland. The full line embraces the ectopic zone, the dotted line embraces the transformation zone.

occur in isolated areas of cervical mucus if the patient is given a small dose of gestagens with a purpose to bring about contraception. This may be a limiting factor for the lowest dose of gestagens possible to give with a safe contraceptive effect.

Time factors

One recently recognized important aspect of gestagenic action is the time relationship. A given gestagen can be metabolized or eliminated rapidly or slowly, and this is valid also for the metabolites of the steroid. If the metabolites have gestagenic or (which may happen) estrogenic action, there may arise a complicated time scale of biological effects. The experimental study of these effects is very difficult. In our laboratory we have developed a method to get some information on this complex phenomenon. We have primed the patients with a constant dose of estrogen to bring about a constant base level. After 5-10 days of priming, a single heavy dose of a gestagen has been added and the various parameters of interest have been studied by repeated samplings (for example from the cervix). In this way we have been able to distinguish short and long biologic action from each other. Two retrosteroids have been investigated, both with short action (about 8 and 18 h respectively) and a 19-nor progestational steroid with a long action time (about 100 h). It is believed that this approach may be of considerable value for the understanding of biodynamics and practical application forms of gestagenic compounds.

Summary

The importance of human studies in the field of gestagens is stressed. Action spectra showing the different effects in the humans may be used. Some aspects of the molecular chemistry of gestagens are presented. The contributions of biophysics to the study of gestagenic action mechanisms are discussed and three new applications are briefly presented: 1. The measurement of ovarian size as an expression of gestagenic action on the hypophyseal system, 2. the molecular biophysics of the cervical mucus under

gestagenic action and its relation to sperm penetration, and 3. the time factors involved in biologic action of gestagenic compounds.

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Discussion

J. HAMMERSTEIN: Professor Odeblad, I think I missed the point. How did you measure the size of the ovary during the cycle? You gave a draft, but I had problems to understand it.

E. ODEBLAD: When we perform the clinical examination of the patient, we apply to the finger an electric coil – on the index finger which is introduced into the vagina –, and we have another coil on the other finger which is applied to the abdomen of the patient, and we catch the ovary between the fingers when doing it by manual examination. We feel the ovary and get a difference between the coils, and we move the fingers to the side of the ovary. Now one coil acts as a primary coil in a transformer, the other coil acts as a secondary coil in a transformer. There is an electric pick-up between the coils. When the coils are separated, the pick-up is reduced. This way we can get a distance between the coils. That is just an electric transformer.

J. HALLER: I am also very much amazed that you are in the position to get significant differences not only within the cycle, but also that you can measure practically quantitatively the effect of steroids by means of the difference of the size of the ovary. I think there may be some pitfalls which may go into your measurements (e.g. if you have adhesions or some kind of adnexal inflammation). Certainly a chronic inflammatory condition or differences in the size according to a previous inflammation of the adnexa may give you maybe not only the size of the ovary but also of a tube which is adherent. Secondly, I think that different obstetricians, who are examining, may exert different amounts of pressure. So I think that the first condition or the first obligatory point would be that always the same man is examining and even then I wonder whether your differences are really significant. I think that in very few patients I would be able to get really quantitative differences. Maybe my ability to palpate is not estimated high enough by myself, but I am certain I would not be able. But I should like to try that.

E. ODEBLAD: Well, I did not have time to go through this subject during my lecture but anyhow this can be done only on very co-operative volunteers. For example, from

100 patients we can select perhaps five patients who are willing to co-operate and have the physical stature for doing this so that the thin abdominal walls can relax completely and tolerate the investigation. Of course, there should be no other pathological signs: no inflammation, no uterine myoma or anything else. But in these very few cases we can perform these studies very well and we have performed a statistical analysis on double tests. Actually the error of measurement is amazingly small: only 1 mm on the side of the ovary. We did not believe it ourselves when we got these very good results. But in fat patients this is not possible to do; only in a few well selected volunteers.

H.-J. STAEMMLER: Wäre es nicht präziser, wenn man die Grösse der Ovarien mit Hilfe der Culdoskopie misst? Man kann diese wiederholt anwenden. Wir haben das getan und einen sehr guten Überblick über die Veränderung der Eierstöcke erhalten.

E. ODEBLAD: Aber die Culdoskopie ist ein operativer Eingriff, und unsere Methode kann zehnmal jeden Monat appliziert werden, ohne dass die Patientin daran Schaden nimmt.

H.-J. STAEMMLER: Die Culdoskopie schadet ihr auch nicht.

E. ODEBLAD: Vielleicht. Wir haben das nicht versucht.

J. HAMMERSTEIN: I wonder whether you correlated your findings in the ovary with a urinary steroid excretion analysis, especially in the cases of anovulatory cycles, because there are not only one but at least three types of the anovulatory cycle on the basis of estrogen excretion. I am a little bit doubtful that all anovulatory cycles will have the steady increase in the size of the ovary as you have shown us in the slide. For example, there is one type with the same estrogen excretion throughout the whole cycle, and I could think that in this case the size of the ovary is constant and not increasing. Have you any indication for this?

E. ODEBLAD: We do not have a lot of cases of anovulatory cycles presently. What I showed you is an average of all the examined cases. I know very well that there are quite big differences between different patients. Maybe we can do something more on this subject in the future.

B. LUNENFELD: Do you really try to claim that the size or the increase in size and the biochemical fate of function have to correlate?

E. ODEBLAD: No. I did not say so, but what I said is that we can do all these things together and try to find out how these things really are.

J. FERIN: What could be the significance of the leukocytic infiltration in the cervical mucus during the progestational phase?

E. ODEBLAD: Well, we have performed quantitative cell countings in the cervical mucus, and we have performed, as far as one can, different cell-countings. Actually, there are very, very great variations in the leucocyte infiltration amounting to about the 20-fold range, but we do not know what the cells do there or why they are there. But there is an enormous range of variation and this speaks against some kind of physiological function. I don't know whether this is just an accidental happening or if it has anything to do with it.

B. LUNENFELD: What you called abnormalities of cervical glands, is this a quantitative element? Would you think that the different glands which open up at the portio have a different sensitivity to progesterone or to progestational agents or, when you say abnormality, are they abnormal whatever amount of progesterone you will give?

E. ODEBLAD: Well, first I must say we have been able to investigate only a few patients with various amounts of gestagens. But if we give a very large amount of gestagens, we may get more but not all glands to respond normally. So, there is a kind of quantitative response. But we have, I guess, only fifteen patients in which we have done this study with various amounts of gestagens.

J. HALLER: Did you also examine the single secretory glands in a normal ovulatory cycle? And did you find that – perhaps according to endogenous progesterone – they were responding in the same percentage? Or were the glands, as you called them, abnormal?

E. ODEBLAD: Yes. We have followed normal cycles too, and I should say there is a similar pattern of response in normal cycles as in gestagen-treated cycles.