

**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)

**Nachwort:** Conclusions [for "Symposion : Wirkung oraler Progestativa bei Zyklusanomalien"]

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## Conclusions

E. DICZFALUSY:

Ladies and Gentlemen,

I was asked to make specific comments, but I do not feel particularly qualified, since I could not be present yesterday. So I would rather like to make some very general comments.

I would like to draw your attention to a speech of some couple of months ago. Mr. McNAMARA, the President of the World Bank, delivered an address at Notre Dame University in which, among others, he urged that the World Bank should start supporting research on human reproduction. It is estimated that by the mid 70ies the costs of such research will be around 150 million dollars per year not including the costs of the pharmaceutical industry.

Now, listening to the discussions this morning, it was quite obvious to me that this is indeed a major field in which a lot of effort is needed. You know that the industry is trying to develop fertility regulating agents which will regulate and modify fertility in both directions. You may wonder why the progress is so slow. Well, one reason is that the mode of action of these fertility regulating agents is incompletely comprehended. This applies to the various types of oral contraceptives just as well as to clomiphene. The other reason is that it takes a very long time to have adequate clinical and pharmacological studies and to derive a concept of what a new compound really does. Many companies in the States calculate that it takes them between seven and nine years to develop and put on the market a new product. Now, if you think back to the meeting of this group a year ago and try to compare what was then the state of affairs concerning this very interesting compound, i.e. the Ro 4-8347 compound, and what it is now, I think it is fair to say that the main difference is that the indications have been narrowed down. However, the optimism which prevailed a year ago, let's say concerning the treatment of severe cases of amenorrhoeas, is perhaps less marked today. I think, however, that it is very important before we part to try to get an objective assessment of where we stand. What does this compound do and what does it not? I would like to suggest to Professor LUNENFELD that he should try to give us his views on this subject before I ask Professor FERIN to close the session.

B. LUNENFELD:

Professor DICZFALUSY is trying to stimulate me to give a provocative summary on the effects of Ro 4-8347 on the basis of the numerous reports presented at this Symposium. This is not an easy task due to three main handicaps:

a) Concepts on the regulation of the menstrual cycle are not so clear as they may seem at a superficial glance.

b) Classification of disorders of the menstrual cycle and classification of patients into the different categories are still rather empirical.

c) Actions of fertility promoting agents in general are incompletely comprehended.

It might be worthwhile to discuss these handicaps in the light of this Symposium before we attempt to summarize and draw our preliminary conclusions on the clinical effects of Ro 4-8347.

The role of gonadotropins in the induction of ovulation, at least from the qualitative point of view, seems rather clear. It is therefore not surprising that when treating hypogonadotropic amenorrheic patients a pregnancy rate of above 70% can be attained. The moment one attempts induction of ovulation with gonadotropins, in patients who are capable of producing and releasing gonadotropins, the pregnancy rate drops to 33%. Also the number of courses necessary for pregnancy increases from 3 in the hypogonadotropic group to 6 in the second group.

This illustrates clearly that, in the absence of endogenous gonadotropic action, one can induce ovulation with surprising ease. On the other hand, the presence of endogenous gonadotropins directly or indirectly interferes with such treatment and reduces its efficiency significantly.

During the first part of this Symposium it became evident that the regulation of gonadotropic release is not yet fully understood. Although probably midcycle LH stimulation is responsible for the final maturation of the follicle, ovulation and corpus luteum function, the available data do not permit final conclusions as to the mechanism of the midcycle release of LH.

The long discussion on the existence of a midcycle FSH peak *seems* to be resolved and the majority of authors believe in the evidence of its existence. As to its role, no experimental data exist, and the mechanism through which it is released is uncertain.

It was with pleasure that we ascertained during this Symposium that a number of excellent groups (BETTENDORF; SCHMIDT-ELMENDORFF; HOHL-

WEG and MAYER; KELLER; FERIN and THOMAS; BLOBEL; STAMM, ZARRO and GERHARD; MANCUSO and MONETA) are investigating the effects of progestational and estrogenic agents on the control of gonadotropins. The aim of such basic research is not only to evaluate the role of naturally occurring hormones in gonadotropic regulation, but also to correlate their structure to function. It is this kind of research that will ultimately permit the preparation of "tailor made" agents for specific therapeutic problems.

One of the essential features of hormone action is that, once it has exerted its effect on the target organ or organs, it is removed or inactivated; however, the effects of free and bound hormones, conjugates and metabolites are not fully understood today.

The papers during this meeting which discussed conjugation, metabolism and fate of naturally occurring hormones and of synthetic steroids such as Ro 4-8347 were, therefore, of great importance (BREUER; LAURITZEN; LUNENFELD, KRAIEM and REICHERT; ADLERCREUTZ, JÄNNE, LAATIKAINEN, LINDSTRÖM, LUUKKAINEN and VIHKO; DARRAGH; DAPUNT and GLEISPACH). Such data will probably help in our overall understanding of regulatory processes.

The knowledge of a certain action of naturally occurring hormones or a synthetic compound sometimes makes one forget that such materials have many other actions. A good ovulation inducer, for instance, which will have a negative effect on cervical mucus may be of little use, since although the patient will ovulate, she will not become pregnant. The multiple actions of progestational agents were well illustrated by ODEBLAD's paper.

By the time we have heard the first part of the Symposium we were surprisingly well equipped with data on the chemistry, metabolism and fate of Ro 4-8347, but realized our limitation in the knowledge of reproductive processes. It could therefore not surprise anyone of us that the clinical information which was submitted to us was not uniform, that results varied between different authors and that some may have questioned the progress achieved between our first meeting last year and today. This, I think, was the tune of Prof. DICZFALUSY's comments. But what did the results really show us?

1. Practically all papers agreed that Ro 4-8347 was a potent progestational agent that in the presence of endogenous estrogenic activity will provoke menstruation.
2. Side effects common to most gestagens were not mentioned for this compound during this meeting.
3. Since this compound provokes no hyperthermic effect and no metabolization to pregnanediol, it does not interfere in clinical and laboratory investigations.
4. Ro 4-8347 will be a potent regulator of the menstrual cycle in a number of groups of patients with menstrual trouble.
5. In the usual dosage scheme Ro 4-8347 will not inhibit ovulation in normally ovulating women.

6. In the usual dosage scheme used, Ro 4-8347 will not inhibit gonadal function.
7. No general agreement was obtained on the action of Ro 4-8347 on gonadotropins.

(STAMM, ZARRO and GERHARD concluded that the compound provokes LH release. MANCUSO and MONETA believe that the compound has a direct stimulatory effect on release and/or production of both FSH and LH. HALLER found stimulation with an 8 mg dosage, and also that with a smaller dosage apparently stimulation of gonadotropic activity may occur. KELLER found that in some of the treatment phases there was a slight increase of LH activity, but concluded that the compound generally provoked *no* significant alterations in the LH excretion pattern. FERIX and THOMAS found no stimulatory action on LH.)

These discrepancies are not specific to this compound; the same problems have arisen with many compounds, even such known compounds as estrogen. Depending on the specific case, dose, duration and time of application, different effects can be obtained.

It can therefore be concluded that Ro 4-8347 fulfils all requirements of a potent progestational agent, having the advantage that it produces no hyperthermia, practically no side effects, and due to its lack of an inhibitory action on gonadotropins can be used on a long-term basis.

It is furthermore a cycle regulator, inducing regular menstrual periods, and possibly stimulates ovulation in certain ill-defined normogonadotropic patients. The types of patients who would fit this category are young girls, unmarried women and married women not over-anxious for pregnancy, with menstrual disorders.

With further know-how on regulatory processes, and better definition of disease, defined groups of patients might be found which would respond by ovulation when given this material in the right dose, at the right time and for a correct period.

It is my hope that I have summarized my views on this compound both from what we heard during this Symposium and from our own experience.

J. FERIN :

I fully agree with what has just been said by my friend, Professor LUXENFELD. But I am supposed to make closing remarks which I hope can be adopted by the majority of us.

Ro 4-8347 doubtless is a progestational agent, i.e. a compound which like progesterone is able to induce the secretory transformation of the estrogenic primed endometrium in the ovariectomized woman. In this connection it is approximately twice as potent as dydrogesterone, in my experience. Furthermore, like progesterone this compound can promote the release of LH and probably also of FSH. On the other hand, this compound can also depress the release of these two factors. The quality of its effect is very dependent on the dose, on the duration of administration, on the precise timing of its administration during the cycle and also on the ovarian follicular status at the beginning of treatment. However, though Ro 4-8347 is an interesting potential ovulation stimulator, its efficacy in this respect is limited and not equivalent to the efficacy of clomiphene.

E. DICZFALUSY :

Ladies and Gentlemen,

It remains only that I should thank all the participants and all the members of the audience; I would like to thank especially all of the speakers for their collaboration. The session is closed.