# EFFECT OF SWITCHING WITH ORAL CONTRACEPTIVES

*by*

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More than 16 million women are having oral contraceptives and it is expected that this number will increase within the next few years. In our country, this method was the main one adopted by the authorities, and at the moment about half a million of Egyptian women are having the contraceptive pill.

Switching from one pill to another is a common practice, which is clinically accompanied with many side-effects. This switching may either be due to medical advice, or unavoidable circumstances such as shortage of one preparation or another from the drug stores and Family Planning Centres due to importation difficulties. It could also occur in response to an unwise friendly advice.

Switching could occur in the following way :

I.—The same chemical composition :

*(a)* from a high to a low dose pill.

*(b)* from a low to a high dose pill.

II.—Different chemical composition, either in :

*(a)* oestrogen.

*(b)* gestagen.

*(c)* both components.

III.—A different scheme, e.g., sequential method.

The purpose of the present study was to investigate some of the main clinicopathological aspects of this important and common phenomenon.

## MATERIALS AND METHODS

Participants in this study were from women requesting family planning advice at the Family Planning Clinic, El-Galaa Hospital, Cairo. They were arranged in the following groups :

Group A : Control :

1. comprised 68 users of Vestalin M for 6 months.
2. comprised 55 users of Vestalin Uno for 6 months.

Group B : High to low dose :

comprised 24 users of Vestalin M for an average period of 11 months switching to Vestalin Uno.

Grop C : Low to high dose :

comprised 26 users of Vestalin Uno switched to Vestain M.

Group D : from one chemical composition to another :

1. comprised 41 users of Gynovlar for an average period of 6 months switched to Vestalin Uno.
2. ( i) comprised 14 users of Chlormadinone for an average period of 24 months switched to Vestalin Uno.

   (ii) comprised 18 users of Chlormadinone for an average period of 18 months switched to Vestalin M.

The duration of use of each type of pills depended mainly on its availability at the Centre. All pills were supplied free by the respective firms and were given to users on the same basis.

The chemical composition of pills used is :

1. Vestalin M : 2.5 mg Vinylestrenelone + 0.1 mg Ethinyl oestradiol
2. Vestalin Uno : 1 mg Vinylestrenelone + 0.1 mg Ethiny oestradiol

3. Chlormadinone : 6-chloro-6-dihydro-17-acetoxyprogesterone (0.5 mg).

4. Gynovlar : 3 m Norethisterone acetate + 0.05 mg Ethinyl bestradiol.

A full case history was recorded for every participant who was asked to report to the Clinic at monthly intervals and any complaints were recorded.

Post menstrual endometrial biopsies, between the 5th and 7th day of the cycle, were obtained before the start of the pills, before the switch and at the end of the trial of the second drug. Paraffin sections were prepared and stained routinely with haematoxylin and eosin. A detailed histopathological examination of the sections was performed which included estimation of the average number of endometrial glands per low power field of the microscope, the hieght of their lining epithelium and the texture of the stroma.

## RESULTS

Table 1 shows the side effects occuring during the adminstration of Vestalin M and Table 2 those with Vestalin Uno. It is apparent that amenorrhea, hypomenorrhea and break through bleeding, the main clinical side effects with which we are concerned in the present study, showed much reduction in their incidence in the second tablet i.e., with Vestalin Uno.

The histopathological features are reported as follows :

Group B : from high to low dose pills :

Fig. 1 shows the endometrial pattern of one of the participants in this group, which represents the rest, before the start of adminstration of pills. A normal pattern is seen and a higher magnification of this is shown in Fig. 2.

Fig. 3 shows her endometrial picture nine months after the start of the pills, when she came complaining of severe hypomenorrhea. Marked reduction in the number and height of the lining epithelium of the glands is quite evident as well as areas of oedema, loose stroma and interstitial haemorrhages. This could explain the hypomenorrhea associated with such an endometrium.

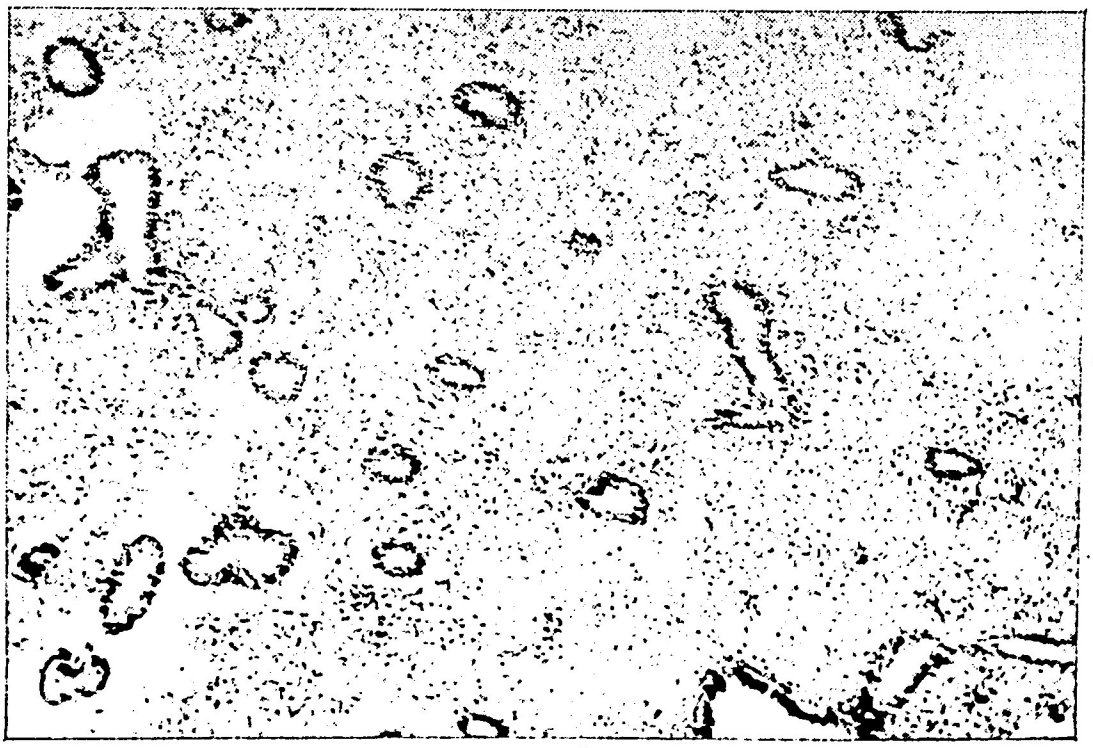
TABLE 1

Vestalin M

Percentage of side-effects according to No. of Participants in each cycle

| | 1st cycle | 2nd cycle | 3rd cycle | 4th cycle | 5th cycle | 6th cycle |
|---|---|---|---|---|---|---|
| Number of cases | 53 | 45 | 40 | 36 | 31 | 25 |
| Side Effects | | | | | | |
| Amenorrhea | 7.5 | 4.4 | 22 | 11.1 | 12.8 | 12 |
| Hypomennorhea | 3.9 | 2.2 | 5.9 | 8.3 | 25.8 | 24 |
| Break Through Bleeding | 9.4 | 11.1 | 7.5 | 0 | 9.3 | 8.0 |
| Spotting | 0 | 0 | 0 | 0 | 3.0 | 4.0 |
| Lactation | 5.6 | 0 | 0 | 0 | 0 | 0 |
| Headache | 9.4 | 11.1 | 15 | 19 | 22 | 28 |
| Dyspepsia | 7.5 | 4.4 | 5.0 | 5.5 | 6.4 | 4.0 |
| Vomiting | 5.4 | 4.5 | 0 | 0 | 0 | 0 |
| Hair loss | 2.9 | 0 | 0 | 0 | 0 | 0 |
| Pregnancy | 0 | 0 | 0 | 0 | 0 | 0 |

Vestalin M : 2.5 mg. Vinylestrenelone + 0.1 mg. Ethinyloestradiol



Flg. 1

TABLE 2

Vestalin Uno

Percentage of side-offects according to Number of Participants in each cycle

| Number of cases | 1st cycle | 2nd cycle | 3rd cycle | 4th cycle | 5th cycle | 6th cycle |
|---|---|---|---|---|---|---|
| | 50 | 40 | 36 | 27 | 24 | 22 |
| Side Effects | | | | | | |
| Amenorrhea | 2.0 | 10 | 16 | 14.5 | 15.4 | 3.5 |
| Hypomenorrhea | 8.0 | 17.2 | 11.1 | 11.1 | 12.2 | 13.5 |
| Break Through Bleeding | 2.0 | 5.0 | 0 | 14.5 | 15.4 | 4.5 |
| Spotting | 0 | 0 | 0 | 3.6 | 4.5 | 4.5 |
| Lactation | 4.0 | 5.0 | 0 | 0 | 0 | 0 |
| Headache | 14.0 | 10.0 | 10.0 | 10.0 | 10.0 | 10.0 |
| Dyspepsia | 8.0 | 5.0 | 2.7 | 0 | 0 | 0 |
| Vomiting | 2.0 | 2.5 | 0 | 0 | 0 | 0 |
| Hair loss | 0 | 0 | 0 | 0 | 0 | 0 |
| Breast atrophy | 0 | 0 | 0 | 0 | 4.2 | 4.5 |
| Pregnancy | 0 | 0 | 0 | 0 | 0 | 0 |

Vestalin Uno : 1 mg. Vinylestrenelone + 0.1 mg. Ethinyloestradiol

Fig. 4 shows larger magnification of the previous section, demonstrating the oedema and in the meantime, an endometrial gland whose lining epithelium shows marked reduction in its height.

When this patient switched to Vestalin Uno, the amount and length of her withdrawl bleedings improved. Fig. 5 represents her endometrial picture four months following the switch, with a compact stroma, a good number of glands in the proliferative phase, having a good height of the lining epithelium. Fig. 6 reveals a higher magnification of the same section.

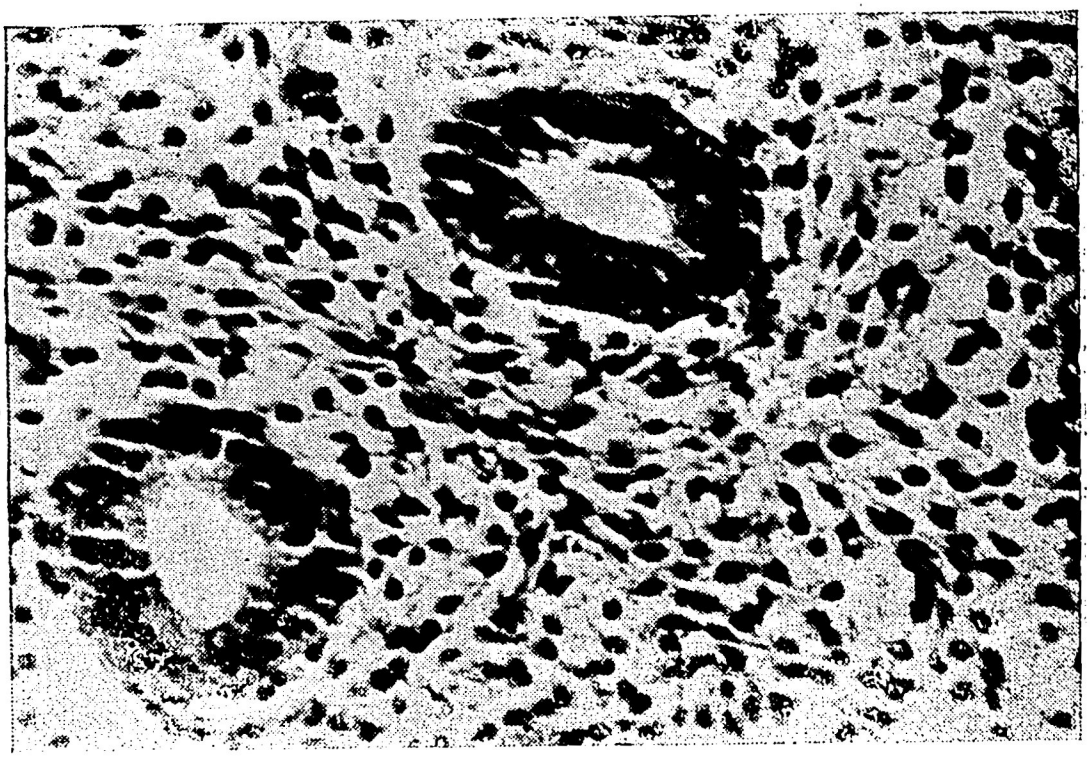


Fig. 2.

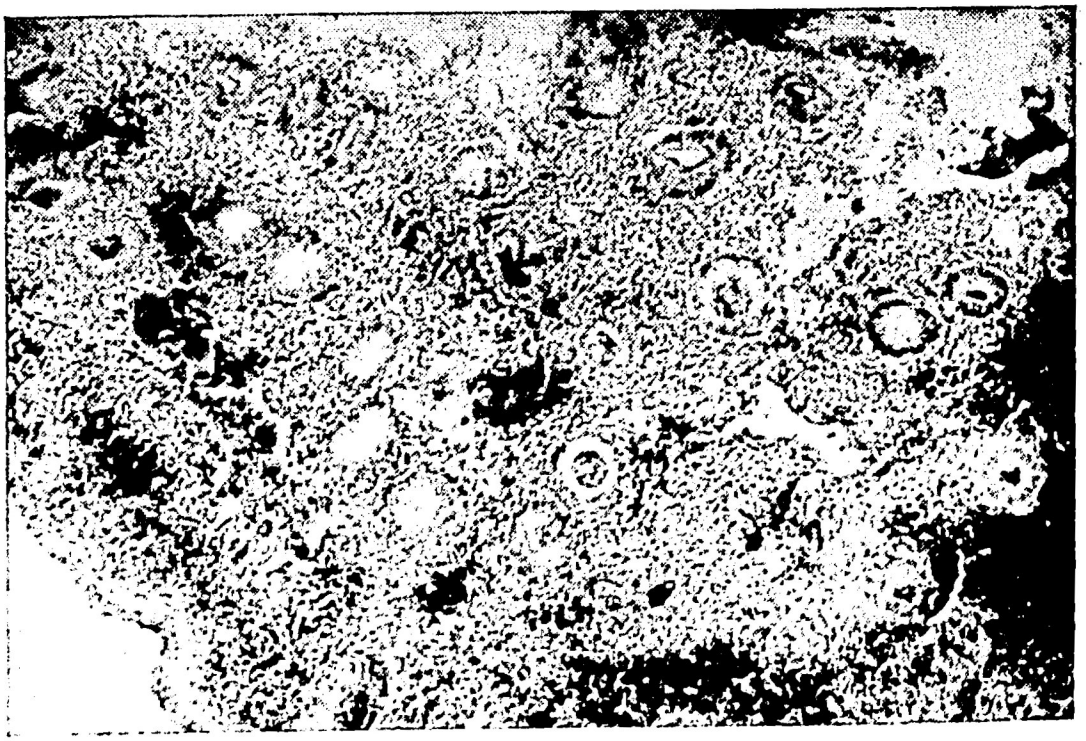


Fig. 3

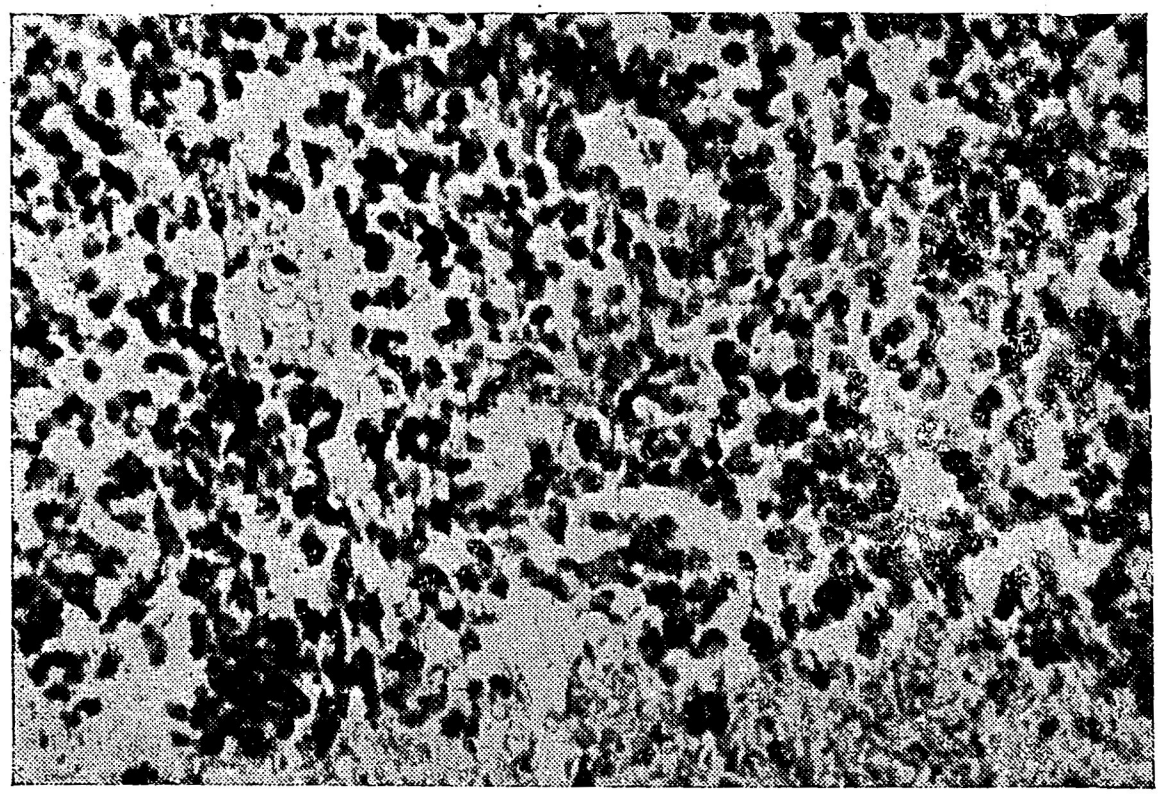


Fig. 4

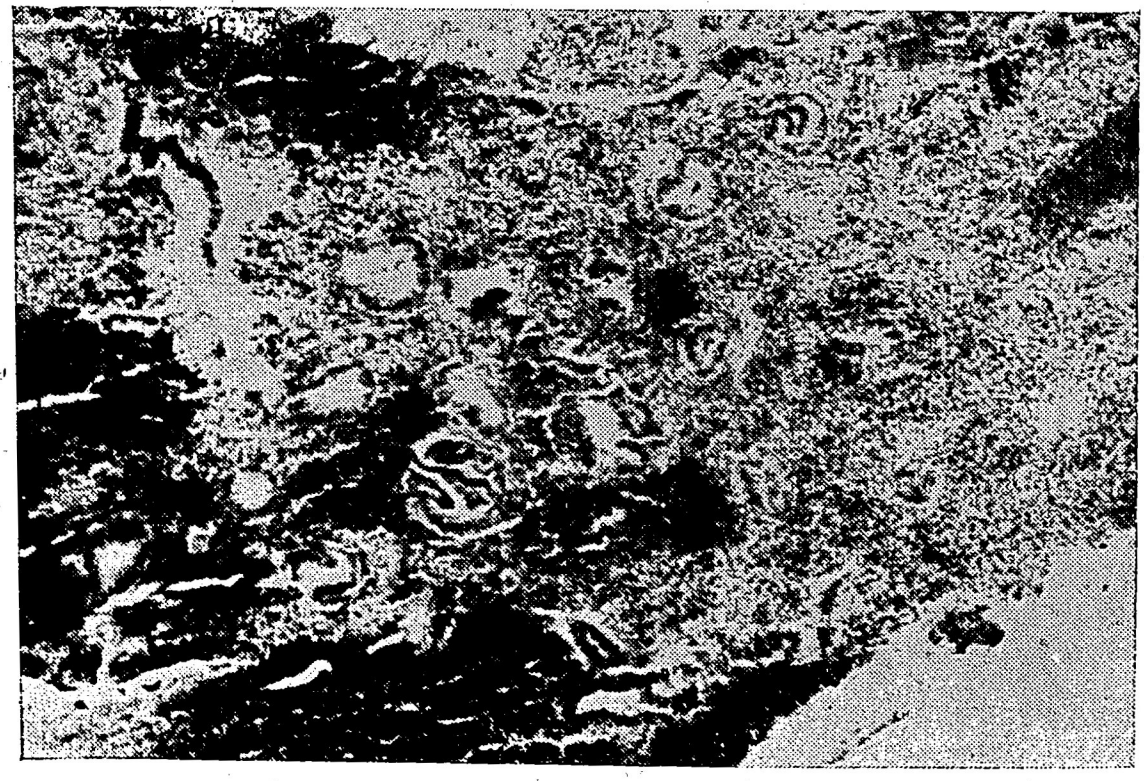


Fig. 5

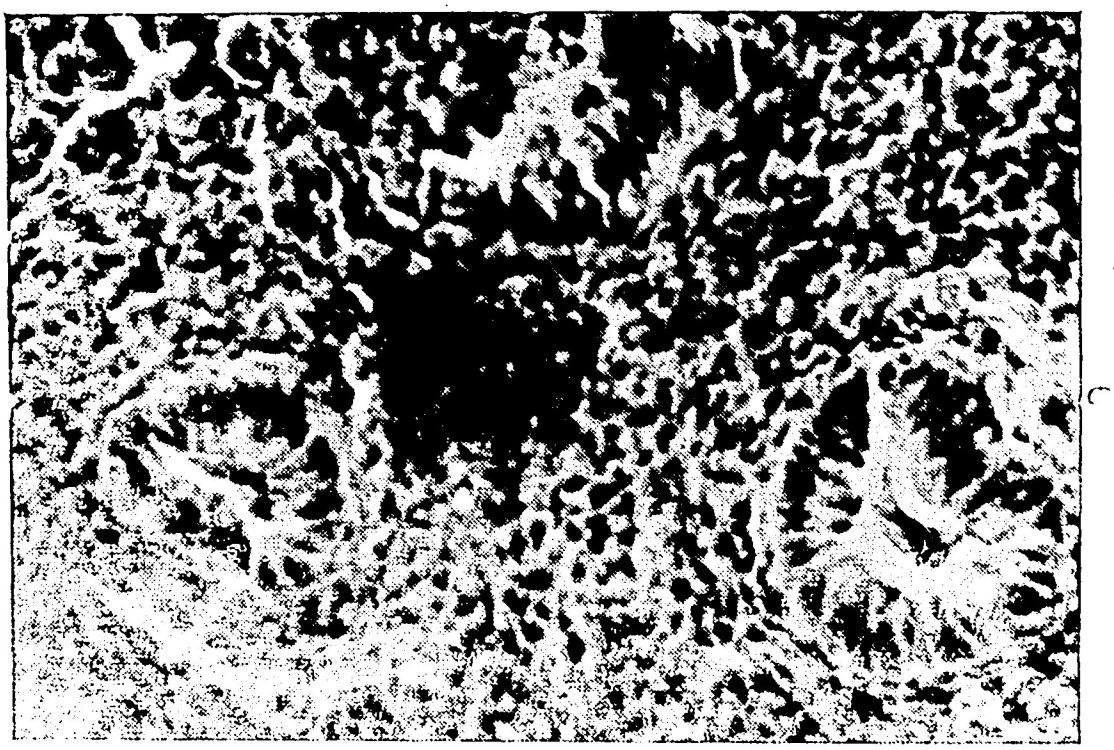


Fig. 6

Group C : from low to high dose pills :

Fig. 7 represents the endometrial features of one of the participants in this group, before the start of having pills, with normal number of glands and compact stroma. Fig. 8 is a higher magnification of the same section.

Fig. 9, reveals her endometrial picture after six months of adminstration of Vestalin Uno, with a compact stroma and almost normal size of the glands with high lining epithelium.

Fig. 10, represents her endometrial picture four months following her switching to Vestalin M, when she started to complain of progressive hypomenorrhea. The stroma is markedly oedematous and loose and the glands are few in number with low height lining epithelium.

Group D : from one chemical composition to another :

Fig. 11, shows the endometrial picture of one of the participants in this group, before having any pills, with a normal pattern. Fig. 12, reveals her endometrial features after 8 months of using Gynovlar when she started to complain of hypomenorrhea. The endometrial stroma is loose, with very few glands, whose lining epithelium is much

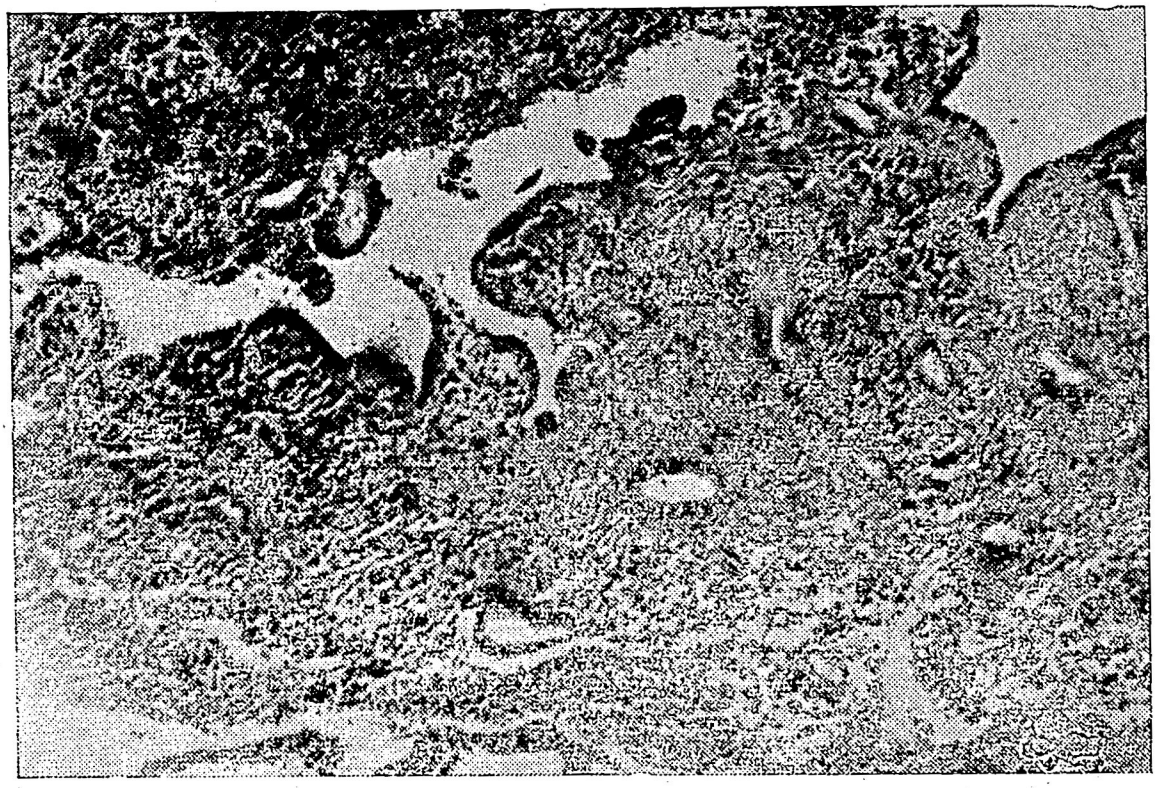


Fig. 7

Fig. 8

Fig. 9

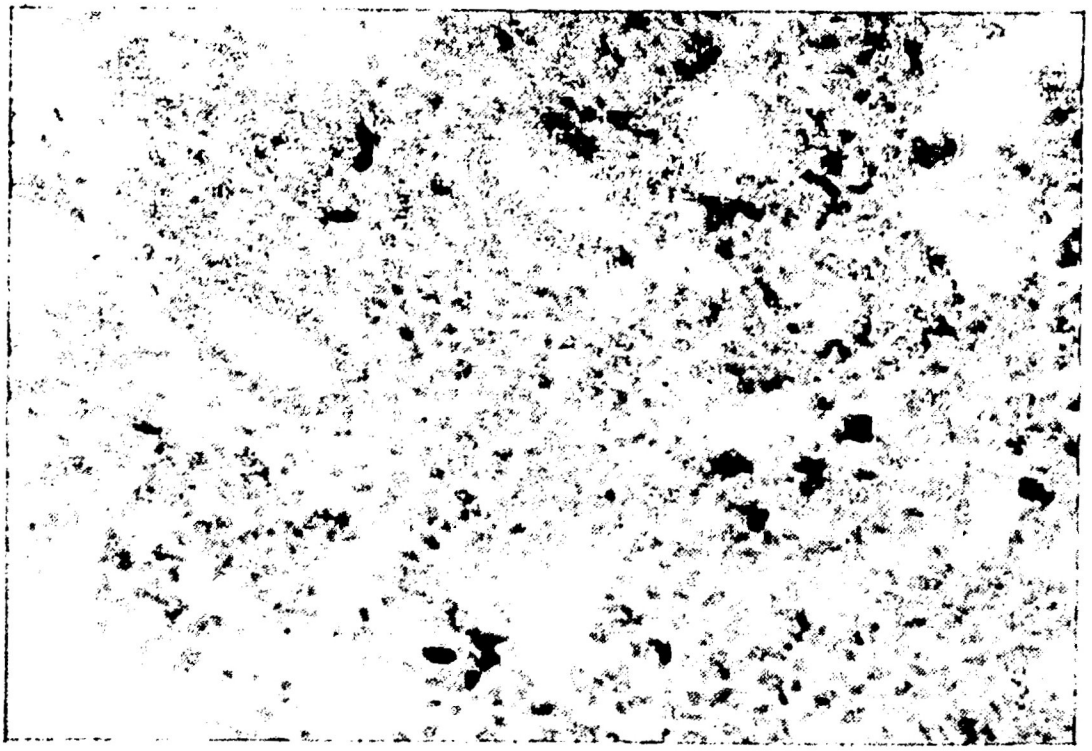


Fig. 10

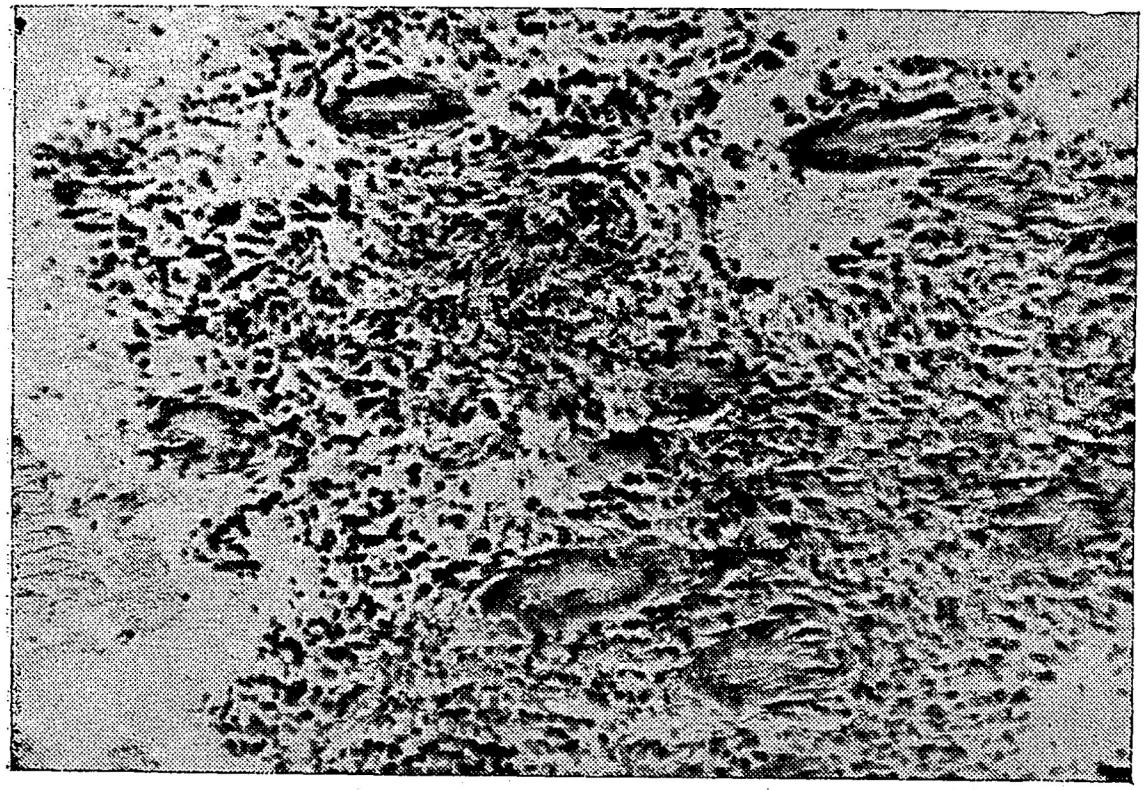


Fig. 11

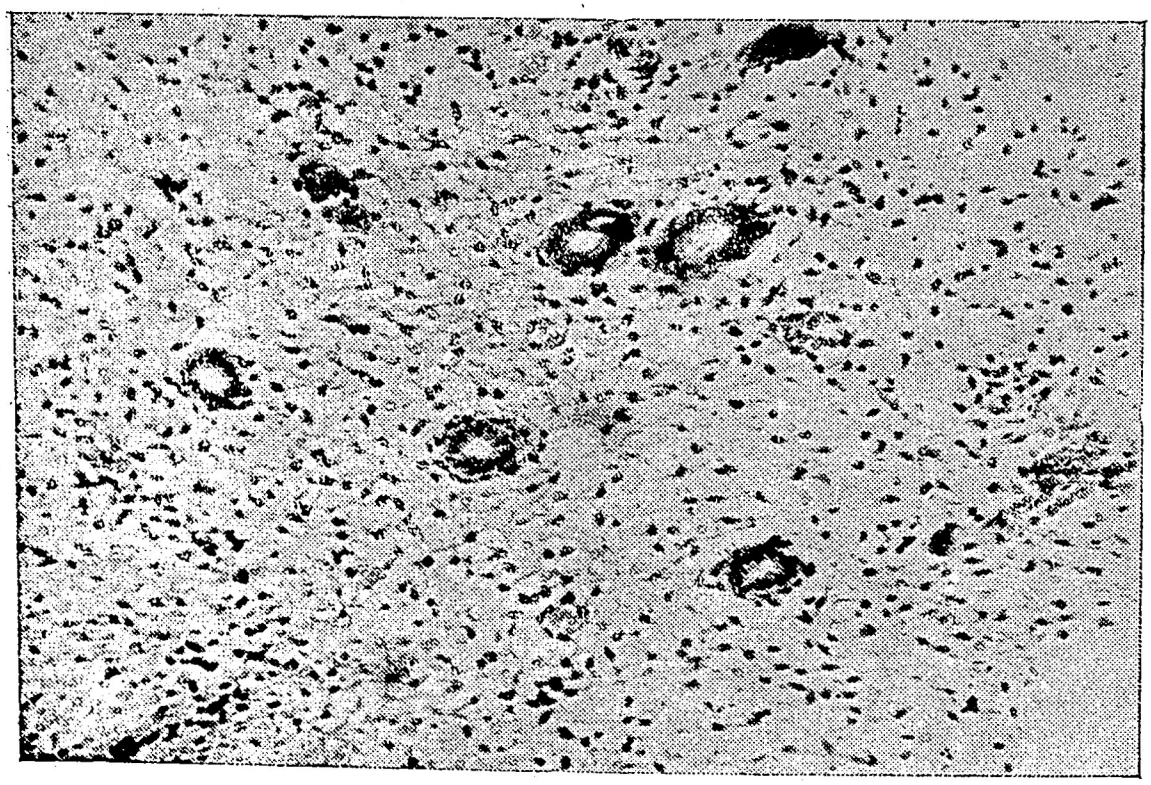


Fig. 12

reduced in height. Fig. 13, represents the endometrium of the same participant four months following her switch to Vestalin Uno When her withdrawl bleeding and endometrial picture returned to almost premedication pattern.

Fig. 13

Group D : from one chemical composition to another :

Fig. 14, shows the endometrial picture of one of the participants in this group before the start of having pills, which is nomal. Fig. 15, reveals her endometrial features six months after the start of having Chlormadinone, with the number of the glands being slightly reduced and the stroma less compact. This is also well demonstrated in Fig. 16. Fig. 17, represents her endometrial picture six months after switching to Vestalin Uno, with the stroma becoming more compact and the height of the lining epithelium of the glands improving. This could probably be due to the presence of the Ethinyloestradiol in the Vestalin Uno.

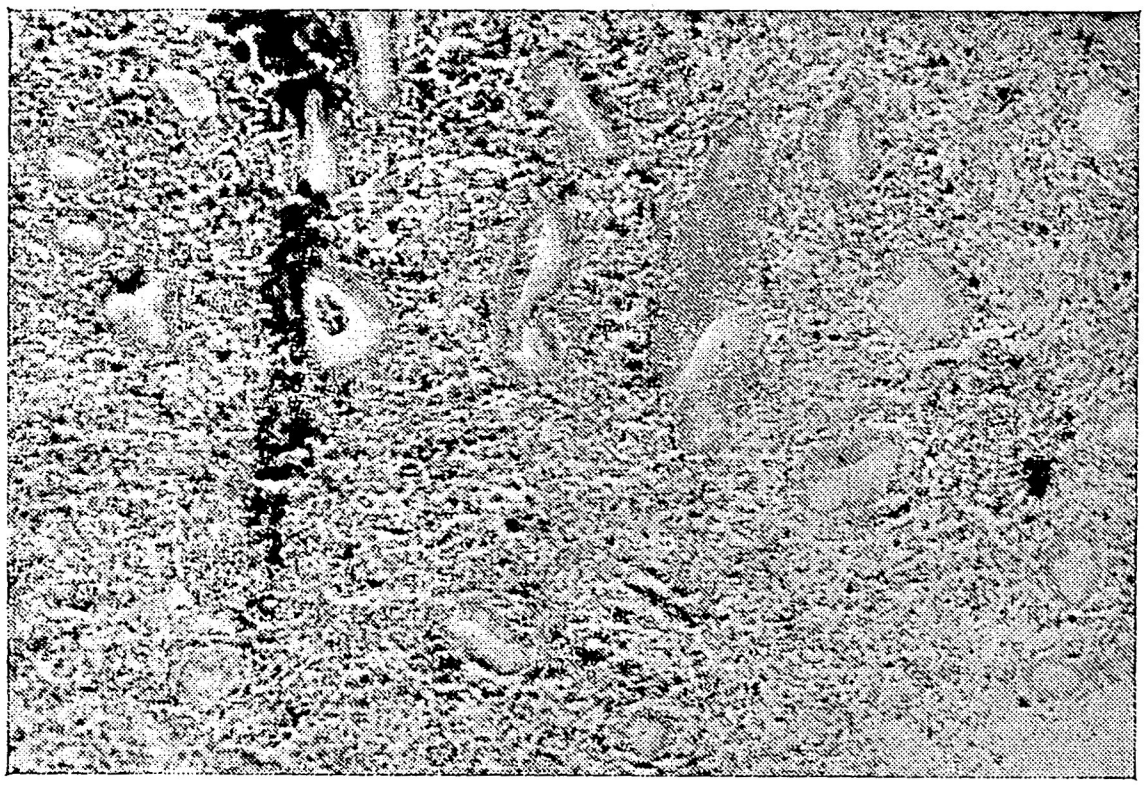


Fig. 14

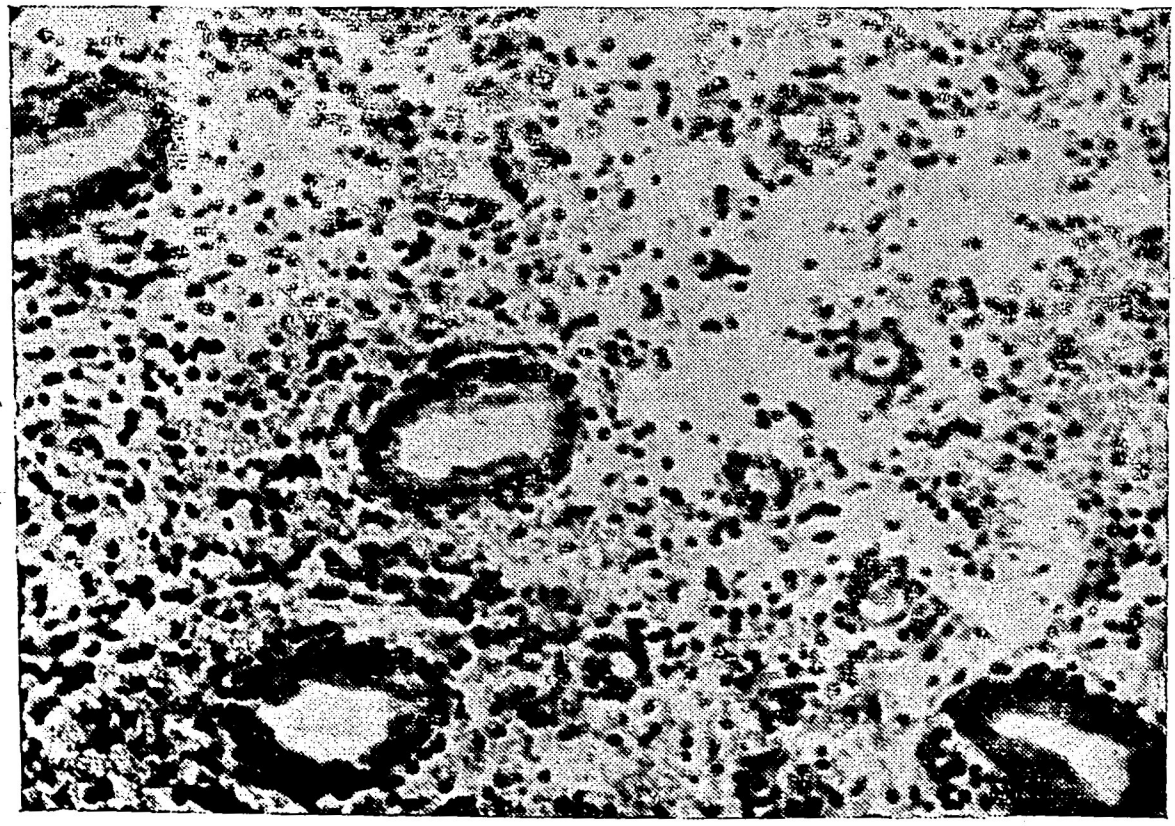


Fig. 15

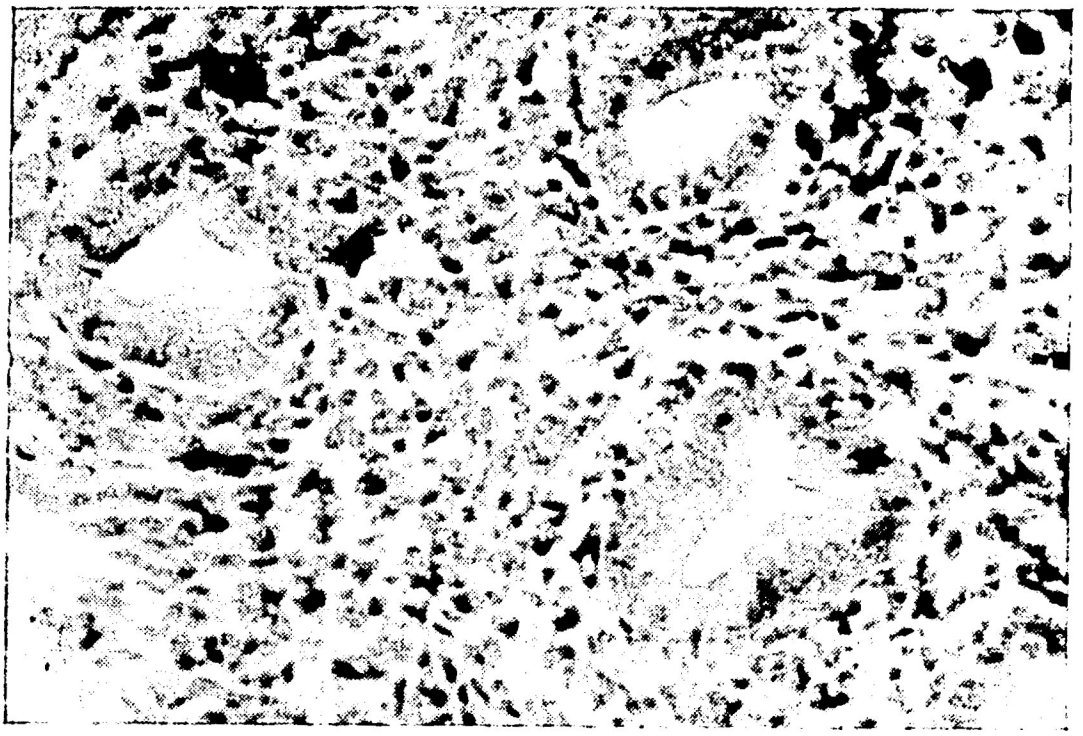


Fig. 16

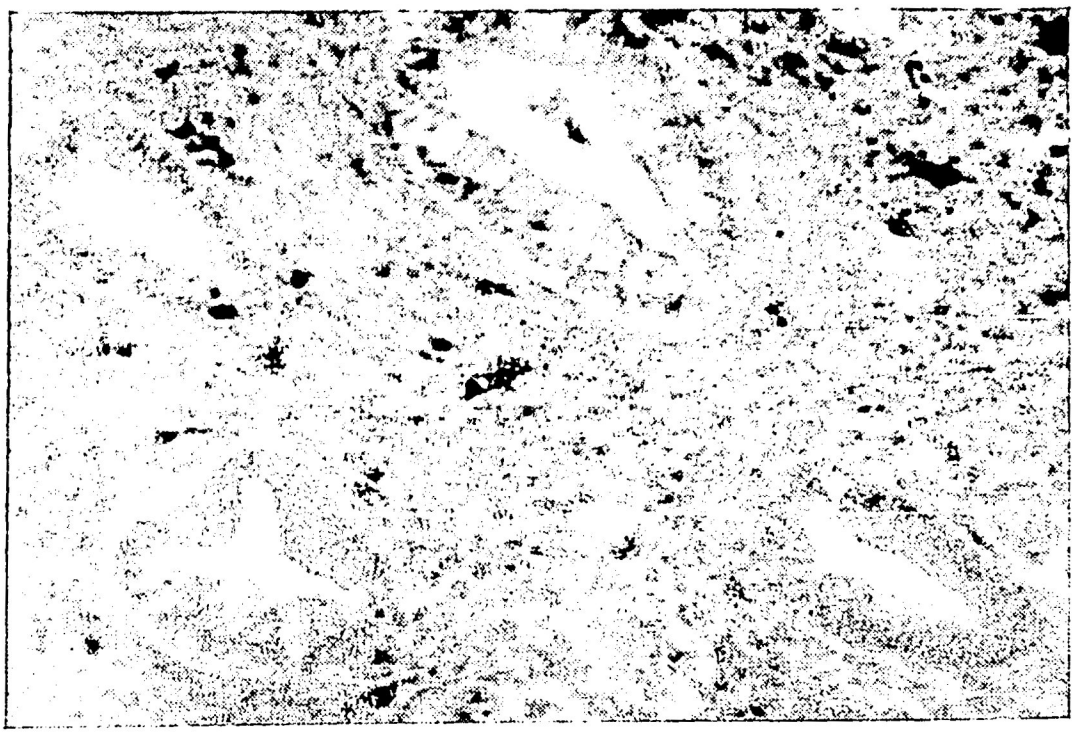


Fig. 17

## DISCUSSION AND COMMENT

Several authors have described the influence of oral progestagens on the endometrium, e.g., Grant (1964), Jackson (1963), Maqueo et al. (1963), Mears (1965), Rice Wray (1963) and Pincus et al. (1958). Some claim that there are features characteristic for the various main types of progestagens, while others as Maqueo (1963) and Rice Wray and co-workers (1963), reported that the endometrial response varies only in minor and relatively insignificant features from one progestational compound to another depending on the specific progestagen.

Very few studies have been devoted to the effect of switching on the endometrium. Mazhar et al. (1965), in their clinical trial found that alteration in the menstrual pattern depended on whether the switch was from a high to a low gestagen level or vice versa. They noted that the higher the gestagen dose and potency, the more the incidence of amenorrhea or hypomenorrhea.

In the present study, the endometrial picture confirms the latter authors findings. The main action of the high dose gestagen level is reduction in the number of the glands as well as the height of the lining epithelium accompanied by an oedematous and loose texture stroma. These findings coincided with the hypomenorrhea and amenorrhea occuring in these women. This is possibly due to the excessive decidual reaction of the stroma as shown in our figures. This reaction gradually involves the compact basal layer of the endometrium, which is not involved in the lutinization process in the secretory phase of the cycle in normal women. It is hence shedded out gradually taking with it the necks of the endometrial glands which are responsible for the regeneration of the endometrium in subsequent cycles. It could be also responsible for the diminution in number of the endometrial glands with the high gestagen level pills and hence the higher incidence of hypomenorrhea and amenorrhea. On switching from a high to a low gestagen level pill, with the oestrogen content being constant, the latter effect predominates resulting in regeneration of the endometrium and marked improvement in the amount and duration of the withdrawl bleedings.

We can conclude, therefore, that women who are happy with a certain type of pill, regardless its high gestagen level should be left alone. Some of these have actually been treated from a pre-existing hypermenorrhea through the therapeutic effect of the high gestagen level in the pill on their endometria. Those complaining of amenorrhea or hypomenorrhea should be advised to have the low level gestagen pill. On the other hand, those switching accidentally to high level gestagen pills may complain of amenorrhea or hypomenorrhea and should be switched to the low level gestagen pill immediately. After all, all actually depends on the hormonal pattern of the certain woman who is having a certain type of pills and her response will therefore depend on such pattern.

Finally, it is interesting to note that none of our participants got pregnant during the period of study with the exception of one case whose endometrial biopsy showed prominent decidual reaction. This occured on the fourth month of use of a low gestagen level pill (Vestalin Uno), after switching from a high dose gestagen pill (Vestalin M). Most probably she got pregnant due to patient failure to have the pills regularily rather than drug failure, although some authors e.g. Dysfalouzy (1969), have drawn the attention to the possibility of occurence of ovulation when switching from a high dose gestagen pill to a low dose one and particularily in the first cycle after the switch.

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