weight of the traumatized horns was 366.4 ± 29.2 mg, and that of the intact horns, 72.1 ± 3.9 mg.

Since, in a majority of these 2 groups of rats, the superficial layers of the vaginal epithelium appeared to have been exfoliated into the lumen before autopsy, in the next series of experiments, 5 OX-DHT-rats and 5 OX-rats were placed on the daily P-OD injection schedule for 5 days, instead of 7 days, after being primed with OD for 3 days from day 60. Uteri were not traumatized.

In 3 of the 5 OX-DHT-rats, vaginal smears were dominated by cornified cells throughout the P-OD injection period. Vaginal cornification on the first 1 or 2 days of the period was undoubtedly due to the residual effects of the OD-priming. Sections through vaginae of these rats, sacrificed on the day following the last P-OD injection, clearly demonstrated a stratified squamous cornifying epithelium and nodular masses consisting largely of lymphocytes and plasma cells embedded in the lamina propria (Figure 3). In the remaining 2 rats which gave leucocytic vaginal smears for the last 2 or 3 days of P-OD injections, the greater part of the vaginal epithelium was stratified squamous but not cornified. Small patches of mucified epithelium were found in the depths of the mucosal folds.

Five OX-rats gave predominantly cornified vaginal smears for the first few days of P-OD injections due to the residual effects of OD-priming, followed by leucocytic smears for the rest of the injection period. At autopsy, the vaginal epithelium was invariably mucified, as evidenced by the positive PAS reaction (Figure 4). Different amounts of amorphous material, not necessarily PAS-positive, and some leucocytes were present in the lumen.

To compare the initial state of the vaginal epithelium, 6 OX-DHT-rats and 5 OX-rats were killed on day 60. At the time of sacrifice, the OX-DHT-rats invariably had the vaginal orifice showing leucocytic vaginal smears, while the OX-rats were still without the aperture. Histological studies revealed a marked difference in structure of the vaginal mucosa between the 2 groups. In OX-rats, the vaginal epithelium consisted of only 2 to 3 layers of small cells (Figure 5). The vaginal lumen was almost empty. By contrast, in the OX-DHT-rats, the vaginal epithelium was decidedly thickened, consisting of 2–6 layers of much larger cells, as compared with that in the OX-rats (Figure 6). Occasionally, areas infiltrated with leucocytes occurred in the epithelium. The vaginal lumen was distended, being filled with numerous leucocytes. The lamina propria was diffusely infiltrated with lymphocytes and plasma cells.

In both OX- and OX-DHT-rats killed on the day following injections of 0.2 µg OD for 3 days from day 60, the vaginal epithelium was always of the stratified squamous cornifying type. The vaginal lumen contained varying amounts of desquamated nucleated and cornified cells. Lymphocytes and plasma cells were not numerous in the lamina propria of the vaginal mucosa in the OX-DHT-rats, except in one animal in which many ovoid masses of the cells were found (Figure 7). In the OX-rats, these types of cells were few, if any, in the lamina propria.

It seems evident that treatment of female rats with DHT during early postnatal life induces a permanent or at least long-lasting alterations in reactivity of the vaginal mucosa to hormones, so that vaginal cornification can occur under hormone conditions which support development of deciduomata. However, it is not presently known whether the effects are specific to DHT.

Possible effects of lymphocytes and plasma cells on the reaction of the vaginal mucosa to hormones also need to be studied. Cyclical changes in accumulation of plasma cells in the lamina propria of the hamster vaginal mucosa in relation to the blood level of oestrogen have been reported[3].

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## Intrauterine Device Increases the Fibrinolytic Activity of the Rat Endometrium at Deciduation, a New Aspect of its Contraceptive Effect

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*Summary.* The fibrinolytic activity of the endometrium of the two uterine horns in the rat was histochemically determined. One of the horns contained a plastic-IUD, the other served as control. The endometrium of the control horn was almost inactive in contrast with that of the IUD-horn in which fibrinolytic activity was apparent. The fibrinolytic activity induced by the IUD might be involved in the prevention of ova implantation.

The mechanism of the contraceptive effect of intrauterine devices (IUDs) is not yet properly understood. Insertion of foreign material into the uterus causes biochemical and cellular reactions to dispose of the provocative agent[2]. According to GREENWALD[3], the presence of a plastic IUD in the rat uterus causes a local increase in the number of the neutrophils with reduction of fertility as a result. PARR[4] thought that the contraceptive effect might be due to products of cellular decomposition.

It has recently been shown that fertilized rat ova possess a high fibrinolytic activity during their passage through the tubes that on implantation of the ova the activity disappears and that the fibrinolytically active endometrium changes into an almost fibrinolytic inactive decidua[5]. Absence of fibrinolytic activity thus seems to be a necessary pre-requisite for implantation of the ova[5]. But IUDs have recently been shown to increase the fibrinolytic activity of the endometrium[6,7]. We thus thought that the increased fibrinolytic activity at the time of implantation and deciduation might be one of the reasons why IUDs have a contraceptive effect. We therefore studied the effect of a plastic device on the fibrinolytic activity of the rat endometrium at the time of implantation.

*Materials and methods.* 13 Sprague-Dawley female rats, weighing 180–220 g were used. They were fed a standard diet and maintained in an artificially illuminated room. Surgery was performed under ether anaesthesia and under

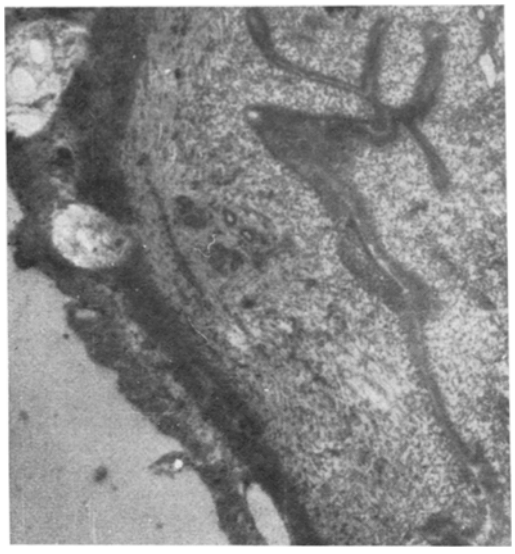

Fig. 1. Fibrinolytic activity of rat uterine horn (control). Note lytic zones confined to small vessels in the outer layer of the uterine wall while the endometrium is inactive even at incubation time 60 min. Magnification 2.5 × 6.3.

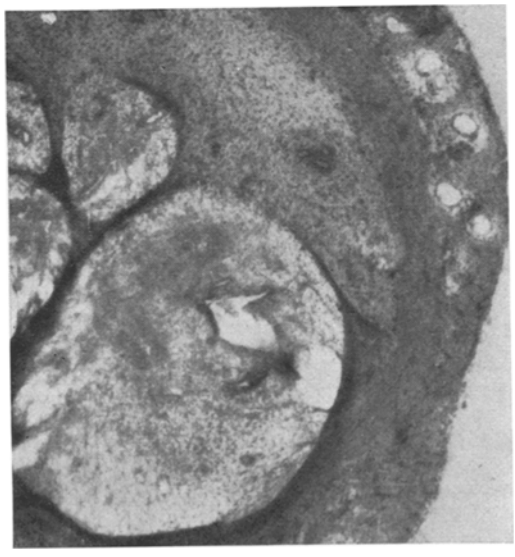

Fig. 2. Fibrinolytic activity of rat uterine horn containing a plastic IUD. Note lytic zones confined to the endometrium already at incubation time 45 min. Magnification 2.5 × 6.3.

Fibrinolytic activity of the rat endometrium at time of implantation of ova

| Rat | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Right horn | 3.5 | 3.5 | 3.5 | 3 | 3 | 3 | 3 | 5.5 | 3.5 | 3 |
| Left horn | 0 | 0 | 0 | 0.5 | 0 | 0 | 0 | 0.5 | 0 | 0 |

Plastic IUD in right horn. Left horn control. (Histochemically determined. Arbitrary units.)

aseptic conditions. The right horn was exposed by a dorso-lateral incision in the flank, and the uterine cavity was opened by a small incision in the antimesometrial wall, about 7 mm below the uterine tubal junction. A plastic IUD 6 mm long and 0.5 mm in diameter was inserted and fixed in position by a nylon thread. The incision in the uterus was closed by a fine silk suture (Ethicon 6:0). The conterlateral horn served as a control. The IUD was left in situ for 3 months.

The females were then caged over night with males of known fertility and every morning they were examined for spermatozoa or a copulation plug. If one or both were present, the animal were regarded as pregnant on day 1.

On day 5 of pregnancy the animals were killed and the uterus was removed. The horns were afterwards immediately frozen in liquid propane. Cryostat sections (8 µm) were placed in a plane through the previous site of the plastic IUD, and in a corresponding part of the control horn. The sections were collected on cleaned glass slides. 4 slides with 8 sections on each were prepared for every sample. The fibrinolytic activity was determined histochemically with the method of TODD[8], as modified and graded in arbitrary units by PANDOLFI[9]. Incubation times of 15, 30, 45 and 60 min were used.

The fibrinolytic activity in the IUD-horn as well as in the control horn was found to be confined to small vessels in the outer layer of the uterine wall. The endometrium of the control horn was almost inactive, even after incubation for 60 min (Figure 1). In contrast, fibrinolytic activity was increased in the endometrium of the IUD-horns (Figure 2). The difference in endometrial fibrinolytic activity of the horns is given in the Table.

Deciduation of the rat endometrium begins on the 5th day of pregnancy. In agreement with previous observations[5], the endometrium in the control horn was almost fibrinolytically inactive on that day. IUDs have been shown to raise the fibrinolytic activity of the human non-pregnant endometrium[6] and in the non-pregnant endometrium of the rat[7]. The present findings show that the IUD also is capable of increasing the fibrinolytic activity of the rat endometrium at the time of implantation of ova.

The proteolytic activity of cells in cultures prevents their adhesion to substrates[10–12], to surfaces and to one another[13–15]. The IUD-induced enhancement of the endometrial fibrinolytic activity might thus prevent adhesion and implantation of ova, and thereby help to explain the contraceptive effect of the IUD.

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