

peutic possibilities of this hormone for the relief of intermittent claudication are being investigated.

It is, of course, well known that the circulation in the skeletal muscles can be increased by chemical means or in response to increased work. The purpose of this presentation is to show that such changes in circulation do not appear to be effected through a nervous mechanism.

9772

Induction of Oestrous Changes in the Monkey and Bitch by Triphenyl Ethylene.* †

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It has been shown previously (Robson and Schönberg¹) that triphenyl ethylene will induce oestrous changes in the genital organs and mating in ovariectomized mice and hypophysectomized rabbits. The effects in mice may last for several months. In the present experiment the action of this substance has been investigated in monkeys and in a bitch.

Two monkeys (*Macacus rhesus*, weighing 4.25 kg. and 3.8 kg. respectively) were ovariectomized and the first injection was given 24 and 31 days later. At the time of the first injection the sexual skin was pale in both animals. The substance was injected subcutaneously in solution in oil.

Monkey I received 1.2 gm. at the first injection, 1.0 gm. 4 days later and 1.2 gm. 8 days after the first injection. Eleven days after the first injection the whole sexual skin, including the base of the tail, became red and somewhat swollen and the redness and swelling increased during the ensuing week and was then maintained until the animal was killed for postmortem examination, 26 days after the first injection. Histological examination showed that the vaginal wall was very thick and consisted of an outer almost completely cornified zone and an inner zone of nucleated cells. The condition was similar to that produced by the injection of oestrin in the ovariecto-

* This is part of work carried out in collaboration with Professor A. Schönberg on the activity of certain synthetic oestrogenic substances.

† The expenses of this investigation have been defrayed by a grant from the Medical Research Council.

¹ Robson, J. M., and Schönberg, A., *Nature*, 1937, **140**, 196.

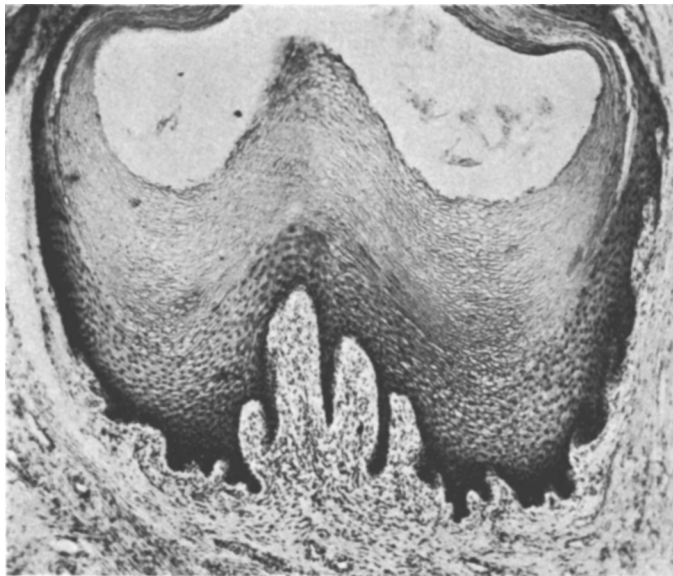


FIG. 1.

Microphotographs of sections from Monkey I treated with triphenyl ethylene.
A. Vagina. $\times 70$.



FIG. 1. B. Cervix. $\times 115$; to show squamous metaplasia.

mized monkey (*e. g.*, Allen²). The cervix showed epithelial hyperplasia and also squamous metaplasia affecting especially the base of the glands such as has been described as produced by the prolonged action of oestrin (Overholser and Allen,³ Engle and Smith,⁴ Zuckerman⁵). Sections of the vagina, of the cervix and of the glandular endometrium are shown in Fig. 1.

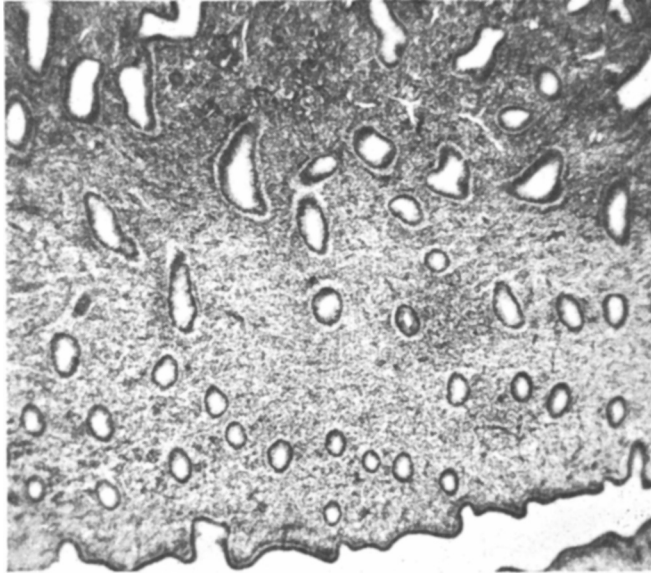


FIG. 1. C. Endometrium. $\times 35$.

The second monkey showed typical changes in the sexual skin (redness and swelling) 7 days after the injection of 1.0 gm. of triphenyl ethylene. This animal has received further injections and is being kept for observation over a more prolonged period. It has received a total of 8.0 gm. of triphenyl ethylene over a period of 4 weeks and has shown no signs of ill health.

No sexual relations were observed when the first monkey was put with a mature male macacus after ovariectomy but before injection. After the typical sexual skin changes had been produced by triphenyl ethylene this monkey was mounted by the male. The second monkey was, however, mounted by the male both before and after the injections and hence the previous result is inconclusive.

² Allen, E., *Am. J. Anat.*, 1928, **42**, 467.

³ Overholser, M. D., and Allen, E., *Surgery, Gyn. and Obstetrics*, 1935, **60**, 129.

⁴ Engle, E. T., and Smith, P. E., *Anat. Rec.*, 1935, **61**, 471.

⁵ Zuckerman, S., *Lancet*, 1937, 435.

A bitch weighing 11.4 kg. and showing no signs of oestrus was ovariectomized. Five days later she received 1.0 gm. of triphenyl ethylene in oil subcutaneously. Four days after the injection some swelling of the vulva was noted and on this and on the next 2 days the vaginal smear contained a number of erythrocytes. Eleven days after the first injection 0.2 gm. of triphenyl ethylene was injected and another 0.2 gm. was given on the next day. The swelling of the vulva gradually increased and attained a maximum 14 days after the first injection; this maximum was maintained for some 10 days and then the swelling gradually decreased. Twelve days after the first injection the animal was put with a male and full mating occurred, lasting some 15 minutes. Mating occurred daily during the next 5 days, but no mating took place later on. The animal was subsequently hypophysectomized, then injected with a total of 5.8 gm. of triphenyl ethylene over a period of 16 days. No toxic effects of any kind were produced. Swelling of the vulva occurred, the animal showed sexual interest when put with the male, but no mating occurred. Eleven days after the last injection the animal was killed for postmortem examination. This showed that the removal of the pituitary had been complete. The uterus was very large, both muscle and endometrium being hypertrophied. The changes were similar to those which can be produced by the injection of oestrin in the hypophysectomized and in the ovariectomized bitch (Robson and Henderson⁶).

Experiments were made to determine whether large doses of triphenyl ethylene exerted any toxic effects. Five mature female mice received 100 mg. of the substance in 0.5 cc. oil subcutaneously. Five other mature female mice each received 10 injections (at daily intervals) of 20 mg. of triphenyl ethylene in 0.1 cc. oil. None of the animals showed any toxic effects. The second group of 5 animals was killed 9 days after the last injection and Professor Drennan very kindly examined the organs histologically (uterus, ovaries, liver, kidney, spleen, lungs, aorta, heart); no toxic changes were found. Squamous metaplasia of the endometrium was found in one of these animals (Fig. 2). This is of interest since McEuen⁷ has described squamous metaplasia occurring after prolonged treatment with oestrin.

Triphenyl ethylene has a low oestrogenic activity. Its activity as estimated by vaginal cornification in mice is about 1/10,000 that of oestradiol.

⁶ Robson, J. M., and Henderson, W. R., *Proc. Roy. Soc.*, 1936, 120 B, I.

⁷ McEuen, C. S., *Am. J. Cancer*, 1936, 27, 91.

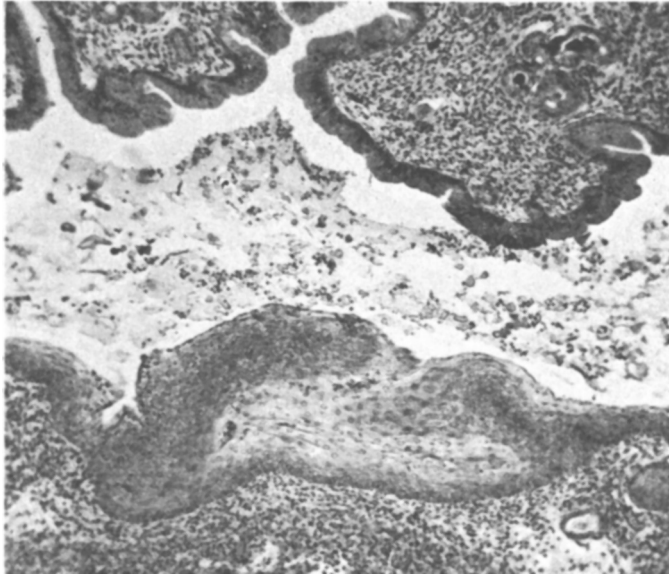


FIG. 2.

Microphotograph of section of uterus of mouse treated with triphenyl ethylene; to show squamous metaplasia. $\times 80$.

The substance is, however, of interest for the following reasons: Its toxicity is very low since no recognizable harmful effects were produced by the following total dosages (subcutaneous injection) 5.8 gm. in the bitch; 8 gm. in a monkey; 0.2 gm. in mice; 20 gm. in a mare. In mice the tolerated dose is at least 400 times as great as the vaginal oestrogenic dose.

The ratio between the dose needed to induce mating and that required to produce vaginal cornification in the ovariectomized mouse appears to be much smaller in the case of triphenyl ethylene than in the case of oestrone.

Finally triphenyl ethylene readily produces effects of long duration and this makes it possible to maintain typical oestrous changes in castrated animals with relatively low doses.

Its activity in primates suggests a possible clinical application but this cannot be considered until experiments on carcinogenic activity, now in progress and negative up to the present, have been completed.

Summary. The administration of triphenyl ethylene to 2 ovariectomized monkeys and one ovariectomized bitch produced changes similar to those brought about by oestrin. The bitch mated. No toxic changes were obtained in these animals or in mice injected with large doses of triphenyl ethylene.