of the glans clitoris in the female and of the penis in the male. In six-month-old, testosterone-treated alligators[5,6], the penes hypertrophied so much that the tips of them protruded from the cloaca; similarly, we have observed that testosterone brings about a considerable hypertrophy of the penis of the pond tortoise *Lissemys punctata* (unpublished observation).

The juvenile crocodiles treated with testosterone propionate also show enlarged kidneys (Figure 1, k). In the alligator, FORBES[6] noted that testosterone had no effect on the mesonephroi, but no mention is made of the kidneys. The preterminal segment of the renal tubule of the kidney does not develop into a sexual segment in males of crocodiles and chelonians, and even a relatively heavy dose of the androgen has not brought about the development of this segment in the juvenile crocodile studied by us.

In the female crocodile, testosterone propionate had no appreciable effect on the ovaries and oviducts, which were well formed. There does not seem to be any reminiscent medulla in the gonad, as the exogenous androgen did not develop this into a testis-like structure. The gonads of testosterone-treated female alligators were also not affected, according to FORBES[5,6], but the oviducts showed considerable hypertrophy and their anterior ends were thrown into irregular folds. Similarly the oviducts are also stimulated by testosterone in the lizard[2,3].

The most pronounced effect of testosterone propionate in the immature female crocodile examined by us is the enormous hypertrophy of the clitoris (Figure 1, c). The clitoris of the injected specimen exceeds even the size of the penis of the control male and compares well with the penis of the injected male. In the six-month-old alligators, testosterone had no effect on the clitorides of the females[5], but in the seventeen-month-old female alligators, the clitorides were stimulated and the tips of these organs protruded out of the cloaca[6]. It is not clear why androgen had no effect on the clitoris of an earlier stage in the alligator; probably it was not sensitive to androgen. In the immature female terrapin[4], testosterone also caused the hypertrophy of the glans clitoris.

To sum up, testosterone propionate induces spermatogenesis in the testes of immature crocodiles and causes enormous development of the penis and clitoris. The Wolffian duct of the male shows slight enlargement, while the ovaries and the Mullerian ducts in the female are not affected on receiving the androgen. The preterminal segment of the renal tubule of the treated kidney did not develop into a sexual segment in the male crocodile, though the kidney itself showed enlargement.

Zusammenfassung. Nicht geschlechtsreifen, zweijährigen Krokodilen aus gleicher Brut wurden je 25 mg (Gesamtdosis) Testosteronpropionat verabreicht. Sektionsbefund 7 Tage nach der letzten Injektion: Spermatogenese und entwickelte Spermien, Rückbildung des interstitiellen Gewebes. Penis und Klitoris hypertrophisch. Nierenvergrösserung, Ovarien und Müllersche Gänge unverändert. Kontrollen ohne Spermatogenese, jedoch mit Vermehrung der Leydigschen Zellen.

L. S. RAMASWAMI and D. JACOB

Department of Zoology, University of Rajasthan, Jaipur (India), September 8, 1964.

Estrogen-Induced Uterine Metaplasia in Rats Given Oral Supplements of Vitamin A[1]

Many investigators[2-4] have noted an apparent antagonism between estrogen and vitamin A with a certain balance between these two substances being required to maintain normal reproductive tract morphology in female rats. A further extension of this concept which has gained some support is that estrogen stimulation of experimental animals may cause a hypovitaminotic A condition. Thus, MCCULLOUGH and DALLDORF[5] and CRAMER[6] speculated that estrogen-induced uterine metaplasia may be a result of a deficiency in vitamin A which develops after prolonged hormone stimulation. The present investigation was designed to test this hypothesis by studying the effect of two levels of excess vitamin A on uterine stratified squamous metaplasia (keratinizing metaplasia) resulting from exogenous estrogen treatment.

Materials and methods. Forty-eight Wistar strain rats were bilaterally ovariectomized at 20 days of age and maintained on a vitamin A-deficient diet thereafter. These animals were divided into five experimental groups as follows: (1) untreated, (2) estrogen treated (2.3 mg estradiol cyclopentylpropionate per week), (3) estrogen treated plus 250 international units (IU) of vitamin A per week, (4) estrogen treated plus 100,000 IU vitamin A per week, (5) 100,000 IU vitamin A weekly. All animals were sacrificed after 60 days (80 days of age). The uteri were embedded in paraffin and sectioned at 8 μ. Every fifth section was mounted and stained with Harris' hematoxylin and eosin.

Results. The data (Table) reveal that when exogenous estrogen is administered to rats deficient in vitamin A (group 2) the uterine lesions are numerous and extensive. The simultaneous administration of moderate amounts of vitamin A suppresses the incidence of the lesions (group 3). In contrast, high doses (group 4) apparently introduce other factors, at present unexplained, and afford very little protection against the adverse effects of prolonged estrogen injections.

Discussion. The high degree of metaplasia observed in the uteri of animals of group 2 was expected since the combination of hypovitaminosis A and excess estrogen stimulation (in amounts used in this investigation) is known to precipitate such lesions[7].

[1] This research was completed while the author was a student in the Department of Anatomy, Bowman Gray School of Medicine, Winston-Salem, N.C. It was supported by a grant from the National Vitamin Foundation. The author is indebted to Dr. W. J. Bo for suggesting the problem and for making himself available for consultation.

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Reports on the vitamin A requirements for the normal albino rat vary widely. However, it appears that 250 IU/week is about twice the normal requirement to maintain the integrity of mucous membranes[8]. The relative inhibition of estrogen-induced endometrial metaplasia by these moderate doses indirectly supports the contention of McCULLOUGH and DALLDORF[5] and CRAMER[6]; i. e. that vitamin A deficiency is an etiological factor in producing these lesions. However, it is certainly not proof of this hypothesis since uterine keratinizing metaplasia never develops in bilaterally ovariectomized rats maintained on vitamin A-free diets for long periods of time, e.g. group 1 of the present investigation. Furthermore, estrogen-treated rats develop keratinizing metaplastic lesions without other gross signs of vitamin A deficiency (unkempt fur, dyspnea, etc.). The absence of heteroplastic changes in the uteri of the ovariectomized, vitamin A-deficient rats supports the suggestion of Bo[9] that a deficiency of this vitamin is not an important factor in producing stratified squamous metaplasia in the uterus of the rat.

Incidence and extent of metaplastic lesions observed in the uteri of the animals within the five experimental groups

Group	Treatment	No. of rats	No. of rats with uterine metaplasia	Extent of lesions [a, b]
1	Ovariectomized Vitamin A-deficient diet	7	0	—
2	Ovariectomized Vitamin A-deficient diet Estrogen	11	10	+++ (4); ++ (5); + (1)
3	Ovariectomized Vitamin A-deficient diet Estrogen 250 IU vitamin A	9	2	+ (2)
4	Ovariectomized Vitamin A-deficient diet Estrogen 100,000 IU vitamin A	15	12	+++ (4); ++ (7); + (1)
5	Ovariectomized Vitamin A-deficient diet 100,000 IU vitamin A	6	0	—

[a] + indicates one to several metaplastic foci of the glandular or luminal epithelium; ++ indicates more numerous small metaplastic lesions; +++ indicates very extensive metaplastic lesions involving the entire or nearly the entire endometrium.
[b] Numbers in parentheses indicate number of animals with a lesion of this extent.

Although the importance of an adequate supply of vitamin A for maintaining most epithelial membranes is well established, evidence is accumulating which indicates that high doses of vitamin A are just as deleterious as an absence of this vitamin. SHERMAN[10] found that by adding large doses of vitamin A to culture media, a significant decrease in the mitotic index of cultured skin, cornea, and trachea was observed. LAWRENCE, BERN, and STEADMAN[11] reported epithelial atrophy of hamster cheek pouch epithelium after applications of high concentrations of vitamin A. The injurious effects of excess vitamin A were recorded also by FELL et al.[12]. They conjectured that the severe effects on tissue explants were related to the influence of excess vitamin A on the permeability of certain subcellular membranes. Since excess estrogen stimulation also causes degeneration of the normal uterine columnar epithelium followed by reparative stratified squamous metaplasia[13], it is not surprising that when the two were administered simultaneously the percentage of animals with uterine changes was high (group 3). In these experiments, however, atrophic or metaplastic changes were not produced in the uterus when large doses of vitamin A were given alone (group 5). The results show that certain levels of vitamin A and estrogen are required to maintain normal endometrial morphology and that a systemic imbalance of these substances can cause pathological alterations in the reproductive tract of the female rat.

Zusammenfassung. An der Ratte wurde der Einfluss von oral verabreichtem Vitamin A auf die Östrogen-induzierte Metaplasie der Uterusschleimhaut untersucht. Kleine Dosen von Vitamin A (250 IE pro Woche) sind zur Vermeidung dieser Metaplasie wirksamer als grosse Dosen von Vitamin A (100000 IE pro Woche).

R. J. REITER

Experimental Zoology Branch, Directorate of Medical Research, Edgewood Arsenal (Maryland USA), November 30, 1964.

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Effect of Agar on Bradykininogen Levels and Esterolytic Activity in Rat Plasma

Previous results[1] have shown that the increased capillary permeability observed during passive cutaneous anaphylaxis (PCA)[2], induced by heterologous antibody and antigen in the rat, could be suppressed in animals which had received an intravenous injection of starch or agar. This inhibitory effect was obtained in spite of undiminished skin histamine levels and of an unimpaired sensitivity of agar-treated animals to histamine release by compound 48/80, dextran or ovomucoid. These findings led to the conclusion that the release of endogenous histamine probably plays no major role in this type of passive anaphylactic reaction. A similar conclusion, extensive to

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