regulating and anti-inflammatory actions for dexamethasone(8), no substantiation either in the clinic(9) or other laboratory assays has been recorded. Divergence in potency estimates between animal and man should not be unexpected when one recognizes the wide disparity in glucocorticoid potency estimates from different assays.

Ringler and Dulin(10), utilizing 2 different liver glycogen bioassay methods, reported that the glycogenic efficacy of a steroid was a function of the assay procedure, and that the degree of divergence was a direct function of the magnitude of the steroid liver glycogen deposition potency; the greater the potency the greater the divergence in the activities estimated by the 2 assay methods.

The present study was conceived to ascertain if a dissociation in thymolytic and glycogenic actions of a steroid could be realized. On the contrary, glycogenic and thymolytic efficacy studies of 64 steroids of diverse chemical structure have illustrated a strong relationship in these estimates when assessed concurrently in the same animal. Though regression analysis showed the glycogenic and thymolytic potencies were not equal (except at $\rho = 16$), inspection of the difference in potency estimates at the extremes of observation for thymus involution ($\rho = 0.5$ and 100.0) indicate potency assessed by liver glycogen deposition and thymus involution vary only 60% and 25%, respectively.

Summary. In a 5-day bioassay, liver glycogen deposition and thymus involution were simultaneously determined in adrenalectomized, immature male rats. The mean index of precision (λ) for the thymus measurement was 0.150 ± 0.009, whereas the index for the glycogen measurement was 0.188 ± 0.009. Glycogenic and thymolytic efficacy ratios of 64 steroids of diverse chemical structure illustrated a strong relationship in these studies. In brief, steroids exhibiting a thymolytic potency equivalent to hydrocortisone, possessed liver glycogen activity averaging 40% higher and for compounds of greater potency the divergence was smaller, reaching zero when the relative thymolytic potency was about 16. Beyond this potency, a reversal was apparent, thus when the thymolytic potency was 100, liver glycogen activity was 75.

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Potency of Vitamin A Acid in the Vaginal Smear Assay. (27869)

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Vitamin A acid fulfills some of the functions of Vitamin A but is neither stored in the body nor converted to Vit. A(1) and attempts to measure its potency have produced extremely variable results. Arens and Van Dorp (2), by means of the growth assay, found Vit.

A acid to be one-tenth as active as Vit. A, its sodium salt equal to Vit. A. Boguth *et al.*(3) found that equal amounts of Vit. A and its acid were required to reverse vaginal cornification caused by oestradiol and testosterone. Large doses of Vit. A acid were more effective than Vit. A in producing toxic symptoms in rats(4) but judged by its capacity to spare liver stores of Vit. A or to prevent the onset of night-blindness, Vit. A acid was completely inactive(5).

It was observed in this laboratory that Vit. A acid reversed, temporarily, the cellular changes of the vagina brought on by Vit. A deficiency. A means was thus afforded to simplify the method of Boguth *et al.*(3) by eliminating the treatment with oestradiol and testosterone. This paper reports the use of such a modified vaginal smear assay in estimation of the potency of all-*trans*, 2-*cis* and 6-*cis* Vit. A acid and an investigation into its sparing action on Vit. A in the vaginal smear assay.

Experimental. Young, female rats of the Food and Drug colony (Wistar strain), fed a Vit. A-free diet from weaning, were ovariectomized when 7 weeks old. Vaginal smears were examined daily until the rats became deficient in Vit. A as indicated by a preponderance of squamous epithelial cells in the smears. A detailed account of this technic has been published by Pugsley *et al.*(6) and, more recently, by Embree *et al.*(7). At this point a single oral dose of Vit. A acetate (reference Standard) or crystalline all-*trans* Vit. A acid* in corn oil was given by means of a tuberculin syringe and blunted needle. Vaginal smears were examined for the 2 following days and a rat was judged to be cured of Vit. A deficiency when the squamous epithelial cells were replaced by leucocytes. The percentage of rats "cured" by the initial dose of Vit. A or Vit. A acid was recorded and as soon as the rats were once more deficient the procedure was repeated with larger or smaller doses. In this manner a range of doses which provided cures of from 0% to 100% was obtained. 2-mono-*cis* and 6-mono-*cis* Vit. A acid were tested in the same manner.

* Distillation Products Industries, Rochester, N. Y.

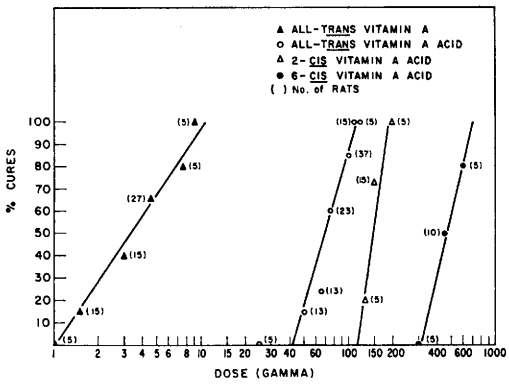

FIG. 1. Percentage of deficient rats cured by various amounts of Vit. A and Vit. A acid.

The sparing effect of Vit. A acid was measured in 2 vaginal smear assays. Twenty deficient rats were dosed with sufficient Vit. A acetate to maintain a non-deficient smear for about one week. In addition Vit. A acid was given daily for 5 days to half of the rats and the number of days required to deplete both groups of animals was recorded.

Results. The smallest dose of Vit. A with any effect on the vaginal smears (Fig. 1) was 1.5 μg (5 I.U.) and 9.0 μg (30 I.U.) gave 100% cures. This latter dose approximates the smallest used in the normal vaginal smear assay and prevents deficiency symptoms for about one week. All-*trans* Vit. A acid had no effect on the vaginal smears in amounts less than 50 μg while 110 μg cured all those treated. The smallest effective dose of the 2 mono-*cis* Vit. A acid was 130 μg and 200 μg provided complete cures while the less complete data on the 6 mono-*cis* acid indicated that 700 μg would cure all of the rats treated. Even the largest doses of Vit. A acid maintained a non-deficient smear for not more than 3 days.

The results of 2 vaginal smear assays in which Vit. A acid was given as a supplement in the first 5 days of the assay period are shown in Table I. Under these circumstances Vit. A acid exerted no effect on the rate at which reserves of Vit. A were expended.

Discussion. It seems characteristic of Vit. A acid that each method used to measure its biological potency provides a different answer. Judged by the amount required to change the smears of all rats in a deficient

TABLE I. Lack of Sparing Effect of Vit. A Acid on Vit. A in Vaginal Smear Assay.

Dose				
Vit. A (μg)	15	15	30	30
Vit. A acid (μg)*	—	50	—	100
Response (days)	7.6	8.3	9.1	8.9

* Administered for first 5 days only.

group Vit. A acid was 8% as active as Vit. A. This is similar to estimates made by the growth assay(2) but differs from the results of Boguth *et al.*(3) who found Vit. A and its acid equal in potency. The technic of Boguth *et al.* required much larger doses and there is some indication that the estimated potency of Vit. A acid varies with the size of the dose, *e.g.*, the slope of the response curve of Vit. A acid was greater than that of Vit. A. The amount of Vit. A required to cure all deficient rats in a group was 6 times that required to cure any, while the same response could be obtained by doubling the smallest effective dose of Vit. A acid. Similarly Matschiner and Doisy(8) found that increasing a dose of Vit. A acid 10-fold had a more marked influence on Vit. K deficiency than did a similar increase in Vit. A. In this respect Vit. A acid differs from other forms of Vit. A, such as the *cis* isomers, which have low biological potency but a response curve of the same slope as the all-*trans* form. Perhaps this characteristic of Vit. A acid is related to the fact that excess amounts cannot be stored but are quickly metabolized.

The 2-*cis* and 6-*cis* isomers of Vit. A acid, for which potencies have not previously been reported, were 50% and 15% as active respectively as the all-*trans* isomer. This relationship resembles that of the same isomers of Vit. A and suggests features common to both in the metabolic pathways of Vit. A and Vit. A acid. This hypothesis is difficult to reconcile, however, with the lack of sparing action of Vit. A acid for Vit. A which has been demonstrated by 3 methods, disappearance of liver stores(5), appearance of night-blindness(5) and by the vaginal smear assay.

Summary. The biological potency of Vit. A acid was measured by a modified vaginal smear assay and found to be 8% that of Vit. A. The results suggested that the potency of Vit. A acid, relative to that of Vit. A, may vary with the dosing level used. 2-*cis* and 6-*cis* Vit. A acid were 50% and 15% respectively as potent as the all-*trans* form. Vit. A was not spared by daily doses of Vit. A acid.

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Arterial Blood Flow During Elevated Intrapulmonary and Intra-Abdominal Pressures. (27870)

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It is now generally recognized that cardiac output decreases in man(1,2) and animals (3,4) during continuous positive pressure breathing (CPPB); however, mainly indirect methods such as skin or muscle temperature (5,6,7), plethysmography(8,9) and local ab-