pteridine is oxidized by xanthine oxidase, although the product was not identified; and recently the production of isoxanthopterin by this reaction has been postulated to take place in the elytra of beetles, although no experimental details were given (*6*).

Since it is likely that a variation in the amount of isoxanthopterin would manifest itself during the synthesis of the eye pigments, 44 eye-color mutants of *Drosophila* (*7*) were tested qualitatively for the presence of the enzyme, in the following way. Larvae (15–20) which were just about to pupate were ground in a small test tube with a small amount of water (0.1 ml) and sand. 2-Amino-4-hydroxypteridine (0.02 ml of a solution of 1 mg/ml in 0.05*N* sodium hydroxide) was added, and aliquots were spotted on Whatman No. 1 filter paper immediately and at the end of 1 hour. The chromatogram was developed and examined in the same way as before. The great majority of the mutants had enzyme activity comparable to the wild-type controls. However, it appeared that maroonlike (*ma-l*) and maroon (*ma*) contained greatly reduced amounts of enzyme activity (*8*). Work is continuing on these phenomena.

There remains the question of the significance of this enzyme in the biosynthesis of pteridines. In order to show that the enzyme is active *in vivo*, white-apricot (w^a) larvae, which normally contain very small amounts of 2-amino-4-hydroxypteridine and isoxanthopterin (*2*, and unpublished data), were allowed to feed on powdered cellulose saturated with an aqueous solution of the former; after they had pupated, they were chromatographed according to the method of Hadorn and Mitchell (*2*). The chromatograms showed that 2-amino-4-hydroxypteridine had been ingested and that isoxanthopterin had been produced. It seems probable, therefore, that this enzyme is important in the biosynthesis of isoxanthopterin, and that 2-amino-4-hydroxypteridine is the immediate precursor.

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8. Since we submitted this paper, Hadorn and Schlink [*Nature* 177, 940 (1956)] have reported that the mutant rosy lacks isoxanthopterin. We have been able to show that this mutant also lacks xanthine oxidase. Further experiments in collaboration with Hadorn are in progress.

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Modification of the Menstrual Cycle in Rhesus Monkeys by Reserpine

Reproductive function in the female rat is modified by reserpine. Gaunt *et al.* (*1*) found an alteration in the estrous cycle and a reduction in fertility. Barraclough (*2*) obtained inhibition of ovulation. Because of these observations, the possible influence of reserpine on the primate reproductive cycle was considered worthy of investigation. The dose used was in excess of that employed in clinical practice but was comparable to the dose used experimentally in rats and monkeys (*1*). Our purpose was to determine whether or not a maximal tranquilizing dose exerted a demonstrable effect on the menstrual cycle.

Adult, rhesus monkeys weighing between 4.4 and 8.6 kg were used. Three of the animals (909, 940, 921) had been pregnant, thus demonstrating their reproductive capacity. Reserpine (Serpasil, *3*) was administered subcutaneously to six monkeys in a dose of 1 mg/kg daily between 11 and 11:30 A.M. for periods ranging from 8 days to more than 100 days, Sundays excluded. The pattern of injection was of two types: (i) in some monkeys, daily injections of the drug were made for more than 100 days; (ii) in other monkeys, the drug was injected for a period of only 8 to 10 days, early in the cycle. Observations were made on (i) duration of the menstrual cycle, (ii) ovulation as ascertained by rectal palpation and checked by laparotomy, (iii) histological examination of ovarian and uterine tissues, and (iv) vaginal desquamation. Measurements of rectal, basal body temperature demonstrated no cyclic fluctuation. Three animals served as controls. Two of these animals later received a placebo, reserpine vehicle, in a volume equivalent to that which they would have received if the drug were being administered. Part of the remainder of the Carnegie colony served as additional controls with regard to length of the menstrual cycle.

Administration of reserpine daily for more than 100 days to three of the experimental monkeys produced a suppression of menstruation in each case (Fig. 1). In monkeys L52 and L53, in which the treatment was initiated toward the end of the summer anovulatory period, the expected bleeding occurred, but it was not followed by another menstruation until the drug was withdrawn. Laparotomy performed at the termination of the reserpine treatment revealed a failure of ovulation in each case (Fig. 1). Histological examination (*4*) in one monkey (L52) revealed a uterus under

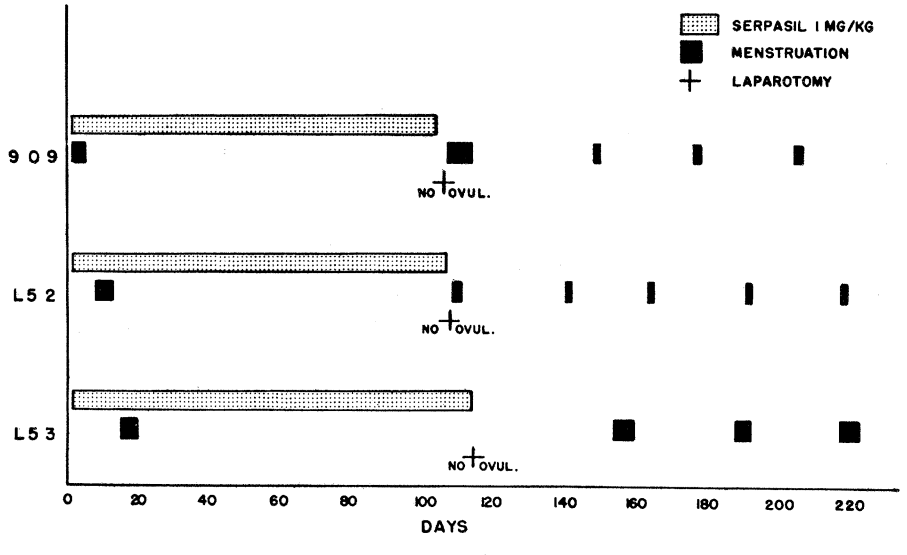

Fig. 1. Prolongation of the menstrual cycle following treatment with reserpine for more than 100 days. Width of the black bar indicates duration of bleeding.

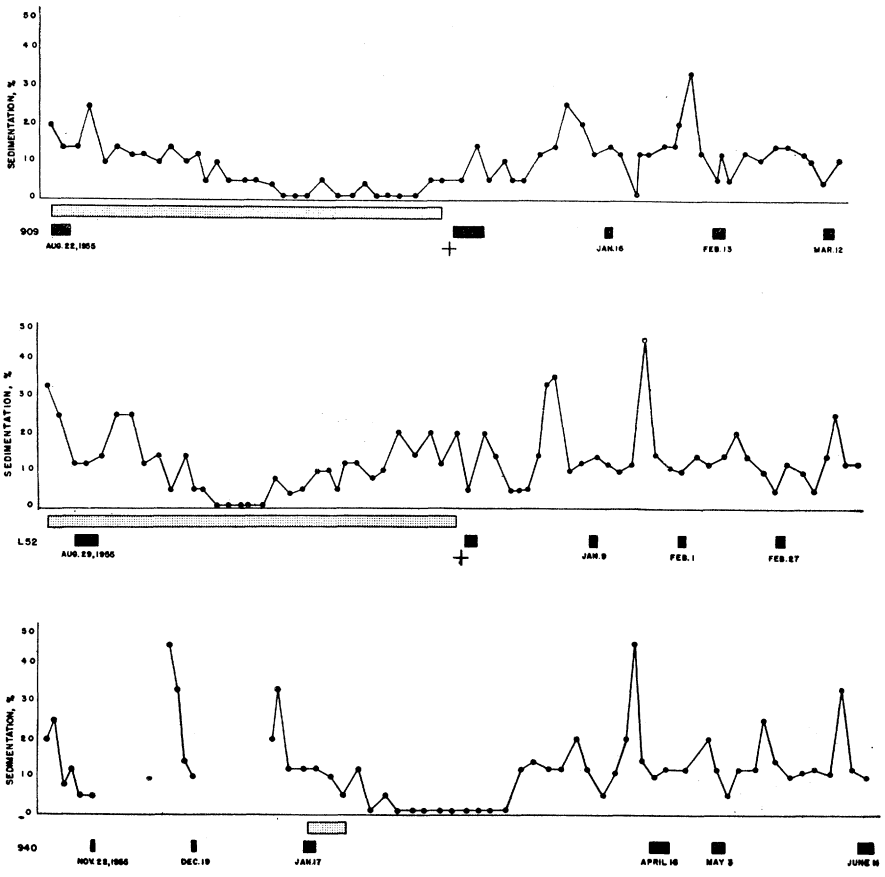

Fig. 2. Influence of reserpine on vaginal desquamation expressed as percent sedimentation (ordinates): (top curve) monkey 909; (middle curve) monkey L52; (bottom curve) monkey 940.

mild estrogenic stimulation. The left ovary showed only 13 growing follicles of 0.8 to 1.9 mm in diameter. Tissues from a second monkey (909) disclosed a thin (1.5 mm) endometrium that was involuted. This animal bled the day following biopsy. In the case in which no uterine biopsy was taken, L53 (Fig. 1), no bleeding was initiated.

Hartman (*5*) showed that a cyclic fluctuation occurred in the percentage of cellular desquamation obtained from daily vaginal lavage, with increased sedimentation on the days subsequent to ovulation. He found that vaginal desquamation in the presence of the "hypotypical" (Hartman) ovaries was zero. In the present experiments, Fig. 2 shows the effect of reserpine on vaginal desquamation. In animals 909 and L52, a low percentage in sedimentation was found during some part of the reserpine treatment. This depression was more prolonged in the case of 909 than in the case of L52 and correlated with the degree of uterine suppression noted for these animals at the time of laparotomy and biopsy.

Administration of reserpine for shorter intervals influenced the cycle, depending on the time of administration of the drug. A prolongation in the cycle occurred following treatment with reserpine from day 2 to day 12 (three cases) or day 2 to day 10 (one case). Laparotomy in two of these animals indicated that they had failed to ovulate by the 23rd day of their cycle. Vaginal desquamation was also influenced, monkey 940 (Fig. 2). Ovulation was not suppressed in two monkeys (data not shown) in which the drug was given from day 8 to day 16 of the cycle. No influence on menstruation was observed following administration of the placebo (vehicle) from day 2 onward.

In seven of the seven experiments in which reserpine was given during the early part of the menstrual cycle, menstruation was suppressed from 47 to 140 days, depending on the length of the treatment. These findings are significant especially when they are compared with the menstrual records of the remainder of the colony. In a total of 114 such cycles obtained from 26 animals between August 1955 and June 1956, 94 percent of the cycles were between 15 and 39 days in length, while only 6 percent were between 48 and 67 days. It is also significant that following withdrawal from this large dose of reserpine, menstrual cycles of normal duration were reestablished quite promptly (Fig. 1). Fluctuations in vaginal desquamation also showed periodic ovarian activity (Fig. 2). During drug treatment, the monkeys were poorly groomed in appearance, but they were able to maintain body weight and good fur growth developed during the winter.

We know of no report on the human being in which an alteration of the menstrual cycle has been produced with reserpine. This may be due to the fact that the clinical dose is usually smaller (0.25 to 5.0 mg/day orally), or that many recipients of the drug may have been in the menopausal or post-menopausal groups, and irregularity in menstrual periods is regarded as incidental and unimportant. Some evidence has been presented by Whitelaw (*6*) which indicates that chlorpromazine, another tranquilizing drug, will delay ovulation and menstruation in women for 8 to 16 days if the drug is given for 1 to 3 days before the expected date of ovulation. Barraclough (*7*) also noted that chlorpromazine blocked ovulation in the rat.

Plans are in progress to determine the minimal effective dose of reserpine in monkeys and the shortest duration of treatment necessary.

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