under the influence of cortisone the cells may support some degree of multiplication to reach levels of virus which result in cellular destruction. Work is being continued to explore these possibilities.

Summary. 1. Treatment of mice with cortisone significantly reduced their resistance to the intravenous toxicity of PR8 influenza A, Lee influenza B, and Newcastle disease viruses. 2. Deaths of cortisone treated mice were prevented by mixing specific immune serum with the viral inoculum or by passive immunization of mice prior to challenge. Immune serum injected intravenously 15 minutes after challenge gave some protection but was without effect when injected 3 hours after challenge. 3. For full effect, doses of 2.5 mg of cortisone had to be used when treatment was begun 24 hours before challenge. Smaller doses were effective if begun earlier. Doses as large as 5.0 mg had no significant effect if given only 3 hours before challenge.

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Progestational Activity of 19-norprogesterone and 19-norethisterone in the Rhesus Monkey. (22927)

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The synthesis of 19-norprogesterone and 19-norethisterone has been previously reported(1,2). These 19-nor steroids have been shown to possess high progestational potency(3,4). 19-norprogesterone was found to be 4 to 8 times as active as progesterone when administered parenterally(3). The degree of endometrial proliferation in the rabbit uterus was used as the criterion of progestational activity. Oral administration of norethisterone (17α-ethinyl-19-nortestosterone) gave a five-fold increase in activity over that of orally administered ethisterone (17α-ethinyltestosterone) in the rabbit assay(4).

This report concerns further observations on these compounds with respect to their relative ability to produce progestational effects in the ovariectomized rhesus monkey.

Materials and methods. Bilaterally ovariectomized rhesus monkeys (*Macacus rhesus*) weighing 3-4 kg were given daily subcutaneous injections of 10 μg estradiol-17β in 0.25 cc sesame oil for 20 days. Beginning on the twenty-first day, daily saline vaginal lavage was used to determine the onset of withdrawal bleeding. This procedure was continued until withdrawal bleeding was completed. The interval between cessation of estrogen administration to the beginning of estrogen-withdrawal bleeding was checked at least twice in each animal before determining the effectiveness of the test compounds in preventing estrogen-withdrawal bleeding. After pretreatment with estrogen as previously indicated, daily administration of test compounds was begun on the twenty-first day. Ethisterone and norethisterone were given orally in tablet form (except as noted in Table I). Solutions of 19-norprogesterone and progesterone were administered subcutaneously in sesame oil. The onset and completion of withdrawal bleeding were determined as noted above.

Results. In Table I, 19-norprogesterone and progesterone have been compared with respect to the characteristic inhibition of estrogen-withdrawal bleeding by progesterone. There was a delay in withdrawal bleeding of

TABLE I. Effect of 19-norprogesterone and Progesterone on Estrogen-Withdrawal Bleeding in the Ovariectomized Rhesus Monkey

Treatment	Daily dose (mg)*	Delay of bleeding (days)	Normal delay of estrogen-withdrawal bleeding (days)
19-norproges-terone	.125	16†	4, 5, 6
	"	31†	5, 8, 7
	"	31†	3, 5, 5
	.0625	11	5, 5, 7, 6, 5
	"	12	5, 6, 7, 5
	.0312	8	8, 8
	"	7	6, 7
	"	8	8, 6
	"	9	8, 8
Progesterone	1.0	42	7, 7, 8
	"	13	7, 7, 6
	"	30	7, 6, 7

* Administered in 0.2 cc sesame oil solution daily subcut.

† Treatment discontinued. Menstrual bleeding occurred 3-4 days later.

13 to 42 days in 3 monkeys receiving daily subcutaneous injections of 1 mg progesterone. A substantial delay in the onset of bleeding was produced by daily injection of 0.125 mg 19-norprogesterone in each of 3 animals. A smaller dose of the latter compound (0.0625 mg) had a marginal effect on the suppression of bleeding whereas one-half this dose (0.031 mg) is subthreshold and menstrual bleeding in this group is within the normal range of estrogen-withdrawal bleeding time in the monkey treated with estrogen alone.

The data for the inhibition of estrogen-withdrawal bleeding by progesterone are in accord with the earlier studies of Hisaw and Greep(5). These authors reported a 9- to 44-day delay of withdrawal bleeding when 1.0 mg progesterone was given subcutaneously daily.

As previously noted, results obtained with the Clauberg rabbit method had indicated that 19-norprogesterone was 4 to 8 times more potent than progesterone. The work of Mardones *et al.*(6) has shown 19-norprogesterone to be more potent than progesterone with respect to antiluteinizing, antihysterotrophic and antifibromatogenic activity in the guinea pig. Results of the present study indicate that 19-norprogesterone is 8 to 16 times more active than progesterone in delaying the onset of estrogen-withdrawal bleeding in the monkey.

Table II presents a summary of experiments in which 19-norethisterone and ethisterone are compared for ability to inhibit uterine bleeding induced by the withdrawal of estrogen.

When these compounds were administered orally, a daily dose of 5 mg norethisterone prevented uterine bleeding until treatment was discontinued. After 15 days treatment with norethisterone (5 mg daily), the uterus of one monkey was biopsied. Histological examination showed a progestational type of endometrium. After 9 days of additional treatment the endometrium exhibited an excellent decidual response. As little as 2.5 mg norethisterone daily produced a definite delay of uterine bleeding in 2 of 3 animals. A daily dose of 1.25 mg was ineffective in maintaining the endometrium. Ethisterone, on the other hand, failed to effect a signifi-

TABLE II. Effect of 19-norethisterone and Ethisterone on Estrogen-Withdrawal Bleeding in the Ovariectomized Rhesus Monkey.

Treatment	Daily dose (mg)*	Post-treatment delay of bleeding (days)	Normal delay of estrogen-withdrawal bleeding (days)
Norethisterone	5	16†	8, 8
	5	20†	5, 7, 8, 7
	5	20†	5, 5, 7, 5
	5	20†	5, 5, 9, 5
	2.5	8	5, 5, 6
	"	14	5, 6, 7, 7
	"	17	5, 5, 6, 8
	1.25	11	8, 8
	"	9	7, 7
	"	6	5, 7
Ethisterone	5‡	5	7, 7
	5‡	9	5, 8, 7
	5‡	8	5, 5, 7, 6
	25	4	3, 5, 5
	"	9	5, 5, 7, 6
	"	7	5, 6, 7, 5
	100	7	5, 5, 9, 5
	"	7	4, 8
	200	7	5, 7, 8, 7
	"	4	5, 5, 7, 5
	"	6	5, 5, 9, 5

* Administered orally by tablet (except as noted).

† Treatment discontinued at this time.

‡ Administered by stomach tube in 5 cc propylene glycol.

cant delay in estrogen-withdrawal bleeding when given in doses ranging from 5 to 200 mg daily. The failure of ethisterone to produce a delay in the onset of bleeding in the rhesus monkey is noteworthy in view of the demonstration of progestational activity in women of an oral dose of ethisterone 6 to 8 times that of the effective intramuscular dose of progesterone(7,8). In addition, ethisterone has been shown to have marked progestational activity in the rabbit(4,9).

Hertz *et al.* have reported that norethisterone is about 4 times more active than ethisterone in the production of progestational changes of the endometrium in women(10). From the data presented here it appears that norethisterone given orally in the monkey has approximately 40% of the activity of progesterone given by the subcutaneous route.

Summary. Two 19-nor steroids have been tested for progestational activity, as measured by inhibition of uterine bleeding following estrogen-withdrawal in the rhesus monkey. 19-norprogesterone was found to be 8 to 16 times as active as progesterone when administered parenterally. Orally administered 17α-ethinyl-19-nortestosterone was active at 2.5 mg daily whereas 17α-ethinyl testosterone was inactive in a range of dosages from 5 mg to 200 mg.

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Elevated Chylomicron Index in Multiple Sclerosis and Its Response to Digestive Enzyme Therapy.* (22928)

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The possibility of an altered lipid metabolism in multiple sclerosis has been suggested by the observations of several groups of investigators. Swank(1) found that a low-fat diet appears to reduce frequency and severity of exacerbations of this disease. Roboz, *et al.* (2) have shown by paper electrophoresis a tendency for greater variability in serum lipoprotein patterns of a series of multiple sclerosis patients than in those of normal individuals; this increased variability appears to be associated with a trend toward increased alpha-1 lipoprotein and corresponding decrease in the lipids of the "gamma" region. Aird, *et al.*(3) produced preliminary evidence which indicates that the relative concentration of the Sf(12-20) serum lipoproteins is elevated in those cases of multiple sclerosis graded "rapidly progressive." Zinn and Griffith(4) have demonstrated that in two conditions in which there exists an altered lipid

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