these should have been protected; although this was not the case there was considerable reduction in duration of ventricular tachycardia in 2 animals (No. 12 and 17). In the remaining 5 the maximum K level was significantly above that of the protected group when ventricular tachycardia occurred. Although the reason for these variations is not clear, the fact that ventricular tachycardia was seen in 5 cases when the maximum K level was near that of their respective controls is at least some evidence for an increase in cardiac irritability being associated with an increase in plasma K.

In recent studies Dresel and Nickerson(7) have noted that some "factor" brought to the heart by the venous blood is probably involved in epinephrine induced arrhythmias during pentobarbital anesthesia. However, they doubted that the rise in arterial plasma potassium caused the arrhythmias. There does, however, seem to be justification for the idea that at least during cyclopropane anesthesia, regardless of what other factors might be involved, the rapid increase in potassium may contribute in part to the production of arrhythmias since protection from these arrhythmias was afforded by elimination of hepatic circulation which also markedly reduced potassium mobilization(5). The present studies tend to confirm this idea with the further indication that the relative increase in potassium may also be of some importance. Whatever the "factor" referred to by Dresel and Nickerson might be, it is possible that it may be associated with the release of potassium from the liver in a large proportion of animals.

Summary. The effect of a low potassium diet of 2 to 3 weeks duration on cyclopropane-epinephrine ventricular tachycardia and arterial plasma potassium has been studied in 20 dogs. Eleven dogs were protected from the arrhythmias while on the diet and 9 were not. In the protected group the K mobilized by epinephrine was considerably reduced. In the non-protected group the per cent rise in K was on the average approximately the same as in control. It is concluded that these studies confirm the view that an actual or relative increase in plasma potassium contributes, at least in part, to the increased cardiac sensitivity to epinephrine during cyclopropane anesthesia.

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Mediation of Progestational Action of Amphenone by the Rabbit Adrenal. (23973)

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Progestational proliferation of rabbit endometrium after parenteral treatment with amphenone* has been described(1). With the exception of certain steroids of gonadal, adrenal or synthetic origin, amphenone is the only compound known to exert progestational activity in the rabbit. This unique action of a non-steroid raises the question whether amphenone exerts a direct effect on the rabbit

* The structural formula for amphenone according to recent revision(2,3) is 3,3-bis(p-aminophenyl)-2-butanone. We have used the dihydrochloride.

TABLE I. Progestational Response to Amphenone in the Rabbit following Alteration of Endocrine Status.

Series	No. of animals	Compound	Total dose (mg)	Operative procedure	Progestational proliferation
I	4	amphenone	3000.0	None	+4, +3, +4, +4
	7	"	2000.0	"	+2, +3, +3, +1, +2, +3, +3
	5	progesterone	.5	"	+4, +4, +4, +4, +4
	5	none		"	0, 0, 0, 0, 0
II	6	amphenone	3000.0	Ad. + Ov.*	0, 0, 0, 0, 0, 0
	4	progesterone	.5	"	+4, +4, +4, +3
	8	amphenone	3000.0	Ov.	+4, +4, +3, +1, +3, +3, +2, +1
III	3	cortisone	27.5	None	0, 0, 0
	4	cortisone + amphenone	27.5 3000.0	"	0, 0, 0, 0
	3	cortisone + progesterone	27.5 .5	"	+3, +4, +4, +4
	3	cortisone + amphenone + progesterone	27.5 3000.0 .5	"	+3, +3, +3
IV	3	ACTH†	500.0	"	0, 0, 0
	3	progesterone	.5	"	+4, +4, +4

* Bilateral adrenalectomy plus bilateral ovariectomy.

† Armour's ACTHAR given daily subcut. in peanut oil with 5% beeswax. Dose in mg equivalents of standard LA-1-A.

uterus or whether its action is mediated indirectly through secretion of progestogens by another endocrine organ. Results here described demonstrate that progestational response to amphenone in the rabbit is dependent on the adrenal glands.

Materials and methods. A modified Clauberg rabbit test was used for determination of progestational activity. Female New Zealand white rabbits from a single colony were used. Initial body weight range was 600-800 g. Ten mcg of estradiol-17 beta were administered in 0.25 ml sesame oil solution daily for 6 days followed by 5 days treatment with the test compound. Amphenone was given in 1 ml aqueous solution for each 100 mg administered. Progesterone, corticosterone and 11β-hydroxyprogesterone were given in 0.2 ml sesame oil solution daily. All injections were subcutaneous unless otherwise specified. Animals were killed with chloroform 20 to 24 hours after the last injection. Body, uterus and adrenal (intact animals) weights were recorded. Uteri and adrenals were fixed in Bouin's solution for histology. Sections were stained with hematoxylin and eosin. The standard scale of McPhail(4) was used in rating progestational proliferation of the endometrium. Quantitative variability in this assay has led to use of 0.5 mg progesterone as a standard for full endometrial proliferation (5). A 2-stage bilateral adrenalectomy and ovariectomy were performed with an interval of 8 to 10 days between each procedure. A lateral approach was used. Intravenous nembutal anesthesia (30 mg/kg) was supplemented with ether as required. Pre-operative treatment consisted of 25 mg hydrocortisone sodium succinate given intravenously 30 minutes to 1 hour before the second adrenal was removed. A 1% saline drinking solution was given *ad libitum* as post-operative treatment. Testing of compounds for progestational activity was not begun for at least one week following the second operation. Completeness of ovariectomy and adrenalectomy was determined at autopsy.

Results. Comparison of the progestational activity of amphenone with that of progesterone was made using unoperated rabbits. These results are shown in Series I (Table I). In this experiment, a total dose of 3.0 g amphenone produced effects comparable to 0.5 mg progesterone. A total dose of 2.0 g amphenone did not evoke the maximum progestational effect.

In several experimental series, the progestational effect of amphenone was compared

with that of progesterone in the adrenalectomized, ovariectomized rabbit. Series II contains results from a representative experiment. Amphenone failed to elicit a progestational response in the endometrium of the adrenalectomized, ovariectomized animal although progesterone produced its characteristic effect under these conditions. Ovariectomy alone did not prevent the progestational response to amphenone.

To determine completeness of adrenalectomy, animals were examined for accessory adrenals at autopsy. In 20 animals only one was found to have an accessory adrenal gland.

To further test the completeness of adrenalectomy, saline was withdrawn from an adrenalectomized, ovariectomized group after amphenone treatment was concluded. The 4 animals died 6 to 12 days after removal of this supportive measure.

In additional experiments (Series III), intact rabbits received a saline suspension of 2.5 mg cortisone acetate daily beginning on the first day of estrogen priming and continuing throughout treatment with amphenone or progesterone. Adrenals from rabbits receiving this dose of cortisone alone showed a 30 to 35% weight loss after 11 days. Cortisone completely suppressed the progestational response to amphenone. At the same dose level, cortisone did not prevent a progestational response to progesterone or a combination of amphenone and progesterone.

An increase in endogenous ACTH production was considered a probable factor in the progestational response to amphenone in the rabbit. Data on the effects of ACTH treatment of the intact rabbit are presented in Series IV. A total dose of 500 mg ACTH did not produce progestational changes in the rabbit endometrium. The adrenal weight range was 182-299 mg in the ACTH-treated group as compared with 66-91 mg in the progesterone-treated group. Total doses of 50 mg ACTH were likewise without effect.

At the total dosage indicated, the following steroids failed to yield a positive response in the Clauberg test using 3 animals for each compound: corticosterone (25. mg), 11β-hydroxyprogesterone (10. mg), 17 hydroxycorticosterone acetate (25. mg), cortisone acetate (50. mg). Ten mg of deoxycorticosterone acetate produced a maximum response comparable to that of 0.5 mg progesterone.

Discussion. Progestational proliferation of the rabbit endometrium in response to amphenone treatment has been demonstrated(1). Following ovariectomy and adrenalectomy, for removal of endogenous progestogen sources, the progestational response to amphenone did not occur although exogenous progesterone exerted its typical uterine effect. It has long been known that progesterone exerts the characteristic uterine effects in the absence of the ovaries(6). Similarly, ovariectomy had no effect on uterine response to amphenone. The progestational response to amphenone, therefore, is dependent on the secretion of the adrenal glands. Biological evidence for an adrenal cortical source of progestogens was obtained in 1930 by Englehart(7). Beall and Reichstein later reported the isolation of crystalline progesterone from adrenal cortical extracts(8).

Lyons *et al.*(9) have reported that treatment with highly purified ACTH preparations sensitizes the uterus of hypophysectomized, ovariectomized rats to the formation of deciduomata. These results indicate that ACTH-stimulated adrenals secrete progestogens.

The suppression of the progestational effects of amphenone by means of cortisone suggested that a decreased rate of secretion of ACTH was responsible for the ineffectiveness of amphenone. Cortisone is known to suppress ACTH production and thereby inhibit the biogenesis of adrenal steroids, including the progestogens. An elevated ACTH level in response to amphenone treatment was considered as a possible explanation for excess adrenocortical progestogen secretion. Decreased synthesis of corticosterone following amphenone has been reported(10). The increase in ACTH secretion subsequent to a reduction in corticosterone level could lead to excess progestogen production. However, in the present experiments, levels of ACTH which caused 2 to 3 fold increments in adrenal weight were incapable of inducing progestational changes in the rabbit endometrium.

Amphenone inhibition of specific enzyme systems in the adrenocortical biosynthetic

pathway of the rabbit would explain the progestational action. Amphenone has been reported to inhibit the synthesis of corticosterone, hydrocortisone, and cortisone in calf adrenal perfusion experiments(10). A block in the biosynthetic pathway between progesterone and corticosterone could result in excess secretion of a potent progestogen in amounts sufficient to induce progestational proliferation of the rabbit endometrium. Adrenocortical progesterone is probably the active progestogen since comparison with the principal adrenal corticosteroids in the Clauberg assay indicated that progesterone was much more potent than any of the active compounds.

Summary. Progestational proliferation of the rabbit endometrium in response to amphenone has been shown to be dependent on the adrenals. The progestational effect of amphenone was prevented by adrenalectomy as well as by cortisone treatment. Large doses of ACTH failed to produce progestational changes in the rabbit endometrium. It was suggested that amphenone exerts its progestational effect on the rabbit uterus by inhibition of specific enzyme systems in the adrenocortical biosynthetic pathway resulting in excess progestogen secretion.

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Genetic Control of Amylase Levels of Mouse Submaxillary Glands.* (23974)

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The amylase level of the submaxillary gland of certain rodents has been shown to be, at least in part, under hormonal control (1). Recent work has suggested that the autonomic nervous system may also play a role in regulating formation of amylase in rodents(2). The extent to which genetic control is involved in regulation of amylase levels is only generally suggested by data which show significant species differences in amylase levels of the submaxillary glands of rabbits, guinea pigs, rats and mice (unpublished data); such differences, however, may be an indirect reflection of genetic control of structural variation in glands of the several species. It was, therefore, considered of importance to determine the role that hereditary mechanisms may have in controlling quantitative differences in amylase level. Furthermore, although proof of a genetic control of biochemical reactions has been demonstrated in certain microorganisms(3,4), little data of such a nature are available concerning such control in higher animals(5). Accordingly, to delineate the genetic role in amylase production, inbred lines of mice, where genetic uniformity is maximum, and where quantitative differences are therefore readily demonstrable (6), were used.

Methods. Adult male mice, 2-4 months old, were used. The animals were fasted for 48 hours, and, under Nembutal anesthesia, the submaxillary-sublingual glands were re-

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