Neither insulin nor glucose alone gave a significant stimulation in any diabetic group.

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Supersensitivity of the Cat Heart to Catecholamine-Induced Arrhythmias Following Reserpine Pretreatment.* (27830)

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It has been shown that reserpine pretreatment increases the sensitivity of the heart to the positive chronotropic(1) and positive inotropic(2) effects of norepinephrine. However, since the cardiac rate(3) and contractility(4) of the hearts of reserpinized animals are reduced below control values, changes in the responses to norepinephrine are difficult to interpret(3). The incidence of an all or none response of the heart, such as arrhythmia, in reserpinized animals therefore seems of value. Supersensitivity to the arrhythmia-inducing action of catecholamines is of further interest since this is a toxic rather than a physiological effect. This report compares the occurrence of ventricular arrhythmias produced by catecholamines in reserpinized cats as compared to untreated cats.

Materials and methods. Cats of both sexes, weighing 2 to 4 kg, were used. Twenty cats served as controls and received no reserpine. Twenty-six cats received reserpine, 0.1 mg/kg/day intraperitoneally, for periods ranging from 7 to 28 days preceding the experiment. This dose of reserpine has been shown to produce nearly maximal depletion (*ca.* 95%) of norepinephrine stores in the cat heart in 24 hours(5).

The cats were pithed under ether anesthesia using the spinal method of Burn(6). Following this operation the cats were maintained on artificial respiration and the etherization discontinued. The hearts were therefore free of effects from anesthetic, neural control, and reflexes resulting from the blood pressure responses to the injected catecholamines. Carotid blood pressure was measured with a Statham transducer and recorded on a Grass polygraph. Needle electrodes were placed subcutaneously on the forelegs and right hindleg and the lead I electrocardiogram recorded on the Grass polygraph.

Consecutive single injections of l-norepinephrine bitartrate (levarterenol) or l-epinephrine bitartrate were given into the femoral vein, beginning with a dose of 0.01 μg/kg (free base) and ending with a dose of 100 μg/kg. No injection was made until the heart and blood pressure effects of the preceding dose had completely subsided. Some cats received only the norepinephrine injections and some received both norepinephrine and epinephrine. When both drugs were used, alternate injections of norepinephrine and epinephrine were made, beginning with the lowest doses. This eliminated the possibility that large doses of one catecholamine might influence the response to a small dose of the other.

Results. The first arrhythmias produced by catecholamine injections were in the form of ventricular premature systoles and extrasystoles. In some of the reserpinized animals, large doses of norepinephrine and epinephrine produced ventricular tachycardia for

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TABLE I. Threshold Doses of Catecholamines Causing Arrhythmias in Control *vs* Reserpinized Cats. Each figure represents the number of cats in which first ventricular arrhythmias occurred at dose indicated.

	Reserpine treatment	Dose of norepinephrine in μg/kg .1	.3	1	3	10	30	100	100+
a. Norepinephrine	None (control)				2	5	5	7	1
	7 days			1	1		2		1
	14 "			1	1	2	1	1	1
	21 "			1	2	1		3	
	28 "	2	1		3	1	1		

Chi square analysis (controls *vs* all reserpine): P = .02.

	Reserpine treatment	Dose of epinephrine in μg/kg .1	.3	1	3	10	30	100	100+
b. Epinephrine	None (control)						3	1	6
	7 days					1	1	2	1
	14 "					4	2	1	1
	21 "					1	3	2	
	28 "		1			3	3		

Chi square analysis (controls *vs* all reserpine): P = .05.

periods of 30 to 60 seconds or longer and in 2 instances ventricular fibrillation. However, these were always preceded by premature systoles and extrasystoles at lower doses. Tachycardia and fibrillation were never observed in control animals. In Table I, under each dose of norepinephrine or epinephrine is presented the number of cats which showed the first cardiac arrhythmias at that particular dose ("threshold dose"). Threshold dose is here defined as the lowest dose producing at least 2 premature or extrasystoles during the positive chronotropic response of the heart. A dose was accepted as threshold only if the next larger dose also produced arrhythmias. In none of the experiments did doses lower than 0.1 μg/kg cause arrhythmias. Cats entered under the column headed 100 + did not have arrhythmias after any of the injections.

The statistical significance of the change in sensitivity was determined by Chi square analyses. In the norepinephrine study, all animals were divided into 2 groups, those in which the threshold dose was 3 μg/kg or lower and those in which the threshold dose was 10 μg/kg or higher. The controls were then compared statistically to all the reserpine-treated cats. The greater sensitivity to norepinephrine in the reserpine animals was significant (P = .02). The epinephrine data were treated similarly, with the exception that, due to a much lower sensitivity of the control animals to epinephrine as compared to norepinephrine-induced arrhythmias, the number of cats in which the threshold dose was 30 μg/kg or lower were compared to the number in which the threshold dose was 100 μg/kg or higher. The sensitivity of the reserpine treated cats to epinephrine was significantly greater (P = .05).

The heart rate and blood pressure were increased by the catecholamines over this same dose range. The maximum heart rate increase was about 60 beats/min and the maximum pressure increase was about 175 mm Hg. The dose response curves for both the positive chronotropic and pressor effect were shifted slightly to the left, indicating supersensitivity, after the 7-day reserpine treatment. The curves for the 14-, 21-, and 28-day treatments were virtually superimposed on those for the 7-day treatment. This is in line with a previous report(3) indicating a maximum supersensitivity of the chronotropic and pressor responses after only 3 days of treatment.

The health of most of the reserpinized animals was fairly good. All animals lost some weight and a few became heavily sedated, developed severe diarrhea and refused to eat or drink. Such animals invariably died in

less than one week of treatment and therefore were not included in the study. The remaining cats showed moderate sedation and mild diarrhea but there was no indication of progressive deterioration with length of treatment nor was there any apparent correlation between these symptoms and the sensitivity to arrhythmias.

Discussion. Reserpine pretreatment causes a significant increase in the sensitivity of the cat heart to arrhythmias induced by norepinephrine and epinephrine. It seems that this sensitivity becomes progressively greater with increasing length of reserpine treatment. However, this later conclusion cannot be proven statistically with the number of experiments reported here. If the sensitivity does increase with the length of reserpine treatment, this would be quite in contrast to the positive chronotropic response of the cat heart. The increase in sensitivity of the cardiac pacemaker in the cat reaches its maximum after only 3 days of treatment with reserpine 0.1 mg/kg/day(3).

The slow onset of supersensitivity to arrhythmias in spite of 95% depletion of norepinephrine occurring within 24 hours(5) is not contrary to existing concepts. Fleming and Trendelenburg(3) have shown that the development of supersensitivity requires time following depletion and that the time required varies considerably from one response to another, supersensitivity of the nictitating membrane contraction reaching maximum much more slowly than that of chronotropic response of the heart.

The ultimate increase in sensitivity to arrhythmias seems rather great, since 2 of the 28-day reserpine cats responded to a dose of norepinephrine (0.1 μg/kg) one-thirtieth of the lowest dose causing arrhythmias in control cats. The increased sensitivity to catecholamine-induced arrhythmias is a hazard worthy of consideration in individuals on reserpine therapy.

Summary. Pretreatment with reserpine (0.1 mg/kg/day) for 7 to 28 days causes a significant increase in the sensitivity of the cat heart to catecholamine-induced arrhythmias. There is some indication that the sensitivity increases progressively with increased duration of reserpine treatment.

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Carbon Dioxide Induced Acidosis in Pregnant Rats and Caries Susceptibility of Their Progeny. (27831)

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The information regarding prenatal influences on tooth development is quite limited. Stein(1) reported 8 cases of enamel hypoplasia and Sheldon *et al.*(2) observed hypoplastic defects of intrauterine origin. The maternal influences of rickets and syphilis were noted by Wolfe(3) and by Diamond and Weinmann(4) while Kreshover(5) observed clinically that metabolic disturbances altered tooth formation. Among other studies are those of Mellanby(6) on abnormally shaped incisors and molars of rats whose mothers were vitamin A deficient during pregnancy, and Kreshover(7) showed that alloxan treatment during pregnancy in the rat produced abnormalities of amelogenesis.