TABLE I.

No. of birds	Treatment	Dose of hormone	Latent period preceding bill pigmentation, days	No. with pigmentation response
4	systemic	8 μg	5-13	3
5	"	4 μg	17-19	3*
3	"	2 μg	25	1†
5	local	2 μg	4-5	5‡

*Very slight response in 1 animal.
† " " "
‡Heavy pigmentation in area at base of bill. No pigmentation on opposite (untreated) side.

Conclusion. Androgenic hormone can act locally to induce deposition of melanin in those cells of the sparrow bill which are capable of producing this pigment.

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Results of Daily Intravenous Injections of Lanatoside C Upon the Heart Muscles of Dogs.

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Bauer, Hu, Buchner and Lindner[1] demonstrated that the daily intravenous administration of one-third or more of a cat unit* of digitoxin per kilo of body weight produces degenerative changes in the heart muscles of dogs in from 5 to 30 days. The coronary arteries of the hearts of the dogs studied were free of any gross or microscopic pathology, but small infarctions and areas of connective tissue replacement were found in the myocardiums.

In repeating these experiments, we gave lanatoside C,† a crystalline derivative of digitalis lanata, by vein to dogs and also attempted to determine the effects, if any, of moderate and large oral doses both of lanatoside C and of digitalis purpurea.

In July, 1938, 9 dogs were digitalized by vein according to their weight. Thereafter, doses of from one-half to 5 cat units of both

[1] Bauer, F., *Arch. exp. Path. Pharm.*, 1934, **176**, 74; Hu, C., Lien, V., and Li, R., *Chinese Med. J.*, Suppl., 1936, **1**, 31; Büchner, F., *Arch. exp. Path. Pharm.*, 1934, **176**, 59; Lindner, W., *Arch. exp. Path. Pharm.*, 1938, **190**, 210.

*"Cat unit" always refers to the Hatcher-Brody unit.

†Cedilanid, Sandoz Chemical Works, Inc.

preparations were administered once daily with the food. Each tablet of lanatoside C contained 0.25 mg and each cc of solution 0.20 mg; 0.281 mg of lanatoside C are equivalent to one Hatcher-Brody cat unit. Each 1½ grain tablet of digitalis purpurea contained one Hatcher-Brody cat unit.

After 30 to 370 days, the animals were sacrificed and representative sections of the myocardiums secured. There were no abnormal gross findings and the microscopic sections were within normal limits.

Twenty-three dogs were given daily intravenous injections of lanatoside C ranging from one-twentieth to three-quarters of a cat unit per kilo of body weight. Nine of these animals died 6 to 12 hours before autopsy and post-mortem changes were too extensive to permit accurate conclusions.

All the animals receiving more than 0.20 of a cat unit per kilo of weight exhibited severe symptoms of intoxication. They developed anorexia, emesis, weight loss, salivation, muscular weakness and attacks of severe dyspnea. The dyspnea was noted late in the experiments, occurred 5 to 10 minutes after the injection of lanatoside C and persisted for from 5 to 45 minutes. It was usually associated with tachycardia or bradycardia and in one instance with a venous pressure of 15 cm of sodium citrate.

The coronary arteries of the hearts of all the dogs were free of any gross or microscopic changes. Subendocardial hemorrhages

TABLE I.
Experiments with Daily Intravenous Injections of Lanatoside C Correlated with Electrocardiography.

Dog No.	Daily dosage in cc	Dosage in cat units per kilo	Duration of experiment, days	Symptoms noted during experiments	EKG changes	Heart muscle pathology
1E	5.0	.25	8	anorexia, emesis wt loss, salivation, dyspnea, muscular weakness	present	none
2E	6.9	.33	8	same as 1E	"	"
3E	12.7	.50	4 (D)	" " "	"	?
4E	12.6	.75	4 (D)	" " "	"	?
5E	3.0	.20	60	same as 1E, except for absence of dyspnea	"	present
6E	6.0	.25	22	same as 5E	"	"
7E	8.0	.33	7	" " 1E	"	"
8E	13.6	.50	7 (D)	" " "	"	?
9E	9.6	.40	8	" " "	"	none

(D) Represents animals dying 6-12 hours before autopsy.
Each cc of solution contains 0.20 mg of crystalline lanatoside C.

were seen in one of the hearts which was otherwise microscopically normal and in 3 of the hearts showing widespread cellular damage. There were no other significant gross autopsy findings in any of the dogs. (Table I.)

The hearts of 4 dogs receiving from one-fifth to one-half a cat unit per kilo of body weight over a period of from 16 to 33 days exhibited diffuse and widespread cellular damage. Numerous small infarctions containing a few mononuclear cells and very occasional polymorphs were noted in most of the sections. Elsewhere there was marked proliferation of young connective tissue replacing some of the necrotic muscle. (Figs. 1 and 2.) An unusual atrophy of cardiac muscle without necrosis was seen in 2 of the sections.

Discussion and Conclusions. Myocardial damage can be produced in the dog heart by daily intravenous injections of lanatoside C in doses greater than 0.20 cat unit per kilo of body weight. There may be subendocardial hemorrhage in animals dying after such injections, but the coronary vessels are entirely free of any gross or microscopic abnormalities. These changes probably result from spasm with local lumen attenuation of the coronary vessels supplying the involved areas. Lanatoside C in large doses probably reduces the

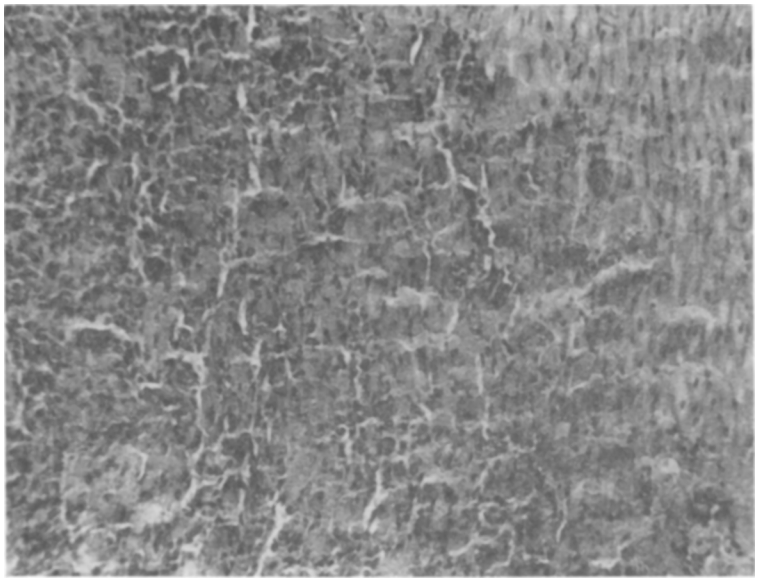

FIG. 1.

Photomicrograph of heart muscle obtained from dog 7E, showing an area of acute myocardial infarction. Note loss of striation of muscle fibers and cellular infiltration. Hemotoxylin-eosin stain was used.

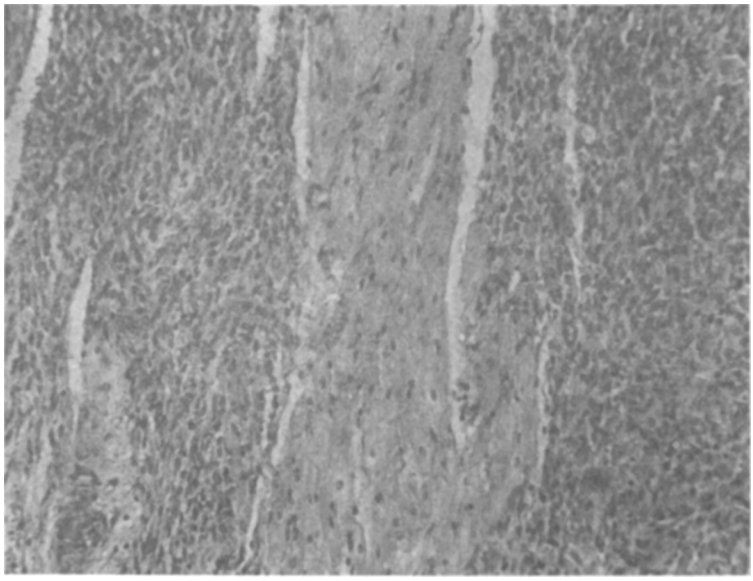

FIG. 2.
Photomicrograph of heart muscle obtained from dog 5E, showing complete replacement of the heart muscle by fibrotic tissue. Note intense cellular reaction. Hemotoxylin-eosin stain was used.

blood supply of the heart muscle by a powerful vasoconstrictor action on the coronary arteries. Essex and Visscher[2] have shown that lanatoside C in therapeutic doses does not restrict the coronary flow as measured by the thermostromuhr.

The myocardial damage which we produced in our experiments is probably not clinically significant, since daily doses approaching the level needed to produce these changes are never given.‡ The importance of producing myocardial infarction without grossly changing or plugging the coronary arteries is, however, emphasized by this study.

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2 Essex, E., Herrick, J., and Visscher, M., *Am. Heart J.*, 1938, **16**, 143.

‡ The single, complete digitalizing dose of lanatoside C in man is 8 cc given intravenously. This is equivalent to a single intravenous injection of 1.33 cc in a 25-pound dog. The digitalizing dose in man is never repeated in the same course of treatment, oral maintenance doses are given thereafter (1 to 5 tablets per day).