# Sensitization of the Pigeon to Epinephrine-Induced Ventricular Fibrillation by a Substituted Propiophenone

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**The cardiac effects of a substituted propiophenone (U-0882) have been studied in the pigeon. The results obtained and the techniques used indicate that a simple test may be employed to evaluate the cardiac-sensitizing propensities of a compound. The test is based on the biological determination of the quantity of epinephrine required to induce ventricular fibrillation in pigeons which have been pretreated with a usually tolerated parenteral dose of the compound being tested.**

PAST INTEREST in cardiac sensitization has been primarily limited to volatile halogenated hydrocarbons in medical anesthesia and industrial toxicology. However, an increasing number of parenterally administered chemical substances have been shown capable of sensitizing the heart to fatal epinephrine-induced ventricular fibrillation (1–4). Moore and Swain (4) recently suggested that compounds under pharmacologic investigation be examined for possible cardiac-sensitizing action in order to prevent the inadvertent induction of ventricular fibrillation. Conventional *in vivo* procedures demonstrating the capability of a substance to sensitize the heart to ventricular fibrillation are unfortunately impractical for routine examination of compounds under investigation because they are expensive, cumbrous, and time-consuming.

Previous studies in this laboratory by Braun and Lusky (5) demonstrated that the action of certain cardiac agents in the pigeon was similar to that in mammals. The pigeon is currently used in the official assay of digitalis (6).

The present communication describes the cardiac effects of alpha-phenoxy-alpha-dimethylaminomethylpropiophenone hydrochloride (hereafter designated as U-0882)[1] in the unanesthetized pigeon. The sensitizing action of this compound on the heart of the dog has previously been reported by Moore and Swain (3).

Although the present paper describes certain toxic manifestations and properties of U-0882, the main purpose of these studies was to devise a feasible method for measuring the cardiac-sensitizing propensities of a compound.

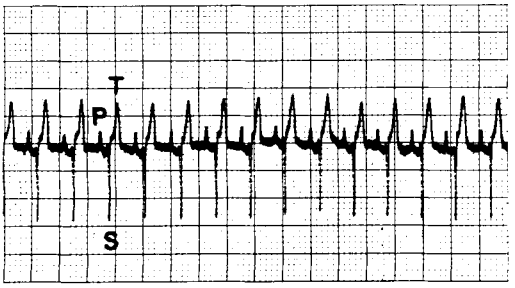



Fig. 1.—Lead II of normal electrocardiogram of pigeon.

## EXPERIMENTAL PROCEDURES AND RESULTS

Unanesthetized, common barn pigeons, predominantly of the male sex, ranging in weight from 290 to 400 Gm. were employed in this study. All pigeons were immobilized and the vagi were intact. Artificial respiration was not employed and tracheal cannulation was not performed. Platinum electrodes were inserted into the right wing base, the left wing base, and the left leg of the pigeon. Standard lead II electrocardiograms were taken using a Sanborn Viso-Cardiette, model 51.

Varying doses of U-0882 and epinephrine were administered through an indwelling polyethylene catheter into an alar vein. Each dose was followed immediately by a 0.2-ml. wash of isotonic saline. All doses of epinephrine hydrochloride were so diluted in physiological saline that each of the test dosage levels was administered in a 1 ml./Kg. volume. The U-0882 was administered as a 1.0% solution in physiological saline.

**Normal Electrocardiogram, Lead II, of the Pigeon.**—The electrocardiogram of a normal, unanesthetized, adult male pigeon taken on lead II is illustrated in Fig. 1. The P, S, and T waves are well defined, but the electrocardiogram differs from that of man in that the pigeon exhibits no Q wave. There is controversy among investigators as to the existence of an R wave in the bird (7, 8).

**Induction of Ventricular Fibrillation by U-0882 Alone.**—When U-0882 was administered intravenously to groups of 12 pigeons each at dose levels of 20, 30, and 40 mg./Kg., ventricular fibrillation was induced in a few of the unanesthetized birds without the use of epinephrine or other triggering agent. The results show that ventricular fibrillation was induced in 1 of 12 pigeons receiving 20 mg./Kg., in 2 of 12 receiving 30 mg./Kg., and in 4 of 12 pigeons receiving 40 mg./Kg. The 40-mg./Kg. dose caused violent clonic convulsions in 8 of 12 pigeons. The convulsions were fatal to 2

Received June 23, 1961, from the Division of Pharmacology, Bureau of Biological and Physical Sciences, Food and Drug Administration, U. S. Department of Health, Education, and Welfare, Washington 25, D. C.
Accepted for publication July 6, 1961.

[1] The compound U-0882 used in this study was kindly provided by the Upjohn Co., Kalamazoo, Mich.

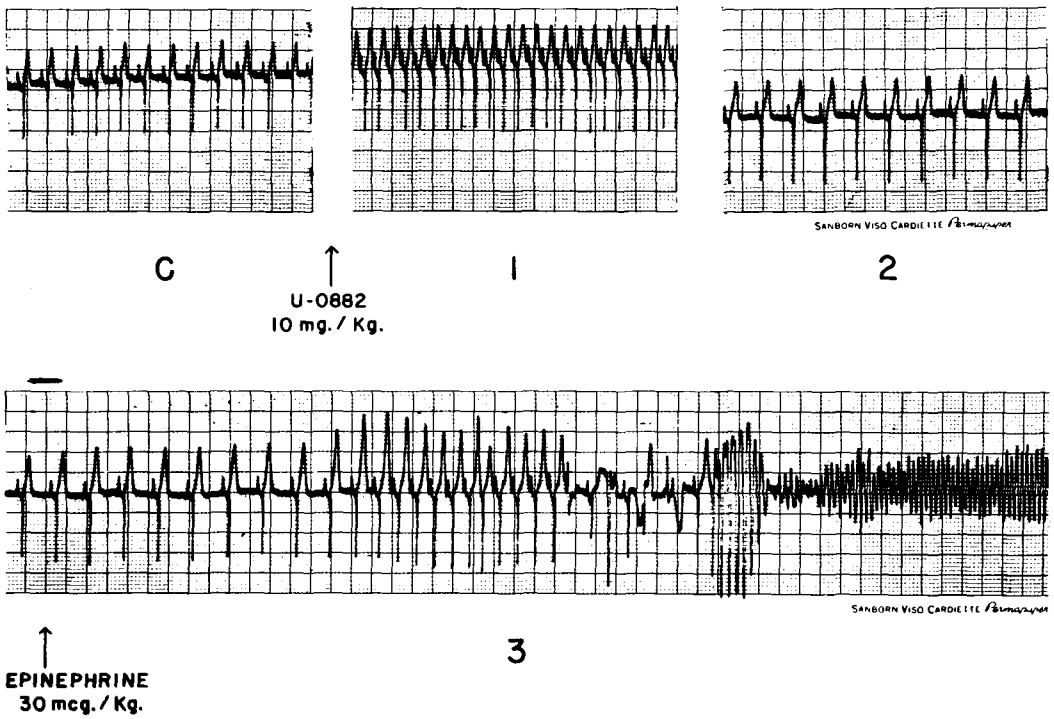



Fig. 2.—Lead II, electrocardiogram of pigeon. C, control; 1, tachycardia following U-0882; 2, bradycardia 2 minutes after U-0882; 3, progression into fibrillation after dose of epinephrine.

of these 8 pigeons; ventricular fibrillation was the cause of death of 2 others, and 4 pigeons recovered from the convulsions. Of the 4 pigeons which did not have convulsions, 2 succumbed from ventricular fibrillation and 2 pigeons did not exhibit any serious toxic effects.

**Influence of U-0882 on the Heart Rate of the Pigeon.**—The heart rate varied from pigeon to pigeon following the administration of 10 mg. of U-0882/Kg. intravenously. Tachycardia occurred in all of the birds within 1 minute after the injection, but by the end of the second minute, the rate either approximated normal or bradycardia ensued (Fig. 2). The electrocardiograms of 59 pigeons were examined to determine whether the reduction of heart rate following the administration of U-0882 bears a relationship to the incidence of ventricular fibrillation induced by a subsequent injection of epinephrine. The dose of 10 mg. of U-0882/Kg. caused cardiac slowing of varying degree in 43 pigeons and no significant change in rate in 16 pigeons. Following the administration of epinephrine, ventricular fibrillation was induced in 25 of 43 pigeons of the first group and also in 8 of the 16 pigeons of the second group. The apparent higher incidence of fibrillation in the group with the bradycardia was not statistically significant ($p = 0.07$).

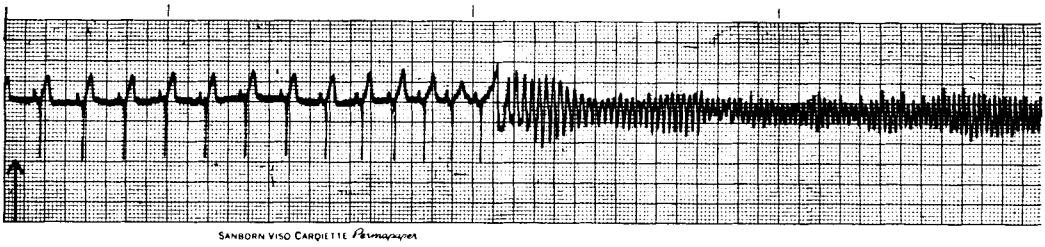
**Epinephrine Dose as Index to Cardiac Sensitizing Activity.**—Six groups of 12 pigeons each were pretreated with 10 mg. of U-0882/Kg. intravenously. Two minutes later these groups received 3, 5, 10, 20, 30, and 40 mcg./Kg. of epinephrine, respectively. Electrocardiograms were taken to observe any effects on the heart. The electrocardiograms in Fig. 3 illustrate the two observed typical progressions into ventricular fibrillation. In the upper panel the onset of fibrillation is sharp and devoid of ectopic beats. The lower panel, in contrast, shows numerous ectopic beats preceding the onset of ventricular fibrillation in the pigeon. Two of the 72 pigeons on experiment were discarded because fibrillation was induced before the injection of epinephrine by U-0882 alone. Ventricular fibrillation was fatal to all pigeons. No deaths were due to other causes.

Figure 4 shows the dose-response curve obtained in these experiments. The dose of epinephrine (HCl) found to produce ventricular fibrillation in 50% of the pigeons, was calculated by the method of least squares to be 8.3 mcg./Kg. with a range of 6.2–12.8 mcg./Kg. The calculated slope was 1.3 probits per log dose.

In general, the onset of ventricular fibrillation occurred 5 to 10 seconds after the injection of epinephrine. For 15 to 20 seconds after the onset of fibrillation the pigeons lay quietly, respiration appeared normal, and there was no overt indication of the toxic manifestation. This was followed by an arching of the head and neck, brief clonic convulsions, and a final gasp. A similar sequence of events is observed in pigeons after toxic doses of digitalis.

## DISCUSSION

The sensitization of the heart to fatal epinephrine-induced ventricular fibrillation by a chemical compound has not been previously described in the pigeon or any other member of the avian genus. The results of the present investigation indicate that the cardiac-sensitizing activity may be evalu-



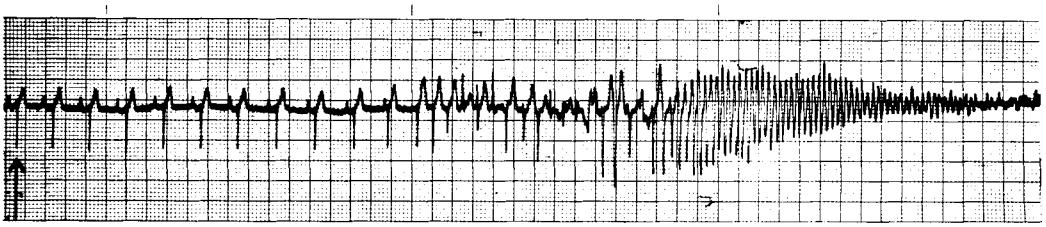




Fig. 3.—Two modes of electrical progression into U-0882–epinephrine ventricular fibrillation.

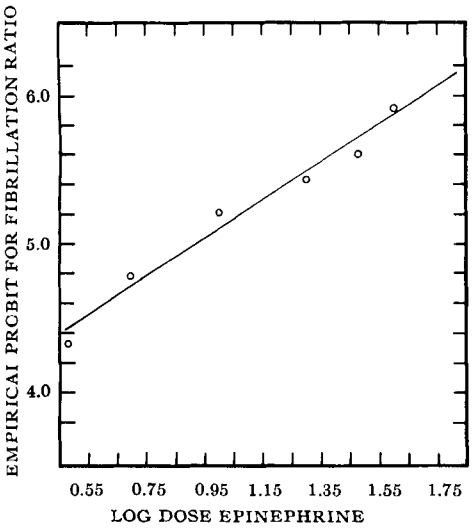



Fig. 4.—Relationship of dosage of epinephrine to incidence of ventricular fibrillation in pigeons sensitized with U-0882.

ated by the dose of epinephrine which will induce fibrillation in 50% of the pigeons previously receiving a usually tolerated dose of the compound under examination.

The observed slope of the dose-response curve obtained from the data of these experiments was 1.3 probits per log dose. This is a relatively flat dose-response curve in comparison with the dose-response curves of various other drugs and their actions. The present data are obviously insufficient to conclude whether this flatness is characteristic of pigeons, epinephrine, U-0882, the combination, or of drug-induced ventricular fibrillation. In any event the low cost of pigeons makes it economically feasible to use relatively large numbers of test animals to attain any desired degree of precision in evaluating the potential of a drug for inducing ventricular fibrillation. The use of the pigeon in cardiac-sensitization studies has other advantages over the use of other species. Artificial respiration often required in other species may not be necessary. The time-saving factor should encourage the use of pigeons. Only 5 to 10 minutes were required for the completion of each individual pigeon test.

## SUMMARY

The sensitizing action of a substituted propiophenone, U-0882, on the heart of the pigeon to epinephrine-induced ventricular fibrillation has been demonstrated.

The results of these experiments suggest a simple, rapid, and inexpensive approach to the detection and evaluation of cardiac-sensitizing properties of compounds as a routine toxicity procedure.

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