

Some β -Adrenergic Responses to Administration of *d,l*-Isoproterenol to Turkeys¹ (39394)

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Administration of the β -adrenergic agonist, isoproterenol, to rats and other mammals induces copious drinking and antidiuresis (1-7). The objective of the experiments described below was to determine whether isoproterenol also stimulated the same responses in a bird, viz, the turkey.

Methods. Experiment 1. Effect of isoproterenol on water intake of turkeys. Sixteen mature female turkeys (broad-breasted white) weighting 7.7 to 8.4 kg were used. The birds were divided equally into two groups. Group 1 served as the control group and was injected sc in the neck with 0.5 ml of isotonic saline. Group 2 was injected sc in the neck with 50 μ g of *d,l*-isoproterenol sulfate dihydrate²/kg. The dose of isoproterenol was calculated as the salt, dissolved in saline, and 0.5 ml was injected. A watering device³ from which the turkeys had been watered since 3 weeks of age was used to measure water intake at hourly intervals for 2 hr. A preliminary study showed that the turkeys would not drink from a watering device with which they were not familiar during the 2-hr test period. Intake of water was determined by weighing the water containers initially and at hourly intervals after administration of isoproterenol. Each turkey was kept separately in a pen 7-ft square. The floor was covered with peanut shells and the watering device was in a corner of each pen. During this study, it was observed that the birds treated with isoproterenol excreted a watery urine, a condition never observed in turkeys under normal circumstances, since these animals excrete a semi-

solid urine with their feces. A separate study was therefore made to determine whether drinking occurred prior to excretion of the watery urine or vice versa. Six control and six treated turkeys were used. The experiment was carried out as above except that a control and a treated turkey were observed continuously by one individual and notations were made of the times that drinking and urination occurred in each bird during the 2 hr following administration of 50 μ g of *d,l*-isoproterenol/kg of body weight, sc.

Experiment 2. Effect of isoproterenol on urine excretion in turkeys. In this study an attempt was made to determine the effect of acute administration of isoproterenol on urine excretion in restrained turkeys.

Three mature female broad-breasted white turkeys weighing 5.0 to 7.1 kg were used. The turkeys were restrained in dorsal recumbency because it was found that they usually lay quietly throughout the 2-hr experiment when their heads were covered with a towel. Before beginning the experiment, each turkey was given an isotonic saline enema to cleanse the cloaca and lower gut of urine and feces. Completeness of the procedure was determined visually with the aid of canine vaginal speculum. Urine was collected continuously in a filtering flask trap by aspiration from the cloaca with a vacuum pump. Urine volume was measured every 30 min throughout the experiment. After an initial 30-min control period, each turkey was injected sc with 200 μ g of *d,l*-isoproterenol sulfate dihydrate/kg body weight. The dose was calculated as the salt.

Experiment 3. Other β -adrenergic responses to administration of isoproterenol in turkeys. Five broad-breasted white turkeys, two male and three female weighing from 5.2 to 7.6 kg were used. The three female turkeys were also used in Experiment 2. In the first study, skin temperature of the left

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² *d,l*-Isoproterenol sulfate dihydrate, Aldrich Chemical Co., Milwaukee, Wisconsin.

³ Little Giant Fountain Bowl #2508, Miller Mfg. Co., South St. Paul, Minnesota.

thigh of the birds was measured while they were restrained on a table. A Yellow Springs Instruments Co. fast-response thermometer probe #423 was taped to the skin of the thigh of each bird and temperature readings were made at 1-min intervals during a 25-min control period and for 44 min after administration of isoproterenol (200 μ g of *d,l*-isoproterenol sulfate dihydrate/kg sc). The dose was calculated as the salt. Mean air temperature of the room during this study was 25.8°.

In the second study, heart rate was recorded by means of needle electrodes implanted in the breast muscles of eight restrained turkeys and recorded on a NarcoBio Systems polygraph. At the end of a 15-min control period, four treated turkeys (three female and one male) were administered 200 μ g of *d,l*-isoproterenol sulfate dihydrate/kg sc in the neck region. The dose was calculated as the salt. Four control female turkeys not used in previous experiments were administered the saline vehicle at the same time. Measurement of heart rate continued for 70–90 min following treatment.

Two weeks later, four turkeys were administered 200 μ g of *d,l*-isoproterenol sulfate dihydrate/kg as the salt and killed 1 hr later. An additional bird was administered saline instead of isoproterenol and killed 1 hr later. The kidneys from each bird were fixed in 10% neutral formalin and embedded in paraffin. Tissue sections were cut at 5 μ m and stained with hematoxylin and eosin.

Statistical analysis of the data included an analysis of variance, and both one- (Experiment 2) and two-tailed Student's *t* tests (Experiments 1 and 3) (8).

Results. Experiment 1.

Administration of isoproterenol to turkeys increased their water intake in a fash-

ion similar to that reported for mammals (Table I). Water intake of treated turkeys was more than fivefold that of controls during the first hour of treatment ($P < 0.05$). During the second hour after treatment with isoproterenol, water intake was significantly ($P < 0.01$) greater than that of saline-treated controls. The cumulative 2-hr water intake of the treated group was also significantly ($P < 0.01$) greater than that of the control group.

In a study separate from that described above, four of six turkeys administered isoproterenol urinated prior to drinking. The time between urination and drinking varied from 1 to 63 minutes. A third turkey drank 5 min after urination while the fourth drank 21 min after urination. In the case of the remaining two turkeys, drinking occurred 8 and 11 min prior to urination. Turkeys treated with saline were never observed to excrete a fluid urine.

Experiment 2. Urine excretion rate increased at each 30-min interval after administration of isoproterenol although the increases were not significant (Table II). In contrast, the change in rate of urine excretion from the preisoproterenol control period increased significantly ($P < 0.05$) at 60

TABLE II. RATE OF URINE EXCRETION IN THREE TURKEYS AFTER SC ADMINISTRATION OF 200 μ g *d,l*-ISOPROTERENOL SULFATE DIHYDRATE/KG BODY WEIGHT

Postinjection time (min)	Urine excretion (ml/30 min)	Δ Urine excretion (ml/30 min)
0	38.3 \pm 6.1*	—
30	74.7 \pm 23.5	38.8 \pm 22.5
60	126.0 \pm 40.3	87.7 \pm 38.7**
90	154.7 \pm 56.0	116.3 \pm 53.4**

* One standard error of mean.

** Significantly different from 0 time ($P < 0.05$); one-tailed Student's *t* test.

TABLE I. EFFECT OF ADMINISTRATION OF *d,l*-ISOPROTERENOL SULFATE DIHYDRATE (50 μ g/kg BODY WEIGHT) ON WATER INTAKE OF TURKEYS DURING 2 HR AFTER DRUG TREATMENT

Experimental group	Number of turkeys	Water intake during:		
		1st hr	2nd hr	(1 + 2 hr)
Control	8	10.5 \pm 4.5*	18.9 \pm 7.9	29.4 \pm 11.5
Isoproterenol tested	8	56.4 \pm 15.6**	105.5 \pm 21.7***	161.9 \pm 27.6***

* One standard error of mean.

** Significantly different from control group ($P < 0.05$).

*** Significantly different from control group ($P < 0.001$).

and 90 min after administration of isoproterenol. It should be pointed out that urine excretion rate found here does not reflect urine excretion rate in the noncatheterized bird whose cloaca normally reabsorbs the water brought to it.

Experiment 3. Administration of 200 μ g *d,l*-isoproterenol/kg sc to turkeys increased the temperature of the skin of the left thigh. Maximal levels were achieved within 40 to 60 min after drug administration. In contrast, administration of saline had no effect. Representative results for three individual turkeys are shown in Fig. 1. In addition to

increasing skin temperature of the thigh, administration of isoproterenol was also accompanied by more than a doubling of the respiratory rate (Fig. 1).

Heart rate increased from levels of 170 to 270 beats per minute approximately 25 min after administration of 200 μ g of *d,l*-isoproterenol/kg sc (Fig. 2). Control turkeys administered saline showed a reduction in heart rate from levels of 165 to approximately 155 beats per minute, 25 min after injection. Heart rate of the treated turkeys had not returned to control level 75 min after administration of isoproterenol.

Histological examination of the kidneys revealed that glomerular and peritubular capillaries were widely dilated in turkeys killed 1 hr after administration of isoproterenol (Fig. 3C). These dilations were not seen in the turkey treated with saline (Fig. 3A).

Discussion. This is the first report of drinking accompanying administration of isoproterenol to a bird. The drinking re-

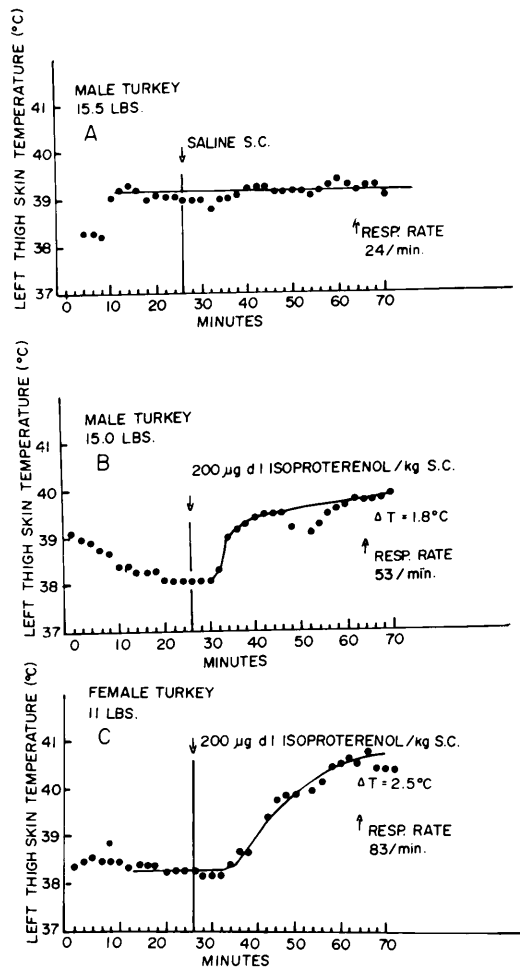


FIG. 1. Effect of sc administration of either saline (A) or *d,l*-isoproterenol sulfate dihydrate (200 μ g/kg body wt) (B,C) on skin temperature of left thigh of turkeys. Respiration rate measured 38 min after treatment is also given in the figure.

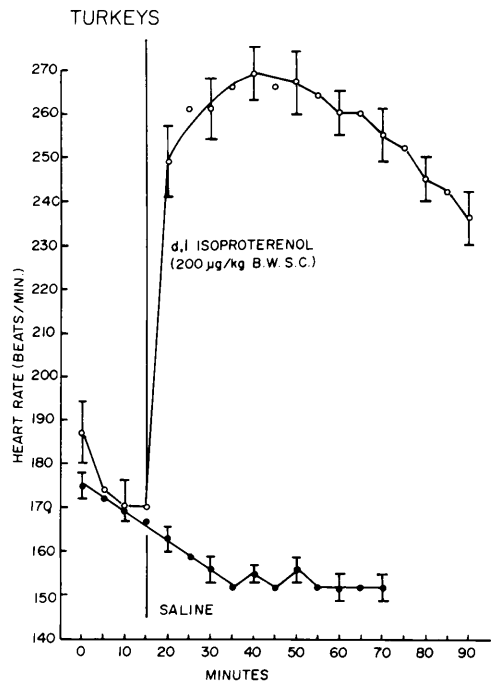


FIG. 2. Effect of sc administration of either saline or *d,l*-isoproterenol sulfate dihydrate (200 μ g/kg body wt) on heart rate of turkeys. Treatment was initiated at the end of a 15-min control period. One standard error is set off at each mean.

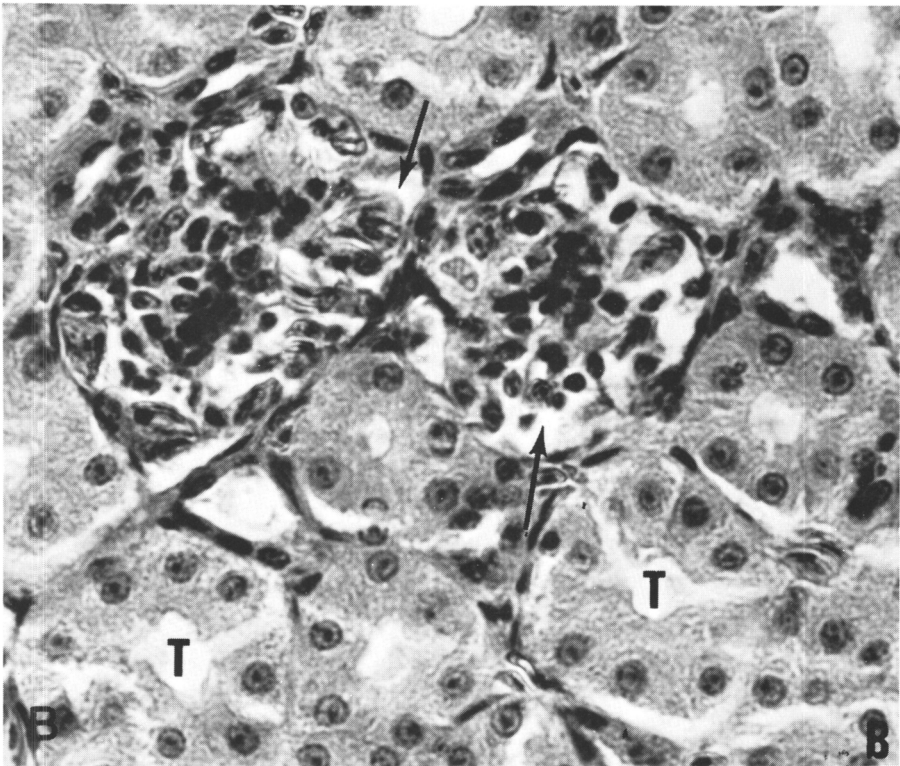
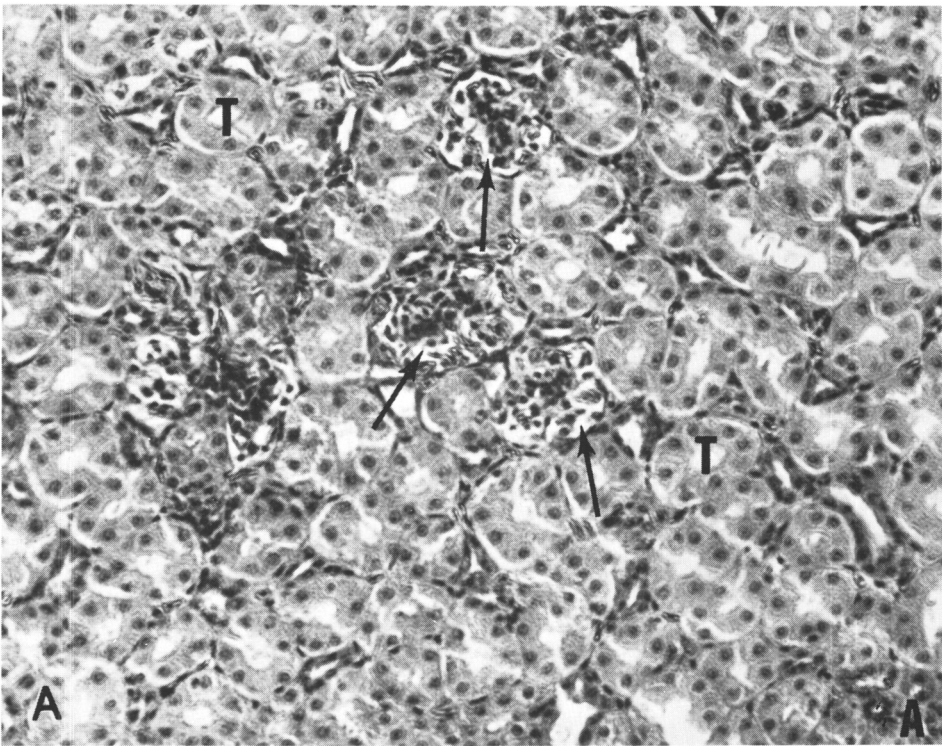


FIG. 3. The effect of a single injection of saline (A and B) or isoproterenol (C and D) on the histological appearance of the kidney of turkeys. (A) The glomeruli (arrows) are compact and tubules (T) are not dilated. H + E stain, $\times 250$. (B) H + E stain, $\times 1300$. (C) The glomeruli are swollen and their capillaries (arrows) dilated. Tubules (T) and peritubular capillaries (C) are also dilated. H + E stain, $\times 250$. (D) H + E stain, $\times 1300$.

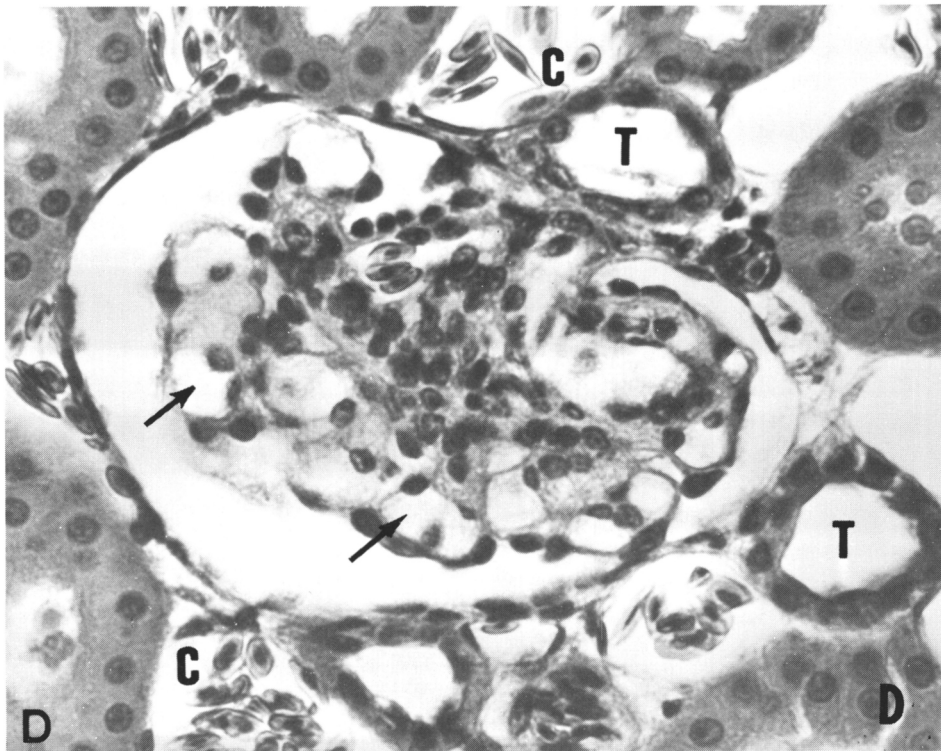
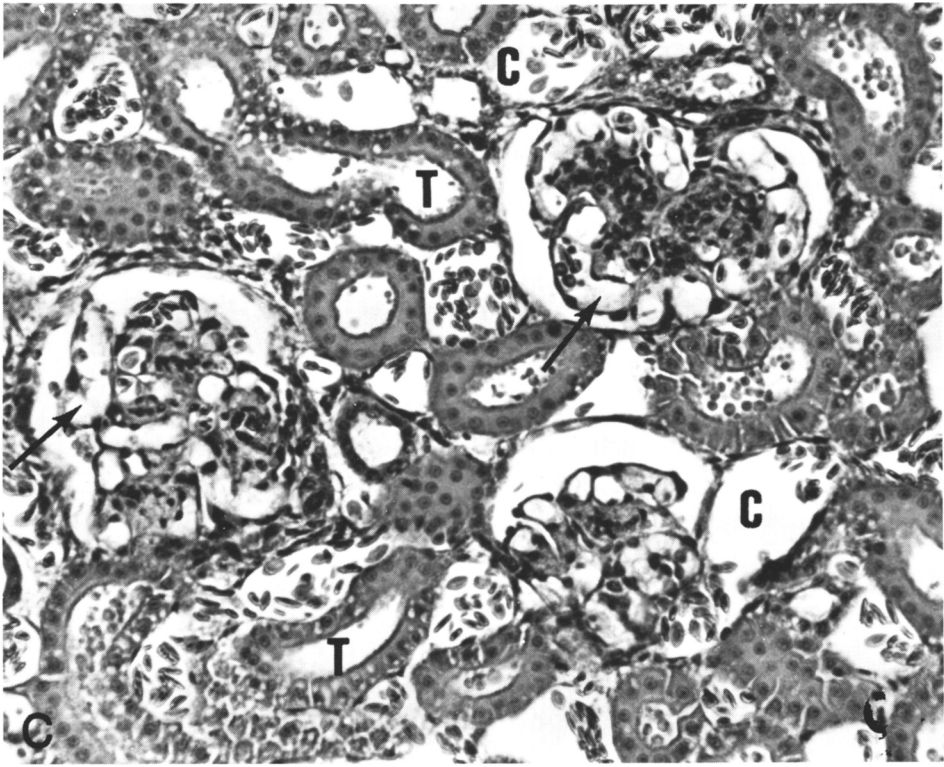


FIG. 3. *Continued*

sponse was similar in character to that observed in mammals (1-5). However, the response of the turkey appeared to differ from that of mammals in that administration of isoproterenol was accompanied by a fluid urine excretion. This is a rare occurrence in birds and contrasts sharply with the prominent antidiuresis accompanying administration of isoproterenol to mammals (3, 6, 7). A possibility exists that drinking may be stimulated indirectly by the increased urine excretion since four of six turkeys studied excreted a fluid urine prior to drinking. However, two other turkeys drank prior to urination.

It cannot be stated with certainty whether the increased urine excretion accompanying administration of isoproterenol was related either to changes in renal hemodynamics or to a reduction in antidiuretic hormone secretion. An increase in glomerular filtration rate and filtration fraction could account for the diuresis as could changes in tubular reabsorption of electrolytes and water. Schrier *et al.* (6) and Berl *et al.* (7) have shown that the antidiuretic effect of isoproterenol in the dog is not related to effects on the kidney but to an increase in the rate of secretion of antidiuretic hormone. The possibility that isoproterenol may have opposite effects in turkeys requires additional study, as does the dilation of glomerular capillaries induced by this drug (Fig. 3C).

In view of the increased urine excretion accompanying administration of isoproterenol to turkeys, it seemed important to study the effect of isoproterenol on some other β -adrenergic responses to determine whether they differed from those customarily seen in mammals. The studies revealed that increases in skin temperature (Fig. 1) and heart rate (Fig. 2) in response to isoproterenol were similar to those reported for mammals (9-11).

Summary. Acute administration of *d,l*-isoproterenol (50 μ g/kg body wt, sc) to turkeys was accompanied by a significant in-

crease in water intake which occurred within 1 h after treatment. This dose of *d,l*-isoproterenol also induced a copious, watery urine excretion. Acute administration of *d,l*-isoproterenol (200 μ g/kg body wt, sc) increased the temperature of the skin of the left thigh within 10 min after treatment. Skin temperature reached maximal levels within 40 to 60 min after treatment. Heart rate of turkeys administered *d,l*-isoproterenol (200 μ g/kg body wt, sc) increased approximately 100 beats per minute within 25 min after treatment. With the exception of the diuresis, the turkey responds to administration of isoproterenol in the same fashion as the mammal.

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1. Lehr, D., Mallow, J., and Krukowski, M., *J. Pharm. Exp. Therap.* **158**, 150 (1967).
2. Lehr, D., and Goldman, W., *European J. Pharmacol.* **23**, 197 (1973).
3. Klein, L. A., Liberman, B., Laks, M., and Kleeman, C. R., *Amer. J. Physiol.* **221**, 1657 (1971).
4. Tang, M., and Falk, J. L., *Pharmacol. Biochem. Behav.* **2**, 401 (1974).
5. Abdeloal, A. E., Mercer, P. F., and Mogenson, G. J., *Canad. J. Physiol. Pharmacol.* **52**, 362 (1974).
6. Schrier, R. W., Lieberman, R., and Ufferman, R. C., *J. Clin. Invest.* **51**, 97 (1972).
7. Berl, T., Cadnapaphornchai, P., Harbottle, J. A., and Schrier, R. W., *J. Clin. Invest.* **53**, 857 (1974).
8. Snedecor, G. W., and Cochran, W. G., in "*Statistical Methods*," 5th ed., p. 237. Iowa State University Press, Ames (1956).
9. Fregly, M. J., Nelson, E. L., Resch, G. E., Field, F. P., and Lutherer, L. O., *Amer. J. Physiol.* **229**, 916 (1975).
10. Black, D. J., Fregly, M. J., Thrasher, T. N., and Moreland, A. F., *J. Pharm. Exp. Therap.* **197**, 362 (1976).
11. Goodman, L. S., and Gilman, A., "*The Pharmacological Basis of Therapeutics*," 3rd ed., p. 498. Macmillan, New York (1965).

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