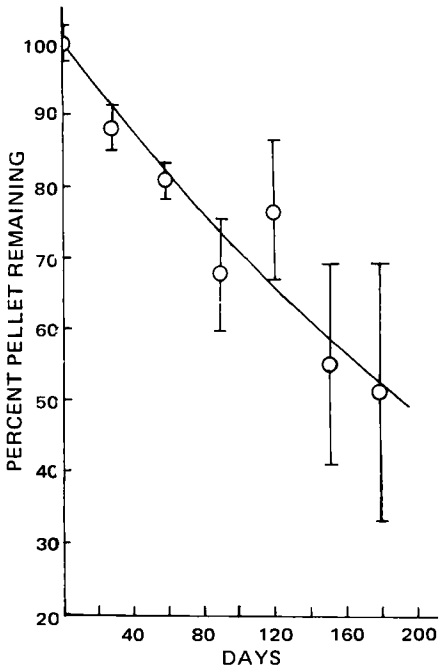


**Figure 5**—*Dissolution profile of delmadinone acetate pellets, Group 5, implanted subcutaneously in rats. Key: O, mean of observations with standard deviation as solid bar; curved solid line is computer fit of data to dissolution model.*

tion medium was ethanol–water (30:70). This test did not show significant differences between groups. A similar result was reported previously (5).

This finding indicates that an *in vivo* dissolution experiment is required to ascertain which physical parameters are important in pellet manufacture that cannot be immediately determined by an *in vitro* dissolution test. In the present study, the low compression group dissolved at a significantly greater rate than those pellets produced at a higher compression load. This result indicates that pellets with the desired dissolution rate could be produced by controlling the compression load (pellet density) without the necessity of an *in vitro* dissolution test.

Future studies will examine the *in vivo* dissolution rate of batches of pellets manufactured under known compression loads in the "standard compression" range and will examine the influence of steroid particle-size distribution on pellet manufacturability and *in vivo* dissolution.

## REFERENCES

(1) D. Deanesly and A. S. Parkes, *Proc. Roy. Soc., Ser. B*, **124**, 279(1937).

(2) E. Ballard and E. Nelson, *J. Pharm. Sci.*, **51**, 915(1962).

(3) H. W. Hays, E. Oppenheimer, D. R. Mathieson, and J. Lein, *Fed. Proc.*, **4**, 123(1945).

(4) A. T. Cowie and S. J. Foley, *J. Endocrinol.*, **4**, 375(1944–46).

(5) E. L. Parrott, D. E. Wurster, and T. Higuchi, *J. Amer. Pharm. Ass., Sci. Ed.*, **44**, 269(1955).

(6) H. J. Ringold, E. Batres, A. Bowers, J. Edwards, and J. Zderic, *J. Amer. Chem. Soc.*, **81**, 3485(1959).

(7) "Report of Biological Activity of Delmadinone Acetate," Bioassay Department, Institute of Biological Sciences, Syntex Research, Palo Alto, Calif, 1968.

(8) H. A. Gerber, W. Jochle, and F. G. Sulman, *J. Small Anim. Pract.*, **14**, 151(1973).

(9) C. M. Metzler, "A User's Manual for NONLIN," Tech. Rep. 7297/69/7297/005, The Upjohn Co., Kalamazoo, Mich., 1969.

## ACKNOWLEDGMENTS AND ADDRESSES

Received December 16, 1974, from the *Institute of Pharmaceutical Sciences, Syntex Research, Palo Alto, CA 94304*

Accepted for publication April 16, 1975.

The author thanks R. E. Jones for help with computer programs and D. Herriott and the staffs of the Department of Toxicology and the Department of Pharmaceutical Analysis, Syntex Research, for their technical assistance.

# Neurogenic Influences of Bilateral Adrenalectomy on Monoamine Oxidase

**DAVID E. CLARKE ˣ and SUMATHY S. SAMPATH ***

**Abstract** □ Bilateral adrenalectomy (10 days) increased the monoamine oxidase activity of the rat heart, vas deferens, spleen, superior cervical ganglion, and hypothalamus but not that of the rest of the brain, kidney, and liver. Experiments were made to determine whether the increased activity was due to neurogenic influences and whether the enhanced activity of monoamine oxidase was intra- or extraneuronally located. Ganglionic blockade with chlorisondamine failed to alter the rise in cardiac monoamine oxidase. Likewise, superior cervical ganglion monoamine oxidase was unaffected by surgical denervation. 6-Hydroxydopamine abolished the increase in monoamine oxidase activity of the vas deferens, spleen, and superior cervical ganglion but failed to alter that of the kidney, hypothalamus, and the rest of the brain. Cardiac monoamine oxidase was reduced markedly by 6-hydroxydopamine, but the remaining activity was still significantly elevated over the respective control values. The data suggest that the increase in organ monoamine oxidase is predominantly of neuronal origin and that this increase is not due to transsynaptic induction.

**Keyphrases** □ Monoamine oxidase—activity, effect of bilateral adrenalectomy, 6-hydroxydopamine, chlorisondamine, rat organs □ 6-Hydroxydopamine—effect on monoamine oxidase activity after bilateral adrenalectomy, rat organs □ Chlorisondamine—effect on monoamine oxidase activity after bilateral adrenalectomy, rat organs □ Adrenalectomy, bilateral—effect on monoamine oxidase activity, rat organs

Bilateral adrenalectomy increases the monoamine oxidase [monoamine: oxygen oxidoreductase (deaminating) EC 1.4.3.4] activity of the rat heart (1–3) and of certain other organs (2). However, the mechanism(s) whereby steroids or steroid insufficiency influences monoamine oxidase remains speculative (4).

In the case of bilateral adrenalectomy, it has been suggested that reflexogenically induced activation of postganglionic sympathetic fibers may be involved (5). If so, a specific transsynaptic induction of intraneuronal monoamine oxidase might follow, assuming no trophic influence of the released transmitter upon the extraneuronal enzyme(s). Indeed, it was shown previously (6) that there is a selective increase in the activity of intraneuronal monoamine oxidase in the rat vas deferens 10 days after bilateral adrenalectomy. Alternatively, indirect evidence exists for an increase in the activity of extraneuronal monoamine oxidase. An enhanced deamination of levarterenol (norepinephrine) was reported during perfusion of isolated hearts taken from bilaterally adrenalectomized rats (1). Since the concentration of the perfused levarterenol was 5 μg/ml, deamination probably occurred primarily, if not entirely, at extraneuronal sites (7, 8).

The present study reports on experiments designed to distinguish between these two possibilities. Neurogenic influences were tested using ganglionic blockade and surgical denervation. In addition, 6-hydroxydopamine was used to assess relative changes in the activity of the intra- and extraneuronal enzymes.

## METHODS

Male albino Wistar rats, 150–200 g, were used. The animal quarters were maintained at 22–24° on a circadian cycle of 12 hr (6:00 am to 6:00 pm, light; 6:00 pm to 6:00 am, dark). A 7–8 day acclimatization period was allowed prior to experimental procedures. Food and water were supplied *ad libitum*.

**Bilateral Adrenalectomy**—Surgical removal of the glands was performed under pentobarbital sodium anesthesia (60 mg/kg ip). Two bilateral incisions were made in the abdomen, and both adrenal glands, along with the periadrenal fat, were removed. The peritoneal cavity was closed with sterile surgical silk, and the skin incisions were closed with wound clips. Sham-operated rats differed only in that the glands were located but not removed. All animals were given tap water containing 0.9% (w/v) sodium chloride as the sole drinking fluid.

**Denervation of Superior Cervical Ganglion**—Surgical section of the preganglionic fibers to the superior cervical ganglion was made under pentobarbital sodium anesthesia, as already described. The trachea was exposed, and the vagus nerve was carefully dissected from the sympathetic fibers and the common carotid artery. A ligature was placed about 2 cm caudal to the ganglion, and the nerves were sectioned above the ligature. The contralateral ganglion was used as a control. A sham operation was carried out in which the nerves were located but not tied or severed. The muscle incision was closed with surgical silk and the skin with wound clips.

The denervated side was varied alternately, and the animals were sacrificed 10 days after the operation. The persistence of complete ptosis was used to verify the completeness of the operation. Bilateral adrenalectomy or sham adrenalectomy was conducted immediately following this procedure.

**Monoamine Oxidase Determinations**—Monoamine oxidase activity was assayed by determining the indoleacetic acid formed from tryptamine in the presence of excess aldehyde dehydrogenase, as described previously (3, 9). Whole tissue homogenates were prepared in 0.25 *M* sucrose, using a homogenizer[1]. A 50-mg/ml homogenate was prepared for all tissues except ganglia. The ganglia were either weighed on a microbalance and assayed individually or pooled and then assayed.

Tissues were checked for linearity with respect to both concentration and incubation time so as to be sure that the initial velocity rate of the reaction was being measured. The indoleacetic acid was measured spectrofluorometrically (excitation at 286 nm, emission at 365 nm, uncorrected), and the values were corrected for extraction losses by running a set of standards through the entire procedure.

**Tissue Water Content**—Wet to dry tissue weight ratios were determined by heating tissues to a constant weight at 85°.

**Drugs**—Chlorisondamine[2] and 6-hydroxydopamine[3] were used. 6-Hydroxydopamine was prepared just before use in 0.001 *N* HCl which had been previously gassed with nitrogen.

**Statistics**—The significance of the difference between means was calculated using the Student *t* test.

[1] Polytron.

Table I—Effect of Bilateral Adrenalectomy upon Monoamine Oxidase Activity of Various Rat Tissues

| Tissue | Percent Increase[a] | *n* | Significance |
|---|---|---|---|
| Heart | 151 ± 13.18 | 18 | $p < 0.001$ |
| Spleen | 46 ± 6.30 | 12 | $p < 0.001$ |
| Superior cervical ganglion | 41 ± 4.52 | 12 | $p < 0.01$ |
| Vas deferens | 39 ± 6.80 | 16 | $p < 0.01$ |
| Hypothalamus | 35 ± 8.78 | 12 | $p < 0.01$ |
| Rest of brain | 6 ± 7.05 | 12 | Not significant |
| Liver | 4 ± 6.55 | 12 | Not significant |
| Kidney | 2 ± 8.00 | 12 | Not significant |

[a] Expressed as a percentage of sham-operated values 10 days after surgery. Shown are mean values ± *SE* for *n* animals.

## RESULTS

The monoamine oxidase activity of various tissues was measured 10 days after bilateral adrenalectomy, and the results are expressed in Table I as a percentage of the respective sham-operated, control means. Heart monoamine oxidase activity was increased markedly. Also statistically significant but smaller elevations were found in the spleen, superior cervical ganglia, vas deferens, and hypothalamus. No changes were obtained in the rest of the brain, liver, and kidney.

Changes in heart monoamine oxidase were controlled using three separate groups of rats. Group I ($n = 6$) received water and no operation; Groups II ($n = 6$) and III ($n = 18$) were sham operated, but Group II was given water while Group III was given saline as the drinking fluid. The monoamine oxidase activity of the three groups was not significantly different, demonstrating that the anesthetic, surgery, or saline did not affect cardiac monoamine oxidase.

No change in the water content of the heart, spleen, or kidney was observed, but 2 and 6% increases over the sham-operated saline controls were obtained in the liver and vas deferens, respectively.

Thus, the results show that bilateral adrenalectomy specifically increased the monoamine oxidase activity of some organs but not others and that this effect was not due to enzyme concentration consequential to an increased tissue mass to water ratio.

An experiment was performed to study the effect of chronic ganglionic blockade upon the increase in cardiac monoamine oxidase activity following adrenalectomy. Sham-operated and bilaterally adrenalectomized rats were injected with chlorisondamine (5 mg/kg ip three times a day) for 10 days. The control groups received the vehicle only. Figure 1 shows that persistent ganglionic blockade, as judged by ptosis, failed to alter the rise in cardiac monoamine oxidase activity. Chlorisondamine also failed to affect the inherent activity of the enzyme in control, sham-operated rats.

A similar result was obtained following preganglionic nerve section to the superior cervical ganglion (Fig. 2). Denervated ganglia showed the same mean increase in monoamine oxidase activity as the intact contralateral controls. In addition, denervation failed to alter the monoamine oxidase activity in the sham-adrenalectomized group, indicating that normal physiological levels of presynaptic input did not affect cell body monoamine oxidase under the present experimental conditions.

[2] Ecolid, Ciba Pharmaceutical Co., Summit, N.J.
[3] Regis Chemical Co., Morton Grove, Ill.

In view of these data, it was important to establish whether bilateral adrenalectomy actually affected intraneuronal monoamine oxidase. Thus, experiments were conducted using 6-hydroxydopamine (100 mg/kg iv) given 9 days after bilateral adrenalectomy or the sham operation. Control groups received vehicle only. The rats were killed 31 hr later, and the results are shown in Table II. Bilateral adrenalectomy alone produced quantitatively similar results to those given in Table I.

The cardiac monoamine oxidase of sham-operated rats was not altered by 6-hydroxydopamine (compare Group III with Group I); but the elevated activity of monoamine oxidase, due to adrenalectomy, was decreased significantly (compare Group IV with Group II). However, the enzymatic activity remained significantly elevated compared with Group III (sham operated, 6-hydroxydopamine treated). In the spleen and superior cervical ganglion, 6-hydroxydopamine abolished completely the rise in monoamine oxidase activity following bilateral adrenalectomy; the activity of monoamine oxidase in spleens and ganglia of sham-operated rats remained unaffected. The vas deferens was most susceptible to 6-hydroxydopamine, and decreases in the monoamine oxidase activity of both the sham-operated and adrenalectomized groups (Groups III and IV) were obtained, with the adrenalectomized group being the most sensitive. The kidney, hypothalamus, and rest of the brain were unaffected by 6-hydroxydopamine.

The adrenalectomized, 6-hydroxydopamine-treated group (Group IV) originally contained seven rats. Subsequent to the administration of 6-hydroxydopamine, three animals died, presumably because of their inability to combat the considerable cardiovascular and general homeostatic changes induced by this compound.

## DISCUSSION

In the present study, cardiac monoamine oxidase activity was increased markedly 10 days after bilateral adrenalectomy, but this increase was not affected by chlorisondamine. Chlorisondamine, a potent and long lasting ganglionic blocking agent, induced a persistent ptosis throughout the course of treatment. Thus, it may be concluded that a transsynaptic induction of monoamine oxidase is not the cause of the elevated activity of this enzyme in the heart. The same conclusion can be made for the superior cervical ganglion, since chronic denervation failed to curtail the rise in monoamine oxidase. In addition, neither chlorisondamine (heart) nor denervation (ganglia) changed the normal level of monoamine oxidase activity in sham-operated rats. Thus, using *in vitro* determinations, no evidence was obtained for any neurogenic influences on monoamine oxidase.

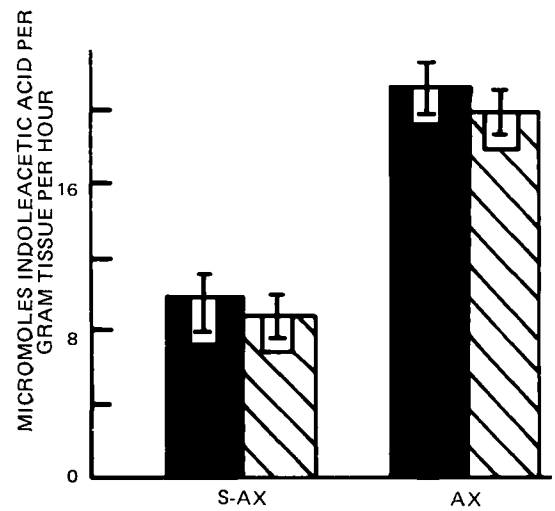


**Figure 1**—*Effect of chronic ganglionic blockade with chlorisondamine (5 mg/kg ip three times daily) for 10 days upon heart monoamine oxidase activity of bilaterally adrenalectomized and sham-adrenalectomized rats. Key: S-AX, sham adrenalectomized, mean values ± SE for five rats; AX, adrenalectomized, mean values ± SE for five rats; ■, without chlorisondamine; and ▨, with chlorisondamine. Significance of differences are: S-AX* versus *AX*, $p < 0.01$; *and S-AX plus chlorisondamine* versus *AX plus chlorisondamine*, $p < 0.01$.

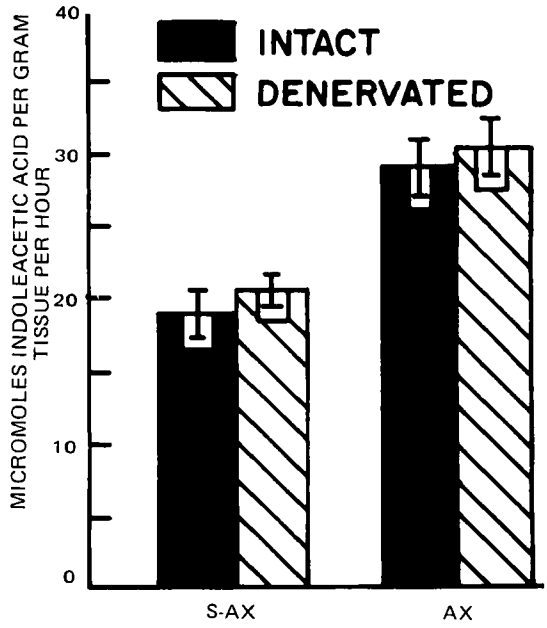


**Figure 2**—*Effect of chronic unilateral denervation for 10 days upon the monoamine oxidase activity of the superior cervical ganglion of bilaterally adrenalectomized and sham-adrenalectomized rats. Key: S-AX, sham adrenalectomized, mean values ± SE for six rats; and AX, adrenalectomized, mean values ± SE for six rats. Significance of differences are: intact S-AX* versus *intact AX*, $p < 0.05$; *and denervated S-AX* versus *denervated AX*, $p < 0.05$.

Sympathectomy, including that following 6-hydroxydopamine, has been used to assess the proportion of intraneuronal monoamine oxidase in sympathetically innervated tissues (10–12). In the present study, the fall in the monoamine oxidase activity of the vas deferens of sham-operated rats (about 30%) was short of the 50% decrease obtained in denervation studies (6, 10). This finding implies that the dose of 6-hydroxydopamine (100 mg/kg) failed to induce a complete sympathectomy. However, this conclusion cannot be extrapolated to all other tissues, since different sensitivities to 6-hydroxydopamine exist.

The heart is very sensitive to 6-hydroxydopamine compared with the vas deferens (13–15) and cardiac tyrosine hydroxylase activity (16), and both levarterenol levels and uptake (16, 17) are depressed markedly after a similar 6-hydroxydopamine dosage to that used in the present study. Thus, a more complete sympathectomy is likely in the heart than in the vas deferens. In fact, the data from sham-operated rats confirm the suggestion that heart (10, 12) and kidney (10) monoamine oxidase is located predominantly at extraneuronal sites, and the lack of any effect upon the brain enzyme is consistent with the inability of 6-hydroxydopamine to cross the blood–brain barrier.

Based upon these considerations, the results obtained with 6-hydroxydopamine in adrenalectomized rats (Table II) suggest that the increased activity of monoamine oxidase is largely of neuronal origin, but this contention is clouded by the unexpected fall in ganglionic monoamine oxidase and by the high mortality encountered. However, this latter phenomenon does not seem to represent a nonspecific cellular toxicity or generalized debilitating effect of 6-hydroxydopamine since brain, and more importantly, kidney monoamine oxidase remained unaffected.

Examination of the data for the vas deferens (Table II) reveals an increased sensitivity to 6-hydroxydopamine in adrenalectomized rats; a complete denervation seems to have been achieved. This finding might indicate that either the neurons or the monoamine oxidase itself is more susceptible to the damaging effects of this drug (6-hydroxydopamine is a substrate for monoamine oxidase). An increased neuronal accumulation of 6-hydroxydopamine is also likely. However, no evidence exists for an enhanced neuronal uptake in the hearts of adrenalectomized rats (1, 2), but differ-

Table II—Effect of 6-Hydroxydopamine on Monoamine Oxidase Activity of Bilaterally Adrenalectomized and Sham-Operated Rats[a]

| Tissue | Monoamine Oxidase Activity, μmoles/g/hr[b] | | | |
|---|---|---|---|---|
| | Group I | Group II | Group III | Group IV |
| Vas deferens | 7.42 ± 0.19[c,d] | 11.09 ± 0.39[e,d] | 5.31 ± 0.31[e,c] | 3.50 ± 0.35[f,e,c] |
| Spleen | 4.05 ± 0.36[c] | 6.11 ± 0.19[e,d] | 3.61 ± 0.30[c] | 3.22 ± 0.08[e,c] |
| Superior cervical ganglion | 9.11 ± 0.38[c] | 13.72 ± 0.62[e] | 9.22 ± 0.64[c] | 8.95 ± 0.37[c] |
| Heart | 8.61 ± 0.55[c] | 19.72 ± 0.83[e,d] | 8.18 ± 0.97[c] | 11.94 ± 0.72[e,c,d] |
| Kidney | 3.22 ± 0.11 | 3.39 ± 0.22 | 3.23 ± 0.09 | 3.39 ± 0.30 |
| Hypothalamus | 8.47 ± 0.49[c] | 11.39 ± 0.37[e,d] | 8.19 ± 0.76[c] | 11.67 ± 0.53[e,d] |
| Rest of brain | 5.08 ± 0.19 | 5.40 ± 0.27 | 5.00 ± 0.16 | 5.16 ± 0.26 |

[a] Group I = sham operated plus vehicle, Group II = adrenalectomy plus vehicle, Group III = sham operated plus 6-hydroxydopamine, and Group IV = adrenalectomy plus 6-hydroxydopamine. Surgical operations were made 9 days prior to the administration of 6-hydroxydopamine or the vehicle, and the rats were killed 31 hr later. [b] Mean values ± *SE* for six rats (Groups I and II), five rats (Group III), and four rats (Group IV). [c] Significantly different from Group II, $p < 0.05$. [d] Significantly different from Group III, $p < 0.05$. [e] Significantly different from Group I, $p < 0.05$. [f] Values expressed per pair × $10^2$.

ences between organs cannot be excluded since uptake mechanisms in peripheral adrenergic neurons may vary (18, 19). Thus, although ganglionic damage with 6-hydroxydopamine is usually considered to be virtually nonexistent (13), similar changes to those proposed for the vas deferens could explain the observed fall in the monoamine oxidase activity of this structure.

It is worth noting that ganglia are not completely resistant to 6-hydroxydopamine (13), especially those of young animals (20–23) where extensive structural, histochemical, and biochemical changes have been observed. Thus, if adrenalectomy caused some reversal of the ganglionic "aging process," damage with 6-hydroxydopamine would be expected. In fact, steroids do appear to exert a marked cellular differentiating effect upon certain ganglionic cells of immature rats (24), but the effects of adrenalectomy on mature ganglia remain to be elucidated.

The data obtained with the heart suggest that both extra- and intraneuronal monoamine oxidase is increased by adrenalectomy. Thus, it is not surprising that Avakian and Callingham (1) found an enhanced deamination of levarterenol (5 μg/ml) during perfusion of isolated hearts taken from adrenalectomized rats. The surprising result is that the normally small proportion of intraneuronal monoamine oxidase is increased to such an extent as to alter significantly the total monoamine oxidase activity of the heart. A similar effect was also obtained in the spleen.

Tryptamine is a substrate for the two major types of monoamine oxidases, A and B (25). Thus, from the present study, no conclusions with regard to preferential influences of adrenalectomy on any particular type or molecular form of monoamine oxidase can be made. However, the intraneuronal enzyme(s) of the superior cervical ganglion and the vas deferens appear to be almost entirely of type A (25, 26).

In conclusion, this study has shown that bilateral adrenalectomy increases the monoamine oxidase activity of some organs but not others. No evidence was obtained for a transsynaptic mediation of this effect, but intraneuronal monoamine oxidase seems to be involved. Of the peripheral organs studied, only those with a fair to high content of endogenous norepinephrine were affected, suggesting that a relationship might exist (10). In addition, the increased monoamine oxidase activity of the superior cervical ganglion is, in itself, suggestive of an intraneuronal locus, since 90% of the monoamine oxidase in this structure is believed to be present within the cell bodies of the adrenergic fibers (26).

Overall, the results support previous findings where surgical denervation of the vas deferens inhibited the rise in monoamine oxidase activity due to bilateral adrenalectomy (6). However, the present results are rendered less conclusive due to the toxicity of 6-hydroxydopamine in adrenalectomized rats. Further investigations will be required to obtain more substantive evidence.

## REFERENCES


(1) V. M. Avakian and B. A. Callingham, *Brit. J. Pharmacol.*, **33,** 211P(1968).

(2) P. M. Caesar, G. G. S. Collins, and M. Sandler, *Biochem. Pharmacol.*, **19,** 921(1970).

(3) D. E. Clarke and S. S. Sampath, *J. Pharmacol. Exp. Ther.*, **187,** 539(1973).

(4) M. B. H. Youdim, M. Holzbauer, and H. F. Woods, in "Neuropharmacology of Monoamines and Their Regulatory Enzymes," E. Usdin, Ed., Raven, New York, N.Y., 1974, p. 11.

(5) T. C. Westfall and H. Osada, *J. Pharmacol. Exp. Ther.*, **167,** 300(1969).

(6) S. S. Sampath and D. E. Clarke, *Life Sci.*, **11,** 1037(1972).

(7) L. L. Iversen, "The Uptake and Storage of Noradrenaline in Sympathetic Nerves," Cambridge University Press, Cambridge, Mass., 1967, p. 108.

(8) S. L. Lightman and L. L. Iversen, *Brit. J. Pharmacol.*, **37,** 638(1968).

(9) L. Lovenberg, R. J. Levine, and A. A. Sjoerdsma, *J. Pharmacol. Exp. Ther.*, **135,** 7(1962).

(10) B. Jarrott, *J. Neurochem.*, **18,** 7(1971).

(11) B. Jarrott and L. L. Iversen, *ibid.*, **18,** 1(1971).

(12) A. Horita and M. C. Lowe, in "Monoamine Oxidases—New Vistas," E. Costa and M. Sandler, Eds., Raven, New York, N.Y., 1972, p. 227.

(13) H. Thoenen and J. P. Tranzer, *Annu. Rev. Pharmacol.*, **13,** 169(1973).

(14) G. Jaim-Etcheverry and L. M. Zieher, *Eur. J. Pharmacol.*, **13,** 272(1971).

(15) G. Burnstock, B. Evans, B. J. Gannon, J. W. Heath, and V. James, *Brit. J. Pharmacol.*, **43,** 295(1971).

(16) J. De Champlain, *Can. J. Physiol. Pharmacol.*, **49,** 345(1971).

(17) H. Thoenen, in "6-Hydroxydopamine and Catecholamine Neurons," T. Malmfors and H. Thoenen, Eds., American Elsevier, New York, N.Y., 1971, p. 75.

(18) S. Spector, J. Tarver, and B. Berkowitz, *Pharmacol. Rev.*, **24,** 191(1972).

(19) D. E. Clarke, B. S. Jandhyala, I. Cavero, B. N. Dixit, and J. P. Buckley, *Can. J. Physiol. Pharmacol.*, **52,** 641(1974).

(20) P. U. Angeletti and R. Levi-Montalcini, *Proc. Nat. Acad. Sci. USA*, **65,** 114(1970).

(21) T. B. Cheah, L. B. Geffen, B. Jarrott, and A. Ostberg, *Brit. J. Pharmacol.*, **42,** 543(1971).

(22) T. Malmfors, in "6-Hydroxydopamine and Catecholamine Neurons," T. Malmfors and H. Thoenen, Eds., American Elsevier, New York, N.Y., 1971, p. 47.

(23) L. Eranko and O. Eranko, *Acta Physiol. Scand.*, **84,** 125(1972).

(24) *Ibid.*, **84,** 115(1972).

(25) N. H. Neff and H.-Y. T. Yang, *Life Sci.*, **14,** 2061(1974).

(26) G. Goridis and N. H. Neff, *Neuropharmacology*, **10,** 557(1971).


## ACKNOWLEDGMENTS AND ADDRESSES


Received February 25, 1975, from the *Department of Pharmacology, College of Pharmacy, University of Houston, Houston, TX 77004*

Accepted for publication April 18, 1975.



* Present address: Department of Pharmacology, University of California Medical Center, San Francisco, CA 94143

ˣ To whom inquiries should be directed.