Proc. Nat. Acad. Sci. USA
Vol. 71, No. 7, pp. 2715–2719, July 1974

Monoamine Oxidase and Cerebral Uptake of Dopaminergic Drugs

(dopamine/noradrenaline/adrenaline/apomorphine/nialamide)

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Contributed by George C. Cotzias, April 10, 1974

ABSTRACT **The brain uptake of amines that do not enter the brain or enter it poorly was promoted by noncompetitive inhibitors of monoamine oxidase, as shown by behavioral and chemical criteria. Mice pretreated with water or enzyme inhibitors other than those mentioned were placid after receiving dopamine (3,4-dihydroxyphenethylamine). Mice pretreated with monoamine oxidase inhibitors (nialamide or iproniazid) showed upon treatment with dopamine the brisk motor responses characteristic of treatment with its precursor, L-dopa (3,4-dihydroxyphenylalanine). After receiving dopamine, intact nialamide-pretreated mice showed marked increases of brain dopamine, in contrast to water-pretreated test mice or water-treated controls. In unilaterally caudectomized, nialamide-pretreated mice, dopamine induced marked lateral curving of the body toward the lesion followed by running in that direction. Noradrenaline or adrenaline induced curving in caudectomized mice, whereas intact ones remained placid.**

These catecholamines are bound and inactivated by monoamine oxidase. The cerebral uptakes of chemicals that are bound but not inactivated by monoamine oxidase were thereafter tested. Nialamide induced increased behavioral responses to apomorphine and to *N*-propyl noraporphine, increased cerebral concentrations of both, and a deep coloration of the brain from methylene blue (bound by monoamine oxidase) but not Evans blue (bound by albumin). Even large doses of nialamide, however, failed to affect the behavioral responses to oxotremorine, which has cholinergic rather than adrenergic or dopaminergic properties. Mitochondrial monoamine oxidase seems therefore to play a specific regulatory role in the transport of substances that it binds, either to inactivate or to release them.

The aim of treating Parkinson's disease with L-3,4-dihydroxyphenylalanine (L-dopa, levodopa) is to replenish the low 3,4-dihydroxyphenethylamine (dopamine) levels in the striatum of the brain (1, 2). This precursor amino acid is used in part because dopamine does not enter except in a few silent areas (3–6). Essential inability to enter the brain also characterizes noradrenaline (norepinephrine) (7) and adrenaline (epinephrine (6), a primary and a secondary catecholamine, respectively. In contrast, similar amines such as mescaline or the amphetamines and tertiary ones such as apomorphine or its congeners enter the brain readily. The effects of mescaline and of the amphetamines are widely recognized but it is worth noting that apomorphine can stimulate the striatum in animals (8, 9) and can alleviate parkinsonism in man (10, 11).

Among the amines mentioned, those that essentially fail to enter the brain are labile in comparison with those that do. The former are readily inactivated, notably by monoamine oxidase (MAO) (12*a*), a mitochondrial enzyme (13). Among the latter, mescaline is a poor substrate for MAO (12*a*), the amphetamines are bound but not inactivated by it (12*c*), and two aporphines were found by us to resemble the amphetamines. This suggested a strong dependence of the entrance of an amine into the brain upon the degree of its inactivation on the way to the brain.

This idea could be tested by protecting labile amines with metabolic inhibitors, as nonlabile ones are protected by their chemical structures. We had hoped thus to demonstrate cerebral effects of labile amines and perhaps the inhibitors that can evoke them. Investigations of the latter, however, have greatly broadened the scope of this work.

Abbreviations: MAO, monoamine oxidase; i.p., intraperitoneally.

MATERIALS AND METHODS

Animals. Male Swiss albino mice were studied either intact or after partial removal of the right caudate nucleus, the success of which was determined by injecting apomorphine (2 μg/g, Merck & Co.) intraperitoneally (i.p.) and observing the conjugate curving of the body to the right detailed below (14). Each dose (Table 1 and 2) was tested on at least two groups, one serving as control.

Protocols. In one series, animals were injected i.p. with water or a metabolic inhibitor. In another, they were pretreated with one of the inhibitors and then injected i.p. with one of the catecholamines; dopamine (Calbiochem) was given also by gastric intubation (p.o.). The interval between pretreatment and treatment was 2 hr for nialamide (Sigma) and iproniazid (Hoffmann-LaRoche); 1 hr for 3,4-dimethoxy-5-hydroxybenzoic acid (Regis); 30 min for tropolone (Aldrich), catechol (Nutritional Biochem. Corp.), and SKF-525A (β-diethylaminoethyl diphenylpropylacetate·HCl,S.K.F. Labs). In another series, apomorphine, *N*-propyl noraporphine (Sterling-Winthrop); methylene blue (J. T. Baker); oxotremorine (Nutritional Biochem. Corp.); or Evans blue (City Chemical Co.) were given instead of a catecholamine.

Behavioral Scores. In intact mice, the components of the behavioral patterns induced by each drug were graded 0–3 and summed. When dopamine was given after a MAO inhibitor, stereotyped movements, hyperactivity, jumping, corkscrew tail, imbalance, panting, salivation, piloerection, red muzzle, or convulsions emerged; the maximal score was 30. The differences between water- and MAO inhibitor-pretreated animals were due to cerebral manifestations in the latter. Both aporphines induced stereotyped movements, gnawing, head bobbing, panting, corkscrew tail, and ataxia; the maximal score was 18. Oxotremorine (15) induced tremor, panting, corkscrew tail, opisthotonus, salivation, swollen con-

TABLE 1. *Behavioral effects of catecholamines—intact mice*

Chemical given	Dose/g	No. of animals	Mean score ± SEM
Water	0.02 ml	12	0
Nialamide	0.5 mg	30	0
Nialamide	0.25 mg	12	0
Nialamide	0.125 mg	6	0
Water + dopamine	0.02 ml 0.2 mg	21	8.2 ± 0.1
Nialamide + dopamine	0.5 mg 0.2 mg	36	16.6 ± 0.3*
Nialamide + dopamine	0.25 mg 0.2 mg	12	15.7 ± 0.4*
Nialamide + dopamine	0.125 mg 0.2 mg	6	14.2 ± 0.4*
Water + dopamine△	0.02 ml 1.0 mg	10	8.1 ± 0.1
Nialamide + dopamine△	0.5 mg 1.0 mg	10	17.8 ± 0.8*
Apomorphine	1.0 μg	21	10.7 ± 0.1
Nialamide + apomorphine	0.25 mg 1.0 μg	9	12.3 ± 0.4*
NPA	1.0 μg	6	10.5 ± 0.4
Nialamide + NPA	0.25 mg 1.0 μg	6	13.83 ± 0.4*
NPA	1.5 μg	6	12.2 ± 0.3
Nialamide + NPA	0.25 mg 1.5 mg	6	14.3 ± 0.2*

All chemicals were given intraperitoneally except those marked △, which were given orally. * = $P < 0.01$ as tested against corresponding controls. NPA stands for *N*-propylnoraporphine.

junctiva, red muzzle, and ataxia; the maximal score was 30. Adrenaline and noradrenaline caused sustained immobility. Methylene blue and Evans blue induced no visible behavioral changes.

The caudectomized animals were observed for curving of the entire body and tail to the right, withdrawal of the right limbs, extension of the left limbs, and circular running to the right. MAO substrates induced these manifestations only in nialamide-pretreated mice, whereas the doses of the aporphines were often lowered so that only the nialamide-pretreated animals reacted.

Analytical Methods. Whole brain dopamine was determined fluorimetrically (16) in intact mice 30 min after the injection of either water or dopamine (17). Cerebral radioactivity was measured periodically on pairs of water- or nialamide-pretreated mice after injection of tritiated apomorphine (18). Statistical significance was determined with groups of at least six animals at the peak of behavioral effects coinciding with the peak of the radioactivity. Whole-brain aporphines were determined fluorimetrically 10 min after injection (manuscript under preparation). Determinations of methylene blue or Evans blue were unnecessary, since the colors of the brains were conclusive. MAO activities were measured in mouse liver homogenates (10% w/v) and in suspensions of mitochondrial fragments (Tris·HCl buffer, pH 7.3, 0.1 M) with dopamine as the substrate (19). Apomorphine (6.4 mM) and *N*-propyl noraporphine (6.4 mM) were tested (37° for 1 hr) both as substrates and for their binding by MAO in both homogenates and mitochondrial fragments. The substrate constant (K_m) of dopamine, and the binding constants (K_i) of the aporphines were determined by the method of Lineweaver and Burk (20).

TABLE 2. *Behavioral effects of catecholamines—caudectomized mice*

Chemical given	Dose/g	No. of animals	Conjugate deviation
Water	0.02 ml	12	0
Nialamide	0.5 mg	15	0
Nialamide	0.25 mg	6	0
Nialamide	0.125 mg	3	0
Dopamine	0.2 mg	9	0
Nialamide + dopamine	0.5 mg 0.2 mg	15	→
Nialamide + dopamine	0.25 mg 0.2 mg	3	→
Nialamide + dopamine	0.125 mg 0.2 mg	3	→
Water + dopamine △	0.02 mg 1.0 mg	12	0
Nialamide + dopamine △	0.5 mg 1.0 mg	12	⇉
Water + noradrenaline	0.02 ml 0.2 mg	6	0
Nialamide + noradrenaline	0.5 mg 0.2 mg	6	→
Water + adrenaline	0.02 ml 0.2 mg	6	0
Nialamide + adrenaline	0.5 mg 0.2 mg	6	→
Water + apomorphine	0.02 ml 0.5 μg	6	0
Nialamide + apomorphine	0.25 mg 0.5 μg	6	→
N-Propylnoraporphine	0.025 μg	6	0
Nialamide + *N*-propylnoraporphine	0.25 mg 0.025 μg	6	⇉

All chemicals were given intraperitoneally except those marked △, which were given orally. → = conjugate curving toward side of caudectomy. ⇉ = running toward side of caudectomy.

Enzyme Inhibitors. Nialamide and iproniazid are noncompetitive inhibitors of MAO (12*b*). Tropolone is an inhibitor (21) and catechol is a competitive substrate for catechol *O*-methyltransferase, a major catabolic enzyme for catecholamines (22). Because MAO inhibitors also block the microsomal oxidase which can dealkylate some catecholamines, SKF-525A was used to block this oxidase (23, 24).

OBSERVATIONS

Injections of dopamine (0.8, 0.4, 0.2, and 0.1 mg/g) in intact mice after injection of water (0.02 mg/g) induced dose-dependent salivation, piloerection, and placidity. Oral administration (1.5, 1.0, 0.5, and 0.25 mg/g) induced sometimes similar manifestations. When intact animals were given nialamide (0.5, 0.25, 0.125, and 0.1 mg/g, i.p.) followed by dopamine, their placidity lasted maximally for 10 min and was followed by dose-dependent motor hyperactivity and the other effects characteristic of L-dopa (17), lasting maximally for 1 hr. With oral dopamine, the quiescent period lasted for 20 min and the hyperactive period for up to 1.5 hr. Replacement of nialamide by iproniazid (0.5, 0.125, 0.1, and 0.5 mg/g, i.p.), did not change these reactions. Since nialamide or iproniazid alone

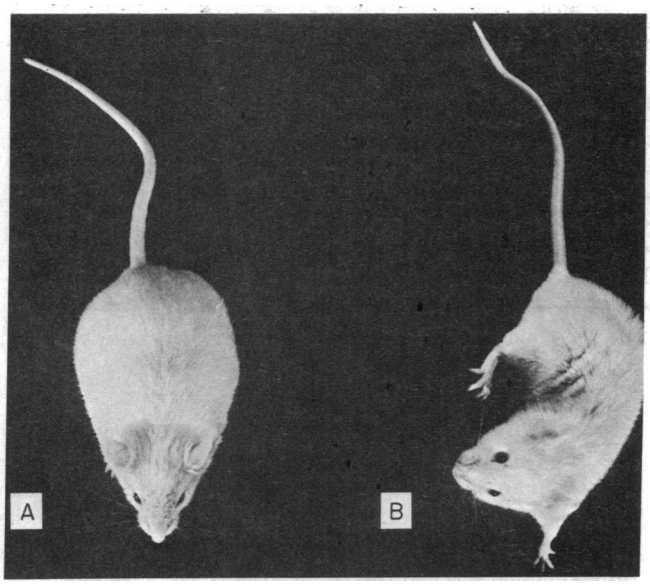

FIG. 1. A right partial caudectomy was performed on mice *A* and *B* a month prior to the experiments. Two and one half hours prior to taking of this picture, mouse *A* received water and mouse *B* nialamide (see *text*), while thirty minutes prior to it both mice received orally dopamine·HCl (0.25 mg/g). Note the marked conjugate deviation in mouse *B* toward the caudectomy (*right*). After this picture was taken, mouse *B* ran for 1 hr in the direction of the lesion, whereas mouse *A* was placid.

were inactive, these experiments suggested that the MAO inhibitors had permitted extensive entrance of exogenous dopamine into brain areas, including the striatum.

To identify the amine as having entered the brain, we did spectrofluorimetric analyses of whole brain on groups of at least six mice receiving the following: (*1*) water (0.02 ml/g, i.p.); (*2*) water followed by dopamine (0.2 mg/g, i.p.); (*3*) nialamide (0.5 mg/g, i.p.); (*4*) nialamide (0.5 mg/g, i.p.) followed by dopamine (0.2 mg/g, i.p.). The corresponding means and standard errors of the dopamine concentrations (μg per brain) were: (*1*) 0.48 ± 0.02; (*2*) 0.52 ± 0.03; (*3*) 0.50 ± 0.02, and (*4*) 1.35 ± 0.17. Group *4* differed from groups *1*, *2*, and *3* ($P < 0.001$), whereas the latter did not differ significantly among each other. Nialamide had, therefore, increased the dopamine taken up by the brain but not the dopamine synthesized by the brain.

The caudectomized mice receiving only dopamine (0.2 mg/g, i.p.) or orally (1.0, 0.5, and 0.25 mg/g) did not show curving of their bodies. Curving was notably absent also after injection of nialamide (0.5, 0.25, and 0.125 mg/g). When however, the i.p. or oral dopamine was given 2 hr after the nialamide, the marked conjugate deviation shown in Fig. 1 was always induced. With the two highest oral doses of dopamine the mice ran circularly to the right for at least 1 hr. The effects were the same when iproniazid (0.5, 0.25, 0.1, and 0.05 mg/g) was substituted for nialamide.

These results suggested that noradrenaline and adrenaline, for which dopamine is a precursor, should be tested. When given noradrenaline (0.4, and 0.2 mg/g) or adrenaline (0.4 and 0.2 mg/g) intact mice pretreated with water or nialamide showed sustained placidity, whereas nialamide-pretreated, caudectomized mice always exhibited the sustained conjugate deviation shown in Fig. 1. Thus, the postural responses to dopamine, adrenaline, or noradrenaline were similar.

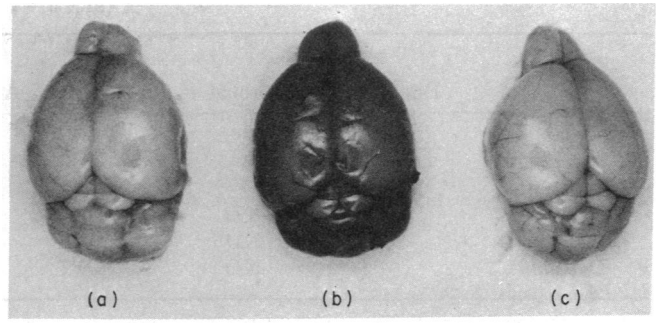

FIG. 2. Two and one half hours prior to taking of this picture donor mice *a* and *c* received water (0.02 ml/g, i.p.), whereas donor mouse *b* received nialamide (0.25 mg/g, i.p.). Thirty minutes prior to the picture mouse *a* received water and mice *b* and *c* methylene blue (0.1 mg/g, i.p.). Note the deep staining of the brain of nialamide-pretreated donor.

If the cerebral effects of these amines were promoted only by their impeded inactivation, one might duplicate them with inhibitors of enzymes that inactivate amines without deaminating them (25). We, therefore, pretreated intact mice with tropolone (40 μg/g), catechol (10, 30, and 50 μg/g), 3,4-dimethoxy-5-hydroxybenzoic acid (0.25 mg/g × 2) (26), or SKF-525A (60 μg/g) without promoting behavioral effects from dopamine (0.2 mg/g). This suggested that MAO played a specific role in promoting the cerebral effects of its exogenous substrates, as could be tested by using compounds reversibly bound by MAO without being inactivated and neuroactive drugs with actions unrelated to that of MAO.

Methylene blue is reversibly bound without being inactivated by MAO (12*d*, 27). After pretreatment with nialamide (0.5, 0.25, 0.125, and 0.1 mg/g), methylene blue (0.1 or 0.05 mg/g) produced a deep coloration of the brain, in contrast to pretreatment with water (Fig. 2). Injections of Evans blue (0.1 and 0.05 mg/g), which is bound to albumin instead of MAO, caused no visible coloration of the brain either with or without nialamide pretreatment (0.5 and 0.1 mg/g).

These results could be extended to the aporphines if these tertiary amines are bound but not deaminated by MAO. Their incubation (6.4 and 25 mM) with mouse liver homogenates or mitochrondrial suspensions revealed no net evolution of volatile amines. Yet reversible binding of these agents by mitochondrial MAO was evident, as shown by the following results. The K_m for dopamine was 0.8×10^{-9} M in the mitochondrial suspensions and 0.91×10^{-9} in the homogenates. The K_i values for apomorphine (6.4 mM) were 1.43×10^{-7} M in the former and 1.10×10^{-7} M in the latter, and for *N*-propyl noraporphine (6.4 mM) were 3.0×10^{-7} M and 2.08×10^{-7} M. Thus, both tertiary catecholamines are competitive inhibitors of MAO, raising the question whether a noncompetitive MAO inhibitor would potentiate their behavioral effects.

Injections of apomorphine in doses of 2.0 μg/g, which yield the highest attainable behavioral scores, produced equal scores in water- and nialamide-pretreated mice. With submaximal doses, however, (1.0 μg/g) significant potentiation of the drug's pharmacological effects by nialamide became apparent. Furthermore, caudectomized mice given apomorphine (0.5 μg/g) failed to show conjugate deviation after water pretreatment but showed it clearly after nialamide pretreatment.

TABLE 3. *Summary of effects*

	Dopamine	Noradrenaline	Adrenaline	Apomorphine	*N*-propyl aporphine	Methylene blue	Evans blue	Oxo-tremorine
Nialamide	+	+	+	+	+	+	−	−
Iproniazid	+	+	+	+	ND	ND	ND	ND
Tropolone	−	−	−	−	ND	ND	ND	ND
SKF-525A	−	ND	ND	−	ND	ND	ND	ND
DMHB	−	ND	ND	−	ND	ND	ND	ND
Catechol	−	ND	ND	ND	ND	ND	ND	ND

List of inhibitors (*columns*) and of substances tested for penetration into the brain (*rows*). + = positive effect; − = negative effect; ND = not done; DMBH = 3,4-dimethoxy-5-hydroxybenzoic acid.

In intact mice, injection of *N*-propyl noraporphine (1.0 μg/g) induced lower behavioral scores in water-pretreated mice than in nialamide-pretreated ones (10.5 ± 0.4 versus 13.8 ± 0.4, $P < 0.001$), whereas 0.05 and 0.025 μg/g produced conjugate deviation only in nialamide-pretreated caudectomized mice.

The coincidence of cerebral effects of apomorphine with its concentration in brain was shown with tritiated apomorphine (2 μg/g) in mice sacrificed every 5–15 min. The percent of the injected radioactivity that was recovered in whole brain 5 min later was 0.62 ± 0.08% for the seven nialamide-pretreated mice (0.5 mg/g) and 0.37 ± 0.02% for the seven water-pretreated ones ($P < 0.001$). These uptakes remained identical in six mice receiving 0.25 mg of nialamide per g. That the radioactivity reflected the concentrations of aporphine was shown by the spectrofluorimetric analysis of individual whole brains 10 min following injection. Each group of mice tested consisted of at least six animals, water- and nialamide-pretreated. The corresponding means and standard errors (μg per brain) for each aporphine were: apomorphine (2 μg/g, i.p.): 0.22 ± 0.01, 0.41 ± 0.03 ($P < 0.001$); *N*-propyl noraporphine (1.0 μg/g, i.p.): 0.08 ± 0.01, 0.17 ± 0.04 ($P < 0.03$); *N*-propyl noraporphine (2.0 μg/g, i.p.): 0.19 ± 0.02, 0.25 ± 0.01 ($P < 0.03$).

The various amines tested, including the aporphines, have dopaminergic or adrenergic properties, whereas oxotremorine is a cholinergic drug. Its effects (0.1 μg/g) on water- and nialamide-pretreated (0.5 mg/g) mice were identical.

DISCUSSION

As Table 3 summarizes, noncompetitive inhibitors strongly bound by monoamine oxidase (MAO), have promoted the cerebral uptake of chemicals loosely or reversibly bound by this enzyme. These strong, noncompetitive MAO inhibitors have revealed cerebral effects of exogeneous MAO substrates and have potentiated cerebral manifestations of noncompetitive inhibitors. This accords with the induction of rotatory behavior by nialamide in nigralesioned rate receiving cocaine (28), which, like methylene blue, apomorphine, and *N*-*n*-propyl noraporphine, is a reversible inhibitor of MAO (12*e*).

Cerebral effects reported here appear to have depended specifically upon MAO and upon substances bound by it, since they could be duplicated neither by substituting amines with a cholinergic agent nor by substituting MAO inhibitors with those of other degrading enzymes. Mitochondrial MAO appears, therefore, to play a specific regulatory role in the transport across the blood brain barrier and other cell membranes of substances which it binds and either deaminates or releases. This notion accords with (*1*) a histochemical study (29) showing increased neuronal fluorescence in nialamide-pretreated animals receiving L-dopa; and (*2*) an investigation which concluded that enzymes like MAO are dominant in the regulation of the disposition of catecholamines, imposed by the abdominal vascular bed studied (30).

Our results do not permit postulation of a molecular mechanism explaining this "opening-up" of the blood–brain barrier by inhibiting a mitochondrial enzyme. They do, however, permit the formulation of therapeutic protocols. It seems desirable, for example, to determine the therapeutic potential of nialamide in patients whose parkinsonism is suboptimally controlled even with the most recent improvement in the L-dopa treatment, a combination of L-dopa with a peripherally acting dopa decarboxylase inhibitor (31). This combination (Sinemet®, Merck Sharp & Dohme) curtails the synthesis of dopamine within peripheral tissues and has thus permitted the safe coadministration of a MAO inhibitor in the experimental animals hitherto studied (32). Furthermore, coadministration of a MAO inhibitor with apomorphine might sufficiently potentiate the central action of this amine to permit circumvention of the dose-dependent azotemia which has disqualified this drug from the treatment of parkinsonism (33).

Mr. Douglas Humphrey secured the photographs, two of which are reproduced here. Mrs. Geraldine Callister assisted with the compilation of the data and the manuscript. This work was supported by the U.S. Atomic Energy Commission; the National Institutes of Health (Grant NA 09492-03); the Charles E. Merrill Trust; Mrs. Katherine Rodgers Denckla; and The American Parkinson's Disease Association. A preliminary report was given by G.C.C. at his Harvey Lecture (Rockefeller Institute, December 14, 1973).

1. Hornykiewicz, O. (1966) *Pharmacol. Rev.* **18**, 925–964.
2. Cotzias, G. C., Papavasiliou, P. S. & Gellene, R. (1969) *N. Engl. J. Med.* **280**, 337–345.
3. Udenfriend, S., Weissbach, H. & Bogdanski, D. F. (1957) *Ann. N.Y. Acad. Sci.* **66**, 602–608.
4. Vogt, M. (1958) in *Symposium on Catecholamines. National Institutes of Health, Bethesda, Maryland, Oct. 16–18, 1958* (Williams and Wilkins Co., Baltimore), p. 487.
5. Welch, B. L. & Welch, A. M. (1964) "Biogenic amines," in *Progress in Brain Research*, eds. Himwich, H. E. & Himwich, W. A. (Elsevier, Amsterdam), Vol. 8, pp. 201–206.
6. Oldendorf, W. H. (1971) *Amer. J. Physiol.* **221**, 1629–1639.
7. Weil-Malherbe, H., Whitby, L. G. & Axelrod, J. (1961) *J. Neurochem.* **8**, 55–64.
8. Ernst, A. M. (1965) *Psychopharmacology* **7**, 391–399.
9. Anden, N-E., Rubenson, A., Fuxe, K. & Hökfelt, T. (1967) *J. Pharm. Pharmacol.* **19**, 627–629.
10. Cotzias, G. C., Papavasiliou, P. S., Fehling, C., Kaufman, B. & Mena, I. (1970) *N. Engl. J. Med.* **282**, 31–33.

11. Duby, S. E., Cotzias, G. C., Papavasiliou, P. S. & Lawrence, W. H. (1972) *Arch. Neurol.* **27**, 474–480.
12. Kapeller-Adler, R. (1970) in *Amine Oxidases and Methods for Their Study* (Wiley-Interscience, New York & London), (*a*) pp. 38–39, (*b*) p. 52, (*c*) p. 55, (*d*) p. 57, (*e*) p. 62.
13. Cotzias, G. C. & Dole, V. P. (1951) *Proc. Soc. Exp. Biol. Med.* **78**, 157–160.
14. Lotti, V. J. (1971) *Life Sci.* **10**, 781–789.
15. Campbell, L. B., Hanin, I. & Jenden, D. J. (1970) *Chem. Pharmacol.* **19**, 2053–2059.
16. Anton, A. H. & Sayre, D. F. (1964) *J. Pharmacol.* **138**, 360–375.
17. Cotzias, G. C., Tang, L. C., Miller, S. T. & Ginos, J. Z. (1971) *Science* **173**, 450–452.
18. Ginos, J. Z., LoMonte, A., Cotzias, G. C., Bose, A. K. & Brambilla, R. J. (1973) *J. Amer. Chem. Soc.* **95**, 2991–2994.
19. Cotzias, G. C. & Dole, V. P. (1951) *J. Biol. Chem.* **190**, 665–672.
20. Lineweaver, H. & Burk, D. (1934) *J. Amer. Chem. Soc.* **56**, 658–666.
21. Belleau, B. & Burba, J. (1963) *J. Med. Chem.* **6**, 755–759.
22. Axelrod, J. (1966) *Pharmacol. Rev.* **18**, 95–113.
23. Axelrod, J., Reichenthal, J. & Brodie, B. B. (1954) *J. Pharmacol. Exp. Ther.* **112**, 49–54.
24. La Du, B. N., Jr., Trousof, N. & Brodie, B. B. (1953) *Fed. Proc.* **12**, 339.
25. Missala, K., Lal, S. & Sourkes, T. L. (1973) *Eur. J. Pharmacol.* **22**, 54–58.
26. Baldessarini, R. J. & Chace, K. J. (1972) *Eur. J. Pharmacol.* **17**, 163.
27. Ehringer, H., Hornykiewicz, O. & Lechnerk, J. (1961) *Arch. Exp. Pathol. Pharmacol.* **241**, 568–582.
28. Christie, J. E. & Crow, T. J. (1973) *Brit. J. Pharmacol.* **47**, 39–47.
29. Bertler, A., Falck, B., Owman, C. H. & Rosengrenn, E. (1966) *Pharmacol. Rev.* **18**, No. 1, Part I, 369–385.
30. Spector, S., Tarver, J. & Berkowitz, B. (1972) *Pharmacol. Rev.* **24**, No. 2, 191–202.
31. Papavasiliou, P. S., Cotzias, G. C., Düby, S. E., Steck, A. J., Fehling, C. & Bell, M. A. (1972) *N. Engl. J. Med.* **286**, 8–14.
32. Calne, D. B. & Reid, J. L. (1973) *Brit. J. Pharmacol.* **48**, 194–197.
33. Cotzias, G. C., Lawrence, W. H., Papavasiliou, P. S., Düby, S. E., Ginos, J. Z. & Mena, I. (1972) *Tran. Amer. Neurol. Ass.* **97**, 156–159.