rimotor integration. The movement disturbances of Parkinson's disease, for example, are attributable to a loss of dopamine-containing neurons that innervate forebrain structures, particularly the neostriatum (*11*). Damage to these neurons of young adult animals results in sensorimotor disturbances similar to parkinsonism (*12*). The symptoms of this clinical disorder (*13*) and its analog in animals (*14*) are frequently controlled by administration of L-dopa, apomorphine, or similar compounds. Our findings suggest that advanced age may represent another link between movement disturbances and the deterioration of dopaminergic neurotransmission. This conclusion is supported by recent clinical investigations that have noted similarities between the movement disturbances of parkinsonism and those of nondiseased elderly individuals (*15*).

The swimming behavior of aged rats is a powerful indicant of age-related disturbances of movement. The impairment observed in aged animals is likely to be symptomatic of a wide-ranging deterioration of sensorimotor integration. The findings offer the opportunity to illuminate the neurological basis for some movement disorders of elderly humans.

JOHN F. MARSHALL
NORBERTO BERRIOS

Department of Psychobiology, University of California, Irvine 92717

References and Notes

1. A. T. Wellford, in *Handbook of the Psychology of Aging*, J. E. Birren and K. W. Shaie, Eds. (Van Nostrand Reinhold, New York, 1977), p. 450.
2. S. Schapiro, M. Salas, K. Vukovich, *Science* **168**, 147 (1970).
3. J. F. Marshall, D. Levitan, E. M. Stricker, *J. Comp. Physiol. Psychol.* **90**, 536 (1976).
4. D. R. Levitt and P. Teitelbaum, *Proc. Natl. Acad. Sci. U.S.A.* **72**, 2819 (1975); C. Ranje and U. Ungerstedt, *Eur. J. Pharmacol.* **43**, 39 (1977).
5. The following rating scales were used. For vigor: 3, continuous movement of all four limbs; 2.5, occasional floating; 2, floating more than swimming; 1.5, occasional swimming using all four limbs; 1, occasional swimming using hind limbs only; and 0, no use of limbs. For success: 3, entire head always above water; 2.5, ears but not eyes usually below water; 2, eyes but not nose usually below water; 1, entire head below water for periods of 6 seconds or longer; and 0, animal on bottom of tank for periods of 10 seconds or longer.
6. Records of rectal temperatures taken immediately before and after each swim test showed that young and old rats lost body heat equivalently during 15 minutes (mean ± standard error, 9.4° ± 0.3°C and 9.5° ± 0.2°C, respectively).
7. Å. Bertler, *Acta Physiol. Scand.* **51**, 97 (1961); A. Carlsson and B. Winblad, *J. Neural Transm.* **38**, 271 (1976); P. Riederer and S. Wuketich, *ibid.*, p. 277; J. A. Joseph, R. E. Berger, B. Engel, G. S. Roth, *J. Gerontol.* **33**, 643 (1978); E. G. McGeer, H. C. Fibiger, P. E. McGeer, V. Wickson, *Exp. Gerontol.* **6**, 391 (1971); P. E. McGeer and E. G. McGeer, *J. Neurochem.* **26**, 65 (1976); C. E. Finch, *Br. Res.* **52**, 261 (1973); V. Jonec and C. E. Finch, *ibid.* **91**, 197 (1975); J. B. Walker and J. P. Walker, *ibid.* **54**, 391 (1973); S. Govoni, P. Loddo, P. F. Spano, M. Trabucchi, *ibid.* **138**, 565 (1977); S. Govoni, P. F. Spano, M. Trabucchi, *J. Pharm. Pharmacol.* **30**, 448 (1978).
8. N.-E. Andén, S. G. Butcher, H. Corrodi, K. Fuxe, U. Ungerstedt, *Eur. J. Pharmacol.* **11**, 303 (1970).
9. G. Bartholini, W. P. Burkhard, A. Pletscher, H. M. Bates, *Nature (London)* **215**, 852 (1967).
10. For example, the most vigorous swimming in aged rats given apomorphine occurred at a dose of 0.25 mg/kg (45 points), whereas that of the young adult rats occurred with 2.0 mg/kg (42 points).
11. O. Hornykiewicz, *Biochem. Pharmacol.* **24**, 1061 (1975).
12. Reviewed by J. F. Marshall and P. Teitelbaum, in *Handbook of Psychopharmacology*, L. L. Iversen, S. D. Iversen, S. H. Snyder, Eds. (Plenum, New York, 1977), vol. 7, p. 201; E. M. Stricker and M. J. Zigmond, in *Progress in Psychobiology and Physiological Psychology*, J. M. Sprague and A. N. Epstein, Eds. (Academic Press, New York, 1976), p. 121; U. Ungerstedt, in *The Neurosciences: Third Study Program*, F. O. Schmitt and F. G. Worden, Eds. (MIT Press, Cambridge, 1974), p. 695.
13. A. Barbeau, *Proc. 7th Int. Congr. Neurol.* **2**, 925 (1961); W. Birkmayer and O. Hornykiewicz, *Wien. Klin. Wochenschr.* **73**, 787 (1961); G. C. Cotzias, M. H. Van Woert, L. M. Schiffer, *New Engl. J. Med.* **276**, 374 (1967); G. C. Cotzias, P. S. Papavasiliou, C. Fehling, *ibid.* **282**, 31 (1970); A. Lieberman, M. Kupersmith, E. Estey, M. Goldstein, *ibid.* **295**, 1400 (1976); T. N. Chase, A. C. Woods, G. A. Glaubiger, *Arch. Neurol.* **30**, 383 (1974).
14. J. F. Marshall and T. G. Gotthelf, *Exp. Neurol.*, **65**, 398 (1979).
15. J. H. Petatjan and L. W. Jarcho, *Neurology* **25**, 866 (1975); E. Evarts, H. T. Teräväinen, D. E. Beuchert, D. B. Calne, in *Dopaminergic Ergot Derivatives in Motor Functions*, K. Fuxe and D. B. Calne, Eds. (Pergamon, New York, in press).
16. Supported by PHS grant AG-00538. We thank A. Rosenstein for technical assistance and R. J. Baldessarini for apomorphine hydrochloride.

10 May 1979; revised 24 July 1979

A Correlation Between Platelet Monoamine Oxidase Activity and Plasma Prolactin Concentrations in Man

Abstract. *Increases in plasma prolactin concentrations produced by α-methyl-p-tyrosine, a catecholamine synthesis inhibitor, varied inversely with baseline platelet monoamine oxidase activity in 12 patients with chronic schizophrenia. In normal volunteers with low monoamine oxidase activity and in unmedicated patients with chronic schizophrenia, plasma prolactin concentrations varied directly with platelet monoamine oxidase activity. No such relationship was found in normal subjects with high platelet monoamine oxidase activity. These data suggest that platelet monoamine oxidase activity reflects monoaminergic activity in the tubero-infundibular system, which in turn affects plasma prolactin concentrations. This relationship may be important in patients with low platelet monoamine oxidase activity, such as some chronic schizophrenics.*

Monoamine oxidase (MAO) (E.C. 1.4.3.4) plays a major role in the degradation of monoamines (*1*). Platelet MAO activity is reduced in some people with a variety of clinical disorders (*2*) including some patients with chronic schizophrenia (*3*). Whether platelet MAO activity reflects monoaminergic activity in the brain or elsewhere has yet to be established.

The release of prolactin from the anterior pituitary is inhibited by the monoamine, dopamine (DA) (*4*). Although increased DA activity has been postulated in chronic schizophrenia, plasma prolactin concentrations, an indirect measure of this activity, are not decreased in schizophrenics (*5*). The three experiments described here suggest that the regulation of prolactin secretion is related to monoaminergic activity as reflected in platelet MAO activity in some normal subjects and schizophrenics.

The first experiment consisted of a retrospective analysis of the effects of α-methyl-*p*-tyrosine (AMPT), a catecholamine synthesis inhibitor, on plasma prolactin concentrations in two studies of chronic schizophrenics maintained on stable doses of conventional neuroleptics (*6*). Increases in plasma prolactin concentrations produced by AMPT (*7*) were found to vary inversely with platelet MAO activity (*8*) (Spearman, $\rho = -.85$, $P < .001$, $N = 12$).

This correlation suggested that platelet MAO activity might reflect MAO activity in the tubero-infundibular system. If so, low platelet MAO activity should be associated with high DA concentrations in the tubero-infundibular system. In subjects with high platelet MAO activity (that is, already low DA concentrations) further decreases in DA concentrations with AMPT could lead to only small increases in plasma prolactin concentrations. Fundamental to this interpretation is the assumption that low platelet MAO activity should be associated with low plasma prolactin concentrations in unmedicated subjects. This hypothesis was tested in two further experiments.

Blood was drawn from 39 normal volunteers (*9*) between 8 and 9 a.m. and processed as described previously (*7*, *8*). Twenty-three of the subjects were chosen specifically from among subjects with platelet MAO activity in the lowest decile (*10*) of 375 previously studied normal subjects (*11*). Sixteen subjects were chosen specifically from the highest decile of this group of normal subjects (*12*). It was hypothesized that the group with low MAO activity would have lower

0036-8075/79/1026-0479$00.50/0

plasma prolactin concentrations than the group with high MAO activity. No such difference was found. Nevertheless, plasma prolactin concentrations correlated directly with platelet MAO activity in the group with low platelet MAO activity ($\rho = .54, P < .01, N = 23$), whereas no such relationship was found in the group with high platelet MAO activity group ($\rho = .05, P < .84, N = 16$) (Fig. 1). For the last experiment we used 19 unmedicated patients satisfying Research Diagnostic Criteria (*13*) for chronic schizophrenia (*14*). Three to seven samples of blood per patient were analyzed for plasma prolactin concentrations during drug-free intervals ranging from 6 to 46 days (*15*). Median prolactin concentrations varied directly with median platelet MAO activity ($\rho = .46, P < .05, N = 19$) (Fig. 2).

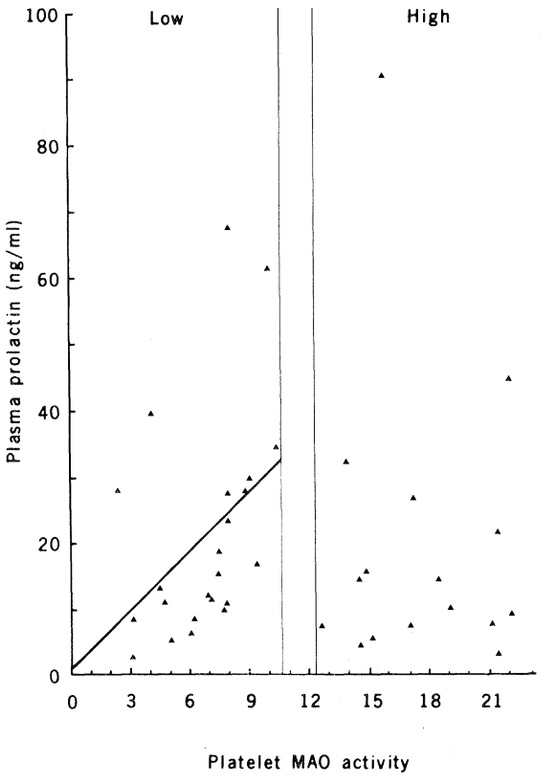

Fig. 1. A direct correlation is shown between platelet MAO activity and plasma prolactin concentration in normal subjects with low platelet MAO activity ($\rho = .54, P < .01, N = 23$). There is no such relationship in normal subjects with high platelet MAO activity ($\rho = .05, P < .84, N = 16$). Platelet MAO activity was determined as nanomoles of benzaldehyde produced per 10^8 platelets per hour.

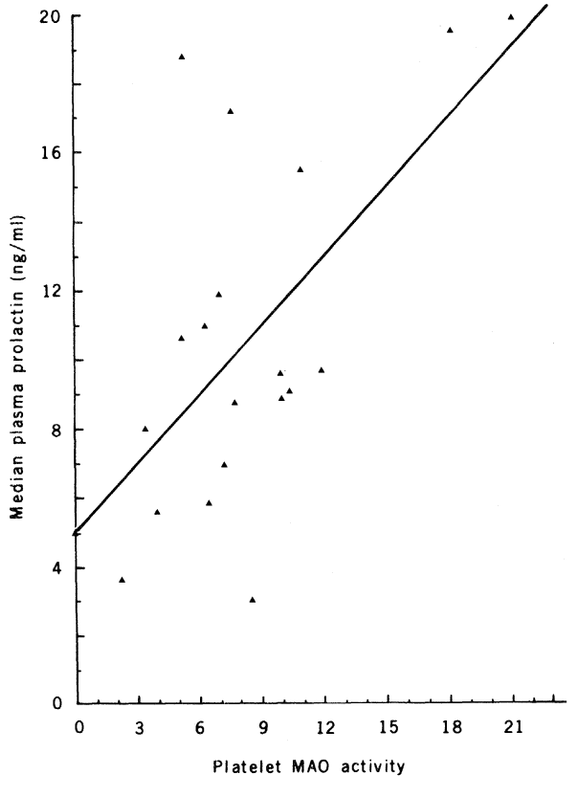

Fig. 2. A direct correlation is shown between platelet MAO activity and plasma prolactin concentrations in unmedicated chronic schizophrenics ($\rho = .46, P < .05, N = 19$).

The data from these three experiments strongly suggest a correlation between platelet MAO activity and plasma prolactin concentration in normal subjects and chronic schizophrenics with low MAO activity. Exactly how this relationship is mediated is a point of interest. Some monoamines that are substrates for MAO include DA, norepinephrine, serotonin, and phenethylamine (*16*). Although it cannot be said with certainty that one of these monoamines is responsible for mediating this effect, there is no monoamine with a more clear-cut inhibitory effect on prolactin release than DA (*4*). Exactly how DA is metabolized by MAO is unclear. There appear to be at least two different types of MAO (MAO-A and MAO-B) as distinguished by substrate and inhibitor characteristics (*16, 17*). Both types have been reported to metabolize DA (*18*). Platelet MAO has the characteristics of MAO-B (*19*). Although in the brain of some species MAO-A predominates (*20*), there is relatively high MAO-B activity in the pituitary (*20, 21*).

It is interesting that in normal volunteers with high platelet MAO activity we found no correlation between plasma prolactin concentration and platelet MAO activity. The absence of this correlation does not appear to result merely from a restriction of platelet MAO activity, since the range was actually larger in the high MAO group than in the low MAO group (*10, 12*). It appears that there is a threshold beneath which platelet MAO activity is associated with plasma prolactin concentrations in this normal population. This does not appear to be the case in the schizophrenic population where two patients with platelet MAO activity in the highest decile had corresponding high plasma prolactin concentrations. Nevertheless, the data suggest a physiological difference between normal subjects with low and high platelet MAO activity. In normal subjects with high platelet MAO activity and presumably low DA concentrations plasma prolactin concentrations appear to be controlled by another mechanism.

Since platelet MAO activity is decreased in some chronic schizophrenics and some normal subjects, such subjects appear to have increased DA activity in the tubero-infundibular system. These findings support the hypothesis that

platelet MAO activity reflects monoaminergic activity in the tubero-infundibular system.

JOEL E. KLEINMAN, STEVEN POTKIN
Laboratory of Clinical Psychopharmacology, Division of Special Mental Health Research, National Institute of Mental Health, Saint Elizabeths Hospital, Washington, D.C. 20032
ALAN ROGOL
Department of Pediatrics, University of Virginia Medical Center, Charlottesville 22908
MONTE S. BUCHSBAUM
Laboratory of Clinical Psychophysiology, National Institute of Mental Health, Bethesda, Maryland 20205
DENNIS L. MURPHY
Laboratory of Neuropharmacology, National Institute of Mental Health
J. CHRISTIAN GILLIN
HENRY A. NASRALLAH
RICHARD JED WYATT
Laboratory of Clinical Psychopharmacology, Saint Elizabeths Hospital

References and Notes

1. I. J. Kopin and J. Axelrod, *Ann. N.Y. Acad Sci.* **107**, 848 (1963); I. J. Kopin, *Pharmacol. Rev.* **16**, 197 (1964).
2. D. S. Robinson, J. M. Davis, A. Nies, C. L. Ravaris, D. Sylwester *Arch. Gen. Psychiatry* **24**, 536 (1971); D. L. Murphy and R. Weiss, *Am. J. Psychiatry* **128**, 1351 (1972); M. Sandler, M. B. H. Youdim, E. Harrington, *Nature (London)* **250**, 335 (1974); M. B. H. Youdim, H. F. Wood, B. Mitchell, *Clin. Sci. Mol. Med.* **48**, 289 (1975); R. H. Belmaker, D. L. Murphy, R. J. Wyatt, D. L. Lorieux, *Arch. Gen. Psychiatry* **31**, 553 (1974); J. B. Brown, *Am. J. Psychiatry* **134**, 206 (1977).
3. D. L. Murphy and R. J. Wyatt, *Nature (London)* **238**, 225 (1972); H. Y. Meltzer and S. M. Stahl, *Res. Commun. Chem. Pathol. Pharmacol.* **7**, 419 (1974); R. J. Wyatt, S. G. Potkin, D. L. Murphy, *Am. J. Psychiatry* **136**, 377 (1979).
4. K. Fuxe, T. Hokfelt, O. Nelson, *Neuroendocrinology* **5**, 257 (1969); S. Mutes and J. Clemens, *Vitam. Horm. N.Y.* **30**, 164 (1972); R. M. MacLeod and J. E. Lehmeyer, *Endocrinology* **94**, 1077 (1974).
5. J. V. Beaumont, G. W. Harris, P. J. Carr, H. G. Friesen, T. Kolakowska, P. C. B. Mackinnon, B. M. Mandelbrote, D. Wiles, *J. Psychosom. Res.* **16**, 297 (1972); H. Y. Meltzer, E. J. Sachar, A. G. Frantz, *Arch. Gen. Psychiatry* **31**, 564 (1974); *Biol. Psychiatry* **10**, 53 (1975); E. J. Johnstone, T. J. Crow, K. Mashiter, *Psychol. Med.* **7**, 223 (1977).
6. H. A. Nasrallah, E. F. Donnelly, L. B. Bigelow, L. Rivera-Calimlim, A. Rogol, S. Potkin, F. P. Rauscher, R. J. Wyatt, J. C. Gillin, *Arch. Gen. Psychiatry* **34**, 649 (1977); J. C. Gillin, J. E. Kleinman, H. A. Nasrallah, L. B. Bigelow, A. Rogol, D. Luchins, J. Carman, D. Weinberger, R. J. Wyatt in *Catecholamines: Basic and Clinical Frontiers*, E. Usdin, I. J. Kopin, J. D. Barchas, Eds. (Pergamon, New York, in press). The 12 patients in these two studies included eight whites and four blacks (11 males and 1 female). Ages ranged from 18 to 35 years. For four subjects who participated in both studies, their values were averaged. All patients received 3000 mg per day orally of AMPT in four divided doses with the exception of one patient who received 1500 mg per day during his second trial because of side effects. Mean plasma prolactin concentration ± the standard deviation on conventional neuroleptics was 47.7 ± 39.7 ng/ml. For patients receiving AMPT plus conventional neuroleptics, the mean plasma prolactin concentration was 101 ± 42.9 ng/ml. The increase in prolactin concentration was calculated by subtracting baseline (conventional neuroleptic) values from AMPT (plus neuroleptic) values for each patient.
7. A. D. Rogol and A. Chrambach, *Endocrinology* **97**, 406 (1975). Blood from fasting subjects was obtained two to three times per week between 7 and 9 a.m. It was placed on ice, centrifuged at 4°C, and plasma was removed by pipette and stored at −70°C. Plasma prolactin concentrations were determined in triplicate by a homologous double-antibody radioimmunoassay by investigators blind to the patient and the drug regimen.
8. D. L. Murphy, C. Wright, M. Buchsbaum, A. Nichols, J. L. Costa, R. J. Wyatt, *Biochem. Med.* **16**, 254 (1976). For all of the normal volunteers and many of the schizophrenic subjects multiple determinations (two, or three to seven, respectively) were made of their platelet MAO activity with ^{14}C-labeled benzylamine being used as a substrate. The median value was used wherever possible because it was least susceptible to the influence of spurious values. This was possible in every instance except in the second study where only two values were available per normal volunteer, necessitating the use of the mean value.
9. The volunteers included 38 whites and 1 black (23 males and 16 females) ranging in age from 18 to 32 years.
10. The lowest decile of MAO activity for males ranged from 2.40 to 7.98 nmole of benzaldehyde produced per 10^8 platelets per hour. For females the range was from 7.14 to 10.47 nmole of benzaldehyde per 10^8 platelets per hour.
11. M. S. Buchsbaum, R. D. Coursey, D. L. Murphy, *Science* **194**, 339 (1976).
12. Platelet MAO activity for the highest decile of males and females ranged from 12.57 to 21.54 and 14.92 to 22.22 nmole of benzaldehyde produced per 10^8 platelets per hour, respectively.
13. R. L. Spitzer, J. Endicott, E. Robins, *Am. J. Psychiatry* **132**, 1187 (1975).
14. The patient group included 15 whites and 4 blacks (14 males and 5 females) ranging in age from 20 to 45 years.
15. Median prolactin concentrations were used rather than mean values to prevent occasional spuriously high values from exerting an unduly large effect.
16. N. Weiner, *Arch. Biochem. Biophys.* **91**, 182 (1960); E. Costa and M. Sandler, Eds., *Monoamines Oxidases—New Vistas* (Raven, New York, 1972); G. F. W. Wolstenholme and J. Knight, Eds., *Monoamine Oxidase and Its Inhibition* (Elsevier, Excerpta Medica/North-Holland, Amsterdam, 1976).
17. J. P. Johnstone, *Biochem. Pharmacol.* **17**, 1285 (1968).
18. H.-Y. T. Yang and N. H. Neff, *J. Pharmacol. Exp. Ther.* **189**, 733 (1974).
19. C. H. Donnelly and D. L. Murphy, *Biochem. Pharmacol.* **26**, 853 (1977).
20. D. J. Edwards and C. W. Malsbury, *Life Sci.* **21**, 1009 (1977).
21. J. M. Saavedra, M. Palkovitz, J. S. Kizer, M. Brownstein, J. A. Zivin, *J. Neurochem.* **25**, 257 (1975).

14 May 1979; revised 23 July 1979

Intrathecal Capsaicin Depletes Substance P in the Rat Spinal Cord and Produces Prolonged Thermal Analgesia

Abstract. *A single intrathecal injection of capsaicin depletes substance P from primary sensory neurons and causes a prolonged increase in the thermal and chemical pain thresholds of the rat but no apparent change in responses to noxious mechanical stimuli.*

Substance P may play a role in the transmission of noxious stimuli at primary afferent synapses in the dorsal horn (*1*). The peptide is located within synaptic vesicles in primary afferent terminals (*2*) and has been observed within neurons of small diameter within the dorsal root ganglion (*3*). The iontophoretic application of substance P excites those neurons that respond to noxious peripheral stimuli (*4*). Recently, we reported that substance P is released in vivo from the cat spinal cord by high-intensity, but not low-intensity stimulation of the sciatic nerve (*5*). Administration of the homovanillic acid derivative, capsaicin, into the spinal perfusate of rats and cats produces a calcium-dependent release of substance P (*5*); whereas repeated subcutaneous administration of capsaicin reduces the concentration of substance P in the dorsal horn (*6*). In addition, systematically administered capsaicin has been reported to alter the response of peripheral nerves to chemical stimuli applied to the skin and to block the animal's thermoregulatory response (*7*).

These observations led us to investigate whether animals treated with capsaicin might display analgesia. To restrict the actions of capsaicin to the spinal cord, we administered the drug directly into the subarachnoid space. In rats under ether anesthesia we implanted a polyethylene catheter by inserting it through the cisterna magna to the rostral edge of the lumbar enlargement in the spinal subarachnoid space (*8*). The rats were allowed to recover for 7 days, after which time they each received an intrathecal injection of 3 or 30 μg of capsaicin in a volume of 15μl (*9*) and then an injection of 10 μl of saline.

Intrathecal injection of capsaicin produced a striking biphasic response. During the first 1 to 3 minutes, the animal showed a strong contracture of the caudal portions of the body; after this period the animals regained coordinated motor control and immediately began biting and scratching at the caudal portion of the body in the dermatomes corresponding to those levels of the spinal cord affected by the intrathecal injection. This severe agitation lasted 5 to 10 minutes, after which the animal sat quietly showing occasional grooming behavior.

Twenty-four hours after the injection of capsaicin, we tested the nociceptive threshold by using the spinally mediated tail-flick response to heat and by measuring the withdrawal latency on a 55°C hot plate. In animals tested before injection of capsaicin, the mean latency on the

0036-8075/79/1026-0481$00.50/0