ference (Institute of Physics and Wiley, London, 1975).
4. R. Tym and P. W. Todd, *Int. J. Radiat. Biol.* **8**, 589 (1964); R. Katz, B. Ackerson, M. Homayoonfar, S. C. Sharma, *Radiat. Res.* **47**, 407 (1971); R. Wideroe, *Radiat. Environ. Biophys.* **15**, 57 (1978).
5. K. H. Chadwick and H. P. Leenhouts, *Phys. Med. Biol.* **18**, 78 (1973); M. G. Payne and W. R. Garrett, *Radiat. Res.* **62**, 388 (1975).
6. P. Todd, J. P. Geraci, P. S. Furcinitti, R. M. Rossi, F. Mikage, R. B. Theus, C. B. Schroy, *Int. J. Radiat. Oncol. Biol. Phys.* **4**, 1015 (1978).
7. J. van der Veen, L. Bots, A. Mes, *Arch. Ges. Virusforsch.* **8**, 230 (1958); G. W. Barendsen, T. L. J. Beusker, A. J. Vergroesen, L. Budke, *Radiat. Res.* **13**, 841 (1960).
8. M. M. Elkind and H. Sutton, *Radiat. Res.* **13**, 556 (1960).
9. P. Todd, *Radiat. Res.* **34**, 378 (1968).
10. J. M. Brown, *ibid.* **71**, 34 (1977); K. Z. Morgan, *Bull. Atomic Sci.* **34**, (7), 30 (1978); J. Rotblat, *ibid.*, p. 41.
11. This research was supported by Public Health Service grant R01-CA-17536 awarded by the National Cancer Institute. We thank J. C. S. Wood, R. M. Rossi, J. J. Jackson, C. B. Schroy, N. Kukulinsky, and M. J. Rowland for technical assistance.
* Present address: Radiological Research Accelerator Facility, Brookhaven National Laboratory, Upton, Long Island, New York 11937.

15 May 1979; revised 6 August 1979

Movement Disorders of Aged Rats: Reversal by Dopamine Receptor Stimulation

Abstract. *When placed in a tank of water, aged rats (24 to 27 months old) showed marked impairments in swimming. Compared with young adult rats (3 to 4 months old), the older animals moved their limbs less vigorously and were less successful in keeping their heads above water. The young, but not old, rats maintained a position nearly horizontal to the water surface and planed across it. These movement dysfunctions of aged rats resemble those seen in young adult animals that have sustained injury to brain dopamine-containing neurons. The swimming impairments of the aged rats were reversed by the dopamine receptor stimulant apomorphine and by the biosynthetic precursor of dopamine,* L-*dopa. Thus, age-related alterations in brain dopaminergic systems may be responsible for some of the movement disturbances associated with senescence.*

While movement disturbances of aged humans have been well documented, those of aged animals have not been systematically examined. As reviewed by Wellford (*1*), elderly persons need more time to carry out movements, pace themselves poorly in tasks requiring continuous performance, and fail to adjust their movements to compensate for their errors. To determine the motor capacities of aged rats, we have examined their capacity to swim. Swimming, which requires the coordinated movement of the limbs and trunk, is a common measure of the motor abilities of rodents. Its ontogeny (*2*) and neurological basis (*3*, *4*) have been investigated. We now report that 2-year-old rats have deficient ability to sustain vigorous and effective swimming. However, when given apomorphine or L-dopa they swim as well as young adult animals, which suggests that a deterioration of brain dopamine neurotransmission may contribute to some of the movement disorders of advanced age.

Male rats (Fischer 344 strain, retired breeders, Charles River) delivered by cesarean section were housed in metal cages. The swimming of rats 24 to 27 months old was compared with that of 3- to 4-month-old rats. Each rat was placed in a cylindrical tank (46 cm in diameter by 46 cm deep) of water (22° to 24°C) for 15 minutes. The rats could not keep their nostrils above water while supporting themselves on the bottom of the tank, nor could they jump out. At 1-minute intervals, the observer rated swimming along two dimensions: (i) the vigor with which the animal moved its limbs, and (ii) the success that each rat had in maintaining its head above the water surface (*5*).

Young adult rats swam with vigorous limb movements and held their heads above water. They typically kept their body axes nearly horizontal to the surface, moving all four limbs so as to plane across it (Fig. 1A). The vigor and success with which the young rats swam declined gradually during the 15-minute test (Fig. 2A). In contrast, the aged animals swam vigorously for a few minutes but were significantly impaired by minute 6 (Fig. 2A). Moreover, the aged rats were unable to sustain a horizontal position in the water. They lapsed into a more vertical posture (Fig. 1C) that necessitated their struggling to keep their heads above water. After several minutes they repeatedly sank and intermittently fought their way back to the surface. For the 15-minute test, the two age groups differed significantly on both measures of swim performance [F (1,17) = 27.8, for vigor, 96.4 for success, $P < .001$] (*6*). The interaction between group and time was significant for both measures, indicating a more rapid deterioration of swim performance in aged than in young adult rats [F (14,238) = 6.80, $P < .001$, for vigor; F (14,238) = 2.35, $P < .005$, for success].

The poor performance of these aged rats resembles the impaired swimming of

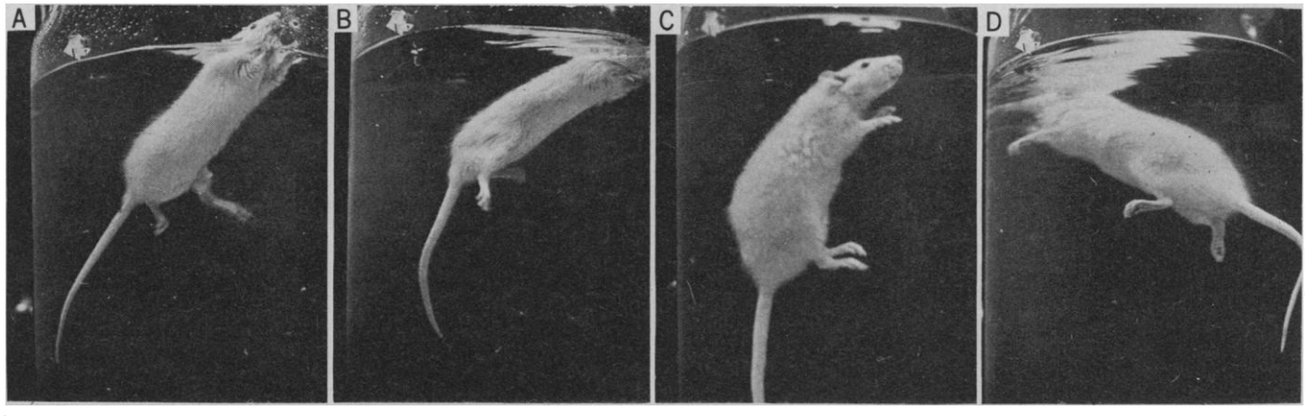

Fig. 1. Swimming of young adult (A and B) and aged (C and D) rats given apomorphine (0.50 mg/kg) or its vehicle. Note the vertical position assumed by the aged rat given vehicle (C). After apomorphine treatment, the aged animal adopted a more horizontal position (D), similar to that of young adult rats given apomorphine (B) or its vehicle (A).

0036-8075/79/1026-0477$00.50/0

young adult rats in which the dopamine-containing terminals of the forebrain have been damaged (*3*, *4*). The swimming of young adult rats with brain dopamine loss, like that of aged animals, deteriorates rapidly during a 15-minute test (*3*); they adopt a vertical position in the water as their performance wanes. In view of these similarities, it seemed that the deficient performance of the senescent rat might be linked to age-related changes in brain dopaminergic neurotransmission (*7*). If so, their swimming should improve after the administration of compounds that enhance brain dopamine receptor stimulation.

Young adult and aged rats were given the dopamine receptor stimulant compound apomorphine (*8*) (0.25, 0.50, or 2.0 mg per kilogram of body weight as free base, injected intraperitoneally) or its vehicle (0.1 percent ascorbic acid in 0.9 percent NaCl) 15 minutes before being placed in the water. The observer, who was not informed as to the drug condition of the animal being tested, rated its vigor and success at each minute of the 15-minute test.

The performance of aged rats given apomorphine was dramatically restored (Fig. 2B). Even the lowest dose induced senescent rats to swim more vigorously and successfully than vehicle-treated young adults [Dunnett's t-tests, t (84) = 10.6 for vigor, 4.6 for success, $P < .005$]. An analysis of the moment-by-moment scores reveals that this improvement is attributable to a prolongation of vigorous and effective swimming. Like young adults, the apomorphine-treated aged animals adopted a more horizontal position (Fig. 1D), keeping their heads above water for most of the test. Apomorphine also enhanced the swimming vigor of young adult rats [F (3,46) = 8.9, $P < .001$] although less markedly and only at doses higher than those required by aged rats.

We determined next whether the swimming of aged rats would be improved after administration of another compound that increases brain dopamine receptor stimulation. The previous experiment was repeated with the biosynthetic precursor of catecholamines, L-dopa. When administered systemically, this amino acid is converted enzymatically to dopamine in the brain (*9*). L-Dopa methyl ester HCl (Sigma, 50 or 100 mg/kg, as free base, injected intraperitoneally) or its vehicle (0.9 percent NaCl) were given 15 minutes before the swim test.

L-Dopa rejuvenated the swimming of aged rats [F (2,24) = 20.9 for vigor, 12.9 for success, $P < .001$] (Fig. 2C). Even at the lower dose (50 mg/kg) the aged animals swam with improved vigor and success [Dunnett's t-tests, t (47) = 4.95 for vigor, 4.77 for success, $P < .005$]. Only at the higher dose (100 mg/kg) was the swimming of the younger rats improved, and even then only in the success measure [Dunnett's t-test, t (47) = 4.84, $P < .005$].

These experiments demonstrate for what we believe to be the first time that aged rats suffer from severe disturbances of movement. The rapid deterioration of their performance during the test suggests that their motor dysfunctions are particularly apparent when prolonged, strenuous movements are required. Not only do they swim with impaired vigor and success, but by adopting a vertical posture, they reduce their buoyancy, an inefficient strategy for coping with the prolonged swim stress.

The dramatic rejuvenation of performance by compounds that enhance the activity of brain dopamine receptors holds potential significance for understanding the movement disturbances of aging. The poor performance of aged rats in the drug-free condition is not attributable solely to peripheral factors, such as diminished muscle mass or increased adiposity; instead, the results suggest a central nervous origin of this deficit. In particular, the poor performance of the aged animal seems linked to the age-related changes in neurotransmission at brain dopaminergic synapses (*7*). Given this background of subnormal dopamine synaptic activity in senescence, low doses of apomorphine or L-dopa appear to facilitate movement by normalizing the stimulation of central dopamine receptors.

The aged rats showed dramatic improvements in swimming at doses of apomorphine or L-dopa that had little or no effect on the performance of young rats. Over the range of doses tested, however, the maximum performance of the two age groups was remarkably similar (*10*). This similarity indicates that the central programs for these movements are intact in aged rats. The dopamine agonist compounds apparently permit the aged animal to activate these central programs under the appropriate circumstances.

The dopamine-containing neurons of the brain have long been known to be essential for normal movement and senso-

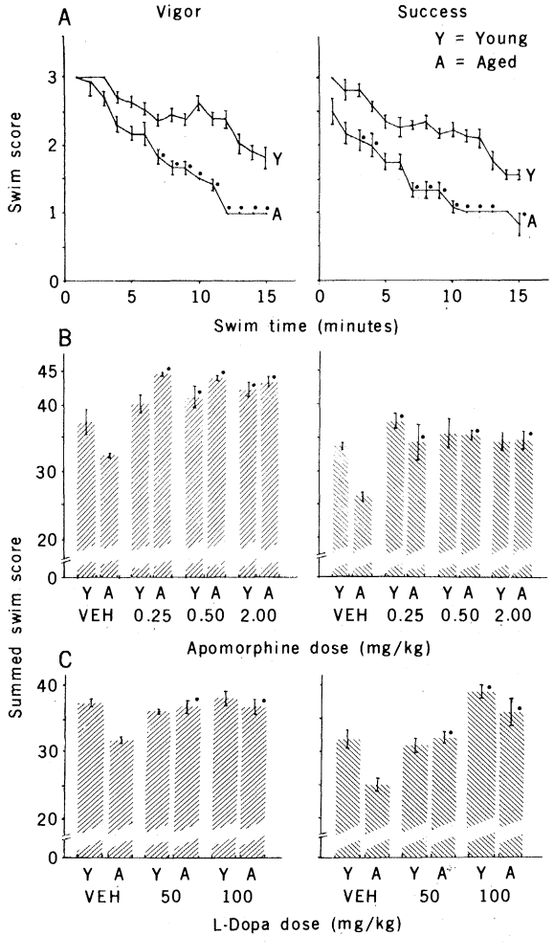

Fig. 2. Mean (± 1 standard error) swim performance of aged (*A*) and young adult (*Y*) rats that received no drugs (A) or were treated with apomorphine (B) or L-dopa (C). (A) Dots indicate significant differences ($P < .05$, Scheffé tests) between 6 aged rats and 13 young adult rats. (B) The effects of age and of drug dose are significant for both measures of swim performance, as are the group-by-dose interactions (analyses of variance, $P < .002$). Dots indicate significant differences (Dunnett's t-tests, $P < .05$) from respective vehicle (*VEH*) control condition. Each group contained from 6 to 25 rats. (C) The effects of age and of drug dose are significant for both measures of swim performance, as are the group-by-dose interactions (analyses of variance, $P < .005$). Dots indicate significant differences (Dunnett's t-tests, $P < .05$) from respective vehicle control conditions. Each group contained 6 to 10 rats.

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