Effects of Age on Dopamine and Serotonin Receptors Measured by Positron Tomography in the Living Human Brain

Dean F. Wong, Henry N. Wagner, Jr., Robert F. Dannals
Jonathan M. Links, J. James Frost, Hayden T. Ravert
Alan A. Wilson, Arthur E. Rosenbaum, Albert Gjedde
Kenneth H. Douglass, John D. Petronis, Marshal F. Folstein
J. K. Thomas Toung, H. Donald Burns, Michael J. Kuhar

Abstract. *D2 dopamine and S2 serotonin receptors were imaged and measured in healthy human subjects by positron emission tomography after intravenous injection of ^{11}C-labeled 3-*N*-methylspiperone. Levels of receptor in the caudate nucleus, putamen, and frontal cerebral cortex declined over the age span studied (19 to 73 years). The decline in D2 receptor in males was different from that in females.*

Earlier we reported the imaging and measuring of neurotransmitter receptors in the living human brain by means of ^{11}C-labeled 3-*N*-methylspiperone ([^{11}C]NMSP), a neuroleptic ligand, and positron emission tomography (PET) (*1*). This ligand binds preferentially to D2 dopamine and S2 serotonin receptors. The results of studies in vivo and in vitro indicate that most of the accumulation of [^{11}C]NMSP in basal ganglia reflects binding to D2 dopamine receptors, whereas most of the accumulation in cerebral cortical areas reflects binding to S2 serotonin receptors (*2–6*). The imaging of neurotransmitter precursors and other receptors in animals and humans has also been reported (*7*).

We now describe our studies of 22 male and 22 female volunteers ranging in age from 19 to 73 years and from 19 to 67 years, respectively [males: mean age, 39 ± 17 years; females: mean age, 36 ± 14 years (±1 standard deviation)]. The volunteers were healthy as determined by medical, neurological, and neuropsychological tests, including a brief mental examination, general health questionnaire, physical and neurological examination, resting electrocardiogram, and computerized tomography (CT) scan. The CT scans were taken of each subject to identify the planes containing the caudate nucleus and putamen (*8*). Subjects were injected with [^{11}C]NMSP (dose range, 0.2 to 2.9 μg/kg) which was synthesized by the *N*-alkylation of spiperone with [^{11}C]methyl iodide (*1*). Multiple, serial PET scans were obtained continuously for 2 hours after injection. Simultaneous venous samples from a heated hand (to simulate arterial blood) or arterial samples or both were obtained in all cases. These samples showed a decrease in the amount of [^{11}C]NMSP in both plasma and whole blood within the first 15 minutes after the injection. Binding to the D2 dopamine receptor was estimated by the ratio of radioactivity in the caudate to that in the cerebellum (A_{ca}/A_{cb}, expressed as mean counts per minute per computer picture element) and by the ratio of radioactivity in the putamen to that in the cerebellum. Binding to the S2 serotonin receptor was estimated by the ratio of radioactivity in the frontal cortex to that in the cerebellum (A_{fr}/A_{cb}).

After the subjects were injected, accumulation of [^{11}C]NMSP within the caudate and putamen, areas rich in D2 receptors, increased progressively with time, whereas binding in the cerebellum, which contains few or no D2 receptors, decreased rapidly. Activity in the frontal, temporal, parietal, and occipital cortex decreased at an intermediate rate, reflecting a decrease both in S2 receptor binding and in nonspecific binding (Fig. 1). These findings are similar to those from other in vivo receptor labeling studies (*1, 3, 5*).

In every subject, the A_{ca}/A_{cb} ratio increased linearly with time after injection (Fig. 2). The slope of this line reflects the rate (sometimes referred to as K_3) of [^{11}C]NMSP binding to the D2 receptor from the exchangeable tissue pool (including nonspecific binding) as derived below (Eq. 1). This linear increase in the A_{ca}/A_{cb} ratio with time has been observed in more than 100 normal volunteers and patients and suggests a three-compartment model (*9, 10*).

$$C_p \underset{K_2}{\overset{K_1}{\rightleftharpoons}} C_e \underset{K_4}{\overset{K_3}{\rightleftharpoons}} C_r \qquad (1)$$

where C_p is the content of tracer in the plasma, C_e is the content of exchangeable (free plus nonspecifically bound) tracer in tissue, and C_r is the content of receptor-bound tracer in tissue. This linearity also confirms that $K_4 \ll K_3$; therefore, we will set $K_4 = 0$.

The equations describing the model are, in the cerebellum,

$$\frac{dA_{cb}(t)}{dt} = K_1C_p(t) - K_2A_{cb}(t) \qquad (2)$$

and in the caudate,

$$\frac{dC_e(t)}{dt} = K_1C_p(t) - (K_2 + K_3)C_e(t) \qquad (3)$$

$$\frac{dC_r(t)}{dt} = K_3C_e(t) \qquad (4)$$

$$A_{ca}(t) = C_e(t) + C_r(t) \qquad (5)$$

where $A_{cb}(t)$ and $A_{ca}(t)$ are the observed activities in the cerebellum and caudate. Integrating and combining these equations yields a theoretical expression for the ratio A_{ca}/A_{cb},

$$\frac{A_{ca}(t)}{A_{cb}(t)} = \left(\frac{K_2}{K_2 + K_3}\right)\left[\frac{C_e(t)}{A_{cb}(t)}\right] + \left(\frac{K_1K_3}{K_2 + K_3}\right)\frac{\int_0^t C_p(t')dt'}{C_p(t)} \qquad (6)$$

D. F. Wong, H. N. Wagner, R. F. Dannals, J. M. Links, J. J. Frost, H. T. Ravert, A. A. Wilson, K. H. Douglass, J. D. Petronis, and H. D. Burns are in the Divisions of Nuclear Medicine and Radiation Health Sciences, Johns Hopkins Medical Institutions, Baltimore, Maryland 21205. A. E. Rosenbaum is in the Division of Neuroradiology, Johns Hopkins University School of Medicine. A. Gjedde is in Medical Physiology Department A, Copenhagen University, Copenhagen, Denmark. M. F. Folstein is in the Department of Psychiatry, J. K. T. Toung is in the Department of Anesthesiology and Critical Care, and M. J. Kuhar is in the Department of Neuroscience, Johns Hopkins University School of Medicine. Correspondence should be directed to D. R. Wong, Nuclear Medicine, Johns Hopkins Hospital, 600 North Wolfe Street, B1-167C Tower Building, Baltimore, Maryland 21205.

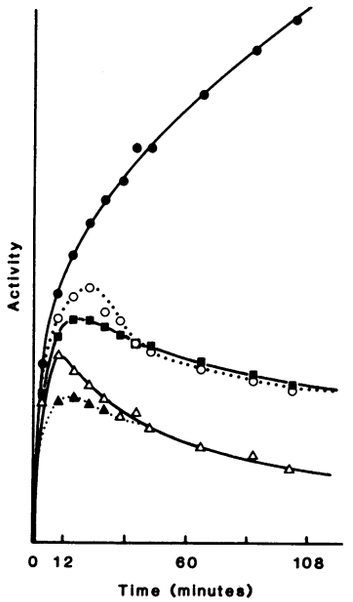


Fig. 1. Decrease in the level of activity in various regions of the brain with time. Data were accumulated as described [see text and (*1*)]. The planes for PET imaging were selected after CT scans had identified planes containing the basal ganglia as well as the location of the basal ganglia within the plane. A headholder was used to ensure ease and reproducibility of locating the planes. The data shown are from a 29-year-old male and are a qualitative representation of the entire group. Activity is reported as counts per minute per pixel (computer picture element). (●) Caudate and putamen, (○) occipital visual cortex, (■) frontal lobe cortex, (△) cerebellar cortex, and (▲) cerebellar white matter.

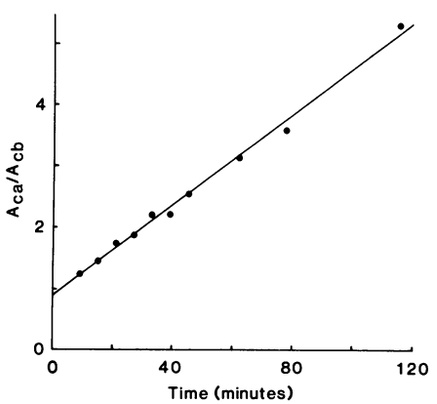


Fig. 2. The ratio A_{ca}/A_{cb}, an estimate of D2 dopamine receptor, increases linearly with time. The ratios are the average value of right and left sides of the brain. The ratios shown are underestimates because of physical factors including partial volume and resolution effects (*1*). By using a life-sized phantom of brain with compartments shaped like the basal ganglia, we found in initial experiments that the recovery coefficients for our NeuroECAT (computerized axial tomography) scanner were 0.68 for the caudate, 0.66 for the putamen, and 1.0 for the cerebellum (*25*). Thus, the actual A_{ca}/A_{cb} ratios are higher than our estimates. Data from the single male subject are qualitatively representative of the entire group and fit a straight line [$m = 0.055$ min^{-1}; standard error (m) = 1.89×10^{-3}; $r = 0.99$]. The slopes of these plots are presumably related to K_3 (*9*).

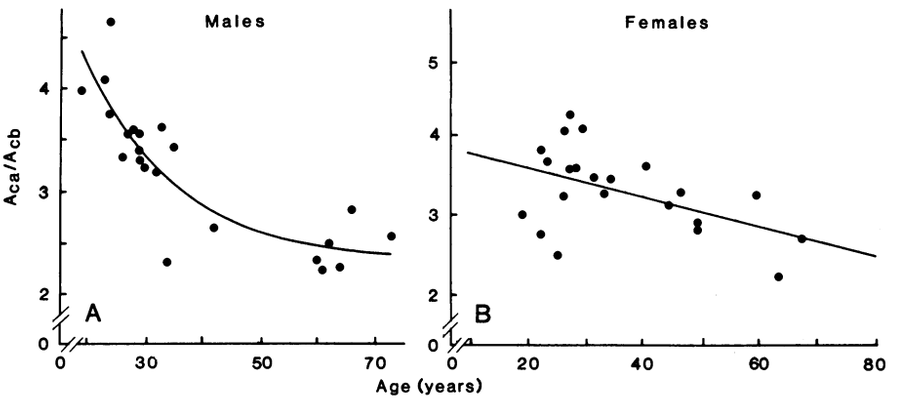


Fig. 3. Decline in D2 dopamine receptor in males (A) and females (B) [see (*23*)]. The graph in (A) shows the exponential fit for the data, since the polynomial fit would indicate a slight increase at older ages which, on the basis of reasonable biological arguments, is unlikely. Furthermore, the slight upturn is at the upper range of the data, and additional studies at older ages would be necessary to determine whether this upturn is real. For the males, the 95 percent confidence limits on the regression line at ages 20, 40, and 65 were 4.30 ± 0.46, 2.91 ± 0.25, and 2.44 ± 0.27, respectively, and the 95 percent prediction limits for a new value of A_{ca}/A_{cb} at these ages were 4.30 ± 0.84, 2.91 ± 0.74, and 2.44 ± 0.75, respectively. For the females, the 95 percent confidence limits on the regression line at ages 20, 40, and 65 were 3.59 ± 0.32, 3.22 ± 0.22, and 2.76 ± 0.48, respectively, and the 95 percent prediction limits for a new value of A_{ca}/A_{cb} at these ages were 3.59 ± 1.02, 3.22 ± 0.99, and 2.76 ± 1.08, respectively.

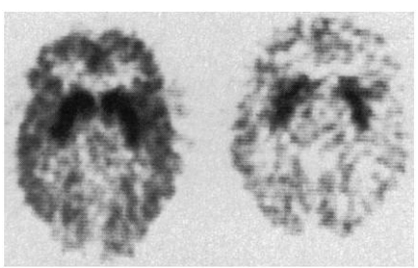
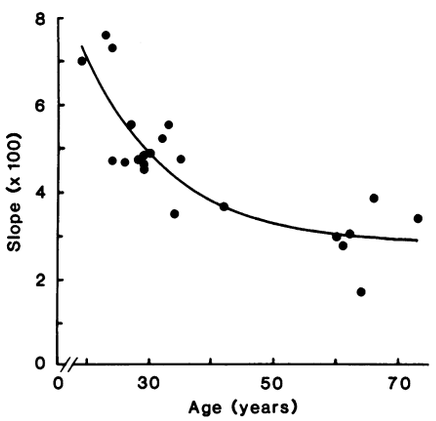


Fig. 4 (left). PET scans of the brain of a young (left) and an old (right) male subject. Fig. 5 (right). The change with age in slopes of plots of A_{ca}/A_{cb} versus time in males. This plot is similar to that in Fig. 3A, showing that these lines for each subject change with age in a manner similar to the change in the ratios [see (*15*)].



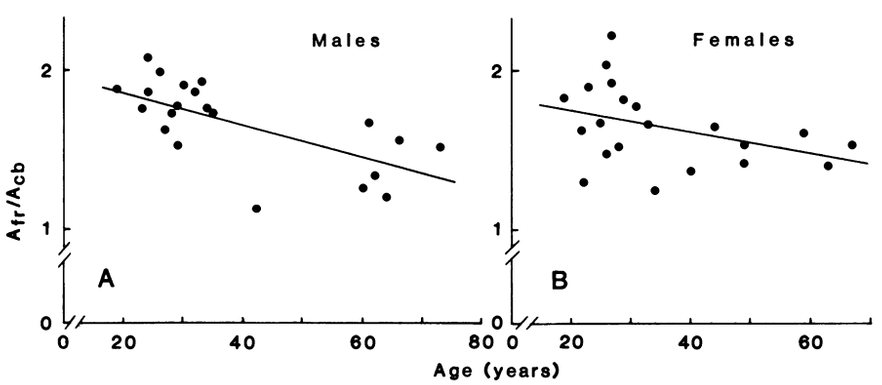


Fig. 6. Change in the ratio A_{fr}/A_{cb} with age plotted separately for males (A) and females (B) [see (*23*)]. These data did not show a significant difference due to sex in the decline of receptor with age, the data for both sexes fitting best to a straight line (see Fig. 5). There was a 29 percent drop for males in the age range of 19 to 73 years and a 19 percent drop for females in the age range of 19 to 67 years [males: $A_{fr}/A_{cb} = 0.01x + 2.05$, standard error ($m$) = 0.0026; females: $A_{fr}/A_{cb} = -0.007x + 1.89$, standard error ($m$) = 0.0036]. For the males the 95 percent confidence limits on the regression line at ages 20, 40, and 65 were 1.85 ± 0.13, 1.65 ± 0.09, and 1.40 ± 0.17, respectively, and the 95 percent prediction limits for a new value of A_{fr}/A_{cb} at these ages were 1.85 ± 0.44, 1.65 ± 0.42, and 1.40 ± 0.45, respectively. For the females the 95 percent confidence limits on the regression line at ages 20, 40, and 65 were 1.73 ± 0.15, 1.60 ± 0.11, and 1.44 ± 0.24, respectively, and the 95 percent prediction limits for a new value of A_{fr}/A_{cb} at these ages were 1.73 ± 0.51, 1.60 ± 0.50, and 1.44 ± 0.54, respectively.

The solution to Eq. 2 shows that at a time $T \gg 1/K_2$, A_{cb} becomes proportional to C_p,

$$A_{cb}(T) = \frac{K_1 C_p(T)}{K_2} \quad (7)$$

and, similarly,

$$C_e(T) = \frac{K_1 C_p(T)}{K_2 + K_3} \quad (8)$$

Physiologically, this limit will be reached if the permeability of the barrier between blood and brain is high enough; the achievement of linearity in about 10 minutes indicates that this is true.

Replacing Eqs. 7 and 8 in Eq. 5 gives

$$\frac{A_{ca}(T)}{A_{cb}(T)} = \left(\frac{K_2}{K_2 + K_3}\right)^2 + \left(\frac{K_2 K_3}{K_2 + K_3}\right) \frac{\int_0^T C_p(t')dt'}{C_p(T)} \quad (9)$$

and if $K_3 \ll K_2$, then

$$\frac{A_{ca}(T)}{A_{cb}(T)} = 1 + (K_3) \frac{\int_0^T C_p(t')dt'}{C_p(T)} \quad (10)$$

Gjedde (*10*) argues that the normalized integral becomes proportional to time; hence, the model predicts a linear increase in A_{ca}/A_{cb} with time, as observed experimentally, with a slope determined by K_3 (*11*). This result indicates that measurement of cerebral blood flow and volume is not required, unlike the situation for other proposed models (*12*).

The lack of proportionality between the amount of [^{11}C]NMSP in the cerebellum and that in the blood evidently results from the presence of nontransportable metabolites in the blood and may serve as a measure of these metabolites (*13, 14*). Although it is possible that the metabolites of [^{11}C]NMSP change as a function of age, the observation that the absolute activity in the cerebellum did not suggests that the effects on input function for the caudate and putamen do not change significantly with age. Hence the decrease in A_{ca}/A_{cb} is primarily due to a decrease in receptor binding.

The ratio A_{ca}/A_{cb} was calculated for the period between 43 and 49 minutes after injection, a time at which NMSP is preferentially associated with D2 receptors (*1, 5, 6*), and was plotted versus the subjects' ages (Fig. 3). The plots revealed a decline in D2 receptor binding. In the 22 males (Fig. 3A), the data were fitted by an exponential function ($A_{ca}/A_{cb} = 2.31 + 6.56e^{-0.061x}$, where x is age; standard errors of coefficients, 0.24, 3.09, and 0.023, respectively). There was a decline of 46 percent in the fitted function over the range of ages (19 to 73 years) (see also Fig. 4). There was a similar (43 percent) exponential decline in the putamen with age. In the 22 females (Fig. 3B), there was a somewhat smaller (25 percent) decrease in receptor binding with age (over the range of 19 to 67 years) in the caudate and putamen [$A_{ca}/A_{cb} = 0.018x + 3.97$; standard error of slope (m) = 0.0072]. When the slopes of plots for A_{ca}/A_{cb} versus time were plotted against age for males, a similar exponential decline was observed (*15*) (Fig. 5). Finally, a plot of A_{fr}/A_{cb} against age revealed a statistically significant linear decline of S2 receptor binding with age ($P < 0.001$) for males and females combined, but there was no significant difference beween males and females (Fig. 6).

A likely explanation for the decline in binding with age is that the number of receptors decreases. Studies in vitro with both animal and human tissues obtained at autopsy have also revealed a decline in D2 and S2 receptor concentration with age (*16*), with no change in the dissociation constant. A decline in cerebral blood flow alone does not seem an adequate explanation of these findings. Cerebral blood flow has been shown to decrease with age, but the decline appears to be less than that in receptor binding (*17*). We estimated cerebral blood flow from the initial distribution of [^{11}C]NMSP at the time of injection to 6 minutes after injection; we believe that this distribution is predominantly determined by blood flow. During this period there was no statistically significant decline in the A_{ca}/A_{cb} ratio (~1) as a function of age in either the males or the females. In addition, the ratio of the activity in the caudate (counts per minute for this period) to the integral of that in the blood, and the ratio of the activity in the cerebellum to the integral of that in the blood, did not decrease with age for either sex. All CT scans were reviewed to determine the size of the caudate nucleus and putamen. There was no observable decrease in size (*18*). Cerebral glucose metabolism, also measured by PET, has been found either not to decrease or to drop only slowly with age (*19*).

Other studies have revealed age-related decreases in various other dopaminergic features. Cell bodies in the substantia nigra and putamen decrease in number and size with age (*20*). There is also an age-related decrease in the levels of neurotransmitter as well as in activities of synthesizing enzymes (*21*) in the caudate, putamen, and nucleus accumbens. These findings may be related to the decline in receptors observed here, since neurons in the basal ganglia and substantia nigra bear D2 receptors (*22*). Our data suggest that the decline in D2 receptor in females was different from that in males (*23*). However, more data is required for complete elucidation of this finding. In studies with other animals there is evidence of functional differences in dopamine receptors with sex and that estradiol can alter levels of dopamine receptor (*24*).

References and Notes

1. H. N. Wagner *et al.*, *Science* **221**, 1264 (1983).
2. T. Lee and P. Seeman, *Am. J. Psychiatry* **137**, 191 (1980); M. Quik *et al.*, *J. Neurol. Sci.* **43**, 429 (1979); I. Creese *et al.*, *Eur. J. Pharmacol.* **60**, (1979); J. Z. Fields *et al.*, *Brain Res.* **136**, 578 (1977); A. Schotte *et al.*, *ibid.* **276**, 231 (1983); A. V. P. MacKay *et al.*, *Life Sci.* **23**, 527 (1978).
3. The pharmacological binding characteristics of [^{11}C]NMSP are similar to those of spiperone in this regard [N. W. Pedigo *et al.*, *Eur. J. Pharmacol.* **50**, 451 (1978); D. Marchais *et al.*, *Brain Res.* **183**, 235 (1980); S. J. Peroutka and S. H. Snyder, *ibid.* **208**, 339 (1981); S. J. List and P. Seeman, *Proc. Natl. Acad. Sci. U.S.A.* **78**, 2620 (1981); R. E. Boehme and R. D. Ciaranello, *ibid.*, p. 3225].
4. P. Seeman *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **73**, 4354 (1976); S. H. Snyder and J. P. Bennett, *Annu. Rev. Physiol.* **38**, 153 (1976); I. Creese *et al.*, *Eur. J. Pharmacol.* **46**, 377 (1977); J. Z. Fields *et al.*, *Brain Res.* **136**, 578 (1977); J. E. Leysen *et al.*, *Biochem. Pharmacol.* **27**, 307 (1978); J. W. Kebabian and D. B. Calne, *Nature (London)* **277**, 93 (1979); M. Titeler, *Multiple Dopamine Receptors* (Dekker, New York, 1983); I. Creese *et al.*, *Annu. Rev. Neurosci.* **6**, 43 (1983).
5. M. Baudry *et al.*, *Life Sci.* **21**, 1163 (1977); V. Hollt, A. Czlonkowski, A. Herz, *Brain Res.* **130**, 176 (1977); P. Laduron and J. Leysen, *Biochem. Pharmacol.* **26**, 1003 (1977); M. J. Kuhar *et al.*, *Life Sci.* **22**, 203 (1978); V. Hollt and P. Schubert, *Brain Res.* **151**, 149 (1978); S. Bischoff *et al.*, *Eur. J. Pharmacol.* **68**, 305 (1980); L. C. Murrin, *Life Sci.* **31**, 971 (1982); J. F. Van der Werf *et al.*, *Eur. J. Pharmacol.* **87**, 259 (1983).
6. The concentration of [^{11}C]NMSP in frontal cerebral cortex in mice 1 hour after injection was 100 times more sensitive to blockade by cinanserin, a serotonergic (S2) drug, than that in the striatum. Conversely, [^{11}C]NMSP in the striatum under similar conditions was about ten times more sensitive to blockade by haloperidol, a dopaminergic (D2) drug (D. F. Wong *et al.*, in preparation).
7. E. S. Garnett *et al.*, *Nature (London)* **305**, 137 (1983); W. C. Eckelman *et al.*, *Science* **223**, 291 (1984); D. Comar *et al.*, *Psychiatry Res.* **1**, 23 (1979); H. K. Kulmala *et al.*, *Life Sci.* **28**, 1911 (1981); C. S. Kook *et al.*, *J. Nucl. Med. Chem.* **18**, 533 (1975); G. A. Digenis *et al.*, *J. Pharmacol. Sci.* **70**, 985 (1981); T. J. Tewson *et al.*, *Brain Res.* **192**, 291 (1980); J. S. Fowler *et al.*, *J. Nucl. Med.* **23**, 437 (1982); B. Drayer *et al.*, *J. Comput. Assist. Tomog.* **6**, 536 (1982).
8. In the CT scans, three slices were obtained parallel to the canthomeatal line. The middle slice passed through the frontal horn at either upper portion or above the third ventricle and also passed through the pineal gland and habenular commissure. This slice permitted maximum visualization of the caudate and lentiform nuclei and corresponded to the middle slice in the PET scan. The other two planes were taken 32 mm above and below this plane. The upper slice was approximately equidistant between the roof of the body of the lateral ventricles and the vertex of the skull. The lower slice passed through the mid-posterior fossa (plane of the fourth ventricle). These planes also corresponded to the upper and lower planes of the PET scanner. Even though intravenous contrast medium was not used, the caudate nucleus could still be identified and usually appeared denser than the lentiform nucleus.
9. L. Sokoloff *et al.*, *J. Neurochem.* **28**, 897 (1977).
10. A. Gjedde, *Brain Res. Rev.* **4**, 237 (1982).
11. This approach is similar in principle to the graphic analysis approach discussed in detail by Patlak *et al.* [*J. Cereb. Blood Flow Metab.* **3**, 1 (1983)].
12. M. A. Mintun *et al.*, *Ann. Neurol.* **15**, 217 (1984).
13. A. Gjedde, W. D. Heiss, K. Wienhard, in *Cerebral Blood Flow and Metabolism Measurement*,

A. Hartmann and S. Hoyer, Eds. (Springer-Verlag, New York, 1984).
14. Under ideal circumstances (in the absence of significant concentrations of metabolite within extravascular brain tissue), it can be shown that the normalized integral of the metabolite concentration in the cerebellum is related to the normalized integral of the free ligand concentration in the caudate (C. S. Patlak, personal communication).
15. The slopes of these plots for males ranged from 0.017 to 0.07 min^{-1} (average, 0.053 min^{-1}) and decreased exponentially with age ($m = 0.0279 + 0.177e^{-0.0715x}$; standard error = 4.6×10^{-3}, 9.0×10^{-2}, and 2.4×10^{-2}). The 95 percent confidence intervals of the experimental regression at ages 20, 40, and 65 years were 0.070 ± 0.01, 0.038 ± 0.0049, and 0.030 ± 0.0064, respectively, and the prediction limits of a new slope value at these ages were 0.070 ± 0.019, 0.038 ± 0.016, and 0.030 ± 0.017, respectively. The slopes of these plots for females ranged from 0.0765 to 0.036 min^{-1} (average, 0.05057 min^{-1}) and had a linear fit ($m = 0.040x + 6.39$; standard error = 0.0002). For the females the 95 percent confidence limits on the straight-line regression at ages 20, 40, and 65 years were 0.056 ± 0.0090, 0.048 ± 0.0061, and 0.038 ± 0.014, respectively, and the prediction limits for a new value of slope at these ages were 0.056 ± 0.029, 0.048 ± 0.028, and 0.038 ± 0.031, respectively.
16. J. A. Severson *et al.*, *J. Neurochem.* **39**, 1623 (1982); J. A. Severson and C. E. Finch, *Brain Res.* **210**, 201 (1980); J. A. Joseph *et al.*, *Life Sci.* **29**, 575 (1981); L. J. Thal *et al.*, *Brain Res.* **192**, 185 (1980); A. DeBlair and T. Menrini, *ibid.* **242**, 361 (1982); J. K. Marquis *et al.*, *Biochem. Pharmacol.* **30**, 1876 (1981); M. Meino *et al.*, *Brain Res.* **202**, 488 (1980); C. H. Misra *et al.*, *Life Sci.* **27**, 526 (1980); J. Marcusson, *Clin. Neuropharmacol.* **7** (suppl. 1), 22 (1984).
17. The declines in cerebral blood flow over a comparable range of ages are variable and in the range of 0 to 29 percent. Also, in some cases the data are not directly comparable [N. A. Lassen *et al.*, *J. Clin. Invest.* **9**, 491 (1960); H. Naritomi *et al.*, *Arch. Neurol.* **36**, 410 (1979); P. Scheinberg *et al.*, *AMA Arch. Neurol. Psychiatry* **70**, 77 (1953); W. D. Obrist, *Aging* **7**, 213 (1978); S. S. Kety, *J. Chronic Dis.* **3**, 478 (1956)].
18. Assessment of CT images of the caudate and putamen did not reveal a decrease in size with age, nor was significant atrophy observed. It is possible that a small decrease in size of the caudate or putamen with age partially contributes to the decrease in the measured activity in these regions because of the so-called partial volume effect. Structures similar in size or smaller than the spatial resolution of the PET scanner result in lower measured activity than the true activity. The lack of evidence from CT scans showing a recognizable decrease in caudate or putamen size suggests that the decrease in activity with age is not solely an effect of size change. This decrease is maximum in the 20- to 40-year age group, where atrophy would be unusual.
19. R. Duara *et al.*, *Brain* **106**, 761 (1983); D. E. Kuhal *et al.*, *J. Cereb. Blood Flow Metab.* **2**, 163 (1982); R. A. Hawkins *et al.*, *ibid.* **3**, 250 (1983).
20. O. Bugiani *et al.*, *Eur. J. Neurol.* **17**, 286 (1978); P. L. McGeer *et al.*, *Arch. Neurol.* **34**, 33 (1977).
21. P. L. McGeer and E. F. McGeer, *J. Neurochem.* **26**, 65 (1976); A. Carlsson and B. Winblad, *J. Neural Trans.* **38**, 271 (1976).
22. S. H. Snyder and R. R. Goodman, *J. Neurochem.* **35**, 5 (1980); R. Schwarcz and J. T. Coyle, *Brain Res.* **127**, 235 (1977); L. C. Murrin *et al.*, *Eur. J. Pharmacol.* **60**, 229 (1979); N. Klemm *et al.*, *Brain Res.* **169**, 1 (1979); M. Quik *et al.*, *ibid.* **167**, 335 (1979); J. W. Kebabian and D. B. Calne, *Nature (London)* **277**, 93 (1979).
23. The relation between the A_{ca}/A_{cb} ratio and age in females is best represented by a straight line. In males a second-degree polynomial regression gave a significantly better fit ($P < 0.01$) than a straight line, thus demonstrating a statistically significant difference between males and females in the decline of receptor with age. An exponential function was approximately as good a fit. (The mean square errors of polynomial and exponential fit were 0.114 and 0.123, respectively). Because of the partial overlap of the data for males and females, the biological significance of this statistical difference has yet to be determined.
24. R. Hruska *et al.*, *Pharmacol. Biochem. Behav.* **16**, 285 (1982); T. DiPaolo *et al.*, *Molec. Cell. Endocrin.* **16**, 99 (1979); J. C. Miller, *Psychoneuroendocrinology* **8**, 225 (1983); T. DiPaolo *et al.*, *Neuropsychopharmacol. Biol. Psychiatry* **6**, 377 (1982).
25. D. F. Wong *et al.*, *J. Nucl. Med.* **25**, 108 (1984).
26. Supported by U.S. Public Health Service grants NS15080 and MH00053. We thank S. Wrightson, M. Flutka, F. Gilbert, M. J. Stumpf, J. K. Rhine, D. Koller, P. Zorich, M. Murrell, M. Bryan, P. D. Wilson, B. Jensen, A. Kimble, G. Pearlson, G. Uhl, P. Worley, R. D. Parker, G. J. Wang, L. Buhle, T. Duelfer, T. K. Natarajan, A. Bice, N. D. LaFrance, J. Alano, G. Wand, R. Ney, H. M. Drew, B. D. Scheinin, K. Stolz, and H. Rothenburg for assistance and S. H. Snyder for general discussions.

11 June 1984; accepted 28 September 1984

Daniel E. Koshland, Jr., New Editor of *Science*

Bruce N. Ames

In January of 1985, Philip Abelson will hand over the reins of *Science* to a new editor to build on the fine foundation he has created for this distinguished magazine. The AAAS has been fortunate to persuade Daniel Koshland to assume this responsibility.

Dan Koshland became interested in science at the age of 13 when he read *Microbe Hunters* and *Arrowsmith*. He obtained at B.S. in chemistry from the University of California, Berkeley, and a Ph.D., also in chemistry, from the University of Chicago. His graduate work under the direction of Frank Westheimer was leaning toward the biological side of chemistry, and it is to the application of chemistry to biology that he has devoted his efforts. After a postdoctoral fellowship at Harvard he had joint appointments at Brookhaven National Laboratory and Rockefeller University until moving to the University of California, Berkeley, as professor of biochemistry in 1965.

Koshland has a tremendous curiosity about all things scientific, and his career has been noteworthy for the contributions he has made to numerous areas of science. His enthusiasm, high energy level, and low activation energy for mastering new fields are ideal characteristics for editorship of a multidisciplinary journal such as *Science*.

His research has been reported in approximately 300 articles, ranging from theoretical papers involving pure mathematics to a paper on "The walking rate of ants." It is impractical to describe all of his contributions here but a few illustrative examples can be chosen.

Koshland's early work was focused on enzyme mechanisms. His first major contribution was the concept of single and double displacement reactions in biology, a concept that applied the stereochemistry of organic chemistry to the understanding of enzymatic mechanisms. It provided a unifying theory to many reactions that seemed widely disparate and was typical of many of his subsequent contributions. In demonstrating the validity of his theories, he developed a number of experimental tools—methods for modifying carboxyl and tryptophan residues in proteins, the all-or-none assay, oxygen-18 isotopic techniques for interpreting mechanisms of muscular contraction, and the first "chemical mutation" (the conversion of a serine to a cysteine residue at the active site of chymotrypsin by chemical modification)—and a theoretical analysis of the "proximity effect."

His next major contribution was the development of the "induced fit" theory, now included in textbooks of biochemistry. At its first promulgation, however, it was not easily accepted, for it proposed that enzymes were flexible molecules, not the classical keylock or template model of Emil Fischer, which was standard doctrine at the time. Koshland's proposal was that the fit between a protein molecule and its substrate was more like the fit of a hand in a glove than the fit of two pieces of a rigid jigsaw puzzle. Moreover, the change in shape of the protein "induced" by the small molecule was essential to its biological properties. Koshland and others, of

Bruce N. Ames is chairman of the Department of Biochemistry, University of California, Berkeley 94720.