Elevated levels of circulating trace amines in primary headaches

G. D'Andrea, MD; S. Terrazzino, PhD; A. Leon, PhD; D. Fortin, BS; F. Perini, MD; F. Granella, MD; and G. Bussone, MD

Abstract—*Background:* Trace amines, including tyramine, octopamine, and synephrine, are closely related to classic biogenic amines. They have been hypothesized to promote migraines and other types of primary headaches, but there is no direct evidence supporting this hypothesis. *Methods:* Using a multichannel electrochemical high-performance liquid chromatography system, the authors evaluated whether changes in circulating trace amines occur in subjects with migraine (with or without aura) during headache-free periods as well as in patients with cluster headache (CH) during the remission and active phases as compared with healthy control subjects. *Results:* Plasma levels of all trace amines were significantly higher in CH patients, in both the remission and the active phases, when compared with control subjects or subjects with migraine. In addition, intraplatelet levels of octopamine, synephrine, and tyramine were higher in CH patients than in control subjects. In migraine patients, plasma levels of octopamine and synephrine were higher compared with controls, although in migraine with aura, the difference was not significant. *Conclusions:* Whereas the elevation of plasma trace amine levels in both migraine and CH supports the hypothesis that disorders of biogenic amine metabolism may be a characteristic biochemical trait in primary headache sufferers, the observation that such alterations are more prominent in patients with CH than migraine patients suggests that they may reflect sympathetic or hypothalamic dysfunction.

NEUROLOGY 2004;62:1701–1705

The hypothesis that trace amines such as tyramine, octopamine, and synephrine, closely related chemically to classic biogenic amines,[1,2] may contribute to the pathogenesis of primary headaches was proposed several decades ago.[3,4] The observation that certain foods rich in tyramine, such as chocolate, citrus fruits, and cheese, caused a hypertensive headache response in depressed patients treated with monoamine oxidase (MAO) inhibitors raised the possibility that the increased sensitivity to tyramine-containing foods in dietary migraine might be due to a deficiency in MAO activity.[5] Thereafter, in view of the time delay from ingestion of provocative foods and the painful attack, accumulation of octopamine, derived from tyramine metabolism, was proposed to be the main causative agent.[6] Trace amines, including octopamine, displace biogenic amines from their storage vesicles, and the depleting agent reserpine precipitates migraine, results in line with the capability of trace amines to act as false neurotransmitters. However, despite evidence showing that levels of trace amines in rodent brain are elevated during inhibition of MAO enzymes (MAO-A and MAO-B) or after selective deletion of MAO genes,[7,8] to date there is no direct evidence supporting the involvement of trace amines in primary headaches. As a matter of fact, the inability to demonstrate specific receptors for these compounds and the lack of sensitive nonradioactive methods for the detection of trace amines in biologic samples have limited their investigation in humans.

Recently, however, G-protein-coupled receptors with high affinity for trace amines have been described in rodents and humans.[9] These receptors, called trace amine receptors (TAR), are distinct from the classic biogenic amine receptors and are found in various tissues and organs, including specific brain areas such as the amygdala, hypothalamus, and locus ceruleus. In addition, effects of trace amines, in particular octopamine, on mammalian α_2- and β_3-adrenergic receptors have emerged.[10,11] All this opens the possibility that one or more trace amines may in humans behave as "bona fide" neurotransmitters or neuromodulators capable of exerting effects independently or in concert with classic biogenic amines.

We have recently devised a sensitive high-performance liquid chromatography (HPLC) method for assessment of trace amines in human plasma and platelets.[12] Utilizing this method, we here questioned whether abnormalities in circulating trace amines are found in primary headache sufferers. To this end, levels of tyramine, octopamine, and synephrine were, in comparison with healthy control subjects, assessed in plasma of patients with migraine with

From the Headache and Comorbidity Center (Dr. D'Andrea, D. Fortin), Department of Clinical Pathology, Este-Monselice Hospital, and Research and Innovation Company (Drs. Terrazzino and Leon), Padova, Headache Center (F. Perini), Neurology Department, Vicenza Hospital, Institute of Neurology (Dr. Granella), University of Parma, and Headache Center (Dr. Bussone), Neurological Institute "C. Besta," Milan, Italy.

Supported in part by "Associazione Antonio R. Cananzi per le Cefalee e le Malattie Cerebrovascolari" and by MIUR grant no. 3933.

Received September 9, 2003. Accepted in final form January 16, 2004.

Address correspondence and reprint requests to Dr. G. D'Andrea, Headache and Comorbidity Center, Department of Clinical Pathology, Este-Monselice Hospital, via San Fermo 10, 35042 Este (PD), Italy; e-mail: giovinavi@libero.it

Table 1 *Patient series*

Data	Control subjects	Migraine without aura	Migraine with aura	Cluster headache patients
Age range, y	30–50	19–38	16–45	22–59
Mean age, y	40.4	28.5	31.7	41.6
No.	36	34	16	44
Sex, M/F	16/20	13/21	8/8	42/2
Duration cluster, y				2–13
Remission period		4–9		20
Active period		35–80		24
Duration of migraine, y		2–9	1–5	
Frequency of attacks		1–4/mo	0.5–2/mo	1–3/d

(MwA) and without (MA) aura during headache-free periods as well as in patients experiencing cluster headache (CH) during both active and remission periods.

Materials and methods. Three groups of headache sufferers (MA, MwA, and CH) and 36 healthy control subjects, age and sex matched, were enrolled into the study (table 1). The diagnosis of migraine MA, MwA, and CH was made in agreement with International Headache Society criteria.[13] No patients complained of any other diseases. All subjects were free of drugs known to affect both MAO activity (e.g., imipramine, amitriptyline, phenelzine, tranylcypromine, selegiline, and moclobemide)[14] and platelet function from at least 2 weeks prior to blood sampling. In addition, to avoid biochemical interference from diet, all subjects avoided food containing biogenic amines (e.g., chocolate, dry fruits, cheese, etc.) from at least 1 week before the hematologic examination. Migraine patients were studied in headache-free periods at least 3 days after the last painful attack. The CH sufferers in active phase were under treatment with verapamil with doses ranging from 240 to 360 mg/day. Migraine and residual attacks of CH were treated with imigran/imitrex subcutaneously. Migraine and CH patients in remission period were free from any drugs. After informed consent was obtained, levels of tyramine, octopamine, synephrine, and were measured in plasma of all subjects (see table 1), and platelet levels were evaluated in CH patients and 22 control subjects.

Peripheral venous blood (30 mL) was drawn from the antecubital vein, following overnight fasting, at 9 AM from subjects after 5 minutes of resting in the supine position. The blood was drawn from the same operator and collected into <fr1/10> volume citric acid/citrate dextrose as anticoagulant for the estimation of trace amines. Platelet-rich plasma (PRP) was obtained by centrifugation (950 rpm for 15 minutes) of whole blood, and after the platelet number was calculated by a platelet analyzer, PRP was centrifuged at higher speed (3,500 rpm × 15 minutes) to obtain a platelet pellet and the platelet-poor plasma (PPP). The platelet pellet was then washed with 3 mL of Tyrode buffer solution, as was previously described.[15] The platelet pellet was sonicated in 1% perchloric acid solution. The mixture was centrifuged (14,500 rpm for 5 minutes) to remove protein fragments. The supernatant was removed and passed through a 0.2-μm nylon filter (Acrodisc; Waters). PPP was obtained by centrifugation of PRP (3,500 rpm × 15 minutes). An aliquot of perchloric acid was added to PPP (total volume 4 mL) for the deproteinization. After brief centrifugation (14,000 rpm for 5 minutes), the supernatant was passed through an ultrafilter membrane.

HPLC method. The chromatographic system consisted of an autosampler (Waters) capable of variable-volume injections, equipped with a 100-μL loop and two-pump separation module (Waters 2695) connected with a C_{18} reverse phase (XTerra) 15 × 4.6–mm, 5-μm column, fitted with a 3.0 × 20–mm, 5-μm precolumn (XTerra). The detection device consisted of a multichannel electrochemical detector system (CoulArray ESA). The autosampler and pumps were monitored and controlled by Millennium 2 software. The multichannel detector was monitored and controlled by a CoulArray for Windows installed in a Pentium 3 computer (Dell). The computer system performed the data storage, analysis, and report generation. The mobile phase, adjusted to pH 3 with phosphoric acid, consisted of sodium phosphate monobasic 10.25 g/L, sodium dodecyl sulfate 250 mg/L, and acetonitrile 11% vol/vol. The instrumental parameters of the separation method were as follows: full-scale sensitivity of all channels, 100 μA; potentials of each of eight channels, starting with channel 1, −100, 0, 50, 300, 380, 780, 890, +920 mV. Three incremental doses of 0.125, 0.250, and 0.500 μg/mL of tyramine, octopamine, and synephrine standard solutions (Sigma, St. Louis, MO) were utilized to obtain the calibration curve to determine the platelet and plasma levels of each substance. The standard solutions were prepared dissolving 10 mg of the components in a solution of 0.1 N perchloric acid and each component was diluted with a solution of 1% perchloric acid to give a final concentration of 1 μg/mL. Aliquots of 80 μL of the standards and extracts from biologic tissues were injected for identification and quantification. The retention times of tyramine, octopamine, and synephrine were 18.50, 6.7, and 7.8 minutes (ratio accuracy 0.75, 0.88, and 0.87). The standard deviation for the calibration of each substance was ±0.00161. The detection limits of the HPLC method were 22 pg for tyramine, 22 pg for octopamine, and 49 pg for synephrine.

Statistical analysis. The results are presented as means ± SD and were assessed with analysis of variance followed by Tamhane test using the SPSS statistical package (SPSS, Chicago, IL) or with unpaired *t*-test, as required. The level of significance was set at $p < 0.05$.

Results. Detectable levels of octopamine and synephrine were found in almost all patients (34/34 and 33/34 MwA patients, 15/16 and 14/16 MA subjects, 39/44 and 41/44 CH patients) and in the majority of control subjects (36/36 and 27/36 subjects). Tyramine, on the other hand, was less frequently detected, particularly in control subjects (14/36) and MA patients (6/16). The latter result is in accord with previous findings showing that tyramine is, in comparison with other amines, biochemically unstable, that is, rapidly metabolized to octopamine or catabolized by MAO activity.[16]

Table 2 reports mean levels of octopamine, synephrine, and tyramine found in plasma of MwA and MA subjects during headache-free periods as well as in CH patients with respect to control subjects. In MwA, plasma levels of octopamine and synephrine are, unlike that of tyramine, significantly more elevated when compared with control values. Although these trace amines were also increased in MA, the difference with respect to controls was not significant. In addition, all three trace amines are severalfold higher in plasma of CH patients as well as significantly more elevated with respect to those found in MwA or MA subjects. This significant difference was observed in CH patients both in remission and in active periods. No signif-

Table 2 *Tyramine, octopamine, and synephrine plasma levels in control and primary headache subjects*

Subjects	Tyramine	Octopamine	Synephrine
Controls, n = 36	1.05 ± 1.78	2.17 ± 1.86	3.12 ± 3.92
Migraine without aura, n = 34	2.02 ± 3.21	4.86 ± 2.80*	9.18 ± 4.64*
Migraine with aura, n = 16	1.42 ± 1.78	6.07 ± 7.10	6.77 ± 6.20
CH patients, n = 44	7.51 ± 7.76*†‡	11.48 ± 8.40*†	15.17 ± 12.45*§‖
CH patients in remission phase, n = 20	4.91 ± 4.36‖¶	9.86 ± 6.74*§	12.56 ± 10.90†
CH patients in active phase, n = 24	9.67 ± 9.67*†‡	12.84 ± 9.50*†	17.34 ± 13.43*§‖

Values are expressed as ng/mL ± SD and were assessed by one-way analysis of variance followed by post-hoc analysis (Tamhane test).

* $p < 0.001$, vs controls.
† $p < 0.05$, vs migraine with aura.
‡ $p < 0.005$, vs migraine without aura.
§ $p < 0.05$, vs migraine with aura.
‖ $p < 0.02$, vs migraine without aura.
¶ $p < 0.01$, vs controls.

CH = cluster headache.

icant difference was found, except for tyramine being higher in the active phase, between levels of octopamine and synephrine of CH patient groups in remission and in the active period.

Previous reports have shown that circulating trace amines such as octopamine are taken up into platelets and stored within the dense bodies.[17,18] Thus, in an attempt to gain further insight into the levels of circulating amines in persons with primary headache and in particular CH, we also measured trace amine levels in platelets of CH patients with respect to controls (table 3). Detectable levels of octopamine, synephrine, and tyramine were, in fact, found in platelets of almost all CH patients (41/41, 41/41, and 37/41), whereas tyramine, unlike octopamine and synephrine, was found only in half of the control subjects (11/22). Furthermore, the mean intraplatelet values of all three biogenic amines were significantly higher in platelets of CH patients when compared with those of control subjects. Again, no significant differences were, as in plasma, evident upon comparison of mean intraplatelet tyramine and octopamine, but not synephrine, levels assessed during remission and active phases of CH.

Table 3 *Platelet trace amine levels in cluster headache patients during remission and active phases in control subjects*

Subjects	Tyramine	Octopamine	Synephrine
Controls, n = 22*	0.045 ± 0.068	0.22 ± 0.16	0.33 ± 0.25
CH patients, n = 44	0.38 ± 0.35†	0.70 ± 0.51†	0.81 ± 0.55†
CH in remission phase, n = 20	0.43 ± 0.42‡	0.75 ± 0.53†	0.98 ± 0.62†§
CH in active phase, n = 24	0.34 ± 0.28†	0.66 ± 0.51‡	0.64 ± 0.43‡

Values are expressed as ng/10^8 platelets ± SD and were assessed by Student unpaired *t*-test.

* 19 males, 3 females.
† $p < 0.0001$, vs controls.
‡ $p < 0.005$, vs controls.
§ $p < 0.05$, vs cluster headache in active phase.

CH = cluster headache.

Discussion. The current study shows that circulating levels of trace amines such as octopamine and synephrine are in primary headache patients significantly more elevated than those found in control subjects. As all subjects rigorously avoided food known to contain relevant amounts of trace amines for at least 1 week prior to the blood sampling, an increased outsource by the diet is unlikely to have affected the determinations. In addition, as platelets do not possess the enzymatic machinery to synthesize trace amines, the high intraplatelet levels observed in CH may, following their uptake, reflect the augmentation in circulating trace amines.[18] All this raises the possibility that alteration in amine metabolism is a distinctive feature accompanying primary headache syndromes. In addition, the observation that subjects affected by CH display severalfold increases in the levels of not only octopamine and synephrine but also tyramine, even when compared with those found in subjects with MA or MwA, suggests that such a metabolic abnormality may be of particular relevance in CH.

In CH, the observation that significantly increased levels of the evaluated trace amines occur during both the remission and the active phases raises the hypothesis that such alterations may reflect the ongoing sympathetic dysfunction.[19] Trace amines are known to be synthesized and stored within the autonomic nervous system.[20] Tyramine, derived from the amino acid tyrosine through tyrosine decarboxylase enzyme activity, is metabolized by dopamine-β-hydroxylase into octopamine, whereas phenylethanolamine *N*-methyltransferase enzyme activity transforms octopamine into synephrine, the final biochemical step in the synthesis of trace amines.[1] Thus, one possibility is that the increased plasmatic trace amine levels found in CH patients may reflect an increase of tyrosine decarboxylase activity or inhibition of tyrosine hydroxylase (TH) enzyme activity. In support of this

hypothesis is the evidence showing that norepinephrine, the major product of TH activity, is decreased in platelets in all phases of CH and in plasma and CSF only in active phase.[21,22] In addition, the TH enzyme within the autonomic nervous system is the major source of norepinephrine in plasma.[20]

Another possibility is that the abnormal trace amine levels in CH may reflect hypothalamic dysfunctions. The hypothalamus and locus ceruleus contain, in humans, the highest level of octopamine,[23] and these areas are connected with the autonomic system.[24] Further, low prolactin levels in CH patients in all phases of the disease and after challenge with TRH have been reported.[25] Although these findings may reflect dopaminergic hyperactivity, no evidence has been provided in support of this possibility. An alternative explanation may be an increased level of octopamine turnover in the hypothalamus. Octopamine, in fact, reduces prolactin secretion from lactotrophic cells via nondopaminergic receptors.[26] In addition, hypothalamic abnormalities play a major role in the pathogenesis of CH. A study with PET has demonstrated that regional cerebral blood flow, an index of synaptic activity, is increased during nitroglycerin-induced CH attacks in the posterior area of the hypothalamus.[27] More recently, the same group, using voxel-based morphometry MRI analysis, has shown an enlarged volume of the gray matter in the same area.[28] A new effective treatment, based on stereotactic stimulation of posterior hypothalamus in patients with intractable chronic CH, also supports a hypothalamic involvement.[29] Interestingly, TAR-1 mRNA is reported to be expressed in hypothalamus as well as in the ventral tegmental area, locus ceruleus, and dorsal raphe nucleus, structures that govern, among other functions, the pain threshold.[10,30] α-Adrenoceptors, including α_{2C}-receptors, are also distributed in these areas.[12] Octopamine acts as agonist of TAR-1 and α_{2C}-receptors.[9,31] It is possible to conceive that alterations in octopamine and other amines may, via specific receptors, interfere with functions of the hypothalamus and perhaps other subcortical circuitries potentially implicated in CH.

The physiopathologic significance of the increased levels of octopamine and synephrine in plasma of MwA and MA patients is unknown. Nevertheless, although it may be similar to CH, the results here reported show that when compared with CH, a minor biochemical shift in amine metabolism occurs in migraine patients. In support of this hypothesis, reduced intraplatelet levels of serotonin and norepinephrine occur before painful attacks in females affected by menstrual migraine.[32,33] Of interest is also that the lower entity of the biochemical alteration is consistent with the occurrence of a mild autonomic system symptomatology in migraine.[34]

Although the underlying causes must be clarified, our results suggest that high circulating trace amine levels may represent an abnormal biochemical phenotypic trait accompanying migraine and, particularly, CH. Whether this abnormality, either alone or in association with other factors, underlies any susceptibility to CH or migraine remains to be determined.

References

1. Trace amines and the brain. New York: Dekker, 1976:21–40.
2. Saaverdra JM. β-Phenylethylamine, phenyletholamine, tyramine and octopanine. In: Trendelemburg V, Weiner N, eds. Cathecholamines II. Berlin: Springer, 1989:181–201.
3. Merikangas KR, Stevens DE, Merikangas JR, et al. Tyramine conjugation deficit in migraine, tension type headache, and depression. Biol Psychiatry 1995;38:730–736.
4. Branchek AT, Blackburn T. Trace amines receptors as targets of novel therapeutics: legend, myth and fact. Curr Opin Pharmacol 2003;3:90–97.
5. Hanington E. Preliminary report on tyramine headache. Br Med J 1967;2:550–551.
6. Sever PS. False transmitters and migraine. Lancet 1979;1:333.
7. Durden DA, Philips SR. Kinetic measurements of the turnover rates of phenylethylamine and tryptamine in vivo in the rat brain. J Neurochem 1980;34:1725–1732.
8. Grimsby J, Toth M, Chen K, et al. Increased stress response and beta-phenylethylamine in MAOB-deficient mice. Nat Genet 1997;17:206–210.
9. Borowsky B, Adham N, Jones KA, et al. Traces amines: identification of a family of mammalian G protein-coupled receptors. Proc Natl Acad Sci USA 2001;98:8966–8971.
10. Rudling EJ, Richardson J, Evans DP. A comparison of agonist-specific coupling of cloned human α_2-adrenoceptor subtypes. Br J Pharmacol 2000;131:933–941.
11. Visentin V, Morin N, Fontana E, et al. Dual action of octopamine on glucose transport into adipocytes: inhibition via β_3-adrenoceptor activation and stimulation via oxidation by amine oxidases. J Pharmacol Exp Ther 2001;299:96–104.
12. D'Andrea G, Terrazzino S, Fortin D, Farruggio A, Rinaldi L, Leon A. HPLC electrochemical detection of trace amines in human plasma and platelets and expression of mRNA transcripts of trace amines receptors in circulating leukocytes. Neurosci Lett 2003;346:89–92.
13. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988;8(suppl 7):1–96.
14. Baldessarini RJ. Drugs and the treatment of psychiatric disorders. In: Hardman JG, Limbird LE, eds. Pharmacological basis of therapeutics. 10th ed. New York: McGraw-Hill Medical Publishing, 2001:447–483.
15. Martignoni E, Blandini F, D'Andrea G, et al. Platelet and plasma catecholamines levels in migraine patients: evidence for a menstrual related variability of the noradrenergic tone. Biogenic Amines 1994;10:227–237.
16. Axelrod J, Saavedra JM. Octopamine. Nature 1977;265:501–504.
17. Morelli A, Frintzilas M, Zimmon SD. Platelet uptake of octopamine and norepinephrine in hepatic encephalopathy. Gastroenterology 1977;73:560–664.
18. Murphy LD, Cahan HD, Molinoff BP. Occurrence transport and storage of octopamine in human thrombocytes. Clin Pharmacol Ther 1975;18:587–593.
19. Fanciullacci M, Pietrini U, Gatto G, Boccuni M, Sicuteri F. Latent dysautonomic pupillary lateralization in cluster headache; a pupillometric study. Cephalalgia 1982;2:135–144.
20. Ibrahim KE, Couch MW, Williams CM, Fregly MJ, Midgley JM. m-Octopamine: normal occurrence with p-octopamine in mammalian sympathetic nerves. J Neurochem 1985;44:1862–1967.
21. D'Andrea G, Cananzi AR, Morra M, et al. Platelet catecholamines in cluster headache. J Neurol Neurosurg Psychiatry 1992;55:308–309.
22. Strittmatter M, Hamann GF, Grauer M, et al. Altered activity of the sympathetic nevous system and changes in the balance of hypophyseal, pituitary and adrenal hormones in patients with cluster headache. Neuroreport 1996;7:1229–1934.
23. Danielson TJ, Boulton AA, Robertson HS. m-Octopamine, p-octopamine and phenylethylamine in mammalian brain: a sensitive, specific assay and effects of drugs. J Neurochem 1977;29:1131–1135.
24. Laorden ML, Fuertes G, Gonzales–Cuello A, Milanes MV. Changes in catecholaminergic pathways innervating paraventricular nucleus and pituitary-adrenal axis response during morphine dependence: implication of α(1)-and α(2)-adrenoceptors. J Pharmacol Exp Ther 2000;293:578–584.
25. Waldelind E, Gustafsson SA. Prolactin in cluster headache: diurnal secretion, response to thyrotropin-releasing hormone and relation to sex steroids and gonadotropins. Cephalalgia 1987;7:43–54.
26. Becu–Villalobos D, Thyssen SM, Rey EB, Lux–Lantos V, Libertun C.

Octopamine and phenylethylamine inhibit prolactin secretion both in vivo and in vitro. PSEBM 1992;199:230–235.
27. May A, Bahra A, Buchel C, Frackowiak SR, Goadsby JP. Hypothalamic activation in cluster headache attacks. Lancet 1998;352:275–278.
28. May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ. PET and MRA findings in cluster headache and MRA in experimental pain. Neurology 2000;55:1328–1335.
29. Leone M, Franzini A, Bussone G. Stereotactic stimulation of posterior hypothalamic gray matter in a patient with intractable cluster headache. N Engl J Med 2001;345:1428–1429.
30. Altier N, Stewart J. The tachinin NK-1 receptor antagonist, RP-67580, infused into ventral tegmental area prevents stress-induced analgesia in the formalin test. Physiol Behav 1999;66:717–721.
31. Rossi EC, Louis G, Zeller EA. Structure activity relationship between catecholamines and the α-adrenergic receptor responsible for aggregation of human platelets by epinephrine. J Lab Clin Med 1979;93:286–294.
32. Fioroni L, D'Andrea G, Alecci M, Cananzi AR, Facchinetti F. Platelet serotonin pathway in menstrual migraine. Cephalalgia 1996;16: 427–430.
33. Martignoni E, Blandini F, Sances S, et al. Platelet and plasma catecholamines levels in patients. Evidence for menstrual-related variability of the noradrenergic tone. Biogenic Amines 1994;10:227–237.
34. Thomsen LL, Iversen HK, Boesen F, Olesen J. Transcranial Doppler and cardiovascular responses during cardiovascular autonomic tests in migraineurs during and outside attacks. Brain 1995;118:1319–1327.

AAN AWARD FOR CREATIVE EXPRESSION OF HUMAN VALUES IN NEUROLOGY

Dr. Michael Smith of Tucson is the winner of the 2003 AAN Award for Creative Expression of Human Values in Neurology (the "Creative Expression Award"). His prizewinning personal history, "A Wise Owl," appears in the November 11, 2003, issue of *Neurology*.

At a reception hosted by the Ethics, Law & Humanities Committee during the 56th Annual Meeting of the AAN in San Francisco, Dr. Smith received a check for $500. A donation of $1500 has also been given in his honor to the charitable organization of his choice, Doctors without Borders/Médecins sans Frontieres.

To learn more about the Creative Expression Award,
visit http://aan.com/professionals/awards/award/awa_cre_exp.cfm