As the premier scholarly publication of the osteopathic medical profession, *JAOA—The Journal of the American Osteopathic Association* encourages osteopathic physicians, faculty members and students at colleges of osteopathic medicine, and others within the healthcare professions to submit comments related to articles published in the *JAOA* and the mission of the osteopathic medical profession. The *JAOA*'s editors are particularly interested in letters that discuss recently published original research.

Letters to the editor are considered for publication in the *JAOA* with the understanding that they have not been published elsewhere and that they are not simultaneously under consideration by any other publication.

All accepted letters to the editor are subject to editing and abridgement. Letter writers may be asked to provide *JAOA* staff with photocopies of referenced material so that the references themselves and statements cited may be verified.

Readers are encouraged to prepare letters electronically in Microsoft Word (.doc) or in plain (.txt) or rich text (.rtf) format. The *JAOA* prefers that readers e-mail letters to jaoa@osteopathic.org. Mailed letters should be addressed to Gilbert E. D'Alonzo, Jr, DO, Editor in Chief, American Osteopathic Association, 142 E Ontario St, Chicago, IL 60611-2864.

Letter writers must include their full professional titles and affiliations, complete preferred mailing address, day and evening telephone numbers, fax number, and e-mail address. In addition, writers are responsible for disclosing financial associations and other conflicts of interest.

Although the *JAOA* cannot acknowledge the receipt of letters, a *JAOA* staff member will notify writers whose letters have been accepted for publication. Mailed submissions and supporting materials will not be returned unless letter writers provide self-addressed, stamped envelopes with their submissions.

All osteopathic physicians who have letters published in the *JAOA* receive continuing medical education (CME) credit for their contributions. Writers of original letters receive 5 hours of AOA category 1-B CME credit. Authors of published articles who respond to letters about their research receive 3 hours of category 1-B CME credit for their responses.

Although the *JAOA* welcomes letters to the editor, readers should be aware that these contributions have a lower publication priority than other submissions. As a consequence, letters are published only when space allows.

Nitric Oxide and Anandamide in OMT Research

To the Editor:

We are writing in response to the June 2005 original contribution by John M. McPartland, DO, and coauthors.[1] We are pleased to have data from our laboratory cited as a means of demonstrating a relationship between endothelial anandamide (AEA) release and constitutive nitric oxide synthase to potentially describe the therapeutic effects of osteopathic manipulative treatment.[2]

We would like to take a moment to briefly clarify and expand on our laboratory's findings. In short, we propose that therapeutic manual manipulations aid in circulation and provide increased blood flow to peripheral vascular tissue, and that these effects are mediated by nitric oxide. These assertions are based on experimental data obtained from our laboratory demonstrating that mechanical perturbance of excised neural and vascular tissue stimulate release of nitric oxide. These findings, when combined with numerous analogous findings,[3–6] support our hypothesis that physical manipulations increase the concentration of nitric oxide in the blood, allowing the recipient to experience the numerous beneficial effects of increased nitric oxide concentrations within the vasculature. These effects are in addition to and in conjunction with the classic vasodilation induced by nitric oxide. Such effects include antiviral, antibacterial, and antioxidant protection in addition to mediating a key signaling molecule in the stress-and-relaxation response.[7] Thus, from our perspective, it is no wonder that, after undergoing osteopathic manipulative treatment (OMT), patients often report feeling "better."

In addition to our findings related to the release of nitric oxide by mammalian and invertebrate tissue—and in further corroboration with the findings of McPartland and colleagues[1]—we demonstrate the presence of numerous other signaling molecules within the blood, notably the endocannabinoids AEA and 2-arachidonylglycerol. These are naturally occurring constitutive nitric oxide synthase–derived, nitric oxide–stimulating signaling molecules that are also constitutively expressed by nervous tissue, which can further initiate profound physiologic effects when stimulated.[7]

The molecule of particular note is AEA, an endogenous endocannabinoid, which can also cause nitric oxide release from human immune cells, neural tissues, and human vascular endothelial cells.[7] Anandamide can also initiate invertebrate immune cell constitutive nitric oxide synthase–derived nitric oxide. These findings lend further credence to and strongly support the findings reported by McPartland and his coinvestigators.[1] In addition, these

results open new doors for the osteopathic physician's use of OMT as an immune system regulator.

As an aside, it is interesting that a new theoretical paradigm is beginning to emerge in the realm of osteopathic medical research—one that has united researchers from the laboratory as well as the clinic in an effort to explore this unique and exciting area of medicine. We look forward to future collaborations.

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Response

I thank Dr Stefano for elaborating on the mechanisms proposed in our June 2005 original contribution.[1] There is "NO" doubt that future research collaborations will open new doors for the osteopathic physicians' use of osteopathic manipulative treatment. Basic scientists with excellent pedigrees are conducting endocannabinoid research at osteopathic medical schools.[2,3] Osteopathic medicine needs outcomes-based research, but we also need to explore the mechanisms by which our treatments work.

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Unsubstantiated Superiority Claims for Rivastigmine Tartrate

To the Editor:

In his March 2005 review article ("Cholinesterase inhibitors in the treatment of dementia." *J Am Osteopath Assoc*. 2005;105:145–158), Jay M. Ellis, DO, writes about treatment of patients with Alzheimer disease using rivastigmine tartrate, stating, "The 4.9 point difference in overall ADAS-Cog [the Alzheimer's Disease Assessment Scale – Cognitive Subscale] score increases in favor of rivastigmine over placebo in this 26-week trial is the largest observed for any of the cholinesterase inhibitors."

The implied message in Dr Ellis' statement is that rivastigmine may be the best acetylcholinesterase inhibitor currently available.

It is important for readers of *JAOA—The Journal of the American Osteopathic Association* to be reminded occasionally that such an implication is inappropriate because head-to-head trials are generally considered the best way to compare medications—and because rivastigmine has not been subjected to this form of trial with the two other cholinesterase inhibitors noted in the aforementioned literature review (ie, donepezil hydrochloride and galantamine hydrobromide).

It is generally inappropriate to compare different medications indirectly based on how each has performed against placebo in separate clinical trials because subjects in the respective study groups may have different baseline characteristics, or their conditions may progress at different rates in the absence of medical treatment. For an indirect comparison of medical interventions to show validity, there must be statistical analysis and adjustment (ie, metanalysis) based on the characteristics of the different study populations.[1]

Under the authority of well-known federal regulations,[2–4] the US Food and Drug Administration regularly sends warning letters to pharmaceutical companies funding advertisements that make unsubstantiated superiority claims similar to those found in this March 2005 *JAOA* article. It is the responsibility of THE JOURNAL's readers to rectify similar situations in the literature, however inadvertent, when articles with unfounded superiority claims slip past the scientific peer review process and into print.

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(continued on the next page)

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Response

The purpose of my March 2005 review article (*J Am Osteopath Assoc*. 2005; 105:145–158) was to make it clear that, among the acetylcholinesterase inhibitors, there is no single "best" agent for the treatment of patients with Alzheimer disease. In my own practice, I use all three agents to treat patients for this condition.

In my article, I diligently avoided recommending any agent preferentially. In fact, to avoid the appearance of favoritism toward any of the agents mentioned, I intentionally rotated the sequence of the names when all three agents were presented together. This personal preference of mine diverges from traditional editorial practice, which places lists of agents in alphabetical order by default when no specific treatment recommendations are being made as a result of differences in efficacy or tolerability, for example. My preference required specific instructions to my manuscript editor at THE JOURNAL (R.J. Fiala, MA, oral communication, March 2005).

Finally, it is the responsibility of biomedical researchers to discover and report treatment differences among pharmaceutical agents, as I did. Drs Shah and Krueger took exception to what they perceived as an implied recommendation of rivastigmine tartrate in my statement about a positive difference in overall ADAS-Cog [the Alzheimer's Disease Assessment Scale - Cognitive Subscale] scores between that agent and placebo. However, my statement accurately reflected the data available at the time of publication[1,2] and in no way indicates (or implies) that this difference should be the basis for recommending rivastigmine tartrate over donepezil hydrochloride or galantamine hydrobromide.

Drs Shah and Krueger accurately report that head-to-head studies for acetylcholinesterase inhibitors were lacking at the time of publication. These data are now available, however. As anticipated, each acetylcholinesterase inhibitor was efficacious. Subsequent researchers have joined me in stating that physicians cannot easily predict which treatment option would be best for any given patient.

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Correction

The *JAOA* regrets an error in terminology that appeared in the following letter to the editor:

> Reeves R. AOA certifying boards are credible and capable [letter]. *J Am Osteopath Assoc*. August 2006;106(8):441. Available at: http://www.jaoa.org/cgi/content/full/106/8/441. Accessed October 20, 2006.

In the following sentence, *Accreditation Council for Graduate Medical Education (ACGME)* should have been *American Board of Medical Specialties (ABMS):*

> Regarding the validity of American Osteopathic Association (AOA) board certification, Dr Mychaskiw concludes that the opinion held by some MDs that AOA certifying boards are "'easier' and less credible" than Accreditation Council for Graduate Medical Education (ACGME) boards may be accurate.

The sentence should have read shown below:

> Regarding the validity of American Osteopathic Association (AOA) board certification, Dr Mychaskiw concludes that the opinion held by some MDs that AOA certifying boards are "'easier' and less credible" than **American Board of Medical Specialties (ABMS)** boards may be accurate.