Letters to the Editor

Hyperbaric oxygen therapy and neurological disease

To the Editor:

Re: Mychaskiw G. A, Message from the editor – HBO_2 and neurological disease: The time has come. Undersea and Hyperbaric Medicine 2010;37(2):xi-xiii [1]

We read this recent editorial with concern. While agreeing it is entirely appropriate that the UHMS actively support the investigation of HBO_2 therapy (HBO_2T) for novel applications, we cannot let the main implications of the editorial pass without remark.

The editorial begins with some pertinent issues about the philosophy and practice of research funding in the United States, which, for the clinical scientist, can be one of the most time-consuming and challenging aspects of modern academic medicine. Dr. Mychaskiw uses the example of autism to illustrate some of the difficulties, and we agree this spectrum of disorders is one in which valid animal models, diagnostic biomarkers or imaging techniques are unlikely to be developed in the foreseeable future. Basic science research into an intervention like HBO_2T is therefore difficult, and clinical studies are the logical option. However, research grants are rarely awarded for clinical studies without solid preclinical science. This "Catch-22" for HBO_2T is one of the reasons we agree the UHMS needs to actively participate in designing, funding and performing good clinical research aimed directly at important clinical questions.

Unfortunately, the editorial then strays into very controversial territory well outside the remit of a hyperbaric medicine journal. It asserts that the role of mercury in vaccines "continues to be debated," then makes the extraordinary suggestion that the volatile anesthetic agent sevoflurane "may be the thalidomide of the new millennium." Both claims require a response.

Vaccines have been subject to rigorous epidemiological examination over many years, and the suggestion that a meaningful scientific debate continues is a false dichotomy. The possible role of vaccines (particularly the combined MMR – measles, mumps, rubella) in the development of autism spectrum disorder (ASD) has been recently reviewed [2,3], including a Cochrane systematic review [4]. None support a causal link between the vaccine and ASD. The idea was popularized in 1998 by Wakefield in a publication that has now been retracted by the *Lancet* and most of the co-authors [5-7]. Subsequently, in the United Kingdom a Fitness to Practise Panel of the General Medical Council has recommended that Dr. Wakefield be removed from the medical register and concluded that he had "shown callous disregard," "abused his position of trust" and "acted in dishonest and misleading ways" during the conduct and reporting of this study (*http://www.gmc-uk.org/Wakefield_SPM_and_SANCTION.pdf_32595267.pdf*).

In a demonstration of the power of both the press and highly motivated lobby groups, the speculation about MMR and ASD quickly degenerated into a causal belief that pervades all the way to the editorial in question here. The result has been described as "a tragic, heart-breaking, and embarrassing public health tragedy" [2]. Predictably, outbreaks of these previously well-controlled diseases have resulted in injury, hospitalization and death [2]. One further consequence was to divert scarce research resources from other promising investigations into the treatment of ASD in order to refute the widely held but unsubstantiated claims.

Sadly, it appears we have learned little from this regrettable sequence of events. In the editorial in question, for instance, the specter of sevoflurane is raised as yet another medical factor associated with the development of ASD. Sevoflurane is the only non-pungent modern anesthetic vapor suitable for inhalational inductions, and it is not surprising that its use in children has grown steadily since its introduction. The editor observes that the incidence of both sevoflurane anesthesia and autism are growing, hence there may be a causal link. He cites two papers [8,9] in support of this assertion, but neither makes that claim. Singh reports post-operative myoclonic seizures in a 14-year-old male following sevoflurane administration [8]. That sevoflurane may on rare occasions be epileptogenic is not new, but that hardly establishes a causal relationship with ASD. Wilder *et al*. reported on a retrospective co-

hort of over 5,000 children under the age of four years in Minnesota. They reported more learning difficulties (LD) in those who had received multiple general anesthetics in the past (35% had LD by the age of 19 years versus 20% in those who did not receive multiple anesthetics) [9]. There are, of course, many potential confounders of this apparent relationship, and the authors concluded that "these data cannot reveal whether anesthesia itself may contribute to LD or whether the need for anesthesia is a marker for other unidentified factors that contribute to LD." The discussion makes it clear, however, that animal data support a common dose-dependent neurodegenerative effect across a wide range of anesthetic agents. This has yet to be demonstrated in humans ("it is not known whether exposure to anesthetics produces neuropathological or neurobehavioral sequelae in humans") [9]. Even if a clinically important pharmacological effect were to be shown, it is unlikely that sevoflurane is particularly problematic in this regard.

The editorial tells us that "we are trying to establish a database of centers in the U.S. utilizing hyperbaric oxygen as part of a treatment regimen for autism." We would be grateful to know who exactly is signified by "we"? Has the UHMS constructed such a database? Again, when it is said that "we" speculate that HBO_2T will prove to be efficacious in a range of (unspecified) neurologic indications, it is not clear whose views are being represented. Although we, too, have no data, it seems doubtful that such a view would be held by a majority of the members of this Society. The correct interpretation, in our view, is that as a Society we have insufficient evidence to speculate one way or the other. Indeed, for the few chronic neurological conditions that have been the subject of methodologically sound clinical investigation (*e.g.*, multiple sclerosis and cerebral palsy), there is little suggestion of clinical benefit. Although the work of Rossignol *et al*. on ASD [10] is of interest, we cannot interpret it as evidence of the benefit of HBO_2T, as neither arm of the study actually delivered this therapy. We refer interested readers to the UHMS position statement on autism on the website for details (*http://www.uhms.org/portals/0/pdf/Autism_POSITION_PAPER.pdf*).

In summary, the *UHM* journal seems to be expressing views in this editorial that are directly at odds with those of the Hyperbaric Oxygen Therapy Committee of the UHMS. Of course, to express such views is part of the free press, but in the pages of the UHMS journal, such views must be clearly identified by the owner. In our opinion, this editorial should not be taken to represent the views of the UHMS scientific community.

Finally, we do support to the call for high-quality scientific work in this area, and of the intent of this Society to promote and publish such work. We agree that it is a vital public health role as well as serving the direct interests of our patients to do so, and we look forward to reading the spring issue of 2011 with great anticipation.

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Hyperbaric oxygen therapy and neurological disease: *Response*

In Response:

I very much appreciate the thoughtful and well-presented commentary by Bennett, *et al.* regarding my recent editorial in *UHM* [1]. The editorial was intended to be controversial and generate discussion, such as elaborated by Dr. Bennett and colleagues, to further interest in and illustrate the need for publication of rigorous scientific work regarding investigational use of hyperbaric oxygen therapy (HBO_2T) for neurologic conditions. In that sense, it has succeeded. However, it is clear that some of the syntax used may have been misunderstood and deserves clarification, along with a few other points.

UHM is a peer-reviewed scientific journal and original articles are presented as such, without regard to the positions of the UHMS, or any other society, but solely on their scientific merit. Editorials contained within, including the one in question, are the opinions of the writer and, unless specifically indicated, are not to be construed as representing any official policy or position of the UHMS. Indeed, as stated quite correctly by Bennett *et al*., views in the editorial are at odds with the Hyperbaric Oxygen Therapy Committee of the UHMS. Unfortunately, my use of "we" was confusing, and it is understandable how this may have been incorrectly taken to mean that the editorial represented the UHMS. In this case, "we" refers to myself and my colleagues at the High Pressure Biology and Neurologic Disease Laboratory in our Department of Anesthesiology. I apologize to the members of the readership who may have been similarly confused.

My point in the editorial remains unchanged. There is a large body of "off-label" HBO_2T administered in the United States and around the world for various neurologic conditions, including autism, stroke, cerebral palsy and multiple sclerosis, to name but a few. In some cases, such as multiple sclerosis, the literature is convincing that hyperbaric oxygen has little, if any, therapeutic effect. In others, the literature is less clear. We do suspect that the volume of this "off-label" use is very high and constitutes the mainstay of business for many clinics. It is even possible that a majority or substantial minority of HBO_2T use is "off-label". Surprisingly, no comprehensive

database of HBO_2T use exists, especially regarding these "off-label" conditions. We believe it is important to properly quantify this in order to understand the public health implications of a widely used therapy that has not been properly validated in controlled scientific studies. Similarly, we believe that it is important to publish rigorous scientific work of high quality regarding these uses – hence the call for papers.

Autism was cited as an example of a condition with considerable emotional overlay complicating and clouding scientific judgment and a condition for which HBO_2T is widely used without firm basis in the literature. Bennett and colleagues illustrate well the issues involved in their response to my syntax regarding debate over the use of mercury in vaccines. We are in agreement that the issue appears scientifically settled, but not all debate is scientific. My use of that phraseology is not to imply agreement with a role of mercury-containing vaccines in the etiology of autism, but rather to illustrate that it remains an issue of "debate" (outside of scientific circles), regardless of evidence to the contrary. We agree that limiting use of vaccinations for these reasons is a public health tragedy.

Finally, sevoflurane was discussed, as it is a particular area of interest in our work examining the role of NMDA receptor antagonists and GABA agonists in neurodegenerative changes in the developing brain. Speculation regarding a possible etiologic role of sevoflurane in neurodegenerative disease, including autism, is another example of the challenges encountered in scientific study of complex neurologic disease in animals and humans. The literature is clear that all of these compounds, including volatile anesthetics, cause widespread neurodegeneration in the developing brain [2]. This has been conclusively demonstrated in rodent and primate models, and we are currently pursuing histopathologic studies in human samples. Clinically, sevoflurane is associated with seizures, perioperative delirium and other effects that may be construed as neurotoxic, or at least neuroexcitatory [2, 3]. There is no question as to whether sevoflurane causes neurodegeneration in the developing brain; it does. The only questions are whether this effect is greater than that seen with other volatile anesthetics, and what, if any, is the clinical consequence in humans. Another issue our laboratories are examining is whether HBO_2T has an ameliorative effect on these neurodegenerative changes. The correlation of the increase in use of sevoflurane with the increase in the incidence of autism is just that, a correlation. It is in no way evidence of a cause and effect, but it is also not exculpatory of cause and effect. History is replete with examples of pharmacotherapies believed safe that are later found to have unintended pathologic side effects. To coin an old phrase, absence of evidence is not evidence of absence. Lest we dismiss a potential clinically significant side effect of sevoflurane in humans, recall that alcohol is also an NMDA receptor antagonist, and fetal alcohol syndrome is a well-known condition. Long-term neurobehavioral change secondary to anesthetic exposure is an area of concern in pediatric anesthesia and is currently the subject of numerous investigations and FDA review [4].

Again, we are grateful to Dr. Bennett and his colleagues for their commentary and bringing some of these issues to light. The Hyperbaric Oxygen Therapy Committee of the UHMS is to be credited for its high standard of scientific evidence in considering what constitutes an approved indication for HBO_2T. We suspect that well-controlled studies of high rigor will demonstrate efficacy in certain neurologic conditions, and we also look forward to the special issue with great interest.

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Dr. Mychaskiw is a consultant to, has received research support and is a member of the speakers bureau of Baxter Healthcare, Inc. and GE Healthcare, Inc.