Letters to the editor

'Hyperbaric oxygen therapy and cerebral palsy'

SIR–As the senior clinicians involved in the largest randomized trial of hyperbaric oxygen (HBO) therapy for children with cerebral palsy (CP)[1,2] as well as in the McGill pilot study[3] we would like to comment on the Annotation by Dr Essex.[4]

It has been taught in medical schools for many years that perinatal brain injury is 'fixed' but if we really want to be honest, we have to recognize the limitations of our knowledge. There is more and more evidence that this assertion is no longer valid. We are learning new facts about human neurophysiopathology and cerebral plasticity as well as discovering unprecedented ways to treat what seemed to be permanent brain injury. We know more about stem cells and their potentially regenerating capabilities and studies are showing that HBO therapy seems to have very promising results in improving brain function in many neurological conditions.

Dr Essex refers to our multicentre trial[1] as being a placebo-controlled study. This is untrue. In fact both groups received a hyperbaric treatment as defined medically. This is the reason why the term placebo and controlled were not used in the paper published in the 'Lancet'. An exposure to compressed air at 1.3ATA will increase the PaO_2 by more than 50% which is a level universally used in treatment throughout the world. Dr Essex does not attempt to qualify the improvements that were measured in our study. It is important to state that everyone who was involved agreed that they were statistically and clinically very significant. Statistics never reveals the whole picture. During this study we have seen many tremendous functional improvements. At an age where we did not expect any dramatic changes, some children started to walk, to speak, or to sit for the first time in their lives. The motor changes that were seen and measured with the GMFM[5,6] were greater, more generalized, and were obtained in a shorter period of time than most of the improvements found in any other studies of recognized conventional therapies in the treatment of children with CP. The children in both groups improved an average of ten times more during the two months of HBO treatment (whilst all other therapies and medication were stopped) than during the three months follow-up (when medication and all the ancillary treatments were restarted). The improvements in gross motor function and in neuropsychological testing as well as with the standardized parent questionnaire (PEDI) were still maintained three months after the HBO treatment.

There are few experts in hyperbaric medicine who are experts in CP and vice-versa. It is then very easy to mislead almost anyone in the scientific community if someone falsely states that 1.3ATA with air is a placebo and if he does not present the improvements measured in our study as they really are, that is clinically and statistically impressive. Many could therefore be persuaded to believe that this study only demonstrated that there were some comparable changes in both groups and that they were certainly related to a placebo effect. It is far from reality.

So far all the studies using HBO therapy to treat children with CP have shown significant and often profound improvements. We do not know on what basis Dr Essex can state that the majority of evidence is based on poor quality trials, as some of the studies have been published in internationally recognized journals. Five recent pilot studies in McGill University,[3] the US Army,[7] the Cornell University, the University of Galveston, and one reported from Cuba[8] together with our randomized multicentre trial have all indicated that the majority of the 200 hundred children evaluated improved significantly. There was no important adverse effect reported from any of these studies. There is therefore not a single published or unpublished research study that has ever refuted these positive changes that we continue to observe and to measure in hundreds of neurologically impaired children.

Regarding the placebo effect, we would have needed a placebo group for it to be a factor! Among the numerous research projects conducted to evaluate the effects of various treatments for CP there is not a single one that has ever shown a placebo or participation effect. The consistently reproducible and long term effects found by HBO treatment research have never been documented using a placebo under any conditions, and certainly not with results superior to those obtained with the recognized therapies for a given condition. In a recent review article, Hrobjartsson and Gotzsche[9] concluded that there was little evidence that placebos in general had powerful clinical effects. They had no significant pooled effect on subjective or objective binary or continuous objective outcomes.

The three hypotheses submitted by Dr Essex to explain the success of the HBO treatment as measured in all the studies cannot withstand scientific scrutiny. He first refers to 'natural progress' to explain the important changes measured in most of the children. As already stated, these children improved ten times more rapidly during the course of the HBO treatment than with their normal regimen. This cannot be a natural evolution and the recent paper by Rosenbaum et al.[10] shows graphics that confirm that fact. Dr Essex then proposes the possibility of a subgroup of children improving more than would be expected over a course of the HBO treatments. However, in the multicentre trial as well as in most of the other studies, all the subtypes of CP were treated and the improvements had the same level of significance in every subgroup.

Dr Essex finally suggests that cognitive dissonance could play a part and that most parents would not admit, after spending a lot of money on HBO treatment that it had not worked. It is simply insulting to the parents and totally contrary to the data of our research which has shown tremendous consistency between the subjective assessments by the parents and the evaluation by the therapists. Dr Essex is also forgetting that the changes were not subjective, but were objectively measured by well trained professionals using internationally accepted and validated tools. It is also very surprising that Dr Essex does not even mention the two conclusions drawn by the authors of the study as summarized in the Lancet editorial:[11] 'The researchers postulate that either the two treatments were equally effective, or that the mere act of participating in a trial that promoted communication with other motivated children and parents had a positive effect'. Even if there is absolutely no evidence to support this participation effect hypothesis and despite the fact that there was no standardization or any measurements of these issues, the Government of Quebec (who funded the research) and some scientists chose to believe solely in this possible cause. In order to have a participation effect we would have had to

create a more stimulating environment than the usual therapy regimen, which was not the case. Many children were treated alone in monoplace chambers with similar results to those who were treated in multiplace chambers. Furthermore, even if we would have hypothetically developed such an environment, it has been reported to accelerate only intellectual, emotional, and social development[12] and would not explain the important motor improvements. This was the main observation and the principal objective of the trial. Most of the main researchers and clinicians involved in the study believed that the cause of these improvements was not clearly identified, in part because of the fact that there was no control group, and postulated that both treatments were possibly equally effective. This is a sound scientific hypothesis supported by more and more research and recent data. A recent study evaluating hyperbaric treatment with or without oxygen in the treatment of cerebral vascular accidents in rats[13] showed that 'hyperbaric oxygen and to some extent hyperbaric pressure reduced ischemic brain damage and behavioral dysfunction'. Recently, Heuser et al.[14] reported clinical improvements after only ten hyperbaric treatments at a pressure of 1.3ATA with 24% O_2 in patients presenting with chronic toxic encephalopathy. The benefits were also documented by positive changes on single photon computed tomography.

Finally, Dr Essex is more than alarmist in his paragraph on HBO treatment complications. He affirms that HBOT in CP is 'potentially very dangerous'. He forgets to say that most of the very rare reported hazards apply to diving and treatments given under much higher pressures (2 to 3 ATA, even up to 6 ATA for gas embolism) than those suggested for the treatment of CP (1.25 to 1.5 ATA). At this lower pressure, oxygen is therapeutic and the incidence of any complications from a change in pressure is very low, much less than most complications associated with so-called safe medications. Our studies were conducted under governmental and university supervision, after reviews by five ethics committees. They thoroughly analyzed all the potential risks for the children and no one felt that it was a potentially dangerous treatment! We were responsible, during the course of the studies, for more than 4500 pressurizations and are aware of more than 30 000 other HBO treatments given to the children with CP that we follow regularly. We did not see a single significant complication or permanent injury. Although in our pilot study thirteen out of twenty five children had grommets inserted in the ears, it was as a preventative measure that is no longer recommended, except in very rare cases.

HBO therapy in CP is a very promising and safe treatment. We certainly support Dr Essex's recommendation for ensuring security and for adequate supervision as well as his recognition of the need for further research. Considering that there are few effective treatments for children with CP we are convinced that research in HBO therapy for treatment of CP must be pursued in order to understand the underlying mechanisms behind all the impressive changes that have been observed in thousands of children, and to better define the indication and dosage of HBO treatment in this condition.

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'Essex replies'

SIR–The letter of Marois and Vanasse contrasts with the personal and professional vilification I have received via e-mail from supporters of hyperbaric oxygen (HBO). In the multicentre trial[1] cited by Marois and Vanasse, of which they were co-authors, children either received hyperbaric oxygen or '…slightly pressurised air…at…the lowest pressure at which pressure can be felt, thereby ensuring the maintenance of masking'. This latter group was the placebo group, albeit not a 'pure' placebo because of the nature of the active treatment. Surely this was the sham treatment, and I find it interesting that Marois and Vanasse claim this was an active treatment arm of the study. 'HBO did not improve the condition of children with cerebral palsy (CP) compared with slightly pressurised air' (p 582). Since both groups improved equally, perhaps therefore children with CP could be given slightly pressurised air rather than HBO therapy with its attendant risks (see below)?

A literature search showed a number of studies on HBO that were poor quality (non randomized; no control group; non blinded, etc) and/or were published in non peer