

*How many deaths will it take till they know? 1*

**Monkeys, madmen and the standard of evidence**

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*Those who act boldly are recognizing right, as well as reality.* – John F. Kennedy

In this issue, we bring you two important articles addressing the “holy grails” of investigational hyperbaric medicine: study design and the control group [2,3]. This is a crucial question, as good science requires properly equivocal, blinded control groups to validate experimental results. In clinical medicine, we think of the placebo effect as applying only to patients, but investigators are also subject to a placebo effect of interpreting data to fit a foregone conclusion. In the case of hyperbaric oxygen, the therapy many “love to hate,” scientific rigor is particularly important. There comes a point, however, when we lose sight of the forest for the trees and chase endless data while lives are lost. Weaver *et al.* discuss very elegantly the design of several clinical trials currently under way investigating the use of HBO<sub>2</sub>T in concussion and traumatic brain injury secondary to explosive blast [2]. Obviously, there are several ways to go about creating a control group for HBO<sub>2</sub>T studies. The most common way, as well illustrated by Weaver's other paper, is by exposing control subjects to pressures less than the pressure being studied and at lower FIO<sub>2</sub> (generally room air) [3]. As he concludes, even experienced divers cannot discern a difference between 1.2 and 1.5 atmospheres absolute (atm abs). Given this relatively small difference, Weaver's conclusions may not be that surprising, although it is conventional wisdom that pressure variation is most noticeable between 1 and 2 atm abs and, once beyond that, becomes much less so (personal communication, K Corson). It would have been interesting to see whether experienced personnel could differentiate between 2 atm abs (or greater) and 1.2 atm abs, and perhaps we will see such work in the future. Unfortunately, in the application of HBO<sub>2</sub>T in neurologic issues, where lower pressures appear to be efficacious, what appears as a control group to those accustomed to indications utilizing HBO<sub>2</sub>T at >2.0 atm abs, is actually a therapeutic group. This leads to confounding results and inappropriate abandonment of HBO<sub>2</sub>T as a potentially valid therapy.

The best example of this is the study of HBO2T in cerebral palsy by Collet *et al.* in 2001 that, for many, is incontrovertible evidence that HBO2T is ineffective for this condition [4]. This study, published in *The Lancet*, demonstrated that HBO2T (100% O<sub>2</sub> at 1.75 atm abs) was no more effective in parameters measured than control. The flaw, however, is that their control group was room air at 1.3 atm abs, which the authors describe as “slightly pressurized” [4]. Obviously the application of HBO2T in neurologic conditions is not an all-or none phenomenon, and it should not be surprising that Collet’s “control” group had therapeutic efficacy. Of course, the fact that both groups improved was relegated to the scientific equivalent of a shoulder shrug: “deserves further consideration” [4]. We find it disconcerting that such a flawed study is forever after held up as the “gold standard” in the proof of HBO2T’s lack of efficacy in cerebral palsy, despite other studies to the contrary [5]. The Navy-VCU study discussed by Weaver *et al.* [2] takes the question of the control group to a much more rigorous (and complicated) level. In this study, pressure is held constant and oxygen concentration is varied to deliver an equivalent of room air at 1 atm abs or 100% oxygen at either 1.5 or 2.0 atm abs. Clearly, this is far more involved than the simple variation in pressure and requires a very sophisticated facility with substantial personnel and material cost. Naturally, this study, in spite of, or rather because of, its design, will not address the question of an effect of pressure independent of inhaled oxygen concentration. Nevertheless, of all the ongoing studies regarding HBO2T and concussion, we await the results of the Navy-VCU study with the greatest anticipation as it appears to be the most rigorous. Weaver *et al.*’s article discussing the various DOD studies [2] is an excellent primer on HBO2T study design and should be required reading for investigators in the field. While we applaud good science, there comes a point, as mentioned earlier, of stagnation as the standard of evidence required for the blessing of organized medicine exceeds reality (where most of us live). The application of HBO2T in neurologic applications is scientifically cumbersome. As we have discussed, study design and control group strategy is a challenge. Outcome measures are not uniform, there is a lack of standardized testing, measurable gains may be small relative to subjective improvement and there are no validated serum biomarkers for either diagnosis or therapeutic evaluation. In an era of economic challenge, with NIH and other funding at historical low levels (as measured by percentage of grant proposals funded) and given the aforementioned complexity of HBO2T studies, it may be some time before true, incontrovertible efficacy data exists, if ever. There are many, however, including your editor, who feel that the burden of proof for the efficacy of HBO2T in neurologic applications has been met, and our intellectual paralysis is causing unnecessary morbidity and mortality for patients suffering from traumatic brain injury and concussion, among other conditions [6]. Of course, hyperbaric medicine does not have the market cornered on intellectual paralysis. This phenomenon is not even limited to medicine, but currently applies to most U.S. scientific and technological development. It is telling to compare medical and scientific innovation in the decade 1960-1970 to the decade 2000-2010. Considering the 1960s, space travel, open-heart surgery, organ transplantation and nuclear propulsion are just a few of the milestones of that remarkable decade. On the other hand, from 2000-2010, accomplishments of similar impact are sadly lacking. The human genome has been decoded and has resulted in precisely nothing. Although I am sure the biologists in the audience would argue against this generalization, it is undeniable that the great promises of gene therapy and individualized medicine have not been realized, to name just one of the disappointments of this lackluster decade. By contemporary measures, Dr. James D. Hardy was a madman. Founder of the Department of Surgery at the University of Mississippi School of Medicine, Dr. Hardy was the author of 23 books and 466 scientific papers. He trained multiple generations of surgeons

throughout the Southeast and was the developer of numerous surgical innovations, including the world's first human lung transplant in June of 1963. On January 23, 1964, Hardy performed the world's first heart transplant. In an era before organ donation and brain death, however, this was a cumbersome undertaking, as a donor needed to suffer cardiopulmonary death at the moment that the recipient was anesthetized and ready. Predictably, this did not occur on that January evening, as the recipient was rapidly deteriorating and the donor stabilized and did not die. As the world knows, Hardy then obtained a heart from a chimpanzee named "Bino" at the Jackson Zoo. Unfortunately, following the transplant, the patient survived only for 90 minutes, expiring from metabolic derangement and an undersized donor heart [7]. The die had been cast, however, and Hardy thus demonstrated that cardiac transplantation was possible, laying the groundwork for Dr. Christiaan Barnard to perform the first successful human heart transplant in South Africa in 1967. Would Dr. Hardy have been able to do this work in 2012? Where are the James Hardys today? Are they still waiting for just the right prospective randomized double-blind study?

In the U.S. criminal justice system, a verdict of guilt requires proof beyond a reasonable doubt, whereas in the civil justice system a preponderance of the evidence is required. We believe that, in the case of HBO2T and concussion, a preponderance of the evidence has been met, and we hope that the DOD studies will provide the proof beyond a reasonable doubt. We have the technology, we have the education and training, we have the evidence: We just need the will to use it. *Mike Webster, Terry Long, Andre Waters, Justin Strzelczyk, Tom McHale, Lou Creekmur, John Grimsley, Chris Henry, Cookie Gilchrist, Wally Hilgenberg, Owen Thomas, Mike Borich, John Mackey, Bob Probert, Reg Flemming, Rick Martin, Derek Boogaard, Rick Rypien, Wade Belak, Andrew "Test" Martin, Chris Benoit, Dave Duerson, Junior Seau.*

How many deaths will it take [1]?

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*Orlando, Florida, June 2012*

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