Chapter 5. Future Research

1. Outcome Studies

We identified several barriers to conducting controlled clinical trials of HBOT for brain injury and particularly cerebral palsy. Strategies can be developed to conduct good-quality studies to overcome each of these barriers.

Lack of agreement on the dosage of HBOT and the duration of treatment is an important barrier to conducting good-quality clinical studies. Oxygen, the "active ingredient" in HBOT, is fundamentally a drug. For new drug therapies seeking approval by the Food and Drug Administration, the dosage and duration of treatment must be determined in carefully designed dose-ranging studies before definitive studies demonstrating clinical efficacy can be started.

Good-quality dose-ranging studies of HBOT for brain injury can be done, based on the model used by pharmaceutical manufacturers and the FDA. It is likely that the dosage of HBOT needs to be individualized based on the patient's age, clinical condition, and other factors. This is the case for many other drugs and does not pose an insurmountable barrier to designing dose-finding trials. In fact, the need to individualize therapy makes it essential to base the design of long-term studies of clinical outcomes on the results of dose-ranging studies.

Lack of independent, reliable data on the frequency and severity of adverse events. Uncertainty about the frequency and severity of serious adverse events underlies much of the controversy about HBOT. The case against HBOT is based on the reasoning that, *because HBOT may be harmful, it must be held to the highest standard of proof.* A corollary is that, if HBOT can be shown to be as safe as its supporters believe it to be, the standard of proof of its efficacy can be lowered.

This reasoning is consistent with the views of most clinicians and with the theoretical underpinnings of rational decision-making (i.e., utility theory). Consider a treatment that has been proven to be harmless and without cost. If there is a 1 percent chance that the treatment works, a rational decisionmaker would try it—there is a potential gain and no potential loss. On the other hand, if there are proven harms, and their severity and frequency are well described, the probability that the treatment works would have to be higher before most people would try it.

A strategy for identifying common adverse events associated with the use of HBOT in each clinical area (brain injury, cerebral palsy, and stroke) should be developed, with the goal of identifying the general level of risk involved. Important potential adverse effects of a drug may not be known or suspected before a study is conducted. For this reason, good-quality studies of adverse effects must be planned to assess harms that may not be known or even suspected. The most common strategy is to use a standard template of several dozen potential adverse effects affecting each organ system. Other characteristics of a good study of adverse events include a clear description of patient selection factors, independent assessment of events by a neutral observer, and the use of measures for the severity (rather than just the occurrence) of each event.

Relevant outcome measures. Some of the most important outcomes of treatment are difficult to measure. Previous trials have relied primarily on standardized measures of motor and neuro-cognitive dysfunction. These measures do not seem to capture the impact of the changes that parents perceive. An apparently "small" improvement can have a big impact on caregivers.

Caregivers' perceptions should be given more weight in evaluating the significance of objective improvements in a patient's function. Unfortunately, studies have not consistently measured caregiver burden, or have assessed it only by self-report. Studies in which the

caregivers' burden was directly observed would provide much stronger evidence than is currently available about treatment outcome.

Patients' unwillingness to be assigned to a placebo or sham treatment group is another barrier to conducting controlled trials. One funded trial of HBOT that incorporated a true placebo group had to be cancelled because patients were unwilling to undergo sham HBOT treatments for several months.

Whether placebo-controlled trials are necessary to evaluate HBOT has received a great deal of attention in discussions about HBOT. Participants on all sides of this debate make the assumption that an "evidence-based" approach implies devotion to double-blind, placebo-controlled trials without regard to practical or ethical considerations. This assumption is false. Double-blind, placebo-controlled trials are the "gold standard" for government regulators overseeing the approval of new pharmaceuticals, but not for clinical decision-making or insurance coverage decisions. Evidence-based clinical decisions rely more heavily on comparisons of one treatment to other potentially effective therapies, not to placebos.

Several alternatives to the double-blind, placebo-controlled trial can be used to examine effectiveness. One approach is to compare immediate to delayed treatment with HBOT, as was done in the Cornell trial. Another is to design a trial in which patients are randomly assigned to several alternative HBOT regimens. Because of uncertainty about the dosage and duration of treatment, such a trial would be preferable to a trial that offered a choice between one particular regimen and no treatment at all. It is also easier to incorporate a sham therapy arm in such a trial: patients may be more willing to enter a trial if they have a 10% or 20% chance of being assigned to sham treatment instead of a 50% chance. Other alternatives to a placebo include conventional physical, occupational, and recreational therapy, or another alternative therapy, such as patterning.

The Collet trial of HBOT for cerebral palsy[119, 120] has important implications for the design of future research. In that trial there was a clinically significant benefit in the control group. Debate about the trial centers largely on how the response in the control group should be interpreted. The trial investigators believe that the beneficial effect was the result of the psychological effect of participating in the trial and extra attention paid the children in and out of the hyperbaric chamber. Alternatively, the slightly pressurized air (that is, "mild" hyperbaric oxygen) may have caused the improvement. A third possibility is that the slightly increased oxygen concentration, not the pressure per se, was responsible for the benefit.

A trial that could sort out which of these explanations was true would have a major impact on clinical practice. Such a trial might compare (1) room air under slightly elevated pressure, delivered in a hyperbaric chamber, to (2) elevated oxygen concentration alone, delivered in a hyperbaric chamber, and to (3) an equal amount of time in a hyperbaric chamber, with room air at atmospheric pressure. From the perspective of a neutral observer, the third group is not a "sham" but rather an attempt to isolate the effect of the social and psychological intervention cited by the investigators.

In addition to improved design, future trials of HBOT need better reporting. This would aid the interpretation and application of research results. Two types of information are essential: a clear description of the research design, particularly of the control and comparison groups, and a detailed description of the patient sample.

2. Studies of Diagnostic Tests and Intermediate Outcome Measures

An independent, critical assessment of the body of animal experiments and human case studies supporting the "idling neuron" theory of brain injury and recovery should been done. A large body of studies supports the theory underlying the use of HBOT, but the interpretation of these studies is also disputed. Most of these studies use experimental animal models of brain injury and are designed to support the hypothesis that HBOT redirects blood flow to, and promotes recovery and growth of, "idling neurons" at the border of the damaged brain tissue.

There is sharp disagreement in the medical literature over the validity of these experimental models. One major issue is the significance of improvements in patterns of cerebral blood flow. The principle that redirecting flow toward ischemic areas can help damaged tissue recover is well established in cardiology. However, in critical care generally, drugs and maneuvers that redirect flow to ischemic organs (e.g., brain and kidney) do not always improve recovery at the cellular level. For this reason, improved blood flow must be linked to other measures of cellular and organ recovery.

HBOT for brain injury is not likely to gain acceptance in routine clinical use until a clinical method of assessing its effectiveness in the individual patient is validated. Specifically, the diagnostic value of SPECT scans and of other intermediate indicators of the effects of HBOT should be examined in good-quality studies. Like all other diagnostic tests, SPECT scans have a measurable false positive and false negative rate in relation to clinical outcomes. Controlled trials are not needed as the ideal study design to measure the accuracy of a diagnostic test. Rather, a longitudinal cohort study in which all patients undergo scans as well as standardized followup tests would be a feasible and ideal approach.