Hyperbaric Medicine's Historial Evolution & Chamber Types

Dick Clarke, CHT

1 History of Hyperbaric Therapy

Dick Clarke

CHAPTER OUTLINE

One of the earliest medical technologies still in use today, the history of hyperbaric medicine extends back almost 350 years. The first recorded attempt to use alterations in atmospheric pressure for therapeutic purposes is attributed to Henshaw, an English physician and clergyman, in 1662.[1] Apparently inspired by the salutary effects some investigators associated with changes in climate, and presumably secondary to differences in barometric pressure, Henshaw sought to artificially control climate. His "domicilium" was nothing more than a sealed room. Attached to it was a pair of large organ bellows. By manipulation of a series of valves and operation of the bellows, the atmosphere within the room could be "condensed" (compressed) or "rarified" (decompressed).

These changes were designed to simulate the effects of climate change experienced as one traveled to higher altitudes (the mountains) or lower altitudes (the coast). Henshaw chose the condensed atmosphere to treat certain acute conditions and the rarified atmosphere for several chronic diseases. There was even an opportunity for the unafflicted. Henshaw suggested,[1] "In times of good health this domicilium is proposed as a good expedient to help digestion, to promote insensible respiration, to facilitate breathing and expectoration, and consequently, of excellent use for the prevention of most affections at the lungs" (p. 10).

It is unlikely that patients experienced anything more than a temporary sense of improvement at best. The degree to which any alteration in the domicilium's pressure could be achieved certainly would have been modest, given the limitations of hand-operated bellows and the integrity of the room. This was probably fortuitous. Too low a pressure could have produced clinically significant hypoxia, or worse. Exposure to too high a pressure could have placed patients at risk for decompression sickness, a complication of compressed air exposure not to be identified for another 200 years. It was also unlikely that the domicilium's

atmosphere was renewed during its occupancy. Consequently, Henshaw's "encouraging" reports of changes in respiration and insensible perspiration were possibly the result of an accumulation of metabolic waste products.

That Henshaw's domicilium produced any meaningful benefits is highly improbable, for it was almost 200 years before any further interest in hyperbaric therapy was recorded. Perhaps the most notable aspect of his work was that it preceded the discovery of oxygen by more than 100 years.

Oxygen was first discovered by Carl Wilhelm Scheele, a Swedish chemist, in 1772. However, he did not publish his observations until 1777.[2] In the meantime, Joseph Priestly, an English chemist, independently discovered oxygen in 1775 and published his findings that same year, 2 years before Scheele.[3] As a result, Priestly is commonly credited with the discovery of oxygen.

There were no other reports of attempts to improve illness or disease with simulated climate change until the 19th century, despite efforts to promote its scientific scrutiny. In 1782, the Royal Society of Sciences, in Haarlem, The Netherlands, introduced a prize for the design of an apparatus that would enable study of the effects of high pressures on animal and vegetable life.[4] There were no applicants, despite the prize being offered again on three other occasions through 1791.

COMPRESSED AIR BATHS

Emile Tabarie, a physician practicing in Montpellier, France, is credited with rekindling interest in hyperbaric medicine.[5] In 1832, he presented to the French Academy of Scientists a detailed description of the workings of a pneumatic laboratory. That same year he undertook a series of studies that investigated the effects of lowered air pressures, both locally and systemically.[5] By generating a reversal of this environment through an increase in ambient pressure, Tabarie hypothesized that healthful conditions would be further improved on and certain diseases might be successfully overcome. He suggested that the "indispensable nature" of atmospheric air would, by its modification, "represent an inexhaustible source of beneficial influence on man."[6] Tabarie claimed to have successfully treated 49 cases of mostly respiratory diseases.[6]

One final comment on Tabarie relates to the procedure he adopted to optimize hyperbaric comfort and safety. He advocated increasing air pressure gradually, maintaining it steadily at a predetermined maximum pressure, often in the order of two fifths of an additional atmosphere, then slowly lowering it. The entire process took approximately 2 hours and was somewhat similar to modern therapeutic dosing schedules, the exception being higher pressures in use today.

Junod, another French physician, is credited with the introduction of the first purpose-built hyperbaric chamber.[7] The chamber was commissioned in 1834, and it was based on a design by James Watt, of steam engine fame. The chamber was spherical, built of copper, and capable of compression to 4.0 atmospheres absolute (ATA). Junod exposed his patients to higher pressures and faster rates of compression and decompression than Tabarie. This apparently caused consistent difficulties sufficient to lead some to state that hyperbaric devices did not belong in the practice of medicine.[1]

Junod believed that a patient's perfusion was enhanced while in his chamber. That patients would report a greater sense of well-being during their occupancy he believed to be proof positive. A more modern analysis might conclude that the narcotic property of nitrogen in air at pressures of 4.0 ATA (reported 100 years later by another Frenchman, Jacques Cousteau, which he termed *rapture of the deep*) was the likely cause of what was certainly only a temporary sense of any such well-being.

The largest chamber complex of this period was built in 1837 by Pravaz and installed in the French city of Lyon.[8] It could accommodate 12 patients. Pravaz named this therapy *"le bain d'air comprime."* He was of the opinion that these "compressed air baths" served to dilate the bronchi, thereby proving beneficial in a wide range of pulmonary and related conditions, including tuberculosis.[9]

By the 1850s, great interest in compressed air therapy was apparent throughout much of

Western Europe. In 1855, Bertin constructed his own hyperbaric chamber and wrote the first textbook describing this medical technology.[10] His facility attracted patients from as far away as North America. In 1875, Forlanini, recognized as the pioneer of artificial pneumothorax in the treatment of tuberculosis, described his "pneumatic institute," which he had installed in Milan, Italy.[11]

As quickly as new diseases and illnesses were discovered, it seemed as if hyperbaric proponents suggested that the chamber represented its treatment or cure. Perhaps not surprisingly, a wave of enthusiasm spread rapidly, and chambers soon became operational in Scandinavia, England, Germany, The Netherlands, Belgium, and Austria.[12]

In 1879, Fontaine introduced a mobile hyperbaric operating room; it was capable of accommodating up to 12 people.[13] He suggested that this would allow surgery to extend from hospitals to sanatoriums, and even into private homes. A prominent surgeon of the day, Pean, used the chamber to perform some 27 different types of surgeries over a 3-month period. All surgeries were considered successful, and it was reported that his hyperbaric patients recovered more quickly from the crude anesthesia of the day, experienced little vomiting, and had no cyanosis. These observations led to the planning of a large hyperbaric surgical amphitheater, one that would hold up to 300 people. It was never completed. Sadly, Fontaine became the first known hyperbaric practitioner fatality after a construction accident while his hyperbaric amphitheater was under construction.

A series of seemingly unrelated events paralleled the introduction of "compressed air baths." These events were soon to converge and would eventually provide hyperbaric medicine with a firm mechanistic basis and its first clear treatment indication.

COMPRESSED AIR CAISSON TECHNOLOGY

During the late 18th century, major changes in European and North American economy and society took place. This period was subsequently termed the Industrial Revolution. These changes resulted from technologic advances in the use of iron and steel, the invention of new machines that would increase production and efficiency, and the introduction of the factory system. Coal replaced wood as the primary energy source.

As these changes became widely adopted, the search for new sources of coal took on the frenetic pace that characterizes today's search for oil and gas deposits. In northern France, sizable deposits of coal were discovered beneath the Loire River and below quicksand. Efforts to mine these deposits were hampered by the surrounding water table, which readily flooded mine shafts that penetrated the ground. Jean Triger, a French paleontologist and mining engineer, introduced a technology that was to overcome the flooding problem.[14] Triger's technique was based on an idea that Sir Thomas Cochrane patented in 1830, which detailed the use of compressed air in tunneling through water-bearing strata.[15]

Triger's design involved the connecting together of a series of 5-foot diameter circular steel rings to form a hollow shaft (Fig. 1.1). This shaft (or *caisson,* French meaning "box") was lowered through mud and quicksand, with additional rings added until the shaft came to rest on coal deposits beneath. The combined weight of the steel rings served to force the shaft down, as loose earth and sand was excavated away. The shaft was sealed with an "air lock." Connected to the shaft and air lock was an air compressor. Compressed air would be introduced until the pressure within the shaft reached the pressure at the bottom of the shaft, expelling whatever water and moist sand was present.

The purpose of the air lock was to allow men to enter and exit the shaft without its loss of pressure and resultant flooding. Once men were inside the air lock and its outer hatch sealed, compressed air would be introduced into the lock until its pressure equaled that of the previously pressurized mine shaft. The inner hatch of the air lock would then be opened and access to the shaft afforded. Excavated materials and coal were transferred out by reversing this sequence of hatch operation. In this manner, "dry" coal mining

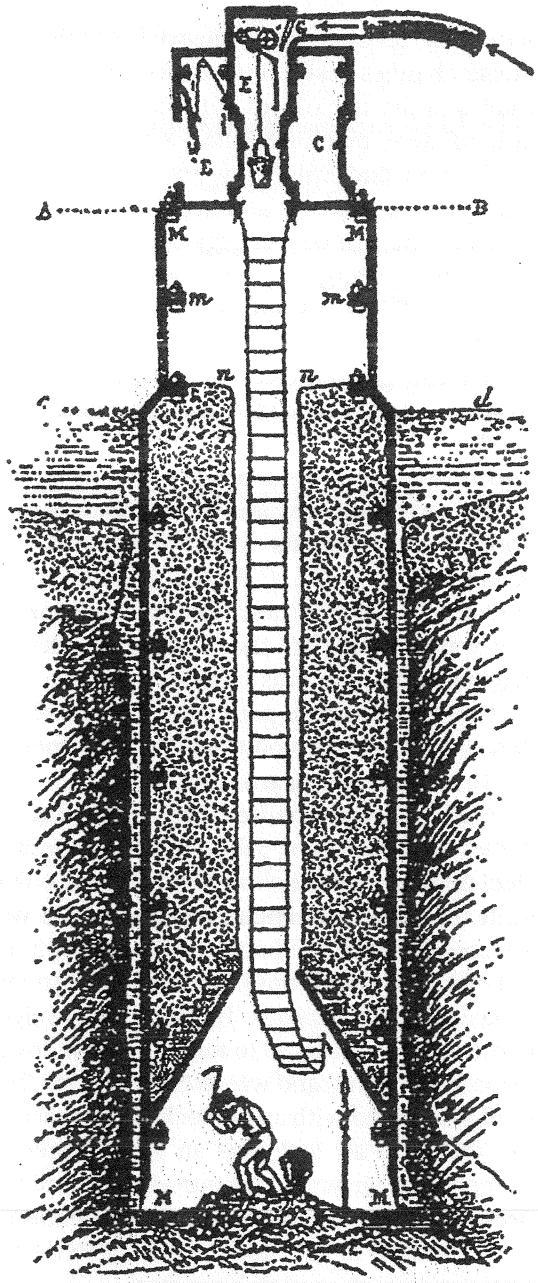

Figure 1.1 One of the first caissons used in France. *(Reprinted with permission of the Undersea and Hyperbaric Medical Society.)*

became possible, and it opened up access to the greater sources of coal needed to fuel the expanding Industrial Revolution.

Ultimately, some of these caissons were pressurized to as high as 4.25 ATA (107 feet of sea water equivalent). With a typical 4-hour work period, these caisson exposures placed the occupants at great risk for decompression sickness.[16] At the time of Triger's pioneering efforts, however, the fact that caisson exposures might result in decompression sickness was not appreciated. After his own exposure on one particular occasion, Triger noted the next day, "[K]nee pains appeared in the left side, and we felt a rather severe painful discomfort for several days afterwards." He went on to note, "After we were quite free of these pains, we were anxious to try the experiment again. At the same hour, this is, 20 hours after our exit from compressed air, we felt in the right side pains just like the former ones, which kept us numb for four or five days."[17]

Today, we recognize these complaints as common clinical manifestations of decompression sickness, a condition unknown to Triger. Similar complaints in compressed-air workers received little sympathy and were frequently considered to have coincided with some nightly excesses by the workers between their caisson shifts![18] Triger was fortunate that his injuries were reversible and not any more severe. However, worse results were soon to follow.

Some 64 workers were eventually employed in the caissons operating in Douchy, northern France. Several of them subsequently complained of similar symptoms to those of Triger; one suffered complete paralysis of his arms and legs, lasting 12 hours, and two died. This newly introduced and valuable engineering technology was clearly outpacing medical science, and with fatal consequences.

By now, a relation between exposure to compressed air and these complaints was being suggested. At the request of Triger, two physicians, Pol and Watelle, went to the Douchy mines to study this phenomenon. Pol and Watelle would subsequently describe the medical problems encountered in these mines. They noted, among other things, "The danger does not lie in going into the compressed air. It is not a disadvantage to stop there a longer or shorter time." Their findings, published in 1854,[19] represented the earliest observations of decompression sickness in humans. Although they missed the significance of increasing exposure times, Pol and Watelle did acknowledge the veracity of

the miners who observed that they "pay only when leaving the caisson."

Based on autopsy observations, Pol and Watelle considered the underlying problem as one of "superoxygenation and congestion."[19] They further noted that decompression was necessary to produce symptoms and recompression reduced symptom severity. This latter observation appeared to be based on statements by injured miners to the effect that their symptoms would improve on returning to the pressurized mine shaft for their next shift.

It was another 15 years before anyone drew attention to a similar presentation to those seen in compressed-air workers and those occurring in divers, who likewise breathed compression air.[20] Paul Bert, the dominant figure of this period, was the first to piece things together. Bert, another Frenchman, is considered by many to be the "father of pressure physiology," yet his early career left no clues as to his ultimate legacy. He was first an engineer, then a law student, before becoming one of Claude Bernard's (the celebrated 19th century physician and scientist) most brilliant pupils. On graduation as a doctor of medicine and a doctor of science, Bert was appointed to successive physiology positions at Bordeaux and the Sorbonne. His scientific activity was diverse, but his main achievements concerned the biological effects of barometric pressure. His classic work, *La Pression Barometrique,*[21] represented an enormously comprehensive investigation of the physiological effects of air under both increased and decreased atmospheric pressures. Applying Dalton's and Henry's gas laws,[16] Bert recognized that too rapid a decompression from the air pressures encountered in these caissons induced a pathophysiologic insult secondary to excess tissue nitrogen tensions.

Some 79% of atmospheric air is composed of nitrogen, which is largely inert. As environmental pressures are raised, increased amounts of nitrogen (and other gases present in air) are delivered to the lung (Dalton's Law). These gases are transferred to the blood and on to the tissues in their soluble state (Henry's Law). Here, nitrogen, being largely inert, accumulates as a function of pressure and time. On return to normal atmospheric pressure (decompression), this accumulated nitrogen begins its return journey, along the same pathway, and still in its soluble state. If the rate of decompression becomes too great, tissues of the body and blood become supersaturated with nitrogen. Nitrogen may then evolve from its soluble form to a gaseous form, in a manner similar to the release of carbon dioxide when one opens a carbonated beverage container. Resulting bubbles may traumatize critical tissues, obstruct vascular flow, or coalesce. Resulting signs and symptoms will vary as a function of the amount of gas involved and its anatomic location. The extent of the injury will range from joint discomfort to death.

Bert noted, "All symptoms, from the slightest to those that bring on sudden death, are the consequences of the liberation of bubbles of nitrogen in the blood, and even in the tissues, when compression has lasted long enough." He added, "The great protection is slowness of decompression. ..."[21] He was of the opinion that slowing the rate of decompression would reduce the likelihood of this injury pattern, yet provided no guidance as to how best to do this. Specific measures would be introduced in the coming decades.

Bert's second significant contribution to the practice of hyperbaric medicine was his identification of the toxicity of oxygen on the central nervous system when applied at pressures in excess of approximately 1.75 ATA.[21] A range of premonitory signs and symptoms now identify such toxicity. Unless the partial pressure of oxygen is quickly reduced, a grand mal seizure may result. This complication of hyperbaric oxygenation is frequently referred to as the "Paul Bert effect." Central nervous system oxygen toxicity would not become clinically important for several decades, when sufficiently high partial pressures of oxygen were used clinically.

The compressed air caisson concept was quickly grasped by civil engineers as a tool that would allow them to undertake projects not otherwise possible. Bridges could now be designed to cross large bodies of water, with submerged caissons providing support for columns

that held up the bridge spans. Underground mass transit systems would now be built within water table areas.

Unfortunately, news of the caisson concept traveled more quickly than news of the complications resulting from inadequate decompression from compressed-air environments. Paul Bert's suggestion that slowed decompression was of value in reducing the incidence of decompression injury was not published for several years, and then frequently not accepted or fully embraced. Not surprisingly, significant morbidity and mortality would plague subsequent compressed-air–based construction projects.

The building of the world's first steel arch bridge span, constructed in St. Louis, Missouri, and crossing the Mississippi River, was a case in point.[22] Construction on the bridge began in 1869. The caisson used for construction had its walls and roof reinforced; however, there was no floor. Once the caisson had been maneuvered into place, weight was added to its roof until it sank. Compressed air was introduced into each caisson to displace the water; then workers entered through an air lock to dig away the loose material beneath. The caisson's weight continued to force it down until bedrock was reached. Once this occurred, the caisson was filled with concrete, which then formed the foundation for each bridge support column (Fig. 1.2). Manned exposures within the bridge support caissons reached 4.45 ATA (the equivalent of 114 feet of sea water.[23]

With exposure times of several hours, resultant nitrogen loading was frequently physiologically intolerable at the higher pressures. Of the 352 workers so exposed, 5% died and another 10% suffered serious forms of decompression sickness. Because construction had commenced before the publication of *La Pression Barometrique,* one might appreciate why morbidity and mortality would be as high as it was. There was simply no local knowledge of an association between decompression from compressed-air exposure and decompression sickness. Further complicating the issue was that this project involved significantly higher pressures (greater nitrogen loading) than its European counterparts. The bridge's designer, and head of its construction, James Eads, for whom the bridge was named, asked his physician friend to investigate these caisson-related mishaps. Dr. Alphonse Jaminet

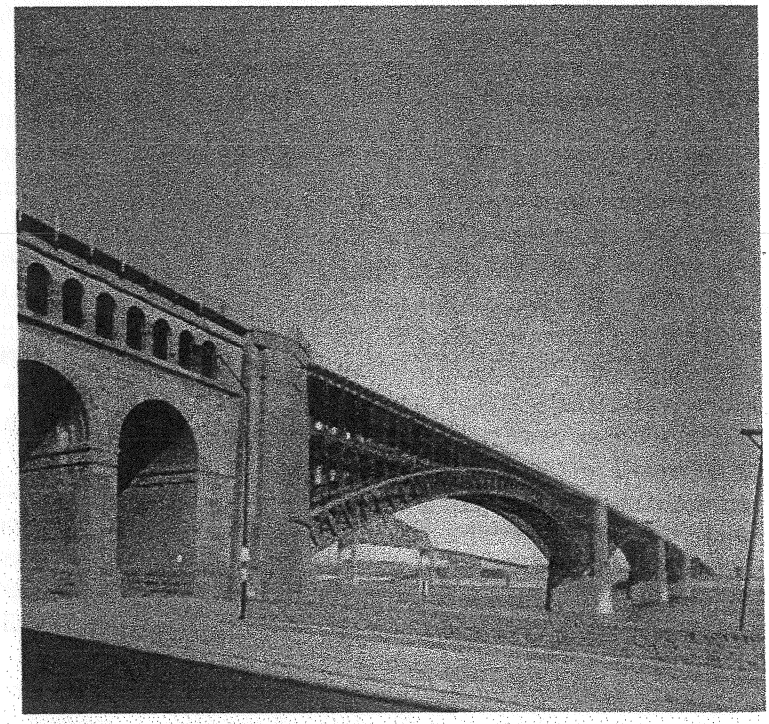

Figure 1.2 The Eads Bridge, the first bridge to span a body of water using caisson technology. *(Courtesy Paul Piaget, Photographer, 1968. Historic American Buildings Survey, HABS No. MO-1190.)*

subsequently made many descents into the Eads Bridge caissons.[23] On one such occasion he spent in excess of 2 hours at a pressure greater than 4.0 ATA. Subsequent decompression took only 4 minutes, which by today's standards would be quite rapid. On exiting the caisson's air lock, Jaminet became paralyzed and aphasic, implying decompression sickness involving the brain and spinal cord.[24] He was fortunate to eventually recover much of his premorbid function.

The second caisson project of note, from a decompression injury perspective, was in the building of the Brooklyn Bridge, which spans the East River.[25] Work began in 1870 and lasted 13 years. As with the construction of the Eads Bridge, the Brooklyn Bridge caissons were much larger than their European counterparts and involved higher ambient air pressures. The Brooklyn Bridge project was supervised by Washington Roebling, who assumed this responsibility on the death of his father John Roebling, one of the bridge's principal designers. The younger Roebling was aware of the serious medical complications associated with the Eads Bridge. He decided, therefore, that an on-site physician was necessary, and engaged Dr. Andrew Smith. Although Smith's tenure lasted only 5 months, he was faced with 110 cases of decompression injury, which he termed *caisson disease.* Smith first published his clinical experiences in 1870.[26] Smith's observations provided early and valuable insight into the various presentations of decompression sickness. Roebling himself suffered permanent paralysis as a result of his visits to the caissons, and ultimately succumbed to sepsis secondary to pressure ulcers.

Of the two Brooklyn Bridge caissons, the one on the Manhattan side ended up considerably deeper, eventually reaching 35 pounds per square inch gauge (psig; 3.38 ATA). Bedrock was first encountered at 33 psig (3.24 ATA). Just 1.0 psig deeper two fatalities occurred, with both men dying soon after exiting the caisson. At 35 psig (3.38 ATA), a third man died. Roebling decided, therefore, to halt any further evacuation even though bedrock was not uniformly exposed across the base of the caisson. This turned out to be a reasonable compromise as both the bridge and Roebling's reputation remain intact today.

One lost opportunity was Smith's recommendation that a recompression chamber, fed by the caisson's air compressors, be made available. He was clearly of the opinion that improvement occurred in injured miners who returned to the pressurized caisson. Smith's position was that an on-site recompression chamber would allow treatment to be instituted immediately on presentation rather than the miner waiting for the next day's shift for possible and likely limited benefit while back in the caisson. Had Smith insisted on its availability, it is possible that one or more of the Brooklyn Bridge fatalities might have been avoided and many of the other serious injuries successfully treated. Had he gone one step further and argued that his chamber idea also be incorporated into the caisson itself, he would have better controlled decompression and been the first to actually prevent many cases of decompression sickness. He had, after all, observed that one clear cause was "the transition to normal atmospheric pressure, after prolonged sojourn in a highly condensed atmosphere."[27]

Controlled decompression via a medical lock built into the caisson first occurred several years after Smith's observations, and just a few miles away. New York's Hudson River tunnel was the first tunnel to be constructed using compressed-air technology.[28] In its latter stages, it was also the first caisson to incorporate a decompression chamber into the top of the caisson shaft. This project was likewise the scene of enormous decompression morbidity and mortality before the decompression chamber became operational. Work commenced in 1879, several years before the completion of the Brooklyn Bridge, and on the opposite side of Manhattan. In 1882, Moir[28] observed that "the men had been dying at a rate of one man per month, out of 45 or 50 men employed, a death rate of about 25% per annum" (p. 574). Work stopped this same year. It was not the result of any medical, legal, or employment issue. It was something more fundamental. The construction company had simply exhausted its funds.

Alternative financial support was acquired several years later, and work recommenced in 1889. At this point, a decompression chamber had been installed into the top of the caisson. It was used to carefully control the decompression rate from pressures now ranging from 30 to 35 psig (3.0–3.38 ATA). It was also used to treat cases of decompression sickness, by recompression. There were only two more deaths in the following 15 months,[29] and cures were affected in some cases of decompression sickness by using the chamber to recompress workers (the forerunner of the work-site recompression chamber). These cases of decompression sickness were successfully treated by using as its mechanistic basis the inverse relation of pressure and volume described by Boyle's Law.[16]

Between 1906 and 1908, construction of two more New York tunnels took place, both under the East River. Pressures reached 42 psig (3.86 ATA) and frequently involved twice-daily exposures. Despite the more gradual decompression process in use at this time, decompression sickness climbed in concert with the higher pressures and twice-daily exposures. Keays reported enormous morbidity and mortality, involving more than 3500 cases and 20 fatalities from some 500,000 manned caisson compressions.[30]

In the following two decades, decompression chambers became an integral part of caisson technology, and an increasing number of these chambers were constructed to function independent of the caisson. This would permit treatment of those who exited the caisson and became symptomatic without the need to return to it, thereby interfering with its routine operation. Although more gradual caisson decompression rates had by now become commonplace, the actual process was by no means uniform.

It was not until 1907 that some form of order was established. The British Admiralty, eager to capitalize on high-pressure environments for military diving, engaged J. Scott Haldane to investigate air decompression procedures. With colleagues Boycott and Damant, Haldane's work led to the first standardized set of decompression tables.[31,32]

From this point forward the navies of the world took a leading role in improving the safety of exposure to compressed-air environments and advancing depth and time exposures, to undertake a wide range of deep-sea diving operations. Civil engineers readily adopted navy decompression procedures and their variants. Testament to the effectiveness of Haldanian-based decompression tables was the subsequent and significant reduction in the incidence of decompression sickness. The construction of the Dartford Tunnel in southern England during the 1950s was characteristic of improved morbidity and mortality. The decompression sickness incidence rate was just 0.50% (689 cases in 122,000 compressions, of which only 35 were considered to be serious).[33]

HYPERBARIC MEDICINE

Several "firsts" are attributed to J. Leonard Corning, a New York neurologist. In the late 1880s, he was the first to introduce "compressed air baths" in the United States.[34] His 6-foot diameter hyperbaric chamber was the first to operate with an electrically powered air compressor, and he would eventually become more widely recognized as the first to use spinal anesthesia.

Corning's interest in hyperbaric medicine stemmed from his visits to the Hudson River Tunnel construction site. He observed numerous cases of paralytic decompression sickness, leading him to consider this condition as essentially an affliction of the spinal cord. Corning clearly saw promise in the ability of air recompression to resolve many of these cases, and he chose to use compressed-air therapy for a broader range of nondecompression-related brain and spinal cord illness and disease. This may have been based on his opinion that compressed-air workers exhibited "a striking exacerbation of mental and physical vigor."[34]

Corning's hyperbaric treatments would last from 1 to 2 hours, involving pressures of up to 3.0 ATA. Corning[34] certainly recognized the risk for decompression sickness and ensured "that fifteen to twenty minutes are consumed in the operation of reducing the pressure in

the chamber" (p. 229). Corning appeared to use the chamber more as a facilitator of various medicinal solutions in the treatment of nervous and mental conditions than as stand-alone compressed-air therapy. Although he appeared to believe that some additive or synergistic benefit existed, his hyperbaric practices failed to impress the medical establishment. Within several years, use of hyperbaric air chambers for conditions other than decompression sickness was largely discontinued; however, chamber use for nondecompression-related conditions would soon return.

In the waning months of World War I an influenza pandemic swept the world. It has been estimated that between 25 and 50 million people died. In the United States alone, more than 500,000 people died of influenza. Orval Cunningham, chairman of the Department of Anesthesiology at Kansas University Medical School who was recognized as an "excellent teacher and practitioner of anesthesiology and remarkably keen clinical observer" (p. 40),[35] noted that the pandemic's morbidity and mortality rates were greater in areas of high elevation than they were in coastal regions. This observation intrigued Cunningham. He considered the only significant variable to be a change in barometric pressure. To determine whether this was a clinically significant event, he borrowed a hyperbaric chamber from a local bridge construction company. Beginning in 1918, he treated moribund influenza patients in the chamber with seemingly encouraging results: "Patients whose lips bore the blue-black livid stamp of the kiss of death and were deeply unconscious, but if not too far beyond the brink, in a matter of minutes were brought back to normal color and to a return of consciousness."[35]

These findings stimulated Cunningham. He eventually acquired a larger chamber and continued to report encouraging improvements in these cases. Cunningham's "validation" of hyperbaric treatments as essential in influenza may have stemmed from one unfortunate and tragic event. His patients would occasionally spend many days to several weeks at a time under the chamber's elevated air pressures. One night a mechanical failure brought the air compressors to a standstill. The chamber's pressure decreased rapidly to normal atmospheric pressure. All its occupants died. Cunningham was now convinced that hyperbaric air alone had kept these patients alive, and they had died because they could not be supported on leaving it.[35] A modern analysis would deduce that death resulted from the overwhelming effects of decompression sickness secondary to high nitrogen tensions, as well as possible cases of pulmonary barotrauma of ascent.

As the pandemic ebbed and pulmonary cases decreased, Cunningham sought out other conditions to treat with hyperbaric air. It was unlikely that he was initially motivated by profit. As an anesthesiologist, he had rarely billed his patients, preferring to accept whatever was offered. He seemed to be of the opinion that inhalation of compressed air offered a meaningful therapeutic option.

Cunningham went on to treat arthritis, glaucoma, pernicious anemia, diabetes, syphilis, and certain cancers. His rationale was that arthritis was likewise influenced by alterations in barometric pressure and anaerobic bacteria were at the center of these other conditions.[35] Cunningham may have based his assumptions, in part, on Bert's observations that oxygen content varied throughout the body, and that lower oxygen tensions were evident in bone and connective tissue.[21]

One grateful patient, a close friend of a wealthy industrialist, who was "cured" by Cunningham, provided Cunningham the financial means to make his hyperbaric treatments more widely available. The result was the construction of the first in a planned series of huge chambers to be located across the country. The Timken-Cunningham Ball stood five stories high and 64 feet in diameter. Each floor had 12 bedrooms and the amenities of a good hotel.[36]

Cunningham's activities generated a great deal of interest within the lay community and an equal amount of concern within the medical establishment.[35,36] Cunningham did nothing to assuage his critiques by submitting clinical data requested of him for peer review. His only report related to hyperbaric medicine was published in 1927.[37] In this report, he argued the basis for his treatment approach

but provided no supportive data and only a passing "outcomes" comment that "we have had encouraging results with five of twenty-seven cases of hopeless carcinoma."[37]

Cunningham was further challenged to produce more substantive data by the American Medical Association's Bureau of Investigation. Efforts by the American Medical Association continued without success, leading them to eventually censor Cunningham in 1928.[38] Cunningham subsequently closed his hyperbaric practice, and finally retired in 1935. Two subsequent owners attempted to keep this hyperbaric facility viable, but it was eventually abandoned in 1936. The chamber was subsequently used as a conventional hospital before closing permanently in 1940. Two years later, it was scrapped. This essentially marked the end of the compressed-air era of hyperbaric medicine for therapeutic purposes other than the treatment of decompression sickness.

EARLY HYPERBARIC OXYGEN THERAPY

The first practice of hyperbaric *oxygen* therapy is attributed to a South American whose contributions remain largely overlooked today. Although he is arguably deserving of the title "father of hyperbaric oxygen therapy," this accolade has been bestowed on the Dutch cardiovascular surgeon Ita Boerema, whose involvement in hyperbaric medicine, albeit considerable, did not begin until more than 20 years later. In 1934, the Brazilian Academy of Sciences held a special meeting in honor of the recently deceased Madam Curie. A Brazilian physician, Álvaro Osório de Almeida, who had trained under Curie (and several of Paul Bert's disciples) and had become her close friend, spoke at the meeting. His presentations were of particular interest to this audience in that they addressed hyperbaric oxygen–induced central nervous system toxicity, work he undertook as a prelude to treating cancer patients with hyperbaric oxygen.[39,40]

It was probably not high ambient air pressures that attracted de Almeida to hyperbaric medicine; rather, it was the ability of the chamber to deliver high amounts of oxygen. De Almeida hypothesized that malignant cells would be sensitive to high doses of oxygen. Initially, he sought to determine whether higher organisms could safely tolerate the levels of oxygen he considered necessary to injure malignant cells.[41,42] De Almeida reported that experimentally implanted tumors in rats invariably "softened" after repeated exposures to 6.0 ATA oxygen for 3 hours. Tumor breakup was perceptible after several days, with some resorption of tumor mass. Encouraged, de Almeida quickly moved on to human studies.[42] This proved more complicated, as 6.0 ATA oxygen was clearly too toxic an exposure level. Greatly increased sensitivity to oxygen was apparent, even when a strict dietary intake (200 daily calories) was enforced.

Not deterred, de Almeida attempted to combine radiation therapy and a hyperbaric dose of 3.0 ATA.[43] Madam Curie was able to make available radium for his studies, which was carried to Rio de Janeiro in the hand luggage of his friends, colleagues, and family members! His human work led him to conclude that the effects of combination hyperbaric oxygen and radium therapy are "greater than just the effects of one summed up with the effects of the other."[43]

De Almeida also studied the effects of hyperbaric oxygen on leprosy[44] and gas gangrene.[45] It was necessary to conduct all of this research in the basement of his home to avoid the stigma of being labeled a "dog doctor," which was commonly directed at academics during this period.

Despite publishing his work in three different languages, de Almeida's pioneering application of hyperbaric *oxygen* therapy goes largely unnoticed today.

DIVING MEDICINE

The U.S. Navy began experimenting with hyperbaric oxygen in the treatment of decompression sickness soon after de Almeida, reporting their early experience in 1937.[46] Behnke and Shaw were clearly cognizant of

the ability of air recompression to resolve many, particularly less severe, cases of decompression sickness. They were dissatisfied, however, with the greatly extended decompressions necessary to safely return the patient and his attendants to the surface. Decompressions in excess of 24 hours were not uncommon.

Others, beginning with Bert,[21] had suggested that oxygen replace air during the treatment process. Behnke and Shaw became the first to attempt this. Their work resulted in treatment recommendations based on severity of injury, and included the first application of nitrogen-oxygen mixtures other than air.[46] An important aspect of this early work was the identification of safe time-dose oxygen exposure limits—that is, exposure to the highest oxygen pressure for the longest period with minimum possible risk for central nervous system oxygen toxicity.[47] Subsequent navy interest in oxygen extended to accelerating the decompression process to improve efficiency (time spent working vs time spent decompressing) and safety (getting the diver out of the water more quickly).[16]

Significant reductions in in-water decompression time resulted. Eventually, the practice of oxygen-enhanced decompression was extended to surface oxygen decompression procedures.[16] With these procedures, the diver exits the water well in advance of the time normally required for standard in-water air decompression to be completed. Once at the surface, the diver is immediately recompressed in a waiting hyperbaric chamber. Oxygen breathing is instituted, and subsequent decompression conducted. The stage used to recover the diver is now free to transport the next diver to the work site. Although this process appears hazardous—that is, exiting the water before elimination of what would normally be considered sufficient tissue nitrogen to surface safely—the incidence of decompression sickness is no greater than that associated with standard in-water air decompression.[47] One might argue that planned surfacing in such a manner would set the disease process in motion and is, therefore, dangerous. Others could counter that it is actually safer to do this, rather than undergo in-water decompression, in that the diver is no longer in a relatively hazardous environment, and his or her subsequent decompression can be more carefully controlled.

The next significant evolution in military diving and oxygen use occurred in 1960. Until that time, recompression of those suffering decompression sickness was commonly accomplished with patients breathing compressed air, with only limited oxygen exposures, despite Behnke and Shaw's[46] encouraging work with animals.

By the 1960s, a disturbing trend in U.S. Navy recompression treatment experience had become apparent. Treatment table failure rates were steadily climbing and were attributed, in part, to increasing intervals between symptom onset and therapeutic compression.[48] Delays were particularly common in recreational divers, whereas military and professional divers invariably work from a diving platform that incorporates recompression capability. The interval between symptom onset and therapeutic compression, therefore, is brief. Recreational divers rarely have such readily available support, frequently diving in medical and geographic isolation. Provision of treatment in these cases can be delayed from many hours to several days.

Goodman, Workman, and their colleagues[49] tackled the issue of lengthy decompressions from treatment pressure and treatment table failure rates. Their work culminated in the adoption by the U.S. Navy of the Minimal-Recompression Oxygen-Breathing treatment tables. These treatment tables remain in use today and are employed internationally.

RADIATION SENSITIZATION

During the early 1950s, several observations laid the groundwork for the introduction of hyperbaric oxygen as a radiation sensitizer. Gray and colleagues[50] observed that curability of small animal tumors with radiotherapy is limited by the radioresistance of the portion of cells that retain their reproductive integrity. Tumor cell sensitivity to irradiation was seen

to increase when experimental mice breathed hyperbaric doses of oxygen.

Gray's group[51] further observed that radiobiological damage demonstrates dependence on the concentration of oxygen in the immediate vicinity of tumor cells at the time of radiation. It soon became evident that many solid tumor cell populations exist within a wide range of oxygen tensions.[52]

These findings were sufficiently encouraging to warrant an early clinical trial. This was undertaken at St. Thomas's Hospital in London, England, by Churchill-Davidson, Sanger, and Thomlinson.[53] Their protocol included placing patients into barbiturate coma to limit the likelihood of oxygen seizures and inserting tympanic membrane ventilation tubes to avoid ear barotrauma. Patients were then placed into a naval diving chamber modified to accommodate a recessed Perspex window, and its pressure was increased with oxygen to 3.0 ATA.[54]

It was through this window that X-rays were delivered in a single treatment to breast and lung cancers, the only tumor sites that would "match" the viewport. A unique method was used to assess any difference afforded by hyperbaric oxygen. Only patients with tumors large enough to be divided into two were recruited. Half of the tumor was irradiated conventionally, whereas the other half was shielded. Shielding was reversed and the second half of the tumor irradiated while the patient was exposed to hyperbaric oxygen.[53] Within 2 years, this group was able to report 35 patients successfully managed in this way.[55] Damage to the tumor areas irradiated in the chamber was more pronounced.

Great interest in this method of radiation delivery resulted,[56-59] but radiation oncologists were invariably frustrated by the lack of "anatomic visibility" afforded by the small and limited number of windows available in the largely steel hyperbaric chambers of the day. Such was the interest in hyperbaric oxygen radiosensitization that access to all tumors, regardless of where they were anatomically, was sought. Industry was challenged, and it responded by adding more windows into purpose-built chambers. By the early 1960s, a completely acrylic hyperbaric chamber had been produced.

Within a decade of the advent of hyperbaric oxygen radiation sensitization, doubts about its safety were being expressed. Some suggested that the incidence of new primary tumors and metastatic disease appeared to be greater in those patients irradiated in hyperbaric chambers.[60,61] Coupled with an apparent lack of consistent survival advantage, the introduction of alternative radiation sensitizers, and a lack of uniformity in radiation dosing (making comparisons difficult), interest in hyperbaric radiation sensitization waned, and had largely ceased by the mid-1970s.

CARDIAC SURGERY

The decade of the 1950s witnessed another significant hyperbaric event, one that resulted in the identification of a second therapeutic mechanism. Boerema's[62] introduction of controlled hypothermia had served to double the ischemic time from normothermic cardiac surgery. This doubling, however, still represented only a total of approximately 5 minutes. Boerema's search for more effective methods led him to consider hyperbaric oxygenation. He was aware of the practice of hyperbaric oxygen therapy as it related to the treatment of decompression sickness.

Using a small-animal chamber, he first demonstrated that dogs could tolerate much longer periods of cardiac arrest when both cooled and exposed to 3.0 ATA oxygen.[62] His foundation for hyperbaric dosing would be the work by Behnke and Shaw,[46] who had proposed 3.0 ATA for 3 hours as the upper safe threshold to avoid overt central nervous system oxygen toxicity. He next exposed pigs to this same pressure where they underwent exchange transfusion, first using plasma. He later switched to Macrodex, adding salts to produce a Ringer's-like solution. Although hemoglobin levels declined to essentially zero, there was clearly sufficient oxygen transport within plasma to support oxygen-dependent functions. This work was published in the first issue of *Journal of Cardiovascular Surgery,* under the title "Life Without Blood."[63]

By 1959, Boerema and colleagues[64] were performing cardiac surgery on infants and adults with a specially built hyperbaric operating room (Figs. 1.3 and 1.4). Successful cross-clamp ischemic times of between 13 and 14 minutes were achieved. Hyperbaric operating rooms were soon installed in many hospitals throughout the world.

Bernhard and colleagues[65] at Harvard Medical School were the first to perform hyperbaric cardiac surgery in the United States in 1963. They developed several complementary techniques, one a miniature extracorporeal circulation oxygenator that they used successfully with hyperbaric oxygenation and hypothermia. Soon thereafter, Bernhard's group[65] was routinely operating on infants with congenital cardiac abnormalities. Pressures between 3.0 and 3.6 ATA were used and titrated to overcome low arterial oxygen levels. The greater the degree of cyanosis, the higher the pressure. In accordance with Boerema's protocol, compression would begin once the chest was opened. Decompression commenced on repair of the defect and before closure of the thoracotomy, and took up to 150 minutes.

During this period of hyperbaric cardiac surgery enthusiasm, steady advances in the development of extracorporeal circulation devices were under way. By 1960, this technology was considered safe enough to support coronary artery bypass grafting, usually in conjunction with controlled hypothermia. Over the ensuing decade, the practice of hyperbaric surgery began to falter. Its disadvantages, namely, higher costs, risk for decompression sickness, ear barotrauma, and confinement anxiety issues (Boerema found that some 50% of those who would otherwise have been considered hyperbaric team members could not sufficiently tolerate its environment), became difficult to justify. Extracorporeal circulation technology eventually won the day.

What remained, however, was a second and important hyperbaric oxygen–induced therapeutic mechanism. Boerema had conclusively demonstrated that large volumes of oxygen could be transported in simple solution and in the absence of hemoglobin.[63] This effect would eventually become the treatment basis for acute carbon monoxide intoxication, crush injuries and other acute ischemias, inadequately perfused skin flaps, and exceptional blood loss anemia.

Although the ability of hyperbaric therapy to increase blood oxygen transport is intuitive today, only 20 years before Boerema's findings this concept had been ridiculed. According to the highly respected chairman of the University of Chicago Department of Medicine in a letter to the editor of *Journal of the American Medical Association*,[66] "[T]he claim that the method (hyperbaric therapy) has any effect on oxygen supply or oxygen tension in the tissues is

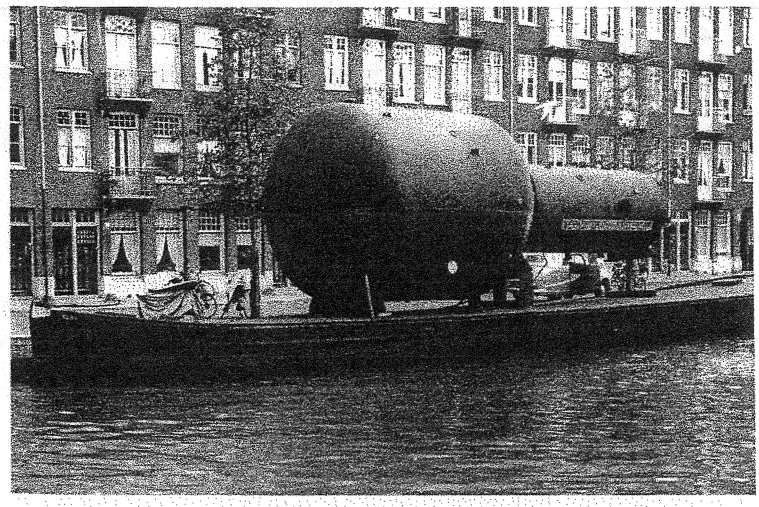

Figure 1.3 Boerema's hyperbaric operating room being delivered via an Amsterdam canal to Hospital Wilhelmina Gasthius. *(Permission granted by Best Publishing Company, Bakker DJ and Cramer FS: Hyperbaric Surgery, Perioperative Care, Flagstaff, Ariz, 2002.)*

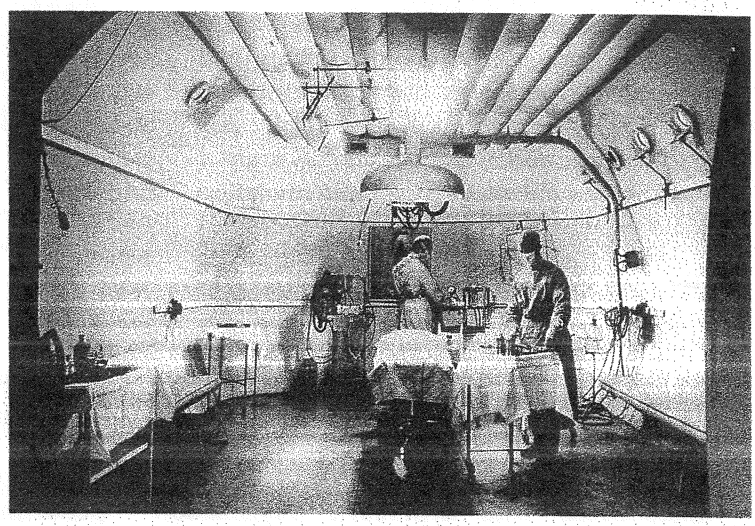

Figure 1.4 Inside Boerema's enormous hyperbaric operating room. *(Permission granted by Best Publishing Company, Bakker DJ and Cramer FS: Hyperbaric Surgery, Perioperative Care, Flagstaff, Ariz, 2002.)*

absurd. To claim that oxygen may be made to reach tissues at higher tensions is only to display ignorance of the mechanism by which oxygen is transported to and given off to the tissues"(p.1808). Even in the 1960s, some scientists remained convinced that the only way to increase oxygen delivery was to increase hemoglobin. They thought that dissolved oxygen was insignificant in oxygen transport.[67]

CLINICAL HYPERBARIC MEDICINE

Several members of Western Infirmary's Department of Surgery, Glasgow, Scotland, extended the investigation of hyperbaric oxygen therapy during this period, with an emphasis on acute ischemias.[68-72] Using a converted autoclave, Smith and Lawson studied the effects of hyperbaric oxygenation in a dog model of coronary artery occlusion.[71] After ligation of the circumflex coronary artery, dogs were randomized to receive 2.0 ATA oxygen or normal atmospheric air. They reported that 90% of the hyperbaric group was protected from the ventricular fibrillation that killed 60% of control animals. Similar findings were reported elsewhere.[73]

The first clinical experience of hyperbaric oxygen in the treatment of acute myocardial infarction was reported in 1962 by the Glasgow group, initially involving a single patient.[70] Within 2 years they were able to report a randomized trial involving 36 cases, 18 treated at 2.0 ATA oxygen and 18 control subjects. No statistically significant difference was observed between the groups.[74]

Hyperbaric oxygen has, however, continued to be of research interest in myocardial infarction over the ensuing years. It has been found somewhat beneficial when used in concert with thrombolytic agents in both animals[75] and humans,[76,77] and as a method to reduce complications after stent placements.[78] The current role of hyperbaric oxygen therapy in acute coronary syndrome has recently been reviewed.[79]

It is somewhat surprising that it took until 1960 to treat the first human carbon monoxide poisoning with hyperbaric oxygen. Haldane[80] had demonstrated its value in animals some 50 years earlier. Subsequent animal studies determined that hyperbaric oxygen hastened the elimination of carbon monoxide from blood and provided sufficient plasma-borne oxygen to overcome failure of hemoglobin transport.[81-83] Pace and coworkers[84] confirmed these effects in healthy human volunteers.

The Glasgow group's first two carbon monoxide patients were particularly compromised. Their prompt recovery was attributed to treatment with 2.0 ATA oxygen therapy, and this dose of oxygen soon became a treatment

standard at Western University. By 1962, their case experience had grown to 22 patients.[85]

ANTIMICROBIAL EFFECTS

Shortly after he introduced hyperbaric cardiac surgery, Boerema[86] used his chamber to treat a "hopeless" case of gas gangrene, that is, hopeless in that limb amputation was not an option. Boerema elected to use hyperbaric oxygen therapy at 3.0 ATA for 2 hours daily. A dramatic arrest of the advancing infection was observed, and systemic toxicity soon resolved. Boerema, Brummelkamp, and colleagues subsequently accumulated 40 cases[87] and then 80 cases.[88] In most patients, *Clostridial perfringens* was the primary organism. The use of oxygen to treat gas gangrene was, however, not new; it too had been injected directly into infected tissues of soldiers during World War I, used by Hinton in the same manner 30 years later,[89] and had already been delivered hyperbarically by de Almeida.[45]

The somewhat arbitrary selection of 3.0 ATA as the treatment pressure appeared fortuitous. Van Unnik[90] subsequently showed that alpha toxin production by *Clostridial perfringens* was inhibited, although not arrested, at 3.0 ATA, but not at lesser pressures.

A growing body of animal and clinical evidence followed. It became apparent that the action of hyperbaric oxygen was based on the formation of oxygen free radicals in the relative absence of free radical degrading enzymes such as superoxide dismutases, catalases, and peroxidases.[91-93] Although hyperbaric oxygen does not kill clostridia directly, it is bacteriostatic in vivo and in vitro.[94-96] In a dog model, the greatest reduction in morbidity was achieved when hyperbaric oxygen was combined with antibiotics and surgery.[97]

Hyperbaric oxygen was subsequently reported to be useful in the treatment of chronic osteomyelitis. Experimental work and clinical experience demonstrated enhanced osteogenesis,[98,99] improved bacterial cell wall antibiotic transport,[100] and heightened leukocyte-mediated killing of aerobic organisms.[101]

Application of the antimicrobial properties of hyperbaric oxygen was extended to the treatment of necrotizing soft-tissue infections caused by aerobic, anaerobic, and mixed bacterial flora.[102-104]

WOUND HEALING

In 1965, in Japan, Wada and colleagues[105] reported an observation that was to have a profound effect on the practice of hyperbaric medicine. Survivors of a coal mine fire with carbon monoxide poisoning were treated with hyperbaric oxygen. Some of these miners suffered concurrent burns. It was the impression of Wada's group that those patients treated with hyperbaric oxygen enjoyed improved burn wound healing compared with those burned miners who did not require hyperbaric oxygen therapy for carbon monoxide poisoning.

This observation prompted several investigators to study the potential of hyperbaric oxygen in animals, invariably involving a second-degree burn model. Hyperbaric oxygen was found to reduce burn wound edema,[106] improve healing time,[107] reduce infection rates,[107] produce an earlier return to capillary potency, and minimize inflammatory response.[108]

Published clinical experience was slow to accumulate. One small, randomized trial demonstrated reduced fluid requirements, faster healing rates, and reduced mortality rates.[109] Other reports, largely retrospective, suggested reduced skin grafting requirements,[110] lowered mortality and reduced hospital stays,[111] reduced infection rates,[112] and lower costs[113] when hyperbaric oxygen was incorporated into standard burn care management.

Despite these purported benefits, hyperbaric oxygen therapy has not been embraced by the burn wound community. It is possible that issues involving patient stabilization and management requirements, patient absence from the tightly controlled burn care environment, and concern about cross-contamination demand better scientific support before hyperbaric oxygen is accepted as treatment for burn victims.

Having initially concerned themselves with acute ischemias, the Glasgow group extended their interest in hyperbaric oxygen therapy to chronic obliterate vascular disorders. Some modest successes were reported in ischemic ulcers, but overall results were disappointing. It was hypothesized by others at Western University that a possible explanation for the lack of apparent benefit from hyperbaric oxygen was due to its vasoconstrictive effect. Blood vessels of the eye had been observed to constrict while volunteers breathed 100% oxygen under normal atmospheric conditions.[114] The same effect was observed within the cerebral vasculature and magnified at 3.5 ATA oxygen.[115] If blood flow to the limb was reduced in the same way, it was proposed that the benefit of hyperbaric oxygen to increase oxygen content might be lost.[116] Should this be the case, it might explain the failure of hyperbaric oxygen to produce improvement in patients with peripheral vascular disease.

Using young healthy volunteers, Bird and Telfer[116] measured forearm blood flow by occlusion plethysmography at 1.0 and 2.0 ATA oxygen. Mean blood flow decreased by 11.2% and 18.91%, respectively. The authors concluded that a homeostatic mechanism existed in ischemic limbs. As oxygen content is increased, blood flow correspondingly decreases, so that hyperbaric doses of oxygen never reach ischemic tissues.

Unfortunately, these researchers were unable to measure oxygen content. Had they been able to do so, they would have observed its profound increase as subsequent authors reported.[117,118] These tissue oxygen increases are largely dependent on adequate large-vessel patency.

Although unhelpful for chronic arterial occlusive disease, the vasoconstrictive effect of hyperbaric oxygen, occurring without concurrent hypoxia, has proved therapeutic elsewhere. Vasoconstriction occurs at the level of the arteriole. Venules are unaffected, so outflow is maintained. The net effect of hyperoxic-induced vasoconstriction, therefore, is to reduce edema. Indications include the impending stage of comportment syndrome,[119] acute thermal burns,[110] and edematous skin flaps.[120]

By the 1970s, the practice of hyperbaric medicine was based on several and frequently complementary effects. The inverse relation of absolute pressure to gas bubble volume (Boyle's Law) served as the mechanistic basis for the treatment of decompression sickness. This effect was enhanced with the provision of oxygen. Hyperoxygenation was used to support hypoxic tissues secondary to acute ischemic events, and to facilitate disassociation and hasten elimination of carbon monoxide. Antimicrobial activities were used in the treatment of both anaerobic and mixed anaerobic and aerobic infections, as well as to support leukocyte-mediated phagocytosis in infected and chronically infected bone. Vasoconstriction reduced compartment pressures and improved edematous states.

During this same period, treatment of conditions related to the above effects brought to light another potential hyperbaric application. It appeared as if some chronic wounds, related or otherwise to the primary hyperbaric indication, were healed as a consequence of hyperbaric oxygen treatments.[67]

This suggestion was counterintuitive to some scientists, who appreciated that the central environment of the healing wound was hypoxia, with resulting accumulations of lactate. Would not hyperbaric oxygen overwhelm the wound and eliminate this presumably normal healing environment?

This answer was no. It became evident that although lactate initiates wound repair, many of its subsequent reparative phases are oxygen dependent.[121-126] If a wound is compromised by local *tissue* hypoxia, it will stall or completely fail to heal. Hyperbaric oxygen, in the setting of adequate regional perfusion, will reestablish the necessary wound oxygen gradient. To determine whether a particular patient has sufficient physiologic capacity to respond locally (the wound) to centrally delivered hyperoxia, transcutaneous oxygen testing proved helpful.[127] The most precise indication for hyperbaric oxygen therapy in the management of a chronic wound is a low (<40 mm Hg) periwound transcutaneous oxygen value that briskly reverses on oxygen inhalation.[128]

Transcutaneous oximetry, applied algorithmically, will aid in patient selection, identify nonresponders, and suggest a therapeutic end point.[129] This screening process serves to enhance clinical outcome and the cost-effectiveness of hyperbaric oxygen therapy.

Hyperbaric wound referrals now extend to arterial insufficiency,[130] diabetic,[131,132] and soft-tissue radionecrosis[133,134] causative agents. Some of the stronger evidence relates to mandibular osteoradionecrosis. A clear understanding of its pathophysiology has emerged,[135] and so, too, has evidence that hyperbaric but not normobaric oxygen will stimulate angiogenesis.[136]

The sixth and most recently identified benefit of hyperbaric oxygen relates to ischemia-reperfusion injury. What was initially considered by some as a harmful effect of high levels of oxygen[137] is emerging as a potentially valuable therapeutic and preconditioning agent.

Prolonged periods of acute interruption in blood flow result in injury to the microcirculation and may lead to cell death. Paradoxically, subsequent reperfusion may actually accelerate these deleterious effects.[138] Reperfusion, by adjuvant therapy, decompression, or revascularization, has the potential to induce a complex interplay between adhesion molecules and neuropils with resulting microvascular plugging. This secondary ischemic state is frequently referred to as the "flow/no reflow phenomenon."

The well-documented deleterious effects of oxygen-derived free radicals might suggest that hyperbaric oxygen as a treatment or preventative measure is counterintuitive. One might expect an exacerbation of ischemia-reperfusion injury secondary to increased production of oxygen-derived free radicals associated with hyperbaric oxygenation. Animal studies have, however, failed to identify any harmful effect; in fact, the reverse has been demonstrated. In rats and rabbits, involving liver, brain, heart, skeletal muscle, small intestine, skin, and endothelial cell ischemia-reperfusion preparations, improved outcome was uniformly noted when hyperbaric oxygen was applied immediately before, during, or immediately after acute ischemia.[139] The effect of hyperbaric oxygen appears principally the result of a down-regulation of adhesion molecule function on leukocytes and vascular endothelium.[140]

These findings suggest a clinical foundation for the employment of hyperbaric oxygen therapy in several high-risk settings for ischemia-reperfusion injury. Examples include acute traumatic peripheral ischemias, compartment surgery, hypoxic birth, injury, and cardiac surgery. This latter example has already been the subject of a randomized clinical trial,[141] with encouraging results. Hyperbaric oxygen is already being advocated in all patients with revascularization or replanted extremities involving ischemia times greater than 6 hours.[142]

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INDICATIONS FOR HYPERBARIC OXYGEN THERAPY

~ Undersea and Hyperbaric Medical Society, 2013

Acute Thermal Burn Injury
Air or Gas Embolism**
Carbon Monoxide Poisoning*
Central Retinal Artery Insufficiency
Clostridial Myonecrosis
Compromised Skin Grafts and Skin Flaps
Crush Injury, Compartment Syndrome/Acute Ischemias*
Decompression Sickness**
Enhancement of Healing, Selected Problem Wounds*
Exceptional Blood Loss Anemia
Idiopathic Sudden Sensorineural Hearing Loss
Intracranial Abscess
Late Radiation Tissue Injury (Bone and Soft Tissues)*
Necrotizing Soft Tissue Injuries
Refractory Osteomyelitis

**High level clinical evidence*
*** Indisputable standard of care*