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The Haldane Effect

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Abstract

John Scott Haldane, British physiologist and philosopher, was born in 1860 in Edinburgh, Scotland. Haldane investigated poisonous gases occurring in coal mines and wells, sunstroke, the physiological action of carbon monoxide and the use of a caged canary for early carbon monoxide detection, the regulation of lung ventilation (with J.G. Priestley), and devised the haemoglobinometer, the apparatus for blood-gas analysis. He also described the effects of oxygen deficiency and exercise on breathing. During the First World War he worked on effects of poisonous gases and designed a portable oxygen administration apparatus. His work on hypoxia and the acclimatization of the human body to high altitude revolutionized concepts in respiratory physiology. Haldane published some landmark books on his philosophical ideas about the true significance of biology. Most importantly, however, Haldane investigated the problems of deep diving for the British Admiralty, developing the 'stage decompression' method, a lasting contribution to the diving world. This elaborate experimental investigation was conducted in part in a steel pressure chamber at the Lister Institute and with divers in Scottish deep-water lochs. In 1908, J.S. Haldane published those results in his seminal paper "Prevention of Compressed-Air Illness" in the Journal of Hygiene with A.E. Boycott and G.C.C. Damant. Stage decompression allowed divers to be safely brought to the surface and made it possible to conduct 120 fsw (37 m) salvage operations on the *Laurentic* to recover over £5,000,000 of gold ingots without recordable incident. One hundred years later, the Norwegian University of Science and Technology in Trondheim convened the Haldane Symposium, December 18-19, 2008, celebrating the past, present, and future directions of environmental physiology research in decompression.

Keywords: decompression, decompression tables, environmental physiology, John Scott Haldane

Introduction

The Haldane Effect

Deoxygenated hemoglobin (Hb) has a greater affinity for carbon dioxide (CO_2) than does oxygenated hemoglobin (HbO_2). Thus, oxygen (O_2) release at the tissues facilitates CO_2 pickup, while O_2 pickup at the lungs promotes CO_2 dissociation from Hb. In reality, the exchange of O_2 and CO_2 is occurring at the same time. In the oxygen-rich capillaries of the lung, this property causes the displacement of CO_2 to plasma as venous blood enters the alveolus and is vital for alveolar gas exchange.

Reduced (deoxygenated) hemoglobin is a better proton acceptor than the oxygenated form ($H^+ + HbO_2 \longleftrightarrow H^+.Hb + O_2$). In red blood cells, carbonic anhydrase catalyzes the conversion of dissolved carbon dioxide to carbonic acid, which rapidly dissociates to bicarbonate and a free proton ($CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$). The majority of CO_2 in the blood is in the form of bicarbonate. Only a very small amount is actually dissolved as CO_2, with the remaining amount bound to hemoglobin. The Haldane effect is not the subject of this paper; the enduring effect of the Haldanes is, of John Scott in particular, as the first environmental physiologist.

Haldane Family History

Haldane Places

Gleneagles in Perthshire, Scotland, was the Haldane family estate since the 13th century, where John Scott was raised. There are named extraterrestrial sites such as the Haldane lunar crater, located in Mare Smythii, near the eastern limb of the Moon, and the Haldane Martian crater. Haldane, Illinois, USA is an unincorporated county. There also exists the small town of Haldane, Southland, New Zealand and a Haldane Ducati motorcycle dealership in Auckland. The Glasgow School of Art, Department of Ceramics is housed in the Haldane Building on Hill Street, Glasgow, Scotland.

The Haldanes' Ancestry

Bernard, son of Brien, during the reign of King William the Lion (1165-1214) was the presumed founder of the Haldane family in Scotland. Almer de Haldane fought with King Robert de Bruce in the 14th century. Sir John Haldane was the third Lord of Gleneagles in the 15th century. Sir James Haldane presided as Governor of Dunbar Castle in the 16th century. The 11th Laird, Chief Sir John Haldane, was knighted by King Charles I in the 17th century. General George Haldane led troops in the Battle of Fontenoy in the 18th century. There is no record of Archibald Haldane, who settled in Virginia in 1655, regarding his relationship to the Haldane family forefathers of John Scott Haldane.

The Haldane Family Tree

John Scott Haldane is of the third generation of this Wikipedia excerpt of the Haldane family tree (Figure 1). Of note is the high level of influential accomplishments of members of this aristocratic Scottish family, in particular, the first through fourth generations.

Robert Haldane (1764-1842) was the brother of J.S. Haldane's grandfather, a Scottish churchman, and Royal Navy mariner.

James Alexander Haldane (1768-1851) was J.S. Haldane's grandfather, brother of Robert Haldane, who married twice and fathered a total of 13 children (obviously not all depicted above). He was an independent Scottish Church leader.

Daniel Rutherford Haldane (1824-1887) was J.S. Haldane's uncle and President of the Royal College of Physicians in Edinburgh.

Richard Burdon Sanderson Haldane (1856-1928) was The Right Honourable Lord Richard Burdon Haldane, 1st Viscount Haldane**,** John Scott Haldane's brother. He was a British politician, lawyer, philosopher and Secretary of State for War in 1909 (Maurice, 1937).

Elizabeth Sanderson Haldane (1862-1937) was J.S. Haldane's sister and the first female Justice of the Peace in Scotland in 1920.

John Burdon Sanderson Haldane (1892-1964), also known as 'Jack,' was J.S. Haldane's son, a prominent scientist in his own right who, with Ronald Fisher and Sewall Wright, was the founder of population genetics. Quite the philosopher, in his essay "When I am Dead" Haldane (1927) opined "If my mental processes are determined wholly by the motions of the atoms in my brain, I have no reason to suppose that my beliefs are true...and hence I have no reason for supposing my brain to be composed of atoms." J.B.S. Haldane also offered a cautionary note on the four stages of the acceptance of a scientific theory: 1) This is worthless nonsense; 2) This is an interesting, but perverse, point of view; 3) This is true, but quite unimportant; and, 4) I always said so. The Cambridge Dictionary of Scientists (2nd ed., 2002) characterizes J.B.S. Haldane as "One of the most eccentric figures in modern science. If his life has a theme, it is of bringing talents in one field of work to the solution of problems in quite a different area. He was self-confident, unpredictable and difficult to work with. His family was wealthy and talented, and his father was Britain's leading physiologist." In addition to his achievements in science and as an author, during much of his life J.B.S. Haldane was a noted atheist, materialist, socialist, and communist. In the field of genetics he was the first to discover linkage in mammals, to map a human chromosome, and to measure the mutation rate of a human gene. Haldane (1924) was also a famous science popularizer and remarkable in predicting many scientific advances, but has been criticized for presenting a too idealistic view of scientific progress. He also coined the term "clone" (Clark, 1969).

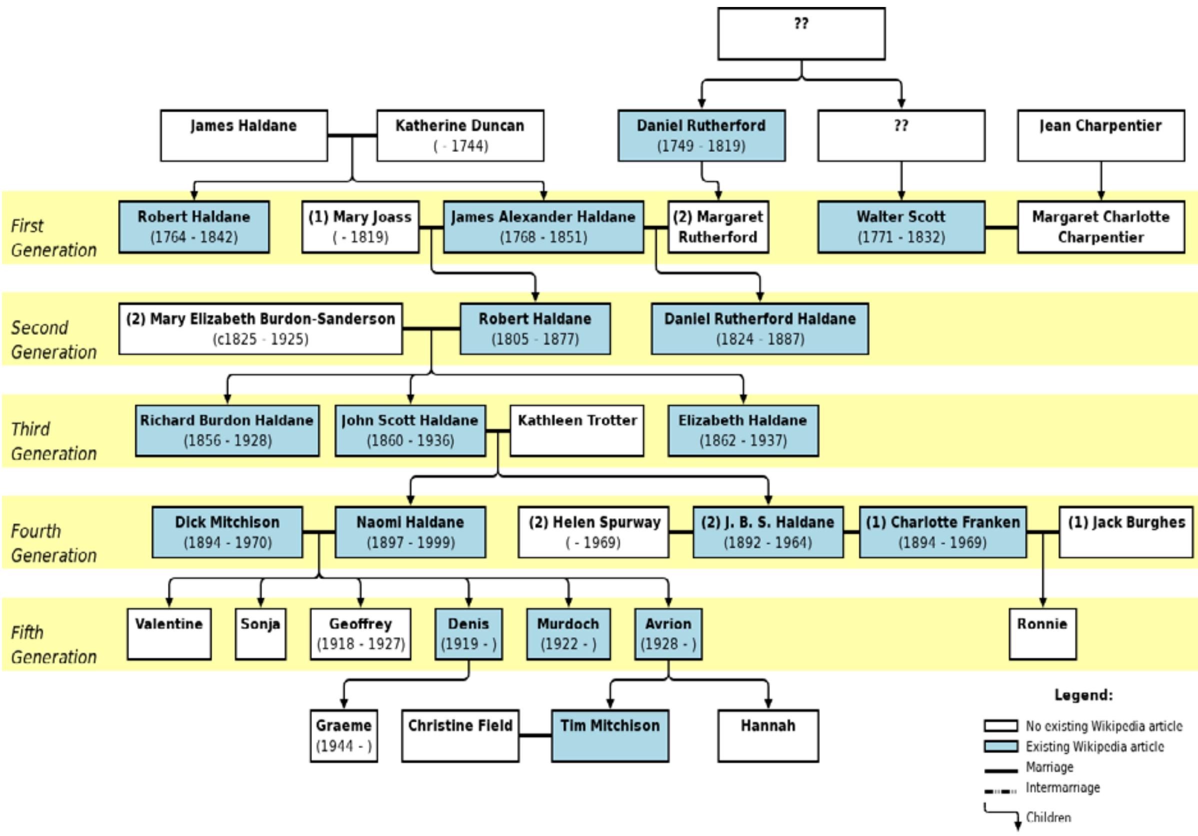

Figure 1. Haldane family tree.

Like his father, Jack Haldane was an enthusiastic experimenter, willing to expose himself to danger to obtain data. One experiment, involving elevated levels of oxygen saturation, triggered a fit which resulted in him suffering crushed vertebrae. In his decompression chamber experiments, he and his volunteers suffered perforated eardrums but Haldane stated that "the drum generally heals up; and if a hole remains in it, although one is somewhat deaf, one can blow tobacco smoke out of the ear in question, which is a social accomplishment."

In a 1923 talk given in Cambridge, Haldane, foreseeing the exhaustion of coal for power generation in Britain, proposed a network of hydrogen-generating windmills. This was the first proposal of the hydrogen-based renewable energy economy.

J.B.S. Haldane became a member of the prestigious Royal Society in 1932. Among the awards he received was the Royal Society's Darwin Medal (1953), the French Government's Legion of Honour (1937), the Academia Nazionale dei Lincei's Feltrinelli Prize (1961), the Weldon Memorial Prize from Oxford University, the Linnean Society's Darwin Wallace Medal, and the U.S. National Academy of Sciences Kimbler Genetics Award (Mahanti, 2006). He served as President of the Genetical Society from 1932 to 1936. Haldane was a friend of the author Aldous Huxley. Jack died on December 1, 1964 and had willed that his body be used for study at the Rangaraya Medical College, Kakinada (Mahanti, 2006). During his life, Jack Haldane wrote 24 books, more than 400 scientific papers, and numerous popular articles.

Naomi Margaret Haldane Mitchison (1897-1999) was J.S. Haldane's daughter, the sister of Jack**.** Naomi was a Scottish novelist and poet with over 90 works to her credit (Calder, 1997). "She was Bohemian, a child of the twenties, she had an open marriage and sexual freedom, taking off corsets, not wearing brassieres long before the 1960s. She believed herself to be part of an intellectual elite and felt empowered to do and be any way she felt" (Benton, 1990). In 1981, she was appointed Commander of the Order of the British Empire (CBE). In 1990, at age 92, Mitchison received an Honorary Doctorate of Letters from Heriot-Watt University, Edinburgh**.** Naomi was also a good friend of the writer J.R.R. Tolkien, serving as was one of the proofreaders of *The Lord of the Rings*.

John Scott Haldane

The Person

John Scott Haldane (1860-1936) is the main focus and anchor of the Haldane effect and arguably the first environmental physiologist. He was born in Edinburgh on 3 May, 1860, the fourth son of Robert Haldane by his second wife Mary Elizabeth, and died March 16, 1936, of pneumonia. Haldane believed that "the aim of the science of physiology is to deliver general principles which shall enable us to predict behaviour of the living body under various physiological conditions." He was considered the father of oxygen therapy: "The first step in good practice is to know what the oxygen is aiming at, where it is going, and in what quantities."

We know about Haldane from his work in developing decompression tables, but his contribution can only be understood if one considers his previous work and interests. First of all, Haldane was an observer and an experimentalist, who always pointed out that careful observation and experiments had to be the basis of any theoretical analysis. "Why think when you can experiment" and "Exhaust experiments and then think." His passion for obtaining data was demonstrated by the fact that during his medical studies in Jena he carefully observed the amount of beer being drunk, noting that the students on the average drank about 20 pints per evening.

Haldane received his education at the Edinburgh Academy, University of Edinburgh (1884), and University of Jena in central Germany, after which he was a Demonstrator at University College, Dundee, and from 1907-1913 a Reader in Physiology at Oxford University where his uncle, John Burdon-Sanderson, was Waynflete Professor of Physiology. J.S. Haldane became a member of the Royal Society in 1897 but had issues such as "The Royal Society system of selecting papers and excluding 'speculative' ones makes the meetings, Proceedings and Transactions as dull as ditch water and quite unrepresentative of the progress of British Science" (Goodman, 2007). Regardless, he was awarded Royal Medallist of the Society in 1916, Copley Medallist in 1934, and in 1928 he was appointed Companion of Honour for his scientific work in connection with industrial disease.

J.S. Haldane was personally gifted with a unique power of encouraging the faculty for research and his teaching was characterized by his efforts to make the students observe and think for themselves**.** He had the great ability to add both force and charm or character, the effect of which was securing the attachment of his pupils. Haldane had a profound sense of public service and he believed passionately that the world could be made a better place through the appliance of science. From miners dying of carbon monoxide poisoning and soldiers being gassed like rats in the trenches, to mountaineers and aviators coping with high altitudes, Haldane showed that science could bring light into the darkness. A friend described him as "almost quixotically anxious to do good to all mankind – and to teach them all a thing or two" (Goodman, 2007).

Haldane was also a philosopher of science and many of his lectures were published in books, including *The Sciences and Philosophy* in 1929, *The Philosophical Basis of Biology* in 1931, and *The Philosophy of a Biologist* in 1935.

The Self-Experimenter

Haldane was "himself such a coalmine canary, putting his own health and life on the line to protect others" (Goodman, 2007). Haldane's own philosophy was "All life is a physiological self experiment." Once, on his way home from his laboratory after such an experiment, he was stopped by an Oxford policeman who had observed the scientist's stumbling progress. Haldane explained that it was not due to alcohol, but gas. His housekeeper offered her sympathies to his wife, Kathleen: "I know how you feel, ma'am. My husband's just the same on a Friday night."

Haldane liked nothing better than to explore dangerous mine shafts and sewers. But it was in the specially constructed, air-tight chamber in his lab that the effects of gases on people were revealed. In an age before risk assessments, institutional review boards and human subject ethics committees, Haldane was a serial self-experimenter. He also thought nothing of exposing his own son Jack to dangerous doses of chlorine and other noxious gases. His young daughter Naomi once told a six-year-old friend outside their house: "You come in. My father wants your blood." Her friend screamed and ran away.

J.S. Haldane's Research

First Paper

Haldane's first essay in 1883, with his brother Lord Haldane, contributed to "Essays in Philosophical Criticism" by examining the relationship of philosophy to science and attempted to answer the questions: "What is man; discover man's relationship to his environment; and, knowing man's relationship to his environment, determine his function, what is he most suited to do in the world?" His real interest was the study of the relationship between the organism and the environment. This, as well as his deep feeling for social issues, would determine the focus of his professional life.

First Study

Haldane as Sherlock Holmes, environmental investigator, asked a) What is bad air? b) What makes air dangerous to breathe? and c) How can its bad effects be prevented? He proceeded by studying the air in overcrowded Dundee slums, turning up without warning in the middle of the night to collect air in bedrooms where eight people were sleeping. His results indicated that rooms of 180 ft^3 (5,097 L) had 65% more carbon dioxide, twice as many molds, 254% more organic matter, including hydrogen sulfide (0.07% can be fatal), and 1000% more bacteria than normal.

Self-Experiments

Some of Haldane's rebreathing experiments revolved around the concept of the good air being used up. His findings included: that oxygen was a gas that supported life longer than an equal amount of air; that carbon dioxide spoils pure air once it was breathed; and that after seven hours, O_2 was down to 13% and CO_2 was up to 6.5% accompanied by symptoms of heavy panting, severe headache, and vomiting; and, that after breathing O_2 of 2%, he went unconscious after 40 seconds. Word of his propensity for experimentation got out prompting one neighbor to knock on his door asking "My wife's cat has been lost and we thought that possibly… it might be here."

The Haldane Apparatus

Haldane invented the haemoglobinometer, the apparatus for blood-gas analysis, and also designed an apparatus for the accurate and fast analysis of air or mixtures of gases (Figure 2).

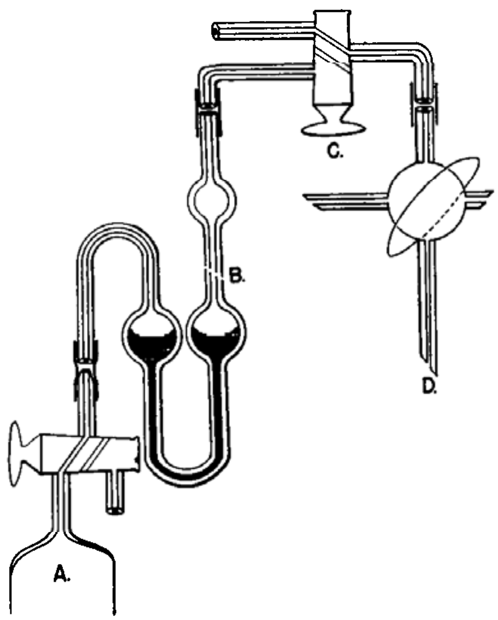

Figure 2. Haldane apparatus (Snyder, 1937): A is the gas-sampling tube; B is made of capillary tubing of 1 mm bore, with two lower bulbs to contain approximately 0.75 cc and an upper bulb to contain about 0.25 cc; C is a two-way stopcock; and, D is the upper part of the Haldane apparatus (Henderson type stopcock).

The Stink

When a Select Committee called upon him to "delve inside the lower depths of government and analyse the stink that flowed beneath," Haldane ventured into the sewers below Westminster Palace. A born iconoclast, he successfully challenged the idea that "sewer air" was a cause of typhoid and other diseases.

Coal Mine Canaries

Serinus canaria is affected by gas 20 times faster than man. Haldane held canaries in the mines in cages not unlike the one in Figure 3. Haldane, being fundamentally a kind man and concerned about the animal's well being, modified the cage so that only the front was open and could be o-ring sealed when closed. He had mounted a small oxygen bottle on top of the cage. When the canary fell off its perch from breathing toxic gas, he would shut the front door and open the oxygen bottle, ensuring the canary's survival.

Figure 3. Antique 19th century coal mine canary cage.

Mine Accident Experiments
In 1896, a mine explosion occurred in Tylorstown Colliery, Rhondda Valley, South Wales, with over 100 men inside. Enter J.S. Haldane, 'medical detective.' The toxic gas after the explosion (afterdamp) had not extinguished miners' lamps, leading Haldane to believe that oxygen was present and suffocation needed to be ruled out. His diagnosis was accurate: 75% of the deaths were attributed not to blast injuries, but to carbon monoxide (CO) poisoning as evidenced by pink and red skin coloration and carmine-red blood samples.

Haldane's continued curiosity about why the miners died led to more self-experimentation. Breathing 0.2% CO for 71.5 min, Haldane's vision became dim, his limbs weak, he had some difficulties in waking up or walking without assistance, and his movements were very uncertain. Afterwards he confessed to feeling confused, making spelling mistakes, experiencing indistinct vision, and not recognizing what he saw. Breathing oxygen produced dramatic improvements. On another occasion, after 29 min of breathing CO, Haldane calmly noted that he felt distinctly abnormal: he was panting, breathing 18 times per minute, his limbs shook and his pulse was racing. Soon, he began to feel unsteady on his feet.

Respiration Studies
Haldane and Priestly (1905) showed that the regulation of breathing is normally determined by the tension of CO_2 in the respiratory center of the brain, and that this nervous center is sensitive to variations in the tension of CO_2 in arterial blood. Since CO_2 is one of the principal products of tissue metabolism, an explanation was afforded of the automatic changes in breathing which occur with alteration in bodily activity.

More Environmental Studies
Haldane conducted other environmental studies on the effects of hyperthermia, nutrition, and in particular, lung disease mechanisms (lack of sunlight, poor ventilation, ladder climbing, infections, smoke inhalation, high and low temperatures, unsanitary conditions and breathing of stone dust - silicosis). Acott (1999) referred to Haldane as "the father of the salt tablet" for his recommendation of salt replacement during excessive sweating.

Haldane's altitude studies consisted of work at Pikes Peak (1911) and Mount Everest of which he said "the highest points of the Earth could be reached without the help of oxygen, providing they had the right men and the right weather." He was further involved with the design of the first prototype space suit (1921) and balloon flights to 90,000 ft (27,430 m) in 1933.

Also, the identification of nitrite (NO_2^-) as the active ingredient in red meat curing procedures dates back to the late 19th century. J.S. Haldane was the first to demonstrate that the addition of nitrite to hemoglobin produced a nitric oxide (NO)-heme bond, called iron-nitrosyl-hemoglobin ($HbFe^{II}NO$). The reduction of nitrite to NO by bacteria or enzymatic reactions in the presence of muscle myoglobin forms iron-nitrosyl-myoglobin. It is nitrosylated myoglobin that gives cured meat, including hot dogs, their distinctive red color and protects the meat from oxidation and spoiling (Gladwin, 2004).

Decompression Studies and Diving Tables

Haldane found that it was not pressure that damaged the body, but differences in pressure. Paul Bert (1878) dived 24 dogs to 290 fsw (88 msw) with rapid decompression, resulting in death by nitrogen bubbles. In his studies using goats at the Lister Institute of Preventive Medicine, Haldane used slow ascent rates of 5.0 $ft{\cdot}min^{-1}$ (1.5 $m{\cdot}min^{-1}$). The results were published in the seminal paper by Boycott, Damant, and Haldane (1908), 100 years ago.

Haldane made the important observation that no diver had "the bends" after rapid decompression from 42 ft (13 m) to the surface leading to the general principle that a 2:1 pressure difference could be tolerated. A staged-decompression technique was developed and tables describing uptake and elimination of nitrogen were developed by his son Jack Haldane at age 13. The body was divided into six compartments with different half times and the deepest dive tested to 210 fsw (64 msw).

Haldane also suggested that oxygen should be used to shorten decompression time provided that the pressure was kept less than 2.0 bar because of the fear of oxygen toxicity. However, Haldane made little contribution to the therapy of decompression sickness although he recognized that recompression was the treatment of choice. Haldane had doubts about the safety and efficacy of 'uniform decompression' practice. Haldane's experiments were conducted at the Lister Institute of Medicine in a recompression chamber and he assumed the following: a) for bubbles to form, the pressure of gas in the tissues must exceed the external pressure; b) that body tissues will hold gas in a supersaturated state unless a certain limit is reached; c) that any decompression is free from risk only if the degree of supersaturation "can be borne with safety;" and, d) that tissue perfusion was the limiting factor in inert gas uptake (Boycott *et al.,* 1908).

His decompression experiments examined the depth and pressure exposure, duration, and the pattern of decompression. Initially, a few experiments were conducted on rabbits, guinea pigs, rats and mice but it was difficult to detect symptoms in these smaller animals. The goat (Figure 4 a, b) was chosen as the experimental model "because they were the largest animals which could be conveniently dealt with" and "those who are familiar with them can detect slight abnormalities with a fair degree of certainty." The dog was rejected because of the findings of Heller *et al.* (1900) who had previously used them to produce 'safe' decompression profiles that failed for humans.

Goats were excluded from the experiments if they were ill. Only five to eight goats were used per experiment. The chamber was not ventilated because they believed CO_2 to have a minimal effect on the susceptibility to decompression sickness. The chamber temperature was not controlled and no allowance was made for any variation in atmospheric pressure. Large pressure variations were used to produce minor to severe symptoms. The compression time of six minutes was neglected in short exposures but included in longer, deeper exposures.

At the time of the experiments, Haldane knew from Naval diving data that decompression from 2.0 bar produced no symptoms irrespective of the duration of exposure. However, decompression from 2.25 bar produced the "occasional slight case;" hence, Haldane's assumption that halving the pressure would not produce symptoms. He used a 'perfusion' mathematical model of gas uptake, the half lives of which were calculated from data available at that time (Acott, 1999).

A common bends symptom in goats was limb pain where the affected limb, often the foreleg, was raised (Figure 4a). Pain was detected by "urgent bleating and continual restlessness" with the goat often gnawing at the affected area "such as the testicles;" temporary paralysis noted about 15 min after decompression with improvement within 30 min and the animal being "quite well" the next day. Permanent post-decompression paralysis also occurred where the hind legs were noted to be paralyzed immediately with any spontaneous improvement followed by a permanent relapse (urinary retention and an acute gut distension were also noted). "Obviously ill" goats were noted to be apathetic, refusing "to move or to be tempted with corn (of which goats are inordinately fond)." Dyspnea, a sinister symptom usually occurring just before the animal died was also observed. Importantly, Haldane's data showed that goats had an individual variability and susceptibility to decompression sickness.

Figure 4a. Bends of foreleg in a goat.
Both figures from Boycott *et al.* (1908).

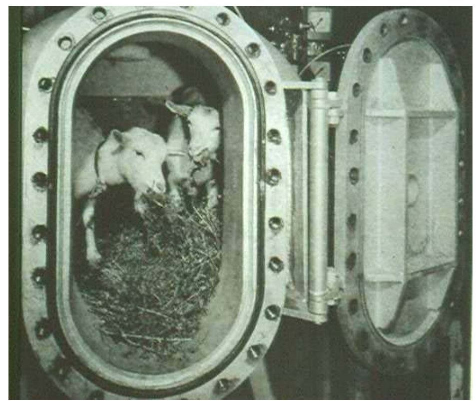

Figure 4b. Goat chamber dives.

Diving tables were published in 1907**,** the Royal Navy adopted them for military divers in 1908, and the U.S. Navy adopted them in 1912. They became the Blue Book for civilian divers who felt no discomfort after ascending from 210 ft (64 m). Referring to applied physiology, Richard Haldane, John Scott's brother, stated "Dr. Haldane has shown yet one more instance of the application of science to practical work." Haldane continued to think about the decompression problem for the rest of his life, considering how to extend and extrapolate the tables.

The S.S. *Laurentic* (White Star Lines), built by Harland & Wolff at their Belfast yard, went down the slipway on 29 April 1909 at the time that construction on the *Titanic* started. Captain Reginald Norton was chosen to carry 43 tons of gold bullion from Great Britain to Canada. On 25 January 1917, she struck a mine and sank within an hour in 130 ft (40 m) of water in Lough Swilly, Donegal, Ireland, with a huge loss of life and all the gold bullion. In 1906, Commander Guybon C.C. Damant had set a world diving record of 210 ft (37 m) during Naval endurance diving tests. His experiences as a salvage diver were well known to the Admiralty. In 1917, the 36-year-old Damant's dive team included Augustus Dent. He was aboard S.S. *Laurentic* when she sank and knew where the bullion room was. Between 1917 and 1924 this incredible salvage operation recovered 3,186 of the 3,211 missing gold bars. In 1932, an additional five bars were recovered by another salvage operation. Twenty gold bars, currently worth some £10 million, are still unaccounted for at the bottom of Lough

Swilly. Over 5,000 salvage dives were conducted using Haldane's tables in a 200 yd^2 working area at 120 ft with no loss of life or serious problems.

Death - The End
Naomi Mitchison reported that her father "had a look of intense interest in his face, as though he was taking part in some crucial experiment in physiology which had to be monitored carefully… It made me feel that was an experience deeply worth having." Born into a Scottish aristocratic family whose motto was "suffer," Haldane certainly suffered for his science (Anon. 1936). His life was "the greatest sustained physiological experiment in the history of the human lung" (Goodman, 2007).

100 Years after Haldane and the Future of Diving

In celebration of Haldane's work, the Baromedical and Environmental Physiology Group of the Norwegian University of Science and Technology, Trondheim, convened the international symposium *The Future of Diving: 100 Years of Haldane and Beyond*, December 18 and 19, 2008 (Lang and Brubakk, 2009). Presented below are some examples of the Haldane Symposium historical and future-direction research highlights to illustrate our trajectory since 1908 and new directions currently being investigated in an effort to increase our understanding of the systemic disease called decompression illness.

The first half of the 20^{th} century was spent adjusting the ratios, the second half with ascent rules, Workman's M-values, the Thalmann algorithm, probabilistic models, bubble models, and deep stops, but HALDANE STILL RULES! (Doolette, 2009).

Wisloff *et al.* (2004) investigated the effects of exercise at different intervals before diving rats to 196 ft (60 m) for 45 min on air. Exercise performed 20 h before diving resulted in lower bubble scan grades and increased survival times. Møllerløkken *et al.* (2006) reported from their diving study using pigs (3 h, 130 ft [40 m] dive - 0.35 ATA PO_2) on the role of nitric oxide (nitroglycerine administered at 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 30 min pre-decompression) in preventing vascular bubble formation after decompression. Richardson (2009) discussed exercise performed 24 h prior to decompression (and during decompression stops) as not harmful, but instead appearing to protect from DCS, reinforcing that a reduction in the number of venous gas bubbles may be related to the reduced risk of DCS. The mechanism appears to be NO-related and thus the administration of an NO donor might be a reasonable pharmacologic alternative to exercise. Dujic *et al.* (2004; 2005a; 2005b; 2006; 2008) concluded from a series of experiments that reducing the number of bubbles could be accomplished by exercise before, during decompression and after diving, and an NO donor. Asymptomatic cardiovascular and endothelial dysfunction after diving lasted for several days after a single field dive with unknown long-term effects. Acute and long-term use of antioxidants may prevent some of these effects, but not all.

Kayar *et al.* (2001) continued investigations of biochemical decompression by asking whether a capsule of *Methanobrevibacter smithii* could stop pathology pathways activated by bubbles (*e.g.*, inflammatory cascade activation**,** platelet activation**,** vascular endothelial biochemistry alterations) by converting inert gas to non-gas molecules. The proof of concept was established in small and large animal models where inert gas was eliminated from tissues by converting hydrogen and carbon dioxide to methane and water. The greater methane release correlated with lower DCS risk.

Perdrizet (1997) continued investigations of heat-shock proteins, cellular response to stress and hyperbaric oxygen therapy stress pre-conditioning. Blatteau *et al.* (2007), on the topic of dehydration prior to diving, observed that the uptake of inert gas by a particular tissue depended on the rate of blood flow to the tissue and dehydration-induced hypovolemia reduced stroke volume. A single predive sauna session significantly decreased circulating bubbles after a chamber dive, which may reduce the risk of DCS. Heat-exposure induced dehydration and NO pathways could be involved in this protective effect. Because heart rate was unchanged after the sauna session, it was hypothesized that blood flow could be reduced at the start and during the dive, thus limiting inert gas load and bubble formation afterwards. A rise in flow-mediated dilation was observed, suggesting an NO-mediated effect on endothelial function after a single sauna session.

Fahlman *et al*. (2006) are convinced of the untapped diving physiological knowledge to be gained from studying natural divers, marine mammals, which probably live with extremely high blood- and tissue-N_2 levels. Diving adaptations such as lung collapse, tracheal compression and behavioral responses may be important in reducing bubble formation. Future marine mammal studies should determine if biochemical adaptations reduce DCS risk.

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