Does the Lung Pump Oxygen?

A short history of a classical controversy.

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In the summer of 1984 we mounted the first British physiological expedition to Pikes Peak in Colorado since the 1911 expedition led by the great Oxford physiologist J S Haldane. Our team included Edward Williams and Michael Ward of the Alpine Club and five other 'Gentlemen Physiologists'. We could find no evidence of the Haldane expedition and the Summit House where he and his team worked has been replaced by a grander tourist shop and cafe. Since returning I have been re-reading his original papers in which he sets out his evidence, gathered on this expedition, for the idea that the lung can pump oxygen into the body when man becomes acclimatized to high altitude.

All readers of the *Alpine Journal* are aware of the way high altitude reduces physical performance. Accounts of climbing on Everest and other very high peaks always emphasize the desperately slow rate of climbing, a few slow steps then a pause for gasps of air. The problem for the body stems, of course, from the lack of oxygen, or strictly from the low pressure of oxygen in the air.

However, while the low oxygen pressure is the same for everyone, people seem to vary a lot in their ability to cope with the problem; also the same individual improves with time spent at altitude due to the process of acclimatization. It was these considerations amongst others that led Haldane to support the theory that the lung was able, if necessary, to pump or secrete oxygen from the air into the blood against a pressure gradient. This ability, like most human (or animal) abilities, would be expected to vary from person to person accounting for the differences in response to high altitude. Also, like athletic training, this ability could develop over time accounting, in part, for the process of acclimatization.

The alternative theory was that oxygen passed from the air in the lungs to the blood by simple diffusion down a pressure gradient. The main protagonist for this 'diffusion only' theory was the equally famous physiologist from Cambridge, Joseph Barcroft. But neither of these men claimed originality for their theories. They represented the last and most colourful antagonists in a controversy which had lasted for at least 40 years before their time.

Up until the mid-nineteenth century if the transport of chemicals across living membranes was considered at all it was assumed to be by passive diffusion. Then it came to be appreciated that in some organs, for instance the kidney and bowel, membranes could pump certain chemicals across against a concentration gradient. In the kidney urea is pumped out in to the urine to a higher concentration than it is in the blood. Various glands were shown to secrete substances out of or into the blood uphill against concentration gradients. Could the lung be considered as an oxygen gland?

Continental Physiologists

Ludwig, a German physiologist in Leipzig seems to have been the first to suggest gas secretion by the lung in the mid-nineteenth century. He and his school published work suggesting that the lung secreted carbon dioxide out of the lung and probably oxygen inwards. This led his rival Pfluger in Bonn with his pupils to carry out experiments to disprove this notion and to their satisfaction they showed in 1871 that simple diffusion was adequate to account for oxygen transport.

However, this work was done with instruments which were far too crude to measure the partial pressure of gases in the blood to the accuracy needed to prove or disprove the rival theories.

Next on the scene in 1890 was the great Danish physiologist Christian Bohr, one of Pfluger's pupils. He improved the instrumentation and with his students carried out more exact experiments and came to the conclusion that under certain conditions carbon dioxide and oxygen were secreted. But in 1894 Fredericq, in Liege, claimed diffusion was adequate. Then in 1897 Haldane and Lorain-Smith published their first studies on the subject claiming the demonstration of oxygen secretion. So about the turn of the century the controversy was nicely balanced.

The Kroghs

August Krogh, a young pupil of Bohr and also a Dane, set out to prove his chief and the secretion theory to be correct. He improved the instrument for measuring blood gases, the aerotonometer, so that he could be certain about the relative values of lung and blood oxygen and carbon dioxide partial pressures. This was the crucial evidence for either theory. To his surprise he found that the blood (arterial) oxygen was always less than the lung oxygen even when the animal breathed a low oxygen mixture. His chief had been wrong.

Before publishing these findings Krogh did a lot more work on the different aspects of the problem. In some of this he was very ably helped by his physician wife Marie. In particular she devised a solution to the problem of estimating the capacity of the lung to diffuse oxygen across into the blood.

One of the arguments in favour of the secretion theory was that it was thought inconceivable that simple diffusion could account for the transfer of as much as five or even six litres of oxygen per minute which is required by a top athlete when running flat out. In order to refute this argument the Kroghs wanted to measure the diffusing capacity of the lung for oxygen, as did other physiologists of the day. To do this they needed to know the amount of oxygen taken in per minute, which was a standard measurement, and the driving pressure for oxygen. To measure this pressure they needed to know not only the pressure of oxygen in the lung, which was not too difficult, but also the mean pressure in the blood capillary. This last was impossible to be certain about. Marie's solution was to bypass this difficulty by using a trace concentration of carbon monoxide in the gas breathed and measuring the diffusing capacity of the lung for this gas. Carbon monoxide is a look-alike to oxygen in that it is taken up by haemoglobin in the blood in the same way as oxygen only more so. The advantage was that one started with no carbon monoxide in the

body and so the driving pressure was simply the pressure in the lung of carbon monoxide. This could be measured. The value of diffusing capacity for carbon monoxide could be converted to that of oxygen from the known physical properties of the gases. The upshot was that the lung was shown to be a very good diffuser of oxygen. This is partly because it has an enormous surface area for gas exchange and partly because haemoglobin is so good at taking up oxygen. They showed that given the diffusing capacity they had measured, simple diffusion alone was adequate to transfer oxygen, even on exercise or when breathing low oxygen mixtures. And so another plank in the oxygen secretion theory was removed.

It is interesting and rather sobering to realize that Marie's work lay ignored by physicians for the next 35 years until it was rediscovered on the other side of the Atlantic in 1950 by Kety working with Comroe. They were interested in tests of lung function for use in patients with various forms of lung disease. What more crucial test of lung function than its ability to transfer oxygen? So Marie's measurement of diffusing capacity for carbon monoxide gradually became a routine clinical test and the total capacity divided by the lung volume is often known now as the 'Krogh factor'.

After August and Marie had amassed all their data on the subject they published their work in 1910 in a series of seven short papers which they afterwards referred to as 'The seven little devils'. August wrote in the introductory paragraph to the first devil; 'The results were contrary to our expectations and the publication has been put off till now in order that the problem might be approached in some other ways and conclusions reached representing, if possible, some sort of finality in the protracted discussion of this most complicated subject.' Wishful thinking on Krogh's part because the controversy in Britain was only just getting started.

J S Haldane

John Scott Haldane was born in 1860 of a distinguished Scottish family. His brother became Secretary of State for War during the First World War. After studying medicine at Edinburgh he worked first at Dundee then moved to Oxford where his uncle was professor of physiology. Haldane had become interested in air and what made it 'foul' under various conditions. He invented an apparatus for the accurate measurement of carbon dioxide and oxygen in air that is still used, in modified form, as the reference method in this field. With this he showed that in stuffy rooms the carbon dioxide level rises (slightly) and oxygen falls. This work led to work on the chemical control of breathing. He showed that carbon dioxide was the main stimulus, oxygen lack being a less sensitive drive (at sea level) as an earlier German physiologist (Mischer Rush) put it. 'Carbon dioxide spreads its wings over the oxygen needs of the body.' Haldane was, of course, fully aware of the importance of oxygen lack, anoxia as it was then called, and wrote, 'Anoxia not only stops the machine, it wrecks the machinery.'

Foul air was a particularly serious problem in the mines and Haldane was soon investigating the different forms of it. 'Black damp' he showed was 87% nitrogen and 13% carbon dioxide. 'After damp', found after an explosion, he

found to have a high percentage of carbon monoxide. He reported after one mine explosion that of 57 bodies recovered only four had died of the violence of the explosion, the rest of carbon monoxide poisoning. He investigated the time course of carbon monoxide poisoning in mice and men; mainly on himself as subject. He showed that in small animals or birds the time course was much faster. He therefore advocated the use of a canary as a test for carbon monoxide.

His work on carbon monoxide poisoning led him to devise a method for using it to calculate the partial pressure of oxygen in the blood. The method was rather indirect compared with Krogh's aerotonometer and until I started this article I thought it had not been used by anyone else. The measurement of carbon monoxide in the blood involved a titration step in which the colour of one tube was matched to that of a standard tube while adding a solution drop by drop. The result is calculated from the amount of solution necessary to achieve a colour match. It is all too easy in such a situation, consciously or unconsciously, to add a drop or two too much or too little according to the result desired.

So using this method he published, first in 1897, his finding that sometimes the arterial oxygen was higher than lung oxygen indicating that oxygen secretion takes place. He later withdrew these results because he had used factors for the oxygen/carbon monoxide relationships in blood derived from ox blood. But in 1912 he published again using values from each subject's own blood. In this study he found that while breathing a low oxygen mixture, especially if some exercise was performed, there was evidence of secretion.

Pikes Peak Expedition 1911

In 1911 Haldane with Douglas, his young colleague from Oxford, joined two American scientists, Henderson and Schneider, for a physiological expedition to Pikes Peak. This is a 4300m peak in the front range of the Rockies in Colorado. Even in those days the summit could be reached by a rack railway in about 3 hours from the town of Colorado Springs. There was a Summit House at the rail terminus on the flat top of the mountain. In this stone building the team lived and improvised their laboratory.

The views from the top were breathtaking. To the east one looked out over the checkerboard of Colorado Springs and over the Great Plains to a straight sea-like horizon. In all other directions were the peaks of the Rockies.

In his hundred page paper on the expedition in the Philosophical Transactions of the Royal Society, Haldane was allowed to expand on all aspects of the expedition in a way that is the envy of present day scientists. He described the symptoms of mountain sickness in his own party and the sufferings of tourists arriving after he had acclimatized. 'The walkers struggled in looking blue, cold, exhausted and miserable often hurrying out again to vomit.' A reporter became blue and faint and had to be revived with oxygen. It is strange how this contrasts with our experience in 1984. Amongst the tourists who only spent an hour or two on the summit we did not see any of these alarming symptoms. But to return to 1911, the physiologists made observations on themselves and one visitor. They noted the progressive decrease in lung carbon dioxide and increase in lung oxygen level from an initial reduced value, with acclimatiza-

tion. They recorded the rise in red cell number and haemoglobin concentration in the blood. They observed the extraordinary periodic breathing during sleep and obtained good records of the breathing pattern showing periods of cessation of breathing for up to 20 seconds. There are photographs of team members puffing up the steep incline of the railway with large rubberised canvas bags on their backs. These were the famous 'Douglas' bags for the collection of expired air.

But the finding which most excited Haldane was the evidence of secretion of oxygen. They carried out fifteen experiments on five subjects. Of these, in four oxygen was added to the inspired air and nitrogen in one. In the remaining nine experiments air was breathed. In all experiments the arterial oxygen was higher than the lung oxygen by an average of 36mm Hg indicating a significant secretion of oxygen by the lungs. Later Haldane was to insist on the importance of acclimatization in order to achieve oxygen secretion but his actual data show a 36mm Hg difference in the first experiment carried out on Pikes Peak. This was on Douglas seven days after arrival on the summit. Subsequent experiments on this subject showed no further 'improvement' with acclimatization. Oxygen breathing reduced but did not abolish oxygen secretion.

Thus by 1914 when the First World War halted much conventional physiology the question of oxygen secretion was very open, with the Copenhagen school maintaining that there was no such thing and the Oxford school insisting that the mechanism was available when oxygen was in short supply as at high altitude.

After the war the last great protagonist in the controversy arrived on the scene, Joseph Barcroft.

Joseph Barcroft

Barcroft was 12 years younger than Haldane. He was from an old Irish family with a country seat at Newry in County Down. He was sent to school in England and then to Cambridge where he read physiology. Though he went back to Ireland for holidays, Cambridge became his home for almost all his long, productive working life. He was soon involved in research and like Haldane did a lot of work on the way haemoglobin carries oxygen in the blood.

His first altitude expedition was in 1910 to Tenerife where at 3300m he studied the effect of altitude on blood/oxygen interactions. The following year while Haldane was on Pikes Peak, Barcroft was on Monte Rosa working from the salubrious hut on the Col d'Olen (3000m) and the far from salubrious hut on the Punta Gnifetti, the Cabana Regina Margherita (4572m). Again the objective was the study of the oxygen/haemoglobin complex in men at these altitudes and the changes in blood acidity.

During the 1914–18 War Barcroft was asked to investigate the problem of soldiers gassed by the Germans (as was Haldane). He realised that the men were dying due to lack of oxygen. The gas irritated the lungs producing excess fluid which hampered the free passage of oxygen. He therefore advised that they be treated in an atmosphere enriched with oxygen. To achieve this an oxygen tent was devised and certainly some lives were saved by these means. He also suggested that the same treatment would be helpful in treating pneumonia as

indeed it is, though we now, of course, use a small face mask rather than a tent enclosing the whole bed.

After the war, perhaps partly as a result of these experiences, he had a 'glass box' constructed in the laboratory at Cambridge in which a man could live and the atmosphere be controlled. Carbon dioxide could be scrubbed out and the oxygen percentage adjusted as desired.

In 1920 Barcroft carried out a six day experiment in this box with himself as the one subject. The objective was to test the oxygen secretion theory. In 1913 he and Cooke had been the first to get blood direct from an artery in a human subject for gas analysis. Using this technique he hoped to provide direct evidence for or against the theory. It was an heroic experiment. He lived for six days in the box while the oxygen percentage was gradually reduced until on the final day it was down to 10%, equivalent to over 5500m. He took exercise on a stationary bicycle and each day withdrew blood from a metal cannula tied into his artery at the wrist. After the experiment the artery had to be tied off. Most people can manage without this artery and fortunately Barcroft was one of these. His programme was full with observations on his pulse, breathing, exercising, collection of expired air, etc. He kept this up for the planned six days although on the last day he felt quite ill, presumably from mountain sickness.

The experiment showed that the pressure of the arterial blood oxygen was always lower than the lung oxygen even on exercise at the highest altitude equivalent. So there was no need to postulate any other mechanism than diffusion. Haldane objected that under laboratory conditions acclimatization might not have occurred and, though Haldane did not make the criticism, there was only one subject who might have been atypical in this respect.

So the next year Barcroft led an international expedition to Peru, one of whose objectives was to test the secretion theory again, this time on more subjects and at real altitude in the field.

The Cerro de Pasco Expedition 1921–22

This expedition was quite an ambitious one with eight scientists, five from the USA and three, including Barcroft, from Britain. The British contingent sailed across the Atlantic, through the Panama and south to Lima. There they met their American colleagues who had gone ahead and made preliminary arrangements.

Their destination was the mining township of Cerro de Pasco situated at 4300m on the Alto Plano over the spine of the Andes from Lima. It is not a pretty place, a high altitude slum, mostly, and even the Andes are not very dramatic at this point. But the drive up from Lima, and even more the rail trip is one of the most spectacular in the world. The great advantage of Cerro for a physiologist is its accessibility from sea level and a large resident population (about 25,000). Barcroft was fortunate in having the full backing of the Railway Company who gave him the use of a couple of box cars which were fitted out as laboratory and living accommodation. In this laboratory they made observations on themselves at Lima and later at Cerro.

There were numerous projects on the various ways in which the body adapts

to the low oxygen pressure. Amongst these were the measurement of arterial and lung oxygen using an improved method of arterial sampling with syringe and needle much as we do today, rather than the tied-in cannula used in the 'glass box' experiments. These measurements again showed in all subjects and under all conditions that the pressure of the arterial oxygen was always lower than the lung oxygen. Barcroft did not make a big issue of this fact in his reports of the expedition. He seemed now to have considered the matter settled in favour of the 'diffusion only' theory.

Barcroft became the authority on altitude physiology and his book *Lessons from High Altitude* became a minor classic. He seems to have been a most likeable man and though famous beyond physiological circles was always ready to listen to ideas and even criticism from younger workers. In the Second World War he did much work on nutrition and before that on neonatal physiology. But we remember him mainly for his altitude work. When asked about the cause of mountain sickness he is reputed to have replied, 'It would betray my nationality if I were to tell you that mountain sickness is caused by the oxygen which isn't there!'

In December 1922 the Royal Society arranged a public discussion in which, besides Barcroft and Haldane, T H Somervell and T G Longstaff took part, the latter two having recently returned from the 1922 Everest Expedition. Haldane maintained that, 'Mr Barcroft's results had not shaken the evidence furnished by the Pikes Peak expedition that increased oxygen secretory activity of the lung epithelium was the main factor in acclimatization', and he maintained that the fact that Somervell with Mallory and Norton had reached the astonishing height of 8200m without supplementary oxygen must mean that oxygen was being secreted by these well-acclimatized men. As late as 1936 the new edition of his book *Respiration* included a chapter on oxygen secretion by the lung. However, by the mid twenties the consensus view of physiologists was against him.

One pleasant aspect of this controversy was the courteous and magnanimous way in which it was conducted at least on the part of Krogh, Haldane and Barcroft. Krogh in the introduction to his 'Seven little devils' paid tribute to his teacher, Bohr, whose views he was about to rebut. Just after the Royal Society meeting mentioned above, Barcroft wrote in a review of Haldane's new book, 'No one who turns over the pages can but be impressed with the enormous advance which has been made in the physiology of respiration within the last thirty years, and the degree to which that advance has been due to Dr Haldane's work and to the stimulating influence which he has wielded over the minds of others.'

Where did Haldane, a brilliant and careful worker, go wrong and why did he persist in clinging to the secretion theory for so long? I have no quick and certain answer to these questions. I have hinted that there may have been bias, probably unconscious, in the rather subjective analysis used in the carbon monoxide method.

However, another possible explanation comes from the work of Ester Killick. She was a student of Haldane and worked as a physiologist in the Mining Department of Birmingham University. In 1938, using herself as

subject, she examined the effect of repeated exposure to carbon monoxide on the relationship between lung and blood levels of carbon monoxide. She used the same method for estimating carbon monoxide as had Haldane. She claimed that with these repeated exposures there developed a gradient of pressure between lung and blood for either carbon monoxide or oxygen! Her analyses were checked independently so there was unlikely to be an error there. An alternative explanation for her results could be that the relationship between carbon monoxide and oxygen affinity for haemoglobin becomes different in the body as compared to the test tube with repeated exposure. Whatever the explanation, Haldane's Pikes Peak results might have been due to this odd effect of repeated exposure to carbon monoxide in himself and his subjects.

But I am sure that Haldane was committed to the secretion theory and the results on Pikes Peak only confirmed his already strongly held view. This goes some way towards answering the second question. Why did he persist in holding to the secretion theory for so long? It was as if oxygen secretion had become an article of faith for him.

In his later years he wrote and lectured extensively about his philosophy of science and of life. Part of this was an abhorrence of what he believed to have been a wrong turning taken by physiology in embracing a highly mechanistic view of the body. A strange view in one who by using a most rigorous experimental approach himself had made so many important advances. However, there is no denying that there was this mystical side to Haldane, at least in his middle and later life when he sought to emphasise the wonder of nature and life. It was therefore more attractive to think of the delicate living membrane that separates air from blood in the lungs as having a secretory function, facilitating the transport of life-giving oxygen into the body, than that it functioned merely as an inert membrane allowing diffusion like an artificial sausage skin.

Haldane died in 1936 and Barcroft in 1947. The oxygen secretion controversy is part of the rich history of science along with the Phlogiston Theory and the Theory of Humours. Like them it was a good idea and though false was valuable in stimulating scientists to devise and carry out experiments to prove or disprove it. In the course of such work techniques were perfected, ideas were refined and science was advanced.