Joseph Barcroft’s studies of high-altitude physiology

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West JB. Joseph Barcroft’s studies of high-altitude physiology. Am J Physiol Lung Cell Mol Physiol 305: L523–L529, 2013. First published August 30, 2013; doi:10.1152/ajplung.00176.2013.—Joseph Barcroft (1872–1947) was an eminent British physiologist who made contributions to many areas. Some of his studies at high altitude and related topics are reviewed here. In a remarkable experiment he spent 6 days in a small sealed room while the oxygen concentration of the air gradually fell, simulating an ascent to an altitude of nearly 5,500 m. The study was prompted by earlier reports by J. S. Haldane that the lung secreted oxygen at high altitude. Barcroft tested this by having blood removed from an exposed radial artery during both rest and exercise. No evidence for oxygen secretion was found, and the combination of 6 days incarceration and the loss of an artery was heroic. To obtain more data, Barcroft organized an expedition to Cerro de Pasco, Peru, altitude 4,300 m, that included investigators from both Cambridge, UK and Harvard. Again oxygen secretion was ruled out. The protocol included neuropsychometric measurements, and Barcroft famously concluded that all dwellers at high altitude are persons of impaired physical and mental powers, an assertion that has been hotly debated. Another colorful experiment in a low-pressure chamber involved reducing the pressure below that at the summit of Mt. Everest but giving the subjects 100% oxygen to breathe while exercising as a climber would on Everest. The conclusion was that it would be possible to reach the summit while breathing 100% oxygen. Barcroft was exceptional for his self-experimentation under hazardous conditions.

Joseph Barcroft (1872–1947) (Fig. 1) was an eminent respiratory physiologist, and information is available about him in an extensive obituary (21) and a biography (13). This article deals with some of his studies at high altitude and related topics are reviewed here. In a remarkable experiment he spent 6 days in a small sealed room while the oxygen concentration of the air gradually fell, simulating an ascent to an altitude of nearly 5,500 m. The study was prompted by earlier reports by J. S. Haldane that the lung secreted oxygen at high altitude. Barcroft tested this by having blood removed from an exposed radial artery during both rest and exercise. No evidence for oxygen secretion was found, and the combination of 6 days incarceration and the loss of an artery was heroic. To obtain more data, Barcroft organized an expedition to Cerro de Pasco, Peru, altitude 4,300 m, that included investigators from both Cambridge, UK and Harvard. Again oxygen secretion was ruled out. The protocol included neuropsychometric measurements, and Barcroft famously concluded that all dwellers at high altitude are persons of impaired physical and mental powers, an assertion that has been hotly debated. Another colorful experiment in a low-pressure chamber involved reducing the pressure below that at the summit of Mt. Everest but giving the subjects 100% oxygen to breathe while exercising as a climber would on Everest. The conclusion was that it would be possible to reach the summit while breathing 100% oxygen. Barcroft was exceptional for his self-experimentation under hazardous conditions.

Barcroft was born in Northern Ireland and spent almost the whole of his working life in the University of Cambridge, UK. He carried out extensive studies in five different areas including metabolism of the submaxillary gland; physiology of hemoglobin including factors affecting the oxygen affinity; high-altitude physiology, particularly the determinants of the arterial PO2; physiology of the spleen; and neonatal physiology. He made important contributions in all of these areas and received many honors during his lifetime including Fellowship of the Royal Society and receipt of its Copley Medal, honorary doctorates from several universities, and a knighthood. The present article concentrates on four projects and relates some aspects that have not previously received much attention.

Glass Chamber Experiment of 1920

This is one of the most colorful episodes in the history of high-altitude physiology. Barcroft was the subject himself, and he lived continuously in a small sealed room for 6 days while subjecting himself to increasingly severe hypoxia. The conditions were heroic. In the process he surrendered ~2.5 cm of his left radial artery, nearly fainted during the blood-drawing procedure, needing brandy to revive himself, and all for a result with an n of 1.

Rationale for the experiment. This is clearly set out at the beginning of the article (5). The study was a direct response to the claim by John Scott Haldane (1860–1936) that the lung actively secreted oxygen across the blood-gas barrier. Much of the evidence for this came from the Pikes Peak expedition of 1911 that included Haldane and three other physiologists (12), and the results were published in 1913, seven years before Barcroft’s experiment. The report from that expedition stated that on the first day of the period of a month on the summit, altitude 4,300 m, the oxygen partial pressure in the blood exceeded that in the alveolar gas by 7 mmHg. Furthermore, as Barcroft noted, after 2 or 3 more days, and during exercise that doubled the oxygen consumption, the arterial PO2 exceeded that in alveolar gas by an average of 32 mmHg.

Haldane had originally become interested in the possibility of oxygen secretion by the lung following a visit to Christian Bohr (1855–1911) in Copenhagen. Haldane and Lorrain Smith carried out a series of experiments on animals that seemed to support the secretion hypothesis. Interestingly, Haldane retained his belief in oxygen secretion despite mounting evidence against it, throughout his life.

Barcroft was not the only person who was skeptical of oxygen secretion but he was determined to test the secretion theory. He pointed out that Haldane and colleagues had calculated the arterial PO2 from the oxygen and carbon monoxide concentrations in the blood after the subject had inhaled a small amount of carbon monoxide, and he argued that this indirect measurement of PO2 might be liable to error. For this reason Barcroft made direct measurements of the oxygen concentration of arterial blood by exposing the blood to a partial vacuum (4). He then calculated the oxygen saturation and derived the PO2 from his own oxygen dissociation curve that he had measured in 1910 during an expedition to Tenerife (1). It should be noted that, despite this direct challenge by Barcroft to Haldane’s belief, the two men were friends and in fact had previously worked together on methods of measuring the PO2 in small samples of blood (4). Although Haldane had his base in Oxford and Barcroft was in Cambridge, and Haldane held to the theory of oxygen secretion by the lung for the remainder of his life, these two eminent scientists remained cordial and spoke highly of each other’s work on several occasions.
Background of the glass chamber. Barcroft’s procedure of placing humans in a small closed glass chamber where they could inspire an altered oxygen mixture can be traced back to his work on gas poisoning during World War I (3). Barcroft’s family had been members of the Society of Friends (Quakers) for generations and were therefore noncombatants. Barcroft resolved this dilemma during the war by acting as a civilian attached to the army. Chlorine gas was initially used by the German army starting in April 1915, although apparently this new form of warfare did not have the support of the German High Command but came about because of a directive from the Kaiser himself (13). The initial physiological studies using the chambers were made on rabbits exposed to chlorine or phosgene, but later soldiers who had been gassed in the trenches were treated with 40–50% oxygen in the chambers. Interestingly, the idea of giving these patients an increased oxygen mixture to breathe was not immediately accepted, although today we would automatically use oxygen in the treatment of patients with acute inflammation of the lung caused by a noxious gas.

The glass chambers were relatively small having capacities of 10 or 12 cubic meters and they were constructed of plate glass supported by iron frames. Three of the chambers could be connected together. Carbon dioxide that accumulated in the chamber was removed by soda lime and excess water vapor was taken out by calcium chloride. Typically the patients remained in the chamber overnight but left it for 8 h during the day. The size of the chamber used in the experiment described here was not given, but the photograph (Fig. 2) shows that it was large enough to contain a bed and other equipment such as a cycle ergometer (19).

In his account of the experiment in 1920, Barcroft contrasts his use of a glass chamber in his laboratory with existing high-altitude facilities. For example, he describes the Margherita Hut on the Monte Rosa, altitude 4,559 m, as “but an improvisation as compared with the modern physiological laboratory.” He goes on to say that “at such places there is usually a certain amount of indigestion, sometimes constipation, sometimes diarrhoea, usually extreme cold. It is therefore open to dispute how far such symptoms as headache are due to disorders not directly connected with anoxic conditions.” By contrast, he claimed that the glass chamber in his laboratory meant that “every sort of convenience was accessible.” However, the limited hygiene facilities for a continuous stay of 6 days and nights in his glass chamber suggests that although laboratory equipment was no doubt accessible, the conditions in the chamber must have been spartan.

The long period of 6 days was chosen because Haldane and his colleagues had reported that the oxygen secretion ability of the lung increased over time at high altitude. For the same reason, Barcroft exercised on a stationary bicycle on the last day because this was also reported to increase oxygen secretion. Throughout the 6 days and nights Barcroft’s activities were closely monitored by 11 university students whose names are duly acknowledged at the end of the article. An interesting sidelight was that although the students reported that Barcroft appeared to sleep well at night, his own belief was different. He stated “My own view of the matter was quite otherwise. I thought I had been awake half the night and was unfreshed in the morning . . . the slumber was very light and fitful with incessant dreams” (2).

Nowhere does Barcroft refer to the difficulties of living continuously in the chamber for 6 days, although one wonders whether the British stiff upper lip attitude was a factor. He claimed that he “had been thoroughly well fed — a rather light breakfast, tea, eggs, bread and butter cooked by the attendant and lunch and dinner sent from the college kitchens.” An exception was when he awoke on the morning of the sixth day with what he refers to as “the typical symptoms of mountain
sickness, vomiting, intense headache and difficulty of vision.” He very reasonably attributed these symptoms to the hypoxia because by then he was at an equivalent altitude of 18,000 ft (5,486 m).

Experimental procedure. Barcroft entered the chamber on February 1, 1920 and the operative procedures to sample arterial blood were carried out during the evening of February 7. When he entered the chamber, the PO₂ of the air was given as 163 mmHg and this gradually fell as nitrogen was pumped in and oxygen was consumed by the subject. Barcroft analyzed the air in the chamber himself throughout the 6 days using a Haldane gas analyzer (14). The lowest inspired PO₂ was 84 mmHg on the morning of February 7. As stated above this was equivalent to an altitude of 18,000 ft (5,486 m), which was far higher than any existing high-altitude laboratory at the time. The removal of CO₂ from the chamber by soda lime was more efficient at the end than the beginning of the experiment, and during the last 48 h the PCO₂ varied from 3 to 5 mmHg.

The actual surgical procedure is described in detail. The operation on the radial artery began at 7:28 PM but by 7:30 to 7:40 it was recorded that the subject was “inclined to be faint” and as a result he was given tea and brandy. As a result he was “sufficiently himself to breathe through valves without the samples being invalid through looseness of grip with the lips.” The left radial artery was exposed for an inch and a half, a ligature was applied to the distal end, and a clip was placed on the proximal end. Then an incision was made in the artery to receive the cannula from which blood was withdrawn. This was done during both rest and exercise on the cycle ergometer, the total volume of blood removed being 83 ml. The exercise protocol was impressive, the total time being 37 min with the work rate varying between 350 and 386 kg·m·min⁻¹ (57–63 W). During the blood draws, alveolar gas samples were collected, thus allowing the difference between the PO₂ in alveolar gas and arterial blood to be measured.

Some details of the operative procedure are puzzling. This must have been carried out in the chamber while Barcroft was exposed to the hypoxia, but it seems unlikely that the person could do the operative procedure when acutely exposed to an altitude of 5,400 m. Perhaps he used an oxygen mask, but in this case it would be difficult to avoid contaminating the chamber with oxygen.

Experimental results. These are described in section 4 of the manuscript with the details given in Table XII. To be frank, the description of the results is not as clear as one would like. First there is a qualitative statement in the first paragraph that might raise eyebrows today. Barcroft stated that with the measured PO₂ in the alveolar gas of 57–68 mmHg, the oxygen saturation of blood with the same PO₂ would be expected to be between 80 and 90%. He then went on to say that when the first sample of arterial blood was drawn, “the blood looked dark” and from this he argued that this was evidence against oxygen secretion since if the PO₂ of the blood were a few mmHg higher than that of the alveolar gas as predicted by Haldane, the blood would be expected to have its usual red color. This is hardly convincing.

Table XII then shows the actual numbers. For the resting subject, the alveolar PO₂ was given as 68.4 mmHg. This comes from a procedure that Barcroft referred to as the Krogh method and consisted of collecting the last 2 ml of gas from each of a series of expirations in a glass tonometer. This value was then compared with the calculated arterial PO₂ of 60 mmHg. This PO₂ was derived from the measured arterial oxygen saturation of the blood sample and then by using a previously determined oxygen dissociation curve from Barcroft’s own blood (1). In this way for the resting subject the arterial PO₂ was calculated as 8.4 mmHg less than the alveolar value.

For the exercising subject, the alveolar PO₂ was given as 56.5 mmHg by the Krogh technique but 54 mmHg by a slight modification of this called the Haldane method. The PO₂ in arterial blood was again calculated from the measured oxygen saturation and oxygen dissociation curve and the value was 48 mmHg. Therefore the arterial PO₂ was some 6 to 8 mmHg lower than that in alveolar gas. Barcroft went on to say that the disparity between the PO₂ in alveolar gas and arterial blood was greater during work than during rest although the actual numbers do not seem to support this.

Barcroft then calculated what he called the “diffusion constant” during work. This was done by dividing the measured oxygen consumption of 750 ml per min by the alveolar-arterial PO₂ difference. The value was given as 107 ml (actually 107 ml/min). However, the basis of this calculation is questionable because the PO₂ of the blood in the pulmonary capillary during the loading of oxygen is not the arterial value but the gradual transition between the PO₂ of mixed venous blood and the arterial blood.

It was concluded that the results of these experiments disproved Haldane’s secretion theory because both at rest and during exercise the arterial PO₂ was less than the alveolar value. But in the final paragraph of the manuscript Barcroft gallantly remarked “We yield to none in appreciation of the accuracy of his observations.”

The reader of today comes away from this paper with somewhat conflicting emotions. Clearly this was a heroic experiment entailing what must have been 6 grueling days in a small enclosed space with the unpleasantness of the worsening hypoxia, not to mention the loss of one radial artery. On the other hand the method of measuring the arterial PO₂ was questionable with the value being derived from an oxygen dissociation curve measured several years previously. Perhaps the biggest limitation of all was that only two measurements were made, one at rest and another at exercise, and in only one subject. It is easy to imagine that Barcroft was looking for an opportunity to obtain additional data, and this was provided by the expedition to Cerro de Pasco that is described below. However, before moving to that, here is a brief description of another remarkable experiment carried out by Barcroft in one of his glass chambers.

Toxicity of Hydrocyanide Gas

As indicated earlier, Barcroft worked on gas poisoning during World War I. One of the gases being considered was hydrogen cyanide (HCN), and Barcroft volunteered to test the effects of this gas on himself and a dog. Although the experiment was carried out in 1917, the full report was not published until 1931 (3).

Barcroft and a dog weighing ~12 kg were simultaneously exposed to an atmosphere containing a concentration of what
was estimated to be 1 part in 2,000 of HCN gas in air. The results of the experiment were set out in Table V, which is reproduced here as Fig. 3. As the table shows, the dog became unsteady by 50 s and was unconscious by 1 min and 15 s. By 1½ min it developed tetanic convulsions and was thought to be nearly dead. A few seconds later Barcroft came out of the chamber, put on a respirator, and removed the dog. Five minutes after the initial exposure Barcroft felt a brief period of nausea and a little later noticed difficulty in maintaining attention during conversation. As the note at the bottom of the table indicates, the apparently dead dog was set aside for burial but in fact was found walking around next morning and fully recovered.

The reason for the striking difference in response of the dog and human to HCN is apparently still not understood. However, the paper states that there are species differences in the toxicity of HCN and, for example, the guinea pig is unusually tolerant. The toxicity of HCN is principally due to its inhibition of the enzyme cytochrome-c oxidase in mitochondria and this is highly conserved so the species difference is puzzling. Although this remarkable experiment is not strictly related to Barcroft’s high-altitude studies, it vividly demonstrates his willingness for self-experimentation and his courage.

### International High-Altitude Expedition to Cerro de Pasco, Peru

Barcroft was the principal organizer of this expedition although it was binational, with the group from Cambridge collaborating with a number of physiologists from Harvard. In all there were eight members of the expedition and the initial planning took place in the early summer of 1921, only a year and a half after the glass chamber experiment described above. The expedition itself was quite short. Barcroft and colleagues from Cambridge arrived in Lima, Peru on December 18, 1921, and they left Peru exactly a month later. The group from Harvard arrived in Peru 3 wk before the Cambridge team.

Cerro de Pasco is a mining town in the Andes ~200 km to the northeast of Lima. The town is on a slope but the altitude is often given as 4,300 m, which is the same as the summit of Pikes Peak. An advantage of the venue was a railway line from Callao, the port of Lima, all the way to Cerro, which greatly facilitated access to this high altitude. This arrangement is similar to that of the Pikes Peak expedition where the cogwheel railway to the summit made that an attractive venue. The railway in Peru was particularly convenient because a laboratory was set up in one of the baggage vans, and accommodation for expedition members was also available in other passenger cars. Figure 4 shows the laboratory.

The account of the expedition was published in the Philosophical Transactions of the Royal Society of London (7); by today’s standards it was extremely long with a considerable amount of narrative that is interesting but largely irrelevant from a scientific viewpoint. The table of contents on the first page essentially sets out all the scientific objectives, which numbered 16. However, it is clear that a major thrust was the issue of oxygen secretion, that is, the relationship between the alveolar and arterial PO2 at high altitude. Barcroft subsequently wrote a book about the expedition findings and added some new material (2).

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* Although the corpse was set aside for burial about 6.30 p.m., the dog did in point of fact recover, and was found walking about next morning. It showed no further symptoms.
Oxygen secretion. In the Cerro de Pasco study the arterial PO2 was determined by the “bubble” tonometric method described by Barcroft and Nagahashi (6). This was a modification of the technique originally introduced by Krogh (16). Table I in the report shows the arterial and alveolar PO2 values that were only measured on five people at high altitude. In the table Category I refers to the expedition members but only the results for Meakins are shown. Category II refers to mining engineers who were originally from low altitude but had been at Cerro for months or years. Category III refers to the high-altitude natives who had been at high altitude for generations. In only one of these was the alveolar PO2 given. As can be seen in the table, the alveolar PO2 exceeded the arterial value by 2, 7, 9, −1, and 1 mmHg.

The results were also shown in Fig. 11 reproduced here as Fig. 5. On the extreme left under the M are the results for Meakins, at sea level, at Cerro, and then on returning to sea level. The alveolar-arterial differences were small and in fact the measurement at high altitude showed an arterial value slightly above the alveolar value. To the right of Meakins' values are those for five engineers. To the right of these are the results of three people who were permanent residents of high altitude. Note that for seven subjects the arterial value was less than the alveolar value. In the case of Villarreal the alveolar value was not available.

The paper goes on to state that two main facts stand out: 1) There is no suggestion of oxygen partial pressures in the blood of 90–120 mmHg such as have previously been alleged to exist in dwellers at high altitudes. (This was a reference to the results of the Pikes Peak expedition.) 2) The pressures of oxygen in arterial blood are such as would naturally be brought about by diffusion.

Measurements of the arterial oxygen saturation were also made and were shown in Table II in the report. In five members of the expedition in whom measurements were made at Cerro during rest, the saturation varied between 81.5 and 91%. In two members measurements were also made during work, the values being 79 and 90.5%. In four mining engineers the saturations were between 86 and 91%. The three people who were permanent residents of the mountains had saturations between 82.3 and 86%. These last low values surprised the investigators because, as they stated in the article, they presumably indicated the low arterial oxygen saturations that these people lived with all their lives.

Other measurements of respiration and circulation. The increased pulmonary ventilation at high altitude was studied by measuring the alveolar PCO2 on many occasions; the mean value was ~28 mmHg as opposed to 40 mmHg at sea level. The discussion of possible causes for the increased ventilation is rather tortured and is reminiscent of a similar discussion by Haldane and his colleagues (12) on the results obtained on Pikes Peak. We now know that the mechanism was the stimulation of the peripheral chemoreceptors by the low PO2 in the arterial blood, but the chemoreceptors were not discovered by the Heymans father-and-son team until four years later (15).

There is a long section on the position of the oxygen dissociation curve at high altitude and the various factors influencing the oxygen affinity of hemoglobin. This was one of Barcroft’s primary interests. The results were somewhat confusing; part of the reason is that the investigators were not aware of the role of 2,3-diphosphoglycerate. Indeed, this was not discovered until 1967 (9, 11). However, the consensus was that the dissociation curve was shifted to the left, probably because of the reduced arterial PO2.

The shape and size of the chest in high-altitude permanent residents was studied in some detail including X-rays of the upper body. It was concluded that many of the highlanders had larger chests than would be expected from their height, which was generally less than that of the investigators.

In a novel series of studies, measurements of the diffusing capacity of the lung for carbon monoxide were made by using the technique developed by Marie Krogh (17). The equipment for this had been made available from Krogh’s laboratory. It was concluded by the investigators that there was no change in the diffusing capacity compared with sea level. However, it was argued that the tendency of the arterial oxygen saturation to fall with exercise could be explained by diffusion limitation across the blood-gas barrier. Barcroft carried out these calculations using the Bohr integration technique (10); his was the first clear demonstration of the diffusion limitation of oxygen uptake at high altitude.

Extensive studies were made of the increase in red blood cell concentration at high altitude. These essentially confirmed previous measurements made on the Pikes Peak expedition and elsewhere.

Neuropsychometric measurements. These studies were some of the most original of this expedition. A large series of mental tests were employed, including recognition of duplicate letters in a sequence; tests of handwriting, memorizing, and multiplication; and a general assessment of mental fatigue. The conclusion was that it was possible to carry out complicated cognitive tests accurately but this took more time than at sea level. Barcroft himself felt that concentration was more difficult and time was wasted in “bungling,” that is, being unable to organize tasks as effectively as at sea level. To quote the study, “Judged by the ordinary standards of efficiency in laboratory work, we were in an obviously lower category intellectually at Cerro than at sea level. By a curious paradox this was most apparent when it was being least tested. For perhaps what we suffered from chiefly was the difficulty of maintaining concentration. When we knew we were undergoing a test, our con-
centration could by an effort be maintained over the length of time taken for the test, but under ordinary circumstances it would lapse. It is, perhaps, characteristic that, while each individual mental test was done as rapidly at Cerro as at the sea level, the performance of the series took nearly twice as long for its accomplishment."

It was interesting that the engineers at the mine who were originally from sea level, but had spent several years at high altitude in some cases, were adamant that they were definitely incapable of doing their own sea-level standard of work at high altitude, whether mental or physical.

Acclimatization and its effectiveness. In the final section on “Summary and Conclusions” the three main factors that had a positive influence in acclimatization were listed as 1) an increase in total ventilation, 2) the leftward shift of the oxygen dissociation curve such that at any given PO2 the oxygen concentration is increased, and 3) the increase in concentration of the red blood cells.

Factors that were not helpful in acclimatization were listed as oxygen secretion, alterations in the lung volumes, diffusion properties of the lung, and the cardiac output, although measurements of the last were made by very indirect methods and conflicting results were obtained.

The final topic that was dealt with is of particular interest because the results were novel and sparked considerable controversy. The issue was whether the acclimatization process allowed the physiological state of people at high altitude to equal that of sea-level residents. As we have seen, Barcroft was able to make measurements on three groups of people at high altitude: the expedition members, the engineers, and the permanent residents.

Barcroft made the famous statement “All dwellers at high altitude are persons of impaired physical and mental powers.” There seemed to be good experimental evidence for this in the expedition members. Although formal measurements of work capacity were not carried out, it was clear to the members when they tried to walk uphill that their exercise ability was substantially reduced. In addition, as we have seen, there was impairment of mental ability.

No formal mental testing was done on the mining engineers. However, as mentioned above, the engineers themselves were adamant that their standard of both mental and physical work at Cerro was clearly less than at sea level.

When we come to the permanent residents at high altitude, the situation is not nearly so clear. Barcroft and his colleagues were very impressed by the ability of young people to carry heavy loads and by the fact that they played football at Cerro. However, no comparisons could be made of either physical or mental performance at high altitude and sea level. Therefore it was not reasonable for the expedition to extrapolate their own physical and mental limitations to the permanent residents. In fact the eminent Peruvian physician Carlos Monge Medrano took great exception to Barcroft’s remarks on the permanent residents and wrote “For our part, as early as 1928 . . . we proved . . . that Professor Barcroft was himself suffering from a subacute case of mountain sickness without realizing it. His substantial error is easy to explain as resulting from an improper generalization on his part of what he himself felt and applying his reactions to Andean man in general” (20).

It should be added that Barcroft took part in two brief earlier expeditions to high altitude, but these will not be described in detail here. The first was in 1910 when he was a member of an expedition to Tenerife in the Canary Islands led by Nathan Zuntz (1847–1920). Barcroft chiefly worked on factors affecting the position of the oxygen dissociation curve (1). However, he also made an interesting observation relevant to the contention of Mosso that the deleterious effects of high altitude were caused by the low PCO2. During this expedition Barcroft, who had an almost normal PCO2 and therefore a low PO2 at high altitude, developed obvious acute mountain sickness. By contrast, Douglas, who remained well, had a much lower PCO2 and higher PO2. Barcroft pointed out that this anecdotal observation supported Paul Bert’s contention that hypoxia was the most important factor rather than Mosso’s suggestion of a low PCO2.

Barcroft also spent some time at the Capanna Margherita in 1911 where again he worked mainly on the oxygen affinity of hemoglobin and the position of the oxygen dissociation curve.

Exercise at Extreme Altitude While Breathing 100% Oxygen

In 1931 Barcroft participated in a remarkable chamber experiment that has received little attention. Unlike the two projects already discussed, the glass chamber experiment and the Cerro de Pasco expedition, Barcroft was not the primary instigator of this study. It was the brainchild of Rodolfo Margaria (1901–1983), who was Professor of Physiology at the University of Milan and who made many important contributions to the physiology of exercise, including exercise at altitude. The study was carried out in a low-pressure chamber in Oxford by Margaria, Barcroft, Douglas, and Kendall (8). Douglas was a longtime associate of J. S. Haldane and was an important member of the Pikes Peak expedition referred to earlier. L. P. Kendal was a colleague of Douglas’s at Oxford.

The low-pressure chamber in which the studies were carried out had an interesting history. It was originally constructed in Lancaster, Pennsylvania, to test the effects of low barometric pressures on US aviators during World War I and train them to deal with these. The chamber was 2.7 m high and 2.1 m in
diameter and was shipped to a US Air Service base in Issoudun in central France, where it arrived in September 1918. However, the Armistice was signed on November 11 of that year and so little use was made of the chamber. With the end of the war the question arose of what to do with it.

Georges Dreyer (1873–1934) was Professor of Pathology at Oxford University and had worked extensively on oxygen equipment for aviators including periods with the US Air Service. The upshot was that the chamber was donated to Oxford in 1919, where it was set up in the Department of Pathology. Interestingly, a series of experiments were carried out on George INgle Finch (1888–1970) in 1921 because he planned to take part in the Everest Reconnaissance Expedition of that year (22). However, the chamber was not extensively used for physiological measurements and indeed the work of Dreyer on the use of oxygen at high altitude has been largely forgotten (23).

Margaria’s interest in exercise at extreme altitude was prompted in part by the early British expeditions to Everest. In 1924 E. F. Norton reached an altitude only 300 m short of the summit (8,848 m) without supplementary oxygen. During the same expedition, Mallory and Irvine set out for the summit using supplementary oxygen but never returned. In 1930 Margaria had studied the effects of reducing barometric pressure on maximum exercise in a low-pressure chamber and concluded that, at a barometric pressure of 300 mmHg, the work rate of humans fell to zero (18). He therefore argued that it would be impossible for climbers to reach the summit of Mt. Everest (barometric pressure ~250 mmHg) without supplementary oxygen, but he wondered to what extent the maximal work rate would be increased during oxygen breathing.

The actual experiment was carried out on February 20, 1931 (8). The exercise protocol consisted of stepping on and off a box 33 cm high every 4 s for an hour. This procedure was chosen because it was thought to be a reasonable estimate of the work rate required for a climber to reach the summit. Barcroft reported the results of the experiment at a meeting of the Physiological Society on March 14, 1931, and Franklin (13) reproduced the blackboard drawing made by Barcroft at the time (Fig. 6). Note that Margaria is stepping on and off the box while breathing 100% oxygen, and Barcroft, also breathing oxygen, is keeping watch within the chamber. Douglas is outside the chamber smoking his pipe.

Two protocols were studied. In the first, the barometric pressure was 240 mmHg, which was equivalent to an altitude above that of the Everest summit, where the pressure is ~250 mmHg. Margaria exercised for 1 h and at the end of that time stated that he could continue indefinitely. However, he complained of acute pain in the extensor muscles of both legs and both knees although he had only been exercising with one leg. Kendall repeated the protocol and also reported the same leg pain.

For the second protocol the pressure was reduced to 170 mmHg and both men were able to complete the 1-h exercise although they felt that they could not have done this at a lower pressure. Near the end of the exercise, Margaria’s pulse rate was only 88 min−1 whereas Kendall’s was 164.

The pain reported by both men is fascinating. In retrospect this was almost certainly due to decompression sickness since they went into the chamber with a full load of nitrogen in their tissues and the combination of the low barometric pressure and oxygen breathing would have greatly accelerated nitrogen elimination. This may have been the first reported instance of decompression sickness caused by a low barometric pressure.

Barcroft went on to calculate the amount of oxygen that would be necessary to reach the Everest summit and return and came up with a figure of 700 liters. He stated that the weight of this would only be a kilogram, a trifling amount, but he recognized that the weight of the cylinders would be substantial. He was not to know that Everest would not be climbed using oxygen for another 22 years, and that it would be another 25 after that before the first ascent was made without supplementary oxygen.

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7. Barcroft J, Binger CA, Bock AV, Doggart JH, Forbes HS, Hartridge H. The work rate required for a climber to reach the Everest summit (8,848 m) without supplementary oxygen. During the expedition, Mallory and Irvine set out for the summit using supplementary oxygen but never returned. In 1930 Margaria had studied the effects of reducing barometric pressure on maximum exercise in a low-pressure chamber and concluded that, at a barometric pressure of 300 mmHg, the work rate of humans fell to zero (18). He therefore argued that it would be impossible for climbers to reach the summit of Mt. Everest (barometric pressure ~250 mmHg) without supplementary oxygen, but he wondered to what extent the maximal work rate would be increased during oxygen breathing.

The actual experiment was carried out on February 20, 1931 (8). The exercise protocol consisted of stepping on and off a box 33 cm high every 4 s for an hour. This procedure was chosen because it was thought to be a reasonable estimate of the work rate required for a climber to reach the summit. Barcroft reported the results of the experiment at a meeting of the Physiological Society on March 14, 1931, and Franklin (13) reproduced the blackboard drawing made by Barcroft at the time (Fig. 6). Note that Margaria is stepping on and off the box while breathing 100% oxygen, and Barcroft, also breathing oxygen, is keeping watch within the chamber. Douglas is outside the chamber smoking his pipe.

Two protocols were studied. In the first, the barometric pressure was 240 mmHg, which was equivalent to an altitude above that of the Everest summit, where the pressure is ~250 mmHg. Margaria exercised for 1 h and at the end of that time stated that he could continue indefinitely. However, he complained of acute pain in the extensor muscles of both legs and both knees although he had only been exercising with one leg. Kendall repeated the protocol and also reported the same leg pain.

For the second protocol the pressure was reduced to 170 mmHg and both men were able to complete the 1-h exercise although they felt that they could not have done this at a lower pressure. Near the end of the exercise, Margaria’s pulse rate was only 88 min−1 whereas Kendall’s was 164.

The pain reported by both men is fascinating. In retrospect this was almost certainly due to decompression sickness since they went into the chamber with a full load of nitrogen in their tissues and the combination of the low barometric pressure and oxygen breathing would have greatly accelerated nitrogen elimination. This may have been the first reported instance of decompression sickness caused by a low barometric pressure.

Barcroft went on to calculate the amount of oxygen that would be necessary to reach the Everest summit and return and came up with a figure of 700 liters. He stated that the weight of this would only be a kilogram, a trifling amount, but he recognized that the weight of the cylinders would be substantial. He was not to know that Everest would not be climbed using oxygen for another 22 years, and that it would be another 25 after that before the first ascent was made without supplementary oxygen.

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