Some facts and some thoughts on the history of oxygen uptake and its measurement

By Dr Paul Older JUNE 2007

Introduction:

Cardiopulmonary exercise testing (CPET), based upon the high-density profiles of the ventilatory and pulmonary gas exchange responses, is a relatively new medical technology and was not used to any extent clinically until 1975. In that year Karlman Wasserman and Brian Whipp wrote a 'State of the Art' paper on "Exercise Physiology in Health and Disease"[1].

This essay traces the history of the physiology and the development of the technology used for CPET in the evaluation of cardiovascular, pulmonary and metabolic functioning. Cardiac failure, for example, is increasingly recognized as a major cause of postoperative mortality[2,3]. Thus CPET embraces both the world of medicine and the world of surgery.

In order to understand the assumptions underlying the use of the metabolic "cart" (the major tool for CPET) it is necessary to be familiar with the history of its development. It is appropriate to start the modern development with the measurement of the uptake of 'dephlogisticated air'[4] in the 18th Century and to continue through to the sophisticated science and technology that it has become in the 21st Century.

This history starts with some details regarding Antoine Laurent Lavoisier (1743-1794) who was the first person to measure oxygen uptake during exercise in 1783[5] in Paris. Therefore, I have chosen the latter part of the eighteenth century as a starting point for this account.

A perspective of Antoine Lavoisier

Much of the detailed information on the 'father of modern chemistry' that is presented in this essay is sourced from three books.

First the work of Robert Kerr (1755-1813) who in 1789 translated the work of Lavoisier, *'Traite elementaire de Chimie, presente dans un ordre nouveau et d'apres les decouvertes modernes'*. This work is often referred to as 'Traite' and is part of his book '*Antoine Lavoisier: Elements of Chemistry*'[6]

Second Lawrence Holmes who, in 1895, published his book *'Lavoisier and the Chemistry of Life. An Exploration of Scientific Creativity'*[5]. The book covers the period of the life of Lavoisier from 1773-1792.

Finally, I am indebted to Douglas McKie who, in 1952, wrote the book *'Antoine Lavoisier. Scientist, Economist and Social Reformer'*[7]

Lavoisier was working in the last three decades of the 'Scientific Enlightenment' in the eighteenth century, an era that commenced with the beginning of the 18th century; a period of major scientific change[8]. At that time the word *'science'* did not have its current meaning, and the term *'scientist'* had not been invented. Not only were there major theoretical and experimental developments throughout the century but also the way in which 'scientists' were working was radically changing. The period from 1750-1830 corresponds to the Industrial Revolution in England. This gave a big boost to scientific research by stimulating interest in such issues as heat in general and thermodynamics in particular. Lavoisier felt that he had also started a revolution in that his new Scientific Order was incompatible with the old[8]. This concept of scientific progress is supported by Thomas Kuhn in his famous book 'The Structure of Scientific Revolution'[9]. Kuhn, I think, would have accepted the work of Lavoisier as a 'Paradigm shift' in knowledge.

At the beginning of the 18th century, science was highly philosophical; at its end, science had added to that philosophy with mathematics (e.g. Jean Fourier 1768-1830, Pierre Laplace 1749-1827) and

mechanics (e.g. Thomas Newcomen 1664-1729, James Watt 1736-1819)♣. At the beginning of the century chemistry was alchemy, at the end it was a science[8].

Lavoisier, who had initially followed in his fathers footsteps and qualified as a lawyer in 1763, rapidly became attracted to chemistry and geology. To understand the genius of Lavoisier it is necessary to see 'science' as it was in the early 1600's up to late 1700's.

The period starting with Johann Van Helmont (1579-1644) and ending with Lavoisier, represented the transition from alchemy to chemistry. Van Helmont was the first person to recognize that 'fixed air' or 'gas sylvestre' (carbon dioxide) was a product of respiration[7]. He also invented the word 'gas' probably from the word 'chaos'.

During this period Isaac Newton (1643-1727) said that *'if I have seen farther than others, it is because I have stood on the shoulders of giants'*[10]. Lavoisier was, in some ways, the Newton of medical physiology. Johann Becher (1635-1682) and his disciple Ernst Stahl (1660-1734) together conceptualized and developed the phlogiston theory.[8] Lavoisier falsified this theory and replaced it with his theory of the composition of air; this was the paradigm shift in knowledge.

The 'discovery' of oxygen and the demise of phlogiston

The situation in 1774 was that it was widely held that there was an element, phlogiston, which was released when a substance underwent combustion. It was thought that animals could only exist for a short while in a limited amount of air as respiration apparently released more and more phlogiston. Respiration thus resembled combustion. When metals were combusted they gave up the phlogiston and formed what was termed 'calces' (literally 'ashes').

Enter, Joseph Priestley (1733-1804): a non-conformist minister, of originally Calvinist background and a staunch supporter of the French and American (1763-1783) Revolutions, had discovered a 'new air' in 1774. This air was prepared from mercuric oxide and was more able to support combustion than 'common air'; this he termed 'dephlogistigated air' and he said that 'the new air was five or six times as good as common air'! This 'new air' was considered to be 'ordinary air' liberated of all its phlogiston.[11] It was remarkable in that it could support respiration better than 'common air' and for that reason it was named by Lavoisier as 'vital air'. Scheele had discovered what he called 'fire air' in 1771 but never published his findings so probably it was Scheele not Priestley who discovered oxygen[5]. It is difficult to be certain who did actually 'discover' oxygen but the work of Scheele ran concurrently with that of Lavoisier and probably Priestley. We do know that these three chemists knew each other. Whilst Lavoisier published his findings on the 'airs' in 1777, there was no publication in French of the work by Scheele until 1780 and 1781 when a French translation of Scheele's original German treatise *"Chemical Treatise on Air and Fire"* was published[5]. This had been written also in 1777. Lavoisier was therefore less than kind when he took the credit for these findings and published that *'M. Scheele has repeated these same experiments'*[5]. The story may not end there for in 1621 a 'Netherlander', Cornelius Jacobszoon Drebel (1572-1633), built a submarine that, with six oar power, was rowed up the Thames at a depth of 4-5 metres. There are several stories about how the crew managed without succumbing to hypoxia. The most beguiling is that he introduced a container of 'aerial nitre' (oxygen, but he did not know that). This, he wrote, could be manufactured from heating saltpeter. It is known that he did create 'aerial nitre' but it is not certain that he used that in his submarine. A less romantic explanation is that he had tubes going to the surface to replenish stale air. Whichever is to be believed, however, he can certainly be considered to have 'discovered' oxygen some 150 years before Scheele or Priestley♠.

A little of French history and the demise of Lavoisier

The middle to late part of the 18th century was a time of great unrest for France as well as for America and England. Louis XVI of France was supplying arms and explosives to America and Lavoisier had performed a lot of work in developing these explosives[8]. The open support by Priestley of both the French and American revolutions was provocative. He openly supported the storming of the Bastille. This and other indiscretions forced him to emigrate to America in 1794[8]. It was the French revolution so beloved by Priestley, which finally saw the demise of his friend Lavoisier.

In 1772 Lavoisier had made a discovery that would forever invalidate the phlogiston theory. In a series of experiments he showed that sulphur and phosphorus actually gained weight during combustion.[6] If

♣ Many of the remarkable machines devised and built by Newcomen and Watt are on display in Manchester (UK) Museum featuring equipment from the Industrial Revolution.
♠ http://en.wikipedia.org/wiki/Cornelius_Drebbel Last accessed 3rd February 2007

this was so then phlogiston, which was always lost during combustion, must have a negative mass! Lavoisier flawed the old theory that the *calces* of metal were lighter than the parent metal by extremely accurate experiments and thus persuaded his peers to accept his new theory. Much of Lavoisier's success came from this ability to measure weights and volumes with great accuracy. In 1779 Lavoisier named the combustible component of air, '*principe acidifiant'* or '*principe oxygine'* (from the Greek, οξυς, acid, and γεινομαι, I beget)[6]. The non-combustible component he named, azote (or no-life).

What was needed now was an alternative theory to explain combustion and respiration. Lavoisier and his colleague Pierre Laplace (1749-1827) suggested, erroneously, that combustion of oxygen took place in the lungs. It was Eduard Fluger (1829-1910) who showed in 1870 that metabolism occurred in the periphery and that the blood merely transported the oxygen and carbon dioxide[12]. In 1783 Lavoisier had performed a series of experiments in conjunction with Laplace. These related more to the question of heat production of small animals during exercise than oxygen uptake.[5] However experiments with similar apparatus was used to investigate the metabolic rate of small animals. Between 1785 and 1789 Lavoisier was more occupied with experimentation in the plant kingdom. This was to have far reaching effects in the world of physics because in 1788 Lavoisier established the Law of Conservation of Mass in a series of experiments with fermentation.[7]

In 1790 Lavoisier again turned his attention to respiration – described by Lawrence Holmes as '*The Animal Economy; 1790-1792 Lavoisier's Return to Respiration*'[5] His new experiments were designed to investigate the changes in human respiration under many differing physiological conditions. At this time he was working with an assistant, Armand Séquin (1767-1835), who later became the 'guinea pig' for many of Lavoisier's experiments.

Together in 1787 they developed a eudiometric device (Greek *eudios* meaning '*goodness of air'*), for the volumetric analysis of air based on an original concept of Joseph Priestly in 1771. Remarkably they produced a eudiometric tube only eight inches by one inch in which they could analyse small samples of air drawn from their breathing apparatus.[5] This apparatus is depicted in the drawings of Lavoisier and Séquin made by Madame Lavoisier[5] and reproduced as Figures 1 and 2. These drawings show Sequin breathing into a face-mask both at rest and during exercise. The notes of Séquin relating to the apparatus, explain that the expired air is bubbled through caustic alkali to absorb the carbonic acid. It was with this apparatus that the experiments were conducted that resulted in a letter to Professor Black[ϑ] (1728-1799) in 1790.[5] This letter will be looked at in detail shortly but it is remarkable that their experiments into oxygen uptake gave results, which are more or less the same as we see today.

In 1793, the early days of the French Revolution, both Lavoisier and Pierre Laplace were expelled from the *'Academie des Sciences'* which required that all members had to be *'by virtue of their Republican ideals and hatred of Kings' worthy of their place in such a Scientific institute'*. Lavoisier was a tax collector for the King – called a 'tax farmer'. He received a small income for doing this and it was this money that he used for his laboratory. He was however perceived as a supporter of the monarchy as many of the tax farmers were. King Louis XVI himself was also condemned by 'La Revolution' and guillotined in January of 1793. In reality Lavoisier had done a lot to improve the living conditions of the French masses. In September 1793 The Tribunal of 'La Revolution' passed a law ordering the arrest of all foreigners born in enemy countries and all their property to be confiscated. A large number of notable chemists including Laplace, Lavoisier and Coulomb, were caught up in this and forced to resign from the *Acadamie des Sciences*.

On May 8th 1794 Lavoisier was beheaded on the orders of Coffinhall made at one of the Revolutionary Tribunals with the statement *'the revolution has no need of men of science*'[7]. (The actual quotation uses the phrase 'no need of savants'. The literal translation of 'savants' is 'men well versed in science', but the term is not really used now). Before Lavoisier went to the guillotine he had interceded with the Tribunal to save the mathematician Joseph Louis Legrange (1736-1813) from the same fate. After the execution, Legrange said of Lavoisier "*It took only a moment to cause this head to fall and a hundred years will not suffice to produce its like."*[7] In 1850 Justus von Liebig (1803-1873), a historian and physiologist, said that Lavoisier was the greatest single casualty of the 'La Revolution'.

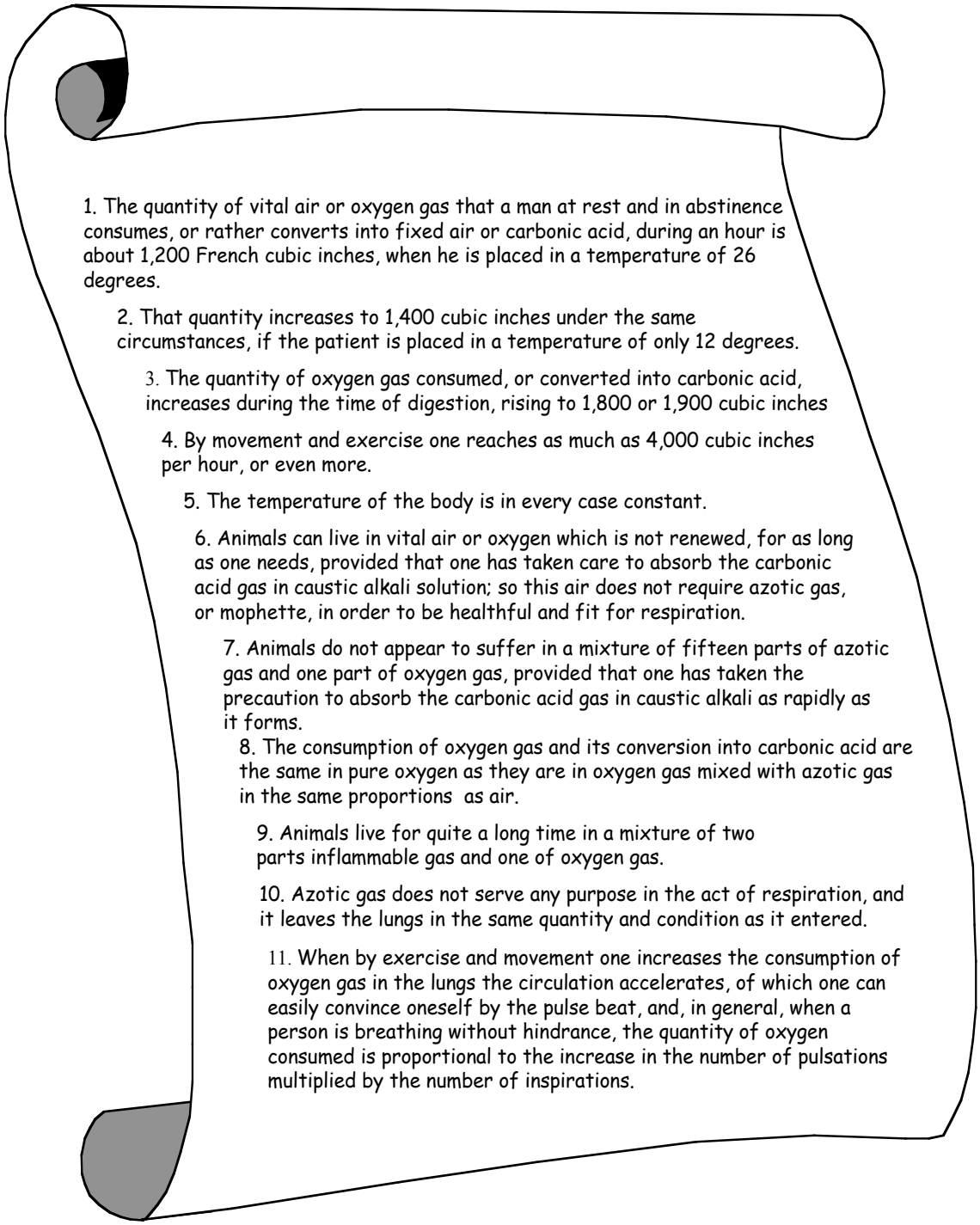
For sake of completion it is of interest that in 1805 Mme Lavoisier remarried, on this occasion, to the Count von Rumford, another distinguished scientist but separated from him four years later.

ϑ In 1756 Black was appointed Professor of Medicine and Lecturer in Chemistry at Glasgow and in 1766 went on to become Professor of Medicine in Edinburgh 8 Gribbin J. *Science A history 1543-2001*: McPherson's Printing Group, Maryborough, Victoria, 2002.

King Louis XVI (1754-1793) had been executed on January 21st 1793 and his wife Marie Antoinette (daughter of the Austrian Archduchess Maria Theresa (1717-1780)), went to the guillotine on October 16th 1793[13].

The French Revolution is relevant to us because it produced a major upheaval in scientific progress for two main reasons. Firstly the French *Acadamie of Science* was a genuine academic institution and its effective disbanding by the Revolution resulted in a major loss of research scientists. It had a limited number of members, each 'branch' of science having only one or at the most two representatives. Secondly many eminent people including Lavoisier were guillotined whilst other scientists such as Priestley had fled overseas. The relationship between Lavoisier, Priestley and Scheele undoubtedly led to fierce competition and now there were very few people left to carry on this work. This time was aptly described by Gribbin as *'the end of an era in chemistry'*[8].

As noted above, Lavoisier wrote a letter to Professor Joseph Black on November 13th 1790. This letter is a remarkable document and warrants further study.



A twenty first century analysis of the eighteenth century work of Lavoisier

Professor Black was a confidant of Lavoisier. This letter discusses many issues that are relevant to the whole concept of Cardiopulmonary Exercise Testing as it is practiced today. It establishes that respiratory gas exchange reflects the metabolic status of the patient in terms of both cardiac function and respiratory function under differing physiological conditions. This is pivotal to the entire science of interpretation of gas exchange as exemplified by cardiopulmonary exercise testing. This is remarkable research and needs closer analysis.

1. The quantity of vital air or oxygen gas that a man at rest and in abstinence consumes, or rather converts into fixed air or carbonic acid, during an hour is about 1,200 French cubic inches, when he is placed in a temperature of 26 degrees.

The term ‘in abstinence’ refers to abstinence of food, as later he describes the effect of food on the metabolic process. Note that he already believes that oxygen is converted to carbonic acid during the act of respiration.

The figure of 1200 cubic inches per hour, quoted by Lavoisier for resting oxygen consumption is based on the French Cubic Inch. If we take the French inch, or ‘pouce’, to be 2.707 cms then 1200 French cubic inches per hour equates to 396 ml/min. in modern terms. (There were 12 ‘pouces’ to the ‘pied’ but since the ‘pied’ had various definitions in different parts of France (!), so did the ‘pouce’. A book published in 1853 has it equal to 1.09 inches or 0.0277 meters.)

Lavoisier was aware of these problems and devised a new system of measures based not on the length of a pendulum but on the circumference of the earth measured through the north and south pole. This became the Metric system that we now know.

Today many laboratories utilize the term ‘met’; short for metabolic equivalent. This is defined as the average resting oxygen consumption for a 70 kg male of 40 years of age. It is quoted as 3.5 ml/min/kg. In absolute terms this is 245 ml/min. In our own Cardiopulmonary Research Laboratory we have found that the average ‘resting’ oxygen consumption is between 275 ml/min and 350 ml/min. These figures are not ‘basal oxygen consumption’ as they are performed on a subject who is often anxious, sitting on a bicycle ergometer and not entirely comfortable. They are therefore higher numerically than basal figures. The accuracy of these calculations by Lavoisier is nevertheless a remarkable piece of research.

2. That quantity increases to 1,400 cubic inches under the same circumstances, if the patient is placed in a temperature of only 12 degrees.

His reference to the ambient temperature shows his understanding of the need for respiration, in its broadest sense, to maintain body temperature.

We have not performed this experiment but it is in keeping with current physiological concepts of heat regulation. Earlier I mentioned that Lavoisier had worked with Laplace on development of heat in exercising animals so it was a reasonable experiment for him to perform. Joseph Black had already mastered the concepts of latent heat and specific heat by 1760[5]. In 1783 Lavoisier and Laplace measured the oxygen uptake of a guinea pig and calculated its heat production; all this using an ice calorimeter well described by Holmes in his chapter entitled ‘The Importance of Melting Ice’[5].

3 The quantity of oxygen gas consumed, or converted into carbonic, increases during the time of digestion, rising to 1,800 or 1,900 cubic inches

The change in metabolic rate induced by differing foodstuffs is well described by Guyton.[14] The metabolic rate increases by about 4% for a meal of fat or carbohydrate but can rise by as much as 30% following a meal predominately of protein. This large rise, referred to the specific dynamic action of protein, is due to a large increase in amino-acid metabolism. Depending on the type of meal ingested the rise in oxygen consumption will clearly be between 4% and 30%.

Lavoisier demonstrated an increase of between 28% and 35% - we must assume that the meal in question had a large proportion of protein!

The changes in metabolism induced by food intake is one reason why it is better to perform a cardiopulmonary exercise test after a short fast – 2-3 hours. Changes induced by metabolism in respiratory exchange ratio can cause problems with interpretation of the test. Respiratory exchange ratio is the ratio of the body’s carbon dioxide output to oxygen uptake, typically measured at the mouth.

4. By movement and exercise one reaches as much as 4,000 cubic inches per hour, or even more.

This figure of 4000 cubic inches per hour quoted by Lavoisier equates to 1320 ml/min. His figure for resting oxygen consumption was 396 ml/min. Thus exercise raised the resting value by over 300% for a period of one hour. The fact that the exercise was performed by Séquin for a period of one hour implies that the subject was very fit and as subjects experience additional stress exercising above their lactate thresholds it is likely that Seguin was exercising at - or conceivably, but less likely, just above - his lactate threshold. (The anaerobic threshold may be defined as the point in exercise when aerobic metabolism cannot maintain, on its own, the energy requirement of the subject. Anaerobic sources will be needed as an adjunct for ATP production.)

The experiment as performed in Figure 2 by Lavoisier is entirely believable. The use of a treadle would bring into play the large muscle mass of the legs in much the same way as a bicycle ergometer.

5. **The temperature of the body in every case remained constant**

Exercise below the anaerobic threshold does not cause a rise in body temperature providing the ambient temperature is not excessive. Lavoisier would clearly have had no concept of 'anaerobic threshold'.

Whilst there may have been no rise in body temperature, exercise will always produce a rise in heat production. Only 40% of metabolic energy produced by oxidation of carbohydrate or fatty acids is converted to ATP; the remaining energy is converted to heat. This heat has to be dissipated which will require an increase in blood supply to the skin.

The issue of heat production is important to modern CPET. It is necessary to maintain exercise laboratories at a constant environmental temperature of 20-25^{0}C. As the skin is the major organ for temperature control, exercise in a hot environment will set up a competition between the skin and active muscles for blood supply In other words cardiovascular dynamics will be changed in a warmer environment.

As an observation and armed with 21st century physiology, it is possible to suggest that all Lavoisier's experiments on exercise appear to have been performed below the anaerobic threshold.

6. Animals can live in vital air or oxygen which is not renewed, for as long as one needs, provided that one has taken care to absorb the carbonic acid gas in caustic alkali solution; so this air does not require azotic gas, or mophette, in order to be healthful and fit for respiration.

Vital air is oxygen; and *azotic gas* or *mophette* is nitrogen. Lavoisier was the first chemist to show that the atmosphere was composed of more than one gas. He showed that oxygen will sustain life on its own, but only if carbonic acid gas is removed. He also showed that nitrogen is not necessary to sustain life. Between 1772 and 1777 Priestley isolated and described seven more 'new airs'. He met Lavoisier in 1774 in Paris and discussed his discoveries with him. In 1773 Priestley had been awarded the Copley Medal for his paper on 'airs'[4], the highest award from the Royal Society of London. As I have said before, it becomes questionable as to precisely who should take credit for some of these discoveries.

It is interesting that even today the limitation on closed circuit diving rigs (re-breathing systems used by the navy frogmen to avoid bubbles and detection) are limited in use by their ability to remove carbon dioxide from the system. For some time the author worked with other scientists to try to overcome this problem; even by the time of the Viet Nam war this problem had not been completely resolved.

7 Animals do not appear to suffer in a mixture of fifteen parts of azotic gas to one part of oxygen gas providing one has taken the precaution to absorb the carbonic acid gas in caustic alkali as fast as it is formed.

Fifteen parts of *azotic gas* (nitrogen) to one part of oxygen is just 6.25% oxygen. Assuming a barometric pressure of 760 mmHg and a saturated water vapour pressure of 47 mmHg this equates to an inspired partial pressure of oxygen of approximately 45 mmHg.

At the first base camp of Mount Everest the altitude is 6012 metres and barometric pressure is halved to 380 mmHg. The inspired oxygen partial pressure is 70 mmHg. No one who is reasonably healthy needs oxygen at that altitude but can an animal go higher than that without oxygen? In December 1987 Sherpa Ang Rita scaled Everest without using supplementary oxygen♣♥. The altitude of Mount Everest is 8850 metres with a barometric pressure of around 250 mmHg. (That figure fluctuates with weather changes).

J B West, one of the greatest authorities in the world on high altitude oxygen uptake and acid-base equilibrium, showed that this altitude results in an inspired partial pressure for oxygen of 43 mmHg.

♣♥ What about the Duke of Abruzzi? – in 1909 he climbed to 6500 metres without additional oxygen

The actual arterial partial pressure for that inspired value would be less than 30 mmHg[15]. Clearly Lavoisier was correct in his observations[♣♣].

8 The consumption of oxygen gas and its conversion to carbonic acid are the same in pure oxygen as they are in oxygen gas mixed with azotic gas in the same proportion as air.

Paraphrased this says that oxygen uptake will be the same if the subject is breathing pure oxygen or air.

Except under very unusual conditions oxygen uptake at rest in a normal environment is not a function of oxygen availability. Increasing inspired oxygen partial pressure will not affect oxygen uptake.

Even under moderate to severe exercise conditions oxygen uptake is still not limited by inspired oxygen concentrations. Hyperventilation does occur during exercise above the anaerobic threshold but it is driven by a metabolic acidosis, produced by lactic acid accumulation, not by hypoxaemia. Hyperventilation will reduce arterial carbon dioxide levels and tend to return the blood pH to normal. Hyperventilation from causes other than hypoxaemia, will increase the alveolar oxygen partial pressure but will not increase oxygen uptake other than by the increase in the oxygen cost of breathing; a fact used as one determinant of anaerobic threshold during cardiopulmonary exercise testing today. End expired oxygen concentration normally rises after the anaerobic threshold as opposed to the subsequent fall in end expired carbon dioxide.

9 Animals live for a quite a long time in a mixture of two parts of inflammable gas and one part oxygen gas

In Lavoisiers' time, the term 'inflammable gas' included all gases that could burn. It included hydrogen which was discovered by Cavendish (1731-1810)[6] in 1766 by treating metal with an acid.

This statement by Lavoisier is merely saying that animals can live in an atmosphere of 33% oxygen and that no other gas is necessary for their survival. Remember that he always absorbed carbon dioxide in his experiments.

10 Azotic gas does not serve any purpose in the act of respiration and it leaves the lungs in the quantity and condition that it entered.

This simple statement is of profound importance.

Azotic gas or nitrogen certainly does not serve any purpose in the act of respiration. Whether it leaves the lungs *'in the quantity and condition that it entered'* is another question.

At that time the other inert gases had not been discovered Whilst nitrogen is inert in terms of metabolism, any change in the *concentration* of nitrogen in expired air does not reflect nitrogen uptake but reflects the fact that the number of oxygen molecules removed from the inspired air are not necessarily replaced by the same number of carbon dioxide molecules produced in metabolism. This results in the volume of expired air being unequal to the inspired volume. The difference being a function of the value of the respiratory quotient (RQ) as reflected by the respiratory exchange ratio (RER). If the RER is less than one then the expired volume will be less than the inspired volume.

This issue is addressed and is critical to the calculations made by many modern metabolic carts. This problem is usually solved by use of the 'Haldane Transformation'. This calculation is based on the assumption that, in steady state, the mass of nitrogen inspired over unit time is exactly the same as that expired. If that is so, then it is not necessary to measure both the inspired and expired volumes and the following equation may be used to derive inspired volumes from expired.

$$\dot{V}_{insp} = \dot{V}_{exp} \times F_{expN_2} / F_{inspN_2}$$

Some errors which may occur in this concept have been well documented[16] but it is still in general use and certainly valid. In fact the Haldane transformation was originally described as follows "*The oxygen content of the expired air does not necessarily indicate how much oxygen has disappeared from the inspired air because the amount of expired air is not equal to the amount of the inspired air, both gases thought to be free of water. Usually, the volume of the expired air will be smaller because more oxygen is taken up than carbonic acid is excreted. Accordingly we can, based on the constant relation of*

[♣♣] It is remarkable that the Bar-headed Goose can actually fly over the summit of Everest – exercise at 9000 metres? Currently oxygen uptake is being studied at 6000 metres by experts in extreme physiology. (Personal communication)

nitrogen in the atmospheric air, calculate the amount of inspired oxygen from the amount of nitrogen in the expired air. We simply have to multiply the number of the latter by that constant of 20.93/79.07".

Unfortunately this was not written by Haldane but by Geppert and Zuntz in 1888[17].

It remains astonishing that Lavoisier had postulated the physiology behind this work in 1790 – more so that it was correct.

11 When by exercise and movement one increases the consumption of oxygen gas in the lungs the circulation accelerates, of which one can easily convince oneself by the pulse rate, and, in general, when a person is breathing without hindrance, the quantity of oxygen consumed is proportional to the increase in the number of pulsations multiplied by the number of inspirations.

Despite the fact that the original statement is inaccurate this statement inexorably ties the uptake of oxygen during exercise to cardiac and pulmonary function. It is this statement that is the basis of modern cardiopulmonary exercise testing; the heart, the lungs and the circulation becoming inexorably linked in function.

It was stated by Frederich Kreysig (1770-1839) in 1819 that *"..as the lungs and heart are linked together and the function of both organs aim at the same purpose, respiration is necessarily troubled if the heart action is altered".*

Henderson in 1929 summarized the state of knowledge in his treatise "Blood: A Study in General Physiology" and proposed the simple but essential concept that "*the lungs, heart and circulation should be thought of as a single apparatus for the transfer of oxygen and carbon dioxide between the atmosphere and the working tissues."*[18]

As may be seen from this data we owe so much of our knowledge of the events that led up to the discovery of oxygen and its uptake by man, to the early Chemists. They pioneered the application of accurate quantitative techniques to chemistry and other amazing applications that were taken up by Medicine. There are many examples. Gabriel Fahrenheit (1686-1736) invented the alcohol thermometer in 1709 and the mercury thermometer in 1714. Anders Celsius (1701-1744) devised the Celsius scale in 1742.

From the 1740's on, progress depended on a handful of men who were not only contemporaries but often knew each other.

William Harvey (1578-1657), a physician to the Monarch James 1st and his son Charles 1st, had proven the circulation of the blood and established the idea of the heart as a pump in 1628. It was then that he published the book that became known as 'De Motu Cordis'[8]. As he had no microscope he was unable to work out how the blood passed from the arteries to the veins. He measured very roughly the volume of blood in a sheep by exsanguination; then by dissection and measurement calculated the rough volume of the sheep's heart. Armed with stroke volume and heart rate he could calculate the cardiac output. Unfortunately as he made no accurate measurements he was unable to give an accurate figure for his estimates. Suffice to say the estimated cardiac output per minute exceeded the blood volume in a very short period. He therefore argued that the blood must be re-circulated[8].

It was left to Marcello Malpighi♥ in 1661 to identify and describe the pulmonary and capillary network connecting small arteries with small veins, one of the major discoveries in the history of science. He did this with the aid of a then recent invention, the microscope, for which work he received the derision of many of his colleagues in Italy.

Humphrey Davy (1778-1829) had detected the presence of oxygen and carbon dioxide in blood in 1799. In 1837 Gustav Magnus (1802-1870) found that there was more oxygen and less carbon dioxide in arterial blood than in venous blood. This clearly showed that carbon dioxide was added to the blood during its passage through the circulation[19].

In 1870 the prophesy of Legrange, mentioned above[7], was fulfilled and Adolf Fick (1829-1901) described what is now called the Fick Principle to establish cardiac output. Fick theorized a method for

♥ **Malpighi**, Marcello 1628–1694. Italian anatomist who was the first to use a microscope in the study of anatomy and the first Italian invited to become a member of the Royal Society, London.

calculation of cardiac output but never actually measured it. He argued that *"It is astonishing that no one has arrived at the following obvious method by which the amount of blood ejected by the ventricle of the heart with each systole may be determined directly, at least in animals. One measures how much oxygen an animal absorbs from the air in a given time, and how much carbon dioxide it gives off. During the experiment one obtains a sample of arterial and venous blood; in both the oxygen and carbon dioxide content are measured. The difference in oxygen content tells how much oxygen each cubic centimeter of blood takes up in its passage through the lungs. As one knows the total quantity of oxygen absorbed in a given time one can calculate how many cubic centimeters of blood passed through the lungs in this time. Or if one divides by the number of heartbeats during this time one can calculate how many cubic centimeters of blood are ejected with each beat of heart. The corresponding calculation with the quantities of carbon dioxide gives a determination of the same value, which controls the first."*[20].
This theory had to wait for the Van Slyke (1833-1971) apparatus for blood gas determination to be published in 1921[21] and the demonstration of the cardiac catheter by Werner Forssman in the 1930's, before it could be conveniently verified in man. Werner Forssman, Andre Cournand and Dickinson Richards were jointly awarded the Nobel Prize in 1956 for the development of the technique for cardiac catheterization[22].

In truth the first verification of Fick in humans was by Baumann and Grollman; *"Verification of the Fick principle in humans was initially accomplished in 1930. It was made possible through the daring exploits of Baumann and Grollman at a time when cardiac catheterization had yet to be established as a clinical tool. They obtained samples of mixed venous blood by inserting a spinal tap needle just to the right of the sternum that entered the right ventricular chamber by puncturing its wall."* This is the precise quote by Grollman.♠

Meanwhile in Denmark August Krogh (1874-1949) had developed a gas-analysis apparatus that could measure respiratory quotient to an accuracy of 0.05%[23]. He had developed a cycle ergometer in 1909-1910 (Figure 3) and was able to undertake gas exchange measurements as well as measure cardiac output during exercise. This he did by measurement of the amount of nitrous oxide that disappeared from the alveoli over a short period. (<30 seconds)[23]. Krogh was probably one of the first men to set up an exercise-testing laboratory. He was able to measure the 'insensible'❦ fluid losses during heavy exercise (Figure 4) which set the stage for our current understanding of fluid changes during exercise.

The big issue of the Fick theory is that it requires knowledge of oxygen content in arterial and mixed venous blood not just partial pressure. To do this it is necessary to calculate haemoglobin saturation against partial pressure *in vivo*. Probably the first to achieve this was the Frenchman Paul Bert (1833-1886). He exposed animals to differing barometric pressures and determined the oxygen content of the blood at those pressures.[19]

In 1904 the so called *Bohr effect* was described by Christian Bohr (1855-1911), Karl Hasselbalch (1874-1962) and August Krogh[19]. The Bohr effect describes the reduction in oxygen affinity of oxyhaemoglobin in the presence of higher levels of CO2 and a low pH. The Bohr effect permits the efficient delivery of oxygen to metabolically active tissues. This effect is crucial for the elite athlete as the tissue and blood pH in these subjects reaches very low figures.

In 1914 Yandell Henderson wrote *'By the term oxygen pulse we mean the amount of oxygen consumed by the body from the blood of one systolic discharge of the heart. Its value is calculated by dividing the amount of oxygen absorbed by the individual per minute by the number of heart beats in that minute.*[24]
Three hundred years after Harvey had described the features of the circulation but had only been able in a very rough way to estimate stroke volume, Yandell Henderson, in 1923, wrote a remarkable article "Volume changes of the heart"[25]. In that article he stated "*The stroke volume of the heart is….the most important quantitative function of the whole body. It is much more important than the exact amount of the arterial pressure…..for the amplitude of the heart's volume change multiplied by the pulse rate gives the total volume of arterial blood supplied to the entire body".* Should one be needed, this is the most perfect endorsement of the importance of measurement of the oxygen pulse in modern CPET. Yandell Henderson linked respiration and cardiovascular function in much the same way that Lavoisier had in 1790 with his statement "*When by exercise and movement one increases the consumption of oxygen gas in the lungs the circulation accelerates, of which one can easily convince oneself by the*

♠ Grollman A: The Cardiac Output in Man in Health and Disease, p11. Springfield, Illinois; Charles C Thomas. 1932

❦ To be pedantic 'insensible loss' actually refers to water lost in respiration; whilst the loss by sweating is more correctly termed 'sensible loss'.

pulse rate, and, in general, when a person is breathing without hindrance, the quantity of oxygen consumed is proportional to the increase in the number of pulsations multiplied by the number of inspirations"!

In 1966 Richard Kelman published a computer subroutine for conversion of partial pressure of oxygen to percentage saturation. This took into account all the known variables such as the Bohr effect[26] and formed the mathematical basis for the development of computer programmes for clinical use by the author.

In 1979 John Severinghaus developed an equation for conversion of partial pressure of oxygen to percent saturation that was accurate over the entire physiological range of oxygen tension[27].

Arterio-venous oxygen content difference is now pivotal to the understanding of the non-invasive measurement of stroke volume during exercise gas exchange.

Finally, implicit in the Fick equation is the principle of all dilution methods for determining blood flow. If one knows the amount of any substance that enters or leaves a stream of fluid and the concentration difference resulting from that entrance or removal, the flow of the stream of fluid can readily be calculated. Fick's equation therefore underlies all of the dilution methods for measuring blood flow including the use of various indicators as well the thermal dilution principle[20] or 'Swan-Ganz' system.

Before the metabolic cart became a clinical reality the only practical way to measure haemodynamics was by dye dilution studies. It was the application of dye dilution and later thermodilution that allowed cardiac output to be measured. If in addition mixed venous and arterial blood samples are taken at the same time it was possible to measure oxygen consumption. The computer subroutines published in the 1960's and alluded to above facilitated more accurate results as they allowed for closer approximation of oxygen content. Thus the physiology and technology could be united to provide for the 'bedside' acquisition of data in both medical and surgical patients.

From 1960 on there has been an increasing interest in post-operative stress physiology. This has been facilitated by the ability to measure cardiac output and oxygen consumption at the bedside as explained above. At around the same time, 1963, the American Society of Anesthesiologists published what was probably the first attempt at quantifying post-operative risk in non- cardiac surgery[28].

The first realization of the substantial increase in cardiac output caused by major surgery came from the work of Clowes and Del Guercio in 1960[29]. The study was performed on very few patients but suggested that the patients who survived major non-cardiac surgery were those in whom the cardiac output rose post-operatively. i.e. an increase in metabolic rate was a physiological response to surgery not pathological. This study was done using dye dilution, which became the 'gold standard' for evaluation of the new thermodilution pulmonary artery catheter of the mid 1970's.

Concepts of respiratory gas exchange so pivotal to the Fick cardiac output determination were largely displaced in favour of the dye and thermodilution techniques. This has resulted in the cardiologist viewing measurements involving respiratory gases as the domain of the respiratory physician and the respiratory physician viewing an exercise test as a means of evaluating gas exchange abnormalities. In reality the cardiopulmonary exercise test remains the one study that evaluates both pulmonary and cardiac function. Cardiopulmonary exercise testing uses the Fick principle in interpretation of some variables.

To this point this essay has concentrated on the physiological changes pertaining to exercise. We now need to see how the technology has advanced over the years.

The technology of CPET

The equipment used for exercise testing is normally referred to as a 'metabolic cart'. Equipment, which is used in Intensive Care Units, is not suited to the exercise laboratory as the analysers are too slow or use 'mixing chamber' technology. This equipment became commercially available in the 1970's. There had existed very sophisticated equipment in laboratories around the world to investigate oxygen uptake. One of the most notable of these was the Exercise Physiology Laboratory at the Harbor-UCLA Medical Centre (Harbor General Hospital at that time), directed by Professor Karlman Wasserman. Professor Wasserman had actually started work on the concept of the anaerobic threshold at UCSF. He continued this work at Stanford and went on to publish his first work on the AT in 1964[30]. The Harvard Fatigue Laboratory was founded in 1927 (1927-1947) by L.J. Henderson, a famous biochemist. It is interesting that D.B. Dill, the director of the Harvard Fatique Laboratory, had a working contact with

both Karlman Wasserman and August Krogh, mentioned above and a Danish Nobel Prize Winner. It is of note that Professor Wasserman and D.B Dill co-authored a paper in 1964 concerning fitness at 90 years of age[30].

The modern metabolic cart requires two quite separate technologies to provide the basis for appropriate interpretation of exercise test data. One is the issue of blood gases and oxygen content of blood. The other is the measurement of oxygen and carbon dioxide content and volume of inspired and expired gas. As we will see later it was the recent development of very fast acting oxygen and carbon dioxide analysers that has allowed the so-called 'breath by breath' metabolic carts to be used clinically. The first computerized breath-by-breath studies were developed by William Beaver, Karl Wasserman and Brian Whipp and the details reported in 1973[30].

The modern cart consists of oxygen and carbon dioxide analysers and a means of measuring gas flows very accurately. To measure oxygen uptake and carbon dioxide elimination during exercise we must be able to measure oxygen and carbon dioxide concentration on a 'breath by breath' basis. Given that the respiratory rate may rise to fifty breaths per minute or higher implies that we need to be able to measure oxygen and carbon dioxide concentrations in well under one second. This is normally discussed in terms of response times and we need a 90% response time of better than 90 ms by the analysers.

These analysers will normally be interfaced with a computer. Sophisticated computer programs analyse and display the data on the screen in addition to storing them. These machines can analyse and store data for each breath. The computer programmes are closely guarded 'secrets' by the various manufacturers. Carbon dioxide analysers are generally infrared devices. To be accurate under exercise conditions they also need to have a 90% response time of better than 80 ms in order to function with breathing rates of up to 60-70 breaths per minute and inspiratory/expiratory ratios of less than 2:1. Distortion of the carbon dioxide wave form is caused by the 'rise time' of the analyser being too slow[31].

There are five or more types of oxygen analyser. Response times are a major reason that most devices are not appropriate for exercise use but the delicacy and sensitivity to vibration is another problem. In our laboratory we choose to use a Zirconium Oxide analyser (high temperature electrochemical analyser). These use a 'solid' electrolyte made of zirconia oxide and stabilized with yttrium oxide. The cell is heated to 750^0C at which temperature the zirconium oxide becomes porous to oxygen ions which move from a high concentration to a low concentration. One side of the electrolyte is exposed to air with a precisely known concentration of oxygen. This movement causes a voltage between two electrodes; one exposed to the 'air' and the other to the gas to be analysed. This analyser has a very fast response time and is accurate from traces of oxygen to 100% oxygen.

Gas flow may be measured in several ways but a pressure differential pneumotachygraph is small and light weight. The 'gold standard' for volume measurement remains volume displacement devices. These are commonly large and too cumbersome to use for exercise purposes. The pressure differential devices need accurate calibration at varying flow rates but are the most convenient for exercise use. The various rotameter devices all had problems with acceleration and deceleration of their rotating components but with modern technology may still provide accurate data.

We now have the technology to measure oxygen uptake on a 'breath by breath' basis and the physiological knowledge to interpret the myriad of variables that the computer is able to generate. Some authorities feel that too many variables are generated in graphic form. This allows for many plots of one variable against another which may lead to misleading correlations. The systems have been minaturised to the point where data acquisition may be done on a device that will fit onto the belt of the subject and the information downloaded to a computer later. Some even allow for radio transmission of data over 1 km or more. This allows for athletes to perform their activities unattached to a machine and for the data to be interpreted later. It also allows patients to go about their normal activities and accurately measure oxygen uptake and anaerobic threshold. There is still a need to have a data interpretation system to allow non-physiologists to understand the data; much like interpretative ECG systems. This is potentially dangerous in that it might encourage acceptance of the machine diagnosis without really understanding how this result was derived. Many purists would rather interpret the data themselves.

We have come a long way since Lavoisier and Sequin used a eudiometric tube and a treadle to calculate oxygen uptake. Certainly Lavoisier caused a Paradigm shift in scientific thinking on oxygen uptake. Has there been one since?

We have not mentioned the electrocardiograph. As Kipling might have said in the Jungle Book through his 'story teller' *"but that Sahib, is another story".*

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FIGURES

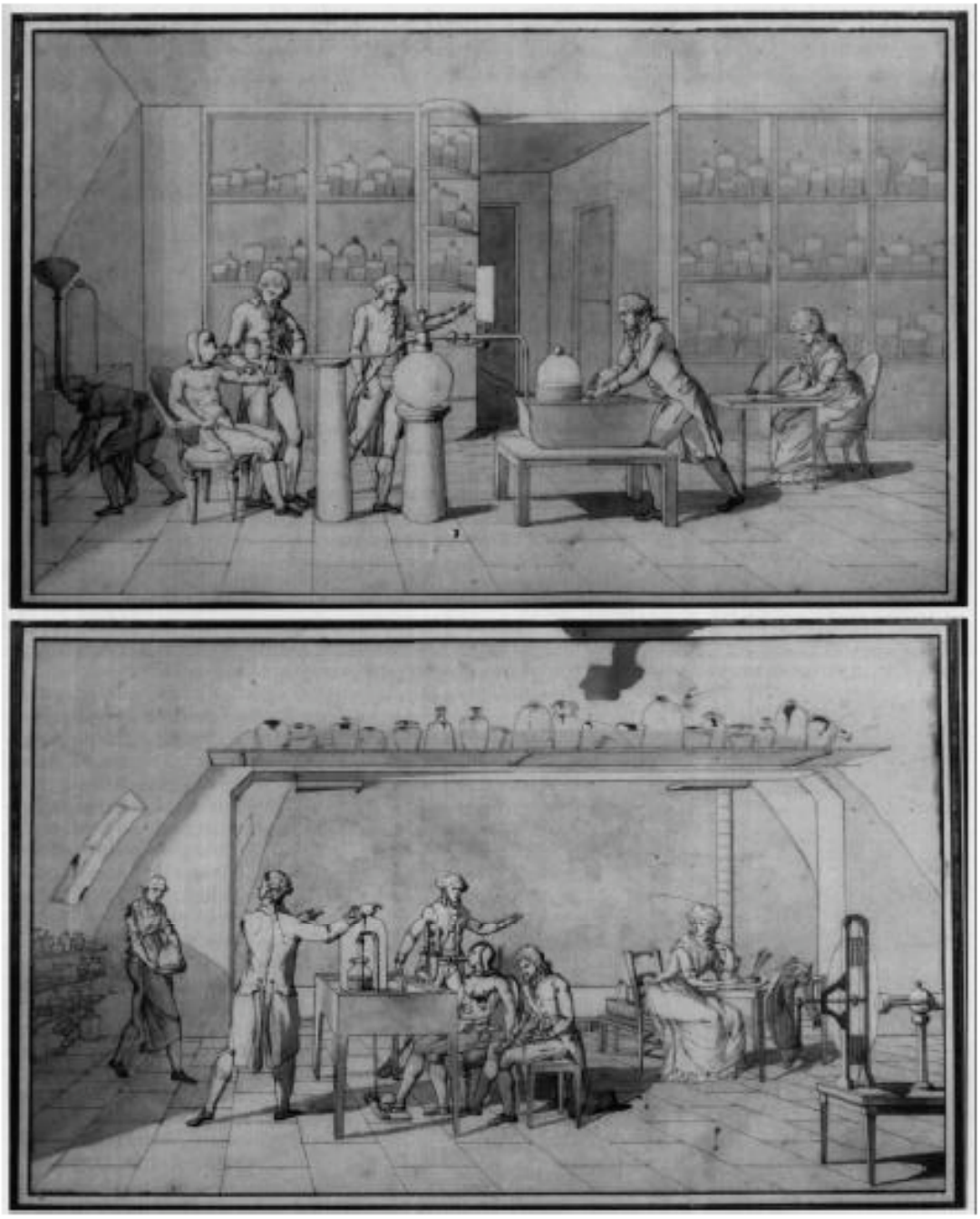

Figure 1 Oxygen uptake at rest. The laboratory of Lavoisier with Sequin as the subject. Circa 1780

Figure 2 Oxygen uptake during exercise. The laboratory of Lavoisier with Sequin as the subject operating a treadle Circa 1780

Figure 3

Showing the early cycle ergometer

of Krogh: Circa 1910

Figure 4

Showing the supine bicycle ergometer with

full weighing facilities: Circa 1930

The pictures depicted in Figure 5 to 7 are reproduced by kind permission of Dr Adrian Hall, a long standing friend and colleague.

Figure 5. Le Musee des Artes et Metier in Paris

Figure 6. The section of the museum devoted to Lavoisier

Figure 7. The 'calorimeter' used in the guinea pig experiments