HIGH ALTITUDE MEDICINE AND PHYSIOLOGY

Fifth edition

John B. West, Robert B. Schoene, Andrew M. Luks
and James S. Milledge

CRC Press
Taylor & Francis Group

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CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20121203

International Standard Book Number-13: 978-1-4441-5433-7 (eBook - PDF)

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Preface

New advances in the areas of high altitude medicine and physiology continue to be made at a rapid pace. For example, since the last edition of this book in 2007, there have been dramatic advances in the area of genetics of high altitude. One of the most important discoveries has been the genetic differences between Tibetans and Han Chinese with the expectation that this will go a long way in explaining the remarkable adaptation of Tibetans to their environment. Additional important advances have been made on the functions of hypoxia-inducible factors which we now realize orchestrate many of the body's responses to hypoxia. Added to this has been a better understanding of the phenotypic differences between Andeans and Tibetans which are the two principal populations of the world that have so successfully adapted to high altitude. All this new work has justified a new chapter on genetics at altitude and this is written in a way that should make this somewhat technical topic accessible to those of us who do not have a strong background in the area.

Additional important advances have been made in the management of high altitude diseases. For example, the value of the different medications available for acute mountain sickness is addressed, together with new information on strategies for acclimatization. Advances in our understanding of the mechanism of high altitude pulmonary edema are discussed together with their therapeutic implications. Extensive additions have been made to the chapter on other high altitude related medical conditions. In addition, the chapter on pre-existing medical conditions has been extensively revised.

Another burgeoning area is the challenge presented to people who need to go to high altitude to work. Mines are being developed at increasingly high altitudes, particularly in South America. There are now very large telescopes located as high as 5000 m in north Chile and effective work at those altitudes is only possible using oxygen enrichment of room air. A striking technological advance is the new Chinese train to Lhasa which passes through an altitude over 5000 m. The ingenious solution has been to increase the oxygen concentration in every passenger car on the train. A sadder event is the continuing dispute between India and Pakistan in the region of the Siachen Glacier where troops are operating at over 6000 m with a correspondingly high morbidity.

For this new edition, all sections of the book have been carefully updated, but great pains have been taken to maintain a reasonable length. There are a number of new illustrations. The references have been brought up to date with some of them so recent that they have been completed in the proof stage.

A welcome addition to the group of editors is Andrew Luks MD from the University of Washington in Seattle. He is an avid mountaineer and has a particular interest in the clinical aspects of high altitude diseases. He has been responsible for updating several of the chapters in this area.

Mountains continue to attract increasing numbers of people for skiing, trekking or climbing. In addition, commercial activities at high altitude are increasing at a rapid rate. Happily, there has been a large increase in research on the diseases that affect permanent dwellers at high altitude, an area that has traditionally received less attention than should have been the case. Our hope is that this new edition will continue to improve the health and safety of all people who live, visit or work at high altitude. It is a pleasure to acknowledge the continuing support of Joanna Koster and her colleagues at Hodder Arnold.

John B West
Robert B Schoene
Andrew Luks
James S Milledge

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Acknowledgements

We acknowledge help from many friends and colleagues who have read and provided comments on parts of the text. Tatum Simonson PhD gave advice in the chapter on Genetics and High Altitude, and Keith Lander provided general editorial assistance. Andrew Luks is grateful to Erik Swenson for support and mentorship through his career. Pat Howell read and corrected the chapters by Jim Milledge.

We would also like to thank all those who contributed to the original work on which much of this book is based. These include Sherpas, porters, climbers, scientists and other supporters who made the projects possible. We remember too, with gratitude, all those who share the adventure of science with colleagues in the high places of the world.

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Conversion tables

Table F.1 Conversion of pressure units mmHg (millimeters of mercury) to kPa (kilopascals)

mmHg	kPa
1	0.133
10	1.33
20	2.67
30	4.00
40	5.33
50	6.67
60	8.00
80	10.7
100	13.3
200	26.7
300	40.0
500	66.7
700	93.3
760	101.3

1 torr = 1mmHg

Table F.2 Conversion of height units and barometric pressure according to the ICAO Standard Atmosphere and the actual pressure on most high mountains at low latitudes (see Table 2.1)

Altitude		Pressure mmHg	
m	ft	Standard	Actual
0	0	760	760
1 000	3 281	674	679
2 000	6 562	596	604
3 000	9 843	526	537
4 000	13 123	462	475
5 000	16 404	405	420
6 000	19 685	354	369
7 000	22 966	308	324
8 000	26 247	267	284
9 000	29 258	231	247

1 Watt = 6.12 kg. m min^{-1}

Table F.3 Conversion of temperature units, °C (degrees Celsius) to °F (degrees Fahrenheit)

°C	°F
−40	−40
−30	−20
−25	−13
−20	−4
−15	5
−10	14
−5	23
0	32
5	41
10	50
15	59
20	68
25	77
50	86
35	95
40	104

1 Watt = 6.12 kg. m min^{-1}

Table F.4 Conversion of energy units, kcal (kilocalories) to kJ (kilojoules)

kcal	kJ
50	209.4
100	418.8
250	1 047
500	2 094
1 000	4 188
2 000	8 375
3 000	12 563
4 000	16 750
5 000	20 938
6 000	25 126

1 Watt = 6.12 kg. m min^{-1}

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List of abbreviations

ACE	angiotensin converting enzyme
ACTH	adrenocorticotropic hormone
ADH	aldosterone
ADH	anti-diuretic hormone
AFC	alveolar fluid clearance
AH	acute hypoxia
Aldo	aldosterone
ALMA	atacama large millimeter/sub-millimeter array
AM	adrenomedullin
AMREE	American Medical Research Expedition to Everest
AMS	acute mountain sickness
ANP	atrial natriuretic peptide
ASHRAE	American Society of Heating, Refrigeration and Air-Conditioning Engineers
ATP	adenosine triphosphate
AVP	arginine vasopressin
BAL	bronchoalveolar lavage
BBB	blood–brain barrier
BCAA	branched-chain amino acid
bFGF	basic fibroblast growth factor
BMEME	British Mount Everest Medical Expedition
BMR	basal metabolic rate
BNP	brain natriuretic peptide
BP	blood pressure
BTPS	body temperature and pressure saturated
CAD	coronary artery disease
CBF	cerebral blood flow
CF	cystic fibrosis
CH	chronic hypoxia
CKD	chronic kidney disease
CMS	chronic mountain sickness
CNS	central nervous system
COLD	chronic obstructive lung disorder
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CSF	cerebrospinal fluid
CT	computed tomography
CTS	comet-tail scores
CXEE	Caudwell Xtreme Everest Expedition
DLCO	diffusing capacity or carbon monoxide
E	estrogen
E+P	estrogen plus progesterone
ECF	extracellular fluid
ECG	electrocardiogram
ECMO	extra-corporeal membrane oxygenation
EEG	electroencephalogram
EMG	electromyography
eNOS	endothelial nitric oxide synthase
EPO	erythropoietin
ERB	endothelin receptor blocker
ERPF	effective renal plasma flow
ESQ	environmental symptom questionnaire
ET	endothelin
ET-1	endothelin-1
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GABA	gamma aminobutyric acid
HACE	high altitude cerebral edema
HAPE	high altitude pulmonary edema
HAPH	high altitude pulmonary hypertension
HAR	high altitude retinopathy
Hb	hemoglobin
[Hb]	hemoglobin concentration
Hct	hematocrit
HCVR	hypercapnic ventilatory response
HIF	hydroxia-inducible factor
HIF-1	hypoxia-inducible factor 1
HIF-1α	hypoxia-inducible factor-1 alpha
HPVR	hypoxic pulmonary vascular response
HRE	hypoxia response element
HVD	hypoxic ventilatory decline
HVR	hypercapnic ventilatory response
I/D	insertion/deletion
ICD	implantable cardiac defibrillator
ICP	intracranial pressure
IH	intermittent hypoxia
IHE	intermittent hypoxic exposure
iNOS	inducible nitric oxide synthase

INR	international normalized ratio
IOP	intraocular pressure
ISMM	International Society for Mountain Medicine
IT	interval training
IUGR	intra-uterine growth retardation
LASIK	laser-assisted in situ keratomeliusis
LH	luteinizing hormone
LHTL	live high, train low
LLS	Lake Louise Score
LLSS	Lake Louise Scoring System
LLTH	live low, train high
LLTL	live low, train low
LT	lactate threshold
LVF	left ventricular failure
MFNS	magnetic femoral nerve stimulation
MIGET	multiple inert gas elimination technique
MR	magnetic resonance
MRI	magnetic resonance imaging
MVV	maximal voluntary ventilation
NESP	novel erythropoiesis stimulating protein
NFPA	National Fire Protection Association
NHE1	sodium/hydrogen ion exchanger isoform 1
NIPPV	non-invasive positive pressure ventilation
NK	natural killer
NO	nitric oxide
NOx	no metabolites
NPY	neuropeptide y
NREM	non-rapid eye movement
NSAIDs	non-steroidal anti-inflammatory drugs
OHD	oxygen–hemoglobin dissociation
ONSD	optic nerve sheath diameter
OPS	orthogonal polarization spectral
PAC	plasma aldosterone concentration
PAL	physical activity level
PAP	pulmonary artery pressure
PASP	pulmonary artery systolic pressure
PCr	phosphocreatine
PCV	packed cell volume
PDE-5	phosphodiesterase type-5
PDGF	platelet-derived growth factor
PFO	patent foramen ovales
PHD	prolyl hydroxylase domain
PRA	plasma renin activity
PRK	photorefractive keratectomy
PV	plasma volume
PVR	pulmonary vascular resistance
RAS	renin–angiotensin system
RBC	red blood cells
RCM	red cell mass
RDBPC	randomized, double-blind, placebo-controlled
REDST	redox state
REM	rapid eye movement
rhEPO	recombinant human epo
RK	radial keratotomy
ROS	oxygen free radicals
ROS	reactive oxygen species
RQ	respiratory quotient
SAH	subarachnoid hemorrhage
SBP	systolic blood pressure
SDF	sidestream dark-field
17-OHCSs	17-hydroxycorticosteroids
SIDS	sudden infant death syndrome
SiEp	serum immunoreactive epo concentration
SL	sea level
SNP	single nucleotide polymorphism
STPD	standard temperature and pressure, dry gas
SWS	slow wave sleep
TBG	thyroxine-binding globulin
TBW	total body water
TEG	thromboelastography
TGF	transforming growth factor
TIA	transient ischemic attacks
TLC	total lung capacity
TRPC	transient receptor potential
TSH	thyroid-stimulating hormone
TT	time trial
2,3-DPG	2,3-diphosphoglycerate
UA	uterine arteries
Ub	ubiquitin
UKIRT	United Kingdom Infrared Telescope
V/Q	ventilation/perfusion
VAS	visual analog scale
VDH	ventilatory deacclimatization from hypoxia
VEGF	vascular endothelial growth factor
VHL	von Hippel–Lindau
WBC	white blood cells

1

History

SUMMARY

The history of high altitude medicine and physiology is one of the most colorful in the whole of the life sciences. Although there were a few anecdotal references to medical problems at high altitude before 1600, Joseph de Acosta's description of acute mountain sickness, originally published in 1590, is a watershed. Shortly after this the mercury barometer was invented by Evangelista Torricelli in 1644, and very quickly it was recognized that barometric pressure declined with altitude. Robert Boyle and Robert Hooke constructed the first air pump for physiological measurements in 1660 and Boyle then proposed his famous law. During the seventeenth and eighteenth centuries the nature of respiration was elucidated and the respiratory gases were first clearly described by Lavoisier in 1777. Soon the effects of acute ascent to high altitude were dramatically shown by the early balloonists including several fatalities from the severe hypoxia. The French physiologist, Paul Bert, was the first to clearly identify the low partial pressure of oxygen as responsible for high altitude illness with his landmark publication *La Pression Barométrique* in 1878.

When climbing became popular in the European Alps in the mid-nineteenth century many instances of acute mountain sickness were described. The construction of the Observatoire Vallot in France and the Capanna Margherita in Italy facilitated early medical and physiological studies of high altitude. The early twentieth century saw the beginning of special expeditions to high altitude to make medical and physiological measurements including the important Pikes Peak Expedition of 1911. A lively topic at this time was the possibility of oxygen secretion by the lung and this was finally resolved in favor of passive diffusion. Attempts to climb the highest mountain in the world, Mount Everest, comprise a great saga culminating in the first ascent in 1953 when supplemental oxygen was used, and the first ascent without bottled oxygen in 1978.

More recently, there have been several dedicated expeditions to explore the physiology of extreme altitude and generally an enormous

increase in high altitude life sciences research. An important area has been the medical and physiological features of permanent residents of high altitude. A recent major advance was the discovery of genetic differences in Tibetans compared with Han Chinese. Another area of study is ways of improving the quality of life for people who are required to work at high altitude.

1.1 INTRODUCTION

This chapter provides an overall view of the history of high altitude medicine and physiology. More information about specific events is given at the beginning of subsequent chapters. Readers who desire more details can find these in West (1998). Table 1.1 shows a chronology of some of the principal events in the development of high altitude medicine and physiology.

1.2 CLASSICAL GREECE AND ROME

It is perhaps surprising that there are so few references to the ill effects of high altitude in the extensive writings of classical Greece and Rome. The Greek epics and myths, in particular, are so rich in the accounts of travels and the foibles of human nature that one might expect there to be a reference to the deleterious effects of high altitude but this is generally not the case. However, seventeenth century writers believed that the ancient Greeks were aware of the thinness of the air at high altitude. For example, Robert Boyle (1627–91) claimed that Aristotle (384–322 BC) held this view when he wrote:

Table 1.1 Chronology of some principal events in the development of high altitude medicine and physiology

Year	Event
c. 30 BC	Reference to the Great Headache Mountain and Little Headache Mountain in the *Ch'ien Han Shu* (classical Chinese history)
1590	Publication of the first edition (Spanish) of *Historia Natural y Moral de las Indias* by Joseph de Acosta with an account of mountain sickness
1644	First description of the mercury barometer by Torricelli
1648	Demonstration of the fall in barometric pressure at high altitude in an experiment devised by Pascal
1777	Clear description of oxygen and the other respiratory gases by Lavoisier
1783	Montgolfier brothers initiate balloon ascents
1786	First ascent of Mont Blanc (4807 m) by Balmat and Paccard
1878	Publication of *La Pression Barométrique* by Paul Bert
1890	Viault describes high altitude polycythemia
1890	Joseph Vallot builds a high altitude laboratory at 4350 m on Mont Blanc
1891	Christian Bohr publishes *Uber die Lungenathmung*, giving evidence for the secretion of both oxygen and carbon dioxide by the lung
1893	High altitude station, Capanna Regina Margherita, is built on a summit of Monte Rosa at 4559 m
1906	Publication of *Hohenklima und Bergwanderungen* by Zuntz *et al.*
1909	The Duke of the Abruzzi reaches 7500 m in the Karakoram without supplementary oxygen
1910	Zuntz organizes an international high altitude expedition to Tenerife
1910	August Krogh publishes *On the Mechanism of Gas-Exchange in the Lungs*, disproving the secretion theory of gas exchange

1911	Anglo-American Pikes Peak expedition (4300 m); participants C.G. Douglas, J.S. Haldane, Y. Henderson and E.C. Schneider
1913	T.H. Ravenhill publishes *Some Experiences of Mountain Sickness in the Andes*, describing *puna* of the normal, cardiac and nervous types
1920	Barcroft *et al.* publish the results of the experiment carried out in a glass chamber in which Barcroft lived in a hypoxic atmosphere for 6 days
1921	A.M. Kellas finishes his manuscript on 'A consideration of the possibility of ascending Mt Everest' which remained unpublished until 2001
1921–22	International High Altitude Expedition to Cerro de Pasco, Peru, led by Joseph Barcroft
1924	E.F. Norton ascends to 8500 m on Mount Everest without supplementary oxygen
1925	Barcroft publishes *The Respiratory Function of the Blood.* Part 1. *Lessons from High Altitude*
1935	International High Altitude Expedition to Chile, scientific leader D.B. Dill
1946	Operation Everest I carried out by C.S. Houston and R.L. Riley
1948	Carlos Monge M. publishes *Acclimatization in the Andes*, about the permanent residents of the Peruvian Andes
1949	H. Rahn and A.B. Otis publish *Man's Respiratory Response During and After Acclimatization to High Altitude*
1952	L.G.C.E. Pugh and colleagues carry out experiments on Cho Oyu near Mount Everest in preparation for the 1953 expedition
1953	First ascent of Mount Everest by Hillary and Tenzing (with supplementary oxygen)
1960–61	Himalayan Scientific and Mountaineering Expedition in the Everest region, scientific leader L.G.C.E. Pugh. Silver Hut laboratory at 5800 m, measurements up to 7440 m
1968–79	High altitude studies on Mount Logan (5334 m), scientific director C.S. Houston
1973	Italian Mount Everest Expedition with laboratory at 5350 m, scientific leader P. Cerretelli
1978	First ascent of Everest without supplementary oxygen by Reinhold Messner and Peter Habeler
1981	American Medical Research Expedition to Everest, scientific leader J.B. West
1985	Operation Everest II, scientific leaders C.S. Houston and J.R. Sutton
1983 to present	Research at Capanna Regina Margherita (4559 m) by O. Oelz, P. Bärtsch and co-workers from Zurich, Bern and Heidelberg
1984 to present	Studies at Observatoire Vallot (4350 m) on Mont Blanc by J.-P. Richalet and co-workers
1985	Studies on Mt McKinley (Denali) at 4400 m, leader P. Hackett
1990 to present	Research at Pyramid Laboratory, Lobuje, Nepal by P. Cerretelli and co-workers
1991	Expedition to Mt Sajama, 6542 m, leader J.-P. Richalet
1994	British Mount Everest Medical Research Expedition, leaders S. Currin, A. Pollard and D. Collier
1997	Operation Everest III (COMEX '97), leader J.-P. Richalet
1998	Medical Research Expedition to Kangchenjunga, leaders S. Currin, D. Collier and J. Milledge
1998	Expedition to Chacaltaya, 5200 m, leader B. Saltin
2007	Caudwell Xtreme Everest Expedition, leader M. Grocott
2010	Reports by several groups of genetic changes in Tibetans compared with Han Chinese

> That which some of those that treat of the height of Mountains, relate out of Aristotle, namely, That those that ascend to the top of the Mountain Olympus, could not keep themselves alive, without carrying with them wet Spunges, by whose assistance they could respire in that Air, otherwise too thin for Respiration: . . .
>
> (Boyle 1660, p. 357)

However, modern historians have not been able to find this statement in Aristotle's extensive writings. Similar attributions to Aristotle can be found in the writings of Francis Bacon (1561–1626) and St Augustine of Hippo (354–430). See West (1998) for additional information.

1.3 CHINESE HEADACHE MOUNTAINS

There is a tantalizing reference to what may have been acute mountain sickness in the classical Chinese history, the *Ch'ien Han Shu*, which dates from about 30 BC. One of the Chinese officials was warning about the dangers of traveling to the western regions, probably part of present day Afghanistan, when he stated that travelers would not only be exposed to attacks from robbers but they would also become ill. One of the translations reads:

> Again, on passing the Great Headache Mountain, the Little Headache Mountain, the Red Land, and the Fever Slope, men's bodies become feverish, they lose colour, and are attacked with headache and vomiting; the asses and cattle being all in like condition. . . .

Several people have tried to identify the site of the Headache Mountains, suggesting for instance that it is the Kilik Pass (4827 m) in the Karakoram Range on the route from Kashgar to Gilgit (Gilbert 1983). However, there is not universal agreement on this.

1.4 POSSIBLE EARLY REFERENCE TO HIGH ALTITUDE PULMONARY EDEMA

Fâ-Hien was a Chinese Buddhist monk who made a remarkable journey through China and adjoining countries in about AD 400. He related that when crossing the 'Little Snowy Mountains' (probably in Afghanistan) his companion became ill, 'a white froth came from his mouth' and he died. It is tempting to identify this as the first description of high altitude pulmonary edema.

1.5 JOSEPH DE ACOSTA'S DESCRIPTION OF MOUNTAIN SICKNESS

Joseph de Acosta (1540–1600) was a Jesuit priest who traveled to Peru in about 1570. While he was there he ascended the Andes and gave a very colorful account of illness associated with high altitude. This was first published in 1590 in Spanish (Acosta 1590) (Fig. 1.1), and an English translation entitled *The Naturall and Morall Historie of the East and West Indies* appeared in 1604 (Acosta 1604). Here are some passages from his account when the party were near the top of Mount Pariacaca.

> I was suddenly surprized with so mortall and strange a pang, that I was ready to fall from the top to the ground. . . .

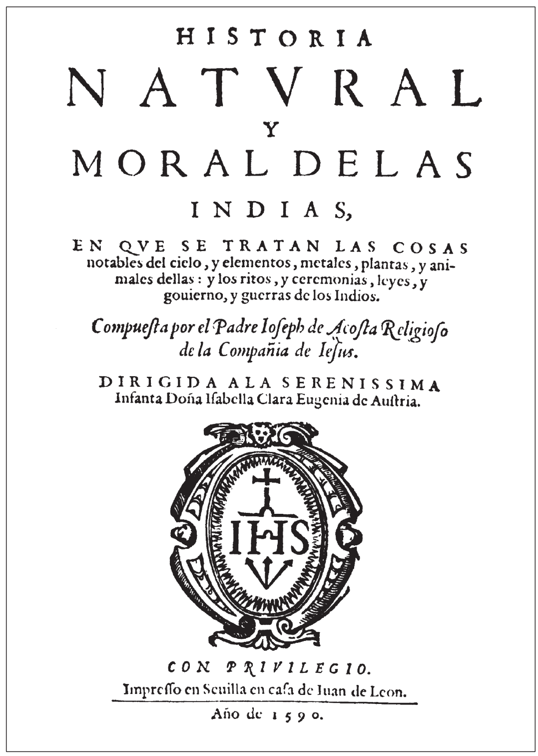
HISTORIA
NATVRAL
Y
MORAL DELAS
INDIAS,
EN QVE SE TRATAN LAS COSAS notables del cielo, y elementos, metales, plantas, y animales dellas: y los ritos, y ceremonias, leyes, y gouierno, y guerras de los Indios.
Compueſta por el Padre Ioſeph de Acoſta Religioſo de la Compañia de Ieſus.
DIRIGIDA ALA SERENISSIMA Infanta Doña Iſabella Clara Eugenia de Auſtria.
IHS
CON PRIVILEGIO.
Impreſſo en Seuilla en caſa de Iuan de Leon.
Año de 1590.

Figure 1.1 Title page of the first edition of the book by Joseph de Acosta published in Seville in 1590.

He then went on to add:

> I was surprized with such pangs of straining & casting, as I thought to cast up my heart too; for having cast up meate, fleugme & choller, both yellow and greene; in the end I cast up blood, with the straining of my stomacke. To conclude, if this had continued, I should undoubtedly have died. . . .

This is followed by an often-quoted passage:

> I therefore perswade my selfe that the element of the aire is there so subtile and delicate, as it is not proportionable with the breathing of man, which requires a more grosse and temperate aire, and I beleeve it is the cause that doth so much alter the stomacke, & trouble all the disposition.

It should be noted that this is not a typical account of acute mountain sickness which usually comes on gradually and is not associated with severe vomiting. The description sounds more like a gastrointestinal upset.

Acosta's book was widely read and, for example, Robert Boyle was familiar with his description of mountain sickness. Various people including Gilbert (1991) have attempted to identify the site of Pariacaca but there is some disagreement over this.

1.6 INVENTION OF THE BAROMETER

A key advance in high altitude science was the recognition that barometric pressure falls with increasing altitude. In 1644 Evangelista Torricelli (1608–47) wrote a letter to his friend Michelangelo Ricci in which he described how he had filled a glass tube with mercury and inverted it so that one end was immersed in a dish of the same liquid (Torricelli 1644) (Fig. 1.2). The mercury descended to form a column about 76 cm high, and Torricelli argued that the mercury was supported by the weight of the atmosphere acting on the dish. His letter included the striking sentence: 'We live submerged at the bottom of an ocean of the element air, which by unquestioned experiments is known to have weight. . . .' This was a conceptual breakthrough. Torricelli also speculated that on the tops of high mountains the pressure might be less because the air is 'distinctly rare'.

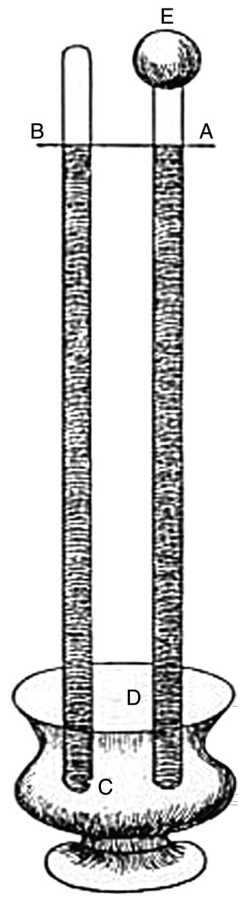

Figure 1.2 Torricelli's drawing of his first mercury barometer, from his letter to Michelangelo Ricci of 1644.

However, it was left to Blaise Pascal (1623–62) to prove that barometric pressure falls with increasing altitude. In 1648 he persuaded his brother-in-law, Florin Perier, to carry a mercury barometer up the Puy-de-Dôme in central France. This was an elaborate experiment with careful controls and he was successful in showing that on the summit the pressure had fallen by approximately 12% of its value in the village of Clermont.

1.7 INVENTION OF THE AIR PUMP

The first effective air pump was constructed by Otto von Guericke (1602–86) who was mayor of the city of Magdeburg in central Germany. In a famous experiment he constructed two metal hemispheres which fitted together accurately when the air within them was pumped out. Two teams of horses were then unable to separate the two hemispheres, graphically demonstrating the enormous force that could be developed by the air pressure.

However, Guericke's pump was cumbersome to operate and it was impossible to place objects in the hemispheres to study the effects of the reduced air pressure. This was first done by Robert Boyle (1627–91) and his colleague Robert Hooke (1635–1703). Hooke was a mechanical genius who designed an air pump consisting of a piston inside a brass cylinder. Above this was a large glass receiver into which various objects and small animals could be placed (Fig. 1.3). In his groundbreaking book *New Experiments Physico-Mechanicall, Touching the Spring of the Air, and its Effects. . .* (Boyle 1660), he demonstrated the effects of a reduced atmospheric pressure in a variety of experiments. In one of these a lark was placed in the receiver and Boyle wrote:

> the Lark was very lively, and did, being put into the Receiver, divers times spring

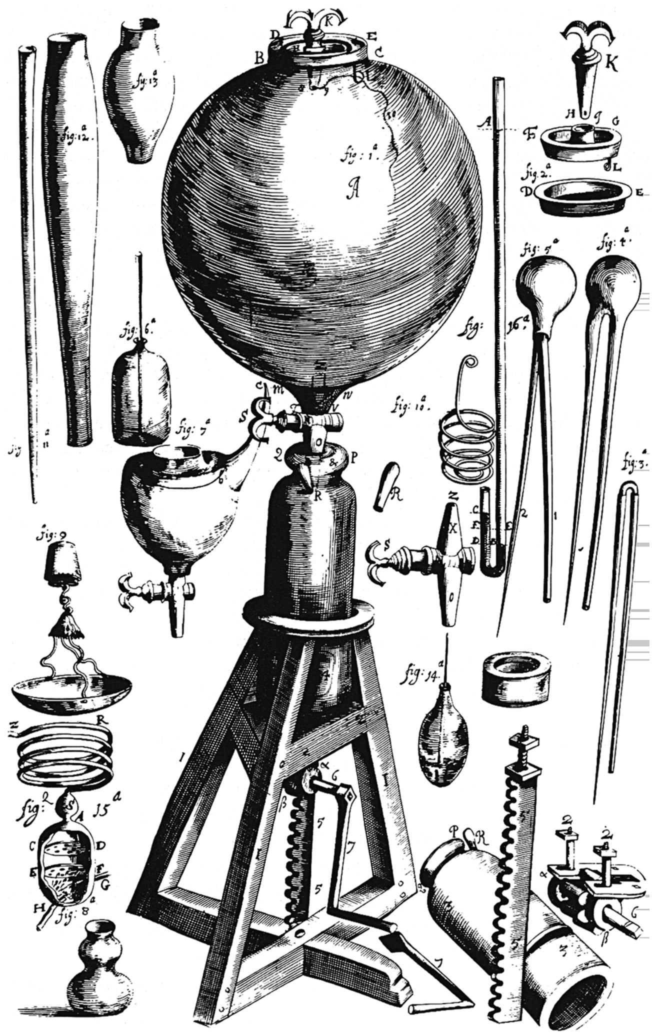

Figure 1.3 Air pump constructed by Robert Boyle and Robert Hooke. This enabled them to carry out the first experiments on hypobaric hypoxia. From Boyle (1660).

> up in it to a good height. The Vessel being hastily, but carefully clos'd, the Pump was diligently ply'd, and the Bird for a while appear'd lively enough; but upon a greater Exsuction of the Air, she began manifestly to droop and appear sick, and very soon after was taken with as violent and irregular Convulsions, as are wont to be observ'd in Poultry, when their heads are wrung off. . . .

Following these experiments Hooke made a chamber large enough for a man to sit in it while it was partially evacuated and he reported to the young Royal Society:

> that himself had been in it, and by the contrivance of bellows and valves blown out of it one tenth part of the air (which he found by a gage suspended within the vessel) and had felt no inconvenience but that of some pain in his ears at the breaking out of the air included in them, and the like pain upon the readmission of the air pressing the ear inwards.

1.8 DISCOVERY OF OXYGEN

Progress in the remainder of the seventeenth century and most of the eighteenth century was largely stymied until the nature of the respiratory gases was characterized. There is not space here to follow the interesting story of the work of Boyle, Hooke, Lower and Mayow in the seventeenth century and the discovery of oxygen by Joseph Priestley (1733–1804), Carl Scheele (1742–86) and Antoine Lavoisier (1743–94). John Mayow (1641–79) was aware in 1674 of what he called 'nitro-aerial spirit', which we now recognize as oxygen but his work was largely ignored for almost a century. Both Priestley and Scheele independently isolated oxygen but Priestley was confused about its nature, believing that it was 'unphlogisticated air', and Scheele's report was delayed because of publication problems. It was left to the brilliant French chemist Lavoisier (Fig. 1.4) to clearly describe the three respiratory gases. In 1777 he stated:

> Eminently respirable air [he later called it oxygine] that enters the lung, leaves it in the form of chalky aeriform acids [carbon dioxide] . . . in almost equal volume. . . . Respiration acts only on the portion of pure air that is eminently respirable . . . the excess, that is its mephitic portion [nitrogen], is a purely passive medium which enters and leaves the lung . . . without change or alteration. The respirable portion of air has the property to combine with blood and its combination results in its red color.

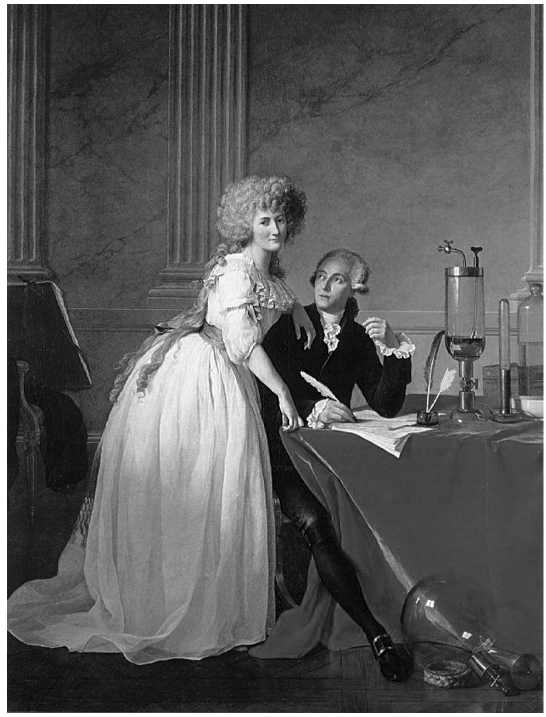

Figure 1.4 Antoine Lavoisier (1747–1794) with his wife Marie-Anne (1759–1836), who was his laboratory assistant. From the painting by David, 1780.

Carbon dioxide had been discovered earlier by Joseph Black (1728–99) while he was a medical student although he used the term 'fixed air'.

1.9 FIRST BALLOON ASCENTS AND THE RECOGNITION OF SEVERE ACUTE HYPOXIA

The Montgolfier brothers, Joseph (1740–1810) and Jacques (1745–99), invented the man-carrying balloon, first using heated air, and later hydrogen. The first free ascent of a manned balloon took place in Paris in 1783. It was not long before these adventurous balloonists became aware of the deleterious effects of high altitude on the body. For example, Alexandre Charles (1746–1823) (of Charles' law) ascended in a hydrogen-filled balloon in December 1783 and reported 'In the midst of the inexpressible rapture of this contemplative ecstasy, I was recalled to myself by a very extraordinary pain in the interior of my right ear. . . .' He correctly attributed this to the effects of air pressure.

However, more ominous effects were soon noted. Jean Blanchard (1753–1809) claimed to have ascended to an altitude of over 10 000 m in 1785 (although the altitude was contested) and reported that 'Nature grew languid, I felt a numbness, prelude of a dangerous sleep. . . .' However, much more dramatic were the events in 1862 when James Glaisher (1809–1903) and Henry Coxwell (1819–1900) rose to an altitude which was estimated to exceed 10 000 m. Glaisher became partly paralyzed and then unconscious, and Coxwell lost the use of his hands, and could only open the valve of the balloon by seizing the cord with his teeth. Glaisher also reported losing his sight before his partial paralysis.

The most famous and tragic balloon ascent was by three French aeronauts, Gaston Tissandier (1843–99), Joseph Crocé-Spinelli (1843–75) and Theodore Sivel (1834–75), in their balloon Zénith in 1875. Paul Bert (see below) had recommended that they take oxygen but they had too little and there were difficulties in inhaling it. Tissandier's report (1875) is dramatic.

> Towards 7500 meters, the numbness one experiences is extraordinary. . . . One does not suffer at all; on the contrary. One experiences inner joy, as if it were an effect of the inundating flood of light. One becomes indifferent. . . . Soon I wanted to seize the oxygen tube, but could not raise my arm. . . . Suddenly I closed my eyes and fell inert, entirely losing consciousness.

When the balloon ultimately reached the ground, Sivel and Crocé-Spinelli were dead, having perished as a result of the severe hypoxia. The disaster caused a sensation in France.

1.10 MOUNTAIN SICKNESS IN MOUNTAINEERS

During the nineteenth century, mountaineering became popular particularly in the European Alps. The result was many descriptions of acute mountain sickness, some of which seem to us today to be greatly exaggerated. One of the first was from the great German naturalist Alexander von Humboldt (1769–1859) when he reached very high altitudes on two volcanoes in South America in 1799. On Chimborazo, at an altitude of about 5540 m, he stated that the whole party felt 'a discomfort, a weakness, a desire to vomit, which certainly arises as much from the lack of oxygen in these regions as from the rarity of the air.' Another early account was by Horace-Bénédict de Saussure (1740–99) on Mont Blanc (4807 m) in 1787. When he was near the summit he stated:

> I therefore hoped to reach the crest in less than three quarters of an hour; but the rarity of the air gave me more trouble than I could have believed. At last I was obliged to stop for breath every fifteen or sixteen steps. . . . This need of rest was absolutely unconquerable; if I tried to overcome it, my legs refused to move. . .

Numerous other reports of the deleterious effects of high altitude while climbing mountains are given in the first chapter of Paul Bert's book *La Pression Barométrique* (1878).

1.11 PAUL BERT AND THE PUBLICATION OF *LA PRESSION BAROMÉTRIQUE*

The French environmental physiologist Paul Bert (1833–86) is often cited as the father of modern high altitude physiology and medicine. The publication of his great book *La Pression Barométrique* in 1878 was certainly an important landmark. One of his principal findings was that the deleterious effects of exposure to low pressure could be attributed to the low $P\mathrm{O}_2$. He did this by exposing experimental animals to a low pressure of air on the one hand (hypobaric hypoxia), and to gas mixtures at normal pressure but with a low oxygen concentration (normobaric hypoxia) on the other. In this way he showed that the critical variable was the $P\mathrm{O}_2$. *La Pression Barométrique* is essential reading for anybody with a serious interest in the history of high altitude medicine and physiology. A good English translation is available (Bert, 1878). For one thing, there is a long introductory section on the history as Bert saw it, and this makes fascinating reading today. Bert wrote with a charming style and urbane wit. The book not only deals with the medical and physiological effects of low pressure but high pressure as well.

Many of Bert's studies were carried out at the Sorbonne in Paris which was equipped with both low pressure and high pressure chambers (Fig. 1.5). At one stage he tested the three French balloonists Tissandier, Crocé-Spinelli and Sivel who were referred to above and he actually warned them that they had insufficient oxygen but the warning letter arrived too late.

La Pression Barométrique includes many interesting passages. For example, it contains the first graphs of the oxygen and carbon dioxide dissociation curves in blood. Bert also speculated that polycythemia might occur at high altitude and this was shown a short time later by compatriots including Viault (1890). At one point Bert speculated on the possible reduction of metabolism in frequent visitors to high altitude and people who live permanently there. This short section will be cited partly because it gives a good feel for the style of Bert and his pungent wit.

> We see that very probably, in the habitual conditions of our life, we commit excesses of oxygenation as well as of nourishment, two kinds of excess, which are correlative. And just as peasants, who eat much less than we do, but utilizing all that they absorb, produce in heat and work a useful result equal, if not superior, to that of city dwellers; just as a Basque mountaineer furnished with a piece of bread and a few onions makes expeditions which require of the member

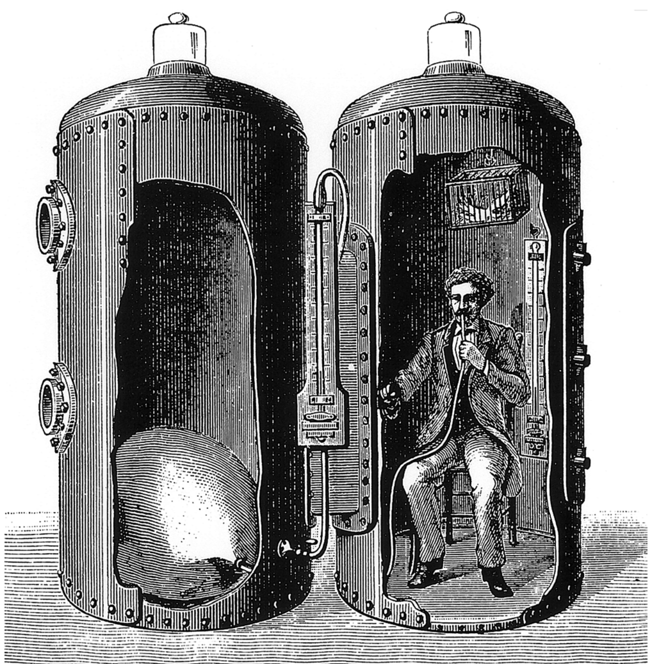

Figure 1.5 Low pressure chambers used by Paul Bert at the Sorbonne. From Bert (1878).

> of the Alpine Club who accompanies him the absorption of a pound of meat, so it may be that the dwellers in high places finally lessen the consumption of oxygen in their organism, while keeping at their disposal the same quantity of vital force, either for the equilibrium of temperature, or the production of work. Thus we could explain the acclimatization of individuals, of generations, of races.
>
> (Bert 1878, p. 1004 in the English translation)

1.12 HIGH ALTITUDE LABORATORIES

1.12.1 Observatoire Vallot

Towards the end of the nineteenth century the pace of discoveries in high altitude medicine and physiology accelerated rapidly partly as the result of the publication of *La Pression Barométrique*. This was a period when two high altitude laboratories were established. The first was the Observatoire Vallot on Mont Blanc which was installed in 1890. Joseph Vallot (1854–1925) conceived the idea of placing a small building at an altitude of about 4350 m, which is about 460 m below the summit of Mont Blanc. With typical French panache he was not satisfied with a simple hut, but in addition there were a comprehensive laboratory, a well-appointed kitchen, and attractive interior decorations including a French tapestry of courtly ladies in the eighteenth century style. The laboratory was used for research in several of the physical sciences, including astronomy and glaciology, but physiological studies were also carried out including some of the first observations of periodic breathing at high altitude (Egli-Sinclair 1893). The Observatoire Vallot is still in use today although it has been considerably modified. Access is challenging because usually a night has to be spent at the Grands Mulets (3050 m) followed by a climb over the snow and ice the next day. Alternatively, a helicopter ascent is possible.

In 1891, a young physician, Dr Jacottet, died in the Observatoire Vallot from what was almost certainly high altitude pulmonary edema. A description of the illness including the post-mortem findings is in Mosso's book *Life of Man on the High Alps* (Mosso 1898) referred to in the next section.

1.12.2 Capanna Margherita

Shortly after the construction of the Observatoire Vallot, an even higher structure was placed on one of the peaks of Monte Rosa in Italy at an altitude of 4559 m. The original hut was completed in 1893 and 10 years later it was enlarged by the influential Italian scientist Angelo Mosso (1846–1910) to include a laboratory for physiological and medical studies. The structure owes its name to Queen Margherita of Savoy who was a lover of alpinism and a generous patron of science. In fact, she visited the Capanna in 1893 and spent the night there.

Mosso was a physiologist with very broad interests, particularly in the area of exercise and environmental physiology. Some of the early studies in the Capanna Margherita were reported in his book *Fisiologia dell'uomo sulle Alpi: studii fatti sul Monte Rosa* (Mosso 1897), and this was translated into English as *Life of Man on the High Alps* (Mosso 1898). Among the projects carried out at the Capanna were some on periodic breathing, and also total ventilation at high altitude. In fact, Mosso believed that the deleterious effects of high altitude were related to the low carbon dioxide levels in the blood rather than the reduced $P\text{O}_2$ as previously proposed by Paul Bert. Mosso coined the term 'acapnia' to describe this condition which he thought was important in the development of acute mountain sickness. An interesting event at the Capanna was the illness of an Italian soldier, Pietro Ramella, who developed what was thought to be a respiratory infection and from which he recovered. In retrospect, this may have been high altitude pulmonary edema as was the case with Jacottet at the Observatoire Vallot. The Capanna Margherita has been enlarged over the years and