Perspectives in Physiology
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Clark M. Blatteis
Nigel A. S. Taylor
Duncan Mitchell *Editors*

Thermal Physiology

A Worldwide History

american physiological society

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Editors
Clark M. Blatteis (deceased)
Formerly at:
Department of Physiology
The University of Tennessee Health
Science Center, College of Medicine
Memphis, TN, USA

This work was completed by

Nigel A. S. Taylor
Dharawal Country (Dapto)
NSW, Australia

Duncan Mitchell
Brain Function Research Group, School of
Physiology
University of the Witwatersrand
Witwatersrand, South Africa

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Following the death of Clark Blatteis in March 2021, Nigel A.S. Taylor (University of Wollongong, Wollongong, Australia) and Duncan Mitchell (University of the Witwatersrand, Johannesburg, South Africa) joined the editorial team, to help the authors to bring their book to completion.

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Prologue

Our father, Clark Blatteis, got the idea for a book on the history of thermal physiology as he approached the end of his professional career. He realised he would soon be leaving behind collegial relationships that he had formed with fellow thermal physiologists from around the globe and enjoyed for over 60 years. Given how little some thermal physiologists knew about each other beyond a level of professional contact, he imagined that they, and others interested in the field, might know even less about their scientific forefathers. He set out to gather the stories that would recall those researchers as individuals, as well as in the context of their most salient contributions to the advancement of the field. With the support of the American Physiological Society and many authors around the world, he began this history of thermal physiology's worldwide forbearers for the archives, and for their professional progeny.

From its early beginnings as a discipline in the eighteenth century, through to becoming a fully established area of study that continues to create new scientific fields of inquiry today, it is clear that there are many more individuals who have contributed to this history than can be included in this book. Indeed, he was unable to complete the list of scientists whom he felt had advanced or inspired further work in the field, before his passing in March 2021. We are very thankful to Suzanne Schneider for finishing the American chapter which our father began, and to Duncan Mitchell and Nigel A.S. Taylor for final editing, revisions, and additions to the work of the many authors who made this a global history. Completing a book posthumously is a delicate task, and we are deeply grateful to them. We are also especially thankful to Larry Tague, our father's close friend and physiology colleague, with whom he discussed his concept of creating an evolving bridge from the past to the future of thermal physiology. Indeed, without the help and support of the scientific community of which our father was proud to be a part, this book would simply not have been completed.

Per our father's wish, we dedicate this work to our mother, Yolanda Blatteis. She counted many of the scientists described in this book as her friends. It could not have been created without the profound love and encouragement during her life's journey with Clark, until her passing in December 2018.

As a scientist, Clark Blatteis has left a legacy of scholarly work, and we are especially proud of what his research has done for the safety of newborns with fevers. Our father retired from the University of Tennessee Department of Physiology many years ago, but he never retired as a thermal physiologist. Just days before he died, he was asked what were the key qualities needed to be a scientist. He answered "*curiosity and perseverance; because, without having questions there would be no interest in seeking answers, and without perseverance there would be no ability to continue when the answers are so often wrong or difficult to find*". He loved his work, and, by extension, he was very curious about his fellow travellers in the field. This history is a result of that curiosity and perseverance. We hope it can aid and inspire the many intrepid scientists pursuing the field of physiology and, especially, thermal physiology today and in the future.

Our father was not the only author to have died during the course of the book's production, and so, with both sadness and admiration, we ask its readers to remember the lives and scientific contributions of Clark Blatteis (1932–2021) and Helen Laburn (1951–2014) from South Africa, who also passed away as the book was being prepared.

Elisa Blatteis Roberts
Charles Blatteis
Beatrice Blatteis

Foreword

Historically, the origin of studies into the thermoregulatory system was the application of temperature measuring devices as diagnostic tools in human diseases. The earliest instruments, technically very large and clumsy, to determine pathological deviations of body temperature from that of a normal healthy individual (e.g. Liebermeister and Wunderlich; see Chap. 3), have become successively refined over the decades, currently ending up with digital infrared thermometers. Well into the twentieth century, the time courses of fever often were essential diagnostic criteria to identify infectious febrile diseases, which were named accordingly (e.g. *tertian malaria, quartan malaria, and continuous typhoid*).

Thermal physiology became very important as an applied science during the late nineteenth and the twentieth centuries, in the context of human exposures to extreme temperatures associated with a multitude of human endeavours: for example, the colonisation of subtropical and tropical regions, exploration of polar regions and, especially, military excursions, such as establishment of military bases in hot or polar environments in the two world wars, and many other military activities (e.g. heat: see Edholm and Schmidt-Nielsen; cold: see Scholander, LeBlanc, and Hammel [see Chaps. 1, 4, 5, 6, 11, 13, and 14]). Thermal physiology also became very important in the context of muscular work; very high metabolic rates even in cool conditions can give rise to excessive heat storage.

As a result of these scientific activities, research has been stimulated concerning the supply of water and electrolytes to balance their loss via sweating (e.g. Adolph; see Chaps. 5 and 11), energy supply to compensate for the metabolic cost of work or cold defence, and control of the circulatory system as the heat-transfer system from the deep-body (core) to the shell tissues (e.g. Rowell; see Chap. 5). In a quite analogous manner, thermal physiology has become an essential aspect of occupational physiology, including industrial work in extreme heat and humidity, and in exercise physiology (e.g. Nadel, Nielsen, Saltin, and Wyndham; see Chaps. 6, 7, and 8). Associated with these topics were studies aimed at understanding the physiological mechanisms involved in adapting to adverse heat, as well as to cold environmental conditions. They comprise a multitude of adaptation studies, both natural and artificial, in humans as well as in other animals, so as to improve the ability of humans and other animals to cope with heat or cold stresses. They have remained topics of research interest, especially from the viewpoint of exercise physiology and biometeorology, but also in the context of global climatic changes (exemplified by the Japanese journal *Global Environmental Research*).

From the therapeutic point of view, body heating to a degree that may precipitate heat stroke has stimulated intensive medical research. A prime example is the extensive logistic effort to treat heat-stroke victims that present whenever the Hajj falls into the hottest part of the year (e.g. Weiner, Khogali; see Chap. 1). On the other hand, induced hyperthermia as a therapeutic tool in the treatment of cancer has remained a substantial research topic (see Chaps. 3 and 9).

The opposite condition, of excessive body cooling, has also become an important topic of research in the course of the twentieth century. The prevention of accidental hypothermia and the treatment of hypothermic patients are still important topics of applied thermal physiological research (see Chap. 12). On the other hand, artificially induced hypothermia initially was under experimental investigation, but has subsequently flourished in clinical investigations (Swan, 1973) as a means to reduce the metabolic oxygen demands in brain-injured patients and, in particular, as the basis for progress in heart and lung surgery, in combination with the development of extracorporeal maintenance of blood flow, oxygenation, and electrolyte balance. The insights obtained in these fields are gaining great attention again in the emergency treatment of severely ill victims of the current SARS-Cov2 pandemic.

It has long been a characteristic of studies in which thermal impacts pose limits to human performances that questions about the mechanisms of temperature regulation (i.e. the physiological functions by which homoeothermic organisms maintain thermal stability over a wide range of external or internal heat loads) have been confined to the analytical background. Exceptions were the control of blood circulation, by which transfer of heat from the inner body to its surface is accomplished, and the maintenance of electrolyte and water balance as the essential basis for heat transfer from the body surface to the environment via evaporative cooling (sweating, panting, saliva spreading), and of their neuronal and humoral control. Research in thermal physiology progressed apparently without requiring detailed insights into the underlying central nervous control mechanisms.

However, starting around the turn from the nineteenth to the twentieth centuries, questions about the central nervous control of body temperature have slowly, but increasingly, gained importance. For example, research into the transmission of thermal afferent information from temperature sensors and the efferent neuronal and humoral control over the mechanisms for producing heat and dissipating it from the body surface has become very important. They proceeded from early central nervous ablation studies (e.g. Isenschmid, Krehl, Thauer, Keller, Bard; see Chaps. 3 and 6) and occasional probing of brain structures in search of nervous structures serving as the deep-body "thermometer" (e.g. Barbour; see Chaps. 3 and 6). Over the course of subsequent decades of investigation, these aspects of temperature regulation have become the subject of a multitude of modern supportive biological disciplines.

It is worth emphasising that most of the chapters in this monograph deal with the insights gained by multidisciplinary approaches. First and foremost, neuro-electrophysiological experiments were vitally important (e.g. Hensel, Iggo, Nakayama; see Chaps. 1, 3, and 9), as they dealt with both peripheral and central neuronal thermosensitivity as afferent inputs. That research also emphasised somatomotor, autonomic nervous, and endocrine control over efferent outputs and central nervous signal processing. Then biochemistry and pharmacology became important, as studies dealt with neurotransmitters involved in temperature regulation and, especially, with pyrogenic substances, cytokines, and prostaglandins as internally generated mediators of fever (see Chaps. 1, 3, 5, and 10).

More recently, studies of molecular receptors and of neurohormones involved in the generation of temperature signals as well as in the processing of those signals, with the aim of generating coordinated responses of the multitude of thermoregulatory effectors, were, and still are, performed. Indeed, the 2021 Nobel Prize was awarded for the discovery of the molecular channels that sense temperature. These approaches have greatly advanced insights into the neurohumoral mechanisms underlying physiological temperature regulation and its pathological disturbances.

Equally relevant are the contributions of comparative physiology. Its early ground-breaking achievements include the discovery of special thermoregulatory effectors (e.g. brown adipose tissue (Smith, Horwitz, Himms-Hagen; see Chaps. 5 and 14), of special vascular mechanisms underlying selective brain cooling as an adaptive mechanism to a multitude of specific environmental impacts (e.g. Jessen, Cabanac, Nielsen; see Chaps. 2, 3, 7, and 8), and the role of thermoregulatory behaviour. Important current topics of relevance for the understanding of body temperature regulation are the circadian, and especially the seasonal, adjustments of body temperature to reduced levels in a controlled manner in states of energy saving (e.g. Kayser, Wang; see Chaps. 2 and 14), a field of research in which many questions remain to be answered.

Max-Planck-Institute for Heart and Lung Research, William G. Kerckhoff Institute, Bad Nauheim, Germany

Eckhart Simon

Preface

"*Wärme ist ein zentral wirkendes Antipyretikum*" (Heat is a centrally acting antipyretic). That is how Henry Gray Barbour described what he saw happen to the deep-body (core) temperature of anaesthetised rabbits in 1912, when he perfused tubes implanted in the hypothalamus with warm water. Barbour was an American pathologist, medical graduate of Johns Hopkins University, and long-time servant of Yale University. Why did he publish in German? Whose idea was it to explore the hypothalamus? Why does the drop in body temperature that he saw have nothing to do with antipyresis?

In the year before, in France, Jules Lefèvre had published his book *La chaleur animale et bioénergétique* (Animal heat and bioenergetics), in which he described an ergometer, for experimental exercise in the laboratory, and calorimetric methods for measuring heat exchange between the body and its surroundings. Do human subjects of the same gender and mass, exercising at the same absolute work rate in the same environment, have the same deep-body temperature? Who showed that the heat balance of the body actually conforms to the laws of thermodynamics, as, of course, it must?

Many thermal physiologists might be taxed to answer such questions. And if thermal physiologists do not know the history of their field, is it surprising that modern climate change scientists so frequently are floundering in basic thermal physiology, as they re-invent it?

A hundred years after Barbour and Lefèvre published their seminal work, Clark M. Blatteis, Professor of Physiology at the University of Tennessee in Memphis (USA), saw an opportunity to overcome such knowledge deficits, and to document the history of thermal physiology. The American Physiological Society's Perspectives in Physiology series of books "*places biomedical science inside a greater historical framework by describing the development of a field of study and highlighting the contributions of prominent investigators in that field*". The Book Committee of that Society agreed to Clark's proposal to add thermal physiology to that series. The book would have chapters describing the history of thermal physiology in different countries. He would write the history of thermal physiology in the USA, and he invited authors from many other countries to contribute chapters. He knew most of those authors personally, through his long association with thermal physiology internationally, including his former chairmanship of the Thermal Physiology Commission of the International Union of Physiological Sciences. The US contribution, along with communications from 13 of the original 14 invited countries, makes up this book. Thermal physiology has a long and distinguished history in many other countries, and we apologise that those histories have not also been recorded in this volume.

Clark took on board the objective of the Perspectives in Physiology series to describe "*development of a field of study*", but also to highlight "*contributions of prominent investigators*". His aim was that the history should recall the workers in the context of their most salient contributions to the advancement of the field. The authors of all the chapters embraced that objective, although some authors elected to focus more on the personages and personalities of the workers, and others more on highlighting their most salient contributions. They set out to compose not simply a list of names and achievements, but rather a dynamic exposition of how ideas, people, and the times in which they lived created the mix that produced the science. In every chapter, readers will meet the real people behind the names that they know as authors of papers in thermal physiology. Two famous thermal physiologists born in the same country married the daughters of their bosses, who were from other countries; who were they? What famous thermal physiologist, not from Norway, was the doctor responsible for the welfare of researchers studying cold acclimation in the 1963 expedition to the Hardanger Plateau in Norway? Why did a thermal physiologist whose father was a diplomat in Tokyo have tears streaming from his eyes in a laboratory in Copenhagen? What thermal physiologist became Prime Minister of the country of his birth?

In a field like that of thermal physiology with ongoing activity, identifying the end of an epoch of history, for the construction of an account of that history, requires an arbitrary decision. Clark's guideline was that the histories should exclude any investigators not "*retired from the bench*" at the time of writing of the chapter. We interpreted that decision to mean excluding anyone for whom data collection still was a major activity in their thermal physiology, but not to exclude investigators still engaged with research writing. Excluding investigators not retired from the bench means that readers may find that the names of the thermal physiologists whom they know best do not appear in this book. They still are making their history. No constraints were placed on what taxa could be included, so decisions such as those to exclude invertebrate thermal physiology, or to exclude ectotherm thermal physiology, were those of the chapter authors.

All but two of the original 14 chapters had been submitted around the date of the original submission deadline. Regrettably, Clark Blatteis did not live to see either the book reach publication or, indeed, the US chapter reach completion. Unfortunate personal and family circumstances intervened. Although, up to then, we had been involved in the book only as enthusiastic authors, when Clark passed away in March 2021, we felt an obligation to preserve all of the work that had been done, and to help get the book to completion. So we offered our assistance to the American

Physiological Society, Springer, and Clark's heirs, and it was accepted. We are very grateful to Suzanne Schneider, who completed the US chapter, and to Victor Candas and Jean-Pierre Libert, who contributed a new French chapter; they were not amongst Clark's invitees but came to the rescue. Authors from other countries who indeed were original invitees returned to the fray and revised their chapters with a commitment and professionalism that we found most remarkable, albeit unsurprising. It is to them that this book owes its revival.

Authors old and new also agreed to us carrying out light edits of their chapters. We did not seek to attain uniformity; rather, we tried to preserve the country flavours. We did try to help authors to maintain internal consistency in their chapters, and we did make suggestions about language and style, bearing potential readers in mind. Many authors had given up the privilege of writing in their home language. We assumed that readers mostly would not be experienced thermal physiologists, and many would not yet be born. We imposed expectations on authors far too advanced in their careers, and indeed in their years, to have to countenance such impositions. We apologise again.

We apologise, too, to those authors whose preference for chapter order, sometimes cogently argued, was not adopted. With the consent of all the authors, the chapters are arranged in date order of the oldest cited reference in the field of thermal physiology, published by someone working in that country. We recognise that the algorithm does not necessarily reflect the extent or strength of the heritage of each country in thermal physiology.

For the benefit of readers, we did try to achieve consistency of technical terminology across chapters. We urged authors to employ the terminology of the Thermal Physiology Glossary of the International Union of Physiological Sciences, with modifications where the Glossary is silent or outdated. In particular, we recommended that authors use either "body core temperature" or "deep-body temperature", terms that we consider synonymous, consistently within a chapter, for the temperature of the tissue mass normally strongly perfused with arterial blood; the internal organs and the brain.

Helping to get the book to completion has required intense activity from both of us, but only for a few months. Apart from that of the company of our fellow authors, we have had generous support from, and collaboration with, the Blatteis family: Elisa Blatteis Roberts, Charles Blatteis, and Beatrice Blatteis. Elisa retrieved material from her late father's computer without which the book would have stalled. We also have had unremitting encouragement, advice, and support from the American Physiological Society, and especially from Dee Silverthorn, the outgoing chair of its Book Committee. The task also has imposed unreasonable expectations on our tolerant, and long-suffering, wives, Lily and Liz. There can be a silver lining, even during a pandemic!

Following the death of the editor, Nigel A.S. Taylor (formerly of the University of Wollongong, Wollongong, Australia) and Duncan Mitchell (University of the Witwatersrand, Johannesburg, South Africa) helped the authors to bring their book to completion.

Witwatersrand, South Africa Duncan Mitchell
Dharawal Country (Dapto), Australia Nigel A. S. Taylor

Contents

Chapter 1
A History of Thermal Physiology in the United Kingdom of Great Britain and Northern Ireland and the Republic of Ireland

Anthony Milton

> "Begin at the beginning", *the King said, very gravely* "and go on till you come to the end: then stop".
>
> *Lewis Carroll (Charles Lutwidge Dodgson, 1865, p. 182).*

1.1 Introduction

Thermal physiology research is entirely dependent on the ability to measure temperature, and that could not happen until the invention of the thermometer by Santorio Santorio in 1612. However, it was not until 1724 that Daniel Gabriel Fahrenheit devised an accurate scale of temperature measurement, followed by the Swedish scientist, Anderss Celsius in 1742, who developed the centigrade (Celsius) scale. It was much later, in 1867, that Sir Thomas Allbutt invented the first practical medical thermometer, and soon after James Joule (1850) demonstrated the relationship between thermal energy and mechanical work. However, with some exceptions (e.g. Blagden, 1775), scientific observations on the physiology of temperature regulation did not really begin in the UK until the end of the eighteenth century. Anyone entering the field of human thermal physiology could adopt the principle of not exposing others experimentally to conditions to which they have not exposed themselves. In preparation, read the well-known heroic tale of how the UK physician and scientist Charles Blagden (Fig. 1.1) exposed himself and other volunteers (including a dog) to air temperatures up to 127 °C, much hotter than modern saunas (see Chap. 4) and enough to cook a steak alongside him, as he demonstrated, and found, to his relief, that sweating kept the deep-body temperatures in the low forties.

A. Milton (✉)
The Old School, Dunbar, East Lothian, UK
e-mail: asmilton27@icloud.com

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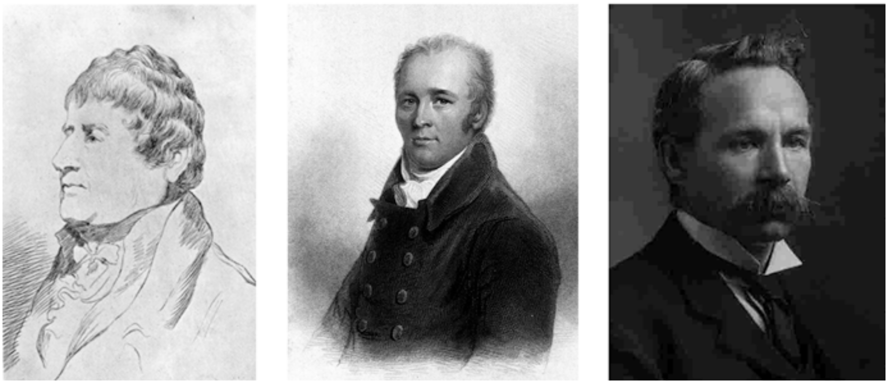

Fig. 1.1 Eminent UK thermal physiologists of the eighteenth and nineteenth centuries. (**a**) Charles Blagden (1748–1820), of the 127 °C exposure (Public domain, by Mary Dawson Turner (née Palgrave), after Thomas Phillips, https://en.wikipedia.org/wiki/Charles_Blagden#/media/File:Blagden_Charles.jpg). (**b**) James Currie (1756–1805), of deep-body temperature in disease (Public domain, London, George Virtue, http://ihm.nlm.nih.gov/images/B05019). (**c**) Marcus Pembrey (1868–1934), of cellular energy and body temperature (Public domain, Wikimedia Commons, https://en.wikipedia.org/wiki/File:MarcusPembury1.jpg)

1.2 Publication of Papers

The Royal Society of London was founded in 1660, and the *Philosophical Transactions of the Royal Society* commenced publication in 1665; it is the world's oldest scientific journal. Virtually all of what we would call physiological research papers during the seventeenth and eighteenth century were published in that journal. In 1800, so nearly a century and a half later, the Royal Society introduced a new journal, called *The Proceedings of the Royal Society*. From that time onwards, *Transactions* has been concerned with the publication of research papers presented by Fellows of the Society, or with papers introduced by Fellows, with each number being primarily restricted to a single theme. Both journals are now divided into two sections, A for mathematics and physics and B for biological sciences. The *Journal of Physiology* was not started until 1878, with the Physiological Society adding the *Quarterly Journal of Experimental Physiology* (now *Experimental Physiology*) in 1908. In addition to submitting papers to the *Philosophical Transactions*, many early scientists published their observations in books, which they published themselves (e.g. Lind, 1771; Crawford, 1779; Hunter, 1786; Currie, 1797).

1.3 Eighteenth Century

The eighteenth century provided several scientists of note for the history of thermal physiology, four of whom are highlighted below; an English country parson, a Scottish surgeon, a Scottish physician and a chemist and physician from Ireland.

1.3.1 Reverend Edward Stone

Edward Stone was born in Princess Risborough near Oxford in 1702, and died in Chipping Norton, which is now a famous tourist village west of Oxford, in 1768. He went to Wadham College, Oxford, in 1720, and later became a Fellow of the college. After entering holy orders, he became chaplain to landowner and politician Sir Jonathan Cope, and held various curacies in and around Chipping Norton. In the year 1763, Stone presented the results of his observations on the use of the bark of the willow tree in the treatment of ague (malaria) to the Royal Society. These results were subsequently published in the *Philosophical Transactions* of the Society, and that constituted the first scientific account published on the use of an antipyretic drug. How Stone came about his discovery is well documented (see Jeffreys, 2004). The active component of this extract of willow bark was subsequently identified as a beta-glucoside, and given the name salicin, after the Latin name for the willow tree, *Salix*.

It was this observation, during the rise of the organic chemical industry, that led to the synthesis of salicylic acid, and subsequently to acetylsalicylic acid (aspirin). It was to take until the 1970s for the antipyretic, analgesic, and anti-inflammatory modes of action of aspirin to be explained, when Vane (1971) showed that aspirin inhibited the cyclo-oxygenase enzymes, responsible for the synthesis of prostaglandins involved in all three conditions, fever, pain and inflammation. Non-steroidal anti-inflammatory drugs (NSAIDs), the family of widely used drugs sharing the ability to inhibit the cyclo-oxygenase enzymes, are now a subject in their own right, but they all stem from the simple observations of an eighteenth-century Minister of the Church of England.

1.3.2 John Hunter

Mister John Hunter was the surgeon in question. Remember that, in the United Kingdom, and other countries in the Commonwealth, surgeons refer to themselves as Mister, a title of which they are very proud. Beware anyone who calls a surgeon "Doctor".

John Hunter was the most famous British surgeon of his era. He was born in Long Calderwood, near Glasgow, in Scotland in 1728. He came to London in 1748 to join his brother, who was a well-known teacher of anatomy. He soon became an assistant in dissection. Having trained at the Chelsea Hospital and St. Bartholomew's Hospital, he ultimately qualified as a surgeon. During his long career, he published a large number of works (see Palmer, 1835). In 1775, he published a paper identifying (but not measuring; see Sect. 1.3.3) the production of heat by animals and plants in the *Philosophical Transactions of the Royal Society*, and in 1778 he published a further paper in the same journal (Hunter, 1775, 1778), in which he described many of his experiments. One of his most important books was published in 1786 (Hunter, 1786); he devoted a whole chapter to heat production in animals, in which he describes his cooling various animals, and measuring the abdominal temperature of dormice.

1.3.3 Adair Crawford

Adair Crawford was born in Crumlin, near Belfast in Ireland, sometime in 1748. He attended Glasgow University, where he studied theology and arts, graduating MA in 1770. He subsequently studied medicine at both Edinburgh and Glasgow, graduating from Glasgow in 1780. He is remembered both as a chemist and a physiologist. He is attributed with being the discoverer of the element strontium. Working at the Royal Military Academy in Woolwich, where he was professor of chemistry, with William Cruikshank, he noted the presence of strontianite in barium-containing minerals. He was also a physician at St Thomas's Hospital in London. He was particularly interested in calorimetry (Fig. 1.2), and, in 1779, that is one year before the description of calorimetry of a guinea pig by Lavoisier and Laplace (see Chap. 2), he published a book entitled "*Experiments and observations on animal heat and the inflammation of combustible bodies*" (Crawford, 1779). He proposed that inhaled air contained more thermal energy than did exhaled air, which resulted in the oxygenated blood leaving the lungs containing more heat than blood pumped into the lungs.

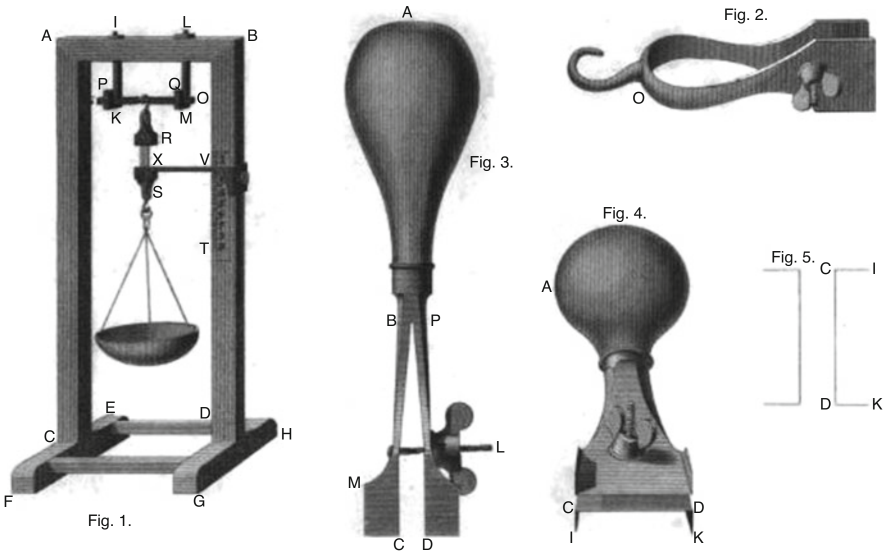

Fig. 1.2 Adair Crawford (1748–1795): equipment for research in thermal physiology. (Public domain, by Adair Crawford and Alexander Crawford, https://commons.wikimedia.org/w/index.php?curid=3513393)

He also indicated that a body's capacity for storing heat is reduced by its chemical combination with "phlogiston", and then elevated by its separation from "phlogiston" (Crawford, 1779). However, despite the title, in that original edition of the book, "*there is no mention whatever of any measurements of the heat produced by living things*" (Blaxter, 1978, p. 2). In 1788, he published a second edition of his book, in which he corrected many of his earlier observations, even though by this time, the phlogiston theory was being disputed. In the second edition, he did include measurements of animal heat production, but also many references to Lavoisier (Blaxter, 1978). Because of ill health he retired to Hampshire, where he died at the age of 46 on the 29 July 1795.

1.3.4 James Currie

The physician in question was James Currie (Fig. 1.1), who was born in Dumfriesshire in Scotland, on the English border, in 1756, and died in Sidmouth (England) in 1825. After leaving school, he went to Virginia (USA) with little success, and returned to Scotland in 1776 to study medicine at Edinburgh University, but he actually graduated from Glasgow University and then moved to Liverpool. It was there that he became interested in the use of cold water in the treatment of fever. He published a classical monograph that contains probably the first report of clinical observations being made in England, if not anywhere, using a thermometer (Currie, 1797). If ever a justification for research into body temperature was needed, then it is contained in the following extracts from that monograph.

> About eighteen years ago when I was at Edinburgh I discovered that the accounts given of the temperature of the human body under disease, even by the most approved authors, are, with few exceptions, founded, not on any exact measurements of heat, but on the sensation of the patient himself, or his attendants. (p. iii)

> Impressed with the belief, that till more accurate information should be obtained respecting the actual temperature in different circumstances of health, and disease, no permanent theory of vital motion could be established, nor any certain progress made in the treatment of those diseases in which the temperature is diminished or increased. (p. iv)

> I have elsewhere observed, that if a definition of life were required, it might be most clearly established on that capacity by which the animal preserves its proper heat under the various degrees of temperature of the medium in which it lives. The most perfect animals possess this power in a superior degree, and to the exercise of their vital functions this is necessary. The inferior animals have it in a lower degree, in a degree however suited to their function. In vegetables it seems to exist, but in a degree still lower, according to their more limited powers, and humbler destination. (p. 173)

> There is reason to believe, that while the actual temperature of the human body remains unchanged, its health is not permanently interrupted by the variation in the temperature of the medium that surrounds it; but that a few degrees of increase or diminution of the heat of the system, produces disease and death. A knowledge therefore of the laws which regulate the vital heat, seems to be the most important branch of physiology. (p. 174)

1.4 Nineteenth Century

1.4.1 Marshall Hall

Marshall Hall was born in Basford near Nottingham in 1790. He studied medicine at Edinburgh University, graduating in 1812. He is best remembered for his research into spinal reflexes, and he was also the first to show that the capillaries were intermediate between arteries and veins. In 1832, he published a comprehensive paper on hibernation, in which he described his experiments on the hedgehog, dormouse and bat. He paid particular attention to whether the animals were in any way asleep, and he casts doubts on the observation of Hunter (1792), who had not recorded whether his animals were in that state. He died in 1857 in Brighton, of a throat infection said to have been aggravated by lecturing.

1.4.2 William Hale White

W. Hale White was born on 7 November 1857 and died at the age of 91 on 26 February 1949. After about 1900, he appears to have hyphenated his name: Hale-White. He worked in the Physiological Laboratory of Guy's Hospital in London. He published a series of papers in the *Journal of Physiology* between 1890 and 1897 on temperature regulation, including the effects of brain lesions (White, 1890, 1891; White & Washbourn, 1891), on the effect of artificial respiration (Fawcett & White, 1897), and on heat regulation in hibernating animals (Pembrey & White, 1896).

1.4.3 Horace Middleton Vernon

Horace Vernon was born on 3 October 1870. After attending Dulwich College, he went to Oxford to study chemistry and physiology. After a stay in Naples, where he was involved in biological research, he graduated in medicine from St George's Hospital in London. He received an appointment in the Physiological Laboratories in Oxford. In 1898, he was elected a Fellow of Magdalene College, and became University Lecturer in Chemical Physiology. From 1894 to 1925, he published over thirty papers in the *Journal of Physiology*, though only three were directly related to thermoregulation, and all three were rather bizarre. The first, in 1894, was concerned with the carbon dioxide produced by frogs within an ambient temperature range of 0–30 °C (Vernon, 1894). The frogs were untreated, curarised or pithed. He continued this research in a second paper, using the frog, newt, toad, axolotl, blindworm, snail, cockroach and earthworm (Vernon, 1897). In 1899, his paper was on what he called the "death temperature" in a number of marine organisms, which he heated until they died. He himself died in Oxford on 11th February 1951. But he made an important contribution to measurement in thermal physiology. He developed the black-globe thermometer (using a float from a toilet cistern) that still is used universally to record the effect of radiant heat (see Vernon, 1932, 1934).

1.4.4 Thomas Clifford Allbutt

Though not a thermal physiologist, Sir Thomas Allbutt deserves his place in this chapter, as he will forever be remembered as the inventor of the clinical thermometer. Sir Thomas was born in Dewsbury in Yorkshire in 1836. He attended Caius College, Cambridge, graduating in 1859 with a first-class degree in Natural Sciences; he then attended St George's Hospital in London and took the Cambridge MB in 1861. From 1861 to 1889, he was a physician in Leeds, and it was during this time that he published his classical contribution, in which he gave a brief outline of the history of thermometry, and where he provided details of his clinical thermometer (Allbutt, 1870). This is the clinical thermometer that we know today, in which a constriction in the tube prevents the mercury running back into the bulb, and so making it possible to read the maximum temperature reached. Allbutt's thermometer was 150 mm long (longer than modern clinical thermometers) and reached the correct temperature in five minutes, compared with the much longer thermometers used in medicine up until that time, which took a considerable time to equilibrate. Allbutt was appointed to the Chair of Physic at Cambridge in 1892, where he remained until his death in 1925.

1.4.5 Marcus Seymour Pembrey

Marcus Pembrey (Fig. 1.1) was one of the foremost British physiologists from the late nineteenth century, and until well into the twentieth century. He was born in Oxford on 28th May 1868. When he was only seventeen years old, he entered Christ Church (Oxford), obtaining a first-class honours degree in physiology in 1889. Three years later, he graduated in medicine from University College Hospital in London. He first appointment was at Oxford University, under John Burdon-Sanderson, then Waynflete Professor of Physiology, but later to become Professor of Medicine, but Pembrey soon took up a lectureship in physiology at Charing Cross Hospital Medical School in 1895. In 1900, he moved to Guy's Hospital Medical School, succeeding Ernest Starling (Law of the Heart), whom he again succeeded as a Professor at London University 20 years later. A full account of his life was written by Douglas (1935). He died at his home near Oxford on 23 July 1934, just a year after he retired.

He published his first paper while he was at Oxford, in collaboration with respiratory physiologist John Scott Haldane, on measuring moisture and carbon dioxide (Haldane & Pembrey, 1890). Haldane subsequently developed an apparatus for measuring respiratory oxygen uptake and carbon dioxide production in animals. Pembrey adapted this apparatus for his own research into small animals. In 1893, he published a paper on the reaction times of mammal to changes in the temperature of their surroundings (Pembrey, 1893).

During the next thirty years, Pembrey was to publish a large number of papers that encapsulate his main interests in the phenomenon of cellular respiration, and the relationship of respiration to energy production and the regulation of body temperature (Pembrey, 1895). He also wrote the chapter on "Animal Heat" in Schafer's "Textbook of Physiology" (Schafer, 1898), which was one of the most comprehensive monographs on physiology up to that time.

In the last paper, which he published in the *Journal of Physiology*, in collaboration with hibernation specialist P.A. Gorer (Gorer & Pembrey, 1927), he recorded his observations on respiratory exchange in hibernating animals. Thirty years earlier, he had published another paper on hibernating animals with physician William Hale White (see Sect. 1.4.2; Pembrey & Hale White, 1896).

1.5 Twentieth Century

1.5.1 Sutherland Simpson

Sutherland Simpson was an Orcadian. He was born at Saraquoy on the small Scottish Orkney Island of Flotta on 3rd February 1863. After schooling in Flotta, and working on his father's farm and fishing boat, he went to Edinburgh in 1892 to train to become a sea captain (see Long, 2013). However, for reasons not fully understood, instead, he became a laboratory attendant to Professor William Rutherford ("Professor Challenger" of the Sherlock Holmes stories) in the Department of Physiology of Edinburgh University. Somehow, he found time to study at Heriot-Watt College, and after some ten years, he obtained a B.Sc. degree at Edinburgh University. Giving up his assistantship and financing himself, he entered medical school. He graduated in medicine (M.B., Ch.B.) in 1899, taking his M.D. degree in 1901 and his D.Sc. in 1903. When Edward Sharpey-Schafer, the discoverer of noradrenaline (norepinephrine), was appointed to succeed Rutherford, he appointed Simpson as one of his four Assistants (see Sharpey-Schafer, 1927).

Simpson's research interests, while in Edinburgh, were many and varied. His published papers include those on the conducting pathways of the pyramidal cortex, secretions from the pancreas, liver, and salivary glands, and on temperature regulation. His first paper on the subject concerned the body temperatures of monkeys (Simpson, 1902a), which was followed by three further papers concerning thermoregulation in this taxon, two in collaboration with departmental colleague J.J. Galbraith (Simpson, 1902b; Galbraith & Simpson, 1904b, 1905a, b). In 1908, he published two papers on the body temperature of fish and marine animals (Simpson, 1908). In collaboration with Galbraith, he published five papers in all between 1903 and 1905. Simpson was lost to British physiology when, on the recommendation of Sharpey-Schafer, he was appointed to the Chair of Physiology at Cornell University (USA), and in the autumn of 1908, he left Edinburgh for Ithaca, never to return. He died there on the 26th March 1926, aged only 63.

1.5.2 J. M. O'Connor

J.M. O'Connor was an Irish physiologist from the Physiological Department of University College (Dublin). He was born in Limerick in 1886, and graduated from the Royal University of Dublin in 1909, the year of dissolution of the University under that name. In 1910, having been awarded a travelling scholarship in physiology, he spent three years in Leipzig and Heidelberg (Germany), before returning to Dublin, to what was to become University College, where he was to spend the rest of his life. In 1915, he published a paper on the influence of body temperature in the secretion of sweat from the foot of the anaesthetised cat. He concluded that, in a cooled animal, sweating occurred only when the temperature was restored to normal, or subcutaneous temperature reached 43 °C. The former he concluded was a protective mechanism to reduce the storage of metabolic heat, the latter was a protective reflex. In 1916, he published a paper on the mechanism of chemical temperature regulation, and a similar paper in 1919. He was not to publish another paper on the subject for another 14 years, until 1932, when he published a paper concerned with the nature of the metabolic regulation of body temperature, and its relation to temperature sensations. From then until 1968, when he was in his eighties, he published more than 30 papers on the subject. The main thrust of his research on temperature regulation assumed that temperature regulation was initially based on a function of the individual cells. This theory was not widely accepted by many thermal physiologists, and his research has been neglected for the most part. In his latter years, he published almost exclusively in the *Proceedings of the Royal Irish Academy*. His last paper (O'Connor, 1968) concerned the influence of pyrogen and an antipyretic on oxygen consumption. The abstract of this paper makes for interesting reading:

> The constancy of the central temperature of the body has been shown to depend on the coincidence of a rise in oxygen consumption with falling temperature which prevents the temperature of the deeper tissues from falling and of increase in the rate of flow of blood with rising temperature to a level capable of abstracting more heat than is produced. It appears probable that febrile temperature might be the result of a change in the temperature at which this coincidence occurs and that the action of antipyretic drugs in restoring the normal relations might be related to this. The influence of Typhoid vaccine and of sodium salicylate on the oxygen consumption of human saliva is examined. These substances cause marked changes in the relation of oxygen consumption to temperature. The relation of these disturbances to the colloidal structure of the mitochondria on the one hand and to fever and inflammation on the other are discussed.

1.5.3 *John Bligh*

Dedicated to the memory of my masters at University College London L.E. Bayliss. G.L. Brown, C. Lovatt Evans (Bligh, 1973, p. vii).

Thus, does John Bligh (1922–2020; Fig. 1.3) begin his book "*Temperature regulation in mammals and other vertebrates*" (Bligh, 1973). What more auspicious a start could one have to one's scientific career than to sit at the feet of these three legends of British physiology. Indeed, Bligh's book has been the bible of so many of us, and even though it is now well over forty years old, I find I still consult it fairly regularly.

Without discounting his many research papers, his greatest contribution to thermal physiology has been his reviews on the subject. John has also contributed as an editor of several monographs and contributed chapters in monographs. In 1973, in collaboration with his Babraham colleague, K.G. Johnson, he published the first glossary of terms for thermal physiology. This was the first definitive publication to be accepted by the *International Union of Physiological Sciences* in the cause of getting thermal physiologists to use a standard terminology (Bligh & Johnson, 1973). In 1990, with Voigt, Bligh edited "*Thermoception and temperature*

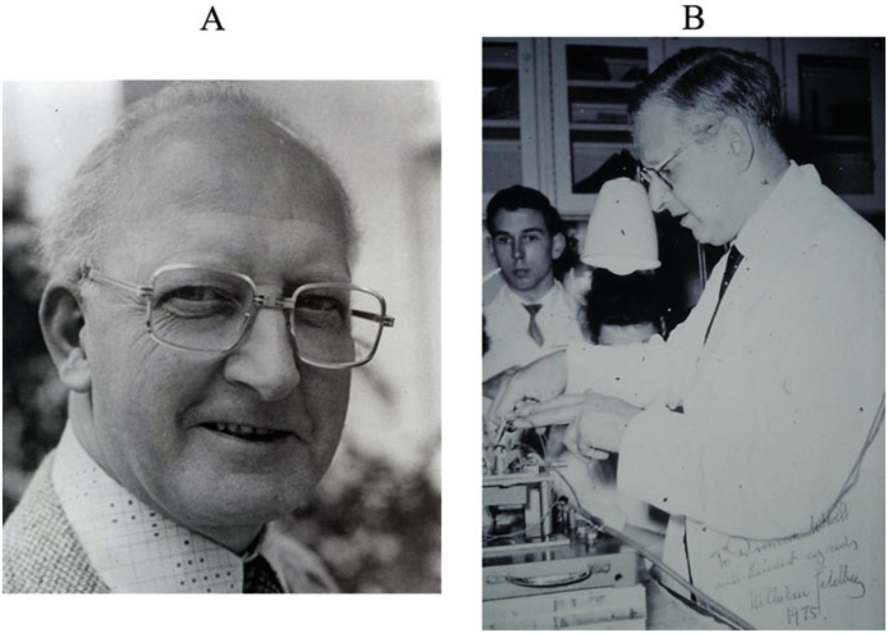

Fig. 1.3 Two 20th Century UK physiologists who contributed to the neurochemistry of thermoregulation. (**a**) John Bligh (1922–2020; photograph taken from Mekjavic [2020] and used with his permission). (**b**) Wilhelm Feldberg (1900–1993) at the bench in 1975 at the National Institute for Medical Research, Mill Hill (London; this photograph is the property of Duncan Mitchell, who retains the copyright, and is used here with his permission)

regulation", which contains chapters by many of the pre-eminent contributors to our knowledge of thermal physiology, many of whom will make appearances within the chapters of this monograph.

John Bligh's research career began in the Department of Physiology at University College London, and his first publications were on choline levels in the body (Bligh, 1952). However, in 1952, he moved to the Hannah Dairy Research Institute in Ayr (Scotland), and this was where his research with large animals, and his interest in temperature regulation, began, interests that were to continue for the rest of his career (see Chap. 8). In 1957, he published a paper (Bligh, 1957) on blood and body temperature in the calf.

John left Ayr for the Agricultural Research Council Institute of Animal Physiology at Babraham, near Cambridge, where he was to spend his time studying temperature regulation in sheep. In a paper in 1959, he showed that, when the sheep was warmed, panting commenced before any change in deep-body temperature was evident, an indication that there were peripheral thermal receptors involved (Bligh, 1959). In 1961, he reported that the apocrine sweat glands of sheep discharged synchronously, accompanied by an increase in skin temperature as the sweat combined with the wool in an exothermic reaction (Bligh, 1961). In 1966, he published his first paper on the effects of neurotransmitters injected into the cerebral ventricles, a subject that was to engage him for the rest of his research career (Bligh, 1966).

After nearly twenty years at Babraham, in collaboration with biochemist J.E. Cremer of the UK Medical Research Council, John published a comprehensive review on body temperature and the response to drugs (Cremer & Bligh, 1969). In one of the figures, he described a simple model of the efferent nervous pathways from what he called the hypothalamic "comparator", with crossed inhibitory connections. He postulated that when "body temperature" exceeds the "set-point temperature", heat loss is increased and heat production is inhibited. When "body temperature" is less than the "set-point temperature", heat production is increased and heat loss inhibited. It is no longer generally accepted that a thermal set-point actually exists, at least as it was originally conceived by Ted Hammel and Jim Hardy (see Chap. 5). Instead, there exist separate and independently adjustable thermoeffector thresholds (see Chap. 3). Indeed, as Romaine Hervey noted in a question to John regarding the "set-point", following one of his conference presentations:

> so, what you are saying is that it is neither a point, nor is it set (personal communication; Michael Tipton).

Using his neural model, he then postulated the site of action of neurotransmitters such as 5-HT, acetylcholine and noradrenaline. With this model in mind, with his protégé Michael Maskrey (who continued a successful career in thermal physiology in Australia; Maskrey & Bligh, 1972) and his Babraham colleague Wally Cottle, soon to emigrate to Canada (see Chap. 14), he investigated the effects of ambient temperature on these neurotransmitters, and how different ambient temperatures may explain differences in the thermoeffector actions of the monoamines (Bligh et al., 1971). John's interests in thermoregulatory neurochemistry extended to prostaglandin (PG) too, as did mine. When he and I infused PGE_1 into the cerebral ventricles of the Welsh Mountain Sheep at a high ambient temperature (40 and 45 °C), when the animal was already panting rapidly, PGE_1 infusion lowered the respiratory rate, and deep-body temperature rose (Bligh & Milton, 1972). In contrast, at a low ambient temperature (10 °C), when the respiratory rate was low and the animals were shivering, then the respiratory rate fell even lower, and violent shivering occurred, and body temperature rose. At 18 °C, when the animal was neither panting nor shivering, PGE_1 produced shivering, vasoconstriction of the cutaneous vessels of the pinna of the ear, and reduced the respiratory rate. At all three ambient temperatures, when the infusion was stopped, respiratory rate increased to the pre-infusion levels, shivering ceased and vasodilatation occurred, until the temperature had returned to pre-infusion levels. We concluded that PGE_1 was acting on the heat gain pathway, before the crossed inhibitory pathway, thus stimulating heat gain and inhibiting heat loss.

John continued his research into central transmission and temperature regulation in the sheep (Bacon & Bligh, 1976; Beal & Bligh, 1979) until he left Babraham in 1977 for Alaska, to take up appointment as Director of the Institute of Arctic Biology in Anchorage (USA; see Chap. 5). There he continued to publish as much as his administrative duties allowed, but his publications were mainly review articles. He remained as Director until 1985, when he returned to England. In England, he continued to live in a village near Babraham until his death in early 2020 (Mekjavic, 2020).

1.5.4 Ainsley Iggo

Ainsley Iggo was a New Zealander. He was born on 2nd August 1924 in Napier, on the east coast of the North Island. He spent his childhood education at local schools. He went to Otago University and Canterbury Agricultural College, and in 1948, graduated with a Master's degree in agricultural science. As he said in his autobiography, which provides a marvellous account of his life (Iggo, 2001, p. 287), he had acquired "*an interest in physiology, some congenial friends and the McMillan Brown Travelling Scholarship*". Before taking up his scholarship, he was to spend a year in the laboratory of Australian neurophysiologist J.C. Eccles, who shared the Nobel Prize with Hodgkin and Huxley. It was under the influence of Eccles that he began to investigate synaptic transmission in autonomic ganglion. When he finally took up his travelling scholarship, he joined the Rowett Research Institute in Aberdeen in Scotland, and he was to spend the remainder of his life in Scotland. After 2 years at the Rowett, he moved to the Physiology Department of Edinburgh University, under the headship of electrophysiologist Professor David Whitteridge. It was at Edinburgh University that he developed his techniques for recording from single nerve fibres (Iggo, 1958). In 1959, he showed that there were several categories of C-fibres, with sensitivities to mechanical, chemical and thermal stimuli.

In 1959, Iggo accepted an invitation to visit Herbert Hensel's laboratory, which had all of the equipment necessary for thermal neurophysiology (see Chap. 3). Again, as he says in his autobiography (Iggo, 2001, p. 291):

> I well remember isolating C cold receptors .... Rigorous testing of C afferent fibres revealed some units with a classical temperature curve .... The skin cold receptors had a peak sensitivity of about 25 °C, a temperature range of 15–36 °C, and dynamic responses only to cooling the skin. Within the next few days, we found "warm receptors". They had a maximum sensitivity at about 42 °C and a thermal range of 35–45 °C. They responded as temperature rose and were insensitive to mechanical stimuli. We had put specific cutaneous thermoreceptors with afferent C fibers on the map. (Hensel et al., 1960).

Subsequently (Iggo, 1963, 1969), he found that, although primate skin had mechanoreceptors similar to those in non-primate species, the cold receptors differed in that they had myelinated afferent fibres.

In 1962, Ainsley Iggo was appointed to the Chair of Veterinary Physiology at the Royal (Dick) School of Veterinary Studies at Edinburgh University, a position he would hold until his retirement in 1990. Throughout that 38-year period, he not only continued his own research, but also built up the department's research reputation. He died in Edinburgh on 25th March 2012.

1.5.5 Wilhelm Sigmund Feldberg

Wilhelm Feldberg will go down in history as one of the great neuropharmacologists and neurophysiologists of the twentieth Century. He was born in Hamburg, Germany, on 19th November 1900, into a wealthy Jewish family. He studied medicine in Berlin, graduating in 1925. In 1931, he came to Cambridge to work with physiologist John Newport Langley, who was the first to conceive of drug receptors. Feldberg returned to Germany, but was dismissed from his post in Berlin by the Nazi authorities. Sir Henry Dale, then Director of the MRC's National Institute for Medical Research in London, and with whom Feldberg had worked after Langley died, sent an intermediary to extract him from Germany, and to bring him to the Institute. Readers are directed to Green (1948) for details concerning the structure and functions of the MRC. Feldberg left Germany with a roll of original Toulouse-Lautrec posters under his arm; they later would be shown proudly to visitors to his home in Mill Hill, London, where so many visitors would be entertained. In England, Feldberg was intimately involved in the research that led to the proof that acetylcholine was the neurotransmitter involved in parasympathetic nerve transmission. After a fellowship at the Walter and Elisa Hall Institute, in Melbourne, Australia, he was appointed Reader in Physiology at Cambridge University. A full account of this research can be found in his own writings (Feldberg, 1977). A summary of his life was written by Milton (1994), and a full account of his life and works was written by Bisset and Bliss (1997). Both contributions provide essential insight into the man and his research.

In 1949, he was appointed at the National Institute for Medical Research, which was to move to Mill Hill in London 1950, and there he was to spend the rest of his working life (Fig. 1.3). He did not become involved in temperature regulation until many years later. In the early 1950s, he started his research on the inner surface of the brain, for which he devised a series of cannulae that could be implanted into the cerebral ventricular system of the cat. He himself later called the cannulae "Collison" cannulae, after the skilled technician who made them. The early experiments were on anaesthetised cats, but later experiments were on conscious cats. He published an account of this research in a book (Feldberg et al., 1963). A part of the research was on tremor, particularly that produced by the intracerebroventricular injection of tubocurarine. In a paper written with physiologist colleague Laurence Malcolm, later to move to the University of Aberdeen, Scotland (Feldberg & Malcolm, 1959), he reported that the tremor produced by tubocurarine could be abolished by adrenaline. He mentioned in this paper that he made no distinction between tremor and shivering. At no time in these early experiments did he record body temperature, yet his experimental approach was the trigger for so much work that was to come.

In 1963, he was joined by R.D. (Bob) Myers, then at Colgate University, Hamilton, USA, but later to be at Purdue University in Indiana (USA). Myers, in collaboration with J. Villablanca, from the University of Chile in Santiago, found that if they injected bacterial pyrogens into the cerebral ventricles, the animals developed a fever (Villablanca & Myers, 1963, 1965). Myers persuaded Feldberg that he should monitor body temperature whenever he performed intracerebroventricular injections. As Feldberg said many times later, though perhaps jokingly, being so persuaded was one of the greatest mistakes of his life. Their experiments together showed that intracerebroventricular injections of either adrenaline or noradrenaline produced a fall in the body temperature of the conscious cat, whereas 5-HT produced a rise in body temperature. They formed a theory that these amines, acting in the hypothalamus, were responsible for the regulation of body temperature (Feldberg & Myers, 1964, 1965). Several more papers were to follow on this subject, reporting investigations of the hypothalamic effects the amines in dogs and monkeys (Feldberg et al., 1966, 1967). However, discord arose in the theory when it was found that in some other species, the effects were different, with noradrenaline producing a rise in body temperature and 5-HT a fall. For example Cooper et al. (1965) found this reversed action to be so in the conscious rabbit, and Bligh (1966) observed the same result in the sheep. These discrepancies were discussed by Bligh et al. (1971), Bligh (1973) and Hellon (1974).

In 1970, Feldberg, Myers and Veale recorded the effects of perfusing the cerebroventricular system of cats with calcium-free artificial cerebrospinal fluid, and showed that an intense hyperthermia occurred, associated with violent shivering. They referred to this phenomenon as a "sodium" fever and considered that calcium was acting as a brake on that fever. They wondered whether these two ions were associated with the "set-point", and also maybe with pyrogen fever. Other workers elsewhere reported that calcium-chelating agents such as EDTA had effects similar to a calcium-free solution. Subsequently Dey et al. (1974) showed that antipyretic drugs did not block this rise in body temperature, nor were any rises in PGE_2 found