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INVITED REVIEW

A century of exercise physiology: concepts that ignited the study of human thermoregulation. Part 1: Foundational principles and theories of regulation

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Abstract

This contribution is the first of a four-part, historical series encompassing foundational principles, mechanistic hypotheses and supported facts concerning human thermoregulation during athletic and occupational pursuits, as understood 100 years ago and now. Herein, the emphasis is upon the physical and physiological principles underlying thermoregulation, the goal of which is thermal homeostasis (homeothermy). As one of many homeostatic processes affected by exercise, thermoregulation shares, and competes for, physiological resources. The impact of that sharing is revealed through the physiological measurements that we take (Part 2), in the physiological responses to the thermal stresses to which we are exposed (Part 3) and in the adaptations that increase our tolerance to those stresses (Part 4). Exercising muscles impose our most-powerful heat stress, and the physiological avenues for redistributing heat, and for balancing heat exchange with the environment, must adhere to the laws of physics. The first principles of internal and external heat exchange were established before 1900, yet their full significance is not always recognised. Those physiological processes are governed by a thermoregulatory centre, which employs feedback and feedforward control, and which functions as far more than a thermostat with a set-point, as once was thought. The hypothalamus, today established firmly as the neural seat of thermoregulation, does not regulate deep-body temperature alone, but an integrated temperature to which thermoreceptors from all over the body contribute, including the skin and probably the muscles. No work factor needs to be invoked to explain how body temperature is stabilised during exercise.

Keywords Body temperature · Exercise · Heat exchange · Homeostasis · Hypothalamus · Thermodynamics · Thermoeffector · Thermoreceptor · Thermoregulation

Abbreviations

C	Rate of convective heat flux
D	Diameter
E	Rate of evaporative heat flux
IL-1	Interleukin-1
IL-6	Interleukin-6
K	Rate of conductive heat flux
M	Metabolic rate
m	Body mass
R	Rate of radiant heat flux
S	Rate of heat storage in the body
TNF	Tumour necrosis factor
W	External work rate
v	Wind speed
$\dot{V}_{O_2}$	Oxygen consumption

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Introduction

Introducing this historical review series

This communication is Part 1 of four historical reviews in which we have endeavoured to weave historical insights into a contemporary perspective of human exercise physiology of relevance to those who work, exercise and compete (occupational and recreational athletes) within thermally stressful conditions. To be consistent with other reviews within this centenary series, our primary, but not our exclusive, emphasis is upon the century of exercise physiology (twentieth century), with a particular emphasis upon work published within the first three decades. During that epoch, the name of this journal was originally *Arbeitsphysiologie* (Work Physiology: 1928–1954), before being absorbed by the *Internationale Zeitschrift für angewandte Physiologie einschließlich Arbeitsphysiologie* (International Journal of Applied Physiology including Occupational Physiology: 1955–1973), which became the *European Journal of Applied Physiology and Occupational Physiology* (1973–1999) and ultimately the *European Journal of Applied Physiology* (1996).

Throughout this series, we will cover both ends of the thermal continuum, with the aim of showing how the key concepts, theories, experimental methods, discoveries (facts) and interpretations, which largely represented the prevailing dogma during the twentieth century, were continually re-evaluated, modified and either discarded or carried through into the twenty-first century. Indeed, embryonic developments of the discipline of exercise physiology arose during the first 30 years of the twentieth century (Lindinger and Ward 2022). Whilst serendipity has always played its role, forward progression along that journey could have occurred only as our understanding of scientific first principles grew (Part 1 of this series), along with our knowledge of how to apply those principles to the derivation of testable hypotheses.

Those principles also dictated the development of tools for quantifying thermal strain and understanding how the body controls the physiological avenues for the exchange of thermal energy (thermoeffector function; Part 2). Since endurance exercise and work often result in thermal stresses that force us beyond our comfort zones, then in Part 3 of this series, we will examine the acute physiological responses to heat and cold stress. Also within that review, we will examine the consequence of thermoregulatory failure and the validity of the many different indices of thermal stress. Our final topic for this series (Part 4) deals with the evolution of our predecessors, leading to the ascent of endurance specialists (*Homo sapiens*), and the historical development of our knowledge of human thermal adaptation to both natural and artificially induced thermal stresses.

One might wonder what can be added to the numerous historical contributions already written (e.g., Wunderlich 1871; Reid 1898; Krogh 1916; Lusk 1922; DuBois 1939; Lee 1948; Burton 1953; Bligh 1966; Wyndham 1973; Horvath 1981a; Åstrand 1991; Buskirk 2003; Schneider and Moseley 2014 [Table 19.1: Milestones of discovery]; Blatteis et al. 2022). Our emphasis is upon exercise-dependent challenges to thermal homeostasis. We have tried to complement, rather than to replicate, previous work, and there are several aspects of this review series that might be considered unique. Firstly, our presentation style has resulted from a merging of the disciplines of science and history so that readers might gain an appreciation of the vastly different social and political environments within which our predecessors lived and worked. To better appreciate their achievements, we must try to imagine their academic environments and their lives. That aspect is more heavily emphasised within Parts 2–4 of this series. Secondly, since we represent three generations, and since we have worked across a wide range of species, then we brought unique, and sometimes quite different, perspectives and priorities to this task. Those differences have provided educational opportunities for ourselves, from which we have emerged unscathed, that enabled us to extend these reviews well beyond that which we might individually have achieved. Thirdly, we have collectively lived, studied and worked in nine countries across five continents. We believe those experiences have helped us to avoid parochialism, while appreciating the contributions of those who have not always been afforded equal scientific status. Fourthly, we knew, and still know, many of the protagonists who worked during our century of exercise physiology. Finally, as co-editors of *Thermal Physiology: A Worldwide History* (Blatteis et al. 2022), we have been able to go beyond our own experiences by following the trails of discovery illuminated by contributing authors from 14 countries.

Our aim is to present the relevant concepts of thermal physiology in such a way that readers with applied research interests will appreciate the importance that a sound understanding of mechanistic physiology and first principles bring to those disciplines. Across this series, we highlight activities that are most likely to give rise to potentially hazardous thermal challenges; longer-duration endurance activities. It is through those pursuits that protracted periods of heat exchange might threaten homeostasis across several regulated variables, and our century of exercise physiology has provided many opportunities to examine the applications of thermal physiology to occupational and recreational athletes. It began immediately after the first Modern Olympic Games (1896, Greece), which included the men's

marathon (women waited until 1984 for their marathon). It included the inaugural *Tour de France* (1903), the most difficult endurance cycling race, as well as Roald Amundsen's (Norway) epic journey to the South Pole (1911), the First World War (1914–1918), the ordeal of Ernest Shackleton and his crew (England), trapped for 2 years in the Antarctic (1915–1917) and the first successful swim across the English Channel by a woman (Gertrude Ederle, 1926, U.S.A.). It concluded with the first *Fédération Internationale de Football Association* World Cup (1930, Uruguay). However, it is not the recreational activities, sport or physically demanding occupations themselves, nor is it the behavioural strategies used therein (e.g., clothing), that are our primary emphasis. Instead, they provide opportunities to explore mechanistic physiology beyond our comfort zones, with those challenges also providing occasions for physiologists to learn about those applications, and the strain that they can exert upon our regulatory systems.

Each paper in this series is structured around three epochs. The keystone (middle) epoch (1900–1930) is most heavily emphasised, and because that period included two Nobel Prizes in Physiology of direct relevance to exercising humans, it has been named the Krogh-Hill epoch. The first prize (1920) was to August Krogh (1874–1949, Denmark; Fig. 1) for his research that showed that oxygen delivery to exercising skeletal muscles was both regulated and effort dependent. The second prize (1922) was awarded to Archibald V. Hill (1886–1977, England; Fig. 1), who discovered that skeletal muscles were significant heat sources during physical exertion. However, thermal physiology can be traced back at least a century and a half earlier, although our understanding of exercise-dependent physiological changes within that first epoch (before 1900) was somewhat rudimentary. Nevertheless, an understanding of the pivotal concepts from that time is essential to contextualise research from both the twentieth and twenty-first centuries, since cornerstone hypotheses and research methods often arose from those foundational experiments. The concepts and hypotheses of those epochs changed as knowledge was acquired, and as thermal physiology moved into the modern epoch (beyond 1930). We have restricted our discussions of that epoch to the critical experiments that led to a re-thinking of ideas and theories from epochs one and two. Others have reviewed the contemporary research more comprehensively.

Since our overall approach is based upon first-principles science, we start this review series by demonstrating how those principles are not just applicable to, but how they provide the very foundation upon which the thermal physiology of exercise is overlaid. When seeking primary-source manuscripts, we have gone deep into the archives from five continents, so the references and recommended readings, both within each review and across the series, include a vast collection of classical resources left by our forebears, including exercise physiologists, ergonomists, engineers, chemists and physicians. Across this series, we have included over 3800 primary sources, with those manuscripts providing a base library around which younger scientists might develop their own collections. As lifelong students, the authors hope to encourage other students to see further by discovering shoulders upon which they might choose to stand. For those wishing to learn more about the scientists and their lives, biographical memoirs have been included.

Scientists are transitory custodians of facts and inquisitors of theories. Our responsibilities are to share knowledge and to test theories without bias, whilst resisting both the temptation to claim ownership over knowledge and the desire to reject the ideas of those with different interpretations of the experimental evidence; science is neither a

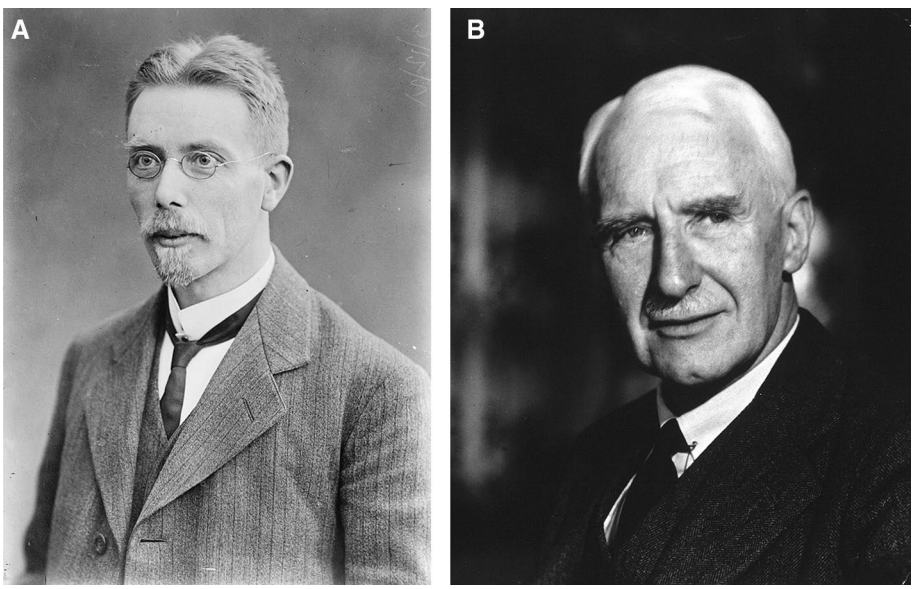


Fig. 1 **A** August Krogh. From the George Grantham Bain (Bain News Service) collection at the United States Library of Congress (Prints and Photographs division; under the digital ID ggbain.32006) and used under Wikimedia Commons agreement (public domain). Source: https://commons.wikimedia.org/w/index.php?curid=6054454 Accessed: July 12th, 2022. **B**: Archibald Hill. From the Welcome Collection, and is in the Public Domain. Source: https://wellcomecollection.org/works/debmyk6s Accessed: March 13th, 2023

democratic process nor is it a combat sport. Accordingly, we have emphasised those inclusive philosophical views throughout this review series, and with that in mind, we open with quotes from three physiologists and a politician. Claude Bernard (France; epoch one) advised students that: "*When we meet a fact which contradicts a prevailing theory, we must accept the fact and abandon the theory, even when the theory is supported by great names and generally accepted*" (Bernard 1949 [P. 164]). Almost a century after Bernard's death, Douglas Wilkie (England), a staunch protagonist for the application of first principles to experimental design and interpretation, wrote that: "*Facts and theories are natural enemies. A theory may succeed for a time in domesticating some facts, but sooner or later inevitably the facts revert to their predatory ways*" (Wilkie 1954 [P. 288]). When speaking at a university graduation about both science and politics, John F. Kennedy (U.S.A.) said: "*The great enemy of truth is very often not the lie—deliberate, contrived and dishonest—but the myth—persistent, persuasive, and unrealistic. Too often we hold fast to the clichés of our forebears. We subject all facts to a prefabricated set of interpretations. We enjoy the comfort of opinion without the discomfort of thought*" (Kennedy 1962). It is fitting to follow with the words of one of our Nobel laureates, who wrote that, as scientists, "*we have all been right sometimes and we have all been wrong often*" (Hill 1965 [P. 167]).

Our target audience for this series includes exercise physiologists wishing to appreciate the origins of human thermal physiology, as applied to exercise, and thermal physiologists wishing to appreciate the origins of the thermal consequences of human exercise. In closing this series introduction, we draw attention to the truism that a lack of awareness of primary-source research demonstrates poor scholarship, and increases the risk of thinking that one's own ideas are original. To assist students wishing to avoid such traps, we have identified classical contributions from scientists who lived and worked in more than twenty-five countries, across all seven continents. However, it can sometimes be useful for researchers new to any field to delay reading the historical literature, so that, when first tackling a research question, they can avoid being blinkered by the methods, ideas and possible bias of their predecessors. Unfettered imaginations can sometimes discover, and then open, once-hidden doors. For instance, the wind-chill index (Siple and Passel 1945), which some still use to assess the risk of outdoor exercise in the cold, arose from the unfettered imaginations of researchers trapped in Antarctica without a library or a computer.

Introduction to part one

We have structured this review series to gradually work through the historical steps that led to our contemporary understanding of how humans work and play within, and then adapt to, a vast array of thermally challenging environments. There is little doubt that the acute and chronic physiological responses will be of greatest interest to most readers, but the precision and validity of those data are determined by the experimental methods used, and whether or not those methods adhered to first principles. We accept that many eyes may glaze over at the mention of first principles, but before that happens, we have raised some interpretative questions that relate to exercising humans.

Examine Fig. 2. The upper panel shows electronically controlled variations in work rate (sinusoidal cycling; 25 °C dry bulb). The lower panel contains the average tissue-temperatures ($N = 8$) of five body regions (labelled A–E). Temperature sensors were positioned within the auditory canal, oesophagus, lower abdomen and the exercising muscles, as well as eight sensors distributed across the body surface, from which a mean skin temperature was derived. Four of those temperatures varied sinusoidally, but the fifth did not. How do you think thermal energy was transferred from the heat source to that unresponsive site? The temperatures of two sites tracked the sinusoidal forcing function, albeit with a slight phase delay. How do you think thermal energy was transferred to those sites? Can you assign body-region names

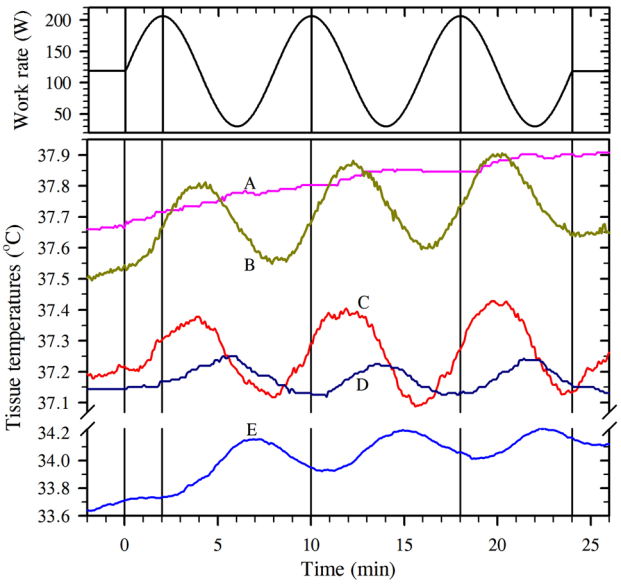


Fig. 2 Simultaneously measured body-tissue temperatures recorded during a non-steady-state experimental treatment. Immediately following a period of steady-state, semi-recumbent cycling at 35% of peak aerobic power (35 min; 25 °C dry bulb), participants were exposed to three consecutive, 8-min blocks of sinusoidally varying work rate (upper panel), with the work rate changing at 1-s intervals. Vertical lines define the start and end points of that sinusoidal treatment (0–24 min), as well as the peak work rates for each wave form (2, 10 and 18 min). The lower panel shows the mean response curves for tissue temperatures obtained for five different body regions, labelled **A**–**E** ($N = 8$, sampled at 5-s intervals); see the text for details. Data were extracted from Todd et al. (2014) and redrawn

to each of those five temperature responses? Can you rank those sites according to their capacity to track variations in heat production? Which of those temperatures might best reflect thermal information that might be transferred to a thermoregulatory centre?

One of those temperature measurements is the index of deep-body temperature most widely used since its first use in the eighteenth century (site A [rectum] Hales 1727; Davy 1814; Allbutt 1867; Wunderlich 1871; Liebermeister 1875), and it is heavily relied upon for athletic and occupational applications. Its popularity has been based upon two assumptions, neither of which has withstood the test of time: it was believed to be the hottest body tissue (Bernard 1876; Pembrey and Nicol 1898; Haldane 1905) and its temperature was thought to be equivalent to the temperature of arterial blood (Bazett 1927; Christensen 1931).

For any temperature measurement to faithfully represent the thermal energy content of another site, that measurement must obey the first-principles physics that govern heat exchanges between those tissues. Measurements that do not satisfy those requirements may provide valid local temperatures, but will be devoid of physiologically useful information. Therefore, before we use any physiological measurement, or accept any published data, we are obliged to understand those principles and the extent to which every measurement conforms to first principles. For any temperature measurement to provide information of relevance to body-temperature regulation, and thereby reflect changes in thermoafferent information, the temperature sensor must have equilibrated with, and responded to rapid changes within, thermally sensitive body tissues. Since endurance athletes and workers regulate, but also routinely challenge the regulation of, their internal environments, then a knowledge of physiological regulation is an essential first principle of exercise physiology.

Homeostasis: the foundation of systems physiology

Only some of the paths along which the investigation and teaching of physiological mechanisms can proceed are based upon first-principles science (Haldane 1916, 1935; Adolph 1954). Whilst the number and names of those physiological principles (concepts) may change over time (e.g., Michael 2007; Michael et al. 2009, 2017; Michael and McFarland 2011), several have appeared consistently as foundational material. One usually finds "homeostasis" (self-regulation of the internal environment [*milieu*]) towards the top of those lists, for it might be argued that it is less important to know how the heart beats than it is to know why its contraction frequency changes during exercise-dependent increments in body temperature. The regulation of human body temperature (homeothermy) is one of those homeostatic processes, and it is an ideal example of integrated physiology, since it has co-opted organs and tissues from other regulatory mechanisms for use in the defence of body temperature. The groundwork that led to our recognition and understanding of homeostasis in general, and of homeothermy in particular, occurred during our first two epochs (Bernard 1879; Cannon 1929).

Revealing homeostasis

For centuries, signs of internal stability were recognised, even within apparently unstable, exercising and unhealthy animals. However, within our first epoch (< 1900), not just physiological interpretations, but actual observations, were heavily influenced, and often held back, by Galenic teachings in the West (Edholm and Weiner 1981), and by ancient Chinese philosophy in the East (Wong and Wu 1932). Both systems appear to have been based upon the impact of opposing forces (*yin* [negative] and *yang* [positive]; Hippocrates 1923; Wong and Wu 1932; Adolph 1961), which may have independently resulted in observations being obliged to conform to those prefabricated interpretations. Then, slowly but surely, the unfettered observations of more enlightened physicians prevented the teachings of our forebears from controlling science, with once-hidden truths being revealed. In the sixteenth century, Jean Fernel (1497–1558, France) introduced the word "physiology" to distinguish between the bodily functions of healthy individuals (Fernel 1547), and the abnormal functions of the infirm, for which he coined the term "pathology" (Sherrington 1946; Fye 1997). Thus emerged our discipline of physiology, from which has arisen various sub-disciplines, based on body systems (e.g., cardiovascular, pulmonary and renal physiology), as well as areas of special interest that crossed several sub-disciplines (e.g., thermal, work and exercise physiology).

During the course of the seventeenth and eighteenth centuries, many pieces of the physiological puzzle were collected, but it is another Frenchman, Claude Bernard (1813–1878), who is universally credited with first gathering those pieces into a unified, physiological theory. Readers seeking detailed examinations of the developments leading up to Bernard, and their implications, are directed to our supplementary resources (e.g., Barcroft 1932, 1934; Adolph 1961; Bligh 1998; Gross 1998; Normandin 2007; Noble 2008; Gomes and Engelhardt 2014; Candas and Libert 2022; also see: Bernard, 1865 [translated 1949], 1876, 1878 [translated 1974], 1879). The amalgamation of ideas arising from his own research, and the experiments of others, led Bernard to believe that the stability of the internal environment was a condition of life ("*la fixité du milieu intérieur est la condition d'une vie libre et indépendante*"; Bernard 1878 [P. 113]). However, he was not the first physiologist to have

addressed the issue, or, indeed, to have arrived at that interpretation of the evidence (e.g., Séguin and Lavoisier 1792 [France]; Bichat 1822 [France]; Davy 1845 [England]; Wunderlich 1871 [Germany]; Pflüger 1877 [Germany]; Fredericq 1885 [Belgium]). Nonetheless, it was he who assembled the evidence most coherently, albeit still in an embryonic state, and ensured that the theory of internal stability became one of the tenets of physiology (Krogh 1934; Adolph 1961; Cannon 1929; Candas and Libert 2022).

Of course, even when we are not challenged physiologically, there is little within our bodies that remains truly stable. Instead, stability is an illusion created by a dynamic equilibrium (Wunderlich 1871; Haldane 1922; Barcroft 1932, 1934; Prosser 1964; also see: Mrosovsky 1990 [*rheostasis*]), with the appearance of stability being attained only if internal processes can counteract stimuli, of either internal and external origin, that tend to induce instability (Bligh 1998). It is as much a temporal phenomenon as it is a physiological state. During exercise, greater instability is observed, yet new equilibria (steady-states) can still be obtained, albeit with the activity of one or more physiological (dependent) variables being increased (a displaced equilibrium). In those states, there are reduced margins for error and increased physiological strain. Indeed, one can imagine that each new equilibrium might resemble an apparently stationary duck, swimming upstream; on the surface, it appears composed and stable, yet under the water, there is considerable activity going on to prevent it from being washed downstream.

For Bernard (1879), the *milieu intérieur* for which he claimed stability was the extracellular fluid compartment (or fluid matrix [Cannon 1929]): the interstitial fluid, blood and lymph. He viewed the composition and volume of that compartment as being sustained by regulatory processes that resisted the consequences of changes that occurred within the *milieu extérieur*. With regard to body temperature, Bernard suggested that warm-blooded animals (a now-obsolete term; Brack et al. 2022) maintained a relatively stable internal heat content ("*les animaux à sang chaud maintiennent la fixité relative de leur chaleur intérieure*"; Bernard 1876 [P. 107]), and it is the chemical activity of the body tissues that higher organisms (birds and mammals) use as a source of heat, which is then retained so that a more or less stable deep-body (core) temperature is attained (38°–40 °C; "*C'est dans l'activité chimique des tissus que l'organisme supérieur trouve la source de la chaleur qu'il conserve dans son milieu intérieur à un degré à peu près fixe, 38 à 40 degrés pour les mammifères*"; Bernard 1878 [P. 117]). As subsequently noted by Haldane (1922 [P. 838]), "*physiological activity is constantly disturbing the internal environment*", and during exercise, metabolic heat production can give rise to potentially lethal elevations in deep-body temperature.

As we entered the Krogh-Hill epoch, several physiologists were taking a special interest in the stability of the internal environment. In England, there was John S. Haldane (1860–1936), whose research embraced both basic and applied physiology (West 2008). He was primarily a pulmonary physiologist, and he recognised that various physiological processes operated to sustain the stability of critical blood-gas partial pressures (Haldane and Priestley 1905; Haldane 1922; Douglas 1936). Haldane also extended his research interests to body-temperature regulation during exercise (Hancock et al. 1929).

Across the Atlantic, Walter B. Cannon (1871–1945, U.S.A.) was similarly investigating physiological equilibria within the *milieu intérieur*. Indeed, it is generally to him that the introduction, and later definition, of the word "homeostasis" is attributed (Cannon 1926), although Robert Tigerstedt (1853–1923, Finland; Tigerstedt 1897) had used an almost identical term ("*homoiothermous*" [Tigerstedt 1906, P. 398]), some 30 years earlier. Cannon used the term to encompass not just thermoregulation, but other physiological mechanisms engaged in regulating the internal environment (Cannon 1926; Dale 1947; Barger 1987). He also used the term to refer to both the state of stability, as well as the processes used to achieve that stability (Brobeck 1965).

Physiological regulation and control

One of the arts of written communication resides within the clarity and consistency of the text, such that both the authors and their readers have the same understanding of the content. Accordingly, we feel obliged to commence this sub-section with a semantic clarification. Whilst the words "regulation" and "control" are frequently used interchangeably, they are not synonymous in physiology. The former refers to the complex array of processes that enable some physiological variables to be kept relatively stable across a range of internal and external stresses (e.g., blood pressure, blood gas and temperature regulation). On the other hand, control implies the active management of specific tissues and organs (effectors; e.g., the heart, cutaneous blood vessels, sweat glands) so that the stability of our regulated variables can be achieved (Brobeck 1965). Distinguishing between those terms has an extensive historical precedent (Séguin and Lavoisier 1792; Bernard 1878; Pembrey 1898; Cannon 1929; Adolph 1961; Brobeck 1965; Cabanac 1997; Bligh 1998), although the distinction is as frequently ignored as it is followed, inadvertently creating confusion.

Resting and exercising humans will try, both behaviourally and autonomically, to limit unnecessary changes to body temperature; we are homeothermic. The components involved within that homeostatic process constitute a thermoregulatory network (Fig. 3). To achieve homeothermy autonomically, humans activate anatomical structures that act to conserve heat (cutaneous vasculature; Bernard 1876; Grant and Bland 1931; Freeman 1935; Clark 1938), to

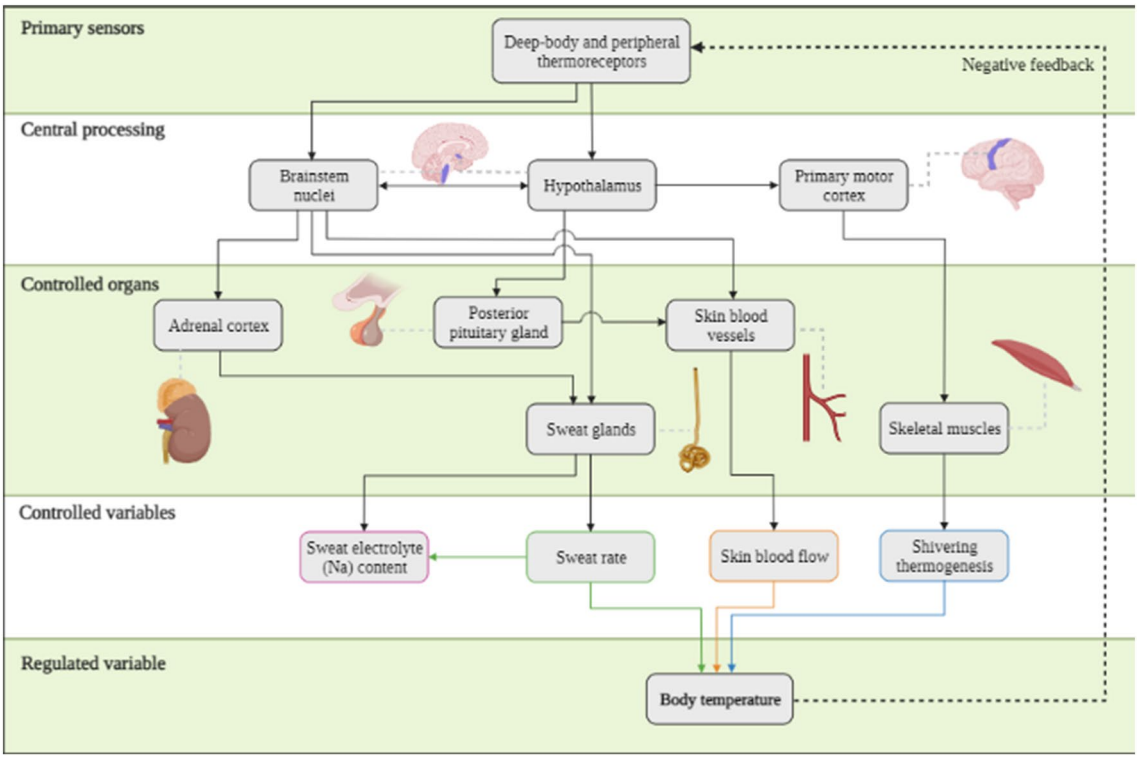


Fig. 3 An overview of human temperature regulation (thermal homeostasis). Modified from the schematics of Werner et al. (2008) and Taylor (2014), and produced using BioRender software (BioRender.com). Sensory feedback ascends to the central integrator and processor which, in turn, modifies the function of the autonomically controlled variables (thermoeffectors)

generate heat (skeletal muscles [Pembrey 1893; O'Connor 1916] and brown adipose tissue [Nedergaard et al. 2007]) or to dissipate heat (cutaneous vasculature [Maddock and Coller 1933; Pickering and Hess 1933; Grant and Pearson 1938; Ferris et al. 1947] and eccrine sweat glands [Ladell 1945; Weiner 1945]). Those structures are our thermoeffectors, and their activities are controlled (modulated) whenever we attempt to regulate body temperatures. Indeed, we can separate the controlled from the regulated variables within any homeostatic process by examining the neural pathways within each regulatory network.

Regulated and controlled variables within homeostatic systems

There are three ways to distinguish a regulated from a controlled variable. Firstly, only the controlled (non-regulated) anatomical structures (tissues, collections of tissues or organs) receive autonomic (efferent) stimulation. During the heat exposure (stress) of resting humans, the initial autonomic response is to withdraw the normal constrictor tone acting on the cutaneous arterioles, which results in a pressure-induced (passive) vasodilatation and increased cutaneous blood flow (Roddie and Shepherd 1956; Blair et al. 1960), thereby increasing heat transfer to the body surface. If the resulting heat loss is not effective enough, autonomically mediated (active) vasodilatation will occur (Lewis and Pickering 1931; Greenfield 1963; Johnson et al. 1995), and cutaneous blood flow is further elevated. If that is not sufficiently effective, then eccrine sweat glands will be activated (Kuno 1934; Ladell 1945). Therefore, the cutaneous vasculature and the sweat glands are autonomically controlled structures, as are the skeletal muscles when they are recruited to elevate heat production (shivering) during cold stress. They are the thermoeffectors.

Thermoeffectors are recruited both gradually and sequentially (Taylor and Gordon 2019) during resting states, according to the size and speed of the change in body temperature (Hensel 1973; Simon et al. 1986, 1998; Boulant 1996; Pierau 1996; Werner et al. 2008; Werner 2010). During exercise, recruitment can appear to be simultaneous, and sweating is activated before the point of maximal cutaneous vasodilatation is attained. In the laboratory, those temperature-dependent effector responses can easily be measured.

What is more difficult to measure is the impact those thermoeffectors have upon the regulated variable of interest (body temperature), not just because changes in that variable often result from the actions of several effectors, but because there is a multitude of thermoreceptors distributed throughout the deep and superficial tissues (Zotterman 1953;

Hellon 1983; Boulant 1996; Pierau 1996). They include both warm- and cold-sensitive receptors, and their distribution is most uneven (Hardy and Oppel 1938), with higher densities within the central nervous system, but also in sites that might require greater thermal protection, or that are used to explore thermal environments. Therefore, for researchers to quantify the effectiveness of sweating (evaporative heat loss) and its impact upon temperature regulation, we must decide which body temperatures to measure, and where to place our temperature sensors. Unfortunately, the methods used to make such measurements are often ill-suited to mechanistic research (Fig. 2).

A further complication is that the regulated variables are whole-body phenomena, as most are attributes of, or reflect changes in, the extracellular fluid. Consequently, the overall temperature of the body, and particularly that of the thermosensitive tissues, is hard to visualise, it is almost conceptual in nature, and it is certainly very hard to measure. Nevertheless, our second distinction between controlled and regulated variables relates to how thermosensitive structures provide neural feedback to the central nervous system concerning the impact of effector activity. That is, for every homeostatic process, its regulatory centre must receive information concerning the status of its regulated variable(s), such as body temperature, blood pressure or blood gas partial pressures. Indeed, it is only the regulated variables that provide neural feedback.

However, feedback is also provided concerning some aspects of the body that do not seem to form part of a regulatory system per se. For example, proprioceptors (muscle spindles and Golgi tendon organs [mechanoreceptors]) provide feedback concerning the movement and position of limbs, while the vestibular labyrinth of each inner ear provides feedback related to head position, movement, orientation with respect to gravity and balance. Clearly, in some circumstances (e.g., free-solo rock climbing), those sensory functions are absolutely vital to the survival of the individual, so it might be said that such feedback participates in regulating the overall status of the body.

Returning to thermoregulation, neural feedback allows the central nervous system to evaluate whether or not thermoeffector activity has halted an elevation (or reduction) in body temperature. Controlled structures lack receptors that respond to changes in their own activity. For example, we possess no physiological mechanism for measuring sweat rate. Thus, thermoeffectors do not provide feedback. On the other hand, thermoreceptors provide a continual flow of sensory information, and it is they that signal the need for thermoeffector activation, as well as providing feedback on the effectiveness of those actions.

Because our thermoreceptors are widely distributed throughout the body, the regulated temperature itself seems to be derived from equally widely distributed thermoafferent signals, many of which converge as they flow upstream (Simon 1974; Simon et al. 1998). The ultimate regulated temperature is not a single deep-body temperature like brain, oesophageal or rectal temperature, or even arterial-blood temperature, but a virtual temperature that represents some combination of all of the deep-body and peripheral signals. We cannot assign the duty of that thermoregulatory feedback to any one tissue bed or organ, and the relative importance of the various tissue temperatures has remained largely unknown. Moreover, the nature of that signal can change, as can the apparent importance of different regions, depending upon which region is experiencing a temperature change, how large that change is and how rapidly it occurs. For example, a marathon runner, having just won a race, may have a deep-body temperature > 40 °C (i.e., low temperatures and winning performances are mutually exclusive phenomena), and will be sweating profusely. Nevertheless, if that athlete immediately has a cold shower, there will occur a sudden and dramatic (albeit transient) bout of shivering, even though that individual will still have a high deep-body temperature. The gradual rise in deep-body temperature drove sudomotor activity, while it was the sudden skin cooling that drove the paradoxical shivering response.

The third distinction relates to neural signals that only the controlled organs and tissues receive. Like other controlled structures, the thermoeffectors are driven by regulation-dependent autonomic traffic, by non-thermal efferents that accompany, and travel in parallel with, motor commands travelling to the skeletal muscles, and by non-thermal feedback that is thought to have arisen from baroreceptors, mechanoreceptors and metaboreceptors (Krogh and Lindhard 1913; Eldridge et al. 1981; Vissing and Hjortsø 1996; Kenny and Journeay 2010; Kondo et al. 2010). For example, when a pre-heated, sweating person either commences or modifies the intensity of exercise, that individual will experience an immediate, intensity-dependent and direction-specific change in sweat rate (van Beaumont and Bullard 1963; Robinson et al. 1965; Jessen et al. 1983; Kondo et al. 2002; Todd et al. 2014).

Thus far, we have identified two (generalised) neural pathways, one that is thermosensitive and one that is not. Human thermoregulation is a multi-level mechanism with bi-directional communication ("Key concepts in exercise thermoregulation: the central regulator is more than a thermostat"). There are sensory (afferent) pathways that convey (upstream) feedback from thermoreceptors, which respond to local changes in temperature and are embedded within different body tissues. We also have feedback arising from body movements, and changes in blood pressure and metabolite concentration. That information is independently converted (transduced) into afferent impulses that travel to the central nervous system (our missing link), which then integrates and interprets those signals, before determining whether or

not effector responses of a corrective nature are required. That central regulator then issues the appropriate efferent (downstream) signals to the controlled structures. All homeostatic regulatory systems contain these components. Consequently, understanding multi-level, control mechanisms forms another first-principles emphasis of physiology. Which other regulated variables are disturbed during work and exercise?

The regulated variables

Claude Bernard (1879) postulated that, in addition to its volume, various properties of the extracellular solvent (water) are regulated at stable and appropriate levels: its solutes (oxygen, carbohydrate, lipid and electrolyte content) and its temperature. Cannon (1929) extended and grouped those variables into classes: the physiological requirements of cells (water, oxygen, nutrients, electrolytes, calcium and endocrine secretions) and environment factors that may influence cellular activity (hydrogen-ion concentration, osmotic pressure and temperature).

Whilst it is important to identify those historical sources, let us jump forward to our contemporary understanding, as depicted in Table 1. That simplification includes eleven regulated variables that may be modified during exercise and thermal stress, the receptors that convert correlates of those regulated variables into neural feedback, and the controlled variables that are managed by centralised controllers. However, knowledge concerning how the different receptors worked has been illusive. For instance, baroreceptors, so named due to their role in blood-pressure regulation, do not measure pressure at all. They are stretch receptors contained within the walls of some large blood vessels and the heart, and they respond to transmural, pressure-related changes in vascular circumference (Angell James 1971). At the other end of that regulatory mechanism are the intravascular smooth muscles that cause vasodilatation and vasoconstriction. In 1840, Benedict Stilling (1810–1879, Germany) named the autonomic neurons responsible for controlling smooth-muscle tension as vasomotor nerves (Stilling 1840), with McDowall (1924) supporting the hypothesis that the feedback signals were coming from the cardiovascular system itself, and were relayed through the vagus nerve.

For thermoreceptors, unravelling the transduction of thermal energy into neural feedback took more than a century, and commenced with the experiments of two Swedish neurophysiologists: Magnus G. Blix (1849–1904; Blix 1882, 1883; Norrsell 2000) and Yngve Zotterman (1898–1982; Zotterman 1953, 1959; Hensel 1974; Pierau 1996). In 2021, the Nobel Prize in Physiology was awarded to David Julius and Ardem Patapoutian (U.S.A.) for their research, which showed that transient receptor potential channels provided a means through which changes in local thermal energy (heat) content could modify ion flux. They had demonstrated a molecular mechanism for detecting changes in tissue temperature.

Where does Table 1 lead us? Each of those regulated variables is a characteristic of the extracellular fluid. That fluid constitutes 20–30% of the adult body mass, and it comes into contact, and therefore communicates with, almost all cells. Thus, those characteristics determine the status of those cells, and, by default, the body itself. Moreover, some of those regulatory processes occur interdependently, as they are integrated processes that often share effector organs and tissues. Therefore, physiological research that is aimed at examining mechanistic relationships requires the manipulation of one or more of those variables whilst quantifying changes in the controlled (effector) variables, regardless of whether the original research question(s) arose from basic or applied interests. Indeed, it can be argued that students of physiology need to understand each of those regulatory mechanisms as parts of the core (first principles) content of

Table 1 Homeostatically regulated variables of relevance to those who work and play in thermally stressful environments

Regulated variables	Sensors	Controlled variables
Blood volume	Baroreceptors	Water loss, sodium loss, skin blood flow
Mean arterial pressure	High-pressure baroreceptors	Heart rate, stroke volume, water loss, sodium loss, skin blood flow
Central venous pressure	Low-pressure baroreceptors	Heart rate, stroke volume, water loss, sodium loss, skin blood flow
Arterial carbon dioxide partial pressure	Chemoreceptors	Ventilatory frequency, tidal volume
Arterial oxygen partial pressure	Chemoreceptors	Ventilatory frequency, tidal volume
Plasma glucose concentration	Chemoreceptors	Secretion of insulin, glucagon, cortisol and adrenaline
Plasma potassium concentration	Chemoreceptors	Potassium secretion and reabsorption
Plasma calcium concentration	Chemoreceptors	Calcium absorption and reabsorption
Plasma hydrogen ion concentration	Chemoreceptors	Ventilatory frequency, tidal volume, hydrogen ion and bicarbonate filtration and secretion
Plasma osmolality	Osmoreceptors	Water loss, sodium reabsorption and excretion, skin blood flow
Body temperature	Thermoreceptors	Skin blood flow, eccrine sweating, thermogenesis

physiology, and thermoregulation is one of those core topics. Since some thermoeffectors are also controlled by other regulatory mechanisms, then it is possible that the demands of those different systems might come into conflict, and so we must now explore the possible existence of homeostatic priorities.

Homeostatic priorities

In Part 4 of this series, we describe, in detail, the protracted and independent evolution of the human thermoeffectors, which did not appear as fully functional, purpose-built mechanisms. Instead, those effectors often served more than one regulatory system. To help understand the ideas developed below, we have briefly summarised the key steps of that evolutionary progression, which commenced with the acquisition of whole-body vascular networks (> 600 million years ago; Monahan-Earley et al. 2013). Those networks allowed reptiles (~ 300 million years ago; Carroll 1970; Simões et al. 2020) to use their cutaneous vasculature to gain thermal energy from their ambient environments (Templeton 1970). Next came evidence for the appearance of endothermy (internal heat production; ~ 200 million years ago; Phillips et al. 2009; Benton 2021), followed by the regulation of body temperature (homeothermy), with the emergence of egg-laying mammals (160–220 million years ago; Phillips et al. 2009; Benton 2021). Endothermy required mammals to switch the direction of those cutaneous vascular heat exchanges so that heat loss could occur, whilst excessive losses, as well as unwanted external heat gains, could be prevented. Hairy mammals evolved ~ 20 million years ago (Pontzer 2012), and they included hominids, which also possessed sweat glands. Body hair was eventually lost from some of the hominids (3–4 million years ago; Reed et al. 2007), giving rise to sweating specialists (*Homo sapiens*), to whom we will assign the pseudonym *Homo sudomotor* when we review how we use that capability to tolerate extended-duration exercise in the heat.

Homeothermy is just one of several homeostatic states that we, and other large mammals, seek to achieve (Table 1). Often, the processes involved in achieving any one of those regulated states require access to anatomical sites, physiological processes or biochemical reactions that must be shared with other regulatory mechanisms (Hensel 1973). Indeed, thermoregulation co-opted structures and processes that had evolved to serve, and continue to serve, other purposes, like the vascular networks of the peripheral tissues. So there inevitably will be competition between different homeostatic processes. In benign circumstances, the sharing of those effectors can occur without the competing needs of any regulatory system being compromised (Hales 1996; Kenney et al. 2014). When athletic and occupational activities are enacted with determination, that sharing may result in regulatory conflicts (Rowell 1977). Examples of those conflicts will be encountered across this historical series, and include, among others, the need to dissipate heat through evaporative cooling, and thereby regulate body temperature, whilst also regulating blood volume and pressure when confronted with an ever-diminishing, body-fluid volume. Similarly, when shivering thermogenesis is required to regulate body temperature in a cold and exercising person, the regulation of blood glucose concentration can often be compromised.

Since our thermoeffectors were sequentially acquired, and overlayed onto existing regulatory mechanisms, then it is just a small step to entertain the possibility that our regulatory systems, when simultaneously disturbed, might not always be afforded equal priority. Indeed, during physiologically stressful states, such as those encountered in physically demanding jobs, endurance racing and cases of human survival, several regulatory systems will be simultaneously disturbed, and an hierarchical ranking seems to now operate across those systems (Bass 1963; Rowell 1977; Satinoff 1978, 1983; Golden and Tipton 2002; Taylor 2015). There is evidence of this ranking across mammalian species. For example, foraging for food and shade-seeking are usually mutually-exclusive activities for antelope, so for them to seek shade, a behavioural form of thermoregulation, it has to be assigned a higher priority than the behaviour of food consumption. The downregulation of one of those behaviours is easy for us to imagine as a matter of choice. But sweating is not optional when exercising in the heat, so how might a change in our autonomic regulatory priorities occur?

Homeostatic priorities might be changed by altering either the sensitivity of the central regulator or the operational range over which the effectors are controlled. These topics are expanded upon in "Key concepts in exercise thermoregulation: the central regulator is more than a thermostat", and they are discussed throughout this review series, as they relate to changes in the thermosensitivity and the inter-threshold zones of our thermoregulatory system. Nevertheless, some homeostatic systems appear more tolerant of downregulation than others. For instance, we can survive much longer without food than without water. When homeothermy comes into conflict for resources with other homeostatic systems, where does it sit within that hierarchy?

Many researchers, and especially some climate-change biologists, believe that homeothermy always ranks highly amongst those regulatory processes. They tend to assume that if animals can regulate body temperature in a given set of environmental conditions, then they will always do so, whenever confronted with those conditions. However, that assumption lacks validity (Boyles et al. 2013; Hetem et al. 2016), as there are many situations in which thermoregulation becomes less rigid, with homeotherms sometimes exhibiting heterothermy, as either an implemented strategy

or as an inevitable consequence. A well-known example is hibernation in small mammals (Storey 2003; Ruf and Geiser 2015), during which body temperature is downregulated, but it is still regulated. Bears exhibit a form of hibernation, during which they reduce metabolic rate, which is advantageous when food is limited, but that change is not caused by a reduced body temperature (Tøien et al. 2011). Non-hibernating, large mammals can become heterothermic when temperature regulation conflicts with body-fluid regulation (Hetem et al. 2010). When homeothermy competes with energy regulation, some large mammals become progressively hypothermic, sometimes with lethal outcomes (Rey et al. 2017). So across mammalian species, thermoregulation is not always afforded the highest priority.

Where does homeothermy rank amongst human homeostatic mechanisms? We certainly do not ever exhibit daily swings of deep-body temperature of > 7 °C that Arabian oryx do during food and water shortages in the desert (body mass 70–100 kg; Hetem et al. 2010). In 2014, this journal published a series of reviews on the theme of competition among our homeostatic processes, with an emphasis on "*Blood pressure regulation outside the comfort zone*" (George et al. 2014; Halliwill et al. 2014; Ichinose et al. 2014; Joyner and Limberg 2014; Kenney et al. 2014; Raven and Chapleau 2014). However, the notion of hierarchical homeostasis in humans, and the ranking of human homeothermy, has received minimal attention, and to illustrate its significance, and its complexity, we provide two examples relevant to exercising humans.

In the first scenario, which is a realistic military example, consider the physiological strain of an extended-duration, load-carriage activity in the heat, performed when wearing impermeable protective clothing. Individuals undertaking that activity will eventually become heat-stressed, fatigued and possibly hypohydrated, quite possibly bringing into conflict temperature and blood pressure regulation. To explore that competition, let us isolate those stresses (exercise, load carriage, heat), and proceed stepwise, starting with a resting (supine), semi-naked, heat-stressed individual exposed to air at 40 °C (dry-bulb temperature). Heart rate and cardiac output will increase, along with a blood-flow redistribution from the visceral to the cutaneous vascular beds (Grollman 1930; Damato et al. 1968; Rowell et al. 1969, 1970). Sweating will eventually start, and the blood volume may gradually decrease. Since that volume is much less than the capacity of the entire vascular network, and since the cutaneous vasculature is highly compliant (Rowell et al. 1970), then tachycardia and a redistribution of blood flow are essential to prevent reductions in mean arterial and central venous pressures (regulated variables).

Now let us add the stress of load-carriage during endurance exercise. That requires an elevated blood flow to the exercising muscles, with that redistribution predominantly aimed at sustaining oxygen delivery to those muscles (Douglas and Haldane 1922; Tschakovsky and Pyke 2008; Ichinose et al. 2014). In our final step, we add impermeable protective clothing, so that the evaporation of sweat no longer dissipates metabolic heat effectively. The thermoregulatory centre responds by further increasing cutaneous blood flow, to convey the heat resulting from exercise to the skin. Hyperthermia is almost inevitable, and, if continued long enough, so too is hypohydration. In those states, we have the vascular beds of the muscles and skin vying for the available cardiac output (Wood and Bass 1960; Rowell 1977; Crandall and González-Alonso 2010; Kenney et al. 2014). As the heart rate approaches 80% of its maximal value, ventricular filling can be compromised (Mortensen et al. 2005), an elevated arterial pressure will increase the afterload (Janicki et al. 1996), and their combined effect is a reduced stroke volume (Mortensen et al. 2005). The superimposed, gradual reduction in the blood volume, due to sweating, can certainly result in compromising the regulation of mean arterial pressure and hypotension (Krediet et al. 2004). In such circumstances, individuals may reach the point of volitional exercise termination. Which straw broke the camel's back? Was it hyperthermia, hypohydration or hypotension? Which regulatory system was given the lowest priority and did that compromise homeostasis?

During such a demanding situation, homoeostasis will be tested on several fronts, with at least five of the regulated variables in Table 1 being disturbed. For each of the controlled variables, an activation level exists beyond which compensatory adjustments become ineffective, with further stress resulting in an ever increasing gap between the required and the deliverable effector response. For example, due to the effects of a reduced stroke volume and simultaneous demands for blood at several locations, an hyperthermic and hypohydrated person may well experience uncompensable hypotension (cardiovascular insufficiency; Barcroft and Edholm 1945; Krediet et al. 2004; also see: Dill et al. 1931), which can result in exercise termination, possibly with presyncopal episodes (Wilson et al. 2006) and sometimes with incapacitation (Noakes 2008; Epstein and Yanovich 2019). When a loaded, exercising, heavily sweating person in a hot environment gives up, heat exhaustion seems the obvious diagnosis, with homeothermy being relegated to a lower priority. But volitional exhaustion is often observed well before deep-body temperatures become problematic (Goldman 2001; Noakes 2008), and our worker may well have given up due to a heat-associated cardiovascular limitation. In that case, blood-pressure regulation was probably given a lower priority, resulting in systemic hypotension. That possibility appears to have been first described by Bass (1963).

Cardiovascular insufficiency would have occurred much later, if at all, had the air temperature been 10 °C (dry bulb). Does that mean that temperature regulation took priority

during heat stress? Perhaps not. When several regulated variables are simultaneously disturbed, each can be brought back towards, if not within, its operational range, without any homeostatic process being sacrificed, or given a supreme role. If that were not so, our species would have succumbed long ago to the pressures of natural selection. Instead, we are regulatory multi-taskers. Our evolution has ensured that healthy individuals have effector reserves that allow us to simultaneously defend several regulated variables adequately, if not perfectly. Therefore, whilst Larry Rowell (1930–2020, U.S.A.; Blatteis and Schneider 2022) once described the intramuscular and cutaneous vasculature as if they were competing remorselessly for blood during exercise in the heat (Rowell 1977), both Bob Hales (1943–2009; Taylor et al. 2022) and Larry Kenney have suggested that, in most circumstances, they compromise to share the available cardiac output (Hales 1996; Kenney et al. 2014).

Nevertheless, something happened to precipitate that cardiovascular insufficiency. The blood volume was progressively modified, due to the independent effects of whole-body heating (Barcroft et al. 1923; Diaz et al. 1979; Harrison et al. 1983; Maw et al. 2000) and exercise (Senay 1972; Edwards and Harrison 1984; Maw et al. 1998), to which we can add the postural change when moving from resting to upright exercise (Waterfield 1931; Harrison 1985; Maw et al. 1998). Those changes are related to both a redistribution of the blood volume, and their impact on the Starling (1896) forces that act across the capillary walls, and to extended-duration sweating (Young et al. 1920; Glickman et al. 1941). Over time, those changes reduce blood pressure, yet we continue to sweat even as we dehydrate (van den Heuvel et al. 2020b); another homeostatic paradox, which is discussed in Part 3 of this series. Since an insufficient intravascular pressure results in inadequate perfusion, which, in turn, progressively impairs cellular functions, then it is possible that cardiovascular insufficiency might fulfill the role of a fail-safe mechanism, which might intervene before cellular damage occurs (Bass 1963; Taylor 2015). In highly motivated individuals, continued exercise can elicit the more catastrophic outcomes of heat illness (e.g., heat stroke, rhabdomyolysis), so homeothermy can indeed fail. Has natural selection supported human survival by providing not just homeostatic priorities, but an hierarchical sequence of systemic failures, such that volitional exhaustion (for whatever reason) is actually a self-preserving outcome?

Our second scenario relates to extended-duration exercise in the cold following a shipwreck. Golden and Tipton (2002) have described many such examples, as have others (Currie and Percival 1792; McCance et al. 1956). We have taken an example from the Krogh-Hill epoch; the survival of the English explorer, Ernest Shackleton (1874–1922), and his crew. Their ship (*Endurance*) was trapped in the Antarctic by moving pack ice (1915), and eventually destroyed (Shackleton and Hurley 2019). During the course of their subsequent ice, land and sea journey to safety, the crew became exhausted and emaciated ("*scarecrows*"), yet most survived until the rescue vessel arrived in 1917. They were repeatedly cold-exposed, so, to have survived, homeothermy must have been given sufficient priority, since it would seem that they continued to regulate their body temperatures, even when malnourished. We have no data, other than their survival, to support that suggestion, nor do we know which body temperatures were being regulated. Nevertheless, keeping metabolic engines running in the face of a shortage of food presents a regulatory conflict. From an evolutionary perspective, that seems foolhardy and illogical, since reducing metabolic rate, as bears do, would conserve energy and increase the chance of surviving protracted cold exposures. Normothermic body-temperature defence is certainly not evident within birds and other mammals during starvation (Graf et al. 1989; Sakurada et al. 2000; Piccione et al. 2002; Rey et al. 2017), although the evidence for its abandonment is much less clear for humans.

Following the Krogh-Hill epoch, Alexander (1945) obtained a cache of records from the Nazi concentration camps, which included Experimental Block Five of the Dachau camp (1942–1945). Among those files was a complete copy of the final report from cooling experiments on prisoners (Holzlöhner et al. 1942 [Alexander 1945; Appendix 7]; also see: Gagge and Herrington 1947). Before proceeding, we acknowledge the people murdered during those horrific trials, the moral dilemma that surrounds those experiments, the validity of data so obtained and the arguments for and against its use (e.g., Berger 1990, 1994; Grunfeld 1991; Drobniewski 1993; Temme 2003; Bogod 2004; Mackinnon 2020; Caplan 2021). From extensive photographic proof (e.g., United States Holocaust Memorial Museum), those prisoners were malnourished to the point of starvation. Yet, from the many Figures and Tables within that report, it would appear that the deep-body (rectal) temperatures approximated those of normothermic individuals, until they were forced into sometimes lethal cooling. Homeothermy seems to have ranked more highly than energy regulation, even during life-threatening starvation.

Moving into the modern epoch, we find the experiments of MacDonald et al. (1984), Mansell and MacDonald (1989) and Vinales et al. (2019) on humans, all of which followed the work of Chossat (1843) on birds. Chossat was perhaps the first to demonstrate nocturnal hypothermia within fasting endotherms. Ian MacDonald is possibly the leading, modern researcher at the interface of nutrition and thermoregulation. He and his colleagues found that, following a 48-h fast, deep-body temperature (zero-gradient aural thermistor; Keatinge and Sloan 1975) was less-well defended in response to external cooling, than it was after a 12-h fast, although the subjects elevated their resting heat production

to a greater extent (MacDonald et al. 1984). They attributed that outcome to fasting disturbing the relationship between body temperature and metabolic heat production in the cold; energy regulation was competing with homeothermy. In their second experiment, both a 48-h fast and 7 days of under-feeding were investigated, in comparison with normal feeding. Starvation again reduced the thermogenic response to cold, but under-feeding had surprisingly little impact (Mansell and MacDonald 1989). However, basal deep-body temperatures were not different across the three treatments. In the third study, fasting was compared with both eucaloric and over-feeding diets, maintained for 24 h (Vinales et al. 2019). Deep-body temperatures (ingestible radio pill) differed by 0.06 °C between those states, although such a change has no physiological significance, given the inherent variations in that temperature as radio pills traverse the digestive tract (Taylor et al. 2014a). From those observations, it would appear that the human evidence remains inconclusive, although it seems to support the suggestion of Golden and Tipton (2002) that thermal homeostasis in humans seems to be maintained, or at least not abandoned, during caloric deprivation. That proposition requires investigation, for it could mean that, during food shortages, humans may indeed be unique in placing a higher priority on thermoregulation. It would be entirely congruent with evolution if the priorities assigned to different homeostatic processes were rearranged depending upon which of those processes contributed most to our welfare at that time and place.

Exercise, especially in the heat, also puts homeothermy into competition with body-fluid regulation. We shall discover, when we discuss the effects of hypohydration on sweating (our third paper in this series), how homeothermy and body-fluid regulation might rank in the priority list of homeostatic processes. As we have noted, we continue to sweat when hypohydrated, and that too might be a physiological phenomenon in which we differ from other large mammals, in which hypohydration typically switches heat loss from evaporative to non-evaporative channels (Mitchell et al. 2002).

First principles: physiological heat exchanges must obey physics

Having introduced some of the first principles of physiology, we now move to first-principles science from the perspective of physics, to briefly examine how thermodynamics dictates heat exchange. There are many excellent resources that provide detailed reviews of the avenues through which all objects, both sentient and insentient, exchange thermal energy with their surroundings (e.g., Kerslake 1972; Monteith and Mount 1974; Buchdahl 1975; Gagge and Nishi 1977; Gonzalez 1988; Gagge and Gonzalez 1996; Monteith and Unsworth 2014). Our brief is to explore the historical development of those fundamental concepts, and Fig. 4 provides a summary timeline of the critical steps within the acquisition of that knowledge. Of greater importance, however, is illustrating how those principles are fundamental to developing sound experimental designs, valid measurement techniques and correct data interpretation when planning, or indeed reading, research of relevance to exercise and occupational physiology.

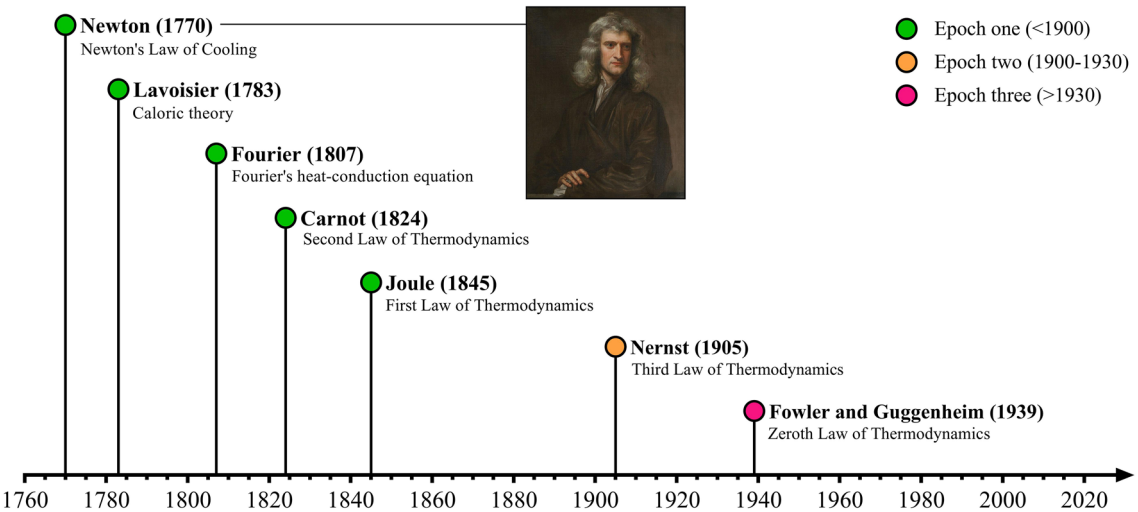


Fig. 4 A timeline for the advancement of knowledge concerning the first principles of thermodynamics. The portrait of Isaac Newton (painted by Godfrey Kneller) is in the Public Domain. Source: https://commons.wikimedia.org/w/index.php?curid=101534333 Accessed: July 22nd, 2022

Thermodynamics and physiology

The *Laws of Thermodynamics* were developed largely during epoch one (< 1900), with contributions during the Krogh-Hill epoch, to define and describe energetic relationships within both thermodynamically closed systems, which do not participate in the exchange of matter, and isolated systems, which do not exchange either matter or energy with their surroundings. Humans are neither thermodynamically closed nor isolated. However, the *Laws of Thermodynamics* still dictate how we exchange heat, both internally, and with our environment. Indeed, those laws are the basis of another first principle of physiology: the conversion of matter into energy, and the conversion of energy from one form to another. As such, they provide the scientific foundation upon which all temperature measurements are based. Those laws are presented below, not in chronological order, but in the numerical sequence in which they were eventually assembled and named. Moreover, the physical principles that dictate the answers to the questions posed in the "Introduction to part one" are revealed, and whenever we make observations, or arrive at interpretations, that do not conform to those laws, it is we who are wrong, due to errors of measurement or of logic; "… *we have all been wrong often*" (Hill 1965 [P. 167]).

The validity of temperature measurement: the *Zeroth Law of Thermodynamics*

Any object warmer than − 273 °C possesses energy, which increases proportionately with the movement speed and collision frequency of its structural particles. Those collisions elevate the thermal energy of that object, which can be quantified either calorimetrically or thermometrically, but, as always, the validity and utility of those measurements is dependent upon satisfying several experimental conditions.

For temperature measurements to provide a valid quantification of the thermal energy content of inanimate objects or living tissues, the temperature sensor must be in thermal equilibrium with its target structure. This, perhaps obvious statement, is the essence of the *Zeroth Law of Thermodynamics*, which was formalised just beyond the Krogh-Hill epoch by Ralph H. Fowler and Edward A. Guggenheim (Fowler and Guggenheim 1939; England). That is, when different energy systems are in thermal equilibrium, they will all have the same temperature and, whilst thermal exchanges will continue, an imbalance of thermal energy across those systems will cease to exist. For inanimate objects (e.g., water in an insulated flask), that criterion is easily satisfied. For living organisms, which have physiological mechanisms that modify the free exchange of energy and matter with their surroundings, which lack thermal homogeneity internally and which continually convert stored chemical into thermal energy, the criterion of thermal equilibration becomes more challenging, and measurements can be made that violate the *Zeroth Law* (Taylor et al. 2014a).

In the first instance, for a temperature sensor to equilibrate with either a tissue or surface temperature, that sensor must have a thermal inertia low enough to allow for rapid thermal equilibration. That inertia is dictated by the size, composition and the specific-heat capacity of the sensor. Measurements taken before equilibration will be invalid representations of the local thermal energy (heat) content. Moreover, since the heat content of living tissues is the result of all heat exchanges that tissue is experiencing, plus its own heat production, then the temperature at any site is merely a transient, turnover index (another first principle). Temperatures represent the balance between heat gains and losses at the time of measurement. If heat exchanges and production are not stable, and they seldom are, then some level of uncertainty must exist concerning the interpretation of any temperature measurement. During dynamic states (Fig. 2), such as variable or progressive (incremental) exercise intensities, that uncertainty is significantly elevated.

A further complication arises when a temperature measurement made in one tissue bed (e.g., the rectum) is then used as a proxy (surrogate) for the temperature of another location (e.g., the brain or arterial blood). For any proxy index to be valid, the two sites must be in thermal equilibrium, and that is most readily obtained when they are both well perfused by blood at the same temperature. Unfortunately, during dynamic thermal states (e.g., exercise or environmental changes), more distant body sites, such as the rectum and brain, are infrequently in thermal equilibrium. Thus, some proxy measurements of temperature, and especially measurements from the rectum, will be inaccurate, except under thermal steady states.

You can always trust a brewer: the *First Law of Thermodynamics*

The total energy possessed by living tissues is the sum of its potential (e.g., stored chemical) and kinetic energies (e.g., molecular motion), and its temperature will vary proportionately with its total thermal (kinetic) energy content. In the middle of the nineteenth century, the English brewer and physicist, James P. Joule (1818–1889), confirmed that kinetic energy could be converted into heat; he heated water simply through its rapid agitation (Fig. 5). In his classical publications (Joule 1845, 1850), Joule rightfully acknowledged his forebears: Thompson, Davy and Mayer. Benjamin Thompson (1753–1814, England; Thompson 1798) explained how frictional forces could generate heat, Humphry Davy (1778–1829, England; Davy 1812) observed that thermal energy and motion were governed by the same physical laws, and J. Robert Mayer (1814–1878, Germany;

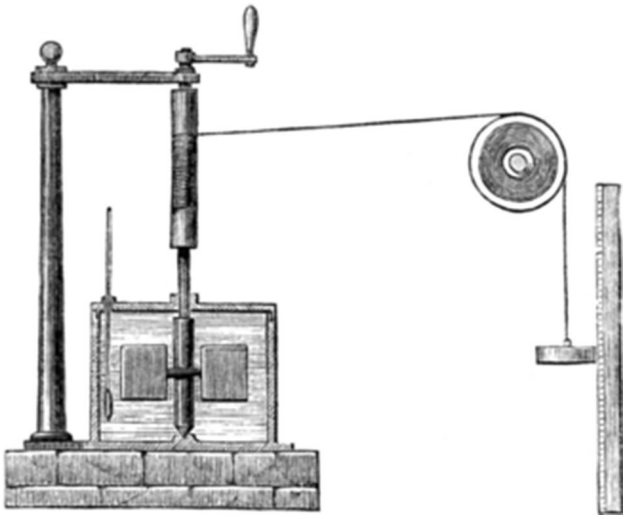


Fig. 5 Apparatus developed by James Joule for measuring the thermal energy liberated when the (gravitational) potential energy of a mass (right side) is converted into kinetic energy. The string attached to that mass caused the paddles in the sealed water bath (left) to spin when the mass was allowed to fall. The change in thermal energy of the water was measured using the thermometer in the water bath. Extracted from Harper's New Monthly Magazine (1869) and used under Wikimedia Commons agreement (Public Domain). Source: https://commons.wikimedia.org/w/index.php?curid=1527228 Accessed: July 22nd, 2021

Mayer 1842) demonstrated that kinetic energy (rapidly agitated water) could be convert into thermal energy. However, it took some time for their ideas to displace the "*caloric theory*" of Antoine-Laurent Lavoisier (1743–1794, France; Lavoisier 1783; Best 2015), which itself had replaced the "*phlogiston theory*" of Georg Stahl (1659–1734, Germany; White, 1932).

Collectively, those ideas led to the eventual formulation of the *Law of Conservation of Energy*, from which we now know that the total energy within a thermodynamically closed system will always remain constant; energy is neither created nor is it destroyed. For Joule's experiment, the water bath resembled a closed system, and kinetic energy was converted into thermal energy, which "*left no doubt on my mind as to the existence of an equivalent relation between force and heat*" (Joule 1850 [P. 64]). This is the *First Law of Thermodynamics*, and readers may recognise it as expressed within the *Heat-Balance Equation* (energy-balance equation). During physiological steady states, that law allows us to quantify the avenues for thermal energy exchange, as well as the conversion of stored chemical energy so that we can perform work on external objects. Since that energy conversion is very inefficient (< 25% efficient), it liberates large amounts of unwanted heat, which must then be either dissipated or stored. Heat storage elevates body temperatures. By simultaneously measuring work performed (ergometry) and the rate of heat exchange (direct calorimetry), one can deduce energy conversion during resting and exercising thermal steady-states.

Determining the direction of heat flow: the *Second Law of Thermodynamics*

During exercise, thermal energy exchange continues even during thermal equilibria, and that energy is continually moving from warmer external objects into the body, and from warmer body tissues (e.g., skeletal muscles) to cooler regions (heat sinks; e.g., cooler tissues), as defined by the *Second Law of Thermodynamics* (Nicolas L.S. Carnot, 1796–1832, France; Carnot 1824). Those energy exchanges are unidirectional, with energy and matter always travelling down transportation gradients (another first principle). That *Second Law* governs physiological heat exchanged by radiation, conduction and convection, whilst heat lost though evaporation may appear to travel against the flow.

All objects that possess thermal energy will absorb and emit some of that energy in the form of electromagnetic waves (photons). The nett result of photon turnover will dictate the kinetic and thermal energies of those objects, which increases when absorption exceeds emission. That is the process of radiative heat exchange. When an object sits in the path of a moving fluid (air or water), the molecules of that fluid will exchange thermal energy with those of the surface of the object. This is a form of convective heat exchange, and it is both flow and gradient dependent. For (stationary) objects that are in physical contact, heat is again transferred from molecule to molecule, and down the thermal gradient. That is thermal conduction. Since the surfaces of objects are generally surrounded by, and in direct contact with, fluids that often have a different temperature, conductive heat exchange results in the establishment of thermal boundary layers next to the surface of that object. The temperature of fluid close to the object will equilibrate with its surface temperature, with fluid layers further away being at progressively different temperatures.

The thickness of a boundary layer is modified by both absolute (air and water currents) and relative movements (locomotion) with respect to the ambient medium. Unless fluid temperature is identical to the surface temperature, even in still conditions, warming or cooling of those layers causes molecular movements within the fluid, the density of those layers will change, and the fluid will start to rise (if heated) or sink (if cooled). That movement creates a natural convection current, which moves thermal energy away from, or back towards, the body. Finally, within the body, a forced-convection current exists within the blood vessels, in the form of mass flow, created by the rhythmical cardiac contractions, and supported by muscle pumping during

exercise. The resulting mass flow of blood redistributes thermal energy throughout the body.

Determining the velocity of heat exchange: Fourier's heat-conduction equation

Convective and conductive heat exchanges are vector quantities, and have both directional and magnitude attributes. The direction of heat flow is dictated by the *Second Law of Thermodynamics*, and its magnitude by *Fourier's heat-conduction equation* (J.-B. Joseph Fourier, 1768–1830, France; Fourier 1807), which determines the rate at which heat travels down a thermal gradient. These principles are applicable to exercising humans, with the rates of tissue-temperature changes being proportional to the size of thermal gradients between the heat sources (muscle mitochondria) and heat sinks (less-active tissues).

Consider the practice of whole-body pre-cooling; the artificial reduction of body temperatures, prior to endurance activities. The aim is to enhance performance by delaying exercise-induced hyperthermia. Whilst improvements in endurance performance associated with that practice are well accepted (Booth et al. 1997; González-Alonso et al. 1999; Kay et al. 1999), they are unlikely to be due to a delayed rise in body temperatures. Instead, the heat-conduction equation dictates that intramuscular temperatures should reach the same, exercise-dependent level at approximately the same time, with or without pre-cooling, and that would be so even if pre-heating was used (Booth et al. 2004, Australia).

Using a simplified physical model (a steel shot [sphere]), with a centrally embedded temperature sensor, the reality of the heat-conduction equation (Fourier 1807) was endorsed experimentally. Three thermal pre-treatments were used to stabilise the central temperature of the sphere at 15°, 25° and 35 °C (separate trials), before it was plunged into hotter water (38.5 °C). On each occasion, the temperature of the sphere equilibrated with that water temperature at approximately the same time (Fig. 6A, B). What changed was the speed with which its central temperature increased, as shown by the grey zones of Fig. 6A (80–150 s; Taylor et al. 2014a). That is, in accordance with Fourier, those rates of temperature change were proportional to the size of the thermal gradients that existed at any point along those warming curves (the difference between any instantaneous temperature and the final temperature). Therefore, when those differences (gradients) were expressed relative to the difference between the initial (time zero) and final temperatures, the three curves were superimposed (Fig. 6B). Of course, those heating rates are also determined by the shape, dimensions, density, thermal conductivity and specific heat capacity of the object, and for exercising athletes, it is not just physical phenomena that dictate tissue heating rates. Indeed, autonomically mediated thermoeffector activity, a redistribution of the cardiac

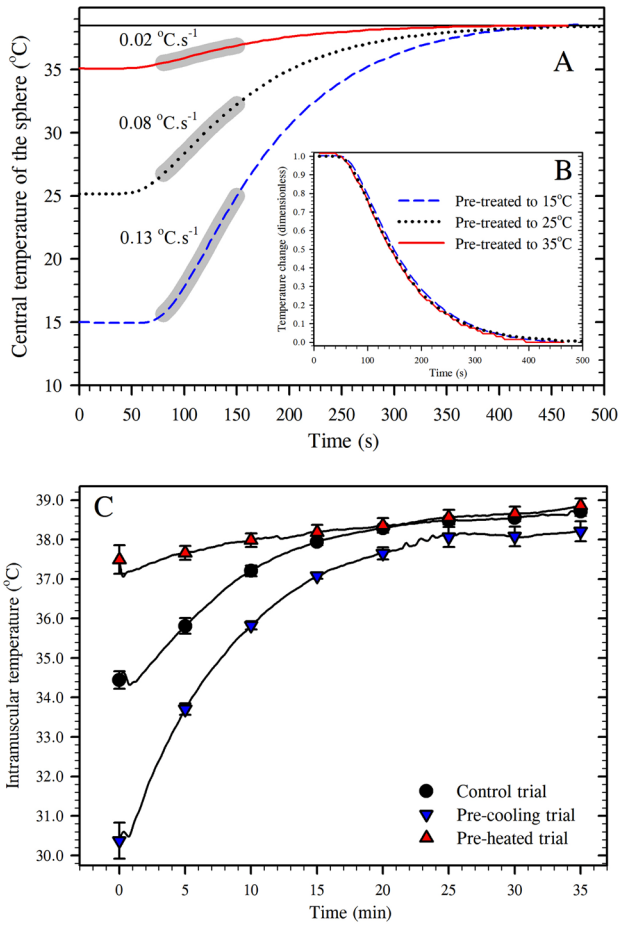


Fig. 6 Fourier's heat-conduction equation in action, physically and physiologically (Fourier 1807). The rate at which the temperature of an object changes (°C s^{-1}) is determined by the size of the thermal gradient between that object and its surroundings. **A** Temperatures recorded from the centre of a steel sphere, and tracked following thermal equilibration in water at each of three temperature (15°, 25° and 35 °C), and then during immersion within a heated water bath (38.5 °C). Those warming curves also show the heating rates for each trial, measured from 80 to 150 s (grey shaded zones). As Fourier would predict, the larger the initial thermal gradient, the greater will be the heating rate. **B** The instantaneous temperatures of the sphere (**A**) expressed as temperature changes derived from the ratio of the difference between each instantaneous temperature and the final temperature (T_i–T_f), and the difference between the initial temperature and the final temperature (T_0–T_f). Thus: temperature change = (T_i–T_f)/(T_0–T_f). Source: Parts **A** and **B** have been modified from a Figure appearing within Taylor et al. (2014a) and used here with permission. **C** Intramuscular temperatures during steady-state cycling in the heat (60% peak aerobic power [maximal oxygen consumption]; 34.6 °C dry bulb). Separate trials were completed following whole-body immersion in cool (pre-cooling: 28.2 °C), warm (control: 34.8 °C) or hot water (pre-heating: 39.1 °C). Subjects provided data for each trial (N = 5), and data are shown as average response curves (15-s sampling) with means and standard errors of the means plotted at 5-min intervals. Modified from Booth et al. (2004)

output towards the active skeletal muscles (to provide fuel and to remove metabolically generated heat) and exercise-related changes in convective heat exchanges with the ambient medium will also influence those temperature changes.

Now consider what happened to the intramuscular temperatures (*vastus lateralis* [3 cm deep]) of participants cycling (35 min; 60% peak aerobic power; 35 °C dry bulb), following three thermal pre-treatments, which elicited muscle temperatures differing by 6.9 °C and a deep-body (oesophageal) temperature difference of 1.3 °C (Booth et al. 2004). The time courses of subsequent exercise-dependent elevations in muscle temperature would have pleased Fourier (Fig. 6C), with the pre-cooled muscles gaining heat almost six times faster (0.23 °C min^{-1}) than did the pre-heated muscles (0.04 °C min^{-1}). Despite the complexities of physiological systems that modify the avenues for heat distribution and dissipation, the experimental evidence shows that the patterns of heat accumulation in both the sphere and muscle tissue were very similar. Indeed, observations such as these resulted in domesticating the hypothesis that pre-cooling can enhance performance by delaying the attainment of a critical (fatigue-inducing) deep-body temperature. Figure 6C has revealed that pre-cooling does not significantly delay the muscle-temperature elevation, and we examine the concept of fatigue-inducing, deep-body temperatures in Part 2 of this series.

At the very limit of heat loss: the *Third Law of Thermodynamics*

All objects with temperatures greater than − 273 °C (0 K) possess energy (the degree symbol is omitted for all temperatures in Kelvin). At that temperature, however, the thermal energy content approaches zero, and that is the essence of the *Third Law of Thermodynamics*, which defines an absolute zero temperature. Guillaume Amontons (1663–1705, France) predicted the existence of absolute zero (Amontons 1695; Candas and Libert 2022), with that state first described by Walther H. Nernst (1864–1941, Germany) within the Krogh-Hill epoch (Nernst 1905; Lindemann and Simon 1942). Its precise value was determined by William Thompson (1824–1907; Lord Kelvin, Scotland), and the unit of thermodynamic temperature was named in his honour (Kelvin [K]) by the *Bureau International des Poids et Mesures* (established 1875). To our knowledge, the *Third Law* has no physiological relevance, although the units reported herein conform to the *Système International d'Unités* (SI units; Royal Society 1975; Bureau International des Poids et Mesures 2019), with temperature being one of the seven base units.

Physical (passive) heat exchanges

In addition to the *Laws of Thermodynamics*, the passive heat exchanges described above are influenced by the shape and dimensions of objects, as well as their thermal conductivities (ability to conduct thermal energy [W m^{-2}]) of the object and its ambient medium. Heat stored within an object is a function of the product of its size and its specific-heat capacity (quantity of heat [J] required to elevate 1 g by 1 K [J g^{-1} K^{-1}]), as well as the density and specific heat of the surrounding medium. During exercise, those exchanges are further modified by changes in posture, clothing that is worn and on moving from air into water, or even into heliox, in the case of saturation divers. These influences modify the precision with which exercising people can be modelled using inanimate objects (e.g., spheres and thermal manikins).

If we pour equal volumes of hot water into a cup and onto a dinner plate, and leave both in a cool room, which will cool faster? Now thermodynamics depends on shape, and especially on the ratio of the mass to the exposed surface area. Larger exposed surface areas cool faster. Similarly, a saucepan containing 2 L of water will take twice as long to boil as will one containing 1 L, on the same heat source. These simple analogies provide first-principles knowledge that enables us to predict differences in passive heat exchange and storage for people of different body size, regardless of age or gender (sex).

For instance, even when at the same tissue temperature, living tissues vary in their specific heat capacities, so equal masses of different body tissues will, at the same tissue temperature, hold different quantities of heat. An homogenised human has an average specific heat of ~ 3.5 J g^{-1} K^{-1} (Pembrey 1898; Gephart and DuBois 1915; Burton 1935). However, that value varies considerably across the body tissues, with adipose tissue being ~ 1.8 J g^{-1} K^{-1} (Karmani 2006; Foundation for Research on Information Technologies in Society 2013), and skeletal muscle, which forms 35–45% (female-male) of a healthy adult's body mass, is ~ 3.6 J g^{-1} K^{-1} (González-Alonso et al. 2000; also see: Xu et al. 2022). Those differences mean that an obese individual will store thermal energy more rapidly than a lean person of the same body mass, assuming equivalent heat losses, when both perform the same amount of external work. Let us now consider differences in body morphology (shape and dimensions) and the thermal properties of air and water.

Morphology defines the relationship between the volume (mass) and surface area of objects, and determines the ease with which heat can be stored and exchanged. For geometrically similar (isometric) objects, such as spheres (the shape with the largest volume per unit area) and rectangular plates (which have the opposite relationship), well-established rules determine how both volume and

area change as size increases. Spheres are highly resistant to passive heat exchange and tend towards thermal stability (e.g., heads), but plates quite readily exchange heat (e.g., hands and feet), and are thermally less stable (Taylor et al. 2014b). Whilst humans have some structures that resemble isometric objects, we are allometrically configured, since we may have different shapes, sizes and segmental proportions, but we all have a recognisable shape. As we grow, our volume (body mass) increases faster than does our skin-surface area. Consequently, larger individuals have smaller mass-specific surface areas (ratio of surface area to mass; Royal Society 1975), and are thermally more stable with regard to passive heat exchanges, whilst smaller people have a tendency to exchange heat more easily.

Let us now examine the fluids in which humans exercise: air and water (Lide 1997). The ability of water to transmit thermal energy (thermal conductivity 631 mW m^{-1} K^{-1}) is 24 times greater than that of air at the same temperature (26 mW m^{-1} K^{-1}). The specific-heat capacity of air is 1.01 J g^{-1} K^{-1}; for water, it is 4.18 J g^{-1} K^{-1}. Air has a density of 0.0012 g.cm^{-3}; water density is 0.9922 g cm^{-3}. Therefore, the volume-specific heat capacity (product of specific heat and density) of water at 37 °C is > 3400 times that of air at that temperature. That capacity determines the amount of thermal energy required to increase the temperature of a given volume by 1 K, so body heat lost into a large water bath hardly affects its temperature. Therefore, whether resting or exercising in water, passive heat losses are many times faster in cool water than in air of the same temperature.

Physiological (active) heat exchanges

Behavioural changes

Discussions of this topic are beyond the scope of this review. However, behavioural strategies (e.g., stress avoidance, artificial heating and cooling, protective clothing) are both more powerful and more efficient than are the actions of our autonomic thermoeffectors, and they permit workers to be productive whilst surviving in places where unprotected humans would perish. Indeed, those behaviours set a demarcation line that separates athletic, but not recreational, pursuits from occupational activities. In affluent countries, behavioural strategies (e.g., central heating or air-conditioning indoor environments) can be so successful in preventing people from activating autonomic thermoregulation, that both total daily energy expenditure and activity-related energy expenditure were found to be independent of environmental dry-bulb temperatures over the range from − 10° to 30 °C (Zhang et al. 2022); the overuse of climatic control is bad for the survival of our planet and our species. A wide selection of manuscripts concerning protective clothing has been included within the recommended readings across the four parts of this series. Readers seeking further resources are directed to the following scientists, for whom selected papers have been included: Victor Candas (France), Ralph Goldman (U.S.A.), Richard Gonzalez (U.S.A.), George Havenith (The Netherlands and England), Ingvar Holmér (Sweden), Elizabeth McCullough (U.S.A.) and Tom McLellan (Canada). Also included are reviews covering a broad range of our behavioural responses.

Metabolic heat production

The energy required to support homeostasis, including growth and repair, work performed by ion-transport systems to maintain electrochemical gradients across cell membranes, the digestion and breakdown of food stuffs and muscular work, is obtained from the breakdown of the energy-rich adenosine triphosphate (ATP) molecule. Unlike plants, animals rely on harvesting energy from the oxidation (catabolism) of carbohydrates, lipids and proteins. During those processes, we produce carbon dioxide and water, but also large quantities of thermal energy (heat). Energy can also be obtained without the participation of oxygen (non-oxidative or anaerobic metabolism), although those short-term energy sources have only a very limited capacity to fuel muscular work (Brooks and Gladden 2003; also see: Hollmann 1995; Gladden 2004; Poole et al. 2021; Katz 2022). Whilst repeated bouts of anaerobic exercise undoubtedly result in significant heat production, which remains unquantified, we restrict our emphasis to heat production during oxidative metabolism.

Metabolic heat production during rest In humans, > 90% of our ingested food is absorbed and oxidised; the balance is lost via faecal and urine elimination (Widdowson 1955; National Research Council 1989). That energy is stored and then expended across three broad functional states: basal metabolism (70%; Ravussin and Bogardus 1992; Donahoo et al. 2004), diet-induced thermogenesis (5–15%; Van Zant 1992; Weststrate 1993; Westerterp 2004; Levine 2005) and exercise-induced energy expenditure. Our focus is upon basal and exercise metabolism, with the former providing an essential primer for the latter, and Fig. 7 provides a summary timeline for the key concepts and historical steps in the acquisition of that knowledge. Those developments are particularly important when we consider how best to compare inter-individual differences in metabolic heat production during exercise.

Basal metabolic rate represents the minimal energy required to sustain physiological function in the absence of physical activity or thermal stress. Basal metabolic rate can

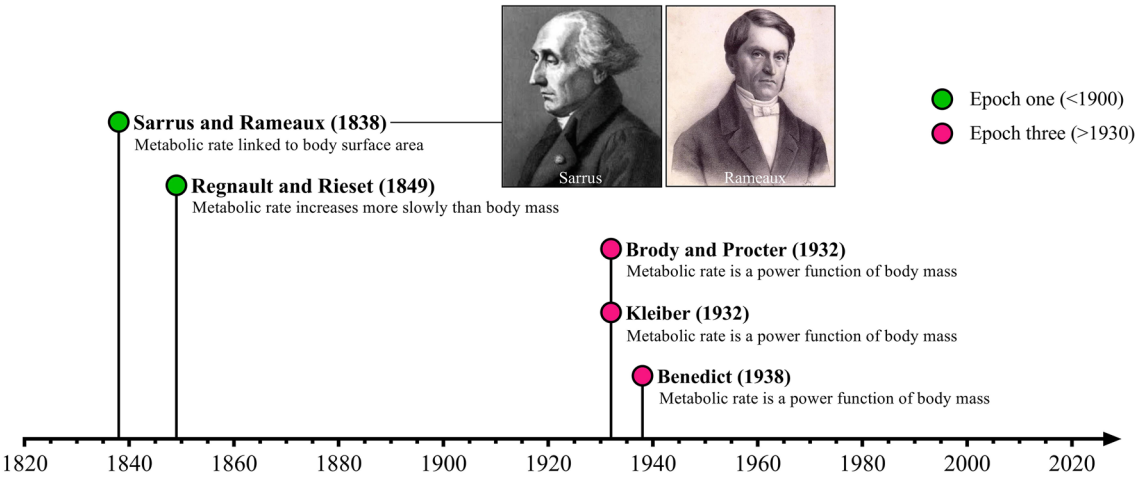


Fig. 7 The sequential acquisition of our contemporary understanding of the dependence of metabolic rate on body size. The portrait of Pierre Frédéric Sarrus is in the Public Domain. Source: https://en.geneanet.org/media/public/screenshot-2020-03-05-pierre-frederic-sarrus-20144788. Portrait of Jean-François Rameaux is in the Public Domain. Accessed: December 22nd, 2022

be measured only under tightly controlled conditions in the laboratory (Mitchell et al. 2018), and those conditions allow for respiratory gas exchanges, measured oronasally, to provide a valid reflection of cellular respiration and metabolic rate. The man first credited with describing those requirements is Adolf Magnus-Levy (1865–1955, Germany; Goldner, 1944), and it is he who, in consultation with Nathan Zuntz (1847–1920, Germany), coined the term "*grundumsatz*" (basal metabolic rate; Magnus-Levy 1947). Those standardised conditions are still used today, albeit with some refinement (Henry 2005; Archiza et al. 2017; Bowes et al. 2021a), and they include: a protracted (supine) steady state, isolation, wakefulness with an absence of muscular activity, a preliminary fast following a normal dietary regimen, minimal psychological or cognitive disturbance, an absence of illness or medications, and the presence of a thermally neutral environment. Although basal metabolic rate is difficult to measure, it is the main determinant of our daily energy expenditure, even in highly active people (Pontzer et al. 2016). Consequently, over our lifetimes, dissipating basal metabolic heat poses a greater load than does dissipating the heat of exercise, however active we are, although the challenge of dissipating heat at an adequate rate is far greater during exercise.

Within the basic and applied sciences, the accepted conventions for reporting basal, resting and exercising rates of metabolic heat production vary from using absolute data (W [J s^{-1}]), to values that have been scaled (standardised or normalised) to some anthropometric attribute, such as body-surface area (area-specific heat production: W m^{-2}) or body mass (mass-specific heat production: W kg^{-1}; IUPS Thermal Commission 2001). With the exception of area-specific normalisation, those conventions are also applied to the reporting of oxygen consumption, with the implicit assumption that metabolic rate and oxygen consumption are uniquely linked to body size (metabolic size). That is, larger individuals invariably consume more oxygen, and produce more carbon dioxide and metabolic heat than smaller individuals, at least in absolute terms, so those variables reflect a positive mass bias. To counteract that bias, scaling is most commonly achieved by dividing the variable of interest by some index of body size (ratiometric scaling; Tanner 1949; Katch 1973), or by using linear regression analysis.

The problem with such linear normalisation arises because those processes will create size-independent data only when a linear relationship actually exists across the full range of those physiological and morphometric data, and when that relationship passes through the origin (Kleiber 1947; Tanner 1949); a scenario that rarely occurs in biology (Schmidt-Nielsen 1984a). Ratiometric scaling results in a zero intercept, but it frequently converts a positive mass bias into a systematic negative bias (Albrecht et al. 1993). On the other hand, linear regression rarely achieves a zero intercept. To illustrate that, we analysed data for both basal metabolic rate (Bowes et al. 2021a) and peak oxygen consumption (Bowes et al. 2021b) obtained from > 60 healthy adults. For an extrapolated body mass of 0 kg, linear regression predicted a basal metabolic rate of 3.7 MJ d^{-1} (Bowes et al. 2021a), and a peak oxygen consumption of 1.05 L min^{-1} (Bowes et al. 2021b). Those biologically impossible outcomes violated the *First Law of Thermodynamics* and those equations could not be used to predict values beyond the mass range of the individuals investigated; "*the true test of any method for the reduction of the metabolism of individuals of different size and shapes to comparable terms is its*

capacity for predicting unknown metabolism" (Harris and Benedict 1919 [P. 182]).

A solution to the errors inherent to linear scaling is to use allometric (non-linear) scaling to normalise physiological data (y) to the appropriate body-size variable (x) adjusted to an exponent (b), using a power function ($y\ x^{-b}$; Huxley 1932; Kleiber 1947; Taylor et al. 1981; Nevill et al. 1992). The justification for that approach is based upon the knowledge that the metabolic rate of mammals shares an allometric relationship with body mass (Taylor et al. 1981; Bergh et al. 1991; Darveau et al. 2002; Weibel et al. 2004; White and Seymour 2005a, b; White and Kearney 2014). Given that many of the formative steps that led to that interpretation occurred in, and around, the Krogh-Hill epoch, we will briefly review that research.

Across the last two centuries, debate arose concerning the nature of the relationship between body size and metabolic rate. Are those variables linearly ($W\ kg^{-1}$) or allometrically linked ($W\ kg^{-0.67}$, $W\ kg^{-0.75}$)? That debate centred on whether to scale those data to the body-surface area or to body mass. The nature of that relationship is certainly of theoretical importance, but it is also of considerable significance during the athletic and occupational pursuits of morphologically diverse groups, that might also involve load carriage. Unless we use appropriate scaling, it will be impossible to provide valid inter-individual, size-independent comparisons of oxygen consumption and metabolic heat production. If basal metabolic heat production is not linearly associated with body size, then it is highly likely that heat production will be not be linearly linked to body size during either exercise or shivering thermogenesis. Whilst it is rare within the applied literature to find examples of scaling that extend beyond linear methods, perhaps it is time to embrace that inevitability.

In the nineteenth century, Pierre F. Sarrus (1798–1861, France), and Jean-François Rameaux (1805–1878, France) observed that the relationship between body size and the metabolic rate of animals seemed to be more closely related to their body-surface area, than to their body mass (Sarrus and Rameaux, 1838–1939). That concept became known as the "*surface law*", but it was not so much a law as a guiding principle (Schmidt-Nielsen 1984a). Similarly, Regnault and Rieset (1849; France) found that the metabolic rate of birds (endotherms) increased disproportionately with body mass, such that the mass-specific metabolic rate of sparrows was ten-fold greater than that of chickens. They proposed that, since heat is lost through the body surface, and since sparrows regulate their body temperatures whilst having much larger mass-specific surface areas, their elevated metabolic heat production was necessary to sustain a stable deep-body temperature (Lusk 1922). Thus, metabolic heat production must have been linearly related to the surface area available for heat loss ($W\ m^{-2}$), which can be approximated using a power function of body mass ($W\ kg^{-0.67}$).

Furthermore, Rameaux (1857) noted that, as endotherms grew, their surface areas increased disproportionately with changes in mass ($mass^{3/4}$ [$mass^{0.75}$]; Shour 2017). Around the same time, Carl Bergmann (1847; Germany) and Müntz (1880; France) supported that surface-area hypothesis, as did Max Rübner (1854–1932, Germany; Rübner 1883), who found that the basal metabolic rates of dogs (3–31 kg) were more alike when normalised to body-surface area than to body mass. Collectively, those communications appear to mark the first scientific descriptions of those non-linear, body-size relationships, and the time beyond which the linear scaling of whole-body metabolic rate (or its respiratory surrogates) should perhaps have been abandoned; "… *we have all been wrong often*" (Hill 1965 [P. 167]).

Within the Krogh-Hill epoch, Gephart and DuBois (1915; U.S.A.) followed that surface-area principle, and normalised their extensive database of metabolic rates to body-surface area. However, because no convenient way to estimate surface area existed, Delafield DuBois and Eugene F. DuBois (1882–1959, U.S.A.; Blatteis and Schneider 2022) developed a successful and long-lived predictive equation using height and body mass (DuBois and DuBois 1916; Aub 1962; Shuter and Aslani 2000). Those who read the original paper may wonder how, when only nine subjects were used, they were able to arrive at such a successful outcome. Had they chosen a typical sample of convenience, they would have been unsuccessful, so we digress briefly to expand upon that point.

The nine subjects used by DuBois and DuBois (1915, 1916) were females and males of vastly different body sizes (mass range 6.3–93.0 kg; height range 73–184 cm), "*including an infant, a child, a sculptor's model, an obese short man, an emaciated diabetic and two double amputees*" (Martin 1984 [P. 143]). Moreover, the general form of their equation was dimensionally correct (e.g., mass is proportional to $length^3$; Martin 1984), and the resulting equation was subsequently verified against surface-area measurements obtained from cadavers (Martin et al. 1984), three-dimensional scanning (Tikuisis et al. 2001) and alginate moulding (Lee et al. 2008). While many alternative formulae exist (Gehan and George 1970; Haycock et al. 1978; Mosteller 1987; Shuter and Aslani 2000; Tikuisis et al. 2001; Lee et al. 2008), the regression equation of DuBois and DuBois (1916) for estimating human surface areas has withstood the tests of time. Nonetheless, direct photometric measurements of body surface area have revealed that it has a tendency to underestimate, with that error increasing with reductions in body size (Mitchell et al. 1971).

During, and immediately following, the Krogh-Hill epoch, three American researchers independently evaluated the validity of the surface-area principle for scaling

metabolic rate: Samuel Brody (1890–1956), Max Kleiber (1893–1976) and Francis G. Benedict (1870–1957). All three challenged the validity of that principle (Harris and Benedict 1918, 1919; Brody et al. 1928; Kleiber 1932, 1947, 1950, 1961; Brody and Procter 1932; Benedict 1938; Brody 1945). If the mechanism that dictated metabolic rate was solely related to surface area, then individuals with the largest surface areas would also have the highest metabolic rates (Kleiber 1932; White and Kearney 2014), but they do not. A century later, the significance of that truism remains infrequently recognised.

In the first instance, Brody et al. (1928) evaluated the relationships between surface area, body mass and metabolic heat production in farm animals, and concluded that "*on mathematical and on biological grounds, that while it may be more convenient, and perhaps more enlightening, to relate heat production to surface area, it is simpler to relate heat production directly to body size raised to some power*" (P. 3). Over the next 15–20 years, Brody and his team further dismantled the surface-area principle (Brody and Procter 1932). Almost a century after Regnault and Rieset (1849) had described the same phenomenon, Brody (1945) noted that "*A most intriguing observation in basal metabolism studies is that basal heat production per unit body weight in homeotherms decreases rapidly with increasing weight … This means that the basal-metabolic significance of a physical weight unit in a canary is about 25 times that in a cow*" (Brody 1945 [P. 354]). That work culminated in the well known log–log plot of metabolic rate and body mass across species that varied in size from a mouse to an elephant

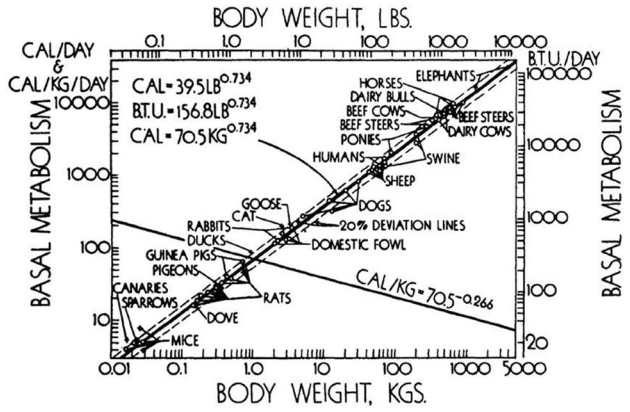


Fig. 8 The 24-h, basal metabolic rates of birds and mammals (cal day^{-1} and cal kg^{-1} day^{-1} [1 cal = 4.186 J]) and its allometric relationship with body mass (kg). From Brody (1945; [Fig. 13.7]), and is in the Public Domain. The positive linear, double logarithmic relationship reveals that the basal metabolic rate increases more slowly than the changes in body mass. The slope of that line provides the exponent of the power function that describes that relationship ($kg^{0.734}$ or $mass^{0.734}$), which dictates that for each 1-kg increment in body mass, metabolic rate will rise by a factor of 0.7

(Fig. 8), and included humans. The slope of that curve was not the 0.67 that the surface-area principle predicted, but 0.73 (Cal day^{-1} $kg^{-0.73}$). That exponent enabled the derivation of size-independent metabolic rates.

Contemporaneously, Kleiber (1932) studied the metabolic rates of animals varying in size from rats to steers. His data indicated that basal metabolism scaled to body mass raised to the exponent 0.74 (W $kg^{-0.74}$). Detailed discussions of that work are contained within Kleiber (1947, 1961). Six years later, Benedict (1938), after modifying his respirometer for use with animals of varying size, produced another curve for animals of widely varying body mass, this time with a body-mass exponent of 0.76 (W $kg^{-0.76}$). Collectively, Brody, Kleiber and Benedict had domesticated the surface-area principle, and a body-mass exponent of 0.75 was adopted; "*Kleiber's law*" or the "*three-quarter rule*". Though it would be treated as a law for many decades, rather than as an experimental result, until it too was ultimately challenged.

Most recently, those inter-specific (among species) comparisons were repeated, but now with greater attention to animal selection, to the achievement of basal states and to the analytical methods used (White and Seymour 2005a, b; Sieg et al. 2009; White et al. 2012). This time, the allometric scaling exponent turned out to be 0.67 ($mass^{0.67}$; White and Seymour 2005a; Australia), and it seemed that we had circled back to surface-area scaling. However, that exponent was derived when all of those species were simultaneously analysed, yet, within each species, there was evidence for some degree of specificity (Heusner 1982; White and Seymour 2003; Sieg et al. 2009), although only a few intra-specific evaluations had been performed (Rübner 1883 [dogs]; Refinetti 1989 [rats; U.S.A.]; Kvist and Lindström, 2001 [birds; Sweden]). Moreover, although it had been shown to be invalid within other species, linear scaling was used most frequently for humans (e.g., Harris and Benedict 1919; Boothby and Sandiford 1922; Durnin 1959; Schofield 1985; Cole and Henry 2005), and it was not until very recently that the possibility was explored that human basal metabolic rates might also scale allometrically (Bowes et al. 2021a; Australia).

Using data obtained from both experimental subjects (basal metabolic rate; 68 males [18–40 years old; 56.0–117.1 kg]) and two historical databases (basal and resting states; 4811 males [2.7–108.9 kg], 2364 females [2.0–96.4 kg]; Schofield 1985), Bowes et al. (2021a) assessed the validity of three different scaling methods: ratiometric scaling, linear regression and allometric regression. For the experimental subjects, allometric regression was the most valid biologically and the most powerful statistically (Eq. 1; Bowes et al. 2021a). Using those criteria, allometric regression also provided the best fit for the historical sample of males (Eq. 2; Bowes et al. 2021a). Those observations

established that the basal and resting metabolic rates of humans also scaled allometrically with body mass, with an exponent between 0.50 and 0.55. Finally, when the historical data of adult males and females (mass range 40–96 kg) were scaled separately (allometrically), a statistically significant sex difference was observed for those body-mass exponents (males: Eq. 3; females: Eq. 4; Bowes et al. 2021a). That difference was congruent with a sex dependency in the mass-specific, metabolic rate of resting adults, as reported elsewhere (Garn et al. 1953; Arciero et al. 1993; Buchholz et al. 2001).

$$\text{Men } (56-117\,\text{kg}):\ \text{M} = 0.739\times \text{m}^{0.55}, \tag{1}$$

$$\text{Men } (3-109\,\text{kg}):\ \text{M} = 0.873\times \text{m}^{0.50}, \tag{2}$$

$$\text{Men } (40-96\,\text{kg}):\ \text{M} = 1.012\times \text{m}^{0.46}, \tag{3}$$

$$\text{Women } (40-96\,\text{kg}):\ \text{M} = 1.094\times \text{m}^{0.40}, \tag{4}$$

where M is the metabolic rate (MJ day^{-1}), m is the body mass (kg).

While basal metabolism represents whole-body energy expenditure, it is important to recognise that some anatomical structures demand relatively more energy than others. In the absence of organ-specific, allometrically scaled data, we must use linearly scaled data, which reveals that the mass-specific metabolic rates of the brain (11.6 W kg^{-1}), liver (9.7 W kg^{-1}) and skeletal muscles (0.6 W kg^{-1}; Elia 1992; Gallagher et al. 1998; Heysmfield et al. 2002; Müller et al. 2011) account for about 75% of the daily, metabolic heat production of humans, when estimated from typical organ masses (Snyder et al. 1975; Later et al. 2010; Molina and DiMaio 2012a, b, c, d). The organs and tissues most active metabolically, on a mass-specific basis, are the heart (21.3 W kg^{-1}) and kidneys (21.3 W kg^{-1}), but their individual masses are relatively low, so, in combination with the adipose tissue (0.2 W kg^{-1}), bone (0.1 W kg^{-1}) and the other body tissues, they account for only about 25% of our daily heat production (Elia 1992; Gallagher et al. 1998; Heysmfield et al. 2002; Müller et al. 2011). Those basal contributions provide important background information that leads us into exercise.

Metabolic heat production during muscular activity

The energy consumed during muscular work is the most variable component of our overall daily energy expenditure, accounting for as little as 15% in sedentary people, and up to 50% in physically active individuals (Levine 2004). The energy expended during a given physical activity is a function of both exercise intensity and muscular efficiency. At rest, whole-body metabolic rate in a healthy, young adult averages ~ 58 W m^{-2} (Gagge et al. 1941), but it can theoretically increase to > 1400 W m^{-2} in highly trained athletes during maximal exercise (Saltin and Åstrand 1967). However, the total daily energy expenditure is not simply the sum of the exercising and resting metabolic rates, because some of that metabolic cost can be met by diverting energy from

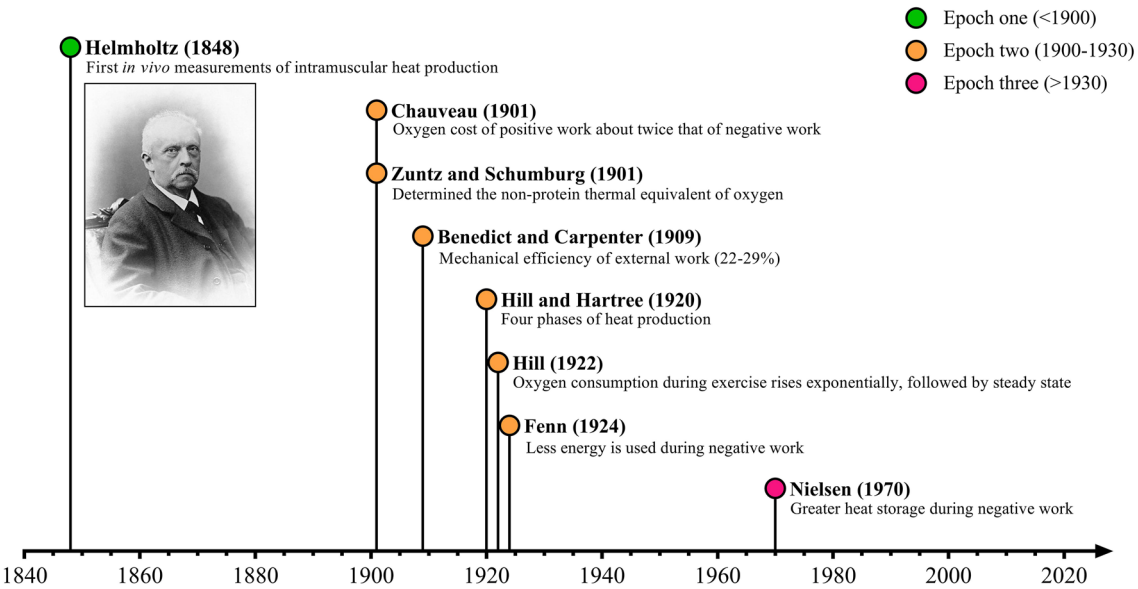


Fig. 9 Timeline of key events in the study of metabolic heat production during exercise; from cellular to whole-body relationships. Portrait of Hermann von Helmholtz (artist: unknown) was obtained from Wikimedia Commons and is in the Public Domain. Source: https://commons.wikimedia.org/wiki/File:Hermann_von_Helmholtz.jpg Accessed: December 22nd, 2022

other purposes, and daily energy expenditure seems to reach a plateau that is independent of the physical-activity level (Pontzer et al. 2016). Nonetheless, even modest exercise intensities (heat production ~ 300 W m^{-2}) can pose a considerable, acute challenge to temperature regulation, especially when work is performed in environments and clothing that reduce heat loss.

The first step in our timeline in Fig. 9 acknowledges the in vivo measurements of heat production during skeletal-muscle activation undertaken by Hermann L.F. Helmholtz (1821–1894, Germany; Helmholtz 1848). A century later, Archibald Hill (England) perfected those temperature measurements, achieving a resolution that contemporary physiologists might find almost inconceivable (10^{-5} °C; Hill 1949). Indeed, the in vitro research completed within the Krogh-Hill epoch provided the essential foundational evidence upon which our contemporary understanding of metabolic heat production in exercising muscle is based.

Research conducted by Hill was instrumental in developing our understanding of intramuscular heat production during the activation and relaxation phases of skeletal-muscle activity (Fletcher and Hopkins 1917; Hill and Hartree 1920; Hill 1965). Hill and Hartree (1920) described four phases of heat production: an initial and very rapid (phosphogenic) heat production, constant (oxidative) heat production during sustained activation, heat produced during muscular relaxation, and its continued production after the muscle had relaxed (oxidative recovery). However, the first convincing evidence of that fourth phase was not published for another 12 years (Hartree 1932), and in that year Hill (1932) described a series of revolutionary steps that changed our understanding of skeletal-muscle energetics. We have limited the following discussion to the thermoregulatory consequences of undertaking work against, and overcoming external forces (positive work), and to the impact of external forces acting on our bodies that produce body movements (negative work).

Metabolic heat production during positive (concentric) work The biochemical processes that occur within the mitochondria (oxidative phosphorylation) enable stored (chemical) energy to be converted into a form (e.g., kinetic energy) that can be used to perform external work. That is, when skeletal muscles are activated concentrically, they develop tension and exert forces against external objects, including water and air. That is positive work, as it results in the transfer of energy from the body to those objects, provided the object in question moves in the direction of the applied force (e.g., pushing a car uphill). In those instances, the external work performed must be subtracted from any measurements of metabolic rate to determine metabolic heat production. The ratio of the external work rate to the metabolic rate is called gross efficiency. If the muscles develop tension against an external force, but that object does not move (static exercise), no physical work is performed, efficiency is zero and all of the metabolic energy appears as heat.

Oxygen plays a vital, yet almost passive, role in those processes, as it is the electron acceptor at the end of the electron transport chain. Indeed, due to the stoichiometric relationship between the rate at which oxygen is consumed and the energy-conversion rate under steady-state conditions, one can determine the rate of energy release using the non-protein respiratory exchange ratio (carbohydrates and lipids; Zuntz 1901; Zuntz and Schumburg 1901; Weir 1949), because the oxidation of those fuels generates a fixed amount of energy, per gram of oxygen consumed. Therefore, the measurement of oxygen consumption became a criterion method for quantifying exercise intensity in the Krogh-Hill epoch, and still is a criterion method for short-term aerobic exercise. As one moves from rest to steady-state exercise, there is an exponential rise in oxygen consumption, followed by the attainment of a steady state. That time-dependent relationship was first described by Hill and Lupton (1922), with the duration of that transition being intensity dependent (Hill 1927). Of course, during all load-bearing activity, oxygen consumption must also be some function of body mass, plus that of any carried load.

Theoretically, gross efficiency cannot exceed 25%, which is dictated by the product of the energy liberated by the breakdown of adenosine triphosphate and the glucose used in its resynthesis (Shephard 1975). However, below that value, gross efficiency can vary greatly, due to variations in both exercise mode and intensity, with the first informative insights into these relationships coming from Francis Benedict and Edward P. Cathcart (1877–1954, Scotland). They used a cycle ergometer (Benedict and Cady 1912) in combination with respirometry (Benedict 1909) to quantify mechanical efficiency at external work rates that ranged from 22 to 29% (Benedict and Carpenter 1909). That work has since been extended to examine the impact of various extraneous factors (Cavagna et al. 1963; Shephard 1975; di Prampero 1986; Böning et al. 2017), with gross efficiency during positive work tending to be lowest during swimming (< 10%; see Part 3 of this series) and highest during cycling (22–25%; di Prampero 1986). Therefore, from the perspective of thermoregulation during exercise, whatever the exercise mode, three-quarters or more of the energy consumed will appear as heat within the body.

Across species, there is consistent evidence that the allometric relationship between metabolic rate and body mass, observed during basal and resting states, is retained during exercise, but now with an elevated scaling exponent (Taylor et al. 1981 [$mass^{0.76–0.79}$; wild and domesticated mammals; U.S.A.]; Bishop 1999 [$mass^{0.88}$; birds and mammals; Wales]; Weibel et al. 2004 [$mass^{0.87}$; mammals; Switzerland]). There

is also human evidence which supports that possibility (Secher et al. 1983 [rowing; Denmark]; Bergh et al. 1991 [running; Sweden]; Nevill et al. 1992 [running; England]; Batterham and Jackson 2003 [running; England]; Markovic et al. 2007 [running; Croatia]; Lolli et al. 2017 [ambulatory and mass-supported exercise; England]). However, due to variations in experimental design, subject selection criteria and differences in exercise mode (supported versus load-bearing), some of that evidence has been inconclusive and unconvincing.

Accordingly, the possibility that the scaling exponent for oxygen consumption might vary across resting, and sub-maximal and maximal ambulatory exercise was recently investigated (Bowes et al. 2021b). Data from 60 men (18–40 years old; 56.0–117.1 kg) showed that the allometric scaling exponent increased significantly from rest (Eq. 5) to maximal exercise (peak aerobic power; Eq. 6). Differences observed between steady-state walking (Eq. 7) and maximal running were not statistically significant. Those observations have established that, across the complete metabolic range (scope) of healthy adults, oxygen consumption (metabolic rate) scales allometrically with body mass. Therefore, when the normalisation of metabolic heat production is required across individuals, one only needs two scaling exponents (rest and exercise). Physiologists unable to measure metabolic rate, but who might wish to model the consequences of variations in metabolic heat production, or to compare heat production across men of widely varying body size, may be able to estimate mass-specific heat production using those equations.

$$\text{Rest}: \dot{V}_{O_2} = 0.023 \times m^{0.57}, \quad (5)$$

$$\text{Maximal exercise (treadmill)}: \dot{V}_{O_2} = 0.160 \times m^{0.75}, \quad (6)$$

$$\text{Horizontal, steady} - \text{state walking } \left(4.8\,\text{km}\,\text{h}^{-1}\right): \dot{V}_{O_2} = 0.023 \times m^{0.87}, \quad (7)$$

where is the $\dot{V}_{O_2}$ is oxygen consumption (L min^{-1}), m is body mass (kg).

Metabolic heat production during negative (eccentric) work Skeletal muscle is lengthened under tension during negative work (e.g., lowering a barbell during arm-flexor exercise), as it exerts force on an external object to control its rate of movement. The muscles are opposing and controlling a moving force, which often is gravity, but no mechanical work is performed on the object, since it does not move in the direction of the force application. Walking, running and skiing downhill generate negative work, as the muscles act to oppose free fall, and the amount of work generated can be calculated from how much work would have to be performed to return the body to its starting position. The energy transferred to the body by the moving external force, or acquired in resisting movement under gravity, appears as heat within the body. So calculations of metabolic heat production require negative work to be added to the measured metabolic rate. That, in turn, results in a negative value for gross efficiency, with values falling below − 50% during downhill walking and − 70% during eccentric cycling (Pimental et al. 1982).

Investigators became interested in the energetics of negative work early during the Krogh-Hill epoch. It is likely that interest commenced with Jean-Baptiste Chauveau (1827–1917, France), who demonstrated that the oxygen consumption for positive work on a motor-driven treadmill was approximately twice that for an equal amount of negative work (Chauveau 1901). Wallace Fenn (1893–1971), who was the first American scientist to work with Archibald Hill (Rahn 1979), subsequently examined (in vitro) the metabolic demands of all three modes of skeletal muscle activation (concentric, eccentric, isometric), discovering what is now known as the "*negative Fenn effect*". That is, when work is performed on the muscle, resulting in its lengthening, less metabolic energy is used, compared with that used in an isometric activation (Fenn 1924).

Another of Hill's students extended that work with a simple, yet elegant, experiment in which two cycle ergometers were placed back-to-back, and connected with a single chain (Abbott et al. 1952). One subject pedalled forwards (positive work) whilst the other resisted, and was driven in reverse (negative work), but both exerted equivalent force on the pedals. About 3.7 times more oxygen was consumed during positive work, with the magnitude of that difference increasing at higher cadences. Those observations were confirmed by Asmussen (1953), and were then extended to other exercise modes (Kamon 1970; Davies and Barnes 1972; Bonde-Petersen et al. 1973). The underlying mechanism was related to a reduction in the number of motor units required to perform the same work during eccentric work (di Prampero 1981; Perrey et al. 2001; Douglas et al. 2017). Such work is accompanied by marked reductions in both heart rate and cardiac output (Dufour et al. 2004). Consequently, it has taken on a therapeutic role for exercise in individuals with limited cardiorespiratory reserve (Camillo et al. 2015; Lindstedt 2016; Mitchell et al. 2017).

Given that physical work is performed on the muscle during eccentric (negative) work, rather than by the muscle, the rate of metabolic heat production is higher than during positive work, when both are performed at same absolute oxygen consumption. The consequence, as demonstrated by Nielsen and Davies (1976, Denmark and England), is a greater heat storage during negative work, which translates to a more pronounced elevation in body temperature and thermoeffector activation (Nielsen 1970; Davies 1979). That

research was extended by Nielsen et al. (1972), who, perhaps unsurprisingly, showed that the higher metabolic heat production associated with negative work at a given oxygen consumption lowered the maximum environmental temperature at which a steady-state body temperature could be achieved. Since both positive and negative work at the same oxygen consumption demanded similar cardiac outputs, but negative work was associated with higher cutaneous blood flows for heat loss, they concluded that a lower blood flow was available for splanchnic perfusion during negative work, in much the same way that Rowell (1977) had hypothesised the competition for blood between skin and muscle during exercise in the heat; a theory no longer universally supported (Hales 1996; Kenney et al. 2014).

The redistribution of metabolic heat

Skeletal muscle metabolism continues, albeit at a much reduced rate, when the muscles are inactive. In that state, muscles behave as sinks for heat produced by the metabolically more active organs (e.g., brain and liver; González-Alonso 2012). That situation reverses dramatically when the muscles become active, whether through purposeful activity or when shivering, with the former sometimes generating sufficient heat to denature intramuscular proteins (Ritchie et al. 1994), if it is not removed. That heat can be dissipated in sufficient quantities only through the skin, but that requires a transport network with an extraordinary topographical distribution and fluid mechanics so that heat can rapidly be delivered, via a convective (mass-flow) mechanism, to the cutaneous tissues.

The rate that heat is transported from the muscle to the skin is reflected in its thermal conductance; the ratio of metabolic heat production rate to the temperature gradient between those sites. Since muscle temperatures are infrequently measured, a deep-body temperature is commonly used as a surrogate index, but since those tissue temperatures will be lower than active muscle temperatures, and since not all metabolic heat is produced in the muscles, those calculations yield imprecise estimates of thermal conductance. Moreover, time delays between changes in muscle temperature and the deep-body surrogate will render those calculations invalid during dynamic exercise states, even when the rapidly responding oesophageal temperature is used (Fig. 2).

Thermal conductance is a property of the whole body, and is not the same as thermal conductivity, which is a property of tissues themselves, and defines how fast heat moves through a specific thickness of each tissue. Thermal conductance, on the other hand, is not influenced by the length of the path between the site of heat generation and the skin, but is linked to variations in regional blood flow. Both conductivity and conductance are important, because not all muscle heat is transported to the skin through the blood. Indeed, there exist parallel paths of tissue conduction and vascular convection for moving heat, with the vascular route capable of moving heat much more quickly, so differences in tissue perfusion can affect the validity of surrogate indices of either muscle or deep-body temperature (Taylor et al. 2014a). Even when active transport is in full operation, the last element in the path from the muscle to the skin surface may be under-perfused, or not perfused at all, so heat then has to be conducted (diffused) across that final layer. That element can be as thin as the thickness of the epidermal *stratum corneum* (typically < 0.02 mm), but can be much thicker, especially in cold environments, in which the body has a distinct, well-perfused core and a poorly-perfused shell (Aschoff and Wever 1958).

According to the physiologist of Mount Everest fame, L. Griffith Pugh (1909–1994, England; Milton 2022), the thermal conductivity of peripheral tissues was first measured satisfactorily by Henry Bordier (1863–1942, France; Hatfield and Pugh 1951; Candas and Libert 2022), who used beef tissues (Bordier 1898). Very soon thereafter, Jules Lefèvre (1863–1944, France) repeated those measurements using living tissues (himself) during water immersion at temperatures from 5° to 30 °C (Lefèvre 1901). Half a century later, Pugh and Henry Hatfield, found muscle to conduct heat nearly twice as quickly as fat (Hatfield and Pugh 1951), as did Bordier (1898). Hatfield and Pugh (1951) considered the results of Hardy and Soderstrom (1938) on beef tissue, which are cited widely, to be incorrect, because that muscle tissue had decayed. Indeed, those erroneous data were used to deny the reality that adipose tissue provided greater thermal insulation than did muscle. Hatfield and Pugh (1951) used human fat and muscle tissues obtained from recently deceased individuals (*post mortem* specimens), and derived the thermal conductivity of human fat as 0.17 W m^{-1} $°C^{-1}$. For human skeletal muscle, conductivity was 0.38 W m^{-1} $°C^{-1}$, and that difference has a significant physiological impact during cold-water exercise. Thus, the thermal conductivity of human adipose tissue is similar to that of dry wood (Suleiman et al. 1999). Nevertheless, the heat-generating organs of the body are surrounded by an excellent thermal insulator. Were it not so, humans would not be able to survive for > 10 h in 17 °C water (Xu and Giesbrecht 2018; also see: Golden and Tipton 2002).

Though thermal insulation is valuable for protection in the cold, it is potentially disastrous during exercise in the heat. Some heat continues to be conducted away from the working muscles through the skin, as they are hotter than the skin (Clark et al. 1977; Formenti et al. 2013; González-Alonso 2012; Fig. 10), but we must rely on perhaps the oldest of all thermoregulatory structures (blood vessels) to transport heat rapidly away from the muscles, bypassing those insulating tissues. Many species evolved with vascular networks (Monahan-Earley et al. 2013), which are used to

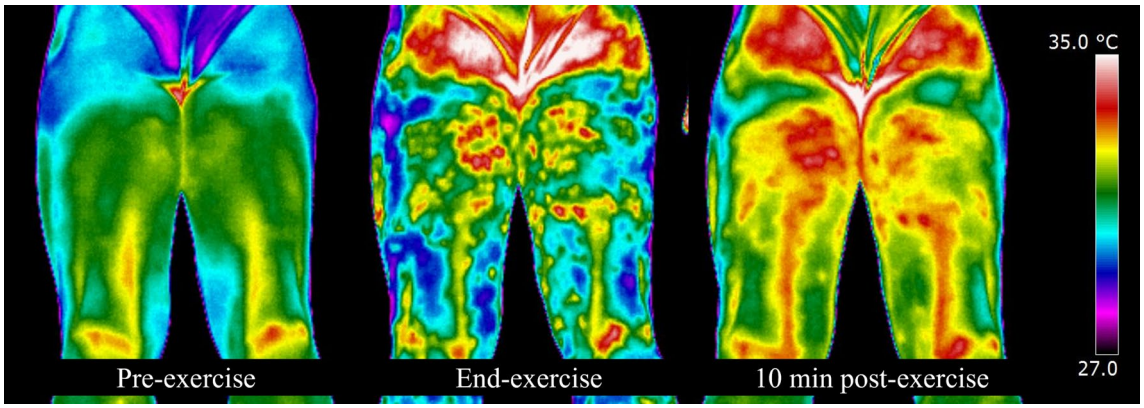


Fig. 10 Skin temperatures from the posterior thigh and buttocks of a male subject, measured using a thermal-imaging camera (FLIR E-60, Flir Systems Inc., Wilsonville, OR, USA) before exercise (rest), immediately following 45 min cycling (138 W) and 10 min after exercise finished. Cycling and photography were performed in an air-conditioned laboratory. Images are unpublished observations provided by, and reproduced with permission from, Jose I. Priego-Quesada (Department of Physical Education and Sports, University of Valencia, Spain), who retains the copyright

deliver, redistribute and remove respiratory gases, nutrients, water, thermal energy and metabolic wastes. Those networks also serve as a means for systemic communication (e.g., endocrine hormones).

As a consequence of those widely variable, forced convection currents, the thermal energy content, and therefore tissue temperatures, of the body are not homogeneous. If that were not so, there would be convective heat flow, but no convective heat transfer from warmer to cooler structures (*Second Law of Thermodynamics*); thermal energy would just be re-circulated. Instead, our bodies have heat sources and heat sinks, and our thermal heterogeneity has implications when a temperature measured at one site is used as a surrogate for the temperature at another site ("The validity of temperature measurement: the Zeroth Law of Thermodynamics").

During exercise, our vascular networks need to transport heat to the skin surface, for either dry or evaporative dissipation. That delivery increases the skin temperature, and reduces the temperature gradient between the muscles and skin, which would reduce heat dissipation, were it not for the fact that the convective transport of heat vastly exceeds (passive) thermal conductance through the tissues, for the same temperature difference between those sites. Thus, reductions in the deep-body to skin temperature gradient may provide a qualitative indicator of peripheral vasodilatation (Hetem et al. 2008 [free-living antelope]), as might the longitudinal temperature gradient along the surface of human forearms (House and Tipton 2002). Whilst those indices are easier to measure than blood flow, such estimations of vasomotor activity require cautious interpretation.

Increases in cutaneous blood flow are first brought about by the removal of sympathetic constrictor tone, and then through active vasodilatation. Where does that extra blood come from? There are three possibilities, they are not mutually exclusive and how they are invoked is critical to the regulation of mean arterial pressure (Table 1). Blood can be diverted (redistributed) away from other tissues, the cardiac output can increase to circulate the available blood faster or the blood volume can increase. Increases in both the cardiac output and blood volume occur without penalty to other tissues, but the diversion of blood away from heat-source tissues can penalise those tissues, sometimes pathologically.

When the sympathetic nervous system dilates peripheral blood vessels during exercise or heat exposure, it simultaneously constricts the arterioles of the gastrointestinal tract, liver, spleen and pancreas (splanchnic blood vessels; Rowell et al. 1968; Perko et al. 1998). That differential sympathetic responsiveness was first recognised by scientists from the Max Planck Institute (Germany; Kullmann et al. 1970; Walther et al. 1970; Simon et al. 2022), and the resulting gut ischaemia can have significant pathological outcomes (Ter Steege and Kolkman 2012). For instance, the gut mucosa may well be the tissue most vulnerable to thermal damage (Braasch 1964), and the leakage of endotoxins, or even micro-organisms, from the gut into the blood is common, especially after sustained heavy exercise in the heat, when blood supply can also be reduced by hypohydration. Indeed, 81% of exhausted runners at the end of one Comrades Marathon (South Africa) exhibited endotoxaemia (Brock-Utne et al. 1988), and both endotoxaemia and septicaemia of gut origin participate significantly in exertional heat stroke (Part 3 of this historical series).

In the next Section, we introduce radiative, convective and evaporative heat exchanges, and examine the historical evidence that revealed those processes.

Convective, radiative and evaporative heat exchanges: in the service of Fourier

Cyclists, as well as athletes in water sports for which competitors are not restricted to lanes, will know how to take advantage of competitors who are prepared to work at the front. Whether the fluid is water or air, working at the front means pushing fluid away and opening an apparent hole, and then dragging some of that fluid along, presumably with opponents in the slipstream or sitting on the wash. If we examined the movement of the fluid in contact with cyclists and watercraft, we would notice that some fluid is travelling in roughly parallel lines (laminar flow), whilst other parts are swirling (turbulent flow). Turbulent flow increases drag, but it facilitates heat loss for the athlete, and it is Reynolds' number that determines whether fluid travelling across a surface will have laminar, at lower air velocities, or turbulent characteristics.

Although that concept originated from the work of George Stokes (1819–1903, Ireland; Ranford 2020), we associate it with another Irish-borne physicist, Osborne Reynolds (1842–1912; Jackson 1995a, b), who described laminar and "*sinuous*" (turbulent) flow around objects (Reynolds 1883). By the early twentieth century, three Germans, Ludwig Prandtl (1875–1953), Wilhelm Nusselt (1882–1957) and Franz Grashof (1826–1893), described how near-stationary (thermal boundary) layers form in the air and water at the surfaces of all stationary, solid objects that differ in temperature from the fluid in which they were immersed (Prandtl 1905). They then related the thermally induced movement of those fluid layers, convective heat flux (W m^{-2}), to the physical properties of the fluid; "flux" is the term for heat flow expressed per unit surface area and the SI units have an area-specific form (e.g., W m^{-2} or W m^{-2} K^{-1}).

Towards the end of the nineteenth century, Jožef Stefan (1835–1893, Slovenia), and his student, Ludwig E. Boltzmann (1844–1906, Austria), published their law relating to the rate at which thermal energy (Stefan 1879), in the form of electromagnetic radiation, is emitted from surfaces (radiant heat flux; W m^{-2}). That heat flux is related to the fourth power of the absolute temperature (K) of the object. Anders Ångström (Sweden) knew enough about radiative, convective and evaporative heat flux to write about measuring heat radiation, and the problems of evaporation and convection from lakes (Ångström 1920). In 1922, Warren K. Lewis (1882–1975, U.S.A.) drew attention to the analogy between heat and mass transfer across thermal boundary layers, which set constraints on evaporative heat flux coefficients (Lewis 1922). That is, there is an inflexible link between evaporative and convective heat flux, resulting from the laws of physics. Those constraints were either ignored by, or remained unknown to, many thermal physiologists of the modern epoch (Mitchell 1974a). Indeed, given the wealth of knowledge about heat transfer by the end of the Krogh-Hill epoch, it is surprising that no one of that era seems to have attempted to quantify the rates of human heat exchange via its convective, radiative and evaporative avenues. However, some scholars of the nineteenth century were aware of the need to do so (Sarrus and Rameaux 1838–1839; Candas and Libert 2022).

Our forebears from the first two epochs would have known that heat exchanges with the environment would have conformed to physical principles that relate heat flux to gradients that dictated both heat or mass transfer. Indeed, that principle, which was a development from *Newton's Law of Cooling* (Isaac Newton, 1643–1727, England; Newton, 1770), had been established by Joseph Fourier (Fourier 1807). However, there was a barrier to writing those equations, because thermal physiologists had not yet measured human radiant and convective heat fluxes, even though engineers of the day were routinely making such measurements. Before the end of the nineteenth century, and without making the necessary measurements, Max Rübner estimated the contribution of sensible heat loss (radiation plus convection combined) to human heat loss (Rübner 1896); sensible heat loss is associated with measurable changes in temperature whilst latent heat loss occurs during phase changes and without the temperature of the water molecules changing. Rübner "*was a genius who could draw correct conclusions from inaccurate and incomplete data whereas most of us draw incorrect or incomplete conclusions from data that are accurate*" (DuBois 1939 [P. 149]).

Early in the twentieth Century, Jules Lefèvre (Candas and Libert 2022) confirmed that human sensible heat loss increased with wind speed (Lefèvre 1911). Towards the end of the Krogh-Hill epoch, L.B. Aldrich (1885–1965, U.S.A.) measured the radiant heat exchange of children in classrooms (Aldrich 1928), although Kuehn and colleagues (1970) described those measurements as "*crude*". Better, but still only approximate, measurements of radiant heat exchange were made on adults in Germany by Bohnenkamp and Ernst (1931).

In the sub-sections that follow, we do not intend to present all that is known today about rates of heat exchange with the environment. Instead, Fig. 11 contains a summary of the key steps concerning the historical development of those principles. We will seek to dispel some misconceptions that confound the views of some concerning thermoregulation during exercise, like the fallacies that damp air is heavy, and that sweat cannot be evaporated into air with 100% relative humidity.

Convective heat exchange In theory, measurements of radiant and convective heat exchanges are physical measurements, but the first such measurements for humans were

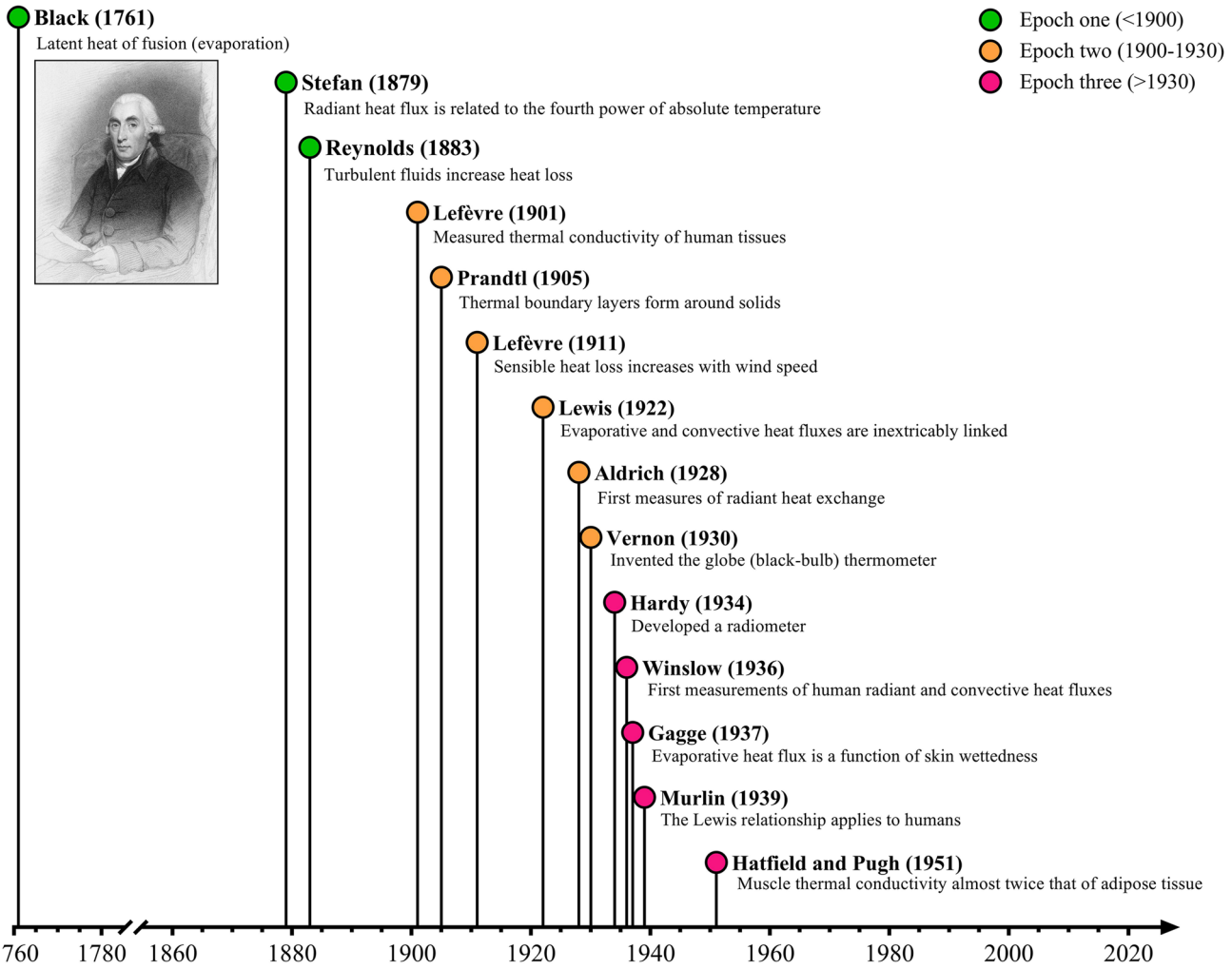


Fig. 11 Steps in the historical development of our understanding of heat exchange during exercise. Portrait of Joseph Black (artist: J. Rogers) was obtained from Wikimedia Commons and is in the Public Domain. Source: https://commons.wikimedia.org/wiki/File:Joseph_Black_b1728.jpg Accessed: December 22nd, 2022

based on physiological experiments, and relied upon several physiological assumptions. The first measurements of radiant and convective heat fluxes were based on the principle of partitional calorimetry, a principle usually attributed to Charles-Edward Winslow (1877–1957, U.S.A.; Winslow et al. 1936a; Blatteis and Schneider 2022), which followed the research of Houghten et al. (1929), who had developed the effective temperature index (Houghten and Yagloglou 1923). In partitional calorimetry, the measurable components of the overall energy exchanges are quantified, with the rate of sensible heat exchange then calculated as the difference.

By that time, resting and exercising metabolic rates could be measured accurately from respiratory gas exchanges. Cutaneous and respiratory water-loss rates could also be quantified from body-mass changes, but calculating evaporative heat loss required the rather dubious assumption that all of that sweat actually evaporated from the body surfaces. The calculation of sensible heat exchange by difference requires the body to be in a thermal equilibrium (steady state). That requirement seems to have been satisfied somewhat infrequently in the modern epoch, and not just within studies involving partitional calorimetry. In Houghten's experiments, equilibria were evaluated from the stability of rectal temperature; another dubious practice (Fig. 2, tissue temperature A). They produced data concerning heat transfer at different dry-bulb temperatures, relative humidities and wind speeds, but with some peculiar outcomes. For example, sensible heat loss increased with wind speed at low dry-bulb temperatures, but not at dry-bulb temperatures > 21 °C (Houghten et al. 1929 [Fig. 14]).

It was only later that researchers were able to distinguish between radiant and convective heat flux rates when using partitional calorimetry. That separation relied on a portable,

infrared thermometer to measure radiant heat flux, which was developed by Jim Hardy (1904–1985, U.S.A.; Hardy 1934a). With radiation measured independently, the only avenue of heat transfer that still required determination by difference was the rate of convective heat flux, but that still relied upon doubtful physiological assumptions (DuBois 1939). Hardy's partitional calorimetry was carried out in the human calorimeter of the Russell Sage Institute of Pathology (U.S.A.), in almost still air (Hardy et al. 1938a). He later imposed forced air currents using fans in the calorimeter (Hardy et al. 1938b), but did not analyse how the rate of convective heat flux varied with wind speed.

Convective heat flux involves heat exchanges with moving fluids, resulting from the creation of kinetic-energy gradients within the molecules of that fluid. The driving force for heat flux is the temperature gradient between the skin and the dry-bulb air temperatures, with thermal energy travelling down that gradient, regardless of which site is warmer. The product of that temperature difference and the convective heat flux coefficient provides a measure of convective heat flux.

Winslow and his colleagues analysed how the convective heat flux coefficient varied with wind speed for men sitting or semi-reclining (naked and clothed) in an air-conditioned chamber (Winslow et al. 1936b, 1939). Airflow was imposed using fans, so it was turbulent and the direction was variable. Winslow's team concluded that the convective heat flux coefficient was non-linearly dependent on air flow (wind speed [v]; $v^{0.6}$). Doubling convective heat flux requires an increase of wind speed of more than three-fold. Others have used the square-root relationship ($v^{0.5}$).

Whichever exponent is used, it also has to apply, inversely to the dimension of the body from which convective heat flux is occurring; the narrowest dimension perpendicular to the wind direction (Mitchell et al. 2018). The narrower the body, the greater is the convective heat flux coefficient. The same rule applies to different body parts, so the heat flux coefficient is much higher for the fingers than for the trunk (de Dear et al. 1997). In the case of a cylinder, to which the overall human shape approximates, the relevant dimension is its diameter (D), and convective heat flux is proportional to the ratio of the wind speed to the cylinder diameter, with an exponent of positive 0.6. Since that diameter is the same for wind blowing perpendicular and parallel to the long axis of the body, heat flux ought to be the same in both cases.

Exponents > 1.5 reported for the convective heat flux of a thermal manikin (Wyon 1989), which resembled an average Scandinavian female, under downward flow from ceiling fans (Kurazumi et al. 2014), seem to be beyond the possible range (Whillier and Mitchell 1968). For a cylinder, the coefficient should be the same for wind blowing from the front or the side, but the human torso is more oblong in shape. Thus, when measurements were taken from a manikin, they revealed a 20% lower coefficient for wind from the side (Xu et al. 2021), which is more or less consistent with differences in the human torso, when viewed from the coronal (frontal) and sagittal (lateral) planes.

The wind speed that determines convective heat flux is the speed of the fluid immediately surrounding the body surface. In the laboratory, that movement is induced by fans and pumps. In the natural environment, it is the prevailing wind, and during exercise, it is the relative wind speed produced by body movements (Givoni and Goldman 1972). That wind can have exercise-specific effects, because it depends upon how the body moves.

A champion marathon runner will generate air movement very similar to that produced by a headwind > 5 m s^{-1}, which is > 100 times higher than the flows in Winslow's chamber. During racquet sports, the body movements result in predominantly turbulent flow over the arms. Experiments with a manikin moving in different directions on a rail have indicated the strong effects of arm movements on convective heat flux (Luo et al. 2014). Only in very few forms of exercise with non-uniform movement has the effect of body movement on the rate of convective heat flux been determined, but those studies have illustrated the complexity of the problem. For example, box stepping in a wind tunnel with imposed flows between 0.5 and 3.5 m s^{-1}, added a further 0.4 m s^{-1} to the overall air flow at 12 steps min^{-1}, and 0.8 m s^{-1} at 24 steps min^{-1} (Galimidi et al. 1979).

Measurements of relative wind speed during box stepping were made in a calorimetric wind tunnel (Mitchell and Laburn 2022). It was in that apparatus that the first direct measurements of the human convective heat flux coefficient were made, as engineers would make them. Those measurements required no assumptions about heat balance, and the instrument designed for that purpose measured the minute changes in air (dry-bulb) temperature that occurred in the wind blowing over the subject, who sat on an upright cycle ergometer (Carroll and Visser 1966; South Africa). For naked men exposed to wind speeds between 0.5 and 5.0 m s^{-1}, the heat flux coefficient was 8.32 W m^{-2} K^{-1}, with convective heat flux then calculated ($8.32.\{v.\text{air pressure}/760\}^{0.6}.\{\text{skin-air temperature}\}$; air pressure is in mmHg; Mitchell et al. 1969; Mitchell and Whillier 1971).

Air pressure appears in the equation because wind speed is not the only environmental variable that affects convection. Many properties of air do so, and especially air density (Mitchell 1974b). Convective flux is proportional to air density because density determines the number of particles per litre of air that might come into contact with the body. Since pressure density is proportional to air pressure, then convective heat flux changes as pressure changes with altitude. Thus, climbers at the top of Mount Everest lose heat to the cold air via convective flow at only about 40% of the

rate that they would at sea level in equally-cold air with the same wind speed.

Another factor that affects air density is its water vapour content, which is temperature dependent. We are amused by cricket commentators who inform audiences that the cricket ball swings (moves laterally) much more on overcast days because damp air is so "*heavy*" (dense). The ball may swing more, but humid air is neither heavier nor denser, as water molecules are lighter than both the oxygen and nitrogen molecules they displace; it is actually less dense than dry air. The more humid the air, the lower is the convective heat flux coefficient.

Since the driving force for convective heat flux is the temperature gradient, we need to know where to measure those temperatures. The ambient air is one site, and the skin surface is the other. However, we can use skin temperature only in naked or near-naked people. For clothed people, it is the clothing-surface temperature that is important. Clothing and posture also affect the area available for convective heat flux. Even in naked people, the area available for convection is only 94% of the total body area in a standing position, because non-ventilated areas exist (e.g., armpits), and 86% when seated (Kurazumi et al. 2014). Clothing adds considerably to that surface area, and far more than one might expect. How much it adds can be measured accurately (Halliday and Hugo 1963). For example, wearing a tracksuit added 41% to the body-surface area (Mitchell and van Rensburg 1973). More typically, clothing area is estimated from the clothing insulation (McCullough et al. 1985; Holmér et al. 1999).

Back to Reynolds. As a general principle, lower air velocities across naked or clothed skin are associated with laminar airflow (lower Reynolds' number). If we could see the molecules moving, they would appear layered, with gradually lower flows as those layers get closer to the body surface. At higher flows, a turbulent pattern would develop, with wind speed and direction varying unpredictably across the flow profile. The transition from laminar to turbulent flow occurs at a flow-boundary layer; our second boundary layer. Turbulent flow is both a friend and foe, since it increases both convective heat flux (when the air is cooler than the skin) and wind resistance (drag). Both flow types are examples of forced convection and both are relevant to athletes. When measured on a thermal manikin, the convective heat flux coefficient was up to 30% higher during turbulent than during laminar flow at the same wind speed (Yu et al. 2020). However, there is another form of airflow across the body surface that occurs in the absence of either wind or body movements.

Every heat-producing object transfers thermal energy to cooler surrounding fluids, thereby creating thermal boundary layers adjacent to its outer surface. The same occurs for objects that are cooler than their surroundings, but the direction of heat flow is reversed. The density of the fluid in those boundary layers changes inversely with temperature, relative to that of more-distant fluid. That causes the boundary layers to rise, or fall, as the boundary fluid gains heat from, or loses heat to, the object that it surrounds (Mitchell 1974b). This form of convection is known as buoyancy, free convection or natural convection.

For humans, natural convection becomes an important component of convective heat flux at forced wind speeds < 0.5 m s^{-1} (Mitchell et al. 1969). In fact, the convective heat flux coefficient observed when standing in wind moving at 0.2 m s^{-1}, with a 5 °C gradient between the body surface and the air (dry-bulb), is almost equivalent to that observed when standing in a 0.3 m s^{-1} wind with a 20 °C difference (Whillier and Mitchell 1968 [Fig. 2]). Nevertheless, natural convection contributes minimally to convective heat exchange in still air, relative to forced convection induced by pedalling, walking or running in still air (Nag 1984).

If changes in air density induce changes in the convective heat flux coefficient, the change in density between water and air should have a much bigger effect, and it does. For near-naked men in water flowing parallel to the long axis of their bodies, as if they were swimming, Boutelier et al. (1977) determined that the convective heat flux was $273.v^{0.5}$ W m^{-2} K^{-1}. So, Michael Phelps (U.S.A.), swimming at his top speed (2.7 m s^{-1}) would have a convective heat flux in water of 450 W m^{-2} K^{-1}, which is 35 times higher than in air at the same speed (13 W m^{-2} K^{-1}). Indeed, the convective heat flux is so high in water that it is impossible to sustain a temperature difference > 1 °C between the skin and the water, even in still water at tolerable temperatures (Boutelier et al. 1977). Thus, skin temperatures rapidly equilibrate with the prevailing water temperature (Rapp 1971).

Humans are not equipped thermally to spend extended periods in water. Thus, attempting to swim to safety in cold water can be lethal (Keatinge 1978; Golden and Tipton 2002), because the extra metabolic heat production of swimming (Schmidt-Nielsen 1972; di Prampero et al. 1974) might not match the extra convective heat lost by movements through the water. Nevertheless, depending upon water temperature, and the morphology and body composition of the swimmer, thermal homeostasis might be achievable (Pugh and Edholm 1955; Keatinge 1960; Golden et al. 1980; Golden and Tipton 1987; Sagawa et al. 1988).

Radiative heat exchange By far the most important avenue of heat transfer, when outside in hot weather, is solar radiation (Mitchell et al. 2018). Therefore, from a physiological perspective, it makes no sense for weather forecasters to tell outdoor workers and athletes what tomorrow's air tempera-

ture will be, when the weather is going to be hot on a cloudless day, although dry-bulb air temperatures still determine convective heat flux. For instance, the dry-bulb temperature required for a naked human to gain heat by convection at the same maximum rate as that gained from direct solar radiation on a cloudless summer day, with a wind speed of 1 m s^{-1}, would be 103 °C (Mitchell et al. 2018). Consequently, in cold weather, solar radiation can off-set the effects of cold air, so going shirtless at the polar-ice caps is not always foolhardy. Although statistically, the dry-bulb air temperature and radiant load are associated (hot days without sunshine are rare), there is no rigorous relationship between that air temperature and the radiant heat load.

Meteorological services do report atmospheric radiant heat flux, but we have no intuitive way of translating those numbers into something that is physiologically meaningful. Since the invention of the globe (black-bulb) thermometer by Horace M. Vernon (1870–1951, England; Vernon 1930, 1932), there has been a simple, cheap and convenient way of measuring environmental radiation, and generating a number (temperature) to which we can relate. Unfortunately, it is seldom that meteorological services measure globe temperature, and it does not feature in weather forecasts. In the third paper of this historical series, we will expand upon the generation of numbers for quantifying thermal stress (environmental impact) and thermal strain (physiological consequences).

Solar radiation may penetrate indoor workplaces, but there are many other potential sources of radiant heat. For example, rock temperatures in deep mines can be > 60 °C, steel-industry blast furnaces operate around 1500 °C (steel is tempered between 200° and 600 °C) and flashover fires produce overhead temperatures of ~ 500 °C (Morrison et al. 1966; Peacock et al. 1999; Rawlins and Phillips 2001). Conversely, homes and offices do not usually have strong sources of radiation, and within those locations, we are unaware of whether we are responding to radiant or convective heat flux.

The transfer of radiant heat (electromagnetic radiation) is identical energetically to the transmission of light; both are conveyed by photons. Radiant heat flux from any surface, including our skin, is a function of the fourth power of its absolute surface temperature (K; Stefan 1879), as well as an optical property of that surface, which defines its efficiency as a radiator. That property is known as its emissivity (range 0–1), and it depends on properties of the surface, but much more on the wavelength of the radiation. Because of that fourth-power relationship, a surface at 40 °C does not emit double the radiant heat as that same surface at 20 °C, but only 30% more.

Radiation emitted by humans is in the infrared waveband, as is radiation emitted by our typical indoor and outdoor surroundings. More than half of the energy from direct solar radiation is also in that waveband (Stuart-Fox et al. 2017). In that waveband, our bodies (naked or clothed), and almost all surrounding surfaces, have an emissivity > 0.95, so they behave as nearly perfect radiators, and absorb nearly all the infrared radiation falling on them. It is only for residual solar radiation (direct or reflected) that emissivity varies with visible colour, and can drop below 0.95. Wearing light-coloured clothing when exercising outdoors reduces the solar radiant heat load, but wearing white clothing certainly does not prevent solar radiation reaching the body surface (Clark and Cena 1978; Havenith and Wang 2005; Kuklane et al. 2006). For instance, the average changes in resting skin temperature were 13% and 12% lower when wearing white clothing compared to the business-as-usual clothing used agriculture and construction, respectively (Ioannou et al. 2021). Furthermore, variations in skin colour have no meaningful impact upon unclothed, radiant heat absorption (Eijkman 1895; Mitchell et al. 1967).

All forms of heat flow, including radiant heat, are gradient dependent, and travel from hotter to cooler objects, and that includes the skin. Like the convecting skin-surface area, the radiating surface area is less than our whole-body surface area, and that difference can be quite large, because several body surfaces at the same temperature face each other (e.g., chest and upper arms, medial thighs surfaces). Those sites do not participate in radiant heat exchange with the environment (van Graan 1969; Kurazumi et al. 2008b). The radiating surface area is highest in the spread-eagle posture, where it can approximate 95% of the total surface area (van Graan and Wyndham 1964). In environments for which the dry-bulb temperature and mean radiant temperature are similar (most indoor environments), and convection is in the natural domain, radiant heat exchange will exceed convective heat exchange in resting people, but not when they are exercising, because of the relative air movement induced by exercise.

Calculating radiant heat exchange under solar radiation is a formidable task. Nonetheless, to fulfil the needs of the photovoltaic energy industry, solar radiant heat flux has been measured very precisely, and can be predicted down to the microclimate level, almost anywhere on earth, at any time, and with adjustments for cloud and dust cover (Kearney and Porter 2017). So the formidable task is not determining the direct solar flux, but determining how much thermal energy is absorbed by the human body.

The first problem relates to the complexity of the radiant environment (Fig. 12). It is a false analogy to think of the sun shining on an exercising person outdoors as if that individual was standing in the beam of a searchlight. Direct radiation from the sun indeed forms a component of the radiant load, but there is solar radiation scattered in the atmosphere, and reflected towards us from the clouds, the ground and our immediate surroundings. There is also infrared radiation from all hotter, surrounding objects, including the ground. There can be diffuse radiation from the atmosphere itself,

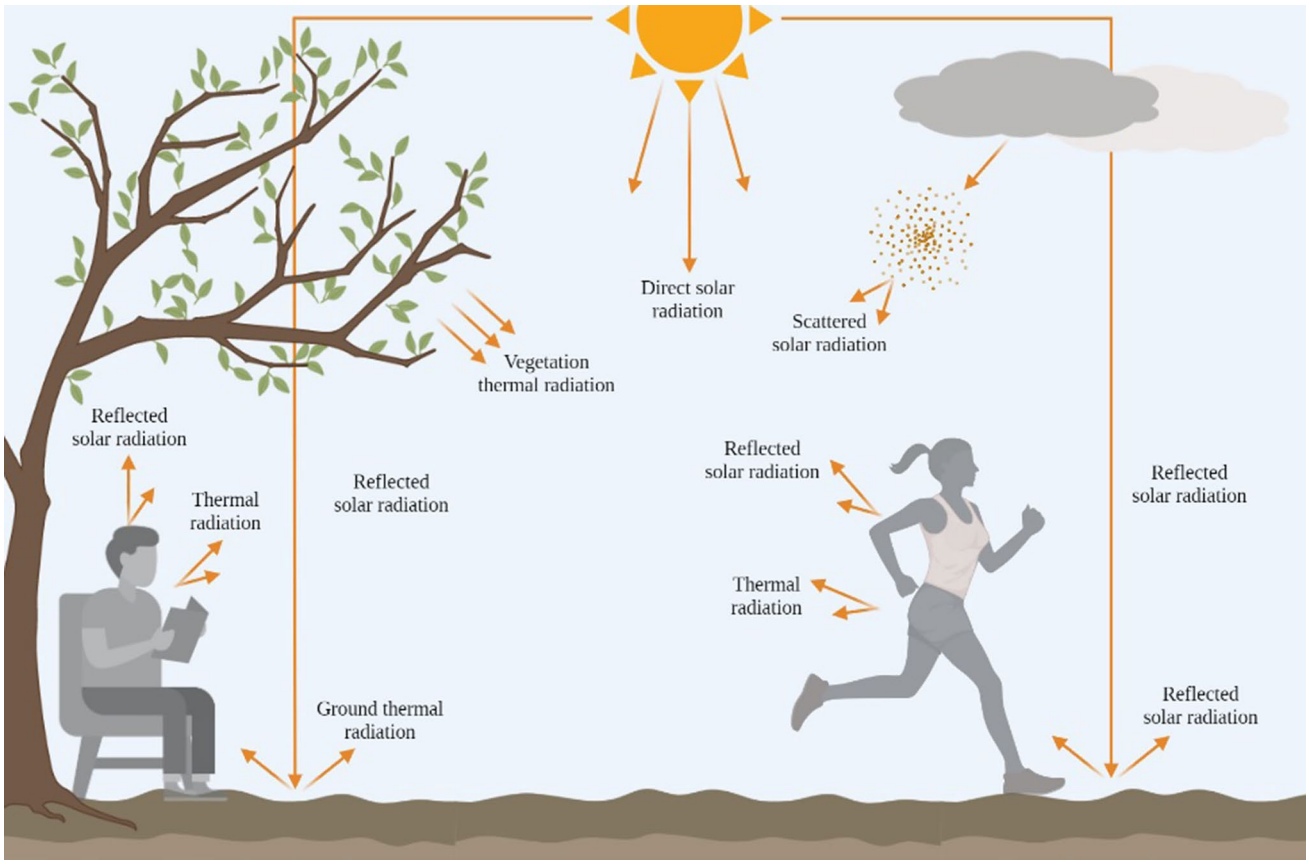


Fig. 12 The many routes by which solar radiation can have a thermal impact upon the body. Modified from Mitchell et al. (2018)

but the atmosphere is more important as a radiation sink at night (e.g., cloudless desert nights), when the night sky behaves like a perfectly absorbing surface at a temperature of about − 30 °C (Swinbank 1963). Indeed, it provides an important route for the dissipation of metabolic heat during nocturnal exercise. As a consequence of those sources of radiation, exercising in the shade does not mean that it occurs without a radiant heat load (Fig. 12).

Calculating the impact of direct solar radiation is not straightforward, because the proportion of the incident radiant heat intercepted by an exercising person depends not just on the sun's position, but on posture, as is evident from changes in the surface area of one's shadow throughout the day. Deriving that proportion was a task that was addressed on both sides of the Atlantic half a century ago. Underwood and Ward (1966, England) used a photographic method, whilst Roller and Goldman (1968, U.S.A.) used a geometric method.

Those, and several other methods, for calculating radiant load were evaluated according to the degree to which the calculated load correlated with the skin temperature of clothed, standing volunteers facing North, in summer in North-East Poland (Blazejczyk et al. 1993). The U.S. approach fared well, as did an approach by Budyko (1959, 1974; Russia). The best correlations, however, were with mean radiant temperature, measured by a complex procedure first advanced by Povl O. Fanger (1934–2006, Denmark; Fanger 1970), and modified for outdoor conditions by Jendritzky (1990, Germany). Given how complex the radiant environment is outdoors, we doubt the value of trying to use predictive equations to calculate radiant load, and believe the best approach is to measure mean radiant temperature, in real time and on site. That requires no complex procedures, just a globe thermometer, as first used during the Krogh-Hill epoch (Vernon 1930, 1932; Bedford and Warner 1934; Kuehn et al. 1970), and a knowledge of dry-bulb temperature and wind speed at that globe temperature. For retrospective analyses, but also for data applicable to test days, one could use meteorological data, although field work is infrequently undertaken in close proximity to local weather stations.

Evaporative heat exchange Another double-edged sword encountered by occupational and recreational athletes, comes in the form of evaporative heat dissipation, which, if lost water is not replenished, will lead to progressive hypohydration whilst simultaneously affecting other regulated

variables (Table 1). Evaporative heat flux plays a multifaceted, special role in thermoregulation during exercise. Not only is it the only route of heat loss available for dissipating metabolic heat during circumstances in which convection and radiation impose external thermal loads on the body, but it takes advantage of a thermally insensible heat-loss mechanism; the phase change of water into vapour, without altering the temperature of the water molecules. In so doing, it gives humans (*Homo sudomotor*) an extraordinary capacity to dissipate heat.

Unfortunately, the physics of evaporative cooling is not always well understood. For example, the gradient that dictates evaporation is a vapour pressure gradient, not a relative humidity gradient, and as long as that pressure gradient is favourable, water vapour will move away from the skin, even into air that has a relative humidity of 100%. Since evaporation, like all phase changes, is an isothermal processes, then within thermally compensable steady states, once sweating is established and the skin is fully wet, and once that sweat is evaporating freely, the temperature of that skin surface will effectively be clamped (Mitchell et al. 1968; Mitchell and Whillier 1971; Stewart and Wyndham 1975; Candas et al. 1979a; Monteith 1981; Baldwin et al. 2023). Evaporation rate can increase further, but skin temperature will not change, and it ceases to respond to changes in ambient temperature. To provide the first-principles base for interpreting evaporative heat flux, we will briefly review the physics of evaporative cooling, and its history.

The cooling effect of evaporation has been known for centuries (e.g., Williams 1793a, b; Bahadori 1978; Delacey 2015), although, before the eighteenth century, western scientists seemed to have only a superficial understanding of the phenomenon. During the eighteenth and nineteenth centuries, that changed. Following a publication by William Cullen (1710–1790, Scotland; Cullen 1756; Comrie 1925; Risse 1974), and through correspondence with Cullen (Thomson 1832; University of Glasgow 2021), Benjamin Franklin (1706–1790, U.S.A.) learned of the cooling effect created by evaporation (Franklin 1758, 1769). Contrary to popular opinion, Franklin did not discover the cooling effect of evaporating alcohol (Thomson 1832). Instead, he credited Cullen (Cullen 1756; Franklin 1769) and John Hadley (1731–1764, England; Franklin 1758), and it was Cullen's students (Dobson and Black) who described, defined and named the mechanism that took up heat when substances changed phase from a liquid to a gas, or from a solid to a liquid.

Firstly, Matthew Dobson (1732–1784, England) "*observed that the thermometer, when lifted out of many of the fluids, and suspended a short time in the air beside them, fell down to a lower degree than that indicated by another thermometer which hung constantly in the same air … it was occasioned by the evaporation*" (Black and Robison 1807 [P. 156]). Secondly, Joseph Black (1728–1799, Scotland; Christie 2014) observed that when "*ice … is changed into water, a quantity of heat must go into this water, without making it sensibly warmer; and when water is changed into ice, a quantity of heat must come out of the freezing water as fast as the ice is formed, and this without leaving it sensibly colder. The absorption of heat, therefore, into the melting ice, is not the cause of its liquefaction, but rather the consequence of it; while on the other hand, the extrication of what I call latent heat from the freezing water, is not the cause of its becoming solid, but the consequence of it.*" (Black and Robison 1807 [P. 136]). Those words are thought to be the first description, dated at 1761 by Tunbridge (1971), of the origin and quantification of the thermal energy required to cause those phase transitions.

Those descriptions provide insight into understanding insensible and sensible heat exchanges. During melting, ice undergoes a phase change, but "*without making it sensibly warmer*". That is, thermal energy is used to break the bonds holding the water molecules in a rigid matrix (latent heat of fusion: 334 J g^{-1}; Lide 1997), but those molecules do not experience a measurable (sensible) change in temperature. So more than two and a half centuries ago, it was recognised that the phase changes of ice melting and freezing were isothermal. This also holds for evaporation, during which thermal energy is converted into kinetic energy, eventually causing the water molecules to move sufficiently rapidly to break away from a liquid, such as sweat, and enter a gaseous state (latent heat of evaporation: 2426 J g^{-1} at 30 °C; Wenger 1972), again without a temperature change.

External energy is required for those phase changes. If either the melting ice or the evaporating water was in contact with one's hand during those transitions, then some of the thermal energy for those conversions would come from that hand, and heat delivered to the hand surface from deeper tissues would be dissipated, by phase change, without its surface temperature changing; the heat loss is insensible. Prior to evaporation being initiated, the skin surface would have been warmer, so evaporation cools the skin initially, after which the skin temperature becomes relatively stable, following the establishment of a thermal steady state. That occurs once the skin is fully wet, once evaporation has become established and when all heat delivered to the skin is being dissipated. If that hand was immersed in cold water, heat delivered to the surface would be conveyed to the cold water, while its surface temperatures would fall and the water temperature would rise; that heat loss is sensible.

The recognition of latent heat, and its implications, eventually contributed to the *Laws of Thermodynamics*. In spite of their importance, Black did not always publish his observations and theories (Christie 2014), so they were known mainly through his lectures (Black and Robison 1807). Our quotes were taken from the posthumous publication of his

lectures by John Robison, a student and colleague (Black and Robison 1807). The reluctance of Black to publish led Robison to note that "*Scarcely did a year pass over … in which some corner of this doctrine was not nibbled off, and appropriated by others; generally by his former pupils*" (Black and Robison 1807 [P. 356]). A similar concern was expressed by William Harvey (1628). Four centuries later, it seems that the more things change the more alike they remain.

Two papers related to latent heat highlight the misattribution of credit (Wilcke 1772; de Luc 1787), and are cited to reduce the probability of its continuation. Johan C. Wilcke (1732–1796, Sweden) discovered that melting snow with an identical mass of hot water was accompanied by a reduction in thermal energy of that water, which was used in melting the snow. He had also encountered the latent heat of fusion (Wilcke 1772), but eight years after Dobson and Black (Black and Robison 1807; Wolf 1938). The second paper was written by Jean-André Deluc (1727–1817, Switzerland; de Luc 1787), who claimed credit for discovering latent heat, and refused to relinquish his claim (Tunbridge 1971).

When sweat evaporates, it extracts latent heat from the body, and the resulting water vapour accumulates in the thermal boundary layer. If it did not move away, evaporation would soon stall. But, in the service of Fourier (1807), it does move away, driven by the vapour pressure gradient between the skin and the surrounding atmosphere (Whillier 1967). For example, skin at 35 °C, and wet with sweat, has a vapour pressure of 5.6 kPa, which is much higher than the surrounding air at 30 °C (dry bulb) and at 100% relative humidity (4.2 kPa). In that scenario, water vapour will move into the air even though it is saturated, although some water will then necessarily condense out of the air.

Our understanding of the speed and ease with which water vapour moves down the vapour pressure gradient owes much to Warren Lewis (1922). He recognised that the thermal boundary layer contained both water vapour (mass) and thermal energy, so factors that affected boundary layer movement would affect water vapour and heat in the same way. Thus, the evaporative heat flux coefficient has to be proportional to the convective heat flux coefficient (Qian and Fan 2006). The Lewis relationship requires air movement, and an object's characteristic dimensions, to affect convection and evaporation in the same way, and it was Murlin (1939) who recognised that the Lewis relationship applied to humans.

Unfortunately, that idea made very little impression until it was couched in physiological language by Woodcock and colleagues (Woodcock et al. 1956; Woodcock and Breckenridge 1965; U.S.A.), and rediscovered by Brebner et al. (1958, England), but without citing Lewis. An example of the delay in awareness appeared in a paper by Nelson et al. (1947), in which the effect of wind speed on evaporation and convection were assigned different exponents, contravening the laws of physics, which dictate that the exponents must be identical.

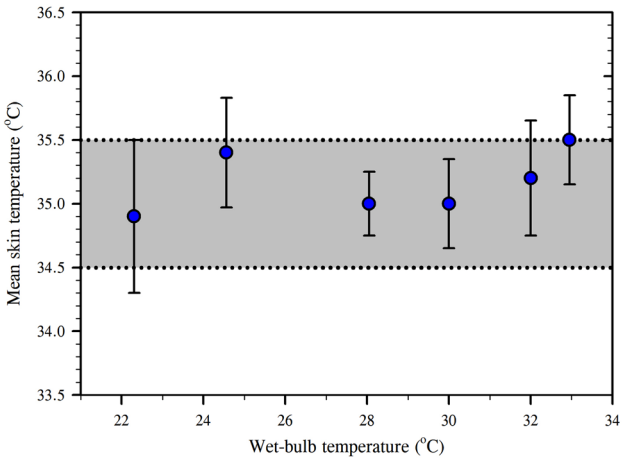


Fig. 13 Mean skin temperatures for two near-naked, heat-adapted males resting and exercising at two different work rates (45 and 113 W) within a calorimetric wind tunnel, in twelve sets of ambient conditions that included two dry-bulb temperatures (36° and 41 °C), three water vapour pressures (2.0, 3.3 and 4.7 kPa) and two laminar-flow wind speeds (0.67 and 3.11 m s^{-1}). As indicated by the grey band, mean skin temperature was effectively clamped across those conditions, at approximately 35 °C, because the skin was saturated with sweat that was freely evaporating. Changes in sweat rate over those conditions were driven only by changes in deep-body temperature. Data are means with standard deviations, and were digitised from Mitchell and Whillier (1971) and replotted

Another flawed assumption is the idea that the sweat rate is equivalent to the rate of evaporation, as was assumed by the early practitioners of partitional calorimetry. There are some circumstances in which that assumption might be correct, but those are rarely seen during exercise, and then only in the driest of air. Indeed, when calculating evaporative heat flux one needs to include a factor that considers skin wettedness (Gagge 1937), which takes account of the skin fraction that is actually wet. Moreover, sweat starts to drip before the skin is completely wet, with sweat dripping commencing when the local skin wettedness approaches ~ 50% (Candas et al. 1979a, 1980), with the resulting extra evaporation cooling the floor and not the person. The magnitude of the error made by assuming that sweat drips only when the skin is fully saturated, will increase as the air humidity rises. Since skin wettedness depends upon how much sweat is produced, it can be considered to be under physiological control.

Whilst whole-body sweat rate can be estimated from mass changes, evaporative cooling cannot, unless one can distinguish between sweat production and sweat drippage (Candas et al. 1979a). A further complication arises when sweat does not evaporate on the body surface, but at some distance from that surface, as it may in a clothed person. For instance, wicking fabrics remove some of the sweat from the skin surface (Hong et al. 1988; Goldman and Kampmann

2007), such that evaporation eventually occurs within, or at the outer surface of, the fabric (Nagata 1978; Havenith et al. 2008; Wang et al. 2014), leading to reduced heat loss from the skin itself. We will examine the control of sudomotor function in "Key concepts in exercise thermoregulation: the central regulator is more than a thermostat", and the measurement of sweat rate in Part 2 of this historical series.

We conclude this Section by drawing attention to the phenomenon that, under steady-state conditions, the evaporation of sweat from fully wet skin will effectively clamp skin temperature. Because the phase change of liquid water to water vapour is an isothermal process, heat delivered to the skin can be conveyed away by evaporation without skin temperature changing. If the skin is wet and evaporating freely, its temperature is resistant to changes in environmental temperature, and to the rate of heat delivery from deep-body tissues. To illustrate that phenomenon, Fig. 13 shows measurements of steady-state mean skin temperatures taken from heat-adapted men exercising at three different work rates, over a range of thermally compensable wet-bulb temperatures (22°–33 °C). Across those conditions, mean skin temperature varied by < 1 °C, despite differences in rate of heat delivery by cutaneous blood flow and differences in evaporation rates (Mitchell and Whillier 1971). Anomalously high skin temperatures have been reported by others (Gagnon et al. 2013; Foster et al. 2021), although the attainment of a thermal steady state was not certain, with those temperatures sometimes being higher than deep-body temperature when exposed to high dry-bulb temperatures.

An overview of thermodynamics, thermoregulation and our route to a retrospective

Our task within this Section was to describe the historical events that led to our contemporary understanding of the physical processes by which heat is transported within the body, especially during exercise, and exchanged with the environment. Our route to this retrospective has been founded on the *Laws of Thermodynamics*, as indeed are all physiologically driven heat exchanges. Our adherence to those laws, and their consequences for thermoregulation during exercise, is not optional, so let us summarise and consolidate what those laws mean for our field.

The *Zeroth Law of Thermodynamics* defines thermal equilibrium. It requires that, if two structures are at the same temperature, neither will experience a nett change in heat content, no matter how far apart the structures are, or the temperatures of intervening structures. So if muscle and skin temperatures at a site are the same, there is no nett heat transfer between those sites. That law forms a fundamental requirement for all contact thermometers. We are not interested in what thermometers indicate, which is always their own temperature. Our interest is the temperature of the tissue with which the thermometer is in contact. For that temperature to be physiologically meaningful, the thermometer needs to be in thermal equilibrium with that tissue, and stay in thermal equilibrium if that tissue temperature changes, even if that change occurs at its maximum feasible, physiological rate. Fulfilling that condition requires heat transfer between the tissue and thermometer to be both rapid and reliable, and the thermometer must have an appropriate thermal inertia. Thermometers used for skin temperature measurements need to have much lower thermal inertia than those used to measure deep-body (core) temperatures.

For valid measurements, the tissue temperature has to be the same with, and without, the thermometer in place. Many skin temperature measurements are rendered invalid because the thermometer, or the device that applies it to the skin, interferes with evaporation from the skin site. Skin thermometers must allow free evaporation at the site of the sensor. Faced with the challenge of securing sensors to rapidly moving body segments during dynamic exercise, and to avoid loose sensors that just measure air temperature, researchers often use impermeable adhesive tape to attach sensors to skin. In those situations, we are obliged to report the method of attachment so that readers will be aware of the shortcomings of those data, which overestimate the actual skin temperature.

Though it may seem counterintuitive, the *Zeroth Law of Thermodynamics* does not reveal the direction in which heat flows. That requires the *Second Law of Thermodynamics*; spontaneous nett transfers of thermal energy always travel down thermal gradients. In the context of that law, we tend to overlook the reality that the most important cooling tissue in the body is arterial blood, which leaves the heart at the temperature of mixed-venous blood, and contains an admixture of blood from both hotter and cooler tissues. Arterial blood travels to, and cools, metabolically active organs (liver and brain), and venous blood leaving the human brain is always warmer than its arterial supply (Nybo et al. 2002b). It is this cooling by the arterial blood that also prevents hard-working skeletal muscles from cooking in their metabolically produced heat (González-Alonso 2012), although that does occur (rhabdomyolysis; Kim et al. 2016; Rawson et al. 2017); heat illnesses are discussed within Part 3 to this series.

If the foetus of a pregnant woman is to dissipate its metabolic heat, the *Second Law of Thermodynamics* dictates that foetal temperature has to be higher than that of the arterial blood reaching the placenta. Fortunately, evolution

has provided mothers with the means to reduce the risk of foetal hyperthermia when they become heat stressed during exercise (Laburn et al. 2002). Moreover, whilst there will be exceptions, it seems there are no serious contraindications to maternal exercise (Mottola 2008), with at least 25 pregnant athletes competing in the modern Olympic Games (https://www.olympedia.org/lists/77/manual).

The consequences of the *Zeroth* and *Second Law* for thermoregulation during exercise are profound, but it is the consequences of the *First Law* that are ubiquitous. That law states that energy can be transferred and converted between different forms, but can neither be created or destroyed. Candas and Libert (2022) believe that the first physiological expression of the *First Law of Thermodynamics* came from Pierre Sarrus and Jean-François Rameaux (France), when they noted that "*If in the instant case we admit that the temperature of the animals is constant, it is known that among them there is a perfect equality between the heat they produce and the heat they emit*" (Sarrus and Rameaux 1838–1839; Shour 2017 [P. 6]). Whilst there are several ways that one might assemble the components of heat production and heat exchange into unifying theoretical and mathematical models, thermal physiologists have settled on the energy-balance (heat-balance) equation for the human body (Eq. 8), with each component expressed as area-specific rates (W m^{-2}; see "Metabolic heat production during rest" [area- versus mass-specific normalisation]).

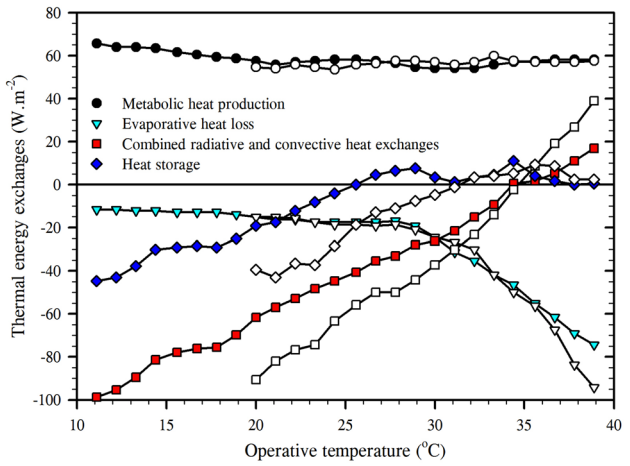


Fig. 14 Physical and physiological avenues for heat exchange in naked (open symbols) and clothed (business suit; closed symbols) individuals resting (semi-recumbent) in a copper chamber, across a range of operating temperatures ("*temperature operating on the exposed surface of the body system, whether it be skin or clothing, or both*" [P. 35]). Data extracted from Gagge et al. (1938; Table 2 [P. 34])

$$S = M + W + R + C + K + E, \quad (8)$$

where S is the rate of heat storage in the body, M is the rate of metabolic heat production, W is the rate of work performed against, or by, external forces, R is the rate of radiant heat flux, C is the rate of convective heat flux, K is the rate of conductive heat flux, E is the rate of evaporative heat flux.

We can ignore conduction because it is unimportant for exercising humans, except when prostrated following exhaustive exercise, though it plays a significant role within many workplaces. Values for heat flowing towards the body are herein given a positive sign. Readers will find others using the plus/minus (±) sign in the energy-balance equation, but that is algebraically unnecessary.

When the body is in thermal equilibrium with its environment, the rate of heat storage is zero. The main goal of our thermoregulatory system, the neural basis of which is examined in "Key concepts in exercise thermoregulation: the central regulator is more than a thermostat", is not to maintain the stability of any particular body temperature, but to restore the overall heat storage to zero, whenever storage, and therefore body temperature, rises or falls. During sustained exercise, that requires the nett rate of heat storage to be zero when muscle temperatures are high. Achieving that equilibrium does not require the returning of muscle temperatures to their resting values. Indeed, elevated muscle temperatures are considered conducive to optimal exercise performance (Bishop 2003). Consequently, the thermoeffectors will not remain silent during exercise, but will be activated to accommodate elevated muscle temperatures, even when heat storage is zero.

To achieve zero nett storage, the thermoregulatory system can manipulate every component of the energy-balance equation, either autonomically or behaviourally. For example, radiative heat flux can be manipulated by changing skin temperature and posture, convective heat flux is altered by changing skin temperature and modifying wind speed (relative or absolute), evaporative heat flux is modified by controlling sweat rate, we can alter our external work rate, and resting metabolic heat production rates can be elevated by shivering (thermogenesis). Typically, the thermoregulatory system will attempt behavioural means (like shade selection and exercise avoidance; Fig. 12) for manipulating those components, before implementing autonomic means, as they are more powerful, more efficient and less resource-wasteful responses. To illustrate how our physical and physiological heat exchanges are modified when exposed to different thermal conditions, we have illustrated the responses of resting individuals (Fig. 14; naked and clothed), measured at the end of the Krogh-Hill epoch (Gagge et al. 1938). In our next section, we will examine how those thermoeffectors are controlled.

It is sometimes difficult to grasp the subtleties of the work rate component of the energy-balance equation. That difficulty stems from the concept of external work and the sign (positive or negative) that must be used. Work can be performed on external structures to overcome forces external to the body (e.g., bicycle pedals, oar handles), but it can also be performed on the body when an external force (gravity) is more powerful. Work performed against gravity (*e.g.*, walking uphill, rock climbing), or against fluid friction (in water [swimming, rowing, kayaking], in air [cycling, running]), results in energy leaving the body. In those situations, the work component of Eq. 8 requires us to use negative values. Ladder mills and inclined treadmills create some consternation because the body's centre of gravity may not change position, but forces are exerted on the moving ladder or belt, and not on the static surrounds. What would happen if exercise stopped, but the belt or ladder continued moving? There is no nett work performed against gravity during level locomotion, even when carrying a load, because the energy spent raising the centre of gravity is recovered within the body when the centre of gravity is restored to its initial level. Internal work, such as stretching tendons or pumping blood, does not contribute to the overall work because it is converted to heat within the body.

Because the *First Law of Thermodynamics* also applies to chemical energy, we can calculate the rate of metabolic heat production from the turnover of the chemical agents involved in energy generation. For long-term measurements (*e.g.*, *Tour de France*), a more practical contemporary technique is to measure the rate of carbon dioxide production using doubly-labelled water (Westerterp et al. 1986; Westerterp 2018). Perhaps counter-intuitively, that method revealed that, over the long term, resting metabolism contributes far more to our 24-h metabolic heat production than does exercise (Speakman and Selman 2003), even in highly-active communities (Pontzer et al. 2015). For short-term measurements, the exchange of respiratory gases is usually measured (Macfarlane 2017; Shephard 2017; Ward 2018; Ferretti et al. 2022), although derivations of metabolic rate are valid only during steady states and when all of the metabolic heat is produced aerobically. Indeed, we still have no way of measuring metabolic heat production in real time when there is significant anaerobiosis. So we do not know how much metabolic heat Tamara Walcott (38-year old mother of three; U.S.A.) generated when she deadlifted 290 kg, or when Usain Bolt (Jamaica) ran 100 m in 9.58 s. We can be sure, though, that the *First Law of Thermodynamics* rules, even during exercise with an elevated anaerobic component.

Key concepts in exercise thermoregulation: the central regulator is more than a thermostat

Precursors to the concept of a human thermostat: epoch one

The Cornish physician and brother of Humphry Davy, John Davy (1790–1868, England), made a revealing statement in 1845, when he said "*it has been too generally taken for granted that the temperature of man in health, as measured by a thermometer placed under the tongue, is a constant one*" (Davy 1845 [P. 319]). That statement reveals that, by the middle of the nineteenth century, and for at least 30 years before Claude Bernard's concept of a stable *milieu intérieur* (1878), a view prevailed that human deep-body temperatures were somewhat stable. However, "*the temperature of the body rises and falls in a perceptible manner with the temperature of the air*" (Davy 1844 [P. 62]), so body temperatures could vary. Davy (1844) also reported the first known observations of the influence of age upon deep-body temperatures, and, following an investigation of the body temperatures of fish, he reported greater temperature variations within those ectotherms than within humans (Davy 1844). How would he have interpreted that observation? As we look backwards, we realise that many developmental steps were required before Davy could interpret his observations, and critical steps within those developments are summarised in Fig. 15.

It was perhaps beyond Davy's understanding that a (neural) regulating centre, which behaved something like a *thermostat*, might have contributed to the stability of human body temperatures. Indeed, it was 16 years later, Carl Liebermeister (1833–1901, Germany) deduced that a *thermostat*-like action could explain his observations of human deep-body temperature changes during fevers (Liebermeister 1860). He concluded that fevers resulted from an upward resetting of the body temperature, presumably by some neural mechanism (Liebermeister 1875), which John Bligh (1922–2020, England; Bligh 1966; Milton 2022) interpreted as Liebermeister appreciating the concept of a *set-point* for the regulation of body temperature. Readers will note that we have italicised the terms *thermostat* and *set-point*, and that convention has been used for similarly troublesome terms throughout this series. To retain historical precision, those terms will still be used when quoting or paraphrasing the words of our predecessors. The preferred terms now are "regulatory centre" (*thermostat*) and temperature "threshold" (*set-point*).

Other researchers, some of whom also preceded Bernard, identified the existence of neural pathways that participated in the regulation of body temperature, but they were more

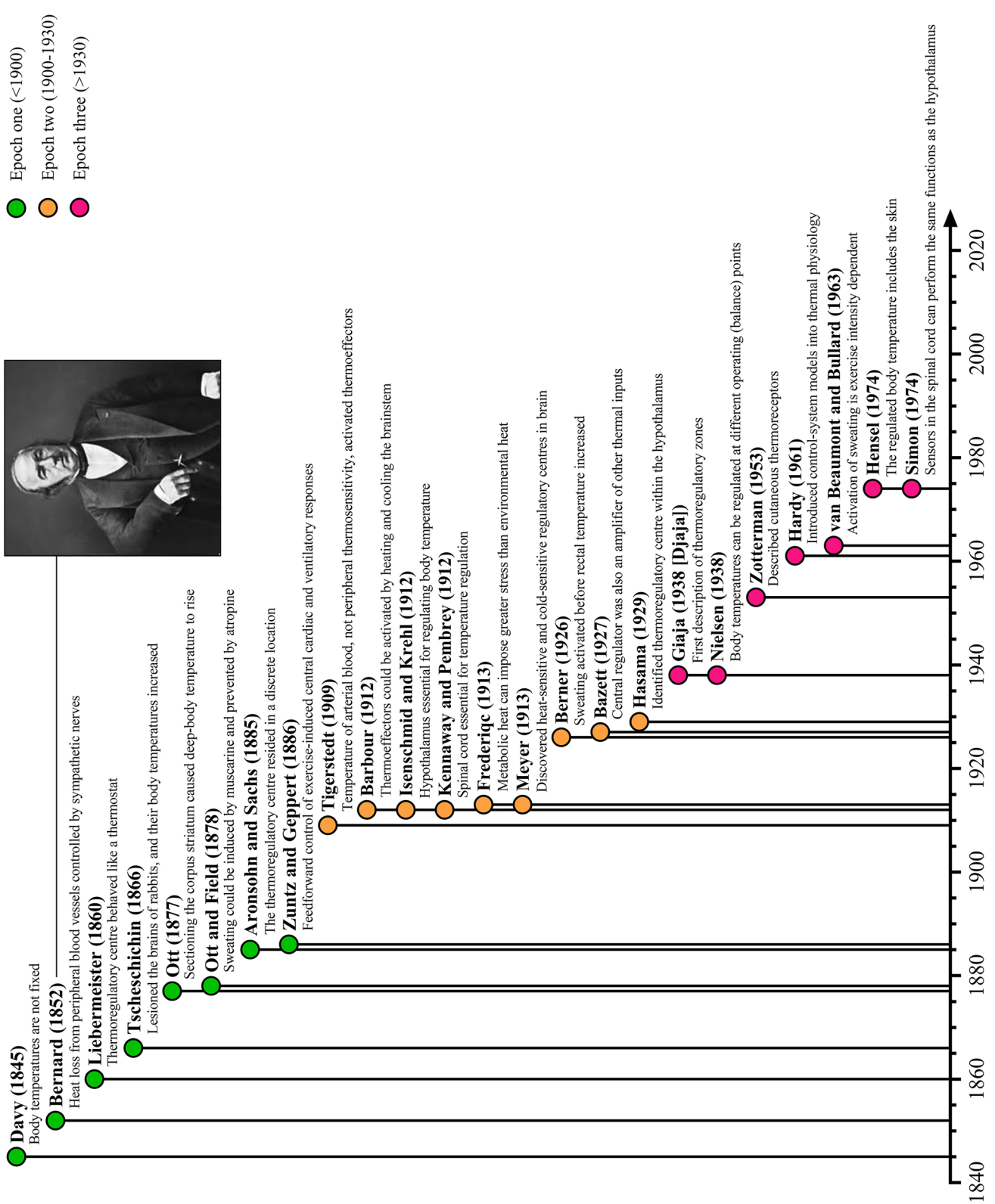


Fig. 15 Principal discoveries and concepts in the development of our understanding of thermoregulation. Portrait of Claude Bernard (photographer: unknown) was obtained from Wikimedia Commons, and is in the Public Domain. Source: https://commons.wikimedia.org/wiki/File:Claude_Bernard.jpg Accessed: December 22nd, 2022

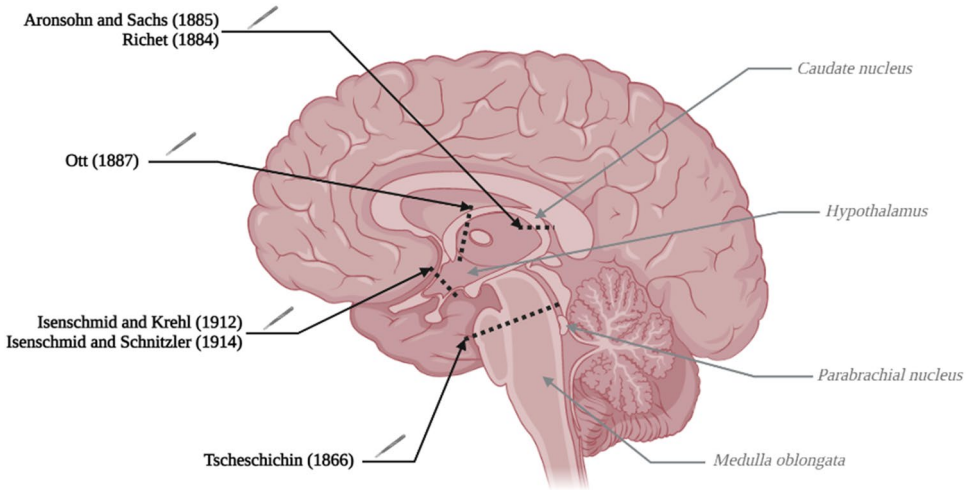


Fig. 16 Outline of the human brain showing sites of the hypothalamus, *medulla oblongata*, caudate nucleus and parabrachial nucleus. Dotted lines show the approximate sites of lesions made by Tscheschichin (1866), Richet (1884), Aronsohn and Sachs (1885), Ott (1887), Isenschmid and Krehl (1912) and Isenschmid and Schnitzler (1914). Those sites were identified from their verbal descriptions. Brain outline from Neuroscientifically Challenged, licensed under Creative Commons Attribution 4.0 International License (https://neuroscientificallychallenged.com/)

concerned with their neuro-anatomical location than with their operation. For example, Brodie (1811) provided evidence that the brain was involved in thermoregulation; decapitated, artificially ventilated animals did not maintain body temperature. Others explored neuro-anatomy, usually in anaesthetised laboratory animals, unaware of the extent to which anaesthesia disrupted the operation of those neural pathways; that was not recognised until the end of the century (Richet 1893). The methods of those early investigators were crude, and typically involved the insertion of mechanical probes to destroy parts of the brain. Perhaps the earliest of those researchers was J. Tscheschichin (1866, Russia), who lesioned the brains of rabbits, just rostral to the *medulla oblongata* (Fig. 16), and observed their body temperatures increased. He proposed that the rostral brain dampened down activity in the more-caudal, central nervous system, so that isolating the rostral brain led to a mild hyperthermia.

Soon afterwards, Bruck et al. (1870; Germany) expressed doubt that the rise in temperature observed by Tscheschichin resulted from an interruption of the neural tracts, because simply puncturing that area had the same effect. With some insight into thermoregulatory mechanisms, they deduced that elevation had originated from increased metabolic heat production, rather than reduced heat loss, because both deep-body and peripheral temperatures increased. Adding to those mechanistic doubts, Dubczcanski and Naunyn (1873) found that mechanically probing the brain seemed to release, within the brain, pyrogenic substances like those responsible for Liebermeister's fevers.

Whatever the mechanism, Isaac Ott (1847–1916), the first American thermal physiologist (Blatteis and Schneider 2022), showed that transverse sectioning of the *corpus striatum* (which includes the *caudate nuclei*, Fig. 16) of experimental animals caused their deep-body temperatures to rise (Ott 1887). There were many other neuro-anatomical studies of the role of the rostral brain in determining deep-body temperature (Ott 1884, 1889; Kornblum 1925), with outcomes usually interpreted in terms of interrupting neural pathways. Nonetheless, it is to the German medical students, E. Aronsohn and J. Sachs (1885), that credit is usually given for identifying that the regulatory function in question was not diffuse, but resided in a discrete location (Bligh 1966). They observed a rise in the deep-body temperature of rabbits following lesions within the *caudate nucleus* (Fig. 16). They concluded that elevation to be induced not by neural damage, but by mechanical excitation of neurons, because they could induce the same rise by electrically stimulating that site. Unfortunately, Charles R. Richet (1850–1935, France), who made extensive contributions to thermal physiology (Candas and Libert 2022), and won a Nobel Prize in Medicine (1913), was incensed at the publication of Aronsohn and Sachs (1885; Richet, 1885a). It seems that then, as now, investigators did not always read the literature thoroughly, as Richet claimed to have published the same conclusion a year earlier (Richet 1884).

Although most nineteenth century researchers were more concerned with identifying the central location of the neurons that played a role in determining body temperature, there was some interest in how those neurons influenced body temperature. For example, Carl Bergmann (1845) proposed that it was the thermosensitivity of the brain that initiated cutaneous vasomotor activity (Bligh 1966), and

Bernard (1852) suggested that heat loss from the skin was controlled by sympathetic nerves, with that neural activity originating within the brain. However, Isaac Ott was not convinced.

By observing the effects of spinal-cord transection on cutaneous vasodilatation in the limbs of heat-stressed (> 50 °C dry bulb), etherised cats, Ott (1879) concluded that vasodilatation was driven, not by centres in the brain, but primarily by centres in the spinal cord, below the cervical spine. He induced sweating on cat paw pads by electrically stimulating the peripheral end of cut sciatic nerves, and was convinced there were sweat-centres distributed throughout the spinal cord, but also in the *medulla oblongata* (Ott 1879). Sweating could also be induced when a recently discovered cholinergic agonist (muscarine; Schmiedeberg and Koppe 1869) was applied to peripheral nerves, and it could be prevented by the cholinergic antagonist atropine (Ott and Field 1878).

Christian Sihler (1879, 1880; U.S.A.) considered the apparent thermosensitivity of the brain to be even less important. He was convinced that it was thermal stimulation of the skin, and not warming of the brain, that caused dogs to pant in the heat. Richet (1893) agreed that it was peripheral stimuli that normally elicited panting and shivering, with the proviso that the brain became involved during extreme heating and cooling.

Thus, by the beginning of the Krogh-Hill epoch, the idea of a stable deep-body temperature had been established well before Bernard's concept of a relative constancy of inner heat ("*la fixité relative de leur chaleur intérieure*"; Bernard 1876 [P. 107]). Yet the idea of homeothermy is usually attributed to Bernard. Certainly, the idea that homeothermy might be beneficial, and that the body temperature might actually be regulated, had to wait for Bernard, but researchers knew there was a discrete area of the brain, in or near the *caudate nucleus*, without which that stable deep-body temperature could not be sustained. They did not know, however, what the function of that area was, when it was intact. Some conceived it to be a temperature-sensing area, but many regarded thermoeffector activities like vasodilatation, panting and shivering to be driven, not by the temperature-sensing area, but by peripheral body temperatures. Some thought that areas in the spinal cord could take over the functions of the certain areas of the brain.

Developments within the Krogh-Hill epoch

The twentieth century began with further neuro-anatomical explorations of sites of the central processing within the brain that supported thermoregulation. There was little progress in the Krogh-Hill epoch about the circuitry that might connect those sites; that topic was pursued in the modern epoch. Work also continued on what the stimulus was for the activation of the thermoeffectors. Ideas accumulated about how a physiological regulatory centre might work, including during exercise. Our forebears of that time were not to know that thermoregulatory mechanisms do not operate like domestic thermostats.

When the epoch began, the geographic centre-of-gravity for neuro-anatomical research was in Europe, and particularly the laboratory of Hans H. Meyer (1853–1939; Austria), and the Medical Clinic in Heidelberg (Germany). By the end of the epoch, the centre-of-gravity had moved to the U.S.A., primarily as a result of one technological advance. That was the Horsley-Clarke stereotactic apparatus for the accurate positioning of micro-devices within the brain. It was first described in 1908 (Horsley and Clarke 1908; Jensen et al. 1996; Compston 2007), but not used for thermoregulatory research until thirty years later (Magoun et al. 1938).

Hans Meyer was neither a neuro-anatomist nor a physiologist, but a pharmacologist (Baehr 1940), yet he was responsible for discovering that two neuro-anatomical regulatory centres existed within the brain: one responsive to heat stimulation and the other to cold (Meyer 1913). Those centres were close to each other, but at distinct anatomical sites, with the apparently cold-sensitive, posterior site subsequently being identified as a thermosensitive relay station. Again, using crude lesioning techniques, Isenschmid and colleagues (Heidelberg) demonstrated that, of the candidate brain regions near the *caudate nucleus*, it was the hypothalamus that was crucial for the regulation of body temperature (Isenschmid and Krehl 1912; Isenschmid and Schnitzler 1914).

Though the regulatory centre was seated within the hypothalamus, it required neural connections with the thermoeffectors, via an intact spinal cord, for that centre to regulate body temperature, as Kennaway and Pembrey (1912; England) confirmed by making spinal lesions in rabbits and mice. They also knew that thermoregulation was compromised in humans with spinal cord lesions, and that they sweated only above the level of such a lesion. Without presenting data, they also remarked that "*It is known also that in man after traumatic section of the spinal cord the temperature may fall to 27° or rise to 43°. Sensations of heat and cold are lost in the paralysed parts and when the temperature of the patient rises sweat breaks out only upon the parts above the lesion; likewise when his, temperature falls he shivers only in the same parts of his body*" (Kennaway and Pembrey 1912 [P. 84]).

That observation was made nearly fifty years before the first Paralympics (Rome, 1960). Athletes with high spinal-cord lesions have now been studied during exercise at 60% of their peak aerobic power (wheelchair ergometer) in hot environments (Price and Campbell 2003). We know that people with cord lesions still sweat in areas supplied by intact sympathetic nerves; tetraplegic patients tend not to

sweat at all, whilst paraplegics sweat above the level of the neural injury, and, on average, from one dermatome below the injury (Trbovich et al. 2021). Tetraplegics and paraplegics do not seem at risk from hyperthermia during exercise because the metabolic heat production of denervated muscles is relatively low (Price 2006), although they are more susceptible than able-bodied people to hyperthermia when at rest, due to their impaired thermoeffector function. Nevertheless, we know that intact connections to the brain are essential for normal thermoregulation, so an understanding of how athletes with spinal transections thermoregulate is fundamental to their welfare (Price 2006; Ko 2019).

Making lesions in the central nervous system is an inexact way of trying to identify the location of any regulatory centre, and can provide evidence only of the consequences of its failure, but not of the functioning of the intact brain. As an experimental approach, it was criticised heavily at the time (Reichert 1902), and there were lengthy discussions about the meaning of rises in body temperature that occurred after brain lesions (Jacobj and Römer 1912; Liljestrand and Frumerie 1914). Better evidence of function could be obtained by thermal stimulation of the putative site of the regulatory centre. That there indeed was a thermosensitive site in the territory of the carotid artery was confirmed by observation of thermoeffector activation when the carotid arterial blood of rabbits (Kahn 1904) and dogs (Moorhouse 1911) was warmed. Robert Tigerstedt claimed that it was the temperature of the arterial blood perfusing the brain, and not peripheral thermosensitivity, that was the over-riding determinant of thermoeffector activity (Tigerstedt 1909; Leppäluoto et al. 2022). His claim was endorsed by Charles S. Sherrington (1857–1952, England; Sherrington 1924).

Henry G. Barbour (1886–1943, U.S.A.), who was working in the laboratory of Hans Meyer (Blatteis and Schneider 2022), and writing in German, used water-perfused thermodes introduced into brain tissue to show that the thermoeffectors of rabbits could be activated by heating and cooling of the brainstem (Barbour 1912). Later Prince and Hahn (1918a, 1918b; U.S.A.) narrowed down that site in cats and rabbits to be close to the *caudate nucleus* (Fig. 16), and even later, Bun-ichi Hasama (1929; Japan) identified it as the hypothalamus in cats. Yet it would take half a century before thermosensitive neurons were found in the hypothalamus, first within anaesthetised (Nakayama et al. 1961; U.S.A.; Nagasaka 2022), and then within unanaesthetised animals (Hellon 1967; England; Milton 2022).

Circumstantial evidence indicated that the hypothalamus also was the site of the thermoregulatory centre in humans, though other brain areas may well be involved. When patients with hypothalamic lesions survive, one might expect them to become poikilothermic, and hypothermic if cold exposed (Fox et al. 1970). If the lesion was caused by a traumatic brain injury, the patient may initially have episodes of hyperthermia (de Tanti et al. 2005), just as happens when mechanical injury is used to disrupt neural pathways in the brains of non-human animals.

Although exploration of thermosensitive sites using thermodes undoubtedly was less crude than brain lesioning, it was not without criticism. Cloetta and Waser (1914) could not reproduce Barbour's (1912) results using diathermic heating of the brainstem. The thermodes available were big, and could not be positioned precisely, and it required much higher and lower temperatures than the brain ever would encounter naturally, to activate the thermoeffectors. Barbour took his thermodes down to 11 °C and up to 51 °C. The in vivo researchers of the Krogh-Hill epoch were far from the exquisite skill of Claus Jessen (1935–2015, Germany; Fuller and Blatteis 2015), who inserted an array of 25 thermodes near the hypothalamus of goats, and activated their thermoeffectors via small changes in temperature, once they had recovered from surgery (Jessen 1976). They were also way behind the thermal precision of physiologists who used in vitro techniques (Hill 1949).

In parallel with activity aimed at identifying the anatomical site of the regulatory centre, there was extensive research aimed at quantifying thermal stress, and at describing thermoeffector functions (Barbour 1921; Bazett 1927). Important for thermoregulation during exercise was the pronouncement by Léon Fredericq (1851–1935, Belgium; Fredericq 1913) that metabolically produced heat imposed a greater stress on the body than did environmental heat. We are also indebted to Fredericq for his advocacy for physiology as a self-standing discipline, and since physiology is centred upon regulating a relatively stable internal environment, then the mechanisms of all regulatory systems, including thermoregulation, must form the core of physiology. From around that core, other disciplines can emerge, such as exercise and occupational physiology.

In that same year, Artur Lippmann (1913; Germany) reported that the rectal temperature of men reached 39 °C after a heavy march, with others reporting similarly elevated temperatures (Young et al. 1920 [39.6 °C; Australia]; MacKeith et al. 1923 [39.4 °C; England]). More extreme temperatures had been observed during classical and exertional heat illnesses: Weaver (1897: 44.3°–46.1 °C), Tigerstedt (1906; 43.6 °C). So researchers of the Krogh-Hill epoch knew that exercise elevated deep-body temperature considerably, and the prevailing view was that the temperature of the entire body, except the skin, followed rectal temperature, which was considered equal to that of aortic blood (Bazett 1927), though liver temperature could be somewhat higher (Barbour 1921).

The circadian variation of deep-body temperature was much greater than had been proposed by Davy; it was "*conservatively placed at 1 °C*" (Barbour 1921 [P. 297]). In other mammals, those peak-to-trough amplitudes can be much

higher, and > 7 °C for free-living Arabian oryx in the hot-dry season (Hetem et al. 2010). But it was also known that, in exercising subjects (cycling), there was a stimulus to sweat (so presumably an input to the regulatory centre) that was activated before rectal temperature had increased by even 0.05 °C (Berner et al. 1926). Barbour thought that the skin could provide the missing stimulus: "*It is probable, however, that application of heat either to the skin or to the base of the brain yields similar results*" (Barbour 1921 [P. 301]). According to Wilhelm Filehne (1910), as translated by Barbour (1921 [P. 301]), "*for the initiation of the processes which regulate against overheating no rise in blood temperature is necessary. For in a bath up to the neck at 41 to 42 °C, sweating of the forehead began prior to any change in rectal temperature; plunging a hand into cold water stopped this sweating at once*". Without actually measuring skin temperature, Marcus S. Pembrey (1868–1934, England; Milton 2022) and his colleagues, concluded that, during exercise, "*discomfort or distress appeared to be more closely associated with a high temperature of the skin than with a high rectal temperature*" (MacKeith et al. 1923 [P. 438]), although the problem of time delays with that surrogate (rectal) temperature were not yet fully appreciated.

However, George N. Stewart (1860–1930, Canada) used his expertise with measuring segmental blood flows, as described in paper two of this series, to examine the neural control of vasomotor activity during locally applied thermal stimuli. He heated and cooled the insentient part of the left hand of an injured student, observing that "*a change is produced in the blood-flow in the right hand when a portion of the left hand, totally insensitive to warmth or cold (as well as to other forms of sensation), is immersed in warm or cold water*" (Stewart and Walker 1913 [P. 392]). According to Alrick B. Hertzman (1898–1991, U.S.A.), Leon Fredericq (1882) correctly suspected that cutaneous vasomotor activity was under centralised neural control as well as localised thermal influences, although he surmised that the regulatory centres for vasomotor control were in the spinal cord (Hertzman 1959). Indeed, McDowall (1935) believed that the spinal centres controlling blood vessels were subsidiary to regulatory centres located in the brain, and existed at some, as yet unlocated, sites above the medulla.

Possibly the most outspoken about the possibility of a thermoregulatory centre within the brain was Karl Kornblum (1893–1944, U.S.A.). He knew about the neuro-anatomical work of the time, but thought it was inconclusive. He considered any deviation in body temperature to be pathological, and suspected that body temperature was regulated by a suite of reflexes distributed throughout the nervous system. About the cerebral heat centre, he was adamant: "*from the review of the literature, as well as the conclusions drawn from my own experimental work, I feel that the use of the term heat or temperature center as indicating a definite spot in the brain whose sole function is the regulation of temperature is misleading, and the term should therefore be dropped from physiologic and clinical considerations of temperature regulation*" (Kornblum 1925 [P. 765]). His experimental work concerned brain lesions in dogs, and, as we know, his admonition failed, with good reason.

Barbour (1921 [P. 306]) had no doubt about "*the existence of a thermostat-like nervous mechanism at the base of the brain*" and, in rabbits, "*warming of this region causes dilatation while cooling causes constriction*". In fever, he concluded that the regulatory centre would set the body temperature at a higher level (Barbour 1921), echoing Liebermeister's propositions from 50 years earlier. With remarkable prescience, but without evidence, Henry C. Bazett (1885–1950, England and U.S.A.) postulated that some *thermostat*-like nervous mechanism might be not just be a sensor of local temperature, but a thermosensitive amplifier, modulating the effects of thermal inputs from elsewhere in the body, on the thermoeffectors (Bazett 1927). Absent in the Krogh-Hill epoch was any quantitative description of the relationship between the body temperatures presumed to drive thermoeffector activity. Indeed, researchers seemed to regard the regulatory centre as operating in an on–off mode ("*inevitably the facts revert to their predatory ways*"; Wilkie 1954 [P. 288]). If body temperatures rose, sweating and peripheral vasodilatation were activated, and if they fell, shivering and peripheral vasoconstriction happened, but no-one had advanced either a conceptual or a mathematical model that might link those effector responses to changes in body

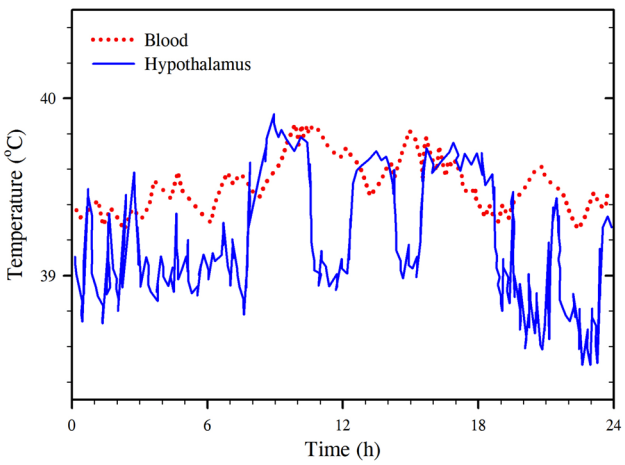


Fig. 17 Five-minute recordings of hypothalamic and carotid artery temperatures of a pig over 24 h. Hypothalamic temperature was much less stable, and showed frequent and rapid reductions, sometimes > 1 °C, without activating the thermoeffectors, most noticeably at night. Those episodes reflect a selective cooling of the brain. Redrawn from Fuller et al. (1999a)

temperature. However, mathematical models were to become standard feedstock of research in thermoregulation during exercise by the middle of the twentieth century.

The modern epoch

In the context of the modern epoch, we will not review all that is known today about how the regulatory centre operates during exercise, but will reflect on the history, and highlight conclusions that have been supported or challenged over time. We will consider four questions. To which body temperatures does the regulatory centre respond, and were our forebears correct in assigning a paramount role to brain temperature, while allowing inputs to that centre from elsewhere in the body? How does that regulatory centre process that information? It is clearly not an on–off controller. Which mechanisms might be involved in determining, and possibly changing, the operating level the regulatory centre, and how are they affected by exercise? Is the process of temperature regulation linked to neural, non-thermal information pertaining to the intensity of exercise?

Which body temperatures stimulate the regulatory centre?

The Krogh-Hill epoch left us with fulsome promises for a cardinal role for the hypothalamus during thermoregulation, both as a sensor of body temperature, and as the site from which the thermoeffectors were controlled. Those promises were based on research in experimental animals, as the human hypothalamus remained inaccessible. In the 1950s and 1960s, Theodor H. Benzinger (1905–1999, U.S.A.; Harsch 2007; Blatteis and Schneider 2022) claimed that he had discovered how to measure the temperature of the human hypothalamus, which he called a *thermostat*, and then proceeded to an extreme interpretation of its cardinal role. What he actually measured was tympanic membrane temperature (Benzinger 1969a), and its extrapolation to hypothalamic temperature depended on the assumption that both the tympanic membrane and hypothalamus were perfused by blood from the internal carotid artery.

It was then known that almost the entire tympanic membrane was perfused by the external carotid artery (Hamberger and Wersall 1964), but there was a segment of the membrane perfused by a branch of the internal carotid artery (the caroticotympanic artery; Standring 2008); the lower, anterior quadrant (Benzinger and Taylor 1963; Brinnel and Cabanac 1989; Brengelmann 1987, 1993; Taylor et al. 2014a). It was at that site that Benzinger placed his thermocouple, which requires an otoscope for positioning (Brinnel and Cabanac 1989) and to confirm the absence of cerumen (ear wax). Tympanic temperature measured using infrared thermometry, as is often performed during rest and exercise (Easton et al. 2007), or using any device not inserted under visual control, will measure the temperature of tissues perfused by the external, rather than the internal carotid artery, including the auditory canal itself (Keatinge and Sloan 1975; Taylor et al. 2014a).

Benzinger (1969a) was targeting internal carotid artery blood as an accurate measurement of deep-body (hypothalamic) temperature. It would have been anathema to him for the regulatory centre in the hypothalamus to be at a temperature not equal to that of its arterial blood, but that is exactly what proponents of human selective brain cooling claim (*e.g.*, Cabanac and Caputa 1979; Cabanac 1995). They believe that human hypothalamic temperature can be lower than arterial blood temperature, and that tympanic thermometers somehow measure hypothalamic temperature directly, rather than blood temperature (Mariak et al. 1999). We are unable to support that possibility.

Benzinger envisaged that the hypothalamus was the only site in the body equipped with sensors and neuronal networks engaged in the human responses to heat, including metabolic heat produced during exercise (Benzinger 1961, 1969b). He postulated that thermoeffector activation during heat stress could be modulated by skin temperature, but only by its cold thermoreceptors; "… *we have all been wrong often*" (Hill 1965 [P. 167]). Although they cannot function

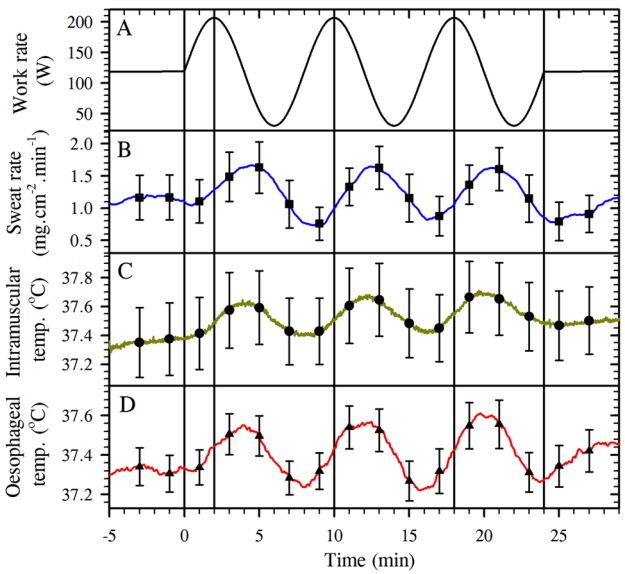


Fig. 18 Variations in external work rate (**A**) during a sinusoid forcing function (semi-recumbent cycling, 25 °C dry bulb, 35% relative humidity), bracketed by steady-state exercise (35% of peak aerobic power; 35 min and 20 min, respectively). Mean response curves, with standard errors of the means at 2-min intervals ($N=8$), are shown for the forehead sweat rate (ventilated capsule; **B**) and for intramuscular (*vastus lateralis*) and oesophageal temperatures (**C**, **D**, respectively). Data were extracted from Todd et al. (2014) and redrawn

if separated from the brain, there are neural sensors and networks in the spinal cord that perform the same functions as the hypothalamus (Simon 1974). The hypothalamic regulatory centre integrates, and responds to, many temperatures from outside the central nervous system, and it can only function successfully if it responds to the entire collection of thermoreceptors distributed throughout the body (Jessen 1996; Werner 2010). That must include temperature sensors in the skin, as the thermoeffectors are sometimes activated far too quickly for changes in deep-body temperature to be the only stimulus (Brown and Brengelmann 1970; Romanovsky 2014).

The hypothalamus is exquisitely sensitive to experimentally-induced local temperature changes in experimental animals, with temperature changes of a few tenths of a degree evoking thermoeffector activity (*e.g.*, van Someren et al. 2002). Mysteriously, it appears not always to be as sensitive to natural variations in its own temperature. Figure 17 shows the instability of hypothalamic temperature in a pig, relative to that of carotid blood. Those natural hypothalamic temperature changes of ~ 1.0 °C occurred without any thermoeffector activation. That phenomenon is not unique to pigs (Bligh 1966). John Bligh remarked that: "*This contrast between the effectiveness of quite small local hypothalamic temperature changes in inducing thermoregulatory responses under experimental conditions and the ineffectiveness of considerably greater changes under conditions comparable to those of normal life, is in urgent need of investigation*" (Bligh 1966 [P. 326]). More than half a century later, it is still in urgent need of investigation.

Figure 17 also reveals periods when hypothalamic temperature was lower than that of the arterial blood destined for the brain. Those were episodes of selective brain cooling, which is prominent in species with a well-developed carotid rete (arterial network within the venous cavernous sinus), notably the artiodactyls (even-toed, hooved animals and cetaceans; Jessen 2001), which allows for a counter-current exchange of heat. Heat is exchanged between cooler venous blood returning from the evaporating, mucosal surfaces of the nasal cavity, which acts as a heat sink for warmer arterial blood, which is cooled slightly, before it enters the brain.

Selective brain cooling was discovered in goats by C. Richard Taylor (1939–1994, U.S.A.; Taylor 1966; Blatteis and Schneider 2022), so, as one of his contemporaries, Benzinger should have known it was possible to uncouple hypothalamic temperature from that of the carotid artery. However, like others, before and after, he appears not to have been sufficiently familiar with the comparative literature. Our reading must be diverse (multidisciplinary), deep and not selective if we are to prevent scientific insularity; a problem that has often held back the applied sciences. Whilst selective brain cooling was once thought to protect the brain during hyperthermia, it is now known to suppress the hypothalamic drive for both forms of evaporative cooling in those mammals, switching cooling to non-evaporative routes, and thereby conserving water (Strauss et al. 2017).

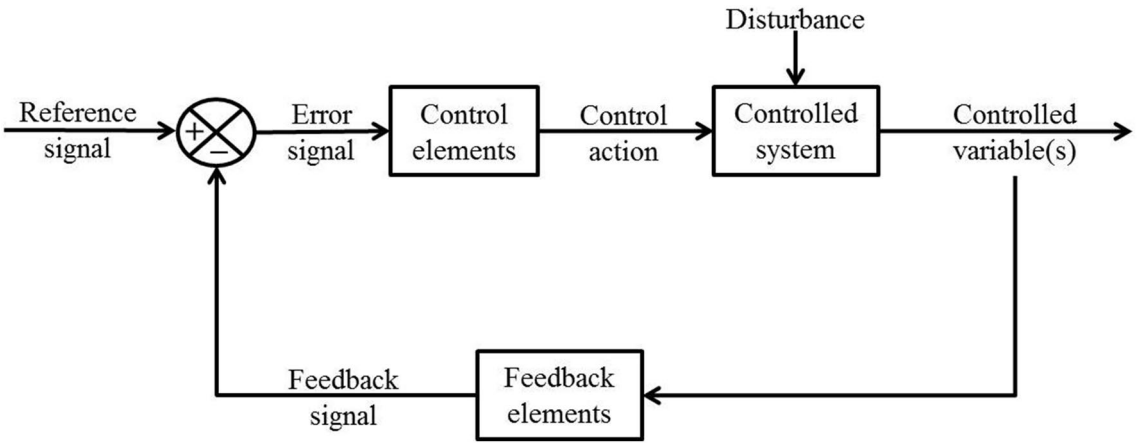


Fig. 19 A conceptual (signal-flow) illustration of the human thermoregulatory system, as understood during the early part of the modern epoch. It illustrates a negative feedback system in which some attribute of the entire body (the controlled or passive system) has been disturbed. Such a change will be induced by heavy exercise, which can modify whole-body temperature. That temperature was then called a controlled variable, but it is now known as a regulated variable. Temperature regulation was thought to occur by the comparison of feedback from the thermoreceptors (feedback elements) with a reference signal (the global *set-point*; now considered to be invalid). Deviations from that reference signal generated a temperature deviation (*error signal*) which led to the activation of one or more controlled variables (thermoeffectors; *e.g.*, sweating) that act to arrest, or at least slow down, further temperature deviations. Whilst some concepts have changed over time, the principle of negative feedback control remains unaltered. Modified from concepts shown in Mitchell et al. (1972)

Researchers who study selective brain cooling in artiodactyls universally do not believe that humans can exhibit selective brain cooling, due to the absence of a carotid rete (Mitchell et al. 2002; Nybo and White 2008; Crandall et al. 2011; Strauss et al. 2017). It is almost impossible, of course, for ethical reasons, to measure hypothalamic temperature and carotid artery blood temperature in intact humans, although Nybo and colleagues measured the temperature of carotid artery blood and jugular venous blood close to the hypothalamus in exercising, heat-exposed humans (Nybo et al. 2002b). They found no evidence for selective brain cooling. Nevertheless, some thermal physiologists contend that humans can exhibit selective brain cooling (Cabanac 1995; Nybo and White 2008; Crandall et al. 2011), and that it might even contribute to ethnic differences in face shape (Irmak et al. 2004). Even if humans did exhibit selective brain cooling, we would expect it to be switched off during strenuous exercise, as it is in artiodactyls when their brain temperature is at its highest (Jessen et al. 1994; Mitchell et al. 2002). Moreover, when we commence exercise, breathing switches from the nasal to an oral pathway very early during that transition (Varène et al. 1986); a fact that has escaped the purveyors of "nasal strips" for athletes.

In the context of exercise, we might also consider whether, amongst the extra-hypothalamic temperature sensors, sensors within skeletal muscle might also provide feedback to the regulatory centre. Skeletal muscles make up about a third of our body mass (Janssen et al. 2000), and, during exercise, they are the primary source of metabolic heat (Pembrey 1898; Buchthal et al. 1945). Leon Fredericq (1913) provided possibly the earliest alert for the physiological significance of muscle temperatures, which can increase by four to six times as much as oesophageal temperature during leg exercise (Kenny et al. 2003). Since control-system engineers might seek to position temperature sensors close to powerful heat sources, then it is not such a huge leap to suggest that natural selection might also have arrived at a similar solution, as there is the potential for a strong feedback signal to the regulatory centre, which, in turn, drives the effectors responsible for dissipating heat.

Thermally responsive receptors have been identified in the leg muscles of cats and dogs. In dogs, their thresholds are in the painful (nociceptive) range (Kumazawa and Mizumura 1977), whilst cats have warm and cold sensors (group III and IV muscle afferents) that respond to non-noxious changes in temperature (Hertel et al. 1976). The synchronisation of sudomotor activity with intramuscular and, to a lesser extent, oesophageal temperature (Figs. 2 and 18), shows evidence consistent with the existence of intramuscular thermoreceptors in humans, that might contribute to thermoefferent drive during exercise. The phase delay between changes in muscle temperature and the discharged sweat rate (Fig. 18; 26 s; Todd et al. 2014), which is delayed relative to the production of primary sweat (Machado-Moreira et al. 2009), was significantly shorter than the delay following oesophageal temperature changes (47 s; Todd et al. 2014). The role of intramuscular sensors in human thermoregulation remains speculative, although their existence has been hypothesised (Robinson et al. 1965; Stolwijk and Hardy, 1966a; Saltin et al., 1968a; Mitchell et al. 1977; Werner 1980; Jessen et al. 1983; Eiken and Mekjavic 2004). Even if intramuscular sensors are involved, we do not know whether their feedback is essential, given the existence of feedback from deep-body thermoreceptors located elsewhere.

We may have temperature sensors in our skeletal muscles, but we remain consciously unaware of muscle temperature. If those sensors do exist, it seems that they might feed information to the regulatory centre, but not to the conscious brain. Neural information from cutaneous thermoreceptors feeds into both the conscious brain and into the regulatory centre in the hypothalamus (Hellon 1970). Cutaneous thermoreceptors were described more than half a century ago (Zotterman 1953, 1959; Hensel 1974; Pierau 1996), and how that information proceeded via the thalamus to somatosensory cortex was established long ago. However, until very recently, no one knew how it got to the regulatory centre. We do now, and we recognise the pivotal role of the *parabrachial nuclei* (Fig. 16).

Those nuclei, situated where the brainstem joins the cerebellum, are the neural equivalents of airline hubs. They receive somatosensory information from the skin and viscera ascending through the spinal cord, and redistribute it to appropriate destinations in the brain, including the thalamus and hypothalamus (Saper 2002). In rats at least, they are responsible for despatching information from peripheral temperature sensors to the hypothalamus, thus providing input to the hypothalamic regulatory centre (Nakamura and Morrison 2008). Rats with thalamic lesions that prevent thermal signals reaching the somatosensory cortex, retain normal behavioural thermoregulation, as it is the projection via the *parabrachial nuclei*, and not via the somatosensory cortex, to the hypothalamus that mediates behavioural thermoregulation (Yahiro et al. 2017).

How does the regulatory centre process thermal information?

Whilst the vocabulary of thermal physiology in the Krogh-Hill epoch did not include terms like "feedback" or "threshold temperatures", contemporary thermal physiologists may not know how to discuss thermoregulation without using at least one of those terms. Figure 19 is a conceptual (signal-flow) model from fifty years ago (Mitchell et al. 1972) that will allow us to introduce those terms, as they were understood at that time, although contemporary thermal physiologists would no longer consider it to be a correct portrayal.

Neural feedback and feedforward to a central regulator Although the concepts and terminology had appeared in an earlier German paper (Wagner 1952; Simon et al. 2022), it usually is to Jim Hardy that the introduction of control-system concepts into thermoregulatory physiology is attributed, as a mechanistic explanation of how the regulatory centre might process information (Hardy 1961, 1965). Those concepts are characterised within Fig. 19, but they were also described quantitatively in terms of transfer functions; mathematical relationships between thermoeffector activation and changes in the regulated variable. Those relationships convert conceptual (didactic) and control-system models into mathematical expressions (Hardy 1961; Hammel et al. 1963; Werner 1996, 2010; Werner et al. 2008; Kanosue et al. 2010; Havenith and Fiala 2016; Wissler 2018).

Borrowing from control engineers of the time, Hardy (1961) advanced four potential mechanisms that could underlie the operations of the regulatory centre. The first was an on–off mechanism, as employed in an electric kettle, in which full heating is either present or absent. That is how we believe that thermoeffector activity was envisaged during the Krogh-Hill epoch and before, but there is no on–off control in autonomic thermoregulation. The second concept was proportional control, in which there is a direct relationship between the magnitude of the temperature deviation (load error in control-systems terminology) of the body (the passive or controlled system) and the magnitude of the thermoeffector response. The proportional descriptor arose because that relationship was originally confined to being linear, but that is now known to not necessarily be the case. The third concept was rate (or derivative) control, in which the magnitude of the control action is related not to the size of the temperature deviation, but to its rate of change. There is vast experimental evidence that thermoregulation operates on the basis of combined proportional and rate control. The fourth possible mechanism advanced was integral control, in which the magnitude of the control action is related to the time integral of the temperature deviation (*e.g.*, the area under a curve of body temperature against time). Integral control is used widely in engineering, but there is no evidence that it operates during thermoregulation.

That thermoregulation operates under proportional and rate control has major implications for how body temperature is regulated. For instance, during steady-state exercise, the body temperature is elevated relative to that at rest, but it then stabilises. It is simply being regulated at a different level; the operating point or new balance point. Similarly, during steady-state, cool-water immersion, we might see a reduced, but stable, body temperature. Those changes in temperature are not signs of regulatory failure (Nielsen 1938), but signs that the regulatory system is working properly. The reason is that, under proportional control, a sustained temperature deviation is required to drive the thermoeffectors, so that further changes in body temperature can be prevented. As a consequence, the body temperature stabilises at an operating point at which a different balance, relative to the normothermic state, is achieved between heat production and heat loss. That operating (balance) point is not the reference point shown in Fig. 19. Thus, the following statements are unsupported by empirical data: "*According to proportional control theory, the aim of the thermal controller is to establish a core body temperature at a given adjustable set point*" (Jay et al. 2008 [P. 1587]), and "*as the corrective effector responses take effect, countering the effect of the perturbation, the regulated variable begins to return towards set point values, and the deviation (error signal) is reduced*" (Ramsay and Woods 2014 [P. 11]). Those statements could be correct if the thermoregulatory system employed integral control, but it does not.

The magnitude of the temperature deviation of the passive system that is necessary for thermoeffector activity to prevent continued deviations in body temperature is not fixed. That is because the sensitivity (or gain) of the control system can change. If sudomotor sensitivity increases, as it does following thermal adaptation (Part 4 of this series), the temperature deviation necessary to drive sweating is reduced. On the other hand, thermoeffector sensitivity may decline with ageing (Tankersley et al. 1991; Inoue et al. 1999; van Someren et al. 2002), so the required deviation might increase.

Whilst the introduction of concepts of engineering control into thermoregulation was revolutionary, Hardy concerned himself with only one type of control, namely negative feedback control, wherein a change body temperature stimulates both behavioural and autonomic thermoeffector actions that might arrest that temperature change (Hardy 1961). The emphasis herein is upon autonomic thermoregulation of exercising humans, for which not just neural feedback, but also feedforward signals, provide inputs. Hardy did not consider feedforward control.

Feedback signals to the central nervous system come from a range of different types of receptors distributed throughout the body. As we have seen, some of those receptors form critical components of our homeostatic regulatory mechanisms (Table 1), they are parts of the somatic sensory system and they respond to stimuli associated with changes in both the internal and external environments ("Homeostasis: the foundation of systems physiology"). In the context of exercise, somatic sensors other than the thermoreceptors also provide important feedback, such as those related to the movement and position of the limbs (proprioceptors [mechanoreceptors]), changes in intramuscular status (metaboreceptors), contact with our surroundings (touch receptors), injury awareness (pain receptors) and receptors for the special senses (*e.g.*, visual and auditory sensors). The

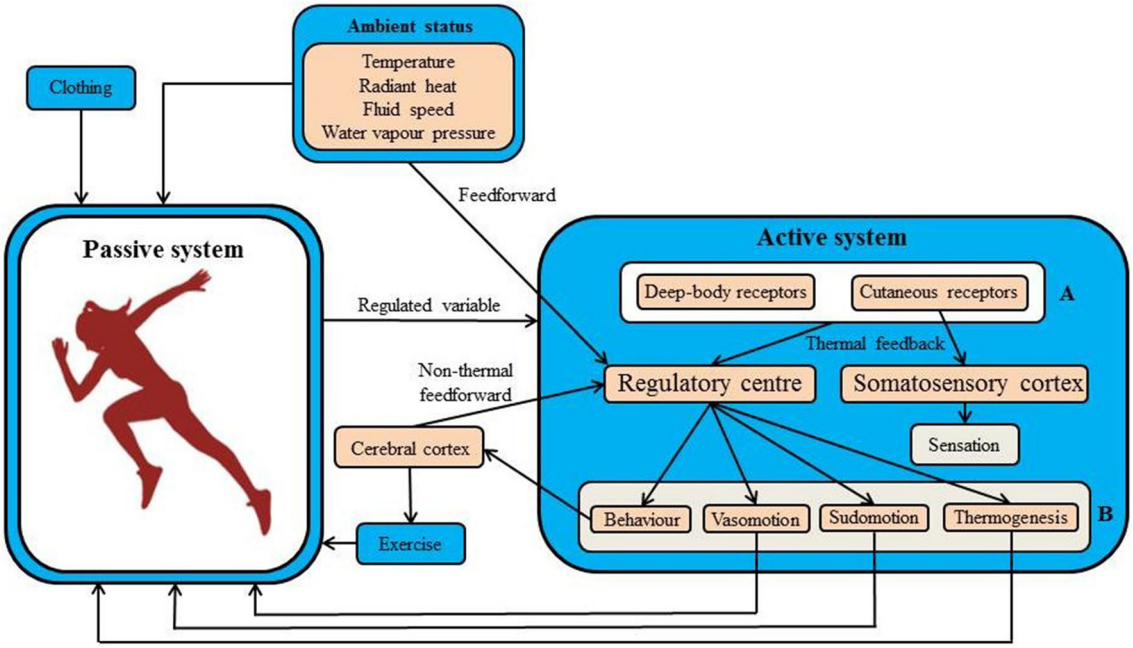
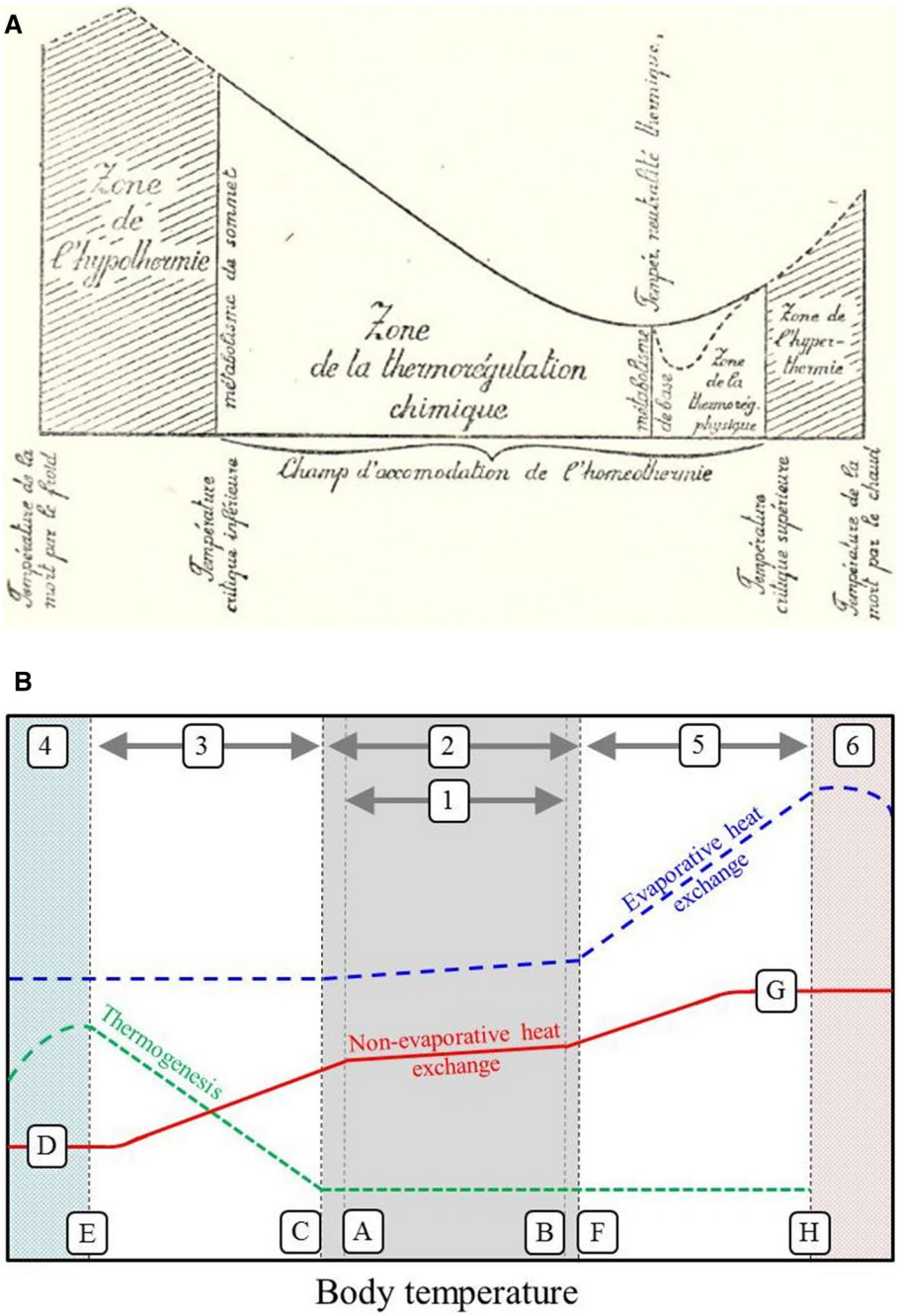


Fig. 20 A contemporary signal-flow model of the human thermoregulatory system, and its interactions with feedback and feedforward signals. The nomenclature follows that used by Werner et al. (2008 [Fig. 18.3]). The thermal energy content of the passive (controlled) system (the body) is affected by changes in the ambient conditions, clothing and exercise, with the resulting variations in body temperature (the regulated variable) being detected by thermosensitive elements within the active system. Block A of that system defines the regulated variable (body temperature), which is derived from thermal feedback to the regulatory centre arising from the deep-body and cutaneous thermoreceptors (thermoafferent flow) distributed throughout the body. In turn, that centre activates the controlled variables (thermoeffectors [control elements]; block B), which then modify the temperature (heat content) of the passive system. Feedforward signals convey pre-emptive or anticipatory information about the ambient conditions (upper block) and exercise-mediated effects of a non-thermal nature, originating within the cerebral cortex (central block). Whilst it is known that exercise-mediated feedforward modifies thermoeffector function, the precise site of that interaction is uncertain. Cutaneous receptors, which communicate with the somatosensory cortex, generate conscious temperature sensations

thermoregulatory system relies predominantly on thermal feedback signals, but it is also influenced by non-thermal signals, which may support, or even interfere with homeothermy, when they provide information about competing homeostatic processes, such as blood pressure regulation.

Neural feedforward signals in thermoregulation provide pre-emptive or anticipatory information concerning changes in the thermal status of our immediate surroundings. They also provide information concerning impending changes in the musculoskeletal and metabolic status of the body. Those changes within an exercising individual may eventually disturb thermal homeostasis, but thermal feedback is not yet available. Those feedforward signals emanate from the cerebral cortex, they are of a non-thermal nature, and they are not related to the sensory feedback from the thermoreceptors that are measuring body temperature. Nevertheless, they alert the thermoregulatory system, and other regulatory systems, to changes in the metabolic demand for energy and heat production, such as the initiation of exercise, variations in exercise intensity or the cessation of exercise. Those signals modulate thermoeffector function (e.g., cutaneous vasoconstriction and sweat production) before there has been any change in body temperature.

At the onset of exercise, in anticipation of blood being redirected to the metabolically active tissues, and a potential fall in blood pressure, those cortical signals induce an almost instantaneous, but intensity dependent, constriction within the cutaneous vascular beds (Christensen et al. 1942; Vissing et al. 1991; Kondo et al. 1998; Shibasaki et al. 2005). That is actually counterproductive to heat dissipation, and since the blood volume is much smaller than the overall capacity of our vascular networks, it was once thought that the exercising skeletal muscles competed with the skin for that limited blood volume (Rowell 1977), although Christensen et al. (1942) believed that "*the skin has no significance as an active blood depot at the transition from rest to exercise*" (P. 170), and that competitive theory has now been domesticated (Hales 1996; Kenney et al. 2014). Furthermore, if the body is sufficiently hyperthermic, and the intensity of the exercise is within the moderate domain, that cutaneous vasoconstrictor response will be reduced, representing a relative constriction, and it may even be prevented (Johnson and Park 1982).



Similarly, there is an intensity-dependent activation of precursor sweating as exercise commences (van Beaumont and Bullard 1963; Kondo et al. 1998, 2002; Shibasaki et al. 2003, 2006), which appears to be effort-dependent, and unrelated to the size of the activated muscle mass. That is, the exercise-related sudomotor response is primarily determined by the relative intensity of the muscle activation (*e.g.*, 50% of maximal voluntary activation), and seems to be uninfluenced by the size of the activated muscle mass (*e.g.*, handgrip versus leg extension) when those muscles are activated at an equivalent intensity (Gordon et al. 2016). In a thermally primed (slightly warm) individual, discharged sweat can appear within 1.5 s of the start of exercise, and long before any body temperature could have changed (van Beaumont and Bullard 1963). Conversely, at the end of exercise, there can be an immediate, sometimes transitory, reduction in sweat rate, which is also well in advance of the body temperatures falling, and it may occur even when body temperatures are still increasing. Whilst that reduction may accompany declining non-thermal feedforward, it is believed to be more

◂**Fig. 21** **A** Djaja's representation of temperature regulation (Giaja 1938a), which is in the Public Domain. Translations (left to right): (1) "*Température de la mort par le froid*" lethal cold temperature, (2) "*Zone de l'hypothermie*" zone of hypothermia (3) "*Température critique inférieure*" lower critical temperature, (4) "*Métabolisme de sommet*" peak metabolism, (e) "*Champ d'accomodation de l'homéothermie*" zone of homeothermic accommodation, (f) "*Zone de la thermorégulation chimique*" zone of metabolic (thermogenic) thermoregulation, (g) "*Métabolisme de base*" basal metabolic rate, (h) "*Température neutralité thermique*" zone of thermoneutrality, (i) "*Zone de la thermorégulation physique*" zone of physical thermoregulation, (j) "*Température critique supérieure*" upper critical temperature, (k) "*Zone de l'hyperthermie*" zone of hyperthermia and (l) "*Température de la mort par le chaud*" lethal hot temperature. **B** A contemporary adaptation of Giaja's (1938a) overview of human thermoregulation and the zones of temperature regulation, incorporating embellishments added by Stanier et al. (1984), Bligh (1987), Mekjavic et al. (2003), Werner et al. (2008) and Taylor and Gordon (2019). All thresholds are referenced to the regulated variable (body temperature). The vasomotor zone (1) sits between the thresholds for cutaneous vasoconstriction (point A) and vasodilatation (point B). It describes the regulatory zone in which physiological heat exchanges occur only through changes in vasomotor activity. Within that zone, there are only slight variations in body temperature. The inter-threshold zone (2) sits between the thresholds for shivering (point C) and sweating (point F), which define the commencement of thermogenic (zone 3) and (zone 5) sudomotor temperature regulation. Evaporative heat exchange includes transepidermal evaporation, which occurs across a broad range of body temperatures and participates in evaporative heat exchange before the sweat glands are activated. The regions of maximal vasoconstriction (D) and vasodilatation (G) are shown as plateaux, whilst the summit values for thermogenesis (E) and sweat secretion (H) set the limits beyond which unregulated hypothermia (zone 4) and hyperthermia (zone 6) will eventually ensue

strongly associated with altered baroreceptor activity at the cessation of exercise (Kenny and Journeay 2010).

By the time that neural feedforward was implicated, and more fully appreciated in thermoregulation, it was a phenomenon that had been known to exist since the first epoch, with regard to exercise-induced changes in the central cardiac and ventilatory responses (Zuntz and Geppert 1886 [Germany]; Johansson 1894 [Sweden]; Krogh and Lindhard 1913 [Denmark]). Since those signals originate from the cerebral cortex, and then activate both the motor neurons and the autonomic nervous system, they are also known as central-command signals (Goodwin et al. 1972; Williamson et al. 2006). That term has also been used within thermal physiology (Kenny and Journeay 2010; Kondo et al. 2010). Part of the logic for the proposition that feedforward signals must also exist, as part of the human thermoregulatory system, was based upon the delay in thermoeffector activation that would occur if that system relied wholly upon feedback signals. Similarly, in the absence of feedforward control, the central cardiac and ventilatory responses to exercise would be delayed, and blood flow to the skeletal muscles would be insufficient for their immediate needs. Presumably, the acquisition of such control mechanisms must have been favoured during natural selection.

The inclusion of thermal feedforward control into concepts of how thermoregulation operates occurred about a century later than its acceptance within cardiovascular and respiratory physiology. Part of that progression might be attributed to Huckaba et al. (1971). In their time, skin temperature was not considered to be part of the regulated temperature; only hypothalamic temperature was regulated. Since skin temperature was influenced by ambient conditions, cutaneous receptors were plausible candidates for providing thermal feedforward control, and that is how Huckaba and colleagues envisaged feedforward control to be implemented during changes in the thermal environment. However, the idea that the regulated temperature was only hypothalamic temperature was soon abandoned, in favour of a less-specific, deep-body temperature being the regulated temperature. Skin temperature was still excluded, though, so the cutaneous thermoreceptors remained as possible candidate sources for thermal feedforward control (Kanosue et al. 2010; Romanovsky 2014).

Our contemporary understanding is that the thermoreceptors responsible for thermoregulation are distributed widely throughout the body, with the regulated temperature including skin temperature (Hensel 1973; Jessen 1996; Werner 2010). Since the firing rates of the cutaneous thermoreceptors are rate sensitive (Hensel 1974, 1981; Pierau 1996), they can alert the central nervous system to small, sudden, localised temperature changes, and thereby elicit corrective actions before deep-body temperatures deviate significantly. But those corrective responses occur only after skin temperature has changed, even if only slightly, so the signal that they provide is a very rapid feedback signal, not a feedforward signal. Also, in conditions of high metabolic or ambient heat loads, during which the thermoregulatory system might most require accurate information about the thermal surroundings, the skin temperature is effectively clamped as a result of evaporating sweat (Fig. 13), so the cutaneous thermoreceptors cannot convey either feedforward or feedback information concerning temperature changes.

Our mechanistic appreciation of how the regulatory centre might process information has advanced appreciably since the time of Hardy (1961), and the simplistic model in Fig. 19, when only thermal feedback was considered within the thermoregulatory system. Indeed, physiologists have now also added the roles of non-thermal feedforward and other forms of non-thermal modulation (Crandall et al. 1998; Kenny and Journeay 2010; Kondo et al. 2002, 2010; Shibasaki et al. 2003, 2005, 2006; Gordon et al. 2016), as well as a role for non-thermal interference with thermoregulation that might result from the activities of other homeostatic processes (Crandall et al. 1998; Mekjavic and Eiken 2006). Particularly important for thermoregulation during exercise

are the activities of the metaboreceptors and mechanoreceptors (Kondo et al. 2002). They alert the thermoregulatory system to changes in exercise state and some of the biochemical consequences of higher-intensity exercise (e.g., changes in metabolite concentration) that almost invariably leads to an increased body temperature. Such signals may be viewed as providing pre-emptive activation of the thermoeffectors, and a contemporary signal-flow model of how all of those signals are believed to interact is presented in Fig. 20.

The examples provided above reveal another important difference between feedback and feedforward control. To the best of our knowledge, all neural feedback signals, including those that stimulate behavioural responses, are processed in the hypothalamus. Feedforward neural signals that modulate the autonomic thermoeffector responses, such as vasoconstriction and sweating, will also be processed within the hypothalamus. Feedforward that leads to behavioural responses also require central processing, because those afferent signals have to be interpreted in the context of stored information about previous experiences, and an appropriate behavioural response has to be initiated, mainly via the motor cortex. One assumes that level of processing occurs outside the hypothalamus, as does the processing of many reflexes. The part of the brain best equipped to integrate afferent signals, stored and efferent information of a behavioural nature is the insular cortex, which connects with both the hypothalamus and the motor cortex (Nieuwenhuys 2012), and it also receives thermosensory information in humans (Craig et al. 2000; Hua et al. 2005).

However, on its own, feedforward control has no capacity to correct regulatory errors in real time. For that to occur, the regulatory centre requires thermoafferent feedback so that it can adjust the effector responses when and where necessary, including adjusting for errors resulting from faulty responses to feedforward signals. We leave this topic with a brief comment concerning other views about neural feedback and feedforward. For example, George Somjen, an influential neurophysiologist, denied any role for feedback control in thermoregulation (Somjen 1992). He considered all thermoregulatory responses, autonomic and behavioural, to be learned responses. He cannot have been right. Ramsay and Woods (2014, 2016) did not deny a role for negative feedback in thermoregulation, but regarded feedforward control as being responsible for the precision of thermoregulation. They attributed any imprecision to inadequate learning. They too cannot be right. Precision in thermoregulation derives from the correction of potentially adverse body temperature deviations, and that is the core responsibility of all feedback systems.

Reference signals, set-points, operating points, critical temperatures and thresholds Feedback and feedforward control are concepts introduced from systems engineering. Of the engineering terminology that has been introduced, none has created more fervour than the term *set-point* (Hardy 1965). Engineering control systems often use a reference signal, against which feedback is compared, which then leads to the creation of a *set-point*. A familiar example is the cruise control of a motor vehicle (Stone et al. 2015), which continually controls engine power to keep vehicle speed at a reference level; the *set-point* of that system. Given that deep-body temperature is so stable, in so many different circumstances, with multiple thermoeffectors in action, it

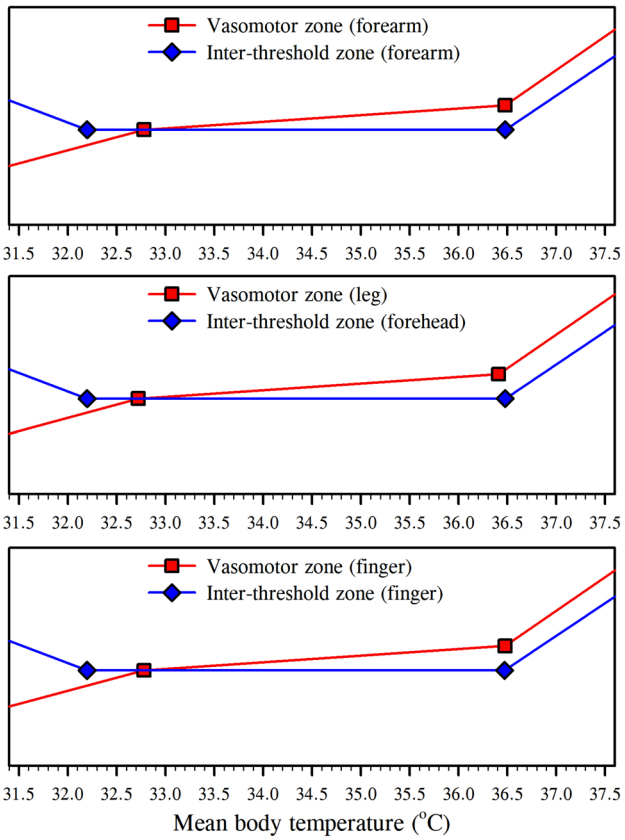


Fig. 22 The vasomotor and inter-threshold zones of resting (supine) adults. The mean body temperature thresholds of the former zone were determined from simultaneously measured variations in the vascular conductance of the forearm (laser-Doppler flowmetry), and from the leg (calf) and finger (venous-occlusion plethysmography). Since physiological heat exchanges in this zone are mediated only via vasomotor activity, it is known as the vasomotor zone. The slopes within those vasomotor zones are qualitative reminders that the cutaneous vasculature is not quiescent, even when normothermic and comfortable. The inter-threshold zones were defined on the basis of the mean body temperatures that coincided with the initiation of shivering thermogenesis (increased whole-body oxygen consumption) and the simultaneously determined thresholds for precursor (primary) sweat production from the forearm, forehead and finger (skin conductance). Those thresholds occur earlier than the appearance of discharged sweat on the skin surface, and more closely reflect changes in sympathetic activity. Data were extracted from the experiment of Taylor et al. (2019), which involved separate trials of passive cooling and heating in supine individuals ($N = 8$)

is no surprise that early researchers considered physiological thermoregulation to operate with a reference signal that might also lead to the generation of a *set-point* (Benzinger 1961, 1969b), as in Fig. 19. So convinced were those early researchers that the reference signal was a physiological reality that the responsibility for generating it was assigned to temperature-insensitive neurons within the hypothalamus (Hardy 1965).

One of the oldest observations of how thermoregulation might involve the elevation of deep-body temperature, was through a coordinated response of several thermoeffectors during a fever. Fevers fitted comfortably into the framework of an elevated *set-point* (Benzinger 1969a). However, as our understanding of human thermoregulation progressed, many thermal physiologists abandoned the idea of a global *set-point* as a foundation for a stable deep-body temperature, even during fever, and they also abandoned the concept of a global regulator (Mekjavic et al. 1991; Kanosue et al. 2010; Werner 2010); though not all contemporary thermal physiologists have done so. Moreover, whilst the *set-point* concept of Benzinger (1961) is certainly now regarded as incorrect, so too is the adjustable *set-point* of Hammel et al. (1963). Indeed, following a conference presentation by John Bligh on, and his explanation of, an adjustable *set-point* for the different thermoeffectors, G. Romaine Hervey made the comment: "*so what you are saying is that it is neither a point nor is it set*" (Michael Tipton, personal communication with Joules). Since "… *we have all been wrong often*" (Hill 1965 [P. 167]), then a thermoeffector "threshold", rather than a *set-point*, is our preferred term, in agreement with Werner (2010).

Contemporary thermal physiologists believe that vasomotor and sudomotor activities, as well as shivering and our thermally driven behavioural responses, are both autonomous and independently controlled (Tansey and Johnson 2015; Taylor et al. 2019). Those thermoeffectors share elements of a common regulatory system, such as the thermoreceptors. Furthermore, those effectors are coordinated to serve a common goal, and that is to manipulate the avenues for exchanging thermal energy, as expressed within the energy-balance equation, such that, whenever possible, the rate of heat storage is reduced to zero, and body temperature is stabilised. As noted above, body temperature can be regulated at either lower or higher operating (balance) points (Werner 2010).

Thermal physiologists of the modern epoch have retained the idea that the thermoeffectors exhibit activation thresholds in response to changing body temperatures (Werner 2010; Tansey and Johnson 2015). Below one threshold, for example, there is no sweating; above that threshold, sweating increases with increments in body temperature. Moreover, thresholds for the different thermoeffectors are not identical (Mekjavic et al. 1991; Taylor et al. 2019). For instance, when cooled from an hyperthermic state through to mild hypothermia, sweating did not cease at exactly the same body temperature that shivering was initiated, as was once believed (Cabanac and Massonnet 1977). Instead, there exists an inter-threshold zone where neither of those thermoeffectors is active (Burton and Bazett 1936; DuBois 1939; Brück et al. 1970; Jessen and Ludwig 1971; IUPS Thermal Commission 2001; Mekjavic and Eiken 2006). That zone is sometimes also called the thermoeffector inter-threshold zone (IUPS Thermal Commission 2001), and it, along with other regulatory zones, was first independently described by the Serbian physiologist, Ivan Djaja (1884–1957, Fig. 21A; Giaja 1938a, 1938b [known as Jean Giaja in other languages]; Andjus

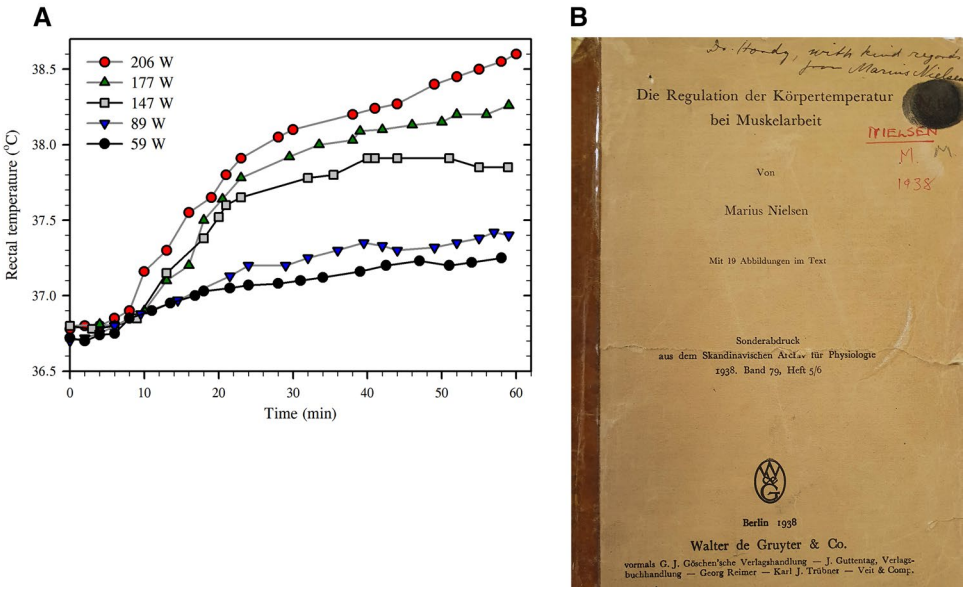


Fig. 23 **A** Rectal temperatures of a man cycling on an ergometer (60 min) at each of five work rates (22°–23 °C dry bulb, 35–45% relative humidity). Data were extracted from Nielsen (1938 [Fig. 2]) and redrawn. Apart from canvas shoes, the subject was unclothed. **B** In the era when reprints were given to colleagues, and often sent by mail, Nielsen gave a (signed) copy of his manuscript to Jim Hardy (U.S.A.). Reprints were sent by surface mail, and would have taken many weeks. In the twenty-first Century, those weeks have been reduced to seconds, but at the expense of reprints being signed personally!

et al. 2016), and Hardy and Soderstrom (1938, Fig. 21B; USA).

Taylor et al. (2019) have recently shown that, when the regulatory zones between shivering and local sweating onset were determined across three body segments, those inter-threshold zones covered, on average, a mean body temperature range of 4.3 °C. Between those thresholds, both passive and physiologically controlled heat exchanges will still occur, with the latter being the result of sympathetically mediated cutaneous vasomotor activity. That second regulatory zone might also be called an inter-threshold zone, but in the parlance of our predecessors, it is known as the vasomotor zone (Hardy and Soderstrom 1938), since it describes a regulatory zone within which physiological heat exchanges are modified only through changes vasomotor activity. The end points of that zone are separated by the thresholds of cutaneous vasoconstriction (heat conservation) and vasodilatation (heat loss), and, in our hands, that zone covered a mean body temperature range of 3.7 °C when averaged across three body segments (Fig. 22; Taylor et al. 2019). Thus, the inter-threshold zone was 0.5 °C larger than the vasomotor zone, and the threshold for shivering activation was 0.5 °C lower than the average threshold for cutaneous vasoconstriction. During heat storage, the average threshold for precursor sweat production was indistinguishable from the average vasodilatation threshold.

Accordongly, there appears to exist a sequential, or cascade of, thermoeffector recruitment (Taylor and Gordon 2019), and since those thermoeffectors were acquired at vastly different times during the evolution of *Homo sapiens* (see "Homeostatic priorities" and Part 4 of this series), that should perhaps not be unexpected, as others have noted (Jessen and Ludwig 1971; Satinoff 1978; Kanosue et al. 2010; Romanovsky 2018). Indeed, that recruitment progression is slower, or even incomplete, in people with larger mass-specific surface areas (Notley et al. 2016, 2017), and, to some extent, must be morphologically linked, since more effective passive heat loss removes, or at least reduces, the need to recruit one or more of the thermoeffectors. Therefore, attempts to explain the intricacies of thermoeffector control, without also controlling for variations in body size, may yield incomplete or possibly misleading outcomes.

Furthermore, there is evidence that those thresholds, and the regulatory zones they define, are adjustable, as occurs during thermal adaptation (Taylor 2014), and those thresholds may even change independently, with the thresholds for heat-loss effectors sometimes moving in different directions (Taylor and Gordon 2019). For example, "*when passive heating followed whole-body pre-cooling, the vasomotor and sudomotor thresholds varied independently, with a reduction in the former and an elevation in the latter*" (Taylor et al. 2019 [P. 43]). Those observations are consistent with the hypothesis that different thermoeffectors are controlled by different components within the regulatory centre (Hammel 1965; Tansey and Johnson 2015; Taylor et al. 2019; Taylor and Gordon 2019). Furthermore, the threshold for one thermoeffector (e.g., sweating) can lie within the thermoregulatory zone of another thermoeffector (e.g., vasomotion), so sweating will begin before vasodilatation is complete.

Campaigners against the global *set-point* concept (including the current authors) tend to forget that, when Hammel (1965) first discussed *set-points*, not only did he regard those points as being synonymous with a thermoeffector threshold, but that he proposed separate thresholds for each thermoeffector. That is exactly the concept to which we have reverted, after years of futile fervour (Gisolfi 1983; Gisolfi and Wenger 1984; Werner 2010; Taylor and Gordon 2019). However, even though the concept of a global regulator has been abandoned, the central role of the hypothalamus, as the anatomical seat of the regulatory centre, is firmly in place. But the role of the hypothalamus in homeostasis extends far beyond thermoregulation (Saper and Lowell 2014).

Particularly important for exercise is the role of the hypothalamus, or the adjacent circumventricular organs, in osmoregulation (Bourque 2008), because thermoregulation and body-fluid regulation are homeostatic processes that both compete for body water (McKinley et al. 2018; Table 1). In most animals that use evaporative cooling, increasing the concentration of the blood (haemoconcentration) and reducing blood volume, as occurs during hypohydration, suppresses evaporative cooling, if fluid loss becomes excessive. Clearly, that must hold in extreme states in humans, but in less-extreme states, whether or not there is suppression of sweating during hypohydration depends on a complex interaction between the direct effects of hypohydration and the secondary effects of hypohydration-induced hyperthermia. We have analysed that interaction in detail in Part 3 of this series, in which we also examine the significance of quantifying sweat rates at the same body temperatures, before and after dehydration, since it is thermoefferent feedback that activates and then drives sweating.

In non-human mammals, the main signal for the suppression of evaporative cooling appears to be an increase in plasma tonicity, not osmolality, because changing the concentration of non-ionic molecules seems to be equally effective (McKinley et al. 2018). There are neurons within the hypothalamus that respond to both high body temperature and hypertonicity (Boulant and Silva 1988), so the hypothalamic regulatory centre has the neuronal capacity to manage possible competition between temperature and body-fluid regulation, although that management may well occur elsewhere, because there is convergence between the efferent pathways from that centre and the pathways originating from the neurons and receptors that respond to changes in tonicity.

Does the regulatory centre reset during exercise?

At he start of the modern epoch, one of the more-influential papers relating to thermoregulation in exercising humans was published by one of August Krogh's assistants, Marius Nielsen (1903–2000, Denmark; Nielsen Johannsen 2022). He showed that, when subjects exercised for 60 min at different external work rates (Fig. 23; 22°–23 °C dry bulb), rectal temperature rose and then stabilised at intensity-dependent plateaux, except at the highest work rate (Nielsen 1938). We often associate both Nielsen (1938) and Saltin and Hermansen (1966) with identifying the exercise-intensity dependence of deep-body temperature, but it was Bardswell and Chapman (1911) who provided possibly the earliest evidence of that relationship. Nielsen (1938) did, however, first describe that change to be independent of air temperature, which he varied between 8° and 29 °C, seemingly divorcing the elevation in rectal temperature from the external thermal load. Earlier, Dill et al. (1931, U.S.A.) had observed that, during exercise "*a constant temperature may be reached if conditions for heat dissipation are favorable; otherwise body temperature rises until exhaustion intervenes*" (P. 517). Nielsen and Nielsen (1962) reinforced that temperature independence, although they tested subjects only at 5°, 20° and 30 °C (Nielsen Johannsen 2022). Nevertheless, those Danish papers are often used to support the notion that deep-body temperature will remain independent of air temperature between 5° and 30 °C (dry bulb), even though only three conditions were investigated.

From the heat-transfer equations, it appears that, at a wind speed of 1.9 m s^{-1}, the combined radiant and convective heat loss rate over that temperature range would have changed by < 100 W (Mitchell et al. 1968), whereas of metabolic heat production changed by > 400 W (Nielsen 1938). Furthermore, since those trials were conducted at 35–55% relative humidity, the ambient conditions were physiologically compensable. Apart from contending that the elevation was independent of ambient temperature, Nielsen's interpretation was that something to do with the exercise, other than the metabolic heat load, was responsible for the elevation in body temperature.

As proposed originally by Sid Robinson (1902–1982, U.S.A.; Blatteis and Schneider 2022), Nielsen believed there was a work-related factor involved in thermoregulation during exercise (Robinson 1949; Smiles and Robinson 1971). Not just Nielsen's results, but subsequent non-human experiments initiated speculation about the possible resetting of the regulated body temperature during exercise by some work factor. Several researchers contended that the regulatory centre incorporated a global *set-point* that was raised during exercise, but just as many contended that it was either lowered or unchanged (Gisolfi 1983; Gisolfi and Wenger 1984). It is counterintuitive for a global *set-point*, even if it existed, to be raised during exercise when more sweating is required to dissipate heat, since an elevated threshold would diminish sudomotor drive (Schneider and Moseley, 2009).

Nielsen's belief that something unusual was happening to the regulatory centre during exercise would have been challenged by evidence from an experiment conducted with his (unrelated) colleague, Bodil Nielsen. They found very similar cutaneous vascular and sudomotor responses during both passive heating (diathermy) and cycling, which were manipulated to elicit equivalent deep-body temperatures in both conditions (Nielsen and Nielsen 1965). C.T. Mervyn Davies (Davies 1979; England) confirmed that result using positive (concentric) and negative (eccentric) work on a treadmill.

Negative work is a useful tool for thermal research, because the rate of internal heat production equals the metabolic heat production plus the heat acquired from negative work (*First Law of Thermodynamics*). Therefore, during positive and negative work at the same steady-state oxygen consumption, one must expect to observe higher deep-body temperatures during negative work (Davies 1979). At that metabolic rate, negative work will also require a greater rate of physical and physiological heat loss for the body temperature to stabilise. Thus, greater sweat rates should be observed during negative work, which is what Davies had observed, leading him to conclude that "*the postulation of specific "work" factors is totally unwarranted*" (Davies 1979 [P. 179]), if muscle temperature was included as an independent component of body temperature. The regulatory centre worked as usual during exercise, without the need for a work factor or a change in the thermoeffector thresholds.

Bodil Nielsen remained convinced that a work factor existed, and its impact extended far beyond negative work. She concluded that "*it seems that the increase of the internal temperatures during work is brought about by some work factor, possibly of chemical nature, liberated by or in proportion to the extent of the oxydative processes. This induces a change in the setting of "the human thermostat", perhaps in a manner similar to the action of a pyrogen in fever*" (Nielsen 1966 [P. 224]). Her conclusion was based on measurements of metabolic rate, sweat rate and deep-body (oesophageal) temperature during uphill, downhill and level treadmill walking. Sweat rate was related to the total heat production, but she made the extraordinary observation that sweat rate was unrelated to deep-body temperature, because body temperature was dependent on metabolic rate (oxygen consumption), and not on the overall heat production. Oesophageal temperatures were equivalent at the same oxygen consumption rate during positive and negative work, though heat production and sweat rates were completely different. Where does that lead us? Is the regulatory centre exercise-intensity sensitive?

Table 2 Examples of the variations in plasma interleukin-6 (IL-6) concentrations (arranged in ascending order) following prolonged laboratory exercise, competitive sporting events and other clinical and experimental procedures that elevate cytokine concentrations

Physical activity and conditions	Plasma interleukin-6 concentration (pg mL^{-1})	Source
Cycling (90 min, 35 °C dry bulb)	3.6	Starkie et al. (2005)
High and moderate-intensity walking	4 (at peak)	Brown et al. (2018)
Running (20 km, < 2 h)	4	Sprenger et al. (1992)
Cycling (60 min, deep-body temperature 39.5 °C)	5 (arterial sample)	Nybo et al. (2002a)
Two-legged knee-extensions (~ 55% maximal, 180 min)	8.5	Steensberg et al. (2002)
Cycling (40 min at 65% peak aerobic power, peak deep-body temperature 39.1 °C)	Increased by 10	Rhind et al. (2004)
Hypoxic running (60 min, 65% normoxic peak aerobic power)	12	Hill et al. (2020)
Running (60 min, 75% peak aerobic power)	12	Shin and Lee (2011)
Cycling (164 km, 4.8–8.9 h, 30.0°–31.5 °C wet bulb)	23	Vingren et al. (2016)
Berlin Marathon (3 h 15 min to 5 h 25 min)	32 (median [interquartile range 21–41])	Bernecker et al. (2013)
Passive, whole-body hyperthermia (chemotherapy)	50	Katschinski et al. (1999)
Passive, whole-body hyperthermia (60 min, deep-body temperature 41.8 °C)	50	Robins et al. (1995)
Patients with haemorrhagic fever	70	Linderholm et al. (1996)
Copenhagen Marathon (2 h 40 min to 4 h 20 min)	75	Ostrowski et al. (1999)
Boston Marathon (2001)	Pre-race: 1.6, post-race 67	Siegel et al. (2007)
Cycling (60 min, 75% of peak aerobic power)	80 (75% quartile 210)	Ullum et al. (1994)
Brussels Marathon (3 h 06 min to 4 h 24 min)	88	Castell et al. (1996)
Beppu-Oita Mainichi Marathon (2 h 25 min to 2 h 40 min)	120	Suzuki et al. (2000)
Recombinant human IL-6 infusion	150 (at peak)	Steensberg et al. (2003)
Endotoxin-induced fever (rats)	450	Cartmell et al. (2000)
Critically ill surgical patients with sepsis	1000 (threshold for increased mortality: peak concentration 500,000)	Damas et al. (1992)

All increases following prolonged exercise were considered significant. [Some of the values were obtained from published graphs, and should be regarded as estimates]

Is temperature regulation linked to exercise intensity?

One might be able to explain the disconnection between sweat rate and deep-body temperature if body temperatures other than those measured were involved, but no simple explanation would account for Nielsen's interpretation (Nielsen 1966). That is, there seemed to be an uncoupling of sudomotor drive from thermal feedback, and an apparent linkage of that drive to the whole-body metabolic rate. That possibility raises some important questions. How does the regulatory centre acquire information concerning exercise intensity? Presumably, that occurs via a non-thermal feedforward mechanism (Fig. 20). How does the centre use that information, in combination with heat storage, to determine the required heat loss (e.g., sweat rate)? We will return to these questions in Part 2 of this series.

Exercise, cytokines and thermoregulation

Within a few years, Bodil Nielsen's (1966) contention, that the regulatory centre might be reset during exercise, received unexpected support from James Haight and Bill R. Keatinge (1931–2007; England; Milton 2022). They found that the rectal temperature of nine men who had completed prolonged exercise (37-km hilly walk in 9 h) was not restored to its basal level, as it was following shorter exercise bouts, but remained elevated for 11 h (Haight and Keatinge 1970; Haight and Keatinge, 1973a). During that period, the deep-body temperature threshold for sweating was shifted upwards, so the body temperature elevation was defended, as it would be in a fever. They concluded that the "*temperature changes are most easily explained by mild pyrexia due to the release of endogenous pyrogen associated with minor tissue damage*" (Haight and Keatinge, 1973a [P. 77]). It is also well established that such exercise is followed by a period of an elevated (excess) post-exercise, resting oxygen consumption, which is also believed to be coupled with an increased body temperature (Gaesser and Brooks 1984).

A decade later, Joseph Cannon and Matthew Kluger (U.S.A.; Blatteis and Schneider 2022) looked for evidence of an endogenous pyrogen that might be released during exercise. They collected plasma and the supernatant from leukocytes, from humans who had just completed 1 h of cycling (60% of peak aerobic power). When those fluids

were transfused into rats, they developed monophasic fever (Cannon and Kluger 1983). Cannon then moved to work with Charles Dinarello (U.S.A.), and, following a hint from the work of Liesen et al. (1977; Germany), they concluded that the cytokine induced by that exercise was interleukin-1 (IL-1), the activity of which was abolished by antibodies that neutralised human IL-1 (Cannon et al. 1986).

Within the next decade, researchers with more sophisticated cytokine assays were unable to find appreciable concentrations of IL-1 in human plasma during, or after exercise (Ullum et al. 1994). They contended that Cannon's methods could not distinguish between IL-1 and interleukin-6 (IL-6; Ostrowski et al. 1999), and suggested they had actually found IL-6. If any cytokine could reset the regulatory centre, it is likely to be IL-6, since it is required for re-setting during a fever (Cartmell et al. 2000). However, most researchers exploring IL-6 release during exercise had no interest or concern in its role during thermoregulation, but it has become a molecule of considerable impact for contemporary exercise physiologists (Pedersen et al. 2007; Pedersen and Febbraio 2008; Pedersen and Hoffman-Goetz 2000; Suzuki 2019). They were justified in their lack of concern, but they were not to know that a priori.

Many researchers of IL-6 release accompanying exercise express its impact in terms of the fold number of concentration increase, relative to its pre-exercise concentration. That approach is highly sensitive to errors in the almost-undetectable background concentration of IL-6 before exercise. A more realistic view of the phenomenon comes from the actual concentrations (Table 2). When analysed in that way, some clear patterns emerge, which do not seem to have been described previously. Firstly, none of post-exercise IL-6 concentrations, for which skeletal muscle is the source, is nearly as high as the IL-6 concentrations in fever or inflammation, for which monocytic cells are the source of IL-6 (Luheshi 1998); muscle is a poor source of IL-6 (Moldoveanu et al. 2001). Secondly, plasma IL-6 concentration after exercise tended to be lower when the exercise was controlled in the laboratory, than when it was measured following self-paced, competitive exercise. Indeed, those lower concentrations were unlikely to have any effect on body temperature, though they may have other actions (Moldoveanu et al. 2001). Thirdly, plasma IL-6 concentration following passive, whole-body hyperthermia exceeded the concentration following most episodes of prolonged exercise in the laboratory.

Interleukin-6 is the main cytokine that acts on the thermoregulatory centre to induce the body temperature changes associated with fever, but its release into the circulation follows the appearance of the pro-inflammatory cytokines, tumour necrosis factor (TNF) and IL-1. Indeed, infusion of recombinant human IL-6 into volunteers had no effect at all on deep-body temperature (Steensberg et al. 2003). Nor did the injection of IL-6 into rats (Cartmell et al. 2000), although it did cause fever if it was accompanied by a sub-pyrogenic dose of IL-1 (Cartmell et al. 2000). During exercise, IL-6 is a primary cytokine (Pedersen and Febbraio 2008). Its appearance in plasma precedes that of both TNF and IL-1 (Brown et al. 2018). That earlier appearance actually suppresses the release of pro-inflammatory TNF and IL-1 from muscle. Exercise also inhibits the release of pro-inflammatory cytokines from blood monocytes (Gleeson 2000), though perhaps not their intracellular synthesis (Moldoveanu et al. 2001), and it promotes the release of anti-inflammatory cytokines (Petersen and Pedersen 2005; Peake et al. 2005; Gleeson et al. 2011). With little or no IL-1 in plasma when IL-6 appears during exercise, IL-6 may then have no effect on body temperature, whatever its concentration.

It was a plausible hypothesis that IL-6 was associated with muscle damage (Ostrowski et al. 1998), but that is now known not to be the case (Pedersen 2000; Toft et al. 2002; Suzuki 2019). There is no correlation between IL-6 concentration and plasma markers of cell lysis. Whatever the source of IL-6 is, it may have nothing to do with muscle activation. For example, when men completed 40 min of cycling at 65% of peak aerobic power in a water bath used to first clamp rectal temperature above 39 °C, IL-6 appeared in their plasma, but when rectal temperature was clamped at 37.5 °C during exercise, none appeared (Rhind et al. 2004). Cold-water immersion (15 °C) following strenuous weight lifting suppressed IL-6 release, 30 min after completing the exercise (Earp et al. 2019). After treadmill running (60 min), lower plasma IL-6 and tympanic temperatures were observed in athletes than a control group (Shin and Lee 2011).

Those results, coupled with the evidence that whole-body hyperthermia, on its own, induces a substantial release of IL-6 (Katschinski et al. 1999; Robins et al. 1995), raise the possibility that it is not muscular activation per se, but muscle hyperthermia (Suzuki 2019) that causes the generation of IL-6. Testing that hypothesis requires measurement of intramuscular and valid deep-body temperatures, which researchers into exercise-associated IL-6 have only occasionally undertaken (Starkie et al. 2005) and infrequently reported (Starkie et al. 2003).

Doubts about a pyrogen-like work factor resetting the thermoregulatory centre during exercise are augmented by the results of pharmacological (anti-inflammatory) interventions, which might have been expected to prevent such an outcome. For example, Downey and Darling (1962) found that aspirin had no effect on the deep-body temperature during treadmill walking, although body temperatures after exercise might have been affected. Johnson and Ruhling (1985) similarly found no effect of aspirin for at least 60 min after exercise. Most recently, Emerson et al. (2021) in an under-powered meta-analysis (Cook and Hatala 2015), concluded that taking a course of non-steroidal,

anti-inflammatory drugs before exercise did not affect deep-body temperature during exercise. So the prostanoid synthesis that would be expected if exercise-associated IL-6 acted on the regulatory centre appears to be missing.

Exercise physiologists who follow the research on IL-6 and exercise, and especially the research from the Copenhagen Muscle Research Centre (Denmark; Joyner et al. 2015), might be tempted to believe that, since muscles generate pyrogenic IL-6, that IL-6 must act to elevate body temperature, just as IL-6 of monocyte origin does in fever. Accordingly, that mechanism might fulfil the role of a pyrogenic work factor postulated by Nielsen (1966). Indeed, Bente K. Pedersen (Denmark) and colleagues actually identified IL-6 as what "*has been called the 'work stimulus', the 'work factor' or the 'exercise factor'*" (Pedersen et al. 2004 [P. 263]), though they did not mention any possible function in thermoregulation. If muscle IL-6 did elevate body temperature during or after exercise, the early hypotheses of Nielsen (1966) and Haight and Keatinge (1973a) of an endogenous pyrogen constituting a chemical work factor, acting during and after exercise, would be vindicated.

On the basis of the evidence assembled here, exercise physiologists should not be tempted to follow that path. Though it is a potent endogenous pyrogen in other circumstances, the IL-6 released into plasma during and after exercise, and generated in small amounts in the brain during exercise (Nybo et al. 2002a), seems to play no role in resetting the thermoregulatory centre. It is unlikely that any work factor does so, if the recognised brain pyrogen IL-6 does not.

Conclusions and recommendations

The objective of this review series is to explore the historical development of the key concepts of human thermoregulation during exercise, but within three epochs, the keystone of which falls within our century of exercise physiology. In laying out that arena, we have positioned homeothermy within the primary physiological construct of homeostasis, acknowledging the contributions of Claude Bernard (1879), Robert Tigerstedt (1906) and Walter Cannon (1929). We have shown that apparent stability within any regulated variable, like body temperature, actually reflects a dynamic equilibrium of components that themselves are in states of flux.

Because homeothermy relies upon anatomical and physiological resources used by other homeostatic processes (Table 1), and since those resources are limited, then homeothermy may have to compete for those resources. Our reliance upon water for evaporative cooling and transporting heat to the periphery sometimes competes with its requirement for osmoregulation and the maintenance of blood pressure, with homeothermy occasionally losing. We have also highlighted the important, but frequently ignored, differences between physiological regulation and control in achieving stability of critical physiological variables, and the *milieu intérieur*.

As a prelude to our review of the historical development of physiological measurement (Part 2), we have outlined the physical and physiological processes by which heat is transported within the body, especially during exercise, and exchanged with our ambient environments. We have demonstrated that those heat exchanges must obey the laws of physics. Indeed, those first principles are the building blocks upon which sound scientific experimentation must be based, and from which valid interpretative evidence can be extracted. For example, if the physics of heat exchange dictates that the size and shape of an object will determine its passive heat exchanges, then, when investigating inter-individual differences in physiological heat exchange, one needs to control for morphological differences. If differences in body composition affect heat storage and transfer, then even when investigating people of the same morphological configuration, the standardisation of body composition becomes important. When looking back on the historical literature, it is sometimes easy to see the limitations of previous experimental designs because "… *we have all been wrong often*" (Hill 1965 [P. 167]). The art is to appreciate how those limitations might affect data interpretation, and to use hindsight to reduce the probability of repeating those flaws.

With respect to the human regulatory centre which responds to changes in body temperature, we have explored the critical steps that led us to our contemporary understanding of the role of the hypothalamus in thermal homeostasis, via the control of our thermoeffectors. During that journey, we discussed and moved beyond *set-point* theory. In Fig. 20, we summarised that knowledge into a contemporary signal-flow model of human thermoregulation during exercise, and its interactions with thermal feedback as well as thermal and non-thermal feedforward signals. In Figs. 21 and 22, we have endeavoured to show that our thermoeffectors are independently activated, and that their activation thresholds are neither single points nor are they set.

In Part 2, the first principles presented herein will be applied to the development of our primary measurement techniques for investigating the thermal physiology of exercising humans. Those methods are fundamental to valid research, since they are used to quantify heat storage and changes in body temperatures. Those variables are regulated (Table 1), so deviations beyond the vasomotor or inter-threshold zones (Fig. 22) will activate one or more of our thermoeffectors (Fig. 21). Therefore, measurement simplifications that may satisfy our pragmatic, but not our mechanistic needs, or failures of those methods to obey physics (thermodynamics), must result in the gathering of questionable,

and quite possibly, uninterpretable data, as illustrated by tissue temperature A (from the rectum) in Fig. 2.

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Author contributions SRN, DM and NAST developed and planned this review, and took part in all phases of manuscript preparation. Each author was responsible for writing specific sub-sections, and for editing all parts of this work. All authors approved the final submission of this manuscript.

Data availability Supplementary data are not provided as this is a review manuscript and not an experimental paper.

Declarations

Conflict of interest There are no conflicts of interest.

References and recommended readings

Abbott BC, Bigland B, Ritchie JM (1952) The physiological cost of negative work. J Physiol 117:380–390. https://doi.org/10.1113/jphysiol.1952.sp004755

Ackerknecht EH (1974) The history of the discovery of the vegetative (autonomic) nervous system. Med Hist 18:1–8. https://doi.org/10.1017/s0025727300019189

Adolph EF (1921) The regulation of the water content of the human organism. J Physiol 55:114–132

Adolph EF (1947a) (ed) Physiology in man in the desert. Interscience, New York

Adolph EF (1947b) Heat exchanges, sweat formation, and water turnover. In: Adolph EF (ed) Physiological of man in the desert. Interscience Publishing Company, New York, pp 33–43

Adolph EF (1954) The physiological scholar. Am J Physiol 179:607–612. https://doi.org/10.1152/ajplegacy.1954.179.3.607

Adolph EF (1961) Early concepts of physiological regulations. Physiol Rev 41:737–770. https://doi.org/10.1152/physrev.1961.41.4.737

Adolph EF (1968) Origins of physiological regulation. Academic Press, New York

Albrecht GH, Gelvin BR, Hartman SE (1993) Ratios as a size adjustment in morphometrics. Am J Phys Anthropol 91:441–468. https://doi.org/10.1002/ajpa.1330910404

Aldrich LB (1928) A study of body radiation. Smithsonian miscellaneous collections, vol 81, number 6. Smithsonian Institution, Washington

Alexander L (1945) The treatment of shock from prolonged exposure to cold, especially in water. CIOS Target Number 24, Medical. Combined Intelligence Objectives Sub-Committee, G-2 Division, Shaef (Rear), APO 413

Allbutt TC (1867) A clinical thermometer. Medical Times and Gazette. J Med Sci Lit Crit News 1:182–183

Allbutt TC (1896) A system of medicine. MacMillan and Company, London

American Institute of Physics (1941) Temperature: its measurement and control in science and industry. Reinhold Publishing Company, New York

Amontons G (1695) Remarques et Expériences Physiques sur la Construction d'une Nouvelle Clepsidre, sur les Baromètres, Thermomètres et Hygromètres. Chez Jean Jombert, Paris

Amontons G (1703) Remarques sur la table des degrés de chaleur. Mémoires de l'Académie Royale des Sciences. 202–212

Andjus PR, Stojilkovic SS, Cvijic G (2016) Ivan Djaja (Jean Giaja) and the Belgrade School of Physiology. Physiol Res 60:S1–S13. https://doi.org/10.33549/physiolres.932180

Angell James JE (1971) The effects of changes of extramural "intrathoracic" pressure on aortic arch baroreceptors. J Physiol 214:89–103. https://doi.org/10.1113/jphysiol.1971.sp009420

Ångström A (1920) Applications of heat radiation measurements to the problems of the evaporation from lakes and the heat convection at their surfaces. Geogr Ann 2:237–252. https://doi.org/10.1080/20014422.1920.11880772

Anonymous (1965) Max Rubner—1854–1932. Energy physiologist. J Am Med Assoc 194:86–87

Archiza B, Welch JF, Sheel AW (2017) Classical experiments in whole-body metabolism: closed-circuit respirometry. Eur J Appl Physiol 117:1929–1937. https://doi.org/10.1007/s00421-017-3735-5

Arciero PJ, Goran MI, Poehlman ET (1993) Resting metabolic rate is lower in women than in men. J Appl Physiol 75:2514–2520. https://doi.org/10.1152/jappl.1993.75.6.2514

Aronsohn E, Sachs J (1885) Die Beziehungen des Gehirns zur Körperwärme und zum Fieber. Archiv Für Die Gesamte Physiologie Des Menschen Und Der Tiere 37:232–301. https://doi.org/10.1007/BF01752423

Aschoff J, Wever R (1958) Kern und schale im wärmehaushalt des menschen. Naturwissenschaften 45:477–485. https://doi.org/10.1007/BF00635546

Asmussen E (1953) Positive and negative muscular work. Acta Physiol Scand 28:364–382. https://doi.org/10.1111/j.1748-1716.1953.tb00988.x

Åstrand P-O (1991) Influence of scandinavian scientists in exercise physiology. Scand J Med Sci Sports 1:3–9. https://doi.org/10.1111/j.1600-0838.1991.tb00264.x

Åstrand P-O, Rodahl K (1986) Textbook of work physiology. Physiological bases of exercise, pp 391–411. McGraw-Hill, New York

Aub JC (1962) Eugene Floyd DuBois—1882–1959. National Academy of Sciences of the United States of America, Biographical Memoirs, pp 124–145

Baehr G (1940) In memoriam, Hans Horst Meyer. Bull N Y Acad Med 16:260–261

Bahadori MM (1978) Passive cooling systems in Iranian architecture. Sci Am 238:144–154

Bainbridge FA (1919) The physiology of muscular exercise. Longmans, Green and Company, London

Bainbridge FA, Bock AV, Dill DB (1931) The physiology of muscular exercise. Monographs in physiology. Longmans, Green and Company, London

Baldwin JW, Benmarhnia T, Ebi KL, Jay O, Lutsko NJ, Vanos JK (2023) Humidity's role in heat-related health outcomes: a heated debate. Environ Health Perspect 131:CID:055001. https://doi.org/10.1289/EHP11807

Barbour HG (1912) Die Wirkung unmittelbarer Erwärmung und Abkühlung der Wärmezentra auf die Körpertemperatur. Archiv Für Experimentelle Pathologie Und Pharmakologie 70:1–26. https://doi.org/10.1007/bf01865333

Barbour HG (1921) The heat-regulating mechanism of the body. Physiol Rev 1:295–326. https://doi.org/10.1152/physrev.1921.1.2.295

Barcroft J (1932) La fixité du milieu intérieur est la condition de la vie libre. (Claude Bernard). Biol Rev 7:24–87. https://doi.org/10.1111/j.1469-185X.1962.tb01036.x

Barcroft J (1934) Features in the architecture of physiological function. University Press, Cambridge

Barcroft J, Binger CA, Bock AV, Doggart JH, Forbes HS, Harrop G, Meakins JC, Redfield AC, Davies HW, Scott JMC, Fetter WJ, Murray CD, Keith A (1923) Observations upon the effect of high altitude on the physiological processes of the human body, carried out in the Peruvian Andes, chiefly at Cerro de Pasco. Philos Trans R Soc Lond Ser b Biol Sci 211:351–480. https://doi.org/10.1098/rstb.1923.0008

Barcroft H, Edholm OG (1945) On the vasodilatation in human skeletal muscle during post-haemorrhagic fainting. J Physiol 104:161–175. https://doi.org/10.1113/jphysiol.1945.sp004113

Bardswell ND, Chapman JE (1911) Some observations upon the deep temperature of the human body at rest and after muscular exertion. BMJ 1:1106–1110. https://doi.org/10.1136/bmj.1.2628.1106

Beretta M (2012) Imaging the experiments on respiration and transpiration of Lavoisier and Séguin: two unknown drawings by Madame Lavoisier. Nunclus 27:163–191. https://doi.org/10.1163/182539112X637200

Barger AC (1987) Walter Bradford Cannon: physiologist and citizen of the world. In: McLennan H, Ledsome JR, McIntosh CHS, Jones DR (eds) Advances in physiological research, pp 19–42. Springer, Boston. https://doi.org/10.1007/978-1-4615-9492-5_3

Bass DE (1963) Thermoregulatory and circulatory adjustments during acclimatization to heat in man. In: Hardy JD (ed) Temperature: its measurement and control in science and industry, vol. 3, Part 3, pp 299–305. Reinhold Publishing Co., New York.

Batterham AM, Jackson AS (2003) Validity of the allometric cascade model at submaximal and maximal metabolic rates in exercising men. Respir Physiol Neurobiol 135:103–106. https://doi.org/10.1016/s1569-9048(03)00027-2

Bayon HP (1938a) William Harvey, physician and biologist: his precursors, opponents and successors—Parts I & II. Ann Sci 3:59–118. https://doi.org/10.1080/00033793800200791

Bayon HP (1938b) William Harvey, physician and biologist: his precursors, opponents and successors—Part III. Ann Sci 3:435–456. https://doi.org/10.1080/00033793900201111

Bayon HP (1939a) William Harvey, physician and biologist: his precursors, opponents and successors—Part IV. Ann Sci 4:65–106. https://doi.org/10.1080/00033793900201341

Bayon HP (1939b) William Harvey, physician and biologist: his precursors, opponents and successors—Part V. Ann Sci 4:329–389. https://doi.org/10.1080/00033793900201341

Bazett HC (1927) Physiological responses to heat. Physiol Rev 7:531–599. https://doi.org/10.1152/physrev.1927.7.4.531

Bazett HC (1949) The regulation of body temperatures. In: Newburgh LH (ed) Physiology of heat regulation and the science of clothing. Hafner Publishing Company, New York, pp 109–192

Bedford T (1951) H. M. Vernon, M.A., M.D. Occup Med 1:47–48. https://doi.org/10.1093/occmed/1.1.47

Bedford T, Warner CG (1934) The globe thermometer in studies of heating and ventilation. Epidemiol Infect 34:458–473. https://doi.org/10.1017/s0022172400043242

Benedict FG (1909) An apparatus for studying the respiratory exchange. Am J Physiol 24:345–374. https://doi.org/10.1152/ajplegacy.1909.24.3.345

Benedict FG (1938) Vital energetics: a study in comparative basal metabolism. Carnegie Institution of Washington, Washington, DC (**Publication 503**)

Benedict FG, Cady WG (1912) A bicycle ergometer with an electric brake. Carnegie Institution of Washington, Washington, DC (**Publication No. 167**)

Benedict FG, Carpenter TM (1909) The influence of muscular and mental work on metabolism and the efficiency of the human body as a machine. Office of Experimental Stations, U.S. Department of Agriculture. Bulletin Number 208. Washington, DC

Benedict FG, Talbot FB (1921) Metabolism and growth from birth to puberty. Carnegie Institution of Washington, Washington, DC (**Publication number 302**)

Benton MJ (2021) The origin of endothermy in synapsids and archosaurs and arms races in the Triassic. Gondwana Res 100:261–289. https://doi.org/10.1016/j.gr.2020.08.003

Benzinger TH (1961) The human thermostat. Sci Am 204:134–149. https://doi.org/10.1038/SCIENTIFICAMERICAN0161-134

Benzinger TH (1969a) Clinical temperature: new physiological basis. J Am Med Assoc 209:1200–1206. https://doi.org/10.1001/jama.1969.03160210032008

Benzinger TH (1969b) Heat regulation: homeostasis of central temperature in man. Physiol Rev 49:671–759. https://doi.org/10.1152/physrev.1969.49.4.671

Benzinger TH, Taylor GW (1963) Cranial measurements of internal temperature in man. In: Hardy JD (ed) Temperature: its measurement and control in science and industry, vol. 3, part 3, pp 111–120. Reinhold Publishing Corporation, New York

Berger RL (1990) Nazi science—the Dachau hypothermia experiments. N Engl J Med 322:1435–1440. https://doi.org/10.1056/NEJM199005173222006

Berger RL (1994) Ethics in scientific communication: study of a problem case. J Med Ethics 20:207–211. https://doi.org/10.1136/jme.20.4.207

Bergh U, Sjödin B, Forsberg A, Svedenhag J (1991) The relationship between body mass and oxygen uptake during running in humans. Med Sci Sports Exerc 23:205–211

Bergmann C (1845) Nichtchemischer Beitrag zur Kritik der Lehre von Calor animalis. Archiv Für Anatomie, Physiologie Und Wissenschaftliche Medicin 1845:300–319

Bergmann C (1847) Über die Verhältnisse der Wärmeökonomie der Thiere zu ihrer Größe. Vandenhoeck und Ruprecht, Göttingen

Bernard C (1852) Sur les effers de la secretion be la portion cephalique du grand sympathique. Comptes Rendus De L'académie Des Sciences 4:168–169

Bernard C (1876) Leçons sur la Chaleur Animale, sur les Effets de la Chaleur et sur la Fièvre. J.-B. Baillière et Fils, Paris

Bernard C (1878) Leçons sur la Phénomènes de la vie, Communs aux Animaux et aux Végétaux. J.-B. Baillière et Fils, Paris

Bernard C (1879) Leçons sur la Phénomènes de la vie, Communs aux Animaux et aux Végétaux II. J.-B. Baillière et Fils, Paris

Bernard C (1949) Introduction to the study of experimental medicine. Translated by Greene, H.C. Henry Schuman, Inc., USA

Bernard C (1974) Lectures on the phenomena common to animals and plants. Translated by Hoff, H.E., Guillemin, R., and Guillemin, L. Charles C. Thomas, Springfield

Bernecker C, Scherr J, Schinner S, Braun S, Scherbaum WA, Halle M (2013) Evidence for an exercise induced increase of TNF-α and IL-6 in marathon runners. Scand J Med Sci Sports 23:207–214. https://doi.org/10.1111/j.1600-0838.2011.01372.x

Berner GE, Garrett CC, Jones DC, Noer RJ (1926) The effect of external temperature on second wind. Am J Physiol 76:586–592. https://doi.org/10.1152/ajplegacy.1926.76.3.586

Best NW (2015) Lavoisier's "Reflections on phlogiston" I: against phlogiston theory. Found Chem 17:137–151. https://doi.org/10.1007/s10698-015-9220-5

Bichat X (1822) Recherches Physiologiques sur la Vie et la Mort. Béchet Jeune, Libraire

Bird M (2008) William Keatinge 1931–2008. Physiol News 71:60–61

Bishop CM (1999) The maximum oxygen consumption and aerobic scope of birds and mammals: getting to the heart of the matter.

Proc R Soc Lond Ser B Biol Sci. 266:2275–2281. https://doi.org/10.1098/rspb.1999.0919
Bishop D (2003) Warm up I: potential mechanisms and the effects of passive warm up on exercise performance. Sports Med 33:439–454. https://doi.org/10.2165/00007256-200333060-00005
Black J, Robison J (1807) Lectures on the elements of chemistry, vol 1. Mathew Carey, Philadelphia
Blair DA, Glover WE, Roddie IC (1960) Vasomotor fibres to skin in the upper arm, calf and thigh. J Physiol 153:232–238. https://doi.org/10.1113/jphysiol.1960.sp006531
Blatteis CM, Schneider SM (2022) Thermal physiology in the USA: a 100-year history of the science and its scientists (1880–1980). In: Blatteis CM, Taylor NAS, Mitchell D (eds) Thermal physiology: a worldwide history. Perspectives in physiology, pp 239–355. Springer, New York. https://doi.org/10.1007/978-1-0716-2362-6_5
Blatteis CM, Taylor NAS, Mitchell D (eds) (2022) Thermal physiology: a worldwide history. Perspectives in physiology. Springer, New York. https://doi.org/10.1007/978-1-0716-2362-6
Blazejczyk K, Nilsson H, Holmér I (1993) Solar heat load on man. Review of different methods of estimation. Int J Biometeorol 37:125–132. https://doi.org/10.1007/BF01212621
Bligh J (1966) The thermosensitivity of the hypothalamus and thermoregulation in mammals. Biol Rev Camb Philos Soc 41:317–365. https://doi.org/10.1111/j.1469-185x.1966.tb01496.x
Bligh J (1987) Human cold exposure and the circumstances of hypothermia. In: Mekjavic IB, Banister EW, Morrison JB (eds) Environmental ergonomics. Taylor & Francis, London, pp 3–21
Bligh J (1998) Mammalian homeothermy: an integrative thesis. J Therm Biol 23:143–258. https://doi.org/10.1016/S0306-4565(98)00014-X
Bligh J, Johnson KG (1973) Glossary of terms from thermal physiology. J Appl Physiol 35:941–961. https://doi.org/10.1152/jappl.1973.35.6.941
Bligh J, Moore R (1972) (eds) Essays on temperature regulation. North-Holland Publishing Company, Amsterdam
Blix M (1882) Experimentela bidrag till lösning af frågan om hudnervernas specifika energi. Uppsala Läkareförenings Förhandlingar 18:87–102
Blix M (1883) Experimentela bidrag till lösning af frågan om hudnervernas specifika energi. Uppsala Läkareförenings Förhandlingar 18:427–440
Blix AS, Folkow LP, Mercer JB (2022) The history of thermal physiology in Norway. In: Blatteis CM, Taylor NAS, Mitchell D (eds) Thermal physiology: a worldwide history. Perspectives in physiology, pp 569–596. Springer, New York. https://doi.org/10.1007/978-1-0716-2362-6_12
Bock AV, Vancaulaert C, Dill DB, Fölling A, Hurxthal LM (1928) Studies in muscular activity: IV. The "steady state" and the respiratory quotient during work. J Physiol 66:162–174. https://doi.org/10.1113/jphysiol.1928.sp002515
Boerhaave H (1746) Dr. Boerhaave's academical lectures on the theory of physic. A genuine translation of his institutes and explanatory comment, vol. V. W. Innys, London
Bogod D (2004) The Nazi hypothermia experiments: forbidden data? Anaesthesia 59:1155–1156. https://doi.org/10.1111/j.1365-2044.2004.04034.x
Bohnenkamp H, Ernst HW (1931) Untersuchungen zu den Grundlagen des Energie-und Stoffwechsels. 2. Uber die Strahlungsverluste des Menschen Die Strahlungsmessung im absoluten Energiemass. Pflugers Archiv Fur Die Gesamte Physiologie Des Menschen Und Der Tiere 228:63–78. https://doi.org/10.1007/BF01755486
Bonde-Petersen F, Henriksson J, Knuttgen HG (1973) Effect of training with eccentric muscle contractions on skeletal muscle metabolites. Acta Physiol Scand 88:564–570. https://doi.org/10.1111/j.1748-1716.1973.tb05485.x
Böning D, Maassen N, Steinach M (2017) The efficiency of muscular exercise. Ger J Sports Med 68:203–214. https://doi.org/10.5960/dzsm.2017.29
Booth JD, Marino F, Ward JJ (1997) Improved running performance in hot humid conditions following whole body precooling. Med Sci Sports Exerc 29:943–949. https://doi.org/10.1097/00005768-199707000-00014
Booth JD, Wilsmore BR, MacDonald AD, Zeyl A, Storlien LH, Taylor NAS (2004) Intramuscular temperatures during exercise in the heat following pre-cooling and pre-heating. J Therm Biol 29:709–715. https://doi.org/10.1016/j.jtherbio.2004.08.044
Boothby WM, Sandiford I (1922) Summary of the basal metabolism data on 8,614 subjects with especial reference to the normal standards for the estimation of the basal metabolic rate. J Biol Chem 54:783–803. https://doi.org/10.1016/S0021-9258(18)85715-5
Boothby WM, Sandiford I (1924) Basal metabolism. Physiol Rev 4:69–162
Bordier H (1898) Conductibilite calorifique des tissus de l'organisme. Archives de Physiologie Normale et Pathologique. Série 5. 10:17–26
Boulant JA (1981) Hypothalamic mechanisms in thermoregulation. Fed Proc 40:2843–2850
Boulant JA (1996) Hypothalamic neurons regulating body temperature. In: Comprehensive physiology. supplement 14: handbook of physiology, environmental physiology, pp 105–126. https://doi.org/10.1002/cphy.cp040106
Boulant JA (2006) Neuronal basis of Hammel's model for set-point thermoregulation. J Appl Physiol 100:1347–1354. https://doi.org/10.1152/japplphysiol.01064.2005
Boulant JA, Silva NL (1988) Neuronal sensitivities in preoptic tissue slices: interactions among homeostatic systems. Brain Res Bull 20:871–878. https://doi.org/10.1016/0361-9230(88)90104-9
Bourque CW (2008) Central mechanisms of osmosensation and systemic osmoregulation. Nat Rev Neurosci 9:519–531. https://doi.org/10.1038/nrn2400
Boutelier C, Bougues L, Timbal J (1977) Experimental study of convective heat transfer coefficient for the human body in water. J Appl Physiol 42:93–100. https://doi.org/10.1152/jappl.1977.42.1.93
Bowes HM, Burdon CA, Taylor NAS (2021a) The scaling of human basal and resting metabolic rates. Eur J Appl Physiol 121:193–208. https://doi.org/10.1007/s00421-020-04515-1
Bowes HM, Burdon CA, Peoples GE, Notley SR, Taylor NAS (2021b) Scaling the peak and steady-state aerobic power of running and walking humans. Eur J Appl Physiol 121:2925–2938. https://doi.org/10.1007/s00421-021-04759-5
Boyle MO (2008) William Harvey's anatomy book and literary culture. Med Hist 52:73–91. https://doi.org/10.1017/s0025727300002064
Boyle MO (2013) Harvey, by Hercules! The hero of the blood's circulation. Med Hist 57:6–27. https://doi.org/10.1017/mdh.2012.78
Boyles JG, Thompson AB, McKechnie AE, Malan E, Humphries MM, Careau V (2013) A global heterothermic continuum in mammals. Glob Ecol Biogeogr 22:1029–1039. https://doi.org/10.1111/geb.12077
Braasch D (1964) Zur Pathogenese des tödlichen Kreislaufkollapses nach Überwärmung einzelner Organe auf 45°C. Archiv Für Die Gesamte Physiologie Des Menschen Und Der Tiere 278:567–574. https://doi.org/10.1007/BF00362324
Brack V, Boyles JG, Cable TT (2022) Warm-blooded mammals: an enduring misconception. Am Biol Teach 84:529–534. https://doi.org/10.1525/abt.2022.84.9.529

Brebner DF, Kerslake DM, Waddell JL (1958) The relation between the coefficients for heat exchange by convection and by evaporation in man. J Physiol 141:164–168. https://doi.org/10.1113/jphysiol.1958.sp005963

Brengelmann GL (1987) Dilemma of body temperature measurement. In: Shiraki K, Yousef MK (eds) Man in stressful environments: thermal and work physiology, pp 5–22. Charles C. Thomas, Springfield

Brengelmann GL (1993) Specialized brain cooling in humans? Fed Am Soc Exp Biol J 7:1148–1152. https://doi.org/10.1096/fasebj.7.12.8375613

Brinnel H, Cabanac M (1989) Tympanic temperature is a core temperature in humans. J Therm Biol 14:47–53. https://doi.org/10.1016/0306-4565(89)90029-6

Brobeck JR (1965) Exchange, control and regulation. In: Yamamoto WS, Brobeck JR (eds) Physiological controls and regulations. W. B. Saunders, Philadelphia, pp 1–13

Brock-Utne JG, Gaffin SL, Wells MT, Gathiram P, Sohar E, James MF, Morrell DF, Norman R (1988) Endotoxaemia in exhausted runners after a long-distance race. S Afr Med J 73:533–536

Brodie BC (1811) The Croonian Lecture, on some physiological researches, respecting the influence of the brain on the action of the heart, and on the generation of animal heat. Philos Trans R Soc Lond 101:36–48. https://doi.org/10.1098/rstl.1811.0003

Brody S (1945) Bioenergetics and growth: with special reference to the efficiency complex in domestic animals. Reinhold Publishing Corporation, New York

Brody S, Comfort JE, Matthews JS (1928) Growth and development with special reference to domestic animals. XI. Further investigations of surface area with special reference to its significance in energy metabolism. University of Missouri, Agricultural Experiment Station. Res Bull 115

Brody S, Procter RC (1932) Growth and development, with special reference to domestic animals. XXIII. Relation between basal metabolism and mature body weight in different species of mammals and birds. University of Missouri, Agricultural Experiment Station. Res Bull 166:89–101

Brooks GA, Gladden LB (2003) The metabolic systems: anaerobic metabolism (glycolytic and phosphagen). In: Tipton CM (ed) Exercise physiology. Springer, New York, pp 322–360

Brown AC, Brengelmann GL (1970) The interaction of peripheral and central inputs in the temperature regulation system. In: Hardy JD, Gagge AP, Stolwijk JAJ (eds) Physiological and behavioral temperature regulation. Thomas, Springfield, pp 684–702

Brown M, McClean CM, Davison GW, Brown JC, Murphy MH (2018) The acute effects of walking exercise intensity on systemic cytokines and oxidative stress. Eur J Appl Physiol 118:2111–2120. https://doi.org/10.1007/s00421-018-3930-z

Bruck L, Günter A, Heidenhain R (1870) Versuche über den Einfluss der Verletzung gewisser Hirntheile auf die Temperatur des Thierkörpers. Archiv Für Die Gesamte Physiologie Des Menschen Und Der Tiere 3:578–584. https://doi.org/10.1007/BF01855777

Brück K, Wünnenberg W, Gallmeier H, Ziehm B (1970) Shift of threshold temperature for shivering and heat polypnea as a mode of thermal adaptation. Pflüg Arch Eur J Physiol 321:159–172. https://doi.org/10.1007/BF00586370

Buchholz AC, Rafii M, Pencharz PB (2001) Is resting metabolic rate different between men and women? Br J Nutr 86:641–646

Buchdahl AA (1975) Twenty lectures on thermodynamics. Pergamon Press, Oxford

Buchthal F, Høncke P, Lindhard J (1945) Temperature measurement in human muscles in situ at rest and during muscular work. Acta Physiol Scand 8:230–258

Budyko MI (1959) About heat balance of living organisms [in Russian]. Izvestiya Akademii Nauk, Seriya Geograficheskaya 1:29–35

Budyko MI (1974) The thermal regime of living organisms. In: Budyko MI (ed) International geophysics, vol 18, pp 371–399. https://doi.org/10.1016/S0074-6142(09)60012-7

Bureau International des Poids et Mesures (2019) The International System of Units (SI). Ninth Edition. Organisation Intergouvernementale de la Convention du Mètre, Paris. https://www.bipm.org/en/publications/si-brochure Accessed 10 Nov 2021

Burfoot A (2007) The history of the marathon. Sports Med 37:284–287. https://doi.org/10.2165/00007256-200737040-00003

Burger HC, Horeman HW, Brakkee AJM (1959) Comparison of some methods for measuring peripheral blood flow. Phys Med Biol 4:168–175. https://doi.org/10.1088/0031-9155/4/2/306

Burton AC (1935) Human calorimetry: II. The average temperature of the tissues of the body. J Nutr 9:261–280. https://doi.org/10.1093/jn/9.3.261

Burton AC (1953) Peripheral circulation. Annu Rev Physiol 15:213–246. https://doi.org/10.1146/annurev.ph.15.030153.001241

Burton RF (2008) Estimating body surface area from mass and height: theory and the formula of Du Bois and Du Bois. Ann Hum Biol 35:170–184. https://doi.org/10.1080/03014460801908439

Burton AC, Bazett HC (1936) A study of the average temperature of the tissues, of the exchanges of heat and vasomotor responses in man by means of a bath calorimeter. Am J Physiol 117:36–54. https://doi.org/10.1152/ajplegacy.1936.117.1.36

Buskirk ER (2003) The temperature regulatory system. In: Tipton CM (ed) Exercise physiology. Springer, New York, pp 423–451

Cabanac M (1972) Thermoregulatory behavior. In: Bligh J, Moore RE (eds) Essays on temperature regulation. North-Holland Publishing Company, Amsterdam, pp 19–36

Cabanac M (1995) Human selective brain cooling. R.G. Landes Company, Austin

Cabanac M (1997) Regulation and modulation in biology. A reexamination of temperature regulation. Ann N Y Acad Sci 813:21–31. https://doi.org/10.1111/j.1749-6632.1997.tb51668.x

Cabanac M, Caputa M (1979) Natural selective cooling of the human brain: evidence of its occurrence and magnitude. J Physiol 286:255–264. https://doi.org/10.1113/jphysiol.1979.sp012617

Cabanac M, Massonnet B (1977) Thermoregulatory responses as a function of core temperature in humans. J Physiol 265:587–596. https://doi.org/10.1113/jphysiol.1977.sp011732

Camillo CA, Burtin C, Hornikx M, Demeyer H, De Bent K, van Remoortel H, Osadnik CR, Janssens W, Troosters T (2015) Physiological responses during downhill walking: a new exercise modality for subjects with chronic obstructive pulmonary disease? Chron Respir Dis 12:155–164. https://doi.org/10.1177/1479972315575717

Candas V, Hoeft A (1995) Clothing, assessment and effects on thermophysiological responses of man working in humid heat. Ergonomics 38:115–127. https://doi.org/10.1080/00140139508925089

Candas V, Libert J-P (2022) Contributions of French research to the knowledge of thermal physiology from the eighteenth to the twenty-first century. In: Blatteis CM, Taylor NAS, Mitchell D (eds) Thermal physiology: a worldwide history. Perspectives in physiology, pp 57–95. Springer, New York. https://doi.org/10.1007/978-1-0716-2362-6_2

Candas V, Libert J-P, Vogt JJ (1979) Human skin wettedness and evaporative efficiency of sweating. J Appl Physiol 46:522–528. https://doi.org/10.1152/jappl.1979.46.3.522

Candas V, Libert J-P, Vogt JJ (1980) Effect of hidromeiosis on sweat drippage during acclimation to humid heat. Eur J Appl Physiol 44:123–133. https://doi.org/10.1007/BF00421090

Cannon WB (1926) Physiological regulation of normal states: some tentative postulates concerning biological homeostatics. In: Pettit A (ed) À Charles Richet: Amis, ses Collègues, ses Élèves. Les Éditions Médicales, Paris, pp 91–93
Cannon WB (1929) Organization for physiological homeostasis. Physiol Rev 9:399–431. https://doi.org/10.1152/physrev.1929.9.3.399
Cannon JG, Evans WJ, Hughes VA, Meredith CN, Dinarello CA (1986) Physiological mechanisms contributing to increased interleukin-1 secretion. J Appl Physiol 61:1869–1874. https://doi.org/10.1152/jappl.1986.61.5.1869
Cannon JG, Kluger MJ (1983) Endogenous pyrogen activity in human plasma after exercise. Science 220:617–619. https://doi.org/10.1126/science.6836306
Cannon WB, Querido A, Britton SW, Bright EM (1927) Studies on the conditions of activity in endocrine glands. XXI. The rôle of adrenal secretion in the chemical control of body temperature. Am J Physiol 79:466–507. https://doi.org/10.1152/ajplegacy.1927.79.2.466
Caplan AL (2021) How should we regard information gathered in Nazi experiments? AMA J Ethics 23:E55–E58. https://doi.org/10.1001/amajethics.2021.55
Caravello V, McCullough EA, Ashley CD, Bernard TE (2008) Apparent evaporative resistance at critical conditions for five clothing ensembles. Eur J Appl Physiol 104:361–367. https://doi.org/10.1007/s00421-007-0655-9
Carnot S (1824) Réflexions sur la Puissance Motrice du Feu et sur le Machines Propres a Développer Cette Puissance. Chez Bachelier, Paris
Carpenter WB (1843) Popular cyclopaedia of natural science. Animal physiology. W.S. Orr and Company, London
Carroll RL (1970) The ancestry of reptiles. Philos Trans R Soc Lond Ser b Biol Sci 257:267–308. https://doi.org/10.1098/rstb.1970.0026
Carroll DP, Visser J (1966) Direct measurement of convective heat loss from human subject. Rev Sci Instrum 37:1174–1180. https://doi.org/10.1063/1.1720451
Cartmell T, Mitchell D (2005) The molecular basis of fever. In: Steckler T, Kalin NH, Reul JMHM (eds) Handbook of stress and the brain: part 2: stress: integrative and clinical aspects. Volume 15. Techniques in the behavioral and neural sciences, pp 193–227. Elsevier Science, Amsterdam. https://doi.org/10.1016/S0921-0709(05)80056-2
Cartmell T, Poole S, Turnbull AV, Rothwell NJ, Luheshi GN (2000) Circulating interleukin-6 mediates the febrile response to localised inflammation in rats. J Physiol 526:653–661. https://doi.org/10.1111/j.1469-7793.2000.00653.x
Cassel J, Casselman WGB (1990) Regulation of body heat: the evolution of concepts and associated research. In: Schönbaum E, Lomax P (eds) Thermoregulation: physiology and biochemistry. Pergamon Press, New York, pp 17–50
Castell LM, Poortmans JR, Leclercq R, Brasseur M, Duchateau J, Newsholme EA (1996) Some aspects of the acute phase response after a marathon race, and the effects of glutamine supplementation. Eur J Appl Physiol 75:47–53. https://doi.org/10.1007/s004210050125
Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D (1997) The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 389:816–824. https://doi.org/10.1038/39807
Cavagna GA, Saibene FP, Margaria R (1963) External work in walking. J Appl Physiol 18:1–9. https://doi.org/10.1152/jappl.1963.18.1.1
Chapman CB (1990) The long reach of Harvard's Fatigue Laboratory, 1926–1947. Perspect Biol Med 34:17–33. https://doi.org/10.1353/pbm.1990.0049
Chatonnet J (1967) Sur les modalités de mise en jeu des commandes nerveuses de la régulation thermique. In: Heim R, Halpern B, Bourges Y (eds) Les Concepts de Claude Bernard sur le Milieu Intérieur: Colloque International Organisé pour la Célébration du Centenaire de la Publication de l' "Introduction à l'étude de la Médecine Expérimentale" de Claude Bernard (1965). Masson et Cie, Paris, pp 399–413
Chauveau A (1901) La dépense énergétique qu'entraînent respectivement le travail moteur et le travail résistant de l'homme qui s'élève ou descend sur la roue de Hirn; évaluation d'après l'oxygène absorbé dans les échanges respiratoires. Comptes Rendus De L'académie Des Sciences 132:194–201
Chossat C (1843) Recherches Expérimentales sur l'Inanition. Imprimerie Royale, Paris
Christensen EH (1931) Beiträge zur Physiologie schwerer körperlicher Arbeit. II. Mitteilung: Die Körpertemperatur während und unmittelbar nach schwerer körperlicher Arbeit. Arbeitsphysiologie 4:154–174
Christensen EH, Nielsen M, Hannisdahl B (1942) Investigations of the circulation in the skin at the beginning of muscular work. Acta Physiol Scand 4:162–170. https://doi.org/10.1111/j.1748-1716.1942.tb01451.x
Christie JRR (2014) An attenuated philosophical gentleman. Notes Rec R Soc Lond 68:193–197. https://doi.org/10.1098/rsnr.2014.0004
Claremont AD, Costill DL, Fink W, Van Handel P (1976) Heat tolerance following diuretic induced dehydration. Med Sci Sports 8:239–243
Clark ER (1938) Arterio-venous anastomoses. Physiol Rev 18:229–247. https://doi.org/10.1152/physrev.1938.18.2.229
Clark JA, Cena K (1978) Net radiation and heat transfer through clothing: the effects of insulation and colour. Ergonomics 21:691–696. https://doi.org/10.1080/00140137808931771
Clark RP, Edholm OG (1985) Man and his thermal environment. Edward Arnold, London
Clark RP, Mullan BJ, Pugh LGCE (1977) Skin temperature during running—a study using infra-red colour thermography. J Physiol 267:53–62. https://doi.org/10.1113/jphysiol.1977.sp011800
Cloetta M, Waser E (1914) Über den Einfluß der lokalen Erwärmung der Temperaturregulierungszentren auf die Körpertemperatur. Archiv Für Experimentelle Pathologie Und Pharmakologie 77:16–33. https://doi.org/10.1007/BF01875079
Cole TJ, Henry CJK (2005) The Oxford Brookes basal metabolic rate database—a reanalysis. Public Health Nutr 8:1202–1212. https://doi.org/10.1079/phn2005806
Collins KJ (1992) Regulation of body temperature. In: Tinker J, Zapol WM (eds) Care of the critically ill patient, pp 155–173. Springer, London. https://doi.org/10.1007/978-1-4471-3400-8_13
Compston A (2007) The structure and functions of the cerebellum examined by a new method. By Sir Victor Horsley, FRS, FRCS and RH Clarke, MA, MB. Brain 1908: 31; 45–124. Brain 130:1449–1452. https://doi.org/10.1093/brain/awm115
Comrie JD (1925) An eighteenth century consultant. Edinb Med J 32:17–30
Cook DA, Hatala R (2015) Got power? A systematic review of sample size adequacy in health professions education research. Adv Health Sci Educ Theory Pract 20:73–83. https://doi.org/10.1007/s10459-014-9509-5
Cooper KE (2002) Some historical perspectives on thermoregulation. J Appl Physiol 92:1717–1724. https://doi.org/10.1152/japplphysiol.01051.2001
Coote JH (2007) Landmarks in understanding the central nervous control of the cardiovascular system. Exp Physiol 92:3–18. https://doi.org/10.1113/expphysiol.2006.035378
Craig AD, Chen K, Bandy D, Reiman EM (2000) Thermosensory activation of insular cortex. Nat Neurosci 3:184–190. https://doi.org/10.1038/72131

Crandall CG, Brothers RM, Zhang R, Brengelmann GL, Covaciu L, Jay O, Cramer MN, Fuller A, Maloney SK, Mitchell D, Romanovsky AA, Caputa M, Nordström CH, Reinstrup P, Nishiyasu T, Fujii N, Hayashi K, Tsuji B, Flouris AD, Cheung SS, Vagula MC, Nelatury CF, Choi JH, Shrivastava D, Gordon CJ, Vaughan JT (2011) Comments on point:counterpoint: humans do/do not demonstrate selective brain cooling during hyperthermia. J Appl Physiol 110(2):575–580. https://doi.org/10.1152/japplphysiol.01375.2010

Crandall CG, González-Alonso J (2010) Cardiovascular function in the heat-stressed human. Acta Physiol 199:407–423. https://doi.org/10.1111/j.1748-1716.2010.02119.x

Crandall CG, Stephens DP, Johnson JM (1998) Muscle metaboreceptor modulation of cutaneous active vasodilation. Med Sci Sports Exerc 30:490–496. https://doi.org/10.1097/00005768-199804000-00004

Cullen W (1756) Of the cold produced by evaporating fluids, and of some means of producing cold. Essays Observ Phys Lit. 2:145–175

Currie J, Percival T (1792) An account of the remarkable effects of a shipwreck on the mariners; with experiments and observations on the influence of immersion in fresh and salt water, hot and cold, on the powers of the living body. Philos Trans R Soc Lond 82:199–224. https://doi.org/10.1098/rstl.1792.0014

Dale HH (1947) Walter Bradford Cannon, 1871–1945. Biogr Mem Fellows R Soc 5:407–423. https://doi.org/10.1098/rsbm.1947.0008

Dale HH (1962) Otto Loewi, 1873–1961. Biogr Mem Fellows R Soc 8:67–89. https://doi.org/10.1098/rsbm.1962.0006

Damas P, Ledoux D, Nys M, Vrindts Y, De Groote D, Franchimont P, Lamy M (1992) Cytokine serum level during severe sepsis in human IL-6 as a marker of severity. Ann Surg 215:356–362. https://doi.org/10.1097/00000658-199204000-00009

Damato AN, Lau SH, Stein E, Haft JI, Kosowsky B, Cohen SI (1968) Cardiovascular response to acute thermal stress (hot dry environment) in unacclimatized normal subjects. Am Heart J 76:769–774. https://doi.org/10.1016/0002-8703(68)90262-7

Darveau CA, Suarez RK, Andrews RD, Hochachka PW (2002) Allometric cascade as a unifying principle of body mass effects on metabolism. Nature 417:166–170. https://doi.org/10.1038/417166a

Darwin CR (1859) On the origin of species by means of natural selection. John Murray, London

Darwin C (1888) The descent of man, and selection in relation to sex, 2nd edn. John Murray, London

Davies CTM (1979) The effects of different levels of heat production induced by diathermy and eccentric work on thermoregulation during exercise at a given skin temperature. Eur J Appl Physiol 40:171–180. https://doi.org/10.1007/BF00426940

Davies CTM, Barnes C (1972) Negative (eccentric) work. II. Physiological responses to walking uphill and downhill on a motor-driven treadmill. Ergonomics 15:121–131. https://doi.org/10.1080/00140137208924416

Davy H (1812) Elements of chemical philosophy. Part 1. Volume 1. J. Johnson and Company, London

Davy J (1814) An account of some experiments on animal heat. Philos Trans R Soc Lond 104:590–603. https://doi.org/10.1098/rstl.1814.0033

Davy J (1844) Miscellaneous observations on animal heat. Philos Trans R Soc Lond 134:57–64. https://doi.org/10.1098/rstl.1844.0005

Davy J (1845) On the temperature of man. Philos Trans R Soc Lond 135:319–333. https://doi.org/10.1098/rstl.1845.0014

de Dear RJ, Arens E, Hui Z, Oguro M (1997) Convective and radiative heat transfer coefficients for individual human body segments. Int J Biometeorol 40:141–156. https://doi.org/10.1007/s004840050035

Delacey L (2015) Aboriginal inventions: 10 enduring innovations. Australian Geographic, Redfern, Australia. https://www.australiangeographic.com.au/topics/history-culture/2015/03/aboriginal-australian-inventions/ Accessed 28 June 2021

de Luc JA (1787) Idées sur la météorologie. Chez la Veuve Duchesne, Paris

De Tanti A, Gasperini G, Rossini M (2005) Paroxysmal episodic hypothalamic instability with hypothermia after traumatic brain injury. Brain Inj 19:1277–1283. https://doi.org/10.1080/02699050500309270

Diaz FJ, Bransford DR, Kobayashi K, Horvath SM, McMurray RG (1979) Plasma volume changes during rest and exercise in different postures in a hot humid environment. J Appl Physiol 47:798–803. https://doi.org/10.1152/jappl.1979.47.4.798

Dill DB (1959) Eugene F. DuBois, environmental physiologist. Science 130:1746–1747. https://doi.org/10.1126/science.130.3391.1746

Dill DB (1964) Physiologists in World War II. Physiologist 18:35–37

Dill DB (1985) The hot life of man and beast. American Lecture Series, Publication Number 1065. Charles C. Thomas, Springfield

Dill DB, Edwards HT, Bauer PS, Levenson EJ (1931) Physical performance in relation to external temperature. Arbeitsphysiologie 4:508–518. https://doi.org/10.1007/BF02010116

di Prampero PE (1981) Energetics of muscular exercise. Rev Physiol Biochem Pharmacol 89:143–222. https://doi.org/10.1007/BFb0035266

di Prampero PE (1986) The energy cost of human locomotion on land and in water. Int J Sports Med 7:55–72. https://doi.org/10.1055/s-2008-1025736

di Prampero PE (2000) Cycling on Earth, in space, on the Moon. Eur J Appl Physiol 82:345–360. https://doi.org/10.1007/s004210000220

di Prampero PE, Pendergast DR, Wilson DW, Rennie DW (1974) Energetics of swimming in man. J Appl Physiol 37:1–5. https://doi.org/10.1152/jappl.1974.37.1.1

Donahoo WT, Levine JA, Melanson EL (2004) Variability in energy expenditure and its components. Curr Opin Clin Nutr Metab Care 7:599–605. https://doi.org/10.1097/00075197-200411000-00003

Dorman LE, Havenith G (2009) The effects of protective clothing on energy consumption during different activities. Eur J Appl Physiol 105:463–470. https://doi.org/10.1007/s00421-008-0924-2

Douglas CG (1936) John Scott Haldane, 1860–1936. Biogr Mem Fellows R Soc 2:114–139. https://doi.org/10.1098/rsbm.1936.0009

Douglas CG, Haldane JS (1922) The regulation of the general circulation rate in man. J Physiol 56:69–100. https://doi.org/10.1113/jphysiol.1922.sp001993

Douglas J, Pearson S, Ross A, McGuigan M (2017) Eccentric exercise: physiological characteristics and acute responses. Sports Med 47:663–675. https://doi.org/10.1007/s40279-016-0624-8

Downey JA, Darling RC (1962) Effect of salicylates on elevation of body temperature during exercise. J Appl Physiol 17:323–325. https://doi.org/10.1152/jappl.1962.17.2.323

Drobniewski F (1993) Why did Nazi doctors break their 'hippocratic' oaths? J R Soc Med 86:541–543

Drury A, Grant RT (1945) Thomas Lewis, 1881–1945. Obit Not Fellows R Soc 5:179–202. https://doi.org/10.1098/rsbm.1945.0012

Dubczcanski X, Naunyn B (1873) Beiträge zur Lehre von der fieberhaften (durch pyrogene Substanzen bewirkten) Temperaturerhöhung. Archiv Für Experimentelle Pathologie Und Pharmakologie 1:181–212

DuBois EF (1939) Heat loss from the human body. Harvey Lecture, December 15, 1938. Bull N Y Acad Med 15:143–173

DuBois D, DuBois EF (1915) The measurement of the surface area of man. Arch Intern Med 15:868–881. https://doi.org/10.1001/archinte.1915.00070240077005
DuBois D, DuBois EF (1916) A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 17:863–871
DuBois EF, Riddle O (1958) Francis Gano Benedict—October 3, 1870–May 14, 1957, pp 67–99. National Academy of Sciences of the United States of America, Biographical Memoirs
Dufour SP, Lampert E, Doutreleau S, Lonsdorfer-Wolf E, Billat VL, Piquard F, Richard R (2004) Eccentric cycle exercise: training application of specific circulatory adjustments. Med Sci Sports Exerc 36:1900–1906. https://doi.org/10.1249/01.mss.0000145441.80209.66
Durnin JVGA (1959) The use of surface area and of body-weight as standards of reference in studies on human energy expenditure. Br J Nutr 13:68–71. https://doi.org/10.1079/BJN19590010
Earp JE, Hatfield DL, Sherman A, Lee EC, Kraemer WJ (2019) Cold-water immersion blunts and delays increases in circulating testosterone and cytokines post-resistance exercise. Eur J Appl Physiol 119:1901–1907. https://doi.org/10.1007/s00421-019-04178-7
Easton C, Fudge BW, Pitsiladis YP (2007) Rectal, telemetry pill and tympanic membrane thermometry during exercise heat stress. J Therm Biol 32:78–86. https://doi.org/10.1016/j.jtherbio.2006.10.004
Edholm OG (1978) Man: hot and cold. Edward Arnold, London
Edholm OG, Bacharach AL (1965) The physiology of human survival. Academic Press, London
Edholm OG, Gunderson EKE (1973) (eds) Polar human biology. In: The proceedings of the SCAR/IUPS/IUBS symposium on human biology and medicine in the antarctic. Butterworth-Heinemann, London
Edholm OG, Weiner JS (1981) Introduction to the history of human physiology. In: Edholm OG, Weiner JS (eds) The principles and practice of human physiology. Academic Press, London, pp 1–18
Edwards RJ, Harrison MH (1984) Intravascular volume and protein responses to running exercise. Med Sci Sports Exerc 16:247–255
Eijkman C (1895) Vergleichende Untersuchung über die physikalische Wärmeregulirung bei dem europäischen und dem malaiischen Tropenbewohner. Archiv Für Pathologische Anatomie Und Physiologie Und Für Klinische Medicin 140:125–157. https://doi.org/10.1007/BF02116129
Eiken O, Mekjavic IB (2004) Ischaemia in working muscles potentiates the exercise induced sweating response in man. Acta Physiol Scand 181:305–311. https://doi.org/10.1111/j.1365-201X.2004.01289.x
Eldridge FL, Millhorn DE, Waldrop TG (1981) Exercise hyperpnea and locomotion: parallel activation from the hypothalamus. Science 211:844–846. https://doi.org/10.1126/science.7466362
Elia M (1992) Organ and tissue contribution to metabolic rate. In: Kinney JM, Tucker HN (eds) Energy metabolism: tissue determinants and cellular corollaries. Raven Press, New York, pp 61–80
Emerson DM, Chen SC, Kelly MR, Parnell B, Torres-McGehee TM (2021) Non-steroidal anti-inflammatory drugs on core body temperature during exercise: a systematic review. J Exerc Sci Fit 19:127–133. https://doi.org/10.1016/j.jesf.2020.12.003
Epstein Y, Yanovich R (2019) Heatstroke. N Engl J Med 380:2449–2459. https://doi.org/10.1056/NEJMra1810762
Fanger PO (1970) Thermal comfort. Danish Technical Press, Copenhagen
Fenn WO (1924) The relation between the work performed and the energy liberated in muscular contraction. J Physiol 58:373–395. https://doi.org/10.1113/jphysiol.1924.sp002141
Fernel JF (1547) De Naturali parte Medicinae libri septem. Joannes Gryphius, Venice
Ferretti G, Fagoni N, Taboni A, Vinetti G, di Prampero PE (2022) A century of exercise physiology: key concepts on coupling respiratory oxygen flow to muscle energy demand during exercise. Eur J Appl Physiol 122:1317–1365. https://doi.org/10.1007/s00421-022-04901-x
Ferris BG, Forster RE, Pillion EL, Christensen WR (1947) Control of peripheral blood flow: responses in the human hand when extremities are warmed. Am J Physiol 150:304–314. https://doi.org/10.1152/ajplegacy.1947.150.2.304
Filehne W (1910) Zur Lehre von der Warmeregulation. Archiv Für Physiologie 1910:551–558
Fletcher WM, Hopkins FG (1917) The respiratory process in muscle and the nature of muscular motion. Proc R Soc Lond Ser B Biol Sci 89:444–467. https://doi.org/10.1098/rspb.1917.0005
Flouris AD (2011) Functional architecture of behavioural thermoregulation. Eur J Appl Physiol 111:1–8. https://doi.org/10.1007/s00421-010-1602-8
Flouris AD, Schlader Z (2015) Human behavioral thermoregulation during exercise in the heat. Scand J Med Sci Sports 25:52–64. https://doi.org/10.1111/sms.12349
Folk GE (1974) Textbook of environmental physiology. Lea & Febiger, Philadelphia
Formenti D, Ludwig N, Gargano M, Gondola M, Dellerma N, Caumo A, Alberti G (2013) Thermal imaging of exercise-associated skin temperature changes in trained and untrained female subjects. Ann Biomed Eng 41:863–871. https://doi.org/10.1007/s10439-012-0718-x
Foster J, Smallcombe JW, Hodder S, Jay O, Flouris AD, Nybo L, Havenith G (2021) An advanced empirical model for quantifying the impact of heat and climate change on human physical work capacity. Int J Biometeorol 65:12151229. https://doi.org/10.1007/s00484-021-02105-0
Foundation for Research on Information Technologies in Society (2013) Database of tissue properties. Zurich, Switzerland. http://www.itis.ethz.ch/itis-for-health/tissue-properties/database/heat-capacity/. Accessed 26 Jan 2022
Fourier J-B-J (1807) Théorie de la Propagation de la Chaleur dans les Solides. Monograph submitted to the Institute de France, December 1807
Fowler RH, Guggenheim EA (1939) Statistical thermodynamics: a version of statistical mechanics for students of physics and chemistry. Cambridge University Press, London
Fox RH, Davies TW, Marsh FP, Urich H (1970) Hypothermia in a young man with an anterior hypothalamic lesion. Lancet 296:185–188. https://doi.org/10.1016/S0140-6736(70)92538-9
Franklin B (1758) Letter from Benjamin Franklin to John Lining, 17 June 1758. Founders Online, The U.S. National Archives and Records, Administration, College Park. https://founders.archives.gov/documents/Franklin/01-08-02-0023. Accessed 28 June 2021
Franklin B (1769) Experiments and observations on electricity. Francis Newbery, London
Fredericq L (1882) Sur la régulation de la température chez les animaux à sang chaud. Arch Biol 3:687–804
Fredericq L (1885) Influence du milieu ambiant sur la composition du sang des animaux aquatiques. Archives De Zoologie Expérimentale Et Générale Série 2:34–38
Fredericq L (1913) Sur la régulation de la température chez les animaux à sang chaud. Arch Int Physiol 13:687–804
Freeman NE (1935) The effect of temperature on the rate of blood flow in the normal and in the sympathectomized hand. Am J Physiol 113:384–398. https://doi.org/10.1152/ajplegacy.1935.113.2.384
Fregly MJ, Fregly MS (1982) Edward F. Adolph. Physiologist 25:1
Fuller A, Blatteis CM (2015) In memory of Helen Laburn and Claus Jessen. Temperature 2:59–60. https://doi.org/10.1080/23328940.2015.1017090

Fuller A, Mitchell G, Mitchell D (1999a) Non-thermal signals govern selective brain cooling in pigs. J Comp Physiol B 169:605–611. https://doi.org/10.1007/s003600050261

Fuller A, Oosthuyse T, Maloney SK, Mitchell D (1999b) Evaluation of miniature data loggers for body temperature measurement during sporting activities. Eur J Appl Physiol 79:341–346. https://doi.org/10.1007/s004210050518

Fye WB (1997) Jean François Fernel. Clin Cardiol 20:1037–1038. https://doi.org/10.1002/clc.4960201214

Gaesser GA, Brooks GA (1984) Metabolic bases of excess post-exercise oxygen consumption: a review. Med Sci Sports Exerc 16:29–43

Gagge AP (1937) A new physiological variable associated with sensible and insensible perspiration. Am J Physiol 120:277–287. https://doi.org/10.1152/ajplegacy.1937.120.2.277

Gagge AP, Burton AC, Bazett HC (1941) A practical system of units for the description of the heat exchange of man with his environment. Science 94:428–430. https://doi.org/10.1126/science.94.2445.428

Gagge AP, Gonzalez RR (1996) Mechanisms of heat exchange: biophysics and physiology. In: Comprehensive physiology. Supplement 14: Handbook of physiology, environmental physiology, pp 45–84. https://doi.org/10.1002/cphy.cp040104

Gagge AP, Herrington LP (1947) Physiological effects of heat and cold. Annu Rev Physiol 9:409–428. https://doi.org/10.1146/annurev.ph.09.030147.002205

Gagge AP, Nishi Y (1977) Heat exchange between human skin surface and thermal environment. In: Comprehensive physiology. Supplement 26: Handbook of physiology, reactions to environmental agents, pp 69–92. https://doi.org/10.1002/cphy.cp090105

Gagge AP, Winslow CE, Herrington LP (1938) The influence of clothing on the physiological reactions of the human body to varying environmental temperatures. Am J Physiol 124:30–50. https://doi.org/10.1152/ajplegacy.1938.124.1.30

Gagnon D, Jay O, Kenny GP (2013) The evaporative requirement for heat balance determines whole-body sweat rate during exercise under conditions permitting full evaporation. J Physiol 591:2925–2935. https://doi.org/10.1113/jphysiol.2012.248823

Galimidi UC, Stewart JM, van Rensburg A (1979) The effect of body motion on convective heat transfer from a nude man. J S Afr Inst Min Metall 79:485–488

Gallagher D, Belmonte D, Deurenberg P, Wang Z, Krasnow N, Pi-Sunyer FX, Heymsfield SB (1998) Organ-tissue mass measurement allows modeling of REE and metabolically active tissue mass. Am J Physiol 275:E249–E258. https://doi.org/10.1152/ajpendo.1998.275.2.E249

Garn SM, Clark LC, Harper RV (1953) The sex difference in the basal metabolic rate. Child Dev 24:215–222. https://doi.org/10.2307/1126247

Gehan EA, George SL (1970) Estimation of human body surface area from height and weight. Cancer Chemother Rep 54:225–235

George KP, Fadel PJ, Taylor NAS (2014) Thematic reviews. Series III: blood pressure regulation outside the comfort zone. Eur J Appl Physiol 114:443–444. https://doi.org/10.1007/s00421-013-2796-3

Gephart FC, DuBois EF (1915) Fourth paper. The determination of the basal metabolism of normal men and the effect of food. Arch Intern Med 15:835–867. https://doi.org/10.1001/archinte.1915.00070240044004

Giaja J (1938a) Homéothermie et Thermorégulation I—L'homothermie. Hermann & Cie, Paris

Giaja J (1938b) Homéothermie et Thermorégulation II—La Thermorégulation. Hermann & Cie, Paris

Giering K, Minet O, Lamprecht I, Müller G (1995) Review of thermal properties of biological tissues. Proc SPIE Int Soc Opt Eng 25:45–65

Gisolfi CV (1983) Temperature regulation during exercise: directions—1983. Med Sci Sports Exerc 15:15–20

Gisolfi CV, Lamb DR, Nadel ER (1993) Exercise, heat, and thermoregulation. Brown & Benchmark, Dubuque

Gisolfi CV, Wenger CB (1984) Temperature regulation during exercise: old concepts, new ideas. Exerc Sport Sci Rev 12:339–372

Givoni B, Goldman RF (1972) Predicting rectal temperature response to work, environment, and clothing. J Appl Physiol 32:812–822. https://doi.org/10.1152/jappl.1972.32.6.812

Gladden LB (2004) Lactate metabolism: a new paradigm for the third millennium. J Physiol 558:5–30. https://doi.org/10.1113/jphysiol.2003.058701

Gleeson M (2000) Interleukins and exercise. J Physiol 529:1. https://doi.org/10.1111/j.1469-7793.2000.00001.x

Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA (2011) The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol 11:607–615. https://doi.org/10.1038/nri3041

Glickman N, Hick FK, Keeton RW, Montgomery MM (1941) Blood volume change in men exposed to hot environmental conditions for a few hours. Am J Physiol 134:165–176. https://doi.org/10.1152/ajplegacy.1941.134.2.165

Golden F, St C, Hampton IF, Smith D (1980) Lean long distance swimmers. J R Nav Med Serv 66:26–30. https://doi.org/10.1136/jrnms-66-26

Golden F, St C, Tipton MJ (1987) Human thermal responses during leg-only exercise in cold water. J Physiol 391:399–405. https://doi.org/10.1113/jphysiol.1987.sp016744

Golden F, Tipton M (2002) Essentials of sea survival. Human Kinetics, Champaign

Goldman RF (1974) Clothing design for comfort and work performance in extreme thermal environments. Trans N Y Acad Sci 36:531–544. https://doi.org/10.1111/J.2164-0947.1974.TB01599.X

Goldman RF (1994) Heat stress in industrial protective encapsulating garments. In: Martin WF, Levine SP (eds) Protecting personnel at hazardous waste sites, pp 258–315. Butterworth-Heinemann, Boston

Goldman RF (2000) Heat stress in industrial protective encapsulating garments. In: Martin WF, Gochfeld M (eds) Protecting personnel at hazardous waste sites, 3rd edn, pp 295–355. Butterworth-Heinemann, Oxford. https://doi.org/10.1016/B978-075067049-4/50012-6

Goldman RF (2001) Introduction to heat-related problems in military operations. In: Pandolf KB, Burr RE, Wenger CB, Pozos RS (eds) Medical aspects of harsh environments, Volume 1. In: Zajtchuk R, Bellamy RF (eds) Textbook of military medicine, pp 3–49. Department of the Army, Office of the Surgeon General, and Borden Institute. Washington, DC

Goldman RF, Kampmann B (2007) Handbook on clothing—biomedical effects of military clothing and equipment systems, 2nd edn. NATO Research Study Group 7 on Bio-Medical Research Aspects of Military Protective Clothing

Goldner MG (1955) Adolf magnus-levy 1865–1955. Diabetes 4:422–424. https://doi.org/10.2337/diab.4.5.422

Gomes MM, Engelhardt E (2014) Claude Bernard: bicentenary of birth and his main contributions to neurology. Arq Neuropsiquiatr 72:322–325. https://doi.org/10.1590/0004-282X20130239

Gonzalez RR (1987) Biophysical and physiological integration of proper clothing for exercise. Exerc Sports Sci Rev 15:261–295

Gonzalez RR (1988) Biophysics of heat transfer and clothing considerations. In: Pandolf KB, Sawka MN, Gonzalez RR (eds) Human performance physiology and environmental medicine at terrestrial extremes. Benchmark Press, Indianapolis, pp 45–95

Gonzalez RR, Cena K (1985) Evaluation of vapor permeation through garments during exercise. J Appl Physiol 58:928–935. https://doi.org/10.1152/jappl.1985.58.3.928
González-Alonso J (2012) Human thermoregulation and the cardiovascular system. Exp Physiol 97:340–346. https://doi.org/10.1113/expphysiol.2011.058701
González-Alonso J, Quistorff B, Krustrup P, Bangsbo J, Saltin B (2000) Heat production in human skeletal muscle at the onset of intense dynamic exercise. J Physiol 524:603–615. https://doi.org/10.1111/j.1469-7793.2000.00603.x
González-Alonso J, Teller C, Andersen SL, Jensen FB, Hyldeg T, Nielsen B (1999) Influence of body temperature on the development of fatigue during prolonged exercise in the heat. J Appl Physiol 86:1032–1039. https://doi.org/10.1152/jappl.1999.86.3.1032
Goodwin GM, McCloskey DI, Mitchell JH (1972) Cardiovascular and respiratory responses to changes in central command during isometric exercise at constant muscle tension. J Physiol 226:173–190. https://doi.org/10.1113/jphysiol.1972.sp009979
Gordon CJ (1982) Open-loop gain of evaporative heat loss during radiant heat exposure in the mouse. Am J Physiol 242:R275–R279. https://doi.org/10.1152/ajpregu.1982.242.3.R275
Gordon CJ (1983) A review of terms for regulated vs. forced, neurochemical-induced changes in body temperature. Life Sci 32:1285–1295. https://doi.org/10.1016/0024-3205(83)90802-0
Gordon CJ (1990) Thermal biology of the laboratory rat. Physiol Behav 47:963–991. https://doi.org/10.1016/0031-9384(90)90025-y
Gordon CJ (2017) The mouse thermoregulatory system: its impact on translating biomedical data to humans. Physiol Behav 179:55–66. https://doi.org/10.1016/j.physbeh.2017.05.026
Gordon CJ, Caldwell JN, Taylor NAS (2016) Non-thermal modulation of sudomotor function during static exercise and the impact of intensity and muscle-mass recruitment. Temperature 3:252–261. https://doi.org/10.1080/23328940.2016.1176102
Gordon CJ, Heath JE (1980) Slow bursting thermal sensitive neurons in the preoptic area of the rabbit. Brain Res Bull 5:515–518. https://doi.org/10.1016/0361-9230(80)90256-7
Gordon CJ, Heath JE (1986) Integration and central processing in temperature regulation. Annu Rev Physiol 48:595–612. https://doi.org/10.1146/annurev.ph.48.030186.003115
Gosselin RE (1947) Heat exchanges in the desert. In: Adolph EF (ed) Physiological of man in the desert. Interscience Publishing Company, New York, pp 77–95
Gourine VN (1997) (ed) Temperature control in health and disease. Institute of Physiology, National Academy of Sciences, Minsk
Graf R, Krishna S, Heller HC (1989) Regulated nocturnal hypothermia induced in pigeons by food deprivation. Am J Physiol 256:R733–R738. https://doi.org/10.1152/ajpregu.1989.256.3.R733
Grant RT, Bland EF (1931) Observations on arteriovenous anastomoses in human skin and in the birds foot with special references to the reaction to cold. Heart 15:385–411
Grant RT, Pearson RSB (1938) The blood circulation in the human limb: observations on the differences between the proximal and distal parts and remarks on the regulation of body temperature. Clin Sci 3:119–139
Greenfield ADM (1963) The circulation through the skin. In: Hamilton WF, Dow P (eds) Handbook of physiology. Circulation. Section 2, Volume II, pp 1325–1351. American Physiological Society, Washington, DC
Grollman A (1930) Physiological variations of the cardiac output in man. X. The effect of variations in the environmental temperature on the pulse rate, blood pressure, oxygen comsumption, arterio-venous oxygen difference, and cardiac output of normal individuals. Am J Physiol 95:263–273. https://doi.org/10.1152/ajplegacy.1930.95.2.263
Gross CG (1998) Claude Bernard and the constancy of the internal environment. Neuroscientist 4:380–385. https://doi.org/10.1177/107385849800400520
Guerlac H (1976) Chemistry as a branch of physics: Laplace's collaboration with Lavoisier. Hist Stud Phys Sci 7:193–276. https://doi.org/10.2307/27757357
Grunfeld GB (1991) Ethics of using Nazi research. J Med Ethics 17:162. https://doi.org/10.1136/jme.17.3.162-a
Gunga H-C (2009) Nathan Zuntz: his life and work in the fields of high altitude physiology and aviation medicine. Academic Press, Burlington
Haight JS, Keatinge WR (1970) Human temperature regulation after prolonged intermittent exercise. J Physiol 206:20P-21P
Haight JSJ, Keatinge WR (1973) Elevation in set point for body temperature regulation after prolonged exercise. J Physiol 229:77–85. https://doi.org/10.1113/jphysiol.1973.sp010127
Haldane JS (1905) The influence of high temperatures No. 1. Epidemiol Infect 5:494–513. https://doi.org/10.1017/S0022172400006811
Haldane JS (1916) The new physiology. Science 44:619–631. https://doi.org/10.1126/science.44.1140.619
Haldane JS (1922) Respiration. Yale University Press, New Haven
Haldane JS (1935) The philosophy of a biologist. Oxford University Press, Oxford
Haldane JS, Priestley JG (1905) The regulation of the lung-ventilation. J Physiol 32:225–266. https://doi.org/10.1113/jphysiol.1905.sp001081
Hales S (1727) Statical essays: containing vegetable staticks; or an account of some statical experiments on the sap in vegetables. W. Innys, London
Hales JRS (1996) Heat-induced conflicts between and within autonomic activities. In: Shiraki K, Sagawa S, Yousef MK (eds) Physiological basis of occupational health: stressful environments. SBP Academic Publishing, Amsterdam, pp 3–12
Hales JRS, Richards DAB (1987) (eds) Heat stress: physical exertion and environment. Excerpta Medica, Amsterdam
Hall TS (1975) History of general physiology, 600 B.C to A.D. 1900, Volume I: from pre-socratic times to the enlightenment. University of Chicago Press, Chicago
Halliday EC, Hugo TJ (1963) The photodermoplanimeter. J Appl Physiol 18:1285–1288. https://doi.org/10.1152/jappl.1963.18.6.1285
Halliwill JR, Sieck DC, Romero SA, Buck TM, Ely MR (2014) Blood pressure regulation X: what happens when the muscle pump is lost? Post-exercise hypotension and syncope. Eur J Appl Physiol 114:561–578. https://doi.org/10.1007/s00421-013-2761-1
Hamberger CA, Wersall J (1964) Vascular supply of the tympanic membrane and the ossicular chain. Acta Otolaryngol 57(Supplement 188):308–318. https://doi.org/10.3109/00016486409134581
Hammel HT (1965) Neurons and temperature regulation. In: Yamamoto WS, Brobeck JR (eds) Physiological controls and regulations, pp 71–97. Philadelphia, Saunders
Hammel HT (1968) Regulation of internal body temperature. Annu Rev Physiol 30:641–710. https://doi.org/10.1146/annurev.ph.30.030168.003233
Hammel HT (1970) The concept of an adjustable set point. In: Hardy JD, Gagge AP, Stolwijk JAJ (eds) Physiological and behavioral temperature regulation, pp 676–683. C.C. Thomas, Springfield
Hammel HT, Jackson DC, Stolwijk JAJ, Hardy JD, Stromme SB (1963) Temperature regulation by hypothalamic proportional control with an adjustable set-point. J Appl Physiol 18:1146–1154. https://doi.org/10.1152/jappl.1963.18.6.1146
Hancock W, Whitehouse AGR, Haldane JS (1929) The loss of water and salts through the skin and the corresponding physiological adjustments. Proc R Soc Lond Ser B Biol Sci 105:43–59. https://doi.org/10.1098/rspb.1929.0028

Hardy JD (1934a) The radiation of heat from the human body: I. An instrument for measuring the radiation and surface temperature of the skin. J Clin Investig 13:593–604. https://doi.org/10.1172/JCI100607

Hardy JD (1934b) The radiation of heat from the human body: II. A comparison of some methods of measurement. J Clin Investig 13:605–614. https://doi.org/10.1172/JCI100608

Hardy JD (1937) The physical laws of heat loss from the human body. Proc Natl Acad Sci USA 23:631–637. https://doi.org/10.1073/pnas.23.12.631

Hardy JD (1949) Heat transfer. In: Newburgh LH (ed) Physiology of heat regulation and the science of clothing. Hafner Publishing Company, New York, pp 78–108

Hardy JD (1954) Control of heat loss and heat production in physiologic temperature regulation. Harvey Lect 49:242–270

Hardy JD (1961) Physiology of temperature regulation. Physiol Rev 41:521–606. https://doi.org/10.1152/physrev.1961.41.3.521

Hardy JD (1965) The "set-point" concept in physiological temperature regulation. In: Yamamoto WS, Brobeck JR (eds) Physiological controls and regulations. Saunders, Philadelphia, pp 98–116

Hardy JD, DuBois EF, Soderstrom GF (1938) The technic of measuring radiation and convection. J Nutr 15:461–475. https://doi.org/10.1093/jn/15.5.461

Hardy JD, Muschenheim C (1934) The radiation of heat from the human body. IV. The emission, reflection, and transmission of infra-red radiation by the human skin. J Clin Investig 13:817–831. https://doi.org/10.1172/JCI100624

Hardy JD, Oppel TW (1938) Studies in temperature sensation. IV The stimulation of cold sensation by radiation. J Clin Investig 17:771–778. https://doi.org/10.1172/JCI101007

Hardy JD, Soderstrom GF (1937) An improved apparatus for measuring surface and body temperature. Rev Sci Instrum 8:419–422. https://doi.org/10.1063/1.1752205

Hardy JD, Soderstrom GF (1938) Heat loss from the nude body and peripheral blood flow at temperatures of 22°C to 35°C. J Nutr 16:493–510. https://doi.org/10.1093/JN/16.5.493

Harris JA, Benedict FG (1918) A biometric study of human basal metabolism. Proc Natl Acad Sci USA 4:370–373. https://doi.org/10.1073/pnas.4.12.370

Harris JA, Benedict FG (1919) A biometric study of basal metabolism in man. Carnegie Institution of Washington, Washington. Publication number 279

Harrison MH (1985) Effects on thermal stress and exercise on blood volume in humans. Physiol Rev 65:149–209. https://doi.org/10.1152/physrev.1985.65.1.149

Harrison MH, Edwards RJ, Cochrane LA, Graveney MJ (1983) Blood volume and protein responses to skin heating and cooling in resting subjects. J Appl Physiol 54:515–523. https://doi.org/10.1007/BF00422158

Harsch V (2007) Theodor Benzinger, German pioneer in high altitude physiology research and altitude protection. Aviat Space Environ Med 78:906–908

Hartley HB (1947) Antoine Laurent Lavoisier 26 August 1743–8 May 1794. Proc R Soc Lond Ser B Biol Sci 134:348–377. https://doi.org/10.1098/rspa.1947.0050

Hartree W (1932) A negative phase in the heat production of muscle. J Physiol 19:104–110

Harvey W (1628) Anatomical exercises on the generation of animals, pp 143–518. In: Willis R (Translator) The works of William Harvey. Sydenham Society, London.

Hasama B-I (1929) Pharmakologische und physiologische Studien über die Schweisszentren. II. Mitteilung: Über den Einfluß der direkten mechanischen, thermischen und elektrischen Reizung auf die Schweißsowie Wärmezentren Naunyn-Schmiedebergs. Archiv Für Experimentelle Pathologie Und Pharmakologie 146:129–161. https://doi.org/10.1007/BF01863269

Hatfield HS, Pugh LGC (1951) Thermal conductivity of human fat and muscle. Nature 168:918–919. https://doi.org/10.1038/168918a0

Houghten FC, Yagloglou CP (1923) Determination of the comfort zone. J Am Soc Heat Vent Eng 29:515–528

Havenith G, Fiala D (2016) Thermal indices and thermophysiological modeling for heat stress. Compr Physiol 6:255–302. https://doi.org/10.1002/cphy.c140051

Havenith G, Fiala D, Blazejczyk K, Richards M, Bröde P, Holmér I, Rintamaki H, Benshabat Y, Jendritzky G (2012) The UTCI-clothing model. Int J Biometeorol 56:461–470. https://doi.org/10.1007/s00484-011-0451-4

Havenith G, Heus R, Lotens WA (1990) Resultant clothing insulation: a function of body movement, posture, wind, clothing fit and ensemble thickness. Ergonomics 33:67–84. https://doi.org/10.1080/00140139008927094

Havenith G, Richards MG, Wang X, Bröde P, Candas V, den Hartog E, Holmér I, Kuklane K, Meinander H, Nocker W (2008) Apparent latent heat of evaporation from clothing: attenuation and "heat pipe" effects. J Appl Physiol 104:142–149. https://doi.org/10.1152/japplphysiol.00612.2007

Havenith G, Wang X, THERMPROTECT network (2005) Interaction effects of radiation and convection measured by a thermal manikin wearing protective clothing with different radiant properties. In: Proceedings of the third international conference on the human-environment system. Tokyo, Japan. September 12th–15th, 2005, pp 47–50

Haycock GB, Schwartz GJ, Wisotsky DH (1978) Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. J Pediatr 93:62–66. https://doi.org/10.1016/s0022-3476(78)80601-5

Haymes EM, Wells CL (1986) Environment and human performance. Human Kinetics Publishers, Champaign

Hellon RF (1967) Thermal stimulation of hypothalamic neurones in unanaesthetized rabbits. J Physiol 193:381–395. https://doi.org/10.1113/jphysiol.1967.sp008364

Hellon RF (1970) The stimulation of hypothalamic neurones by changes in ambient temperature. Pflügers Arch Eur J Physiol 321:56–66. https://doi.org/10.1007/BF00594122

Hellon R (1983) Thermoreceptors. Comprehensive physiology. Supplement 8: Handbook of physiology, the cardiovascular system, peripheral circulation and organ blood flow, pp 659–673. https://doi.org/10.1002/cphy.cp020318

Helmholtz H (1848) Ueber die Wärmeentwickelung bei der Muskelaction. Archiv für Anatomie, Physiologie und wissenschaftliche Medicin. 144–164

Helmholtz H (1861) On the application of the law of the conservation of force to organic nature. Proc R Soc 3:347–357

Henry CJK (2005) Basal metabolic rate studies in humans: measurement and development of new equations. Public Health Nutr 8:1133–1152. https://doi.org/10.1079/phn2005801

Hensel H (1973) Neural processes in thermoregulation. Physiol Rev 53:948–1017. https://doi.org/10.1152/physrev.1973.53.4.948

Hensel H (1974) Thermoreceptors. Annu Rev Physiol 36:233–249. https://doi.org/10.1146/annurev.ph.36.030174.001313

Hensel H (1981) Thermoreception and temperature regulation. Academic Press, London

Herrington LP (1949) The range of physiological response to climatic heat and cold. In: Newburgh LH (ed) Physiology of heat regulation and the science of clothing. Hafner Publishing Company, New York, pp 262–276

Hertel HC, Howaldt B, Mense S (1976) Responses of group IV and group III muscle afferents to thermal stimuli. Brain Res 113:201–205. https://doi.org/10.1016/0006-8993(76)90020-2

Hertzman AB (1959) Vasomotor regulation of cutaneous circulation. Physiol Rev 39:280–306. https://doi.org/10.1152/physrev.1959.39.2.280

Hetem RS, Maloney SK, Fuller A, Mitchell D (2016) Heterothermy in large mammals: inevitable or implemented? Biol Rev 91:187–205. https://doi.org/10.1111/brv.12166

Hetem RS, Mitchell D, Maloney SK, Meyer LC, Fick LG, Kerley GI, Fuller A (2008) Fever and sickness behavior during an opportunistic infection in a free-living antelope, the greater kudu (*Tragelaphus strepsiceros*). Am J Physiol 294:R246–R254. https://doi.org/10.1152/ajpregu.00570.2007

Hetem RS, Strauss WM, Fick LG, Maloney SK, Meyer LCR, Shobrak M, Fuller A, Mitchell D (2010) Variation in the daily rhythm of body temperature of free-living Arabian oryx (*Oryx leucoryx*): does water limitation drive heterothermy? J Comp Physiol B 180:1111–1119. https://doi.org/10.1007/s00360-010-0480-z

Heusner AA (1982) Energy metabolism and body size. I. Is the 0.75 mass exponent of Kleiber's equations a statistical artifact? Respir Physiol 48:1–12. https://doi.org/10.1016/0034-5687(82)90046-9

Heysmfield SB, Gallagher D, Kotler DP, Wang Z, Allison DB, Heshka S (2002) Body-size dependence of resting energy expenditure can be attributed to nonenergetic homogeneity of fat-free mass. Am J Physiol 282:E132–E138. https://doi.org/10.1152/ajpendo.2002.282.1.E132

Hill AV (1927) Muscular movement in man: the factors governing speed and recovery from fatigue. McGraw-Hill Book Company Inc., New York

Hill AV (1932) The revolution in muscle physiology. Physiol Rev 12:56–67. https://doi.org/10.1152/physrev.1932.12.1.56

Hill AV (1949) Myothermic methods. Proc R Soc Lond Ser B 136:228–2241. https://doi.org/10.1098/rspb.1949.0022

Hill AV (1950) August Schack Steenberg Krogh, 1874–1949. Biogr Mem Fellows R Soc 7:220–237. https://doi.org/10.1098/rsbm.1950.0014

Hill AV (1965) Trails and trials in physiology. A bibliography, 1909–1964; with reviews of certain topics and methods and a reconnaissance for further research. Williams and Wilkins Company, Baltimore

Hill GW, Gillum TL, Lee BJ, Romano PA, Schall ZJ, Hamilton AM, Kuennen MR (2020) Prolonged treadmill running in normobaric hypoxia causes gastrointestinal barrier permeability and elevates circulating levels of pro-and anti-inflammatory cytokines. Appl Physiol Nutr Metab 45:376–386. https://doi.org/10.1139/apnm-2019-0378

Hill LE, Griffith OW, Flack M (1916) V. The measurement of the rate of heat-loss at body temperature by convection, radiation, and evaporation. Philos Trans R Soc Lond Ser B 207:183–220. https://doi.org/10.1098/rstb.1916.0005

Hill LE, Hargood-Ash D (1919) On the cooling and evaporative powers of the atmosphere, as determined by the kata-thermometer. Proc R Soc Lond Ser B 90:438–447. https://doi.org/10.1098/rspb.1919.0004

Hill AV, Hartree W (1920) The four phases of heat-production of muscle. J Physiol 54:84–128. https://doi.org/10.1113/jphysiol.1920.sp001913

Hill AV, Lupton H (1922) The oxygen consumption during running. J Physiol 56:xxxii–xxxiii

Hippocrates (1817) The aphorisms of hippocrates. Translated by Marks, E. from the Latin version of Verhoofd, L. Collins and Company, New York

Hippocrates (1923) Hippocrates. Translated by Jones, W.H.S. Loeb Classical Library 148. Harvard University Press, Cambridge

Hollmann W (1985) Historical remarks on the development of the aerobic-anaerobic threshold up to 1966. Int J Sports Med 6:109–116. https://doi.org/10.1055/s-2008-1025823

Holmér I (1988) Assessment of cold stress in terms of required clothing insulation-IREQ. Int J Ind Ergon 3:159–166. https://doi.org/10.1016/0169-8141(88)90017-0

Holmér I (2006) Protective clothing in hot environments. Ind Health 44:404–413. https://doi.org/10.2486/indhealth.44.404

Holmér I, Nilsson H, Havenith G, Parsons K (1999) Clothing convective heat exchange-proposal for improved prediction in standards and models. Ann Occup Hyg 43:329–337. https://doi.org/10.1093/annhyg/43.5.329

Holmes FL (1985) Lavoisier and the chemistry of life. An exploration of scientific creativity. University of Wisconsin Press, Madison

Holzlöhner E, Rascher S, Finke E (1942) Bericht über Abkühlungsversuche am Menschen. [Report on cooling experiments on humans]. Munich

Hong K, Hollies NRS, Spivak SM (1988) Dynamic moisture vapor transfer through textiles: Part I: clothing hygrometry and the influence of fiber type. Text Res J 58:697–706. https://doi.org/10.1177/004051758805801203

Horowitz M (2022) The history of thermal physiology in Israel. In: Blatteis CM, Taylor NAS, Mitchell D (eds) Thermal physiology: a worldwide history. Perspectives in physiology, pp 541–567. Springer, New York. https://doi.org/10.1007/978-1-0716-2362-6_11

Horsley VA, Clarke RH (1908) The structure and functions of the cerebellum examined by a new method. Brain 31:45–124. https://doi.org/10.1093/brain/31.1.45

Horvath SM (1981) Historical perspectives of adaptation to heat. In: Horvath SM, Yousef MK (eds) Environmental physiology aging, heat and altitude. Elsevier North Holland Inc, New York, pp 11–25

Horvath S, Horvath E (1973) The harvard fatigue laboratory: its history and contributions. Prentice-Hall, Englewood Cliffs

Houghten FC, Teague WW, Miller WE, Yant WP (1929) Thermal exchanges between the human body and its atmospheric environment. Am J Physiol 88:386–406. https://doi.org/10.1152/ajplegacy.1929.88.3.386

House JR, Tipton MJ (2002) Using skin temperature gradients or skin heat flux measurements to determine thresholds of vasoconstriction and vasodilatation. Eur J Appl Physiol 88:141–145. https://doi.org/10.1007/s00421-002-0692-3

Hua LH, Strigo IA, Baxter LC, Johnson SC, Craig AD (2005) Anteroposterior somatotopy of innocuous cooling activation focus in human dorsal posterior insular cortex. Am J Physiol 289:R319–R325. https://doi.org/10.1152/ajpregu.00123.2005

Huckaba CE, Downey JA, Darling RC (1971) A feedback-feedforward mechanism describing the interaction of central and peripheral signals in human thermoregulation. Int J Biometeorol 15:141–145. https://doi.org/10.1007/BF01803888

Hunter RA, MacAlpine I (1958) William Harvey and Robert Boyle. Notes Rec R Soc Lond 13:115–127

Huntington E (1924) Civilization and climate. Yale University Press, New Haven

Huxley JS (1932) Problems of relative growth. Methuen and Co., Ltd., London

Ichinose M, Maeda S, Kondo N, Nishiyasu T (2014) Blood pressure regulation II: what happens when one system must serve two masters—oxygen delivery and pressure regulation? Eur J Appl Physiol 114:451–465. https://doi.org/10.1007/s00421-013-2691-y

Inoue Y, Shibasaki M, Ueda H, Ishizashi H (1999) Mechanisms underlying the age-related decrement in the human sweating response. Eur J Appl Physiol 79:121–126. https://doi.org/10.1007/s004210050485

Ioannou LG, Tsoutsoubi L, Mantzios K, Gkikas G, Piil JF, Dinas PC, Notley SR, Kenny GP, Nybo L, Flouris AD (2021) The impacts of sun exposure on worker physiology and cognition: multi-country evidence and interventions. Int J Environ Res Public Health 18:7698. https://doi.org/10.3390/ijerph18147698

Irmak MK, Korkmaz A, Erogul O (2004) Selective brain cooling seems to be a mechanism leading to human craniofacial diversity observed in different geographical regions. Med Hypotheses 63:974–979. https://doi.org/10.1016/j.mehy.2004.05.003

Isenschmid VR, Krehl L (1912) Über den Einfluß des Gehirns auf die Wärmeregulation. Archiv Für Experimentelle Pathologie Und Pharmakologie 70:109–134. https://doi.org/10.1007/BF0187388

Isenschmid VR, Schnitzler W (1914) Beitrag zur Lokalisation des der Wärmeregulation vorstehenden Zentralapparates im Zwischenhirn. Archiv Für Experimentelle Pathologie Und Pharmakologie 76:202–223. https://doi.org/10.1007/BF01864729

IUPS Thermal Commission (1987) Glossary of terms for thermal physiology. Second edition. Revised by The Commission for Thermal Physiology of the International Union of Physiological Sciences. Pflüg Arch Eur J Physiol 410:567–487

IUPS Thermal Commission (2001) Glossary of terms for thermal physiology. Third edition. Revised by The Commission for Thermal Physiology of the International Union of Physiological Sciences. Jpn J Physiol 51:245–280.

Jackson JD (1995a) Osborne Reynolds: scientist, engineer and pioneer. Proc R Soc A Math Phys Eng Sci 451:49–86. https://doi.org/10.1098/rspa.1995.0117

Jacobj C, Römer C (1912) Beitrag zur Erklärung der Wärmestichhyperthermie. Archiv Für Experimentelle Pathologie Und Pharmakologie 70:149–182. https://doi.org/10.1007/BF01940635

Jackson JD (1995b) Osborne reynolds: scientist, engineer and pioneer. Proc R Soc Lond Ser A 451:49–86. https://doi.org/10.1098/rspa.1995.0117

James JP (1845) On the existence of an equivalent relation between heat and the ordinary forms of mechanical power. Lond Edinb Dublin Philos Mag J Sci 27:205–207

Janicki JS, Sheriff DD, Robotham JL, Wise RA (1996) Cardiac output during exercise: contributions of the cardiac, circulatory, and respiratory systems. In: Rowell LB, Shepherd JT (eds) Comprehensive physiology. Supplement 29: Handbook of physiology, exercise: regulation and integration of multiple systems, pp 649–704. https://doi.org/10.1002/cphy.cp120115

Janssen I, Heymsfield SB, Wang Z, Ross R (2000) Skeletal muscle mass and distribution in 468 men and women aged 18–88 yr. J Appl Physiol 89:81–88. https://doi.org/10.1152/jappl.2000.89.1.81

Jay O, Gagnon D, DuCharme MB, Webb P, Reardon FD, Kenny GP (2008) Human heat balance during postexercise recovery: separating metabolic and nonthermal effects. Am J Physiol 294:R1586–R1592. https://doi.org/10.1152/ajpregu.00717.2007

Jendritzky G (1990) Bioklimatische Bewertungsgrundlage der Räume am Beispiet von mesoskaligen Bioklimakarten. In: Schirmer H (ed) Methodik zur raumlichen Bewertung der thermischen Komponente im Bioklima des Menschen, pp 7–69. Akademie fiir Raumforschung und Landesplanung, Hannover

Jensen RL, Stone JL, Hayne RA (1996) Introduction of the human Horsley-Clarke stereotactic frame. Neurosurgery 38:563–567. https://doi.org/10.1097/00006123-199603000-00029

Jessen C (1976) Two-dimensional determination of thermosensitive sites within the goat's hypothalamus. J Appl Physiol 40:514–520. https://doi.org/10.1152/jappl.1976.40.4.514

Jessen C (1996) Interaction of body temperatures in control of thermoregulatory effector mechanisms. In: Comprehensive physiology. Supplement 14: Handbook of physiology, environmental physiology, pp 127–138. https://doi.org/10.1002/cphy.cp040107

Jessen C (2001) Selective brain cooling in mammals and birds. Jpn J Physiol 51:291–301. https://doi.org/10.2170/jjphysiol.51.291

Jessen C, Feistkorn G, Nagel A (1983) Temperature sensitivity of skeletal muscle in the conscious goat. J Appl Physiol 54:880–886. https://doi.org/10.1152/jappl.1983.54.4.880

Jessen C, Laburn HP, Knight MH, Kuhnen G, Goelst K, Mitchell D (1994) Blood and brain temperatures of free-ranging black wildebeest in their natural environment. Am J Physiol 267:R1528–R1536. https://doi.org/10.1152/ajpregu.1994.267.6.R1528

Jessen C, Ludwig O (1971) Spinal cord and hypothalamus as core sensors of temperature in the conscious dog. II. Addition of signals. Pflüg Arch Eur J Physiol 324:205–216. https://doi.org/10.1007/BF00586419

Johansson JE (1894) Ueber die Einwirkung der Muskelthätigkeit auf die Athmung und die Hertzhätigkeit. Skandinavisches Archiv Für Physiologie 5:20–66. https://doi.org/10.1111/j.1748-1716.1894.tb00192.x

Johnson JM, Park MK (1982) Effect of heat stress on cutaneous vascular responses to the initiation of exercise. J Appl Physiol 53:744–749. https://doi.org/10.1152/jappl.1982.53.3.744

Johnson JM, Pérgola PE, Liao FK, Kellogg DL, Crandall CG (1995) Skin of the dorsal aspect of human hands and fingers possesses an active vasodilator system. J Appl Physiol 78:948–954. https://doi.org/10.1152/jappl.1995.78.3.948

Johnson SC, Ruhling RO (1985) Aspirin in exercise-induced hyperthermia. Evidence for and against its role. Sports Med 2:1–7. https://doi.org/10.2165/00007256-198502010-00001

Joule JP (1845) On the existence of an equivalent relation between heat and ordinary forms of mechanical power. Lond Edinb Dublin Philos Mag J Sci 27:205–207. https://doi.org/10.1080/14786444508645256

Joule JP (1850) On the mechanical equivalent of heat. Philos Trans R Soc Lond 140:61–82. https://doi.org/10.1098/rstl.1850.0004

Joyner M, Kjaer M, Larsen PO (2015) The Copenhagen Muscle Research Centre (CMRC) 1994–2004. Scand J Med Sci Sports 25(Supplement 4):22–28. https://doi.org/10.1111/sms.12598

Joyner MJ, Limberg JK (2014) Blood pressure regulation: every adaptation is an integration? Eur J Appl Physiol 114:445–450. https://doi.org/10.1007/s00421-013-2636-5

Kahn RH (1904) Uber die Erwarmung des Carotidenblutes. Archiv Für Anatomie Und Physiologie 28(Supplement):81–134

Kamijo Y, Okumoto T, Takeno Y, Okazaki K, Inaki M, Masuki S, Nose H (2005) Transient cutaneous vasodilatation and hypotension after drinking in dehydrated and exercising men. J Physiol 568:689–698. https://doi.org/10.1113/jphysiol.2005.090530

Kamon E (1970) Negative and positive work in climbing a laddermill. J Appl Physiol 29:1–5. https://doi.org/10.1152/jappl.1970.29.1.1

Kanosue K, Crawshaw LI, Nagashima K, Yoda T (2010) Concepts to utilize in describing thermoregulation and neurophysiological evidence for how the system works. Eur J Appl Physiol 109:5–11. https://doi.org/10.1007/s00421-009-1256-6

Kanosue K, Yanase-Fujiwara M, Hosono T (1994a) Hypothalamic network for thermoregulatory vasomotor control. Am J Physiol 267:R283–R288. https://doi.org/10.1152/ajpregu.1994.267.1.R283

Kanosue K, Zhang YH, Yanase-Fujiwara M, Hosono T (1994b) Hypothalamic network for thermoregulatory shivering. Am J Physiol 267:R275–R282. https://doi.org/10.1152/ajpregu.1994.267.1.R275

Karmani S (2006) The thermal properties of bone and the effects of surgical intervention. Curr Orthop 20:52–58. https://doi.org/10.1016/J.CUOR.2005.09.011

Katch VL (1973) Use of the oxygen-body weight ratio in correlational analyses: spurious correlations and statistical considerations. Med Sci Sports Exerc 5:253–257

Katschinski DM, Wiedemann GJ, Longo W, d'Oleire FR, Spriggs D, Robins HI (1999) Whole body hyperthermia cytokine induction: a review, and unifying hypothesis for myeloprotection in the setting of cytotoxic therapy. Cytokine Growth Factor Rev 10:93–97. https://doi.org/10.1016/S1359-6101(99)00006-4

Katz B (1978) Archibald Vivian Hill, 26 September, 1886–3 June 1977. Biogr Mem Fellows R Soc 24:71–149. https://doi.org/10.1098/rsbm.1978.0005

Katz A (2022) A century of exercise physiology: key concepts in regulation of glycogen metabolism in skeletal muscle. Eur J Appl Physiol 122:1751–1772. https://doi.org/10.1007/s00421-022-04935-1

Kaufman WC (1994) Pharo Gagge and aeromedical research. Aviat Space Environ Med 65:1161

Kay D, Taaffe DR, Marino FE (1999) Whole-body pre-cooling and heat storage during self-paced cycling performance in warm humid conditions. J Sports Sci 17:937–944. https://doi.org/10.1080/026404199365326

Kayser C (1970) The French contribution to the progress in thermoregulatory research. In: Hardy JD, Gagge AP, Stolwijk JAJ (eds) Physiological and behavioral temperature regulation, pp 11–21. C.C. Thomas, Springfield

Kearney MR, Porter WP (2017) NicheMapR—an R package for biophysical modelling: the microclimate model. Ecography 40:664–674. https://doi.org/10.1111/ecog.02360

Keatinge WR (1960) The effect of subcutaneous fat and of previous exposure to cold on the body temperature, peripheral blood flow and metabolic rate of men in cold water. J Physiol 153:166–178. https://doi.org/10.1113/jphysiol.1960.sp006526

Keatinge WR (1978) Survival in cold water: the physiology and treatment of immersion hypothermia and of drowning. Blackwell Scientific Publications, Oxford

Keatinge WR, Sloan RE (1975) Deep body temperature from aural canal with servo-controlled heating to outer ear. J Appl Physiol 38:919–921. https://doi.org/10.1152/jappl.1975.38.5.919

Keele K (1957) William Harvey: the man and the college of physicians. Med Hist 1:265–278. https://doi.org/10.1017/s0025727300021335

Kennaway EL, Pembrey MS (1912) Observations upon the effects of section of the spinal cord upon temperature and metabolism. J Physiol 45:82–105. https://doi.org/10.1113/jphysiol.1912.sp001538

Kennedy JF (1962) Commencement address at Yale University, New Haven, Connecticut, 11 June 1962. https://www.jfklibrary.org/asset-viewer/archives/JFKWHA/1962/JFKWHA-104/JFKWHA-104 Accessed 10 Sep 2021

Kenney WL, Stanhewicz AE, Bruning RS, Alexander LM (2014) Blood pressure regulation III: what happens when one system must serve two masters: temperature and pressure regulation? Eur J Appl Physiol 114:467–479. https://doi.org/10.1007/s00421-013-2652-5

Kenny GP, Journeay WS (2010) Human thermoregulation: separating thermal and nonthermal effects on heat loss. Front Biosci 15:259–290. https://doi.org/10.2741/3620

Kenny GP, Reardon FD, Zaleski W, Reardon ML, Haman F, Ducharme MB (2003) Muscle temperature transients before, during, and after exercise measured using an intramuscular multisensor probe. J Appl Physiol 94:2350–2357. https://doi.org/10.1152/japplphysiol.01107.2002

Kerslake DM (1972) The stress of hot environments. Cambridge University Press, Cambridge

Key JD, Keys TE, Callahan JA (1979) Historical development of concept of blood circulation. An anniversary memorial essay to William Harvey. Am J Cardiol 43:1026–1032. https://doi.org/10.1016/0002-9149(79)90370-9

Kim J, Lee J, Kim S, Ryu HY, Cha KS, Sung DJ (2016) Exercise-induced rhabdomyolysis mechanisms and prevention: a literature review. J Sport Health Sci 5:324–333. https://doi.org/10.1016/j.jshs.2015.01.012

Kleiber M (1932) Body size and metabolism. Hilgardia 6:315–353. https://doi.org/10.3733/hilg.v06n11p315

Kleiber M (1947) Body size and metabolic rate. Physiol Rev 27:511–541. https://doi.org/10.1152/physrev.1947.27.4.511

Kleiber M (1950) Physiological meaning of regression equations. J Appl Physiol 2:417–423. https://doi.org/10.1152/jappl.1950.2.7.417

Kleiber M (1961) The fire of life: an introduction to animal energetics. Wiley, New York

Ko H-Y (2019) Thermoregulatory dysfunction. In: Ko H-Y (ed) Management and rehabilitation of spinal cord injuries, pp 305–309. Springer, Singapore. https://doi.org/10.1007/978-981-10-7033-4_23

Kondo N, Horikawa N, Aoki K, Shibasaki M, Inoue Y, Nishiyasu T, Crandall CG (2002) Sweating responses to a sustained static exercise is dependent on thermal load in humans. Acta Physiol Scand 175:289–295. https://doi.org/10.1046/j.1365-201X.2002.00994.x

Kondo N, Nishiyasu T, Inoue Y, Koga S (2010) Non-thermal modification of heat-loss responses during exercise in humans. Eur J Appl Physiol 110:447–458. https://doi.org/10.1007/s00421-010-1511-x

Kondo N, Shibasaki M, Aoki K, Koga S, Inoue Y, Crandall CG (2001) Function of human eccrine sweat glands during dynamic exercise and passive heat stress. J Appl Physiol 90:1877–1881. https://doi.org/10.1152/jappl.2001.90.5.1877

Kondo N, Takano S, Aoki K, Shibasaki M, Tominaga H, Inoue Y (1998) Regional difference in the effect of exercise intensity on thermoregulatory sweating and cutaneous vasodilation. Acta Physiol Scand 164:71–78. https://doi.org/10.1046/j.1365-201X.1998.00407.x

Kornblum K (1925) A clinical and experimental study of hyperthermia. Arch Neurol Psychiatry 13:754–766. https://doi.org/10.1001/archneurpsyc.1925.02200120075007

Kozyreva TV (2022) Development of research on thermoregulatory system in Russia. In: Blatteis CM, Taylor NAS, Mitchell D (eds) Thermal physiology: a worldwide history. Perspectives in physiology, pp 597–619. Springer, New York. https://doi.org/10.1007/978-1-0716-2362-6_13

Krediet CTP, Wilde AA, Wieling W, Halliwill JR (2004) Exercise related syncope, when it's not the heart. Clin Auton Res 14:25–36. https://doi.org/10.1007/s10286-004-1005-1

Krogh A (1913) A bicycle ergometer and respiration apparatus for the experimental study of muscular work. Skandinavisches Archiv Für Physiologie 30:375–394. https://doi.org/10.1111/j.1748-1716.1913.tb00681.x

Krogh A (1916) The respiratory exchange of animals and man. Longmans, Green and Company, London

Krogh A (1920) A gas analysis apparatus accurate to 0.001% mainly designed for respiratory exchange work. Biochem J 14:267–281. https://doi.org/10.1042/bj0140267

Krogh A (1934) Principle of regulation in the organism. Features in the architecture of physiological function. Nature 134:340–341. https://doi.org/10.1038/134340a0

Krogh A, Lindhard J (1913) The regulation of respiration and circulation during the initial stages of muscular work. J Physiol 47:112–136. https://doi.org/10.1113/jphysiol.1913.sp001616
Kuehn LA, Stubbs RA, Weaver RS (1970) Theory of the globe thermometer. J Appl Physiol 29:750–757. https://doi.org/10.1152/jappl.1970.29.5.750
Kuklane K, Gao C, Holmér I, THERMPROTECT network (2006) Effects of natural solar radiation on manikin heat exchange. In: Protective clothing—towards balanced protection: proceedings of the 3rd European conference on protective clothing (ECPC) and NOKOBETEF 8. Warsaw, Poland. May 10–12; 2006
Kullmann R, Schönung W, Simon E (1970) Antagonistic changes of blood flow and sympathetic activity in different vascular beds following central thermal stimulation. Pflüg Arch Eur J Physiol 319:146–161. https://doi.org/10.1007/BF00592493
Kumazawa T, Mizumura K (1977) Thin-fibre receptors responding to mechanical, chemical, and thermal stimulation in the skeletal muscle of the dog. J Physiol 273:179–194. https://doi.org/10.1113/jphysiol.1977.sp012088
Kuno Y (1934) The physiology of human perspiration. J. & A. Churchill, London
Kuno Y (1956) Human perspiration. C.C Thomas, Springfield
Kurazumi Y, Tsuchikawa T, Matsubara N, Horikoshi T (2008) Effect of posture on the heat transfer areas of the human body. Build Environ 43:1555–1565. https://doi.org/10.1016/j.buildenv.2007.09.001
Kurazumi Y, Rezgals L, Melikov AK (2014) Convective heat transfer coefficients of the human body under forced convection from ceiling. J Ergon 4:126–131. https://doi.org/10.4172/2165-7556.1000126
Kvist A, Lindström Å (2001) Basal metabolic rate in migratory waders: intra-individual, intraspecific, interspecific and seasonal variation. Funct Ecol 15:465–473. https://doi.org/10.1046/j.0269-8463.2001.00549.x
Laburn HP, Faurie A, Goelst K, Mitchell D (2002) Effects on fetal and maternal body temperatures of exposure of pregnant ewes to heat, cold, and exercise. J Appl Physiol 92:802–808. https://doi.org/10.1152/japplphysiol.00109.2001
Ladell WSS (1945) Thermal sweating. Br Med Bull 3:175–179. https://doi.org/10.1093/oxfordjournals.bmb.a071905
Ladell WSS (1955) The effects of water and salt intake upon the performance of men working in hot and humid environments. J Physiol 127:11–46. https://doi.org/10.1113/jphysiol.1955.sp005235
Lane JE (1919) Daniel Turner and the first degree of Doctor of Medicine conferred in the English colonies of North America by Yale College in 1723. Ann Med Hist 2:367–380
Larsen EH, Hoffmann E, Hedrick MS, Wang T (2021) August Krogh's contribution to the rise of physiology during the first half the 20th century. Comp Biochem Physiol Part A Mol Integr Physiol 256:110931. https://doi.org/10.1016/j.cbpa.2021.110931
Later W, Bosy-Westphal A, Kossel E, Glüer C-C, Heller M, Müller MJ (2010) Is the 1975 Reference Man still a suitable reference? Eur J Clin Nutr 64:1035–1042. https://doi.org/10.1038/ejcn.2010.125
Lavoisier A-L (1783) Réflexions sur le Phlogistique, pour Servir de Suite à la Théorie de la Combustion et de la Calcination. Académie des Sciences, Paris
LeBlanc J (1975) Man in the cold. Charles C. Thomas Publisher, Springfield
Lee DHK (1948) Heat and cold. Annu Rev Physiol 10:365–386. https://doi.org/10.1146/annurev.ph.10.030148.002053
Lee DHK (1964) Terrestrial animals in dry heat: man in the desert. In: Dill DB, Adolph EF (eds) Handbook of physiology. Section 4. Adaptation to the environment, pp 551–582. American Physiological Society, Washington, DC
Lee J-Y, Choi JW, Kim H (2008) Determination of body surface area and formulas to estimate body surface area using the alginate method. J Physiol Anthropol 27:71–82. https://doi.org/10.2114/jpa2.27.71
Lefèvre J (1898) Influence des réfrigérations sur la topographie et la marche des températures. Résistance thermogénétique de l'organisme humain. Archives de Physiologie Normale et Pathologique. Série 5. 10:1–16
Lefèvre J (1901) Reserches sur la conductabilité de la peau de l'organisme vivant et sur ses variations en fonction de la température extérieure. Étude Sur L'homme. J Phys 10:380–388. https://doi.org/10.1051/jphystap:0190100100038001
Lefèvre J (1911) Chaleu Amimale et Bioénergétique. Masson et Cie, Paris
Leppäluoto J, Hirvonen J, Hohtola E, Huttunen P, Rintamäki H, Hassi J (2022) Not only winter, not only cold: history of thermal physiology in Finland. In: Blatteis CM, Taylor NAS, Mitchell D (eds) Thermal physiology: a worldwide history. Perspectives in physiology, pp 201–237. Springer, New York. https://doi.org/10.1007/978-1-0716-2362-6_4
Levine JA (2004) Non-exercise activity thermogenesis (NEAT). Nutr Rev 62:S82–S97. https://doi.org/10.1053/beem.2002.0227
Levine JA (2005) Measurement of energy expenditure. Public Health Nutr 8:1123–1132. https://doi.org/10.1079/PHN2005800
Lewis WK (1922) The evaporation of a liquid into a gas. Trans Am Soc Mech Eng 44:325–340
Lewis T, Pickering GW (1931) Vasodilatation in the limbs in response to warming the body; with evidence for sympathetic vasodilator nerves in man. Heart 16:33–51
Lide DR (1997) CRC handbook of chemistry and physics. CRC Press, Boca Raton
Liebermeister C (1860) Physiologische Untersuchungen über die quantitativen Veränderungen der Warmeproduction. Erster, Zweiter und Dritter Artikel. Archiv für Anatomie und Physiologie. 1860, 1861:520–541, 589–623, 661–683
Liebermeister C (1875) Handbuch der Pathologie und Therapie des Fiebers. F.C.W. Vogel, Leipzig
Liesen H, Dufaux B, Hollmann W (1977) Modifications of serum glycoproteins the days following a prolonged physical exercise and the influence of physical training. Eur J Appl Physiol 37:243–254. https://doi.org/10.1007/BF00430954
Liljestrand G, Frumerie K (1914) Untersuchungen über den Wärmestich 1. Skandinavisches Archiv Für Physiologie 31:321–366. https://doi.org/10.1111/J.1748-1716.1914.TB00690.X
Linderholm M, Ahlm C, Settergren B, Waage A, Tärnvik A (1996) Elevated plasma levels of tumor necrosis factor (TNF)-α, soluble TNF receptors, interleukin (IL)-6, and IL-10 in patients with hemorrhagic fever with renal syndrome. J Infect Dis 173:38–43. https://doi.org/10.1093/infdis/173.1.38
Lindemann FA, Simon FE (1942) Walther Nernst, 1864–1941. Obit Not Fellows R Soc 4:101–112. https://doi.org/10.1098/rsbm.1942.0010
Lindinger MI, Ward SA (2022) A century of exercise physiology: key concepts in …. Eur J Appl Physiol 122:1–4. https://doi.org/10.1007/s00421-021-04873-4
Lindstedt SL (2016) Skeletal muscle tissue in movement and health: positives and negatives. J Exp Biol 219:183–188. https://doi.org/10.1242/jeb.124297
Lippmann A (1913) Ergebnisse vergleichender Untersuchungen von Achsel-und Rektumtemperatu nach einem großen Marsche. Dtsch Med Wochenschr 39:1496–1497. https://doi.org/10.1055/s-0028-1128631
Little MA, Collins KJ (2012) Joseph S. Weiner and the foundation of post-WW II human biology in the United Kingdom. Am J Phys Anthropol 149:114–131. https://doi.org/10.1002/ajpa.22164

Lolli L, Batterham AM, Weston KL, Atkinson G (2017) Size exponents for scaling maximal oxygen uptake in over 6500 humans: a systematic review and meta-analysis. Sports Med 47:1405–1419. https://doi.org/10.1007/s40279-016-0655-1

Lotens WA, Havenith G (1991) Calculation of clothing insulation and vapour resistance. Ergonomics 34:233–254. https://doi.org/10.1080/00140139108967309

Luheshi GN (1998) Cytokines and fever: mechanisms and sites of action. Ann N Y Acad Sci 856:83–89. https://doi.org/10.1111/j.1749-6632.1998.tb08316.x

Luo N, Weng WG, Fu M, Yang J, Han ZY (2014) Experimental study of the effects of human movement on the convective heat transfer coefficient. Exp Therm Fluid Sci 57:40–56. https://doi.org/10.1016/j.expthermflusci.2014.04.001

Lusk G (1922) A history of metabolism. In: Barker LF (ed) Endocrinology and metabolism, vol. 3, pp 3–38. D. Appleton and Company, New York

MacDonald IA, Bennett T, Sainsbury R (1984) The effect of a 48 h fast on the thermoregulatory responses to graded cooling in man. Clin Sci 67:445–452. https://doi.org/10.1042/cs0670445

Machado-Moreira CA, Barry RJ, Vosselman MJ, Taylor NAS (2009) Thermal and non-thermal sweating: what you see is not necessarily what you get. J Physiol Sci 59(Supplement 1):167

Machle W, Hatch TF (1947) Heat: man's exchanges and physiological responses. Physiol Rev 27:200–227. https://doi.org/10.1152/physrev.1947.27.2.200

Macfarlane DJ (2017) Open-circuit respirometry: a historical review of portable gas analysis systems. Eur J Appl Physiol 117:2369–2386. https://doi.org/10.1007/s00421-017-3716-8

MacKeith NW, Pembrey MS, Spurrell WR, Warner EC, Westlake HJWJ (1923) Observations on the adjustment of the human body to muscular work. Proc R Soc Lond Ser B 95:413–439. https://doi.org/10.1098/rspb.1923.0046

Mackinnon S (2020) When medical information comes from Nazi atrocities. BMJ Clin Res. 368:l7075. https://doi.org/10.1136/bmj.l7075

Maddock WG, Coller FA (1933) The role of the extremities in the dissipation of heat. Am J Physiol 106:589–596. https://doi.org/10.1152/ajplegacy.1933.106.3.589

Magnus-Levy A (1947) Energy metabolism in health and disease. J Hist Med Allied Sci 2:307–320. https://doi.org/10.1093/jhmas/ii.3.307

Magoun HW, Harrison F, Brobeck JR, Ranson SW (1938) Activation of heat loss mechanisms by local heating of the brain. J Neurophysiol 1:101–114. https://doi.org/10.1152/jn.1938.1.2.101

Mansell PI, MacDonald IA (1989) Effects of underfeeding and of starvation on thermoregulatory responses to cooling in women. Clin Sci 77:245–252. https://doi.org/10.1042/cs0770245

Mariak Z, White MD, Lewko J, Lyson T, Piekarski P (1999) Direct cooling of the human brain by heat loss from the upper respiratory tract. J Appl Physiol 87:1609–1613. https://doi.org/10.1152/jappl.1999.87.5.1609

Markovic G, Vucetic V, Nevill AM (2007) Scaling behaviour of O_2 in athletes and untrained individuals. Ann Hum Biol 34:315–328. https://doi.org/10.1080/03014460701219358

Martin AD (1984) An anatomical basis for assessing human body composition: evidence from 25 dissections. Doctoral Dissertation, Simon Fraser University, Canada

Martin AD, Drinkwater DT, Clarys JP (1984) Human body surface area: validation of formulae based on a cadaver study. Hum Biol 56:475–488

Maw GJ, Mackenzie IL, Taylor NAS (1998) Human body-fluid distribution during exercise in hot, temperate and cool environments. Acta Physiol Scand 163:297–304. https://doi.org/10.1046/j.1365-201x.1998.00380.x

Maw GJ, Mackenzie IL, Taylor NAS (2000) Can skin temperature manipulation, with minimal core temperature change, influence plasma volume in resting humans? Eur J Appl Physiol 81:159–162. https://doi.org/10.1007/PL00013790

Mayer JR (1842) Bemerkungen über die Kräfte der unbelebten Natur. Annalen Der Chimie Und Pharmazie 42:233–240

McCance RA, Ungley CCJWL, Widdowson EM (1956) The hazards to men in ships lost at sea, 1940–44. Special report series. Medical Research Council, No. 291. HM Stationery Office, London

McCullough EA, Jones BW, Huck J (1985) A comprehensive data base for estimating clothing insulation. ASHRAE Trans 91:29–47

McCullough EA, Rohles FH (1983) Quantifying the thermal protection characteristics of outdoor clothing systems. Hum Factors 25:191–198. https://doi.org/10.1177/001872088302500206

McDowall RJS (1924) A vaso-pressor reflex. J Physiol 59:41–47. https://doi.org/10.1113/jphysiol.1924.sp002161

McDowall RJS (1935) The nervous control of the blood vessels. Physiol Rev 15:98–174. https://doi.org/10.1152/physrev.1935.15.1.98

McKemy DD, Neuhausser WM, Julius D (2002) Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature 416:52–58. https://doi.org/10.1038/nature719

McKie D (1952) Antoine Lavoisier: scientist, economist, social reformer. Henry Schuman, New York

McKinley MJ, Martelli D, Pennington GL, Trevaks D, McAllen RM (2018) Integrating competing demands of osmoregulatory and thermoregulatory homeostasis. Physiology 33:170–181. https://doi.org/10.1152/physiol.00037.2017

McLellan TM, Daanen HAM, Cheung SS (2013) Encapsulated environment. Comp Physiol 3:1363–1391. https://doi.org/10.1002/cphy.c130002

McLellan TM, Havenith G (2016) Protective clothing ensembles and physical employment standards. Appl Physiol Nutr Metab 41:S121–S130. https://doi.org/10.1139/apnm-2015-0474

Mekjavic IB, Eiken O (2006) Contribution of thermal and nonthermal factors to the regulation of body temperature in humans. J Appl Physiol 100:2065–2072. https://doi.org/10.1152/japplphysiol.01118.2005

Mekjavic IB, Sundberg CJ, Linnarsson D (1991) Core temperature "null zone." J Appl Physiol 71:1289–1295. https://doi.org/10.1152/jappl.1991.71.4.1289

Mekjavic IB, Tipton MJ, Eiken O (2003) Thermal considerations in diving. In: Brubakk AO, Neumann TS (eds) Bennett and Elliott's physiology and medicine of diving, 5th edn, pp 115–152. Saunders, Edinburgh

Meyer HH (1913) Theorie des Fiebers und seiner Behandlung. Verhandlungen Des Deutschen Kongresses Für Innere Medizin 30:15–17

Michael J (2007) Conceptual assessment in the biological sciences: a National Science Foundation-sponsored workshop. Adv Physiol Educ 31:389–391. https://doi.org/10.1152/advan.00047.2007

Michael J, Cliff W, McFarland J, Modell H, Wright A (2017) What are the core concepts of physiology? In: The core concepts of physiology, pp 27–36. Springer, New York. https://doi.org/10.1007/978-1-4939-6909-8_3

Michael J, McFarland J (2011) The core principles ("big ideas") of physiology: results of faculty surveys. Adv Physiol Educ 35:336–341. https://doi.org/10.1152/advan.00004.2011

Michael J, Modell H, McFarland J, Cliff W (2009) The "core principles" of physiology: what should students understand? Adv Physiol Educ 33:10–16. https://doi.org/10.1152/advan.90139.2008

Milton A (2022) A history of thermal physiology in the United Kingdom of Great Britain and Northern Ireland and the Republic of Ireland. In: Blatteis CM, Taylor NAS, Mitchell D (eds)

Thermal physiology: a worldwide history. Perspectives in physiology, pp 1–56. Springer, New York. https://doi.org/10.1007/978-1-0716-2362-6_1
Mitchell D (1974a) Physical basis of thermoregulation. In: Robertshaw D (ed) Environmental Physiology. MTP International Review of Science, Physiology Series One, vol , pp 1–327. Butterworths, London
Mitchell D (1974b) Convective heat transfer from man and other animals. In: Monteith JL, Mount LE (eds) Heat loss from animals and man. Butterworths, London, pp 59–76
Mitchell D, Atkins AR, Wyndham CH (1972) Mathematical and physical models of thermoregulation. In: Bligh J, Moore RE (eds) Essays on temperature regulation. North-Holland Publishing Company, Amsterdam, pp 37–54
Mitchell D, Laburn HP (2022) South African thermal physiology: highlights from the twentieth century. In: Blatteis CM, Taylor NAS, Mitchell D (eds) Thermal physiology: a worldwide history. Perspectives in physiology, pp 435–491. Springer, New York. https://doi.org/10.1007/978-1-0716-2362-6_8
Mitchell D, Maloney SK, Jessen C, Laburn HP, Kamerman PR, Mitchell G, Fuller A (2002) Adaptive heterothermy and selective brain cooling in arid-zone mammals. Comp Biochem Physiol B Biochem Mol Biol 131:571–585. https://doi.org/10.1016/S1096-4959(02)00012-X
Mitchell JH, Reardon WC, McCloskey DI, Wildenthal K (1977) Possible role of muscle receptors in the cardiovascular response to exercise. Ann N Y Acad Sci 301:232–242. https://doi.org/10.1111/j.1749-6632.1977.tb38202.x
Mitchell D, Snelling EP, Hetem RS, Maloney SK, Strauss WM, Fuller A (2018) Revisiting concepts of thermal physiology: predicting responses of mammals to climate change. J Anim Ecol 87:956–973. https://doi.org/10.1111/1365-2656.12818
Mitchell D, Strydom NB, Van Graan CH, Van Der Walt WH (1971) Human surface area: comparison of the Du Bois formula with direct photometric measurement. Pflüg Arch Eur J Physiol 325:188–190. https://doi.org/10.1007/BF00587008
Mitchell WK, Taivassalo T, Narici MV, Franchi MV (2017) Eccentric exercise and the critically ill patient. Front Physiol 8:120. https://doi.org/10.3389/fphys.2017.00120
Mitchell D, van Rensburg AJ (1973) Assessment of clothing insulation: the problem and its solution using direct calorimetry on exercising men. Arch Sci Physiol 27:149–162
Mitchell D, Whillier A (1971) Cooling power of underground environments. J S Afr Inst Min Metall 72:93–99
Mitchell D, Wyndham CH, Atkins AR, Vermeulen AJ, Hofmeyr HS, Strydom NB, Hodgson T (1968) Direct measurement of the thermal responses of nude resting men in dry environments. Pflüg Arch Eur J Physiol 303:324–343. https://doi.org/10.1007/BF00596389
Mitchell D, Wyndham CH, Hodgson T (1967) Emissivity and transmittance of excised human skin in its thermal emission wave band. J Appl Physiol 23:390–394. https://doi.org/10.1152/jappl.1967.23.3.390
Mitchell D, Wyndham CH, Vermeulen AJ, Hodgson T, Atkins AR, Hofmeyr HS (1969) Radiant and convective heat transfer of nude men in dry air. J Appl Physiol 26:111–118. https://doi.org/10.1152/jappl.1969.26.1.111
Moldoveanu AI, Shephard RJ, Shek PN (2001) The cytokine response to physical activity and training. Sports Med 31:115–144. https://doi.org/10.2165/00007256-200131020-00004
Molina DK, DiMaio VJ (2012a) Normal organ weights in men: Part I—the heart. Am J Forensic Med Pathol 33:362–367. https://doi.org/10.1097/PAF.0b013e31823d298b
Molina DK, DiMaio VJ (2012b) Normal organ weights in men: Part II—the brain, lungs, liver, spleen, and kidneys. Am J Forensic Med Pathol 33:368–372. https://doi.org/10.1097/PAF.0b013e31823d29ad
Molina DK, DiMaio VJ (2012c) Normal organ weights in women: Part I—the heart. Am J Forensic Med Pathol 36:176–181. https://doi.org/10.1097/PAF.0000000000000174
Molina DK, DiMaio VJ (2012d) Normal organ weights in women: Part I—the brain, lungs, liver, spleen, and kidneys. Am J Forensic Med Pathol 36:182–187. https://doi.org/10.1097/PAF.0000000000000175
Molnar GW, Wilson O, Goldman RF (1969) Application of Newton's Law to body cooling. Pflüg Arch Eur J Physiol 311:16–24. https://doi.org/10.1007/BF00588059
Monahan-Earley R, Dvorak AM, Aird WC (2013) Evolutionary origins of the blood vascular system and endothelium. J Thromb Haemost 11:46–66. https://doi.org/10.1111/jth.12253
Monteith JL (1981) Evaporation and surface temperature. Q J R Meteorol Soc 107:1–27. https://doi.org/10.1002/qj.49710745102
Monteith JL, Unsworth MH (2014) Principles of environmental physics: plants, animals, and the atmosphere. Academic Press
Monteith JL, Mount LE (1974) (eds) Heat loss from animals and man: assessment and control. Butterworths, Oxford
Moorhouse VHK (1911) Effect of increased temperature of the carotid blood. Am J Physiol 28:223–234. https://doi.org/10.1152/ajplegacy.1911.28.4.223
Morimoto T (2015) History of thermal and environmental physiology in Japan: the heritage of Yas Kuno. Temperature 2:310–315. https://doi.org/10.1080/23328940.2015.1066920
Morrison SF (2018) Efferent neural pathways for the control of brown adipose tissue thermogenesis and shivering. Handb Clin Neurol 156:281–303. https://doi.org/10.1016/B978-0-444-63912-7.00017-5
Morrison JF, Mitchell D, Strydom NB (1966) The determination of the heat load on labourers when near submerged arc furnaces. J S Afr Inst Min Metall 67:115–121
Mortensen SP, Dawson EA, Yoshiga CC, Dalsgaard MK, Damsgaard R, Secher NH, González-Alonso J (2005) Limitations to systemic and locomotor limb muscle oxygen delivery and uptake during maximal exercise in humans. J Physiol 566:273–285. https://doi.org/10.1113/jphysiol.2005.086025
Mosteller RD (1987) Simplified calculation of body-surface area. N Engl J Med 317:1098. https://doi.org/10.1056/NEJM198710223171717
Mottola MF (2008) Performance in the pregnant woman. In: Taylor NAS, Groeller H (eds) Physiological bases of human performance during work and exercise, pp 225–237. Churchill Livingstone Elsevier, Edinburgh
Mrosovsky N (1990) Rheostasis: the physiology of change. Oxford University Press, Oxford
Müller MJ, Langermann D, Gehrke I, Later W, Heller M, Glüer CC, Heymsfield SB, Bosy-Westphal A (2011) Effect of constitution on mass of individual organs and their association with metabolic rate in humans—a detailed view on allometric scaling. PLoS ONE 6:e22721. https://doi.org/10.1371/journal.pone.0022732
Müntz A (1880) Recherches sur l'alimentation et sur la production du travail. Annales De L'institut National Agronomique 3:23–61
Murlin JR (1939) Skin temperature, its measurement and significance for energy metabolism. Ergeb Physiol Biol Chem Exp Pharmakol 42:153–227. https://doi.org/10.1007/BF02322566
Nag PK (1984) Convective and evaporative heat transfer coefficients of the persons in different activities. J Hum Ergol 13:43–49. https://doi.org/10.11183/jhe1972.13.43
Nagasaka T (2022) Japanese contributions to the development of knowledge of thermal physiology in the 20th century. In: Blatteis CM, Taylor NAS, Mitchell D (eds) Thermal

physiology: a worldwide history. Perspectives in physiology, pp 493–515. Springer, New York. https://doi.org/10.1007/978-1-0716-2362-6_9
Nagata H (1978) Evaporative heat loss and clothing. J Hum Ergol 7:169–175
Nakamura K, Morrison SF (2008) A thermosensory pathway that controls body temperature. Nat Neurosci 11:62–71. https://doi.org/10.1038/nn2027
Nakamura K, Morrison SF (2011) Central efferent pathways for cold-defensive and febrile shivering. J Physiol 589:3641–3658. https://doi.org/10.1113/jphysiol.2011.210047
Nakayama T, Eisenman JS, Hardy JD (1961) Single unit activity of anterior hypothalamus during local heating. Science 134:560–561. https://doi.org/10.1126/science.134.3478.560
Nakayama T, Hammel HT, Hardy JD, Eisenman JS (1963) Thermal stimulation of electrical activity of single units of the preoptic region. Am J Physiol 204:1122–1126. https://doi.org/10.1152/ajplegacy.1963.204.6.1122
National Research Council (US) Committee on Diet and Health (1989) Calories: total macronutrient intake, energy expenditure, and net energy stores. In: Diet and health: implications for reducing chronic disease risk. National Academies Press, Washington. https://www.ncbi.nlm.nih.gov/books/NBK218769/. Accessed 29 August 2022
Nedergaard J, Bengtsson T, Cannon B (2007) Unexpected evidence for active brown adipose tissue in adult humans. Am J Physiol 293:E444–E452. https://doi.org/10.1152/ajpendo.00691.2006
Nelson N, Eichna LW, Horvath SM, Shelley WB, Hatch TF (1947) Thermal exchanges of man at high temperatures. Am J Physiol 151:626–652. https://doi.org/10.1152/ajplegacy.1947.151.2.626
Nernst WH (1905) Physikalisch-chemische Betrachtungen über den Verbrennungsprozess in den Gasmotoren. Springer, Berlin
Nevill AM, Ramsbottom R, Williams C (1992) Scaling physiological measurements for individuals of different body size. Eur J Appl Physiol 65:110–117. https://doi.org/10.1007/BF00705066
Newton I (1700) Scala graduum caloris. Calorum descriptiones & figna. Philos Trans R Soc Lond 22:824–829.
Nielsen M (1938) Die Regulation der Köerpertemperatur bei Muskelarbeit. Skandinavisches Archiv Für Physiologie 79:193–230. https://doi.org/10.1111/j.1748-1716.1938.tb01246.x
Nielsen B (1966) Regulation of body temperature and heat dissipation at different levels of energy and heat production in man. Acta Physiol Scand 68:215–227. https://doi.org/10.1111/j.1748-1716.1966.tb03420.x
Nielsen B (1970) Heat production and heat transfer in negative work. In: Hardy JD, Gagge AP, Stolwijk JAJ (eds) Physiological and behavioral temperature regulation. C.C. Thomas, Springfield, pp 215–223
Nielsen B (1990) Solar heat load: heat balance during exercise in clothed subjects. Eur J Appl Physiol 60:452–456. https://doi.org/10.1007/BF00705036
Nielsen B, Nielsen M (1962) Body temperature during work at different environmental temperatures. Acta Physiol Scand 56:120–129. https://doi.org/10.1111/j.1748-1716.1962.tb02489.x
Nielsen B, Nielsen M (1965) Influence of passive and active heating on the temperature regulation of man. Acta Physiol Scand 64:323–331. https://doi.org/10.1111/j.1748-1716.1965.tb04186.x
Nielsen B, Nielsen SL, Petersen FB (1972) Thermoregulation during positive and negative work at different environmental temperatures. Acta Physiol Scand 85:249–257. https://doi.org/10.1111/j.1748-1716.1972.tb05258.x
Nielsen Johannsen B (2022) History of thermal physiology in Denmark. In: Blatteis CM, Taylor NAS, Mitchell D (eds) Thermal physiology: a worldwide history. Perspectives in physiology, pp 405–434. Springer, New York. https://doi.org/10.1007/978-1-0716-2362-6_7
Nieuwenhuys R (2012) The insular cortex: a review. Prog Brain Res 195:123–163. https://doi.org/10.1016/B978-0-444-53860-4.00007-6
Nishi Y (1981) Measurement of thermal balance in man. In: Cena K, Clark J (eds) Bioengineering, thermal physiology and comfort. Elsevier, New York, pp 29–39
Nishi Y, Gagge AP (1970) Direct evaluation of convective heat transfer coefficient by naphthalene sublimation. J Appl Physiol 29:830–838. https://doi.org/10.1152/jappl.1970.29.6.830
Nishi Y, Gagge AP (1973) Moisture permeation of clothing: a factor governing thermal equilibrium and comfort. Mem Fac Eng 13(Supplement 2):5–13
Noakes TD (2008) A modern classification of the exercise-related heat illnesses. J Sci Med Sport 11:33–39. https://doi.org/10.1016/j.jsams.2007.02.009
Noble D (2008) Claude Bernard, the first systems biologist, and the future of physiology. Exp Physiol 93:16–26. https://doi.org/10.1113/expphysiol.2007.038695
Normandin S (2007) Claude Bernard and an introduction to the study of experimental medicine: "physical vitalism", dialectic, and epistemology. J Hist Med Allied Sci 62:495–528. https://doi.org/10.1093/jhmas/jrm015
Norrsell U (2000) Magnus Gustaf Blix (1849–1904); neurophysiological, physiological, and engineering virtuoso. J Hist Neurosci 9:238–249. https://doi.org/10.1076/jhin.9.3.238.1781
Notley SR, Park J, Tagami K, Ohnishi N, Taylor NAS (2016) Morphological dependency of cutaneous blood flow and sweating during compensable heat stress when heat-loss requirements are matched across participants. J Appl Physiol 121:25–35. https://doi.org/10.1152/japplphysiol.00151.2016
Notley SR, Park J, Tagami K, Ohnishi N, Taylor NAS (2017) Variations in body morphology explain sex differences in thermoeffector function during compensable heat stress. Exp Physiol 102:545–562. https://doi.org/10.1113/EP086112
Nunneley SA (1989) Heat stress in protective clothing: interactions among physical and physiological factors. Scand J Work Environ Health 15:52–57
Nybo L, Nielsen B, Pedersen BK, Møller K, Secher NH (2002a) Interleukin-6 release from the human brain during prolonged exercise. J Physiol 542:991–995. https://doi.org/10.1113/jphysiol.2002.022285
Nybo L, Secher NH, Nielsen B (2002b) Inadequate heat release from the human brain during prolonged exercise with hyperthermia. J Physiol 545:697–704. https://doi.org/10.1113/jphysiol.2002.030023
Nybo L, White MD (2008) Do humans have selective-brain cooling? In: Taylor NAS, Groeller H (eds) Physiological bases of human performance during work and exercise, pp 473–479. Churchill Livingstone Elsevier, Edinburgh
O'Connor JM (1916) On the mechanism of chemical temperature regulation. Proc R Soc Lond Ser B Biol Sci 89:201–212. https://doi.org/10.1098/rspb.1916.0006
Ogata K (1970) A review of Japanese research on the body temperature regulation. In: Hardy JD, Gagge AP, Stolwijk JAJ (eds) Physiological and behavioral temperature regulation, pp 5–10. C.C. Thomas, Springfield
Ostrowski K, Rohde T, Asp S, Schjerling P, Pedersen BK (1999) Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. J Physiol 515:287–291. https://doi.org/10.1111/j.1469-7793.1999.287ad.x
Ostrowski K, Rohde T, Zacho M, Asp S, Pedersen BK (1998) Evidence that interleukin-6 is produced in human skeletal muscle during

prolonged running. J Physiol 508:949–953. https://doi.org/10.1111/j.1469-7793.1998.949bp.x
Ott I (1879) Observations on the physiology of the spinal cord. J Physiol 2:42–90. https://doi.org/10.1113/jphysiol.1879.sp000045
Ott I (1884) The relation of the nervous system to the temperature of the body. J Nerv Ment Dis 11:141–152. https://doi.org/10.1097/00005053-188404000-00001
Ott I (1887) The heat-centre in the brain. J Nerv Ment Dis 14:152–162. https://doi.org/10.1097/00005053-188703000-00002
Ott I (1889) The thermo-polypneic centre and thermotaxis. J Nerv Ment Dis 16:238–250
Ott I, Field GBW (1878) Sweat centres: the effect of muscarin and atropin on them. J Physiol 1:193–198. https://doi.org/10.1113/jphysiol.1878.sp000016
Packard GC, Boardman TJ (1988) The misuse of ratios, indices, and percentages in ecophysiological research. Physiol Zool 61:1–9. https://doi.org/10.1086/physzool.61.1.30163730
Pandolf KB, Burr RE (2001) (eds) Textbooks of military medicine. Medical aspects of harsh environments, vol 1. Borden Institute, Washington
Pandolf KB, Burr RE (2002) (eds) Textbooks of military medicine. Medical aspects of harsh environments, vol 2. Borden Institute, Washington
Pandolf KB, Sawka MN, Gonzalez RR (1988) (eds) Human performance physiology and environmental medicine at terrestrial extremes. Benchmark Press, Indianapolis
Parkes EA (1869) A manual of practical hygiene, for use in the medical services of the army, 3rd edn. Taylor and Francis Limited, London
Peacock RD, Reneke PA, Bukowski RW, Babrauskas V (1999) Defining flashover for fire hazard calculations. Fire Saf J 32:331–345. https://doi.org/10.1016/S0379-7112(98)00048-4
Peake JM, Suzuki K, Hordern M, Wilson G, Nosaka K, Coombes JS (2005) Plasma cytokine changes in relation to exercise intensity and muscle damage. Eur J Appl Physiol 95:514–521. https://doi.org/10.1007/s00421-005-0035-2
Pedersen BK (2000) Exercise and cytokines. Immunol Cell Biol 78:532–535. https://doi.org/10.1111/j.1440-1711.2000.t01-11-.x
Pedersen BK, Akerstrom TC, Nielsen AR, Fischer CP (2007) Role of myokines in exercise and metabolism. J Appl Physiol 103:1093–1098. https://doi.org/10.1152/japplphysiol.00080.2007
Pedersen BK, Febbraio MA (2008) Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiol Rev 88:1379–1406. https://doi.org/10.1152/physrev.90100.2007
Pedersen BK, Hoffman-Goetz L (2000) Exercise and the immune system: regulation, integration, and adaptation. Physiol Rev 80:1055–1081. https://doi.org/10.1152/physrev.2000.80.3.1055
Pedersen BK, Steensberg A, Fischer C, Keller C, Keller P, Plomgaard P, Wolsk-Petersen E, Febbraio M (2004) The metabolic role of IL-6 produced during exercise: is IL-6 an exercise factor? Proc Nutr Soc 63:263–267. https://doi.org/10.1079/PNS2004338
Peier AM, Moqrich A, Hergarden AC, Reeve AJ, Andersson DA, Story GM, Earley TJ, Dragoni I, McIntyre P, Bevan S, Patapoutian A (2002) A TRP channel that senses cold stimuli and menthol. Cell 108:705–715. https://doi.org/10.1016/s0092-8674(02)00652-9
Pembrey MS (1893) On the reaction-time of mammals to changes in the temperature of their surroundings. J Physiol 15:401–420
Pembrey MS (1898) Animal heat. In: Schäfer EA (ed) Text-book of physiology. Young J. Pentland, Edinburgh, pp 785–867
Pembrey MS, Nicol BA (1898) Observations upon the deep and surface temperature of the human body. J Physiol 23:386–406. https://doi.org/10.1113/jphysiol.1898.sp000736
Pennes HH (1948) Analysis of tissue and arterial blood temperatures in the resting human forearm. J Appl Physiol 1:93–122. https://doi.org/10.1152/jappl.1998.85.1.5
Perko MJ, Nielsen HB, Skak C, Clemmesen JO, Schroeder TV, Secher NH (1998) Mesenteric, coeliac and splanchnic blood flow in humans during exercise. J Physiol 513:907–913. https://doi.org/10.1111/j.1469-7793.1998.907ba.x
Perrey S, Betik A, Candau R, Rouillon JD, Hughson RL (2001) Comparison of oxygen uptake kinetics during concentric and eccentric cycle exercise. J Appl Physiol 91:2135–2142. https://doi.org/10.1152/jappl.2001.91.5.2135
Petersen AMW, Pedersen BK (2005) The anti-inflammatory effect of exercise. J Appl Physiol 98:1154–1162. https://doi.org/10.1152/japplphysiol.00164.2004
Pflüger EFW (1877) Die Teleologische Mechanik der lebendigen Natur. Max Cohen & Sohn, Bonn, Germany
Phillips MJ, Bennett TH, Lee MS (2009) Molecules, morphology, and ecology indicate a recent, amphibious ancestry for echidnas. Proc Natl Acad Sci USA 106:17089–17094. https://doi.org/10.1073/pnas.0904649106
Piccione G, Caola G, Refinetti R (2002) Circadian modulation of starvation-induced hypothermia in sheep and goats. Chronobiol Int 19:531–541. https://doi.org/10.1081/cbi-120004225
Pickering GW, Hess W (1933) Vasodilatation in the hands and feet in response to warming the body. Clin Sci 1:213–223
Pierau F-K (1996) Peripheral thermosensors. Comprehensive physiology. Supplement 14: Handbook of physiology, environmental physiology, pp 85–104. https://doi.org/10.1002/cphy.cp040105
Pimental NA, Shapiro Y, Pandolf KB (1982) Comparison of uphill and downhill walking and concentric and eccentric cycling. Ergonomics 25:373–380. https://doi.org/10.1080/00140138208925003
Pollitzer S (1884) On the temperature sense. A contribution to the physiology of the skin as an organ of sense. J Physiol 5:143–194. https://doi.org/10.1113/jphysiol.1884.sp000161
Pontzer H (2012) Overview of hominin evolution. Nat Educ Knowl 3:8
Pontzer H, Durazo-Arvizu R, Dugas LR, Plange-Rhule J, Bovet P, Forrester TE, Lambert EV, Cooper RS, Schoeller DA, Luke A (2016) Constrained total energy expenditure and metabolic adaptation to physical activity in adult humans. Curr Biol 26:410–417. https://doi.org/10.1016/j.cub.2015.12.046
Pontzer H, Raichlen DA, Wood BM, Emery Thompson M, Racette SB, Mabulla AZ, Marlowe FW (2015) Energy expenditure and activity among Hadza hunter-gatherers. Am J Hum Biol 27:628–637. https://doi.org/10.1002/ajhb.22711
Poole DC, Rossiter HB, Brooks GA, Gladden LB (2021) The anaerobic threshold: 50+ years of controversy. J Physiol 599:737–767. https://doi.org/10.1113/JP279963
Prandtl L (1905) Über Flüssigkeitsbewegung bei sehr kleiner Reibung. In: Krazer A (ed) Verhandlungen des Dritten Internationalen Mathematiker-Kongresses in Heidelberg. B.G. Teubner, Leipzig, pp 484–491
Price MJ (2006) Thermoregulation during exercise in individuals with spinal cord injuries. Sports Med 36:863–879
Price MJ, Campbell IG (2003) Effects of spinal cord lesion level upon thermoregulation during exercise in the heat. Med Sci Sports Exerc 35:1100–1107. https://doi.org/10.1249/01.MSS.0000074655.76321.D7
Prince AL, Hahn LJ (1918a) The effect on body temperature induced by thermal stimulation of the heat center in the brain of the cat. Am J Physiol 46:412–415. https://doi.org/10.1152/ajplegacy.1918.46.4.412
Prince AL, Hahn LJ (1918b) The effect on the volume of the hind limb induced by heating and cooling the corpus striatum of the rabbit. Am J Physiol 46:416–419. https://doi.org/10.1152/ajplegacy.1918.46.4.416
Prosser CL (1964) Perspectives of adaptation: theoretical aspects. In: Dill DB, Adolph EF (eds) Handbook of physiology. Section 4.

Adaptation to the environment, pp 11–25. American Physiological Society, Washington, DC
Pugh LGCE, Edholm OG (1955) The physiology of channel swimmers. Lancet 266:761–768. https://doi.org/10.1016/S0140-6736(55)92454-5
Qian X, Fan J (2006) Interactions of the surface heat and moisture transfer from the human body under varying climatic conditions and walking speeds. Appl Ergon 37:685–693. https://doi.org/10.1016/j.apergo.2006.01.002
Rahn H (1979) Wallace Osgood Fenn: 1893–1971. Natl Acad Sci Biogr Mem 50:140–173
Rameaux J-F (1857) Des lois, suivant lesquelles les dimensions du corps, dans certaines classes d'animaux, déterminent la capacité et les mouvements fonctionnels des poumons et du coeur. Bulletins De L'académie Royale Des Sciences, Des Lettres Et Des Beaux-Arts De Belgique 3:94–103
Ramsay DS, Woods SC (2014) Clarifying the roles of homeostasis and allostasis in physiological regulation. Psychol Rev 121:225–247. https://doi.org/10.1037/a0035942
Ramsay DS, Woods SC (2016) Physiological regulation: how it really works. Cell Metab 24:361–364. https://doi.org/10.1016/j.cmet.2016.08.004
Ranford P (2020) Sir George Gabriel Stokes, Bart (1819–1903): his impact on science and scientists. Proc R Soc A Math Phys Eng Sci 378:20190524. https://doi.org/10.1098/rsta.2019.0524
Rapp GM (1971) Convection coefficients of man in a forensic area of thermal physiology: heat transfer in underwater exercise. J Physiol (paris) 63:392–396
Raven PB, Chapleau MW (2014) Blood pressure regulation XI: overview and future research directions. Eur J Appl Physiol 114:579–586. https://doi.org/10.1007/s00421-014-2823-z
Raven PB, Kjaer M, Hellsten Y (2014) Contributions from Copenhagen Muscle Research Center. In: Tipton CM (ed) History of exercise physiology, pp 89–104. Human Kinetics, Champaign
Ravussin E, Bogardus C (1992) A brief overview of human energy metabolism and its relationship to essential obesity. Am J Clin Nutr 55:242S-245S. https://doi.org/10.1093/ajcn/55.1.242s
Rawlins CA, Phillips HR (2001) Reduction of mine heat loads. In: Wasilewski S (ed) Proceedings of the 7th international mine ventilation congress. June 17–22, 2001, Cracow, Poland, pp 381–389
Rawson ES, Clarkson PM, Tarnopolsky MA (2017) Perspectives on exertional rhabdomyolysis. Sports Med 47(Supplement 1):33–49. https://doi.org/10.1007/s40279-017-0689-z
Reed DL, Light JE, Allen JM, Kirchman JJ (2007) Pair of lice lost or parasites regained: the evolutionary history of anthropoid primate lice. BMC Biol 5:1–11. https://doi.org/10.1186/1741-7007-5-7
Refinetti R (1989) Body size and metabolic rate in the laboratory rat. Exp Biol 48:291–294
Regnault HV, Reiset J (1849) Recherches chimiques sur la respiration des animaux des diverses classes. Annales De Chimie Et De Physique 26:299–519
Rehberg PB (1951) August Krogh, November 15, 1874–September 13, 1949. Yale J Biol Med 24:83–102
Reichert ET (1902) The ponto-bulbar heat center. J Am Med Assoc 38:143–148. https://doi.org/10.1001/jama.1902.62480030001001
Reid EW (1898) Secretion and absorption by the skin. In: Schäfer EA (ed) Text-book of physiology, pp 669–691. Young J. Pentland, Edinburgh
Rennie DW (1987) Tissue heat transfer during exercise in water. In: Shiraki K, Yousef MK (eds) Man in stressful environments: thermal and work physiology, pp 211–223. Charles C. Thomas, Springfield
Rey B, Fuller A, Mitchell D, Meyer LCR, Hetem RS (2017) Drought-induced starvation of aardvarks in the Kalahari: an indirect effect of climate change. Biol Lett 13:20170301. https://doi.org/10.1098/rsbl.2017.0301
Reynolds O (1883) XXIX. An experimental investigation of the circumstances which determine whether the motion of water shall be direct or sinuous, and of the law of resistance in parallel channels. Philos Trans R Soc Lond 174:935–982. https://doi.org/10.1098/rstl.1883.0029
Rhind SG, Gannon GA, Shephard RJ, Buguet A, Shek PN, Radomski MW (2004) Cytokine induction during exertional hyperthermia is abolished by core temperature clamping: neuroendocrine regulatory mechanisms. Int J Hyperth 20:503–516. https://doi.org/10.1080/02656730410001670651
Richards MG, Rossi R, Meinander H, Broede P, Candas V, den Hartog E, Holmér I, Nocker W, Havenith G (2008) Dry and wet heat transfer through clothing dependent on the clothing properties under cold conditions. Int J Occup Saf Ergon 14:69–76. https://doi.org/10.1080/10803548.2008
Richet CR (1884) De l'influence des lésions du cerveau sur la température. Comptes Rendus De L'académie Des Sciences 98:827–829
Richet C (1885) Die Beziehungen des Gehirns zur Körperwärme und zum Fieber. Archiv Für Die Gesamte Physiologie Des Menschen Und Der Tiere 37:624–625. https://doi.org/10.1007/BF01752446
Richet C (1893) Le frisson comme appareil de regulation thermique. Archiv Für Anatomie Und Physiologie 5:312–326
Riedman SR (1957) Antoine Lavoisier: scientist and citizen. Thomas Nelson & Sons, New York
Risse GB (1974) "Doctor William Cullen, physician, Edinburgh": a consultation practice in the Eighteenth Century. Bull Hist Med 48:338–351
Ritchie KP, Keller BM, Syed KM, Lepock JR (1994) Hyperthermia (heat shock)-induced protein denaturation in liver, muscle and lens tissue as determined by differential scanning calorimetry. Int J Hyperth 10:605–618. https://doi.org/10.3109/02656739409022441
Robertshaw D (1974) (ed) Environmental physiology. Physiology series one, vol 7. Butterworths, London
Robins HI, Kutz M, Wiedemann GJ, Katschinski DM, Paul D, Grosen E, Tiggelaar CL, Spriggs D, Gillis W (1995) Cytokine induction by 41.8°C whole body hyperthermia. Cancer Lett 97:195–201. https://doi.org/10.1016/0304-3835(95)03976-4
Robinson S (1949) Physiologic adjustments to heat. In: Newburgh LH (ed) Physiology of heat regulation and the science of clothing. Hafner Publishing Company, New York, pp 193–231
Robinson S, Meyer FR, Newton JL, Ts'ao CH, Holgersen LO (1965) Relations between sweating, cutaneous blood flow, and body temperature in work. J Appl Physiol 20:575–582. https://doi.org/10.1152/jappl.1965.20.4.575
Rocha-Homem T (2015) Robert Mayer: conservation of energy and venous blood colour. Adv Hist Stud 4:309–313. https://doi.org/10.4236/ahs.2015.44020
Roddie IC, Shepherd JT (1956) The blood flow through the hand during local heating, release of sympathetic vasomotor tone by indirect heating, and a combination of both. J Physiol 131:657–664. https://doi.org/10.1113/jphysiol.1956.sp005490
Roller WL, Goldman RF (1968) Prediction of solar heat load on man. J Appl Physiol 24:717–721. https://doi.org/10.1152/jappl.1968.24.5.717
Romanovsky AA (2014) Skin temperature: its role in thermoregulation. Acta Physiol 210:498–507. https://doi.org/10.1111/apha.12231
Romanovsky AA (2018) The thermoregulation system and how it works. Handb Clin Neurol 156:3–43. https://doi.org/10.1016/B978-0-444-63912-7.00001-1
Rossi R (2014) Clothing for protection against heat and flames. In: Wang F, Gao C (eds) Protective clothing: managing thermal

stress. Woodhead Publishing Series in Textiles. Elsevier, Amsterdam, pp 70–89
Rowell LB (1974) Human cardiovascular adjustments to exercise and thermal stress. Physiol Rev 54:75–159. https://doi.org/10.1152/physrev.1974.54.1.75
Rowell LB (1977) Competition between skin and muscle for blood flow during exercise. In: Nadel ER (ed) Problems with temperature regulation during exercise. Academic Press, New York, pp 49–77
Rowell LB (1986) Human circulation. Regulation during physical stress. Oxford University Press, New York
Rowell LB (1993) Human cardiovascular control. Oxford University Press, New York
Rowell LB, Brengelmann GL, Blackmon JR, Murray JA (1970) Redistribution of blood flow during sustained high skin temperature in resting man. J Appl Physiol 28:415–420. https://doi.org/10.1152/jappl.1970.28.4.415
Rowell LB, Brengelmann GL, Murray JA (1969) Cardiovascular responses to sustained high skin temperature in resting man. J Appl Physiol 27:673–680. https://doi.org/10.1152/jappl.1969.27.5.673
Rowell LB, Brengelmann GL, Blackmon JR, Twiss RD, Kusumi F (1968) Splanchnic blood flow and metabolism in heat-stressed man. J Appl Physiol 24:475–484. https://doi.org/10.1152/jappl.1968.24.4.475
Royal Society (1975) Quantities, units and symbols. A report by the Symbols Committee of the Royal Society. Royal Society, London
Rübner M (1883) Über den Einfluss der Köpergröße auf Stoff- und Kraftwechsel. Z Biol 19:535–562
Rübner M (1896) Zur Bilanz unserer Wärmeökonomie. Archiv Für Hygiene 27:69–89
Ruf T, Geiser F (2015) Daily torpor and hibernation in birds and mammals. Biol Rev 90:891–926. https://doi.org/10.1111/brv.12137
Rykaczewski K, Bartels L, Martinez DM, Viswanathan SH (2022) Human body radiation area factors for diverse adult population. Int J Biometeorol 66:2357–2367. https://doi.org/10.1007/s00484-022-02362-7
Sagawa S, Shiraki K, Yousef MK, Konda N (1988) Water temperature and intensity of exercise in maintenance of thermal equilibrium. J Appl Physiol 65:2413–2419. https://doi.org/10.1152/jappl.1988.65.6.2413
Sakurada S, Shido O, Sugimoto N, Hiratsuka Y, Yoda T, Kanosue K (2000) Autonomic and behavioural thermoregulation in starved rats. J Physiol 526:417–424. https://doi.org/10.1111/j.1469-7793.2000.00417.x
Saltin B (1970) Circulatory adjustments and body temperature regulation during exercise. In: Hardy JD, Gagge AP, Stolwijk JAJ (eds) Physiological and behavioral temperature regulation, pp 193–203. C.C. Thomas, Springfield
Saltin B, Åstrand P-O (1967) Maximal oxygen uptake in athletes. J Appl Physiol 23:353–358. https://doi.org/10.1152/jappl.1967.23.3.353
Saltin B, Hermansen L (1966) Esophageal, rectal and muscle temperature during exercise. J Appl Physiol 21:1757–1762. https://doi.org/10.1152/jappl.1966.21.6.1757
Saltin B, Gagge AP, Stolwijk JAJ (1968) Muscle temperature during submaximal exercise in man. J Appl Physiol 25:679–688. https://doi.org/10.1152/jappl.1968.25.6.679
Saper CB (2002) The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. Annu Rev Neurosci 25:433–469
Saper CB, Lowell BB (2014) The hypothalamus. Curr Biol 24:R1111–R1116. https://doi.org/10.1016/j.cub.2014.10.023
Sargent F, Tromp SW (1964) A survey of human biometeorology. WMO-No. 160. TP 78. World Meteorological Organization, Geneva
Sarrus F, Rameaux J (1838–1839) Rapport sur un mémoire adressé à l'Académie Royale de Médecine. Commissaires Robiquet et Thillaye, rapporteurs. Bulletin de l'Académie Royale de Médecine 3:1094–1100.
Satinoff E (1978) Neural organization and evolution of thermal regulation in mammals. Science 201:16–22. https://doi.org/10.1126/science.351802
Satinoff E (1983) A reevaluation of the concept of the homeostatic organization of temperature regulation. In: Satinoff E, Teitelbaum P (eds) Handbook of behavioural neurobiology. Motivation, vol 6. Plenum Press, New York, pp 433–472
Schäfer EA (ed) (1898) Text-book of physiology. Young J. Pentland, Edinburgh
Scheffler RW (2015) The power of exercise and the exercise of power: the Harvard Fatigue Laboratory, distance running, and the disappearance of work, 1919–1947. J Hist Biol 48:391–423. https://doi.org/10.1007/s10739-014-9392-1
Schlader ZJ, Vargas NT (2019) Regulation of body temperature by autonomic and behavioral thermoeffectors. Exerc Sport Sci Rev 47:116–126. https://doi.org/10.1249/JES.0000000000000180
Schmidt-Nielsen K (1972) Locomotion: energy cost of swimming, flying, and running. Science 177:22–228. https://doi.org/10.1126/science.177.4045.222
Schmidt-Nielsen K (1984a) Scaling: why is animal size so important? Cambridge University Press, Cambridge
Schmidt-Nielsen B (1984b) August and Marie Krogh and respiratory physiology. J Appl Physiol 57:293–303. https://doi.org/10.1152/jappl.1984.57.2.293
Schmidt-Nielsen B (1995) The zoophysiological laboratory and the beginning of exercise physiology (1910–1916). In: August and Marie Krogh, pp 95–111. Springer, New York. https://doi.org/10.1007/978-1-4614-7530-9_11
Schmiedeberg O, Koppe R (1869) Das Muscarin Das giftige Alkaloid des Fliegenpilzes (*Agaricus muscarius* L.). F.C.W. Vogel, Leipzig
Schneider S, Moseley P (2014) The temperature regulatory system. In: Tipton CM (ed) History of exercise physiology. Human Kinetics, Champaign, pp 477–506
Schofield WN (1985) Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr 39:5–41
Schönbaum E, Lomax P (1990) (eds) Thermoregulation: physiology and biochemistry. Pergamon Press, New York
Secher NH, Vaage O, Jensen K, Jackson RC (1983) Maximal aerobic power in oarsmen. Eur J Appl Physiol 51:155–162. https://doi.org/10.1007/BF00455178
Séguin A, Lavoisier A-L (1792) Premier mémoire sur la transpiration des animaux. In: Lavoisier A-L (ed) Les Maitres de la Science, pp 90–105. Libraire de l'Académie de Médecine, Paris
Selle WA (1952) Body temperature: its changes with environment, disease and therapy. Charles C. Thomas, Springfield
Senay LC (1972) Changes in plasma volume and protein content during exposures of working men to various temperatures before and after acclimatization to heat: separation of the roles of cutaneous and skeletal muscle circulation. J Physiol 224:61–81. https://doi.org/10.1113/jphysiol.1972.sp009881
Senay LC, Christensen ML (1965) Cardiovascular and sweating responses to water ingestion during dehydration. J Appl Physiol 20:975–979. https://doi.org/10.1152/jappl.1965.20.5.975
Shackleton EH, Hurley F (2019) South: the illustrated story of Shackelton's last expedition 1914–1917. Voyageur Press, Stillwater
Shephard RJ (1975) Efficiency of muscular work: some clinical implications. Phys Ther 55:476–481. https://doi.org/10.1093/ptj/55.5.476

Shephard RJ (2017) Open-circuit respirometry: a brief historical review of the use of Douglas bags and chemical analyzers. Eur J Appl Physiol 117:381–387. https://doi.org/10.1007/s00421-017-3556-6

Sherrington CS (1924) Notes on temperature after spinal transection, with some observations on shivering. J Physiol 58:405–424. https://doi.org/10.1113/jphysiol.1924.sp002143

Sherrington C (1946) The endeavour of Jean Fernel: with a list of the editions of his writings. University Press, Cambridge

Shibasaki M, Secher NH, Selmer C, Kondo N, Crandall CG (2003) Central command is capable of modulating sweating from non-glabrous human skin. J Physiol 553:999–1004. https://doi.org/10.1113/jphysiol.2003.051102

Shibasaki M, Secher NH, Johnson JM, Crandall CG (2005) Central command and the cutaneous vascular response to isometric exercise in heated humans. J Physiol 565:667–673. https://doi.org/10.1113/jphysiol.2005.083535

Shibasaki M, Wilson TE, Crandall CG (2006) Neural control and mechanisms of eccrine sweating during heat stress and exercise. J Appl Physiol 100:1692–1701. https://doi.org/10.1152/japplphysiol.01124.2005

Shin Y-O, Lee J-B (2011) Effects of exercise training on plasma cytokine and chemokine levels, and thermoregulation. J Therm Biol 36:219–224. https://doi.org/10.1016/j.jtherbio.2011.03.001

Shiraki K, Sagawa S, Yousef MK (1996) (eds) Physiological basis of occupational health: stressful environments. SBP Academic Publishing, Amsterdam

Shiraki K, Yousef MK (1987) (eds) Man in stressful environments: thermal and work physiology. Charles C. Thomas, Springfield

Shour R (2017) Sarrus and Rameaux, 1838 [translated into English]. https://doi.org/10.13140/RG.2.2.26197.27363

Shrivastava D (2018) (ed) Theory and applications of heat transfer in humans, vol 2. Wiley, Hoboken

Shuter B, Aslani A (2000) Body surface area: Du Bois and Du Bois revisited. Eur J Appl Physiol 82:250–254. https://doi.org/10.1007/s004210050679

Sieg AE, O'Connor MP, McNair JN, Grant BW, Agosta SJ, Dunham AE (2009) Mammalian metabolic allometry: do intraspecific variation, phylogeny, and regression models matter? Am Nat 174:720–733. https://doi.org/10.1086/606023

Siegel AJ, Verbalis JG, Clement S, Mendelson JH, Mello NK, Adner M, Shirey T, Glowacki J, Lee-Lewandrowski E, Lewandrowski KB (2007) Hyponatremia in marathon runners due to inappropriate arginine vasopressin secretion. Am J Med 120:461.e11-461.e17. https://doi.org/10.1016/j.amjmed.2006.10.027

Sihler C (1879) On the so-called heat-dyspnoea. J Physiol 2:191–201. https://doi.org/10.1113/jphysiol.1879.sp000056

Sihler C (1880) Some further observations on heat-dyspnoea. J Physiol 3:1–10. https://doi.org/10.1113/jphysiol.1880.sp000079

Simões TR, Vernygora O, Caldwell MW, Pierce SE (2020) Megaevolutionary dynamics and the timing of evolutionary innovation in reptiles. Nat Commun 11:3322. https://doi.org/10.1038/s41467-020-17190-9

Simon E (1974) Temperature regulation: the spinal cord as a site of extrahypothalamic thermoregulatory functions. Rev Physiol Biochem Pharmacol 71:1–76. https://doi.org/10.1007/BFb0027660

Simon E, Pierau F-K, Taylor DM (1986) Central and peripheral thermal control of effectors in homeothermic temperature regulation. Physiol Rev 66:235–300. https://doi.org/10.1152/physrev.1986.66.2.235

Simon E, Gerstberger R, Roth J (2022) A history of physiological research on temperature regulation in Germany. In: Blatteis CM, Taylor NAS, Mitchell D (eds) Thermal physiology: a worldwide history. Perspectives in physiology, pp 97–200. Springer, New York. https://doi.org/10.1007/978-1-0716-2362-6_3

Simon E, Schmid HA, Pehl U (1998) Spinal neuronal thermosensitivity in vivo and in vitro in relation to hypothalamic neuronal thermosensitivity. In: Sharma HS, Westman J (eds) Progress in brain research, vol 115. Elsevier, Amsterdam, pp 25–47

Siple PA, Passel CF (1945) Measurements of dry atmospheric cooling in subfreezing temperatures. Proc Am Philos Soc 89:177–199

Slonim BB (1974) (ed) Environmental physiology. C.V. Mosby Company, St. Louis

Smiles KA, Robinson S (1971) Regulation of sweat secretion during positive and negative work. J Appl Physiol 30:409–412. https://doi.org/10.1152/jappl.1971.30.3.409

Snyder WS, Cook MJ, Nasset ES, Karhausen LR, Howells GP, Tipton IH (1975) Report of the task group on reference man. International Commission on Radiological Protection, Publication 23. Pergamon Press, Oxford

Somjen GG (1992) The missing error signal-regulation beyond negative feedback. Physiology 7:184–185. https://doi.org/10.1152/physiologyonline.1992.7.4.184

Speakman JR, Selman C (2003) Physical activity and resting metabolic rate. Proc Nutr Soc 62:621–634. https://doi.org/10.1079/PNS2003282

Sprenger H, Jacobs C, Nain M, Gressner AM, Prinz H, Wesemann W, Gemsa D (1992) Enhanced release of cytokines, interleukin-2 receptors, and neopterin after long-distance running. Clin Immunol Immunopathol 63:188–195. https://doi.org/10.1016/0090-1229(92)90012-D

Standring S (2008) Gray's anatomy: the anatomical basis of clinical practice, 14th edn. Churchill Livingstone Elsevier, Edinburgh

Stanier MW, Mount LE, Bligh J (1984) Energy balance and temperature regulation. Cambridge texts in Physiological Sciences 4. Cambridge University Press, Cambridge

Starkie RL, Hargreaves M, Rolland J, Febbraio MA (2005) Heat stress, cytokines, and the immune response to exercise. Brain Behav Immun 19:404–412. https://doi.org/10.1016/j.bbi.2005.03.005

Starkie R, Ostrowski SR, Jauffred S, Febbraio M, Pedersen BK (2003) Exercise and IL-6 infusion inhibit endotoxin-induced TNF-α production in humans. Fed Am Soc Exp Biol J 17:1–10. https://doi.org/10.1096/fj.02-0670fje

Starling EH (1896) On the absorption of fluids from the connective tissue spaces. J Physiol 19:312–326. https://doi.org/10.1113/jphysiol.1896.sp000596

Steensberg A, Fischer CP, Keller C, Møller K, Pedersen BK (2003) IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. Am J Physiol 285:E433–E437. https://doi.org/10.1152/ajpendo.00074.2003

Steensberg A, Keller C, Starkie RL, Osada T, Febbraio MA, Pedersen BK (2002) IL-6 and TNF-α expression in, and release from, contracting human skeletal muscle. Am J Physiol 283:E1272–E1278. https://doi.org/10.1152/ajpendo.00255.2002

Stefan J (1879) Über die Beziehung zwischen der Wärmestrahlung und der Temperatur. Sitzungsberichte der Kaiserlichen Akademie der Wissenschaften: Mathematisch-Naturwissenschaftliche Classe 79:391–428

Stewart GN, Walker OC (1913) Vasomotor reflexes elicited by heat and cold from areas deprived of temperature sensibility by a traumatic lesion. Arch Intern Med 11:383–394. https://doi.org/10.1001/archinte.1913.00060280020002

Stewart JM, Wyndham CH (1975) Suggested thermal stress limits for safe physiological strain in underground environments. J S Afr Inst Min Metall 76:334–338. https://doi.org/10.10520/AJA0038223X_569

Stilling B (1840) Physiologische, pathologische und edicinisch-practische Untersuchungen über die Spinal-Irritation. von Otto Wigand, Leipzig

Stoll AM, Hardy JD (1950) Study of thermocouples as skin thermometers. J Appl Physiol 2:531–543. https://doi.org/10.1152/jappl.1950.2.10.531

Stolwijk JAJ, Hardy JD (1966) Temperature regulation in man—a theoretical study. Pflüg Arch Eur J Physiol 291:129–162. https://doi.org/10.1007/BF00412787

Stone DJ, Celi LA, Csete M (2015) Engineering control into medicine. J Crit Care 30:652-e1-652-e7. https://doi.org/10.1016/j.jcrc.2015.01.019

Storey KB (2003) Mammalian hibernation. In: Roach RC, Wagner PD, Hackett PH (eds) Hypoxia. Advances in experimental medicine and biology, vol 543. Springer, Boston. https://doi.org/10.1007/978-1-4419-8997-0_3

Strauss WM, Hetem RS, Mitchell D, Maloney SK, O'Brien HD, Meyer LCR, Fuller A (2017) Body water conservation through selective brain cooling by the carotid rete: a physiological feature for surviving climate change? Conserv Physiol 5:cow078. https://doi.org/10.1093/conphys/cow078

Strydom NB, Wyndham CH, van Graan CH, Holdsworth LD, Morrison JF (1966) The influence of water restriction on the performance of men during a prolonged march. S Afr Med J 40:539–544. https://doi.org/10.10520/AJA20785135_37303

Stuart-Fox D, Newton E, Clusella-Trullas S (2017) Thermal consequences of colour and near-infrared reflectance. Philos Trans R Soc B Biol Sci 372:20160345. https://doi.org/10.1098/rstb.2016.0345

Suleiman BM, Larfeldt J, Leckner B, Gustavsson M (1999) Thermal conductivity and diffusivity of wood. Wood Sci Technol 33:465–473. https://doi.org/10.1007/s002260050130

Suzuki K (2019) Characterization of exercise-induced cytokine release, the impacts on the body, the mechanisms and modulations. Int J Sports Exerc Med 5:122. https://doi.org/10.23937/2469-5718/1510122

Suzuki K, Yamada M, Kurakake S, Okamura N, Yamaya K, Liu Q, Kudoh S, Kowatari K, Nakaji S, Sugawara K (2000) Circulating cytokines and hormones with immunosuppressive but neutrophil-priming potentials rise after endurance exercise in humans. Eur J Appl Physiol 81:281–287. https://doi.org/10.1007/s004210050044

Swinbank WC (1963) Long-wave radiation from clear skies. Q J R Meteorol Soc 89:339–348. https://doi.org/10.1002/qj.49708938105

Székely M (2022) Thermoregulatory studies in Hungary: historical background. In: Blatteis CM, Taylor NAS, Mitchell D (eds) Thermal physiology: a worldwide history. Perspectives in physiology, pp 517–539. Springer, New York. https://doi.org/10.1007/978-1-0716-2362-6_10

Talbot GR, Pacey AJ (1972) Antecedents of thermodynamics in the work of Guillaume Amontons. Centaurus 16:20–40. https://doi.org/10.1111/j.1600-0498.1972.tb00163.x

Tankersley CG, Smolander J, Kenney WL, Fortney SM (1991) Sweating and skin blood flow during exercise: effects of age and maximal oxygen uptake. J Appl Physiol 71:236–242. https://doi.org/10.1152/jappl.1991.71.1.236

Tanner JM (1949) Fallacy of per-weight and per-surface area standards, and their relation to spurious correlation. J Appl Physiol 2:1–15. https://doi.org/10.1152/jappl.1949.2.1.1

Tansey EA, Johnson CD (2015) Recent advances in thermoregulation. Adv Physiol Educ 39:139–148. https://doi.org/10.1152/advan.00126.2014

Taylor CR (1966) The vascularity and possible thermoregulatory function of the horns in goats. Physiol Zool 39:127–139. https://doi.org/10.1086/physzool.39.2.30152426

Taylor NAS (2014) Human heat adaptation. Compr Physiol 4:325–365. https://doi.org/10.1002/cphy.c130022

Taylor NAS (2015) Overwhelming physiological regulation through personal protection. J Strength Cond Res 29:S111–S118. https://doi.org/10.1519/JSC.0000000000001030

Taylor NAS, Gordon CJ (2019) The origin, significance and plasticity of the thermoeffector thresholds: extrapolation between humans and laboratory rodents. J Therm Biol 85:102397. https://doi.org/10.1016/j.jtherbio.2019.08.003

Taylor NAS, Groeller H (2008) (eds) Physiological bases of human performance during work and exercise. Churchill Livingstone Elsevier, Edinburgh

Taylor NAS, Machado-Moreira CA, van den Heuvel AMJ, Caldwell JN (2014a) Hands and feet: physiological insulators, radiators and evaporators. Eur J Appl Physiol 114:2037–2060. https://doi.org/10.1007/s00421-014-2940-8

Taylor CR, Maloiy GMO, Weibel ER, Langman VA, Kamau JMZ, Seeherman HJ, Heglund NC (1981) Design of the mammalian respiratory system. III. Scaling maximum aerobic capacity to body mass: wild and domestic mammals. Respir Physiol 44:25–37. https://doi.org/10.1016/0034-5687(81)90075-X

Taylor NAS, Nykvist Å, Powers N, Caldwell JN (2019) Thermoeffector threshold plasticity: the impact of thermal pre-conditioning on sudomotor, cutaneous vasomotor and thermogenic thresholds. J Therm Biol 83:37–46. https://doi.org/10.1016/j.jtherbio.2019.05.001

Taylor N, Pörtner H (2021) Obituary: Christopher J. Gordon (1953–2021). J Therm Biol 99:103053. https://doi.org/10.1016/j.jtherbio.2021.103053

Taylor NAS, Taylor EA, Maloney SK, de Dear RJ (2022) Contributions from a land down under: the arid continent. In: Blatteis CM, Taylor NAS, Mitchell D (eds) Thermal physiology: a worldwide history.Perspectives in physiology, pp 357–404. Springer, New York. https://doi.org/10.1007/978-1-0716-2362-6_6

Taylor NAS, Tipton MJ, Kenny GP (2014b) Considerations for the measurement of core, skin and mean body temperatures. J Therm Biol 46:72–101. https://doi.org/10.1016/j.jtherbio.2014.10.006

Teitlebaum A, Goldman RF (1972) Increased energy cost with multiple clothing layers. J Appl Physiol 32:743–744. https://doi.org/10.1152/jappl.1972.32.6.743

Temme LA (2003) Ethics in human experimentation: the two military physicians who helped develop the Nuremberg Code. Aviat Space Environ Med 74:1297–1300

Templeton JR (1970) Reptiles. In: Wittow GC (ed) Comparative physiology of thermoregulation, vol I. Academic Press, New York, pp 167–223

Ter Steege RWF, Kolkman JJ (2012) The pathophysiology and management of gastrointestinal symptoms during physical exercise, and the role of splanchnic blood flow. Aliment Pharmacol Ther 35:516–528. https://doi.org/10.1111/j.1365-2036.2011.04980.x

Thompson B (1798) An inquiry concerning the source of the heat which is excited by friction. Philos Trans R Soc Lond 88:80–102. https://doi.org/10.1098/rstl.1798.0006

Thomson J (1832) An account of the life, lectures and writings, of William Cullen. William Blackwood, Edinburgh

Tigerstedt R (1897) Lehrbuch Der Physiologie Des Menschen. S. Hirzel, Leipzig

Tigerstedt R (1906) A text-book of human physiology. Translated by Murlin, J.R. D. Appleton and Company, New York

Tigerstedt R (1909) Die Wärmeökonomie des Körpers. In: Nagel W (ed) Handbuch der Physiologie des Menschen, vol 1. Vieweg, Brunswick, pp 557–608

Tikuisis P (2022) Contributions from the land of the maple leaf: Canada. In: Blatteis CM, Taylor NAS, Mitchell D (eds) Thermal physiology: a worldwide history. Perspectives in physiology,

pp 621–652. Springer, New York. https://doi.org/10.1007/978-1-0716-2362-6_14
Tikuisis P, Meunier P, Jubenville CE (2001) Human body surface area: measurement and prediction using three dimensional body scans. Eur J Appl Physiol 85:264–271. https://doi.org/10.1007/s004210100484
Todd G, Gordon CJ, Groeller H, Taylor NAS (2014) Does intramuscular thermal feedback modulate eccrine sweating in exercising humans? Acta Physiol 212:86–96. https://doi.org/10.1111/apha.12327
Toft AD, Jensen LB, Bruunsgaard H, Ibfelt T, Halkjær-Kristensen J, Febbraio M, Pedersen BK (2002) Cytokine response to eccentric exercise in young and elderly humans. Am J Physiol 283:C289–C295. https://doi.org/10.1152/ajpcell.00583.2001
Tøien Ø, Blake J, Edgar DM, Grahn DA, Heller HC, Barnes BM (2011) Hibernation in black bears: independence of metabolic suppression from body temperature. Science 331:906–909. https://doi.org/10.1126/science.1199435
Trbovich M, Ford A, Wu Y, Koek W, Wecht J, Kellogg D (2021) Correlation of neurological level and sweating level of injury in persons with spinal cord injury. J Spinal Cord Med 44:902–909. https://doi.org/10.1080/10790268.2020.1751489
Trbovich M, Wu B, Koek W, Wecht J, Kellogg D (2022) Are thermoregulatory sweating and active vasodilation in skin controlled by separate nerves during passive heat stress in persons with spinal cord injury? Top Spinal Cord Inj Rehabil 28:84–95. https://doi.org/10.46292/sci21-00063
Tschakovsky ME, Pyke KE (2008) Cardiovascular responses to exercise and limitations to human performance. In: Taylor NAS, Groeller H (eds) Physiological bases of human performance during work and exercise, pp 5–27. Churchill Livingstone Elsevier, Edinburgh
Tscheschichin J (1866) Zur Lehre von der thierischen Wärme. Archiv Fiir Anatomie Und Physiologie Von Reichert Und Du Bois-Reymond 11:151–179
Tuckey H (2013) Everest—The First Ascent. The Untold Story of Griffith Pugh, the Man Who Made it Possible. Random House Group, London
Tunbridge PA (1971) Jean André De Luc, F.R.S. (1727–1817). Notes Rec R Soc Lond 26:15–33. https://doi.org/10.1098/rsnr.1971.0003
Ullum H, Haahr PM, Diamant M, Palmo J, Halkjaer-Kristensen J, Pedersen BK (1994) Bicycle exercise enhances plasma IL-6 but does not change IL-1 alpha, IL-1 beta, IL-6, or TNF-alpha pre-mRNA in BMNC. J Appl Physiol 77:93–97. https://doi.org/10.1152/jappl.1994.77.1.93
Underwood EA (1944) Lavoisier and the history of respiration. Proc R Soc Med 37:247–262
Underwood CR, Ward EJ (1966) The solar radiation area of man. Ergonomics 9:155–168. https://doi.org/10.1080/00140136608964361
University of Glasgow (2021) William Cullen. https://www.universitystory.gla.ac.uk/biography/?id=WH0013&type=P. Accessed 28 June 2021
van Beaumont W, Bullard RW (1963) Sweating: its rapid responses to muscular work. Science 141:643–646. https://doi.org/10.1126/science.141.3581.643
van den Heuvel AMJ, Haberley BJ, Hoyle DJR, Croft RJ, Peoples GE, Taylor NAS (2020) Hyperthermia and dehydration: their independent and combined influences on physiological function during rest and exercise. Eur J Appl Physiol 120:2813–2834. https://doi.org/10.1007/s00421-020-04493-4
van Graan CH (1969) The determination of body surface area. S Afr Med J 43:952–959
van Graan CH, Wyndham CH (1964) Body surface area in human beings. Nature 204:998. https://doi.org/10.1038/204998a0
van Someren EJ, Raymann RJ, Scherder EJ, Daanen HA, Swaab DF (2002) Circadian and age-related modulation of thermoreception and temperature regulation: mechanisms and functional implications. Ageing Res Rev 1:721–778. https://doi.org/10.1016/S1568-1637(02)00030-2
Van Zant RS (1992) Influence of diet and exercise on energy expenditure—a review. Int J Sport Nutr Exerc Metab 2:1–19. https://doi.org/10.1123/ijsn.2.1.1
Varène P, Ferrus L, Manier G, Gire J (1986) Heat and water respiratory exchanges: comparison between mouth and nose breathing in humans. Clin Physiol 6:405–414. https://doi.org/10.1111/J.1475-097X.1986.TB00071.X
Vernon HM (1930) The measurement of radiant heat in relation to human comfort. J Physiol 70:xv
Vernon HM (1932) The measurement of radiant heat in relation to human comfort. J Ind Hyg 14:95–111
Vinales KL, Begaye B, Thearle MS, Krakoff J, Piaggi P (2019) Core body temperature, energy expenditure, and epinephrine during fasting, eucaloric feeding, and overfeeding in healthy adult men: evidence for a ceiling effect for human thermogenic response to diet. Metabolism 94:59–68. https://doi.org/10.1016/j.metabol.2019.01.016
Vingren JL, Budnar RG, McKenzie AL, Duplanty AA, Luk HY, Levitt DE, Armstrong LE (2016) The acute testosterone, growth hormone, cortisol and interleukin-6 response to 164-km road cycling in a hot environment. J Sports Sci 34:694–699. https://doi.org/10.1080/02640414.2015.1068440
Vissing SF, Hjortsø EM (1996) Central motor command activates sympathetic outflow to the cutaneous circulation in humans. J Physiol 492:931–939. https://doi.org/10.1113/jphysiol.1996.sp021359
Vissing SF, Scherrer U, Victor RG (1991) Stimulation of skin sympathetic nerve discharge by central command. Differential control of sympathetic outflow to skin and skeletal muscle during static exercise. Circ Res 69:228–238. https://doi.org/10.1161/01.res.69.1.228
Vogt JJ, Meyer JP, Candas V, Libert J-P, Sagot JC (1983) Pumping effects on thermal insulation of clothing worn by human subjects. Ergonomics 26:963–974. https://doi.org/10.1080/00140138308963425
Wagner R (1952) Über ein Prinzip biologisches Regelungen. Wien Klin Wochenschr 64:627–628. https://doi.org/10.1007/BF01471455
Walther OE, Iriki M, Simon E (1970) Antagonistic changes of blood flow and sympathetic activity in different vascular beds following central thermal stimulation. Pflüg Arch Eur J Physiol 319:162–184. https://doi.org/10.1007/BF00592494
Wang F, Annaheim S, Morrissey M, Rossi RM (2014) Real evaporative cooling efficiency of one-layer tight-fitting sportswear in a hot environment. Scand J Med Sci Sports 24:e129–e139. https://doi.org/10.1111/sms.12117
Ward SA (2018) Open-circuit respirometry: real-time, laboratory-based systems. Eur J Appl Physiol 118:875–898. https://doi.org/10.1007/s00421-018-3860-9
Waterfield RL (1931) The effects of posture on the circulating blood volume. J Physiol 72:110–120. https://doi.org/10.1113/jphysiol.1931.sp002765
Watmough DJ, Oliver R (1968) Emissivity of human skin in vivo between 2.0μ and 5.4μ measured at normal incidence. Nature 218:885–886. https://doi.org/10.1038/218885a0
Weaver WH (1897) The rational treatment of sunstroke. J Am Med Assoc 29:620–621. https://doi.org/10.1001/jama.1897.02440390010002b

Weibel ER, Bacigalupe LD, Schmitt B, Hoppeler H (2004) Allometric scaling of maximal metabolic rate in mammals: muscle aerobic capacity as determinant factor. Respir Physiol Neurobiol 140:115–132. https://doi.org/10.1016/j.resp.2004.01.006

Weiner JS (1945) The regional distribution of sweating. J Physiol 104:32–40. https://doi.org/10.1113/jphysiol.1945.sp004103

Weir JB (1949) New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol 109:1–9. https://doi.org/10.1113/jphysiol.1949.sp004363

Wenger CB (1972) Heat of evaporation of sweat: thermodynamic considerations. J Appl Physiol 32:456–459. https://doi.org/10.1152/jappl.1972.32.4.456

Werner J (1980) The concept of regulation for human body temperature. J Therm Biol 5:75–82. https://doi.org/10.1016/0306-4565(80)90003-0

Werner J (1996) Modeling homeostatic responses to heat and cold. In: Comprehensive physiology. Supplement 14: Handbook of physiology, environmental physiology, pp 613–626. https://doi.org/10.1002/cphy.cp040128

Werner J (2010) System properties, feedback control and effector coordination of human temperature regulation. Eur J Appl Physiol 19:13–25. https://doi.org/10.1007/s00421-009-1216-1

Werner J, Mekjavic IB, Taylor NAS (2008) Concepts in physiological regulation: a thermoregulatory perspective. In: Taylor NAS, Groeller H (eds) Physiological bases of human performance during work and exercise, pp 325–340. Churchill Livingstone Elsevier, Edinburgh

West JB (2008) J.S. Haldane and some of his contributions to physiology. In: Poulin MJ, Wilson RJA (eds) Integration in respiratory control. Advances in experimental medicine and biology, vol 605. Springer, New York. https://doi.org/10.1007/978-0-387-73693-8_2

Westerterp KR (2004) Diet induced thermogenesis. Nutr Metab 1:1–5. https://doi.org/10.1186/1743-7075-1-5

Westerterp KR (2018) Exercise, energy expenditure and energy balance, as measured with doubly labelled water. Proc Nutr Soc 77:4–10. https://doi.org/10.1017/S0029665117001148

Westerterp KR, Saris WH, van Es M, Ten Hoor F (1986) Use of the doubly labeled water technique in humans during heavy sustained exercise. J Appl Physiol 61:2162–2167. https://doi.org/10.1152/jappl.1986.61.6.2162

Weststrate JA (1993) Resting metabolic rate and diet-induced thermogenesis: a methodological reappraisal. Am J Clin Nutr 58:592–601. https://doi.org/10.1093/ajcn/58.5.592

Widdowson EM (1955) Assessment of the energy value of human foods. Proc Nutr Soc 14:142–154. https://doi.org/10.1079/pns19550031

Whillier A (1967) The calculation of heat exchange between air and wet surfaces. J S Afr Inst Min Metall 67:396–402

Whillier A, Mitchell D (1968) Prediction of the cooling rate of the human body. J South Afr Inst Min Metall 68:103–114

White CR, Frappell PB, Chown SL (2012) An information-theoretic approach to evaluating the size and temperature dependence of metabolic rate. Proc R Soc Lond Ser B Biol Sci 279:3616–3621. https://doi.org/10.1098/rspb.2012.0884

White CR, Kearney MR (2014) Metabolic scaling in animals: methods, empirical results, and theoretical explanations. Compr Physiol 4:231–256. https://doi.org/10.1002/cphy.c110049

White CR, Seymour RS (2003) Mammalian basal metabolic rate is proportional to body mass$^{2/3}$. Proc Natl Acad Sci USA 100:4046–4049. https://doi.org/10.1073/pnas.0436428100

White CR, Seymour RS (2005a) Allometric scaling of mammalian metabolism. J Exp Biol 208:1611–1619. https://doi.org/10.1242/jeb.01501

White CR, Seymour RS (2005b) Sample size and mass range effects on the allometric exponent of basal metabolic rate. Comp Biochem Physiol A Mol Integr Physiol 142:74–78. https://doi.org/10.1016/j.cbpa.2005.07.013

Wilcke JC (1772) Om snöns kyla vid smältningen. Kungliga Svenska Vetenskaps Akademiens Handlingar 33:97–120

Wilkie DR (1954) Facts and theories about muscle. Prog Biophys Biophys Chem 4:288–324

Williams JL (1793a) Account of the method of making ice at Benares. Philos Trans R Soc Lond 83:56–58. https://doi.org/10.1098/rstl.1793.0009

Williams JL (1793b) Additional observations on the method making ice at Benares. Philos Trans R Soc Lond 83:129–131. https://doi.org/10.1098/rstl.1793.0012

Williamson JW, Fadel PJ, Mitchell JH (2006) New insights into central cardiovascular control during exercise in humans: a central command update. Exp Physiol 91:51–58. https://doi.org/10.1113/expphysiol.2005.032037

Wilson TE, Cui J, Zhang R, Crandall CG (2006) Heat stress reduces cerebral blood velocity and markedly impairs orthostatic tolerance in humans. Am J Physiol 291:R1443–R1448. https://doi.org/10.1152/ajpregu.00712.2005

Winslow C-EA, Herrington LP, Gagge AP (1936a) A new of partitional calorimetry. Am J Physiol 116:641–655. https://doi.org/10.1152/ajplegacy.1936.116.3.641

Winslow C-EA, Herrington LP, Gagge AP (1936b) The determination of radiation and convection exchanges by partitional calorimetry. Am J Physiol 116:669–684. https://doi.org/10.1152/ajplegacy.1936.116.3.669

Winslow C-EA, Gagge A, Herrington LP (1939) The influence of air movement upon heat losses from the clothed human body. Am J Physiol 127:505–518. https://doi.org/10.1152/ajplegacy.1939.127.3.505

Wissler EH (2018) Human temperature control: a quantitative approach. Springer-Verlag GmbH, Berlin

Wolf A (1938) A history of science technology and philosophy in the eighteenth century. Routledge, London. https://doi.org/10.4324/9780429059667

Wong KC, Wu L-T (1932) History of Chinese medicine: being a chronicle of medical happenings in china from ancient times to the present period. Tientsin Press Ltd, Tientsin

Wood JE, Bass DE (1960) Responses of the veins and arterioles of the forearm to walking during acclimatization to heat in man. J Clin Investig 39:825–833. https://doi.org/10.1172/JCI104102

Woodcock AH, Breckenridge JR (1965) A model description of thermal exchange for the nude man in hot environments. Ergonomics 8:223–235. https://doi.org/10.1080/00140136508930794

Woodcock AH, Powers JJ, Breckenridge JR (1956) Man's thermal balance in warm environments. Technical Report EP-30. Quartermaster Research and Engineering Command, Natick

Wunderlich CA (1871) On the temperature in diseases: a manual of medical thermometry. Translated by Woodman, 2nd edn. W.B. New Sydenham Society, London

Wunderlich CA, Seguin E (1871) Medical thermometry, and human temperature Second Edition. Translated by Woodman. W.B. New Sydenham Society, London

Wyndham CH (1973) The physiology of exercise under heat stress. Annu Rev Physiol 35:193–220. https://doi.org/10.1146/annurev.ph.35.030173.001205

Wyon DP (1989) Use of thermal manikins in environmental ergonomics. Scand J Work Environ Health 15(Supplement 1):84–94

Xu X, Giesbrecht GG (2018) A new look at survival times during cold water immersion. J Therm Biol 78:100–105. https://doi.org/10.1016/j.jtherbio.2018.08.022

Xu J, Psikuta A, Li J, Annaheim S, Rossi RM (2021) A numerical investigation of the influence of wind on convective heat transfer from the human body in a ventilated room. Build Environ 188:107427. https://doi.org/10.1016/j.buildenv.2021.107778

Xu X, Rioux TP, Castellani MP (2022) The specific heat of the human body is lower than previously believed: the journal temperature toolbox. Temperature. https://doi.org/10.1080/23328940.2022.2088034

Yahiro T, Kataoka N, Nakamura Y, Nakamura K (2017) The lateral parabrachial nucleus, but not the thalamus, mediates thermosensory pathways for behavioural thermoregulation. Sci Rep 7:1–10. https://doi.org/10.1038/s41598-017-05327-8

Yoshimura H, Ogata K, Itoh S (1960) (eds) Essential problems in climate physiology: a tribute to Professor Yas Kuno in celebration of his seventy-seventh birthday. Nankodo, Kyoto

Young WJ (1920) The metabolism of white races living in the tropics. III. The influence of external temperature and rate of cooling upon the respiratory metabolism. Ann Trop Med Parasitol 13:313–337. https://doi.org/10.1080/00034983.1920.11684207

Young WJ, Breinl A, Harris JJ, Osborne WA (1920) Effect of exercise and humid heat upon pulse rate, blood pressure, body temperature, and blood concentration. Proc R Soc Lond Ser B Biol Sci 91:111–126. https://doi.org/10.1098/rspb.1920.0004

Yu Y, Liu J, Chauhan K, de Dear R, Niu J (2020) Experimental study on convective heat transfer coefficients for the human body exposed to turbulent wind conditions. Build Environ 169:106533. https://doi.org/10.1016/j.buildenv.2019.106533

Zhang X, Yamada Y, Sagayama H, Ainslie PN, Blaak EE, Buchowski MS, Close GL, Cooper JA, Das SK, Dugas LR, Gurven M (2022) Human total, basal and activity energy expenditures are independent of ambient environmental temperature. Iscience. 25:104682. https://doi.org/10.1016/j.isci.2022.104682

Zotterman Y (1953) Special senses: thermal receptors. Annu Rev Physiol 15:357–372. https://doi.org/10.1146/annurev.ph.15.030153.002041

Zotterman Y (1959) Thermal sensations. In: Field JF, Magoun HW, Hall VE (eds) Handbook of physiology: neurophysiology. Section 1, vol 3, pp 431–458. American Physiological Society, Washington

Zuntz N (1901) Über die Bedeutung der verschiedenen Nährstoffe als Erzeuger der Muskelkraft. Pflüg Arch Eur J Physiol 83:557–571

Zuntz N, Geppert J (1886) Ueber die Natur der normalen Athemreize und den Ort ihrer Wirkung. Archiv für die gesamte Physiologie des Menschen und der Tiere. 38:337–338. https://doi.org/10.1007/BF01654665

Zuntz N, Schumburg WAEF (1901) Studien zu einer Physiologie des Marsches. August Hirschwald, Berlin