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INVITED REVIEW

A century of exercise physiology: concepts that ignited the study of human thermoregulation. Part 3: Heat and cold tolerance during exercise

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Abstract

In this third installment of our four-part historical series, we evaluate contributions that shaped our understanding of heat and cold stress during occupational and athletic pursuits. Our first topic concerns how we tolerate, and sometimes fail to tolerate, exercise-heat stress. By 1900, physical activity with clothing- and climate-induced evaporative impediments led to an extraordinarily high incidence of heat stroke within the military. Fortunately, deep-body temperatures > 40 °C were not always fatal. Thirty years later, water immersion and patient treatments mimicking sweat evaporation were found to be effective, with the adage of cool first, transport later being adopted. We gradually acquired an understanding of thermoeffector function during heat storage, and learned about challenges to other regulatory mechanisms. In our second topic, we explore cold tolerance and intolerance. By the 1930s, hypothermia was known to reduce cutaneous circulation, particularly at the extremities, conserving body heat. Cold-induced vasodilatation hindered heat conservation, but it was protective. Increased metabolic heat production followed, driven by shivering and non-shivering thermogenesis, even during exercise and work. Physical endurance and shivering could both be compromised by hypoglycaemia. Later, treatments for hypothermia and cold injuries were refined, and the thermal after-drop was explained. In our final topic, we critique the numerous indices developed in attempts to numerically rate hot and cold stresses. The criteria for an effective thermal stress index were established by the 1930s. However, few indices satisfied those requirements, either then or now, and the surviving indices, including the unvalidated Wet-Bulb Globe-Thermometer index, do not fully predict thermal strain.

Keywords Body temperature · Cold injuries · Exercise · Heat exchange · Heat illness · Hyperthermia · Hypothermia · Non-shivering thermogenesis · Sweating · Shivering thermogenesis · Vasomotor

Abbreviations

BAT	Brown adipose tissue
EHS	Exertional heat stroke
E_{max}	Maximal attainable evaporation
E_{req}	Required evaporation
HSI	Heat stress index
IREQ	Required clothing insulation
$IREQ_{min}$	Minimal required clothing insulation
$IREQ_{max}$	Maximal required clothing insulation
$IREQ_{neutral}$	Clothing insulation required for thermal comfort
ISO	International Standards Organization
PHS	Predicted Heat Strain
UTCI	Universal thermal climate index
WBGT	Wet-bulb globe thermometer

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Introduction

This review is Part 3 of four historical manuscripts that focus on the thermal physiology of most relevance to recreational and occupational athletes. Our use of those terms is deliberately inclusive and relates to adults of varying abilities who are exposed to thermally stressful conditions during work (e.g., emergency workers and military personnel) and exercise. In Part 1 (Notley et al. 2023a), we described the scientific steps that revealed the principles of thermodynamics which govern thermal energy exchanges. Those exchanges must obey physics. We also summarised the research that led to our contemporary understanding of body temperature regulation, by controlling physiological (thermoeffector) responses that produce, conserve or eliminate heat (Notley et al. 2023a [Figs. 20 and 21]). Armed with that information, we reviewed and critiqued the historical development of physiological measurements that were based upon those principles, and that withstood scientific scrutiny to become valid and reliable tools for measuring body temperatures and our thermoeffector responses (Notley et al. 2023b).

We will now explore the physiological strain experienced by, as well as the external stresses imposed upon, the men and women who rest, work and compete in thermally challenging environments. We again focus on three epochs, as defined by the research of two Nobel laureates, August Krogh (1874–1949; Denmark) and Archibald V. Hill (1886–1977; England), from the century of exercise physiology: before 1900, the years 1900–1930 (the Krogh–Hill epoch) and the modern epoch (beyond 1930). We do not doubt that Krogh and Hill would feel comfortable being described as physiologists with passionate interests in exercise and body temperatures.

In Part 1 of this series, we introduced the Serbian physiologist Ivan Djaja (1884–1957 [Jean Giaja]), who established the first Institute of Physiology in the Balkans during the Krogh-Hill epoch (Andjus et al. 2011). We return again to Djaja, but now to one of his publications at the start of the modern epoch (Giaja 1938), and his schematic representation of the zones of temperature regulation (Notley et al. 2023a [Fig. 21]). In this third part of our historical series, we will initially travel beyond the zone of thermoneutrality ("*Température neutralité thermique*"; thermoneutrality), through the "*Zone de l'hyperthermie*" (hyperthermia) and into the region of potentially lethal hyperthermia ("*Température de la mort par le chaud*"). We will then leave the thermoneutral zone for a second time, and pass through the zone of hypothermia ("*Zone de l'hypothermie*") to arrive at potentially lethal states of hypothermia ("*Température de la mort par le froid*"). Since recreational and occupational athletes, by definition, may spend hours beyond, and sometimes well beyond, their comfort zones, they may experience levels of physiological strain that can have serious pathophysiological consequences.

Whilst this review series was written to facilitate their independent reading, each of its four parts builds upon, and is linked to, its predecessor. Across the series, we have gone deep into the archival resources of over 25 countries, across five continents, with the aim of providing a significant collection of primary-source references and recommended readings (> 3800 across the series) that represent the foundations upon which our understanding of human thermal physiology during exercise sits. That work was undertaken by exercise and thermal physiologists, as well as by ergonomists, engineers, chemists and physicians, and we have woven their work into the geopolitical and technological climates of their times. It is our aim that those resources, along with the stories that lay behind that research, might be part of the antidote for scientific insularity. It is further hoped that readers might appreciate that, as sub-disciplines become progressively narrower in their foci, they often become less able to tackle complex physiological questions. That reality was emphasised by Nathan Zuntz (1847–1920) during the Krogh–Hill epoch (Gunga 2009).

Beyond the summer stroll—accommodating, tolerating and suffering exercise in the heat

Our journey beyond the summer stroll could be said to have begun in France, in the late eighteenth century, when the polymath, Antoine-Laurent Lavoisier (1743–1794), and his collaborator, Armand J.F. Séguin (1767–1835), discovered that oxygen consumption, and therefore metabolic heat production, increased during physical activity (Séguin and Lavoisier 1789; Candas and Libert 2022). Well before the construction of the *First Law of Thermodynamics* (Joule 1850), they observed that heat production was accompanied by increased evaporative cooling (Candas and Libert 2022), although it was not until 1845 that the retention of that metabolic heat was associated with an increase in deep-body (core) temperature. A Cornish physician, John Davy (1790–1868, England; Davy 1845), made that connection, although the elevations of deep-body temperature that he observed were too small to have any pathophysiological consequences, and he would not have any concept of the potentially fatal aftermath of very high body temperatures, though lethal heat stroke would be reported by other British doctors within 15 years (Gordon 1860).

This summer journey will reveal the potentially fatal consequences of excessively elevated body temperatures, but winter strolls can also be perilous ("Beyond shivering—accommodating, tolerating and suffering exercise in the cold"). The association of exercise with thermal strain will lead us to physiologists, physicians and engineers who

have explored human thermoregulation. Before setting off, we provide road maps (Figs. 1 and 2) with sign posts to highlight the main protagonists and their critical observations, discoveries and hypotheses.

Since physiologists commenced their journeys on the heels of physicians, who were concerned with the pathophysiological consequences of excessive heat storage, then our journey also commences with those physicians, and their recommended treatments for hyperthermia that varied from dousing with water (Gordon 1860) to opium administration (Wrench 1868). Those physicians may have been the first to treat, but they were far from the first to encounter, heat illnesses, which are perhaps among the oldest known diseases (Osler 1893; Wakefield and Hall 1927).

Heat illness in epoch one: treatments with water and opium

Heat illness: killed by forced marches and military uniforms?

There are ancient allusions to heat illnesses, with possibly the earliest report appearing in the Book of Judith (King James Bible; Chapter 8): "*And her husband was Manasses, who died in the time of the barley harvest; for he was standing over them that bound sheaves in the field; and the heat came upon his head, and he died in Bethulia*" (Wakefield and Hall 1927 [P. 94]). Some important words were missing from that quote, which originally read: "*heat came upon his head, and he fell on his bed, and he died*" (Horowitz 2022 [P. 541]). Those missing words told us that deaths from heat illness are not necessarily immediate, but can occur several days later.

Somewhat later, we discover that heat illness compromised the military campaign of the Roman Governor of Egypt, Gaius Aelius Gallus (26–24 BCE): "*for the desert, the sun, and the water (which had some peculiar nature) all caused his men great distress, so that the larger part of the army perished. The malady proved to be unlike any of the common complaints but attacked the head and caused it to become parched, killing forthwith most of those who were attacked, but in the case of those who survived this stage it descended to the legs, skipping all the intervening parts of the body, and caused dire injury to them*" (Jarcho 1967 [P. 767]). Had Gallus also provided the first record of rhabdomyolysis? Although it had been known from the time of Hippocrates that cold-water affusions might have helped those victims (Hippocrates 1817), cold water is not easily accessible to desert sojourners, even though it may well have been just below their feet.

Heat casualties also afflicted the crusaders in the Middle Ages, who were unacclimatised, heavily armoured and exercising in Middle-Eastern weather. There were catastrophes further east too: "*In Peking, in July 1743, 11,000 persons are said to have perished on the streets from the effects of heat*" (Wakefield and Hall 1927 [P. 94]). At the end of the eighteenth century, that perfect storm also compromised Napoleon's forces in Egypt (Steinman 1987). Bonaparte's Chief Surgeon, and the originator of the flying ambulance and medical triage (Wood 2008), Dominique-Jean Larrey (1766–1842, France), described heat disorders that varied from ophthalmia to testicular atrophy (Commission des Sciences et Arts d'Egypte 1809), although his thermal contributions are best known for increasing our understanding of cold injuries and their treatment ("Beyond shivering: the descent into hypothermia"). It was another Frenchman, Gabriel Andral (1797–1876), who was perhaps the first person to formally associate high ambient temperatures with heat stroke (Andral 1843 [Pp. 113–116]). In the context of our current interests, heat illness in well-prepared workers and athletes, it is often the highly motivated who are at greatest risk (Sonna 2001).

Manasses perished from the heat, and the sun caused the Roman soldiers much distress, but it was when our journey entered tropical climates that we encounter the fatal consequences of elevated body temperatures that were not necessarily caused by the sun. It was the British military physicians, during the colonisation of India, who observed and described those scenarios (e.g., Martin 1837). They lacked the support of a framework for understanding thermoregulatory function, but by observing their successes and failures, we can see how knowledge accumulated, and we might also appreciate why some, such as Edward Wrench (1833–1912; England), might recommend strange treatments: "*the sheet-anchor in such cases, if you can get hold of them before coma or convulsions have come on, is opium. I tried it over and over again and found it answer*[s] *in a most marvelous manner*" (Wrench 1868 [P. 179–180]). In the following year, another English physician prescribed "*large doses of quinine by the mouth, or hypodermically*" (Waller 1869 [P. 132]). At that time, physicians could not distinguish between malaria and heat stroke. Fortunately, quinine is efficacious in patients with malaria and harmless in those with heat stroke.

In the ninteenth century, the term applied to a suite of heat illnesses was heat apoplexy, and was coined by the military surgeon Charles Gordon (1820–1899, England and India; Gordon 1860). The French term was "*coup de soleil*", and other terms include insolation, apoplexy of the hot winds, *erythismus tropicus*, heat stroke, *coup de chaleur*, *Hitzschlag*, sunstroke, *Sonnenstich*, heat exhaustion, heat prostration, *solis ictus*, thermic fever and thermoplegia (Gordon 1860; Pembrey 1914; Casa et al. 2010a). In the ninteenth century, no distinction was made between potentially lethal sunburn, which we now know to be a toxic condition caused by photochemical rays of the sun and unrelated to body temperature, and heat stroke, in which hyperthermia

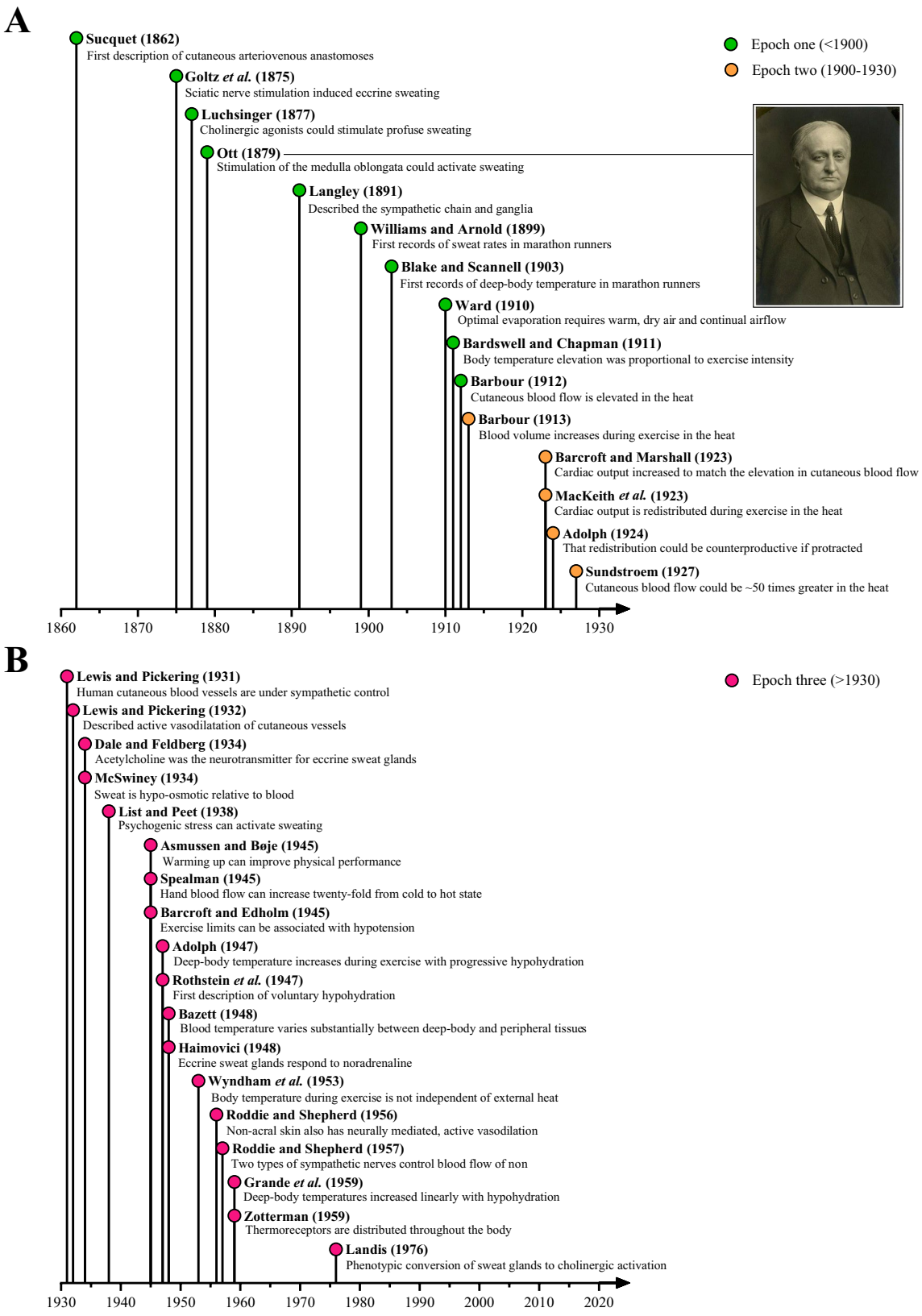


Fig. 1 Historical timelines: three epochs of discovery related to human heat stress during exercise. **A** Epochs one and two. The photograph of Isaac Ott was obtained and used under the Wikimedia Commons agreement (Public Domain). *Source:* https://en.wikipedia.org/wiki/Isaac_Ott#/media/File:Isaac_Ott.jpg Accessed: December 30th, 2022. **B** Discoveries during the modern epoch

is the cardinal event (Mitchell and Laburn 1985). Thus, heat stroke and sunstroke were often used interchangeably (Levick 1859), with that lack of differentiation is still evident within the contemporary glossary of thermal physiology (IUPS 2001).

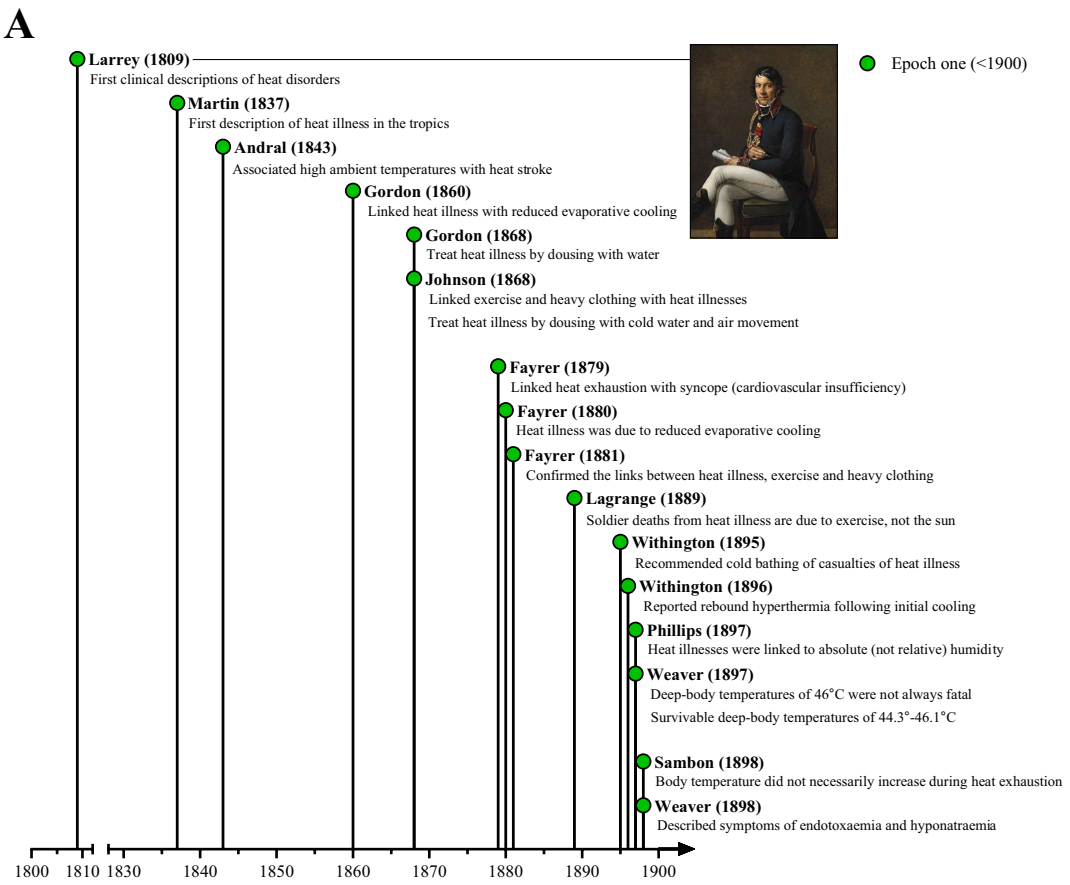
Gordon reported heat apoplexy in 0.5% of his regiment, with an appalling mortality rate of 88% (Gordon 1860). Waller (1869) reported a mortality rate of 51%. Gordon associated the condition in some regiments with exercise in the heat: "*soldiers were most liable to the disease when, after a debauch of spirits over night, they were forced to march armed and accoutred during the heat of the succeeding day*" (Gordon 1860 [P.989]). In less active regiments, he observed that "*… it is among those who, from compulsion or inclination, are much within doors during the intense heat of the day that it principally occurs*" (Gordon 1860 [P. 986]). In 12 years in India, he saw no cases of heat apoplexy in women; their work was conducted inside. He identified the meteorological conditions with the highest risk to be oppressive days with cloudy skies and little wind. Soldiers were at higher risk when forced to march along narrow roads in dense brushwood than in open country, and he correctly concluded that "*diminished evaporation from the skin in a most hot condition of atmosphere thus explains why we then suffer most (in health), and why hot climates are most unwholesome*" (Gordon 1860 [P. 990]). However, Gordon incorrectly concluded that diminished evaporation imposed a threat because it failed to carry away toxins, and we revisit those ninteenth century European perspectives (e.g., Lind 1771; Balfour 1923) when discussing heat adaptation in the last of these historical communications. Nevertheless, Gordon described a method for the successful treatment of a heat-stroke patient, which has withstood the test of time: "*two mussucks* [skin bags] *of water were immediately thrown over him*" (Gordon 1860 [P. 993]).

George Johnson (England; Johnson 1868), agreed with Gordon's risk assessments, noting that muscular exertion and fatigue, hot clothing, alcohol and close over-crowded rooms, always with very high air temperatures, were associated with heat illnesses. His explanation was that hot blood relaxed the pulmonary arteries, flooding the capillaries and causing pulmonary congestion. He proposed that "*hot air and hot blood are the cause of this form of apnoea, so cold air and cold blood are the chief means of cure*" (Johnson 1868 [P. 103]). His recommended treatment, which has also stood the test of time, was to lay the patient in the coolest place, with free-air current, wetting the entire body with cold water (without necessarily removing the clothes), giving cold water by mouth or by injection, and ceasing only when the skin was cool and moist.

William Strange (1816–1893, England) agreed about the circulatory problem, as did Wrench (1868), but not necessarily with its site being the lungs (Strange 1868). Strange also pointed out the vast inter-individual differences in symptoms, possibly due to confusing sunburn and heat stroke, and the difficulty of distinguishing heat illness from the fever of tropical infections (Fayrer 1879, 1882). The British Surgeon-General, Joseph Fayrer (1824–1907), did not consider lethal sunburn and heat stroke as different conditions, but regarded them as the second and third stages of sunstroke, with the first stage being heat exhaustion and syncope (Fayrer 1879). Syncope was due to cardiovascular insufficiency (uncompensable hypotension) resulting from over-exertion in the heat and typically seen in furnace stokers on steam ships in the tropics. Other casualties were labourers, factory workers and farm workers. The second stage resulted from "*exposure to the direct action of the sun's rays when the atmospheric temperature is also high, and especially when unusual exertion is made*" (Fayrer 1879 [P. 800]). Many thought that the sun's rays directly affected the brain and spinal cord, and that misconception led to the wearing of pith helmets to cover the head and neck (Fig. 3A), which became a feature of many caricatures of the British Army; "*Mad dogs and Englishmen go out in the midday sun*".

The third stage of Fayrer's sunstroke could occur without exposure to the sun (so-called heat apoplexy): "*the most serious cases are those that come on under cover by night as well as by day, and apart from the direct solar rays … Heat alone, especially when the atmosphere is loaded with moisture so as to prevent evaporation from the person, is the real cause of the disease*" (Fayrer 1879 [P. 301–302]). He later had doubts about heat alone being the cause, because the heat was accompanied by many other atmospheric changes (Fayrer 1884). He said that body (presumably sublingual) temperature could rise to 43 °C, the skin was hot and sometimes dry, and delirium, coma and convulsions were common, as were fatalities, with hundreds of deaths per year (Fayrer 1882). In India, those fatalities occurred predominantly amongst recently arrived Europeans, but if the heat was severe enough, even the local residents would succumb (Fayrer, 1884). He reported that, at *post mortem*, "*the blood is dark and grumous* [clotted]*, often imperfectly coagulated, and effused in patches of ecchymosis* [bruising]*, rendering the body rapidly livid*" (Fayrer 1879 [P. 303]). We might associate his description with the coagulopathy of heat stroke. He recognised army clothing as an agent of heat illness (Fig. 3B): casualties "*were brought to me, and laid out in rows, perfectly unconscious, in their red coats and black leather stocks (they wore them, in those days, even in action under a tropical sun)*" (Fayrer 1879 [P. 304]). In agreement with Johnson (1868), and as we would agree today, he noted that "*heat being the primary cause of the disease, the object is to reduce temperature as speedily as possible and before tissue changes have been caused*" (Fayrer 1879 [P. 305]).

Heat waves were another phenomenon known to those whose summer stroll took them eastwards. G. Douglas


A
Larrey (1809)
First clinical descriptions of heat disorders
Martin (1837)
First description of heat illness in the tropics
Andral (1843)
Associated high ambient temperatures with heat stroke
Gordon (1860)
Linked heat illness with reduced evaporative cooling
Gordon (1868)
Treat heat illness by dousing with water
Johnson (1868)
Linked exercise and heavy clothing with heat illnesses
Treat heat illness by dousing with cold water and air movement
Fayrer (1879)
Linked heat exhaustion with syncope (cardiovascular insufficiency)
Fayrer (1880)
Heat illness was due to reduced evaporative cooling
Fayrer (1881)
Confirmed the links between heat illness, exercise and heavy clothing
Lagrange (1889)
Soldier deaths from heat illness are due to exercise, not the sun
Withington (1895)
Recommended cold bathing of casualties of heat illness
Withington (1896)
Reported rebound hyperthermia following initial cooling
Phillips (1897)
Heat illnesses were linked to absolute (not relative) humidity
Weaver (1897)
Deep-body temperatures of 46°C were not always fatal
Survivable deep-body temperatures of 44.3°-46.1°C
Sambon (1898)
Body temperature did not necessarily increase during heat exhaustion
Weaver (1898)
Described symptoms of endotoxaemia and hyponatraemia
Epoch one (<1900)
1800 1810 1830 1840 1850 1860 1870 1880 1890 1900
B
Mayer (1900)
Sweat removes more water than solutes, and can lead to hypertonic hypovolaemia
Pembrey (1902)
Heat stroke was linked to heavy military clothing
Pembrey (1903)
Recommended wetting and fanning heat-stroke casualties
Pembrey (1914)
Advised against water-restriction practices
Simpson (1914)
First psychrometric chart for environments during exercise
Melville (1916)
Recommended drinking requirements for soldiers
Pattison (1920)
Recommended rubbing ice on the skin of heat-illness casualties
Willcox (1920)
Exertional heat stroke does not necessarily impair sweating
Levine et al. (1924)
Fatigue in marathon runners associated with hypoglycaemia
Mavrogordato and Pirow (1927)
Recommended heat adapting workers to reduce heat illness
Ferris et al. (1938)
Ice-water immersion to treat heat-illness casualties
Barcroft and Edholm (1945)
Exercise limits can be associated with hypotension
Buskirk and Beetham (1960)
Post-race, body-mass deficits of 6% in marathon runners
Pugh et al. (1967)
Post-race, rectal temperature >41°C in a marathon runner
Hart (1982)
Classical heat-stroke patient survived with a deep-body temperature of 47.0°C
Epoch two (1900-1930)
Epoch three (>1930)
1900 1910 1920 1930 1940 1950 1960 1970 1980 1990 2000 2010 2020

◂**Fig. 2** Historical timelines: three epochs of discovery related to heat illness during exercise. **A** Epoch one. The portrait of Dominique-Jean Larrey was painted by Larrey's sister-in-law, Marie-Guillemine Benoist (1804). The work was obtained and used under the Wikimedia Commons agreement (Public Domain). *Source:* https://commons.wikimedia.org/wiki/File:Portrait_of_Baron_Larrey_by_Marie-Guillemine_Benoist.jpg Accessed: December 30th, 2022. **B** Discoveries during the Krogh-Hill and modern epochs

Hunter (England) recorded the consequences of the heat wave of June 1886 (Egypt; minimum nightly 31 °C, maximum daily 50 °C [dry bulb]). Of the 2469 men in the army garrison, 48 developed heat stroke and 25 died; most were under the influence of alcohol (Hunter 1887). He railed against the bleeding of casualties, which accelerated death in heat-stroke casualties. Some of his intoxicated casualties may have preferred that outcome to his treatment: immediately strip the patient, lie him in the coolest place possible, splash cold water on the head and spine, and give a large cold-water enema (Hunter 1887).

Theo Hyslop (1863–1933, England) reported 55 cases of insanity following sunstroke, 23 of whom were Europeans in India (Hyslop 1890), and he believed sunstroke and heat stroke to have different causes, but the same symptoms. Hyslop suggested sunstroke was due to the rays of the sun, which affected "*the vasomotor centre in the medulla oblongata, especially by striking on the unguarded occiput and neck*" (Hyslop 1890 [P. 495]), whilst heat stroke was caused by hot air and the "*heat of the body produced by exercise which is not attended by perspiration*" (Hyslop 1890 [P. 494]). However, at the end of the ninteenth century, Louis (Luigi) W. Sambon (1867–1931, England) caused an upset and damaged his career, by contesting that sunstroke had anything to do with the action of the sun or heat on the body (Sambon 1898a). He also challenged the view that Europeans could not tolerate or adapt to hot-tropical climates (Sambon 1898b).

Sambon was born in England, trained in London and Naples (Italy), began his medical career in Rome and then worked in England as a tropical medicine specialist (Holdroyd 1931). He classified heat illnesses on the basis of deep-body temperature changes. If the body temperature did not rise, the condition was classified as heat exhaustion, which was common in soldiers forced to march in close order with heavy clothing and equipment. He considered that term to be a misnomer since, if body temperature did not rise, the condition could not have been caused by heat; we return to this concept in "Warmed to the work". For conditions in which deep-body temperature did rise, he resurrected the ancient name of siriasis. The "*ancients called it siriasis because of its prevalence during the hottest season, when Sirius, the dog star, rises and sets with the sun*" (Sambon 1898a [P. 748]). Siriasis was also characterised by coma, pulmonary congestion, and high mortality, and dark blood and venous engorgement at *post mortem*. It did not always occur on the hottest days, but high water vapour content imposed a serious risk. Sambon concluded that siriasis had the characteristics of an infectious disease prevalent in India, but absent in Europe, which he incorrectly attributed to a soil microorganism that flourished when the air was wet.

Sambon's paper (1898a) solicited a flurry of rejoinders. For example, O'Grady (1898; Royal Navy, England) reported a fatal case of heat stroke in a ship's stoker in European waters. McCartie (1899a, b) dismissed arguments about the hottest days, pointing out that heat stress also depended on wind speed and humidity. He also identified long forced marches and the tight army uniforms as causal agents of heat illness, noting that "*every workman in the world strips to the waist except the soldier, who is trussed and swathed up as if his life depended on it*" (McCartie 1899a [P. 191]).

Across the Atlantic, Theodore Deecke (1866–1882, U.S.A.) reviewed cases of fatal heat stroke (Deecke 1883), and reported deep-body temperatures of up to 44 °C, with regular observations of dark blood *post mortem*. Much higher deep-body temperatures (46 °C), which were not always fatal, were reported by Weaver (1897), who reviewed 2038 U.S. cases of fatal sunstroke. He diagnosed death to be due to the absorption of toxic products through a stomach wall, which had been damaged due to the loss of sodium chloride. Those toxins needed to be made innocuous, and "*Nature attempts to do it by burning it up with a high fever*" (Weaver 1897 [P. 621]). Weaver mistakenly attributed the reduced sodium chloride concentration to sweating, which actually induces an hypertonic hypohydration, but he correctly identified drinking too much water as a potential pathophysiological problem. We now know that to be hyponatraemia ("How should the fluid lost in sweat be replaced?"), but did he also describe endotoxaemia ("Have early ideas about exertional heat stroke been supported?")?

William Phillips (1863–1935, U.S.A.) reviewed those same fatalities, finding that 72% had occurred in low-lying western cities, and he gave readers a lesson in the first principles and the psychrometry of heat stroke: "*the action of heat is much influenced by the hygrometric condition of the atmosphere. A dry, hot air, it is claimed, is better tolerated than a moist one at a lower temperature, because it favors perspiration, and thereby keeps the body cool, while damp air diminishes evaporation and the refrigerating processes of the body*" (Phillips 1897 [P. 225]). He correctly identified that the risk factor associated with damp air was absolute humidity (proportional to water vapour pressure), not relative humidity.

Charles Withington (1862–1917, U.S.A.) analysed 100 cases of *heat prostration* (1882–1894; Withington 1895), which included 28 fatalities, 20 of whom died unconscious, with 11 of those surviving > 24 h. All casualties presenting with rectal temperatures > 43.3 °C died, whilst all those with

Fig. 3 **A** An Indian shola-style pith helmet, worn to protect the head and back of the neck from direct solar radiation. Creative Commons Attribution 2.0. **B** A British officer in the uniform of the 74th Highland Regiment. The tight woollen clothing covering almost all of the body impeded evaporation and did not allow air circulation near the skin. John Opie, Wikimedia Commons and in the Public Domain. **C** The cotton uniform and felt hat worn by Robert Baden Powell, which replaced the redcoat, woollen uniform and pith helmet. Painting by John Edward Chapman: Baden-Powell in the Uniform of the South African Constabulary, Standing by His Charger. The Scout Association: Creative Commons CC0 1.0 Universal Public Domain Dedication

temperatures < 39.4 °C survived. Some casualties reported a cessation of sweating: "*in one such case a longshoreman while "tending hatch" on deck of a vessel at 3 P. M., had been sweating profusely. This suddenly stopped and he "felt cold", then lost consciousness*" (Withington 1895 [P. 513]). Treatment consisted of cold and ice-cold water bathing, sometimes with ice rubbing. Withington reported the consequences of over-cooling: "*sometimes the chilling of the surface drives the blood in upon the viscera, and collapse occurs*" (Withington 1895 [P. 513]). He noticed, but did not attempt to explain, rebound hyperthermia, sometimes back to the temperature at admission, which could occur following bouts of cooling. By the end of the ninteenth century, cold water and ice were established firmly as treatments for exertional heat stroke (Costrini 1990).

Insights and blind spots about thermoregulation during exercise

We introduced T. Clifford Allbutt (1836–1925; England), the inventor of the first practical, clinical thermometer, in our previous communication (Notley et al. 2023b). He was also interested in the physiology of thermoregulation during healthy exercise, and, when contemplating what determined human body temperature, he noted that "*the effects of hard and prolonged exercise upon the body had not been tested, and this seemed a serious omission*" (Allbutt 1872 [P. 106]). Allbutt, along with Séguin and Lavoisier (1789), would have been dumbfounded by the ideas of Austin Flint (1812–1886, U.S.A.), who was soon to become President of the American Medical Association. Flint rejected the idea that physiology had to conform to the laws of physics: "*our physiological facts, if definite and well established, should be treated as facts not to be distorted into arguments in favour of laws which we have enacted rather than discovered*" (Flint 1877 [P. 95]). One of those laws was the *First Law of Thermodynamics*: "*If a man take a certain amount of food, and should do no work except that required to maintain circulation respiration, and assimilation, there is no evidence that the force "locked up" in the food is evolved in the form of heat*" (Flint 1877 [P. 94]). Flint also denied that exercise could elicit hyperthermia; "*… we have all been wrong often*" (Hill 1965 [P. 167]).

The views of Flint (1877) were not shared by Fernand Lagrange (1845–1909, France), whom we would recognise as an exercise physiologist. He said that "*if to the action of high temperature there is added that of muscular work, the organism has not to fight against the heat of the surrounding medium, it has also to defend itself against the increased heat developed in its own organs*" (Lagrange 1889 [P. 151]). He had no doubt that "*excessive temperature is a consequence of excessive vital combustion*" (P. 152) or that "*a man who succumbs during a forced march, under the hot sun, is not killed by the sun, but by the forced march*" (Lagrange 1889 [P. 151]).

That exercise caused hyperthermia was the unqualified conclusion of two British thermal physiologists, who provided further insights about thermoregulation during exercise. The first was William Hale White (1857–1949 [hyphenated after 1900]; Milton 2022). He developed a gravimetric method for measuring local sweat rates (Hale White 1897), which was possibly the forerunner of the absorbent-patch (pouch) method (Notley et al. 2023b). He had the physiological insight to say that if the skin temperature, deep-body temperature and sweat rate all increase within a fixed environment, then metabolic heat production must also have

increased. The second physiologist was Marcus S. Pembrey (1868–1934; Douglas 1935; Milton 2022). He and his student showed that "*muscular work causes a marked rise in the internal temperature*" (Pembrey and Nicol 1898 [P. 392]).

By the end of the ninteenth century many, but certainly not all, would have agreed with Pembrey and Nicol (1898) that a hallmark of thermoregulation during exercise was an elevated deep-body temperature. That elevation was exacerbated by suppression of evaporative cooling, either by ambient conditions (high water-vapour pressure, low wind speed) or by clothing, and it could lead to fatal heat stroke. An important cautionary message emerged concerning the ventilatory artefacts accompanying oral thermometry during exercise, although it took some time for that message to be realised across the Atlantic. In perhaps the first deep-body (sublingual) temperature measurements taken before and after running a marathon (Boston Marathon), Harold Williams and Horace Arnold (1899, U.S.A.) arrived at the incorrect conclusion that deep-body temperature actually decreased over the course of the race (air temperature 7 °C). They also measured body-mass changes, with 10 of the 17 runners losing an average of 1.6 kg. Whilst that paper offers little to modern physiologists, it sets a marker close to the commencement of applied research in exercise physiology (Maron and Horvath 1978).

Both sublingual and rectal temperatures were reported for the next three Boston Marathons (1900–1902; Blake and Larrabee 1903), from which the authors concluded that "*mouth temperature is not a reliable factor*" (P. 197). Five runners had post-race, rectal temperatures of 40 °C in 1900 (2.5 kg body-mass loss), whilst the mean temperatures for all runners studied in 1901 were remarkably low (38.4 °C; 1.8 kg mass loss). Such low temperatures imply a slow pace; the authors were not to know how high deep-body temperatures would be in the modern epoch, nor how much sweat could be lost. Indeed, water restriction was often considered a sign of fortitude, and the Oxford University rowing crew of 1860 were restricted to two pints a day during training (Noakes 1995), although other fluids appear not to have been restricted.

During marathon racing, "*contestants may and probably did drink certain amounts of brandy while running*" (Blake and Scannell 1903 [P. 198]). If for no reason other than it compromises thermoregulation and increases the risk of exertional heat stroke (Yeo 2004; Yoda et al. 2005), that practice would be unthinkable today, yet competitors often consumed alcohol in early marathons, and wine was available along the route of the 1924 Paris Olympic Games (Peiser and Reilly 2004). In a curious twist to this story, Levine et al. (1924) would soon describe fatigue-related hypoglycaemia in runners at the end of the Boston marathon ("Fuelling the fires: the competition for blood glucose";) a state that has an adverse impact on thermoregulation in the cold and which is tightly linked to alcohol consumption.

In spite of their impressive insights at that time, the ninteenth-century physiologists who recognised that exercise elevated deep-body temperatures, also considered hyperthermia to reflect a failure of thermoregulation: "*the resisting power of the heat regulator fails or becomes exhausted and the man's temperature rises to pyrexia or hyperpyrexia*" (McCartie 1899b [P. 436]). It was only well into the twentieth century that the connection was made between elevated body temperatures, thermoeffector activation and heat balance during exercise. The contemporary term, "regulatory failure", does not imply regulatory collapse, but a reduced ability to defend a stable body temperature, regardless of its level.

Epoch two: exercise hyperthermia, friend, foe or fiction?

Heat stroke in the Krogh-Hill epoch: a military perspective

In the Krogh-Hill epoch, research concerning thermoregulation during exercise in the heat continued to be dominated by an emphasis on heat illness, and particularly when the British military arena of interest shifted from India to Mesopotamia and the Middle East. According to Alexander (England), "*heat waves (locally known as "date ripeners") occur, when the temperature keeps up for about a fortnight at 124 to 128 °F. (51–53 °C), and it is during these distressing periods that most of the heatstroke cases occur*" (Alexander 1922 [P. 358]). Unfortunately, many protagonists of applied research at that time showed only a scant acquaintance with physiology.

In a different class, however, were the contributions of physiologists such as Marcus Pembrey and Joseph Barcroft. In an observation that will soon ring an identical bell for cold injuries ("Beyond shivering—accommodating, tolerating and suffering exercise in the cold"), Pembrey observed that "*in many an army heat-stroke has been more fatal than the bullets of the enemy*" (Pembrey 1902 [P. 261]). Pembrey dismissed the pronouncement that the blame for heat stroke lay with the chosen lifestyle of the soldiers. He had no doubt that exercise, even without ambient heat, could elevate deep-body temperature "*as high as 101 F (38.3 C)*" (Pembrey 1902 [P. 263]), but he did not consider that elevation as pathological. Indeed, he thought it was beneficial to skeletal muscle activation. Joseph Barcroft (1872–1947, England), and his student showed that elevated temperatures shifted the oxygen haemoglobin dissociation curve to the right, facilitating the offloading of oxygen within exercising muscles (Barcroft and King 1909); some degree of body-temperature elevation was indeed advantageous.

Pembrey (1902) doubted that the exercise-induced elevation of body temperature would attain heat-stroke levels during exercise, even on a hot day, if the air was dry. What caused heat stroke was exercise in the heat when the water-vapour content (absolute humidity) was high, which inhibited evaporative cooling. Farm labourers seldom developed heat stroke even if they worked all day in the sun, so he laid blame squarely on the army: "*the soldier on the march and under the order and care of his officers is clothed in open defiance of common sense and physiological principles*" (Pembrey 1902 [P. 265]). He recognised that coping with exercise in the heat required increased cardiac output and coordinated thermoeffector activation. Whilst his expertise far exceeded that of army doctors, neither he nor his contemporaries understood thermoregulatory function properly. Nonetheless, Pembrey (1902) dismissed the contemporary belief that drinking cold water during hyperthermia could be fatal; soldiers died from what made them drink, but not because they drank. His recommended treatment was wetting heat-stroke casualties with water and creating an airflow over them: "*under no other treatment do so many patients recover*" (Pembrey 1902 [P. 269]). He also recommended: "*light clothing, light loads, open order, a proper supply of water, and training on hot as well as on cold days*" (Pembrey 1902 [P. 269]).

Pembrey credited the British Army with the development of methods for cooling heat-stroke casualties (Pembrey 1914), but he used the words of the military surgeon, James R. Martin (1796–1874, England), to chastise the military for its regulations: "*Parades, formalities, the majestic English march, "Regulations" and appearances, must here be utterly and at once discarded; for it is a question of life and death. The open, disorderly-looking order of march, however slovenly it may seem to the lieutenant-colonel, must here be used, the close order being nothing short of stifling and sickening the men "by Regulation"*" (Martin 1861 [P. 409]). Pembrey knew that sweating was under neural control, but he thought it was influenced by the temperature and composition of the blood. He would find allies among a small group of thermal physiologists, but not the majority. In his view, the brain temperature could be lowered selectively by external cooling: "*the application of ice to the head and neck seems to give prompt results owing probably to the fact that the high temperature especially affects the brain*" (Pembrey 1914 [P. 634]).

Pembrey also advised against the practice of restricting drinking and was clearly contradicting the contemporary dogma, which advocated water restriction. For example, James Sullivan, an organiser of the 1904 Summer Olympics in St. Louis (U.S.A.), pronounced: "*don't get in the habit of eating or drinking in the Marathon race; some prominent runners do, but it is not beneficial*" (Sullivan 1909; cited by Noakes 1995 [P. 124]). Sullivan also campaigned against women participating in the Olympic Games.

Leonard Rogers (1908, England) evaluated the hypothesis that heat stroke had a microbial origin (Sambon 1898a, b). He studied 425 fatal cases, and correlated those data with changes in the weather (Bengal Meteorological Office, India), finding that he could explain the heat-stroke incidence "*on purely physiological grounds, without the assistance of a hypothetical microbe*" (Rogers 1908 [P. 30]), and asserted "*there is a most intimate relationship between heat-waves, the degree of moisture in the air … and the prevalence of heat-stroke; and all the facts are readily explainable on the hypothesis that the hyperpyrexia is produced by a failure of the cooling mechanism of the body during exposure to great heat, especially if accompanied by much moisture in the air and of prolonged duration*" (Rogers 1908 [P. 32]). Rogers was not alone (Buchanan 1900; Duncan 1908), although Milner attributed the cessation of sweating, and the resultant heat stroke, to a "*paralysis of the heat-regulating centre, due to intoxication by the parasite of malignant tertian malaria*" (Milner 1918 [P. 639]). He claimed that quinine reduced mortality substantially. Inhibition of the heat-loss effectors is indeed one consequence of pyrogens, but Leonard Hill (1866–1952, England; Douglas 1953) pointed out that many heat-stroke cases occurred in malaria-free troops who recently had arrived in Mesopotamia from England (Hill 1920).

In a debate that continued within the modern era, Pembrey (1914) believed that dry skin was a hallmark of heat stroke and that it allowed one to distinguish heat stroke from heat exhaustion. Similarly, Hearne (1919, 1920) claimed that a cessation of sweating occurred 1–48 h before other symptoms of heat stroke, and urged that the temperature of anyone with dry skin be monitored. He contended that he had not seen a heat-stroke casualty with a deep-body temperature of 43.3 °C, or higher, who still was sweating. Hill (1920) pointed out that it was not the sympathetic nervous system that failed in heat stroke, but the sweating system. The view that sweating always failed in heat stroke was challenged by Willcox (1920a; London), who noted that: "*suppression of sweating did not, in my experience, always precede heat hyperpyrexia, and though it is undoubtedly an important predisposing cause it cannot be regarded as the primary one*" (Willcox 1920a [P. 648]).

British Army physicians working in the Middle East discovered differences in the prevalence of heat illnesses when compared to India. For example, Willcox (1920b) recorded that, for equally high ambient temperatures (July–August, 1917), there were 3156 heat-stroke cases with 458 deaths (15%), whilst in India, there were just 601 cases, with 62 deaths (10%), and it was not just soldiers who suffered. In 1916, the co-inventor of the Horsley-Clarke stereotactic apparatus that enabled many advances in neural and thermal

physiology (Notley et al. 2023a), Victor Horsley (Semon, 1916), was a volunteer surgeon in Mesopotamia. That role required walking long distances daily, with shade temperatures often exceeding 43.3 °C: he became ill, was admitted to hospital, lost consciousness and died (MacNalty 1957). Whatever the cause of his and other heat-stroke deaths, it was not the direct effect of the sun on the brain and spinal cord (Alexander 1922); "*the Eastern sun is not, as so many people think, a strange avenging deity with totally different powers from those met with in England*" (Finny 1918 [P. 369]).

Army physicians knew that recovery from heat stroke required prompt cooling (Turner 1917), and reducing the period of unconsciousness seemed to be associated with a better chance of recovery (Rogers 1908), but how can that best be achieved? Some used evaporative cooling, with water thrown over the casualty (dousing) and increased air movement (ventilation). One physician used a water-filled trench to successfully treat 40 heat-stroke cases (McIntosh 1920). The Persian Oil Company built a cooled, anti-heat stroke ward (Rennie 1930). Others insisted that rubbing the body surface with ice was the best option (Withington 1895; Pattison 1920; Hehir 1922; Wakefield and Hall 1927).

Not only did ice rubbing result in subsequent rebound hyperthermia (Gauss and Meyer 1917; Hehir 1922), it was irrational on physical grounds. The latent heat of fusion of water, the discovery of which Tunbridge (1971) attributed Joseph Black in 1761 (Notley et al. 2023a), is ~ 334 $J.g^{-1}$, but its vaporisation would dissipate seven times more heat (2426 $J.g^{-1}$). Nonetheless, ice rubbing was not as irrational as another popular cooling method; ice-water enemata (Beamish 1907; Howard 1920). According to Hill (1920), 70 g of water evaporated from the skin took away as much heat as a 1-kg, ice-water enema. Ice-water enemata also prevented measuring rectal temperatures and sometimes had pathological consequences. In one patient who died, "*post-mortem the rectum was found to be partly gangrenous, the pathology being probably identical with the gangrene following frostbite, and due to prolonged exposure of the mucous membrane to a very low temperature*" (Hull and Reed 1907 [P. 341]). Ice water was not the only noxious enema. Some used turpentine (Duncan 1903) and others brandy (Henderson 1902), but the physiology underlying those noxious treatments remains a mystery.

The British army was also engaged in the South African War (the Anglo-Boer War; 1899–1902); to the Boers, it was the second war of independence. Heat illnesses again occurred, although cases were remarkably rare. Hospital admissions were 1625 (1899–1902), or 2.7 per 1000. Only 15 deaths were recorded; case mortality < 0.1% (Simpson 1909). Protagonists of the malaria hypothesis might have attributed that low mortality to an absence of the parasite over the combat zone. Thermal physiologists might prefer the interpretation of Simpson (England): "*the service dress in South Africa could hardly have been improved on; it was eminently suited to the climate. At the beginning of the war there was a tendency to too close fitting, and the helmet was generally worn, but these two faults were eliminated very early; the felt hat in particular was far better suited to the climate than the helmet*" (Simpson 1909 [P. 260]; Fig. 3C).

If 15 British soldiers died of heat illness in that war, and heat-related deaths in India and the Middle East ran into the thousands, why did just four heat-stroke deaths in South African gold mines (1925–1927; Village Deep mine, Johannesburg) generate so much attention (Mavrogordato and Pirow 1927)? In the first instance, heat illnesses reduced productivity, but the real significance was that those deaths changed the way that occupational heat illnesses were reduced and prevented, using regimented artificial heat-adaptation (acclimation) procedures. Indeed, at the end of the Krogh-Hill epoch, there was a paradigm shift, and almost the entire underground workforce of South Africa's gold mining industry was heat acclimated under the supervision of thermal physiologists. That programme was hailed by Jim Hardy (U.S.A.) as the greatest achievement in applied physiology (Mitchell and Laburn 2022).

Mavrogordato and Pirow were not physiologists, but they understood heat transfer, although they thought that all body temperature elevations were pathological. Those four casualties had been engaged in hard physical work underground, and it became apparent that the wet-bulb temperatures were > 30.0 °C, with air movement < 0.2 $m.s^{-1}$. Most importantly, they had been working in their first or second shifts, after periods away. Mavrogordato and Pirow recommended that air movement at hot sites underground should be increased and that men, new or returning to work, be eased into work in the heat by first working at cooler sites: "*it is neither kind nor wise to set a raw boy to learn lashing* [rock shovelling] *at 86F. wet-bulb*" (Mavrogordato and Pirow 1927 [P. 110]).

At the end of the Krogh-Hill epoch, there was a body of knowledge about the circumstances in which heat stroke occurred, and about how it can be prevented and treated. The causal agents were a combination of hard physical work and the wearing of clothing in conditions that prevented the evaporation of sweat at rates sufficient to dissipate metabolic heat and that acquired from the environment. It did not escape Charles Martin (England) that "*The coolie works with his nice brown body exposed and covered with sweat, and is jolly, whereas the white man distressfully labours in a hyperthermic condition, straining his heart to work a refrigerating plant which he has rendered inefficient because his sense of dignity forbids him to expose his skin*" (Martin 1930 [P. 677]).

For sweat to evaporate efficiently, the boundary layer of warm, moist air around the body has to be removed, which

requires air movement. In that era, all elevations of deep-body temperature were considered to result from a failure of the thermoregulatory centre, though some considered limited elevations to be beneficial to exercise. Fatalities resulted from thermal damage to body tissues. Although recovery was once thought to be impossible from rectal temperature > 43.3 °C, survivable, deep-body temperatures of 46 °C were reported (Weaver 1897; Tigerstedt 1906). Heatstroke risk could be reduced by wearing lighter clothing, by frequent drinking and by easing people into working in the heat. The most successful cooling treatment mimicked the evaporation of sweat, whilst aggressive surface cooling often resulted in rebound hyperthermia (e.g., Withington 1895).

Further contributions to heat illness of occupational relevance

Like their colleagues in the military, civilian researchers of the Krogh-Hill epoch knew that it was not just the dry-bulb temperature that determined the physiological impact of the climate. Robert Ward (1867–1931; U.S. climatologist; Rohli and Bierly 2011), reminded us that "*the hotter the air, the greater its capacity for water vapour; the drier the air, the more water can still be evaporated into it; the more wind, the greater the opportunity for evaporation into the fresh supply of air which is constantly brought to the body*" (Ward 1904 [P. 131–132]). Contrary to the views of Haldane (1905), not even the wet-bulb temperature indicated how readily the air would accept heat. Simpson (1914) concluded that the risk of heat stroke was greatest when the absolute air humidity was 25–30 $g.m^{-3}$. Whilst absolute humidity was not a concept familiar to either physicians or physiologists of that time, he showed how it was related to dry-bulb temperature and relative humidity using a psychrometric chart (Simpson 1914). He had also identified hypohydration as a greater challenge to athletes and workers than was a hindrance to evaporation when exercising in hot-dry environments.

But other occupational environments could be just as challenging. Leonard Hill had observed that sailors (stokers) worked with wet-bulb temperatures never lower than 26.7 °C, and sometimes reaching 36.7 °C, and presumably with little air movement (Hill 1912). Watkins (1917) noted heat hazards in U.S. factories after they changed from water power to steam power. Like Finny (1918), Watkins had understood the role of the boundary layer in evaporative cooling: "*in hot working zones, if the air be still, even though it be dry, the body becomes quickly surrounded by an air envelope, saturated with body moisture, which, acting like a blanket, prevents the cooling of the body by evaporation*" (Watkins 1917 [P. 2119]). Horace M. Vernon (1870–1951, England; Milton 2022) identified problems in cotton-weaving sheds, which were humidified to prevent the cotton breaking, so wet-bulb temperatures were only 1.1 °C below the dry bulb (Vernon, 1921). He also found that the work efficiency of miners increased with wind speed (Vernon 1928). Of course, evaporation can occur in saturated air, as long as the vapour pressure gradient is favourable (Mitchell et al. 2018).

Pembrey was convinced that deep-body temperatures were elevated during exercise (up to 38.9 °C), and he believed "*there is no evidence to show that the rise in the internal temperature is injurious; evidence is gradually forthcoming to show that it may be beneficial*" (Pembrey 1904 [P. 476]). The benefit was being pre-warmed and ready to commence work (Cook and Pembrey 1913). Those elevations were believed to be independent of the external work rate, but the rate of heat production was dependent upon that work rate (Lippmann 1913; Melville 1910, 1916). We will meet Charles Melville again ("Water loss, thirst and drinking: "a pint at the half-way halt""), and it is presumed here that he meant that the temperature elevation was independent of both the environment and the exercise intensity, and was regulated at that level by controlling heat loss at a rate required for that work intensity. So elevated body temperatures during exercise not only were normal, rather than pathological, but they were maintained physiologically.

A substantial further advance during exercise came from an experiment at a tuberculosis hospital, where the physicians measured their own rectal temperatures whilst walking on a level road. Those temperatures increased during exercise and then reached a plateau (Bardswell and Chapman 1911; England). Those plateaux were intensity (walking speed) dependent (Fig. 4), and they were so consistent that they could reproduce any rectal temperature up to 39.6 °C in themselves "*simply by prescribing to ourselves varying degrees of muscular effort*" (Bardswell and Chapman 1911 [Pp. 1107–1108]). Those observations were made 27 years ahead of Marius Nielsen (1903–2000, Denmark; Nielsen 1938; Nielsen Johannsen 2022), who also reported that deep-body temperature was determined by exercise intensity. Indeed, most researchers, including ourselves (Notley et al. 2023a), usually attribute that discovery to Nielsen (1938). Accordingly, an elevation of deep-body temperature not only occurred during exercise, but it was proportional to the exercise intensity, although Bardswell and Chapman (1911) made no connection between that elevation and the excitation of heat-loss mechanisms.

The data in Fig. 4 are not from exercise in the heat. Those data were subsequently presented by Young et al. (1920) and Nielsen (1938). The former were researchers from the Australian Institute of Tropical Medicine (Townsville; Taylor et al. 2022), who measured the deep-body (rectal) temperatures during outdoor walks at the hottest time of the day and year; wet-bulb temperature 27.2 °C. They compared those data with values obtained for subjects resting in an iron chamber in the sun, in which water was boiled to achieve

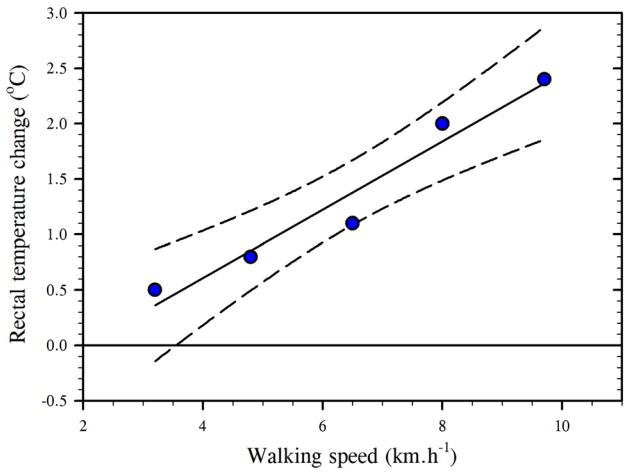


Fig. 4 Exercise-induced and intensity-dependent changes in rectal temperature for men walking outdoors on a level road ($N=3$), including the authors (Bardswell and Chapman 1911). Over walking speeds from 3.2 to 9.7 km.h^{-1}, rectal temperature averages were a linear function of walking speed, and have been plotted, with 95% confidence limits, from tabulated data

a wet-bulb temperature of 38.9 °C. Body temperatures did not stabilise in the chamber, but they did during exercise outdoors, following an elevation of 1.1–1.7 °C over the first half of walks lasting 2.0–3.5 h, after which temperatures rose only a few tenths further.

What did researchers of the Krogh-Hill era know about the thermoeffectors? They knew that cutaneous blood flow was elevated in the heat (Barbour 1912; Stewart, 1913a, b, c; Sundstroem 1927), but were uncertain about the thermoregulatory vasomotor responses to exercise in the heat. They could have measured cutaneous blood flow, at least in the arms and feet, because plethysmographic and calorimetric methods were well established (Notley et al. 2023b). However, those investigating exercise tended not to measure cutaneous blood flow, but inferred changes from other variables, like skin temperature and heart rate. That approach was confounded somewhat by the heterogenous nature of skin temperatures (Benedict and Slack 1911; LeFèvre 1911; Werner and Reents 1980), though it is less so in the heat.

Henry C. Bazett (1885–1950, U.S.A.; Blatteis and Schneider 2022) predicted that the skin temperature of working limbs would increase during exercise because he had assumed that the blood passed through the working muscles *en route* to the skin (Bazett 1927). He expected general vasodilatation of the cutaneous vasculature during exercise, so he would have expected skin temperature to rise elsewhere too, though not as much. One of his contemporaries was Francis G. Benedict (1870–1957, U.S.A.; Blatteis and Schneider 2022), who measured 13 different skin temperatures on a man cycling in the air at 20 °C (Benedict 1925). Benedict indeed found that the skin temperature over working muscles increased, but skin temperatures elsewhere fell.

Regardless of the environmental temperature, researchers of the Krogh-Hill epoch knew that metabolic heat was carried by the blood to the body's surface (Melville 1910). The primary means for increasing cutaneous blood flow was via dilatation of peripheral arterioles and venules (Adolph 1924; Winslow 1926). Without cardiovascular compensation, that diversion of blood to the periphery was thought to compromise blood flow elsewhere; "*when in a hot and humid atmosphere the blood vessels of the skin are dilated and overcharged with blood, the brain and spinal cord among other organs are rendered correspondingly anemic*" (Lee 1912 [P. 866]). One form of compensation would be an increase in cardiac output, and, based on experiments carried out on themselves, Barcroft and Marshall (1923) found that, during body warming, the cardiac output increased by an amount equal to the elevation in cutaneous blood flow. Sundstroem (1927) suggested cutaneous blood flow could be ~50 times greater in the heat, which Rowell et al. (1969a) confirmed experimentally.

Another compensatory adjustment involves a redistribution of the available cardiac output (MacKeith et al. 1923). Indeed, splanchnic blood flow, which supplies the gastrointestinal tract, liver, spleen, pancreas and kidneys, is dramatically reduced when skin blood flow is significantly elevated, and when humans exercise in the heat (Rowell 1973, 1986; Rowell et al. 1968, 1969a, 1970; Perko et al. 1998). That redistribution can, if protracted, result in localised underperfusion, and Adolph (1924) thought that such increases in cutaneous blood flow could be counterproductive. Other compensatory adjustments relate to intravascular changes, such as an increased blood volume (Barbour 1912; Hamilton et al. 1924), which accompanies an elevation in plasma protein content (Bazett 1927). In a now-classical paper, August Krogh showed that some of those compensations, which included changes in the ventilatory and heart rates, were initiated very soon after exercise started (Krogh and Lindhard 1913), and presumably before any substantial change in deep-body temperature. They had demonstrated feedforward thermoregulatory control (Notley et al. 2023a).

Feedforward control was neither widely known, nor was it fully understood by researchers of that epoch, and some thought that an accelerated heart rate might be attributable to increased blood temperature (Mansfeld 1910). That possibility was evaluated by Martin et al. (1914) who dismissed the hypothesis. On the other hand, Adolph (1924) found a better association between heart rate and superficial temperature, but he thought that the control mechanism was that "*the heart gradually compensates for the lack of venous return of the blood by beating faster*" (Adolph 1924 [P. 584]). We now know that the low-pressure baroreceptors will drive the heart rate to regulate central venous pressure (Rowell 1993).

At least part of the confusion about the origin of the increased heart rate resulted from uncertainty about how the thermoeffectors were controlled. Indeed, by 1912, it had not only been established that a thermoregulatory centre existed, but it was located within the hypothalamus (Notley et al. 2023a). Unfortunately, many of those investigating human thermoregulation during exercise in the heat were either unaware of, or not familiar with, earlier non-human research, although Barbour (1912) was an exception. In Bazett's (1927) review, Isaac Ott (1847–1916, U.S.A.; Blatteis and Schneider 2022), who was responsible for pioneering work in the U.S.A. on that regulatory centre, was not cited, although Bazett acknowledged the existence of such a centre.

To illustrate the state of the art at that time, we provide the following examples, with a more detailed discussion contained within Notley et al. (2023a). Isaac Ott had proposed that a hypothalamic regulatory centre was responsible for the production of sweat in cats, whilst Leonard Rowntree (1883–1959, U.S.A.) proposed that spinal centres excited the sweat glands of humans. Barbour (1912) recognised that warming and cooling a site at the base of the brain influenced vasomotion (rabbits), but still asked whether sweating was "*primarily set into action through the temperature-sense nerve endings and the central nervous system?*" (Barbour 1912 [P. 303]). Edward F. Adolph (1895–1986, U.S.A.) stated "*that the dilatation reflex does not concern any part of the central nervous system has been shown by various authors who obtained the response of sweating and of capillary dilatation after central connections were cut*" (Adolph 1924 [P. 581]), adding "*that the three primary responses to high temperatures are initiated by temperature conditions in the skin, and not by those in the central organs*" (Adolph 1924 [P. 584]). Mavrogordato and Pirow (1927), as well as most contemporary thermal physiologists, hold the view that a regulatory centre within the brain controls the blood vessels, respiratory muscles and sweat glands.

Water loss, thirst and drinking: "*a pint at the half-way halt*"

Whilst Marcus Pembrey condemned the British practice of restricting water for soldiers, the German approach during the First World War was diametrically opposed: "*on hot or long marches, mounted or cycle orderlies shall be sent ahead to warn the villagers to turn out and line the streets with tubs and buckets of water so that the men may get some as they pass through*" (Melville 1916 [P. 69]). Though it would have been clear to physiologists and physicians of our first epoch that exercise in the heat led to progressive dehydration (hypohydration), they did not know its consequences for osmoregulation or thermoregulation. Nor did they know which fluid, how much or on what time schedule fluid should be administered to correct water deficits, or whether one could simply rely upon thirst to maintain water balance. Herein, we have adopted the recommendation of Michael Sawka (1992, U.S.A.) that "hypohydration" is preferable entomologically, for referring to reductions in body-fluid content, whilst "dehydration" should refer to the process involved in the progression towards hypohydration. In the past, we have not consistently applied that distinction.

For the South African gold miners, Mavrogordato and Pirow (1927) recommended replacing lost fluids with 0.4% sodium chloride solution, which has a salinity nearly half that of blood. In Britain, there was controversy about the pathophysiology of hypohydration and rehydration. For example, Rayner Thrower (1928) identified salt and water loss as a cause of heat cramps, while John S. Haldane (1860–1936, England) was adamant that the cause was acute poisoning by water (Haldane 1928), which could be prevented by eating "*red herrings or highly salted bacon*" (Hancock et al. 1929, [P. 55]; "*… we have all been wrong often*" (Hill 1965 [P. 167]).

Charles Melville (1863–1943, Scotland) was the British expert on the physiology of the route and forced marches during the Krogh-Hill epoch (Melville 1910, 1916); his German counterpart was Nathan Zuntz (Zuntz and Schumburg 1901). Melville attempted to analyse fluid losses and replacement during marching, and, for a typical soldier (male 68 kg), whom he presumed would be 67% water (45 kg; total body water for lean males is ~ 650 $mL.kg^{-1}$; Maw et al. 1996, Australia), he predicted that a fluid loss of 4.5 kg (10% of body water) could be tolerated without the risk of death. Almost a century later, the World Health Organisation (2005) classified that level of hypohydration as "*Severe dehydration*" (P. 7). Melville (1916) also believed that a 3.4-kg (5%) loss should neither reduce work efficiency nor induce intolerable suffering in well-trained soldiers, while a loss of only 1.1 kg (1.6%) would have similar effects in poorly trained individuals (Melville 1916). The possibility that hypohydration might compromise physical performance is taken up again in "Does hypohydration compromise exercise performance?".

Based on the estimated energy cost for a loaded soldier during a forced march, Melville estimated that it would require sweat to evaporate on the skin at a rate of 118 $mL.km^{-1}$ to dissipate that metabolic heat. So even a poorly trained man should be able to march 11 km (50% of the daily marching distance) without a significant loss of work efficiency (body-mass loss: 1.2 kg). Accordingly, Melville recommended drinking a little less than "*a pint at the half-way halt*" (11 km; Melville 1916 [P. 67]), which would also suffice for the next 11 km. For longer marches, he insisted that soldiers drank every hour and on command. Presumably, he ignored both the presence or absence of thirst: *"no man should be allowed to use his water-bottle without orders, any more than he is allowed to fire a round*

of ammunition without orders" (Melville 1916 [P. 70]). He also advised against drinking larger amounts, because excess water "*merely passes through the kidneys, without doing the body much permanent good*" (Melville 1916 [P. 70]).

Melville did not address water loss in the heat, but Edward Adolph did (Adolph 1921). He established the Rochester Desert Unit (U.S.A.; Blatteis and Schneider 2022) from which arose numerous contributions to our understanding of exercise in the heat (Adolph 1947a). Since sweat is hypotonic with respect to blood (Hunt 1912), heavy sweating leaves the remaining body fluids hypertonic, so Adolph expected renal chloride loss to increase, but he actually found that it decreased (Adolph 1921).

In an experiment in which one of Haldane's students "*refrained from bathing for 1 week*" (he truly was English; Hancock et al. 1929 [P. 45]), and then sweated in a chamber with air saturated at 33.3 °C, sweat chloride concentration increased with sweat rate, which they attributed to sweat-gland fatigue. We now know that electrolyte reabsorption within the sweat duct is inversely related to flow (Dill et al. 1938; Kuno 1956; Sato and Dobson 1970). Hancock et al. (1929) also found that the chloride concentration in urine decreased, as would be expected from reductions in splanchnic blood flow (MacKeith et al. 1923; Rowell 1973, 1974; Rowell et al. 1968).

Adolph made two other announcements that are relevant to an ongoing debate. Firstly, he said that hypohydration induced by sweating had no consequences for body temperature: "*In dehydration I have not found a poorer regulation of temperature than in plethora; the limits to the body's use of water for regulating temperature were not reached*" (Adolph 1921 [P. 126]). He conceded that he may not have dehydrated his participants enough to affect body temperature, and subsequently changed his view when he, and others from his group, found evidence linking an elevation in rectal temperature to hypohydration (Adolph 1947e; Brown 1947c; Rothstein and Towbin 1947). Secondly, he said that hypohydration did not reduce sweat rates in standardised conditions. As we shall see, it may or may not. Like most others of the time, Adolph worked on the assumption that the water in sweat came from the blood, at least initially. Of course, body water, as well as its location within the body-fluid compartments, urine and sweat, is an entirely passive molecule that obeys changes in osmotic pressure (Starling 1896). Contrary to Adolph's second statement, William Marriott (U.S.A.) wrote: "*When the blood and tissues become concentrated by water loss the amount of water available for evaporation is diminished and ultimately becomes less than that required for removal of the heat of metabolism. Fever then occurs.*" (Marriott 1923 [P. 286–287]). He considered evaporative cooling to be compromised by reduced body water, but since the total body water of a lean, 70-kg individual would be ~ 45 L (Maw et al. 1996), we have a large, accessible water volume.

Nevertheless, body-water loss and the accompanying increase in plasma (serum) osmolality result in the sensation of thirst. Walter B. Cannon (1871–1945, U.S.A) confirmed that thirst was not a sensation of local origin: "*the thirsty man does not complain of these general conditions. He is tormented by a parched and burning throat, and any explanation of the physiological mechanism for maintaining the water content of the body must take into account this prominent fact*" (Cannon 1918 [P. 293]). He attributed the parched sensation to the paucity of saliva, which was confirmed by Rowntree (1922), in his translation of a statement by Schiff and Levier (1867, Germany): "*the feeling of dryness in the mouth, although it accompanies thirst, has only the value of a secondary phenomenon, and bears no deeper relation to the general sensation than the heaviness of the eyes bears to the general sensation of sleepiness*" (Rowntree 1922 [P. 126]). Whether thirst could be trusted to maintain water balance, or whether that maintenance required coercion, of which Melville was convinced, was not debated in the Krogh-Hill epoch, but it certainly has been in the modern epoch.

With the exception of a few planned experiments, attention to thermoregulation during exercise in the heat had largely been devoted to men at work, sometimes in industry, but mostly in the military. In their analysis, Mavrogordato and Pirow remarked that the deep-body temperatures observed in miners were the same as those "*found in athletes during violent exercise on the surface*" (Mavrogordato and Pirow 1927 [P. 111]). They seem to have possessed information that was not generally available, presumably because research on thermoregulation during exercise was almost devoid of experiments conducted during recreational exercise. After a brief period of intense interest in thermoregulation during the Boston Marathon, interest waned (Maron and Horvath 1978). However, there was one significant paper in which the poor physical condition of runners at the end of that marathon was attributed to hypoglycaemia, rather than to heat strain (Levine et al. 1924), and we shall return to that paper in "Fuelling the fires: the competition for blood glucose".

Epoch three and a touch of politics for exercising in the heat

Let us advance our journey whilst looking back at the observations and interpretations that have been supported over time. We will linger at several mileposts along the way at which our understanding of thermoregulation during exercise in the heat was advanced substantially, but readers are also directed to Rowell (1974, 1993), Gisolfi and Wenger (1984), Montain et al. (1994), Hales et al. (1996), Sawka et al. (1996, 2011), Taylor et al. (2008c), Crandall and

González-Alonso (2010), González-Alonso (2012), Johnson et al. (2014), Nybo et al. (2014), Taylor (2019) and Cramer et al. (2022). Because some topics have no counterpart in the Krogh-Hill epoch, we will not address some prominent features of the contemporary landscape, such as thermoregulation during exercise in the aged (Hellon and Lind 1956; Dill and Consolazio 1962; Kenney 1997; Inoue et al. 1999b; Meade et al. 2019) and in children (Rowland 2008; Notley et al. 2020a, b), thermoregulation during anaerobic exercise (Cheuvront et al. 2006; Zhao et al. 2013), sex (gender) differences (Kenney and Anderson 1988; Gagnon and Kenny 2012; Notley et al. 2017) and differences due to ancestry (Samueloff 1987; Taylor 2006a, 2014; Lambert et al. 2008; Muia et al. 2020). Another view of this journey can be found in Schneider and Moseley (2014).

Body temperature elevation during exercise in the heat is physiological and essential

The very clear message from some of the most accomplished researchers across our three epochs (e.g., Marcus Pembrey, John Haldane, Erik Christensen [1904–1996, Denmark] and Marius Nielsen), was that exercise could elevate body temperatures independently of the ambient heat load. That message was not accepted universally at the time. Those who opposed the view did so not because they had contrary data, but on theoretical grounds and a partial understanding of thermoregulation. If body temperature is regulated, then surely it would be regulated during exercise too? Thus, body-temperature deviations would be opposed and overcome by heat-loss thermoeffectors, and then restored or maintained at its basal level. That view is still held today by some (e.g., Ramsay and Woods 2014).

Researchers of the Krogh-Hill epoch had no concept of either control theory or negative-feedback control. They did not know what the stimulus was for the excitation of sweating or cutaneous vasodilatation, and some even denied that the nervous system was involved. Though some had the necessary data, nowhere in the papers cited thus far does one find the development of a clear linkage between deep-body temperature and a heat-loss mechanism. That was provided by Cyril H. Wyndham (Fig. 5; Wyndham 1967) from South Africa (1916–1987; Anonymous 1987; Wolstenholme 1987; Mitchell and Laburn 2022).

Figure 5 represents an important milepost along our journey, and it showed that feedback from the deep-body thermoreceptors alone seemed to drive sweating. As we established within our first communication (Notley et al. 2023a), that interpretation is no longer considered valid, although it could be derived from those data because, in all trials, the participants had approximately the same skin temperature (~ 35.0 °C; Notley et al. 2023a [Figure 13]), so feedback from the peripheral thermoreceptors would have remained

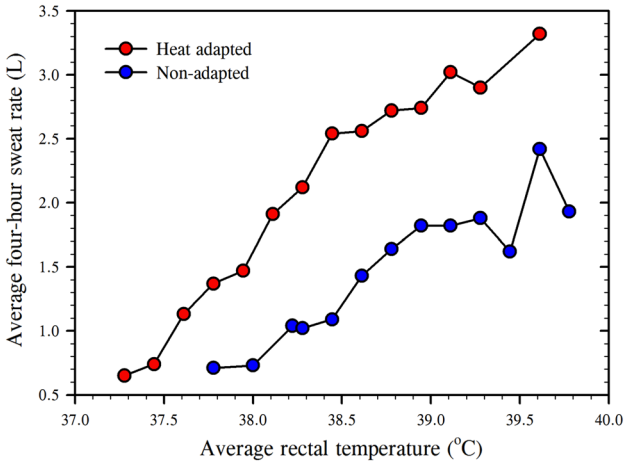


Fig. 5 Sweat rates for exercising men in saturated conditions (box stepping) plotted as a function of deep-body (rectal) temperatures. Data points are four-hour averages, with sweat rates grouped in class intervals (0.3 °F) of rectal temperature, obtained from 13 heat adapted and 353 non-adapted miners of African ancestry. Data were collected across 45 different combinations of wet-bulb temperature, wind speed and work rate, with 465 data pairs for the adapted miners and 262 data pairs for those who were not heat adapted. Drawn using data extracted from Wyndham (1967 [Table 2])

stable. Today, we know that feedback comes from thermoreceptors distributed throughout the body (Werner 1980, 2010; Jessen 1996; Werner et al. 2008). But the principle stands. Elevations of body temperature during exercise are essential, because those changes excite the thermoreceptors that provide the feedback needed to recruit, and then maintain, the activity of our heat-loss mechanisms. Under the constant load of an elevated metabolic-heat production during exercise, sustained body-heat balance is possible only if the appropriate temperature deviation is also sustained. Without that feedback, our thermoeffectors are turned off, and heat loss becomes wholly dependent upon passive exchanges. In addition to demonstrating that relationship (Fig. 5), it is clear that heat-adapted individuals were sweating more profusely at the same deep-body temperature, and we return to that topic in Part 4 of this historical series.

Bardswell and Chapman (1911) drew our attention to the fact that, after some time at each walking speed, rectal temperatures would stabilise at levels determined by walking speed (Fig. 4). That intensity dependence was made famous by August Krogh's assistant, Marius Nielsen (1938; cycle ergometry; Notley et al. 2023a [Figure 23]). With Erling Asmussen, Nielsen later reported that, at the same external work rate (cycling), both rectal and gastrointestinal temperatures were lower, when work was performed using the arms, than with the legs (Asmussen and Nielsen, 1947). That contrasted with evidence reported by Erik Christensen (1931; Notley et al. 2023b), from the same institute. Bodil Nielsen (1968), also from

that institute, replicated the observation of Asmussen and Nielsen (1947), but now using oesophageal temperature. However, the interpretations of those more recent studies were domesticated by Sawka et al. (1984c). He also measured both rectal and oesophageal temperatures and found that the deep-body thermal responses were not exercise-mode specific, but work-rate dependent. Curiously, none of those papers cited Christensen (1931). Sawka et al. (1984c) attributed those different observations to underpowered experimental designs, not achieving physiological steady states, difficulty using the arm-crank ergometer, or some combination of those factors. One can imagine some interesting conversations in the family home since Bodil Nielsen is Asmussen's daughter.

As noted by Notley et al. (2023a), Marius Nielsen is also credited with the claim that the deep-body (rectal) temperatures reached during steady-state exercise were not influenced significantly by the dry-bulb temperature. However, dry-bulb temperatures were varied only between 8 and 29 °C (Nielsen 1938), and in a companion investigation, only three temperatures were used: 5, 20 and 30 °C (Nielsen and Nielsen 1962). From those investigations, arose the belief that deep-body temperature would be independent of air temperatures from 5 to 30 °C (Nielsen Johannsen 2022). But is the deep-body temperature during exercise in the heat truly independent of the ambient thermal load?

Credit for revealing the fallacy of that independence is generally given to Alexander Lind (1925–1990, U.S.A.; Blatteis and Schneider 2022). Lind was then working in England, and by extending the ambient conditions above those imposed by the Danish duo, he established a region of ambient conditions, which he called the *prescriptive zone*, in which the rectal temperature of just three individuals seemed to be independent of the ambient heat load. Above that zone, deep-body (rectal) temperature rose above the level expected for the metabolic-heat production; a very important observation, but was it original? We must also consider the possibility that those data may not have reflected true thermal steady states, since those trials lasted just 60 min, and we know that rectal temperatures can take longer to stabilise (Notley et al. 2023b). One of the earliest observations that demonstrated that reality was provided by Withington (1895), who recorded deep-body temperatures prior to, and for some time after, death due to heat stroke: "… *the thermometer continued to show per rectum, at five-minute intervals for fifteen minutes after death, the same temperature of 107*° [41.7 °C]" (P. 514).

To address both the originality and the methodological (steady-state) limitation, we must travel 13,000 km to Johannesburg (South Africa), and set our next milepost. A decade before Lind (1963), Cyril Wyndham and his team reported the same phenomenon, but now in miners working in the heat (Fig. 6; Wyndham et al. 1953 [4 h, $N = 13$]). At lower ambient heat loads, deep-body temperatures stabilised, after about 60 min, at levels that depended upon the work rate, and were not significantly influenced by the ambient heat load. At higher heat loads, those temperatures either stabilised at a higher level, or did not stabilise at all, but became dependent upon the ambient heat load.

Wyndham's paper was not published in an easily accessible journal. However, we are obliged to seek out and familiarise ourselves with all possible resources. Notwithstanding, the principal conclusion from both groups remains unchallenged. Deep-body temperature is stable and elevated during exercise for physiological, not pathological reasons. The level of that temperature is a function of metabolic heat production, and is dependent upon the physics of heat transfer and the constraints of negative-feedback control.

Curiously, Lind and Wyndham knew each other quite well, and they even worked together (U.K. Climatic and Working Efficiency Unit; Milton 2022), yet, whilst Lind cited Wyndham's paper, he confused the author sequence, misspelt one author's name and underplayed its outcome. That led to tension between Lind and Wyndham (Mitchell and Laburn 2022). Opportunities to conduct experiments similar to those led by Wyndham were only possible because they were funded by a mining company. The company itself was perhaps not so interested in basic science, but in how the acquired knowledge might be applied to reduce work-related heat illness and to simultaneously increase productivity.

Clinically relevant deep-body and skin temperatures

Although Wunderlich reported that the "*highest temperature yet met in a living man, noted by a trustworthy observer, amounted to 112.55 °F (= 44.76 °C)*" (Wunderlich 1871 [P. 2]), we will soon describe still higher temperatures from both the Krogh-Hill (Tigerstedt 1906; 46 °C [possibly malaria]) and modern epochs (Hart et al. 1982; 47.0 °C [classical heat stroke]). Wunderlich (1871) classified deep-body temperatures from 38.5° to 39.0 °C as states of moderate fever, > 39.5 °C in the morning as high fever and those > 42.0 °C as probably being fatal. Contemporary clinical classifications provide us with broad classifications of deep-body temperatures for use with the general population, which might then be used to determine treatment strategies: > 40 °C (profound clinical hyperthermia), > 39.5 °C (profound hyperthermia), 38.5°–39.5 °C (moderate hyperthermia), 37.2°–38.5 °C (mild hyperthermia) and 36.5°–37.0 °C (normothermia; Taylor et al. 2008c). From an occupational perspective, deep-body temperatures of 38.0°–38.5 °C are widely accepted as an upper limit for worker health and safety (Jacklitsch et al. 2016), although such thresholds appear to be directed at preventing not only heat stroke, but also less-severe heat illnesses (e.g., syncope, heat exhaustion) in nearly all workers (Malchaire

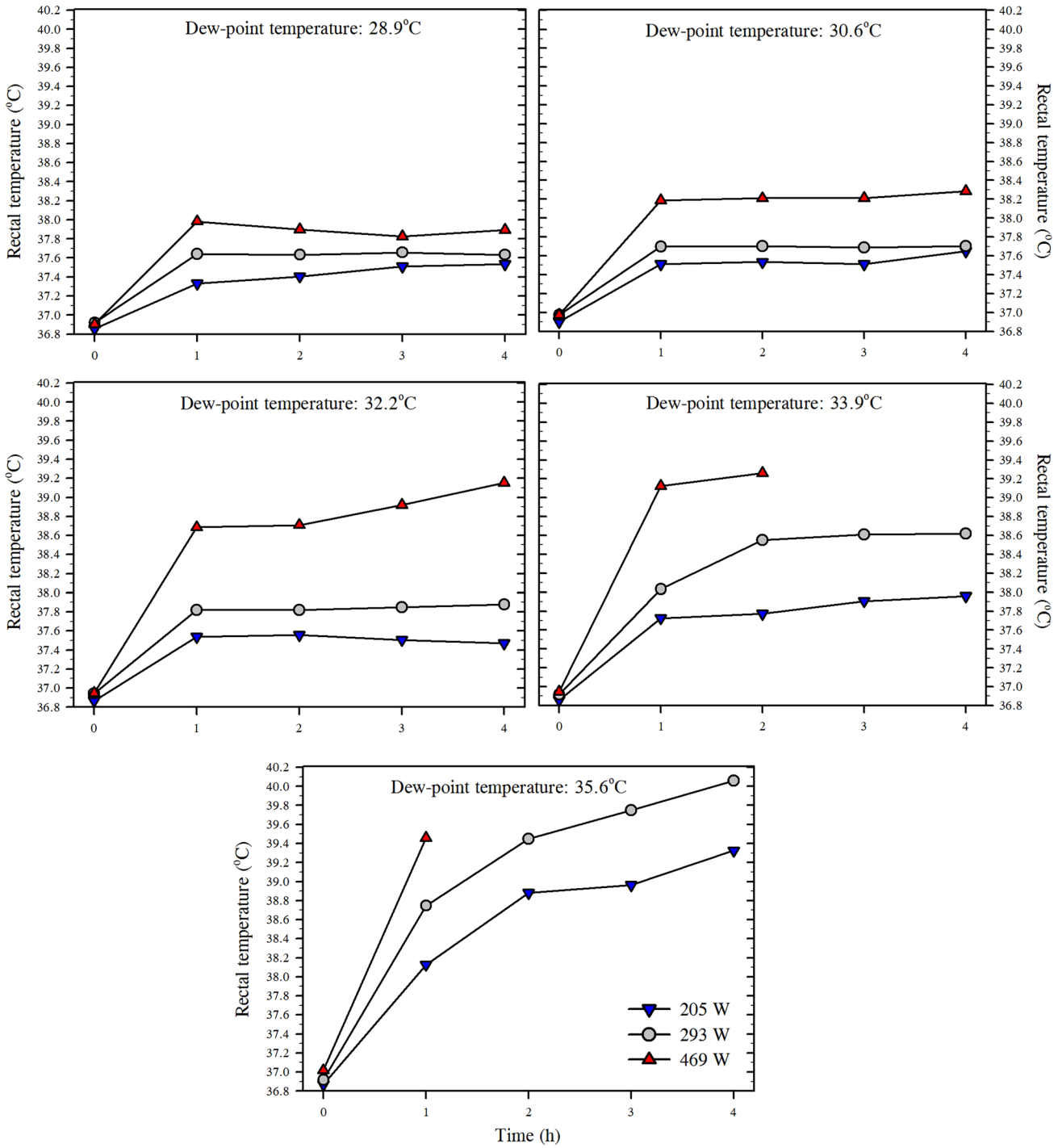


Fig. 6 Deep-body (rectal) temperatures of 13 heat-adapted miners across four hours of exercise (box stepping in an underground climatic chamber) at each of three work rates, across five different dew-point temperatures (saturated air) and with a wind speed of 0.77 m. s^{-1}. Redrawn from Wyndham et al. (1953)

et al. 2000). To achieve the same objective, some have indicated that threshold may be even lower (e.g., 37.5 °C; Sawka et al. 2001a), which would be inappropriately restrictive. Furthermore, we would expect most competitive marathon runners to have deep-body temperatures > 40 °C at the end of their races, but without *sequelae* ("Exertional heat stroke in sport"). This raises a larger issue as to whether deep-body temperature should even be the variable of primary interest when setting limits to mitigate injury risks in occupational athletes, although we are currently without a suitable

alternative. For clinically relevant skin temperatures, we have the following general classifications: > 50 °C (second-degree), > 45 °C (tissue damage), 41°–43 °C (burning pain), 39°–41 °C (pain) and 33°–39 °C (warm to uncomfortably hot; Taylor et al. 2008c).

Practice improves thermoregulation during exercise in the heat

When Marcus Pembrey recommended "*training on hot as well as on cold days*" (Pembrey 1902 [P. 269]), as a way of improving the resistance of soldiers to heat stroke, he did so by intuition. He had no knowledge of the physiology of thermal adaptation. Does physiological adaptation to exercise in the heat require training in the heat, or can it be achieved by passive heat exposure? Does training on cold days have any benefit for our capacity to exercise in the heat without harm? These and other questions concerning natural and artificially induced adaptations to both heat and cold are addressed in Part 4 of this review series.

Warmed to the work

Our sub-title is taken from the catchphrase that Marcus Pembrey (Cook and Pembrey 1913) used to encapsulate his view that the elevation of deep-body temperature during exercise was beneficial physiologically. It would have been evident that an upper limit to that elevation should exist, because excessive elevations caused heat illness. Pembrey believed that, between those limits, either the capacity for exercise or the efficiency of exercise would be enhanced by increasing (warming) body temperatures.

Archibald Hill received a Nobel Prize in 1922 for his discoveries that contracting muscle converted chemical energy into work and heat. At the most fundamental level, we must ask how skeletal muscle activation might be affected by muscle temperature. Whilst we know more about the relationship between muscle function and muscle temperature within poikilotherms (Bennett 1985; James 2013; James and Tallis 2019), it seems that the temperature dependence of in situ muscle activation in homeotherms, and especially the static properties of muscle, is quite weak (Racinais et al. 2019a). We do know that muscle tension tends to be maximal at resting muscle temperatures and declines a little at higher temperatures (Rall and Woledge 1990). Circulating water at 44 °C around the forearm appeared to make no difference to the isometric force developed by the forearm muscles (Mallette et al. 2019), although changes in muscle temperature were not actually measured. Rates of muscle activation and relaxation, and consequently the development of maximal power output, are more dependent on muscle temperature and are accelerated at higher temperatures (Bennett 1984). The temperature of resting muscle usually is a few degrees below rectal or oesophageal temperature (Booth et al. 2004), and resistance to fatigue is better at that temperature than at higher temperatures (Malak 2020). So Pembrey may have been disappointed if he had known how little being "*warmed to the work*" affected the contractile machinery of skeletal muscle.

Of course, there is far more to musculoskeletal performance during exercise in the heat than how the muscle fibres respond to being warm. The turnover of oxygen and nutrients could be influenced by temperature, as could energy delivery and the removal of metabolic wastes. Muscular activity requires activation of the motor nerves, which also could be influenced by temperature. Coordinated exercise also requires optimal cognitive function, particularly during teams sports, which could be affected by body temperature (Schmit et al. 2017; van den Heuvel et al. 2017). According to Cook and Pembrey (1913), the nett outcome of those temperature dependencies would be improved performance. That view was shared by Asmussen and Bøje (1945), who showed that the performance of a 100-m sprint (cycling) and a 1500-m run were improved when the body was warmed, either by prior exercise or by diathermy. They associated that improvement with elevated muscle temperature, which approached 39 °C (Asmussen and Bøje 1945). If muscle temperatures had exceeded 39 °C, they might have come to the opposite conclusion.

In the same Danish laboratory, Bengt Saltin (1935–2014; originally from Sweden; Nielsen Johannsen 2022) and colleagues asked subjects to cycle to exhaustion at work rates of 90%, 100% and 115% of peak aerobic power, but in different air temperatures, with and without pre-heating (Saltin et al. 1972). The higher the external heat load, the sooner the subjects stopped work, and always at leg-muscle temperatures of 39°–40 °C, irrespective of workload, work time and ambient temperature. D. Bruce Dill (1891–1988, U.S.A.; Blatteis and Schneider 2022) had previously encountered premature exhaustion during exercise in the heat, and attributed it to the heart reaching its pumping capacity (Dill et al. 1931). If that limit resulted in blood pressure regulation being compromised, then participants might well have terminated exercise due to uncompensable hypotension (cardiovascular insufficiency; Barcroft and Edholm, 1945; Bass 1963; Krediet et al. 2004), possibly accompanied by pre-syncopal episodes (Wilson et al. 2006) and even incapacitation (Noakes 2008a; Epstein and Yanovich 2019). In the workplace, miners shovelling rock under thermally stressful conditions reduced their performance as ambient conditions became more stressful (Strydom et al. 1963). So being "*warmed to the work*" was not necessarily beneficial. On the contrary, being too warm can compromise performance, and it is well established that marathon race times increase, particularly within sub-elite runners, with greater external thermal loads (Ely et al. 2007a, b).

Over time, a pattern emerged concerning exercise performance and body warming, which Marcus Pembrey would have supported. Firstly, warming up can improve exercise performance (Asmussen and Bøje 1945; McGowan et al. 2015), although the benefits are often hard to demonstrate, and they may involve injury prevention (Maughan and Shirreffs 2004). When warming up is beneficial, those changes are mainly related to increased body temperature, but they may be quite small; a 1 °C increase in exercising muscle temperature enhanced subsequent performance by 2–5% (McGowan et al. 2015). However, at the level of elite sport, such marginal benefits may be crucial, especially in explosive events. In a cool environment, cyclists achieved higher peak power in an ergometer sprint test if their leg muscles were prevented from cooling between their warm-up and the actual event (Faulkner et al. 2013). That benefit has to be traded off in hot weather, especially in humid conditions, because elevated body temperatures can compromise performance (McGowan et al. 2015). In hot weather, warm-up practices should be tailored so as not to raise body temperatures markedly (Maughan and Shirreffs 2004).

One potential way of preparing for endurance exercise without inducing a body temperature elevation would be to cool the body artificially before exercising in the heat. Such pre-cooling has attracted considerable attention, as has per-cooling; artificial cooling during exercise itself. Neither concept is new, and they come from applied physiologists seeking to reduce thermal strain in the workplace. For instance, water-cooled garments were used in hot industries in the 1960s, and soon replaced ineffective gas-cooled garments designed for the pre-flight cooling of astronauts (Nunneley 1970). Water-cooled garments can reduce thermal strain in workers wearing impermeable protective clothing (Tokizawa et al. 2020; Ryan et al. 2023) or costumes (Wang et al. 2019). It was also known that, when working (300 W) in hot-humid conditions, an ice vest could reduce deep-body (rectal) temperature and sweat rates to levels observed in thermoneutral environments (van Rensburg et al. 1972; Strydom et al. 1975).

David Costill (1936-present, U.S.A.) and his colleagues suggested the benefits of pre-cooling were so transient that it was unlikely to have any thermoregulatory benefits for endurance exercise (Bolster et al. 1999). Irrespective of the degree of pre-cooling, athletes tend to feel hot after ~ 15 min of intense exercise (Gibson et al. 2020). Moreover, when cycling in the heat (35 °C dry bulb) following pre-cooling, pre-heating and normothermic treatments (water immersion), which elicited a difference of ~ 7 °C in *vastus lateralis* temperature, those muscle temperatures "*climbed towards a common asymptote, with pre-cooling offering no thermal protection beyond 40 min*" (Booth et al. 2004 [P. 709], Australia). A similar pattern was evident for deep-body temperatures, so in accordance with Fourier's heat-conduction equation, the observations of Bolster et al. (1999) and Booth et al. (2004) were obeying physics. That compliance does not exclude the important interactions of other physical characteristics (e.g., body shape, dimensions, density, thermal conductivity, specific heat capacity) and physiological responses (e.g., thermoeffector activity, redistribution of the cardiac output, exercise-related changes in convective heat exchanges).

The practicalities of pre-cooling and per-cooling are discussed elsewhere (Flouris and Cheung 2006; Xu et al. 2021; Yang et al. 2021; Sajjad et al. 2022), and are not a central interest here. Nor is external cooling the only way to achieve deep-body cooling (Berg et al. 1966; Nadel and Horvath 1969; Lee et al. 2015; Burdon et al. 2013; Zimmermann et al. 2017; Gibson et al. 2020; Alhadad et al. 2021). In the current context, we are concerned with whether or not those cooling strategies might prove beneficial by reducing thermoregulatory strain during exercise in the heat, and there are papers that would appear to support that possibility. Cooling just the neck, which often has no effect on deep-body temperature, seemed that it might be beneficial across a range of sporting events (Cao et al. 2022). The application of 4% menthol to the skin (torso), which activates the peripheral cold receptors chemically, seems to exert some ergogenic affect (Hermand et al. 2020), presumably by bluffing the body that it was being cooled.

Now for a grain of salt! Across many applied studies, we see limitations that can influence how one interprets observations. From a methodological perspective, we must examine whether or not each measurement, as applied in the investigation, provided a valid and reliable index of the dependent variable of interest (e.g., neuromuscular function, cognitive function, work or athletic performance). From a thermal perspective, we must ask: how was deep-body temperature measured, what was the time delay of that measurement, was that delay considered in the experimental design and how were the results interpreted? Was the experiment well designed to test the working hypotheses?

The negative impact on physical performance from ambient and body temperatures that are too high far exceeds the potential benefits of warming up. Ambient heat tends not to compromise short-duration exercise (Maughan and Shirreffs 2004), but not because there is insufficient time for the deep-body temperature to rise. For example, pre-heating does not affect performance in 3-min, all-out cycling efforts (Kaiser et al. 2021), but it seems to affect performance during exercise lasting 15 min (Ely et al. 2010). To put that time into context, the men's Olympic record for 5000 m (running) is slightly < 13 min. For exercise of that duration and longer, there is ample evidence that heat strain can, and does, reduce endurance performance (MacDougall et al. 1974; Galloway and Maughan 1997; Tatterson et al. 2000), as well as peak aerobic power (Klausen et al. 1967; Rowell et al. 1969b; Pirnay et al. 1970; Sawka et al. 1985a; Nybo et al. 2001;

Arngrímsson et al. 2004). In the most recent of those studies, Sigurbjörn Arngrímsson (Iceland), along with American colleagues, described equivalent, stepwise reductions in the peak aerobic power of their participants with increasing dry-bulb temperatures (50% relative humidity): − 4% at 35°, − 9% at 40° and − 18% at 45 °C (Arngrímsson et al. 2004). Hypohydration, on the other hand, appears not to exert a similarly adverse influence on either steady-state exercise (Sawka et al. 1985a; González-Alonso et al. 1997; Tan et al. 2021) or peak aerobic power (Nybo et al. 2001; Cheuvront and Kenefick 2014; Pethick et al. 2019).

The question of interest is whether or not high deep-body temperatures compromise exercise performance centrally. That was certainly the view of Christensen (1931), with that theory reinforced by other Danish thermal physiologists (Nielsen et al. 1993; González-Alonso et al. 1999; Nybo et al. 2002b, 2014; Nybo 2012). That hypothesis did not withstand the tests of time (González-Alonso et al. 2008; Ely et al. 2009), and is covered in detail in Notley et al. (2023b). It seems likely that neither a single central nor a peripheral factor can account for fatigue during exercise in the heat (Cheung and Sleivert, 2004; Todd et al. 2005), although that interpretation is not without dissenters (Marino 2004; Lee et al. 2010; Schlader et al. 2011).

Ely and colleagues (2010, U.S.A.) used a pre-trial warm-up (30 min, 50% peak aerobic power) prior to subjects performing 15 min of self-paced, maximal cycling (21 and 40 °C dry bulb). Whilst deep-body (rectal) temperatures were recorded, the time delay of that index is equal to, if not longer than, the exercise duration, so those temperatures are uninterpretable. However, participants completed 17% less work in the hotter condition, so what was their exercise impediment? There are many physiological ways that excessive heat storage could reduce peak aerobic power, and we agree with the multi-factorial nature of exercise intolerance in the heat, for which we believe that cardiovascular insufficiency and blood pressure regulation provide a viable explanation for terminating exercise in many circumstances (Barcroft and Edholm, 1945; Bass 1963; Krediet et al. 2004)?

Could elevations in skin temperature impose an exercise-tolerance limit? Part of that explanation may include the diversion of blood flow to the skin, and away from the skeletal muscles, the brain and the heart, by the thermoregulatory system (Ely et al. 2010). Skin hyperthermia would divert blood flow to the skin, but that might only be problematic if the cardiac reserve, or the redistribution of the available cardiac output, were insufficient to accommodate that diversion. In more recent work on this topic, Trangmar et al. (2017, England) designed a study from which it appears they were able to separate the effects of skin hyperthermia from those of combined skin and deep-body hyperthermia. They found that skin hyperthermia alone did not reduce peak aerobic power. However, it was reduced when both skin and deep-body temperatures were elevated, and was associated with a reduction in mean arterial pressure, decreased blood flow to the exercising muscles and less blood flowing through the middle cerebral artery (an index of brain perfusion).

During heat exposure, higher skin temperatures buffer against external heat gains and simultaneously increase cutaneous water-vapour pressure, which, if the ambient vapour pressure remains constant, will increase evaporative cooling. Whilst those responses are protective, elevated skin temperatures reduce the thermal gradient between the deep-body and cutaneous tissues and, as a consequence, the flow-specific transfer of heat from the deeper tissues to the skin surface is reduced. To counteract that, cutaneous blood flow must increase, and it does (Wyss et al. 1974; Taylor et al. 1984; Pérgola et al. 1993; Shibasaki et al. 2005; Johnson et al. 2014). However, a reduction of that thermal gradient to values close to, or below, 1 °C was thought to limit exercise tolerance in the heat, with that hypothesis being put forward > 50 years ago (Iampietro and Goldman 1965).

It is reasonable to suggest that, over those years, the main protagonists of that gradient hypothesis were U.S. physiologists: Pat Iampietro, Ralph Goldman, Kent Pandolf, Michael Sawka, Samuel Cheuvront and Robert Kenefick. Some of their stories have been told by Blatteis and Schneider (2022). Following a series of experiments (Iampietro and Goldman 1965; Iampietro 1971; Pandolf and Goldman 1978), that group arrived at, and presented their thermal-convergence hypothesis. It has not been unequivocally supported, although it might be more applicable to high deep-body temperatures (Nunneley et al. 1992; Trangmar et al. 2017), and it might be of greater relevance to occupational scenarios that involve protective clothing (McLellan et al. 2013).

In their latest contribution, Sawka et al. (2012) used theoretical data from Rowell (1986) to show that, at stable, but elevated deep-body temperatures (38° and 39 °C), the cutaneous blood flow of exercising individuals would increase almost two-fold for a 2 °C elevation in skin temperature. Thus, that local effect might counteract a reduction in the core-periphery thermal gradient. Those theoretical data led to the conclusion that, at the same skin temperature, an elevation in deep-body temperature appeared to reduce the predicted cutaneous blood flow, from which they concluded that it was the high skin temperature, rather than a high deep-body temperature, that impaired performance (Sawka et al. 2012).

Most recently, however, Caldwell et al. (2014, 2016; Australia) measured the cutaneous blood flows of resting participants who were thermally clamped at a deep-body temperature of ~ 38.5 °C, whilst local skin-temperature treatments that covered a 35 °C range (5°–40 °C) were applied to four limb segments. Under such conditions, the requirement

for blood flow to the skeletal muscles was minimal, so one would have expected a near-maximal cutaneous vascular response, yet, when averaged across the forearm, hand, calf and foot, cutaneous blood flow increased slightly less than three-fold over that 35 °C range. It is hard to imagine that during exercise, with a parallel demand for blood to the active muscles, a 2 °C elevation in skin temperature might elicit a two-fold increase in the cutaneous vascular response (Sawka et al. 2012). A resolution to that dilemma requires experimental, and not theoretical data.

Cutaneous vasomotor activity during heat exposure

Activation of the autonomic thermoeffectors, following changes in body temperature, occurs in the form of a recruitment cascade (Taylor and Gordon 2019; Notley et al. 2023a; [Figs. 21 and 22]). That sequence usually commences with changes in vasomotor activity, regardless of whether one is heated or cooled, although it has long been known that sweating sometimes can precede vasodilatation (Grant and Holling 1938). Since the thermoeffectors are also influenced by exercise-dependent, non-thermal feedforward (Notley et al. 2023a [Fig. 20]), we first need to understand how the effectors are controlled in resting individuals, as those non-thermal influences can mask the thermally mediated sequence of effector activation.

We emerged from the Krogh-Hill epoch with a relatively poor understanding of cutaneous vasomotor control during exercise in the heat. As noted above, one reason was that the researchers tended not to measure vasomotor function, but drew conclusions about that activity from surrogate indices (e.g., skin temperature). Even in unclothed, normothermic individuals resting at a comfortable air temperature, there is a wide distribution of skin temperatures (Fig. 7), which can span > 15 °C during cold-air exposures (Benedict and Slack 1911; Lefèvre 1911; Burton 1935; Aschoff and Wever 1958; Werner and Reents 1980; Webb 1992). It is clear from Fig. 7 just how fraught with difficulties was the drawing of inferences about vasomotor activity from skin temperature. Even at dry-bulb temperatures as high as 30 °C, skin temperatures can vary by ~ 5 °C. Before the Krogh-Hill epoch, it was known that peripheral vasomotor activity was controlled by the sympathetic nerves, but it was not until the end of that epoch that the sympathetic control of cutaneous blood vessels was confirmed for humans (Lewis and Pickering 1931). Only very recently has it been confirmed that the nerves that control peripheral blood vessels also carry the neurons that innervate the eccrine sweat glands (Trbovich et al. 2021).

Many of the non-invasive tools with which scientists could measure peripheral vasomotor activity directly were developed within our first epoch (Notley et al. 2023b). Of those methods, the plethysmographic technique of Angelo Mosso (1846–1910, Italy; Mosso 1875, 1878) stood out,

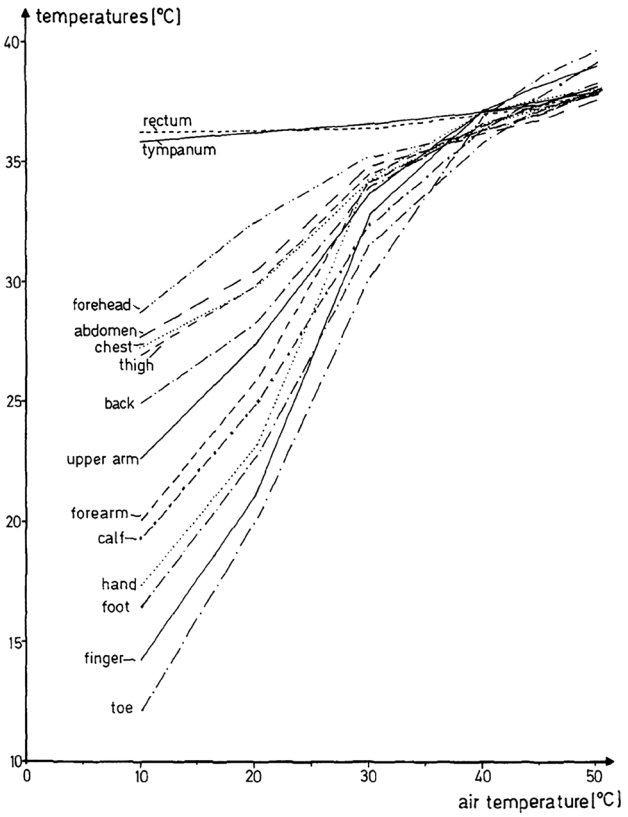


Fig. 7 A topographical distribution of local skin temperatures (uncovered thermocouples) during exposures to each of seven air temperatures (10°, 20°, 30°, 35°, 45° and 50 °C). Subjects were supine and semi-naked ($N = 6$), and were exposed to each condition (90–120 min) after having first reached a thermal steady state in the air at 30 °C. Reproduced from Werner and Reents (1980) and used with permission

with that method being significantly improved during the Krogh-Hill epoch, firstly with the use of venous occlusion to temporarily prevent the return of venous blood from the limb segment of interest (Brodie and Russell 1905). Very soon thereafter came the development of plethysmographic cuffs (Lewis and Grant 1925) and then the mercury-in-rubber strain gauge (Whitney 1949, 1953), which allowed greater movement by the experimental subject, opening the way for measurements to be made during exercise. A further step came in the form of laser-Doppler velocimetry (Nilsson et al. 1980), which enabled the quantification of direction-specific flow (flow velocity), not simply flow.

Despite the improved techniques, acquiring valid data about cutaneous vasomotor activity in exercising humans remained technically challenging, but it has been achieved (e.g., Brengelmann et al. 1977), with the requirement then to separate the thermal- from the exercise-dependent effects adding another layer of complexity. Most would suggest that measurements of peripheral blood flow in the field are still impossible. Accordingly, we have to rely mainly upon that

which has been revealed from laboratory research on resting individuals exposed to heat, applied either to the entire body or to separate limb segments. We do not expect that the way in which the cutaneous blood vessels respond to sympathetic nerve activity would differ between rest and exercise, but there is a caveat, in that it is, as yet, still unclear whether or not the control of cutaneous vasodilatation differs between resting and exercising states (Wong and Hollowed, 2017).

Cutaneous blood flow, particularly that of the hands and feet, is rarely stable (Grant and Pearson 1938; Blair et al. 1961), even when thermally neutral. Instead, local flow variations subtly modify the convective delivery of thermal energy to those segments, and, without heat or cold stress, that might be all that is required to sustain a thermal equilibrium. But those flow variations can produce large artefactual effects during measurements of forearm and leg blood flows when using venous-occlusion plethysmography (Notley et al. 2023b). For that reason, a downstream, supra-systolic occlusion cuff (wrist or ankle) was introduced to remove flow artefacts (Grant and Pearson 1938).

Most of the data upon which we will rely were obtained using venous-occlusion plethysmography to examine the vascular responses of the distal limb segments. It is an implicit assumption of that method that, for resting individuals, thermally induced changes in segmental blood flows are restricted to the cutaneous compartment (Edholm et al. 1956; Roddie et al. 1956; Detry et al. 1972; Johnson et al. 1976a, b). That is not strictly true, although Cooper et al. (1955) observed that cutaneous blood flow, during a vasomotor blockade (adrenaline iontophoresis), was about ten times greater than muscle blood flow when expressed as tissue-specific volume flows. Skin heating, if used to test the sensitivity of the cutaneous blood vessels to local temperature, should not be high enough to induce flow changes within the underlying muscles, although that effect is not very strong (Kunkel et al. 1939). Nevertheless, for those assumptions to apply to exercising individuals, the muscles of the limb segment under examination must remain inactive (Johnson and Rowell 1975), rendering our understanding of muscle blood flow somewhat imprecise (Johnson et al. 2014; Crandall and Wilson 2015). To more fully understand the thermal influences on cutaneous vascular activity, and the mechanistically driven heat loss (or conservation), it is instructive to revisit the anatomical characteristics of the cutaneous vasculature.

An anatomical overview Human skin is often classified as being of either a glabrous (smooth, acral or non-hairy) or a non-glabrous (hairy) form, and those skin types differ in the neural control of their vasculature. By 1948, Alrick B. Hertzman (1898–1991, U.S.A.) and Walter C. Randall (1916–1993, U.S.A.; Blatteis and Schneider 2022) had established that blood flow tended to be higher in glabrous skin (Hertzman and Randall 1948). For both skin types, blood is delivered towards the skin surface through subcutaneous arterioles (within the hypodermis), which feed sequentially into the *rete cutaneum* and the *rete subpapillare* (within the dermis), before forming papillary capillaries that loop up through the papillary layer of the dermis towards, but not into, the epidermis, and then descend back to the subpapillary venous plexus within the dermis (Standring 2008). For details on regional variations in cutaneous capillary densities, readers are directed to Grant and Bland (1931), Lamah et al. (1999), Bukhari et al. (2000), Zhong et al. (2000) and Mørk et al. (2002).

On average, those cutaneous capillaries have internal diameters of ~ 10 µm (Molyneux and Bryden 1981), and it is through their walls that exchanges occur between the blood and the interstitial compartment (Starling 1896). Our interests are centred upon the exchange of thermal energy, which flows down local, transepidermal thermal gradients, firstly between the blood and the epidermal tissues, and then between those tissues and the ambient medium. The direction of heat flow is determined by the ambient temperature, but since the papillary layer of the dermis is not well perfused, then its temperature, as well as that of the overlying epidermal layers, is often more heavily influenced by the ambient temperature, than it is by that of the blood, especially in cold conditions, when cutaneous perfusion is sometimes barely enough to support the local metabolic needs of those tissues (Abramson 1965). Together, those states dictate that papillary blood temperatures rapidly equilibrate with the extravascular tissue temperatures (Conrad 1971; Hales 1985). By introducing thermocouples into the superficial veins and arteries, Henry Bazett showed that the temperatures in those blood vessels varied substantially between the deep-body and peripheral tissues, according to the thermal state of the body, and he drew attention to the "*chaos introduced into physiology by the fictitious assumption of a constant blood temperature*" (Bazett et al. 1948 [P. 19]).

Heat exchanges between blood and the cutaneous tissues are modified, significantly and independently, by the opening and closing of cutaneous arteriovenous anastomoses, found within the dermis (internal diameters 25–125 µm; Hales 1985). Those vessels are vascular shunts that run perpendicular to and connect with, the plexi of the dermal and epidermal arterioles and venules. They were initially described during our first epoch (Sucquet 1862; Hoyer 1877), and are found almost exclusively within the glabrous skin of the hands, feet, ears, lips and nose (Clark 1938; Nagasaka et al. 1987; Walløe, 2016). The most complex and largest of those anastomoses are thought to exist within the volar skin of the hands and feet (Masson 1937; Clark 1938; Abramson 1965), and in the nail beds (Grant and Bland (1931). Heat-induced dilatation of those anastomoses, which occurs both through direct thermal action on those vessels and through

thermally induced changes in sympathetic (vasomotor) tone, shunts blood between the cutaneous arteries and venules, reducing blood flow through the papillary capillaries. Those actions deliver more blood to the deep venous plexus, in which blood flow is much slower, allowing better thermal equilibration between the blood and the surrounding tissues (Midtgåtrd 1980; Nuzzaci et al. 1999). That paradox can be explained using another first principle; *Poiseuille's Law* (1838; Sutera and Skalak 1993). Since those anastomoses have diameters that are about ten-fold larger than the capillaries, then for the same pressure head, a blood flow that is 10,000-fold greater will pass through the anastomoses than through capillaries of the same length (Nelms 1963; Molyneux and Bryden 1981). So, whilst opening the anastomoses keeps blood a little further from the skin surface, it greatly increases how much heat the blood can deliver to the skin.

The veins of the skin are well innervated via sympathetic neurons, and they are very responsive to changes in sympathetic tone (Zimmerman 1966; Webb-Peploe and Shepherd 1968). During pressure-induced dilatation (minimal sympathetic tone), the cutaneous veins have a considerable capacity (Roddie 1983; Rowell 1993). Not surprisingly, the primary role of the cutaneous veins, which are found in the hypodermal and dermal layers, is body temperature regulation, a conclusion that is supported by the consequences of physiological variations in the volume of slowly moving blood within those tissues (Rothe 1983; Rowell, 1983). Indeed, in a resting, normothermic person with an average overall cutaneous blood flow of ~ 350 mL.min^{-1} (Rowell 1974, 1993), and a deep-body-to-skin thermal gradient of 4 °C (37°–33 °C), ~ 83 W of thermal energy can be transferred to the skin for dissipation. That is about equivalent to the resting metabolic heat production. Both the blood flow and size of the thermal gradient change substantially when we deviate from normothermia, thereby modifying the rate at which heat can be transferred to the skin.

Sympathetic vasomotor activity is dictated by the thermoregulatory centres (Werner 1980, 2010; Notley et al. 2023a) in response to input from thermoreceptors distributed throughout the body (Hensel 1973; Jessen 1996), including those within the dermis (Zotterman 1953, 1959; Pierau 1996). That sympathetic control has a powerful influence on vasomotor activity (Barcroft and Edholm 1943; Roddie 1983; Pérgola et al. 1993; Charkoudian 2003; Burdon et al. 2017). For instance, forearm blood flow can be increased simply by heating one leg (Barcroft and Edholm 1946), even if the venous return from that leg is occluded (Kvale and Allen 1939; Kerslake and Cooper 1950). Similarly, hand blood flow can be increased by heating the other hand (Ferris et al. 1947), but it is feedback from the deep-body tissues that is generally regarded as having the most powerful influence on cutaneous vasomotor tone, and for defending body temperature when we not exposed to external heat or cold stresses (Wyss et al. 1974; Proppe et al. 1976; Mercer and Simon 1984; Jessen 1996).

When ambient temperatures change, the cutaneous thermoreceptors, which respond quickly and powerfully to the rate of local temperature change (dynamic activity), increase their contribution to the overall thermal feedback and the control of cutaneous vasomotor activity. However, during physiologically compensable endogenous and exogenous heat stress within sweating individuals, whose unclothed skin surfaces are fully wet, and that sweat is freely evaporating, the rates of convective and conductive thermal energy delivery to the skin surface will be matched by its rate of dissipation. The result of that thermal equilibrium is that the temperature of those skin sites will be stable, and effectively clamped (Notley et al. 2023a [Fig. 13]). In that state, the change in cutaneous receptor activity from those sites can no longer provide significant thermoafferent feedback to the central regulator. That role is now primarily performed by the deep-body thermoreceptors.

At the end of the Krogh-Hill epoch, George W. Pickering (1904–1980, England) believed that the only thermal control of those cutaneous blood vessels emanated from the thermoregulatory centres: "*in man temperature is regulated by a central mechanism which reacts to changes in blood temperature by appropriate vasomotor responses*" (Pickering 1932 [P.128]). McDowall (1935) thought there was an additional local effect of temperature on cutaneous blood flow, but he offered no explanation, though there are many ways that such an effect might occur in the heat. For example, it could modulate the effect of sympathetic fibres on the vessels, induce local neural activity, modulate the effect of circulating vasoactive agents on the vessels or influence blood-vessel walls directly.

Local warming of the skin induces localised vasodilatation, which was once thought to be maximal in normothermic individuals when the skin was heated to 42 °C (Taylor et al. 1984). That theory was domesticated by Caldwell et al. (2014, 2016), who investigated both sympathetically and locally mediated changes in the cutaneous blood flow of the forearm (as per Taylor et al. 1984), hand, leg (calf) and foot of thermally clamped hypothermic, normothermic and hyperthermic participants (Fig. 8). Certainly, the highest segmental blood flows were achieved at a local skin temperature of 40 °C, but across each limb segment, maximal cutaneous vascular conductance (pressure-specific blood flow) could be achieved only if local skin heating was applied during a state of moderate hyperthermia. That truism was applicable to both the non-glabrous and glabrous vascular beds. Indeed, the forearm vascular conductance of a moderately hyperthermic individual, treated with a local skin temperature below 10 °C, was higher than if that person was normothermic and the forearm was heated to 42 °C (Taylor et al. 1984). Those rapid vasomotor responses to locally

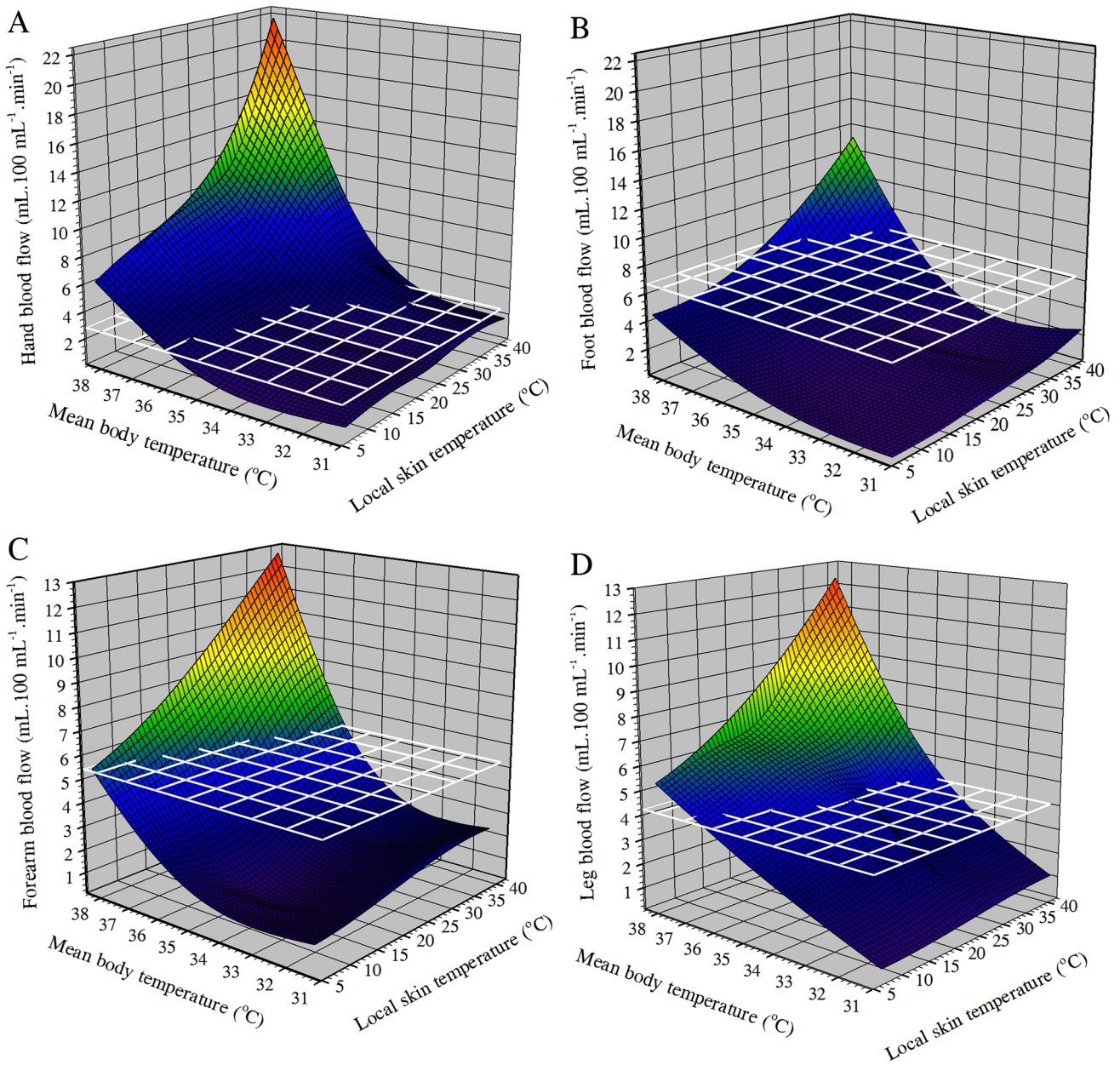


Fig. 8 Three-dimensional surfaces for cutaneous blood flows measured from the hands (**A**), feet (**B**), forearms (**C**) and legs (**D** [calves]) of eight resting participants (semi-nude, supine), during each of three, thermally clamped, whole-body states: mild hypothermia (mean body temperature 31.4 °C), normothermia (control: 36.0 °C) and moderate hyperthermia (38.3 °C). Mean body temperature taken as the weighted sum of oesophageal and area-adjusted skin temperatures, using the deep-body and skin coefficients appropriate for each thermal state (Vallerand et al. 1992). Each state was initially induced using pre-experimental treatments (whole-body water immersion), and then clamped, using both a climate chamber and a water-perfusion garment. Within each condition, five localised thermal treatments were independently applied to the skin of each segment (5°, 15°, 25°, 33°, 40 °C; see Caldwell et al. 2014, 2016 for details). Data are averages for the 15, three-dimensional coordinates with extrapolation used to generate lines between those coordinates. The colour spectra indicate flow graduations (red for highest flows), whilst the transparent (white) planes are thermoneutral (control) blood flows for the same segment on the ipsilateral limb (hand versus foot and forearm versus calf). Reproduced from Caldwell et al. (2014, 2016) and used with permission

applied thermal treatments do not involve neural activity, since the effects are still apparent following the application of a topical anaesthetic (Minson et al. 2001). It seems that dilatation requires the synthesis of the potent, endogenous vasodilator, nitric oxide (Kellogg et al. 1999; Wong and Hollowed 2017). Whilst we do not yet fully understand those mechanisms, a clue might come from patients with Type 2 diabetes. They seem to have a reduced response to local

heating, even if they show no evidence of peripheral neuropathy (Charkoudian 2003).

When whole-body heating is applied, the thermoregulatory centres first release the basal sympathetic tone acting on the cutaneous blood vessels (passive vasodilatation; Bodelsson et al. 1990; Kellogg 2006; Johnson et al. 2014), the skin anastomoses will then dilate and then, at some body sites, there will occur active vasodilatation of the cutaneous vessels (Lewis and Pickering 1931; Greenfield 1963; Johnson et al. 1995). Compared with cold stress, in which there is potent cutaneous vasoconstriction, with the resulting blood flow being as low as 0.8 mL.100 mL^{-1}.min^{-1}, and well below that required to serve the metabolic requirements of the local tissues (Abramson 1965), during profound heat stress, whole-body cutaneous blood flow can reach 7–8 $L.min^{-1}$ (Sundstroem 1927; Rowell et al. 1969a, 1970). Hand blood flow at rest in an uncomfortably warm environment can be about twenty times higher than within an uncomfortably cold environment (Spealman 1945; Caldwell et al. 2014). Cardiac output during exercise can easily reach 25 $L.min^{-1}$, so the heart is easily able to meet those demands for blood to be delivered to the skin. During exercise, cutaneous blood flows tend to be lower than, and perhaps half those observed when resting under high ambient heat stress (González-Alonso et al. 2008). Whilst that is due to the added demand for blood by the exercising muscles (Wood and Bass 1960; Bevegård and Shepherd 1967; Rowell, 1977; Crandall and González-Alonso 2010), it does not necessarily imply the establishment of a conflict (Hales 1996; Kenney et al. 2014).

With the combined demands of servicing the vascular requirements of the skeletal muscles during exercise, whilst preventing excessive deep-body temperature elevations, thermoregulation is sometimes given a lower priority. Indeed, George Brengelmann (1935-present, U.S.A.), with colleagues John Johnson (1944-present, U.S.A.), Lars Hermansen (1933–1984, Norway) and Larry Rowell (1930–2020, U.S.A.; Blatteis and Schneider 2022), reported that, during cycling, no further increase in forearm blood flow occurred after the deep-body (oesophageal) temperature reached 38 °C, regardless of the skin temperature (Brengelmann et al. 1977). Even with that restriction, some vasoconstrictor tone has to be maintained in the skeletal muscles during exercise, to prevent unsustainable hypotension (Barcroft et al. 1943; Rowell, 1997).

One thermoregulatory mechanism that supports the muscles during exercise is an upward displacement of the body-temperature threshold for active, cutaneous vasodilation (Kellogg et al. 1991; González-Alonso et al. 2008). Another support mechanism takes the form of a redistribution of the cardiac output. Savard et al. (1988) provided a nice example of that, when subjects, cycling in a water-perfused suit, were exposed to a skin temperature elevation from 31° to 38 °C. Cutaneous blood flow increased, but neither cardiac output nor total blood flow in the exercising legs changed, so blood must have been diverted to the skin from vascular beds other than within the exercising muscles (Savard et al. 1988).

Although skeletal muscles might seem to be favoured during exercise in the heat, compared to the skin, they are not fully protected from those competitive demands. For example, when heat-adapted subjects were cycling (submaximally) in air at 34 °C (dry bulb), they had higher rectal temperatures, but lower rates of oxygen consumption (heat production), than when working at the same intensity in cooler conditions (Williams et al. 1962). In those circumstances, they were relying upon a greater glycolytic contribution to supply that energy.

An elegant demonstration of the cutaneous vasomotor responses of different body sites to thermal stimuli was provided by Ian Roddie (1928–2011, Ireland; Roddie 1983; Wallace 2011; Milton 2022; also see: Johnson et al. 2014; Blessing et al. 2016). From a series of earlier experiments (Roddie and Shepherd 1956, 1957; Roddie et al. 1957a), Roddie had demonstrated that, relative to the thermoneutral state, blood flow to the glabrous (acral) skin regions, as represented by the hand, was significantly reduced during whole-body cooling. That was not novel (Lewis 1930). However, when the activity of the sympathetic nerves that innervated those blood vessels was blocked, several novel observations emerged (Roddie 1983). Those studies could only have been performed under resting conditions since neural feedforward to the cutaneous vasculature that accompanies exercise would have masked cold-induced vasoconstriction (Notley et al. 2023a).

The first of those observations was revealed when a neural blockade was applied to normothermic individuals, causing immediate cutaneous vasodilatation, with hand blood flow rising almost three-fold (Fig. 9; upper panel, left side). Thus, during normothermia, the cutaneous vasculature of the hand is under a strong, but not maximal, basal level of vasoconstrictor tone (Roddie 1983). Secondly, when those individuals were cooled (whole-body), vasoconstriction did not occur (dashed line), so the blocking agent prevented constrictor activity; we now know that all cutaneous vasoconstriction is noradrenergically driven (Bodelsson et al. 1990; Kellogg 2006; Johnson et al. 2014). Thirdly, regardless of whether whole-body heating was applied in the presence, or the absence, of that blockade, hand blood flows did not exceed those observed when either the normothermic or cooled states were studied during the blockade (dashed line). Therefore, thermally induced cutaneous vasodilatation of the hand is a passive, pressure-driven phenomenon, attributable wholly to the release of vasoconstrictor tone (Roddie 1983).

When those trials were performed on the forearm (Fig. 9; lower panel), as a representative site for non-glabrous (non-acral) tissue, there was evidence that a separate branch of the sympathetic nervous system seemed to control cutaneous

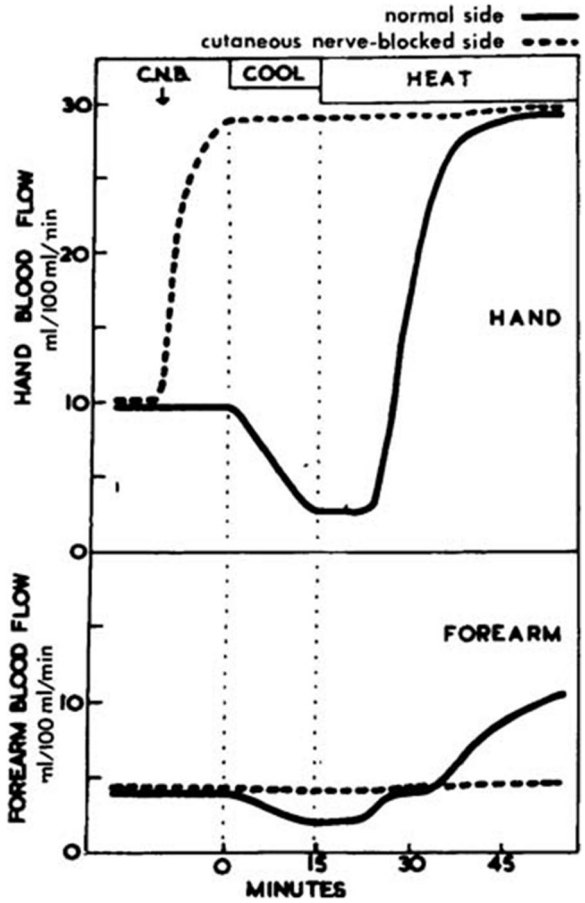


Fig. 9 A schematic illustration of the changes in hand and forearm blood flows induced by whole-body cooling and heating with, and without, the presence of a neural blockade of the cutaneous vasomotor nerves. From Roddie (1983) and reproduced with permission

vasomotor tone (Roddie and Shepherd 1956, 1957; Roddie et al. 1957a). Unlike the hand, the cutaneous vasoconstrictor tone of the forearm is minimal during thermoneutral states (Grant and Holling 1938; Blair et al. 1960), so the neural blockade had minimal impact on forearm blood flow (dashed line). Indeed, regardless of whether the participants were heated or cooled during that blockade, local blood flows matched those of the normothermic state. When whole-body cooling was used without the blockade, cutaneous vasoconstriction occurred (solid line), and when whole-body heating was applied to those cooler participants, again without the blockade, a bi-phasic vasodilatation was observed (Fig. 9; lower panel, right side). That second, active dilatation had a much greater impact on cutaneous blood flow than did releasing the vasoconstrictor tone.

Evidence from subsequent research was consistent with active vasodilatation accounting for 80–90% of the cutaneous vasodilatation that occurs during whole-body heat stress (Charkoudian 2003). Furthermore, that vasodilatation was not noradrenergically mediated, as it was unaffected by the adrenergic blockade. Instead, another sympathetic neurotransmitter was responsible (Roddie 1983). Subsequent research by Johnson and his colleagues expanded our understanding of these mechanisms (Johnson et al. 1995, 2014; Kellogg 2006), but the identity of the neurotransmitter has remained elusive (Wong and Hollowed, 2016; Francisco and Minson 2018), and there may be more than one neurotransmitter involved (Charkoudian 2010).

Does what happened in the hand and forearm also happen in the foot and leg (calf)? Answering that question required tightly controlled experiments, with a water-filled, temperature-controlled, displacement plethysmograph used for measuring the blood flow of those four limb segments (Caldwell and Taylor 2014, 2016; Notley et al. 2023b [Figure 19]). Measurements of cutaneous blood flows were obtained across a 2.4 °C range of thermally clamped deep-body (oesophageal) temperatures and at local skin temperatures manipulated over 35 °C (5°–40 °C; Fig. 8). Regardless of either the whole-body thermal state or the local skin temperature, hand blood flows exceeded those of the foot for all but one comparison, supporting observations first reported in the 1930s (Kunkel et al. 1939; Allwood and Burry 1954; Savard et al. 1985; Wallin 1990). Those systematic flow differences were not evident between the forearm and leg (calf). The cutaneous vascular responses of both the glabrous and the non-glabrous skin sites were again dominated by changes in deep-body temperature, rather than by the local skin temperature. That too had been demonstrated previously, across mammals and birds (Wyss et al. 1974; Proppe et al. 1976; Mercer and Simon 1984; Jessen 1996). Thus, the vasomotor responses to local skin temperature changes are highly variable, site-specific and largely dictated by centrally driven variations in vasoconstrictor and venoconstrictor tone (Caldwell et al. 2014, 2016).

During normothermia, it was really only the hand that displayed physiologically meaningful dilatation of the cutaneous vasculature during localised heating. The rapid, and presumably selective, restoration of blood flowing to the hands, which are critical to the manipulation of our immediate environment and for tool use, may well have provided a selective advantage for our ancestors. It is certainly one of the characteristics of the hands that allows them to be used as sites for heat exchange (Taylor et al. 2014b), similar to the large, well-perfused, but poorly insulated ears of elephants (Phillips and Heath 1992) and the large bills of toucans (Tattersall et al. 2009). Though their vascular responses were less than those of the hand, the other limb segments became more sensitive to local heating during moderate whole-body hyperthermia. Abramson (1942) suggested that hyperthermia sufficient to induce generalised sweating was required before sites other than the hand responded to local temperature. Recent measurements, which included both venous-occlusion plethysmography (forearm) and laser-Doppler

flowmetry (opposite forearm), have shown the forearm vascular conductance to be exquisitely thermosensitive, but unresponsive to changes in hydration state (van den Heuvel et al. 2020b, Australia).

Activating eccrine sweating: *Homo sudomotor*

If the travellers on our journey looked back about four million years, they would find a key event that led to the emergence of what has been given the pseudonym *Homo cursor* (Sands 2010); an animal uniquely equipped for endurance exercise in the heat. The evolution of *Homo cursor* is described in Part 4 of this series, and that transition involved the replacement of apocrine sweat glands with eccrine glands, an event coincident with becoming hairless, or, more accurately, most of our body hair becoming miniaturised. We could call our ancestral, sweating specialists *Homo sudomotor*, and they would have preceded *Homo cursor* by at least two million years. They had the capacity to dissipate all of the metabolic heat produced during maximum aerobic exercise transcutaneously, using evaporative cooling, even whilst continuing to exercise in the sun. That provided a huge selective advantage, although we know that capacity was not always protective, since *Homo cursors* have, and still do, succumb to exertional heat stroke ("Heat stroke in the Krogh-Hill epoch: a military perspective").

In Part 1 (Notley et al. 2023a), we reminded ourselves that sweat cools the body only if it evaporates on, or very near to, the body surface. In fact, sweat begins to drip long before the body surface is fully wet (Candas et al. 1979, 1980). So whilst the rate of body-mass reductions during exercise can be used to estimate sweat loss, they cannot be used to calculate evaporative cooling rates. Evaporation occurs down a water-vapour pressure gradient, not a relative humidity gradient, so there is not an absolute barrier to evaporation when the air has a relative humidity of 100%, provided the water-vapour gradient remains favourable. That thermodynamic fact emerged soon after the Krogh-Hill epoch (Rees 1935), but it is not universally recognised by applied scientists and climate-change biologists. We have described elsewhere how evaporation from our sweat glands might be measured (Notley et al. 2023b), and we recommend using direct calorimetry for exploring differences in evaporation rate, although very few have access to such systems.

In Notley et al. (2023a [Table 1]), we identified situations during which the various homeostatic regulatory systems might come into a state of regulatory conflict, with homoeostasis being simultaneously tested on several fronts. In such scenarios, the outcome of that contest might be determined by the assignment of priorities among those regulatory systems. In "Cutaneous vasomotor activity during heat exposure", we described possible conflicts between the cutaneous vascular beds and those of the exercising skeletal muscles for cardiac output. That has been regarded as a competition by some (Rowell 1974, 1977), which might result in thermoregulation being given a lower regulatory priority during endurance exercise. Others agree that those dual, possibly competing, requirements do exist, but not that they take the form of a conflict until we reach high levels of thermal strain. Instead, they suggest that, at lower levels of strain, the cardiac output is shared without either function being compromised (Hales 1996; Kenney et al. 2014).

Another regulatory conflict can arise when heat exposure and extended-duration endurance exercise co-exist, because thermal sweating depletes body water, which is required for both evaporative cooling and body-fluid regulation. That conflict is exacerbated by carrying loads and wearing protective clothing (Taylor et al. 2021). In subsequent sections, we will discuss the outcomes of that conflict, and how emerging experimental evidence influenced scientific interpretations over time. Before doing so, let us examine how our understanding of human eccrine sweating has emerged.

On the neural control of eccrine sweating In non-human animals, eccrine sweating has long been known to be activated by sympathetic neurons, but it was not dependent upon a sustained peripheral circulation, since sweating could be induced in the paws of amputed limbs (cats). Unlike most tissues innervated by sympathetic nerves, eccrine sweat activity was eventually found to be activated by the neurotransmitter acetylcholine, although the concepts of chemical neurotransmitters and neuroglandular junctions were unknown until the Krogh-Hill epoch. As noted elsewhere in this series, even some of the best human physiologists sometimes overlook, disregard or ignore research conducted on animals other than humans. Let us try to adjust that mind set, as we explore the control of sweating during the nineteenth century.

In that century, several foundational communications regarding the neural control of sweating appeared in quick succession. In the first of those, Goltz et al. (1875; Germany) showed that stimulating the sciatic nerve of cats and dogs induced eccrine sweating from their paws. Kendall and Luchsinger (1876; Switzerland) verified that effect, and reported that neurally induced sweating could be elicited even when paw temperatures were rapidly falling, even when blood flow to the limbs had been occluded and even 60 min after the limb had been amputated. So, the secretion of eccrine sweat appeared to occur independently of a functional circulatory network, at least within the short term. The sweat glands did not need a supply of water from the blood in the short term. Water could be obtained from another source. But the glands were not fully independent; they needed neural activation.

In subsequent papers, Luchsinger (1877a, 1878) identified fibres within the ulnar nerve, which appeared to arise from the spinal cord, and could activate sweating from cat paws. He found those neural pathways also carried vasomotor neurons. Accordingly, he developed a theory for the activation of sweating which included a centrally located (sudomotor) control centre, although he suggested that centre was located within the spinal cord. Beyond his writing, little is known of Balthasar Luchsinger (1849–1886). Nevertheless, his view of thermoregulation prevailed well into the Krogh-Hill epoch, and it strikes chords with the ideas of Eckhart Simon (1933-present, Germany; Simon 1974; Simon et al. 1986, 1998, 2022), to the effect that the spinal cord could behave as an extrahypothalamic thermoregulatory centre.

Across the Atlantic, Isaac Ott verified the observations of Kendall and Luchsinger (1876) concerning the neural dependence of sweating, and its relative independence of a viable blood supply (Ott 1879). He also stimulated sweating from an amputated limb and a deceased animal. To remove the possibility that residual blood within vessels close to those glands could provide a water source, he applied local compression to expel that blood; again, sweating could be elicited. Conversely, when he induced local vasodilatation to supply the sweat glands with blood, sweating did not commence in the absence of neural stimulation. Nevertheless, after a long absence of a local blood supply, sweating eventually decreased, even though neural function had not deteriorated (Ott 1879).

Perhaps more significantly, and within just a few years after the extraction and naming of muscarine (Schmiedeberg and Koppe 1869) and pilocarpine (Gerrard 1875), Ott used those agonists for the sweat-gland receptors to stimulate profuse sweating in cats. Sweating from the paws could be activated when those agents were applied near the terminal points of a sciatic nerve that had been sectioned several days earlier (Ott 1879). He also showed that atropine (first extracted in 1831; Mein 1833), known now to be a muscarinic receptor blocker, completely inhibited sweating. Thus, the tools for developing the experiments necessary to explore human eccrine sweating had been assembled before the end of our first epoch, but that potential had not yet been realised.

A few years before Ott, Luchsinger (1877b) had demonstrated those pharmacological effects on sweating, noting that the application of more pilocarpine could overcome the impact of atropine. That is, atropine was a competitive blocking agent of acetylcholine. It seems probable, therefore, that those experiments of Luchsinger and Ott mark another milepost on our journey, confirming that the neural drive of eccrine sweating required a neurotransmitter, and that was acetylcholine (Luchsinger 1877b; Ott 1879). Imagine the difficulty that Luchsinger and Ott had when explaining their observations, in the absence of the concept of neurochemical synapses and neuroglandular junctions, which they predated by 25 years (Langley 1905, 1906; Dale and Laidlaw 1912; Loewi 1921, 1922; Dale 1934, 1962; Feldberg 1970). Collectively, the observations of Kendall and Luchsinger (1876), Luchsinger (1877b) and Ott (1879) have shown that eccrine sweating is a true secretory process; it is neither an excretory nor is it a filtration process.

Although the observations and interpretations of Ott represented critical stepping stones, with modern hindsight, it seems that he also had blind spots ("*let him who is without sin cast the first stone*"). He concluded incorrectly that both excitatory and inhibitory neurons modulated sweat secretion (Ott 1879). He believed that inhibitory neurons, now known not to exist, were associated with non-sweating fever; the suppression of sweating in the rising phase of fever is a phenomenon that certainly exists (Mitchell and Laburn 1985). He did, however, domesticate Luchsinger's hypothesis (1877a, 1878) that the control centre for sweating lay wholly within the spinal cord. Instead, Ott (1879) found that stimulations applied to the *medulla oblongata* activated sweating and that thermally induced sweating on individual limbs could be prevented by sectioning the efferent nerves that innervated their eccrine sweat glands.

Next, John Langley (1852–1925, England; Maehle 2004) explored the anatomical configuration of the efferent sympathetic nerves (Langley 1891, 1894). Whilst the details of that research are beyond our current focus, it forms another milepost and one upon which contemporary physiological understanding is based. He described the sympathetic chain and its ganglia, along with its spinal-cord connections. During those experiments, Langley (1891) topically treated the sympathetic ganglia with the cholinergic agonist nicotine, which was first extracted by Posselt and Reimann (1828), and he even administered it intravenously. However, he reported minimal sudomotor activity following those treatments, as others have confirmed more recently (Fujii et al. 2019), since the cholinergic activation of eccrine sweat glands is strictly muscarinic, not nicotinic.

Neither Langley nor his contemporaries knew the difference between the muscarinic and nicotinic forms of the cholinergic receptors, but it is now more than a century since the experimental hypotheses arose that led to our current understanding of neurochemical transmitters and their receptors (Bennett 2000). Those chemical transmitters have unique molecular structures, which allow them to combine with, and therefore stimulate, a very precise group of molecules, found on those target cells. For the eccrine sweat glands, that neurotransmitter is acetylcholine (Dale and Feldberg 1934; Chalmers and Keele 1952), which targets the muscarinic (M3) glandular receptors (Hulme et al. 1990). So eccrine sweating can be suppressed using atropine, administered either topically or systemically, to block those receptors (Foster and Weiner 1970; Machado-Moreira et al. 2012). Atropine has no effect on cutaneous blood flow. Many of the nerve gases (e.g., sarin and novichok) act by

over-stimulating the muscarinic receptors (Takala and de Jong 2003), so profuse sweating is one of their many actions, which is prevented militarily using auto-injectors of atropine (Ziemba 2012). Patients using antimuscarinic medications are at risk of heat illness (Cheshire and Fealey 2008), and must avoid heavy exercise in the heat.

The paradox of sympathetic, cholinergic stimulation We would expect to find acetylcholine as a neurotransmitter within the parasympathetic nervous system, but not within the sympathetic nervous system, since its primary postganglionic, sympathetic neurotransmitter is noradrenaline. So the discovery that acetylcholine was the neurotransmitter for the eccrine sweat glands (Dale and Feldberg 1934) appeared somewhat paradoxical. It is interesting to note that our sweat glands also have receptors for noradrenaline (Reddy et al. 1992; Weihe et al. 2005), which is the neurotransmitter for sweating in other large mammals (e.g., cattle and horses), and there is evidence for the existence of noradrenergic neurons close the eccrine glands, although their distribution is much less dense (Uno 1977; Donadio et al. 2006). Since exercise (Zouhal et al. 2008) and heat stress (Brenner et al. 1998) both increase circulating catecholamine concentrations, is it possible that some eccrine sweating is mediated adrenergically?

Eccrine glands secrete sweat following elevated circulating and topically applied noradrenaline, and its agonists (Haimovici 1948, 1950; di Sant'Agnese et al. 1953; Allen and Roddie 1972; Wolf and Maibach 1974; Sato and Sato 1981), but the effect is small, and some say non-existent (Foster and Weiner 1970; Ogawa 1976). Even when subcutaneously administered adrenaline activates sweating, that effect may be secondary to the actions of adrenaline elsewhere (Ogawa 1976). Nevertheless, some hypothesised that human eccrine glands are cholinergically and noradrenergically innervated, with both having sudorific affects (Robertshaw 1977; Noppen et al. 1997; Nakazato et al. 2004).

Though adult human eccrine glands are predominantly, if not entirely, cholinergic, it may not always have been thus, ontogenetically. Indeed, there is much evidence showing that, *in utero*, the sympathetic neurons that will eventually innervate the eccrine sweat glands of rodents have noradrenergic properties (Landis and Keefe 1983; Guidry and Landis 1998). Yet, when examined *post utero*, those neurons had a cholinergic phenotype in rodents (Landis and Keefe 1983) and primates (Uno 1977; macaques and humans). It appeared as though a phenotypic conversion had occurred, with the transition from functionally noradrenergic to cholinergic glands being initiated by the sweat glands themselves (Johnson et al. 1976a, b; Landis and Keefe 1983; Schotzinger and Landis 1988).

Histological examination of antenatal tissues showed that the innervating neurons are not in physical contact with the glands, but are separated slightly from their target receptor cells (Landis and Keefe 1983). It appears that, in utero, the sympathetic neurons grow towards the eccrine glands, only reaching their targets postnatally, whereupon their ability to synthesise noradrenaline is gradually suppressed, and a phenotypic conversion occurs (Landis 1990; Guidry et al. 2005). That conversion results in those neurons losing their ability to synthesise, store and release functionally meaningful amounts of noradrenaline (Landis 1976; Reichardt and Patterson, 1977). The mechanism driving those events seems to reside within the sweat glands, which, following their initial adrenergic stimulation, release a chemical trigger that produces a gland-driven phenotypic conversion to a neuron with cholinergic traits (Schotzinger and Landis 1988; Guidry et al. 2005). Whether the same process occurs in humans is not known yet, but the likelihood that it does again highlights the importance of reading the comparative physiology literature.

Assembling the components of thermoregulation and evaporative cooling Researchers of our first two epochs knew that neural centres, in some centralised location, collected and integrated information about body temperatures, and then activated sweating. But thermal physiologists were unable to make quantitative connections between body temperature and sweating. Into that breach strode Yas Kuno (1882–1977); the father of Japanese thermal physiology (Yoshimura et al. 1960; Morimoto 2015; Nagasaka 2022).

In his seminal monograph (Kuno 1934), Kuno dismissed the idea that skin temperature was the principal thermal input to sweat-gland activity, but he did not relate sweat rate quantitatively to deep-body temperature (Shibasaki et al. 2006). That such connections existed and were crucial to understanding the control of sweating was a discovery of the modern epoch. One example of that connection appears in Fig. 5 (Wyndham 1967), which shows a visual (statistical) relationship between body temperature and sweat rate, but it did not explain that relationship. What is the physiological link? As we have seen (Notley et al. 2023a [Fig. 20]), various receptors within the body, including metaboreceptors and mechanoreceptors (van Beaumont and Bullard 1963; Kenny and Journeay 2010; Kondo et al. 2010), can initiate sweating within thermally primed individuals ("*warmed to the work*"). Cholinergic sweating can even be induced during psychogenic stress (List and Peet 1938; Abram et al. 1973; Machado-Moreira et al. 2012; Schwarck et al. 2019), but the only receptors that participate in both the control of sweating and temperature regulation are the thermoreceptors.

In thermally compensable environments, only when negative feedback from the thermoreceptors allows the regulatory centre to determine that the body temperature has stabilised, will sweating stabilise. If one then measures sweat evaporation rate, it will, by definition, be the required evaporation

rate (Belding and Hatch 1955); the evaporative heat transfer rate that balances exactly the nett rate of heat gained from metabolism and the thermal environment. That is not a physiological triumph. It is the *First Law of Thermodynamics* in action (Notley et al. 2023a). The relationship between sweat rate and the required rate of evaporation is a necessary outcome, but it is not a mechanism of control. When researchers say that sweating is determined by the required evaporation rate independently of measured body temperatures, what they are really saying, quite possibly without being aware, is that the body measures its own temperature better than they can.

Of course, we do not yet know the precise form of the thermal feedback signals that our thermoregulatory system receives, although we assume those signals relate to an overall body temperature, since we have thermoreceptors distributed throughout the body (Zotterman 1959; Hensel 1973; Jessen 1996; Pierau 1996), including locations where we cannot put thermometers. Whilst those sensors provide some measure of the overall thermal status of the body, we cannot accurately represent that by any linear combination of deep-body and mean skin temperatures, although many of us have used those over simplifications. That conclusion was reached by the Dutch thermal physiologist Jan Snellen (1925–2000, South Africa and Canada; Snellen 1966, 1969; Tikuisis 2022), and reconfirmed more recently (Jay et al. 2007). Yet, in many steady-state conditions, linear combinations of deep-body temperature and mean skin temperature have correlated remarkably well with sweat rate (Shibasaki et al. 2006; Werner 2010). When that happens, we should be thankful for our good fortune, but we have not resolved the neural control of sweating. Nevertheless, it does not seem profitable to measure the temperature of tissues that either lack thermoreceptors or are not maintained in a state of thermal equilibrium with thermosensitive tissues.

That sweat rate exhibits a linear relationship with skin temperature is surprising, because skin temperatures play a dual role in controlling sudomotor activity. As well as contributing to the overall thermal feedback, they can elevate and suppress local sweat rates as local skin temperatures rise and fall, even without a change in the sympathetic drive to those glands. It is with Ethan R. Nadel (1941–1998, U.S.A.; Blatteis and Schneider 2022) that the phenomenon of the local control of sweating usually is linked (Nadel et al. 1971). The mechanism is different from the local control of cutaneous vasomotor tone, in that it is strictly a modulation of the effects of sympathetic nerve activity on the glands themselves. Heating a sweat gland does not make it secrete sweat, nor does local heating activate neurons that stimulate the glands. We must remember that, once sufficient sweat covers the unclothed and freely sweating, whole-body skin surface, any effect of skin temperature on the control of sweating will be disguised because the skin temperature will be effectively clamped (Notley et al. 2023a [Fig. 13]).

In a regulatory system for which there are no inherent delays, controlled variables will change almost instantaneously with changes in exercise intensity or an experimental forcing function (Whipp and Ward 1980). However, whilst some non-thermal feedforward signals, which travel in parallel with motor commands, will elevate thermoeffector activity, those changes are merely preparation for, and not responses to, thermoregulatory disturbances. Thus, those instantaneous responses are transient, and the full response must wait until the regulated variable (body temperature) has been disturbed. Within all regulatory systems, there are inherent, and widely variable, delays between the application of a stimulus, the resulting homeostatic disturbance and the effector responses that it elicits.

During a sufficiently large increase in body temperature, sweat secretion will be initiated and synchronised across the body surface (Fig. 10A). That synchronisation reflects waves of sympathetic impulses travelling to, and then almost simultaneously activating, the eccrine sweat glands at different body surfaces. We can evaluate the sensitivity of that control mechanism, in the form of a change in sweat rate per degree elevation in whole-body or local skin temperature (thermosensitivity or gain), and that sensitivity can reflect changes within either the regulatory centre itself or the sweat glands at each site.

Whilst we are currently unable to quantify precisely changes in the regulated variable of interest (body temperature), we can easily induce changes in the thermal status of different body tissues. That can be achieved through the application of forcing functions that elicit those changes, and then observing how the controlled variable of interest (sweating) tracks, or possibly ignores, the resulting temperature variations. A particularly useful function is a sinusoidally varying external work rate, which induces cyclical changes in body temperatures. Indeed, intramuscular (*vastus lateralis*), oesophageal, insulated auditory canal and mean skin temperatures have all been shown to vary sinusoidally during such an experiment (Todd et al. 2014 [Australia]; Notley et al. 2023b [Fig. 16]). The exception was rectal temperature, which slowly crept upwards over the 25-min treatment period; it was neither being regulated nor was it driving eccrine sweating. We will now examine how those temperature changes influenced sweating from five different skin regions (Fig. 10B), which was probably also driven by neural feedforward control.

The average phase delay (lag) between the change in work rate (Fig. 10B; top trace) and the heart-rate response was 26 s. The phase delay between changes in the work rate and the averaged sudomotor response for the forehead was 153 s (trace B). Similar delays were apparent for the other sites. Of particular note are the strong correlations between the

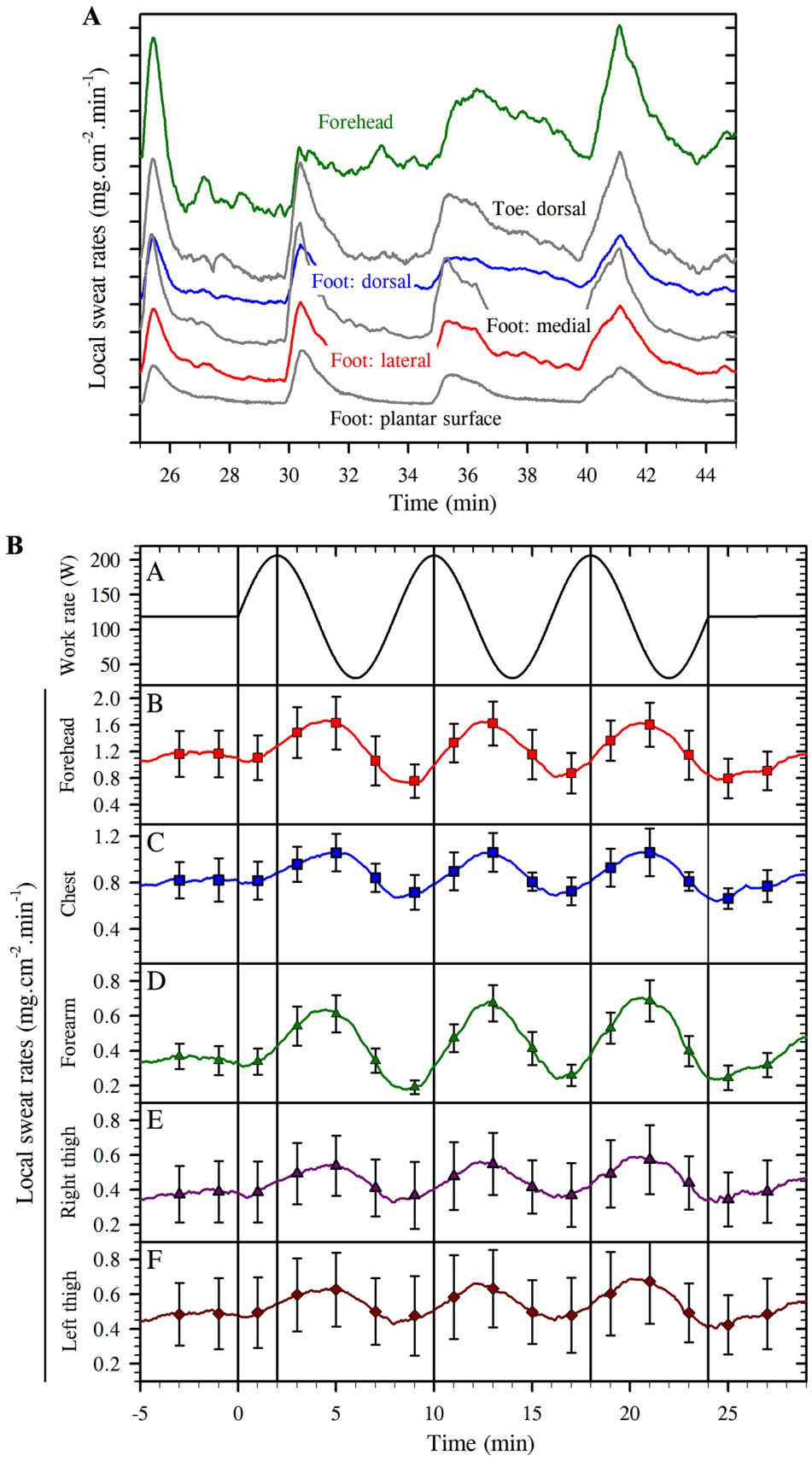


Fig. 10 **A** Synchronous variations in eccrine sweating observed across different body segments during thermal loading at rest. Data are from one individual, collected using ventilated sweat capsules, taken from Taylor and Machado-Moreira (2013) and reproduced with permission of the authors, who retain the copyright. **B** Sinusoidal changes in eccrine sweating during a sinusoidally varying forcing function (semi-recumbent cycling; 25 °C). The top panel shows work-rate variations induced using a pre-programmed, electronically braked ergometer, with time referenced to the start of the first sinusoidal waveform (0 min). Before commencing, the participants were pre-heated using 35 min of steady-state cycling, as reflected within the thermally primed sweat rates before the first waveform. Data are average response curves for each of five, simultaneously recorded local sweat rates (ventilated capsules), with standard errors of the means at 2-min intervals ($N = 8$). Reproduced from Todd et al. (2014) with permission

intramuscular and oesophageal temperatures and those variations (Todd et al. 2014), with the phase delay between intramuscular temperature and sweating (26 s) being significantly shorter than that for oesophageal temperature (50 s; Notley et al. 2023b [Fig. 16]). It is our contention that oesophageal temperature, but certainly not rectal temperature, provided a reasonable approximation of the thermal energy content of the blood that would soon perfuse the hypothalamus. The shorter intramuscular delay is consistent with the possibility that thermosensitive elements might exist within skeletal muscles that might also contribute to thermal feedback as part of the regulated variable, as others have suggested (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).

Following this overview of thermoeffector control during exercise in the heat, it is time to return to our theme of heat illness, and to examine the possibility that occupational and athletic exercise in the heat might result in thermoregulation being challenged, and even compromised. In tackling those possibilities, we first return to the topic of homeostatic prioritisation, which we introduced in Notley et al. (2023a). When several regulated variables are simultaneously and significantly disturbed during stressful, emergency and highly competitive scenarios, which, if any, of those variables might be given a lower priority to ensure survival?

Homeostatic priorities: body temperature, plasma osmolality and blood pressure

Many mammals use evaporative cooling to regulate their body temperatures: dogs pant, warthogs wallow in mud, kangaroos spread saliva on their forelimbs. Humans do not pant, but we can use behavioural strategies. We are a sweating specialists. However, the body water required for evaporative cooling is also necessary for regulating our blood volume, plasma osmolality and our mean arterial and central venous pressures (Notley et al. 2023a [Table 1]). It is a characteristic of all non-human mammals studied so far, free-living in their natural habitats, that they reduce evaporative cooling during water shortages, even in hot environments. Inadequate evaporative cooling results in an elevation of the peaks of the nychthemeral rhythms of deep-body temperature (circadian variations as affected by external influences); they become temporally heterothermic (Fuller et al. 2021).

In arid zones, food availability for herbivores declines during the hot seasons, so they face food and water shortages simultaneously. When faced with a lack of metabolic fuel, those animals also reduce the priority of thermoregulation, they develop deeper troughs in their nychthemeral rhythms, and they can become even more heterothermic. For example, the free-living Arabian oryx exhibited nychthemeral peak-to-trough amplitudes > 7 °C in the hot-dry season (Hetem et al. 2010); humans have a normal amplitude of ~ 1 °C (Notley et al. 2023b [Fig. 11]). Whether or not that heterothermy is inevitable or implemented (Hetem et al. 2016), it is certainly advantageous for thermal balance, because the temperature gradients for heat exchange are reduced during the day and night. So whatever the advantages of homeothermy are, and they are not as obvious as is usually assumed (Mitchell et al. 2018), those advantages are sometimes abandoned during homeostatic conflicts. Homeothermy typically is given a low priority, but exceptions do exist.

Had comparative physiologists been active in the Krogh-Hill epoch, they would have endorsed Pembrey's advice not to restrict access to water (Pembrey 1914), but they would have been astounded to hear Edward Adolph say that, in his experience, hypohydration affected neither the ability to regulate body temperature nor sweat rate (Adolph 1921). Like other good scientists, Adolph modified his ideas about the effects of hypohydration in the light of new evidence, as described below. Comparative physiologists might be even more astounded when encountering contemporary physiologists advising that drinking should be restricted in hypohydrated athletes exercising in the heat. The contemporary physiologists who agreed with Adolph's early views are in the minority, but that does not mean they are wrong; science is a meritocracy, not a democracy.

There is no disagreement about the physiological consequences of sweating for body fluids. It can result in progressive hypovolaemia, putting stress on the regulation of blood pressure. Although the concentration of sweat varies, it is always hypo-osmotic relative to the blood, and we have known that for almost a century (McSwiney 1934). Sweat removes proportionally more water than solutes, and can lead to hypertonic (hyper-osmotic) hypovolaemia (Mayer 1900; Fitzsimons 1972; Morimoto 1990; Cheuvront and Kenefick 2014). The disagreements hinge around three questions. Firstly, does hypohydration lead to hyperthermia and does it suppress sweating, as it does in other large mammals? Secondly, does hypohydration compromise exercise performance? Thirdly, if hypohydration has deleterious consequences, how should the fluid lost in sweat be replaced?

Before addressing those questions we note that the World Health Organisation, when recommending procedures for identifying hypohydration in children suffering diarrhoeal diseases, seems to be much less anxious than some sporting and occupational health organisations: "*The goal of drinking during exercise is to prevent excessive (> 2% body weight loss from water deficit) dehydration*" (American College of Sports Medicine, 2007 [P. 377]). Almost counter-intuitively for more vulnerable children, the World Health Organisation (2005) classifies body-mass reductions < 5% (< 50 mL.kg^{-1}) as showing "*No signs of dehydration*", deficits of 5–10% are classified as evidence of "*Some dehydration*" and it is not until the water deficit exceeds 10% that hypohydration is

classified as "*Severe dehydration*" (World Health Organisation 2005 [P. 7]). Do those other organisations have information that is not available to the World Health Organisation? Of course, there are some athletic pursuits for which body-mass reductions are part of the preparation for competing (mass-dependent divisions), or when one's body mass can be disadvantageous (track sprints, kayaking, rowing), so guidelines, regardless of who writes them, are generalisations that are obliged to err towards conservatism.

Does hypohydration lead to hyperthermia and does it suppress sweating? There is ample evidence to show that deep-body temperature appears to inexorably increase during exercise in which there is progressive hypohydration. Despite his earlier contention to the contrary, perhaps the earliest evidence for that was actually presented by Adolph and his colleagues, in a compendium on human work physiology in the desert (Adolph 1947e; Brown 1947c; Rothstein and Towbin 1947). Others reinforced those observations (Buskirk and Beetham 1960; Strydom and Holdsworth 1968; Wyndham and Strydom 1969a; Greenleaf and Castle 1971; Sawka et al. 1984b; Montain and Coyle 1992), and from that body of work, we have extracted evidence obtained from marathon runners (Fig. 11; Wyndham and Strydom 1969a).

The variations in deep-body (rectal) temperature with sweat-related mass reductions reported by Wyndham and Strydom (1969a) revealed a bi-phasic response (Fig. 11), with rectal temperature consistently increasing only after a body-mass deficit (threshold) was surpassed. Such a threshold is not always evident within the literature. A decade earlier, Grande and colleagues (1959, U.S.A.) reported that the rectal temperatures of soldiers on a water-restricted diet, walking on a treadmill (25.5 °C dry bulb) were linearly related to hypohydration, although they only had two data points > 39 °C, with another two between 38.5° and 39 °C. Grande et al. (1958) also showed that sweat rates (mass losses) declined linearly with hypohydration, and claimed that a water-deficit threshold for that reduction did not exist. However, Wyndham and Strydom (1969a) reported that, for water deficits < 3%, deep-body temperature appeared to be well regulated around 38.5 °C. Such a thermal load would be expected, and necessary, if sweating and evaporative cooling were to be sustained. Beyond that water deficit, however, deep-body temperatures rose, with ~ 50% of that elevation being explained by sweat-related mass reductions, although correlations do not necessarily reveal mechanistic relationships. Similarly, Greenleaf and Castle (1971; U.S.A.) observed that the steady-state, deep-body (rectal) temperatures of their hypohydrated cyclists (23.6 °C dry bulb), were elevated 0.1 °C for every 1% body-mass deficit. These three investigations represent mile posts in our modern epoch

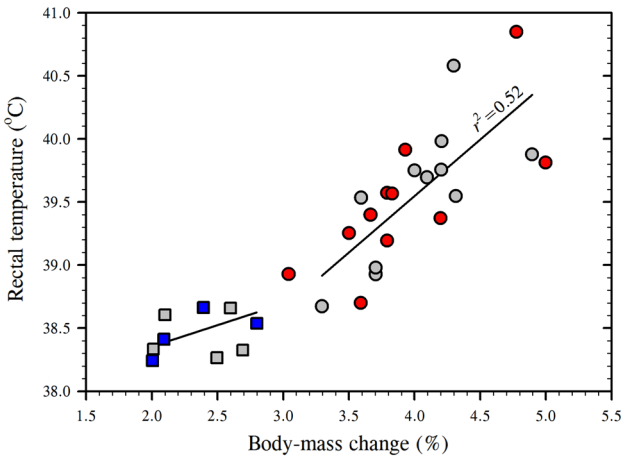


Fig. 11 Deep-body (rectal) temperatures of marathon runners at the end of a 32-km run in cool conditions, as a function of body-mass change (water deficit). Data were obtained from different runners on two different days (coloured versus grey symbols). Subjects sustained thermal steady-states when mass deficits were < 3 kg (squares), but experienced progressive hyperthermia when body-mass losses were greater. Two runners had rectal temperatures > 40 °C without *sequelae*, and one ended without a body-mass deficit. Redrawn from Wyndham and Strydom (1969a)

that seemingly contradicted two of the early contentions of Adolph (1921).

Interestingly, the observations of Wyndham and Strydom (1969a) would lead to an expectation that hypohydration-induced hyperthermia would not occur at body-mass deficits < 3%. That is exactly what Tim Noakes (South Africa) observed in recreational runners (Noakes et al. 1991) and soldiers during a forced march (Nolte et al. 2011a). Contrary to those expectations, hyperthermia has sometimes been reported during exercise with body-mass deficits < 2% (Adams et al. 2019), although it is also occasionally absent at deficits of nearly 4% (Nolte et al. 2011b; Valentino et al. 2016).

Back in South Africa, Strydom et al. (1966a) studied euhydrated and hypohydrated soldiers during a 29-km, loaded forced march (24 kg, 6.6 km.h^{-1}; 22–32 °C dry bulb). One group of height- and mass-matched subjects was allowed to drink ad libitum, while a second group received just 1 L (almost twice Melville's "*pint at the half-way halt*"). Of those who completed the task, their mass deficits were 4.8% (water-restricted) and 3.9% (drinking group). The ad libitum drinkers had incurred what is now called voluntary hypohydration (Rothstein et al. 1947; Greenleaf 1992), which "*serves no useful purpose and should be avoided at all costs*" (Strydom et al. 1966a [P. 543]). Whilst rectal temperatures increased linearly with decreases in body mass (Strydom et al. 1966a), resulting in hypohydrated subjects having higher rectal temperatures at the end of the march, there was no difference in sweat rate between those groups.

Although the subtlety may not have been appreciated, Adolph's interpretation was correct: temperature regulation had not failed, nor was it adversely affected. Body temperatures were being regulated at higher levels (Werner 2010) during its sharing of the available body water with another regulatory system; body-fluid regulation (Notley et al. 2023a [Table 1]).

Some numbers for accountants. Bedouin goats deprived of water for 72 h (desert summer) have lost 19.5% of their body mass without either their total evaporation rate or deep-body temperature being affected (Dmi'el, 1986). They can even tolerate body-mass deficits of 40% due to water loss without *sequelae* (Silanikove 1994; Choshniak et al. 1995), as can camels and kangaroo rats (Schmidt-Nielsen and Schmidt-Nielsen 1952), but humans would not survive that level of hypohydration. During heavy exercise and competitive sport in the heat, human sweat rates can easily reach 2–4 $L.h^{-1}$ (Eichna et al. 1945; Weiner and Hellmann 1960; Armstrong et al. 1986; Rehrer and Burke 1996), and 10–16 $L.d^{-1}$ during occupational pursuits in similarly stressful conditions (Ladell 1945; Latzka and Montain 1999). Survivable human body-mass deficits of 10–15% have been described in such circumstances (Speedy et al. 1999; Armstrong 2021).

Let us now consider Adolph's second proposition; hypohydration does not reduce the sweat rate of exercising humans (Adolph 1921). We could not imagine that Adolph was saying that hypohydration would never impair sudomotor function. It must at some point affect sweating, he would have known that, and there is ample evidence of that effect (Hertzman and Ferguson 1960; Greenleaf and Castle 1971; Fortney et al. 1984; Sawka 1992; Montain et al. 1995; Nose et al. 2018), although that effect might be small. Instead, we believe that, in his hands, as well as in those of others, the experimental conditions used did not reveal that effect, and it was to those conditions that he was referring, whilst avoiding extrapolations beyond his experimental evidence. Indeed, there is a collection of papers from the modern epoch that agree with Strydom et al. (1966a); hypohydration-associated hyperthermia during exercise can occur without suppressing sweat secretion. Let us explore that collection. Later we shall demonstrate that hypohydration without a suppression of sweating is not an anomaly, but a necessary consequence of the *First Law of Thermodynamics*.

The first paper from that collection is by W.S.S. Ladell (England). He manipulated the hydration status of men working in the heat by withholding water or by providing water of different salinities (Ladell 1955). Those who did not drink had higher deep-body (rectal) temperatures. However, "*abstention from water had no effect on the sweat rate until water debts of more than 2.5 1. had been incurred*" (Ladell 1955 [P. 43]). Ladell did not regard the lack of an effect of hypohydration on sweat rate to convey any deviation from a physiological principle. Instead, he attributed it to his experimental design: "*any failure to show deterioration in sweat rate when subjects abstain from water is probably due to their having failed to contract a sufficiently large water debt*" (Ladell 1955 [P. 30]).

Ten years later, Senay and Christensen (1965; U.S.A.) studied resting subjects (semi-reclined) over 12 h at 28 °C (wet bulb). In that environment, they were expected to lose 0.5% of their initial body mass each hour due to sweating. Deep-body (oral) temperature rose with each degree of hypohydration, and "*one is tempted to assign this increase to a deficit in sweating due to dehydration. However, there is no evidence in the presented data that such was the case*" (Senay and Christensen 1965 [P. 281]). Not only was the sweat rate unaffected by hypohydration, but so too was cutaneous blood flow.

In those two studies, different treatments were used to induce hypohydration: exercise in the heat and passive heating (respectively). It is probable that physiological strain differed between those studies, although both reflected actual human experiences. During exercise, water stored with glycogen in the skeletal muscles (Olsson and Saltin 1970) is released, which may interfere with the experimental treatment by providing fluid that was previously not available. In a different approach, Claremont et al. (1976, U.S.A.) attempted to isolate hypohydration from the separate exercise and thermal stresses. They dehydrated subjects using diuretic administration, reducing body mass by 3% before subjects cycled (35% peak aerobic power) in humid heat. Cutaneous blood flow was reduced, but not sweat rate, whilst deep-body (rectal) and intramuscular temperatures were higher when hypohydrated.

There are caveats concerning diuretic-induced hypohydration, as the consequences for body-fluid balance are not the same as those induced by sweating, nor do they necessarily reflect hypohydration experienced during work or sport (Sawka et al. 2001b; Cotter et al. 2014). For instance, whilst diuretics tend to elicit an isotonic (iso-osmotic) reduction in the blood volume, there is evidence of a relatively greater reduction in the plasma volume, which can be almost three-fold greater than that resulting from prolonged exercise (Kubica et al. 1983). Secondly, diuretics do not increase the osmolality of the extracellular fluid, but sweating does, so the osmotic gradient for intracellular dehydration is lacking (Cheuvront and Kenefick 2014). Interpretative caution is required with such research.

Using a combination of dietary (food and water) restrictions and prior exercise in the heat, Sawka et al. (1985b, U.S.A.) dehydrated heat-adapted subjects to body-mass deficits of 3%, 5% and 7%, before they walked (140 min) in a hot-dry environment (49 °C dry bulb). With a 7% mass deficit, only two of the eight volunteers completed that task. Deep-body (rectal) temperature increased with the mass deficit. However, the whole-body sweat rate for the cohort

was unaffected by dehydration, though within each volunteer it decreased with increasing plasma osmolality. Whilst the authors endeavoured to show that sweating at an equivalent body temperature was impaired when hypohydrated, there was considerable overlap among those data, such that isothermal comparisons would be tenuous.

Montain and Coyle (1992; U.S.A.) investigated four levels of hypohydration, up to 4.2%, during endurance cycling (120 min, ~ 65% peak aerobic power, 33 °C dry bulb). Progressive dehydration occurred during, rather than before those trials commenced, and it was achieved using four fluid-replacement volumes (0%, 20%, 50% or 80% of the body-mass change), delivered at six points within each trial. Subjects completed all trials as their own controls. Forearm blood flow declined linearly with hypohydration and, as Nielsen (1974) had shown earlier, deep-body (oesophageal) temperature rose linearly with serum osmolality, but sweat rates were almost identical at each level of hydration.

In Japan, Kamijo and colleagues (2005) combined diuretic administration with saline administration and the withholding of water, to independently manipulate hypovolaemia and hyperosmolality. Subjects then performed semi-recumbent cycling (~ 50 min, 60% peak aerobic power, 30 °C dry bulb) until deep-body (oesophageal) temperature stabilised, at which point they consumed 200 mL of body-temperature water. Hyperosmolality, but not hypovolaemia, led to a suppression of sweating on the chest (ventilated capsule), while deep-body temperature rose with both hyperosmolality and hypovolaemia. Finally, Cramer et al. (2017), used pharmacologically induced hypohydration, finding that neither forearm (ventilated capsule) nor whole-body sweat rates were affected by changes in hydration state.

What is apparent across those projects is that the experimental designs were often dictated by applied, rather than mechanistic outcomes. That is not problematic, unless one is investigating physiological mechanisms. As a consequence, most groups combined two or more stresses (e.g., progressive hyperthermia and hypohydration), and generally within exercising subjects. Since body temperature, blood volume, plasma osmolality and blood pressure are all independently regulated (Notley et al. 2023a [Table 1]), although they share some effectors, and since each of those regulated variables can, and will, be disturbed by exercise, hyperthermia and hypohydration, then untangling and interpreting the evidence is challenging, and sometimes impossible. If those combined stresses modified physical performance, which stress actually caused that change? If hyperthermia and dehydration have opposite effects, will one stress negate the impact of the other when they are combined? When body temperature and hydration state are progressively changing during exercise, is it the size of those regulated-variable changes, or the rate at which they change, which dictates the effector responses? One might untangle those complexities using physiological clamping, for the true test of whether or not sweat rate is affected by hypohydration must surely be to evaluate sudomotor activity at a stable (clamped or isothermal) body temperature.

Recognising some of those limitations, van den Heuvel and colleagues (2020b, Australia) used passively induced (heated water bath) changes in hydration state (euhydrated, 3% and 5% hypohydrated), followed by similarly induced thermal pre-conditioning (normothermia and moderate hyperthermia). Those states were then clamped, using controlled drinking and a thermally regulated climatic chamber and water-perfused garment, which provided six combinations of experimental treatments, during which those clamps were sustained. Resting physiological responses were measured (30 min): deep-body temperatures (oesophagus, insulated auditory canal, rectum), local and whole-body sweat rates (four ventilated capsules, body-mass change) and cutaneous vasomotor responses (laser-Doppler, venous-occlusion plethysmography). Subjects acted as their own controls. There was no effect of hydration state on sweat rate, either at rest during normothermia and moderate hyperthermia (Fig. 12A), or during normothermic, incremental cycling to exhaustion; exercise in the heat was not explored. As observed by Senay and Christensen (1965), cutaneous blood flow was not affected by hypohydration, although severe hypohydration was not induced in either study.

Does hypohydration lead to hyperthermia and does it suppress sweating? We believe that hypohydration does lead to progressive hyperthermia during exercise in the heat. However, the studies reported above support Adolph's contention that hypohydration does not necessarily lead to a suppression of sweating, at rest or during exercise in the heat (also see: Candas et al. 1986; Montain and Coyle 1992). Some authors even state that cutaneous blood flow may not be compromised. Of course, it is possible that the maintenance of sweating might be confined to low levels of hypohydration, although Sawka and colleagues (1985b) noted that sweating was maintained at a 7% body-mass deficit.

In a study in which participants were taken to that same level of hypohydration using exercise and controlled fluid replacement, Taylor et al. (2009, 2012) used deep-body (insulated auditory canal) temperature clamping (38.5 °C), which was achieved using intermittent exercise, to progressively dehydrate volunteers to body-mass deficits of 3% in one trial (> 2 h), and then to 7% on each of two different days (> 6 h each trial). In the 3% trials, subjects consumed isotonic fluid volumes that represented 60% of their body-mass reduction, after reaching each 1% mass reduction. For the 7% trials, an isotonic drink (50 mL) and food (90 g) were provided at each 1% mass reduction. The emphasis was on evaluating indices of hypohydration, although local sweat rates (ventilated capsules) were recorded during structured rest intervals during the 3% trial and one of the 7% trials.

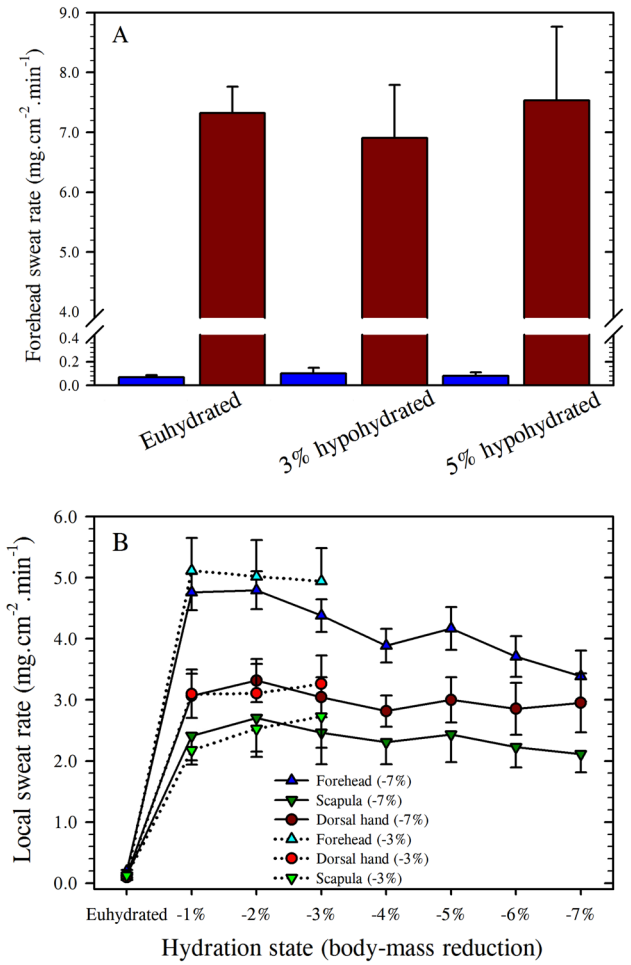


Fig. 12 Local sudomotor responses (ventilated capsules) of hyperthermic individuals before and following hypohydration. **A** Forehead sweating during the final 10 min of seated rest (30 min) in each of six physiological states. Two thermally clamped states (normothermia [blue bars; mean body temperature 36.1 °C] and moderate hyperthermia [red bars; mean body temperature 38.2 °C]) were investigated within each of three (clamped) levels of whole-body hydration: euhydrated (0%), as well as 3% and 5% hypohydrated. Data are means with standard errors of the means ($N=8$). Modified from van den Heuvel et al. (2020b) and used with permission. **B** Local sweat rates obtained during brief rest intervals, across each of the seven stages of exercise-induced (intermittent cycling) hypohydration in the heat (35.6 °C dry bulb, 56% relative humidity). Data were collected with deep-body (insulated auditory canal) temperatures elevated and stabilised at 38.5 °C ($N=12$), and are shown as means with standard errors of the means, with each hypohydrated target being a relative body-mass reduction (1–7%). Data are shown for two trials only: 3% hypohydrated with 60% fluid replacement (2.37 h) and one of the 7% hypohydrated trials with minimal fluid replacement (6.15 h; see Taylor et al. 2012 for details)

Those data were not published, but are now presented in Fig. 12B. Whilst it took gradually longer to attain successive body-mass deficits (mean delay 2.9 min), it is apparent that the sweat rates of the dorsal hand and back (scapula) were sustained, while forehead sweating slowly decreased beyond the 2% mass reduction. That decline was not apparent in thermally clamped, resting subjects following a 5% mass reduction (van den Heuvel et al. 2020b [Figure 3]). Whilst Sawka (1992) and Nose et al. (2018) identified studies in which reduced sweat secretion accompanied hypohydration, without thermal clamping, the physiological impact of hypohydration on sweating was unlikely to have been isolated.

These interpretive differences, and their underlying explanations, might have been avoided with closer attention to the dictum that heat exchanges have to obey physics, and to the insights of pioneers from the modern epoch. The first of those insights came from Grande and colleagues (1959), who believed that even if hypohydration did not suppress sweating, it must have affected thermoregulation, because, at the higher body temperatures that accompany hypohydration, sweating should have increased. Strydom and colleagues echoed that conclusion: "*sweat rate is decreased with increased dehydration. Opposing this effect, however, is the increased body temperature which tends to increase the sweat rate … the one tending to cancel the effect of the other*" (Strydom et al. 1966a [P. 543]; also see: Strydom and Holdsworth 1968). Senay and Christensen (1965) recognised that constancy of sweat rate and cutaneous blood flow, while deep-body temperatures rose, constituted a change in the operating point of the thermoregulatory system (Werner 2010) in the face of competition from other homeostatic systems, suggesting that the change was "*probably derived from the algebraic influences of volume, osmo- and chemoreceptors as well as the direct effect of blood osmolarity, pH, and* pCO_2*, both at the local level and in the central nervous system*" (Senay and Christensen 1965 [P. 281]).

If hypohydration reduces either evaporative or dry heat loss to levels below that required to regulate body temperature, then, unless we also reduce metabolic heat production, the body temperature must rise. The resulting thermoafferent flow will further increase sweating, and, in compensable thermal environments within which evaporation is also elevated, the sweat rate will stabilise when a thermal equilibrium is achieved; heat storage is zero. If hypohydration has not altered any of the other components of the energy-balance equation (metabolic heat production, external work rate, sensible heat transfer), and if it has not altered how much sweat drips without evaporating, then, according to the *First Law of Thermodynamics* (Notley et al. 2023a [Eq. 8]), the level at which sweat rate stabilises during hypohydration must be at the same level observed during euhydration. Therefore, observations that hypohydration does not necessarily change sweat rate are not anomalies, but a consequence of the laws of physics when exercising in compensable conditions.

If any other variables of the energy-balance equation change with hypohydration (e.g., altered sensible heat loss due to a change in skin temperature), or if less sweat drips,

then the level at which the sweat rate stabilises will be below that observed during euhydration, for the equation to balance. In compensable environments, what the body temperature becomes will be determined by the level that provides the thermal feedback necessary for the regulatory centre to drive the thermoeffectors towards the attainment of a thermal equilibrium. So the elevation of body temperature at thermal equilibrium during hypohydration will be variable. However, in compensable environments, and provided sufficient sweat is available, as Adolph asserted correctly, the regulatory centre does not fail during hypohydration; it simply is being regulated at a different level.

Therefore, hypohydration appears to have adjusted the relationship between body temperature and sweat rate. That change is not believed to occur at the glands themselves, but at the regulating centre (Strydom and Holdsworth 1968). Similarly, it may also have adjusted the relationship between body temperature and cutaneous blood flow, again at the regulatory centre. What does hypohydration do, in terms of how the regulatory centre manages the relationship between body temperature and thermoeffector activity?

Reductions in thermoeffector function at a particular body temperature can be achieved by shifting the thermoeffector activation threshold upwards, or by reducing the effector sensitivity (gain) to changes in body temperature (Werner 2010; Notley et al. 2023a). Several groups have concluded that the hyperosmolality accompanying hypohydration can shift the sudomotor threshold upwards (Fortney et al. 1984; Sawka et al. 1985b; Lynn et al. 2011), while others contend that the gain is reduced (e.g., Montain and Coyle 1992). Isotonic hypovolaemia seems to have reduced the gain for chest and arm sweating, but not that of the legs (Fortney et al. 1981). Hyperosmolality also seems to either shift the threshold for cutaneous vasodilatation upwards (Fortney et al. 1984; Charkoudian 2010) or to shift both the threshold and reduce the vasomotor thermosensitivity (Charkoudian 2010). Whether hypohydration elevates the sudomotor threshold or reduces its gain, the evaporation rate necessary to restore energy balance must be associated with a body temperature that is higher than was observed in the euhydrated state.

We conclude this sub-section with the recommendation that testable hypotheses should be developed pertaining to hypohydration-induced changes in both central thermoregulatory and peripheral thermoeffector function. Those hypotheses should lead to experiments in which changes in thermoeffector thresholds and gains are evaluated across different levels of hypohydration. We further recommend that, following the lead of Claus Jessen (1935–2015, Germany; Jessen 1976, 1981; Fuller and Blatteis 2015; Simon et al. 2022), physiological clamping should be used to control unwanted variability in regulatory feedback. Such studies should commence in resting states, then progress into exercise stress, resulting in the heat source coming primarily from an elevated metabolic rate.

Does hypohydration compromise exercise performance? There are two contexts in which our question may be asked. One context is whether or not hypohydration affects the physiological processes involved in muscular exercise. To the extent that progressive hypohydration leads to hyperthermia, the answer to that question has to be in the affirmative, whenever hyperthermia has an adverse affect on physical exercise. But does hypohydration affect muscular exercise in other ways, such as a prioritisation among our regulatory systems for body temperature, plasma osmolality and blood pressure? Our concern is upon the impact of variations in hydration state upon endurance performance in the heat. Charles Melville (1916) was convinced that soldiers would be unable to effectively perform forced marches when hypohydrated, yet body-mass deficits that approach, or exceed, 5% are commonly encountered within endurance sport and some workplaces (Eichna et al. 1945; Ladell 1945; Armstrong et al. 1986; Rehrer and Burke 1996; Latzka and Montain 1999; Speedy et al. 1999; Beis et al. 2012; Armstrong 2021).

It seems that ~ 50% of the plasma-volume reduction observed during normothermic cycling, when hypohydrated, is due to the impact of exercise alone, which is well known to cause a fluid shift from the vascular space into the intracellular compartment (Sejersted et al. 1986; Björnberg 1990; Maw et al. 1998). That effect is intensity-dependent (Miles et al. 1983). During progressive hypohydration, all body-fluid compartments are reduced, since sweat is drawn from across those compartments (Kozlowski and Saltin 1964; Morimoto et al. 1981; Maw et al. 1998). Thus, no one compartment is sacrificed to preserve the integrity of another, although the volume lost from the interstitial space exceeds 65%, whilst that drawn from the plasma represents ~ 15%, at least during shorter-term activities (90 min; Patterson et al. 2014). Since venous pooling also occurs, hypohydration in the heat will also tax blood-pressure regulation (Sawka 1992).

However, it is only at body-mass deficits > 4% that the cardiac output declines (González-Alonso 2012; England), and it can decline substantially (González-Alonso et al. 1997). Whilst exercise-induced muscle pumping enhances venous return, in more extreme situations, the available cardiac output may not be enough to optimally perfuse both the active skeletal muscles and the cutaneous vasculature (Rowell 1974, 1977), although, in most circumstances, there is sufficient reserve to ensure the sharing of that resource (Hales 1996; Kenney et al. 2014). At body-mass deficits of 4% and more, muscle blood flow may be compromised (González-Alonso et al. 1998; Denmark). The consequences of heat transfer from the working muscles are not dramatic, however, because an increased thermal gradient

can compensate for reduced blood flow (González-Alonso 2012). When cycling in the heat, it appears that < 40% of the metabolic heat produced by the legs was transported away in the blood, with the rest being dissipated through the surrounding tissues (González-Alonso et al. 1999). Does the apparent under-perfusion of those muscles have consequences for metabolic-heat production?

Surprisingly, the experimental evidence is that metabolic-heat production is minimally affected (González-Alonso et al. 1999; Trangmar and González-Alonso 2017). Hypohydration to a body-mass deficit of 4% had no significant effect on the steady-state oxygen consumption of trained cyclists working in humid heat (120 min; González-Alonso et al. 1997), nor did it seem to affect the performance of marathon runners in humid heat (Tan et al. 2021; Singapore). Even mass deficits up to 7% seemed not to affect oxygen consumption during treadmill walking in dry heat (Sawka et al. 1985a). Similarly, hypohydration up to a 4% mass deficit added little to the physiological impact of hyperthermia on peak aerobic power (Nybo et al. 2001; Cheuvront and Kenefick 2014; Pethick et al. 2019). Not surprisingly, the onset of "*some dehydration*" and even "*severe dehydration*" (World Health Organisation 2005) does not seem to prevent highly motivated athletes from racing at the front and winning endurance races (Armstrong et al. 1986 [8.1% mass deficit]; Speedy et al. 1999 [10–12%]; Beis et al. 2012 [9.8%]). In fact, moderate hyperthermia and significant hypohydration are concomitants of success, with the fastest finishers being among the most hypohydrated (Sawka and Noakes 2007; Zouhal et al. 2011). Indeed, they are racing against opponents in very similar physiological states; a reality that is lost within the general classifications of hyperthermia and hypohydration.

The metabolic adjustments that skeletal muscles make during hypohydration may accelerate muscle fatigue, so hypohydration will have greater consequences for both whole-body endurance activities and muscle-endurance exercise, than it does for strength or power activities (Institute of Medicine 2005; Cheuvront and Kenefick 2014). Those effects are more pronounced during exercise in the heat than within temperate conditions (Institute of Medicine 2005; Cheuvront et al. 2010; Cheuvront and Kenefick 2014), although hypohydration that develops during exercise is unlikely to affect performances lasting < 60 min. For example, a 75-kg, euhydrated person, sweating at 2 $L.h^{-1}$, without fluid replacement, will take 90 min to reach a 4% mass deficit. Indeed, pre-exercise hypohydration, which some sprint athletes use, is unlikely to influence either performance or deep-body temperature if the subsequent exercise is short, no matter how intense. For example, Che Muhamed et al. (2019, Malaysia) found that the time to exhaustion in an incremental running protocol (~ 10 min) was unaffected by the hydration state. That test was followed by 60 min running (70% peak aerobic power, 30 °C dry bulb) with fluids withheld.

When Wall et al. (2015) tested the time-trial performance (25 km; 33 °C dry bulb, fan-induced wind [32 km h^{-1}]) of cyclists, they found that hydration state (euhydrated, 2% and 3% hypohydrated) had no effect on performance. In 15 studies from which aerobic exercise performance could be assessed, pre-exercise hypohydration to a 4% body-mass deficit led to peak aerobic power decreasing only 2.4% (Deshayes et al. 2020; also see: Institute of Medicine 2005), so the impact of hypohydration on peak aerobic power is much less than that of hyperthermia. In Part 4 of this historical series (physiological adaptation), attention is drawn to the reality that peak aerobic power has limited, if any, prognostic utility for the performances of elite athletes (Noakes and Ekblom 2008).

It might have surprised Melville (1916), as it once surprised us, just how little extra damage hypohydration does to physiological function, over and above that elicited by hyperthermia, in activities involving exercise in the heat. Within resting states, van den Heuvel et al. (2017, 2020a, 2020b) isolated the impact of those two stresses, which are often experienced simultaneously, on some cognitive and physiological functions. They observed that, whilst the sudomotor and cutaneous vasomotor responses were both very sensitive to hyperthermia, the cutaneous vascular and central cardiac responses were largely unresponsive to hypohydration, and it did not appear to affect either whole-body or regional sweat rates during exercise. During self-paced exercise in the heat, evidence from 18 studies in which hypohydration represented body-mass reductions of 3% or more, Périard et al. (2021 [Table 4]; Australia and The Netherlands) found that performance typically decreased by < 5%, although larger effects have been reported elsewhere (Institute of Medicine 2005). Since most occupations involve self-paced work, and since hypohydration seems not to participate significantly to the heat strain of outdoor workers (Ioannou et al. 2022a), then health and safety officers might perhaps contemplate whether the time and cost of maintaining euhydration are justifiable.

The adverse impact of hypohydration on performance is much greater for exercise performed at a constant work rate in the heat than for self-paced work. Such constant work rates are closer to the demands encountered in the military, with most cases of exertional heat illness occurring following forced marches (Shibolet et al. 1964; Alele et al. 2020), as first described before 1900 (Commission des Sciences et Arts d'Egypte 1809; Martin 1837; Gordon 1860). In such scenarios, performance sometimes deteriorates by > 30%, even at body-mass deficits of 2% or less (Périard et al. 2021 [Table 3]), with an extreme case of a 62% deterioration with a mass deficit of 4% (Baker et al. 2008, U.S.A.). In that investigation, well-trained volunteers ran intermittently at 70% of peak aerobic power

(seven, 15-min bouts with 2-min rest, 30 °C dry bulb) while manipulating mass deficits by drinking saline solutions, and then ran to exhaustion at 85% of peak aerobic power. A 4% mass deficit resulted in exhaustion in just 8 min, compared with 26 min when euhydrated. Similarly, hypohydration of < 2% was associated with reduced tolerance times (treadmill walking) in the heat when wearing impermeable clothing (Cheung and McLellan 1997; Canada). Does hypohydration compromise exercise in the heat, independently of hyperthermia? It does, and seriously, but only if the pace is forced and not self-determined.

How should the fluid lost in sweat be replaced? Relying on there being no physiological harm associated with experiencing low levels of hypohydration, and with great faith in a number, Scott Montain and Samuel Cheuvront (U.S.A.) contend that "*if the combination of environment, exercise intensity and duration results in fluid losses of < 2% of body mass without drinking, then fluid intake can be ignored during exercise*" (Montain and Cheuvront 2008 [P. 570]). Now for some context. Consider the rate at which a resting individual loses body water during a day sitting in a chair. From the water losses provided in physiology books (respiratory 0.3 $mL.kg^{-1}.h^{-1}$, transepidermal 0.3 $mL.kg^{-1}.h^{-1}$, urinary 0.89 $mL.kg^{-1}.h^{-1}$ and faecal 0.09 $mL.kg^{-1}.h^{-1}$), our hypothetical 75-kg person would, simply by sitting, approach 2% hypohydration in 13 h, and 4% in 24 h. Those losses gradually elevate the concentration of the blood, which stimulates the central osmoreceptors (Jewell and Verney 1957), giving rise to thirst sensations at about 2–3% hypohydration (Adolph and Wills 1947; Fitzsimons 1972; Denton et al. 1996; Zimmerman et al. 2017; Armstrong and Kavouras 2019) and the release of antidiuretic hormone (Andreoli et al. 2000). If we have water available, we drink (Cannon 1918; Wolf 1958). However, such water deficits are far from incapacitating, and they are well tolerated. Nevertheless, thirst is an extraordinarily complex sensation (Cannon 1918; Andreoli et al. 2000), with very large inter-individual differences in its relationship to body-fluid regulation, such that relying on thirst alone to replace lost fluids during long-duration exercise in the heat can sometimes be precarious. Indeed, thirst is alleviated well before lost fluids have been restored (Silanikove 1994; Kenefick 2018).

Why is thirst so complex? Our regulatory mechanisms are neither on–off controllers, nor are they fine-control systems. For temperature regulation, we do not move from maximal sweating to maximal shivering when our body temperature drops 0.1 °C. Instead, there is an inter-threshold zone separating the activation of those thermoeffectors, which, on average covers a body temperature range of ~ 4.5 °C (Taylor et al. 2019 [Fig. 6]). When recruited, the intensity of thermoeffector activity is proportional to the size and speed of the thermal disturbance (Werner 2010; Notley et al. 2023a; [Fig. 21]). Similarly, thirst is not activated after we lose just 200 mL of water, regardless of how it is lost, since fine-control regulatory systems would not have withstood the pressures of natural selection.

Drinking when thirsty is an attempt to replace lost body fluids (Cannon 1918; Wolf 1958; Fitzsimons 1972), and that behavioural response is subject to the vagaries of other conscious interferences. The deviation threshold for thirst, which is quite variable in healthy adults (Thompson et al. 1986; Danziger and Zeidel 2015), seems to correspond to a 2–3% increase in plasma osmolality (Wood et al. 1982); ~ 280–290 $mOsm.kg\ H_2O^{-1}$ (Thompson et al. 1986). That value is ~ 10 $mOsm.kg\ H_2O^{-1}$ higher than the threshold for an elevation in antidiuretic hormone secretion (Robertson and Berl 1986). The regulatory cells for activating thirst are located on the anterior wall of the third ventricle, and within the anterior cingulate, the parahippocampal gyrus, the insula and the cerebellum (Egan et al. 2003). Unlike its activation, thirst suppression seems to result, not from changes in osmolality, but from more subjective mechanisms (e.g., the presence of water in the mouth; Geelen et al. 1984), including cognitive process (e.g., an awareness of drinking). Thus, thirst suppression can often precede the restoration of lost body fluids (Danziger and Zeidel 2015). As Walter Cannon (1918) told us, relief of the parched sensation of a dry mouth does not imply adequate body-fluid restoration.

Whilst some might suggest there is no reason to sustain either exercise-induced hyper-osmolality or hypovolaemia deliberately, others might challenge that view when applied to competitive athletes (e.g., Mosler et al. 2019), especially if the replacement fluid is water. As will become apparent in Part 4, animals adapt to stresses that regularly disturb our regulated variables. Therefore, whilst excessive hypohydration can absolutely be lethal, its consistent avoidance prevents physiological adaptation, without which individuals, and our species, lose the ability to tolerate stress (Selye 1973). Would anyone recommend athletes and workers to avoid heart-rate elevations? In a rapidly warming world, the avoidance of opportunities to adapt cannot be beneficial. So we might add a rhetorical modifier to our section heading: how often should lost fluids be replaced?

Even if we wished to replace fluid losses, it may not be possible to replace all that is lost during heavy sweating. There are both pragmatic and physiological justifications for that reality. Our focus is on the latter, but fluid replacement is not dictated by how fast we drink. Instead, both fluid replacement and its evaporation at the skin surface are dictated by factors such as the presence of recently ingested fluid, gastric emptying rates, the rate of water absorption from the gastrointestinal tract during exercise, the delay between water absorption and it reaching the sweat glands, the delay before that fluid appears as discharged sweat, absolute air humidity

and the relationship between the volume consumed and the sweat rate required to prevent the development of uncurbed hyperthermia. Fortunately, research from the modern epoch has provided the pieces for this puzzle.

Three of those unknowns were explored in a unique human study, in which Carl V. Gisolfi (1942–2000, U.S.A.) and his team quantified the rates of gastric emptying and water absorption from the duodenum and upper jejunum (Lambert et al. 1996). Data were collected at 10-min intervals during cycling (65% of peak aerobic power, 85 min, 22 °C dry bulb; Gisolfi et al. 2001). Five different fluids (10–15 °C) were consumed across separate trials, and at 10-min intervals (1.1 $L.h^{-1}$). None of the fluids affected either the gastric emptying time (13 $mL.min^{-1}$) or water absorption from the small intestine (~ 7–14 $mL.cm^{-1}.h^{-1}$). The combined duodenal-jejunal absorption rate was 550 $mL.h^{-1}$, which represented 86% of the fluid lost in sweat. That deficit tells us that fluid uptake will not keep pace with water loss, even at low exercise intensities. Others have suggested that the maximum rate of fluid absorption from the gastrointestinal tract is 1.0–1.5 $L.h^{-1}$ (Sawka 1992), and much less during competitive exercise (Costill 1972; Murray 1987) or if the fluid contains glucose (Fordtran and Saltin 1967). One might think that gastric emptying would be faster when hypohydrated, but it is significantly slower (van Nieuwenhoven et al. 2000). Since those absorption rates are much less than the average sweat rate of 3.7 $L.h^{-1}$ of Alberto Salazar in an Olympic marathon (Armstrong et al. 1986), there is some futility in attempts to fully replace water loss in athletes. Indeed, such efforts are incompatible with successful racing.

We know from studies in hypohydrated humans, and other mammals in the heat, that sweat rates suppressed by hypohydration can be restored within minutes of drinking, with restoration occurring well before any fluid is absorbed. That topic is covered in Part 4 of this series, with that anticipatory sweating relying on a promise of fluid to come; a promise that has to be fulfilled. How soon can it be fulfilled following drinking?

Once that fluid enters the blood, there are two more steps before it appears as discharged sweat. The first was revealed serendipitously by Machado-Moreira et al. (2012 [Brazil and Australia]). When investigating the neural control of thermal sweating, atropine sulphate was administered intravenously (dorsal hand), with the aim of blocking whole-body sweating in hyperthermic subjects. Figure 13 shows the time course of that effect, averaged across nine individuals, with infusion commencing at 0 min and the first evidence of a sudomotor suppression at the forehead appearing ~ 40 s later (dotted line). For that to occur, the blood-borne atropine returned to the heart, where it released the parasympathetic brake on the heart rate, which increased by > 40 $beats.min^{-1}$, and then travelled to the cutaneous capillaries of the forehead, left the blood, moved through the interstitial fluid to the sweat glands and attached to the cholinergic receptors of those glands. That attachment blocked sympathetic stimulation, with the forehead sweat rate rapidly decreasing. Thus, once ingested fluid enters the blood, the sweat glands can get access to, and process, that water very quickly. The final piece of our puzzle was provided, in part, by Armstrong et al. (2010, U.S.A.), who gave subjects labelled water (deuterium oxide) immediately before cycling (28.7 °C dry bulb). Since sweating was not primed and body temperatures were not instantaneously increased, sweating was not immediately activated. Nevertheless, that labelled water appeared in the discharged sweat in < 10 min.

Now to some politics. Fluid replacement during recreational exercise, competitive sport or occupational duties is potentially clouded by commercial, and possibly self-interests. We will confine ourselves to the physiological principles and mechanisms behind fluid replacement. Of particular relevance is the notion of Melville (1916), that drinking should be controlled externally and not left to thirst, and whether or not that recommendation has been supported over our century of exercise physiology.

A major limitation, which has sometimes muddied the water, arose from the difficulty of performing the necessary measurements in the field. Fluid loss is typically calculated from body-mass changes, which are generally, but not always, corrected for other sources of water turnover (Cheuvront and Montain 2017). Those changes convey no information about the source of that fluid: intracellular, extracellular, interstitial or intravascular. On first principles, fluid lost by sweating should be replaced by fluid of the same composition as sweat, but that would be unpalatable (Hubbard et al. 1984). Though the manufacturers of commercial drinks might wish it otherwise, by far the most-common

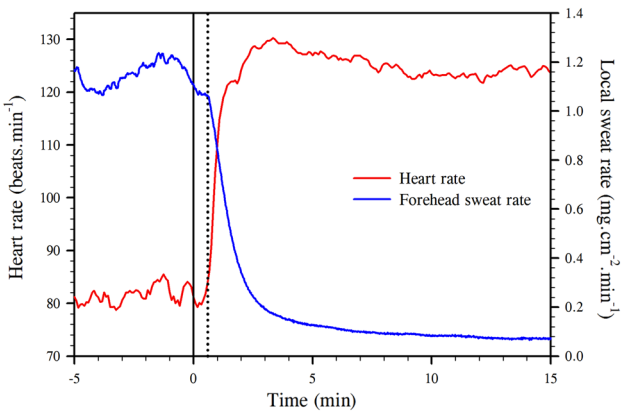


Fig. 13 Local sudomotor and heart-rate responses during thermal clamping with deep-body temperatures elevated 0.5 °C (0–5 min), and followed by an intravenous infusion of atropine sulphate (0 min). Data are average response curves ($N = 9$), extracted from Machado-Moreira et al. (2012) and used with permission

replacement fluid, across the villages, fields and factories of the world, is water. Indeed, why is it that humans, but not other animals, require drinks other than water? That so many humans continue to work and play in the heat indicates that water has been remarkably successful as a replacement fluid, although it may not be ideal for outliers like elite endurance and occupational athletes.

Early in our modern epoch, it was recognised that, even if fluid was readily available, those who engaged in endurance exercise in the heat typically did not consume enough to maintain body mass (Rothstein et al. 1947); they voluntarily hypohydrated (Rothstein et al. 1947; Strydom et al. 1966a; Greenleaf 1992), or did they involuntarily hypohydrate? It seems that thirst alone may not be a sufficiently strong signal to maintain body mass during exercise in the heat, at least during that exercise. Over time, and certainly following food consumption, humans will adequately rehydrate (Adolph 1947a; Rothstein et al. 1947; Maughan et al. 1997); natural selection would have eliminated a sweating specialist incapable of rehydrating. Thus, voluntary hypohydration is not inevitable, with Armstrong et al. (1997) observing that, following pre-exercise hypohydration to a body-mass deficit of 4%, exercising men (90 min treadmill walking, 33 °C dry bulb) restored those mass deficits during exercise whilst drinking ad libitum. So inadequate rehydration during exercise in the heat is not because thirst is absent, but because we choose to ignore it.

Areas of disagreement centre on the possible adverse consequences of voluntary hypohydration, and, more controversially, whether there are adverse and potentially lethal consequences of over-consuming water when exercising. The idea that thirst was a sufficiently strong signal that would terminate exercise in the heat before the damage occurred, was dismissed (Sawka and Noakes 2007). What gained traction was the idea that over-consuming water during exercise can be so dangerous that it should be prevented, and enforcing unnecessary water consumption was probably reprehensible.

The danger arises from exercise-associated hyponatraemia, a condition defined by a serum sodium concentration < 135 mmol.L^{-1}, which is usually, but not always, asymptomatic (Armstrong 2021; Rangan et al. 2021). It can sometimes be fatal due to cerebral oedema (Beltrami et al. 2008; Burke 2019), especially if it develops rapidly (Knechtle et al. 2019). Exercise-associated hyponatraemia was first reported amongst runners in the Comrades Marathon in South Africa (Knechtle et al. 2019; Scheer and Knechtle 2020). Rosner and Kirven (2007) thought that it had caused eight deaths; compare that to the 2,038 fatal heat stroke cases in August of 1896 (Weaver 1897; U.S.A.). In a London marathon (England) run in cool, wet and windy conditions, 12.5% of the competitors had asymptomatic hyponatraemia (Kipps et al. 2011; also see: Knechtle et al. 2011; Rüst et al. 2012). By contrast, in the Rio Del Lago 100-Mile (161 km, U.S.A.) ultra-marathon, run in hotter conditions, asymptomatic hyponatraemia was discovered in 51% of 145 finishers (Lebus et al. 2010; also see: Hoffman et al. 2012).

Symptomatic hyponatraemia is a rare clinical condition, and hyponatraemia resulting from psychogenic polydipsia is nearly five times more common than exercise-associated hyponatraemia, and it tends to lead to more severe signs and symptoms (Rangan et al. 2021). Not everyone who develops the disorder requires medical care (Montain et al. 2001), and the signs and symptoms are no different from those of other conditions which might take participants to a medical tent (Rosner and Kirven 2007; Scheer and Knechtle 2020). Debate continues about whether hyponatraemia is more common in women (Knechtle et al. 2019).

Since its recognition in athletes, hyponatraemia has been reported exuberantly, but the resulting morbidities and mortalities seldom matched the consequences of sustained hypohydration, which can be equally lethal. It is perhaps wise to accept that some comments, such that "*the avoidance of over-drinking can absolutely prevent the development of exercise-associated hyponatraemic encephalopathy*" (Noakes 2007 [P. 791]), have greater historical significance than prophetic relevance. Although it does occur in those with normal renal function (Montain et al. 2001), one reason for the kidneys not correcting the hypovolaemic haemodilution (Kipps et al. 2011) is that inappropriate secretion of antidiuretic hormone can sometimes occur during exercise (Siegel et al. 2007; Rosner and Kirven 2007; Hew-Butler 2010). That problem can lead to the kidneys excreting sodium, even without excess fluid intake. Even in those with normal hormonal secretion who develop hyponatraemia, it is not caused by low sodium intake during exercise (Hoffman and Stuempfle 2015), it is not prevented by sodium supplementation (Hoffman et al. 2015) and it is not necessarily corrected by sodium chloride administration following diagnosis, though the symptoms do resolve (Mitchell et al. 2000; Goudie et al. 2006). It is not even confined to those on programmed drinking protocols (Hew-Butler et al. 2015; Burke 2019). Thus, exercise-associated hyponatraemia is much more complex than water intoxication.

What is the solution? If left to their own devices, those exercising in the heat may not drink enough to avoid hypohydration. Drinking as much as possible may elevate the risk of hyponatraemia in a few. So what is the appropriate fluid-replacement regimen? In our first two epochs, many considered that drinking during exercise was a form of feebleness. Contrary to that perception, Marcus Pembrey advised that soldiers "*must drink copiously in order to maintain the reserves of water in his tissues*" (Pembrey 1914 [P. 636]). Similarly, the provision of water during athletic events was once considered to bestow an unfair advantage on competitors. Late in the twenteeth century, the *International Amateur Athletics Federation* prohibited the provision of refreshments in the

first 15 km of long-distance races and forbad the carrying of water (Noakes 1995). It probably was the research of Cyril Wyndham (Wyndham and Strydom 1969a; Wyndham 1977) that excited interest in the dangers of hyperthermia and hypohydration during competitive running, and also led to that athletic federation changing its rules about drinking (Noakes 1995). Thus, the contemporary view is that prescribed drinking is sometimes required while drinking as much as possible is no longer advised. For work- and exercise-related stresses < 1 h, there in no need to replace lost fluids, other than for personal comfort. When exercise is continuous and more protracted (> 1–2 h), or involves exposures over consecutive days, fluid replacement should be implemented, but the debate about how it should be implemented rages.

That debate hinges on the relative merits of two drinking regimens: programmed drinking or ad libitum drinking. Though some regard the concepts as interchangeable (Kenefick 2018), drinking ad libitum includes, but is not confined to, drinking as motivated by thirst. If water is available, we may choose to drink even if we are not thirsty. Ad libitum drinking has long been associated with voluntary hypohydration (Rothstein et al. 1947; Strydom et al. 1966a; Greenleaf 1992), but is that state severe enough to compromise performance or induce harmful hyperthermia?

Although confining body-mass deficits to < 2% does not guarantee the prevention of hyperthermia (Adams et al. 2019), and voluntary over-drinking does not necessarily compromise performance (Sawka et al. 2007; Montain and Cheuvront 2008; Hillman et al. 2013; Cotter et al. 2014), the advice given to athletes and workers is to limit deficits to < 2% whilst avoiding over-drinking (Sawka et al. 2007; Noakes 2008b; Montain and Cheuvront 2008; Kenefick 2018; Cheuvront and Kenefick, 2021). Most recently, Hess et al. (2022) offered cool, 237-mL drinks (15-min intervals) during treadmill walking (240 min, heat production 450–480 W). Across different thermal loads, ad libitum drinking kept body-mass deficits < 1%, although subjects drank only about half of the 3.6 L offered.

Ad libitum drinking does not always restrict body-mass deficits to < 2%. During self-paced marching (4 h, 29 °C Wet-Bulb Globe Temperature), that practice resulted in average mass losses of 3.8%, with some exceeding 6% (Nolte et al. 2011b). Nor does ad libitum drinking necessarily prevent over-drinking (Tan et al. 2016). Programmed drinking is more likely to result in the attainment of targeted body-mass deficits because it removes spontaneity. What Melville (1916) had in mind was a form of externally dictated programmed drinking. Today, programmed drinking usually would be autonomous, but it has to be learned and rehearsed. It also requires an estimate of sweat rate, for which we have no physiological sensors.

Valid estimations of sweat rates may be achieved from body-mass changes (Gosselin, 1947; Baker et al. 2009; Cheuvront and Montain 2017), although that is frequently inconvenient. Even less convenient are the high-validity measures of plasma and serum osmolality (Adolph 1947b; Sawka et al. 1983). That leaves the much less valid urine indices: colour, specific gravity and osmolality (Zambraski et al. 1975; Armstrong et al. 1994). Perhaps less valid still are salivary flows and osmolality (Gregerson and Bullock 1933; Walsh et al. 2004; Taylor et al. 2012), and bioelectrical impedance (Kushner and Schoeller 1986; Ellis and Wong 1998; Liu et al. 2011). Readers are directed to reviews in which the strengths and limitations of those indices have been reported (Oppliger and Bartok 2002; Shirreffs 2003; Armstrong, 2005; Institute of Medicine 2005; Cheuvront and Kenefick 2014; Hew-Butler et al. 2018).

One reason the debate about drinking strategies can be sustained is because the differences in performance between ad libitum and programmed drinking regimens, at least during running and cycling (Burke 2019), are small. If ad libitum drinking led to better performance and eliminated the risk of both hyponatraemia and hyperthermia, there would be no debate. But it achieves none of those goals. For example, performance on simulated cycling hill-climbs in the heat was slightly worse (and final hydration worse) with ad libitum drinking (Bardis et al. 2017). In other competitive-exercise simulations in the heat, no performance differences existed between those drinking strategies (e.g., Dion et al. 2013), although Dugas et al. (2009) found that ad libitum drinking resulted in slightly better performance, and equal to the somewhat trivial mean benefit (1%) calculated by Goulet and Hoffman (2019), although we counsel against the injudicious use of systematic reviews in Part 4 of this review series. Whatever the consequences of ad libitum drinking are for performance, that practice is associated with higher deep-body temperatures than is programmed drinking. That was known nearly 80 years ago (Pitts et al. 1944), and it has been reinforced in the modern epoch (e.g., Bardis et al. 2017). Since those temperature differences have often been small, they do not generally cause alarm (Marino et al. 2004; Dugas et al. 2009; Bardis et al. 2017).

For endurance exercise in the heat that lasts < 60 min, regardless if its intensity, fluid replacement is not required. Beyond that duration, and when sweating at 2 $L.h^{-1}$, it will take 90 min to reach a body-mass deficit of 4% without fluid replacement. Of course, as noted earlier, many elite endurance athletes will almost double that sweat rate, and we have already described body-mass deficits of 8–12% (Armstrong et al. 1986; Speedy et al. 1999; Beis et al. 2012). We have now entered the zone where fluid replacement should occur, but not commencing at 90 min; drinking needs to commence early to avoid the effects of delayed absorption rates. The volumes consumed should relate to both the environmental conditions and the exercise demand. In occupational settings, we recommend programmed drinking. That

also extends to recreational activities, although the capacity to implement that practice is often restricted by factors beyond the control of the athlete (e.g., positioning of drink stations, opportunities to drink in team sports). What are the solutions?

To estimate the required fluid volumes, we could use body-mass targets, with the aim of preventing mass decrements > 2–3%. Alternatively, we could assume a fluid loss of 30 mL.kg^{-1}, which would represent a 3% mass deficit, but how frequently should we drink? As an illustrative example, we will use data from long-duration exercise during which deep-body temperatures were sustained at 38.0°–38.5 °C, which was consistent with the recommended health and safety upper limit for physically demanding occupations (Jacklitsch et al. 2016). Participants ($N = 12$) performed intermittent cycling (35.6 °C dry bulb) to sustain that deep-body temperature target in each of three trials. In two trials, body-mass deficits of 7% were achieved (> 6 h), whilst the third trial was aimed at a mass deficit of 3% (Taylor et al. 2009, 2012). Body masses were measured at each 1% target and corrected for food and fluid intakes as well urine output. The average whole-body sweat rate was ~ 1.2 L.h^{-1} (95% confidence interval 0.10 L.h^{-1}) and the lower confidence interval (95%) for reaching a 3% body-mass deficit was 115 min. Higher sweat rates would be expected for competitive endurance athletes. For the individuals just described, a fluid consumption of 300–600 mL every 15–30 min would offset those fluid losses, but since Gisolfi et al. (2001) found their exercising participants only absorbed 550 mL.h^{-1}, then fluid consumption beyond that would seem futile. One solution is a fluid intake of 30 mL.kg^{-1} of body mass every 115 min, provided in smaller volumes at 15–30 min intervals (Taylor et al. 2021), in agreement with Latzka and Montain (1999). Sex-dependent fluid requirements are not apparent (Maughan et al. 1997). This is not rocket science.

Marcus Pembrey (1914) would be gratified that his campaign to encourage free access to water had succeeded, though it may have taken a century. Charles Melville (1916) would be incensed that the responsibility for drinking would no longer reside with those in charge. He would, however, recognise the drinking stations used in modern endurance events, since that is what his opponents from the First World War had in mind. He would have no concept that, one day, people would die because they drank too much water.

What should our drinks contain? In addition to fluid replacement, we must also consider the electrolytes lost in sweat and metabolic fuel used during exercise. In another illustration that this too is not rocket science, Ron Maughan (England) advised that it is absolutely unnecessary to consume any substances for which it has not been established that their absence will limit workplace or athletic performance (Maughan 2003). Extended-duration work (> 2–3 h), particularly if meals are delayed, should be accompanied by sodium, chloride and carbohydrate supplementation (Maughan et al. 1997; Burke, 2008; Montain and Cheuvront 2008). If regular meals are possible, then water is all that is needed, as the electrolytes lost in sweat are replaced when eating (Pitts et al. 1944; Rothstein et al. 1947; Maughan et al. 1997). Extended-duration, high-intensity exercise will deplete muscle glycogen and plasma glucose concentrations, and that can even lead to hypoglycaemia, as well as to central and peripheral fatigue (Levine et al. 1924; Christensen and Hansen, 1939; Allen et al. 2008; Hargreaves 2008; Taylor et al. 2008b). However, for activities lasting 60–90 min, carbohydrate supplementation appears to be unnecessary (Hawley et al. 1997). For longer activities (> 4–5 h), electrolyte supplementation may be required (Maughan 2003), but for most people, electrolyte replacement is not essential (Lamb and Brodowicz 1986). Whilst sodium in drinks was believed to enhance gastrointestinal water absorption (Lamb and Brodowicz 1986; Montain and Cheuvront 2008), the evidence of Gisolfi et al. (2001) is inconsistent with those interpretations. The presence of carbohydrates in drinks seems to enhance both water and sodium uptake (Maughan et al. 1997; Gisolfi et al. 2001), although Fordtran and Saltin (1967) thought otherwise.

To estimate the electrolyte requirements of drinks, we require knowledge of both sweat rates and sweat composition. Sweat sodium and chloride compositions are flow-dependent (Dill et al. 1938; Kuno 1956; Sato and Dobson 1970), but not potassium concentration (Ohara et al. 1974). Since temperature-dependent sweat rates can vary twofold, even within the same person (Allan and Wilson 1971), then analyses of sweat composition must be determined simultaneously, and also reported, with sweat rates. Sweat compositions in the absence of flow data have no physiological relevance. With that in mind, Taylor and Machado-Moreira (2013) found six studies that satisfied the necessary criteria. When averaged across those studies, the 95% confidence intervals for sweat sodium, chloride and potassium losses were 26.5–49.7, 26.8–36.7 and 2.7–4.5 mmol.L^{-1} (respectively) for whole-body sweat rates from 0.72 to 3.65 mg.cm^{-2}.min^{-1} (0.78–3.96 L.h^{-1} for an adult 1.8 m^2). Sex differences at similar sweat rates are minimal (van den Heuvel et al. 2007; Baker et al. 2018), with differences in whole-body sweat rate primarily being a function of body size among men and women of similar aerobic fitness (Notley et al. 2017).

To move from rocket science to reality, let us conclude by stating that commercial sports drinks are unnecessary. The evidence shows that carbohydrate supplementation is not required for activities lasting 60–90 min (Hawley et al. 1997), while activities lasting > 4–5 h may require electrolyte supplementation (Maughan 2003). A cheap and effective solution is to make drinks that can be adjusted to individual

taste preferences: add 50 g of glucose to each L of tap water, add 0.5–1.0 g of table salt (sodium chloride) and flavour as desired (Taylor et al. 2021).

Exertional heat stroke: not killed by the sun, but by the forced march

A substantial body of knowledge had been accumulated about heat stroke before the Krogh-Hill epoch. Thankfully, the heat-stroke epidemics in India and the Middle East have not recurred in the modern epoch, although heat waves still claim lives, and not always in regions where they might be expected (Perčič et al. 2018; Zhang et al. 2018; Oudin et al. 2020). With anthropogenic climatic disturbances, that may change (Intergovernmental Panel on Climate Change 2021, 2022; Bouchama et al. 2022). There are notable isolated events that are associated with heat illnesses, and one of those involves the world's largest human gathering; the annual Hajj pilgrimage to Mecca (Saudi Arabia). Its timing is determined by the Islamic calender, and when it coincides with summer, pilgrims are faced with air temperatures averaging 43 °C. During the 1985 Hajj, there were 1012 heat-stroke deaths (Al-Khawashi et al. 1983; Ghaznawi and Ibrahim 1987). Let us now follow the journey of exertional and classical heat stroke, and other less-catastrophic heat illnesses, into the modern epoch (also see: Kosaka et al. 2004; Leon and Bouchama 2015; Laitano et al. 2019; Epstein and Yanovich 2019; Bouchama et al. 2022; DeGroot et al. 2022). Given that our focus is upon exercise, our discussion is restricted to exertional heat stroke.

Have early ideas about exertional heat stroke been supported? To answer that question, we require an understanding of the relevant physiology and pathophysiology. In other areas of thermal physiology, such knowledge usually has emerged from controlled experiments, often by amalgamating data from experiments on humans and other animals. One limitation of non-human research is that no other animal sweats like a human, but experiments mimicking exertional heat stroke (EHS) are unthinkable in humans, so most of our knowledge is anecdotal in nature or comes from military personnel and athletes. Supplementing that knowledge is a substantial collection of research from the mining industry (Wyndham 1974; Mitchell and Laburn 2022).

Physicians and physiologists had provided an admirable understanding of heat stroke when we emerged from the Krogh-Hill epoch. We knew that heat stroke occurred when the regulation of body temperature was overwhelmed by heat and when body temperatures rose above 40 °C (Weaver 1897; Tigerstedt 1906). What usually was overwhelmed was evaporative cooling, either because not enough sweat was produced, because clothing prevented its evaporation at the skin, or because evaporation was impaired by high absolute humidity or low wind speeds. The heat source was usually metabolic and it typically affected otherwise-healthy young people, but it was not restricted to those of European ancestry. Athletes had not yet been recognised as candidates for heat stroke, but that would change (Hughson and Sutton 1978; Sutton 1979; Hart et al. 1980). The heat source could also be external, as in classical heat stroke (Bouchama et al. 2022), but the populations at risk from that had not yet been identified. Severe heat stroke led to delirium, coma and convulsions, and fatal heat stroke often was associated with blood coagulation (Bouchama et al. 1996), usually presenting 18–36 h later (Shibolet et al. 1962). Death often did not occur when thermoregulation was first overwhelmed, but 24 h or more later (Wakefield and Hall 1927; Horowitz 2022). Heat-stroke risks could be reduced by providing water and permeable clothing, and through heat adaptation, but if it occurred, then passive cooling of the skin was a generally successful therapy, either by mimicking the evaporation of sweat using skin wetting and fanning or by cold-water immersion or ice rubbing (Withington 1895; Pembrey 1902; Fantus 1934; Ferris et al. 1938).

From our heritage concerning heat stroke, we highlight the following points. Women indeed are vulnerable to exertional heat stroke, in the same circumstances in which men are, but epidemiologically, men are about twice as likely to experience the condition (Gifford et al. 2019). Tonic and clonic seizures occur frequently in serious cases, but are amenable to treatment with medication used for seizures in other circumstances (Leon and Bouchama 2015). In classical heat stroke, the skin invariably is hot and dry (e.g., Ferris et al. 1938), and it can be in exertional heat stroke too (Pembrey 1914; Hearne 1919, 1920), although we have long known that the skin can be wet (Willcox 1920a; Shibolet et al. 1964), and some individuals will still be sweating profusely when they collapse (Epstein and Yanovich 2019). Indeed, among 36 cases of exertional heat stroke, with 7 deaths, only one of the 29 casualties, for whom skin wetness was recorded, had dry skin at the time of collapse (Shibolet et al. 1967). Marcus Pembrey's (1902) conclusion that the risk of exertional heat stroke could be reduced by regularly working in the heat has been supported, with the most complete support coming from the South African gold mines (Wyndham 1974). Pembrey correctly claimed that the risk could be reduced through hard work on cold days (Leon and Bouchama 2015), because those adaptations also elevate heat dissipation and tolerance (cross-adaptation; Eichna et al. 1945; Allan 1965; Piwonka et al. 1965; Strydom et al. 1966b; Irion 1987; Houmard et al. 1990).

With regard to deep-body temperatures and exertional heat stroke, we must consider three critical issues: which body temperature should be measured, at what threshold does heat stroke occur and what is the highest temperature

from which recovery is possible. There is no doubt that the best deep-body sites for measuring true body temperature are those that rapidly equilibrate with, and then faithfully track, temperature changes within the body tissues of greatest pathophysiological relevance (Taylor et al. 2014a; Notley et al. 2023b). The rectum is not such a site, although it might be an essential first-response measurement. If one can be certain that the patient has been thermally stable for at least 60 min, then we would agree. However, thermal stability is highly unlikely for casualties of exertional heat stroke in the field, but it may exist for individuals with classical heat stroke. Does a low rectal temperature remove concern, or is it a false negative in a dangerously over-heated individual? Does a high rectal temperature confirm heat illness, or is it a false positive in a person who is already cooling? How do we interpret Withington's (1895) report of rectal temperature stability "*for fifteen minutes after death*" (P. 514)? By all means, take a measurement. We recommend, as have others (Shapiro and Seidman 1990), that if someone has been in a situation that could lead to heat illness, and is displaying signs and symptoms of heat illness, whilst other life-threatening illnesses can be excluded (e.g., cardiac arrest), then that person should be treated for heat illness, whatever the rectal temperature, since appropriately applied passive cooling is unlikely to cause further harm.

Whilst high temperatures raise an alarm in suspected heat-stroke cases, the temperature itself is not pathognomonic for heat stroke (Laitano et al. 2019), and we are unable to agree with the proposition that "*the determination of hyperthermia (as identified with an immediate rectal temperature) before treatment is a foolproof manner for identifying EHS victims (along with the presence of CNS changes)*" (Casa et al. 2010b [P. 1251]; U.S.A.). Also, if the patient has been cooled properly at the site of the incident, that individual will arrive at the hospital normothermic, or close to it, and that is why a non-thermal biomarker of heat stroke is essential (for legal purposes) for a positive diagnosis (Mitchell and Laburn 2022). Our position does not deny that high body temperatures are the root cause of heat stroke, but we are certain that, in the field, we cannot define a threshold temperature at which heat stroke can be reliably diagnosed.

What then can we say about deep-body temperatures during exertional heat stroke from which recovery without *sequelae* has been possible? For accountants, there are numerous signposts along that journey, from which we highlight the following contributions: Weaver (1897) described survivable temperatures of 44.3°–46.1 °C; Tigerstedt (1906) reported authenticated and survivable temperatures of 43.6 °C ("*sunstroke*"), 44 °C ("*scarlatina*" [scarlet fever]) and 46 °C (possibly malaria); Hehir (1922) thought that a survival limit was 43.9 °C; Dreosti (1937) found that recovery did not occur when temperatures were > 41.7 °C; Ferris et al. (1938) had four patients with temperatures of 44.4 °C, two of whom survived; Shibolet et al. (1964) described 20 cases in heat-adapted soldiers, with temperatures from 40.0° to 41.8 °C; Hart et al. (1982) reported 24 cases of survivable, classical heat stroke within the temperature range 41.4°–47.0 °C; Slovis et al. (1982) described recovery of a man from classical heat stroke with a temperature of 46.5 °C; Epstein and Yanovich (2019) told us of temperatures in marathon runners close to 43 °C (also see: Kenney et al. 2004); and temperatures of 43°–45 °C are used in the topical treatment of cancer patients (Werner 2014; Simon et al. 2022). Thus, it is clear that we do not know precisely from which deep-body temperature a casualty of exertional heat stroke can recover successfully; temperatures seems to be case-specific and there is no absolute threshold (e.g., < 45 °C). Furthermore, we do not know why deep-body temperatures well over 40 °C can apparently be tolerated without harm. In the days of the British army in India, heat-stroke mortality rates were as high as 51–88% (Gordon 1860; Waller 1869). Today, largely because of successful cooling practices, the mortality rate is probably < 5% (Epstein and Yanovich 2019), and is much less than that of classical heat stroke (Leon and Bouchama 2015). For those casualties of exertional heat stroke who do come to harm, what harm is it and why does that harm occur?

In accounts of human thermal physiology, one encounters statements to the effect that cell chemistry collapses at temperatures > 40 °C, with those effects including the irreversible denaturation of proteins, blood coagulation, skin haemorrhages, a decreased ability to form and pass urine, gastrointestinal bleeding, muscle damage (rhabdomyolisis), neural necroses, myoglobin in the urine and myocardial inflammation (Vertel and Knochel 1967; Ellis 1976; Hart et al. 1980; Hales et al. 1996; Gaffin and Hubbard 2001; Leon and Bouchama 2015; Wesdock and Donoghue 2019). Some generalisations may have arisen through a lack of familiarity with comparative thermal physiology. With fundamentally the same cell chemistry, including proteins, some invertebrates have fully functional sensory and motor systems when their body temperatures exceed 50 °C (Mitchell et al. 2018).

Another frequent pronouncement is that the brain is exquisitely thermally sensitive. In one sense it is: the earliest signs of impending heat and cold illnesses are abnormal behaviours, such as confusion, aggression and slurred speech, with delirium, seizures and coma being signs of severe exertional heat stroke (Bouchama et al. 2022). But those signs arise because brain function is thermally sensitive, not because the brain tissue is thermally vulnerable. Perhaps with the exception of the Purkinje cells of the cerebellum (Leon and Bouchama 2015), brain tissue is much less sensitive to thermal damage than many other body tissues (Burger and Engelbrecht 1967), and the accompanying

thermoregulatory aberrations are not the result of hypothalamic-tissue damage (Sawka et al. 2011; Leon and Bouchama 2015; Laitano et al. 2019).

The heat-stroke deaths in South African gold mines were generally fast deaths (Mitchell and Laburn 2022), presumably resulting from thermal damage to sensitive organs. Most heat-stroke deaths are not immediate, and the harm is multi-organ failure and disseminated intravascular coagulation (Sawka et al. 2011; Leon and Bouchama 2015; DeGroot et al. 2022), which is considered to emanate from thermal damage to the gastrointestinal tract. Gut endotoxins enter the blood stream (Epstein and Yanovich 2019; Adams et al. 2020), and, if severe enough, gut micro-organisms will also invade (Sawka et al. 2011; Leon and Bouchama 2015). Activation of the innate immune functions follows, with cytokine release (Sawka et al. 2011; Bouchama et al. 2022) and diffuse inflammation. The resulting endotoxaemia often leads to endotoxic shock (Bouchama et al. 2022). If the liver remains functional, which it can do for at least 48 h (Sawka et al. 2011), endotoxins are cleared rapidly from the circulation, and may not be detected when patients are hospitalised (Laitano et al. 2019), though they will have initiated a sequence of adverse changes.

Those effects can be compounded by rhabdomyolysis (Sawka et al. 2011; Epstein and Yanovich 2019), which has unique features in cases of exertional heat illness (Oh et al. 2022), and the contents of ruptured muscle cells can cause, or exacerbate, kidney damage (Bouchama et al. 2022). The delayed liver dysfunction that is part of the multi-organ failure has an important diagnostic corollary, with extraordinary and long-lasting elevation of liver enzymes (Sawka et al. 2011; Abriat et al. 2014) serving as identifiers of heat stroke, even if a patient presents in a normothermic state, after successful cooling (Kew et al. 1971; Mitchell and Laburn 2022). Though Schlader and colleagues (2011) do not mention any liver biomarkers of heat stroke, liver enzymes (alanine aminotransferase and aspartate aminotransferase) can have elevated blood concentrations for many days, even after successful cooling (Ward et al. 2020). Resolution of the signs, symptoms and biomarkers does not necessarily imply a readiness to resume exercise in the heat (Adams et al. 2020). Those who recover from exertional heat stroke appear to have an elevated risk of experiencing further episodes (DeGroot et al. 2022; Schermann et al. 2020).

Exertional heat stroke in the workplace The heat-stroke casualties from our first two epochs often were soldiers and miners, although they were not the only workplace casualties (Yang et al. 2017; Ioannou et al. 2021, 2022a), and so it was the prevention of occupational heat illnesses that drove research towards identifying high-risk situations. In the penultimate section of this communication, we review and critique the indices of thermal stress and strain that arose from that research. The most widely used of the heat-stress indices is the Wet-Bulb Globe Temperature index developed by Yaglou and Minard (1957) after the Second World War, with a focus on preventing heat illness in occupational athletes within the military.

Exertional heat stroke continued to occur in the military in the modern epoch (Shibolet et al. 1964), with 4,188 cases in the U.S. military between 2008 and 2018 (Filep et al. 2020). One might have thought those most at risk would have been engaged in active combat. Indeed, 6% of military patients, over a two-year period during the British campaign in Afghanistan, had heat illness, an incidence second only to infective diarrhoea (Cox et al. 2016). Of the 1,531 patients at one British field hospital during the first year of the second Gulf War, 16% had exertional and classical heat illness whilst 31% had diarrhoea and vomiting (Grainge and Heber 2005). Most cases of exertional heat stroke have been associated with military training, and ought to have been preventable, yet they have occurred within many military forces: the U.S. (Malamud et al. 1946; Donham et al. 2020), Israel (Rav-Acha et al. 2004), Thailand (Sithinamsuwan et al. 2009), France (Abriat et al. 2014; Gasc et al. 2022), India (Deshwal et al. 2017) and many other countries (Alele et al. 2020). From those, we have extracted some common themes and some discrepancies.

The true incidence of exertional heat stroke has been underestimated because threshold deep-body temperatures of 40 °C (Donham et al. 2020; Schermann et al. 2020), or 39 °C in France (Abriat et al. 2014), have sometimes been a requirement of diagnosis. So a dehydrated soldier outside France, who presents with neurological signs and perhaps convulsing, but with a deep-body temperature of 39 °C, might not be diagnosed with exertional heat stroke. We maintain, as do Belval et al. (2018), that deep-body temperature thresholds should not be used for diagnosis, and especially on presentation at the hospital.

Although perhaps half of the exertional heat-stroke cases would have been missed (Donham et al. 2020), there has been a huge reduction in military mortalities to ~ 5% (Rav-Acha et al. 2004; Donham et al. 2020), with some considering that its elimination as a cause of death is attainable (Deshwal et al. 2017). Although Yang and colleagues (2017) deny that proper cooling is the explanation, rapid on-site cooling seems to explain the mortality reduction, and also the resolution of neurological signs (Abriat et al. 2014), as well as disseminated intravascular coagulation (Donham et al. 2020).

The preferred cooling method in the military has been passive, cold-water immersion (Gasc et al. 2022). On a first principles basis, immersion in the coldest water possible should facilitate the most rapid heat removal (Fourier 1807), but, whilst physiological heat exchanges have to obey thermodynamics (Notley et al. 2023a), colder water does

not automatically mean faster heat removal, because thermal energy must first be brought to the cutaneous tissues. That requires sustained cutaneous vasodilatation, and we will return to that point in due course. Typically, immersion cooling is aimed at reducing deep-body (rectal) temperature to 38 °C within 30 min. Cold-water immersion is not always feasible, but even if it was used, that cooling target was seldom achieved (Sithinamsuwan et al. 2009; Gasc et al. 2022). A convenient and successful alternative to cold-water immersion is water spraying and fanning (Pembrey 1902; Fantus 1934; Deshwal et al. 2017).

The typical casualties of exertional heat stroke during military training were fit young men, with high self-motivation to perform (Deshwal et al. 2017), possibly compounded by questionable management practices (Rav-Acha et al. 2004; Gasc et al. 2022). Motivation can be maladaptive, particularly during competitive events (Shapiro and Seidman 1990) or when job security is uncertain. Moreover, lessons from the ninteenth century about the inappropriateness of military clothing for exercise in the heat had not always been learned and carried into the modern epoch (Abriat et al. 2014; Deshwal et al. 2017).

As we have long known, the source of damaging heat was metabolic (Shibolet et al. 1964), not ambient heat; one group found that 19% of heat-stroke cases occurred at ambient temperatures < 15 °C (Abriat et al. 2014). Casualties frequently were dehydrated (Deshwal et al. 2017; Alele et al. 2020), contrary to the earlier evidence and subsequent observations that "*dehydration, hypovolemia and electrolyte derangement are not common in heat stroke*" (Clowes and O'Donnell 1974 [P. 566]). Dry skin was common (Ferris et al. 1938; Deshwal et al. 2017; Alele et al. 2020), but military casualties were often sweating profusely when they collapsed (Shibolet et al. 1964; Abriat et al. 2014); "*in most cases the sweat glands are still very active at the stage of heat stroke collapse, and profuse sweating is likely to be present in most patients. Dry skin is a late phenomenon of heat stroke*" (Shapiro and Seidman 1990 [P. 6]).

Another occupation in which the risk of exertional heat illness is elevated is deep mining (> 3 km; Mavrogordato and Pirow 1927). However, while dry-bulb temperatures in those mines do not attain the levels associated with military casualties (< 37.3 °C; Krige 1939; Dreosti 1950), ambient water-vapour pressures approach saturation point due to water spraying for dust suppression. Thus, a high absolute humidity reduces the dissipation of metabolic heat and was the primary casual agent of heat illness (Cluver 1932; Dreosti 1950; Mitchell and Laburn 2022). Although the number of heat-stroke cases was small, it attracted attention and investment in mine cooling and heat-stroke research, because it had the potential to affect > 300,000 employees of private, profit-oriented industries, in which men worked at the limit of physiological tolerance.

Eustace H. Cluver (1895–1982, South Africa; Gear 1982; Mitchell and Laburn 2022) described 92 fatalities of exertional heat stroke that occurred underground (1924–1932; Cluver 1932). Underground supervisors carried some responsibility for those cases, as complaints of thirst and fatigue were "*unsympathetically received by an efficient boss-boy* [onsite supervisor]*, even though he has been warned about the symptoms of impending heat stroke*" and the miner "*will be urged none too gently to resume his work*", and occasionally with "*blows*" (Cluver 1932 [P. 19]). Similarly, Aldo O. Dreosti (1902–1971, South Africa; Orenstein 1971; Mitchell and Laburn 2022) reported 71 cases at one mine hospital, of whom 31 died, whilst Cyril Wyndham presented 126 cases (1956–1959), of whom 27 died (Wyndham 1966). From those data, he suggested that only a 50% survival rate could be expected for those with rectal temperatures on admission of 42.2 °C, whilst he estimated the probability of death to be 100% at 45 °C. Most cases occurred in new miners or in those returning from a period away, but self-motivation was not the precipitating factor. That led Dreosti (1937) to suggest that heat stroke in the mines was preventable.

At that time, the practice was to rapidly transport casualties to hospital, which could take hours, with deaths frequently occurring before, or soon, after arrival. There were formal enquiries into all deaths, as there was then a strong labour movement represented in the government. In Wyndham's time, supervisors were held responsible for deaths and could be charged criminally (Mitchell and Laburn 2022). Amongst the practices introduced by Cyril Wyndham was obligatory cooling at the site of the incident (water splashing and forced evaporation with compressed air), until rectal temperature dropped to 38.3 °C, if a thermometer was available, or for two hours if not (Wyndham 1966; Mitchell and Laburn, 1985). But those benefits were overshadowed by his introduction of supervised heat adaptation in climatic chambers, sometimes holding 1000 miners and running four shifts a day (Mitchell and Laburn 2022); no one is ever again likely to run heat-adaptation programmes for hundreds of thousands of individuals (Wyndham and Strydom 1969b; Wyndham et al. 1973). Through that work, Wyndham demonstrated that exertional heat illness in miners was indeed preventable (Wyndham 1974). We will return to that research in Part 4 of this series, in which we describe and discuss thermal adaptation.

Exertional heat stroke in sport One of our earliest exercise physiologists was Fernand Lagrange (1846-1909, France). He knew that "*the indispensable condition of movement in the human body, just as in all other heat engines, is the production of heat*" (Lagrange, 1889 [P. 34]). He would not have realised that metabolic heat production during exercise, and particularly during competition, could

Fig. 14 Heat exhaustion during distance running. Jim Peters (England) in the men's marathon of the 1954 Empire Games (Vancouver, Canada; 28 °C dry bulb). Peters was then the world marathon champion. As was his habit, he drank nothing during the race, and entered the stadium 17 min ahead of the next runner. He then covered 200 m in 11 min, staggered and fell. In hospital, 68 min after collapsing, he was hypernatraemic and his rectal temperature was 39.4 °C (Noakes et al., 2008). Noakes and colleagues, one of whom had been a competitor in that marathon, dismissed the diagnosis of heat stroke in favour of transient encephalopathy. Because we do not accept that a temperature threshold is required for that diagnosis, we do not dismiss heat stroke as a possibility. Jim Peters never ran competitively again. Reproduced with permission of the Commonwealth Games Federation. Source: https://thecgf.com/stories/commonwealth-sports-moments-5-jim-peters-collapses-end-marathon-1954-british-empire-games Accessed: November 21st, 2022

impose a heat load on the body greater than even tropical, solar radiation. Lagrange would have been very concerned about what was happening to Gabriela Andersen-Schiess when she was trying to complete the final 400 m (4 min 45 s) of the first women's Olympic marathon in 1984 (https://www.youtube.com/watch?v=LTLBejleWiI). "*Hyperthermic, dehydrated and hemi-paretic, her extreme distress drew disgust and dismay from helpless onlookers … this hapless, ataxic athlete crossed the finish line to collapse into the arms of waiting medics, a vision indelibly etched in the memories of spectators and television viewers alike*" (Gerrard, 2020 [P. 45]). When she reached the medical tent, her rectal temperature was 38.7 °C (Murphy, 1984), but she returned to racing 2 weeks later. Lagrange would also have been worried for Jim Peters (Fig. 14), the one-time world record holder for the men's marathon, when he was racing 30 years earlier. The former example was unfortunate, not just for the athlete, but because it appeared to support the misguided prejudice that the marathon was too difficult for women! Curiously, those striking examples attracted far more attention than did heat stroke on the battlefields or in the mines.

When we engage in endurance pursuits, we rely heavily upon our oxidative energy sources. Compared to other large mammals, evolution has left us rather poor at converting fuel into energy anaerobically, but very good at utilising our aerobic energy sources, and *Homo sapiens* is the only animal that engages in endurance exercise for recreational purposes. Whilst natural selection has endowed us with the potential to perform that exercise in the heat, we do have limits, and we can come to grief when challenging those limits. Perhaps Lagrange would not be surprised to find that exertional heat stroke is exceeded only by cardiac conditions and brain injury as a cause of fatalities in sport (Filep et al. 2020).

Although football (soccer) is the most-popular team sport, running is the recreational exercise in which the greatest number of us engage. We evolved to jog, but since we are a competitive species, merely jogging could never satisfy our urges, and races of ever-increasing distance began. To our knowledge, the earliest scientific communications concerning marathon runners, and their physiology, were written by physicians (Boston Marathon; Gordon et al. 1924; Levine et al. 1924; U.S.A.). After a substantial gap, two important papers on marathon running appeared in the 1960s: Buskirk and Beetham (1960, U.S.A.) and Pugh et al. (1967, England). Recreational running bloomed world-wide in the 1970s, as described in the entertaining writing of Peiser and Reilly (2004), and the first guidelines for the protection of distance runners from heat illness appeared in 1975 (American College of Sports Medicine 1975). Very soon thereafter another important paper on marathon running appeared: Maron et al. (1977, U.S.A.).

Those papers set important mileposts for students of exercise and thermal physiology. For instance, Buskirk and Beetham (1960) reported post-race, body-mass deficits of 6%, with deep-body (rectal) temperature elevations of 2 °C. Pugh et al. (1967) told us of a winning marathoner who finished with a rectal temperature of 41.1 °C and a mass deficit of 6.7%. In accordance with the regulations of the time, runners were permitted to drink only at three checkpoints, where observers recorded water consumption and sweat rates were calculated. The sweat rate of the winner was 1.8 $L.h^{-1}$; "*tolerance of a high body temperature is a necessary condition of success in marathon running. Another condition of success seems to be a high tolerance to fluid loss*" (Pugh et al. 1967 [P. 350]). Post-race rectal temperatures of 40 °C were reported by Maron et al. (1977), and they noted that it took 35–45 min for the rectal temperature to stabilise during a marathon. In the next decade, and competing at the 1984 Olympics, Alberto Salazar (U.S.A.) revealed the extraordinary sweat rates (3.7 $L.h^{-1}$) of highly trained, heat-adapted athletes (Armstrong et al. 1986).

Though the marathons we have described were run in cool weather, we are concerned with exercise in the heat. By analysing the outcomes and prevailing weather of seven marathons races in North America, Ely and colleagues (2007b) revealed a progressive reduction in running speed as the Wet-Bulb Globe Temperature increased from 5° to 25 °C.

Possible physiological explanations for performance decrements were hypohydration and the dual demands for blood flow, but the barrier was not a critical deep-body temperature (González-Alonso et al. 2008; Ely and Ely 2020; Notley et al. 2023a). The organisers of early marathons could not have envisaged there would eventually be 136,161 starters in Boston Marathons between 2015 and 2019, during which there were 31 cases of exertional heat stroke, with younger and faster runners being more at risk (Breslow et al. 2021). There were also serious cases amongst 137,580 participants in Tel Aviv (Israel) marathons (2007–2013), two of which were fatal (Yankelson et al. 2014). Whilst some might expect a lower risk of heat stroke in races run in mild weather, in the 2009 Great North Run (north-east England), the world's largest half-marathon race, there were 55 cases from 54,000 runners (Hawes et al. 2010), with four apparently being fatal (Yankelson et al. 2014).

Treating heat-stroke casualties: cool first, transport later In considering how best to treat heat-stroke casualties, let us return to the South African gold miners and what worked for them. Despite the benefits of heat-adapting miners, heat stroke still occurred, so Wyndham and his team tackled the problem by emphasising early recognition and cooling on-site (Wyndham et al. 1959). Recognition clues: aberrant behaviour (e.g., aggression), futile activity and irrational behaviour. Cooling was immediately initiated, although options underground were limited, and so arose a question that has engaged many contemporary thermal physiologists. How do we most effectively cool victims of exertional heat stroke? That question covers four topics: heat removal from the body, heat transfer within the body, the practicalities of cooling and evidence for successful outcomes. In addressing those topics, physiologists followed the steps of their predecessors (e.g., Pembrey 1902; Fantus 1934; Ferris et al. 1938; Wyndham et al. 1959), and recommended cold (e.g., Pryor et al. 2015; Belval et al. 2018) and ice-water immersions (McDermott et al. 2009). Are those treatments physiologically justifiable?

Heat transfer and dissipation are dictated by thermodynamics and by centrally driven thermoeffector control, which is then locally modified (Notley et al. 2023a). As described earlier, ice-water enemata were recommended for heat-stroke patients of the British Army (Beamish 1907; Howard 1920), but dismissed on the basis of first principles (Hill 1920), since evaporating 70 g of water could extract as much heat as a 1-kg enema of iced water. Using that calorimetric argument, the heat extracted by raising the temperature of 100 L of bath water from 15° to 38 °C is equivalent to that extracted by evaporating just over 1 L of water from the surface of the skin. Extracting the same amount of heat by melting ice would require nearly 8 kg of ice. Therefore, evaporative cooling is the most effective of those three ways for removing heat from the body's surface.

When resting in still water, the convective heat transfer coefficient (230 $W.m^{-2}.^{o}C^{-1}$) is roughly 60 times that of still air (Nadel et al. 1974). But moving the water across the body surface at 0.5 $m.s^{-1}$ will increase that coefficient 2.5 times, so if cold water immersion is to be used to cool patients, the water should be stirred continuously (Filep et al. 2020). Indeed, to optimise heat transfer, dousing with cold water ("*two mussucks* [skin bags] *of water were immediately thrown over him*" (Gordon 1860 [P. 993]) is more effective than bathing, because the heat transfer coefficient is higher and its temperature increases minimally, although continual dousing would be required and that will be unpopular.

The advantage that water immersion may have over evaporative cooling relates not to heat removal, but to our second consideration; heat transfer within the body. Because of the high convective heat transfer coefficient into the water, skin temperatures rapidly approach that of the water, but heat can still be dissipated into the water, even though the skin-to-water temperature gradient is relatively small. As a consequence of the lower skin temperature, the temperature gradient between the muscles and the skin will be much higher during cold-water immersion, than it is when using evaporative cooling from the skin. How fast heat flows from muscles to the skin depends upon the temperature gradient between those tissues, but also on whether heat is conveyed convectively (blood borne) or by conduction. Convective transfer is always faster. High rates of convection between the deep body and skin are characteristic of hyperthermia, but what happens when those individuals are immersed in cold or even ice-cold water?

Cutaneous blood flows depend primarily on vasomotor signals emanating from the thermoregulatory centre, in response to thermoreceptor feedback. If the deep tissues are still hot, input from the deep-body thermoreceptors may dominate that received from cooler peripheral tissues during water immersion, and cutaneous blood flow will be sustained. But the concept that the control of the cutaneous vascular tone is always dominated by the central thermoreceptors (Proulx et al. 2003; Casa et al. 2007) does not hold for dynamic thermal states involving the skin, since both localised (Caldwell et al. 2014, 2016) and whole-body skin cooling (Caldwell et al. 2018) induce significantly more powerful vasoconstriction within hyperthermic, than within normothermic individuals. Indeed, the phasic signal received from the cutaneous thermoreceptors during skin cooling is the strongest feedback that the regulatory centre ever receives (Notley et al. 2023a). Furthermore, post-exercise, cold-water immersion also reduces muscle blood flow in mildly hyperthermic individuals (Mawhinney et al. 2013). Thus, if the input from the skin thermoreceptors dominates,

then cutaneous vasoconstriction will be implemented, and heat transfer to the skin must now rely more upon conduction. That possibility was enough for Wyndham and his team (1959) to reject cold-water cooling for hyperthermic miners. Pharmacological agents that prevent peripheral vasoconstriction appear attractive (Mitchell and Laburn 1985), but none has been proven to accelerate cooling (Epstein and Yanovich 2019).

What actually happens to cutaneous blood flow during the cooling of exertional heat-stroke casualties is largely unknown. Predicting those vascular responses is complicated by the circulatory failure that sometimes occurs in severe cases (Epstein and Roberts 2011; Epstein et al. 2015; Tipton et al. 2017), although that is by no means universally observed (Al-Khawashi et al. 1983; Hales et al. 1996). Although we are not aware of any evidence, others seem to have access to information about cutaneous blood flow in heat-stroke patients being cooled. For example, "*peripheral vasoconstriction and shivering occur in normothermic individuals, but EHS* [exertional heat-stroke] *patients either do not exhibit these physiologic responses or if they do, rapid cooling is not impeded*" (McDermott et al. 2009 [P. 89]; U.S.A.), and the effect of ice-water on cutaneous vasoconstriction is "*relatively negligible*" (Noakes 1986 [P. 373]; South Africa); "*… we have all been wrong often*" (Hill 1965 [P. 167]).

Though cutaneous blood flow has not been measured in heat-stroke casualties, it has been measured during the cooling of profoundly hyperthermic volunteers, who were heated to an average oesophageal temperature 39.4 °C (rectal temperature 39.7 °C), using a combination of exercise and ambient heat stress (Caldwell et al. 2018; Australia). During post-exercise cooling in stirred water regulated at 26 °C (temperate) and 14 °C (cold water; separate trials), significantly stronger cutaneous vasoconstriction was observed in the colder water. Consequently, despite the difference in water temperatures, and the resulting skin-water thermal gradients, reducing oesophageal temperatures to 37.5 °C in two different population samples, using those same water temperatures, took only 45–54 s longer in temperate water (Taylor et al. 2008a [45 s]; Caldwell et al. 2018 [54 s]). Since the probability of saving any individual who is < 60 s away from death is negligible in the field, then we remain unconvinced by any evidence that the water needs to be either cold or ice-cold. It is important to note that, even though the oesophageal temperatures had reached 37.5 °C, rectal temperatures were still > 39.0 °C, and did not drop below that value for another 3.8 min (Taylor et al. 2008a). From observed rectal cooling rates of 0.10 °C.min^{-1} (temperate) and 0.18 °C.min^{-1} (cold water; Taylor et al. 2008a), the projected times to reach a rectal temperature of 37.5 °C would have been 14 min (14 °C) and 26 min (26 °C). Proulx et al. (2006, Canada) reported that rectal cooling to that same level took 17.3 min in 14 °C water. Delays of those magnitudes can have significant implications for emergencies, but, as we will soon discuss, rectal cooling rates are often unhelpful, and can even be misleading.

To our knowledge, the first use of ice rubbing and ice bathing was reported by Withington (1895, U.S.A.), with water immersion that "*generally started at 70° or 75°* [21–24 °C]*, and rapidly cooled down by the addition of ice*" (Withington 1895 [P. 513]), but that was not without risk: "*the ice-bath sometimes caused a sudden drop of the temperature to a dangerously low figure, 96°* [35.6 °C]" (P514). Perhaps unsurprisingly, Ferris et al. (1938, U.S.A.) found that excessive cooling often resulted in fatalities. They reported a 32% mortality rate when using ice-water cooling, which may be attributable to complications accompanying a post-immersion thermal after-drop (Currie and Percival 1792; Golden and Hervey, 1981), a phenomenon described in "Deep-body and skin temperatures during and following cold exposure". In one of those fatalities, the casualty was removed from the ice bath with a rectal temperature of 37.2 °C, but it kept falling to 35.6 °C and he developed circulatory failure (Ferris et al. 1938 [P. 258]). As is clear from this historical evidence, a knowledge of when to stop cooling is required. In ice water, that must be well before a rectal temperature of 37.2 °C temperature is reached!

Wyndham (1966) recommended cooling until the rectal temperature reached 38.3 °C. Casa and colleagues (2007) suggest that "*lowering the core body* [rectal] *temperature to less than 40 °C (104 °C) within 30 min should be the primary goal of EHS* [exertional heat-stroke] *treatment*". They subsequently recommended cooling in ice-cold water to a rectal temperature of 38.6 °C (Gagnon et al. 2010), whilst Shapiro and Seidman (1990) suggested terminating at a rectal temperature of 38.5 °C to avoid an "*hypothermic over-shoot*" (P. 10). That termination point was endorsed by Epstein and Yanovich (2019, Israel), and we also endorse that recommendation, regardless of the cooling method used. However, we cannot endorse the following statement from the *American College of Sports Medicine* expert committee on heat illness: "*The recommendation to stop active cooling at ~ 38 °C (101 °F) to prevent hypothermic overshoot is empirical and not based on data showing adverse outcomes. There are no known disadvantages or adverse outcomes from cooling below 38 °C and most "overcooled" athletes will be in the 35–37 °C (95–97 °F) range, which has no adverse physiological effect*" (Roberts et al. 2021 [P. 474]). The 32% mortality rate in heat-stroke patients, following ice-water cooling and reported almost a century earlier (Ferris et al. 1938), is both empirical and adverse, although DeGroot and colleagues (2022) reminded us of the absence of scientific evidence to justify any particular deep-body cooling target. A better indicator for terminating cooling is

perhaps the restoration of normal behaviour (Laitano et al. 2019).

In the field or factory, cold-water immersion or dousing may not be practical, while finding water at 26 °C will be far easier. With the high incidence of diarrhoea and vomiting in heat-stroke casualties (Grainge and Heber 2005), the management of water immersion is both unpleasant and difficult for conscious individuals. Nevertheless, organisers of planned events, in which there is a risk of heat illness, have a duty of care to make available the best options for protecting and treating casualties (e.g., Richards et al. 1979), with cooling facilities possibly being widely distributed as global heating takes hold (Widerynski et al. 2017). In the Krogh-Hill epoch, the Persian Oil Company constructed an anti-heat stroke ward in anticipation of cases (Rennie 1930). Joseph S. Weiner (1915–1982, South Africa and England) and his colleague, Mustafa Khogali (Kuwait), designed a bed in which cooling could be achieved using fine water spray in warm air, in anticipation of heat illnesses during the Hajj (Weiner and Khogali 1980).

But unpredicted exertional heat illnesses will occur, and the requirement for on-site and immediate cooling must prevail, using the best method available. Marcus S. Pembrey (1902) recommended skin wetting and ventilating, which uses water of any temperature and ventilation by any means, and that method is still recommended (Wyndham et al. 1959; Harker and Gibson 1995; Hadad et al. 2004; Yoram Epstein, personal communication). In fact, simply removing the casualty from the heat source, in combination with evaporative cooling, even with minimal air movement across the skin surface, may induce rapid deep-body cooling. Indeed, Caldwell et al. (2018) observed that, during the transition, and preparation of hyperthermic individuals (< 10 min), from a climate chamber (36 °C dry bulb) to water immersion in an air-conditioned laboratory (22 °C), those profusely sweating participants experienced an oesophageal temperature reduction of 0.75 °C. Rectal temperature remained unresponsive (− 0.05 °C). In the field, it is harder to isolate casualties from ambient heat sources, but reducing metabolic heat production, taking advantage of shade, removing clothing and fanning to increase air flow are generally feasible.

Ultimately, treatment decisions need to be based upon evidence obtained from experiments in which valid measurements were first performed on profoundly hyperthermic, asymptomatic volunteers, then verified in casualties of exertional heat stroke. Outcomes from that second stage should be judged on morbidity and mortality outcomes (e.g., Ferris et al. 1938; Wood et al. 2022), and not on surrogate outcomes, such a rates of body cooling. Statistical correlations between the rectal cooling rates and a favourable treatment outcome (e.g., Filep et al. 2020) do not imply either causal or mechanistic links. Not surprisingly, we are unable to accept the validity of evidence-based merely upon rates of rectal cooling, which have been used to defend the merits of a preferred cooling technique (e.g., Casa et al. 2005, 2007, 2017; Casa and Kenny 2009; Leyk et al. 2019). Our reservations are scarcely new (Withington 1895). Almost 50 years ago, when ice-water baths were used to treat heat-stroke patients, it was reported that "*rectal temperature does not accurately reflect rapidly falling core temperature*" (Clowes and O'Donnell 1974 [P. 566]). The suggestion that cold-water immersion is the gold standard for exertional heat-stroke treatment was based primarily on rates of rectal temperature reduction obtained from laboratory evidence (Casa et al. 2007).

Further justification for our reluctance to use rectal cooling rates to evaluate the merits of cooling methods is illustrated in Fig. 15. Delays in the rectal responses to sudden changes in the thermal status of the body are protracted (Fig. 15A). Since those temperatures are poorly synchronised with changes in heat storage (Fig. 15B), they are useful only under thermal steady-states (Taylor et al. 2014a). The possibility of data misinterpretation was confirmed by direct measures of heat extraction. For example, when hyperthermic subjects were cooled to rectal temperatures of 37.5 °C in water at different temperatures (2°–20 °C; Proulx et al. 2006), the observed rectal cooling rates were always less than those predicted for the whole body on the basis of measured heat-extraction rates. That effect is indicated by the line of identity in Fig. 15C, and inset Fig. 15D, which shows that those underestimations were inversely related to the water temperature. During cold-water cooling, most of the heat will be extracted from the peripheral tissues, with rectal temperatures responding too slowly to provide a valid index of that cooling rate. Therefore, a rectal cooling rate of 0.35 °C min^{-1}, which has been used to support the apparent superiority of ice-water immersion (Casa et al. 2007; Belval et al. 2018), does not reflect the true rate at which the body temperature drops when immersed in ice water, and cannot convey information of relevance to either how fast heat was extracted or the duration for which immersion should continue.

The inconvenient reality is that, if deep-body cooling rates are determined only from rectal temperature changes, which show cooling times to reach 37.5 °C of 14.4–17.3 min in water at 14 °C (Proulx et al. 2006; Taylor et al. 2008a) and 26.0 min in temperate water (26 °C; Taylor et al. 2008a), then one might well be driven to seek more rapid cooling strategies. If, however, the cooling times to that same deep-body temperature target were < 5 min, then the risk of adverse clinical outcomes would be minimised, along with the urgency of the treatment. In our hands, the oesophagus is certainly cooled that rapidly, and we believe those changes reflect the thermal status of venous blood returning to the heart, which would soon travel to the central nervous tissues. Nevertheless, those rapidly falling

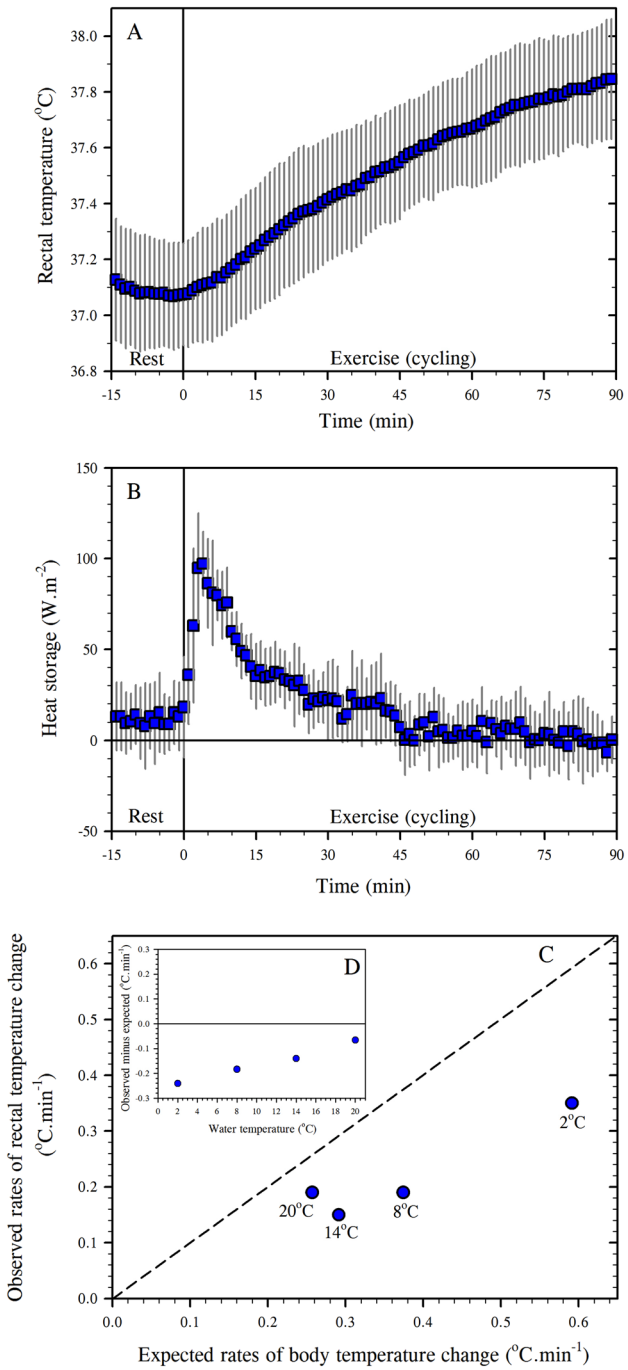


Fig. 15 **A** The average rectal temperatures of young men resting, and then cycling at an external work rate of 40 W.m^{-2} (90 min, 40 °C dry bulb; metabolic heat production 200 W.m^{-2}; $N=8$). Data extracted from Notley et al. (2020a, b) and used with permission. Whole-body heat storage (**B**), as measured within a direct (whole-body) calorimeter, peaked within 7 min, reaching ~ 100 W.m^{-2}. Those data show that a thermal equilibrium was obtained after ~ 45 min of exercise, yet rectal temperatures (**A**) increased inexorably over those 90 min, and without evidence of stabilising. **C** The observed rates of rectal temperature change plotted against expected (predicted) rates if rectal temperature accurately reflected body temperatures during ice-cold and cold-cool water immersions. Subjects with exertional hyperthermia were immersed at four water temperatures (separate trials: 2°, 8°, 14° and 20 °C) until rectal temperatures reached 37.5 °C. Heat extraction was estimated using 11 heat-flux transducers mounted on the skin, and those data were used to derive expected reductions in body temperature using an average specific heat of 3.5 J.g^{-1}.K^{-1}. Data were taken from Proulx et al. (2006 [Tables 2 and 3])

oesophageal temperatures will not be indicative of the heat content of poorly perfused tissues. Those tissues absolutely include the gastrointestinal tract, with splanchnic blood flow being dramatically reduced when humans exercise in the heat (Rowell 1973, 1986, 1993; Rowell et al. 1968, 1969a, 1970; Perko et al. 1998). Whilst extended gastrointestinal underperfusion can result in endotoxins passing into the blood, the site of that leakage is not the rectum. Can rectal temperature provide an index for the thermal status of the rest of the gastrointestinal tract? It may do, but only if those sites are in thermal equilibrium, and we are unaware of any evidence to support that proposition.

Oesophageal temperature, which is a better index of intra-thoracic temperatures (Cooper and Kenyon 1957; Severinghaus 1959; Whitby and Dunkin 1971), falls faster during cold-water immersion than does rectal temperature, but never in parallel with rectal temperature (Proulx et al. 2006; Caldwell et al. 2018). However, that very rapid cooling from ~ 39.5° to 37.5 °C (<5 min) during the temperate-water immersion (26 °C) of experimentally induced hyperthermic subjects (Taylor et al. 2008a; Caldwell et al. 2018), must not be interpreted to mean that whole-body cooling was achieved that quickly. Instead, those times show only that temperate water was equally as effective as cold water (< 60 s slower) in cooling the intra-thoracic blood. Cooling should continue much longer if the poorly perfused tissues are to be cooled.

When contemplating cooling-time differences on the basis of different indices of deep-body temperatures, we need to focus on the primary aim of cooling heat-stroke casualties during an emergency. Is the aim to prevent damage to the central nervous tissues, to prevent rhabdomyolysis or to prevent gastrointestinal damage and endotoxaemia? Those objectives can and should be achieved by extended cooling in cool-temperate water. However, we can evaluate the efficacy of various cooling treatments only if we can validly determine changes in the temperatures of those targeted body regions. Oesophageal temperature, but not that of the rectum, is powerfully influenced by the thermal status of the intra-thoracic blood (Cooper and Kenyon 1957 [humans during aortic surgery]; Gollan 1959 [extracorporeal cooling of dogs]; also see: Lees et al. 1980; Hayward et al. 1984; Shiraki et al. 1986; Nybo et al. 2002). Since that blood will soon perfuse the central nervous tissues, then we can assume that index can be used as a surrogate for those temperatures.

Conversely, Todd et al. (2014) have shown that, whilst oesophageal and rectal temperatures both respond to heat

storage, neither can be used interchangeably to track deep-body temperature changes during dynamic states (Notley et al. 2023b [Fig. 16]). Instead, the thermal time delay at the rectum creates the appearance that those two sites behave as thermally independent tissues. It is likely that thermal independence might extend to the gastrointestinal tract, particularly when splanchnic blood flow is dramatically reduced, as it is during exercise-induced hyperthermia (Rowell 1993). The question now is whether or not rectal temperatures provide useful information concerning the temperatures of thermally vulnerable gastrointestinal *loci*. Whilst that is possible if both sites are sufficiently and consistently perfused with blood of the same temperature, temperature similarities between sites cannot be interpreted to mean that those temperatures are mechanistically linked and can be used interchangeably. The true test of a mechanistic connection is obtained by artificially and dynamically manipulating the temperature of one site, whilst examining the capacity of another site to track those changes. If that has not been demonstrated, then it is misleading to suggest that thermal equivalence between any two indices validates either measurement.

Irrespective of which surrogate site is used to track deep-body temperature during cooling, we conclude that the rate at which rectal temperature falls cannot be used to justify the choice of the water temperature used during immersion cooling. Therefore, in our view, the consensus statement of the *International Olympic Committee* concerning the rapid cooling of exertional heat-stroke casualties using ice-cold water (Casa et al. 2007; Racinais et al. 2022) was not based upon a thorough interrogation of the available evidence. Instead, it seems to have been based on the belief that the rate at which rectal temperature falls provides a valid reflection of heat extraction from tissues other than itself.

We have little doubt that rapid, on-site detection and treatment have reduced the morbidity and mortality of exertional heat stroke by an order of magnitude, compared with our first two epochs, an improvement that must rank amongst the notable successes of modern health care (Wyndham 1966; Filep et al. 2020). What is crucial is for cooling to start immediately and on site, which precludes cold-water immersion, except when prepared in advance. Where practical, we support the use of both stirred water immersion (temperate or cool), as well as water dousing and fanning. We remain unconvinced by any evidence that the water actually needs to be either cold or ice-cold (Taylor et al. 2008a; Casa et al. 2010b; Caldwell et al. 2018; Choo et al. 2018). Since sudden cold-water immersion can precipitate adverse pathophysiological *sequalae*, such as cardiac arrhythmia, reduced cerebral blood flow, hypertension and endotoxaemia (Tipton 1989; Mantoni et al. 2007; Shattock and Tipton 2012; Johnson et al. 2016), then we support the less-aggressive cooling methods recommended by our predecessors (Currie 1805; Pembrey 1902; Fantus 1934; Wyndham et al. 1959; Weiner and Khogali 1980). Unfortunately, in some countries, both the incidence of, and mortality from, exertional heat stroke remain unacceptably high (Tustin et al. 2018; Ioannou et al. 2021, 2022a).

Out of the heat and into the cold And so this journey in the heat has drawn to a close. In the next section, our marathon-running theme will continue, at least to the extent that it provides an example of exercise-induced fatigue, which is linked to hypoglycaemia. In that section, some of those athletes will be swimmers, and from their stories will emerge the link between hypoglycaemia and the inability of our thermoregulatory system to sustain shivering thermogenesis when endeavouring to defend the body temperatures of occupational and recreational athletes.

Beyond shivering—accommodating, tolerating and suffering exercise in the cold

From the scientific literature, it is apparent that more scientists have focussed on the thermal problems accompanying excessive heat storage, rather than excessive heat loss. That imbalance does not reflect their relative importance. They are equally important, although humans have a much greater tolerance for reductions in deep-body temperature, as illustrated by the temperatures of people who recovered from accidental hypothermia (Mroczek et al. 2020 [rectal temperature: 11.8 °C; a change of ~ 25.0 °C) and hyperthermia (Hart et al. 1982 [rectal temperature: 47 °C; a change of ~ 10.0 °C]). Unfortunately, that imbalance in the literature can mean that some readers will be less familiar with the problems of exercise in cold weather and in cold water. Therefore, we open this section with illustrative examples of people who were fit and healthy when cold exposed, and who were performing athletic, occupational or military activities, yet they went well beyond shivering and slipped into hypothermia, or they succumbed to cold injury, perhaps even without shivering. Also included is another historical timeline, to highlight critical steps within the development of our current understanding (Fig. 16).

Seafarers are familiar with the risks of their chosen, and sometimes enforced (pressed), occupation. Many of the early open-sea voyages, although not the first (Cane 2013), originated in cold European waters, so shipwrecks in the cold sea were feared. During our first epoch, Currie and Percival (1792) described physiological changes within shipwrecked mariners that accompanied their descent into hypothermia. A similar disaster occurred at the beginning of our century of exercise physiology; the sinking of the *Titanic* (1912). All who were in the water (1489 souls) when the first rescue

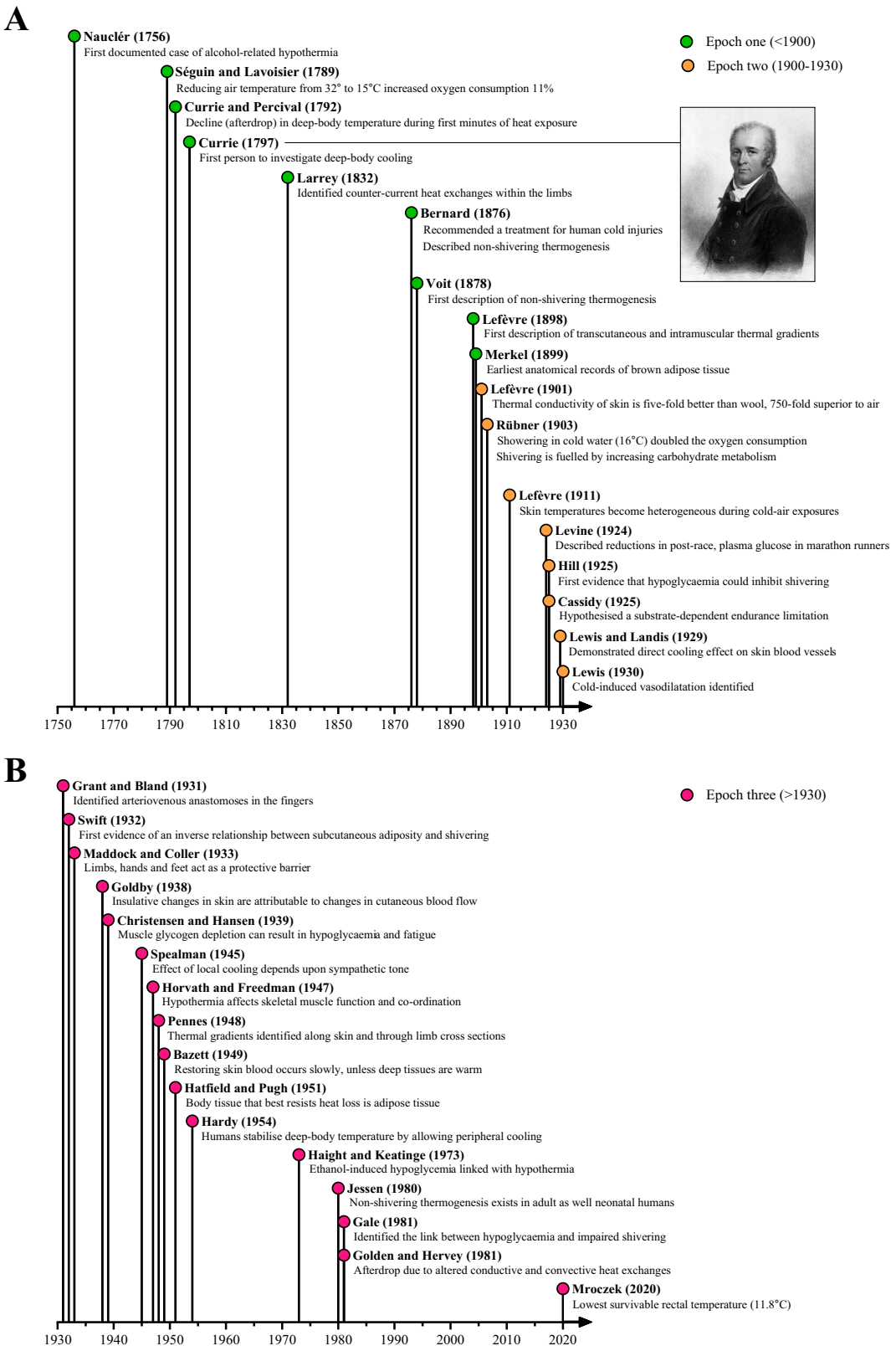


Fig. 16 Historical timelines for human cold stress, cold tolerance and cold injuries. **A** Developments during epochs one and two. The portrait of James Currie (unknown artist) was obtained and used under the Wikimedia Commons agreement (Public Domain). *Source*: https://commons.wikimedia.org/wiki/File:James_Currie_b1756.jpg Accessed: December 30th, 2022. **B** Critical observations and hypotheses during the modern epoch

boat (*Carpathia*) arrived < 2 h later, perished; "*that cold caused these deaths is so obvious that it needs no further comment, but there is hardly a mention of this in the investigations and reports*" (Keatinge 1978 [P. 2]). With hindsight gained over the next century, that omission was corrected (Shetty 2003), but before and during that century, military battles were won and lost by those who either did, or did not, appreciate the impact of environmental changes on the welfare of their personnel or equipment (Guderian 1952; Francis 1984; Paton 2001).

> "*The cold made the telescopic sights useless; the salve which was supposed to prevent this had also not arrived. In order to start the engines of the tanks fires had to be lit beneath them. Fuel was freezing on occasions, and the oil became viscous. This unit, too, lacked winter clothing and anti-freeze ... Before judging their performance, it should be borne in mind that each regiment had already lost some 500 men from frostbite ...*" (Guderian 1952 [P. 131]; German General).

During wars within our three epochs, significant numbers of cold-related injuries occurred: the Crimean War (1853–1856; Paton 2001), the First World War (1914–1918; Atenstaedt 2006), the Second World War (White and Scoville 1945; Shirer, 1959) and the Falkland Conflict (1982; Golden et al. 2013). During the Second World War, an Englishman (Henry Bazett; Roguin 2011), who became one of America's more famous thermal physiologists (Notley et al. 2023a, b), was shot and left for dead, due to his heavy blood loss. He survived because he was hypothermic (Blatteis and Schneider 2022). Hypothermia can support life as well as take life.

In Notley et al. (2023b), we introduced the case of a skier trapped in a semi-frozen stream in Norway, and who showed no signs of life 160 min after her accident, yet she recovered fully (Gilbert et al. 2000; also see: Eidenbenz et al. 2021). Now we travel to Lake Michigan (U.S.A.), where, in 1984, a father and his four-year-old son accidentally broke through the winter ice. The boy remained beneath the ice for almost 30 min (UPI 1984). He too survived. Back to Scandinavia, we find the case of a young Swedish girl (7 years old) submerged in icy seawater for at least 83 min (Romlin et al. 2015). When found, she had ice in her upper respiratory tract, yet she also survived. What did these victims have in common? All had a body morphology conducive to rapid physical heat loss; a large mass-specific surface area. Rapid cooling would have significantly reduced both whole-body and cerebral metabolic rates. Those changes can facilitate survival (Black et al. 1976; Tveita and Sieck 2022). In the case of the children, cold-water inhalation may have induced pulmonary cooling of the central blood volume, due to the aspiration of water that accompanies post-immersion ventilatory efforts (Conn et al. 1995; Golden et al. 1997).

Back on land, readers may not be surprised to hear that athletes have succumbed to hypothermia in inclement weather during a walking event (72.5 km; Pugh 1964). They might, however, be surprised to hear that, during a 100-km, ultra-marathon running race through the mountains, twenty-one runners died from hypothermia in 2021 (Zhang et al. 2021; Sun 2022). Of course, we are all aware of deaths that occur on our highest mountains, and Firth et al. (2008) provided an insight into those deaths that may be attributed to extreme cold. They examined the mortality rates of Mount Everest climbers and Sherpas listed on expedition permits from 1921 to 2006: 212 deaths, with a mortality rate of 1.3% for incidents at altitudes above base camp. Hypothermia was identified as the cause of 11 deaths above base camp, with two of those occurring above 8000 m.

Having set the scene for this section, we will explore the historical steps that led to our contemporary understanding of exercise physiology in the cold; a topic that ignited research interests across several continents. Our emphasis is upon thermal physiology, and not the almost-instantaneous, cold-shock responses that accompany sudden and stressful cold-water immersions (Tipton 1989; Shattock and Tipton 2012; Tipton et al. 2013, 2017). We will present some situations during which homoeostasis might be simultaneously challenged across several regulatory systems, possibly resulting in states of regulatory conflict. For instance, in the first paper of this series (Notley et al. 2023a), we described the survival of a two-year ordeal in the Antarctic by the English explorer, Ernest Shackleton, and his crew (1915–1917). They would have experienced a regulatory conflict between homeothermy and energy balance. They were severely malnourished, but required an elevated metabolic heat production to regulate their body temperatures. Whilst the evidence for humans is limited, it appears that when fasting, but perhaps not during other forms of caloric restriction, thermal homeostasis may be compromised, but not abandoned (MacDonald et al. 1984; Mansell and MacDonald, 1989; Vinales et al. 2019). While we do not intend to examine all possible regulatory conflicts, it is important to appreciate that such struggles may exist during extreme recreational and emergency activities.

Before shivering: cutaneous vasoconstriction

Before we can fully understand the interactive effects of exercise and thermal stress on cutaneous vasomotor activity during cold exposure, we need to understand the effects of cold in the absence of exercise. Evidence from the modern epoch shows that the thermoeffectors are recruited sequentially, in the form of a recruitment cascade, following changes in body

temperature (Taylor and Gordon 2019; Notley et al. 2023b). That cascade, when examined in air, commences with vasomotor activation, which precedes the recruitment of shivering thermogenesis by a body temperature of ~0.5 °C (Taylor et al. 2019). However, we would expect those effector responses to be modified during exercise, and also by the ambient medium within which exercise is performed.

Revisiting first principles: cooling in air, helium, water and snow

The principles that dictate heat flow and heat flux were discussed in Notley et al. (2023a), but since humans exercise and work across a variety of challenging environments, it is important to briefly examine how those exposures might influence thermal balance in scenarios of interest to applied physiologists; we must be good scientists before we can be good applied practitioners. Let us consider the following scenarios: cold-water immersion, air pressurised to a simulated depth of 50 m of the seawater (the air-breathing safety limit for scuba diving), hyperbaric heliox exposure (commercial saturation divers live in helium and oxygen gas mixtures) and survival in a snow cave.

During cold-water immersion, heat is rapidly lost since its thermal conductivity is ~ 25 times greater than that of air at the same temperature (Lide 1997). Its volume-specific heat capacity (the product of specific heat and density) is > 3400 times that of air, and since that capacity increases proportionately with changes in air density, it will be 5.8 times greater at 50 m of seawater than at 1 atmosphere. There will now be almost six times the number of molecules with which to exchange thermal energy, so heat loss will be faster for the same thermal gradient. During scuba diving, respiratory heat loss increases as cylinder air temperature equilibrates with water temperature (Piantadosi et al. 1981). Within hyperbaric chambers at that air density, transcutaneous heat losses will also increase. However, saturation divers, who live and work within enclosed heliox environments, face the opposite problem. The volume-specific heat capacity of air is ~ 1.5 times greater than that of heliox, which means that heliox environments equilibrate with body temperature more rapidly than do similarly enclosed air environments. When that occurs, metabolic heat loss ceases and workers face the problems of rising ambient and body temperatures. Across those scenarios, differences in the rates of heat loss mean that to sustain thermoneutrality, ambient temperatures need to be kept between 28° and 33 °C for water, 31°–32 °C for heliox and 23°–26 °C for air (Burton and Bazett 1936; Winslow et al. 1937; Rennie et al. 1962; Craig and Dvorak 1966; Webb 1982).

If we replace air and water with uncompressed snow, then the size of the air spaces among snow crystals will dramatically modify its thermal conductivity, relative to liquid water. Uncompressed snow has a thermal conductivity of about 5.5 times greater than air, and its specific-heat capacity is about two-fold greater. Its volume-specific heat capacity is ~ 1,380 times that of air at the same temperature. These differences mean that, for a person covered with uncompressed snow, heat loss will be more than five times faster than in air at the same temperature, but it will be < 25% of the rate experienced in water at that temperature. Together, these differences can have a life-saving effect which highlights the survival advantage afforded by building a snow cave during an emergency.

Body morphology and composition: physical and physiological interactions

The shape that is least influenced thermally by the state of its surroundings is the sphere, and the body tissue that best resists heat transfer is adipose tissue (Hatfield and Pugh 1951). It is not surprising that resting, unclothed, larger individuals, who have smaller mass-specific surface areas, and who might also have more adipose tissue, will be thermally more stable during cold exposures (Keatinge 1960; White et al. 1992). Objects that are more plate-like in morphology, and with little adipose tissue, are less thermally stable. That is a characteristic of uncovered hands and feet, which can rapidly lose heat in the cold (Taylor et al. 2014b; Cheung 2015). Such heat losses can lead to localised pain and a loss of manual dexterity, and eventually to non-freezing and freezing cold injuries. Recreational and occupational athletes, on the other hand, tend to be neither spherical nor overweight.

Limb and whole-body movements accompanying recreational and occupational activities modify the physical characteristics of the boundary layer next to the skin ("Further contributions to heat illness of occupational relevance"). Under still conditions, only natural convection currents occur across the skin, and rates of convective heat exchange are low for any given surface-to-ambient temperature gradient (Notley et al. 2023a). However, when flows become laminar in moving fluids, and more so when flows become turbulent, as they must when cycling, rowing, walking or running in still air, or when swimming, there is a significant elevation in convective heat exchange (Nag 1984). These physical influences will also interact with exercise-dependent changes in muscle blood flow and with exercise-dependent and thermally mediated variations in cutaneous vasomotor activity.

Those vascular changes modify the insulation of our peripheral tissues. Tissue insulation is sometimes described as if it were of a fixed form; it is only fixed *post mortem*. Instead, the insulation provided by any living tissue is determined not just by the composition and physical properties of those tissues (anatomical insulation), but by physiological

changes that occur within those tissues. Indeed, increases in peripheral tissue insulation during cold-water immersion exceed that which body fat alone could explain (Carlson et al. 1958), with perfusion variations modifying the insulative power of all tissues. Therefore, our preferred phrase for this interaction of physics and physiology is physiological insulation.

When physiological insulation was investigated in water temperatures slightly lower than those that induced shivering (28°–33 °C), Veicsteinas et al. (1982, U.S.A., and Italy) found that the insulation provided by the peripheral tissues (skin plus subcutaneous adipose tissue of the arms, hands, legs and feet; average tissue depth 2.9 mm) explained only about 10–15% of the physiological insulation of the torso during resting states. On the other hand, the skeletal muscles of the torso and the upper limbs, which are somewhat underperfused at those water temperatures, seemed to account for 85–90% of that insulation. When exercising, heat lost from the skeletal muscles is significantly elevated, due to its elevated blood flow (Cannon and Keatinge 1960 [England]; Nadel et al. 1974 [U.S.A.]), and the insulative power of muscle is significantly diminished. Thus, Veicsteinas et al. (1982) found that, during underwater cycling at a metabolic rate three times the resting level, the contribution of peripheral skin and subcutaneous adipose tissues to whole-body insulation increased to 35–40%. Therefore, whilst our physiological insulation when resting in normothermic water is more heavily influenced by that of the skeletal muscles, our overall insulation is reduced when we start to exercise, with skin and adipose tissues contributing proportionally more, and skeletal muscles proportionally less, to our overall insulation.

Deep-body and skin temperatures during and following cold exposure

In the context of our contemporary understanding of the neural processes involved in thermoregulation during exercise (Notley et al. 2023a [Fig. 20]), let us examine how cold exposures modify the temperatures of the tissues from which thermal feedback arises: the deep-body and subcutaneous tissues. In most circumstances, one can generally see three tissue-cooling phases during cold exposure, with the first tissues affected being those at the periphery, with the cooling of progressively deeper tissues occurring thereafter, ending with deep-body cooling (our third phase).

The speed of our first (peripheral) cooling phase is a function of the size of the thermal gradient, the thermal properties of both the cutaneous tissues and the ambient medium (conductivity, specific-heat capacity, density), and how that medium moves across the skin (laminar or turbulent). During unclothed, normothermic rest at a comfortable air temperature (23°–26 °C), a heterogeneous distribution of skin temperatures is seen (Fig. 7), which becomes progressively more homogeneous as air temperatures rise, but even more heterogeneous when it cools (Benedict and Slack 1911; Lefèvre 1911; Burton 1935; Aschoff and Wever 1958; Werner and Reents 1980; Webb 1992). During water immersion, however, the surface temperatures of all immersed skin regions will rapidly assume a temperature at, or close to, that of the water (Rapp 1971; Boutelier et al. 1977), regardless of the thermal energy content of the water, due to the high rates of heat exchange that occur between the body surface and that medium. Because of the thermal gradient that exists during immersion in any water cooler than the skin, it is not just the surface, but also the subcutaneous tissue temperatures that are modified during water immersion.

We introduced Jules Lefèvre (1863–1944, France) in Notley et al. (2023a), and he is now required for his significant observations at the start of our Krogh-Hill epoch, presumably again on himself. In 1898, using a thermoelectric needle (Fig. 17A), Lefèvre provided our first depiction of the transcutaneous thermal gradient from the skin surface through to the dermal layer, and then through to the intramuscular tissues. He described thermal gradient changes during water immersions from 5° to 35 °C (Fig. 17B; Lefèvre 1898).

Our second cooling phase occurs because the peripheral tissues have cooled, which reduces both the thermal gradient with the ambient medium and peripheral heat loss (Fig. 17B), so it is protective. In his 1901 paper, Lefèvre described how the thermal conductivity of normothermic skin was very low, and about the same as that of wood, yet it was five-fold higher than that of wool and 750-fold higher than air (Lefèvre 1901), reinforcing a truism ignored by so many for more than a century. That is, the best thermal insulation of clothing comes from trapping air between the heat source and the heat sink; the thermal properties of the materials (fabrics) used to achieve that trapping are of minimal importance. Lefèvre also observed, perhaps for the first time, that the thermal conductivity of the skin was not constant, but was almost halved, when measured during immersion in water at 5 °C, relative to water at 35 °C (Lefèvre 1901). Indeed, whilst "*skin exposed to the cold is arranged to lose minimum heat on the external side, it is also arranged to receive as much as possible on the inside*" (translated from Lefèvre 1901 [P. 388]).

We now know that the insulative change he observed (cooling phase two) was entirely attributable to changes in cutaneous blood flow (Goldby et al. 1938; LeBlanc, 1956; Hammel et al. 1959; Keatinge 1978) that result from a localised (direct) effect on those blood vessels, as well as from sympathetically mediated vasoconstriction. That direct effect is quite powerful (Lewis and Landis 1929; Perkins and Li 1948; Webb-Peploe and Shepherd 1968; Roddie 1983; Taylor et al. 1984; Pérgola et al. 1993; Johnson and Kellogg 2010),

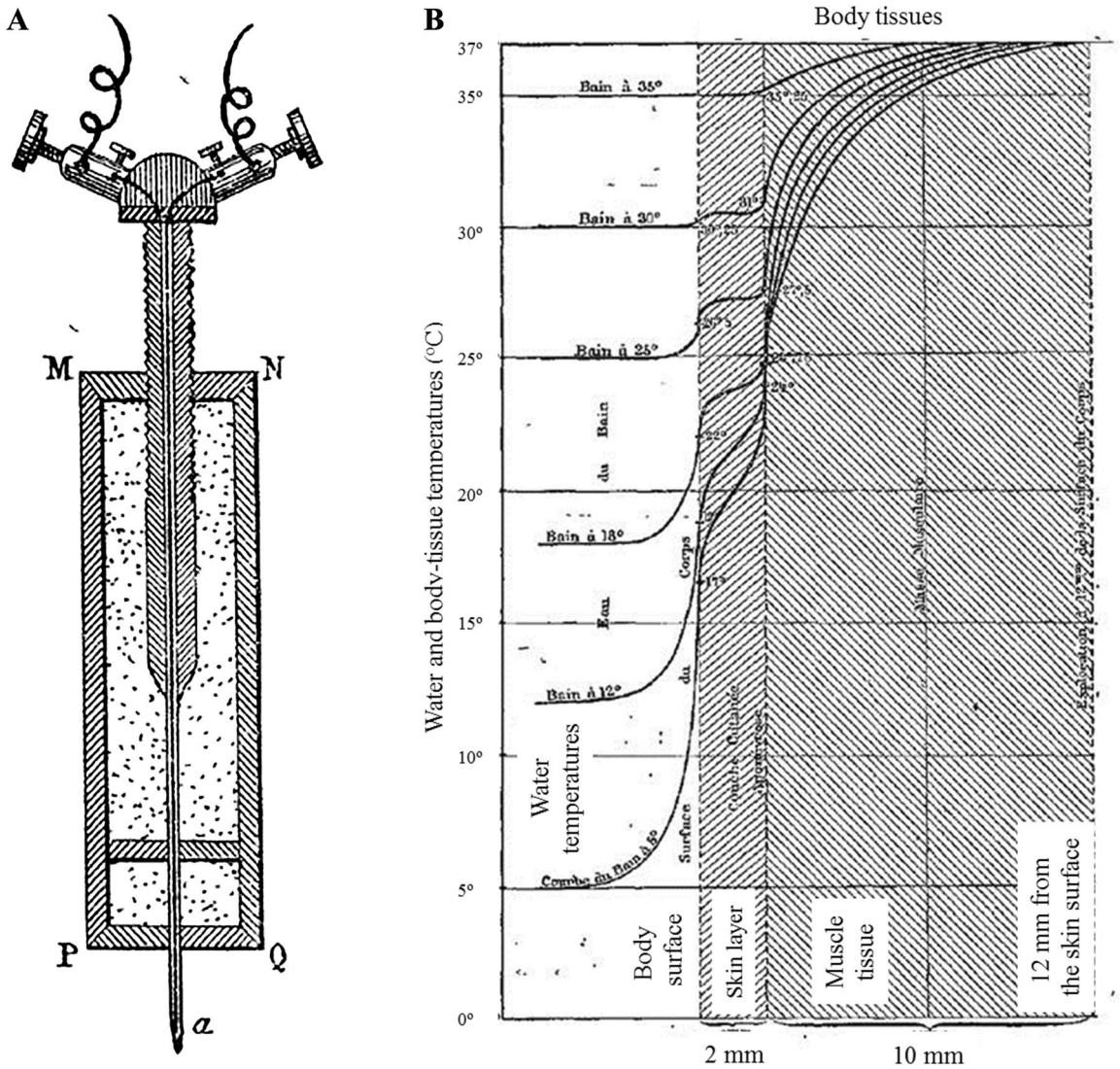


Fig. 17 **A** A longitudinal section through the thermoelectric needle, which housed a thermocouple at the tip, and its casings, used by Jules Lefèvre (1898) to measure the thermal gradient from the skin surface through to a depth of 1 cm (intramuscular temperature). **B** A schematic of changes to the transcutaneous temperature distribution during water immersions in baths (*bain*) at six different temperatures (5°–35 °C). Hatched zones indicate the skin surface (*surface du corps*), the dermal layer (*couche cutanée* [0–2 mm]) and intramuscular tissues (*masse musculaire* [*biceps brachii*; 10 mm]), with extrapolations from 10 to 12 mm. Reproduced by Lefèvre (1898), and is in the Public Domain. English translations and annotations added by the current authors to increase the visual clarity of this Figure

but its effectiveness is related to the overall level of sympathetic tone at that time (Spealman 1945; Pérgola et al. 1993). The resulting cutaneous vasoconstriction transiently, but instantaneously, alters heat balance by reducing transcutaneous heat losses, while metabolic heat production continues.

Because that metabolic heat is now largely contained internally, deep-body heat storage is transiently elevated, albeit slightly, and that elevation continues until the normothermic thermal gradient across the peripheral tissues is re-established. Before that occurs, and as a direct result of that powerful, peripheral vasoconstrictor response, a paradoxical elevation in deep-body temperature can sometimes be observed. Again, it was Lefèvre (1898) who first described that effect, now during water immersion at 22 °C, from measures recorded from the rectum, buccal cavity, axilla and groin. Those elevations lasted ~ 14 min. Indeed, Hardy (1954) suggested that paradoxical elevation emphasised the "*ability of man to stabilize internal temperature at the sacrifice of peripheral body heat*" (P. 248). He had observed an elevation in rectal temperature (0.5 °C) following the transfer of a resting, semi-naked individual into a cold room from a warm room, where he had rested for 3 h.

Eventually, that paradoxical elevation will be reversed, as the deeper tissues lose heat (cooling phase three). The first

person to formally investigate deep-body cooling appears to have been James Currie (1756–1805, Scotland; Currie 1797; Milton 2022). His interest was in relieving fever, which we now know cold-water immersion cannot achieve (Mitchell and Laburn 1985). Of particular importance to thermoregulation is the eventual cooling of the central-nervous tissues, which activates constriction of the veins and arteries of the cutaneous vascular beds, increases physiological insulation (Cannon and Keatinge 1960; Nadel et al. 1974; Veicsteinas et al. 1982) and reduces heat flux. No better example of this effect exists than that provided by polar mammals, such as seals, that have neither dense nor long fur, yet they sit upon the ice, swim in near-freezing water and withstand polar gales, all while successfully regulating their body temperatures more than 40 °C above ambient temperatures (e.g., Blix et al. 1979).

Having not evolved with the insulative capability of seals, we have substituted behavioural strategies to prevent, or at least reduce, heat loss. If those strategies are unsuccessful, then very low, and sometimes fatal, deep-body temperatures can occur. During the Krogh-Hill epoch, Robert Tigerstedt (1853–1923, Finland; Leppäluoto et al. 2022) reported a survivable, deep-body temperature reduction to 24 °C, and "*a man who retained consciousness with a temperature of only 26.7 °C*" (Tigerstedt 1906 [P. 401]). During the Second World War, similarly low temperatures were induced in many of the Holocaust victims (1942–1945; Holzlöhner et al. 1942; Alexander 1945; Gagge and Herrington 1947); the moral dilemma surrounding the use of those data is discussed elsewhere (e.g., Berger 1990, 1994; Grunfeld 1991; Drobniewski 1993; Temme 2003; Bogod 2004; Mackinnon 2020; Caplan 2021). Most recently, we have the survival of individuals who were unintentionally cold exposed: an adult, female skier (rectal temperature 13.7 °C; Gilbert et al. 2000), a young girl submerged in icy seawater (nasopharyngeal temperatures 13.8 °C; Romlin et al. 2015) and a very young boy (2 years; rectal temperature 11.8 °C; Mroczek et al. 2020).

If we rapidly transfer our cold-exposed person into the heat, we should observe a continued reduction in deep-body temperature during the first minutes of heat exposure. That paradoxical reduction was first reported by Currie (Currie and Percival 1792; also see: Currie 1797; Alexander 1945), it is known as a thermal after-drop (Golden and Hervey, 1977) and it is associated with altered conductive and convective heat exchanges across the tissue layers (Golden and Hervey, 1981; Webb 1986; Mittleman and Mekjavic 1988). To illustrate how conduction effects produce an after-drop, and in the spirit of athletic pursuits, we examined the thermal characteristics of a shot put (Fig. 18). A heated metal shot (sphere) was plunged into the water at 15 °C for 35 s, to initiate cooling, then immersed into water at 38.5 °C. The shot lacked internal convective currents, yet its centre continued cooling for another 85 s, even though it was in warm water. Central cooling continued until the thermal gradient that caused heat loss no longer existed, or was reversed, in the form of a series of infinitesimally small, concentrically arranged warmer fronts that moved towards the centre of the shot until thermal equilibration was complete. Golden and Hervey (1977, 1981), using mathematical and physical models (living and euthanased pigs), first described that conductive process. "*Although blood flow undoubtedly alters tissue insulation, … the occurrence of an after-drop did not appear to depend upon the existence of a circulation, but could be explained by a thermal conduction mechanism*" (Golden and Hervey, 1977 [P. 27P]). Others insisted that the after-drop must have a circulatory component (Behnke and Yaglou 1951; Romet 1988; Giesbrecht and Bristow 1992).

In the context of exercise in the heat, it follows that an after-rise must also exist when hyperthermic individuals are immersed in cold water ("Treating heat-stroke casualties: cool first, transport later"). However, our ability to observe and quantify both phenomena is dictated by the indices of deep-body temperature we use. For sites that are affected by both conduction and convection, those phenomena will occur quickly, and may not be seen when deep-body temperatures are measured from sites that rapidly equilibrate with intra-thoracic blood.

Cutaneous vasomotor activity during cold exposure

"An anatomical overview" contains some relevant anatomical details concerning the configuration of the cutaneous vasculature, including the arteriovenous anastomoses. During cold exposures, constriction of the cutaneous arterioles and those anastomoses dramatically reduces cutaneous blood flow, especially flows to the volar surfaces of the hands (palms) and feet (soles). Those reductions are particularly pronounced for the sites with the highest densities of anastomotic vessels (Fig. 19): the volar surfaces of the second toes, the distal phalanges of the fingers and the nail beds. That was known at the end of the Krogh-Hill epoch (Grant and Bland 1931), and was subsequently verified (Masson 1937; Clark 1938; Abramson 1965). Indeed, during maximal vasoconstriction, blood flow may be reduced to levels well below that required to support cellular requirements, even when those cells are in a basal metabolic state (Abramson 1965).

Whilst those responses conserve heat, protracted underperfusion can have potentially debilitating consequences. Those effects range from impaired manual dexterity, which can be life-threatening when critical tasks can no longer be performed, through to peripheral pain, impaired work and athletic performance, and eventually to cold injuries (Gaydos 1958; Enander and Hygge 1990; Heus et al. 1995; Stocks et al. 2004b; Imray et al. 2011; Golden et al. 2013). Particularly vulnerable to cold injuries are the occupational and recreational athletes who pursue their activities outdoors

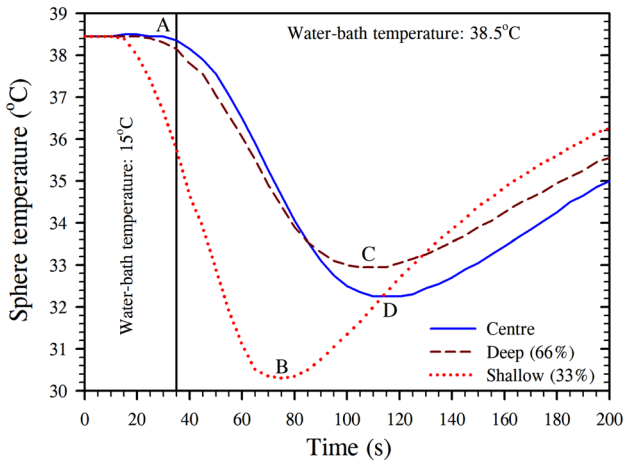


Fig. 18 The thermal characteristics of a metal sphere (shot). A steel ball (mass 7 kg, radius 61 mm) containing thermistors embedded at its centre, and at 33% (shallow: 20 mm) and 66% (deep: 41 mm) of the distance from the surface to its centre, was heated to a steady-state temperature of 38.5 °C (stirred water bath). Following thermal equilibration, the shot was transferred to a cooler, stirred water bath (15 °C: time zero) until the temperature of the central sensor first started to decrease (position A). It was then moved back into the first water bath (38.5 °C). The temperatures of each sensor were recorded at 5-s intervals. As predicted, the shallow sensor cooled most rapidly and further (position B), and was 2.7 °C and 1.9 °C cooler than the thermal troughs of the deep (position C) and central sensors (position D, respectively). Cooling continued, in the form of a thermal afterdrop, until a warmer front reached each of the deeper sensors (points B, C and D). This simulation was inspired by Golden (1979) and Golden and Hervey (1981), and has been modified from Taylor et al. (2014a) and used with permission

in cold weather, either because their peace-time occupation requires them to do so (Mäkinen and Hassi 2009), because they are engaged in military conflicts (Thomas and Oakley 2001; Golden et al. 2013), or because they participate in recreational and sporting events (Sallis and Chassay 1999; Cappaert et al. 2008; McMahon and Howe 2012; Ingram and Raymond 2013). Winter Olympic Games regularly take place at sub-freezing ambient temperatures (Castellani and Young 2012), so cross-country skiers in thin, tightly fitting clothing may even suffer the embarrassing misfortune of genital cold injuries (Hixson 1981).

Fortunately, when extended cold-induced under-perfusion of the skin occurs, the anastomoses will intermittently open, with each surge of warm blood helping to protect the surrounding tissues. That is the phenomenon of cold-induced vasodilatation, discovered in the Krogh-Hill epoch by Thomas Lewis (1881–1945, England; Lewis 1930) and developed by others (Wilson and Goldman 1970; Nuzzaci et al. 1999; Daanen 2003; Cheung 2015). Readers wishing to explore cold-induced vasodilatation in depth are referred to the following resources: Burton and Edholm (1955), Edwards and Burton (1960), Livingstone (1976), Lindblad et al. (1990), Bergersen et al. (1999), Daanen and Ducharme (1999), O'Brien (2005), Van der Struijs et al. (2008), Cheung and Mekjavic (2007), Flouris and Cheung (2009) and Keramidas et al. (2010).

The veins of the hypodermal and dermal layers are well innervated, and, like the anastomoses, respond to sympathetic stimulation (Zimmerman 1966; Webb-Peploe and Shepherd 1968), and participate in thermoregulation. In addition, the veins found deeper within the body, particularly those of the limbs, may participate in counter-current heat exchanges with the arterial vessels with which they are in intimate contact, and presumably have the form of a fine arteriolar network (rete; Nunneley and Nelson 1994). That exchange reduces peripheral heat loss, it was first identified by Claude Bernard (1813–1878, France; Bernard 1876) and it transfers heat from within the arterial blood, via conduction, to the cooler venous blood returning to the deep tissues. That exchange reduces heat delivery to, and heat loss from, the periphery. Many subsequent investigators have elaborated on that heat-conservation process (e.g., Forster et al. 1946; Scholander and Krog 1957). Indeed, it was the classical work of Scholander and Schevill (1955) that demonstrated its powerful physiological significance for diving mammals.

Collectively, cutaneous vascular constriction reduces the convective transport of heat from the deeper tissues to the skin, it elevates physiological insulation (Veicsteinas et al. 1982), it reduces the thermal gradient between the skin and the ambient medium, and it conserves body heat. Local variations in the transcutaneous heat loss were estimated for humans by Cannon and Keatinge (1960) during resting water immersions (22°–38 °C). They used heat-flux disks attached to the index finger (dorsum), forearm (flexor surface), sternum, abdomen and right foot (dorsum). Those data were used to calculate thermal conductivity, but also as a surrogate for cutaneous vasomotor activity. During immersion in water at 22 °C, heat loss from the finger and foot was minimal, whilst heat lost from the chest, and possibly the abdomen, remained almost as high as it was when immersed in water 10 °C warmer. At the other extreme, heat loss from the forearm was, on average, greater in water at 22 °C than it was in water at 31°–33 °C.

Notwithstanding the methodological assumptions and possible sources of error (Wissler and Ketch 1982; Ducharme et al. 1990), that research has several implications. Firstly, it shows that whole-body heat losses during cooler exposures, just like sweat rates in the heat (Taylor and Machado-Moreira 2013), cannot be estimated from single-site measurements. Secondly, it shows that heat loss from the torso remains stable across a wide range of thermal challenges, whilst that of the hands and feet is highly variable, and can be reduced to negligible levels in the cold. It seems that, at rest, the insulation of the torso relies on

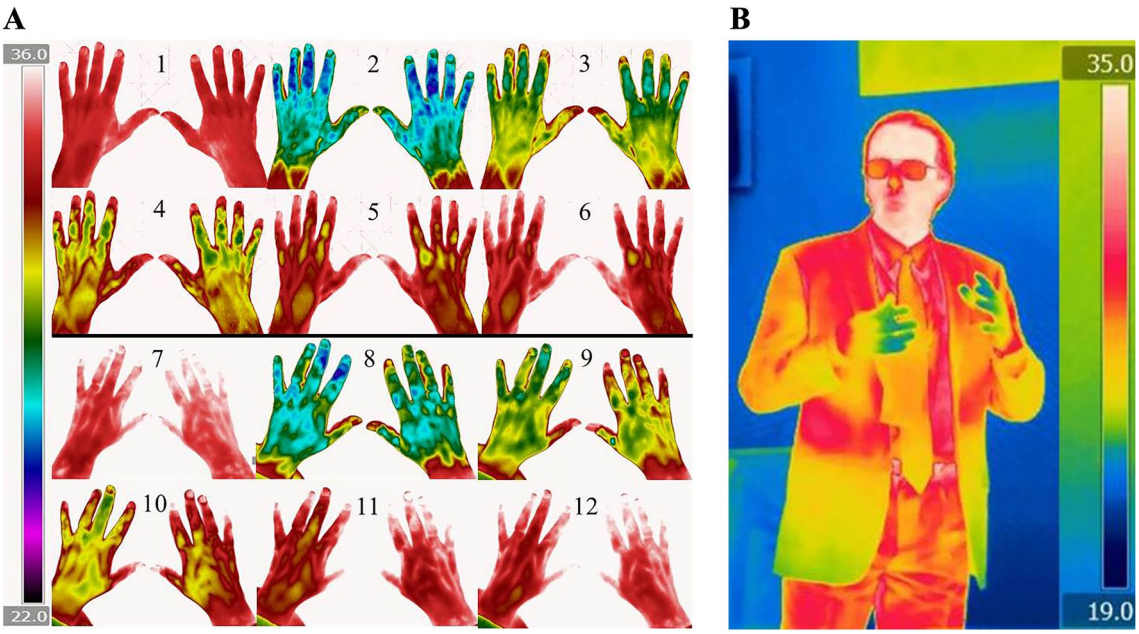


Fig. 19 **A** Thermal images from both dorsal hands of two healthy individuals, one of whom had suffered non-freezing cold injury (images 7–12). Each sequence contains images taken before (1 and 7), immediately following (2 and 8) and then at 1, 2, 4 and 6 min during spontaneous recovery (3–6 and 9–12) from water immersion at 20 °C (wearing plastic bag). Typically, rewarming commences at the finger tips (images 3 and 4) and coincides with the opening of the arteriovenous anastomoses, which usually occurs symmetrically within and between hands (images 3–5). Images 9 and 10 show an asymmetrical rewarming pattern in the left hand of the cold-injured person, with the middle finger being most affected. Images provided and reproduced courtesy of James Mercer (Institute of Health Sciences, UiT The Arctic University of Norway) and Louis de Weerd (Department of Plastic and Reconstructive Surgery, University Hospital of North Norway), who retain the copyright. **B** A thermal image of one of the authors in a thermally comfortable room. He has a history of non-freezing cold injury to the hands and feet from winter kayak training. That effect is evident from the very cool fingers, and has been reported in 23% of paddlers who train in cool-to-cold conditions (Oakley et al. 2022). From the private collection of, and used with permission from Joo-Young Lee (Korea), who retains the copyright

conduction more than on reduced peripheral circulation in the cold (Hayward and Keatinge 1981), and it appears that most heat loss during stationary cold-water immersion is from the torso (Hayward et al. 1973; Keatinge 1978; Wade et al. 1979; Hayward and Keatinge 1981). Thirdly, heat loss from the limbs, proximal to the hands and feet, represents a further avenue for heat loss in the cold, especially during exercise in water, due both to increased convection at the surface and to elevations in blood flow in the working muscles of the limbs (Cannon and Keatinge 1960; Nadel et al. 1974; Veicsteinas et al. 1982).

During cold exposures, thermal gradients are established along the skin surface (Freeman and Nickerson 1938; Werner and Reents 1980) and across torso and limb cross-sections (Pennes 1948; Webb 1992). Those gradients result from increased cutaneous vasomotor tone as our regulatory centre attempts to conserve deep-body heat by reducing peripheral heat loss. That is particularly noticeable in the hands and feet (Maddock and Coller 1933) which might appear as though they have undergone a physiologically amputating (Fig. 19; Forster et al. 1946; Hardy 1954; Scholander and Krog 1957).

Severe cold is not necessary for cold-induced cutaneous vasoconstriction and venoconstriction to be maximal (Bittel et al. 1988). If we did not have a capacity to modify insulation physiologically, then our forebears would probably not have migrated beyond their tropical and temperate climates, unless they had access to appropriately insulated clothing, and particularly hand and footwear. Access to clothing appears was achieved between 83,000 and 170,000 years ago (Allen et al. 2013; Gilligan 2018; Hallett et al. 2021), and humans used thermal protective clothing at least 5000 years ago (Dickson et al. 2005).

Following strong and protracted vasoconstriction, the restoration of blood flow to the cutaneous vasculature occurs rather slowly (Fig. 19; Bazett 1949), and requires deep-body temperatures close to their normothermic values. Consequently, the peripheral tissues can remain cool for some time, and those low temperatures can inhibit the relaxation of muscles within blood vessel walls, delaying passive dilatation. Indeed, blood flow to the hands and feet of a previously hypothermic individual is fully restored only when the deep-body temperature has been returned to its normothermic state (Savard et al. 1985; Caldwell et al.

2014). That relationship is examined more closely in the next section.

The differential impact of deep-body and skin temperature modifications We will now return to an experiment described in "An anatomical overview", the results of which are presented in Fig. 8. Peripheral blood flows for the forearm, hand, leg (calf) and foot were measured using segment-specific, venous-occlusion plethysmography (Caldwell et al. 2014, 2016; Notley et al. 2023b [Fig. 19]). Those measurements could be made only under resting states and it was assumed that thermally induced blood-flow changes were restricted to the cutaneous compartment (Edholm et al. 1956; Roddie et al. 1956; Detry et al. 1972; Johnson et al. 1976a, b). Participants were pre-treated to induce mild hypothermia, normothermia or moderate hyperthermia, and then thermally clamped. Five thermal treatments were applied to each limb segment (5°, 15°, 25°, 33°, 40 °C), giving 15 deep-body and skin temperatures combinations. Our interest is now in the hypothermic state.

The sensitivity of the cutaneous vasculature of each body segment, to increments in local skin temperature, was derived over a 35 °C treatment range. Unlike the impact of local skin heating during hyperthermia, when participants were mildly hypothermic (oesophageal temperature 36.1 °C, mean skin temperatures 22.2 °C), changes in local skin temperature had minimal effect on cutaneous blood flow. Indeed, the thermosensitivity to those treatments was close to zero for the hand, foot and leg, and negligible for the forearm (0.04 mL.100 $mL^{-1}.min^{-1}.{}^{o}C^{-1}$). Thus, with the cutaneous vasculature powerfully constricted during hypothermia, and local heating, even with water at 40 °C, was unable to release the constrictor tone of those limb segments (lower right corners of Fig. 8A–D). Therefore, restoring limb perfusion within hypothermic casualties requires deep-body heating, which must be a therapeutic priority. In fact, during hypothermia, and regardless of the local skin temperature treatment, no segmental flows exceeded 2.5 mL.100 $mL^{-1}.min^{-1}$; a value that is within the error range for those measurements.

To emphasise that need, the vascular thermosensitivities to skin heating during normothermic clamping varied from < 0.1 mL.100 $mL^{-1}.min^{-1}.{}^{o}C^{-1}$ for the forearm and calf, to 0.1 mL.100 $mL^{-1}.min^{-1}.{}^{o}C^{-1}$ for the foot. Those sites were unresponsive, whilst the hands were more sensitive (0.2 mL.100 $mL^{-1}.min^{-1}.{}^{o}C^{-1}$). Such low flows are a double-edged sword, as they can compromise the peripheral tissues if sustained, but they have a powerful, thermo-protective influence on the deeper tissues. That effect was most apparent for the feet, which were unresponsive to local skin heating until whole-body heating released the prevailing constrictor tone (Fig. 8B). The other edge of that sword has occupational health and tissue-injury implications. Those aspects will be expanded upon in "Beyond shivering: the descent into hypothermia", but we close this section with a comment on sustaining manual dexterity of the hands. Whilst that can be achieved during extremely cold exposures by heating only the hands (Brajkovic and Ducharme 2003), the application of that prophylactic measure must commence before deep-body cooling and vasoconstriction of the periphery have occurred.

Igniting thermogenesis

The other autonomic thermoeffectors activated when body temperatures decline involve shivering and non-shivering thermogenesis. In resting subjects exposed to very gradual reductions in body temperature, shivering occurs after that temperature falls by ~ 0.5 °C below the threshold for cutaneous vasoconstriction (Taylor et al. 2019; Notley et al. 2023a; Fig. 22]). Nevertheless, shivering can sometimes occur almost instantaneously during sudden and intense thermal challenges, and before a change in deep-body temperature (Tikuisis et al. 1991), but when deep-body cooling does occur, the rate at which cooling occurs can also modify the intensity of the thermogenic response (Mittleman and Mekjavic 1991). But shivering is not the only way of igniting thermogenesis. The adipocytes are not a metabolically inert form of insulation; they are sources of heat and "*one wonders whether one shouldn't think of the subcutaneous tissue of the homotherms not as an insulating blanket, but rather as a heat-producing or "electric" blanket*" (Cahill 1961 [P. 25]). We return to this concept in "Igniting a second fire: non-shivering thermogenesis".

When did you last shiver whilst playing tennis or squash? Shivering and non-shivering thermogenesis would warrant only a passing mention in a paper celebrating exercise physiology if they did not occur during exercise, but they do occur (Nadel et al. 1973). Of course, the metabolic heat production of exercise can offset the need for shivering during cold exposures (Hardy et al. 1938; Fujimoto et al. 2019), and exercise enhances non-shivering thermogenesis in those adipocytes whose primary role is thermogenesis (Virtanen 2014), at least in the early stages of exercise (Zhu et al. 2022). We begin this journey by examining shivering thermogenesis during rest.

To our knowledge, the first experiments to reveal the role of shivering in elevating metabolic (endogenous) heat production were performed in our first epoch by Armand Séguin and Antoine-Laurent Lavoisier (Séguin and Lavoisier 1789; France; Underwood 1944; Kayser 1970; Candas and Libert 2022). Their initial research on metabolic heat was with small mammals, which was extended to humans, with Séguin as the subject (Underwood 1944; Beretta 2012). After observing that external work (raising and lowering a fixed mass,

15 min) elevated oxygen consumption 170% (from 0.40 to 1.08 L.min^{-1}), they found that reducing the air temperature from 32° to 15 °C resulted in an 11% increase in resting oxygen consumption (Séguin and Lavoisier 1789): "*Though these results are remarkably accurate, it is of more importance that Lavoisier established—and recognized that he had established—the fact that the amount of oxygen absorbed depends upon the three factors, temperature, food and work*" (Underwood, 1944 [P. 258]). Of those factors, our interests are with the first and last.

Jump forward 100 years to Carl Voit (1831–1908, Germany; Voit 1878) and Max Rübner (1854–1932, Germany; Rübner 1903), each of whom investigated aspects of exercise and ambient temperature on metabolic rate. For example, Rübner (1903), a student of Voit, found that showering with cold water (16 °C) more than doubled the oxygen consumption of his participant. More importantly, his respiratory exchange ratio increased from 0.87 to 1.03. We believe that milepost defines the first simultaneously recorded estimation of cold-induced, shivering thermogenesis and its use of carbohydrate metabolism as a principal energy source. That observation was reinforced by another of Voit's students, Graham Lusk (1866–1932, U.S.A.; C.E.P., 1933; DuBois 1940). He immersed three individuals in cold water (8°–10 °C), and observed pronounced elevations in both heat production (181%) and carbohydrate metabolism (Lusk 1911; also see: Benedict 1915; Cannon et al. 1927).

In a significant break from most research of our first two epochs, in which physiologists typically used very small population samples, Raymond Swift (U.S.A.) used respirometry (indirect calorimetry) to evaluate changes in the respiratory exchange ratios of 21 participants during cold-air exposures (2 °C, 75 min; Swift 1932a). Unlike Rübner (1903) and Lusk (1911), he did not observe a systematic shift towards carbohydrate oxidation, although his subjects were comfortably dressed ("*shoes and stockings, light underwear, trousers, shirt, vest, and service coat*"; Swift 1932a [P. 214]), so the physiological impact of the cold air was masked. In his companion paper, he reported no reductions in the deep-body (rectal) temperature (Swift 1932b), even though shivering was observed in six subjects, which was presumably stimulated by low skin temperatures. The significance of this work was the provision of possibly the first evidence of an inverse relationship between subcutaneous adiposity and shivering (Swift 1932b), which has been confirmed many times since (Winslow et al. 1937; Pugh and Edholm 1955; Cannon and Keatinge 1960; Pugh et al. 1960; Wade et al. 1979; Golden et al. 1980; Hayward and Keatinge 1981).

Some investigators reported increased metabolic rates even in the absence of shivering. For instance, Voit (1878) described a 30% elevation in carbon dioxide production, and presumably a proportional increase in oxygen consumption, without apparent shivering. Campbell and colleagues (1921) followed suit, as did Swift (1932b), who reported an 11% elevation in heat production across eight individuals in whom overt shivering was not observed. Thus arose the possibility of a non-shivering form of thermogenesis.

Swift (1932b) believed that shivering could be induced by reductions in skin temperature alone, as rectal temperatures remained stable. We do not contest that possibility, which others have reported (Tikuisis et al. 1991), but we retain our caveat about rectal temperature time delays. If shivering is induced or enhanced by a fall in deep-body temperature, the temperatures of primary importance for activating the thermoeffectors must be those of the central thermosensitive tissues, or of sites in thermal equilibrium with those tissues. Deep-body temperature would not necessarily fall during all cold exposures, and there might even be a paradoxical elevation (Lefèvre 1898; Hardy 1954; Young et al. 1986).

Once initiated, shivering starts with increased muscle tension (pre-shivering tone and tremor; Burton and Bronk 1937; Petajan and Williams 1972; Clark and Edholm 1985). It commences in the torso, where, once established, muscle tension remains higher, and can reach ~ 15% of maximal voluntary contraction for *pectoralis major* (Bell et al. 1992 [Canada]; 2 h, 10 °C dry bulb). Shivering then spreads to the limbs (Burton and Bronk 1937; Spurr et al. 1957; Horvath, 1981b), where its intensity in the distal muscle groups is much lower; < 5% of maximal voluntary contraction (Bell et al. 1992). It appears that ~ 70% of the shivering-dependent heat production is generated from the torso, with ~ 20% coming from the thighs and < 10% from the smaller limb muscles (Bell et al. 1992).

Shivering is an involuntary muscular activity (Pozos et al. 1986) that oscillates in well-defined, wave-like patterns (Clark and Edholm 1985). Indeed, Israel and Pozos (1989, U.S.A.) found shivering to be synchronised across six different muscle groups distributed across the torso and limbs, with peaks in muscular activity occurring approximately 6–12 times.min^{-1} (0.1–0.2 Hz). However, that outcome may have been a function of the specific muscles investigated, since peak shivering activity of the simultaneously examined elbow flexors and extensors was 180° out of phase (Bawa et al. 1987, Canada). Whilst shivering is largely involuntary, it is possible, during low-to-moderate intensities, to exert some voluntary, albeit transient, control over those oscillations (Glickman et al. 1967; Mekjavic and Eiken 1985; Israel et al. 1993; Fujimoto et al. 2019).

Since human thermoregulation operates with proportional and rate control characteristics (Notley et al. 2023a), then the intensity of cold-induced shivering will correspond with the extent of the thermal disturbance, as reflected within in the size and rates of change of the deep-body and skin temperatures. Whilst these descriptive studies neither elucidate nor explain the thermoregulatory mechanism, they allow us to assess the power of shivering as a thermoeffector. We have included such descriptive evidence in Table 1, as did

Hemingway (1963 [Table 1], U.S.A.) for cold-exposed mammals (including humans) and birds. When averaged across those human experiments, the resting metabolic rates were elevated 2.9-fold during shivering (Hemingway 1963).

When comparing the strength of the thermogenic response across participants and investigations, we recommend three strategies. Firstly, the size of each response should be referenced to body temperatures (deep or peripheral) in the form of a change relative to the normothermic state. Secondly, to quantify the thermoregulatory process, a shivering threshold and gain (thermosensitivity) should be calculated, relative to body temperature. For instance, when oxygen consumption is used as a surrogate for shivering intensity, we recommend reporting indices of thermogenic sensitivity, as used by Janský et al. (1996 [Fig. 2]), Regan (1998 [− 0.63 $L.min^{-1}.{}^{o}C^{-1}$]) and Fujimoto et al. (2019 [− 0.41 $L.min^{-1}.{}^{o}C^{-1}$]). We note that any estimate of body temperature used in such a calculation is only an approximation to the input that the constellation of thermoreceptors provides to the regulatory centres. Finally, thermal clamping will minimise, if not eliminate, variability resulting from differences in measurement time delays across various physiological events.

Since our emphasis is thermal strain during athletic and occupational pursuits, it is informative to compare the rate of heat production (or its equivalent) during aerobic exercise (oxygen consumption) with that of shivering. For the 12 studies reported in Table 1, the average elevation was > 2.5 times the pre-exposure oxygen consumption. Those data can also be reported relative to peak aerobic power (maximal oxygen consumption). For endurance-trained athletes (Robinson et al. 1937 [runners]; Clark et al. 1983 [rowers]) and other wild mammals (Taylor et al. 1981 [bovids]), peak aerobic power can reach ~ 20 times the oxygen consumption observed at rest. The metabolic outcomes in Table 1 (two- to five-fold elevations) would correspond with 10–25% of the peak aerobic power of those individuals. So shivering is not a trivial source of metabolic power. Moreover, that power output can be sustained for a very long time without fatigue. For sedentary individuals, whose peak aerobic power is typically only about ten times their resting oxygen consumption, those same metabolic outcomes would represent 20–50% of their peak aerobic power, as observed by Golden et al. (1979a), so those higher relative intensities would not be sustainable. Indeed, one of their participants had a cold-induced oxygen consumption of 2.16 $L.min^{-1}$ (46% of peak aerobic power), which might approximate a seven-fold elevation (resting data were not reported; Golden et al. 1979a).

What would happen to Golden's male participant, shivering to 46% of his peak aerobic power, if he started running at a rate that required an oxygen consumption greater than the residual 54% of his aerobic power? Would he reduce shivering to fuel that exercise? Presumably, he would not need to shiver to regulate body temperature, because all of the energy required to run would degrade to heat, and would exceed that which he had been generating by shivering. But

Table 1 An overview of the experimental evidence for the impact of cold exposure on oxygen consumption and metabolic heat production (also see: Hemingway 1963 [Table 1])

Source	Conditions	Metabolic outcome
Séguin and Lavoisier (1789, France)	Clothed, air: 15 °C	Oxygen consumption: 1.1-fold increase
Rübner (1903, Germany)	Cold-water shower: 16 °C	Oxygen consumption: two-fold increase
Swift (1932b, U.S.A.)	Business clothes, air: 2 °C	Metabolic heat production: almost two-fold increase
Adolph and Molnar (1946, U.S.A.)	Underwear, outdoors, air: 0.6 °C	Oxygen consumption: five-fold increase
Iampietro et al. (1960, U.S.A.)	Nude, air: − 1 to 4 °C	Metabolic heat production: five-fold increase
Glickman et al. (1967, U.S.A.)	Military thermal clothing, air: − 28.9 °C	Metabolic heat production: more than two-fold increase
Young et al. (1986, U.S.A.)	Swimming costume, air: 5 °C	Metabolic heat production: two-fold increase
Young et al. (1989, U.S.A.)	Swimming costume, water: 18 °C	Metabolic heat production: three-fold increase
Tipton et al. (1997, England and Canada)	Swimming costume, water immersion plus agitation to elicit three shivering intensities	Oxygen consumption: two-fold increase
Regan (1998, Australia)	Swimming costume, water: 18 °C	Oxygen consumption: more than four-fold increase
Tikuisis et al. (1999, Canada)	Shorts, t-shirt, gloves and boots: air (10 °C) then shower (10 °C)	Metabolic heat production: more than three-fold increase
Tikuisis et al. (2002, Canada)	Swimming costume, water: 20° gradually reduced to 8 °C	Oxygen consumption: more than four-fold increase

Observations relate to resting individuals only, with changes expressed relative to pre-exposure, normothermic baselines. Metabolic heat productions were derived by the original authors from oxygen consumption using either measured or assumed respiratory exchange ratios, and the formulae of Zuntz and Schumburg (1901), Weir (1949) or Péronnet and Massicotte (1991), although those conversions were not always stated

what if he exercised at 30% of peak aerobic power, with the heat generated by running no longer matching that produced by shivering? Would he then continue to shiver while running, but at a lower level? Since cold water imposes a far bigger drain on body heat than does cold air, what would happen if he swam at 30% of his peak aerobic power in water so cold that it required shivering at (an impossibly high) 70% of his peak aerobic power just to maintain homeothermy? Would he shiver maximally while swimming and still become hypothermic, or would homeothermy be given priority and the energy deficit prevent effective swimming?

Metabolic heat production during swimming

The earliest measurement of peak aerobic power made during exercise (cycling), of which we are aware, was accomplished by Leo Zuntz (1898, Germany), the son of Nathan Zuntz (Gunga 2009). The corresponding data for swimming were collected by Johannes Lindhard (1870–1947, Denmark), a colleague of August Krogh. He undertook a series of historically significant projects, and with G. Liljestrand and N. Stenström provided the first compendium of research on the physiology of walking, running, rowing, skating, skiing and swimming (Lindhard 1915; Liljestrand and Lindhard 1920a, b; Liljestrand and Stenström, 1920a, b, c), all of which were published in a single volume (*Skandinavisches Archiv Für Physiologie*). Our other main protagonist from this epoch, Archibald Hill, brought those observations together into his description of the "*maximum oxygen intake*" (Hill and Lupton 1923 [P. 152–155]; peak aerobic power).

For maximal swimming in non-elite swimmers, Karpovich and Millman (1944) reported that the peak metabolic rates represented a ten-fold elevation in oxygen consumption, relative to a resting state. Whilst it is generally accepted that the peak oxygen consumption rates for swimming are significantly lower than those for other exercise modes (Åstrand and Saltin 1961; McArdle et al. 1971; Holmér et al. 1974), those work rates are unsustainable, even for well-trained swimmers. Indeed, swimming speeds at which peak oxygen consumption is observed can be maintained only for 5–6 min (Holmér and Bergh 1974; Billat et al. 1996; Fernandes et al. 2008). For other exercise modes, tolerance times at peak oxygen consumption speeds seem to be 3.7 min (cycling), 5.4 min (running) and 6.3 min (kayaking; Billat et al. 1996).

Fortunately, from a thermoregulatory perspective, swimming is metabolically wasteful, and heat production can approach several times that of running at the same speed (Schmidt-Nielsen 1972; di Prampero et al. 1974). That overflow of thermal energy makes homeothermy achievable, as long as the water temperatures are not too low (Golden and Tipton, 1987; Sagawa et al. 1988), with heat production supplemented by shivering. Whether homeothermy actually is achieved during endurance, open-water swimming depends upon the water temperature and the sustainable swimming speed. Not only can hypothermia be avoided but, during swimming in water > 20 °C, elevations in deep-body temperature may occur (Trappe et al. 1995).

To illustrate the interplay between swimming speed and water temperature, we examined five studies from three countries, which, with one exception, were performed at three, almost identical water temperatures: 17.4°–18 °C, 25°–26.8 °C and 33°–34 °C. Two studies involved stationary, underwater ergometers. The other three used swimming flumes, which add significantly to convective heat losses. In the first project, Costill et al. (1967, U.S.A.; $N = 8$) studied breaststroke swimming (ergometer) at an intensity that elicited heart rates of 150 beats.min^{-1} (~ 75% maximal intensity, 20 min). They found the oxygen consumption of swimming was not significantly influenced by water temperature, across our three temperatures: 3.01, 3.00 and 2.77 L.min^{-1} (respectively). Subsequently, Nadel et al. (1974, U.S.A. and Sweden; $N = 3$) used the same swimming stroke (flume) and exercise duration, but the swimming intensities approximated 40%, 60% and 100% of peak aerobic power. Whilst the results are largely descriptive, due to the sample size, the oxygen consumption of their participants was consistently higher at each of the lower water temperatures, implying a contribution from thermogenesis.

In our third study (Holmér and Bergh 1974; Sweden; $N = 5$), carried out by two investigators from the previous project (Nadel et al. 1974), participants swam (unspecified stroke; flume) at both 50% (20 min) and 100% (5–8 min) of their peak aerobic power. In the coolest water, oxygen consumption was ~ 0.5 L.min^{-1} higher, relative to the warmer waters, during submaximal swimming. More importantly, they observed that oxygen consumption increased linearly with reductions in deep-body (oesophageal) temperature, once it dropped below ~ 37.3 °C. They further observed that oxygen consumption was elevated even during maximal exercise, so the metabolic heat production of maximal exercise can be supplemented by thermogenesis. In our fourth study (McArdle et al. 1976; U.S.A.; $N = 3$), which is also descriptive, subjects performed combined upper- and lower-body ergometer exercise at six work rates (0–120 W; 5 min), applied in a randomised sequence and separated by 10 min rest in air. The highest work rate approximated maximal intensity. Oxygen consumption was elevated at the two cooler water temperatures, relative to that observed at 33 °C, with a 9% increase at 25 °C and 25% at 18 °C. However, the brevity of the exercise periods, in combination with the intermittent-exercise design, renders those observations difficult to compare with the others experiments. More recently, Tipton et al. (1999; England and Sweden; $N = 10$) replaced the thermoneutral immersion (25°–27 °C) with water at

10 °C. They found that oxygen consumption increased by 45% during self-paced breaststroke (flume) in water at 10 °C, relative to that at 25 °C, even though swimming speed was only 14% faster. Presumably shivering thermogenesis again supplemented exercise-related metabolic heat production.

Together, those projects illustrate that, at some submaximal exercise intensities in cool-to-cold water, there is a superimposition of shivering thermogenesis onto the oxygen cost of swimming, which combines to support thermal homeostasis. Paolone and Paolone (1995) reported the same thermoregulatory phenomenon during walking; a 35% elevation in oxygen consumption when walking in cold air (5 °C), relative to walking at the same work rate (18 $W.m^{-2}$) in temperate conditions (25 °C). Pugh (1967; $N = 3$) had previously observed that effect in wet participants walking in cold air (2 °C), as did Weller et al. (1997a, b; $N = 10$; 5 °C), although that effect was not evident at higher work rates, when thermal supplementation was not necessary.

Some investigators have implied that an absolute oxygen consumption ceiling might exist for that thermal effect (2.8–3.0 $L.min^{-1}$; Nadel et al. 1974; Tipton and Bradford 2014), although that would mean that, in both smaller and sedentary individuals (e.g., peak aerobic power 2.5 $L.min^{-1}$), there would not be a ceiling, whilst in elite endurance athletes (e.g., peak aerobic power > 6.0 $L.min^{-1}$), a ceiling might occur at an intensity of ~ 50% of their peak aerobic power. Our interpretation is that, if a ceiling does exist, it is unlikely to be determined by an absolute oxygen consumption, because whether or not the regulatory centre activates shivering will depend upon exercise-related heat production and heat loss, both of which vary with body size and shape. Beyond that point, the exercise would produce enough heat to offset heat losses, so shivering becomes redundant.

With shivering thermogenesis apparently being relevant only at slower swimming speeds, these studies appear to provide different messages to slower recreational and to faster competitive swimmers, but a recent study from Japan has provided a caveat to that interpretation. Fujimoto et al. (2019) found that, when rest and low-intensity exercise (unloaded cycling) were compared during temperate-water immersions (25 °C), the body-temperature threshold at which thermogenesis began was lower during exercise than it was when resting. But there was no difference in the sensitivity of the thermogenic response above that threshold, so those authors suggested that threshold reduction might predispose slower swimmers to hypothermia. The possibility that thermoeffector thresholds are altered during exercise is contentious, and we are unable to support that hypothesis (Notley et al. 2023a).

If one remains long enough in cold water, deep-body temperatures will be reduced, sometimes to < 35.0 °C (hypothermia: Pugh and Edholm 1955; Keatinge 1960; Pugh et al. 1960; Golden et al. 1980; Keatinge et al. 2001; Diversi et al. 2016), and even to lethal levels (Molnar 1946; Gagge and Herrington 1947; Tipton et al. 2017). The critical determinants of that outcome are well known (*First Law of Thermodynamics* and the energy-balance equation; Notley et al. 2023a), highly predictable and do not require repetitious verification. But now consider the interaction of thermodynamics (Pendergast et al. 2003) and physiology when swimming the English Channel, with water temperatures that vary between 15° and 18 °C during the racing season.

The current records are 7 h 25 min (Yvetta Hlavacova, France) and 6 h 55 min (Trent Grimsey, Australia). The first successful channel swim was made in 1875 (21 h 45 min) by Matthew Webb (1848–1883, England; Fig. 20A), the Channel Swimming Club was formed in England in 1906 and the first woman to complete the swim was Gertrude Ederle in 1926 (1905–2005, U.S.A.; Fig. 20B). One of the more famous open-water swimmers of his era was Zasson Zirganos (1910–1959, Greece; Fig. 20C; Pugh and Edholm 1955; Noakes 2000), and he is noted here to emphasise both his morphology and the use of grease to supplement his physiological insulation; we will return to Zirganos in due course. We also note the important contributions of Lewis Pugh (South Africa), who is famous not just for his cold-water swims (including both polar regions), but for his efforts to protect our planet from global warming. Pugh swam in ice water according to the rules of the *Channel Swimming Association* which excludes the use of thermal protective and buoyancy clothing.

The association of body shape and composition with cold tolerance has long been recognised (Swift 1932b; Pugh and Edholm 1955; Keatinge 1960; Pugh et al. 1960; Golden et al. 1980; Baldassarre et al. 2017), although, as often occurs in physiology, there are lean individuals (Fig. 20; Golden et al. 1980) who challenge our "*prefabricated set of interpretations*" (Kennedy 1962). When swimmers are racing, they can offset convective heat loss by swimming faster, and thereby produce more heat, or they can reduce it by adding to, or modifying, their physiological insulation. For instance, the international organisation that overseas water sports (*Fédération Internationale de Natation*; founded 1908) has mandated the wearing of thermally protective suits for water temperatures < 18 °C; the early open-water swimmers used grease. Conversely, the *International Winter Swimming Association*, which governs racing in ice water (−2° to 2 °C), freezing water (2.1°–5.0 °C) and cold water (5.1°–9.0 °C), excludes the use of thermal protective and buoyancy clothing, as does the *Channel Swimming Association*.

Without adequate metabolic heat production or insulation during cold-water swimming, the progressive encroachment of hypothermia affects skeletal muscle

function and co-ordination (Horvath and Freedman 1947; Clarke et al. 1958; Clarke and Stelmach 1966; Vincent and Tipton 1988), which decreases swimming efficiency and increases the cold-exposure duration (Tipton et al. 1999). For workers exposed to cold water or air, those effects appear in the forms of reductions in strength and manual dexterity (LeBlanc, 1956; Thompson and Hayward 1996; Brajkovic and Ducharme 2003; Zander and Morrison 2008; Wheelock et al. 2021; Sullivan-Kwantes et al. 2021).

Before leaving swimming, we will briefly touch on training-induced increases in endurance fitness. Endurance training increases both metabolic efficiency and the sustainable, steady-state speed of athletes (Hagerman 1984; Baldassarre et al. 2017; Sandbakk and Holmberg 2017). Within sub-elite athletes, it can also increase peak aerobic power somewhat (Saltin et al. 1968b; Ekblom 1969). Whilst that elevation will support greater heat production, it is less likely to be seen in highly trained individuals (Sjödin and Svedenhag 1984; Noakes and Ekblom 2008). By extrapolation, improvements in aerobic power might be even more beneficial for cold-water endurance in recreational swimmers. Bittel et al. (1988, France) described precisely that relationship, finding that the heat production of their thermally non-adapted participants, who varied in endurance fitness, was correlated with peak aerobic power, with the unexplained variance decreasing from 52% in water at 10 °C to 31% at 1 °C. However, Keatinge (1961) observed that, whilst peak aerobic power might be elevated following endurance training when cold-stressed in air, his resting, endurance-trained subjects displayed a reduced metabolic (thermogenic) response within the first 30 min of a 7.5-h cold exposure. The metabolic response of his cold-adapted

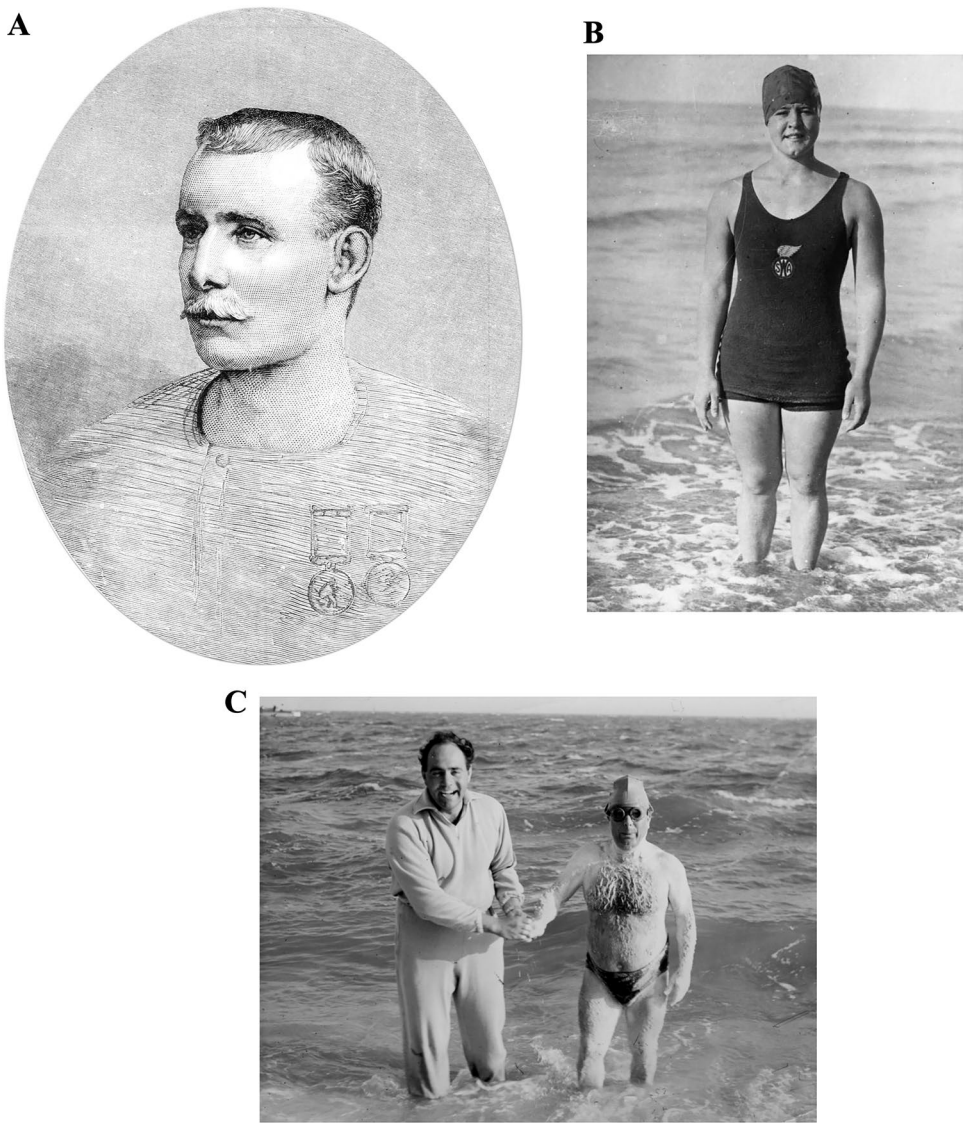


Fig. 20 **A** The first successful English Channel swimmer: Matthew Webb. Obtained from the Illustrated London News (Royal Museums Greenwich, CC BY-SA 3.0) and used under the Wikimedia Commons agreement (Public Domain). *Source:* https://commons.wikimedia.org/wiki/Category:Matthew_Webb#/media/File:Captain_Matthew_Webb.jpg Accessed: April 28th, 2023. **B** The first woman to successfully swim the English Channel swimmer: Gertrude Ederle. Obtained and used under the Wikimedia Commons agreement (Public Domain). *Source:* https://commons.wikimedia.org/wiki/File:Bundesarchiv_Bild_102-10212,_Gertrud_Ederle.jpg Accessed: April 28th, 2023. Part C: Zasson (Jason) Zirganos (Greece) at the completion if his English Channel swim from Dungeness Point (France) to Folkestone (England; 1951 [14 h 10 min]). This image is in the Public Domain. *Source:* https://www.channelswimmingdover.org.uk/content/photo/major-jason-zirganos-of-greece-with-sam-rockett Accessed: July 11th, 2022

subjects initially increased to a greater extent during resting cold exposures, but it was reduced towards the end of those exposures. Similar observations were made by others who studied cold-exposed, endurance-trained individuals (Kollias et al. 1972; Dressendorfer et al. 1977), with the latter reporting both reduced thermogenesis and evidence of a greater vasoconstrictor response. Thus, endurance training appeared to suppress cold-induced thermogenesis.

Fuelling the fires: the competition for blood glucose

During extended-duration activities performed without energy replacement, there is an "*exhaustion of the material of the muscle*" (Hill 1925 [P. 422]). That material is muscle glycogen, which is replaced, in the first instance, by glucose carried in the blood. Glycogen depletion can result in hypoglycaemia and fatigue (Christensen and Hansen, 1939), which can be delayed through glucose ingestion (Coyle et al. 1983). If we jump back to Rübner (1903) and Lusk (1911), who showed that shivering is fuelled via carbohydrate metabolism, then we can see that the combination of protracted endurance exercise and shivering might exacerbate glucose depletion. Collectively, they increase the possibility of developing hypoglycaemia, which might limit exercise and possibly even shivering thermogenesis.

Indeed, in the same year that Hill (1925) hypothesised a substrate-dependent endurance limitation, there appeared evidence that hypoglycaemia could inhibit shivering (Cassidy et al. 1925). It seemed possible that a competition might exist wherein glucose, an energy source for exercise and shivering, must serve two masters, with its depletion resulting in the failure of both forms of muscle activity. How dependent is shivering thermogenesis on intramuscular glycogen and blood glucose?

To answer that question, we will jump over our century of exercise physiology, and into the modern epoch, and we start that journey with a Canadian group led by Ira Jacobs (Jacobs et al. 1994; Tikuisis 2022). They investigated an applied problem using necessarily invasive procedures. In the first study, Martineau and Jacobs (1988) estimated substrate utilisation during shivering using respirometry and muscle biopsies. Resting cool-water immersion (18 °C) induced a 3.5-fold elevation in metabolic rate and increased the respiratory exchange ratio from 0.80 to 0.85, relative to pre-immersion baselines. Those changes were accompanied by a 20% reduction in intramuscular glycogen (*vastus lateralis*) and plasma glucose concentrations and thereby established the role of intramuscular glycogen as a metabolic substrate during strong shivering.

In a follow-up investigation in air (10° versus 29 °C), Vallerand and Jacobs (1989) described a 2.5-fold elevation in resting metabolic rate and the respiratory exchange ratio increased from 0.77 to 0.86. Lipid oxidation also increased, but only by ~ 65%, compared to an almost six-fold rise in carbohydrate oxidation; protein metabolism was not significantly changed. So carbohydrate oxidation, which represented < 20% of the metabolised substrate under normothermic conditions, fuelled > 50% of cold-induced shivering. Martineau and Jacobs (1989a, b) confirmed those observations in cool water (18 °C).

Another Canadian group qualitatively supported those observations (Haman et al. 2005), observing that the intramuscular and plasma glucose stores were oxidised at rest during both lower-intensity (water immersion 10 °C) and higher-intensity (5 °C) shivering (2.3 versus 3.5 times resting metabolic rate, respectively). The use of both energy sources doubled in the colder water, but intramuscular glycogen was metabolised at about three times the rate of plasma glucose. Moreover, the overall contribution of carbohydrates increased from ~ 35% (10 °C) to ~ 55% (5 °C). Those observations do not mean that reductions in either blood glucose or intramuscular glycogen necessarily mean an impediment to shivering unless there is also frank hypoglycaemia.

Does carbohydrate use during exercise have any consequences for shivering? In an elegant experiment, Young et al. (1989, U.S.A.) manipulated the intramuscular (*vastus lateralis*) glycogen stores of their participants using rigid dietary and exercise interventions. Pre-experimental glycogen differences varied by a factor > 3.5, before commencing cool-water immersions (18 °C, 180 min, rest). When glycogen stores were low, mimicking those observed following extended-duration exercise (Coyle et al. 1986), the respiratory exchange ratios were generally < 0.80, before, during and after immersion. When intramuscular glycogen was elevated, the exchange ratios were > 0.90, except during the post-immersion state (< 0.90). Metabolic rate increased > 2.5-fold and was almost identical across both trials. Whilst muscle glycogen was significantly reduced in the low-glycogen trial, plasma glucose concentration did not change throughout either trial and hypoglycaemia did not eventuate. There was no evidence for an intramuscular substrate limitation to shivering thermogenesis, although a connection with hypoglycaemia could not be excluded, as participants remained euglycaemic throughout both trials.

The missing link in those Canadian and U.S. studies was exercise. Indeed, the changes in metabolic rate were rather modest, relative to those expected during exercise undertaken in highly motived athletes and workers. Furthermore, unlike the brain, skeletal muscles have a greater flexibility in their use of metabolic fuels, although that flexibility becomes more limited as exercise or shivering intensity rises (Haman et al. 2005). The key factor to the continuation of either exercise or shivering might be whether or not hypoglycaemia occurs (Haight and Keatinge, 1973; Thompson and Hayward 1996).

One of the seminal experiments concerning the interaction of shivering and plasma glucose concentration was performed by Edward Gale and colleagues (1981; England), but it was from supplementary manipulations that a new and unexpected way of thinking about shivering and plasma glucose arose, and how shivering might be affected by endurance exercise. They used intravenous insulin infusions to artificially induce hypoglycaemia in resting participants (25 °C dry bulb), which elicited cutaneous vasodilatation and sweating. Deep-body (insulated auditory canal) temperature started to decrease 60–80 min after infusion, which activated mild shivering and increased metabolic heat production (~ 25%; Gale et al. 1981). In a subsequent investigation of the impact of different plasma glucose concentrations on normothermic subjects, they found that hypoglycaemia varied in its impact across regulatory systems; there was not a universal response threshold (2.0–2.5 mmol.L^{-1}). Instead, responses were graduated, and they were particularly strong with regard to thermal homeostasis (Gale et al. 1983).

As part of their first experiment, they investigated the impact of insulin infusion on mildly hypothermic subjects (18°–19 °C dry bulb; Gale et al. 1981). Metabolic heat production (shivering) had already increased two-fold, which stabilised deep-body temperature and prevented its further decline. However, 10–15 min after insulin infusion, hypoglycaemia developed and shivering was completely inhibited (confirmed electromyographically). Deep-body temperature decreased rapidly to < 35 °C, yet shivering was not reactivated. Two hypothermic and hypoglycaemic participants were then infused with a glucose solution, and shivering recommenced in both. On one individual, a supra-systolic occlusion cuff was applied around one upper thigh prior to the glucose infusion. Infused glucose could not reach the muscles of that leg, yet it commenced shivering at the same time as the other leg. Hypoglycaemia had exerted a central, but not a localised influence on the muscles. What was that central mechanism? Is this an example of "hitting the wall"?

There certainly is a mechanistic clue within that possibility, to which we will return, but first, let us quickly jump back to the depletion hypothesis of Hill (1925), and our story on marathon running. Could there be a connection with cold tolerance? In the year preceding Hill's hypothesis, three American physicians described marked reductions in the post-race, plasma glucose concentrations of six runners who had just completed the Boston Marathon, noting that "*Such figures are rarely encountered in human experience except with excessive doses of insulin*" (Levine et al. 1924, [P. 1778]). They described an apparent correlation between hypoglycaemia and the physical condition of the runners, yet the winner, Clarence DeMar (U.S.A.), who broke the world record, had a normal plasma glucose concentration. That prompted the authors to recommend carbohydrate consumption before and during marathon racing to prevent "*hypoglycemia and accompanying development of the symptoms of exhaustion*" (Levine et al. 1924 [P. 1779]).

That recommendation led to the development of glucose supplementation strategies for endurance racing (Sherman and Costill 1984). Indeed, strategies to prevent hypoglycaemia in the *Tour de France* are obvious to even unfamiliar observers. Without supplementation, depletion of muscle glycogen leads to precipitous reductions in endurance performance intensity (Bergström et al. 1967; Bosch et al. 1993; Hargreaves 2008; Katz 2022). In the absence of hypoglycaemia, however, supplementing glucose does not appear to enhance shivering thermogenesis (Mittleman et al. 1990; Jacobs et al. 1994). When hypothermia and hypoglycaemia coexist, supplementation may prevent journeying beyond hypothermia.

Let us join the dots. Extended-duration exercise depletes muscle glycogen and plasma glucose concentrations, particularly when exercise intensities are driven by competitive or emergency priorities (Levine et al. 1924; Hargreaves 2008). Blood glucose is the principal energy source for the brain (Mergenthaler et al. 2013) for its homoeostatic regulation (Notley et al. 2023a [Table 1]), and that is why hypoglycaemia has central, as well as peripheral fatigue influences during exercise (Allen et al. 2008; Taylor et al. 2008b). Hypoglycaemia in resting individuals leads to cutaneous and intramuscular vasodilatation, as well as sweating (Allwood et al. 1959; Molnar and Read, 1974; Gale et al. 1981), which promotes heat loss (Kedes and Field 1964), but it also inhibits shivering during hypothermia (Gale et al. 1981). Shivering in euglycaemic people increases plasma glucose consumption (Rübner 1903; Lusk 1911; Martineau and Jacobs 1988, 1989a, b), and when shivering is combined with long-duration exercise, and particularly during potent levels of cold stress, it leads to rapid reductions in muscle glycogen and plasma glucose. Therefore, although Gale et al. (1981) could not explain how hypoglycaemia inhibited shivering centrally, it might be related to reduced availability of plasma glucose for the hypothalamic thermoregulatory centre, which then hits the wall.

To explore that possibility, Passias et al. (1996, Greece and Canada) used the plasma-glucose clamping procedure (see DeFronzo et al. 1979), to maintain euglycaemic and hypoglycaemic states (44% reduction in plasma glucose concentration) throughout their experiment. They then measured the temperature thresholds for three thermoeffectors whilst sustaining those clamps. Shivering was reduced (20%), but not abolished, resulting in more rapid cooling. That was attributed to a reduced shivering threshold (0.6 °C, oesophageal temperature), and was thought to result from a modulating effect on centrally located, cold-sensitive neurons, many of which are glucosensitive (Silva and Boulant 1984). Accordingly, hypoglycaemia has been suggested as an effective predictor of imminent hypothermia (Passias

et al. 1996; Thompson and Hayward 1996), and alcohol-induced hypoglycaemia has been identified as a primary cause of accidental hypothermia.

Extinguishing the fire with alcohol: *"Don't walk and drink"* We believe that the first documented case of alcohol-related hypothermia was reported by Nauclér (1756, Sweden), who rescued a drunken man who appeared frozen to death, but he survived. This topic is peripheral to our central interests, but it would not have been in the Krogh–Hill epoch, when it was a common custom to consume brandy or other alcohol when running marathons (Blake and Scannell 1903; "Insights and blind spots about thermoregulation during exercise"). Our interest is linked to alcohol-induced hypoglycaemia in people exercising in challenging wintery conditions, who, despite their metabolic heat production, can descend into hypothermia. Indeed, Pembrey (1898) recognised the adverse effect of alcohol on cold tolerance, describing its impact as accelerating heat loss via cutaneous vasodilatation and sweat secretion. Thus, it is relevant to recreational athletes on long hikes, and it is not confined to one sex (Laufman 1951 [woman; rectal temperature 18 °C]). For those reasons, we borrowed our subtitle from a light-hearted, but serious commentary in *The Lancet* concerning the hazard of drinking and walking for recreational walkers in cold climates (Anonymous 1973).

The phenomenon of ethanol-induced hypoglycemia has long been known (Brown and Harvey 1941; Field et al. 1963; Madison 1968), and its association with hypothermia, which was unknown to Nauclér (1756) and not considered by Laufman (1951), was confirmed by Haight and Keatinge (1973). They studied two subject groups during cold-air exposures (14.5 °C) in each of three treatments: semi-naked rest (30 min), exposure preceded by strenuous exercise (120 min) and exposure following the same exercise, but with glucose supplementation (50–65 g). One group (control) completed all trials without alcohol consumption, while the second group consumed alcohol (ethanol 30–40 mL) before each trial. Our interests are in the second and third exposures of the second group, in comparison with data from the first exposure of the controls. When alcohol was consumed without glucose, the cold-induced metabolic rate as reduced by 43%, plasma glucose was halved and rectal temperature dropped by 2.2 °C. Conversely, glucose supplementation following alcohol consumption resulted in all variables being elevated during those exposures (16%, 43% and 0.3 °C, respectively). Those deleterious outcomes are clear, and they arose due to alcohol-induced hypoglycaemia, so our subtitle should perhaps be revised: if you are going to walk and drink, then drink, eat and walk!

Igniting a second fire: non-shivering thermogenesis

Claude Bernard (1876) knew that some mammals could generate significant amounts of heat, over and above their basal metabolic heat production, without actually shivering. Some of that heat comes from white adipocytes and triglyceride metabolism, but much more comes from brown adipocytes during cold exposures. That non-shivering form of thermogenesis is our second fire. During the stress-induced release of catecholamines (adrenaline and noradrenaline), the metabolic activity of brown adipocytes is dramatically elevated. All of that energy is converted to heat. Two of those stresses are directly relevant to exercise physiologists: high-intensity exercise, and acute and stressful cold exposures. When cold exposure is protracted, non-shivering thermogenesis can help defend body temperature. In the Krogh-Hill epoch, Walter Cannon and his colleagues (1927) suggested that the mechanism represented the first defensive strategy of cold-exposed homeotherms. The activation of brown adipose tissue (BAT) is neurally mediated (increased sympathetic activity), with those signals coming from the hypothalamus and *medulla oblongata* (Nakamura and Morrison 2011; Morrison and Madden 2014; Morrison 2018).

Possibly the earliest anatomical evidence of brown adipose tissue in humans appeared at the start of our century of exercise physiology (Merkel 1899 [adult, Germany]; Hatai 1902 [infant, U.S.A.]; Fig. 21), with early examples of non-shivering thermogenesis in cold-exposed, resting adults revealing 11–40% increases in metabolic heat production, but they were not shivering (Voit 1878; Campbell et al. 1921; Cannon et al. 1927; Swift 1932b). Those values seem modest when compared with neonates. Within the first hour after their emergence, into air temperatures that are comfortable for adults, but invariably cooler than their previous residence, neonatal heat production can increase to 112–173% of its basal level (Brück et al. 1958). Similarly, Dawkins and Scopes (1965) reported an almost doubling of the oxygen consumption of older infants (air 25°–26 °C).

Non-shivering thermogenesis has rarely entered the domain of exercise physiologists, largely because it was assumed adult humans did not possess sufficient amounts of brown adipose tissue to have a physiological impact (Dawkins and Hull 1965; Toner and McArdle 1988; Young et al. 1996). In fact, evidence for its existence in adults has existed for over a century (Merkel 1899; Bonnot 1908; Jessen 1980) and continues to be supported (Nedergaard et al. 2007; Cypress et al. 2009; Saito et al. 2009; Ouellet et al. 2012). Brown-fat agnostics need look no further than the investigation of Jessen et al. (1980; Denmark) to be convinced of its functional presence in adult humans.

Every decade or so, there is an experiment that domesticates a theory or settles a debate, providing our minds are open to seeking out and accepting facts that challenge

our prefabricated interpretations. The experiment conducted by Jessen et al. (1980) was one of those investigations. They examined thermogenesis in four patients on life support with irreversible brain damage. They were artificially ventilated, administered a neuromuscular blocking agent (*d-tubocurarini chloridum* [curare]) that induced skeletal-muscle paralysis, and exposed to cool air (16 °C). The experiment was reported as conforming with the *Declaration of Helsinki*, as it existed at the time, and with the informed consent of all legal guardians. Deep-body temperatures (oesophagus, tympanic membrane, rectum) decreased 0.7 °C and the plasma concentrations of noradrenaline and non-esterified fatty acids increased by 130% and 44% (respectively). Whole-body oxygen consumption increased by 25%. Electromyography was used to verify that shivering thermogenesis had been eliminated. Clearly, non-shivering thermogenesis exists in adults as well as neonatal humans, and it was quantitatively similar to the observations of Voit (1878), Campbell et al. (1921), Cannon et al. (1927) and Swift (1932b). Whilst it was not trivial, those increases in heat production were far less than those accompanying shivering, and they did not match the increase seen during slow walking (Mansoubi et al. 2015).

In another approach, Paolone and Paolone (1995, U.S.A.) used propranolol (a ß-adrenergic blocker) to reduce non-shivering thermogenesis by reducing lipolysis in the liver and adipose tissues, but without affecting shivering. Subject were studied in four conditions (t-shirts and shorts): standing (50 min) and walking (40 min) at two air temperatures (5° and 25 °C dry bulb). Trials were repeated with and without (placebo) propranolol. Resting oxygen consumption at 5 °C was reduced by 11% following *beta* blockade, but that treatment produced a non-significant reduction in oxygen consumption during exercise, presumably due to exercise compensating for the blockade of non-shivering thermogenesis.

So non-shivering thermogenesis adds minimally to metabolic heat production during exercise in the cold, but can habitual exercise behaviours change the metabolic activity of human brown adipocytes? There is a growing body of evidence showing that white adipocytes can be "browned" following exercise training (Scheel et al. 2022). The primary function of white adipocytes is energy storage, but habitual exercise seems to bestow upon those cells some of the biochemical attributes of brown adipocytes; "browning". At the commencement of exercise, brown adipocytes are stimulated to generate extra heat, but they may be suppressed during extended-duration exercise and excessive heat production (Zhu et al. 2022). Working skeletal muscles use irisin to signal a need for fuel, and Virtanen (2014) believes that biochemical messenger increases the activation of brown adipocytes. Zhu et al. (2022) suggest there is insufficient evidence to support that role.

Do human brown adipocytes make a meaningful contribution to cold thermoregulation in resting states? In other mammals, there can be no doubt that heat production is important, and it may even be essential (Janský, 1973; Himms-Hagen 1996; Horowitz 1996). The role of brown adipocytes in the thermogenesis of human neonates is significant (Brück et al. 1958; Dawkins and Scopes 1965), but that role is smaller in resting adults (Nedergaard et al. 2007; van Marken Lichtenbelt and Schrauwen 2011; Blondin et al. 2014b).

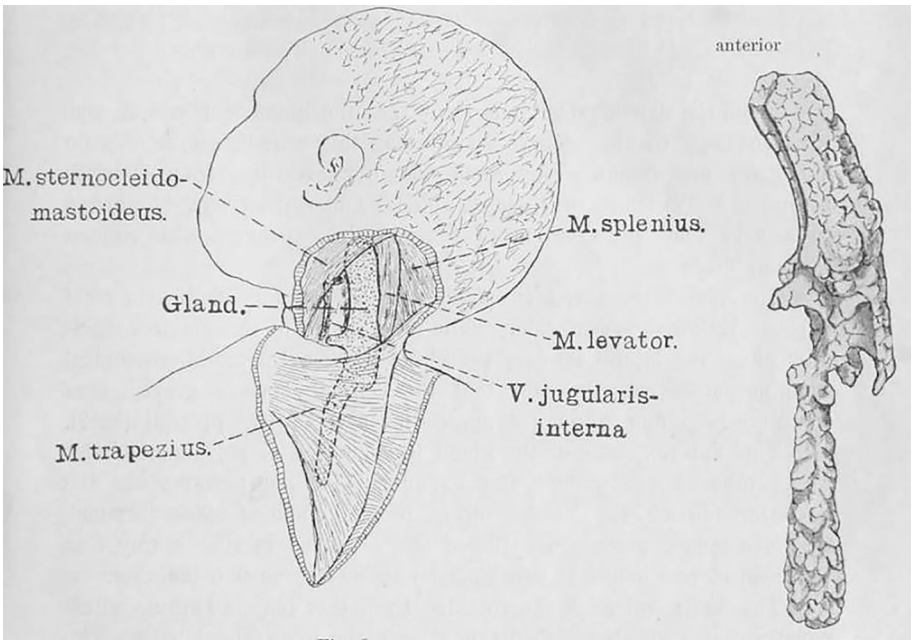


Fig. 21 A sketch, from the early Krogh-Hill epoch, of the location of brown adipose tissue (the hibernating gland) found in the inter-scapular region of an infant, and of its anterior and posterior components. From Hatai (1902 [Figs. 2 and 3]), and is in the Public Domain. Merkel (1899) described that brown adipose tissue, in the same location on an adult, as an elongated fat pad running between the scapula and the base of the skull

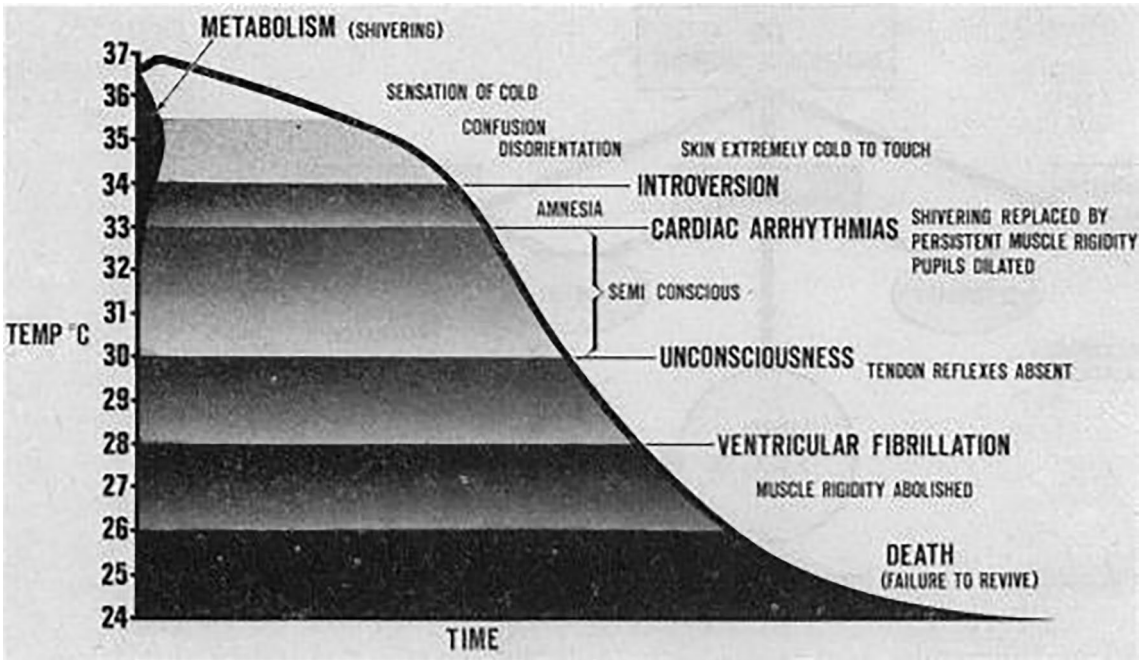


Fig. 22 Deep-body temperature zones wherein the progressive and clinically relevant signs, symptoms and consequences of hypothermia might appear. Taken from Golden (1973) and is freely accessible

Do brown adipocytes usefully contribute to heat production in cold-exposed humans engaged in recreational and occupational pursuits? At this time, we are unable to provide a definitive answer. The anatomical and metabolic adaptations of brown adipose to repeated cold exposures relate only to resting individuals. Whether or not white adipocyte "browning" is real remains speculative, although it is tempting to entertain the notion that, if the thermogenic characteristics of adipocytes can be enhanced by endurance training, then maybe their metabolic role during exercise in the cold can also be enhanced.

Beyond shivering: the descent into hypothermia

The literature is replete with examples of people who have descended into, and ascended back from, seriously hypothermic states. Some examples have already been described (Nauclér, 1756; Pembrey, 1898; Tigerstedt 1906; Laufman 1951; Pugh 1964; UPI 1984; Gilbert et al. 2000; Romlin et al. 2015; Mroczek et al. 2020; Zhang et al. 2021; Sun 2022), and in the sections that follow, others will be highlighted. Before doing so, we remind ourselves of the tissue temperatures that have clinical significance.

Clinically relevant deep-body and skin temperatures

It was again Wunderlich (1871) who provided an early categorisation of clinically relevant deep-body (rectal) temperatures within the hypothermic range. He classified temperatures < 33.5 °C as being fatal, those between 33.5° and 35.0 °C are accompanied by possibly dangerous collapse and temperatures from 35.0° to 36.0 °C are associated with non-fatal collapse. Those zones have been superseded by temperature ranges that are normal clinically. However, those values relate to the general population, but not necessarily to recreational or occupational athletes, who can represent a very skewed subset. Indeed, the high body temperatures of clinical significance, can, and will, be exceeded by enthusiastic athletes and workers, without *sequelae*. Nevertheless, the deep-body temperature zones in Fig. 22 provide us with useful, albeit somewhat plastic, markers of the physiological consequences of hypothermia. John Castellani (U.S.A.) has categorised the early signs of those who have descended into accidental hypothermia as the "*umbles*": the "*grumbles, mumbles, fumbles, and stumbles*" (Castellani 2020 [P. 86]).

To our knowledge, the lowest deep-body temperature survived by an adult was observed following an alpine skiing accident in Norway (Gilbert et al. 2000). The casualty (a young female physician) was reported as clinically dead by the rescue team. After being flown to Tromsø University Hospital, and ~ 160 min after the accident, she had "… *no spontaneous respiration or circulation, her pupils were widely dilated and unresponsive to light. Electrocardiography was isoelectric …*" (Gilbert et al. 2000 [P. 375]). She had displayed some markers of dangerous hypothermia, before skipping over the death zone (Fig. 22). Extracorporeal heating (cardiopulmonary

bypass) was commenced on admission (Farstad et al. 2001), at which point her rectal temperature was 14.4 °C. It was Jean-François Heymans (1859–1932, Belgium) who introduced an extracorporeal heat exchanger to modify deep-body temperatures (Heymans 1919). Full blood flow was restored 40 min later, but her rectal temperature had then fallen to 13.7 °C, 3.5 h after the accident. Her heart was now spontaneously beating and she had a palpable pulse. However, when her oesophageal temperature had risen to 31.5 °C, her rectal temperature was only 14.2 °C, reminding us of the limitations of that surrogate. After 3 h of extracorporeal heating, her rectal temperature reached 36.0 °C. She was ventilated for 35 days, commenced rehabilitation on day 60 and eventually returned to work, hiking and skiing (Gilbert et al. 2000). From that incident and others, the maxim arose that now guides rescuers and those in emergency medicine: "*nobody is dead until warm and dead*" (Hilmo et al. 2014 [P. 1204]; also see: Auerbach 1990; Granberg 1991; Taylor et al. 1994; Ko et al. 2002; Centers for Disease Control and Prevention 2005; Kieboom et al. 2015; Kosiński et al. 2015; Romlin et al. 2015).

If that case is not enough to illustrate the breadth of inter-individual variability outside the normal range, then consider Guðlaugur Friðþórsson, an Icelandic fisherman, who, in 1984 swam for 5–6 h in the sea (5°–6 °C, air − 2.0 °C [dry bulb]; Keatinge 1986; Park 2020) following a boating accident. As Nauclér (1756) had already shown, "*they breed 'em tough up north*", and Friðþórsson was a big man (193 cm, 125 kg), and morphologically suited to endure cold exposure. He produced appreciable heat when swimming, and his clothing provided some thermal protection. We suspect that he must have been approaching failure, and was possibly hypoglycaemic. His two companions perished within 10 min. For comparative purposes, consider an open-water, ultra-endurance swimmer (53-year-old male, 111 kg), who swam 15 km in Lake Constance (Germany; water temperature 9.9 °C) at the about same time. Continuous records of his initial rectal temperature show that it climbed from 37.8° to 38.1 °C after about 20 min, dropped to 36.3 °C at the end of the swim and continued to decrease to 36.0 °C, 35 min after finishing (Rüst et al. 2012).

At the other end of the morphological spectrum are our American (4 years; UPI 1984), Swedish (7 years; Romlin et al. 2015) and Polish children (2 years; Mroczek et al. 2020). We described the first two cases earlier. Our Polish boy wandered away from his home at night (− 7 °C dry bulb; December 2014) and was thought to have been missing for 180 min before his absence was discovered. He was found (unconscious, pupils dilated and fixed) 120 min later, and entered the hospital 110 min later. Extracorporeal oxygenation (reperfusion; Farstad et al 2001) was commenced, at which time his rectal temperature was 12.6 °C, and decreased to 11.8 °C after 10 min. Rewarming commenced 60 min after reperfusion. He also survived, spending nine days in intensive care, and was discharged after 64 days. In the 5-year clinical follow-up, he showed no overt limitations and displayed above average psychological development (Mroczek et al. 2020). But how low can you go?

Zafren et al. (2022, U.S.A.) described case reports for artificially induced hypothermia. Such deliberate, clinically supported treatments and accidental cases in the absence of medical support are neither equally survivable nor physiologically equivalent. Nonetheless, the evidence from Zafren et al. (2022) might lead us to believe that the lowest survivable deep-body temperature for humans now sits at 3 °C (oesophageal; Sealy et al. 1960). We are unable to accept that number, although the deep-body temperatures of hibernating Arctic ground squirrels go below 0 °C (Barnes 1989). If we read the original paper (Sealy et al. 1960), it becomes evident that the temperatures most frequently described were for the blood, cooled using an extracorporeal heat exchanger prior to, and during, heart surgery. Given the intimate contact between the oesophagus, the heart and the large arteries and veins of the heart, then oesophageal temperature rapidly tracks changes in blood temperature, independently of its own perfusion (Notley et al. 2023b). The authors described two cooling methods: whole-body and selective cardiac cooling (Sealy et al. 1960). In the latter, the heart is cooled, but the rest of the body was kept warmer than 26–28 °C. We suspect their magical 3 °C was associated with cardiac-only cooling. Indeed, Gibson and Simpson (1962) described an extracorporeal technique with deep-body temperature reduced to ~ 15 °C, resulting in pericardial temperatures between 10° and 14 °C, although they did report one instance with a pericardial temperature of 5 °C. To our knowledge, the coldest externally cooled, patient was a woman of 51 years, cooled to a rectal temperature of 9 °C (rubberised blanket and refrigerant [− 1° to − 7 °C]). As planned, her heart ceased beating at 10.5 °C, remained silent for 45 min and restarted during rewarming (Niazi and Lewis 1958; U.S.A.). She recovered from the procedure, but not from her cancer.

From these extreme cases, we move to clinically relevant skin temperatures that occur below our level of thermal comfort: 23°–26 °C in air and 34°–36 °C in water ("Revisiting first principles: cooling in air, helium, water and snow"). In air at those temperatures, our skin temperatures vary from ~ 25 °C for exposed toes, through to ~ 34 °C for the uncovered forehead (Fig. 7). When exposed to very cold air, cutaneous vasoconstriction, in combination with heat loss, will result in skin temperatures approaching that of the ambient environment. That effect is most pronounced at the extremities, and results in their thermal isolation (amputation) from the deep tissues (Forster et al. 1946; Scholander and Krog 1957). In cold water, the skin temperature is rapidly reduced, and will often be within 1 °C of water temperature (Rapp 1971; Boutelier et al. 1977). During skin cooling,

localised discomfort occurs at a skin temperature of ~ 25 °C, there is an impairment of manual dexterity at ~ 20 °C, local pain can occur following extended time at ~ 15 °C, there is loss of feeling in the fingers at ~ 10 °C, and the time-dependent development of non-freezing (~ 5 °C) and freezing cold injuries follow (< 0.6 °C; Margaria 1930; Mackworth 1953; Teichner 1957; Keatinge and Cannon 1960; Francis and Golden, 1985; Enander and Hygge 1990; Havenith et al. 1992; Brajkovic and Ducharme 2003; Taylor et al. 2008d). The end result is peripheral incapacitation, which is accelerated by fluid movement over the skin, with the "*effects of raising the wind speed from still air to only a few miles an hour were just as important as the effects of lowering the air temperature by 5 °C*" (Mackworth 1953 [P. 543]). Those effects have both physiological and clinical significance.

The other side of the coin Can hypothermia be protective? Yes, and there are several sides to this coin. Artificially induced hypothermia is an established medical practice with generally beneficial, but sometimes adverse outcomes (Ganong et al. 1955; Hume and Egdahl 1959; Trede et al. 1961; van Brunt and Ganong 1963; Nealon and Gosin 1965; Sessler 1995; Tveita and Sieck 2022). However, systemic hypothermia and localised cold exposures, beyond the clinical environment, can increase the probability of wound infections, delay blood clotting and lead to the development of gangrene within cold-injured tissues (Fuhrman and Crismon 1947; Sessler 1995), as did ice-water enemata used to teat heat stroke ("Heat stroke in the Krogh-Hill epoch: a military perspective"). Those outcomes can have serious implications for recreational and occupational athletes who are unable to immediately remove themselves from their cold surroundings.

Hypothermia during athletic competitions

During our discussions about exercise in the heat, we described how marathons carried a risk of potentially lethal hyperthermia. Do marathons run in the cold carry a risk of hypothermia? They do, but hypothermia requiring hospitalisation is rare (Porter 1984). Cooler conditions favour marathon performances, with the fastest times for marathons typically being set at dry-bulb temperatures of 10°–12 °C (Roberts 2000; Ely et al. 2007a, b; Castallani, 2020). For the Boston Marathon, records were set in light drizzle at dry-bulb temperatures of 5°–10 °C (Trapasso and Cooper, 1989).

Athletes of ultra-marathons and long-distance events in the water do not escape the risk of serious hypothermia. To be consistent with our first-principles approach, four scenarios in which heat loss exceeded heat production will be highlighted, resulting in the development of hypothermia during endurance-dependent athletic competitions. In all cases, we believe that hypoglycaemia contributed to the descent of those athletes into seriously hypothermic states, although we have no data to unequivocally support that interpretation. Four sports have been selected, across which heat exchanges varied considerably. Whilst each scenario absolutely challenged thermal homeostasis, three very different types of exposures have been chosen: air with rain and strong winds, water immersion, and mixed air and water exposures with strong wind. These cases provide opportunities for students to consider physiological function at the limits of human tolerance.

In our first scenario, 240 competitors (17–24 years), in teams of three, took part in a 72.5-km, cross-country walking race over hilly (400 m) moor country (March 1964; The Four Inns, England). Teams are required to remain together and to register at designated checkpoints *en route*, four of which are located at inns. In the 1964 race, there was heavy rain and strong winds (air temperature 1°–4 °C), with sleet and snow falling the previous night. Several walkers required evacuation whilst two (21 years) were missing. Their bodies were found two days later, and a third walker died before reaching the hospital. An official report on the tragedy is available (Pugh 1964).

Our second example occurred in more mountainous terrain (2230 m), during the 100-km, Gansu ultra-marathon (May, 2021; Gansu Province, China). Over the preceding night, a cold front passed through the region, and air temperatures fell to 3 °C with wind speeds gusting to 11.2 $m.s^{-1}$ (Zhang et al. 2021). When the apparent air temperature was calculated (Steadman 1984; "Algebraic stress indices of positive heat load"), its minimum value was – 5 °C and the climatic conditions were classified as extreme (Zhang et al. 2021). There were 172 starters, twenty-one of whom perished due to hypothermia (Zhang et al. 2021; Sun 2022). Included among those was China's top ultra-marathoner, the race record holder and race leader when last seen. Presumably, he was also the producing the most heat.

We introduced Zasson Zirganos (Greece; Fig. 20C) in "Metabolic heat production during swimming". He completed four English Channel swims (fastest 14 h 10 min) with three unsuccessful attempts. He completed only two of the Oceans Seven swims (English Channel [33.5 km] and Catalina Channel [Santa Catalina Island to mainland California, U.S.A., 32.3 km]). To date, only 21 people, including seven women, representing 13 countries, have completed all seven swims. Griffith Pugh and Otto Edholm (England) studied Zirganos during a race record attempt in Lake Windermere (16.2 km, England; water temperature 15.8 °C) as well as swimmers from the 1954 English Channel race (Pugh and Edholm 1955). In 1959, Zirganos died when attempting the North Channel swim; "*he swam for 16 h 23 min and was 3 miles from the Scottish Coast when he was taken from the sea exhausted. He died within minutes. A Doctor performed an emergency operation with a pen-knife but could not restore the heart-beat*" (https://

www.channelswimmingdover.org.uk/content/swimmer/zirganos-major-zasson-jason).

Our last example pales into insignificance with those above, but is included because it occurred during an Australian summer (January 1997), it was a sunny day (strong radiant heating), the sport was rowing (competitors generally remain dry) and one of the victims was a thermal physiologist who had just participated in a cold-adaptation experiment (15-d, cold-water [18 °C], 90 min; Stocks et al. 2001, 2004a, b; Australia). He is an experienced open-water rower who first completed the event in 1979 and should have known the insidious nature of hypothermia, even in warmer ocean waters (20°–24 °C; the Y chromosome is not protective). The race was the biennial George Bass Surfboat Marathon (1975-present; Batemans Bay to Eden, Australia); 190 km completed as seven daily races. Teams have 6–8 rowers, depending on daily distances, with four rowers in the boat at any time. Crew changes, sometimes 1–2 km offshore, occur without stopping and with fresh rowers waiting in the water. On the fourth day (24 km, record 1 h 42 min), a cold front passed through before racing commenced, bringing southerly gales, but clear skies. The winning crew took 3 h. Three rowers from the team in question succumbed to hypothermia: one was unable to complete a crew change, and another lost consciousness in the boat and required rescuing. The crew then completed the race, but, on reaching the beach, the physiologist had the "*mumbles, fumbles, and stumbles*" (Castellani 2020 [P. 86]). Forty rowers were treated for hypothermia that day, but all continued racing and completed the event. How did that happen? Inadequate protective clothing, insufficient energy replacement and an inability to get dry and stay dry in rough seas. Was hypoglycaemia a factor? We suspect so. As a postscript, the physiologist completed the 2023 race without incident.

Beyond shivering: non-freezing and freezing cold injuries

The mechanisms of cold-induced tissue damage

Quite obviously, the primary causal agent for cold injuries is the exposure to thermal gradients that facilitate heat loss between the skin and the adjacent fluid. If air is that fluid, that gradient could approach − 90 °C in Antarctica, which requires the wearing of clothing to establish a protective (limiting) layer of warmer air next to the skin. When immersed in water, which freezes at temperatures from 0 to − 1.8 °C, depending upon its salinity, unclothed skin temperature will approach that of the water (Rapp 1971; Boutelier et al. 1977). The limiting gradient now becomes the tissue layers between the deeper and superficial tissues. In both scenarios, the critical factors for initiating cold-induced tissue damage are the tissue temperatures at which cellular damage starts, and the depth and mass of the body tissues that reach those temperatures. Unfortunately, human tissues cannot withstand freezing without damage, as can the tissues of many animals living in freezing environments (e.g., Storey and Storey 1988), so cell damage starts before tissues freeze (non-freezing cold injuries), although freezing causes greater damage.

In our first epoch, it was Napoleon's chief surgeon (Dominique-Jean Larrey, France; "Beyond the summer stroll—accommodating, tolerating and suffering exercise in the heat"), who provided the first description of, and the recommended treatment for, human cold injuries (Larrey 1832; Francis 1984; Paton 2001), although reports of cold injuries can be traced back to the ancient Greeks (Paton 2001). During the trench warfare of the Crimean and First World Wars, the incidence of non-freezing cold injuries (trench foot) reached almost epidemic proportions (Lorrain Smith et al. 1915; Atenstaedt. 2006; Golden et al. 2013; Anonymous 2018), and readers are directed elsewhere for details concerning the pathophysiology non-freezing cold injuries (Ungley et al. 1945; White and Scoville 1945; Francis and Golden, 1985; Purdue and Hunt 1986; Kennett and Gilliatt, 1991a, b; Irwin et al. 1997; Thomas and Oakley 2001; Imray et al. 2011; Heil et al. 2016b).

The consensus of those reports is that those injuries are due to tissue damage, especially to the large, myelinated nerve fibres, caused by repeated and sustained bouts of maximal cutaneous vasoconstriction, followed by reperfusion. Local tissue blood flows can be reduced below that required to meet the metabolic needs of the local tissues, with reperfusion leading to the appearance of reactive oxygen species and tissue damage (Bhaumik et al. 1995). A sure sign that one has entered that territory is the intense, almost crippling, pain experienced when blood flow returns to numb, superficial tissues, and they slowly rewarm. Repeated cold exposures of that intensity can lead to chronic vascular problems of the hands and feet (Fig. 19), and which is much worse than the pain associated with immersion in cold water (Behnke and Yaglou 1951). A recent epidemiological study has revealed that 23% ($N = 609$) of athletes from paddle sports have symptoms consistent with the presence of non-freezing cold injuries (Oakley et al. 2022).

As the body cools further, tissue freezing can result. The freezing point of human peripheral tissues was once thought to be the same as that of blood (− 0.55 °C; Margaria 1930; Smith 1954), but in another example of self-experimentation, Keatinge and Cannon (1960; England) immersed the distal phalanx of their little fingers into brine at − 1.9 °C (4–7 min), observing the freezing point to sit between − 0.53 and − 0.65 °C, although human skin seldom freezes without first supercooling (Wilson et al. 1976). For our purposes, we can settle for − 0.6 °C for freezing without supercooling, so

human skin tissues can freeze in seawater, even though the water itself has not yet frozen (Keatinge and Cannon 1960).

Details of the pathophysiology of freezing injuries have also been covered by others (Ungley et al. 1945; Mills 2001a; Hutchison 2014; Heil et al. 2016a, b). Tissue freezing occurs in several stages, starting with maximal cutaneous vasoconstriction. The extracellular, but not the intracellular, fluid starts to freeze, leading to ice formation. Those crystals take water from the adjacent cells as they grow, and the cell walls rupture (lysis). Blood trapped within the affected tissues increases in viscosity and blood clots form, further impairing perfusion. Eventually, more and more tissue freezes.

Cold injuries in the workplace

The women and men with physically demanding jobs, during which they will be exposed to cold, now become our focal point. In many of those high-risk jobs, workers will regularly be exposed to whole-body or localised cooling, with those exposures presenting significant health hazards (Mäkinen and Hassi 2009). When repeatedly experienced, adaptations will follow, and that is the emphasis of Part 4 of this historical series.

To illustrate the occupational problem, we have chosen another military example. This choice was based upon three factors: the availability of injury statistics, the precision of those records and the number of active military personnel. Using data from 168 countries, it seems there are currently 20 million active military personnel worldwide (0.3% of the world population; World Population Review 2022). The First World War (1914–1918) was fought between the Allied and Central Powers, with casualty data being more readily available for the former. Across both sides, 65 million personnel were mobilised from 16 countries, with 42 million Allied personnel (Simkin 1997). It was fought largely from trenches that extended from the English Channel almost to the Swiss Alps (Fig. 23).

During that trench warfare, the incidence of non-freezing cold injuries was so high, hence the name trench foot, that it was managed as an epidemic (Lorrain Smith et al. 1915; Paton 2001; Atenstaedt. 2006; Golden et al. 2013; Anonymous 2018; Sabbatani et al. 2019). Just as we have seen with the COVID-19 pandemic, the media were called to action (Fig. 24), although there was no unique pathological mechanism in trench foot. Instead, trench foot is just one of a suite of non-freezing injuries, all with similar pathophysiology, that affect our hands and feet: immersion foot, immersion hand (Ungley et al. 1945) and polar hand (Ayton 1993 [associated with repeated irritation and dermatitis]; Fig. 24).

Using historical data, Paton (2001) provided a detailed collection of data for cold injuries during military conflicts from 400 B.C.E. through to the Falkland Conflict, with Golden et al. (2013) adding further information. The First World War resulted in the following casualty counts due to cold injuries: Britain 100,777, France 79,465, Italy 38,000 and U.S.A. 1992 (Paton 2001 [Table 10–1]; Golden et al. 2013 [Table 1]). On the eastern front, the Russians had 12,000 frostbite cases whilst the Germans suffered 10,000 cases in just one night (Paton 2001). Along the Strait of Gallipoli (Turkey) on November 27 (1915), Australian and New Zealand soldiers had 14,584 frostbite cases.

Those are horrendous injury counts, yet cold-injury reports from the twenty-first century lead us to believe that more lessons need to be learned (DeGroot et al. 2003; Williamson and Izard 2007). Or do we need to revise lessons from 100 years earlier, just as the COVID-19 pandemic reminded us that politicians should revise lessons from the 1918 Spanish (American actually) influenza pandemic (Ott et al. 2007)? Those lessons require dissemination beyond the military, as cold injuries also occur within the general population, and are particularly relevant to those in pursuit of active and adventurous living.

By the end of the Krogh-Hill epoch, no one had climbed Mount Everest (8,849 m), as far as is known. Between 1950 and 2021, > 19,000 climbers had reached 8,000 m or higher in the Himalayas, but hypothermia prevented far too many descents (Szymczak and Blazejczyk 2021). In the twenty-first century, swimming the "Ice Mile" (1.6 km, water < 5° C, swimwear only) has become surprisingly popular, at least amongst larger swimmers (> 100 kg; Knechtle et al. 2015, 2021). Those swims may take 40 min, whereas the predicted 50% survival time in 5° C water is 60 min (Molnar 1946; Golden, 1976), although others have predicted > 120 min (Hayward et al. 1975b; Tikuisis 1997; also see: Golden and Tipton 2002). Using survival times of cold-water immersion victims with and without thermal protective clothing ($N = 122$), Xu and Giesbrecht (2018 [Fig. 2]) developed the latest predictive equation, which provided maximal survival times of ~ 5 h in water at 5 °C, and ~ 12 h in 10 °C water. So the survival of Guðlaugur Friðþórsson (5°–6 °C water; Keatinge 1986; Park 2020), whilst remarkable, was not beyond the realm of human survival. Other examples of thermoregulation during adventurous living in the cold are contained in the following: Hixson (1981; skiers), Valnicek et al. (1993; general population), Harirchi et al. (2005; mountaineers), Laden et al. (2007; sport scuba divers), Mäkinen et al. (2009; general population) and Oakley et al. (2022; paddle sports).

Ötzi: the athletic, Neolithic hunter and farmer

In the true spirit of an historical review, and before coming out of the cold, let us travel way back in time. Our first stop is the Atacama Desert (Chile), from which archeologists retrieved the mummified remains of the Chinchorro people (Underwood 2012); > 7000 years old. Amongst those was a man who lived around 1 B.C.E. Radiological examination revealed evidence

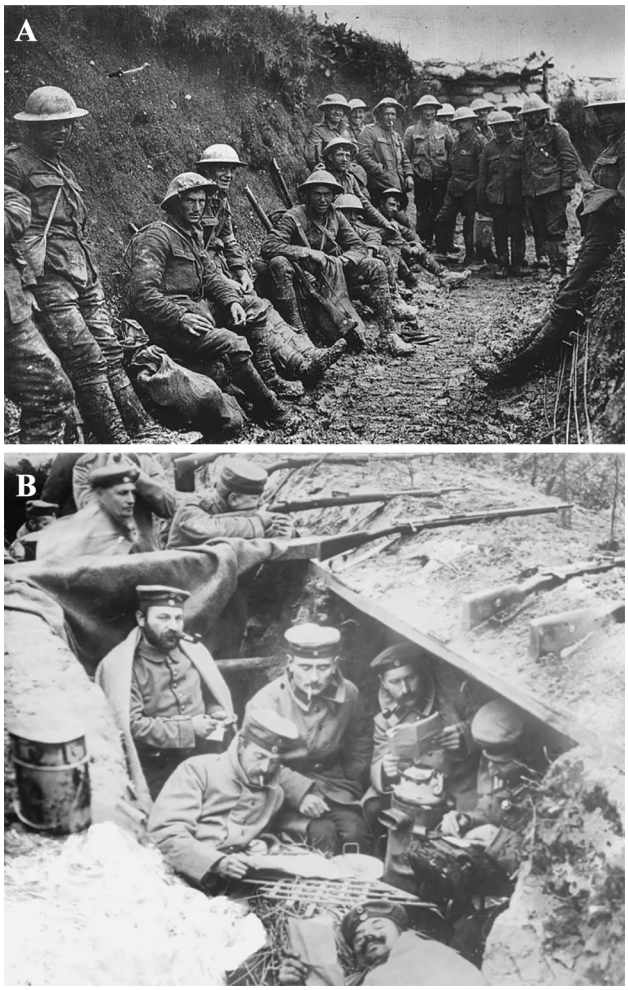


Fig. 23 **A** Royal Irish Rifles is the trenches (Somme, France; July 1916). When it rains or when the snow melts, where does the water go? Obtained and used under the Wikimedia Commons agreement (Public Domain). *Source:* https://commons.wikimedia.org/wiki/File:Royal_Irish_Rifles_ration_party_Somme_July_1916.jpg Accessed: April 28th, 2023. **B** A quiet moment in the German trenches. Obtained from Bain News Service and used under the Wikimedia Commons agreement (Public Domain). *Source:* https://commons.wikimedia.org/wiki/File:A_quiet_moment_in_German_trenches_LCCN2014699064.jpg Accessed: April 28th, 2023

of toe removal (both feet), which preceded death, with skeletal remains providing evidence "*consistent with a diagnosis of circulatory changes (gangrene) resulting from frostbite*" (Post and Donner 1972 [P. 187]). Is that the oldest example of frostbite?

Move forwards ~ 2000 years, and across to Europe to meet a person mummified in a glacier > 3000 years B.C.E. He is Ötzi, an athletic hunter and farmer, who was believed to have been wounded in a fight (Kutschera and Rom 2000; Dickson et al. 2005; Nerlich et al. 2021), and became trapped in ice in the Ötztal Alps (Niederjoch glacier, Italy). His mummified remains were discovered in 1991 by German hikers (Erika and Helmut Simon). What is unique about Ötzi is that he was preserved with his layered protective clothing: loincloth, jacket (goat and deer hides), thigh-high leggings, cape (tree bark), bearskin hat and insulated skin shoes (bear, goat and grass). Also preserved were his equipment: wooden handled dagger (ash and flint), copper ax, longbow (yew), a quiver (14 arrows, 2 with flint arrowheads and feathers), a belt pouch (tinder fungus, flints for sparking and iron pyrites) and the remnants of hide thongs and a backpack for carrying other essential items (Dickson et al. 2005). This man was well-equipped for his alpine journey. Ötzi was an occupational athlete of his time, and he provided the earliest example of clothing that was intended to be thermally protective during exercise in the cold.

Give us a number: indices of thermal stress and strain

Our journeys through both hot and cold environments have delivered us to a time when we might be able to predict, and adequately prepare for, thermally stressful conditions. Predictive indices of thermal stress are aimed at conveying, in a single number or combination of numbers, the effect of a thermal environment on an organism. Together with a number for the rate of metabolic heat production, either during rest or physical work, thermal stress indices are intended to predict the thermal strain exhibited by our physiological or psychological reactions to that stress. Such indices can be measured with purpose-built instruments, or calculated from onsite temperatures and microclimate variables, or even calculated, but less accurately, using data from meteorological stations (Shock et al. 2016). Thermal stress indices have many applications (Lee 1980), which can be "*diagnostic, therapeutic, or prognostic*" (MacPherson 1962 [P. 152]), including the assessment of the risk (probability) of developing thermal illnesses or injuries, predicting the capacity to perform physical work in a particular thermal environment, assessing the safety of athletic or other recreational activities, providing thermal comfort to passengers in transit, and assessing thermal impacts on reproductive function and on building design.

The relationship between thermal strain (the effects) and thermal stress (the cause) depends upon the physiological, anatomical and ecological status of the organism. Some stress indices are used routinely for particular organisms, for example, the Temperature-Humidity Index, which is now used for livestock (e.g., Vitali et al. 2009), although it originated as a human indoor thermal discomfort index (Thom 1959). Since we are concerned with exercising humans, our focus is on thermal stress and strain indices applicable to physical activity. In that realm, the principal aim is to identify, and if possible to avoid, environments that exercising humans might find thermally uncompensable or intolerable.

Fig. 24 **A** A poster to combat the almost epidemic occurrences of non-freezing cold injuries (trench foot or immersion foot) during the First World War. U.S. National Archives and Records Administration, Public Domain. *Source*: https://commons.wikimedia.org/w/index.php?curid=16941901 Accessed: June 21st, 2022. **B** Trench foot (unidentified soldier; 1917). Public Domain. Source: Library and Archives Canada/PA-149311. Reference number: 3192141. Accessed: July 21st, 2022. Also see the pictorial atlas of Mills (2001b). **C** Polar hands a century later (2017). These are the hands of Alex Gregory, a dual Olympic Gold Medallist (rowing), following an extended rowing adventure in Arctic waters. Photograph taken by Alex Gregory, who retains the copyright, and is reproduced with his permission

Figure 25 contains a timeline for the development of such thermal stress and strain indices.

The quality of any thermal stress index is judged by the accuracy with which it predicts strain in population samples (miners, runners, footballers), rather than individuals. Over our century of exercise physiology, > 187 human thermal indices have been developed (Ioannou et al. 2022b), with production peaking in the second half of the twentieeth century (Lazaro and Momayez 2021). Some indices that have been called stress indices are actually strain indices, or mixed stress and strain indices, because they incorporate physiological variables not as outcomes, but into their calculations. Since our communication is primarily a historical review, we have retained the terms used by the originators of those indices.

A few stress indices are based on the physiology of human energy balance (Belding 1970), and might therefore be called rational indices (McGregor and Vanos 2018). Very few thermal indices ever have been used by anyone other than their developers, and only a tiny handful will be encountered by contemporary users. Those that have been used by more than a handful are the Wet-Bulb Globe Temperature (WBGT) index (d'Ambrosio Alfano et al. 2014), the Wind Chill factor (Shitzer and Tikuisis 2012) and the Heat Index of the U.S. National Weather Service (Weinberger et al. 2018). They have been joined by a few indices of more-recent heritage, like the Universal Thermal Climate Index (UTCI; Havenith and Fiala 2016) and the Predicted Heat Strain (PHS) index (Malchaire et al. 2001). Nevertheless, we, and many other thermal physiologists, would not consider any of the thermal indices currently available to be sufficiently accurate and convenient for predicting thermal strain. Let us explore what has been developed previously, how and why it may have under-achieved its objective, and how that work might be improved.

Thermal indices before 1900: epoch one

In 1775, Charles B. Blagden (1748–1820, England) exposed himself, his colleagues and his dog to a room so hot that the ivory frames of their thermometers were warped. He

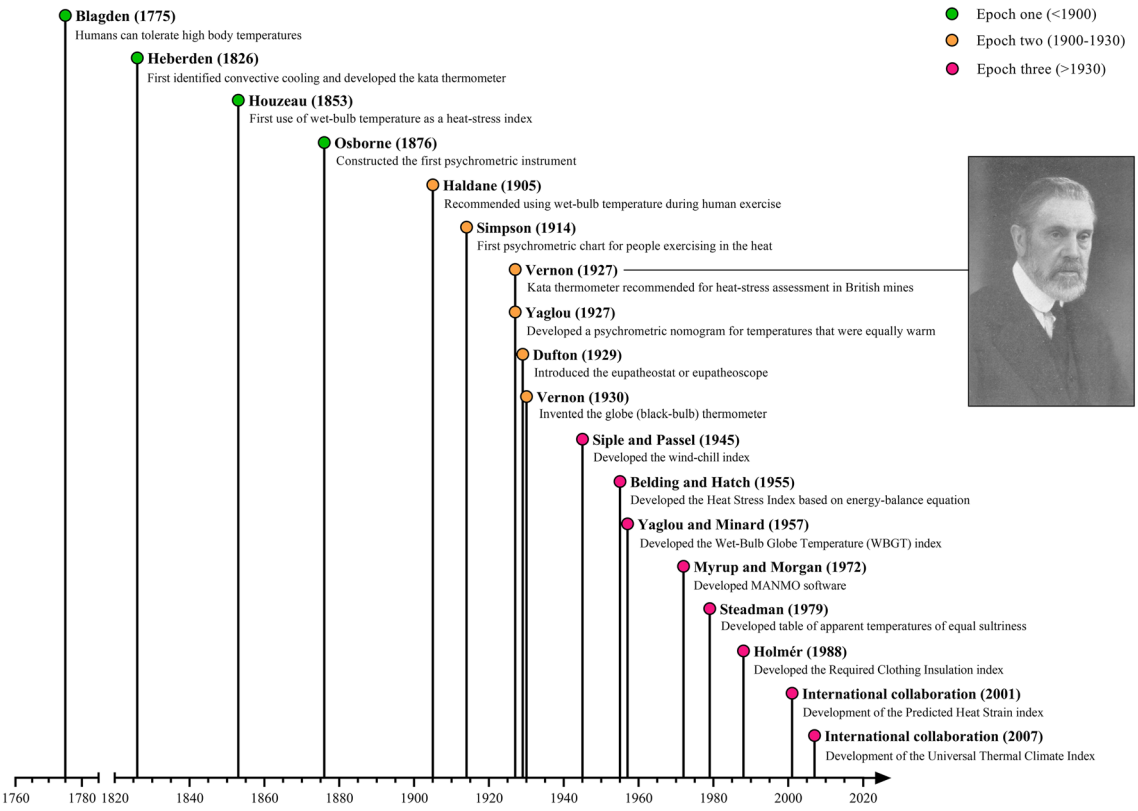


Fig. 25 A summary timeline for the historical development of thermal stress and strain indices across three epochs. The photograph of Horace Vernon was obtained from Bedford (1951) and used with permission

reported only the dry-bulb temperature (Blagden 1775a; Milton 2022), but he left information that allows us to estimate the relative humidity during one of those experiments: "*a Florence flask was brought in, by his order, filled with water heated to 100°* [Fahrenheit]*, and a dry cloth, with which he wiped the surface of the flask quite dry; but it immediately became wet again, and streams of water poured down its sides; which continued until the heat of the water within had risen to 122°*" (Blagden 1775a [P. 115]). Without knowing it, Blagden had told us the dew-point temperature of the room was 50 °C (or below), and psychrometric calculations give relative humidity of at least 80% and a wet-bulb temperature of ~ 50 °C. Such a wet-bulb temperature is considered incompatible with human survival (Sherwood and Huber 2010). Even though he lacked the capacity to measure humidity (Shaw 1888), Blagden was aware that thermal strain depended on both air humidity and dry-bulb temperature. Consequently, any meaningful heat-stress index would have to incorporate some measure of either absolute or relative water-vapour pressure (humidity).

About 50 years later, William Heberden (1767–1845, England) knew that thermal stress indices needed to take into account wind movement over the body: "*it cannot have escaped the attention of any person moderately conversant with natural philosophy, that the index of a thermometer is a very imperfect measure … while the thermometer truly marks the temperature of the medium in which it is placed, the sensations of the body depend altogether upon the rapidity with which its own heat is carried off*" (Heberden 1826 [P. 71]). With remarkable prescience, he recognised that heat loss depends on relative airflow, or airflow that arises from the environment (absolute air flow) or from body movements: "*by walking, or riding ….. we produce on our bodies a current of moist air, which is then felt in proportion to the rapidity with which we pass through it*" (Heberden 1826 [P. 74]). Notwithstanding its significance, "*his valuable conception fell into oblivion*" (Hill et al. 1916 [P. 185]) for nearly a century. Indeed, it was Heberden who devised the principle of an instrument that became popular for measuring heat stress and took account of air movement; the kata thermometer ("Thermal indices in the Krogh-Hill epoch"). He heated a hand-held thermometer up to body temperature and measured how fast it cooled (Heberden 1826).

In Blagden's footsteps, the highly influential Scottish physiologist, John Haldane (Douglas 1936), described "*a great lack of information as to the exact limits of the air temperature and humidity which can be borne for considerable periods without serious physiological disturbance*" (Haldane

1905 [P. 495]). He was wrong about the "*great lack*". A great deal was known about the stress imposed by air temperature, humidity and wind. But Haldane cited none of the earlier work, although he recommended using the wet-bulb temperature as a heat stress index. That earlier work was recognised soon afterwards by Anton Breinl (1880–1944, Australia). In his papers on thermal problems encountered in tropical Australia (Breinl and Young 1919a, b, c, 1920), Breinl relied heavily on a German review on climatology (Hann 1908) for his analysis of earlier work on thermal stress, rather than on the original publications, some of which were, and still are, difficult to obtain.

Breinl would have done better to consult an English review by Edward Titchener (Titchener 1909; U.S.A.), since his paper provided an annotated bibliography of 39 manuscripts on the measurement of what he, and others at the time, called "*sensible temperature*" (the perceived thermal state of the environment). He began with Heberden (1826) but omitted Haldane (1905). Titchener attributed the idea of using a wet-bulb thermometer to measure "*sensible temperature*" to Jean-Charles Houzeau (1853, Belgium), > 50 y before Haldane. Other major contributors to the science of measurement of "*sensible temperature*" were Cleveland Abbe, J.W. Osborne, Mark Harrington and William Phillips, all from America.

Cleveland Abbe (1838–1916) initiated the practice of weather forecasting, and Harrington used wet-bulb temperature to determine how much evaporative cooling was possible in the different regions of the U.S.A. (Harrington 1893). Osborne was not impressed, and his view of the physiological usefulness of those data was damning: "*It is hardly too much to assert that, at the present day, after years of laborious research, the meteorologists furnish no data from which it is possible to deduce the subjective character of any given climate, or its effect upon the human body*" (Osborne 1876 [P. 60]). The meteorologists had not given us a number, so Osborne constructed what may well have been the first psychrometric instrument to incorporate more than a thermometer (Fig. 26). Foreshadowing the wet kata thermometer, it incorporated a porous paper drum through which water, initially heated to above deep-body (core) temperature, could evaporate, and was allowed to cool in the environment being examined, whilst that cooling rate was measured (Osborne 1876). It did not receive universal acclaim: "*for the time being we have no index of sensible temperature, and the use of the indications of any one meteorologic instrument for such purpose can only give, under the most favourable conditions, but a rude approximation to the truth and too remote to be of much practical service*" (Phillips 1896 [P. 23]).

It has become customary to attribute to Haldane (1905) not just the introduction of a wet-bulb temperature into thermal-stress indices, but also to recognising the influence of water-vapour pressure on that stress (e.g., Eissing 1995). But by the end of the ninteenth century, it was well established that heat-stress indices needed to incorporate a measure of water-vapour pressure, and wet-bulb thermometry was routinely used for that purpose (Titchener 1909). What apparently had not been considered was the potential use of the wet-bulb temperature as an index of, or limits to, human exercise performance in the heat. That seems to have been an innovation legitimately attributable to Haldane (1905). Based primarily on the rectal temperatures of men exposed to humid heat in Cornish mines, heated rooms and a Turkish bath, Haldane concluded that the wet-bulb temperature was an appropriate tool with which to assess the thermal stress imposed upon men working in humid heat (Haldane 1905). Those studies launched a compendium of heat-stress indices for exercising humans that incorporated the wet-bulb temperature, which is thermodynamically defined as the lowest temperature to which air would cool just by the evaporation of water. There is an intuitive appeal in using the wet-bulb temperature as an index of heat stress because it combines both a dry-bulb temperature and the effect of air humidity, but, as we shall see, following that intuition without attention to detail has been one of the obstructions to the derivation of an accurate heat-stress index.

Thermal indices in the Krogh-Hill epoch

When the Krogh-Hill epoch began, it was known that dry-bulb and wet-bulb temperatures (or another measure of air humidity) and wind speed needed to be incorporated into any valid thermal stress index, but radiation had not yet been considered. The concept of a quantitative index as a predictor of comfort, physical performance or the risk of injury had not yet emerged, though Haldane foresaw the need for thermal limits to "*work in the stoke-holds and engine-rooms of steamers, in drawing the ovens used for firing pottery, in the drying of salt*" (Haldane 1905 [P. 494]), and he also recognised a military requirement. But the American climatologist, Robert Ward considered the idea of a quantitative index to be preposterous, and that the suggestion "*that a single statement "would express just what people mean when they say that the day is hot or cold," is absurd on the face of it. The sensible temperature is so complex and so individual that no such forecast can be made which would be of any general value whatever*" (Ward 1904 [P. 137]).

Early in the twentieeth century, physiologists were engaged in the assessment of thermal stress in homes and industry, and they developed purpose-built instruments for those purposes. The first was the kata thermometer (Fig. 26B), invented by Leonard Hill ("Heat stroke in the Krogh-Hill epoch: a military perspective"). While it was announced during the First World War, its intended application was public hygiene (Hill et al. 1916). It was advanced as

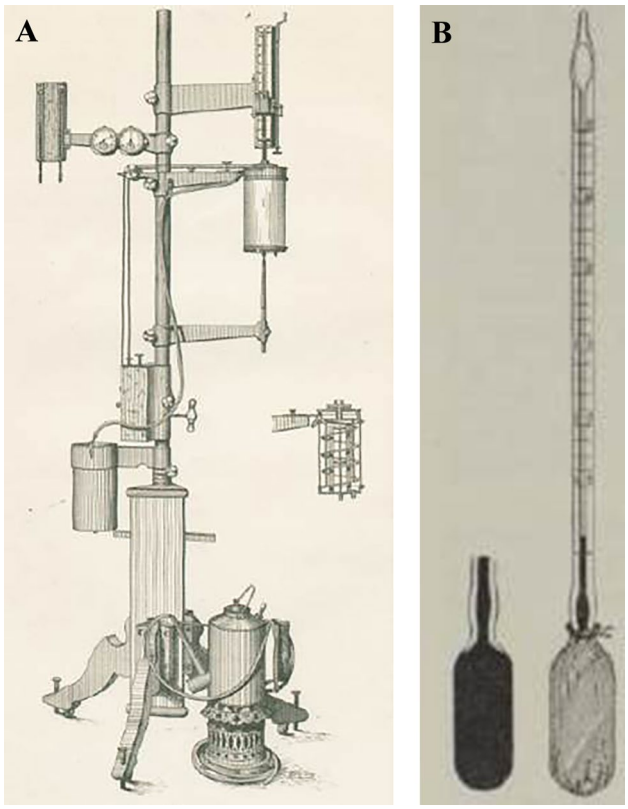


Fig. 26 **A** Osborne's "*new meteorological instrument*", used to assess "*sensible heat*" as the rate of cooling of a porous paper drum heated to above deep-body temperature. From Osborne (1876), and is in the Public Domain. **B** Hill's kata thermometer (40 mm long, 20 mm diameter). Right: wet kata thermometer with an evaporating sock around the bulb. Left: dry kata thermometer. From Hill et al. (1916), and reproduced with permission

an instrument suitable for heat-stress assessment in British mines (Vernon 1927), and soon became a standard instrument in the South African gold mines (Mavrogordato and Pirow 1927), an application for which it was still considered valid 65 years after its invention (Stewart 1981).

The kata thermometer (*kata* [Greek] "down") is an alcohol thermometer with an expanded bulb, calibrated over the normal range of human deep-body temperatures. The bulb could be bare (dry kata thermometer) or covered with a cotton sock (wick; wet kata thermometer). At the time of measurement, the bulb was plunged into water hotter than deep-body temperature, allowed to equilibrate and then removed and allowed to cool in the environment being tested. Cooling was under the influence of local convective, radiative and evaporative heat exchanges, and the time taken to cool from one temperature to another was measured. That measurement was reminiscent of Osborne's earlier instrument (Fig. 26A). The implication was that the slower the cooling, the greater would be the heat stress imposed on humans by that environment. Each kata thermometer was calibrated to convert cooling time to an area-specific cooling flux; the definitive calibration (Hill and Hargood-Ash 1919) was carried out within an aeronautical wind tunnel.

In the year of its announcement, Charles-Edward Winslow (U.S.A.; Notley et al. 2023a) published the comfort votes of men, resting on his porch, and in his office and laboratory, along with data for the kata cooling power (Winslow 1916). He concluded that "*this instrument is of great value in measuring the actual influence of air conditions upon the body*" (Winslow 1916 [P. 719]), though the data scarcely supported that conclusion. Indeed, despite his reliance on the instrument, Cyril Wyndham cautioned that "*it cannot be assumed that the cooling power measured on such a simple physical entity necessarily bears a close relationship to the cooling power of the same atmosphere on the human body without rigid scientific testing and this information cannot be regarded as available*" (Wyndham 1950 [P. 217]). When evaluating thermal stress indices, de Freitas and Grigorieva (2017) classed the kata cooling power amongst indices that had never been validated as a predictor of human thermal strain, either at rest or during exercise.

Soon after the invention of the kata thermometer, Horace Vernon found that coal extraction in British mines fell as heat stress indicated by a kata thermometer increased (Vernon 1928). Earlier, Orenstein and Ireland (1922, South Africa) showed that one's ability to exercise in a gold mine declined as heat stress measured by a kata thermometer increased: "*They put a native boy to work a rotary ergometer for four hours daily in working places at various depths, and they found that in air with a dry kata cooling power of 1, 2, 3, 4 and 5 his working efficiency was reduced by 50, 40, 30, 20 and 10 percent respectively below that experienced in air with a cooling power of 6*" (Vernon 1928 [P. 139]).

The second purpose-built instrument was the eupatheostat or eupatheoscope (Dufton 1929), a device that controlled the surface of a blackened cylinder at 25 °C. A room was considered thermally comfortable if that surface temperature could be maintained by a power input of 55 $W.m^{-2}$ to the cylinder. A higher power requirement indicated cold stress. Like that of the kata thermometer, its inventor was British. It is no more than a collector's item today.

To our knowledge, the first psychrometric chart to describe the environments of people exercising in the heat was developed by Simpson (1914, England), based upon the chart developed by Karl Jelinek (Austria) for meteorological purposes (Jelinek, 1876). But across the Atlantic, at the laboratories of the *American Society of Heating and Ventilating Engineers*, the first of the true algorithmic thermal stress indices was devised. It was the effective temperature index, in the form of a scale on a psychrometric chart (Lee 1980) or a psychrometric nomogram (Yaglou 1927). It depicted combinations of dry-bulb temperature, air water content (proportional to water-vapour pressure) and air movement that subjects judged to be equally warm (Houghten and

Yagloglou 1923a). Their "*judges*" operated in groups of three, and were described in a summary of that work as 85 men, stripped to the waist and engaged in light work (Yaglou 1927). They transferred back and forth between two adjacent climatic chambers as conditions within those chambers were changed, until they voted the conditions in both chambers were equally warm.

Although their title refers to "*lines of equal comfort*" (Houghten and Yagloglou 1923a), the study was more closely related to thermal sensation rather than to comfort (discomfort). Researchers of the time did not distinguish between sensation and comfort, though thermal sensation and thermal discomfort are very different psychophysical variables. The former concerns the perception of the thermal environment and is determined from thermoreceptor feedback (Zotterman 1959; Hensel 1981). Thermal comfort is associated with past experiences (de Dear and Brager 2001), and how pleasurable a particular thermal state feels. Both thermal sensation and discomfort differ from thermal strain, which is a quantification of how much the thermoregulatory variables have deviated from basal values. Numbers can be given to sensation, discomfort and strain, but they are neither numerically nor physiologically equivalent. Perhaps surprisingly for a thermal sensation scale, but gratifyingly for Houghten and Yagloglou, their effective temperature correlated better than did either the dry-bulb or wet-bulb temperatures with thermal strain, as reflected in the rate of deep-body temperature elevation (Yaglou 1927).

In a follow-up study, groups of subjects from a cohort of 130 employees, dressed in their (self-selected) normal indoor clothing, were used to identify what was called a "*zone of comfort*" for clothed Americans, which was definable by its effective temperature (Houghten and Yagloglou 1923b). There followed a plethora of papers about effective temperature (1923–1925; MacPherson 1962), many originating from Constantin P. Yagloglou (also known as Yaglou; 1897–1960, U.S.A.; Whittenberger et al. 1961). He features, along with David Minard (1913–2005, U.S.A.), as a co-inventor of one of our surviving heat-stress indices, the WBGT index (Yaglou and Minard 1957). Those papers (https://catalog.hathitrust.org/Record/004351322) expanded the arena in which the effective temperature was claimed to be a valid index, even for men engaged in heavy physical work, for whom the author asserted it correlated better with thermal strain than did the wet-bulb temperature (Yaglou 1927).

Pre-empting future concerns about wet-bulb temperature, the proponents of the effective temperature index believed that, in dry and humid environments with the same wet-bulb temperature, heat stress would be higher in the dry environment. Those researchers did not expect the limits of effective temperature that were considered comfortable, or safe, in America, would necessarily be applicable in the U.K.: "*in our opinion, the British comfort zone is lower than the American comfort zone, largely on account of the difference in clothing, particularly underclothing, worn in the two countries*" (Yaglou 1927 [P. 299]). A transatlantic dispute developed, not related to underwear, clean or dirty, but to the relative merits of the kata cooling power and the effective temperature index, as heat-stress indices (Vernon 1926; Vernon et al. 1926; Yaglou 1927). Contemporary thermal physiologists ought to reject one of Vernon's objections to the effective temperature index, namely that it did not take account of thermal adaptation. He confused heat stress with strain. Adaptation affects both the physiological and psychophysical responses to thermal stress, but not the intensity of the stress itself. de Freitas and Grigorieva (2017) classed the effective temperature index as a validated index.

Both the kata cooling power and the effective temperature index were developed for indoor environments. In theory, both should have been applicable in outdoor environments, with radiation being a further factor influencing both the kata bulb and the assessment of warmth, but their proponents did not use them outdoors. Users of the kata thermometer were instructed to shield it from solar radiation, and neither group had a convenient way of measuring mean radiant temperature. Researchers were aware that solar radiation was an independent heat source when humans exercised outside, which was even comparable to the endogenous heat load induced by the exercise. They were aware of the complexity of radiant heat flux, the rate of which depended on the body's surface area exposed to radiant flux (view factor or shadow area), and the emissivity of the skin or clothing, which differs with the wavelength of the radiation (Martin 1930). It may have been because they did not know how to apply heat-stress indices outdoors that, at the beginning of our century of exercise physiology, heat-stress indices, by then established for industrial use, had not been implemented in the realm of sport, or indeed in any recreational activity.

Convenient measurement of radiant heat load became possible only after Vernon presented his ingenious globe thermometer to the U.K. *Physiological Society* (Vernon 1930, 1932), and it remains in widespread use almost a century later. Vernon recognised not just the complexity of radiant heat load, but that radiant heat was not always a load; heat could be lost via radiation to surfaces that are cooler than the skin (Notley et al. 2023a [Fig. 12]). He concluded that it is "*necessary to devise some convenient portable instrument which will record in a single measure the summated effect of the diverse radiations from all sources, negative as well as positive*" (Vernon 1932 [P. 96]). He chose a hollow sphere (globe) with a thermometer bulb at its centre. He experimented with various materials, various diameters (64–229 mm) and various external coatings, and one of his options is still today's version: the 150 mm globe of thin

copper painted with matt-black paint, a version that Vernon attributed to Scottish meteorologist John Aitken (Aitken 1887). Today such globes usually have to be manufactured (spun), at considerable cost. Back then, they were the standard floats in toilet cisterns (two of the current authors may have inadvertently acquired such equipment from workplace toilets). Vernon's initial interest was in measuring radiation emitted from indoor heating systems, so as to arrive at the best way of achieving thermal comfort, but he did remark that "*the globe thermometer should prove useful to meteorologists for outdoor observations*" (Vernon 1933 [P. 110]), which he subsequently undertook. Thermal physiologists, exercise scientists and climate-change biologists now use globe thermometers for outdoor observations (Figs. 26B, 27A).

Vernon was aware that the temperature of his globe thermometer depended on both radiant and convective heat exchanges, and he referred to that temperature as the "*radiation-convection-temperature*". The term "*globe thermometer temperature*" was introduced by his colleagues at the British *Industrial Health Research Board*, Thomas Bedford and C.G. Warner (Bedford and Warner 1934b), who also realised that, with the simultaneous measurement of dry-bulb temperature and wind speed, globe temperature could be used to calculate the mean radiant temperature. When globe temperature was constant, the sum of its radiant and convective heat exchanges had to be zero. The convective heat flux coefficients of spheres now are well established, but Bedford and Warner (1934b) measured the coefficient of their globes under forced convection. They also determined the physical energy-balance equation for the globe and solved for mean radiant temperature under steady states. Today, globe temperature is used as an integrated measure of radiant and convective heat exchange as a form of operative temperature (Mitchell et al. 2018).

Thermal indices from the modern epoch

Algebraic stress indices of positive heat load

By the early 1930s, thermal physiologists had the capacity to measure, with considerable precision, dry-bulb, wet-bulb and globe temperatures. Those temperatures are now used to calculate the Wet-Bulb Globe Temperature (WBGT), which is the most widely used of the surviving heat-stress indices. The kata thermometer joined the eupatheostat as a collector's piece, and the effective temperature scale had demised, although Bedford suggested substituting globe temperature for the dry-bulb temperature to derive an effective temperature that might be applicable to industries with substantial sources of radiant heat (Macpherson 1962). Yaglou suggested manipulating the observed wet-bulb temperature (Macpherson 1962; Yaglou et al. 1950). Nevertheless, that artificial life support failed to resuscitate the index, and the facts have "*reverted to their predatory ways*" (Wilkie 1954 [P. 288]).

With regard to its use during exercise in the heat, effective temperature suffered from another weakness. Whilst it predicted thermal strain (e.g., rectal temperature elevation) surprisingly well within indoor environments without radiant heat stress, it was an index not of heat stress, but of warmth sensation. At the time, researchers seemed still not to distinguish between indices of heat stress that might influence physiological strain, indices for predicting psychophysical and psychological strain (e.g., thermal discomfort or cognitive performance), and indices of thermal sensation. Today, we recognise that those indices, and their numbers, are not equivalent (Coccolo et al. 2016; Fantozzi and Rocca 2020). Contemporary thermal physiologists would not consider "*warm and comfortable*", or even "*sweating and comfortable*", to be contradictions within the sensory and comfort domains. Though it had been tested against other heat strain variables, the ability of the effective temperature to predict the risk of heat stroke apparently has never been tested.

It was for exactly that purpose that the WBGT index was devised, and specifically for the prevention of heat casualties in the military (Yaglou and Minard 1957). Haldane (1905) had foreseen the need for such an index, and Gordon (1860) and Waller (1869) might have been able to reduce their heat-stroke mortality rates if they could predict the most stressful days. Today, the WBGT index is the mainstay for assessing thermal risks during recreational and occupational activities. During their analysis of the causes of military heat casualties, Yaglou and Minard (1957) introduced the WBGT as a back-up to their definitive index, which was Yaglou's manipulated effective temperature (Yaglou et al. 1950). They calculated the WBGT as: 0.7 * psychrometric wet-bulb temperature + 0.3 * globe temperature. Their "*psychrometric wet-bulb temperature*" was the ventilated wet-bulb temperature measured with a sling psychrometer.

The U.S. *National Institute for Occupational Safety and Health* (NIOSH) soon "*recommended the WBGT index as the standard heat stress index for industrial use*" (Beshir and Ramsey 1988 [P. 93]; Egypt and U.S.A.), but with important modifications, and a decade later it was adopted by the *International Standardization Organization* (ISO 7243:1982). The weightings used by Yaglou and Minard (1957) were reserved for indoor use, or outdoor use without solar heat load (an unintended application), and substituted the natural (unventilated) wet-bulb temperature for the psychrometric (ventilated) wet-bulb temperature (Eq. 1). That substitution was needed because the WBGT was unresponsive to wind speed when the globe temperature and dry-bulb temperature were equal (Budd 2008), but it was also for convenience. It allowed the WBGT to be measured with three thermometers in a stationary,

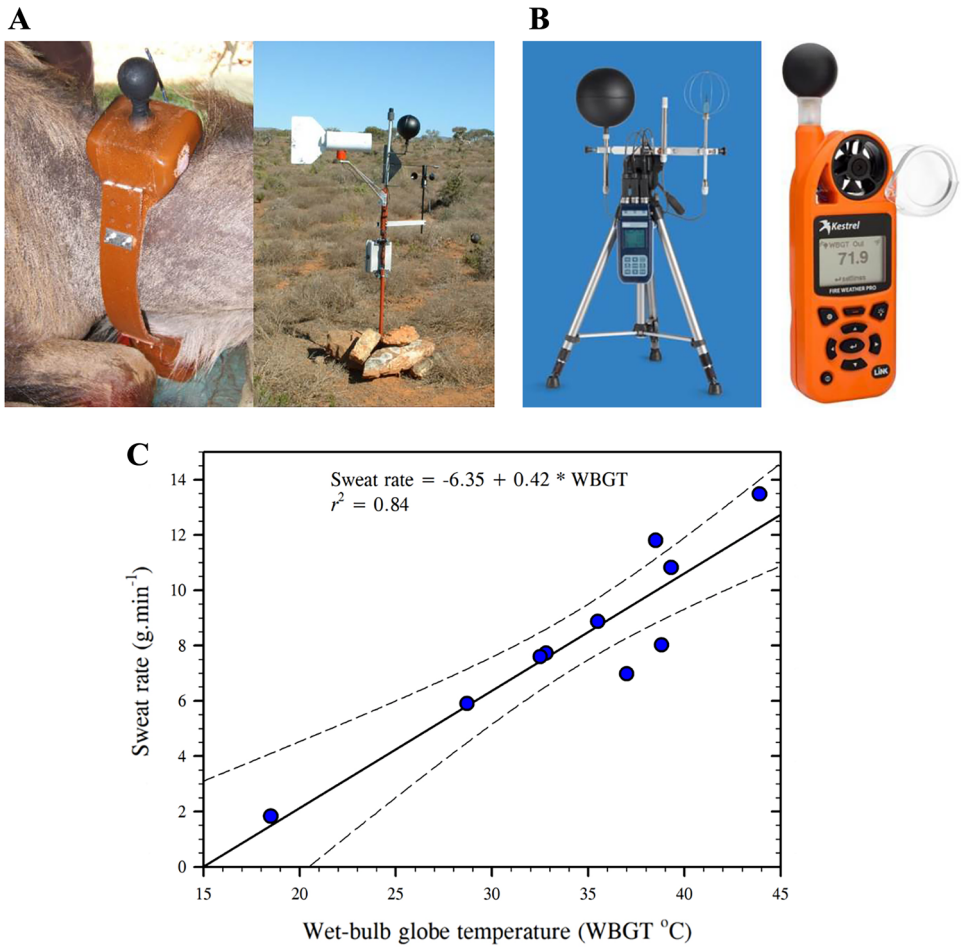


Fig. 27 **A** A miniature globe thermometer on an antelope collar (left) and a globe thermometer for a field weather station (reproduced with permission from the Brain Function Research Group, University of the Witwatersrand, South Africa, which retains the copyright). **B** A field station (standard 150 mm diameter globe) and a hand-held (25 mm diameter globe) wet-bulb globe-thermometer (WBGT) instrument (right). The hand-held instrument incorporates a separate vane anemometer, and has been reproduced with permission from Nielsen-Kellerman, which retains the copyright. **C** Mean sweat rate plotted against the WBGT for lightly-clothed young men walking at 20% of peak aerobic power on a treadmill in a climatic chamber, in which conditions were varied. Globe temperature was changed between 23 and 74 °C, with dry-bulb temperatures at 23°, 38° or 49 °C. WBGT accounted for about 84% of the variation in sweat rate. Data extracted from Kamon et al. (1982 [Table 2]). **A** A miniature globe thermometer on an antelope collar (far left), then, moving rightwards, a globe thermometer for a field weather station (reproduced with permission from the Brain Function Research Group, University of the Witwatersrand, South Africa, which retains the copyright). **B** A field station (standard 150 mm diameter globe) and a hand-held (25 mm diameter globe) wet-bulb globe-thermometer (WBGT) instruments (far right). The Kestrel™ hand-held instrument incorporates a separate vane anemometer, and has been reproduced with permission from Nielsen-Kellerman, which retains the copyright. **C** Mean sweat rate plotted against the WBGT for lightly-clothed young men walking at 20% of peak aerobic power on a treadmill in a climatic chamber, in which conditions were varied. Globe temperature was changed 23 °C and 74 °C, with dry-bulb temperatures at 23 °, 38 ° or 49 °C. The WBGT accounted for about 84% of the variation in sweat rate. Data extracted from Kamon et al. (1982 [Table 2])

unpowered device. Unfortunately, that substitution had profound physiological implications. Except at environmental wind speeds > 3 m.s^{-1} (heat stress is usually highest at low wind speeds), natural wet-bulb temperatures are higher than ventilated temperatures, and the difference can be much larger at wind speeds < 0.5 m.s.$^{-1}$. That error may have health and safety implications (d'Ambrosio Alfano et al. 2012)

$$\begin{aligned}\text{WBGT} = {} & (0.7 * \text{ natural wet-bulb temperature}) \\ & + (0.2 * \text{ globe temperature}) \\ & + (0.1 * \text{ dry-bulb temperature}).\end{aligned} \quad (1)$$

Although there are many published formulae for its calculation (Lemke and Kjellstrom 2012), the natural wet-bulb temperature cannot be calculated accurately from other psychrometric variables (d'Ambrosio Alfano et al.

2012), and the errors underlying that assumption are greatest at the lowest wind speeds. Consequently, if the WBGT is calculated from meteorological variables (Lemke and Kjellstrom 2012), or from meters that do not measure natural wet-bulb temperature directly, the indicated WBGT is at risk of being wrong (Havenith and Fiala 2016).

There is another consequence of the practicalities of devices used for measuring the WBGT. For convenience, when using hand-held instruments and to reduce the response time of the device (d'Ambrosio Alfano et al. 2014), the globe diameters of contemporary WBGT instruments may be less than the 150 mm used by Vernon (Fig. 27B). Vernon's globe required ~ 20 min to stabilise (Hellon and Crockford 1959). Changing the globe diameter changes the relative contributions of radiant and convective heat flux at the globe. If manufacturers do not make the necessary correction (such information is rarely disclosed), smaller globes will deliver a false WBGT (Juang and Lin 2007), and the error can be an underestimate of ~ 3 °C, or more, for a 38-mm globe (d'Ambrosio Alfano et al. 2014). Corrections for differences in globe diameter require an independent measure of wind speed (Hetem et al. 2007; d'Ambrosio Alfano et al. 2014), and only some hand-held instruments incorporate separate anemometers (Fig. 27B).

The WBGT index cannot function adequately as a heat-stress index if it is not measured correctly, and it may not even predict heat strain reliably even if measured correctly (Wenzel 1978; Budd 2008). It is not a rational index based on human energy balance, but it is what has been called an empirical or an "*algebraic or statistical*" index (de Freitas and Grigorieva 2015). No justification has ever been given for the weightings of its three temperatures (Eq. 1), and there is doubt about the fidelity with which it measures heat stress at the high humidity and low wind-speed end of the spectrum, and also at the high dry-bulb temperature and high wind-speed end (Brotherhood 2014; Budd 2008; d'Ambrosio Alfano et al. 2014; Ramanathan and Belding 1973; Smolander et al. 1991). Those conditions often are encountered by recreational and occupational athletes.

Environments with the same WBGT can offer different capacities for evaporative cooling, depending upon air humidity (Vanos and Grundstein 2020), so they will not necessarily be equally stressful (Stapleton et al. 2012). Its main advantage over earlier heat-stress indices is that it incorporates radiant heat exchange, and especially solar radiation, and so it might have been suitable for outdoor work, sporting events and recreational activities. However, an analysis of 357,896 runners covering eight years of the Gothenburg half marathon (Sweden), showed that variations in the WBGT explained only about half of the variance in athlete collapse or required medical assistance, and it underestimated heat stress under higher solar radiation (Thorsson et al. 2021). Are we comfortable with 50–50 predictions?

Equally unfortunately, studies to test the utility of the WBGT index are typically carried out in climatic chambers with neither radiation sources nor sinks (e.g., Iampietro and Goldman 1965). Only rarely is the WBGT correlated with physiological strain (Foster et al. 2021), nor is it incorporated into generalised models of heat-associated morbidity and mortality (Lotens and van Middendorp, 1986; Heo et al. 2019). Rather, its impact on heat strain is expressed in terms of the WBGT limits to work at different intensities (Armstrong et al. 2007; Racinais et al. 2015 [published in three different journals that year, and again in 2022]). Just how those limits have been derived is shrouded in mystery.

The original WBGT limits (Bernard 2012) were based on the prescriptive zone (Lind 1963; Notley et al. 2019), and identifying the upper boundary of heat stress at which deep-body temperature during exercise would cease to depend only on metabolic rate (Dukes-Dobos and Henschel 1973). According to Francesca d'Ambrosio Alfano (Italy), those limits relied on data from just one person (d'Ambrosio Alfano et al. 2014). Without citing sources, some consider the limits to be those at which subjects would attain a deep-body temperature of 38 °C (d'Ambrosio Alfano et al. 2014), but no one appears to have repeated the rigorous statistical analysis undertaken by Wyndham and Heyns (1973), who identified the hot-humid conditions in which miners would have a one in a million probability of attaining a rectal temperature of 40 °C ("Body temperature elevation during exercise in the heat is physiological and essential", and Wenzel et al. (1989).

The reliability of the WBGT, like that of any global thermal index, in predicting thermal strain is compromised if the assumption is made that "*one size fits all*", without taking account of factors like age or chronic disease (Notley et al. 2019). There is considerable discourse about how the limits should be adjusted for different types of clothing worn (Goldman 2000; Bernard et al. 2005, 2008), whether or not sex differences should be incorporated into those limits (Ashley et al. 2008) and how to take account of differences in heat adaptation (Grundstein et al. 2015). Nevertheless, the current authors question the logic of fine-tuning the output from any index that was not itself founded on first principles and mechanistically linked with indices of physiological strain. Furthermore, one should not expect any atmospheric thermal stress index to apply to the wearers of chemical, biological or other forms of impermeable clothing, which create independent microclimates within the clothing (Bernard 1999; Goldman 2000; Taylor et al. 2021).

The stamp of authority given to WBGT limits by organisations responsible for health and safety, like the *International Standardization Organization*, conceals the paucity of data backing up those limits (Brocherie and Millet 2015).

In spite of its long heritage and endorsement by standards authorities, de Freitas and Grigorieva (2017, New Zealand and Russia) classify the WBGT index as an unvalidated index. But there are appropriate data in the literature to test its validity. Figure 27C contains data extracted from Kamon et al. (1982), from a chamber study of exercising men, in which globe temperature was varied while dry-bulb temperature was held constant at each of three levels. The WBGT index predicted the sweat rate remarkably accurately. In a similar study conducted at identical WBGT values, but without added radiation, rectal temperature, heart rate, sweat rate and exercise endurance time were significantly higher at a relative humidity of 70% than at 30%, especially when the WBGT was > 30 °C (Claassen and Kok 2007). Indeed, it is a fallacious to think that conditions with equal WBGT numbers are equally stressful.

The wet-bulb temperature accounts for 70% of the WBGT index, whether radiation is present or absent. However, there are reasons to question the validity of the wet-bulb temperature itself, or any index that is heavily dependent on the wet-bulb temperature in hot-dry environments. The wet-bulb temperature determines the capacity of the environment to accept evaporated water from the body surface. In hot-dry environments, though, adequate evaporative cooling depends not just on the capacity of the environment, but for evaporation to occur at the skin surface, as well as the capacity of athletes and workers to produce enough sweat, a capacity that is unrelated to the wet-bulb temperature.

A second surviving heat-stress index is one that is more likely to be encountered by citizen scientists; the Heat Index of the U.S. *National Weather Service*. That index originated in the 1970s from the work of Robert Steadman, who was then working in Australia. In confronting the problem of large variations in air humidity, Steadman set out to relate the psychophysical perception of "*sultriness*" to environmental variables. So, like developers of the effective temperature index, he was concerned with how the thermal environment was perceived, rather than how it affected physiological strain. Using published data, he modelled the resistance to heat transfer for a clothed man walking outdoors at 1.4 $m.s^{-1}$, and created a table of apparent temperatures of equal sultriness (Steadman 1979a). He defined equal sultriness in terms of the dry-bulb temperature and a measure of humidity, and followed up with calculations that accounted for radiation and wind speed (Steadman 1979b, 1984), although he did not attempt to predict the risk of heat disorders.

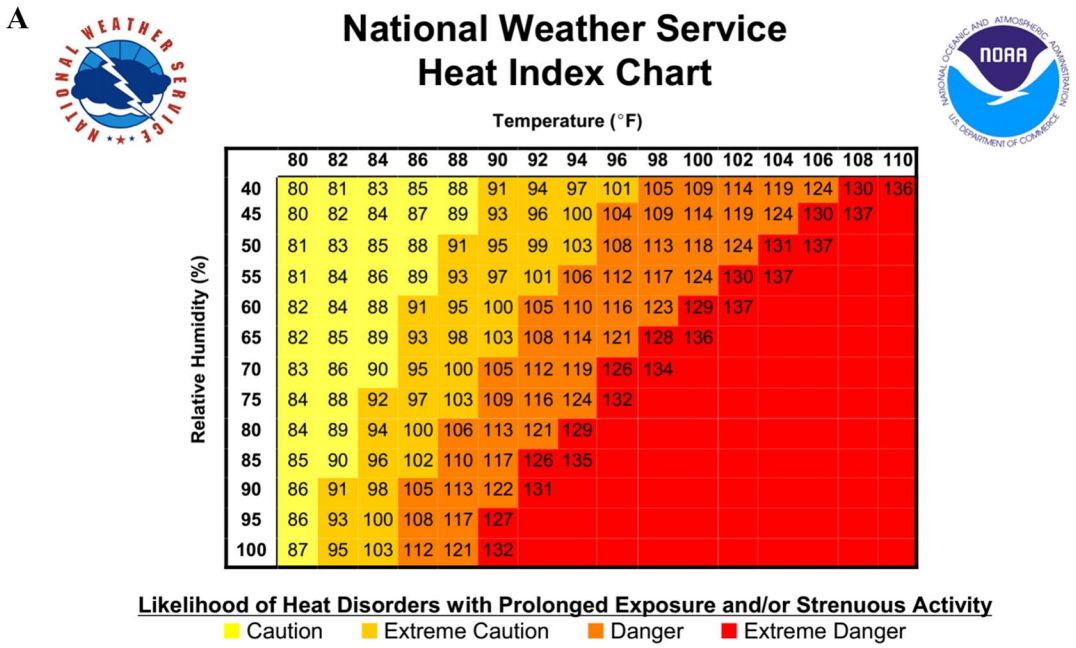
The index of U.S. *National Weather Service* provided numbers from 77 to 187 on a matrix of dry-bulb temperature and relative humidity (Fig. 28A), and was based on Steadman's index (Steadman 1979a, b, 1984). Those numbers, along with coloured zones, identified conditions that varied in severity from the possibility of fatigue through to heat stroke. Those zones were derived from figures published by Quayle and Doehring (1981), although those zones were presented without supporting data or citations. On the basis of their zones, the U.S. *Occupational Safety and Health Administration* charged the U.S. *Postal Service* (2016 and 2017) with contravening workplace regulations. Those charges were dismissed by a judge acting for the *Occupational Safety and Health Review Commission*, noting that the *National Weather Service* had no scientific basis for its zones (Sapper 2020). Though those findings were appealed, the ruling that its zones lacked scientific support were not contested (Sapper 2020).

The risk categories of the U.S. *National Weather Service* apply to apparently undefined, high-risk groups. The Service warns that heat stroke is possible with prolonged exposure or physical activity. Nonetheless, at dry-bulb temperatures < 40 °C (104 °F on the Figure), the extreme caution limit corresponds quite closely to a wet-bulb temperature of 25 °C, where, according to the upper limit of the prescriptive zone, even non-acclimatised adults walking at approximately 30% of peak aerobic power would be unlikely to have unexpectedly high deep-body temperatures (Kenney and Zeman 2002). Heat stroke would be extremely unlikely. Below 40 °C (dry-bulb temperature), the danger limit corresponds quite well with a wet-bulb temperature of 30 °C, and is well below the threshold for survival in the heat (35 °C) suggested by Sherwood and Huber (2010). That the curves depicting limits derived from the U.S. *National Weather Service* chart run approximately parallel to the upper limit of the prescriptive zone implies a reasonable correlation between those limits. So there is indeed scientific evidence for the use of the zones as heat-stress indices, although the risks of heat illness for healthy, non-adapted young women, exercising at light-moderate rates, are far lower than those claimed by the Service for high-risk groups. The fact that neither the upper limit of the prescriptive zone, nor the curve of limits proposed by the *National Weather Service*, run parallel to the wet-bulb temperature lines seems to confirm the inadequacy of the wet-bulb temperature as a heat stress index, and implies that it underestimates heat strain in environments with high dry-bulb temperature and low vapour pressure. Wet-bulb temperature is not a valid heat-stress index in its own right.

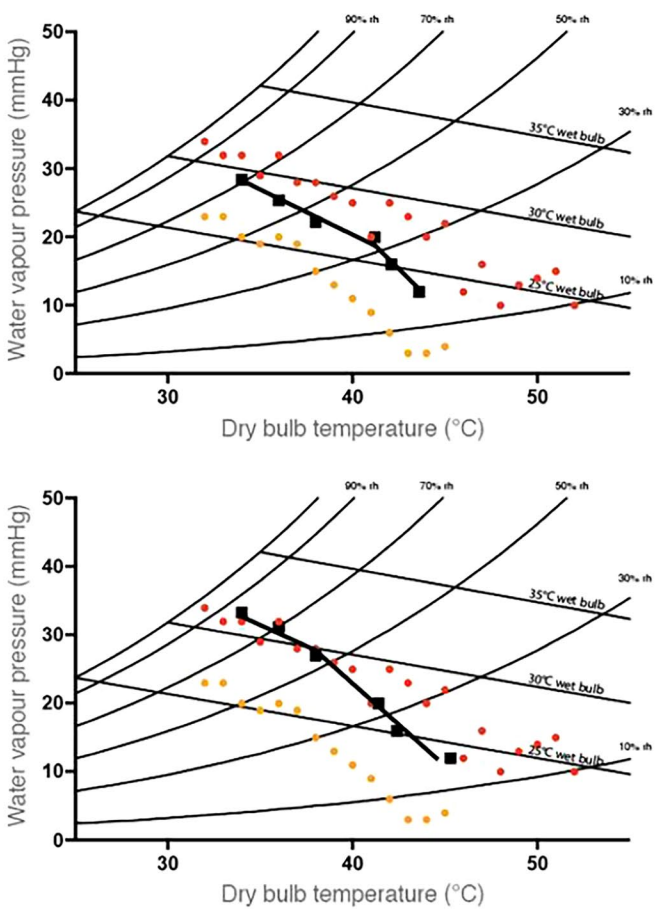
Algebraic stress indices of negative heat load

The indices of cold stress that are in use today have a history of less than a century's duration, and before his engagement with sultriness, Steadman contributed to another surviving index, the wind-chill index (Steadman 1971). Although the effect of wind on human heat stress was well recognised by the Krogh-Hill epoch (Titchener 1909), it took more than a century after Heberden's (1826) observation of the role

A


National Weather Service
Heat Index Chart
Temperature (°F)
Relative Humidity (%)
80 82 84 86 88 90 92 94 96 98 100 102 104 106 108 110
40 80 81 83 85 88 91 94 97 101 105 109 114 119 124 130 136
45 80 82 84 87 89 93 96 100 104 109 114 119 124 130 137
50 81 83 85 88 91 95 99 103 108 113 118 124 131 137
55 81 84 86 89 93 97 101 106 112 117 124 130 137
60 82 84 88 91 95 100 105 110 116 123 129 137
65 82 85 89 93 98 103 108 114 121 128 136
70 83 86 90 95 100 105 112 119 126 134
75 84 88 92 97 103 109 116 124 132
80 84 89 94 100 106 113 121 129
85 85 90 96 102 110 117 126 135
90 86 91 98 105 113 122 131
95 86 93 100 108 117 127
100 87 95 103 112 121 132
Likelihood of Heat Disorders with Prolonged Exposure and/or Strenuous Activity
Caution
Extreme Caution
Danger
Extreme Danger

B


Water vapour pressure (mmHg)
Dry bulb temperature (°C)
35°C wet bulb
30°C wet bulb
25°C wet bulb
Water vapour pressure (mmHg)
Dry bulb temperature (°C)
35°C wet bulb
30°C wet bulb
25°C wet bulb

◂**Fig. 28** **A** Heat index chart of the U.S. National Weather Service, reproduced with permission of the U.S. National Oceanic and Atmospheric Association. Risk levels in the different zones are for (undefined) high-risk groups. (*Source*: https://www.weather.gov/safety/heat-index). **B** Psychrometric charts showing the upper limits of the U.S. National Weather Service "danger" zone (red symbols) and "extreme caution" zone (orange symbols), together with the upper limit of the prescriptive zone (Dukes-Dobos and Henschel, 1973) for non-adapted (upper panel) and heat adapted (lower panel) young women walking at 30% of their peak aerobic power in still air (data extracted from Kenney and Zeman, 2002). Below the upper limit of the prescriptive zone, exercising healthy people can maintain a stable deep-body temperature at a level determined by the metabolic rate, so they should be under no thermal threat. Above the upper limit of the prescriptive zone, they will become hyperthermic, but will not immediately be at risk of heat illness. Figures constructed by Shane Maloney (University of Western Australia, Perth), who retains the copyright, and are used here with permission

of wind in body cooling, before an index of cold stress that might give a number for that wind factor was developed.

Paul Siple and Charles Passel from the 1939–1941 U.S. Antarctic Service Expedition set out to measure the cooling induced by the sub-freezing Antarctic wind. Their aim was to predict the risk of frostbite. They had no guidance on how to make the measurement: "*Lacking adequate library facilities during the years 1939–1941 at Little America III, Antarctica, it was impossible for us to acquaint ourselves with past experimentation in the measurement of the cooling power of the atmosphere at the beginning of our research. Consequently, the selection of a new and different means of measurement of cooling power, unbiased by historical developments herein described, was to be expected*" (Siple and Passel 1945 [P. 179]).

Showing the same kind of ingenuity as Horace Vernon, they put 250 g of water into a plastic cylinder (57 mm diameter, 149 mm length), together with a resistance thermometer. They hung their "*relative comfort cylinder*" outside at roof level, in the dark of the Antarctic winter, and measured the time that it took the water to freeze, which varied between 30 min and 3 h. They then derived the area-specific cooling rate of the cylinder and related that to wind speed, calculating what Siple called "*wind chill*" (Dixon and Prior 1987). Siple and Passel (1945) then estimated heat loss from the skin. They assumed that the temperature of exposed skin was 33 °C, although, even at 10 °C, one would not expect any exposed skin to be > 30 °C (Fig. 7). As Randall Osczevski (Canada) remarked 50 years later; "*it makes no sense to assume that the skin is at 33 °C and then to claim that in some combinations of wind and temperature it is in danger of freezing*" (Osczevski 1995 [P. 373]). Skin cannot freeze when its temperature is 33 °C.

Siple and Passel (1945) then gathered descriptors from the personnel at the base of how they perceived cold environments with different wind chills, using terms such as "cold, very cold and bitterly cold". They knew there was an anomaly with their equation because it predicted less cooling at very high wind speeds. The fact that the predicted heat loss hardly changed at wind speeds higher than ~10 $m.s^{-1}$ matches that which one would expect from the effect of wind on thermal boundary layers (Osczevski 1995). Even though it was devised for sub-freezing, Antarctic winds, wind chill became an established index of wind-induced cooling (e.g., https://www.weather.gov/safety/cold-wind-chill-chart). The effects of wind and air temperature on that cylinder turned out to be very similar to their effects on a thermal manikin's face turned to the wind (Osczevski 1995). Because users found it difficult to relate to an index with units showing an area-specific cooling rate, it became customary to use a wind-chill equivalent temperature, which is the dry-bulb temperature that would lead to the same cooling rate in the absence of air movement. We do not know who made that suggestion, though it may have emerged from the U.S. armed forces (1960s).

The errors and uncertainties of the wind-chill index are as rife as those of the WBGT, and they are also as concealed by its popular appeal and apparent usefulness. The meteorologist Edwin Kessler said an employee of the U.S. National Weather Service once stated that wind chill did not "*serve any purpose other than to provide the news media with a tool with which to excite the general public*" (Kessler 1993 [P. 1744]). Weather forecasters do not necessarily agree, but recognise the hype around wind chill (Horstmeyer 1995). Requiring the equivalent temperature to be "*in the absence of air movement*" introduced one of the problems of the index, because one never encounters perfectly still people in perfectly still air. So the wind-chill equivalent temperature was redefined for low wind speeds, but not zero wind speed. Depending on who calculated the equivalent temperature, those low wind speeds were taken to be 2.2 $m.s^{-1}$ (Osczevski 1995), 1.78 $m.s^{-1}$ or 1.34 $m.s^{-1}$ (Osczevski and Bluestein 2005). As Steadman (1971) pointed out, wind speed could not be taken from meteorological service data, because standard meteorological wind speed is measured 10 m above ground and that wind speed is much higher than at face level, so meteorological wind speed would yield falsely low values of wind-chill equivalent temperature.

At the instigation of *Environment Canada* and the U.S. *National Weather Service*, Osczevski and Bluestein (2005) re-analysed heat loss at the face, correcting for height above the ground, and for minimum air movement, and generated a new chart and formula for wind-chill equivalent temperature. For the same dry-bulb temperature and wind speed, their formula gave less-extreme values for wind-chill equivalent temperature. "*It would seem that winter may not be as cold as previous wind chill calculations have led us to believe, which should be good news to many*" (Osczevski 1995 [P. 381]). The new wind-chill equivalent temperature was not the finished product, however. For example, it is a

steady-state calculation, and, in the very cold and high wind-speed conditions in which its use might be most necessary, it is unlikely that exposures long enough to achieve a steady state can be endured (Shitzer and Tikuisis 2012).

Even after revision, the wind-chill index lends itself to misunderstandings; "*if the wind speed actually reduced the air temperature, then why do we need a freezer, when all we should need would be a fan in a fridge*" (Michael Tipton, personal communication over another Joule). Faces do not freeze in an environment with a wind-chill equivalent temperature of − 30 °C if dry-bulb temperature is 5 °C (Horstmeyer 1995). As with the effective temperature index and the WBGT index, the pressure to provide a number has resulted in wind chill being called into action for purposes for which it was never intended, and for which there is no evidence. Michael Sawka and Andrew Young (U.S. Army Research Institute of Environmental Medicine) noted that the "*wind chill provides no meaningful estimate of the risk of hypothermia*" (Sawka and Young 2006 [P. 553]).

When the wind-chill equivalent temperature is used for hazard reduction during work and exercise in the cold, it should be used only to predict the consequences of having a cold-exposed face, which could include frostbite. The wind-chill equivalent temperature chart has been modified to predict finger cooling and frostbite potential (Tikuisis 2004), and that is how those indices should be applied (Castellani et al. 2021), with the proviso that movement due to the exercise itself should be taken into account in the wind speed (Castellani 2020; Noakes 2000). Runners are never in still air, and a marathon runner's speed is typically 14–17 km. h^{-1}, which is equivalent to Force 3 on the Beaufort Scale ("*leaves and small twigs are in constant motion*"; Porter 1984 [P. 261]). To account for relative and absolute wind speeds, the combination of ambient wind speed and body movements should be performed using vector analysis (e.g., Havenith et al. 2012). Predicting the consequences for a cold-exposed face is how wind-chill equivalent temperature is positioned within responsible advice to competitive and recreational athletes exercising outdoors in cold weather (Fudge 2016; Bushman 2018). Confining their wind-chill index to the role of predicting the risk of frostbite is not what Siple and Passel (1945) had in mind. They envisaged it as a thermal-comfort index, and it is sometimes still proposed as a comfort index (Nimmo 2004), but without compelling evidence.

Indices based on the energy-balance equation

None of the preceding stress indices had a mechanistic relationship with physiological strain, although statistical correlations often existed, and most seem largely unrelated to the human energy-balance equation (Notley et al. 2023a [Eq. 8]). Not surprisingly, we are unable to support statements such as this: "*all occupational heat-stress indices are based, explicitly or implicitly, on the human heat balance equation*" (Brake and Bates 2002 [P. 165]). Indeed, almost all of the > 187 indices of human thermal stress listed by Ioannou et al. (2022b) still have no mechanistic relationship with physiological strain, and pay little, if any, respect to the human energy-balance equation. Such indices never have been suitable for use with exercising humans. The association of environmental thermal variables with variables of physiological strain, including hyperthermia and hypothermia, would be reliable only if those variables were linked to heat transfer between the body and its environment, and coupled with the processes of human temperature regulation. Indices based on those requirements are called rational indices (Belding 1970; Lee 1980), but are better called energy-balance indices (de Freitas and Grigorieva 2015). It took a third of our century of exercise for the first rational index to emerge. Enter Harwood S. Belding (1909–1973) and Theodore F. Hatch (1901–1986; Belding and Hatch 1955) from the Harvard Fatigue Laboratory (U.S.A.; Blatteis and Schneider 2022; Notley et al. 2023b [Table 2]).

According to the energy-balance equation (Notley et al. 2023a), if metabolic heat production, external work rate, and radiative, convective and conductive heat exchanges are specified, then there is just one value of evaporative heat exchange that can result in the overall body-heat storage being zero. At that cooling rate, no nett heat gains or losses will occur and the body temperature will remain stable. Belding and Hatch (1955) designated that value as the required evaporation (E_{req}). Those heat-transfer components depend upon body morphology (they assumed a standard male: body mass 70 kg, height 1.7 m, surface area 1.8 m^2), the clothing worn (they specified shorts and sports shoes), the physical characteristics of the thermal environment and the mean skin temperature of the person (they assumed 35 °C). Vogt et al. (1982) suggested 36 °C would be more realistic for mean skin temperature, whilst we support 35 °C for the fully wet, bare skin of freely sweating individuals (Notley et al. (2023a [Fig. 13]). For a known environment (water-vapour pressure, wind speed) and a pre-determined skin temperature, evaporative heat loss would be maximal if the skin was uniformly and fully wet with sweat. Belding and Hatch defined that evaporative heat loss as the maximal attainable evaporation (E_{max}), and defined their Heat Stress Index (HSI) as the ratio of the required evaporation to the maximal attainable evaporation, expressed as a percentage (Eq. 2).

$$\text{Heat Stress Index} = \left(100 * E_{\text{req}}/E_{\text{max}}\right), \tag{2}$$

where E_{req} is the required evaporation, E_{max} is the maximal attainable evaporation.

Belding and Hatch (1955) considered an HSI of 100 to represent the maximal heat stress tolerable by a healthy young man for 8 h of physical work, and that required evaporative cooling to equal the maximum possible evaporative cooling for those conditions. Values > 100 would be physiologically uncompensable. Since the required evaporation was determined not just by the variables related to stress, but limited by how much sweat a standard man could produce over 8 h, Belding and Hatch (1955) set a maximum allowable sweat rate of 1 $L.h^{-1}$ ("Does hypohydration lead to hyperthermia and does it suppress sweating?"), and calculated that evaporating sweat at that rate would generate an evaporative heat loss rate of about 700 W. They were guided in their understanding of the relationship between evaporation rate and sweat rate by the concept of skin wetness, as advanced by A. Pharo Gagge (1908–1993, U.S.A.; Gagge 1937; Blatteis and Schneider 2022). They did not appreciate that sweat starts to drip from the skin well before it reaches 100% wettedness (Candas et al. 1979, 1980), and that, in hot-humid environments with low wind speed, only ~ 60% of the sweat produced actually evaporates (Stewart 1981). Thus, sweating at 1 $L.h^{-1}$ would actually generate just a bit more than 400 W of evaporative cooling, and about 0.4 $L.h^{-1}$ of unevaporated (futile) sweat.

The HSI of Belding and Hatch (1955) was an elegant concept. Whilst it is a rational heat index, it is not a stress index because it includes physiological variables. Unfortunately, it is difficult to apply accurately in practice, because of the need to calculate various forms of heat transfer, which requires an accurate knowledge of the heat-transfer coefficients and then considerable arithmetic. Those coefficients vary not just with atmospheric conditions, but with body size and shape, posture and clothing. Perhaps surprisingly, given that spreadsheets have existed since the late 1970s, those calculations have been a barrier to its widespread use, and it has been superseded by other rational indices.

Three indices applicable to human exercise that readers may encounter are the Predicted Heat Strain (PHS) for heat exposures, the Required Clothing Insulation (IREQ) for cold exposures and the Universal Thermal Climate Index (UTCI) for all conditions. All are relatively recent developments, they all have a solid heritage in our century of exercise physiology, and de Freitas and Grigorieva (2017) consider all three to have been validated. The contention that they have been validated should be treated with caution because, in some validation trials, rectal temperature was used as the primary index of thermal strain, which is a questionable practice during the dynamic states of interest to applied physiologists.

The Predicted Heat Strain index (PHS) is a modern extrapolation of the HSI, and its main output variable is the predicted sweat rate. The index also provides predictions of deep-body and skin temperatures, even in clothed subjects, and for uncompensable states it offers predictions of possible endurance limits. It incorporates a physiological cut-off for body-water loss that coincide with a 7.5% body-mass loss. Collaborations are pleasingly common in the field of the thermal physiology of exercise, but it was an exceptional collaboration that delivered the PHS. Researchers from Belgium, England, Germany, Italy, Sweden and The Netherlands derived a much improved numerical analysis of human energy balance, with the combined data from 672 laboratory and 237 field experiments then used to test that index (Malchaire et al. 2001; Malchaire 2006).

Although based upon energy balance, it would be a stretch for us to classify it as a rational index when, for example, skin temperature is predicted from an equation unrelated to any physical or physiological processes of heat transfer. Though reasonable, linear correlations between predicted and observed thermal strain emerged, the index was far from perfect, and ominously inaccurate at high heat loads. In both laboratory and field validation experiments, it overestimated the observed rectal temperature by as much as 2 °C. Similarly, the PHS predicted sweat rates of 0.5 $L.h^{-1}$ when the observed sweat rates were 1.1 $L.h^{-1}$. We conclude, from inspection of those validation data, that the PHS is a reasonably accurate heat-strain index, as long as it is not applied to serious heat. Nevertheless, the *International Standards Organization* adopted it and recommended its use in preference to the WBGT in severe working conditions (ISO 7933:2004). Student readers may wonder why that might have occurred, whilst experienced investigators often lack signs of surprise.

For cold conditions, the *International Standards Organization* recommends the Required Clothing Insulation (IREQ) index, which was developed by Ingvar Holmér (1988, Sweden), who also was an originator of the PHS index. The principle and associated calculations were embedded within Steadman's wind-chill paper: "*the thickness of clothing required to maintain thermal equilibrium provides a single index of cold and wind*" (Steadman 1971 [P. 681]). Holmér acknowledged others in the development of the concept, most notably U.S. thermal physiologists Carl Givoni and Ralph Goldman (e.g., Givoni and Goldman 1972; Blatteis and Schneider 2022). His approach differed from that used in both the HSI and the PHS indices, in that he used a variation of the energy-balance model.

Holmér used heat-transfer equations to predict the minimum clothing insulation ($IREQ_{min}$) necessary to achieve, not a stable deep-body temperature, but a stable mean skin temperature of 30 °C. He assumed that the deep-body temperature would be stable if the skin temperature was stable at 30 °C. Holmér calculated the minimum insulation required to sustain thermal comfort ($IREQ_{neutral}$), assuming that skin

temperature was a linear function of metabolic rate. He also estimated endurance limits for circumstances in which stable skin temperatures could not be maintained. Based on the IREQ, the *International Standards Organization* (ISO 11079:2007) also sets minima for the temperature of extremities (Holmér, 2009). The IREQ turned out to be very sensitive to metabolic rate (Griefahn 2000), but, anomalously it seems to us, only slightly sensitive to wind speeds between 0.2–5.0 $m.s^{-1}$ (Holmér, 1988 [Figure 2]).

In the more than 30 years since IREQ was put on the map, improvements have been made to the calculations, largely described in technical reports that are not easily accessible (d'Ambrosio Alfano et al. 2013), but they apparently have been incorporated into international standards (ISO 11079:2007). During actual work in the cold, contrary to the assumption in the calculation of $IREQ_{min}$, workers did not maintain a skin temperature of 30 °C (Gavhed and Holmér, 1998), and overdressed in less-extreme cold. Workers chose to wear clothing that provided more insulation than predicted by IREQ (Aptel 1988; Griefahn 2000), because they were uncomfortably cold at rest when wearing clothing that corresponded to $IREQ_{min}$ (O'Leary and Parsons 1994). Accurate calculation of IREQ requires valid measurement of clothing insulation as well as accurate measurements of the degree to which clothing ensembles modify the body-surface area. Those measurements are made best on exercising subjects wearing those ensembles, and they have been made (Mitchell and van Rensburg 1973), but the equipment was dismantled (Mitchell and Laburn 2022) and instruments for the direct and separate measurement of convective, evaporative and radiative heat transfer on exercising subjects have not been replicated. The IREQ index is far from a finished product (d'Ambrosio Alfano et al. 2013; Xu and Tikuisis 2014).

Ingvar Holmér did not develop, but he did contribute to, the development of the third of our indices based on the concept of Belding and Hatch (1955); the Universal Thermal Climate Index (UTCI; Jendritzky et al. 2007). That index is more ambitious than the others, in that it was aimed at covering both heat and cold stress in outdoor environments, as they changed with global warming. It is not the first of the modern indices to be based on the energy-balance equation, and that might be used for exercising people in both hot and cold thermal states. Steadman's "*universal scale of apparent temperature*" covered dry-bulb temperatures between −40 °C and + 50 °C, wind speeds up to 20 $m.s^{-1}$ and changes in humidity (Steadman 1984; Dixon and Prior 1987), and it is still used to assess heat stress for some outdoor sports (e.g., Huang et al. 2021). However, the UTCI is more comprehensive, since it considers heat exchanges with the environment, as well as within the body, under physiological control. The aim is to predict whole-body thermal responses as well as local reactions (Havenith and Fiala 2016), and it also takes account of solar radiation, making it suitable for both indoor and outdoor environments.

The UTCI is expressed as a single number, the dry-bulb temperature of a reference environment in which the physiological model has the same thermal response as it does in the actual conditions. The reference environment has a specified meteorological wind speed, mean radiant temperature (equal to dry-bulb temperature) and water-vapour pressure, and there is also a reference activity; a person walking outdoors at 1.1 $m.s^{-1}$. The complex issue of clothing was addressed separately and subsequently integrated within the model (Havenith et al. 2012). The thermal response was measured as a linear combination of rectal and mean skin temperatures, face temperature, sweat production, skin wettedness, cutaneous blood flow and shivering intensity, with weighting coefficients determined using principal components analysis (a statistical concept with no physiological interpretation). While the thermal response was modelled dynamically, analysis showed that no important information was lost if measurements were confined to exposures of 30–120 min.

Calculating UTCI for different scenarios defied algebraic solution, as well as the computing prowess of potential users, so another statistical procedure was made available. That alternative produced a regression equation and a look-up table that related the UTCI to the dry-bulb temperature, the difference between the mean radiant temperature and the dry-bulb temperature, wind speed and water-vapour pressure (Bröde et al. 2012a). The developers provided online access to both the equation and table, and a special issue of the *International Journal of Biometeorology* (2012) was devoted to reflections on the performance of the UTCI, written largely by the researchers themselves (McGregor 2012).

The UTCI is also an unfinished product. For example, the clothing that it incorporates is European seasonal clothing, which is understandable. The UTCI correlated reasonably well with thermal sensation and the choice of clothing in a city in southern Brazil, where European-like clothing is worn (Bröde et al. 2012b). The vast majority of the world's population, and especially those living in thermally-stressful tropical and polar regions, do not wear such clothing. Indeed, more than 50% of the world's population live within the Asia–Pacific countries. What is needed is research conducted in those regions, in which the ability of the UTCI to predict physiological thermal strain, like deviations in deep-body temperature, is investigated. Whether the UTCI is manageable by users other than its developers is another question that needs to be asked.

If you cannot give us a number, what should we do?

Indices of thermal stress and strain have an illustrious past, and a prolific and creative present, but "*any reader who was hoping for the evolution of a single heat index applicable*

to all aspects of human endeavour must by now be sadly disappointed" (Lee 1980 [P. 352]). What will be the future of thermal indices? Rather than continuing to improve indefinitely, we anticipate that they are all likely to become obsolete.

Since all thermal indices are surrogates, then it is possible that they might be replaced by strain predictions derived from the actual analysis of physical heat transfer in each situation. That has not been possible in the past because the heat-transfer equations for exercising people, especially people clothed and outdoors in the sun, have not been known well enough, but probably more so because carrying out the arithmetic in a reasonable time was beyond office computers. That no longer is a problem, and those calculations can be performed using smartphone applications, such as that available for the UTCI (Heusinkveld et al. 2017). The heat-transfer equations are becoming known with more accuracy, but applied thermal physiology for humans is lagging behind that of comparative thermal physiology, particularly with regard to making predictions of thermal strain in real-life situations without perfect knowledge of heat transfer. Enter the comparative physiologists.

Comparative physiologists can now predict the deep-body temperatures of exercising, free-living, wild primates from biophysical measurements (Mathewson et al. 2020). That ability has arisen from the work of Michael Kearney and Warren Porter (Kearney and Porter 2009; Australia and U.S.A.). They developed freely available software (Niche Mapper: https://mrke.github.io/) that uses meteorological variables and terrain characteristics to predict local microclimates, above and below the ground surface, and combines those predictions with properties of the animal of interest to predict physiological variables (e.g., body temperatures, evaporative water loss) as well as ecological variables (e.g., population distributions and densities). That software was a natural extension of a model developed half a century ago (Myrup and Morgan 1972), which has been applied to estimate the implications of environmental changes on human heat balance (Morgan and Baskett 1974; Maloney and Forbes 2011; Glass et al. 2015). If Niche Mapper can be applied to humans during exercise, we see no further need for other surrogate predictive indices.

It is in such applications for the biophysical analysis of real-life situations that we foresee the future of predicting human thermal reactions during exercise. Despite the popularity of some thermal stress indices, and their continued use, we expect those indices to eventually lose their utility, because they cannot compete with the full and instantaneous biophysical analysis of thermal status. Few of the > 187 different human thermal indices (Ioannou et al. 2022b) have ever enjoyed sustained and widespread support. There may be a role for wearable devices to monitor thermal strain in real time for high-risk individuals (Notley et al. 2018, 2019), although their utility for estimating body temperature still lacks the rigour required for research. One might also question the validity of deep-body temperature as an index of impending heat stroke, as there is no threshold body temperature above which heat stroke is inevitable and below which it is absent ("Exertional heat stroke: not killed by the sun, but by the forced march").

Conclusions and recommendations

In Part 1 of this historical series (Notley et al. 2023a), we introduced the principles that govern the way in which we work and play in thermal extremes. We then examined how those principles influenced the development of physiological measurements, and we described the limitations associated with surrogate indices for quantifying changes within the regulated and controlled variables of thermoregulation (Notley et al. 2023b). In this third contribution, we used that background to extract and describe validated contributions, across our three epochs, that shaped our understanding of heat and cold tolerance, and intolerance during occupational and athletic pursuits. We described some developments in the treatment of thermal injuries, along with thermal stress and strain indices used to characterise the impact of thermal stress upon recreational and occupational athletes.

From this contribution, we offer the following conclusions and recommendations with regard to heat stress and exercising humans.

- In occupational scenarios, heat strain and incapacitation are due primarily to suppressed evaporative cooling, as dictated by ambient conditions or clothing, coupled with heavy muscular work and load carriage, and can result in exertional heat stroke.
- Performance degradations that may result in the termination of endurance exercise or work are not associated with the attainment of a critical deep-body temperature, although that must eventually occur in many heat-stroke casualties.
- We believe that incapacitation is more likely to be of a cardiovascular origin, mostly probably in the form of unsustainable hypotension.
- Deep-body temperatures < 40 °C are rarely fatal, although we cannot point to a specific temperature that might be used to diagnose heat stroke.
- Whilst we accept that ad libitum drinking is rarely problematic, we suggest that prescribed drinking is preferable for protracted athletic and occupational pursuits.
- For individuals displaying signs and symptoms consistent with heat illness, and when other life-threatening conditions can be excluded, we recommend immediate cooling, regardless of their deep-body temperature, with that cooling continuing until the slowly responding surrogates

of deep-body temperature (e.g., rectal temperature) reach 38.5 °C.
- Our recommendations for cooling hyperthermic individuals are either skin wetting and ventilating, or whole- or partial-body water immersion, with those treatments being made using water of any temperature cooler than the skin.
- We are unable to support ice-cold water immersion, either on the basis of first principles or on the possibility that it imposes minimal risk.
- Of the many heat stress and strain indices that exist, we only support the use of indices based upon the energy-balance equation: the Heat Stress Index and the Universal Thermal Climate Index. Accordingly, we caution against relying on the Wet-Bulb Globe Temperature (WBGT) for recreational and occupational pursuits, and dismiss the use of wet-bulb temperatures as indices of heat stress.

With regard to exercise during cold exposures, we have drawn the following conclusions.

- Shivering thermogenesis can and does supplement metabolic heat production in humans during both rest and exercise.
- We have provided historical and contemporary evidence to show that adult humans possess brown adipocytes, which we believe can support metabolic heat production in resting humans, and particularly neonates, although their contribution during exercise remains uncertain, and is presumably small.
- Thermoregulatory failure during protracted cold exposures is likely to be due to the suppression of shivering that accompanies blood-glucose depletion, which itself may be due to exercise-induced or alcohol-associated hypoglycaemia.
- The restoration of cutaneous blood flow in hypothermic casualties is almost entirely dependent upon first restoring a normothermic deep-body temperature.
- Apparently lifeless hypothermic victims must not be pronounced dead unless they have been rewarmed and still show no signs of life.
- We support the Universal Thermal Climate Index and the Required Clothing Insulation index for reducing strain in recreational and occupational athletes.
- We are unable to support the use of the Wind-Chill Index for predicting hypothermia, although it seems suitable for predicting the risk of frostbite.

In our final contribution to this review series, we will move from the impact of acute thermal stress to explore how humans adapt to chronic thermal exposures. Attention will first be directed to the evolutionary developments that allowed our species to survive and thrive during endurance activity in thermal extremes, including the progression of our ancestral sweating specialists (*Homo sudomotor*) through to *Homo cursor* (running man). With that foundation, and against that genetic background, we will explore the mechanisms of thermal adaptation that will allow us to undertake both the natural and artificially induced phenotypic enhancement of those attributes, and thereby improve our tolerance of acute thermal stresses during recreational and occupational pursuits.

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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.

Declarations

Conflict of interest There are no conflicts of interest to declare.

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