Experimental Physiology

G. L. Brown Prize Lecture

Environmental extremes: origins, consequences and amelioration in humans

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New Findings

- **What is the topic of this review?**
  This review concerns human responses to extreme environmental stresses.
- **What advances does it highlight?**
  This review highlights the following factors: the relatively limited and varying value of adaptation; the value of research in this area to inform other medical conditions; the physiological pathways to drowning; the importance of multistressor studies and multistressor adaptation; and the need for a better understanding of the metabolomic and biomolecular basis of responses and their variation in extreme environments.

Professor Sir George Lindor Brown (1903–1971) is known for his pioneering research into cholinergic neuromuscular transmission. However, during World War II he worked in hyperbaric physiology, and his research into underwater physiology greatly improved the safety of divers. It is perhaps fitting, therefore, that this review, which accompanies the Physiological Society's G. L. Brown Prize Lecture for 2015, explores the impact and mitigation of the environmental stresses which, to varying extents, have shaped our past, threaten our present and inform our future. From a whole-body, integrative perspective, this review examines our current understanding of microgravity, hypo- and hyperbaria, heat, cold air and cold water as both individual and combined stresses. Consideration is given to ways of mitigating the threat posed by environmental extremes, including the differing extents to which humans can demonstrate adaptation to them. Finally, recommendations for further study are suggested that might result in both direct and indirect insights.

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Introduction

Ever since the iconic picture, 'Earthrise', was taken from Apollo 8 as it orbited the moon in 1968, we have considered our world a 'blue planet', an oasis amongst otherwise inhospitable and indifferent spheres. However, the idea of an Eden-like home that we have evolved to be in harmony with, that nurtures us as we care for it, is some way from the truth. On one side of the ecological coin, we have the damage we do to our world by our existence. On the other side, we have the fact that 70% of our planet is covered in water, with an average ocean depth of 4000 m. Light penetrates up to about 80 m into water, so most of our planet is in permanent darkness; the rest of it is in intermittent darkness with day and night. Only

The G. L. Brown Prize Lecture is given in memory of the distinguished physiologist Sir George Lindor Brown (1903–1971). It is aimed at a younger audience with a view to stimulating an interest in physiology. M. Tipton gave the G. L. Brown Prize Lecture in 2015 at (in chronological order) the Universities of: Keele, Cambridge, Westminster, Bath, Portsmouth, Trinity College Dublin, Brighton and Sheffield and at the Physiological Society, London.

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15% of the surface of the Earth is not water, desert, ice or mountain. For man, a subtropical, 1***g***, low-altitude, air-breathing homeothermic animal, most of our home represents an 'extreme environment', defined as a place where it is difficult to survive.

Whilst we can, to differing extents, demonstrate physiological adaptation to heat, cold and altitude, if constrained by these capacities we would still inhabit a very small portion of our planet, close to our equatorial origins. The 3- to 4-million-year evolution of humans has been influenced and determined by the environment. The migration from our equatorial origins was primarily determined by the ability to adapt behaviourally; it was this, underpinned by intellect and invention, that allowed us to protect ourselves, recreate our desired macro- and microclimates and, thereby, colonize most of the rest of the planet and even play one-handed golf on the Moon (Alan Shepard, NASA astronaut, 1971). So it is that, wherever in the world you take the measurement, if resting humans report being 'comfortable', they will have a deep body temperature of 37°C and mean skin temperature of 33°C, exactly as they would have had living naked in their ancestral home with its air temperature of 28°C.

The technical abilities that have enabled us to inhabit the rest of the planet have also made us dependent on that technology and, thereby, limited the extent of our physiological adaptation. Indeed, there is an argument that those stressors that humans have historically been most able to counter are also the ones to which it is most difficult to identify an adaptation. The oldest building made by homonids was a windbreak constructed by *Australopithecus* ∼3.25 million years ago. Over a million years ago, *Homo erectus* was building huts from stones, branches and furs. The earliest evidence for the use of fire, a source of light and radiant heat, comes from China (600,000 BC), whilst the oldest clothed body yet discovered was that of a man who died about 35,000 years ago (Tipton *et al.* 2008). Conversely, those environmental stressors that were more difficult for our ancestors to mitigate (e.g. heat, altitude) can produce significant physiological adaptation with repeated exposure. Our technical abilities also explain why humans do not possess the morphological and anatomical adaptations observed in other species.

The problem comes when things go wrong and we have to fall back on our relatively primitive, unevolved, physiological defences. The consequences of their limitations include drowning, hypothermia, cold injury, hyperthermia and barotrauma. These pathophysiological threats can arise in natural as well as man-made environments, from deserts to space craft. A simple hierarchy of survival is presented in Table 1; although the threats differ, the ultimate problem is usually hypoxia.

Table 1. The hierarchy of survival

Threat	Survival time
Lack of oxygen (respiratory/circulatory impairment)	Minutes
Thermal imbalance (hyperthermia or hypothermia)	Hours
Fluid imbalance (dehydration)	Days
Energy imbalance (starvation)	Weeks

The lack of precision in the 'survival times' in Table 1 is indicative of the large variation in the responses of humans to environmental threats. This variability is caused by a combination of environmental factors (water/air temperature, humidity, pressure etc.) and individual phenotypical and genotypical factors (sex, race, health, fitness, acclimatization status etc.). For example, survival time from dehydration differs in a marine (∼6 days) compared with a desert environment (∼3 days; Golden & Tipton, 2002). The variation is not only apparent between environments and individuals, but also within individuals on different occasions. Thus, an experienced mountaineer, with no previous history of acute mountain sickness, may succumb to it on a subsequent visit to altitude. The reasons for this are not clearly understood; the role of subtle predisposing changes in the physiology of the climber, including asymptomatic infection, have not been elucidated. The coexistence of additional stresses may result in a problem that does not exist otherwise; those who are most likely to become hypothermic in a life raft at sea are also those who are seasick and hungry; motion illness impairs the heat-loss defence mechanisms (decreased vasoconstriction; Mekjavic *et al.* 2001), and hypoglycaemia impairs shivering (Gale *et al.* 1981). Motion illness also decreases vasoconstriction and arterial pressure and this, in turn, decreases G-tolerance (Eiken *et al.* 2005).

The investigation of the impact of the environment on human physiology has been undertaken for a variety of reasons, including the following: (i) to gain an understanding of the physiology and pathophysiology surrounding a specific threat; (ii) to prepare and protect those entering extreme environments for occupational or leisure reasons (this applies to groups as diverse as the chemical, baking, canning and energy industries, as well as the military and sports enthusiasts ranging from outdoor pursuits to fencing); and (iii) to obtain insights into other medical conditions.

Starting from a high point, the remainder of this article briefly examines different extreme environments with a view to highlighting these aspects.

Microgravity

One has to travel 6.37 million km into space to reach a point where the gravitational pull from the Earth is

one millionth of that at the surface. As spacecraft orbit 200–450 km from the surface, astronauts experience apparent weightlessness or 'microgravity' rather than zero gravity, and orbit is equivalent to free fall. The resultant reduction in hydrostatic gradients and loading act upon the body to produce a range of cardiovascular, pulmonary, musculoskeletal, hormonal, vestibular, neurosensory, haematological, thermoregulatory, fluid and electrolyte changes (Lujan & White, 1994; Convertino, 2000; Mekjavic *et al.* 2005). The time courses of these alterations vary, with the fluid shifts and cardiac deconditioning happening earlier (days to weeks) and muscle and bone mass changes later (months). These changes are less significant when astronauts are in microgravity than when they return to 1***g***, where the physiological deconditioning they have experienced can become pathological. This has led to many studies examining possible interventions to mitigate the reduction in the anatomical and physiological status caused by exposure to microgravity. Given that the changes seen mimic those observed with detraining, inactivity and immobilization, most interventions involve careful crew preselection and the completion of ingenious forms of exercise in space to try to reduce the deleterious effects of microgravity (Nicogossian *et al.* 1994).

The expense and logistical demands of spaceflight mean that other methodologies have been employed to simulate exposure to microgravity; these include parabolic flight, immersion, immobilization and bed rest. It is the last of these methodologies that is most widely used, and it also provides an alternative rationale for the study of microgravity. The investigation of physiological aspects of space travel is seldom justified in terms of the future of our species. The need to leave the solar system within the next 4.5 billion years is a powerful argument, but is a little too far outside 5 year spending plans. Instead, the relevance of such investigations for other conditions, such as ageing, bone changes (osteoporosis) in postmenopausal women and extended bed rest in critical care patients, is emphasized.

Vico *et al.* (2000) reported a 25% loss of bone density after 6 months of space travel in 11 cosmonauts in the Russian MIR space station. This is somewhat more than the 5–10% seen in postmenopausal women and occurred in the legs rather than arms, with large interindividual variation. The time to recover fully was longer than the mission. The cause of the reduction in bone mineral density has been a matter of some debate, with mechano-adaptation following the loss of muscle contractions/strength now being preferred to fluid shifts and changed perfusion pressure gradients as the primary mechanism (Rittweger *et al.* 2010). This 'muscle–bone' hypothesis is supported by the finding that exercise that maintains muscle strength is an effective countermeasure to bone loss (Shackelford *et al.* 2004).

Bed-rest studies modelling the impact of microgravity can also provide valuable information for acute muscle wasting in critical illness (Puthucheary *et al.* 2013), with some of the countermeasures being applicable to both microgravity and the care, maintenance and rehabilitation of the long-term critically ill (Greenleaf, 1997; Parry *et al.* 2012).

Hypobaria

Barometric pressure decreases according to an approximately exponential function with distance above the earth. One atmosphere is the pressure exerted by the 38 km of air above us and is equal to ∼760 mmHg (101.33 kPa; 14.7 p.s.i.); because air is compressible, half an atmosphere is at an altitude of ∼5500 m.

The primary problem associated with altitude is the reduction in barometric pressure and the consequent reduction in the arterial partial pressure of oxygen (P_{aO_2}) and oxygen availability at the tissues; this problem is compounded when oxygen demand is increased by exercise. The problem is characterized by the S-shape of the oxyhaemomoglobin dissociation curve, which means that normally, at sea level, small reductions in the P_{aO_2} have relatively little impact on the saturation of haemoglobin; however, below a P_{aO_2} of ∼50 mmHg (equivalent to an altitude of ∼5486 m), such reductions have a more significant impact on the percentage haemoglobin saturation; this represents the highest elevation with permanent residents (slightly below half an atmosphere; Fig. 1).

Above 1500 m, maximal aerobic capacity decreases by about 7.7–11% for every 1000 m increase in altitude up to 6300 m, at which point it declines at a greater rate (Fulco *et al.* 1998). The symptoms of hypoxia progress with increasing altitude, with the major dangers being high-altitude cerebral oedema and high-altitude pulmonary oedema. The pathogenesis of these conditions has been something of a mystery; however, there is a mounting body of evidence of a relationship between genotype and mountain sickness. Several authors have reported a relationship between the angiotensin-converting enzyme (*ACE*) genotype and high-altitude pulmonary hypertension and between endothelial nitric oxide synthase gene polymorphisms and high-altitude pulmonary oedema (Morrell *et al.* 1999; Aldashev *et al.* 2002; Droma *et al.* 2002).

Two further areas of high-altitude research with the possibility of illuminating pathological states include studies into the regulation of cerebral blood flow at high altitude and the individual and temporal response to hypoxia. The initial increase in cerebral blood flow on exposure to high altitude (Severinghaus *et al.* 1966) and the change in the cerebrovascular response to

arterial partial pressure of carbon dioxide (P_{aCO_2}) at high altitude can influence breathing responses (Ainslie & Duffin, 2009). The altered cerebrovascular reactivity to CO_2 and breathing instability seen at high altitude may have implications for unstable breathing patterns in patients with congestive heart failure (Xie *et al.* 2005) and obstructive sleep apnoea (Burgess *et al.* 2010). The mechanisms underlying the changes in cerebral blood flow at high altitude remain to be elucidated fully; 40% of the increase in cerebral blood flow at 5050 m appears to be related to the balance of P_{aO_2} and P_{aCO_2} and to be determined by ventilatory sensitivity. Whilst the other 60% is thought to be due to neuronal and local (e.g. endothelium-derived nitric oxide) factors (Lucas *et al.* 2011), 7–9 days of acclimatization leads to normalization of cerebral blood flow as a result of hypoxia-induced increases in ventilation, with a consequently higher $P_{aO_2} : P_{aCO_2}$ ratio, resulting in less hypoxia-induced dilatation and more hypercapnia-induced constriction in the cerebral circulation (Lucas *et al.* 2011).

Another justification for high-altitude research has been its relevance for intensive care medicine. This is part of a hypothesis that suggests that the physiological and pathophysiological responses to extreme environments may be similar to those seen in critical illness (Grocott *et al.* 2007). The cellular hypoxia associated with critical illness and the responses to high altitude may have parallels in terms of the progression from acute responses that attempt to overcome tissue hypoxia by increasing oxygen delivery to longer-term responses that reduce oxygen utilization by increasing efficiency (Hochachka *et al.* 1996). Furthermore, a better understanding of the variability observed in the response of individuals to altitude may help to explain the variability in the outcome from critical illness founded on hypoxia. For example, the genes identified as assisting high-altitude performance might also improve outcome in critical illness. The *ACE* gene insertion allele improves performance at altitude and lowers mortality from various conditions, including acute respiratory distress syndrome (Marshall *et al.* 2002).

Finally, there remains some debate about the validity of using normobaric hypoxia as a model for hypobaric hypoxia (Beidleman *et al.* 2014). A recent systematic review and evaluation of 13 studies (Coppel *et al.* 2015)

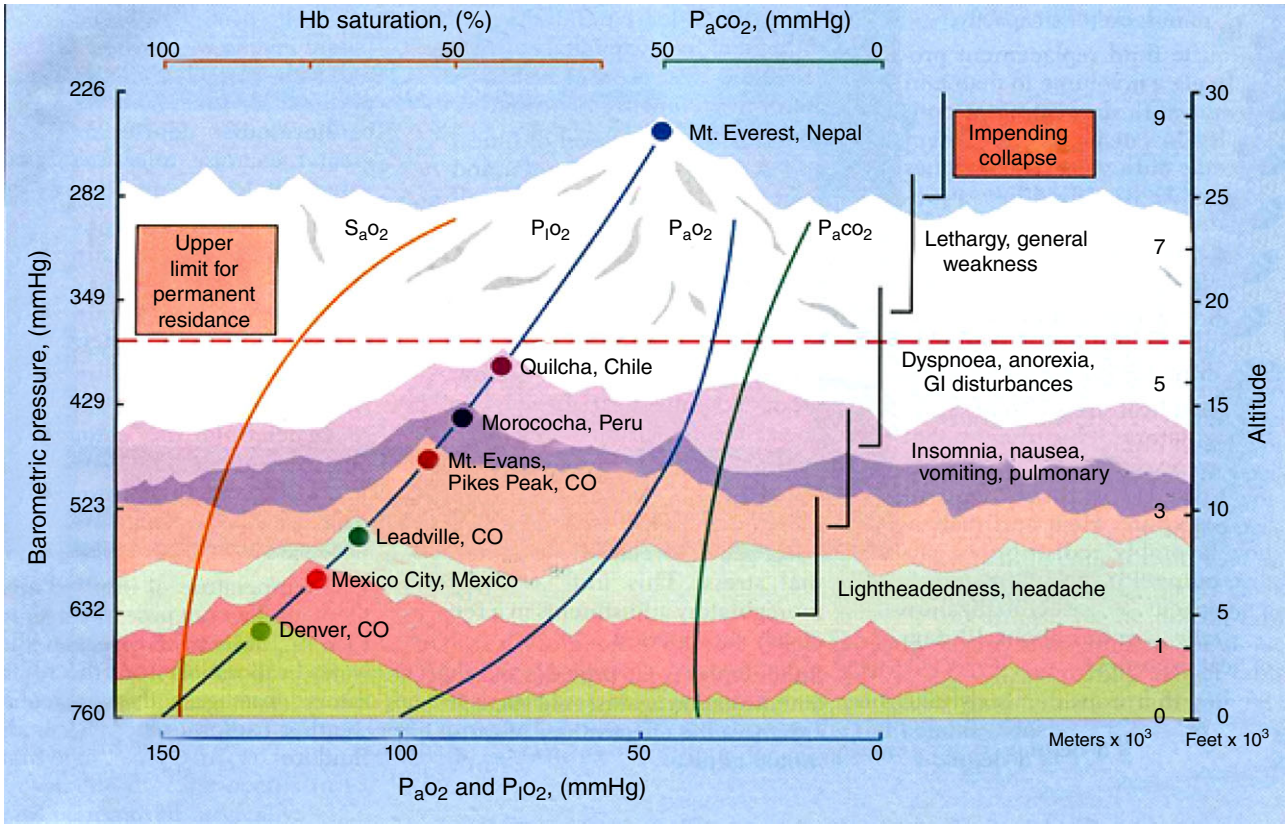

Figure 1. The physical, physiological and pathophysiological consequences of going to altitude
[From McArdle *et al.* (2001), with permission.] Hb = haemoglobin; P_aCO_2 = arterial partial pressure of carbon dioxide; S_aO_2 = arterial haemoglobin oxygen saturation; P_IO_2 = Inspired partial pressure of oxygen; P_aO_2 = Arterial partial pressure of oxygen.

suggested that there were differences between the two in a number of variables, including minute ventilation and nitric oxide levels, suggesting the presence of a physiological difference. However, the authors were unable to draw a definitive conclusion owing to a lack of methodological standardization between the studies.

Hyperbaria

Diving has a long history; Greek sponge divers of 2500 years BC are mentioned in Homer's Illiad and Odyssey. In 1500, Leonardo da Vinci designed the first snorkel, with fins for hands and feet. In 1650, Von Guericke developed the first air pump, which was used by Robert Boyle and led to his first description of decompression sickness with the appearance of bubbles in the eyes of a viper following compression and decompression. Sir Edmund Haley patented the first diving bell in 1690, and the first confirmed submarine battle (US Turtle *versus* HMS Eagle) took place in 1776. The first prototype self-contained underwater breathing apparatus (SCUBA) was invented by James in 1825 and developed by Fleus in 1878. In 1873, Smith reported decompression sickness in workers leaving their pressurized caisson working on the Brooklyn Bridge. The workers bent forward from sudden joint pain; this resembled the fashionable 'Grecian bend' of the tightly corseted New York society women. The term 'bends' remains to this day. In 1878, Paul Bert published '*La Pression Barometrique*', suggesting that nitrogen bubbles cause decompression sickness and that gradual ascent and recompression help to alleviate the condition. This was confirmed by Boycott *et al.* (1908) with the suggestion of staged decompression.

The physiology and pathophysiology associated with the hyperbaric environment are dominated by the physical Laws of Boyle (barotrauma), Dalton (oxygen toxicity and nitrogen narcosis) and Henry (decompression sickness) and, more than any other environment mentioned in this review, are inextricably linked to the associated technology. Indeed, the development of new techniques and equipment in diving usually preceded an understanding of the possible physiological consequences of their use (Brubak & Neuman, 2003).

Perhaps the most important diving-related response to mention within the confines of this review is pulmonary barotrauma resulting in air embolism. This is the second leading cause of death after drowning for those entering the water. The greatest change in lung volume occurs near the surface (Boyle's Law: between 10 m and the surface, the pressure is halved so the volume doubles). Having taken a breath from a source of compressed air, breath holding during ascent can lead to rupture of the alveolar membrane and air emboli entering the pulmonary vasculature and systemic circulation, where blockage of the pulmonary, coronary or cerebral circulation results in symptoms ranging from confusion and weakness to death. The shallowest depth from which this has occurred is thought to be 1 m (Tipton *et al.* 1995), and the most unfortunate death occurred in a diver at a fixed shallow water depth who happened to hold his breath whilst concentrating on his camera as the peak and then trough of a wave passed above him, effectively reducing his depth of immersion and causing pulmonary barotrauma (Shilling *et al.* 1984).

In most regions, the thermal consequences of diving have to be considered. At depths of >180 m, a diver requires 1.2–1.3 kW of external heating to maintain

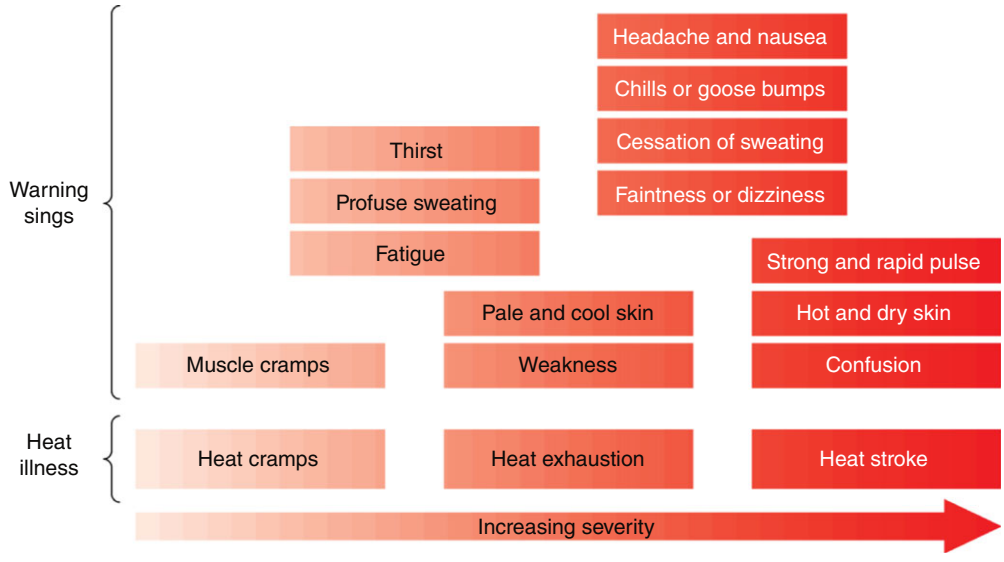

Figure 2. The physiological and pathophysiological signs and symptoms of increasing heat illness

thermal balance. At depths of >100 m, heating the inspired gas is mandatory because heat loss from the respiratory passages changes from primarily evaporative to convective (owing to increased gas density) and becomes a major route of heat loss. At 30 atm, divers breathing gas at a temperature of 4°C will lose all of their metabolic heat via the respiratory tract, independent of the insulation provided at the skin surface. Respiratory heat loss can be reduced by breathing less dense gas mixtures, but even when using helium–oxygen mixtures ('heliox') at depths of 250 m hypothermia can occur in <20 min when breathing unheated gas, despite normal skin temperatures (Hoke *et al.* 1976).

Hyperbaric oxygen therapy has been recommended for a wide range of conditions. However, in some cases the definitive experimentation underpinning these treatments is either missing or lacking the necessary control of normobaric oxygen (Kindwall & Whelan, 2008).

Heat

Despite being a 'tropical animal', designed to live naked in air temperatures around 28°C and possessing powerful effector mechanisms for heat loss, humans can suffer heat illness, including heat stroke and death (Fig. 2). This usually occurs when individuals choose, or are required, to exercise in hot and/or humid environments or when they exercise when wearing thermally inappropriate clothing (e.g. chemical, biological, radiological or nuclear protective clothing). If the body were prevented from losing any of the heat it produced, a fatal level of heat storage would be reached in ∼4 h at rest or 25 min with moderate exercise. Some cases of exertional heat illness occur as a result of malignant hyperthermia, an inherited pharmacogenetic disorder of skeletal muscle characterized by an elevated calcium release from the skeletal muscle sarcoplasmic reticulum. This condition has been associated with pathogenic variants in the *RYR1* and *CACNA1S* genes (Fiszer *et al.* 2015).

The problems caused by heat result from decreased circulating blood volume, alterations in regional blood flow, increased blood viscosity and the direct effect of temperature on the respiratory centres and proteins. Lower levels of heat stress, particularly when compounded by dehydration, can cause physiological changes, including cardiovascular insufficiency, that impair exercise performance (Tipton, 2015; Table 2).

Various options for the active cooling of hyperthermic individuals exist. Of these, whole-body fanning and hand immersion in cold water, which use the physiological responses of the body (sweating and peripheral blood flow) are quick and efficient (Barwood *et al.* 2009). If the victim is suffering heat stroke, with an absence of sweating and compromised peripheral blood flow, conductive cooling by immersion in cool water is required.

Cold air

Provided adequate and appropriate (windproof/waterproof) thermal protection is worn and metabolism is maintained though exercise, hypothermia is rarely a problem even in very cold environments. The problem comes when injury or exhaustion intervenes and limits the metabolic production of heat. The signs and symptoms of hypothermia are presented in Fig. 3. Hypothermia decreases cellular metabolism, blood flow and neural activation.

A more likely risk in very cold environments is cold injury of the peripheral tissue. 'Frostbite' is a well-known and well-understood condition, with the pathology resulting from intracellular freezing during rapid cooling and direct mechanical disruption. During slow cooling, extracellular water crystallization causes osmotic outflow, leading to intracellular dehydration, damage to the capillary wall endothelium and cell death. As a consequence, there is a local release of inflammatory mediators (such as prostaglandin F_2, thromboxane A2 and oxygen radicals), a reduction in plasma volume, oedema, reduced local blood flow, capillary sludging, platelet aggregation, vessel thrombosis, local hypoxia and gangrene (Reamy, 1998; Handford *et al.* 2014).

A much less well-known and well-understood condition is non-freezing cold injury (NFCI), in which the tissues are damaged by long-term exposure to cold and often wet environments, without tissue freezing. The long-term sequelae of NFCI include cold sensitivity (exaggerated cold-induced vasoconstriction), hyperhidrosis and intractable pain in the injured area. The symptomatology of NFCI suggests neuropathy and vascular endothelial damage associated with impaired nitric oxide-dependent endothelial function, tipping the balance in favour of Rho kinase activity, leading to increased vasoconstriction (Wettschureck & Offermanns, 2002). Some support for this mechanism comes from the finding that the impairment in the vasodilator response seen in individuals with cold sensitivity can be overcome by the use of exogenous sublingual glyceryl trinitrate, an endothelium-independent NO donor (Hope *et al.* 2014). A better understanding of the pathological mechanism associated with NFCI may shed light on the microvascular disorders associated with other conditions, such as diabetes and Raynaud's phenomenon.

Cold water

Despite an historical preoccupation with hypothermia as the primary cause of death on immersion in cold water, a significant amount of anecdotal, statistical and experimental evidence points to the initial minutes of immersion being the most hazardous. It takes at least

Table 2. Physiological changes when hot compared with cool (Rowell, 1986; Tipton, 2015)

Variable	Consequences
Central venous pressure is reduced Central blood volume is reduced Heart rate is higher Stroke volume is reduced/unchanged Cardiac output is reduced	Submaximal exercise performance can be affected, e.g. marathon performance declines by ~1 min for each 1°C increase in air temperature above 15°C
Arterial blood pressure is reduced Oxygen consumption is the same Arteriovenous O_2 difference is the same Splanchnic blood flow is reduced	Compromised muscle and liver blood flow results in an earlier onset of anaerobic metabolism and blood lactate accumulation
Splanchnic blood volume is reduced Renal blood flow is reduced Muscle blood flow is reduced Skin blood flow is increased Skin blood volume is increased	Muscle glycogen utilization is increased, and fatigue occurs earlier during prolonged moderate exercise in the heat

30 min for an adult to become hypothermic in cold water, yet ~55% of the annual open-water deaths in the UK occur within a few minutes and within 3 m of a safe refuge. The initial inspiratory 'gasp' and uncontrollable hyperventilation on immersion in cold water ('Cold shock'; Tipton, 1989), evoked by the dynamic response of the peripheral cold receptors with rapid skin cooling, can be the precursors to drowning. Cold shock is followed by cooling of the superficial nerves and muscle, particularly in the limbs, resulting in swim failure and, in the absence of airway protection, drowning (Tipton *et al.* 1999). Cold shock and neuromuscular incapacitation can both occur without deep body temperature falling to hypothermic levels (<35°C). When hypothermia does eventually occur, and unconsciousness is lost (Fig. 3), drowning again intervenes unless the airway is supported by a lifejacket (Fig. 4).

Drowning remains the third most common cause of death by unintentional injury worldwide (7% of all injury-related deaths), with a conservatively estimated 372,000 (1020 per day) drowning deaths worldwide in 2012 (World Health Organization, 2014). It is a 'disease of youth'; 64% of those who drown are <30 years of age and 25% are <5 years old.

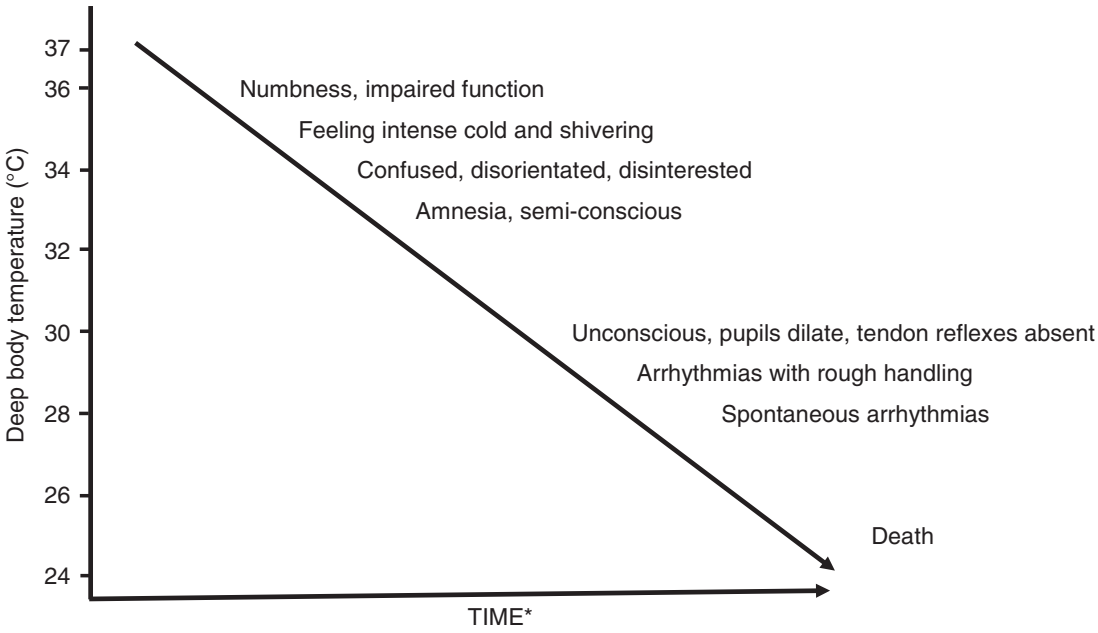

Figure 3. The physiological and pathophysiological signs and symptoms of hypothermia
*Time varies according to individual and environmental factors.

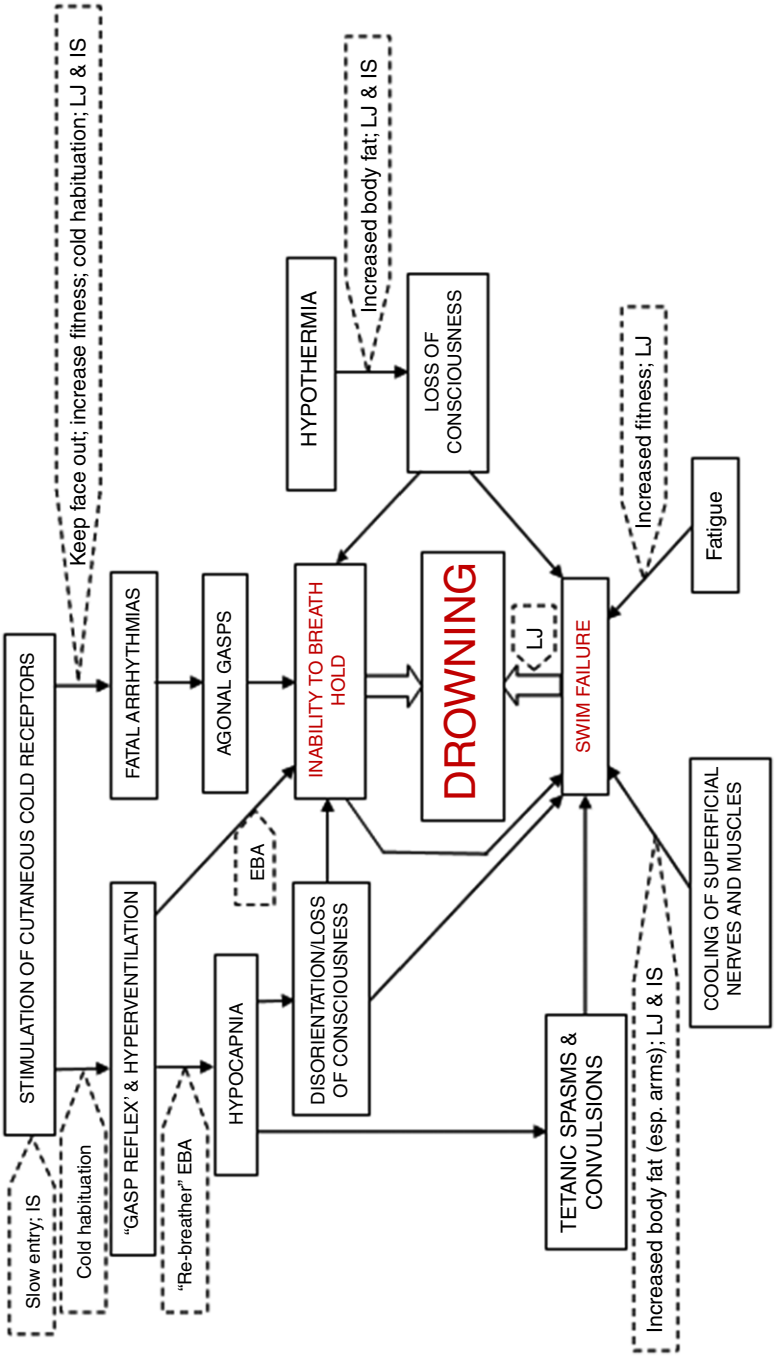

Figure 4. The 'physiological pathways to drowning' following immersion/submersion in cold water, with possible interventions for partial mitigation (dashed boxes)
Abbreviations: EBA, emergency breathing aid; IS, immersion suit; and LJ, lifejacket.

Cardiac problems on immersion have probably been underestimated owing to the fact that electrical disturbances of the heart that result in agonal gasps and aspiration of water (Fig. 4) are likely to be considered as drowning deaths. Also, young, fit and healthy volunteers are tested in the laboratory. Even then, head-out immersion results in arrhythmia and dysrhythmia in about 1–3% of immersions (Datta & Tipton, 2006). This figure increases to >80% if maximal breath holding and submersion are undertaken; coincidental activation of the cold shock response (sympathetic activation) and 'diving response' with face immersions (vagal activation) causes 'autonomic conflict' (Shattock & Tipton, 2012; Tipton, 2013). It is thought that the arrhythmias caused by autonomic conflict can, in the presence of predisposing factors, descend into fatal arrhythmias (Fig. 5); it is suggested that the same mechanism may initiate sudden cardiac death in other situations (Shattock & Tipton, 2012).

On rare occasions, individuals, particularly children, survive prolonged submersion and make a full recovery. The current 'record' is 66 min in a 2.5-year-old female (Bolte *et al.* 1988). It has been suggested that cold water entering the lungs during the 2 min it takes to drown selectively cools the heart and the brain via the carotid artery and, via this mechanism, the hypometabolic consequence of hypothermia extends the hypoxic survival time of the brain (Tipton & Golden, 2011). The critical water temperature for this mechanism to operate appears to be ~6°C, and the larger surface area-to-mass ratio of smaller individuals, which promotes faster supplementary surface cooling, helps to explain why those who have survived prolonged submersion have tended to be children or small adults. This information has been communicated

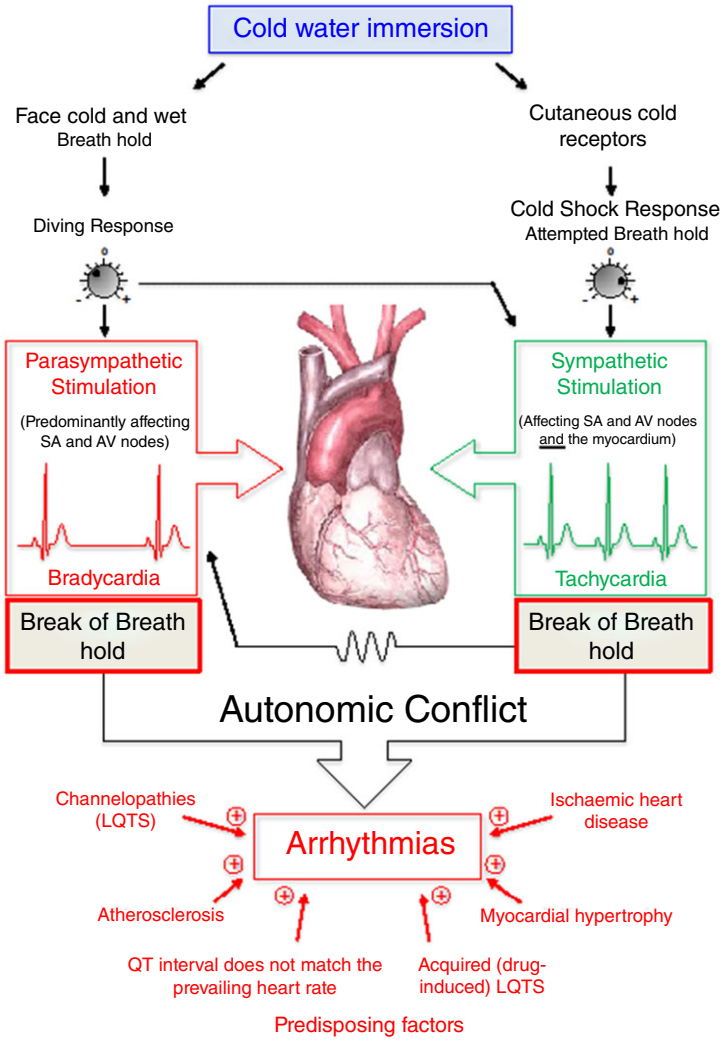

Figure 5. Autonomic conflict; a proposed mechanism for sudden cardiac death
[From Shattock & Tipton (2012), with permission.] SA = sinoatrial node; AV = atrioventricular node; LQTS = long QT syndrome.

to the search and rescue community in the form of a decision-making guide for the rescue and resuscitation of submerged individuals (Tipton & Golden, 2012). Thus, an understanding of the physiological and pathophysiological processes associated with immersion helps with the prevention and treatment of these fatalities, sheds light on sudden death in other situations and helps to inform search and rescue.

Adaptation

As mentioned, to a greater or lesser extent humans can, following repeated exposure, adapt physiologically to the environmental stressors described in the foregoing sections. These adaptations may take the form of inherited (genotypic) or acquired (phenotypic) variations (Tipton *et al.* 2008). Adaptation theory (Fig. 6) addresses most of the applied questions surrounding adaptation.

The capacity of any stress to induce an adaptation is a function of its application frequency, duration, intensity and variability. The time course of adaptation has the following six general characteristics (Adolph, 1964).

i. The stimulus (forcing function) has to be greater than an 'adaptation threshold' to induce adaptation.
ii. Variable phase delay ('adaptation latency') exists before adaptation.
iii. For each effector organ, there is a physiological and possibly a genetically determined maximum.
iv. The speed of adaptation varies between stressors and individuals.
v. Optimal adaptation occurs when the cumulative adaptation impulse is maximized, whilst ensuring that the physiological strain is tolerable.
vi. Cessation of the adaptation stimulus results in variable decay.

The most common applied questions concerning adaptation are: "How long does it take?" and "How long does it last?" The traditional answers with regard to heat and altitude are 10–14 days, with major benefits retained for about a week, but 75% lost within 3 weeks (Armstrong & Maresh, 1991; Tipton *et al.* 2008). More recent evidence suggests that short-term heat acclimatization (plasma volume expansion, reduced exercise heart rate, increased forearm perfusion, lower deep body temperature and improved rowing performance in the heat) can be achieved in 5 days (Garrett *et al.* 2014); the value of concurrent permissive dehydration in this response is a matter for debate (Neal *et al.* 2015). There is also recent evidence that heat acclimatization can be used as an ergogenic aid for performance in cool conditions (Lorenzo *et al.* 2010; Corbett *et al.* 2014).

Some of the adaptations to altitude, heat and cold (water and air) are listed in Table 3. For the reasons suggested

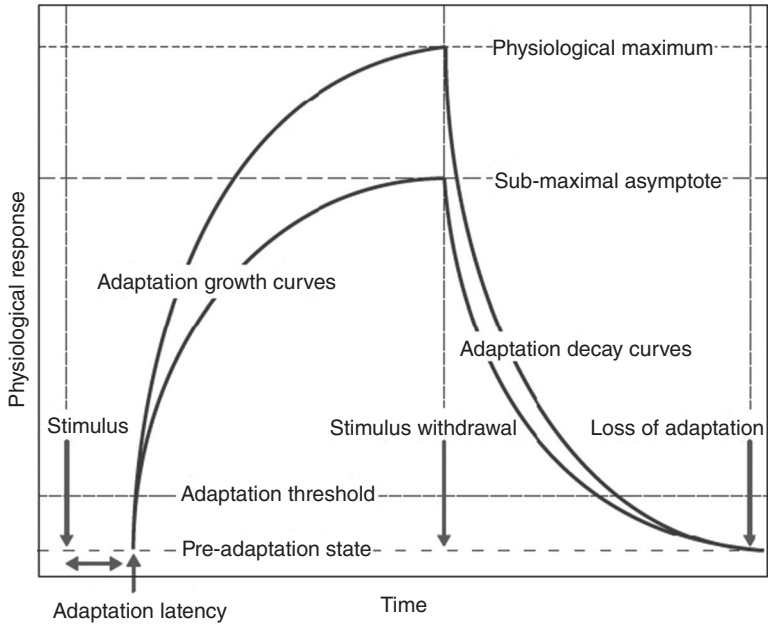

Figure 6. General adaptation theory, showing adaptation threshold, physiological response and decay with time
[From Taylor & Cotter (2006), with permission.]

Table 3. Changes in, and consequences of, the responses to different environmental stresses with adaptation (Armstrong & Maresh, 1991; Milledge, 1998; Tipton *et al.* 2008)

Environmental stressor	Alteration	Consequence
Altitude >2300 m		
Immediate	Hyperventilation; body fluid alkalosis; Increased submaximal HR and $\dot{Q}$; SV and maximal $\dot{Q}$ same or slight reduction	Increased supply of oxygen to tissues; improved efficiency of oxygen utilization; improved work capacity
Longer term	Hyperventilation; right-to-left shift in oxyhaemoglobin dissociation curve; excretion of base (HCO_3^-) by kidneys; decreased alkaline reserve; increased sympathetic neurohumoral activity; submaximal HR remains increased; submaximal and maximal $\dot{Q}$ decrease; SV and PV decrease; mass and lean body mass decrease. Increased: haematocrit, haemoglobin concentration, red blood cell count and 2,3-diphosphoglycerate concentration, skeletal muscle capillarization, mitochondrial density and aerobic enzyme concentrations	Increased supply of oxygen to tissues; improved efficiency of oxygen utilization; improved work capacity
Heat	Increased secretion and sensitivity to aldosterone increased → sodium and chloride reabsorption in sweat ducts and renal tubules → sweat sodium reduced → osmotic expansion of plasma volume. Sweating: earlier onset, greater rate and gland recruitment	Improved salt balance; greater cardiovascular stability, less cardiovascular strain; better distribution of cardiac output; improved cutaneous blood flow; lower resting and exercising deep body temperature; lower skin temperature for a given level of exercise; improved work capacity; decreased perceived exertion; carbohydrate sparing
Cold: peripheral	Increased skin temperature; cold-induced vasodilatation; thermal comfort. Decreased pain; cold pressor response; sympathetic activation	Warmer extremities → decreased chance of cold injury; greater thermal comfort in heat
Cold: whole body	Water: cold shock response reduced (decreased ventilatory, cardiac, blood pressure and catecholamine response to cold immersion). Shivering: delayed onset (same sensitivity) Air: delayed onset of shivering; increased sympathetic activation, plasma noradrenaline, catecholamine sensitivity; decreased skin temperature and blood pressure response to cold; greater amount/activation of brown adipose tissue (non-shivering thermogenesis)	Decreased risk of drowning on initial immersion. Either: a. faster reduction of deep body temperature on exposure to cold (hypothermic adaptation); b. decreased reduction of deep body temperature on exposure to cold (insulative adaptation); or c. increased metabolism in cold (metabolic adaptation). Increased thermal comfort in cold; increased cold-induced vasodilatation

Abbreviations: HR, heart rate; PV, plasma volume; $\dot{Q}$, cardiac output; and SV, stroke volume.

in the Introduction, the picture for adaptation to cold is somewhat more confused than that for heat or altitude.

There is increasing evidence of a genetic contribution to the adaptation of those living at high altitude in terms of variations in the function of factors such as hypoxia-inducible factor 1α (Suzuki *et al.* 2003) and the endothelial nitric oxide synthase gene (Droma *et al.* 2006; Simonson *et al.* 2010). Climate also appears to have been an important selective factor acting on genes responsible for common metabolic disorders (Hancock *et al.* 2008).

The methodologies used to induce adaptation have been varied and, thereby, a source of some confusion. In general, two techniques prevail, namely repeated exposure to a constant stimulus or repeated achievement of a constant physiological strain (e.g. deep body temperature, heart rate, level of exertion). The second approach maintains the stimulus to adapt and provides more effective physiological adaptation (Taylor, 2014) but, at least in terms of the heat, as long as the method employed provides a threshold stimulus, it does not appear to make a difference to the improvement in thermal tolerance as represented by leucocyte *hsp72* mRNA (Gibson *et al.* 2015). The relationship between physiological adaptation and thermal tolerance requires further investigation.

Multistressor studies

A weakness in the field is the relative paucity of studies investigating combined environmental stresses, despite

their prevalence in nature. Excluding heat and humidity, which are usually regarded as a single entity, between 1948 and 2012 there were only 43 published human studies involving combined stresses (Tipton, 2012). Whilst recent work has begun to investigate the combinations of bed rest and hypoxia or cold and hypoxia (e.g. McDonnell *et al.* 2014; Keramidas *et al.* 2014), it is an area that is worthy of more attention, as is the associated field of 'cross-adaptation'. Lunt *et al.* (2010) reported that cold habituation reduced the catecholamine response and the number and severity of symptoms on exposure to hypoxia. These data suggest a generic autonomic cross-adaptive effect between cold habituation and exposure to acute hypoxia in humans.

Conclusion

The investigation of the impact of extreme environments on human physiology has historically been justified in terms of the pathological consequences of such exposures. As areas such as the Arctic and other hazardous and remote areas are considered for occupational and leisure use, this justification remains extant. In addition, and increasingly, the responses of fit and healthy individuals to extreme environmental stress are being used to gain insights into other pathological conditions. This appears to be a helpful approach, but more time is required to evaluate its overall utility. In the future, a better understanding of the metabolomic and biomolecular bases of responses and their variation in extreme environments, and the influence of multiple concurrent environmental stressors and their cross-adaptation, should help to demonstrate the benefit of extreme environmental research for other conditions and processes.

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Additional information

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