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Homeostasis in the laboratory, the clinic and our academic institutions!

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There is nothing so constant as change

I am fascinated by homeostasis, a term coined by Walter B. Cannon nearly 100 years ago (Cannon, 1926), popularised in his book *The Wisdom of the Body* (Cannon, 1932). Building on the early teachings of Claude Bernard, Cannon drew focus to the body's agencies, the control systems that strive for balance and stability in the face of stress, generally emphasized as maintenance of the constancy of the internal environment. Subsequent considerations of homeostasis during the cybernetics movement that followed, provided a narrower perspective concerned with the regulation of set-points by hierarchical control achieving 'negative feedback' regulation of physiological parameters. This theoretical framework applies today as a centrepiece in the appreciation of integrative control systems, with the control of breathing considered an exemplar in negative feedback regulation of arterial partial pressure of CO_2 and pH. Revision followed over about a 50-year period serving to supplement or at times supplant homeostasis by way of expanding concepts to better capture the complex independent, yet interdependent control systems that subserve control of a range of *variable* set-points in the face of a multitude of complex stressors faced by organisms (see Bechtel & Bich, 2024). Borne of this fruitful era is recognition of a reliance in biological organisms of heterarchical control and a value set of physiological processes that necessarily shift in priority in the face of stressors to ensure resilience and survival. Kelvin Davies wrestled these concepts back towards early musings presenting them as 'adaptive homeostasis' (Davies, 2016). More recent scholars, Bechtel and Bich (2024) elegantly argued, in a sympathetic view of Cannon's thesis, recognising *stability* in the place of *constancy*, that homeostasis provides a framework for the consideration of how organisms survive and even thrive despite perpetual challenges to their internal balance. Stability emerges because of constant change, the dynamic flux of physiological and biochemical processes that underpin the coping

strategies of the organism. In essence, homeostasis is best considered the maintenance of the organism (Bechtel & Bich, 2024); sometimes against all odds! Below I describe three examples that illustrate homeostasis in full throttle. These and many others that readers can readily draw from provide a framework for how one might consider stability in other systems of organisation, including academic institutions and by extension society per se.

Preservation in a place of profound stress

The first example stems from my relatively newfound interest in cerebrovascular physiology and control of cerebral blood flow. The three pillars of cerebrovascular control are autoregulation, cerebral vessel reactivity and neurovascular coupling. The example, described below, is demonstration of remarkable preservation of neurovascular coupling in the context of profound hypoxia.

First, however, it is worth acknowledging that homeostatic control of cerebral blood flow can fail. Impaired cerebral perfusion relating to orthostatic hypotension leading to syncope is an excellent example. Conversely, at high altitude, autoregulatory control of cerebral blood flow is overwhelmed or dispensed with, increasing brain blood flow, with a consequential risk of developing cerebral oedema. These divergent examples of inadequate and ‘excess’ cerebral blood flow share the common denominator of the brain’s need and greed for oxygen. The profound behavioural change in fainting, which depending on circumstances could be life-threatening, is borne of inadequate cerebral perfusion that is typically ‘corrected’ by the act of fainting and restoration of brain blood flow. In the case of familial dysautonomia, homeostatic control is perturbed from birth with labile blood pressure due to absent baroreflex control of blood pressure and impaired sympathetic control (Macefield et al., 2014). The hyperperfused brain at high altitude delivers precious oxygen to the brain limiting the extent of brain hypoxia, an example of a shift in homeostatic hierarchies, with consequential risk as a trade-off. The phenomenon is adjusted over the course of acclimatisation to high altitude (Hoiland et al., 2018). Indeed, improved dynamic regulatory capacity and cerebrovascular reactivity emerges as an adaptation in highlanders (Stacey et al., 2023). These mechanisms ultimately subserve tight control of brain oxygen delivery. By extension, many will be familiar with the selfish brain hypothesis (Cushing’s

mechanism) driving neurogenic hypertension (Hart, 2016). So, homeostasis can clearly fail over different trajectories.

However, there are also scenarios where homeostatic control of cerebrovascular function is remarkably resilient. Neurovascular coupling is the tight matching of blood flow to regions of the brain with enhanced neuronal activity. Precision in the regional delivery of brain blood flow to match metabolic demand is achieved through complex feedforward and feedback mechanisms at the level of the neurovascular unit comprising neurons, astrocytes, glia, pericytes and endothelial cells of the vasculature. Cerebrovascular control including neurovascular coupling is perturbed in type 2 diabetes, neurocognitive disorders, stroke and brain injury. We are interested in the effect of high-altitude exposure on neurovascular coupling particularly given that facets of cerebrovascular control are known to be altered at high altitude, given the nature of the profound stress encountered in the high mountains. Our laboratory in the sky was the austere but beautifully dramatic landscape of the Himalaya. We assessed neurovascular coupling using transcranial Doppler ultrasound to measure the velocity of blood in the posterior cerebral artery before and in response to repeated intermittent visual stimulation. During incremental ascent to ~4,000m we showed that neurovascular coupling was remarkably intact despite exposure to severe hypoxia (Leacy et al., 2018), a finding that has been reported by others (Caldwell et al., 2017; Stacey et al., 2023). These studies demonstrate a central tenet of homeostatic regulation, that is, preservation of a physiological mechanism in the face of profound stress. Indeed, high altitude presents a confluence of stressors changing temporally in dynamic fashion. An understanding of the mechanisms serving to maintain neurovascular coupling, as well as factors that contribute to the unravelling of same, will provide better insight into the factors that drive maladaptive processes in ageing and disease. It remains to be determined if our observations reflect a prioritisation of neurovascular coupling per se in the brain at high altitude, or prioritisation of neurovascular coupling in distinct regions of the brain.

Breathing with Duchenne muscular dystrophy: A new perspective on the elaboration of disease

A second example comes from our work exploring breathing in neuromuscular disease, with studies of respiratory system performance across the natural history of Duchenne muscular dystrophy in the *mdx* mouse model of the disease. We determined that there is a remarkable capacity to preserve peak inspiratory performance despite profound dysfunction in the diaphragm muscle, the primary muscle of inspiration (Burns et al., 2019). Compensation is evident early in dystrophic disease owing to the concerted activity of accessory inspiratory and abdominal muscles, which collectively carry the burden of diaphragm dysfunction (O'Halloran et al., 2023). Our work established that the subsequent elaboration of respiratory compromise in *mdx* mice arises from a progressive loss of compensation. Viewed through the lens of homeostasis, our observations are a striking reminder that physiological systems are remarkably resilient, often capable of maintaining function despite profound dysfunction in the primary control mechanisms. Physiology finds a way, until it cannot! Erosion of secondary compensatory mechanisms are responsible for the elaboration of disease and the tragic spiral of disability that manifests. Our fresh perspective on the progression of Duchenne muscular dystrophy is important in the consideration of established and emerging therapies to treat the disease. It reminds us that an understanding of physiology is crucial to the understanding of disability and disease.

A critical conundrum: A curious case of physiological adaptation as a cause of dysfunction

A third example comes from the domain of critical care. Mechanical ventilation is lifesaving, but it comes with a sting in the tail. Unloading of the respiratory musculature, wreaks havoc by instigating diaphragm muscle atrophy and weakness, which depending on the duration of respiratory support, can severely curtail the capacity for independent breathing following withdrawal of mechanical ventilation (Powers, 2024). Weaning failure delays discharge from intensive care units and contributes to morbidity and mortality. In a seminal study by Lindqvist et al. (2018), the authors demonstrated that positive end-expiratory pressure, commonly employed during mechanical ventilation to prevent alveolar collapse, flattens the dome-shaped diaphragm, with resultant shortening of diaphragm muscle fibres. This results in

crowding at the subcellular level of the sarcomere, the functional unit of contraction. Malalignment of the contractile proteins, actin and myosin, owing to too many sarcomeric units in series in the shortened fibres, is sensed by the sarcomeric protein titan triggering proteolytic degradation and a restructuring of the sarcomeres to provide for optimal alignment of the contractile proteins. In essence, sarcomeres are removed to prevent over-crowding. The issue is largely moot for the patient who is supported by the ventilator, rather than the diaphragm for breathing. However, the physiological adaptation, termed longitudinal atrophy, is a homeostatic response to stress, seeking to optimise diaphragm performance. Interestingly, this adaptation proves problematic when positive end expiratory pressure is acutely withdrawn in anticipation of termination of mechanical ventilation. Removal of positive pressure lengthens diaphragm fibres (relieves the shortening), which because they have remodelled, are now stretched such that in effect there are too few sarcomeres per unit length of muscle fibre. This curious example illustrates how physiological adjustments in response to a stressor can, somewhat paradoxically, result in vulnerability of the system to a sudden restoration of 'normal' conditions. The study is a striking reminder for the physician of the complexity of physiology in disability and disease, requiring careful consideration in the context of interventional strategies, both their introduction and removal.

Institutional homeostasis: Lessons from physiology for university strategists

Academic institutions in the UK and Ireland face a perpetual funding shortfall. The chronic crisis has led to various re-structuring strategies and concerns among academics of an increasingly corporate flavour to proceedings. Although change is at the core of our being, it is nevertheless nearly always perceived as unsettling. In the epilogue to *Wisdom of the Body*, Cannon wonders if lessons from biological homeostasis might be relevant to other forms of organisation considering 'analogies between the body physiologic and the body politic' (Cannon, 1932). Indeed, it is evident that there are many lessons for university decision makers that could be readily learned.

For starters, it is a major mistake to assume or conclude that because academic units have shown remarkable resilience to recurrent stressors that such stoicism is

indefatigable. Like physiological systems, notwithstanding some redundancy, in the face of recurrent challenges things may appear well, until they do not. Once the levee is breached, failure is swift and it can be catastrophic.

Leaders fond of hierarchical control ought to recognise that a central tenet of such systems is feedback. Control is notoriously unstable in the absence of real-time, real-world messaging of the efficacy of top-down guidance. Adjusting to the error signal is how the goal is achieved. Feedback may necessarily curtail enthusiasm of efferent command. Therefore, we might best consider constructive criticism of directives as a form of ‘negative’ feedback. It should be sought after by decision makers and it should be listened to and acted upon!

Academic institutions invariably operate as heterarchical entities in one way or another. This offers consolation to most that the institution will inevitably survive, as leaders come and go. At academic unit level, a more dire reality has manifest in several UK institutions with the loss, not just of identity or expertise, but of entire disciplines including, rather bizarrely, high performing units with long-standing tradition and international recognition for excellence. Whilst some solace may be drawn from recognition that order and balance is likely to be achieved in the fulness of time, this provides little reprieve for those affected in the here and now. At the heart of homeostasis is a cooperative enterprise of inter-related control systems that strive to survive and thrive. The corporate brain will soon be poisoned if it strategically dispels with the need for functioning kidneys, and so on. And even if some bludgeoning or selective lesioning is tolerated, watch out! And that might even mean prepare for disappointment when the good times return.

Lest this latter polemic serve to boil our blood, we should consider where best to focus our efforts. Predicaments peculiar to our respective institutions, although mirrored, are best dealt with parochially. However, a common global problem is the gross underfunding of higher education institutions. A century ago, Cannon hinted that physiologists might be well placed to inform the narrative. I strongly agree and encourage a collective call to action!

Conflicts of Interest

None.

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