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UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

The Journal of Physiology

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

Ken D O'Halloran
DOI: 10.1113/JP288466

Corresponding author(s): Ken O'Halloran (k.ohalloran@ucc.ie)

The following individual(s) involved in review of this submission have agreed to reveal their identity: Philip N Ainslie (Referee #2)

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Senior Editor: Kim Barrett

Reviewing Editor: Vaughan Macefield

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(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. Depending on transfer agreements, referee reports obtained elsewhere may or may not be included in this compilation. Referee reports are anonymous unless the Referee chooses to sign their reports.)

Dear Ken,

Re: JP-OP-2025-288466 "Homeostasis in the laboratory, the clinic, and our academic institutions!" by Ken D O'Halloran

Thank you for submitting your manuscript to The Journal of Physiology. It has been assessed by a Reviewing Editor and by 2 expert referees and we are pleased to tell you that it is acceptable for publication following satisfactory revision.

The referee reports are copied at the end of this email.

Please address all the points raised and incorporate all requested revisions or explain in your Response to Referees why a change has not been made. We hope you will find the comments helpful and that you will be able to return your revised manuscript within 4 weeks. If you require longer than this, please contact journal staff: jp@physoc.org.

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We look forward to receiving your revised submission.

If you have any queries, please reply to this email and we will be pleased to advise.

Best wishes,

Kim Barrett
Senior Editor
The Journal of Physiology

EDITOR COMMENTS

Reviewing Editor:

Thank you for submitting your Opinion piece to The Journal of Physiology. While the writing is engaging and the content topical, I believe you should emphasise failings of homeostasis: there are countless examples in physiology, not just those you cite from your own work, that would be better served for illustration (fainting is one common example).

And while we all share the concerns about funding short-falls in academia - which is certainly not limited to the UK and Northern Ireland - I think it is a stretch to add this to an opinion about homeostasis, though I certainly see your point. You will see that the two independent reviewers have their own ideas as to how to improve your article, and I'd like to give you the opportunity to revise your submission to make it punchier and even more engaging. One option would be just to talk about funding cuts in physiology, emphasising how, like failure of homeostasis, this leads to deleterious outcomes.

REFEREE COMMENTS

Referee #1:

This appears to be an invited commentary, summarizing an invited lecture given at the UCC College of Medicine & Health Annual Research Day.

The topic is homeostasis, and how homeostasis is often maintained through compensatory mechanisms which can/will eventually fail - with potentially catastrophic results. The article is easy to read, and the section on academia is an interesting parallel.

Overall I have no issues and can recommend no major edits.

Referee #2:

The goal, I think, of this unsolicited opinion piece is to use three disparate examples to illustrate homeostasis to provide a framework for how one might consider stability in other systems of organization, including academic institutions and by extension society per se. Unfortunately, on many levels, this piece falls short of a meaningful contribution.

1. The author does not provide anything new about homeostasis apart from reiterating some of the key messages of the elegant review by Bechtel and Bich (2024) in this Journal. I am unsure what is new in this section?

2. the three examples to illustrate homeostasis are disparate and largely reads as a self-fulfilling quest by the author to cite their own work. It also also disingenuous as, for example the first example of a study of neurovascular coupling at high altitude ((Leacy et al., 2018) was simply a confirmation of a earlier study on this topic (PMID: 28965918). The links wth pathology, cerebrovascular mechanisms, aging and high altitude in this section are simply over-reaching. The next self-citing example is a pre-clinical study in dystrophic mdx mice. The link to the clinic (per title) and hemostasis is again lacking. The final example, in the domain of critical care, does not even mention hemostasis and the tentative links of the opinion piece are lost. The goal of the final few paragraphs "Lessons from physiology for university strategists" is difficult to reconcile, especially in the context of the other the disparate examples.

END OF COMMENTS

EDITOR COMMENTS

Reviewing Editor:

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RESPONSE:

Thank you for the positive appraisal of the article. Yes, of course there are many examples of failure in homeostatic control. Disruptions to cerebral perfusion relating to orthostatic hypotension leading to syncope is an excellent example. I have incorporated this into the revised text in the context of dysautonomia. This change encouraged me to expanded briefly on a point alluded to previously but now developed, which is that cerebral blood flow increases at high altitude with attendant risk of oedema but the advantage of maintained cerebral oxygenation. These two divergent examples of inadequate and 'excess' cerebral blood flow reveal the hierarchical pressure driven by the brain's need and greed for oxygen. I extend the point to draw focus to the 'selfish brain hypothesis' that contributes to another breakdown in homeostasis evident in hypertension. I had already flagged the breakdown in neurovascular coupling in disease. These points make it clear that very often homeostasis is overwhelmed. Thank you for the suggestion.

And while we all share the concerns about funding short-falls in academia - which is certainly not limited to the UK and Northern Ireland - I think it is a stretch to add this to an opinion about homeostasis, though I certainly see your point.

RESPONSE:

And the Republic of Ireland!

It may be a stretch, but that's a matter of 'Opinion', and that is the essence of the article. If you can see my point, then the message has been conveyed. But, of course, you may not agree with it. As I understand it, given the scope of Opinion articles, this is to be expected among the readership, and we might expect opinions to be divided.

You will see that the two independent reviewers have their own ideas as to how to improve your article, and I'd like to give you the opportunity to revise your submission to make it punchier and even more engaging.

RESPONSE:

Thank you. I have addressed the referees' comments below.

One option would be just to talk about funding cuts in physiology, emphasising how, like failure of homeostasis, this leads to deleterious outcomes.

RESPONSE:

The message is broader than funding cuts to physiology. It speaks to failings in organisational behaviour that mirror biological processes (or so the opinion goes), such that there are lessons from one for the other. The argument is more nuanced than the generally well recognised truism that a lack of resourcing typically leads to poor (restricted) outcome just as homeostasis can fail leading to deleterious physiological function. So, I would prefer to keep the narrative of the original article but of course can revise the text if you insist.

REFEREE COMMENTS

Referee #1:

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RESPONSE:

Thank you for your positive appraisal of the article.

Referee #2:

The goal, I think, of this unsolicited opinion piece is to use three disparate examples to illustrate homeostasis to provide a framework for how one might consider stability in other systems of organization, including academic institutions and by extension society per se.

RESPONSE:

I disagree that the examples are disparate. They can be readily compared and have a common thread—homeostasis. They each provide insight that is drawn from and presented in the final section of the article contextualised to organisational behaviour (institutional homeostasis), which I accept and indeed anticipated may not be to everyone's liking.

Yes, the goal was to illustrate three examples of homeostasis "*to provide a framework for how one might consider stability in other systems of organisation, including academic institutions and by extension society per se*", which is text from lines 50-52 of the original article.

Unfortunately, on many levels, this piece falls short of a meaningful contribution.

RESPONSE:

Perhaps in the context of my Opinion this statement would be better put (or at the very least, more graciously put) as: "In my opinion, unfortunately…..". As written, the above statement is declarative and claims to be true! It seems we differ in our opinions. If published, the readers will decide its value to them. As written, what a profound statement to make! But, how readily it is tempered if you acknowledge that you are simply sharing your perspective as it applies to you. I have no beef with you holding your opinion, but I do object to the declaration of it as a fact!

1. The author does not provide anything new about homeostasis apart from reiterating some of the key messages of the elegant review by Bechtel and Bich (2024) in this Journal. I am unsure what is new in this section?

RESPONSE:

I don't claim to offer anything new in this paragraph. I provide the reader with a succinct summary and interpretation (neither of which evidently troubled you) to provide an introduction and framework for the examples that follow, acknowledging Bechtel and Bich (2024). My reading of Bechtel and Bich (2024), whom I describe as 'scholars who elegantly argued' (line 42 of the original article), is that for all the convoluted dialogue in the 100 years since Cannon's argument, the term homeostasis remains an entirely appropriate and adequate term today. The Opinion article is not a review of homeostasis, nor is it a thesis to challenge concepts of homeostasis, nor a new perspective on a defence of homeostasis from those seeking to challenge it.

2. the three examples to illustrate homeostasis are disparate and largely reads as a self-fulfilling quest by the author to cite their own work.

RESPONSE:

This quip doesn't deserve a fulsome response. But, hey, everyone's got an opinion!

I cited one article from a series of papers we have published arising from several high-altitude expeditions. The senior author of that article is Professor Trevor Day, Mount Royal University, Canada. I cited 2 of our J Physiol articles from a subset of 6 J Physiol articles on mdx/DMD, which are part of a wider portfolio of our relatively recent work on this topic. At this stage of the game, I have many other citable articles to draw from so the record will show that if I was on a quest to cite my own work, I succeeded in showing remarkable restraint!

Alas, you appear to me to have completely missed the point of the article if you think the exercise was motivated by a desire to cite a few of my own papers. Really!

I am happy to let readers decide for themselves.

It also also disingenuous (sic) as, for example the first example of a study of neurovascular coupling at high altitude ((Leacy et al., 2018) was simply a confirmation of a earlier study on this topic (PMID: 28965918).

RESPONSE:

Of the three examples of homeostasis described in the article, the first example describes stability in neurovascular coupling during incremental ascent to above 4,000m (Leacy et al., 2018). It does not claim to be the first demonstration of the phenomenon. A similar outcome can be taken from Caldwell et al., 2017 measured on days 3 and 7 of residency at 3,800m (cited in Leacy et al., 2018). Since presumably there is less concern with studies confirming the findings of other studies, given the genuine reproducibility crisis we face in biomedical science, I can only surmise that you are suggesting that Caldwell et al., (2017) could and should be appropriately cited and my description of the first example of homeostasis need not be restricted to Leacy et al. (2018) even though the intent to the reader should be obvious, i.e., that the example provides for consideration of a concept, described in this section as preservation (of function) in a place of profound stress (the title to the section). I fail to see how this is disingenuous. I fear at this juncture you may have utterly missed the whole point of the article. Nevertheless, Caldwell et al., (2017) is now cited in the revised article and I am grateful to you for this helpful (indirect) suggestion.

The links wth pathology, cerebrovascular mechanisms, aging and high altitude in this section are simply over-reaching.

RESPONSE:

The explicit criticism or cause for concern here is unclear to me. Neurovascular coupling is perturbed in several disease states. But in the severe hypoxia of high altitude, it is preserved. Understanding how it is preserved and factors that lead to it unravelling in disease would be useful to determine. What part of that conclusion is overreaching?

The next self-citing example is a pre-clinical study in dystrophic mdx mice.

RESPONSE:

The referee appears to have taken umbrage with the fact that I cited my own work. I acknowledge in the article that there are (of course) many examples of homeostasis that one could draw from (line 50 of the original article), but I reasonably (in my view) rely on examples, borne of my own work, for 2 of the 3 shared examples in the piece. This hardly warrants mentioning let alone criticism from the referee, unless the referee's statement is to be read entirely blandly as a statement of fact. The examples I draw from are examples I have spent a lot of time thinking about. They have shaped the narrative central to the Opinion article. They are not, and I suspect would not be taken by readers, as an attempt to suggest they are exemplars in the field. O'Halloran et al., 2023 published in J Physiol is a study of respiratory control across the natural history of disease in the *mdx* mouse model of DMD, a comprehensive study involving 384 mice in a programme of work that extended for 3-4 years. I performed most of the experiments myself. I posit that I owe it the occasional mention! It provides an example that I draw from later in the article.

Of course, the central argument of the Opinion piece, that draws from homeostasis per se, could be made without reference to these studies and instead drawn from other examples. In my view, this is a strength of the article as readers can draw from their preferred examples of homeostasis to extrapolate to my suggestion that it is mirrored in organisational behaviour.

The acknowledgement section of the original article reveals that the article arose following my delivery of a lecture on the topic, where understandably (and expectedly) I gave examples from my own work. I'm a physiologist fascinated by homeostasis. I make no apologies for that or for sharing evidence from my own work that has shaped my perspective.

The link to the clinic (per title) and hemostasis (sic) is again lacking.

RESPONSE:

The third example in the article drawn from the setting of critical care *is* the link to 'the clinic'. This is the work of Coen Ottenheijm and colleagues.

The final example, in the domain of critical care, does not even mention hemostasis (sic) and the tentative links of the opinion piece are lost.

RESPONSE:

Line 121-122 of the original article stated: “However, the physiological adaptation, termed longitudinal atrophy, is a homeostatic response to stress, seeking to optimise diaphragm performance”.

I disagree with your opinion that the argument is lost. Rather, in my view, and as argued in the article, this is a classic example of physiological remodelling in response to a prevailing set of circumstances (stressor) that establishes vulnerability in the system, which curiously is revealed upon acute return to the original control (normal) environment. It provides a very important message of the need to recognise that physiological remodelling provides for functional trade-offs. And in this case, it is a matter of life or death! This example establishes a principle that I argue applies to organisational behaviour shared in the final section of the Opinion piece. (Line 166-167 of the original article: “And that might even mean prepare for disappointment when the good times return”).

Again, you appear to have a different opinion (although an argument that contradicts mine has not been presented), but it does not mean that your opinion (or mine) is definitively true. Your statements are declarative. You offer no explanation for how you have arrived at them, and you do not provide suggestions for how I might revise my text.

The goal of the final few paragraphs "Lessons from physiology for university strategists" is difficult to reconcile, especially in the context of the other the disparate examples.

RESPONSE:

From my perspective, I have made the case coherently in the article. The message also appears to have landed with the editor and other referee. So again, it is evident that you disagree with my opinion, such that it is understandably difficult for *you* to reconcile. The Opinion is that there are lessons from biological organisation for institutional organisation. Cannon thought as much nearly 100 years ago, and I galvanise my thoughts on the matter in the final section of the article.

END OF COMMENTS

Dear Ken,

Re: JP-OP-2025-288466R1 "Homeostasis in the laboratory, the clinic, and our academic institutions!" by Ken D O'Halloran

We are pleased to tell you that your paper has been accepted for publication in The Journal of Physiology.

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Best wishes,

Kim Barrett
Senior Editor
The Journal of Physiology

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EDITOR COMMENTS

Reviewing Editor:

Thank you for submitting your revised manuscript to The Journal of Physiology. As you can see, Reviewer 1 is satisfied with your responses, while Reviewer 2 feels your presentation of physiology is basic. I disagree with the latter appraisal and endorse acceptance as is.

REFEREE COMMENTS

Referee #1:

I apologize I misunderstood in my earlier review, that this opinion piece was not invited by the journal in response to an invited lecture. Because of this, I agree with Reviewer 2 that the first sections of the piece primarily cite seemingly unrelated projects completed by the author. The author does attempt to correct this with new edits related to the first project introduced, which is appreciated.

I find the discussion of homeostasis in academic institutions to be the most interesting and provocative component of the article. This idea is clearly reflected in the title.

As it is an opinion piece, I have no requests for edits.

Referee #2:

Thank you for your sharp response and revisions. The author is correct about personal opinion and this is a fair point. I still feel, however, that these opinion pieces and editorials are best done by experts in their related field. I hope you are correct in that this will be of interest to others.