The legacy of A. V. Hill's Nobel Prize winning work on muscle energetics

Chris Barclay and Nancy A. Curtin
DOI: 10.1113/JP281556

Corresponding author(s): Chris Barclay (c.barclay@uq.edu.au)

The following individual(s) involved in review of this submission have agreed to reveal their identity: David C Poole (Referee #1); L. Bruce Gladden (Referee #2)

Review Timeline:

| Event                        | Date       |
|------------------------------|------------|
| Submission Date              | 03-Nov-2021|
| Editorial Decision           | 22-Nov-2021|
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Senior Editor: Ian Forsythe

Reviewing Editor: Bruno Grassi

Transaction Report:

(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 Dr. Barclay,

Re: JP-TR-2021-281556 "The legacy of A. V. Hill's Nobel prize winning work on muscle energetics" by C.J. Barclay and Nancy A. Curtin

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

The reports are copied at the end of this email. Please address all of the points and incorporate all requested revisions, or explain in your Response to Referees why a change has not been made.

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I hope you will find the comments helpful and have no difficulty in revising your manuscript within 4 weeks.

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Yours sincerely,

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EDITOR COMMENTS

Reviewing Editor:
Both reviewers, very expert in the field, express their enthusiasm for the manuscript, which nicely summarizes and puts into perspective AV Hill's legacy in the field of exercise physiology. I concur with their opinion and express my congratulations to the authors for an excellent submission. Both reviewers raised only relatively minor comments/suggestions for changes, which the authors should take into consideration.

REFEREE COMMENTS

Referee #1:

GENERAL COMMENTS

This paper is well conceived, crisply written and delivers a wealth of personal and scientific insights into Hill's work and canonical position in the field of muscle energetics. Even though the reader may have read many of Hill's papers and books the distillation of ideas and appraisal of their present-day consequences is extremely valuable and testament to the authors' deep knowledge of this topic and personal involvement with Hill's legacy. Criticisms are minor and should be taken as suggestions for improving clarity/correctness of delivery, broader interpretation and potential impact as well as accessibility to the non-specialist in this fascinating arena.

SPECIFIC COMMENTS

Page/para/line(s)

2/1/6-8 Beautifully posited.
3/4/5 "other" books. Please provide a title or two here.
5/1/8 Perhaps state "Manchester University" or ?
5/1/9 "from trams and experiments were..."
7/Figure 4 Please increase label clarity on axis. It looks rather fuzzy.
8/1/5 Delete "very." Unnecessary hyperbole.
8/2/9 "a number of times" Please be specific. A colleague and contemporary of Hill's used to admonish folks who used such with the retort "0 is a number!" - and he was right.
8/Figure 5 legend. Perhaps define "Pt" as platinum.
9/1/3 Briefly describe the Peltier effect here?
11/Figure 6 and equation 2 Please consider unifying terms, if possible, between figure & equation.
11/3/end Does it make sense to present this equation here rather than on page 20?
12/end When I think of the formative experiments that demonstrated unequivocally the fate of lactate in vivo George Brooks' work with radiolabeled tracers stands out in humans and animals. Is it worth a brief mention here?

Brooks GA, Gaesser GA. End points of lactate and glucose metabolism after exhausting exercise. J Appl Physiol Respir Environ Exerc Physiol. 1980 Dec;49(6):1057-69. doi: 10.1152/jappl.1980.49.6.1057. PMID: 7440296.

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13/3 "Legacy paragraph. Outstanding!

15/1/2 "no changes in [ATP]." Occasionally I review papers that don't recognize this. A crisp statement as to its acceptance today might be valuable here.

16/3 lines from bottom Perhaps identify them as Earl and Jack, as appropriate here.

17/1/12 Can you give a known compartmentalization for parvalbumin?

17/3/end Personal bias here - but it would be valuable to state that one primary limitation of isolated muscles is the inability
to create in vivo oxygenation conditions and it is now appreciated that cellular energetics and mitochondrial regulation are extremely PO2 dependent. Both hyperoxia and hypoxia/anoxia are non-realistic.

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Referee #2:

Overall, an interesting review that integrates A.V. Hill's research on the energetics of muscle contraction with subsequent and contemporary work.

I have no major criticisms of the manuscript and offer only some minor comments:

Page 5 - Reference is made to Hill "serving on the Committee". Please specify exactly what committee.

Page 7, Line 19 - Remove "and". "...provided a practical guide, which is still relevant..."

Page 9, Line 19 - Perhaps should more correctly say "O2 uptake" since the measurement is being made at the mouth? It accurately represents O2 consumption because the O2 uptake and CO2 output remain steady over a period of minutes.

Page 9, Line 21 - Perhaps should add that the notion of a lack of O2 (i.e., hypoxia/dysoxia) was subsequently questioned, and that the O2 debt is the result of processes in addition to those representing repayment of any so-called debt accrued.

Page 12, bottom - should note here that this hypothesis of lactate oxidation amounting to only 1/6 to 1/5 of the lactate disappearance was a result of the preparation and perhaps the species. It is now well known that in intact, whole mammals, the majority of lactate disappearance in recovery from exercise of most types is due to oxidation.

Page 15, middle - Cain and Davies, and Cain, Infante, and Davies typically receive credit for verifying the immediate role of ATP in muscle contraction but should some credit also go to Lange, Biochem Z 326(3):172-186, 1955, who observed a decrease in [ATP] and an increase in [ADP] after muscle contraction with a blocking combination of iodoacetate and nitrogen mustard?
Is Na+/K+ ATPase not a factor in ATP hydrolysis?

Although you clarify this two paragraphs later, to avoid confusion, should you say, "Ca2+ binding by parvalbumin in amphibian muscle is now recognised..."?

"...was used to calculate the heat..."

here and in the reference list, this should be Liebig, not Leibig. Two lines further down, "...was an elastic body, in which the force..."

"...the latter facilitates fast computation..."

is there anything unique to amphibian as opposed to mammalian muscle that should be noted here, other than the previously mentioned parvalbumin difference?

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END OF COMMENTS

Confidential Review 03-Nov-2021
EDITOR COMMENTS

Reviewing Editor:

Both reviewers, very expert in the field, express their enthusiasm for the manuscript, which nicely summarizes and puts into perspective AV Hill's legacy in the field of exercise physiology. I concur with their opinion and express my congratulations to the authors for an excellent submission. Both reviewers raised only relatively minor comments/suggestions for changes, which the authors should take into consideration.

Just to note, we deliberately didn’t focus on exercise physiology – this has been covered previously. Rather we focus on muscle physiology, which was Hill’s core business.

REFEREE COMMENTS

Referee #1:

GENERAL COMMENTS

This paper is well conceived, crisply written and delivers a wealth of personal and scientific insights into Hill's work and canonical position in the field of muscle energetics. Even though the reader may have read many of Hill's papers and books the distillation of ideas and appraisal of their present-day consequences is extremely valuable and testament to the authors' deep knowledge of this topic and personal involvement with Hill's legacy. Criticisms are minor and should be taken as suggestions for improving clarity/correctness of delivery, broader interpretation and potential impact as well as accessibility to the non-specialist in this fascinating arena.

SPECIFIC COMMENTS

Page/para/line(s)

2/1/6-8 Beautifully posited.

3/4/5 "other" books. Please provide a title or two here.

We have added an Appendix with brief summaries of each of AV Hill’s books

5/1/8 Perhaps state "Manchester University" or ?

Done

5/1/9 "from trams and experiments were..."

Done

7/Figure 4 Please increase label clarity on axis. It looks rather fuzzy.

8/1/5 Delete "very." Unnecessary hyperbole.

Done
It's difficult to be specific because it pops up in so many papers. But, to be specific, we have replaced “a number” with “many” and provided references to six papers which include detailed descriptions of calibration methods.

8/Figure 5 legend. Perhaps define "Pt" as platinum.

Done

9/1/3 Briefly describe the Peltier effect here?

Done

11/Figure 6 and equation 2 Please consider unifying terms, if possible, between figure & equation.

11/3/end Does it make sense to present this equation here rather than on page 20?

Yes. Not sure that it would be in context on p. 20.

12/end When I think of the formative experiments that demonstrated unequivocally the fate of lactate in vivo George Brooks' work with radiolabeled tracers stands out in humans and animals. Is it worth a brief mention here?

Brooks GA, Gaesser GA. End points of lactate and glucose metabolism after exhausting exercise. J Appl Physiol Respir Environ Exerc Physiol. 1980 Dec;49(6):1057-69. doi: 10.1152/jappl.1980.49.6.1057. PMID: 7440296.

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The importance of Hill and Meyerhof’s work wasn’t the actual fraction of lactic acid oxidised; rather it was that in the preparation under consideration, independent analyses had produced the same quantitative result concerning the fate of lactic acid. In fact, that the amount oxidised under those conditions was a strange fraction makes the concordance of the results from the two labs more convincing. This was a demonstration of the First Law of Thermodynamics in a biological system; Liebig and Helmholtz had predicted that the heat production and chemical change in contracting muscle should be directly related and here, over 50 years later, was confirmation of that idea.

13/1/3 At that time (1923), I believe that WW1 was known as "The Great War"

Indeed. But from today’s perspective, WW1 seems appropriate.

13/3 "Legacy paragraph. Outstanding!"

15/1/2 "no changes in [ATP]." Occasionally I review papers that don't recognize this. A crisp statement as to its acceptance today might be valuable here.

Done

16/3 lines from bottom Perhaps identify them as Earl and Jack, as appropriate here.
17/1/12 Can you give a known compartmentalization for parvalbumin?
Not entirely sure what is meant but perhaps that it is a myoplasmic component? This has been added.

17/3/end Personal bias here - but it would be valuable to state that one primary limitation of isolated muscles is the inability to create in vivo oxygenation conditions and it is now appreciated that cellular energetics and mitochondrial regulation are extremely PO2 dependent. Both hyperoxia and hypoxia/anoxia are non-realistic.

The counter argument is that with some reasonable modelling the state of oxygenation of an isolated muscle can be characterised (e.g. Hill, 1928, 1965); this is much more difficult to define or infer in vivo. In fact, in vivo conditions appear much more likely to have muscle cells operating in the low PO2 range where mitochondrial function is PO2-sensitive. Secondly, in much isolated muscle work the aim is not to mimic in vivo conditions but rather to investigate muscle physiology per se under well-defined experimental conditions with fewer uncontrolled variables than is possible with an in situ or in vivo preparation. This is the rationale for the reductionist approach to investigating physiology. For heat measurements this approach is essential as the requirement is to accurately measure the heat produced by a muscle in response to contraction (or at rest) without contamination of heat from any other muscles or other sources and without losing heat to the surroundings (tissues or atmosphere). This can only be achieved using an isolated muscle.

18/Fig 9 legend/3 "calculate"

18/2 Excellent!

19/1/2 If I recall correctly, in a UCLA grad class with Earl Homsher, these overstretched muscles are completely non-physiological and led to a gross overestimation of the "non-contractile" costs. Moreover, some muscles, when stretched in excess of 3.0 microns sarcomere length (diaphragm, for example) never function normally again.

Hopefully, this is a confused memory because nearly all of it is wrong! The original experiments describing this approach were those of Smith (1972) J Physiol 220:583-599 and Homsher et al. (1972) J Physiol 220:601-625), published simultaneously in J Physiol. First, although non-physiological, these experiments were not intended to mimic a physiological situation. Rather the protocol very cleverly took advantage of the then fairly recent linking of the force-length relationship to sliding filaments (Gordon et al. 1966 J Physiol 184:170-192) and allowed cross-bridge cycling to be inhibited by eliminating overlap between the myosin and actin filaments. Second, the method provided what is regarded as the “gold standard” determination of non-cross-bridge contribution to muscle energy output (at least for frog muscle); there is no overestimate, gross or otherwise.

Consistent with that idea, we published a paper in which it was shown that non-cross-bridge-related energy costs are the same whether determined by eliminating filament overlap or by pharmacological inhibition of cross-bridge cycling (Barclay et al. 2008 Acta Physiol 193:381-391.). Finally, a feature of the original studies was the use of semitendinosus muscle, rather than the classical sartorius, precisely because that muscle could be stretched to long lengths without damage. However, you are correct in that not all muscles can be stretched without damage.

22/Figure 11 Dots on "Vs" to indicate flow.
These are in the original figure which we are presenting thus not under our control.

25/2/1 "a number" How many?

26/1/4 from bottom "comparable". Anything is "comparable" - what is meant is "similar".

A dictionary will show that comparable can mean either “able to be compared” or “similar”.

For overall efficiency in intact humans I would consider George Brooks paper as setting a precedent for the field -
Gaesser GA, Brooks GA. Muscular efficiency during steady-rate exercise: effects of speed and work rate. J Appl Physiol. 1975 Jun;38(6):1132-9. doi: 10.1152/jappl.1975.38.6.1132. PMID: 1141128.
Indeed, good work but not greatly different to the earlier work of Whipp and Wasserman (1969) J Appl Physiol 26:644-648). The problem of deciding on an appropriate baseline is obviously an issue when attempting to extract muscle efficiency from whole body measurements using cycling (an advantage of an isolated muscle preparation!)

Referee #2:

Overall, an interesting review that integrates A.V. Hill's research on the energetics of muscle contraction with subsequent and contemporary work.
I have no major criticisms of the manuscript and offer only some minor comments:

Page 5 - Reference is made to Hill "serving on the Committee". Please specify exactly what committee.
Rewritten to clarify

Page 7, Line 19 - Remove "and". "...provided a practical guide, which is still relevant..."
Done

Page 9, Line 19 - Perhaps should more correctly say "O2 uptake" since the measurement is being made at the mouth? It accurately represents O2 consumption because the O2 uptake and CO2 output remain steady over a period of minutes.
Done

Page 9, Line 21 - Perhaps should add that the notion of a lack of O2 (i.e., hypoxia/dysoxia) was subsequently questioned, and that the O2 debt is the result of processes in addition to those representing repayment of any so-called debt accrued.
We have deliberately avoided entering such debates; they have been well discussed in the Exercise Physiology literature and the reviews cited.

Page 12, bottom - should note here that this hypothesis of lactate oxidation amounting to only 1/6 to 1/5 of the lactate disappearance was a result of the preparation and perhaps the species. It is now well known that in intact, whole mammals, the majority of lactate disappearance in recovery from exercise of most types is due to oxidation.
First, the conclusions of Hill and Meyerhof regarding the fate of the lactate formed are not a hypothesis, they are experimentally-determined facts for frog muscle under the conditions used in the study. This is not to be confused with the hypothesis that the breakdown of glycogen to lactic acid was the source of energy for contraction. Second, it is rather missing the point to say that the numbers are different for different muscles/conditions. The importance of the Hill/Meyerhof work was that
using different techniques – one biochemical analysis, the other heat production – the same quantitative conclusions were reached. That the fraction of lactic acid oxidised was an odd, fractional amount makes the Hill/Meyerhof convergence an even more convincing demonstration! From a contemporary perspective, maybe this doesn’t seem a great achievement but at the time it represented a quantitative confirmation the idea, proposed by Liebig (Liebig 1843 Animal Chemistry) and Helmholtz (see pp. 30-32, McKendrick 1899 Hermann Ludwig Ferdinand von Helmholtz), that the heat and chemistry must be directly related, a fundamental idea about how muscle worked.

Page 15, middle - Cain and Davies, and Cain, Infante, and Davies typically receive credit for verifying the immediate role of ATP in muscle contraction but should some credit also go to Lange, Biochem Z 326(3):172-186, 1955, who observed a decrease in [ATP] and an increase in [ADP] after muscle contraction with a blocking combination of iodoacetate and nitrogen mustard? We refer to the assessment of this work by Mommaerts: A separate demonstration of the priority of ATP breakdown remained desirable, however. This demonstration was first given by Lange in the experiments discussed earlier, although these suffered somewhat from the circumstance that they were not obtained on all-or-none contractile responses and that it was not clear why in these slow contractions the transphosphorylation reaction did not keep up with the ATP breakdown, a question still deserving attention. This experiment in which the reformation of ATP was blocked was clearer, though the underlying enzymatic inhibition was not further clarified. In some efforts made during the late 1950’s (unpublished), we did not readily succeed in adapting Lange’s inhibition procedures to the study of twitch responses, nor were we successful in the use of by-products of the preparation of ryanodine, among which there appears to be an inhibitor of the ATPcreatine phosphoryltranspherase as described by D. L. Hill et al. The first clear success, therefore, was that announced by Davies...

(Mommaerts, Physiol Rev 49, 427-508, 1969)

Page 16, Table 1 - Is Na+/K+ ATPase not a factor in ATP hydrolysis? Indeed! Added.

Page 17, Lines 12-16 - Although you clarify this two paragraphs later, to avoid confusion, should you say, "Ca2+ binding by parvalbumin in amphibian muscle is now recognised..."? To clarify, after “…in fast-twitch muscle”, we have added, “…not only of amphibians but also fish and (at least, small) mammals...”.

Page 18, Fig. 9 legend - "...was used to calculate the heat..." Corrected

Page 19, middle of page - here and in the reference list, this should be Liebig, not Leibig. Two lines further down, "...was an elastic body, in which the force...” Corrected

Page 22, Line 9 - "...the latter facilitates fast computation..." Done

Page 23, bottom - is there anything unique to amphibian as opposed to mammalian muscle that should be noted here, other than the previously mentioned parvalbumin difference? We have expanded this to emphasise that frog muscle still remains the modelling bench-mark due to the comprehensive body of information available: “Although models have been applied to muscles other than those of the frog, taking account of differences in structure and physiology, frog muscle remains the modelling bench-mark due to the comprehensive body of structural, physical and biochemical information relating to frog skeletal muscle.”
Dear Dr Barclay,

Re: JP-TR-2022-281556R1 "The legacy of A. V. Hill's Nobel Prize winning work on muscle energetics" by Chris Barclay and Nancy A. Curtin

I am pleased to tell you that your Topical Review article has been accepted for publication in The Journal of Physiology, subject to any modifications to the text that may be required by the Journal Office to conform to House rules.

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Yours sincerely,

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EDITOR COMMENTS

Reviewing Editor:

The (minor) referees' comments were adequately addressed. Excellent review on AV Hill's muscle work, put in today's research perspective.

Senior Editor:

Thank you for a fascinating review.

1st Confidential Review

20-Jan-2022