*J Physiol* 600.7 (2022) pp 1555–1578

TOPICAL REVIEW

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

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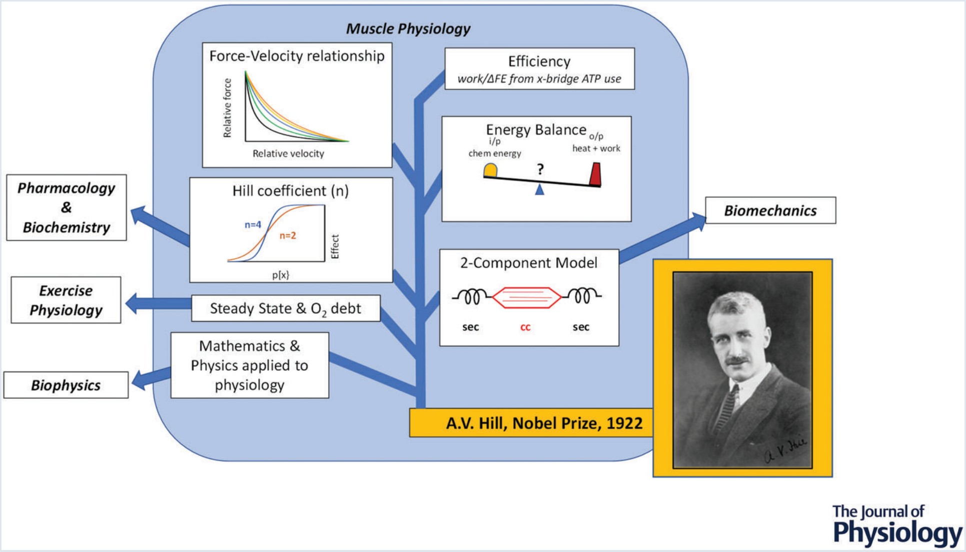
Edited by: Ian Forsythe & Bruno Grassi

The peer review history is available in the Supporting Information section of this article (https://doi.org/10.1113/JP281556#support-information-section).



**Abstract** A. V. Hill was awarded the 1922 Nobel Prize, jointly with Otto Meyerhof, for Physiology or Medicine for his work on energetic aspects of muscle contraction. Hill used his considerable mathematical and experimental skills to investigate the relationships among muscle mechanics, biochemistry and heat production. The main ideas of the work for which the Nobel Prize was awarded were superseded within a decade, and the legacy of Hill and Meyerhof's Nobel work

**Nancy Curtin** has worked on muscle energetics throughout her career. Her PhD work, supervised by R. E. Davies FRS at the University of Pennsylvania, revealed the low rate of ATP use during stretch of active muscle. Subsequently, at University College London, Nancy worked with Roger Woledge on 'energy balance' experiments. This expanded to include the study of mechanics and efficiency of muscles of different species while at Charing Cross & Westminster Medical School, Imperial College London, the Marine Biological Association (Plymouth) and, since retirement, at The Royal Veterinary College. Nancy was an Editor and Distributing Editor of *The Journal of Physiology*. **Chris Barclay** trained in New Zealand, did post-doctoral studies in the UK, with Roger Woledge and Nancy Curtin, and in Australia, with Colin Gibbs. His interests are cellular aspects of muscle energetics and the molecular basis of energetic differences among muscles. In retirement, he maintains interests in theoretical and historical aspects of muscle energetics.

DOI: 10.1113/JP281556

was not a set of persistent, influential ideas but rather a prolonged period of extraordinary activity that advanced the understanding of how muscles work far beyond the concepts that led to the Nobel Prize. Hill pioneered the integration of mathematics into the study of physiology and pharmacology. Particular aspects of Hill's own work that remain in common use in muscle physiology include mathematical descriptions of the relationships between muscle force output and shortening velocity and between force output and calcium concentration, and the model of muscle as a contractile element in series with an elastic element. We describe some of the characteristics of Hill's broader scientific activities and then outline how Hill's work on muscle energetics was extended after 1922, as a result of Hill's own work and that of others, to the present day.

(Received 3 November 2021; accepted after revision 24 January 2022; first published online 3 February 2022)

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**Abstract figure legend** A. V. Hill's scientific legacy. A. V. Hill (pictured) and his colleague Otto Meyerhof shared the 1922 Nobel Prize for Physiology or Medicine. Seven enduring elements of Hill's legacy to muscle physiology are shown. Arrows link concepts and approaches to related disciplines where they have been foundational and highly influential.

## Introduction

A. V. Hill was one of the foremost physiologists of the 20th century. His main scientific interest was muscle energetics, in particular the relationship between muscle mechanical function and heat production, but his attention ranged widely around the general topic of muscle energetics. For example, he was a pioneer in the fields of exercise physiology, biophysics and quantitative pharmacology. His scientific longevity is apparent in a publication list that spans the period from 1909 to 1976.

In 1923, it was announced that, together with Otto Meyerhof from Germany, Hill had been awarded the Nobel Prize in Physiology and Medicine for the previous year, 1922[1] (Fig. 1). Hill and Meyerhof had worked on complementary areas of muscle energetics, with Hill focused on physical (i.e. thermal and mechanical energy) aspects of contraction and Meyerhof on chemical aspects. The Nobel citations stated that Hill's award was '…for his discovery relating to the production of heat in the muscle.', and Meyerhof's '… for his discovery of the fixed relationship between the consumption of oxygen and the metabolism of lactic acid in the muscle.'.

In this article we only briefly describe the work that led to Hill's Nobel Prize. Detailed descriptions of that work have been given by Hill (Hill, 1922, 1926*a*) and others (Katz, 1978; Bassett, 2002) and were described in Hill's Nobel speech (Hill, 1965*a*). We concentrate on subsequent progress in the areas of muscle energetics that Hill worked on and we highlight contemporary research areas that remain heavily influenced by Hill's ideas.

A. V. Hill's life and many achievements have been described in detail and with insight by Bernard Katz (1978). His life and that of Otto Meyerhof are the subject of a forthcoming biography, *Bound by Muscle*, by Andrew Brown (Oxford University Press, USA) to be published in 2022. Hill himself wrote a very personal autobiography (Hill, 1970*a*) and his book *Trails and Trials in Physiology* (Hill, 1965*b*) is an essential companion to his scientific work, both published and unpublished. His other books (Hill, 1926*b*, 1927*a*,*b*, 1931, 1960, 1970b) cover other aspects of his scientific work and thinking (for brief summaries of his books, see the Appendix). The Churchill Archives Centre (University of Cambridge, UK) holds a collection of original documents by Hill[2]. In addition to his scientific work based on muscle physiology, Hill was involved in extensive non-laboratory-based work that brought a scientific perspective to other issues of his time. Although we do not cover this in detail, we do wish to draw attention to this, perhaps less well-known, side of his life. For example, during the two World Wars when laboratories were closed, there was much war-related scientific work and science was in the public eye much as it is today. During World War 1, Hill led a team developing anti-aircraft gunnery, the 'dawn of operations research', vividly described by van der Kloot (2011). This naturally led to his involvement with Sir Henry Tizard's Aeronautical Research Committee, which was overseeing the development of radar prior to World War 2. Also between the wars, he started his work for refugee and interned scientists which was recently

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[1] https://www.nobelprize.org/prizes/medicine/1922/summary/

[2] The papers of Professor A. V. Hill, https://archivesearch.lib.cam.ac.uk/repositories/9/resources/1410

described by Rall (2017). Before the USA entered the war, Hill visited Washington DC and laid the foundations for the 1940 British Technical and Scientific Mission (also known as the Tizard Mission) involving the UK and USA governments. This Mission eventually resulted in British scientific and technological secrets relevant to military use being shared with the USA, where development, which was impossible in wartime Britain, could proceed. During World War 2, Hill was an active Member of Parliament. As a representative of the Royal Society, Hill provided advice on the development of science to the Indian government. Throughout his career, he also served on numerous committees for the government, the Physiological Society and the Royal Society; a description of this huge range of activities, along with extensive references, is given by Katz (1978).

In the next section, we describe some general characteristics of Hill's work and career. We have made a personal selection of four important aspects of Hill's work: (i) embracing the international character of science, (ii) a commitment to technological development, (iii) extrapolating knowledge from isolated muscle work to human exercise and (iv) application of mathematics to the study of physiology. These characteristics were established early and remained central throughout his long career. In subsequent sections, we describe the post-Nobel progress in three areas of Hill's muscle research: (i) the relationship between muscle heat production and the underlying chemical reactions, (ii) the relationship between heat production and mechanical function and (iii) the efficiency of contraction.

## A. V. Hill's approach to science

### Science is international

> *… the community of scientific people throughout the world is convinced of the necessity of international collaboration; has practised such collaboration for many years … and has built up an elaborate system of congresses and unions, of standard units and nomenclature, and of abstracting journals together with widespread interchange of research workers and ideas from one country to another.*
>
> (Hill, 1960, pp. 45–46)

Hill was strongly committed to the international nature of science throughout his career. Many scientists from all over the world came to work with him and he remained in close contact with many of them. *Trails and Trials* (Hill, 1965*b*) includes an 'Author Index' of 104 individuals who published from Hill's laboratory, including visitors and colleagues from many continental European countries, from North America, Russia, China and Japan. Some, for example Detlev W. Bronk, Wallace O. Fenn, Ralph W. Gerard, Rodolfo Margaria and Jeffries Wyman, like Hill, combined a career of hands-on-science with outstanding leadership roles in scientific, research and educational institutions. Some went on to win Nobel Prizes themselves, for example Bernard Katz and Herbert Gasser.

One of the earliest visitors to Hill's laboratory was Viktor Weizsäcker, from Heidelberg, who had already researched oxidative metabolism in frog heart and wanted to follow-up his ideas with Hill's myothermic methods.

**Figure 1. A. V. Hill's Nobel medal**
Photo: N. A. Curtin, personal collection. Used with permission from the Nobel Foundation.

Together they devised a modified thermopile chamber that allowed solution changes during experiments on frog skeletal muscle in which both force and heat were measured. The results (Hill & Weizsäcker, 1914; Weizsäcker, 1914) provided conclusive evidence '…that the chemical reactions which liberate energy for the initial process of contraction are altogether non-oxidative in character'. In *Trails and Trials*, 50 years later (Hill, 1965*b*, p. 42), Hill stated that Weizsäcker's '…conclusion stands today without qualification.', high praise indeed!

Many of Hill's visitors, like Weizsäcker, were already established scientists when they joined Hill and undertook projects that he suggested and using equipment he supplied. Among the plethora of contributions to muscle energetics by Hill's visitors, the following are of particular note in that aspects of their work were especially influential: Fenn's work on the energetics of shortening muscle (Fenn, 1923, 1924), described in more detail later in this article, overturned accepted models of force generation by muscle and was the antecedent of Hill's seminal 1938 and 1964 papers; explorations by Feng (1932) and Solandt (1936) of the effects on resting metabolism of muscle length and potassium, respectively, were important early works on muscle basal metabolism; Bozler (1930) pioneered the study of smooth muscle energetics, measuring the heat production of a snail muscle; Wyman (1926), in a study of tortoise muscle energetics, conceived of plotting muscle length change during shortening as a function of the force developed as a means of graphically displaying muscle work output, a depiction now known as a 'work loop' and a standard method in investigations focused on muscle action during locomotion; and Aubert (Abbott & Aubert, 1951; Abbott *et al.* 1951), who characterized energy changes associated with changes in muscle length, both shortening and lengthening, thus extending and refining Fenn's observations. On at least one occasion the investigation required considerable fortitude on the part of his visitor: Wallace Fenn's famous experiments (Fenn, 1923, 1924) were performed in the cellar of Hill's house near Manchester where Hill was at the time Head of Manchester University's Physiology Department. The cellar location was chosen to avoid electrical interference from trams and experiments were carried out at room temperature which ranged from 0 to 15°C, depending on the season! Some of those who worked with Hill, such as Vic Howarth and Roger Woledge, entered his laboratory in the role of research trainee/assistant and became outstanding muscle physiologists, taking their PhD degrees later with other supervisors. This is a noteworthy sign of the times because, unlike today, a PhD was not required in Britain in the early 20th century when Hill entered science. In fact, he never did a PhD himself and was not a strong believer in the degree.

Hill was a very active member of the Physiological Society from 1912, serving on its Committee, as Chief Editor of *The Journal of Physiology* and as Foreign Secretary. He participated in and organized International Physiological Congresses. Perhaps most notable was his involvement in the first Congress to be held in North America in Boston, Massachusetts, in 1929. Hill had the unusual task of organizing the transport for hundreds of physiologists to cross the Atlantic. The result was the voyage on the *SS Minnekahda*, which today sounds like a dream (Fig. 2). It was single-class ship and most of the passengers were physiologists and their families bound for the Congress. From accounts of this very successful voyage (Zotterman, 1968; Rall, 2016), it is clear that Hill was in his element as international friendships thrived amid 'talking shop', various games (deck tennis, shuffleboard, tug-of-war) and dancing in the evenings. Rall (2016) describes the Congress as marking the 'coming of age' of American Physiology. His lively account gives the background of the Congress, along with the adventures (and some misadventures) of the participants, many of whom were visiting the USA for the first time.

A few years after the 1929 Congress in Boston, Hill began assisting scientists and other scholars who became refugees in the face of persecution of Jews and others that began with the Nazi rise to power in Germany in 1933. Hill's Huxley Memorial Lecture in late 1933 entitled 'The International Status and Obligations of Science' raised the profile of his humanitarian project in the scientific press. Extracts of the lecture were published in *Nature* (Hill, 1933) and were followed by an exchange of letters in *Nature* between Prof. Johannes Stark defending the actions of the National-Socialist Government in Germany (Stark, 1934), and replies from Hill (Hill, 1934*a*,*b*). The

**Figure 2. A. V. Hill (centre) and other physiologists aboard the SS *Minnekahda* on the voyage to the first International Physiological Congress to be held in North America in 1929**
From the Physiological Society's Photographic Collection with permission.

entire lecture and the *Nature* correspondence are glimpses of an emerging situation and make fascinating reading (Hill, 1960, pp. 205—226).

Rall (2017) described how Hill's efforts for refugee scholars continued for several years and evolved as the political situation worsened. It started with the formation of the Academic Assistance Council, which later became the Society for the Protection of Science and Learning and eventually included efforts on behalf of 'enemy aliens' interned in the UK. Hill's positions as Biological Secretary of the Royal Society (1935–1945) and as a Member of Parliament (1940–1945) (Fig. 3*A*) contributed to his effectiveness on behalf of the refugees and internees. He used his leadership and organization skills, both well-honed from his scientific work, and he had an exceptional natural understanding of the debating style that succeeds in Parliament and a flare for good use of the media.

This work was characteristic of Hill's innate commitment to tolerance and intellectual freedom, and is high among the 'wider issues, outside the boundaries of his own research, through which he exerted his most important influence on other people's lives and on the course of events' (Katz, 1978).

In 1943–44, Hill visited India (Fig. 3*B*), '… not as a political observer, but as a colleague representing the Royal Society which was concerned with the development of scientific collaboration with the Commonwealth, especially during the imminent post-war period.' (Katz, 1978, p. 119). Hill was much in demand during the visit; he later wrote '… in reply to pressing invitations from Indian friends I had frequently to tell them that even a physiologist cannot be in more than two places at once.' (Hill 1974, p. 318). The longer-term and lasting successes of the visit arose from his report to the Indian government. It included suggestions to reform medical education so that teaching was done by full-time, well-trained staff. 'The nucleus for creating such people was to be "a great All-India Medical Centre", with highly selected students for whom adequate scholarships or bursaries should be made available.' (Katz, 1978). Among other recommendations were a central organization of scientific research and formation of research councils in India, and opportunities for training in the UK for Indian post-graduates. 'Many of the suggestions in Hill's report acted as a stimulant and were put into practice after Independence in 1947.' (Katz, 1978).

## Improving technology for measuring muscle heat production

For his work on muscle heat production, Hill used isolated muscle preparations. This approach, pioneered by Helmholtz in the 1840s (for a description, see McKendrick, 1899), was used because only with an isolated muscle maintained in a thermally stable environment can the heat produced by the muscle be measured precisely. The development of chambers, thermal sensors and apparatus to allow simultaneous measurement of heat output and mechanical performance (e.g. force developed and change in muscle length) was

**Figure 3. Among many other roles during World War 2, Hill served as Member of Parliament for Cambridge University and visited India on behalf of the Royal Society to research and prepare recommendations for the future of science and medical education**
*A*, A. V. Hill entering Parliament in 1940. Used with permission from the Churchill Archives Centre, The Papers of Professor A. V. Hill, AVHL II 5/123. *B*, Hill during his Indian visit in 1944 with Dr S. S. Bhatnagar FRS, the first Director-General of the Indian Board of Scientific and Industrial Research. Used with permission from the Churchill Archives Centre, The Papers of Professor A. V. Hill, AVHL II 5/119.

central to progress in understanding energetic aspects of contraction.

Developing myothermic (i.e. heat measuring) methods that were more sensitive, faster and free from artefacts was a goal that Hill pursued throughout his working life (Katz, 1978, p. 80). Hill's heat measurements were made using thermopiles, which are thermal sensors consisting of an array of thermocouples. Hill's development of thermopiles included trials of many different types of thermocouples, seeking optimal combinations of metals that provided high thermal sensitivity, low thermal conductivity, and electrical resistance appropriate for the galvanometers used to amplify the thermopile output and that were suited to the hand-fabrication techniques used by Hill's thermopile maker A. C. Downing. Hill summarized the evolution of thermopiles in *Trails and Trials* (Hill, 1965*b*, Chapter 8) and Howarth (1970) provided a practical guide, which is still relevant, to the many decisions required when designing and making thermopiles. The most notable improvement in thermopile performance that Hill and Downing achieved was to improve the speed of response to changes in muscle temperature (Fig. 4*A*). Hill's first device had a time constant, with the muscle in place, of ∼20 s (Hill, 1910*a*); by 1937, this had been reduced to just 20 ms (Hill, 1937). Hill and colleagues generally used whole muscles, though he clearly recognized the advantage of smaller preparations from the point of view of the limitations of diffusive oxygen supply to isolated muscles (Hill, 1965*b*, p. 354). Only 4 years after Hill died, the first measurements of heat production by

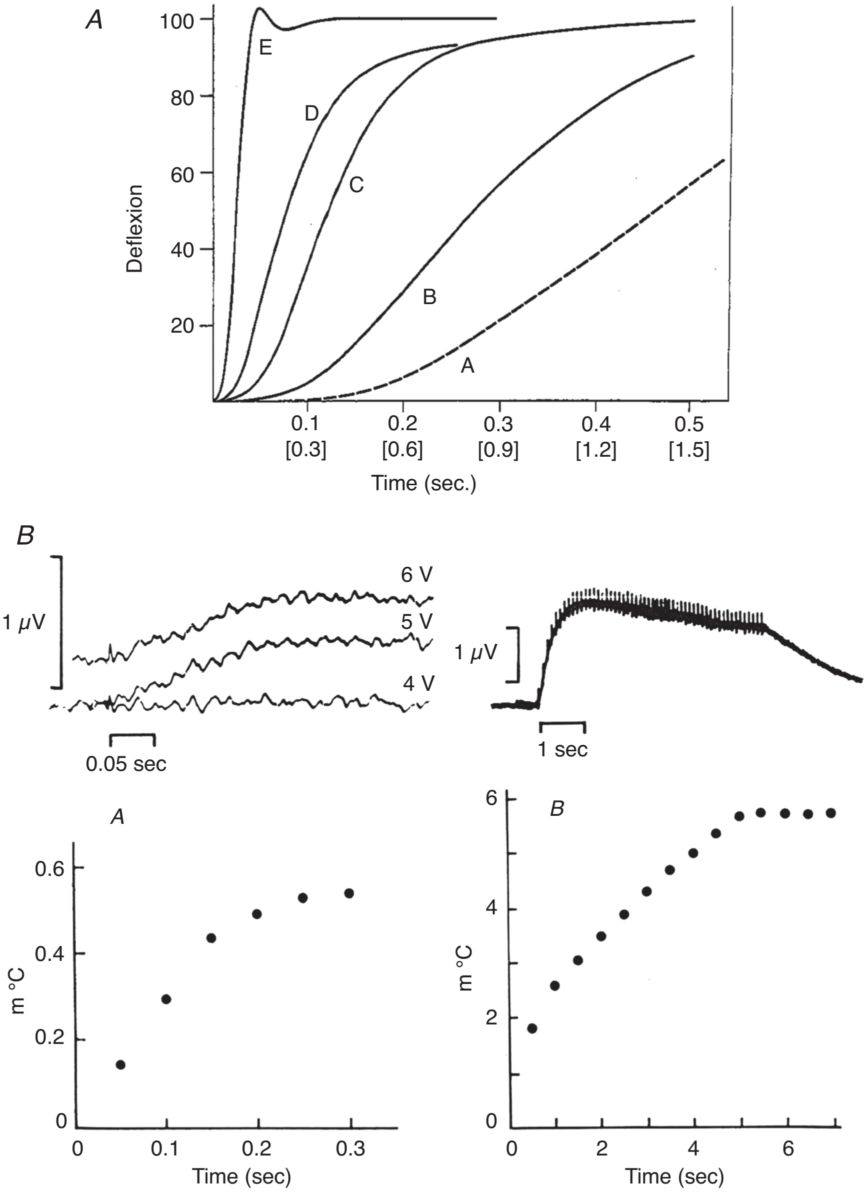

**Figure 4. *A*, improvements in the speed of thermopile response**
Records showing time course of thermopile output in response to a brief heating pulse. A, 1920 (lower time scale); B, 1933; C, 1933, D, 1937; E, 1938. Reproduced from Hill (1939*b*), used with permission from IOP Publishing. *B*, the first heat records from a single frog muscle fibre. Top left: thermopile output in response to single stimulus pulses, showing the all-or-none response (4 V, no response; 5 and 6 V, same amplitude response) at 15°C. Top right: thermopile output during 5 s stimulation at 3°C. Lower records show signals adjusted to account for heat lost during recording and converted to temperature units for twitch (left) and tetanus (right). Fibre dimensions: length, 4.3 mm; diameter, 150 μm; mass, 80 μg. From Curtin *et al*. (1981) used with permission from John Wiley & Sons.

a single fibre from frog muscle (Fig. 4*B*) were made using a Hill–Downing-type thermopile constructed by Vic Howarth (Curtin *et al.* 1981).

For fast measurement of muscle heat production, the style of thermopile developed by Hill and Downing remains the instrument of choice, though with many improvements. Figure 5*A* shows a diagram of the thermopile used by Fenn (1923) and Fig. 5*B* a smaller modern thermopile, constructed using vacuum deposition to produce much thinner thermocouples (Mulieri *et al.* 1977). The galvanometers Hill used to amplify the thermopile output have been superseded by electronic amplifiers (Gibbs *et al.* 1967; Gower & Kretzschmar, 1976).

The *accuracy* of measurements was a continuing concern particularly when combining or comparing quantities of energy measured by different methods, such as work, from the product of force and distance moved, and heat based on the temperature change. Improved calibrations and recognition of, and correction for, artefacts were a high priority. Calibration of temperature measuring devices was a particular challenge and was revisited many times (e.g. Hill, 1928*b*, 1937, 1949, 1965*b*; Bozler, 1931; Hill & Woledge, 1962). In retrospect, it was apparent that in most studies from Hill's lab between 1921 and 1932 the amount of heat produced was overestimated. In a comprehensive analysis of calibration methods, Hill & Woledge (1962) concluded that this was probably due to underestimating the combined heat capacity (from the muscle, adhering solution and underlying thermopile) with which the heat produced by the muscles was shared. Hill also comments on individual publications from his laboratory in *Trails and Trials in Physiology* (Hill, 1965*b*), usefully indicating where a calibration error had been discovered later. The difficulty of calibrating thermopiles and measuring muscle heat capacity was ultimately resolved by the development of a new calibration method that uses the Peltier effect [i.e. heat is produced (or absorbed) at a thermocouple when current is passed through the circuit] to heat the muscle and thermopile at a known rate (Kretzschmar & Wilkie, 1972).

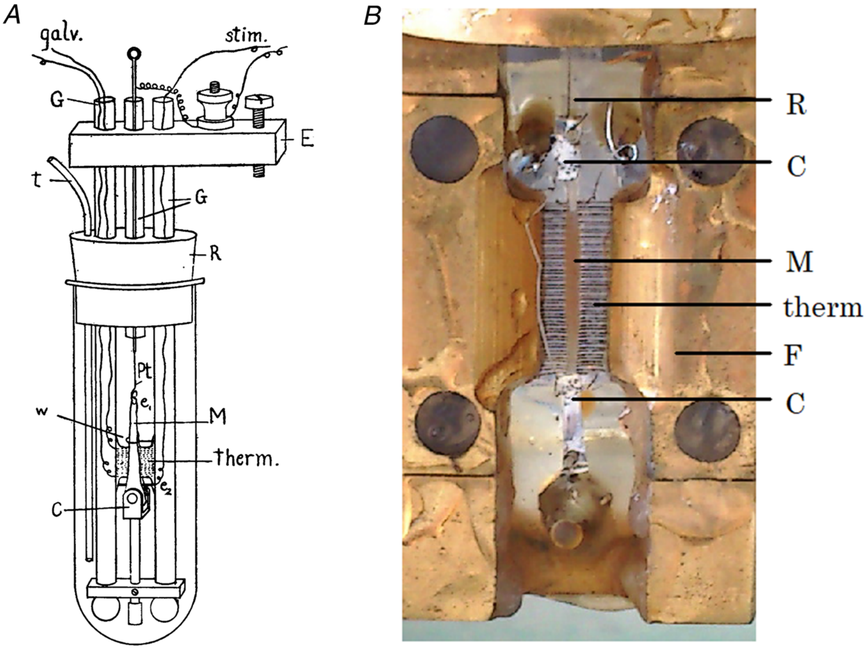

**Figure 5. Thermopiles for measuring muscle heat production**
*A*, diagram of chamber and thermopile used by Fenn (1923). A pair of sartorius muscles (only one shown, labelled 'M') lie along each surface of a thermopile (therm), over the active thermocouples. The thermocouples were composed of constantan-silver created by electroplating (Wilson & Epps, 1919). The thermopile is held between two paraffin-filled glass tubes; these serve to keep the reference thermocouples at a constant temperature. The muscle is stimulated via fine platinum wires ($e_1$ and $e_2$). The thermopile and muscle are enclosed in a glass chamber that allows the apparatus to be immersed in an isothermal water bath. Figure from Fenn (1923) used with permission from John Wiley & Sons. *B*, a contemporary thermopile (Barclay, 2015), consisting of antimony–bismuth thermocouples created using vacuum deposition (Mulieri *et al.* 1977). The reference thermocouples are clamped in a gold-plated brass frame (F). A muscle fibre bundle (M; from a mouse soleus, length, ∼10 mm) lies along one surface of the thermopile (therm) over the active thermocouples. The muscle is connected, using aluminium T-clips (C), at one end to the frame and at the other end to a rod (R) connected to the arm of an ergometer (not visible). The frame was housed within a chamber similar to that used by Fenn. Photo: C. J. Barclay, personal collection.

## Using principles from isolated frog muscle to understand muscular exercise in man and other animals

As a keen runner, though he says '… not…a first-class runner', Hill was interested in human exercise. In particular, he was curious about the 'effects of speed of muscular movement on work done, on force exerted and on energy expended' as well as the 'limits of athletic performance' (Hill, 1965*b*, p. 84).

In his early experiments on human exercise, he wanted to see whether what he had discovered about isolated frog muscle also applied during human running. The frog muscle experiments showed that contraction could occur without oxygen, but oxygen was required for removal of the lactic acid during recovery after contraction. His first report on human exercise was entitled 'The oxygen consumption during running' and was presented as a communication at a meeting of the Physiological Society (Hill & Lupton, 1922). Hill and Lupton measured $O_2$ uptake and $CO_2$ elimination from respiratory gas measurements during running at different speeds. Katz (1978) concluded that, although not identified in the publication, the subject was 'presumably A.V. himself'. On the basis of their results, they defined the useful concepts of (i) *steady-state* exercise in which the rate of $O_2$ consumption is steady and running could be continued indefinitely, and (ii) *oxygen debt* incurred at higher speeds of running at which the '… subject was using more energy than was accounted for by the $O_2$-supply.' (Hill & Lupton, 1922). The latter case was that most analogous to the frog muscle experiments.

Hill was involved in many follow-up and further experiments and has been hailed as an 'exercise physiology pioneer' (Bassett, 2002). Forty-five papers on humans and some on other animals are included in his list of publications in *Trails and Trials* (Hill, 1965*b*). Two recent reviews have discussed Hill's contributions to exercise physiology (Bassett, 2002; Hale, 2008).

The muscles of different animal species also intrigued him because of the huge variation in their 'intrinsic speeds'. His sustained interest in the subject culminated in his 1950 publication 'The dimensions of animals and their muscular dynamics' (Hill, 1950*b*). This work initiated research on allometric aspects of muscle physiology, which remains a dynamic scene (Kram & Roberts, 2016).

## Applying mathematics to physiology

Much of Hill's work in physiology was founded on mathematics and physics. As a schoolboy he showed natural talent, thriving under the instruction of the inspiring mathematics master at Blundell's School in Tiverton, Devon, UK (Hill, 1970*a*). Having won a scholarship to Trinity College, Cambridge University, Hill completed the Mathematics Tripos (roughly equivalent to a bachelor's degree) in 2, rather than the usual 3, years. At this point, however, Hill changed course.

> *… during my first year I began to lose interest in some of the things that to me seemed rather remote from reality and hankered after something more practical. I realize now that I was much better fitted to engineering than to mathematics, but physiology proved in the end to be much like engineering, being based on the same ideas of function and design.*
>
> (Hill, 1969, p. 9)

Consequently, he did the Natural Sciences Tripos: physiology, chemistry and physics. This was an unconventional route into physiology; at that time, a medical degree was widely regarded as essential. However, following his degree studies, Hill was advised by J. N. Langley, who was head of the Physiological Laboratory in Cambridge (and at the time owned and edited *The Journal of Physiology*), to '… settle down to investigate the efficiency of cut-out frog's muscle as a thermodynamic machine.' (Hill, 1970*a*, p. 37). To that end, Hill joined the Physiological Laboratory and became part of a diverse and international group of physiologists with whom he worked as a 'mathematical whizz-kid' providing 'theoretical foundations' and making his colleagues' 'ideas more testable in quantitative terms' (Katz, 1978, p. 77).

Hill's application of mathematics to physiological issues was well illustrated in his first paper, in which he addressed the question of whether the actions of nicotine and curare on muscle force production were limited by binding kinetics or diffusion (Hill, 1909). He derived mathematical expressions for the rate of rise of force for both cases and then determined which best described the measured force development. In a second test, he used the temperature sensitivity of the rate of force development to distinguish between processes limited by chemical or physical processes. Both approaches showed that the drug actions were consistent with rates determined by binding kinetics rather than diffusion. Echoes of this early work are evident in many subsequent studies and in particular in Hill's studies of diffusion of $O_2$ into, and metabolites out of, isolated tissues (Hill, 1928*a*, 1965*b*).

**The Hill equation and Hill coefficient.** A notable outcome of this period was his paper concerning the binding of $O_2$ to haemoglobin (Hill, 1910*b*). Central to that work was an equation relating the per cent saturation of haemoglobin with $O_2$ ($y$) to the partial pressure of $O_2$ ($x$):

$$y = 100 \cdot \frac{K \cdot x^n}{1 + K \cdot x^n} \tag{1}$$

where $K$ and $n$ are fitted constants. Hill demonstrated that this equation accurately described experimental results obtained under a variety of conditions. Hill's mathematical treatment of a dose–response curve was an important step for biochemistry. The Hill equation has been described as '…the first exact (quantitative) receptor model in pharmacology' and '…the first milestone in quantitative pharmacology' (Gesztelyi *et al.* 2012). The many uses of the Hill equation and ways in which it can be interpreted, particularly in light of developments in pharmacology since Hill's publication, have been described by Goutelle *et al.* (2008).

In muscle physiology the equation is familiar as the usual description of the relationship between force produced by a skinned fibre and the concentration of $Ca^{2+}$ around the myofilaments (Fig. 6). In that context, the equation is typically used in the form

$$Force = 100 \cdot \frac{[Ca^{2+}]^n}{{K_{50}}^n + [Ca^{2+}]^n} \tag{2}$$

where $K_{50}$ is the $Ca^{2+}$ concentration at which force output is 50% of the maximum force and is related to $K$ from Eq. (1) as $K_{50} = \sqrt[n]{1/K}$.

Importantly, Hill noted that if the form of a relationship was known, then the parameter values could be determined from just a small number of experimental measurements. This approach to characterizing the properties of a physiological system based on finding a relatively simple equation that accurately described experimental results and could then be used as a predictive tool became a feature of Hill's work. Perhaps the best known example is the 1938 force–velocity equation (Hill, 1938).

## Experiments leading to the Nobel Prize

Given Hill's background, when he started to work on muscle it was natural for him to investigate its *physical* properties. His early work on muscle energetics saw him measure the force and heat produced by muscle and how these varied between stimulated, resting and rigor (dead) muscle (Hill, 1912). Hill saw the physical output from muscle as 'the end-products of activity' separate from but dependent on the 'chemical events that evoke contraction' (Hill, 1965*a*). He recognized that the chemistry and physics were united by thermodynamics and he regarded the Principle of Conservation of Energy as 'firm ground' (Hill, 1965*a*). This was an important element in his Nobel Prize work (described in the next paragraph). Indeed, it remained firm ground through numerous revolutions over the identity of the chemical reaction that acts as the immediate source of the physical energy released during contraction.

In his Nobel Lecture (Hill, 1965*a*), Hill described the consequences of muscle stimulation as consisting of two parts, initial and recovery, with the initial part being unaffected by the presence or absence of oxygen and the recovery requiring oxygen. Fletcher & Hopkins (1907) had already shown that contraction produces lactic acid and that 'from a fatigued muscle, placed in oxygen, there is a disappearance of lactic acid already formed.' A crucial question about recovery in the presence of oxygen was the fate of the lactic acid: was it 'burned' (i.e. completely oxidized to $CO_2$ and $H_2O$) or used to rebuild its precursor? Hill measured the heat produced during recovery and found that the numbers did not match with the complete oxidation hypothesis; the observed heat was much too small to have arisen from the complete oxidation of the lactic acid formed. The conclusion of this early energy balance experiment was the same as Meyerhof's conclusion from completely independent chemical experiments which showed that only about 1/5 or 1/6 of the lactic acid was oxidized (Meyerhof, 1965). It was for this body of work, which showed the power of combining physical and chemical approaches, that Hill and Meyerhof shared the Nobel Prize.

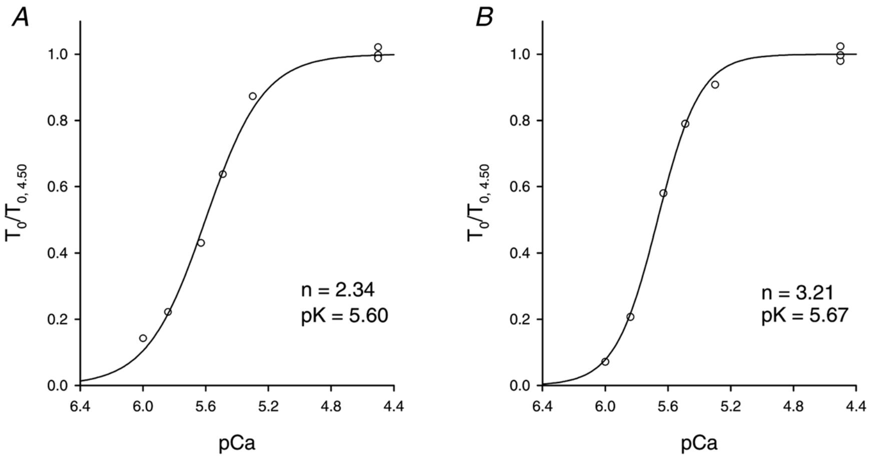

**Figure 6. Use of Hill's equation to describe the relationship between fibre force output and $Ca^{2+}$ concentration**
The examples are from skinned single fibres of human vastus lateralis and show examples of a slow-twitch fibre (*A*) and a fast-twitch fibre (*B*). $[Ca^{2+}]$ is expressed in logarithmic form, where $pCa = -\log_{10}([Ca^{2+}])$. The values of the two parameters of the Hill equation are shown in each panel. The curve for slow fibres is less steep (lower *n*) but reaches 50% of maximum force at a similar $[Ca^{2+}]$ as for fast fibres. From Linari *et al.* (2004), used with permission from John Wiley & Sons.

Hill and Meyerhof had not worked together, but had communicated about their work both before and after World War 1. As was typical of Hill, his relationship with Meyerhof was one of cooperation and friendship rather than competition (Fig. 7). Their work was a success of international science, unclouded by the nationalism that troubled the early years after that war (Katz, 1978, p. 27).

Throughout his scientific career Hill continued devising and improving mathematical descriptions of muscle's physical responses to a single stimulus and to tetanic (repeated) stimulation. He was particularly interested in the time course of these responses and recognized three phases: rapid onset, maintenance and relaxation. The time-course equations for heat production went through several iterations as methods improved. The elements of these equations were not necessarily intended to imply separate underlying mechanisms but often were assumed to, sometimes for better, other times for worse (i.e. false trails). Hill (1939*b*) wrote about his attitudes about facts (experimental evidence) and theories:

> *… I do not believe that we have yet a sufficient basis for a theory. Physiology is not yet ripe for overmuch hypothesis. What is wanted still is a more precise and quantitative knowledge of the facts; and we have seen to-day how much more easily facts can be fitted together, once they are accurately known.*

That idea that accurate experimental data are of prime importance is reflected in much of Hill's later work on muscle energetics.

## The legacy of A. V. Hill's Nobel Prize work

Hill's pre-Nobel Prize work on muscle energetics can be broadly divided into two themes: (i) heat production and chemical change, founded on the lactic acid hypothesis of energy supply, and (ii) heat production and mechanical performance, founded on the viscoelastic model of muscle mechanics. In the decade following the Nobel Prize, both the lactic acid hypothesis and the viscoelastic model were overturned. Hill summarized the rapid development of ideas in that decade in an article entitled, 'The revolution in muscle physiology' (Hill, 1932*b*). Therefore, the legacy of the Nobel work of both Hill and Meyerhof was not a set of persistent, influential ideas but rather was a prolonged period of extraordinary activity that advanced the understanding of how muscles work far beyond the concepts that led to the Nobel Prize. In the following sections, we outline 100 years of progress in the above-mentioned two branches of muscle research.

## Heat production and muscle chemistry

**Biochemistry of contraction.** Hill's primary interest was to understand the relationships among mechanical function, heat production and the chemical processes underlying contraction. Hill (1959) summarized the importance of heat measurements as follows.

> *… the special value of heat … is its intimate relation to the mechanical and chemical changes involved, and the sensitivity and speed of the methods available. Measurement of the heat admittedly does not point unequivocally to the actual chemical processes that occur, but it does provide a framework into which they must be fitted.*

Progress towards the objective of developing a coherent scheme that integrated biochemistry and heat output was limited while the known biochemical scheme remained incomplete. In essence, the lactic acid hypothesis was, as Mommaerts (1969) said, '…based only on the fact that no other substances were known'. However, in 1927, phosphocreatine (PCr; then known as phosphagen) was identified in muscle (Eggleton & Eggleton, 1927; Fiske & Subbarow, 1927) and its breakdown during a brief contraction and its subsequent rapid regeneration

**Figure 7. Nobel Prize winners A. V. Hill (left) and Otto Meyerhof photographed in Highgate, London, where the Hill family lived during his time at University College London**
Image used with permission from the Churchill Archives Centre, The Papers of Professor A. V. Hill, AVHL II 5/119.

in aerobic conditions were demonstrated (Eggleton & Eggleton, 1927). Not long after, ATP was discovered (Fiske & Subbarow, 1929; Lohmann, 1929). The function of these compounds was not clear but the possibility that they played a role in energy supply in muscle became more worthy of consideration when Lundsgaard provided striking evidence against Meyerhof's lactate theory (for reviews, see Hill, 1932*b*; Needham, 1956). Lundsgaard showed that when glycolysis, and thus the formation of lactic acid, was inhibited pharmacologically using iodoacetate, muscles still contracted; that is, the conversion of glycogen to lactate was not required for contraction. Furthermore, he showed that PCr was broken down during contraction and the extent of breakdown was proportional to the tension produced (Needham, 1971, see fig. 14). On the basis of these experiments, Lundsgaard suggested that PCr breakdown was the primary energy-providing reaction and that this initiated the lactate-forming reactions which regenerated PCr. In his 1932 review, Hill gave a lucid review of the rise and fall of the lactic acid theory.

Despite the focus on phosphagen, there was some evidence that ATP was also involved. A critical step towards understanding the order of the reactions of the phosphate compounds was taken by Lohmann in 1934, who deduced that PCr breakdown required ADP:

$$\mathrm{PCr} + \mathrm{ADP} \rightarrow \mathrm{ATP} + \mathrm{Cr} \tag{3}$$

He proposed that the reaction, at the time called Lohmann's reaction and now the creatine kinase reaction, would have to be *preceded* by ATP hydrolysis to provide ADP as a reactant. By this logic, ATP hydrolysis would be the reaction closest to the contraction process. Over the next 15 years, this idea received support from finding that myosin itself was an ATPase, that ATP could induce shortening of threads formed of actin and myosin that had been extracted from muscle (Rall, 2018) and could cause contraction in muscles in which all but the contractile filaments had been removed by glycerination. Indeed, by this stage it was accepted in many quarters that ATP was the primary energy supply reaction and that PCr breakdown must be the immediate regeneration or recovery reaction. However, direct evidence on whether this was the case in muscle was lacking.

In contracting muscle, decreases in PCr could be measured but no changes in ATP concentration could be observed. More than 20 years after ATP was first discovered, Hill (1950*a*) summarized the situation:

> *In the lactic acid era the evidence that the formation of lactic acid was the cause and provided the energy for contraction seemed pretty good. In the phosphagen era a similar attribution to phosphagen appeared even better justified. Now, in the adenosine triphosphate era lactic acid and phosphagen have been relegated to recovery and ATP takes their place. Those of us who have lived through two revolutions are wondering whether and when the third is coming.*
>
> *It may very well be the case, and none will be happier than I to be quit of revolutions, that the breakdown of ATP really is responsible for contraction or relaxation: but in fact there is no direct evidence that it is.*

In that paper, Hill challenged biochemists to show that ATP was broken down during contraction and suggested experimental strategies by which that might be achieved. Over the next decade, considerable effort was expended on this task with the consistent conclusion that no ATP breakdown could be observed (for reviews, see Needham, 1956; Davies *et al.* 1959; Mommaerts, 1959). In fact, it was not until more than 30 years after the discovery of ATP that Davies and colleagues, after numerous unsuccessful attempts, finally provided an unambiguous demonstration that ATP hydrolysis was the primary reaction powering contraction. The breakthrough was founded on unearthing a compound, 1-fluoro-2, 4-dinitrobenzene (DNFB), that inhibited Lohmann's reaction (Eq. 3). Davies and colleagues (Cain & Davies, 1962; Cain *et al.* 1962) showed that when a muscle was exposed to DNFB (i) contraction still occurred, (ii) no PCr breakdown occurred, (iii) there was a decrease in ATP and increases in ADP and AMP, and (iv) the extent of ATP breakdown was proportional to the work performed by the muscle.

These observations are consistent with a coherent biochemical scheme (Table 1) in which ATP hydrolysis is the only reaction that provides the energy required for contraction and that, under normal cellular conditions and in the absence of pharmacological inhibitors, ADP formed during contraction is rapidly rephosphorylated at the expense of PCr (Cain & Davies, 1962; Cain *et al.* 1962; Davies, 1964); this accounts for the constancy of ATP concentration during all but the most exhaustive activity. Clarification of the biochemical reactions underlying contraction paved the way for perhaps the most important development of Hill's ideas, the so-called 'energy balance' experiments of the 1970s and 1980s.

**Energy balance in frog muscle.** In 1971, Roger Woledge laid out a framework for comparing the extent of biochemical changes with the heat produced in isometric contraction. The central tenet, which can be traced back to Hill's Nobel work, was that if the molar heat production (i.e. the heat produced per mole of reaction) associated with each reaction was known and the extent of all the energetically important reactions was measured, then the amount of heat expected to be produced could be calculated and compared to the actual heat produced. However, Woledge also pointed out that the molar heat production of the main heat-producing

**Table 1. Energetically important reactions that can occur during a brief contraction**

| | | | |
|---|---|---|---|
| 1 | ATP hydrolysis | ATP → ADP + Pi | Actomyosin and ion pumping ATPases |
| 2 | Creatine kinase reaction | PCr + ADP → ATP + Cr | Blocked by DNFB |
| 3 | Net initial reaction | PCr → Cr + Pi | |
| 4 | Myokinase reaction | 2ADP → ATP + AMP | Occur only with inhibition of CK or depletion of PCr |
| 5 | | AMP → IMP + $NH_3$ | |
| 6 | Anaerobic glycolysis | Substrate + ADP → ATP + La | La, lactic acid |
| 7 | Oxidative phosphorylation | Substrate + ADP + $O_2$ → ATP + $CO_2$ + $H_2O$ | |

reaction, the breakdown of PCr (Reaction 2, Table 1), under the conditions prevailing in muscle was not known with enough precision to make meaningful comparisons between the heat and chemical change possible. Woledge and colleagues iteratively improved the precision of the value (Woledge, 1973; Curtin & Woledge, 1978; Woledge & Reilly, 1988), greatly increasing the confidence with which energy balance analyses could be made. In parallel, Roger Woledge and Nancy Curtin in the UK and Earl Homsher, Jack Rall and colleagues in the USA set about measuring the heat production and chemical change in frog sartorius muscle (for reviews, see Curtin & Woledge, 1978; Kushmerick, 1983; Woledge *et al.* 1985; Barclay & Loiselle, 2021).

Using the revised molar heat value for PCr, it was immediately apparent that more heat was produced than expected from the chemical breakdown (see Fig. 8), indicating the presence of at least one unknown heat-producing reaction (Gilbert *et al.* 1971). Over many studies, the characteristics of the unknown reaction were mapped in detail, revealing that the unknown reaction was (i) not directly related to cross-bridge cycling, (ii) produced heat at a progressively declining rate during the first 5 s of contraction and (iii) was reversed, absorbing heat and using ATP, over ~30 s after the end of contraction. It was subsequently found that these characteristics largely matched those associated with $Ca^{2+}$ binding by the then newly discovered myoplasmic protein parvalbumin (Fig. 9). $Ca^{2+}$ binding by parvalbumin is now recognized as a mechanism for accelerating the decrease in free myoplasmic $Ca^{2+}$ concentration after contraction of fast-twitch muscles not only of amphibians but also fish and (at least, small) mammals, enabling more rapid termination of contraction than could be achieved by pumping $Ca^{2+}$ from the myoplasm directly into the sarcoplasmic reticulum (SR) (for a review, see Rome, 2006).

The body of work comprising the classical energy balance studies provides the method for characterizing an unknown heat-producing reaction. This includes determining whether its origin is related to force generation or not, mapping the time course with which the heat from the unknown reaction is evolved and absorbed, and establishing whether its reversal is associated with ATP consumption. These remain basic requirements of any future investigation into the origins of an imbalance between heat production and chemical change.

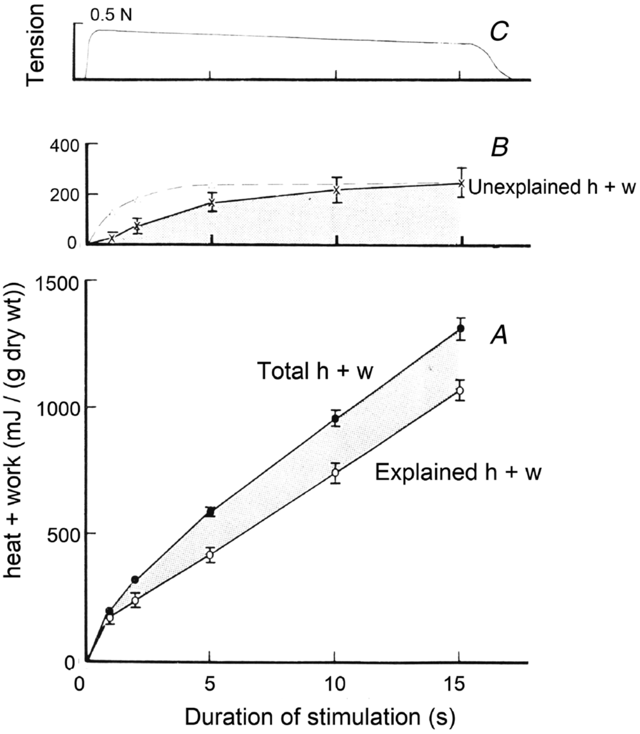

**Figure 8. Energy balance during a 15 s isometric tetanus of frog muscle at 0°C showing some characteristics of its time course**

*A*, solid symbols show the observed heat + work ($h + w$) output, open symbols show the $h + w$ explained by the observed chemical reactions. In *A*, the area between the curves is the unexplained $h + w$. *B*, the time course of unexplained $h + w$; it is produced at a high rate at the start of contraction and then the rate progressively slows over 5–10 s. Beyond that time, no further unexplained $h + w$ is produced. Dashed line is the time course of the labile heat. *C*, representative record of tension produced during the contraction. Figure from Curtin & Woledge (1979) used with permission from John Wiley & Sons.

**Energy balance experiments on mammalian muscle.** A small number of experiments similar to those used for frog muscle have been performed using mammalian muscles. The results for rat soleus, obtained using exactly the same equipment, methods and protocols as used for frog muscles, were very like those for frog muscle: more heat was produced than could be accounted for by the net breakdown of PCr (Gower & Kretzschmar, 1976). Another experiment, using nuclear magnetic resonance rather than conventional chemical analysis to determine the extent of chemical change, confirmed this result (Phillips *et al.* 1993). One might be tempted to say that, as for frog, this excess heat production must also reflect $Ca^{2+}$ binding to parvalbumin; however, rat soleus does not contain parvalbumin (Heizmann *et al.* 1982). Where does the excess heat come from? This is still an open question; no detailed characterization of the unexplained heat produced by rat soleus muscle has yet been performed.

Using mouse fast- and slow-twitch muscle, Crow & Kushmerick (1982) made a different comparison, measuring chemical breakdown during a contraction and the post-contraction oxygen consumption. This technique had previously been used with frog muscles; in that case, more oxygen was consumed than expected from the extent of chemical breakdown, consistent with extra ATP consumption during recovery to move $Ca^{2+}$ from parvalbumin to the SR. However, in the case of the mouse muscles, the amount of oxygen consumed was consistent with the extent of chemical breakdown. For the slow-twitch soleus muscle, this result contrasts with that for rat soleus whereas for the fast-twitch EDL (extensor digitorum longus), the result is not what is expected for a muscle containing parvalbumin.

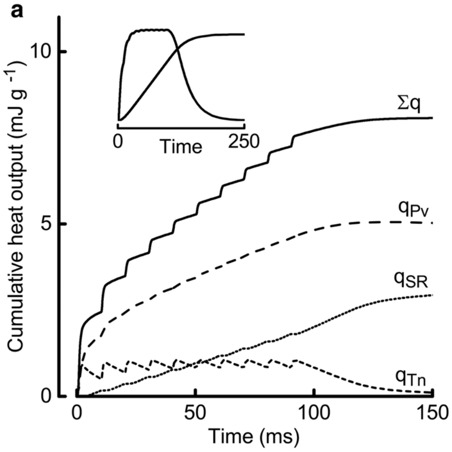

**Figure 9. Time courses of heat output from $Ca^{2+}$-related reactions**
A mathematical model of $Ca^{2+}$ movements within a fibre in response to stimulation was used to calculate the heat produced by $Ca^{2+}$ binding to troponin-C (labelled '$q_{Tn}$') and parvalbumin ($q_{Pv}$) and by the $Ca^{2+}$ pump that returns $Ca^{2+}$ to the sarcoplasmic reticulum ($q_{SR}$). The sum of the heat from these sources is the line labelled Σq, usually referred to as the activation heat. $Ca^{2+}$ binds rapidly to TnC and relatively slowly to parvalbumin. Inset: calculated time courses of force and initial heat output (from cross-bridge cycling and $Ca^{2+}$-related reactions). Mouse extensor digitorum longus muscle at 20°C. From Barclay & Launikonis (2021), used with permission from Springer Nature.

Thus, on the question of whether there is an energy balance in mammalian skeletal muscle, the results are equivocal. We have an example of more heat than can be accounted for by chemical change in a muscle that does not contain parvalbumin, an energy balance in a muscle that does contain parvalbumin, and contradictory results in slow muscles from mouse and rat (for a review, see Barclay & Loiselle, 2021). This remains a fertile area for further investigation.

**A contemporary energy balance approach.** In the energy balance experiments as done in the 1970s and 1980s, the chemical measurements were done on protein-free muscle extracts. Although many different chemicals could be measured in the extract, each muscle extract gave data for only one time point in the contraction. Many muscles and animals were needed to get, for example, the time course of chemical change during a contraction (Fig. 8). The logistics of such experiments may discourage comprehensive studies of that type in the future. However, West *et al.* (2004) used a different approach. In that study, heat production of intact dogfish muscle fibres was compared to the rate of ATP splitting in skinned fibres, with ATP turnover measured using a fluorescent, Pi-sensitive probe. Pi is a product of ATP hydrolysis (Reaction 1, Table 1) and the rate at which it appears during contraction is an index of the rate of ATP splitting. The focus of the study was energy use by cycling cross-bridges (thus excluding heat and ATP use related to intracellular $Ca^{2+}$). The skinned fibres were prepared so that cross-bridge cycling was the only source of ATP splitting. For the intact fibres, the heat production associated only with cross-bridge cycling was determined by subtracting from the total heat production the non-cross-bridge-related heat, with the latter determined by measuring heat output with cross-bridge cycling eliminated by pre-stretch of the fibres to eliminate filament overlap (an approach pioneered by Homsher *et al.* 1972). An energy balance was found: cross-bridge heat production matched that expected from cross-bridge ATP splitting in both extent and time course. Therefore, all the heat produced by cross-bridge cycling could be accounted for by the measured ATP turnover in dogfish muscle.

In summary, although the time course of heat production during a brief (i.e. <5 s) contraction of frog and dogfish muscle is complex (Hill & Hartree, 1920; Curtin & Woledge, 1979; Homsher *et al.* 1979), the information from the energy balance experiments show that it is, in fact, consistent with the expected thermal effects arising from time-varying rates of (i) ATP use by cycling cross-bridges, (ii) ATP use by the SR $Ca^{2+}$ pump, (iii) rapid binding of $Ca^{2+}$ to troponin-C at the start of contraction and dissociation within the time course of force relaxation, and (iv) $Ca^{2+}$ binding relatively slowly to parvalbumin and then dissociating over some 30 s following relaxation (Fig. 9) (Barclay & Launikonis, 2021).

## Heat production and mechanical function

**Elastic models of contraction, 1919–1922.** It has long been recognized that the heat produced by a muscle must be related to the mechanical output (e.g. force produced or work performed) (Liebig, 1842). In exploring the nature of this relationship, some idea of the mechanism by which muscles do mechanical work is required. In the first two decades of the 20th century, the prevailing view was that muscle was an elastic body, in which the force generated during contraction depended on muscle length, or, to account for experimental observations at odds with purely elastic behaviour, a viscoelastic body, for which force depended not only on length but also on the velocity of length changes. For these models, it was envisaged that at the start of a contraction chemical processes generated mechanical potential energy, which was then available to be converted into work or otherwise to heat (for a detailed description, see Hill, 1922).

> *In the resting state a muscle is an elastic and slightly viscous body, with a natural length $l_0$. In the active state it suddenly becomes a new elastic and highly viscous body, with a natural length l, considerably less than $l_0$. It develops a force therefore and tends to shorten.*
>
> (Hill, 1939*b*)

A key feature of these models was that the total energy liberated during a contraction, as work and heat, was determined by the conditions at the *start* of the contraction and was unaffected by events during the contraction. The amount of work that the muscle performed was thought to depend '…upon the art of the experimenter arranging his levers and had no relation to the total energy liberated.' (Fenn, 1923).

**Hill's two-component model of contraction.** When Hill was awarded the Nobel Prize, one of his overseas visitors, Wallace O. Fenn from the USA, was working with Hill to clarify the relationship between heat output and work output. In a large number of experiments, Fenn demonstrated that when shortening, muscles utilized extra energy, above that used for isometric contraction. This was evident not only as work output but also as an increase in the heat produced (Fig. 10). Furthermore, this energy was mobilized only when the shortening commenced (Fenn, 1923, 1924) rather than being determined at the start of the contraction as specified in the elastic or viscoelastic theories. Fenn explicitly stated that his results were not compatible with the viscoelastic theory of contraction. This should have spelled the end of the viscoelastic theory but it did not. In discussing Fenn's findings, Hill (1926*a*) stated:

> *It is difficult to see any simple explanation of these, and of other even more complex phenomena discovered by Fenn …. There are too many factors at work.*

Thus, perhaps because no alternative model was suggested directly by Fenn's results, experimental data continued to be interpreted using the viscoelastic model for some years (e.g. Hill, 1926*a*; Levin & Wyman, 1927). Finally, in 1938 Hill published a paper in which he described further experiments that reinforced and extended Fenn's conclusions, providing the evidence Hill required to finally bury the viscoelastic theory (Hill, 1938).

For this work, Hill used a much improved heat-measuring apparatus (Hill, 1937) and a muscle lever system, described as an ergometer, that allowed precise control of the extent and velocity of muscle shortening (Levin & Wyman, 1927). Importantly, he made his measurements of shortening during a tetanic contraction

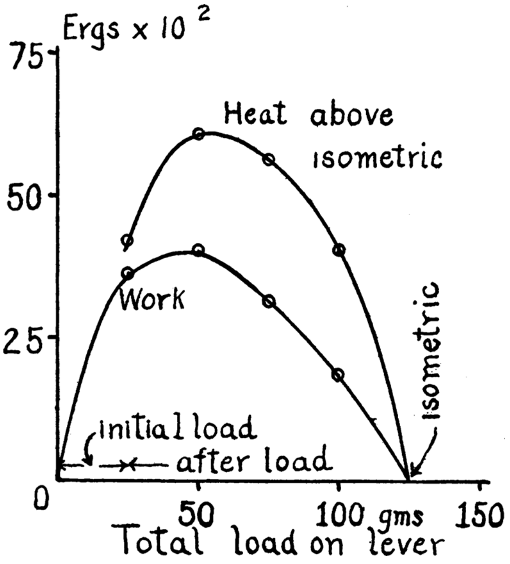

**Figure 10. Fenn's demonstration that performance of work is accompanied by an increase in heat production**
Energy output, as work or heat, is shown on the *y*-axis and the load lifted on the *x*-axis. The heat is shown as the amount in excess of that produced in an isometric contraction (which was 193 × $10^2$ ergs). The work and heat were the totals produced in an afterloaded isotonic twitch of a frog muscle at 0°C. Correction for a calibration error (Hill & Woledge 1962) would require the heat values to be 0.65 of the values shown. Figure from Fenn (1923) used with permission from John Wiley & Sons.

and ensured that force was constant during shortening. He characterized the force–velocity relationship and measured the rate and amount of heat produced during shortening. He formalized the relationship between force ($P$) and shortening velocity ($v$) in what he called the characteristic equation:

$$(P + a) \cdot (v + b) = (P_0 + a) \cdot b \tag{4}$$

$P_0$ is the isometric force and $a$ and $b$ are constants; the right side of the equation is a constant. This expression has proved applicable to all types of striated muscle, with appropriate values of $a$ and $b$ for different muscles, and continues to be the most commonly used mathematical description of force–velocity curves. The ratio $a/P_0$ provides an index of the curvature of the relationship, which is useful for comparisons among muscles. For Hill, the importance of the equation was far greater than simply describing force–velocity data; the equation provided evidence of a direct link between mechanical performance and heat production. Hill (1939*b*) stated:

> *… the constants a and b can be determined independently by measuring the heat of shortening and the rate of energy liberation … and the values so determined prove to be the same as those found by fitting the equation to the purely mechanical observations of load and speed.*

Hill's energy output results were qualitatively consistent with Fenn's but were clearer through the improved control of the timing and extent of shortening provided by the Levin–Wyman ergometer. If the muscle was allowed to start shortening only after a period of isometric contraction, there was a clear increase in the rate of heat output when the shortening started and the amount of extra heat produced was proportional to the extent of shortening. The idea that energy output dynamically follows and is intimately related to the mechanical activity of a muscle *within* the time course of a contraction was a critical step in understanding muscle energetics and remains central to current models of contraction.

In the final section of the 1938 paper, Hill described a new phenomenological model for muscle mechanics, thereby finally spelling the end of the viscoelastic era.

> *The muscle clearly consists of two parts in series, a purely contractile part governed by the characteristic equation, and a purely elastic part governed by ordinary elastic rules.*

This conceptual model explained Hill's use of a protocol in which the force was kept constant during shortening: if the force output is constant, the length of the series elastic component is constant and all the change in muscle length is due to change in the length of the contractile element. In that case, the force–velocity relationship, and the associated energy liberation, can be fully attributed to the contractile element. Hill derived the differential equation required to predict muscle mechanical responses for this model and demonstrated that it provided reasonable simulations of several aspects of mechanical performance (e.g. the time course of force development, power output–velocity relationship). This model was further explored in several subsequent papers and the definitive experimental determination of the characteristics of the contractile and elastic components in isolated frog muscle was presented by Jewell & Wilkie (1958). Hill's 1938 paper arguably has the greatest continuing influence of any of his work: it has been cited almost 7000 times, including over 2500 citations in the last decade (Google Scholar, 13 July 2021). An important component of this ongoing interest is the adoption of the two-component, or Hill-type, model into many models of muscle-generated movement.

**Hill-type muscle models.** In developing computational approaches to analysing movement, it is necessary to have a model of muscle mechanical performance that balances accuracy with computational tractability (for a review, see Zahalak, 1990). Although molecular (i.e. cross-bridge) models of the contractile element (e.g. Piazzesi & Lombardi, 1995; Smith, 2014) can predict a wider range of muscle fibre behaviours, albeit generally without consideration of a series elastic component, than the simpler phenomenological model, the latter facilitates fast computation of the temporal evolution of muscle force and length changes for systems involving multiple simultaneously active muscles. The basic Hill model has been expanded to reflect properties such as the dependence of force output on length, activation and prior activity (e.g. Winters, 1990; Brown *et al.* 1999). Virtual muscles reflecting Hill's two-component concept now reside in complex, comprehensive models of human movement (Cheng *et al.* 2000; Delp *et al.* 2007). Hill's 1938 idea that muscle heat output could be calculated directly from the force–velocity relationship would have made incorporation of energetics into movement models relatively simple. However, the more complex relationship between heat production and force output during shortening described by Hill in 1964 discouraged that approach. Consequently, incorporating energetics into models that include composite changes in muscle length and activation is a challenge (Miller, 2014). Nevertheless, some biomechanical models specifically focus on energetics, typically using empirical energetic profiles of isolated muscles (usually those of small animals) to make reasonable predictions of energy requirements for multi-muscle movements (Fig. 11) (Umberger *et al.* 2003; Tsianos *et al.* 2012; Tsianos & MacFadden, 2016). This evolution seems entirely aligned with Hill's own interests, encompassing the energetics of isolated muscles, moving animals and exercising humans.

**Mechanistic models of muscle contraction.** The other major line of muscle modelling, development of mechanistic models as a tool to understand the molecular basis of the contractile element, also owes a great debt to Hill. In 1957 A. F. Huxley presented the first mathematical treatment of a cross-bridge model of contraction, in which a molecular mechanism was proposed to account for force generation and the associated energy output (due to ATP splitting by cycling cross-bridges) (Huxley, 1957). With selection of suitable rate constants for cross-bridge cycling, the muscle behaviour predicted by Huxley's model accurately matched Hill's force–velocity data and the dependence of heat output on the rate and extent of shortening. Note that at that time it was not known that ∼30% of the ATP turnover in an isometric contraction arose from sources other than cross-bridge cycling (i.e. ion pumping; Homsher *et al*. 1972; Smith, 1972).

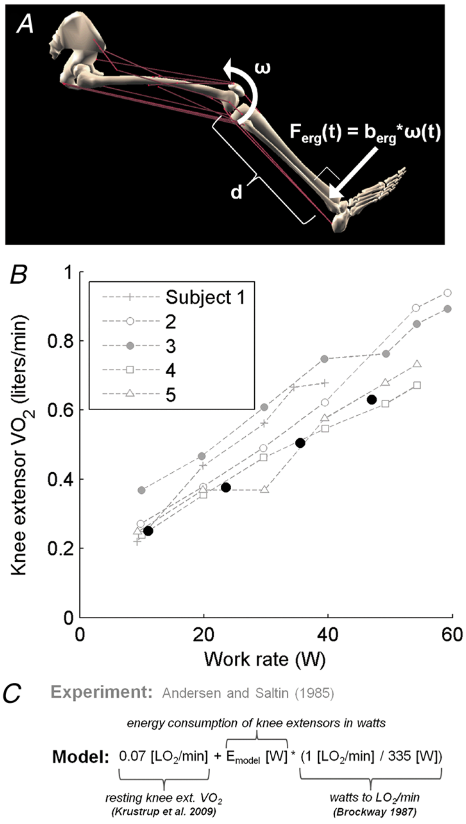

**Figure 11. Example of a biomechanical model used to simulate human knee extensions from Tsianos & MacFadden (2016)**
Top panel: schematic diagram of the dynamic model of human knee extension. Middle panel: comparison between model prediction (filled black symbols) and experimental data for the rate of $O_2$ uptake at different work rates by knee extensors for five human subjects (grey symbols connected by broken lines). The predicted values take account of resting metabolism, energy use by cycling cross-bridges, activation costs and the dynamics of the oxidative recovery system. The experimental data are from Andersen & Saltin (1985) (used with permission of John Wiley & Sons) and the model prediction and figures are reproduced from Tsianos & MacFadden (2016), © 2016 Tsianos, MacFadden under the Creative Commons Attribution 4.0 International licence.

It is interesting that Hill did not appear to embrace the mechanistic cross-bridge ideas. In his revised analysis of the velocity dependence of rate of heat output (Hill, 1964*a*), there is no reference to Huxley's model. Instead, the data were analysed as in 1938 by, at least implicitly, regarding energy output during shortening as arising from a process that occurs in addition to an underlying steady isometric energy output, an idea not consistent with Huxley's model. This is all the more surprising given that Hill had in fact suggested a mechanism to account for his 1938 results that bore some similarities to the Huxley cross-bridge model.

> *Imagine that the chemical transformations associated with the condition of activity occur by passage through, or perhaps by the catalytic effect of, certain active points in the molecular machinery: and that when the tension in the muscle is high the affinities of more of these points are being satisfied by the attractions they exert on one another, and fewer of them are available to take part in chemical transformation. When the tension is low, less of these affinities are being involved in mutual attraction, and more of them are exposed to, or ready to take part in, chemical reaction. The rate at which chemical transformation would occur, and therefore at which energy would be liberated, would be directly proportional to the number of exposed affinities or catalytic groups, and so would be a linear function of the force exerted by the muscle, increasing as the force diminished*
>
> (Hill, 1939*b*).

There are echoes here of Hill's early work on binding kinetics, and the main ideas, namely force being related to the fraction of 'active sites' filled (i.e. cross-bridges attached) and the rate of energy output depending on the number of (actin) sites available for binding, certainly gel with aspects of Huxley-type cross-bridge models.

Contemporary cross-bridge models are more complex than Huxley's original but the predictions of a comprehensive model must still be consistent with measured energy output profiles, and Hill's (1938, 1964*a*) comprehensive data for frog muscle remain the gold standard for demonstrating the validity of most cross-bridge models (e.g. Huxley, 1974; Eisenberg & Hill, 1978; Piazzesi & Lombardi, 1995; Smith, 2014). 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 benchmark due to the comprehensive body of structural, physical and biochemical information available.

## Efficiency of muscle contraction

**Mechanical efficiency.** The efficiency of muscle contraction was a topic that Hill addressed multiple times, starting with one of his earliest muscle papers (Hill, 1913) and concluding with one of his last papers (Hill, 1964*b*). The efficiency of a system is the ratio of the useful energy output from the system to the energy input required to produce that output. For muscle, the output is mechanical work ($w$) or power; the input is less easily defined. Hill reasoned that, in accord with the First Law of Thermodynamics, the total energy output [i.e. the sum of the heat ($q$) and $w$)] provides a direct measurement of the thermal change associated with the 'input' chemical reactions. The 'mechanical' efficiency, as he called it, was then $w/(w + q)$. An advantage of this definition is that $w$ and $q$ have the same units (Hill, 1965*b*).

Efficiency values vary with the velocity of shortening or, alternatively, the load against which the muscle shortens. Efficiency is 0 when muscle work output is 0: that is, if either the velocity of shortening is 0 (i.e. an isometric contraction) or the load lifted is 0 (as when shortening at maximal velocity) and rises to a maximum value between these limits (Fig. 12*A*). Efficiency values for isolated frog muscles reported in papers from Hill's laboratory between 1921 and 1932 were affected by calibration errors that resulted in an overestimate of the heat produced (Hill & Woledge, 1962). Taking that into account, the maximum initial mechanical efficiency of frog muscles was consistently between 35% and 40% (Fenn, 1923; Hartree & Hill, 1928; Hill, 1939*a*, 1964*b*). If the additional energy required for reversal of the initial chemical changes is taken into account, then the overall mechanical efficiency is about half as great, ∼20% (Hill, 1939*a*).

Mechanical efficiency was the definition most often used in experiments on isolated muscle until recently because both $q$ and $w$ could be measured simultaneously and it provided a relatively simple index for making comparisons between, for example, conditions, different anatomical muscles or muscles from different species. However, since the term 'mechanical efficiency' was introduced, much progress has been made in understanding muscle contraction, and the limitations of 'mechanical efficiency' have become obvious (Wilkie, 1974; Barclay, 2019).

**Thermodynamic efficiency.** The discoveries of the cross-bridge cycle as the source of mechanical work and of $Ca^{2+}$ reactions that control activation and relaxation showed that, on its own, mechanical efficiency is not useful for gaining insights into the mechanisms underlying work production. The cross-bridge cycle is the fundamental process that converts chemical energy into work. Its efficiency is termed 'thermodynamic efficiency' and is defined as $w/\Delta G_{\mathrm{ATP}}$, where $\Delta G_{\mathrm{ATP}}$ is the free energy change from ATP hydrolysis (Wilkie, 1960, 1974). Any valid theory of the cross-bridge cycle must be consistent with thermodynamic efficiency values. A crucial difference between mechanical and thermodynamic efficiency is that the definition of the latter excludes from 'input' the energetic costs of $Ca^{2+}$ reactions

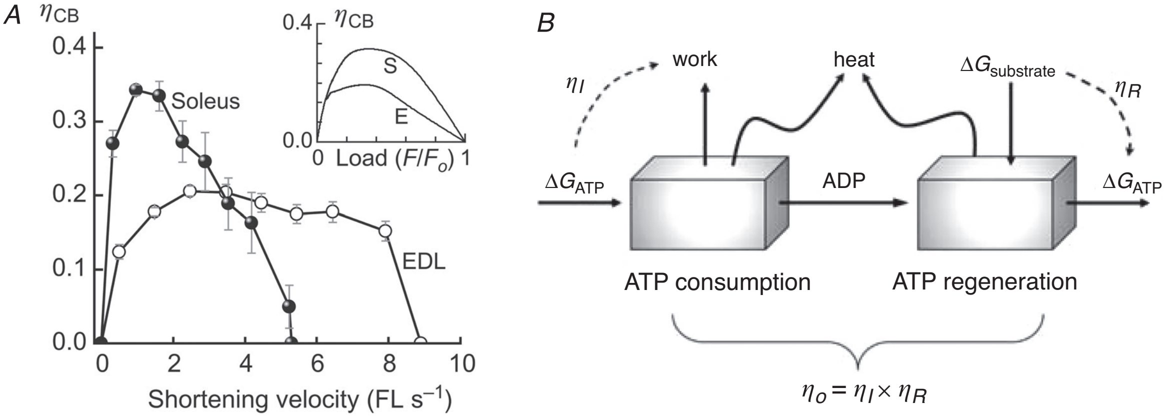

**Figure 12. *A*, efficiency depends on the velocity of shortening**
The figure shows data for cross-bridge thermodynamic efficiency of fast-twitch extensor digitorum longus muscle (open symbols) and slow-twitch soleus muscle (filled symbols) of the mouse. For fast muscle, the peak efficiency is lower than that for slow muscle but remains close to its maximum over a broader range of shortening velocities than that for the slow muscle. Inset: the same curves drawn as a function of the load opposing shortening (S, soleus; E, extensor digitorum longus); load and shortening velocity are related according to the muscles' force–velocity curves. *B*, the series arrangement of the processes of ATP consumption and regeneration. In the diagram the box on the left represents the conversion of a fraction ($\eta_I$; initial thermodynamic efficiency) of the free energy from ATP hydrolysis ($\Delta G_{\mathrm{ATP}}$) into mechanical work; the remainder of the free energy is converted into heat. ADP produced in that reaction is rephosphorylated (box on the right) using free energy extracted from metabolic substrates ($\Delta G_{\mathrm{Substrate}}$) ($\eta_R$; recovery thermodynamic efficiency). The overall efficiency, $\eta_O$, is $\eta_I \times \eta_R$. Both figures from Barclay (2019) in *Muscle and Exercise Physiology*, ed. J. A. Zoldadz, used with permission from Elsevier.

and other overheads necessary for, but not directly part of, the work-generating process. These overheads typically account for 10% of the initial ($q + w$) when shortening with maximum efficiency (Barclay, 2019). Furthermore, the 'input' is $\Delta G_{\text{ATP}}$, recognizing that only free energy can be converted to work, whereas in the case of mechanical efficiency some (i.e. the entropy component) of the 'input' $q + w$ cannot be converted into work (Wilkie, 1960).

Thermodynamic efficiency values have been calculated for skeletal muscles from a number of animals (for reviews, see Smith *et al.* 2005; Barclay, 2017, 2019). These values show that there are considerable differences among muscles from different species and between muscles of different fibre types within a species. For example, the highest cross-bridge thermodynamic efficiency is that of the slow-contracting tortoise rectus femoris muscle, the cross-bridges of which convert 45% of $\Delta G_{\text{ATP}}$ into work. Values only slightly lower have recently been reported for wildebeest locomotor muscle (Curtin *et al.* 2018). At the other extreme, the lowest maximum thermodynamic efficiency is for the fast-twitch mouse muscle at 23%; in comparison, the thermodynamic efficiency of mouse slow-twitch muscle is 35% (Barclay *et al.* 2010). The maximum cross-bridge thermodynamic efficiency for human fast-twitch muscles fibres was reported to be ∼35% (He *et al.* 2000). There appears to be an inverse relationship between power output and efficiency; that is, muscles with a high maximum power output (and thus a relatively flat force–velocity curve, a characteristic of fast-contracting muscles) tend to have lower maximum thermodynamic efficiency than those with low maximum power output (and a more curved force–velocity curve, a characteristic of slow-contracting muscles) (Woledge, 1968; Barclay, 2017).

**Overall efficiency.** It is of practical relevance to know the maximum overall efficiency, in which the 'input' energy cost includes both the energy costs associated with ion pumping and that for the oxidative reversal of the initial chemical change. Including ion pumping costs increases the energy cost of shortening muscle by ∼10% and thus initial thermodynamic efficiency is 2–5% lower than cross-bridge thermodynamic efficiency. The efficiency of processes connected in series (such as initial and recovery processes in muscle, Fig. 12*B*) is the product of the efficiencies of the component processes (Wilkie, 1960, 1974). That is, for muscle the overall efficiency is the product of the initial thermodynamic efficiency and the thermodynamic efficiency of the recovery processes. The latter is the fraction of the free energy change from oxidation of the metabolic substrate that is conserved as free energy available from hydrolysis of the ATP produced by the substrate oxidation. The efficiency of oxidative phosphorylation in muscle is ∼0.8 (for discussions, see Barclay, 2017; Barclay & Loiselle, 2020) so that maximum overall efficiency values, taking account of ion pumping costs, range from 17% for fast mouse muscle to 35% for tortoise muscle. These values correspond to those that would be obtained if the overall cost was calculated from the energetic equivalent of the oxygen consumed to perform the work. In the spirit of Hill, an estimate of the overall efficiency of human muscle can be made using data from isolated fibres (He *et al.* 2000): initial thermodynamic efficiency would be $35/1.1 = 32\%$ and, taking recovery efficiency to be 0.8, then overall efficiency is $32 \times 0.8 = 25\%$ (for further discussion, see Barclay, 2019).

## Summary

In retrospect, the work for which Hill was awarded the Nobel Prize did not mark the pinnacle of his scientific achievements. Instead, the Nobel Prize marked the end of a period in which Hill had largely developed pre-existing ideas – the lactic acid hypothesis of energy supply and the various elastic-based models of contraction – using his combination of experimental and mathematical skills. Hill's most influential and enduring work, at least with regard to muscle physiology, came after 1922. Discoveries by Hill and others between 1922 and 1938 laid the foundations of the modern era of muscle physiology by establishing many of the ideas that underpin our current understanding of muscle mechanics and energetics. Hill's own contribution to these developments was substantial, primarily in establishing the idea that energy use during contraction is driven by the mechanical conditions a muscle encounters during contraction, that the principles established from experiments with isolated muscles can be usefully extrapolated to the energetics of a whole organism during exercise, and that muscle mechanics can be understood as the output of a contractile element in series with an elastic element. This last idea, seemingly quite simple and described in just a few paragraphs near the end of a long paper (Hill, 1938), is now central to the burgeoning field of mathematical modelling of movement, and the Hill-type model continues to be refined to produce a more sophisticated understanding of how multiple muscles act in concert to generate movement and consume energy.

The current technology for measuring muscle heat is highly refined and has the precision, in both time and quantity, required to perform comparisons with chemical breakdown. However, it would be naïve to imagine that improved technology will not contribute to future developments in understanding muscle energetics. For example, there are descriptions in the recent literature of temperature-sensitive fluorescent compounds that can measure the thermal consequences of ATP splitting at the SR (Arai *et al.* 2014), sensitive thermopiles constructed using nanofabrication techniques with novel materials (Peng *et al.* 2018) and chip-based microcalorimeters (Feng *et al.* 2021). Advances in monitoring the extent of the biochemical reactions (such as fluorescent probes for ATP hydrolysis products) are also likely to enhance measurement of the time courses of biochemical changes. Regardless of the methods used, the issues that concerned Hill will continue to be important: accurate calibration of temperature measuring devices, determination of the volume of tissue giving rise to the heat and with which the heat is shared, and accurate identification of the sources of heat. These will be as much of a challenge with new technologies as they were for Hill, but at least as a guide there are Hill's descriptions of his thorough, analytical and critical approach to quantifying muscle energetics.

As we have described, A. V. Hill's scientific achievements, and their ongoing influence, are exceptional. But when, in addition, the scope of his military research, humanitarian work, and his political and diplomatic achievements are taken into account, then, even amongst the ranks of Nobel laureates, A. V. Hill's achievements were truly extraordinary.

## Appendix

### A. V. Hill's books

Hill, A. V. (Hill, 1926*b*). **Muscular Activity**. This book is the publication of the four Herter Lectures given in October 1924 at Johns Hopkins University. This annual lecture series had been endowed in 1902 with the aim of promoting 'a more intimate knowledge of the researches of foreign investigators in the realm of medical science'.

In his preface Hill refers to his interest and involvement in track and field as having motivated him to 'ask many questions which I have attempted to answer here.' The answers used a combination of experiments on frog muscle (first three lectures) and on healthy young athletes (last lecture). The first two chapters/lectures are largely about how force and heat produced by isolated frog muscle can be described by the (later discredited) viscoelastic model of resting and contracting muscle. At that stage, heat measurements were still very slow compared with force measurements. Fenn's 1923 results were shown and recognized as not explicable by the viscoelastic model, but were left as 'a very mysterious problem'. The third chapter is about chemical change with lactic acid production from glycogen being the main focus, in the absence of evidence about other the relevant reactions. The last chapter/lecture returns to the theme set out in the preface and describes studies of exercise by healthy young athletes, covering the concepts at steady state, oxygen debt, etc., as understood at that time.

Hill, A. V. (1927*b*)**. Muscular Movement in Man: the factors governing speed and recovery from fatigue**. The book is based on a lecture series Hill gave at Cornell University, Ithaca, NY, USA, in 1927 under the Non-Resident Lectureship in Chemistry scheme endowed by Mr George Fisher Baker. The first three-quarters of the book is about the 'science of muscular exercise in man'. The final quarter is about experiments on isolated muscle from frog. The first part of the book included results of experiments Hill had done with student athletes during his time at Cornell. Focusing on human exercise was novel at that time; even textbooks of human physiology described muscle physiology in terms of the properties of muscle isolated from frog. Hill's intention was to enhance the scientific status of human exercise studies and to stimulate the interest of chemistry students in the physiology of muscle.

Hill, A. V. (1927*a*). **Living Machinery. Six Lectures delivered before a 'juvenile auditory' at the Royal Institution, Christmas 1926**. In the introduction to the published lectures Hill states: 'It is remarkable how little most people know about their own bodies … I shall try to give you some idea of the workings of two of the most important parts … the muscles which move it about, and the nerves which arrange where and how it shall be moved.' His daughter, Janet (8 years old), proposed that he do experiments on her during the lecture, and her proposal was 'seized upon at once' by the other three children. Their pet dog also joined in. Hill covered a wide range of topics: nerves, muscles, the heart, lungs, blood, speed, strength and endurance. The Royal Institution Christmas Lectures continue, now televised, as an annual event with enthusiastic participation by the 'juvenile' audience.

Hill, A. V. (1931). **Adventures in Biophysics**. This is series of five lectures given at the invitation of The Johnson Foundation of Medical Physics at the University of Pennsylvania, Philadelphia, PA, USA, in October 1930. The chapters cover experiments on vapour pressure changes associated with muscle contraction and recovery, state of water in tissues, concept of the steady state, time-related events and the mechanics of contraction. In addition to describing fast-moving research areas, Hill's aim was to describe 'scientific adventures', in other words the human side of research including 'perplexities that beset us' and 'joy of occasional success'.

Hill, A. V. (1932*a*). **Chemical wave transmission in nerve**. The Liversidge Lecture given at the invitation of Christ's College, Cambridge, UK, and specifically aimed at chemists. By describing the basic facts and characteristics of nerve activity (the realm of physiologists at that time), Hill aimed to attract the interest and participation of chemists, and also physicists and engineers in research on this 'difficult-and therefore the most attractive-of all scientific problems…the nature of the change… which is transmitted in nerve'.

Hill, A. V. (1960). **The Ethical Dilemma of Science**. This book is a wide-ranging collection of writings: addresses to organizations, speeches in Parliament, extracts from official reports and letters to the scientific press. His letters to newspapers often showed his skilful use of wit.

AV wrote in the introduction to the final chapter, but this applies to most of the book, that his motivation was 'the conviction … that application of scientific discovery and method could greatly improve the lot of man anywhere, and… that science itself can serve uniquely as a bond of interest and co-operation between sensible people everywhere.'

The book's title comes from his presidential address to the British Association in 1952. It is included in Chapter 1 which is 'composed of philosophical… reflexions'.

Chapter 2, 'Trailing one's coat', contains mostly writings about the role of science in society.

Chapter 3, 'About people', 19 essays 'about various friends'.

Chapter 4, 'Refugees'.

Chapter 5. 'Science in two world wars'.

Chapter 6. 'Science in the Commonwealth'.

Hill, A. V. (1965*b*). **Trails and Trials in Physiology. A Bibliography, 1909–1964**; this reviews certain topics and methods and a reconnaissance for future research. The sub-title describes the contents very well. The bibliography of publications from his laboratory includes a few sentences after each entry indicating its significance in retrospect.

Hill, A. V. (1970*b*). **First and Last Experiments in Muscle Mechanics** is about his investigations of the mechanics (force, velocity shortening) of contracting muscle, and the roles of the series elastic component and the 'active state'. It was written after Hill had retired to Cambridge having left his UCL laboratory. It was based on a 'vast amount of experimental material …results and conclusion too variegated to put into ordinary scientific papers.' He wrote the book because it was 'better to speculate rather at large, to "let oneself go" in a way that editors of scientific journals… forbid.'

**Memories and Reflections**. After retiring back to Cambridge, Hill put together *Memories and Reflections* mostly from earlier writings. In 1974 he gave the typescript with his hand-written annotations to the Archive Centre at Churchill College, Cambridge, UK. In 2017, Prof. Roger Thomas (Department of Physiology, Development and Neuroscience, University of Cambridge) gave a newly transcribed and edited version to the Archive. The three original volumes as well as the new one can be downloaded from www.chu.cam.ac.uk/archives/collections/memoirs-v-hill/. The Churchill Archive holds the copyright.

In Hill's Preface to *Memories and Reflections* he wrote that although a physiologist, '…at intervals I was persuaded, or was conscripted, or even deliberately chose, to do something quite different; which provided many friendships and adventures, as well as disappointments. These are reflected in various things I have written…' *Memories and Reflections* is a collection of some of these writings. Hill continues that there is a strong element of humour, sometimes 'just for fun. But there was usually a better reason. Over the years I have been in frequent conflict with the inhumanity of nonsense, ranging from Hitler's to anti-vivisection, …Nonsense is generally best defeated by counter nonsense, or derision; that is better than arguing about it seriously.'

*Memories and Reflections* consists of 132 numbered essays in eight Chapters, 357 pages of typescript.

Chapter 1, About People. Essays (1)–(44), pp. 6—120.

Chapter 2, Politics. Essays (45)–(62), pp. 121—161.

Chapter 3, Science, Citizenship, Morality and History. Essays (63)–(78), pp. 162—210.

Chapter 4, Experiments on Animals and Man. Essays (79)–(91), pp. 210—242.

Chapter 5, War. Essays (92)–(107), pp. 243–284.

Chapter 6, Grave or Gay. Essays (108)–(130), pp. 285—330.

Chapter 7, Autobiographical Sketch revised from first version published. Essay (131).

Chapter 8, Notes on Eight Books. Essay (132), pp. 347—357.

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## Additional information

### Competing interests

The authors declare that there are no conflicts of interest.

### Author contributions

Both authors contributed equally to all aspects of the work involved in preparing this paper, qualify for authorship, and approved the final version of the manuscript.

## Funding

None.

## Acknowledgements

The authors thank Dr Andrew Brown for helpful comments on the manuscript.

Open access publishing facilitated by The University of Queensland, as part of the Wiley – The University of Queensland agreement via the Council of Australian University Librarians.

## Keywords

muscle, muscle efficiency, muscle energetics, muscle heat production, Nobel Prize in Physiology or Medicine 1922

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