

# historical perspectives

## Scientific contributions of A. V. Hill: exercise physiology pioneer

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**Bassett, David R., Jr.** Scientific contributions of A. V. Hill: exercise physiology pioneer. *J Appl Physiol* 93: 1567–1582, 2002; 10.1152/jappphysiol.01246.2001.—Beginning in 1910, A. V. Hill performed careful experiments on the time course of heat production in isolated frog muscle. His research paralleled that of the German biochemist Otto Meyerhof, who measured the changes in muscle glycogen and lactate during contractions and recovery. For their work in discovering the distinction between aerobic and anaerobic metabolism, Hill and Meyerhof were jointly awarded the 1922 Nobel Prize for Physiology or Medicine. Because of Hill's interest in athletics, he sought to apply the concepts discovered in isolated frog muscle to the exercising human. Hill and his colleagues made measurements of O<sub>2</sub> consumption on themselves and other subjects running around an 85-m grass track. In the process of this work, they defined the terms "maximum O<sub>2</sub> intake," "O<sub>2</sub> requirement," and "steady state of exercise." Other contributions of Hill include his discoveries of heat production in nerve, the series elastic component, and the force-velocity equation in muscle. Around the time of World War II, Hill was a leading figure in the Academic Assistance Council, which helped Jewish scientists fleeing Nazi Germany to relocate in the West. He served as a member of the British Parliament from 1940 to 1945 and as a scientific advisor to India. Hill's vision and enthusiasm attracted many scientists to the field of exercise physiology, and he pointed the way toward many of the physiological adaptations that occur with physical training.

history; O<sub>2</sub> intake; O<sub>2</sub> debt; maximum O<sub>2</sub> uptake; running economy; muscle; heat production; lactic acid; anaerobic

ARCHIBALD VIVIAN (A. V.) Hill (1886–1977), the British physiologist, has been referred to as "the giant in the field of exercise physiology" (12). In the 1920s, his writings and lectures brought recognition to the emerging discipline of exercise physiology (76). For many years, Hill (Fig. 1) was regarded as the world's foremost authority on muscular activity (100, 111).

Modern-day physiologists can benefit from knowledge of Hill's scientific discoveries. His most important and lasting contributions were in the areas of muscle

calorimetry, muscle mechanics, and applied exercise physiology. Previous authors have successfully chronicled A. V. Hill's life (45, 78) and scientific career (58, 77, 78), and it would be difficult to improve on their efforts. Instead, this article will attempt to summarize his most important contributions and place them in historical perspective by viewing them in the context of more recent findings. Hill introduced many physiological concepts, and he established enduring paradigms that, with modification, are still in use today.

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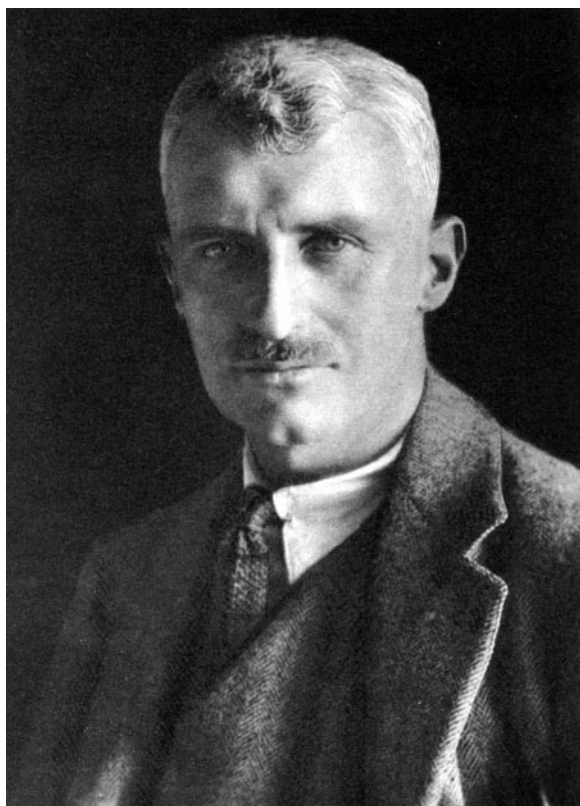


Fig. 1. A. V. Hill, Nobel Laureate (Physiology or Medicine, 1922). Photograph from *Muscular Movement in Man* (55). According to a newspaper account of 1928, "The convention of a dry-as-dust professor was never shattered more completely than by Prof. Hill. He is still a youngish man and has the frame and figure and complexion of a man who rarely leaves work in his garden or of a cricketer. His hair is almost white and contrasts in an extraordinary way with the great vigour and freshness of the man." From Margaret Hill and Margaret Keynes (68).

Although Hill's initial attempts to understand a problem were sometimes proven wrong, his strengths were knowing how to state a hypothesis clearly and concisely and his insistence on rigorous testing of the hypothesis. As one of his colleagues, Bernard Katz, put it

A.V. loved to make provocative statements and did not mind "sticking his neck out", sometimes to inflict the punishment himself later on! If one reads his commentary in *Trails and Trials in Physiology*, it is clear that he regarded errors in interpretation and the "built-in obsolescence" of scientific theories as an inevitable and indeed necessary part of progress and the more provocative the statement, the better it was in jollying progress along. (78)

#### HEAT PRODUCTION IN ISOLATED MUSCLE

Hill is best known for his work on measurement of heat production in frog muscle. The unique property of heat production in muscle that fascinated him was "its intimate relation to mechanical and chemical changes involved, and the sensitivity and speed of the methods available" (58). He collaborated with the biochemist Otto Meyerhof to unravel the distinction between aerobic and anaerobic metabolism, for which they were

awarded the 1922 Nobel Prize. Many years later, with the discovery of phosphagen compounds in muscle by biochemists, Hill was involved in clarifying the roles of adenosine triphosphate (ATP) and phosphocreatine (PCr) in muscle contraction (78).

*Historical background.* A. V. Hill was born in Bristol, England in 1886. His family had little money, but Hill paid for his education by winning one scholarship after another, a "professional schoolboy" of sorts (11). As a teenager he attended Blundell's school in Tiverton. He was awarded a scholarship to Trinity College in Cambridge, England (1905–1909), where he completed a double major in mathematics and the natural sciences (chemistry, physics, and physiology). He later accepted a fellowship in physiology that allowed him to stay on for four more years (45, 78).

After arriving at Trinity College, Hill began studying under Fletcher and Hopkins. These two researchers had already conducted studies on the effects of  $O_2$  on muscle contraction. In 1907 they published a paper showing that muscles can continue contracting in the absence of  $O_2$  and that lactic acid is formed under these conditions (35). The laboratory director at that time was Dr. John Langley, who owned and edited the *Journal of Physiology* from 1894 to 1925. Langley suggested to Hill that he should follow up on this work and "settle down to investigate the efficiency of cut-out frog's muscle as a thermodynamic machine" (Ref. 58). He also provided Hill with a device that consisted of a thermocouple and galvanometer for conducting these experiments.

The first successful attempt to measure heat production in isolated muscle occurred in 1848. Over the next half-century, German and Swedish investigators continued to investigate the problem. These researchers established several important facts: 1) heat is produced in muscle in response to a twitch or a tetanus, 2) in tetanus the rate of heat production declines as the stimulation continues, and 3) the ratio of work to total energy in contraction is dependent on the load and has a maximum value of 0.30 (58).

Despite these advances, there were many misconceptions about biochemistry. In the late 1800s, it was believed that the chemical processes that occurred during muscle contractions were entirely oxidative. A popular theory held that the energy needed for cellular metabolism was provided by the explosive splitting of "inogen" and "biogen," hypothetical giant molecules made unstable in the presence of  $O_2$  (35, 82). Lactic acid had been found in the muscles of hunted deer (96), but the significance of this acid remained unclear. In short, the presence of an anaerobic pathway in muscle was not suspected.

*Temperature-recording devices.* In 1911 Hill traveled to Tübingen, Germany to visit Karl Burkner's laboratory (110). There he received instruction on methods of constructing thermopiles, which are sensitive instruments capable of measuring very small changes in temperature (Fig. 2). Hill also met Friedrich Paschen, a physicist who taught him about moving-magnet galvanometers. The temperature recording of the muscle

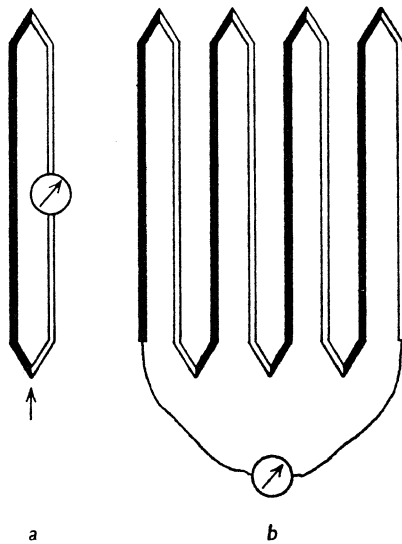


Fig. 2. *a*: Illustration of a thermocouple. Arrow indicates the junction between two dissimilar metals (1 represented as black, the other as white). If the temperature of the 2 junctions is different, an electric current is generated. *b*: 4 thermocouples in series, also known as a thermopile. From Aidley (2). Reprinted with the permission of Cambridge University Press.

was converted to a voltage, which was measured by using the galvanometer (Fig. 3). A light beam was projected onto a mirror affixed to a wire, and small movements due to voltage changes were then projected onto a revolving drum or an oscilloscope (2).

The thermogalvanometer given to Hill by Langley could only measure the total heat produced in a muscle tetanus. In 1912, using the improved methods of Burker (14) and Paschen, Hill was able to show that heat was produced both during and after a muscle contraction. Later refinements allowed improvements in the speed and sensitivity of the temperature-recording devices. By 1931, Hill was able to measure the

change in temperature during a single frog muscle twitch to the nearest  $0.00015^{\circ}\text{C}$  (58).

In 1937, Hill introduced his own invention, a special “protecting” region to solve a problem often seen during isotonic contractions (58). As the muscle shortened, different regions of it would come into contact with the thermopile. Small differences in temperature along the surface of the muscle tended to create artifacts in the readings. But with the advent of the protecting region, the artifacts could be avoided. These continual improvements in temperature-measuring devices made possible the discoveries that will be discussed next.

*Phases of heat production, 1920.* Hill’s physiology career was interrupted by the outbreak of World War I, and his physiology research was put on hold from 1914 to 1919. He devoted himself instead to the war effort, and he was put in command of an anti-aircraft experimental section. But after the war ended, Hill returned to Cambridge and soon thereafter accepted a faculty chair at Manchester University (1920–1923).

In 1920, Hill and Hartree (60) examined the rate of heat production in isometric muscle contractions (Fig. 4). This paper is of historic importance because it distinguished the various phases of heat production in isolated skeletal muscle during contraction, relaxation, and recovery. In addition, it showed that heat production during contraction and relaxation is independent of  $\text{O}_2$ , i.e., anaerobic.

Hill and Hartree (60) observed that the initial heat (heat produced during contraction and relaxation) was not affected by lack of  $\text{O}_2$ . Previously, Weizsacker’s laboratory had reported that the heat generated during a contraction was independent of  $\text{O}_2$ , but their instruments did not have the time resolution needed to separate out the various phases of contraction. Hill and Hartree confirmed that regardless of whether the muscle was placed in  $\text{O}_2$  or  $\text{N}_2$ , the initial heat was identi-

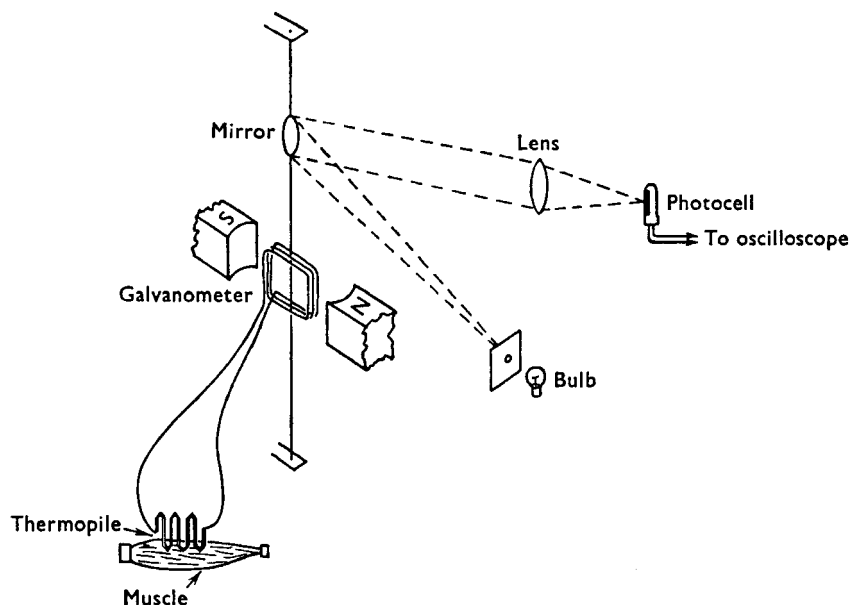


Fig. 3. Moving magnet galvanometer used to record heat production in muscle. From Aidley (2). S, south; N, north. Reprinted with the permission of Cambridge University Press.

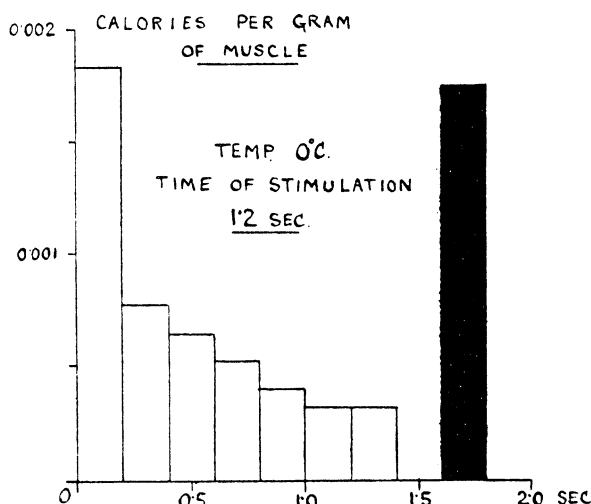


Fig. 4. Heat produced in an isolated frog sartorius during an isometric tetanus. The muscle was electrically stimulated for 1.2 s. There is a large immediate release of heat on contraction, followed by a gradually diminishing rate of heat output, which falls to zero when stimulation ceases. Solid bar represents the amount of heat produced in the first few seconds of recovery; thus it represents only a portion of the recovery heat. (For the time course of the recovery heat, see Fig. 6.) From Hill and Hartree (60), with the permission of the Physiological Society.

cal. However, the recovery heat was much greater in the presence of  $O_2$ .

**Nobel Prize, 1922.** Hill received the 1922 Nobel Prize for Physiology or Medicine "for his discovery relating to the production of heat in muscle." He shared the prize with the German biochemist Otto Meyerhof (Fig. 5), who demonstrated that, in the recovery phase, lactic acid can be reconverted to glycogen or combusted by oxidative metabolism. Hill and Meyerhof (65) published a paper summarizing what was known (or believed) about muscle contraction up to that time. Although some of the details were later shown to be incorrect, the underlying theme was that two distinct pathways are responsible for supplying the energy need for muscle contraction.

Meyerhof and Hill traveled to Stockholm in 1923 to receive their Nobel prizes. In his Nobel Prize lecture, Hill (53) stated

One of the fundamental characteristics of striated muscle, and the one involving the greatest difficulty in investigation, is the great rapidity with which changes take place in it. There is no doubt that ultimately the muscle is a chemical mechanism, in the same way for example as a Daniell's cell or an accumulator is a chemical mechanism. If we were aware of all the chemical events, we should know all that was necessary about the machine which we are studying. Unfortunately, the investigation of chemical events is a slow and laborious process.

Meyerhof and Hill's combined talent was to bring together information from the fields of biochemistry and thermodynamics, to yield a unique view of the energetic processes in muscle. Hill later wrote, "measurements of heat production are no substitute for direct chemical analysis. But they do suggest problems

to the chemist, and provide a framework into which his detailed machinery must be fitted" (58).

At the time of their Nobel prize, Hill and Meyerhof proposed that the energy needed for muscle contraction came directly from the breakdown of a lactic acid precursor. A few years previously, Embden and Laquer (31, 32) had discovered "lactacidogen," a hexose-diphosphate compound formed from glycogen (fructose-1,6-diphosphate). Hill (53) believed that breakdown of this compound to lactic acid caused a release of energy, which was then used in muscle contraction. Over the next decade, additional steps in the glycolytic sequence were discovered, and by 1932 Embden had



Fig. 5. A. V. Hill and Otto Meyerhof, on a road trip to Stockholm for the Physiological Congress in Stockholm in 1926. They coauthored only 1 paper during their careers, but Hill kept a stack of 200 reprints by Meyerhof and his colleagues next to his desk and referred to them constantly. They maintained a close correspondence and had many reunions after the war, in London, Plymouth, Barcelona, Heidelberg, Berlin, and Rome. Reprinted from Hill (46), copyright 1950, with permission from Elsevier Science.

proposed the overall scheme for the glycolytic pathway (81). However, it was not until 1942 that Meyerhof and other workers succeeded in identifying all of the glycolytic intermediates and enzymes (36).

In 1923, shortly before the Nobel prize was announced, Hill accepted a professorship at University College, London, where he remained until 1951. Hill (54) recalled, "When I got to University College, the students made a terrific rumpus about it. I have some beautiful photographs of me being carried on their shoulders around the college." The students had been told how, on one occasion, E. H. Starling had (jokingly) remarked to Hill, whose main training was in mathematics and physics, that Hill knew not a word of physiology. Now the students carried Hill up to Starling's room and began chanting, "We want Starling, we want Starling!" Starling came out and the students cried: "Who said he didn't know any physiology?" Starling replied, "I said he didn't. He doesn't know a damn word!" After that, Hill said, "The students carried me out on to Gower St. and stopped the traffic and showed me to the taxi drivers and people like that. Finally they returned me to my usual place of residence" (54).

*Revolution in muscle physiology, 1932.* In 1932, Hill published a paper entitled "The Revolution in Muscle Physiology" (57). It described new developments in biochemistry in the previous 5 years concerning the fuels for muscle contraction. In 1927, the presence of "phosphagen" was discovered in muscle (29); it would later become known as PCr. Meyerhof (95) then measured the heat of hydrolysis for PCr and found it to be extremely high. Soon after that, ATP was discovered. Then, in 1929, Lundsgaard (85–89) showed that lactic acid is formed in recovery, with simultaneous resynthesis of phosphagen. Finally, the distinction between

anaerobic glycolysis and breakdown of high-energy phosphate compounds had been made.

Previously, Hill and Hartree (60) in 1920 had noted a strange finding. Even in the absence of  $O_2$ , there was a small level of heat production in the first 3 min of recovery. They called this the "delayed anaerobic heat" production, but they were at a loss to offer any biochemical explanation for it. Because of technical problems in measuring the small magnitude of the delayed anaerobic heat and the lack of a plausible mechanism, many researchers were skeptical of its existence. Even Hill himself could not be sure that it existed (58). But, with the advent of more sensitive and stable measuring devices, they later confirmed its presence (41, 42) (Fig. 6).

Now Hill concluded that the delayed anaerobic heat was due to anaerobic glycolysis, with simultaneous restoration of high-energy phosphates (57). During a contraction, the initial heat production is due to breakdown of high-energy phosphates. With recovery in  $O_2$ , these compounds are regenerated by aerobic metabolism. However, in the absence of  $O_2$ , the muscle is forced to rely on anaerobic glycolysis to regenerate ATP and PCr. The discovery by Hartree and Hill (41) of the delayed anaerobic heat in 1920 was one of the first signs that two distinct anaerobic pathways existed (58).

*Discoveries in muscle mechanics, 1938.* Physiologists had long attempted to explain the mechanical properties of muscle in relation to heat production (2, 67). Early theories held that a stimulated muscle was like an elongated spring that has the capacity to shorten and do work. The force exerted by a pure elastic body is dependent solely on its length; however, in muscle, force is dependent on the velocity of contraction. Thus

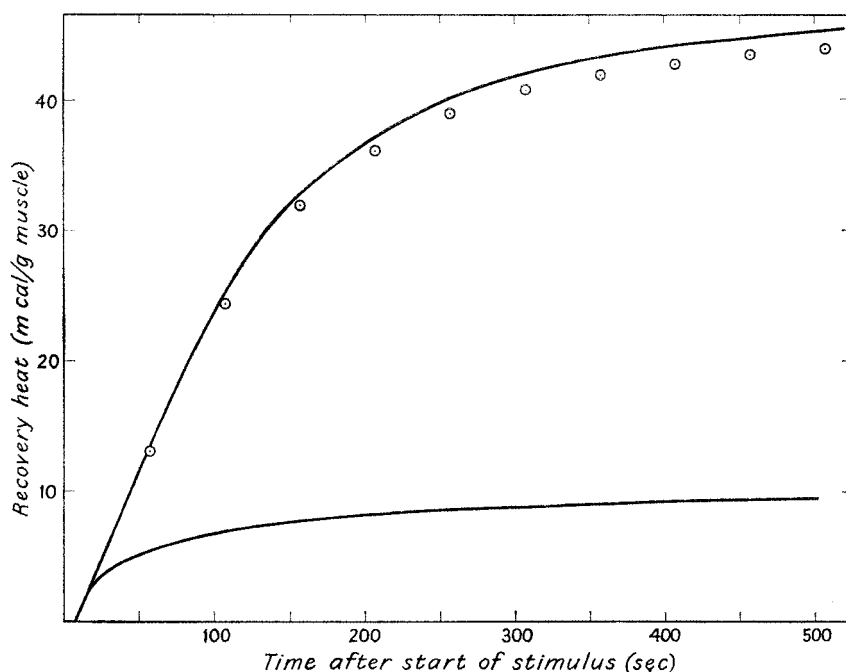


Fig. 6. Time course of the recovery heat production after 1.5-s tetanus in frog sartorii. Upper curve illustrates the recovery heat production when the muscle is placed in  $O_2$ . Lower curve shows the recovery heat production in  $N_2$  (also called the "delayed anaerobic heat production"). From Hill (58), with permission of Lippincott Williams and Wilkins.

the “elastic” theory could not be true. Gasser and Hill (37) then proposed that some of the elasticity of the muscle is dampened by an internal viscosity. They imagined that “any change of shape of the muscle would require the viscous fluid to pass, more or less rapidly, into a new configuration.” At rapid speeds, less tension was left over to appear at the ends of the muscles (2).

In 1923, Fenn (33, 34) disproved the viscoelastic theory, but others were slow to see the importance of his findings. He showed that a muscle releases more heat during a shortening contraction than during an isometric one (the “Fenn effect”). Fenn likened muscle, from an energetic standpoint, to a windlass and chain, where “every link of the chain which is wound up involves the expenditure of so much energy at the moment of winding. The chain may be under great tension, but being inextensible it possesses no potential energy.”

In 1938, Hill (48) published a paper, “The heat of shortening and the dynamic constants of muscle.” The major finding in Hill’s 1938 paper was that, even in “isometric” contractions, the muscle fibers initially shorten. Building on Fenn’s work, Hill now had an explanation for why the initial heat is so much higher than the maintenance heat during an isometric tetanus. Hill proposed that skeletal muscles have two distinct components in series with each other: a contractile component that shortens when stimulated and an elastic component that lengthens under tension (Fig. 7). This simple finding had escaped Hill and other researchers for years. In retrospect, Hill wondered

Why did it take so long to realize that the series elastic component of muscle (or of its recording devices) exerts a dominating influence on the observed form of a contraction; that an isometric contraction is not isometric at all so far as the muscle fibers are concerned; that the

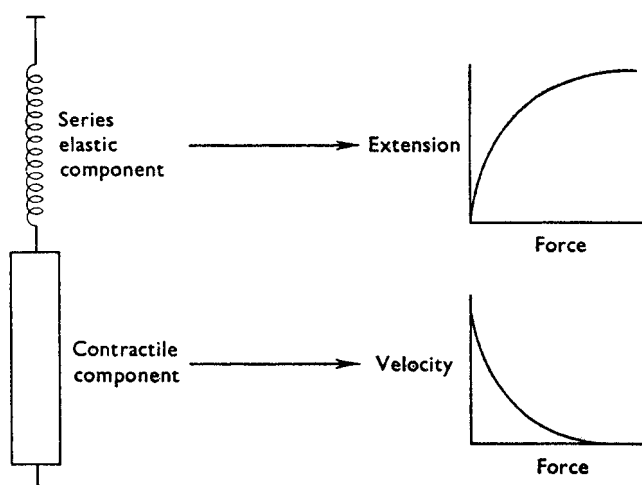


Fig. 7. Hill’s 2-compartment model of contracting muscle, showing the “series elastic” and contractile components. The force-velocity curve defines the properties of the contractile component, whereas the force-extension curve defines the properties of the series elastic component. From Aidley (2). Reprinted with the permission of Cambridge University Press.

mechanical work performed may not be far short of a maximum . . . ? (58)

Hill (48) proposed an empirical relation for the force-velocity curve that emphasized the hyperbolic form of the data. This equation is still commonly used today:  $(\text{force} + a)(\text{velocity} + b) = (\text{force}_{\text{max}} + a)b$ , where  $a$  and  $b$  are constants. The functional importance of the Hill equation is that it allowed scientists to clearly distinguish between slow-twitch and fast-twitch muscles and, using this relationship, develop force-power curves and determine peak power (R. Fitts, personal communication). The Hill curve applies to isolated muscle fibers, whole muscles, and living organisms. Hill’s curve has withstood tremendous scrutiny over the years, and it is widely regarded as a robust descriptor of muscle mechanics (40). The lasting impact of Hill’s 1938 paper is evidenced by the fact that it was cited 1,920 times between the years of 1970 and 2000.

*Hill’s challenge to biochemists, 1950.* In 1950, Hill published “A challenge to biochemists” (46). The discovery of ATP had led researchers to propose that this compound was the immediate supplier of energy for muscular contraction (84). Hill reasoned that, if this were true, one could show that ATP is used up in the process of contraction. He proposed stimulating a muscle, rapidly freezing it to prevent further biochemical changes, and then performing assays to determine the amount of high-energy phosphates present (2).

Hill joked that the “stimulus” was ineffective at first, but it eventually created the desired “response” and several groups began working on the problem (2). In the presence of iodoacetic acid (which blocks glycolysis and prevents PCr from being resynthesized), muscle contraction was shown to cause breakdown of PCr (17, 18). But this finding did not help discern whether ATP or PCr was the immediate supplier of energy for contraction. Hill’s challenge was finally met by Cain and Davies in 1962 (16). They poisoned muscles with fluoro-dinitrobenzene, thus preventing PCr from re-converting ADP to ATP. The amount of ATP lost with each muscle twitch was determined and was found to account for the energy needed to cause the muscles to shorten (2). Finally, ATP had been shown to be the direct source of energy for muscle contraction (Fig. 8).

In the 1950s, Hill continued to pursue the methods of learning about muscle that he believed were the most important: heat production, biochemistry, and force measurements (78). At that time, other investigators began using new techniques like X-ray diffraction and electron micrography. Ultimately, the ultrastructure of striated muscle turned out to have crucial importance for the sliding-filament theory, which was independently proposed by H. E. Huxley and Hanson (75) and A. F. Huxley and Niedergerke (74) in 1954 (28). With the advent of the sliding-filament theory, investigators became more interested in the molecular basis of muscle contraction and the events that regulate actin and myosin binding (78).

Hill continued to be held in high esteem, even by the sliding-filament generation. This was in evidence at a

## THE HISTORY OF BIOENERGETICS

Substances thought to directly provide  
the energy for muscle contraction:

1800's	"Intramolecular" Oxygen
1923	Lacticacidogen
1930	Phosphocreatine
1950	Adenosine Triphosphate

Fig. 8. History of muscle bioenergetics. At turn of the 20th century, "intramolecular oxygen" was thought to directly provide the energy needed for muscle contraction. In 1923, the work of Embden, Meyerhof, and Hill led to the view that "lacticacidogen" (an energy-rich compound intermediate between glycogen and lactate) provided the energy needed for muscle contraction. At that point,  $O_2$  was relegated to the recovery phase. Then, with the revolution in muscle physiology (1927–1932), "phosphagen" (i.e., phosphocreatine) rose to supremacy, only to be replaced later by ATP (74).

1964 conference, "A discussion of the physical and chemical basis of muscular contraction." In his opening remarks, A. F. Huxley (73) explained that the title of the conference was almost the same as that of a 1949 meeting organized by A. V. Hill. He gladly noted A. V. Hill's presence in the audience and remarked that one of the papers was to be presented by one of A. V.'s sons, David K. Hill (66). A number of A. V. Hill's important contributions to muscle physiology were acknowledged, including the celebrated "A challenge to biochemists" (46).

### APPLIED EXERCISE PHYSIOLOGY

Although Hill excelled at basic science, he sought to extend his discoveries to the applied physiology of exercise and  $O_2$  uptake ( $\dot{V}O_2$ ) in humans (11). The study of athletic performance captured Hill's interest, and he was delighted when his experiments on isolated contracting muscle and exercising humans "confirmed and threw light on one another" (58).

From 1922 to 1924, Hill and co-workers (59, 61–64) published a series of papers on muscular exercise, lactic acid, and the supply and utilization of  $O_2$ . These papers were landmark studies in the field of exercise physiology. They helped establish the concept of "anaerobic" energy production during exercise, with oxidative restoration in recovery. Ever since Lavoisier's experiments in the 1780s, it had been known that animals consume  $O_2$  and produce  $CO_2$  and heat in respiration (12). However, the concept of an  $O_2$ -independent energy pathway had not yet been recognized. The general view was that energy was produced via aerobic metabolism on a "pay-as-you-go" basis. Hill's

unique contribution was that he showed the existence of a "buy now, pay later" method of producing energy by anaerobic pathways.

Hill's interest in the physiology of athletics was a result of having competed in cross-country and track in his earlier years (78). He recorded personal records of 53 s in the 440-yd dash, 4:45 in the mile, and 10:30 in the 2-mile (63). Hill was characteristically modest about his running accomplishments. In one article (64), the physical characteristics of a research subject identified as A. V. H. are described: "the subject is of athletic build, 11 [and] 1/2 stone (73 kilos), fairly fit, 35 years of age, and used to running; he is not however, and never has been, a first class runner. . . ." In another article we learn that the subject had a maximal  $O_2$  uptake ( $\dot{V}O_{2\max}$ ) of 4.175 l/min (or 57 ml·kg<sup>-1</sup>·min<sup>-1</sup>), despite the fact that his only training was running 1 mile slowly before breakfast (63)!

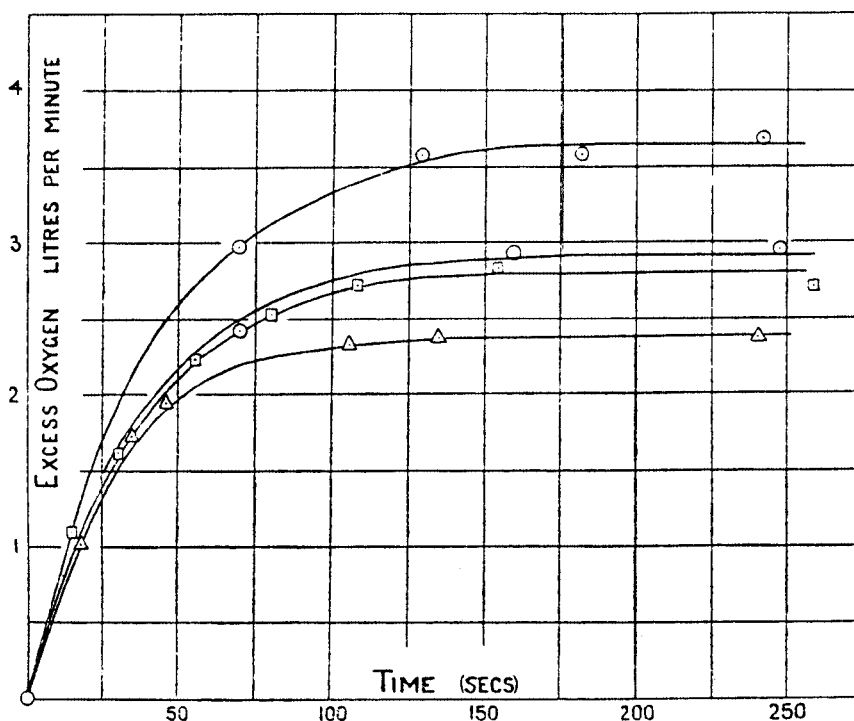
Hill's digression into applied exercise physiology was puzzling to some. In his lectureship at Cornell University in 1927, Hill (55) elaborated on this

The complaint has been made to me—"Why investigate athletics, why not study the processes of industry or of disease?" The answer is twofold. (1) The processes of athletics are simple and measureable and carried out to a constant degree, namely to the utmost of a man's powers: those of industry are not; and (2) athletes themselves, being in a state of health and dynamic equilibrium, can be experimented on without danger and can repeat their performances exactly again and again. I might perhaps state a third reason and say, as I said in Philadelphia, that the study of athletes and athletics is "amusing": certainly to us and sometimes I hope to them. Which leads to a fourth reason, perhaps the most important of all: that being "amusing" it may help to bring new and enthusiastic recruits to the study of physiology, which needs every one of them, especially if they be chemists.

Despite the skepticism of some of his colleagues, Hill always remained optimistic and never allowed himself to doubt the importance of his research (78). His work in athletic performance served to legitimize the field of exercise physiology as a new scientific discipline (76). In the United States, D. B. Dill credited Hill's "bold attack on the physiology of sport" with inspiring much of the work that came out of the Harvard Fatigue Laboratory (5, 26).

$\dot{V}O_{2\max}$ . At Manchester University, Hill and colleagues conducted a classic set of experiments, in which they measured  $\dot{V}O_2$  on themselves and others running around an 85-m grass track (Fig. 9). The expired air samples were collected in a Douglas bag strapped to the subject's back. This required a series of five to six trials at a single running speed, with the subject opening and then closing the three-way valve over a brief (30 s) time interval. The Douglas bags were then carefully analyzed for percentage of  $O_2$  and  $CO_2$  by use of a Haldane gas analyzer. The bag volume was measured by means of a Tissot gasometer (55).  $O_2$  intake was calculated by the Haldane transformation of the respiratory Fick equation, using a slide rule. By

Fig. 9. "Steady state" that occurs while running at various constant speeds. Data on the y-axis reflect "excess"  $O_2$  intake (the  $O_2$  cost of standing rest has been subtracted out). Speeds of 181, 203, 203, and 267 m/min were used. The lower 3 curves reflect a true steady state. The lag in  $O_2$  uptake at the onset of exercise results in an "oxygen deficit," but eventually a steady state is reached in which the actual  $O_2$  intake equals the  $O_2$  requirement. The top curve reflects only an "apparent" steady state in which the maximal  $O_2$  uptake has been reached and a continuing oxygen deficit is accumulating. From Hill and Lupton (63), by permission of Oxford University Press.



repeating this whole procedure several times, they were able to study the time course of the increase in  $O_2$  intake at various running speeds (63).

Hill and colleagues were the first to clearly describe the concept of the maximum  $O_2$  intake (98, 103). They described the notion of an upper limit on the body's ability to take in  $O_2$  in their 1923 paper on "Muscular exercise, lactic acid, and the supply and utilization of oxygen," stating

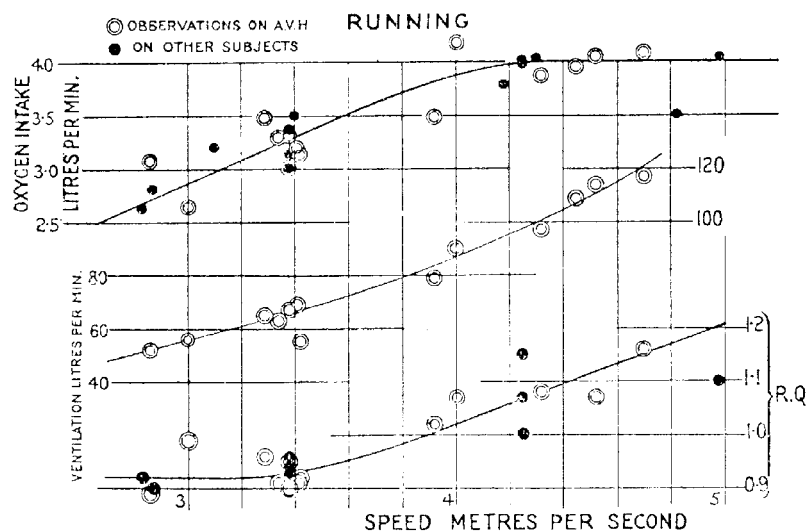
In running the oxygen requirement increases continuously as the speed increases, attaining enormous values at the highest speeds; the actual oxygen intake, however, reaches a maximum beyond which no effort can drive it . . . The oxygen intake may attain its max-

imum and remain constant merely because it cannot go any higher owing to the limitations of the circulatory and respiratory system . . . (63)

In a companion paper in 1924, Hill et al. (59) presented data on seven subjects, showing the relation of running speed to  $\dot{V}O_2$  (l/min) (Fig. 10). The accompanying table showed that, in two subjects (A. V. H. and one other), the measured  $\dot{V}O_2$  leveled off at higher running speeds. The plateau in the graph of  $\dot{V}O_2$  vs. speed was consistent with their 1923 suggestion of an upper ceiling for  $\dot{V}O_2$ .

Åstrand and Saltin (3) later reexamined the relationship of  $\dot{V}O_2$  vs. time at various work rates. They found that the rate of rise in  $\dot{V}O_2$  is a function of the work

Fig. 10. Relationship between running speed and measured  $O_2$  intake, pulmonary ventilation, and respiratory quotient (RQ). Double circles are observations on subject A.V.H. (presumably Hill himself), whereas the closed symbols reflect data on other subjects. Data on some of the lighter subjects were "adjusted" to reflect an  $O_2$  intake (l/min) for someone of Hill's body weight. This approach to handling the data was used because they had not yet thought of expressing  $O_2$  consumption ( $\dot{V}O_2$ ) in  $ml \cdot kg^{-1} \cdot min^{-1}$ . From Hill et al. (59), with the permission of the Royal Society.



requirement, and beyond a certain work rate the  $\dot{V}_{O_2}$  cannot be driven to higher levels. This confirmed that there is an upper limit on an individual's ability to take in and consume  $O_2$ , and today this concept is universally accepted.

**Determinants of  $\dot{V}_{O_2 \max}$ .** In 1924, Hill et al. (59) suggested that four factors determined  $\dot{V}_{O_2 \max}$ : 1) arterial  $O_2$  saturation, 2) mixed venous saturation, 3) the  $O_2$  capacity of the blood, and 4) the circulation rate. For the purposes of our discussion, the word "determinant" refers to a potential limiting factor. Despite their inability to measure some of these variables, they made quantitative estimates that were very accurate.

Hill et al. (59, 63) proposed that maximal cardiac output ( $\dot{Q}_{\max}$ ) was an important determinant of  $\dot{V}_{O_2 \max}$ . Given the level of technology that existed at that time, it is interesting that they were able to deduce that athletes have hearts with larger pumping capacities than untrained subjects. In 1915, Lindhard (83) had measured cardiac outputs of 20 l/min in average-fit individuals and observed the cardiac output-to- $\dot{V}_{O_2}$  relationship. Hill and Lupton (63) speculated that  $\dot{Q}_{\max}$  values of 30–40 l/min were possible in athletes. More recently, Rowell (102) has shown that  $\dot{Q}_{\max}$  and  $\dot{V}_{O_2 \max}$  are closely related. Furthermore, in studies in which  $\dot{Q}_{\max}$  is acutely altered,  $\dot{V}_{O_2 \max}$  changes in the same direction (107).

Hill and Lupton (63) identified the  $O_2$  carrying capacity of the blood as another determinant of  $\dot{V}_{O_2 \max}$ . In 1976, Ekblom et al. (30) demonstrated this by reinfusing 800 ml of whole blood into the body several weeks after its withdrawal. This procedure resulted in an increase in the  $O_2$  carrying capacity, and  $\dot{V}_{O_2 \max}$  increased by 8%.

Hill and colleagues considered the possibility of a pulmonary limitation to  $\dot{V}_{O_2 \max}$ . However, they believed that, in most people, the lungs perform their job of oxygenating the arterial blood extremely well. This view was based on the appearance of their subjects, "who have never, even in the severest exercise, shown any signs of cyanosis." This was an incredible insight, arrived at by using the color of the face, lips, and fingernail beds in place of a pulse oximeter! Nevertheless, Hill and co-workers (59, 63) cautioned against assuming that a complete equilibrium exists between the lungs and arterial blood in maximal work, because of the rapidity of the passage of the red blood cells within the pulmonary capillary. This prediction was confirmed many years later, when researchers showed that elite athletes with high cardiac outputs may experience a fall in arterial  $O_2$  saturation due to a decrease in the mean red cell transit time (19, 25).

Recent studies have noted the presence of a peripheral diffusion limitation in muscle (69, 72, 101). Honig et al. (72) reported that the principal site of resistance is located between the surface of the red blood cell and the sarcolemma. They found a large drop in  $P_{O_2}$  over this short distance and concluded that a low cell  $P_{O_2}$  relative to blood  $P_{O_2}$  drives diffusion and enhances  $O_2$  conductance. In the isolated dog hindlimb, Hogan et al. (69) reduced the  $P_{O_2}$  gradient (and thus the driving

force for  $O_2$  diffusion) while keeping  $O_2$  delivery constant. This procedure caused a decline in  $\dot{V}_{O_2 \max}$ , showing the presence of a peripheral diffusion limitation. Even this was foreseen by Hill and Lupton (63), who stated: "However much the speed be increased beyond this limit, no further increase in oxygen intake can occur: the heart, lungs, circulation and the diffusion of oxygen to the active muscle fibers have attained their maximum."

A modern-day view of the limiting factors for  $\dot{V}_{O_2 \max}$  is provided by Wagner et al. (109). These authoritative researchers conclude that there is no single limiting factor and that it is important to consider all steps in the pathway for  $O_2$ . From ambient air  $\rightarrow$  alveolus  $\rightarrow$  pulmonary capillary  $\rightarrow$  systemic capillary  $\rightarrow$  mitochondria, they conclude that, "each and every step contributes in an integrated way to determining  $\dot{V}_{O_2 \max}$  and a reduction in the transport capacity of any of the steps will predictably reduce  $\dot{V}_{O_2 \max}$ ." This integrated view is based on the fact that a decrease in inspired  $P_{O_2}$ , lung diffusing capacity, hemoglobin concentration, or  $\dot{Q}_{\max}$  will systematically decrease the  $\dot{V}_{O_2 \max}$  (108). There is tremendous support in the literature for this view. Thus, after nearly eight decades of research, the accumulated evidence supports Hill's view of the determinants of  $\dot{V}_{O_2 \max}$ . However, the relative importance of each of these determinants, under any given set of circumstances, remains a topic of great debate.

**Determinants of performance.** Hill and Lupton (63) stressed the importance of  $\dot{V}_{O_2 \max}$  and other variables in athletic performance. They observed, "A man may fail to be a good runner by reason of a low oxygen uptake, a low maximum oxygen debt, or a high oxygen requirement; clumsy and uneconomical movements may lead to exhaustion just as well as may an imperfect supply of oxygen."

Three things are evident in this statement. First, they recognized the interindividual variability in  $\dot{V}_{O_2 \max}$  and its significance for performance. Second, they established the concept of "running economy," which they expressed as the amount of  $O_2$  used to run a given distance. [Hill's group studied the  $O_2$  cost of walking and running and discovered that fast walking requires more energy than slow jogging at the same speed (59).] Third, Hill and Lupton correctly attributed variation in running economy to biomechanical factors, rather than altered muscular efficiency. This view is strongly supported by the work of Daniels et al. (23) showing that highly economical runners tend to have average economy in other exercise modes (bicycling, uphill walking, and arm cranking).

More recent studies have built on the framework that Hill established (4). In addition to  $\dot{V}_{O_2 \max}$  and running economy, another variable that has been shown to influence performance is the "fractional utilization of  $\dot{V}_{O_2 \max}$ ." In the 1970s, researchers found that some athletes are able to sustain 85% of  $\dot{V}_{O_2 \max}$  for extended periods, whereas average-fit individuals can only sustain  $\sim 60\%$  of  $\dot{V}_{O_2 \max}$  over 2–3 h (20, 97). Endurance training increases both  $\dot{V}_{O_2 \max}$  and the percentage of  $\dot{V}_{O_2 \max}$  that can be sustained. This re-

lates to an increase in the “lactate threshold,” consequent to an increase in mitochondria and capillary density (21, 70, 71). However,  $\dot{V}O_{2\text{ max}}$  is still seen as an important variable because it sets the upper limit for endurance performance (i.e., one cannot sustain exercise in excess of 100%  $\dot{V}O_{2\text{ max}}$  for prolonged bouts).

**Theory of  $O_2$  deficit and debt.** In 1920, Krogh and Lindhard (79) introduced the term “oxygen deficit” to represent the difference between the  $O_2$  requirement of an exercise bout and the measured  $\dot{V}O_2$ . They clearly identified the oxygen deficit with energy production by anaerobic pathways, and stated that “This deficit must represent the anoxybiotic reactions which take place during the first phase of the contraction process and which are not finally made up by oxidation until after the work has ceased.”

In 1922–23, Hill and Lupton (63, 64) studied the time course of the change in  $\dot{V}O_2$  in the recovery period. The elevated  $O_2$  intake in recovery, in excess of resting  $\dot{V}O_2$ , was labeled the “oxygen debt” (63) (Fig. 11). After strenuous exertion, the magnitude of the oxygen debt was much larger than that seen after moderate exercise. In his Nobel Prize acceptance speech delivered in 1923, Hill (53) remarked

a man may use as much as 4.2 litres of oxygen per minute, after his circulation and respiration have been worked up by running fast for three to four minutes. This, you will remember, is about the amount which the body requires in recovery from 11 seconds of severe exertion. Were it not for the fact that the body is able, so to speak, to take its exercise on “credit,” instead of paying for it out of “income,” it would be impossible for a man to take anything but quite moderate exercise. The body is capable of running up an oxygen “debt” which must be repaid during the recovery process. The maximum “debt” which we have found is 15 litres, which is nearly four minutes supply at the maximum rate.

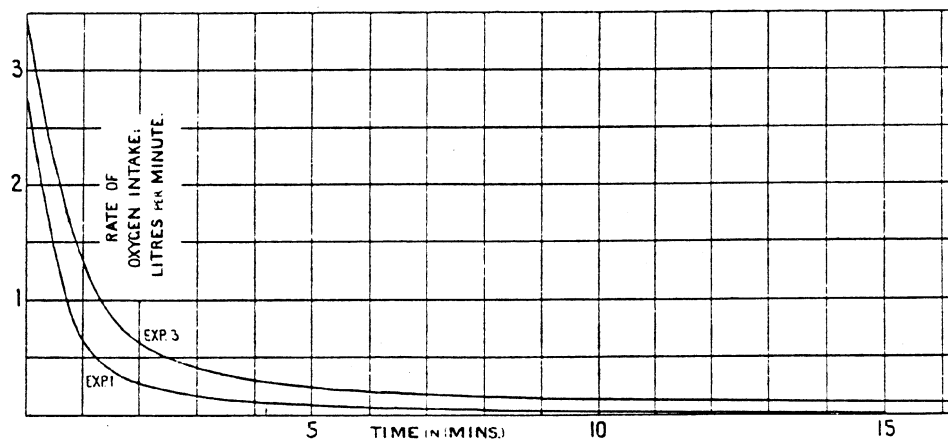
Hill and colleagues (59, 63, 64) believed that the ratio of oxygen deficit to oxygen debt was strictly 1:1. This ratio holds true for light-to-moderate exercise of several minutes’ duration. However, in strenuous exercise, the ratio may become 1:2 or even 1:3. Thus measurements of the oxygen debt in the recovery phase

are not always equal to the oxygen deficit. Even though Hill and Lupton (63) stated that the oxygen deficit could reach 13.25 liters (63), this is misleading. In this case they were using the terms “deficit” and “debt” interchangeably, and it was actually the oxygen debt that was being measured. Recent studies show that the maximal accumulated oxygen deficit can reach values of up to 4 or 5 liters of  $O_2$  in bouts lasting 2–6 min (90, 91). These values are considerably lower than those proposed by Hill and Lupton.

**Fate of lactic acid.** Meyerhof (92–94) performed frog muscle experiments on the fate of lactate in recovery. With repeated contractions, lactic acid appeared and glycogen disappeared in precisely equal quantities. In recovery, Meyerhof observed that 25% of the lactate was oxidized, and 75% reappeared as muscle glycogen. Hartree and Hill (42) performed similar experiments on isolated frog muscle. Using Meyerhof’s value for the “heat of combustion” of lactic acid (3,788 calories/g), they determined that only a small portion of the lactate produced in exercise was oxidized in recovery. The recovery heat accounted for only one-fifth or one-sixth of the amount that would have been required for oxidation of the lactic acid.

Current research suggests that Hill’s and Meyerhof’s findings apply to isolated amphibian muscle, but not to whole humans and other mammals (12). Brooks and co-workers (13, 27) infused isotopically labeled lactate into rats and humans and observed that most of the label appeared in the form of  $CO_2$  given off in respiration, and only a small portion was reconverted to glycogen. This finding is just the opposite of what Meyerhof observed in the isolated frog muscle. There are two explanations for these discrepant findings. The first is that mammalian skeletal muscles readily oxidize lactate, but they have poor capacity for gluconeogenesis. [Reptilian and amphibian muscles, on the other hand, have a greater ability to reconvert lactate to glycogen (12).] The second explanation is that isolated muscle preparations differ from an intact organism (in which lactate can be shuttled to other parts of the body and then oxidized).

Fig. 11. Time course of “excess”  $O_2$  intake during recovery. Lower curve represents recovery from moderate exercise, and the  $\dot{V}O_2$  rapidly returns to the resting level. Upper curve represents recovery from a longer bout of severe exercise. The excess  $O_2$  consumption in recovery was termed the “oxygen debt,” and it was proposed that there is a 1:1 relationship of oxygen deficit to oxygen debt. From Hill and Lupton (63), by permission of Oxford University Press.



In any case, Hill and Lupton (63) sought to apply the results obtained in isolated frog muscle to exercising humans. They made theoretical calculations based on blood lactate levels and the elevation in  $\dot{V}O_2$  during recovery. Hill and Lupton stated

No process is known to occur in muscular exercise in man which is not apparent in isolated muscle, and we shall now assume that the recovery oxygen, measured as above, is used entirely in the oxidative removal of lactic acid. The oxidation is as follows:  $C_3H_6O_3 + 3O_2 \rightarrow 3CO_2 + 3H_2O$ . Now, if the efficiency of recovery be assumed to be six in the sense defined above, i.e. oxidized, then six molecules of LA will be removed for every 3 molecules of  $O_2$  used, or 2 gramme-molecules of LA (i.e. 180 g) for every gramme-molecule of oxygen (i.e. 22.2 litres). This means that an oxygen debt of 1 litre betokens the presence in the body, at the end of exercise, of about 8.1 grm. of lactic acid

Thus Hill and Lupton (63) assumed that one-sixth of the lactate produced in exercise would be combusted in recovery. We now know this value to be incorrect, but this should not overshadow their brilliant application of the concept of anaerobic metabolism to exercising man. They showed that a person can work at energy requirements that far exceed the maximum capacity for aerobic metabolism, for a short time. They also showed that the higher the exercise intensity, the higher the blood lactate levels and the greater the oxygen debt in recovery. Hill and Lupton concluded

Were it not for the fact that the body is able thus to meet its liabilities for oxygen considerably *in arrears*, it would not be possible for man to make anything but the most moderate muscular effort. It is obvious . . . that we must regard the muscle as capable of going into debt for oxygen, of *committing itself to future oxidations on the security of lactic acid liberated in activity*.

The "oxygen debt" theory of Hill and Lupton (63) has undergone substantial revision in recent years. They attributed the oxygen debt to lactic acid, stating "lactic acid then forces the body later to pay off its debt out of income, in oxidative recovery." However, Brooks and colleagues (12) maintain that lactic acid is not the cause of the elevated  $\dot{V}O_2$  in recovery but merely serves as a convenient substrate for the increased metabolic rate. For this reason, Brooks selected a more neutral term, the "excess post-exercise oxygen consumption." The mechanisms cited for the elevated  $\dot{V}O_2$  in recovery are the increased respiratory and circulatory work, restoration of  $O_2$  stores on myoglobin and in venous blood, hormonal responses, and the elevated body temperature. This refinement is generally accepted today, and it helps to explain why the ratio of oxygen debt to oxygen deficit is not always 1:1.

**Other studies in athletic performance.** In 1925, Hill delivered a presidential address called "The physiological basis of athletic records" (56) to the annual meeting of the British Association for the Advancement of Science. It contained a graph of world-record speeds for athletic events of varying duration. Hill presented data on ath-

letic records for running, walking, swimming, and rowing. On the x-axis, event duration was expressed on a logarithmic scale. On the y-axis, speed was expressed in yards per second. The graph is the forerunner to the modern "power curves" obtained by Wilkie (112). Hill explained the speed difference between short and long races in terms of the  $O_2$ -dependent and -independent systems, although he noted that the cause of the further decline in power for events over 10 miles was unknown. The lecture brought "worldwide recognition of exercise physiology as a discipline of its own" (76).

Hill (44) conducted the first study on the effects of air resistance in running. In 1927, Hill placed a 20-cm wooden model of a runner in a small wind tunnel, measured the aerodynamic drag forces, and computed the energy expenditure that would be required to overcome air resistance. He estimated that air resistance would account for 3% of the total energy expenditure at middle-distance speeds (6 m/s) and 4% at sprinting speeds (10 m/s). This paper was the forerunner of a 1980 paper by Davies (24), who placed runners on a treadmill in a wind tunnel and measured the change in  $\dot{V}O_2$  created by headwinds or tailwinds of varying speed. Other studies have directly compared the  $O_2$  cost of overground and treadmill running (22, 99). In general, these studies find that air resistance accounts for 2% of the total energy cost at marathon speeds, 4–8% at middle distance speeds, and 8–15% at sprinting speeds. Thus Hill probably underestimated the effects of air resistance, but he nevertheless raised an interesting question that caused others to pursue this line of research (24, 80, 99, 104).

In 1927, while completing a one-semester guest lectureship at Cornell University, Hill (55) measured the acceleration of sprinters (Fig. 12). The method consisted of large wire coils set up at 1- to 10-yard intervals alongside a track. These were connected to a galvanometer. As a runner wearing a magnetic band around his chest passed by the wire coil, a deflection was recorded on the galvanometer. Velocity could be computed by dividing the distance between each coil by the elapsed time. This method was the forerunner of the modern technique utilizing high-speed video cameras (1).

**Adaptations to training.** Although Hill himself performed no longitudinal studies of physical training, he stimulated a great deal of interest in this area. In his lecture delivered in 1927 he said

You will ask—I have often asked—what happens to the body in training? I am sorry, I do not know. Perhaps the blood supply to the active muscles becomes better, the capillaries responding more rapidly to the needs of the muscles; perhaps more alkali is deposited in the fibres to neutralise the acid formed by exertion. More glycogen seems to be laid down in them as a store of energy, and certainly, they and the nervous system which governs them learn in training to work more economically. Perhaps by training the recovery process is quickened. Maybe the actual mechanical strength of the muscle-fibre and its surrounding membrane (sarcolemma) is increased by training so that it can stand, without injury, the strains and stresses of violent effort. All these factors may

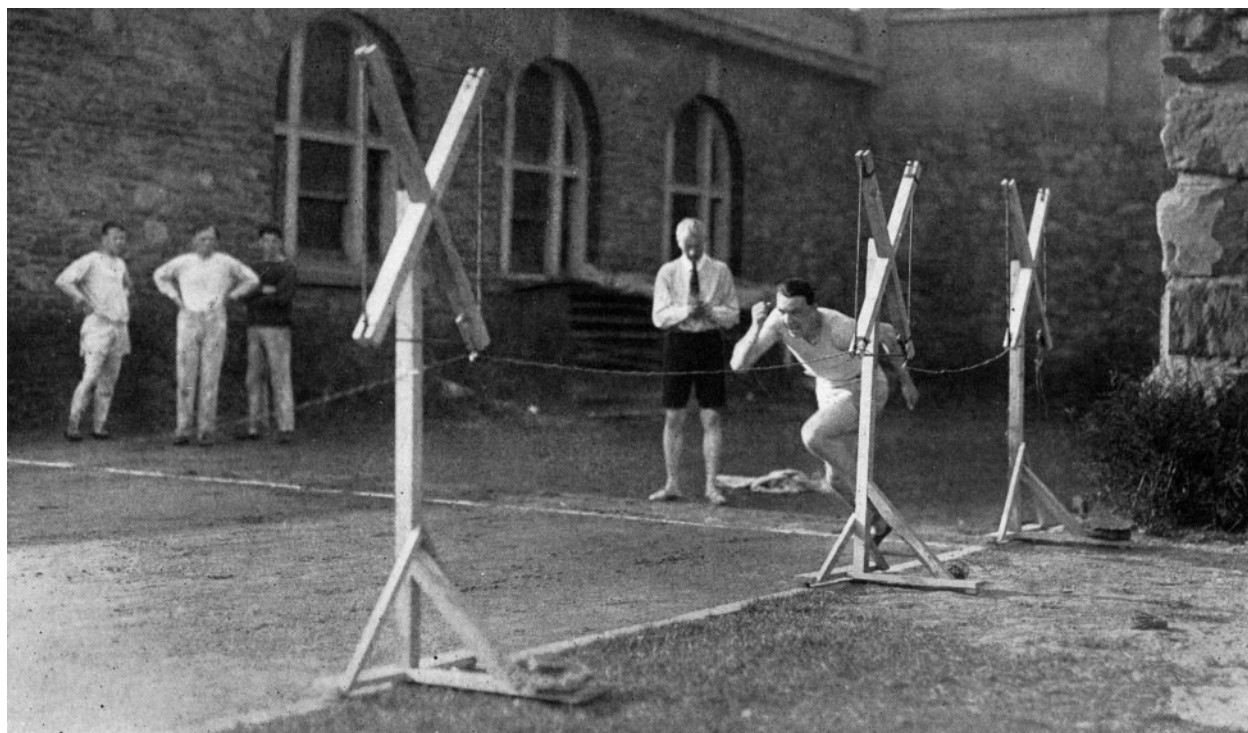


Fig. 12. Testing the acceleration of sprinters at Cornell University, Ithaca, NY, in the spring of 1927, when Hill was completing the George Fisher Baker lectureship in chemistry. The large coils of wire were used to detect a magnet worn by the runner as he sprinted past them. Velocity and acceleration were calculated by knowing the distance between the wire coils. From Hill's *Muscular Movement in Man* (55).

be at work, but at present we can only point to the importance and interest of the problem, and suggest that someone should investigate it properly.

When one considers Hill's list of predictions in light of what we know today, it appears most impressive indeed. Hill predicted the increased buffer capacity of muscle brought on by sprint training, later shown by Costill's laboratory in 1986 (105). In fact, these researchers credited Hill with putting forth the hypothesis that led to their study. He hinted at training adaptations such as a faster heart rate recovery. Hill also predicted that "the stresses and strains of violent effort" can lead to microscopic injury to the muscle fiber (38, 43). Not only that, but he correctly predicted that muscle adapts to these stresses, because it is now known that a single bout of eccentric exercise can protect against muscle soreness and damage from future bouts for up to 6 wk (15).

Hill's predictions demonstrate the tremendous insights he had into applied athletic performance. These insights were shaped by years of personal experience in athletics and by his laboratory studies. Hill pointed the way for future generations of exercise physiologists, by steering them toward interesting questions. E. J. Hamley (39) stated

When one considers [Hill's] criteria and looks at the list of his students it is obvious that he passed on an impressively broad view of "muscle" to his "academic sons." Most of the applied physiology we see in physical

education and sport owes its origins to these 'sons.' The literature is studded with their names and they are distributed around the world.

#### OTHER DISCOVERIES

Hill first measured the heat production in nerve in 1925 (49). Although researchers had tried to do this for about half a century, it was not possible until the development of rapid galvanometers and very sensitive thermopiles. Hill later noted that if large crustacean nerves had been used instead of frog nerves, he would have been able to record it in 1912. Hill interpreted the heat production in nerve as evidence that the process of nerve transmission is a chemical one, not simply a mechanical one (like a "wave" moving along a string). However, according to Katz (78), the high temperature coefficient of conduction velocity in nerve does not by itself enable one to distinguish between these two possibilities. The refractory period was another major clue that chemical processes must be involved (58).

Measurement of heat production in nerve proved an enormous technical challenge, because the amount of heat liberated is so small. Hill wrote

For example, when a single impulse travels down a medullated nerve there is an immediate rise of temperature of the order of  $10^{-7}$  degrees C (one ten millionth of a degree) . . . One gram-calorie would send it  $10^8$  kilometres, about half the distance to the sun. Clearly, communication by nerve fibre is not very expensive! (58)

Hill's laboratory was one of two groups that pioneered the use of pulse-wave velocity as a measure of arterial compliance (47, 47a). Hill used a hot-wire sphygmograph to detect the arterial pulse wave. The hot wire was mounted at the end of a stethoscope, where it was able to detect sudden changes in air pressure. By timing the arrival of the arterial pulse wave in two different locations along an artery, a measure of the arterial elasticity could be obtained. J. C. Bramwell (a cardiologist in Manchester, England) and Hill published five papers between 1922 and 1923 using this technique (6–10). The principle of using pulse-wave velocity as a noninvasive technique for measuring arterial compliance is still in use today.

### SCIENTIFIC ETHICS

Hill had an extremely broad view of science, and he believed in the moral obligation of scientists to speak out on social issues. In his Huxley memorial lecture delivered in November of 1933 (shortly after Hitler came to power), Hill (50) denounced the Nazi persecution of Jewish people, especially scientists who had been forced out of Germany. Mixing science with politics was considered unconventional at the time (78), but Hill's stature and reputation afforded him the opportunity of being heard.

Hill's lecture, published in abridged form in *Nature*, brought a sharply worded rebuttal from Johannes Stark. Stark had recently been appointed president of the Physikalisch-Technische Reichsanstalt in Germany (replacing Hill's friend Paschen). In a letter to the editor in 1934, Stark (106) claimed

In his Huxley Memorial Lecture, extracts from which were published in *Nature* of December 23, Prof. A. V. Hill has made detailed statements regarding the treatment of German scientists by the National-Socialist Government. These statements are not in accordance with the truth. As a scientist, whose duty it is to discover and proclaim the truth, I venture to place on record the following facts as against the inaccurate assertions of Prof. Hill . . .

Stark rationalized the Nazi's treatment of Jewish people by saying that the Jews had created a virtual monopoly in many hospitals and academic institutions around Germany. He went on to dispute Hill's assertion that more than a thousand scholars and scientific workers had been dismissed and suggested that these scientists had voluntarily left their jobs. He discounted Hill's claim of 100,000 political prisoners in concentration camps in Germany, stating that there were not even 10,000 in the concentration camps and they were guilty of high treason.

Hill (51) immediately replied

With Prof. Stark's political anti-Semitism I need not deal: to an unrepentant Englishman (without any Hebrew ancestry or Marxist allegiance) it appears absurd. It is a fact, in spite of what he says, that many Jews or part-Jews, have been dismissed from their posts in universities . . . As regards "high treason" and concen-

tration camps, in England we do not call liberalism or even socialism by that name . . . No doubt in Germany, after this reply, my works in the *Journal of Physiology* and elsewhere will be burned.

Hill was a founding member of the Academic Assistance Council, a group that aided in relocating Jewish scientists from Germany to England and the United States. He solicited contributions from *Nature* subscribers and helped to divert funds that the Rockefeller Foundation had originally slated for research in Germany to help get Jewish refugees relocated at British universities (77).

A young scientist named Bernard Katz read Hill's comments in *Nature* and came to his laboratory in 1935. Although Katz had few credentials of any kind, Hill welcomed him with open arms, showed him around the laboratory, and immediately created a place for him to work (78). Katz developed a close friendship with A. V. and Margaret Hill and later went on to win a Nobel prize in 1939 (for the physicochemical mechanism of neuromuscular transmission). Hill had a considerable impact on the careers of many scientists who came to work in his laboratory or who corresponded with him.

During World War II, Hill shut down his laboratory and went to work assisting the British government. In 1935 he was appointed to the Tizard committee, a group of physicists who served at the bequest of Churchill. They conducted the first successful test of radar to detect incoming airplanes. Soon afterward radar stations were established along the coasts of England; the new technology played an important strategic role when conflict erupted in 1939. From 1940 to 1945, Hill served as the Cambridge representative to the British Parliament (all of the major universities had representation at that time). He also served as a scientific advisor to India and mapped out plans for an All-India medical school in New Delhi. After India established its independence, many of the components of Hill's scientific plan (including the All-India medical school) were put into place (78).

Although Hill remained committed to his own line of research throughout his career, he was also concerned with broader scientific and humanitarian principles (78). He served as president of the British Society for the Advancement of Science (1952), as secretary general of International Council of Scientific Unions (1952), and president of the Society for the Protection of Science and Learning (1963). Katz (78) remarked that

it was [Hill's] concern for others, the encouragement he gave younger colleagues, his upright defence not only of the cause of science, but of scientific men who had been driven from their places of work and needed help, in short it was his devotion to such 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.

## POSTSCRIPT

On the basis of the available knowledge at that time, Hill used his considerable powers of logical deduction to propose hypotheses that would best fit the facts. Sometimes the initial hypotheses were proven wrong, as newer techniques and knowledge became available. Other times his instincts turned out to be correct, and his views were confirmed. He was able to integrate information on physics, mathematics, physiology, and biochemistry to yield a unique view of muscular activity.

In the preface to *Trails and Trials in Physiology* (58), Hill wrote

The implication of "trails" is obvious, sometimes false sometimes genuine. That of "trials" is deliberately equivocal; mostly the word relates quite simply to tests, to experiments, but it would be a reminder also of vexations, failures, and frustrations that were part of the job. How often did one waste a day, or a month, in fruitless experiments? How often were one's facts misinterpreted or one's theories found wanting? (and one was lucky if one discovered that for oneself). In undertaking difficult experiments (and few others are really much fun) such trials are inevitable, and it may be comforting for people to realize that others have experienced them too. Often I have told my young friends that when they have found something they cannot understand at all, instead of being cast down they should jump in the air for joy; for that is how discoveries are made. Research must indeed be planned; but the most interesting things can emerge when the plan does not work, providing a test not only of tenacity but of understanding.

In addition to the creation of new knowledge, Hill brought a new rigor to the study of exercise physiology. He collaborated with scientists from around the world, sharing information and engaging in a lively give-and-take process as they struggled to understand the mechanisms of muscle contraction and cellular bioenergetics. The discovery of anaerobic metabolism in muscle, the concept of maximum  $O_2$  intake, and the Hill equation describing force-velocity curves in muscle were major milestones in exercise physiology. They paved the way for other investigators who advanced the state of knowledge even further. Hill's view was that science moves forward by continual action and reaction between hypothesis on the one hand and critical experimentation and analysis on the other (58). His career exemplified the scientific process in action, and his discoveries advanced our understanding of how the human body functions during exercise.

The main sources used in the writing of this article were the scientific writings of A. V. Hill and his co-workers. Hill's career spanned over 50 years (1910–1965), and he authored more than 200 scientific publications and eight books. *Trails and Trials in Physiology*, a book written toward the end of his career, contains an annotated bibliography of scientific articles by Hill and colleagues (from 1909 to 1964), along with reviews on selected topics and suggestions for further research. Another important source is *The Physiology of Excitable Cells* by D. J. Aidley, which describes Hill's discoveries in the area of calorimetry and muscle mechanics. The definitive chronological biography of A. V. Hill's life was written by Sir Bernard Katz, a Nobel prize winner (1970) who trained under Hill. It was

published in *The Biographical Memoirs of Fellows of the Royal Society* in 1978, one year after Hill's death.

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