
Arshad M. Khan, *University of Southern California*
Neurognostics Question


ARSHAD M. KHAN

Department of Biological Sciences, University of Southern California, Los Angeles, CA, USA

This British pioneer of biophysics and physiology was born in Bristol, England, on September 26, 1886. He was an avid sportsman and athlete, loved the outdoors and was especially fond of mathematics and physics. When he was 19, he joined Trinity College, Cambridge. In 1910, he received a fellowship to pursue graduate work at Trinity in the Physiology Department headed by John Newport Langley, where he used his mathematical skills to first provide theoretical contributions to the ongoing work of other scientists, such as Keith Lucas and Joseph Barcroft. These original contributions included the first mathematical formulation of drug/receptor interactions and the first kinetic model for a cooperative biochemical reaction involving the binding of multiple molecules to a single receptor complex. A mathematical coefficient in these binding equations was later named after him in his honor.

His first entry into experimental physiology involved using sensitive galvanometers to measure thermal changes from contracting muscle, a line of work that would continue throughout his life. In 1912, he also made his first attempt to measure heat from conducting nerves. This had been tried as early as 1848 by Hermann Helmholtz, and subsequently by many other physiologists, but had never been achieved successfully up to that time. Like his predecessors, he reported that his attempt was unsuccessful.

In 1913, he married Margaret Neville Keynes, sister of the famous economist, John Maynard Keynes. With the outbreak of World War I, he joined the military in August, 1914, serving first as a captain and later as a musketry instructor. In 1916, he directed a small group of mathematicians and physicists within the first “Operational Research” team in modern military history, working to develop anti-air defenses to stop Zeppelin incursions into British air space.

In 1920, he left Cambridge to become Chair of Physiology at the University of Manchester and began what was perhaps the most intense research period of his career, publishing no less than 12 full-length studies between 1920–1922. This work included a detailed examination of the phases of heat production in muscle and a “delayed” heat production of muscle under anaerobic conditions. By the end of this period, it was clear that these “external”...
measurements of muscle energy agreed very nicely with the “internal” biochemical measurements of energy consumption being independently published by his colleague and friend Otto Meyerhof. In 1923, this distinguished physiologist, together with Meyerhof, shared the Nobel Prize in Physiology or Medicine for their work on muscle energetics.

In 1926, by now a Chair of Physiology at University College London and armed with much more sensitive instruments than those he used 14 years earlier, he became the first individual to successfully measure the heat production from a firing nerve and oversaw the further refinement of these measurements by his students, Ralph W. Gerard and T. P. Feng. These nerve heat experiments were significant in that they suggested that biochemical processes may accompany nerve impulses.

In 1933, he became a founding member of the Academic Assistance Council, which helped support refugee scientists who fled Nazi-occupied Europe, and also delivered an important scientific lecture in which he sharply criticized the Nazi regime. The text of this lecture reached a young medical student, who, at the time, was making plans to leave Nazi-controlled Germany. This young student was greatly moved by the lecture and arrived in England as a refugee to join the laboratory of our distinguished biophysicist. Around this time, our pioneering biophysicist was then appointed to serve as Biological Secretary of the Royal Society. During the outbreak of the World War II, he again distinguished himself by becoming a Member of Parliament, and also by serving as a scientific liaison between the British and U.S. governments as a member of the famous “Tizard Committee,” a high-level government panel of scientists, led by Sir Henry Tizard, which reported directly to Sir Winston Churchill with recommendations about radar defense.

Following the war, this scientist-statesman, by now nearly 60 years old, faced the difficult decision of whether to reestablish his laboratory after its closure for nearly six years during the war. Remarkably, he decided to do so and also made great efforts to bring into his research unit a new group of talented young colleagues to reestablish biophysics and physiology in the laboratory. To this end, he also successfully re-recruited his former pupil, the medical student who had first joined his laboratory in 1935 after fleeing Germany. This former student returned to become Deputy Director, and later Director, for the biophysics research unit his elder mentor had headed at University College London. In 1951, the biophysics research unit was formally established as the Biophysics Department and was the first such regular department to be established in England.

Our pioneering biophysicist spent his “retirement” years actively engaged in laboratory and international scientific work. On his ninetieth birthday, over a hundred of his closest friends and colleagues, including scientists who had escaped racial persecution largely through his efforts, paid tribute to their revered mentor by presenting him with a bound volume of letters of appreciation and gratitude. This gift honored his many services as a father figure, scientist, advisor, mentor, and friend. After a productive life spanning nearly a century, during which he engaged himself in upright service to science and humanity for seven decades, he died on June 3, 1977.

Questions
1. Who was this pioneer of biophysics and nerve/muscle physiology?
2. What mathematical coefficient in biophysics is named after this scientist?
3. What were his scientific contributions to muscle and nerve physiology?
4. Who was the student that left Germany to join his lab, and who later succeeded him in becoming Director of the Biophysics Unit at University College London?
5. What were some of his nonscientific accomplishments in the political and international arenas?

ARSHAD M. KHAN

Department of Biological Sciences, University of Southern California, Los Angeles, CA, USA

Though known primarily for his work on muscle energetics, Archibald Vivian Hill, as discussed below, also made important scientific and pedagogic contributions to nerve physiology.

Keywords Archibald Vivian Hill (1886–1977), Bernard Katz, biophysics, nerve energetics, neurophysiology, heat production, metabolism

Archibald Vivian Hill (1886–1977; see Figure 1) had a long and distinguished career as a physiologist, helping many students realize successful careers in physiology along the way. He was a pioneer of the newly emerging field of biophysics, established the first regular university biophysics department in England and made fundamental contributions to nerve and muscle energetics. He also was an officer of the Royal Society, a Member of Parliament, and a devoted public servant. He distinguished himself in both world wars—first as a soldier, then as a scientific advisor and diplomat. This short summary of Hill’s accomplishments as a scientist and statesman is part of a larger, ongoing project (e.g., see Khan, 2007; 2008) that attempts to contextualize Hill’s life within a broader historical exploration of nerve energetics.

Early Career (1905–1913)

Hill’s childhood and early schooling, described in detail by Katz (1978), were instrumental in developing his talents for mathematics and athletics. In 1905, he began his undergraduate studies at Trinity College, Cambridge, where his tutor, Sir Walter Morley Fletcher, introduced him to physiology. Fletcher himself had been recruited to Trinity by the physiologist Michael Foster, who helped the Physiology Department at Trinity become “the leading center for physiological research in the English-speaking world and a school of international renown” (Geison, 1978, p. 5). The landmark 1907 paper on lactic acid production in isolated frog muscle, published by Fletcher and biochemist Sir Frederick G. Hopkins, made a lasting impression on Hill (1965). He passed the Mathematical Tripos examinations that same year and resolved to prepare himself for a career in physiology by studying for the Natural Sciences Tripos, which he passed two years later.

Address correspondence to Dr. Arshad M. Khan, Department of Biological Sciences, University of Southern California, 3641 Watt Way, Hedco Neurosciences Building - MC 2520, Los Angeles, CA, 90089–2520, USA. Tel.: +1-213-740-1501. Fax: +213-741-0561. E-mail: arshadk@usc.edu
His first research efforts in the physiology department, now headed by John Newport Langley, were largely of a theoretical nature. Hill provided a mathematical description of the actions of nicotine and curare on muscle (Hill, 1909) that anticipated, by four years, the model for enzyme-substrate binding furnished by Leonor Michaelis and Maud Menten (Katz, 1978; Nelson & Cox, 2000). With Joseph Barcroft, he explored the binding of oxygen to hemoglobin aggregates (Hill & Barcroft, 1910), providing the first description (Hill, 1910a) of the “cooperative” nature of this reaction, which occurs if the number (n) of molecules that bind is greater than 1 (Nelson & Cox, 2000). The value for n is now called the “Hill coefficient” in his honor. With Keith Lucas, Hill modified Nernst theory (Hill, 1910b).

After receiving a Physiology fellowship at Trinity (Hill, 1969), Hill used a galvanometer (Figure 2), originally constructed by the Swedish physiologist Hans Gustaf Blix, to perform his first experiments in muscle thermodynamics (Hill, 1910c, 1911). In 1911, Hill began corresponding with Otto Meyerhof, a young biochemist. This began a friendship and collaborative relationship that would span four decades and both world wars. During this time, Hill also visited Germany, where he learned about thermopile and galvanometer construction in the laboratories of Karl Bürker and Friedrich Paschen, respectively (Hill, 1965). Hill returned to England and used this knowledge to construct new equipment for making more detailed measurements of heat from muscle but still did not have equipment sensitive enough to measure heat from nerve preparations (Hill, 1912).

**Marriage, Children, World War I Service**

In August 1914, approximately one year after his marriage to Margaret Keynes and two months after the birth of his first child, Polly, A. V. Hill began active military duty during World War I, serving as a regimental Captain and later as Brigade Musketry Instructor. In 1915, A. V. and Margaret were blessed with a second child, David, who later became an outstanding biophysicist in his own right (two more children, Maurice and Janet, would
become later additions to the Hill family). In 1916, Hill organized and directed a team of mathematicians and physicists, including Ralph H. Fowler and E. Arthur Milne, in a new Anti-Aircraft Experimental Section within the Munitions Inventions Department. Known informally as “Hill’s Brigands,” they used their scientific and technical skills to generate effective strategies of anti-aircraft defense (Hartcup, 2000; Smith, 1990).

**Nobel Prize, First Measures of Nerve Heat**

Elected as a Fellow of the Royal Society in 1918, Hill resumed his myothermic work at Cambridge following the war. Together, with former “Brigand” William Hartree, he constructed more equipment to measure thermal changes in muscle, which resulted in a rather intensive research effort over two years (Hill & Hartree, 1920a, 1920b; Hartree & Hill 1921a, 1921b, 1921c, 1921d, 1922a, 1922b), during which Hill left Cambridge to chair the Physiology Department at the University of Manchester (Katz, 1978). This effort led to an understanding of the phases of heat production in muscle, especially the “recovery” heat produced by a contracting muscle under anaerobic conditions. Hill successfully interrelated his measurements of the externally released heat with those being obtained by Otto Meyerhof, which detailed the biochemistry underlying muscle heat production. For their joint contributions to muscle energetics, Hill and Meyerhof were awarded the Nobel Prize in Physiology or Medicine in 1923.
Shortly after receiving the Nobel, Hill moved to University College London (UCL), where he succeeded Ernest Henry Starling as the Jodrell Chair in Physiology and returned to the problem of measuring nerve heat production. Now with more sensitive equipment, Hill was at last successful in making these measurements using frog nerves (Hill, 1926). Later, he was assisted by his student, Ralph W. Gerard, in further refining these measurements. Gerard described “initial” and “recovery” phases of nerve heat production and the dependence of heat production on stimulus frequency; he also obtained a value for the absolute heat produced by a single nerve impulse (Downing et al., 1926; Gerard et al., 1927; Gerard, 1927a, 1927b, 1927c). Importantly, these findings suggested that nerve activity was accompanied by an energy release that may not fully be accounted for by electrical events. This work was summarized in a lecture delivered by Hill on May 13, 1932, on “Chemical Wave Transmission in Nerve,” which formed the basis of a monograph published with the same title soon thereafter (Hill, 1932). Hill’s doctoral student, T. P. Feng (1988), showed further that frog nerve remained active for several hours in the presence of lactic acid (Feng, 1932) and also measured heat produced at a steady state, as a function of stimulation frequency, and in terms of the relations between its initial and recovery phases (Feng & Hill, 1933a, 1933b, 1933c; Hill, 1933a; discussed in Hill, 1965).

Academic Assistance Council, Huxley Lecture, and Bernard Katz

When Hitler rose to power in Germany in 1933, he began systematically dismissing German-Jewish academics from the country’s universities and research institutes (Pyke, 2000). In response to this action, the Academic Assistance Council (AAC) was founded in England for the purpose of providing assistance to refugee scientists fleeing Germany. Hill, who was among the signatories of the original communication calling for the AAC’s establishment, worked diligently as AAC vice president to secure positions for these scientists in England (Zimmerman, 2006).

In his November, 1933, Thomas Huxley Memorial Lecture on “The International Status and Obligation of Science,” Hill sharply criticized Germany for their dismissal of scientists. Bernard Katz, who was then a young student in Germany, read an abridged transcript of this lecture published in the journal Nature (Hill, 1933b) and also read a series of follow-up letters, also published by Nature, exchanged between A. V. Hill and Johannes Stark, a pro-Nazi Nobel laureate in Germany. Stark had taken issue with Hill’s lecture and denied charges that the National Socialist government was being deliberately racist. Hill replied to Stark by mentioning the AAC and how the association required financial assistance and later ended a follow-up exchange of correspondence on a humorous note by thanking Stark for the financial assistance he did end up receiving as a result of Stark’s angry letters.

Hill’s principled stand against Nazi policies targeting German-Jewish scientists, coupled with his use of wry humor to terminate an otherwise absurd debate, deeply impressed Katz, who resolved to join Hill’s laboratory as soon as possible. Katz arrived there in February of 1935 and quickly began immersing himself in physiology. He soon met Alan Hodgkin during his summer research excursions to the Marine Biological Laboratory in Plymouth. Hodgkin, who had read Hill’s 1932 book Chemical Wave Transmission in Nerve with great interest (Hodgkin, 1992), became close friends with Katz and together with Andrew Huxley made seminal contributions to neurophysiology.
Tizard Committee, Central Registry, Diplomatic Mission to the United States

Shortly before Katz’s arrival in Hill’s laboratory, Hill was assigned to be a member of a special scientific advisory committee; the purpose of which would be to inform the government about suitable methods for air defense. The “Tizard Committee,” which consisted of Hill, the physicist Patrick Blackett, and Sir Henry Tizard, met for the first time in January of 1935 and were influential in supporting a national system for RDF (“Radio Direction Finding”; now known as radar) during World War II (Clark, 1965). In 1939, Hill was nominated by the Royal Society President, Sir William Bragg, to serve as a chairman of a scientific research committee responsible for the construction of a Central Registry of individuals who could perform wartime services in their various professional capacities as scientists or scientific advisors (Katz, 1978; McGucken, 1978; The Royal Society of London, 1939). This registry recorded those scientific talents of enlisted personnel that could be wasted if the individuals were to be dispersed for other duties or sent to the front lines during the war.

In 1940, Hill was elected as a Member of Parliament by Cambridge University. During this time, under the authority of the Tizard Committee and as a special Air Attaché to the British Embassy in Washington, Hill traveled on a fact-finding mission to the United States to improve British-American scientific cooperation for the war effort (Cameron, 2004; Clark, 1965; Zimmerman, 1996), and he also used this tour to visit Canadian officials as well (Avery, 1998). Hill’s trip paved the way for a larger delegation, headed by Tizard, to be sent shortly thereafter to the United States, and it helped to establish what was perhaps the most influential and historic scientific collaboration to ever take place between two great nations during wartime conditions.

Postwar Restoration of UCL Biophysics, Return to Nerve Heat

Perhaps Hill’s most underappreciated achievement in his long and illustrious career was his ability to reestablish his laboratory following the Second World War, after a period of nearly six years during which the Biophysics Unit had been shut down, and most of the personnel (and students) at University College London (UCL) evacuated or relocated to other less vulnerable locations. By the war’s end, Hill was approaching his sixtieth birthday. Rather than retire, he decided instead to set up his lab once again, and with his assistant, J. L. Parkinson, acquired new instruments or constructed them from surplus machinery left after the war (Katz, 1978). It took a period of about two and a half years for work to properly resume and to enter the published literature once again (Hill, 1965). In the years preceding his retirement, Hill also managed to recruit “several very bright young colleagues from war service in telecommunications and the like” (Hill, 1965, p. 66), including Sir Eric Denton, J. Murdoch Ritchie, and Bernard C. Abbott. During this period, Hill also managed to re-recruit Bernard Katz, who had been in working on neurotransmission in Australia and serving as a radar officer in New Guinea. Katz returned to England, re-joining UCL as Hill’s Deputy Director for the Biophysics Unit. In 1951, this research unit was transformed into the first regular Biophysics Department in England, with Hill serving as its first director for a few months until his official retirement in December of that year (Hill, 1956; Katz, 1978). Katz then succeeded Hill as director of the new department. Although officially “retired” from administration, Hill continued to produce very significant scientific work for several years, including a reexamination, after nearly 25 years, of heat production in crab nerve. Abbott and colleagues (1958) measured the
positive and negative phases of heat production from a single action potential at 0°C and found that the “initial heat” associated with the nerve impulse could be separated further into positive and negative phases (Hill, 1965).

Concluding Remarks
In these short pages, it is impossible to do justice to the life and achievements of a person as accomplished as A.V. Hill. He not only was a distinguished scientist but also a husband, father, soldier, military advisor, department administrator, scientific society secretary, Member of Parliament, ambassador, and statesman. It is fascinating that in most, if not all of these capacities, Hill never shied away from connecting his duties to the scientific enterprise: he was a leader who asserted the larger role of science within solutions to the social and political challenges of his time. Although recognized primarily for his work on muscle, Hill also demonstrated that nerve impulse propagation is associated with a measurable production of heat; a significant finding for the time because it suggested that biochemical mechanisms may exist that might account for the heat produced. However, later work by Hill’s student, J. Murdoch Ritchie (and his colleagues) concluded that the initial heat produced during the passage of the nerve impulse likely represented entropic changes associated with the depolarization and repolarization of the membrane (Howarth et al., 1968). Thus, as Ritchie himself has noted, Hill’s careful thermal measurements were, on some level, “disappointing” (Ritchie, 1995). However, the precise molecular events occurring during initial heat production are still not fully accounted for and remain poorly understood. Perhaps Hill’s famous 1950 “Challenge to Biochemists,” in which he called for the biochemical investigation of ATP’s role in muscle contraction, should be extended to neurophysiologists today in relation to nerve heat production. They may be able to determine with faster and more sensitive techniques the molecular mechanisms underlying the measured initial heat production in nerves. As both our distinguished scientist and his science have shown, the propagation of such impulses will yield much in the way of energy that could drive efforts forward.

References


