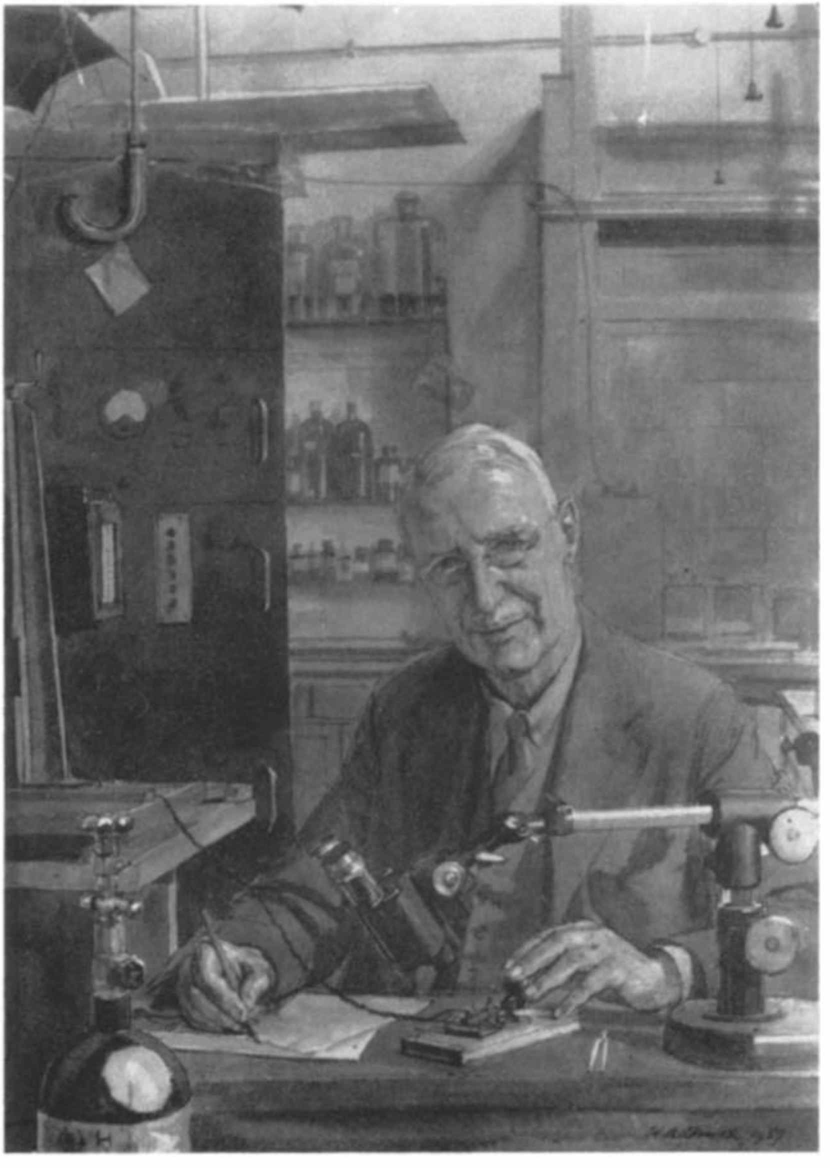

A. V. HILL, from a portrait by H. Andrew Freeth, A.R.A., 1957,
in the possession of King's College, Cambridge.

THE HEAT PRODUCTION OF MUSCLE AND NERVE, 1848–1914[1]

THE FIRST CHAPTER OF A FUTURE MONOGRAPH

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In 1848 Helmholtz[2] published the first recorded experiments on the heat production of isolated muscle (30). Using three thermocouples in series with a galvanometer, he measured the rise of temperature in prolonged contractions of the muscles of a frog's leg. He was then 27 years old and still in the Prussian Army Medical Service, though he was allowed to retire later in the same year. In 1847 he had published his famous monograph *Ueber die Erhaltung der Kraft* (29), one of the epoch-making scientific contributions of the nineteenth century; though addressed to physicists, this had been prepared largely in consultation with physiologists, particularly his friend E. duBois-Reymond. The measurements of muscle heat had clearly been undertaken while his mind was revolving on the conservation of energy.

Helmholtz's paper in 1848 recorded also the first attempt to measure the heat production of stimulated nerve. Contrary to his expectation he could detect nothing; the sensitivity of his instruments was only about one thousandth, as we know now, of what was needed. He published no further experiments on either subject, though in 1850 he was the first to determine the velocity of conduction of a nerve impulse (31, 32). In 1851 he invented the ophthalmoscope, and, as professor of physiology successively at Königsberg, Bonn, and Heidelberg, he devoted himself mainly to vision and hearing. In 1871 he was called to the chair of physics in Berlin, and in 1888 was appointed also President of the newly formed Physikalisch-Technische Reichsanstalt at Charlottenburg. But by his early work on muscle heat production he had lighted a flame which, with a latent period of 15 years, burnt brightly in Germany till the end of the century.

Fifty years later, in June 1898, at about the time when this German work on heat production was coming to an end, a paper (17) of 90 pages (with 47 figures!) on *The Survival Respiration of Muscle* was published in the *Journal of Physiology*. Its author, Walter Morley Fletcher,[3] nearly 25 years old, was then a medical student at St. Bartholomew's Hospital in London, where he had gone after election in 1897 to a fellowship at Trinity College, Cambridge. His research had started in 1895; he had chosen for himself to work on the

[1] The numbers in superior position in this chapter refer to the footnotes, which are mainly biographical.

[2] Helmholtz, Hermann (1821–1894). See Koenigsberger, L., *Hermann von Helmholtz* (Welby, F. A., Transl., Clarendon Press, Oxford, Engl., 1906); A.W.R. *Proc. Roy. Soc.* (*London*), **59**, xvii-xxx (1895–96).

[3] Fletcher, Walter Morley (1873–1933). See Elliott, T. R., *Obituary Notices Roy. Soc.*, **1**, 153–63 (1933); and Fletcher, M., *The Bright Countenance* (Hodder & Stoughton, London, Engl., 1957).

chemistry of muscle, which was outside the current interest of the Cambridge physiological laboratory of those days. Probably, however, Michael Foster[4] had had something to do with it; certainly Foster's thoughts must have been on physiological chemistry, for in 1898 he invited F. G. Hopkins[5] to Cambridge. Moreover, Fletcher told a story that, when he once inquired whether there was really anything more to be got out of chemistry for physiology, Foster rolled his great beard up with both hands over his mouth and emitted his characteristic chuckle.

Foster's answer may have helped to determine Fletcher's choice, and so to decide the sequence of research on the chemistry of muscle, at Cambridge and elsewhere. Doubtless Fletcher had other reasons. Perhaps a lively interest in athletics had biassed him towards muscle; one reason may have been a leaning towards chemistry derived from his father; certainly, however, his direction was partly a result of the guidance of a botanist, F. F. Blackman,[6] whose apparatus for measuring the respiration of plant leaves he borrowed and adapted for muscles. A photograph of Fletcher with that apparatus, in the physiological laboratory at Cambridge in 1897, is given in Maisie Fletcher's book, *The Bright Countenance*.[3]

As W. B. Hardy wrote in 1933, after Fletcher's death,

> the subject was then stagnant, it was lost in all sorts of dead ends. . . . Fletcher gave it new life. Taking one thing with another we know more [today] of muscle and especially of the chemistry of movement than of any other form or activity of living matter. Origins are as difficult in science as in literature. Here, however, it is safe to credit Fletcher with that first step that counts.

Thus, in 1895 a young man of 22 took the first step that started off afresh an activity which is going on today wherever physiologists and biochemists are at work. Spallanzani (1800), Liebig (1850), Hermann (1870), Pflüger (1880) and many others had worked on the chemistry of muscle; but it had been served by inadequate methods and sterilized by fanciful theories embodied in words like "inogen" and "biogen"—hypothetical "giant molecules within which inscrutable chemical changes took place" (Dale[5]). In 1900 Fletcher got back to his muscles, having completed his medical examinations; in 1902 he published two papers (18, 19) on the influence of oxygen on their respiration, and in 1904 another (20) on their osmotic properties in fatigue and rigor.

Since 1898 Hopkins had been in Cambridge, and the community between them, evident in their close collaboration later in the work of the Medical Research Council, must have led Fletcher to discuss his problems with

[4] Foster, Michael (1836–1907). Foster, a pupil of Sharpey, in 1870 had taken the gospel of physiology from University College, London, to Cambridge and was professor there from 1883 to 1903. See Langley, J. N., *J. Physiol. (London)*, **35**, 233–46 (1907); and Gaskell, W. H., *Proc. Roy. Soc. (London)*, B**80**, lxxi–lxxxi (1908). Gaskell's paper is a very striking tribute to Foster's influence.

[5] Hopkins, Frederick Gowland (1861–1947). See Dale, H. H., *Obituary Notices Roy. Soc.*, **6**, 115–45 (1948).

[6] Blackman, Frederick Frost (1866–1947). See Briggs, G. E., *Obituary Notices Roy. Soc.*, **5**, 651–58 (1948).

Hopkins. Indeed, those of us who were fortunate enough to know Hopkins always wanted to discuss our problems with him. About 1905 they began to work together on lactic acid in muscle, and in March, 1907, their famous paper (24) was published in the *Journal of Physiology*. Few papers in the history of physiology can have had so great an influence. Fletcher contributed his special knowledge of muscle, and his conviction that something rather momentous was waiting there to be found out; Hopkins provided the precise methods of chemical analysis; together they realized the importance, and the possibility, of arresting chemical changes in a living tissue before, and while, the destructive manipulations required for quantitative determinations were made. The work was done in Langley's laboratory (he had succeeded Foster in 1903), but he had no part in it except, as was his custom, to admire it from afar. Fletcher continued, amid many distractions, with the study of muscle, and three more papers (21, 22, 23) of his were published. However, in 1914 he became the secretary of the newly formed Medical Research Committee in London, and no more experimental work came from his own hands. Hopkins also never touched the subject again, but his experience with it must have helped to guide him in his later work on intermediary metabolism. In 1915, however, Fletcher & Hopkins jointly gave a Croonian Lecture (25) to the Royal Society on *The Respiratory Process in Muscle and the Nature of Muscular Motion*, an admirable summary, though impaired in its conclusions by their too generous acceptance of Parnas' results (see below). This, apart from the guidance and support they always gave to others, was their last direct contribution to the subject.

In November, 1909, Langley[7] wrote me a letter proposing that I should "settle down to investigate the efficiency of cut-out frog's muscle as a thermodynamic machine." "There is," he said, "an especial problem suggested by Fletcher and Hopkins' work, as to the efficiency of the muscle

[7] Langley, John Newport (1852–1925). See Fletcher, W. M., *J. Physiol. (London)*, 61, 1–27 (1926); and Fletcher, W. M., *Proc. Roy. Soc. (London)*, B101, xxxiii–xli (1927).

From 1894 until his death in 1925, Langley owned and edited the *Journal of Physiology*. That he felt very keenly about the decencies of scientific publication is shown by the following remarks that exploded at the end of his presidential address in 1899 to the Physiology Section of the British Association. They are not less pertinent today, unless editors have abandoned hope.

"I am tempted, before ending, to make a slight digression. Those who have occasion to enter into the depths of what is oddly, if generously, called the literature of a scientific subject, alone know the difficulty of emerging with an unsoured disposition. The multitudinous facts presented by each corner of Nature form in large part the scientific man's burden today, and restrict him more and more, willy-nilly, to a narrower and narrower specialism. But that is not the whole of his burden. Much that he is forced to read consists of records of defective experiments, confused statement of results, wearisome description of detail, and unnecessarily protracted discussion of unnecessary hypotheses. The publication of such matter is a serious injury to the man of science; it absorbs the scanty funds of his libraries, and steals away his poor hours of leisure."

working with and without oxygen. . . . Once started there are plenty of further experiments to do and the question is a very important one for muscle physiology." "It would," he added, "be an advantage that Fletcher and Hopkins have done a good deal of work closely connected with this, so that you would have people interested in the subject to talk it over with."

I was then in the state of exaltation and relief that succeeded my last examination, Part II of the Tripos in Physiology, following Part I in Mathematics (the latter, in those days, with its Senior Wrangler and all, was rather like the Derby). After that nothing seemed too difficult, but fortunately there were plenty of people about to keep one on the rails. Indeed in the Cambridge Physiological Laboratory of that time, apart from one's contemporaries,[8] there were more physiological giants to the square yard than in any other laboratory before or since, not only because there were very few square yards but also because there were so many giants.[9] And within easy distance were plenty of other people available for advice and help.[10] The environment is vividly described by Adrian in his contribution to Alys Keith-Lucas'[11] book, and by Maisie Fletcher[3] in hers.

Looking back on it now over half a century, it seems remarkable that Langley, who was very far from being a biophysicist or biochemist, should have proposed a subject of research so different from his own, yet so exactly fitted to the Cambridge atmosphere of that time and to my own inclinations: one moreover, which had been so fully exploited by the great German physiologists of the nineteenth century that nothing more might have seemed possible, when in fact the subject was ripe for development through the new ideas and methods then beginning to appear. And, no less remarkable, Langley produced, as though by magic, an apparatus (4) designed by Magnus Blix[12] of Lund, which he had acquired, goodness knows why, after some

[8] Among others, V. H. Mottram, G. R. Mines, Geoffrey Evans, J. R. Marrack, H. Hartridge, George Winfield, E. D. Adrian, J. H. Burn, and R. A. Peters. These were not all there in 1909; several came later.

[9] H. K. Anderson, J. Barcroft and his innumerable colleagues all shaking blood-gas apparatus; W. M. Fletcher, W. H. Gaskell, W. B. Hardy, F. G. Hopkins, J. N. Langley, and Keith Lucas.

[10] For example, F. F. Blackman (botany), W. E. Dixon (pharmacology), H. O. Jones (chemistry), Bertram Hopkinson (engineering), C. G. Darwin (mathematics), T. B. Wood (agriculture), Horace Darwin and C. C. Mason (Cambridge Scientific Instrument Co.). The Cambridge Instrument Company, as it is now called, was started in the 1870's by A. G. Dew-Smith, a pupil and colleague of Michael Foster, largely for the purpose of making instruments for the physiological laboratory. Most of the earliest instruments had physiological and biological applications: this special interest was strongly maintained till his death ten years later, by the appointment, in 1906, of Keith Lucas as a director of the Company.

[11] Lucas, Keith (1879–1916). See Darwin, H., and Bayliss, W. M., *Proc. Roy. Soc.* (*London*), B90, xxxi-xlii (1919); Langley, J. N., *J. Physiol.* (*London*), **51,** 35 (1917); and Lucas, Alys, *Keith Lucas* (Heffer & Sons, Cambridge, Engl., 1934).

[12] Blix, Magnus Gustaf (1849–1904). See Tigerstedt, R., *Skand. Arch. Physiol.*, **16,** 334–47 (1904).

international physiological congress (Blix died in 1904). This beautiful little instrument, a thermocouple and galvanometer in one, was sensitive enough, so Blix had told him, to allow the heat produced in a single muscle twitch to be read (though it lacked its galvanometer magnets, and provided for a time rather a puzzle as to how it worked). After that, Langley took no further part in the research, except to advise me to apply to the Royal Society for a grant, to display occasionally a friendly interest in the results, and to rewrite, and make me rewrite and re-rewrite, the papers which I gave him at intervals for the Journal. Many of my younger colleagues since must have suffered from the editorial peculiarities I thus acquired, though I never took as much trouble for them in rewriting their papers as Langley[7] did for most of us.

There were nearly five years before the First World War and innumerable opportunities of talking it over with Fletcher and with Hopkins. For Fletcher had been my tutor at Trinity (a Cambridge tutor is *in loco parentis* to his pupils), and he became, as it were, an elder brother, while Hopkins' rats (with which he was discovering vitamins) lived in cages around my instruments in a cellar. The cellar was odorous and overcrowded, but inspiring—inspiring not only for its frequent contacts with Hopkins, but because Keith Lucas[11] worked on the other side of a partition there, where he was later joined by Adrian and J. C. Bramwell. Their only entry was past the rats and instruments, which led to frequent and, to me, invaluable discussion. Not least among the benefits occurred when Lucas lent me the revolving contact-breaker which, apart from its idleness during two world wars and its daily activity for 14 years with Hartree, I have used ever since. Characteristic of Lucas' craftsmanship is the fact that, after nearly half a century and still on loan, this simple device works better for its purpose of controlling time intervals, from milliseconds to seconds, than any instrument I have known. Even electronic merchants have been known, reluctantly, to admire it.

Langley's intuition was right, and the use of the myothermic method led soon to critical experiments on the effect of oxygen. These were not usually thought out in advance, they were certainly not "planned" as doctrinaires profess to plan research, they arrived quietly by noticing odd things that turned up, by trying to understand them, and then seeing how they could be used. For example, the deflection of a galvanometer resulting from heat produced by stimulating a live muscle was observed to last considerably longer than that caused by the heat (mainly physical) liberated by an excessive direct stimulus. The latter, a casual observation, led to the use of the "heating control" and the method of electrical calibration; the former prompted the recognition of the "recovery heat" (37, 38, 41, 42), since the longer-lasting deflection could not be explained except by a slow, continuing heat production. This delayed heat, moreover, was found to occur only in the presence of oxygen, and the total amount of it could be measured; it was about equal to the "initial heat" which appeared impulsively during contraction. This led to the conclusion, which Fletcher & Hopkins (24) had been inclined to favour in 1907, that the lactic acid liberated during contraction is not oxidized but resynthesized, restored to its initial state. This conviction was strengthened later by Peters' (48) rather exact calorimetrical measurements of the heat produced in muscle by prolonged stimulation, and a comparison with the heat of combustion of lactic acid.

It is now known that the conclusion is not really so simple as we thought then; and today one would probably say that in such short contractions as mine no lactic acid at all was liberated but that, as a net result, only creatine phosphate was split (and later resynthesized with the aid of energy supplied by oxidation). But the recovery heat in the presence of oxygen, under all sorts of conditions, is still about equal to the initial heat, and its implications after the war of 1914–18 led to a long and happy connexion with Otto Meyerhof.[13]

Another critical result with oxygen was obtained by Viktor Weizsäcker[14] who worked at Cambridge in 1914. Weizsäcker, at Heidelberg, had been occupied (55) with a comparison of mechanical work and oxygen consumption in frogs' hearts and also with the inhibiting effects of cyanide. At Cambridge he made the fundamental observation (56, 57) that the "initial" heat is independent of the presence of oxygen and is unaltered by a heavy dose of cyanide. The chemical reactions, therefore, which liberate energy for the primary process of contraction are altogether nonoxidative in character. This result has been amply confirmed since; even the detailed time-course of the initial heat production, not merely its total amount, is independent of the availibility of oxygen. As a result of the war, and later of his interest in clinical neurology (*die geistige Bedeutung der Krankheit*), Weizsäcker almost abandoned physiology from 1914 onwards. However, his final contribution to it (at the age of 28) was a fundamental one; its merit lay in asking (in Heidelberg) the right question and then going where the technique was available to answer it.

Since Fletcher and Hopkins' work, there had been much discussion of whether the removal of lactic acid from strongly fatigued muscle was caused by its oxidation within the muscle cells, or by its resynthesis into some "lactic acid precursor". They had stated the problem themselves and given their tentative answer. J. K. Parnas had come to Cambridge in 1914, shortly before the war, in order, as he hoped, to decide the question by thermal measurements. He had recently shown at Strassburg [Parnas & Wagner (47)] that, under most conditions of activity and breakdown, frogs' muscles

[13] Meyerhof, Otto (1884–1951). See Peters, R. A., *Obituary Notices Roy. Soc.*, **9**, 175–200 (1954).

[14] Weizsäcker, Viktor (1886–1957). He studied physiology with J. von Kries, medicine with L. von Krehl; and did early research on mechanical work and gas exchange in the frog's heart. In 1920 he went over to neurology in the Heidelberg clinic. He was the grandson and great-grandson of Schwabian theologians and this was reflected in his philosophical and moral approach to illness. In 1941 he was appointed to the Chair of Neurology at Breslau; when Breslau was lost to Germany in 1945 he was given a special chair in general clinical medicine at Heidelberg. In both wars he was a prisoner of the United States Armies.

exhibit parallel changes of lactic acid formation and carbohydrate loss. Under some conditions, however, the correspondence had failed, and Parnas concluded that the precursor of lactic acid was not carbohydrate but something compounded of it. At Cambridge he made parallel determinations, on "completely fatigued" frogs' gastrocnemii recovering in oxygen, (*a*) of the extra oxygen used in 20 hours recovery, and (*b*) in a calorimeter, of the extra heat liberated. He found (*a*) that the extra oxygen was sufficient to burn the lactic acid that disappeared and (*b*) that the extra heat was about half the heat of combustion. He concluded, first, that the lactic acid of fatigue is completely burnt and not rebuilt, and, second, that about one-half of the energy so liberated is stored as potential energy in the muscle.

Parnas' experiments, for so difficult an investigation, were made in a very short time and were ended by the outbreak of war, so that I had no opportunity of discussing them with him. He, as a German citizen, was interned (and later repatriated) while I was in the Army. The state of his "completely fatigued" muscles may have been abnormal, as compared with that of the very moderately stimulated muscles used in my experiments in 1912 and after, and their recovery took 20 hours as compared with the few minutes of mine. His extra oxygen and extra heat may have been attributable to processes other than the normal removal of lactic acid and so have been too large. At any rate, his conclusions were wrong. However, they were communicated to the Physiological Society (45) and published in greater detail later (46) in Germany. They were accepted by Fletcher & Hopkins (25) in their Croonian Lecture (and seriously affected their deductions), and, at first, by Meyerhof; but in 1920, on closer examination, Meyerhof (44) showed beyond doubt that in the recovery of muscles from fatigue the oxygen used, the heat produced, the lactic acid removed, and the carbohydrate reformed all fitted into a consistent scheme. When lactic acid disappeared under the influence of oxygen, only a third or a quarter of it was burnt (or a corresponding amount of carbohydrate); the rest reappeared in carbohydrate form.[16]

So the circle was completed, back to Fletcher and Hopkins' original

[16] An entertaining personal story may be added of the conflict of conclusions between Parnas and Meyerhof. In July 1920 an "International" Congress of Physiologists was to be held in Paris, from which "enemy" scientists were to be excluded. In March 1920 Meyerhof had sent his results for publication to *Pflügers Archiv*, and he complained to me bitterly in a letter that he was not to be allowed to attend the Congress and report them, whereas Parnas, no longer a German "enemy" but now a Polish "ally", was intending to read a paper on his contrary findings of 1914, based on much less critical evidence than Meyerhof had obtained. Yet Parnas, in Cambridge from Strassburg in 1914, had been an open and vigorous supporter of German militarism, which Meyerhof had always deplored. In the event, however, neither of them went to the Congress, for Parnas was cut off in Warsaw by the Russian armies which had invaded Poland in July, and it was left to the Congress at Edinburgh of 1923, under the presidency of Sharpey-Schafer (who himself had lost two sons in the war) to become properly international again.

tentative explanation of their results, that lactic acid is not burnt during recovery but rebuilt. It had been difficult not to accept that view, anyhow, once the heat of formation of lactic acid in muscle was known and compared with its heat of combustion. Teleological arguments are notoriously dangerous, but it was difficult to believe that an important constituent of the muscle mechanism, containing a large amount of energy, had to be burnt every time it was produced, in order merely to get rid of it, thereby placing a heavy extra load on the respiratory and circulatory system. From the engineering standpoint, the design of muscles is not so stupid as that [Hill (43)].

The experiments discussed so far were made on isolated muscle; but, just when it was realized that in such muscle a considerable amount of heat is liberated in recovery after contraction, two papers appeared, by Barcroft[16] and his colleagues, describing analogous results on whole, but anaesthetized, animals. In the first, Verzàr (54) showed that, after a rather long tetanus of a cat's muscle, excess oxygen continued to be used for several minutes; in the second, Barcroft & Piper (1), studying the extra oxygen consumption resulting from stimulation of the submaxillary gland of the cat, found that oxygen was used for some time after saliva had ceased to flow. They concluded

> the oxygen appears to be used not in directly providing the energy necessary for the secretion of saliva, but rather for re-establishing the potential energy of the physical or chemical system which performs the complex function of secretion.

The phenomenon, in fact, is rather a general one: it is very evident after severe muscular exercise in man (where it led later to the concept of "oxygen debt"); it occurs in nerve after stimulation. It would be interesting to know whether there are exceptions to the rule that when physiological activity is provoked suddenly through a nerve, it is followed by a slower chemical process of recovery.

Let us return now to the earlier part of this story. After Helmholtz's original publication in 1848, there was an interval of 15 years during which nothing important appeared, then in the 1860's a long series of papers began. The greatest contributor was Adolf Fick,[17] whose name, curiously enough, is perpetuated not in physiology but in physics, in Fick's Law of Diffusion which he announced in 1855 when he was 26 (11, 12). The German physiologists of that era were certainly accomplished physicists. But physiologists also should remember him, for he was the originator of terms they use every day, "isometric" and "isotonic" applied to muscular contraction (13, pp. 112, 131).

Fick was preceded by a few years in publication on muscle heat by Rudolf Heidenhain[18] whose remarkable monograph (27) in 1864, when he

[16] Barcroft, Joseph (1872–1947). He was Langley's successor, 1926 to 1937. See Roughton, F. J. W., *Obituary Notices Roy. Soc.*, **6**, 317–45 (1949).

[17] Fick, Adolf (1829–1901). See Schenk, F., *Arch. ges Physiol.*, **90**, 313–61 (1902); this article is reprinted in Fick, A., *Gesammelte Schriften*, **1** (Stahel, Würzburg, Germany, 1903).

was 30 years old, contained practically his first and last words, apart from controversy, on the subject. Heidenhain had originally expected that with a constant stimulus the total energy in a contraction, i.e., the sum of work and heat, would be constant too. He was astonished to find that when the initial tension was altered in an isometric contraction, or the work was altered by changing the load, the total energy changed too; that the muscle contained a "governor" by which the energy used was largely determined by length and load. With a technique which today would be regarded as primitive, with a sensitivity which gave only about seven scale-divisions for a muscle twitch (subject also to serious thermal disturbances, described as "*negative Wärmeschwankungen*"), he nevertheless arrived at a result which Fick (13, p. 179) described as "*eine der bedeutsamsten physiologischen Entdeckungen der Neuzeit.*" Heidenhain even went so far as to test his conclusions chemically. If two similar gastrocnemii were similarly stimulated to 100 or 120 twitches under two different loads, great and small, so that one of them did much more work than its companion, the one doing the greater work gave a greater colour change to litmus. This might be a good class-demonstration today! In a final chapter on the theory of muscle force, he concluded that the processes that occur when a muscle is stimulated have a different nature and origin from those that cause a stretched rubber band to shorten. He was completely right, though the matter has often been debated since. Heidenhain's conclusions, and similar results obtained by Fick, were discussed by W. O. Fenn (10) in 1923 in an introduction to his own important work on the subject.

Unlike Heidenhain's, Fick's contributions to muscle heat, with those of his pupils, extended over many years. The results are described in his monograph (13) in 1882, in his *Myothermische Untersuchungen* (15) in 1889, and in his *Gesammelte Schriften* (16, Vol. 2). His best known pupil was Magnus Blix,[12] a Swede, who worked with him in 1880–81, and later devised the apparatus referred to on p. 4 above. Curiously enough, Blix published only two important papers (3, 4) on muscle heat (17 years apart, in 1885 and 1902), though there were several others on muscle elasticity. His paper in 1885 discussed the question whether, in muscular contraction, heat is transformed into work. It is strange that this question should ever have been debated seriously, though it was, again and again; for, if muscle were a heat engine, differences of temperature of at least 100°C. would have to exist within a muscle fibre, to explain an observed "thermal efficiency" of 25 per cent. His paper of 1902 contained a detailed account of technique and a long discussion of previous results. His epigrammatic conclusion that "*Länge macht Wärme*", which meant that the amount of energy liberated is determined by the "chemically active surface" during contraction, is far too simple a description of the true facts.

Apart from the work of Heidenhain, the chief conclusions (so far as they

[18] Heidenhain, Rudolf (1834–1897). He studied in Königsberg and Halle/Saale; was Assistant (1854–56) to E. du Bois-Reymond; Professor at Breslau (1859–97); chiefly known for his work (1867–97) on gland secretion. See Grutzner, P., *Arch. ges. Physiol.*, **72**, 221–65 (1898).

were correct) can be summarized as follows. (*a*) In a maximal twitch, the heat produced is about three millicalories per gram of muscle. (*b*) Direct stimulation and stimulation through the nerve give the same heat, provided that the mechanical response is the same. (*c*) In a tetanus, the longer a muscle is stimulated the greater is the total heat produced, but the rate of heat production decreases continually as stimulation continues. (*d*) In a tetanus, the heat production is independent of the frequency of stimulation, so long as the mechanical response is the same. (*e*) The work done in contraction is not derived from heat but directly from chemical reactions. (*f*) The ratio of work to total energy in contraction depends on the load and has a maximum value of about 0.3. (*g*) When a muscle is stimulated, the chemical processes providing mechanical work occur during the actual performance of that work. They do not create a store of potential (e.g., elastic) energy which can be used for doing work later on. (*h*) A muscle poisoned with veratrin, giving a prolonged contraction in response to a single shock, produces much more heat than a normal muscle. (*i*) A frog's muscle at rest shortens on warming, lengthens on cooling. (*j*) Conversely, when a muscle at rest is extended its temperature rises, when released its temperature falls. This seems a meagre harvest from the expenditure of so much effort, ingenuity and learning over so long; but a great deal has been omitted from the list which is now known to be wrong, or to have no special significance today. In fact, of the material included some was not very firmly established. A brief summary by Sanderson (50) appeared in *Schäfers Text Book of Physiology* in 1900, and a rather detailed discussion and criticism of Fick's experiments and arguments on the mechanical efficiency of muscle were given in my paper (39) in 1913 under that title. My own experiments and conclusions of that time are now of little value, because of technical errors which were overcome only many years later, because their discussion was obsessed by the false idea that during activity a muscle produces elastic potential energy which can be turned into work if the mechanical conditions allow, and because of failure to realize that an ordinary "isometric" contraction is not nearly isometric so far as the muscle fibres are concerned. But my criticism was mostly valid.

The most substantial account (26) of the whole of the earlier work is that published by Otto Frank[19] in 1904. Frank himself had never worked on the subject; but the fact that he came to it without personal bias, together with his critical integrity and unrelenting reliance on precision in experiment and argument, may have helped him to sort out the pertinent results and fruitful ideas from an alarming mass of conflicting evidence and doubtful conclusions. The same obstinate integrity led him 30 years later into conflict with the Nazis. That he was not unsympathetic to those whom he regarded as the chief contributors to the subject is shown by some concluding remarks:

[19] Frank, Otto (1865–1944). See Wezler, K., *Z. Biol.*, **103**, 91–122 (1950). This is a notable biography.

It has been my essential purpose to ensure that the fundamental ideas and the exact methods of these authors should not be destined to oblivion. In that sense these pages are dedicated to their memory.

Yet he had written in his introduction:

When I undertook this task it did not seem so difficult as I have since realized it to be. One became frankly dismayed at the appalling uncertainty which still affects all aspects of the subject. . . . It was essential not to restrain one's criticism. . . .

Many of the questions which had been asked could not be answered by methods available then or for many years after, some needed more precise formulation in chemical or physicochemical terms, others had to wait for better knowledge of the plain mechanics of contraction. Fick himself had confessed in 1884, in the introduction to his paper (14) *Myothermische Fragen und Versuche*,

as the title shows I lay at least as much weight on asking the questions and discussing them as on the actual results of the experiments described.

In his final chapter Frank discussed one of Fick's questions,

Do the thermal phenomena in active muscle give an answer to the problem of whether two separate chemical processes are involved, one in contraction, the other in relaxation?

The question was well put, and has a very modern sound; but with the evidence at hand, and with the methods available, no answer could be given till many years had passed. Frank's final sentence, in this supremely good survey, was:

Perhaps—and that is the highest aim of my efforts—future investigation can derive a stimulus from this review.

I discovered Frank's paper in 1911, 167 pages of long and elegant German sentences, at a time when my knowledge of German was very meagre: and in tribute to his memory I can claim emphatically that it did.

In 1908 Karl Bürker[20] published in *Tigerstedt's Handbuch* a very full account (5) of *Methoden zur Thermodynamik des Muskels*, describing the methods used by all previous investigators. This makes it unnecessary to refer here to the methods used before 1908, and they have in fact been altogether superseded by others developed since. Muscle heat is a subject in which the closest attention to experimental technique, and a real understanding of it, are necessary. It is dangerously easy to get beautiful "thermomyograms"; the problem is to know what, if anything, they really mean, to transform them into absolute units of heat and time, and to be sure what errors affect them. The chief weaknesses of the older methods were the following. (*a*) They were extremely slow, so that it was scarcely possible, and

[20] Bürker, Karl (1872–1957). He studied in Tübingen, became (1904) a.o. Professor there, and then in 1917 was called to the chair of physiology in Giessen; in 1945 he retired to Tübingen. His best known work was on the heat production of muscle and on the physiology of blood.

in fact no attempt was made, to determine the time-course of the heat production during and after a contraction. Investigators were content with a single maximum deflection, representing more or less nearly the total heat produced up to the time when the deflection was read. The essential contribution in more recent times has been to provide a picture of the whole time-course of the heat, in relation to stimulus and mechanical response; and most of our knowledge today results from bringing in that other dimension of time. (*b*) No accuracy was possible in determining either the rate of heat production at rest, or the heat produced over a long interval, e.g., in recovery. These calculations required a degree of thermal stability which could not be attained without a far-reaching redesign of the instruments. (*c*) Calibration in absolute units of heat was inadequate; no account was taken either of the heat capacity of the instruments, or of heat loss up to the moment when a deflection was read. Accurate calibration is essential in comparing thermal and mechanical effects. (*d*) Close and consistent contact of muscle with thermopile is necessary if true records are to be obtained, and this contact must be made over an area large enough to give a reasonable average of the change of temperature. Many of the muscles used, and the thermopiles, did not meet this requirement. (*e*) When muscles are allowed to move, as in doing mechanical work, pre-existing differences of temperature along their length may cause grave errors impossible to allow for or sometimes even to detect. Such errors are avoided today by a special provision in the instruments, also by placing the thermopile and muscle in a container at constant temperature. (*f*) The electrical insulator shielding the thermopile from direct contact with a wet muscle either had to be thick, thus introducing delay and unnecessary heat capacity, as if it was thin, bad electrical leaks might occur. With modern insulating materials the situation is altogether easier.

Moreover subsidiary methods, e.g., of stimulating, mechanical recording, and timing, have added a new order of facility to the complex business of combined mechanical and thermal observation, while a much better knowledge of the physiology of muscle not only can guide one to asking the right questions, but can provide a consistency and reliability comparable with that of more ordinary physical measurements.

Returning now to Bürker, his 1908 paper led me in 1911 to spend two months with him in the pleasant little university town of Tübingen. There I learnt about his methods of constructing thermopiles and had the great good fortune to meet Friedrich Paschen,[21] the professor of physics and a famous contributor to infrared spectroscopy. Later, from 1924 on, Paschen was Director of the Physikalisch-Technische Reichsanstalt in Berlin until he was dismissed by the Nazis in 1933 and replaced by the notorious Johan-

[21]Paschen, Friedrich (1865–1947). In 1888 he received his doctorate in Strassburg with Kundt and Kohlrausch; in 1900, he became Professor of Physics at Tübingen; in 1924, director of the Physikalsich-Technische Reichsanstalt, Charlottenberg; and in 1933 he was dismissed by the Nazis. "A giant among spectroscopists". See the charming biography by Tolansky, S., *Nature*, **159**, 529–30 (1947).

nes Stark; in 1928 he was Rumford medallist of the Royal Society. With characteristic good nature, and often with loud shouts of laughter, Paschen taught me about his fine moving magnet galvanometers, and he allowed me to carry away in my bag (for 80 marks) a beautiful iron-shielded instrument made in his laboratory. This galvanometer lived three and one-half years in my cellar, among the cages of Hopkins' rats, and in 1914 was used by Weizsäcker and Parnas to make their experiments too. Paschen's generous advice was available again, from 1920, when we started constructing galvanometers like his in England. Bürker later published another paper (6) on methods, but it contained little new. The kindly help of Bürker & Paschen in 1911 gave a start (35, 38) to the improvements of technique which have continued since for many years, largely at other people's hands: Weizsäcker's in 1914, Fenn's in 1922, Hartree's from 1919 to 1933, and Downing's from 1920 to the present day. But that is another story which will be told later.

Rutherford once remarked to me, apropos of nothing in particular, "I've just been reading some of my early papers; and when I'd read them for a bit I said to myself 'Ernest my boy, you used to be a damned clever fellow.' " I could not imitate Rutherford's charming egotism; but in rereading for the present purpose those of my own papers which come into the period of this Chapter, written between the ages of 24 and 27, I have been interested to find how much in them, of ideas and method, has proved to be the basis of what has been done since. That, perhaps, is not an unusual experience. Of course it is quite untrue that most of the best original research is done by quite young people. I should myself have been a very unhappy man had I been unable to return at 59 to the work which was suddenly cut short by the Second World War at 53. But it is true that the lines of one's original thinking are generally laid down when one is quite young. However, if one is lucky with the subject and one's colleagues, and with the manner in which an improving technique continues to open up new ways of testing ideas, then one's actual published work before the age of 30 may look naive and unfinished in comparison with that of later years. That at least is my experience, but I have been very lucky.

Another thought that often comes to one's mind as one reads one's own, or anyone else's, earlier papers is the question, why on earth didn't we recognize then what is perfectly apparent now? Why did it take me, for example, 25 years to discover the simple device (a "protecting" region) by which the serious technical error caused by movement of a muscle over a thermopile can be avoided? Much effort and printer's ink would have been saved had this been introduced in 1912 instead of 1937, and the true relations between heat, work, load, and shortening could have been settled many years earlier. Or again, why did it take so long to realize that the series elastic component of muscle (or 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 fibres are concerned; that the mechanical work performed in it is not zero but may be not far short of a maximum; that the emergence of the "active state" after a stimulus is very rapid, and does not follow at all the ordinary form of a contraction? Why do ideas, later seen to be obvious, often come so slowly, to young and old alike, to one's colleagues as well as oneself? I have no answer to suggest, but perhaps by keeping the question continually in mind one may help to obviate the need of one.

In my papers of 1910–1914, there is much that is now known to be wrong, some of the "facts" and several of the assumptions and conclusions. But there are some that are right: apart from those already mentioned, the general idea that a slower twitch is associated with the more economical maintenance of a tetanus; the laying of the ghost of intramolecular oxygen; the emphasis on physical chemistry and thermodynamics. The things that are right—and pertinent—have since been confirmed and extended by better methods; they will be discussed later in my monograph and there is no need to refer to them further here. But some people may still wish to see the original papers, and for that purpose Table I may be useful. They may find occasional flashes of amusement, e.g., in the provocative claim (34, p. 43) by a

TABLE I

INDEX TO TOPICS IN PAPERS OF A. V. HILL ON HEAT PRODUCTION OF MUSCLE

(Papers are those of A. V. Hill except where otherwise noted.)

Topic	Reference numbers
Absolute values of the heat, for comparison with work and tension	(39, 40)
Heat in prolonged contractions: influence of duration, frequency of stimulation, temperature, previous activity	(34, 40)
Effect of length and load	(34, 40) and Evans & Hill (9)
Time at which heat is produced	(33, 34, 38)
Recovery heat	(37, 38, 41, 42)
Initial process nonoxidative	(37) and Weizsäcker (56, 57)
Intramolecular oxygen	(38)
Heat production of anaerobic survival, fatigue and rigor, contrary to Dybowsky & Fick (8)	36) and Peters (48)
Physical chemistry and thermodynamics	Appendix (36, 39)

youngster of 24: "a complete investigation of these facts will give us more real insight into the nature of the muscular machine . . . than any theories of contraction ever founded by ingenious minds upon insufficient knowledge." Langley must have liked that sentence, or he would never have allowed me to finish my paper with it; but it nearly led to blows, at a meeting of the Physiological Society, with the author of one such theory. In fact I have always been ready to defend the proposition that all theories of contraction are wrong—including any of my own. It seems to be a general characteristic of the family, but perhaps some day a viable hybrid will be produced.

Langley had told me in 1909, "there are plenty of further experiments to do." It seems strange, looking back, that so many of them could have been made in less than five years; but they are not finished yet, and it may be worth while, before ending this Chapter, to include a few general reflections on the "philosophy" of them that emerged, chiefly later on, as knowledge and experience grew, as technical developments occurred, and as other lines of progress were disentangled. Let us assume that the primary purpose of biophysics and biochemistry is to relate observed physiological phenomena to physical and chemical events and causes at a molecular level. Muscular contraction is among the most evident of such phenomena, and for exact experimentation it has two special advantages: (*a*) that its end results, force, movement and work, can be accurately and rapidly measured in absolute terms, and (*b*) that they can be elicited at will by an electric stimulus. An obvious and immediate interest is to relate the mechanical occurrences, particularly the work, to the exchanges of total energy involved. That energy, however, is derived from chemical change; and a problem of equal importance, but much more troublesome, is to connect the mechanical events with the chemical ones.

The difficulty is that chemical methods are usually extremely slow and insensitive compared with those of recording mechanical events: e.g., work measured in tens or hundreds of ergs is easily recorded without significant delay, but the chemical reaction which produced it might involve only thousandths of a microgram of substance. Even if chemical changes of such magnitude could be measured, it is scarcely conceivable that this could be done in the small fraction of a second occupied by the mechanical event, particularly since most chemical estimations in living cells involve the destruction of the material itself. The only method usually available is to measure the chemical changes that accrue during a series of contractions; and this involves the danger, almost the certainty, that the finer and more fundamental details will be obscured or distorted by examining only the end products, not the primary processes, of the reaction. The astonishing thing, indeed, is that biochemistry has gone as far as it has, in its analysis of intermediate events.

For measuring heat, however, the methods available are very sensitive, and can be made very rapid—not indeed as sensitive and rapid as those for recording mechanical changes, but incomparably better in both respects than usual chemical methods. The heat is related to the chemical exchanges, not always indeed in a specific way, but at least in a manner which provides a firm outline that must not be overstepped and can be filled in as knowledge accrues. In nerve, where no aid is derived from mechanical manifestations of activity, and the electric change is the only immediate sign, the heat provides a valuable further object of study, for comparison with ionic exchanges, and eventually, when they are successfully measured, with chemical exchanges too.

To summarize, therefore, the special value of the heat as an object of research and an index of activity in muscle and nerve 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.

For many years attempts were made to measure the heat production of stimulated nerve. Helmholtz (30) in 1848 had failed to find any in frogs' nerves, but he could read only to 0.002°C.; about 1000 times this sensitivity was needed. Valentin (53) in 1863 and Schiff (51) in 1869 claimed to have obtained positive results. However, Valentin's results must certainly have been caused by the Joule's heat of the stimulating current (which is not easy to avoid), while Schiff's were not quantitative, and no precautions against leak of heat from the stimulus were described. Heidenhain (28) in 1868, with about ten times Helmholtz's sensitivity, again obtained a negative result. In 1890 Humphrey Rolleston[22] in Cambridge turned to the subject (49); it is an intriguing question what led him to it, in view of his later clinical interests. He used a platinum resistance thermometer, with which he could read to 0.0002°C., about the same as with Heidenhain's thermopile. Taking care to avoid the Joule's heat of the stimulating current, he found no measurable heat produced by the nerves; he needed 100 times the sensitivity, which no resistance thermometer could possibly have provided. In the following year, also at Cambridge, G. N. Stewart (later Professor of Physiology at Western Reserve University) tried again (52), with similar instruments, on mammalian nerve; he also was unsuccessful. Finally in 1897 Max Cremer (7), thinking that nonmedullated nerves might give more heat than medullated ones (which later events confirmed), tried the olfactory nerves of pike, carp, and barbel. Reading to 0.0001°C., he concluded that the heat, if any, was certainly less than the disturbance caused by the Joule's heat of the stimulating current.

Why did people go on trying to measure the heat production of nerve, in spite of repeated failure? Chiefly, I suppose, in order to settle the question of whether the nerve impulse is the sort of physical wave in which the whole of the energy for transmission is impressed on the system at the start. Various properties of nerve, superficially at least, favoured this view, particularly the classical demonstration of its "infatigability". Against it was the existence of an absolute refractory period, during which, after the passage of one impulse, a second one cannot be carried; in this property the nerve impulse is unlike any physical wave in which the energy is supplied at the start. If it could be shown that heat really was produced all along a nerve during transmission, then the purely physical theory of conduction would be untenable. A distributed relay system would be required, with energy derived presumably from chemical change.

With such ideas in mind, though not so clearly as today, in 1912 I made another unsuccessful attack (35) on the problem, using the improved thermoelectric instruments constructed after my visit to Bürker and Paschen in 1911. Once more, nothing was found, though success was really rather near. The thermal stability was poor, and the real sensitivity must have been considerably less than I estimated, because of factors not properly realized

[22] Rolleston, Humphrey Davy (1862–1944). He was a physician; Fellow of St. John's College, Cambridge; President, Royal College of Physicians, 1922–26; Regius Professor of Physic, Cambridge University, 1925–32.

at that time. Making a rough allowance now in retrospect, what was really shown was that 600 impulses did not cause a heat production of more than about 3×10^{-5} cal. per gm. or for one impulse 5×10^{-8} cal. per gm. As a matter of fact heat is produced, and I had very nearly measured it; for 20 years later the heat per impulse at the same frequency was found to be about 6×10^{-8} cal. per gm. Had the limb nerves of spider crabs been used instead of the sciatic nerves of frogs, the heat would have been large and obvious.

Bayliss was quick to see the implications of this new failure, at a much higher sensitivity, to detect any heat and in 1915 in his *Principles of General Physiology* (2, p. 378) he wrote:

> The result makes it impossible to suppose that any chemical process resulting in an irreversible loss of energy can be involved [in the transmission of a nerve impulse], and indicates that a reversible physicochemical one of some kind is to be looked for.

I had made originally a similar claim myself, but when the excitement died down I could not really believe it, particularly in face of the absolute refractory period and its consequences. Many things occur in nerve which are quite unlike what happens in the transmission of an ordinary physical wave, while the supposed physicochemical changes were so rapid that they were rather unlikely to go on "reversibly" in such a medium as nerve. Anyway at intervals, after the war of 1914–1918, I went on trying, now with Downing's help; and in 1926 at last positive results were obtained.

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