Historical note on the translation of H. P. Bowditch's paper 'Über die Eigenthümlichkeiten der Reizbarkeit, welche die Muskelfasern des Herzens zeigen' (On the peculiarities of excitability which the fibres of cardiac muscle show)[1]

Berichte der Königlich-Sächsischen Gesellschaft der Wissenschaften, Mathematisch-physische Classe, 1871, 23, 652–689

J. SCHAEFER, W. DEPPERT, R. K. LIE, B. LOHFF AND M. I. M. NOBLE

For some discoveries in science, it seems to take decades before their importance is recognised, and before they gain the acknowledgement denied to them at the time of first publication. The 'staircase' phenomenon which was described in Bowditch's paper of 1871 belongs in this category. While other important observations in the publication immediately earned a wide recognition, the importance of the 'Treppe-Phänomen', though mentioned, was not recognised for a long time. It was Hadju & Szent-Györgi (1952) who pointed out that 'whatever is the ultimate cause, the staircase must be the direct impression of the functional state of the actomyosin system, which is governed mainly by the temperature and ions'. It was probably because of Hadju & Szent-Györgi's

[1] The original translation was accomplished under the auspices of the International Institute for Theoretical Cardiology, and presented to members of the British Society for Cardiovascular Research at an Interval–Force Symposium in 1988. That was a literal translation which of necessity retained the somewhat obscure style of the original (high) German. In the present book, we have tried to reduce this basic text to a more understandable modern English form. This has included some shortening and paraphrasing of the original, and occasional judgements about Bowditch's meaning in the presence of some uncertainty. This may inadvertently have changed his meaning in some instances, but we think that the new version will nevertheless be more useful. The interested reader is referred to the original translation, accompanied by the original German version, which is available from Professor Schaefer at the IIfTC.

publication that Bowditch's description of the relationship between stimulus interval and force development became recognised as relevant to modern cardiovascular research. Fishman & Richards (1964) stated that 'the staircase effect . . . received little investigative attention for over half a century, but suddenly revived due to work by Szent-Györgi & Hadju, and it may turn out to be a way to penetrate the profound problems of the relation between stimulus and response'. Actually, a study of the physiological literature of the late nineteenth century shows that this statement is not quite correct, in that Bowditch's paper was discussed by Aubert (1880), Landois (1900), Tigerstedt (1913), Höber (1922), Trendelenburg & Loewy (1924), and especially Abderhalden (1925). However, the staircase phenomenon itself is only marginally mentioned in all these discussions. A detailed historical analysis of the reasons why Bowditch did not take up the results of his paper of 1871 in his next publication (Bowditch, 1872), and why the work of Luciani (1872) gained more importance would be of great interest to the scientific community.

During our intensive involvement with this 120-year-old text, we were surprised by the wealth of original observations and experimental findings, as well as by the careful methodological work, which was included. Some of the principal findings are summarised in Table 1.

Thus Bowditch's observations, and the assessment he offered of factors that characterise the force–interval relation, anticipated modern concepts of electromechanical coupling and contractility. In approaching the 1871 paper with today's knowledge, therefore, one cannot help asking the question: 'Why did the force–interval relationship, as described by Bowditch, not receive recognition for so long, or, what are the reasons why the force–interval relationship disappeared from light for so long?'

We would like to deal with these questions in the form of four theses:

Thesis 1: *The objects of scientific inquiry with which Bowditch was occupying himself did not fit into the general system of work and thought of his time.*

This does not seem to have been the case. When Bowditch writes in the introduction to his publication that he is interested 'to study the conditions under which the excitable and stimulatable pieces of heart fatigue and recover', he is in complete accord with the research efforts of Ludwig's laboratory in Leipzig (the list of publications from Ludwig's laboratory studying the activity of the heart have been elegantly summarised by Schröer, 1967). Many other researchers in

Table 1. *Contents of Bowditch's 1871 paper*

(*a*) *Main interval–force contributions*
Staircase (Treppe) phenomenon
Post-extrasystolic potentiation
Definition of the 'optimum interval' (a prequisite for the concept of mechanical restitution)
Description of accumulating positive and negative inotropic processes with *different* time constants during artificial stimulation of the heart (precursors of the PIEA and NIEA concepts of Koch-Weser & Blinks, 1963)
(*b*) *Other important contributions*
Differentiation between artificial and endogenous excitation of the heart and their different pathways
The use of toxicological and pharmacological interventions as tools to study the relationship between interval and force
Establishment of the relationship between excitation and contraction as a determinant of physiological function
All-or-none law
(*c*) *Aspects which were alluded to*
Problems caused by the isolation of tissues
Difficulties in the extrapolation of results from isolated tissues to the intact organism
Differences between blood and serum perfusion versus perfusion with artificial solutions
The limitations which are imposed by apparatus, and which have to be respected by experimenters

cardiac physiology at that time, and for some years afterwards, were preoccupied with relating changes in cardiac rhythm to alterations in the force of contraction. In the period from 1866 (Cyon & Ludwig) to 1902 (Woodworth), a variety of research approaches dealing with the relationship between stimulation and activity of the heart were pursued, and a great deal of knowledge about the relationship between stimulation of the heart and the developed contractile force was gained. However, from the point of view of the philosophy and history of science, the impact of these findings has not been adequately analysed. All the prerequisites for the recognition of the principle of electro-mechanical coupling seem to have been available, but no-one seems to have taken this step. Perhaps further work on the question was limited by methodological difficulties. Recording equipment and methods of calibration were at an early stage of development, and each scientist had to make or develop his own apparatus to tackle a specific question (Schröer, 1967). In addition, it became more and more difficult to form a coherent picture of the activity of the heart from the increasing but fragmented body of knowledge which was accumulating. As Abderhalden (1925) pointed out '... a study of this discipline [physiology] which is so fundamental for the understanding of medicine, can only be successful if logical reasoning and the tying together of the innumerable individual facts will lead to a vivid picture of the whole organism'. A limiting factor may also have been that this research seemed to offer relatively few insights into the importance of the activity of the heart for the body (as relevant then as today).

Thesis 2: *Bowditch's work suffered under the influence of contemporary controversies.*

Langendorff (1885, 1898) explained the increased force of contraction of the beat following a premature beat as a 'compensatory effect', i.e. compensating for the weaker premature beat and the missed regular beat. He postulated that the heart strives to conserve both its rhythm and the force of the contraction. This kind of explanation was quite popular during the next few decades (see Kaiser, 1892; Botazzi, 1896; Cushny & Matthews, 1897; Bornstein, 1906; Cushny, 1912), although they were rejected by Woodworth (1902), who in 1897 began to work systematically on the effects that had been described by Bowditch and to restudy them in both the amphibian and mammalian heart. He came to the conclusion that 'the great force of the beat following the extra contraction is dependent, in the frog's ventricle, mostly on the prolonged compensatory pause. It is not directly dependent, as Langendorff supposes on the weakness of the extra contraction'. In addition he confirmed the staircase phenomenon, as well as Bowditch's observations on the 'all-or-none' law, in the mammalian heart. He further observed that the spontaneous beat following an extra contraction of the apex was much stronger than the regular beat, and that the 'hastened' extra contraction had a stimulating effect which was proportonal to its prematurity, and persisted on average for about eight subsequent beats. He noted too that there was an optimal interval between beats which was shorter in the dog than in the frog. However, even though these observations were reproduced (Rihl, 1906), they were not regarded as important.

One should also note that surrounding much of this research was a controversy between the myogenic and neurogenic schools concerning the origin of the heart beat. We would like to suggest that preoccupation with this controversy, and the dominance of the concept of 'compensation' made it difficult for researchers to accept other determinants of the force of contraction.

Thesis 3: *New concepts in cardiovascular physiology began to displace other approaches.*

This indeed seems to have happened. The concept of regulation of the work of the heart through the end-diastolic fibre length (Starling's Law of the heart; Starling, 1918) dominated cardiovascular research in the first half of the twentieth century. Starling's concept incorporated an intrinsic myocardial response as one feature of a highly complex control system (Chapman, 1975), and seemed, at least to the community of scientists interested in the cardiovascular system, to explain practically all important phenomena which characterised the regulation of cardiac force. It thus gained lasting importance in the practice of medicine (Fye, 1983). Preoccupation with Starling's concept led to new ways of viewing the role of the activity of the heart for the body, thus influencing the 'Denkstil' (way of thinking) of the community of scientists ('Denkkollektiv', Fleck, 1935), which narrowed new research approaches. This is vividly illustrated in textbooks of physiology and cardiology from 1920 to the present day. There was a tendency to explain *all* changes in myocardial contraction in terms of changes in the initial length of the fibre, including the dependence of the force of contraction in the interval between beats. Wiggers (1925) for example, studied the ineffectiveness of premature beats with great skill, but did not really seriously concern himself with post-extrasystolic potentiation (Cranefield, 1965), arguing that the post-extrasystolic beat was stronger because the ventricle was more distended at the end of the longer interval before the beat.

Thesis 4: *Realisation of the interdependence of cardiac electrical and mechanical phenomena allowed the re-assessment and re-discovery of Bowditch's findings.*

As it became increasingly evident that cardiac rhythm and cardiac contraction influence each other via electro-mechanical coupling, the findings of Bowditch and Woodworth became relevant again, as they still are today. Several factors contributed to this 're-discovery' and 're-assessment'. First, the development of pacemaking systems opened up the possibility of inducing artificial alterations in rhythm of the heart to treat cardiac arrythmias. The advent of cardiac pacing renewed interest in the fundamental principles underlying the relationship between interval and developed force.

Secondly, renewed interest in cardiovascular pharmacology made it necessary to define the conditions under which drugs could be tested and compared with each other. In a superb review Koch-Weser and Blinks (1963) drew attention to the importance of the interval between beats in the assessment of the inotropy of various substances and the tremendous difference of effects in different species.

Finally, there was a renewed interest in what has been termed 'contractility'. A number of observations made prior to those of Starling had indicated that cardiac muscle was able to alter its intrinsic contractile properties. In 1977 Katz wrote '. . . the importance of these early observations did not become apparent until a symposium on this subject was organised in 1955 at which Sarnoff presented the concept of a 'family of Starling curves', which clearly integrated knowledge of the length-dependent changes in contractile performance, described half a century before by Otto Frank & E. H. Starling, with scattered bits of evidence pointing to a significant role for alterations in 'myocardial contractility'. It was recognised that conditions quite apart from the cellular environment, such as the experimental conditions chosen by the investigator, partly determine the particular combination of force and shortening that the muscle exhibits (Milnor, 1982). Milnor further observed that this dichotomy – the division of factors that determine myocardial function into two classes – has become a central concept in cardiac physiology. In effect, it becomes a distinction between the capability of the muscle and its actual performance in a given situation. The first of these, the *potential* for contraction that the muscle possesses by virtue of local physicochemical conditions, has become referred to as *contractility* (another term which is a source of controversy). The second is the actual *performance* of the muscle in a given setting. This is attributable to the limitations imposed by external mechanical conditions in the ability of the muscle to respond.

Aware of these approaches to the study of contraction and performance, and of the emergent role of calcium in the contractile process, scientists came to recognise the possibility of using the force–interval relationship to extend their understanding of excitation–contraction coupling in the mammalian heart *in situ*. Thus Yue & Sagawa (1987) wrote: 'The beautifully ordered fashion in which the strength of contraction of mammalian cardiac muscle responds to changes in stimulation pattern has long engendered the hope that clarification of these phenomena, known as the interval–force relationship, would lead to understanding the fundamental mechanisms underlying cardiac contraction.'

Conclusion

The pattern which we have outlined, and which in essence shows a neglect of the important insights made available by Bowditch 120 years ago, is very familiar to philosophers of science. It is due to the fact that a certain way of thinking determines the extent to which scientific insights will be accepted, rejected or neglected. If researchers belong to a certain community then they will communicate according to the rules which have been developed in that community. Observations and hypotheses which do not fit into the pattern which dominates the contemporary research approach are either rejected, not acknowledged, or even forgotten. This seems to have happened to the knowledge of the force–interval relationship which had been accumulated up to 1902. With the emergence and general acceptance of Starling's concept a completely different approach to understanding the function of the heart was established.

References

Abderhalden, E. (1925). *Lehrbuch der Physiologie in Vorlesungen*. Teil II. Berlin: Urban.

Aubert, H. (1880). Innervation der Kreislauforgane. In: *Handbuch der Physiologie*, Band 4, hrsg. von L. Hermann, pp. 348–80. Leipzig: Vogel.

Bornstein, A. (1906). Die Postextrasystole. *Zentralblatt Physiologie*, **20**, 401–5.

Botazzi, F. (1896). Über die 'postcompensatorische' Systole. *Zentralblatt Physiologie*, **10**, 401–5.

Bowditch, H. P. (1870). Letter from Leipzig, March 8th 1870. *Boston Medical and Surgical Journal*, 305–7.

Bowditch, H. P. (1871). Über die Eigenthümlichkeiten der Reizbarkeit, welche die Muskelfasern des Herzens zeigen. *Berichte der Königlich-Sächsischen Gesellschaft der Wissenschaften, Mathematisch-physische Classe*, **23**, 652–89.

Bowditch, H. P. (1872). Über die Interferenz des retardirenden und beschleunigten Herznerven. *Arbeiten aus der Physiologischen Anstalt zu Leipzig mitgetheilt von C. Ludwig*, pp. 259–80. Leipzig: Hirzel.

Chapman, C. B. (1975). Ernest Henry Starling. In: *Dictionary of Scientific Biography*, vol. XII, ed. Gillespie, Ch. C., pp. 617–19. New York: Scribner.

Cranefield, P. F. (1965). The force of contraction of extrasystoles and the potentiation of force of the post-extrasystolic contraction. A historical review. *Bulletin of the New York Academy of Medicine*, **41**, 419–27.

Cushny, A. R. (1912). Stimulation of the isolated ventricle with special reference to the development of spontaneous rhythm. *Heart*, **3**, 257–78.

Cushny, A. R. & Matthews, S. A. (1897). On the effect of electrical stimulation of the mammalian heart. *Journal of Physiology*, **21**, 213–30.

Cyon, E. & Ludwig, C. (1866). Die Reflexe eines der sensiblen Nerven des Herzens auf die motorischen Blutgefäße. *Berichte über die Verhandlungen der Königlich-Sächsischen Gesellschaft der Wissenschaften zu Leipzig, Mathematische-physische Classe*, 307–29.

Fishman, A. P. & Richards, D. W. (1964). Circulation of the blood. *Men and Ideas*. New York: Oxford University Press.

Fleck, L. (1935). *Erfahrung und Tatsache*. Frankfurt: Suhrkamp, 1983.

Fye, W. B. (1983). Ernest Henry Starling, his law and its growing significance in the practice of medicine. *Circulation*, **68**, 1145–48.

Hadju, S. & Szent-Györgi, A. (1952). Action of DOC and serum on the frog heart. *American Journal of Physiology*, **168**, 159–63.

Höber, R. (1922). *Lehrbuch der Physiologie des Menschen*. 3. Auflage, Berlin: Springer.

Kaiser, K. (1892). Untersuchungen über die Rhythmicität der Herzbewegungen. *Zeitschrift für Biologie*. Neue Folge, **11**, 203–26.

Katz, A. M. (1977). *Physiology of the Heart*. New York: Raven Press.

Koch-Weser, J. & Blinks, J. R. (1963). The influence of the interval between beats on myocardial contractility. *Pharmacological Reviews*, **15**, 601–52.

Landois, L. (1900). *Lehrbuch der Physiologie des Menschen*. 10. vermehrte und verbesserte Auflage, Berlin: Urban.

Langendorff, O. (1885). Über die elektrische Reizung des Herzens. *Archiv für Physiologie, Leipzig*, **8**, 284–7.

Langendorff, O. (1898). Untersuchungen am überlebenden Säugethierherzen. III. Abhandlung: Unregelmäßigkeiten des Herzschlages und ihre Ausgleichung. *Pflügers Archiv für die gesamte Physiologie*, **70**, 473–86.

Luciani, L. (1872). Die periodische Function des isolirten Froschherzens. *Arbeiten aus der Physiologischen Anstalt zu Leipzig mitgetheilt von C. Ludwig*, pp. 113–96. Leipzig: Hirzel.

Milnor, W. R. (1982). *Hemodynamics*. Baltimore: Williams & Wilkins.

Rihl, J. (1906). Zur Erklärung der Vergrößerung der postextrasystolischen Systole des Säugethierherzens. *Zeitschrift für Experimentelle Pathologie und Therapie*, **3**, 1–18.

Schröer, H. (1967). Carl Ludwig. *Begründer der messenden Experimentalphysiologie: 1816—1895*. (Große Naturforscher, 33). Stuttgart: Wiss. Verlagsgesellschaft.

Starling, E. H. (1918). *The Linacre Lecture on the Law of the Heart given at Cambridge 1915*. London: Longmans and Green.

Tigerstedt, R. (1913). *Lehrbuch der Physiologie*. 7. Auflage. Leipzig: Hirzel.

Trendelenburg, W. & Loewy, A. (1924). *Lehrbuch der Physiologie des Menschen* 4. Auflage des Lehrbuches von Zuntz und Loewy. Leipzig: Vogel.

Wiggers, C. J. (1925). The muscular reaction of the mammalian ventricles to artificial stimuli. *American Journal of Physiology*, **73**, 346–78.

Woodworth, R. S. (1902). Maximal contraction, 'staircase' contraction, refractory period and compensatory pause of the heart. *American Journal of Physiology*, **8**, 213–49.

Yue, D. T. & Sagawa, K. (1987). Insight into excitation–contraction coupling of heart derived from studies of the force–interval relationship. In *Activation, Metabolism and Perfusion of the Heart*, ed. S. Sideman & R. Beyar, pp. 261–77, Dordrecht: Martinus Nijhoff.