PRELUDES AND PROGRESS

Ernest Henry Starling, his law and its growing significance in the practice of medicine

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THE DRAMATIC advances that have characterized cardiovascular medicine and surgery since World War II have been, in many instances, the result of the clinical application of discoveries or concepts derived from basic scientific research. Those concerned with the care of patients and health care delivery, whether they are physicians, laymen, or legislators, would benefit from an enhanced awareness of the importance of basic biomedical research to advances in clinical medicine. Comroe and Dripps1 have published a major study that demonstrates the relationship of basic scientific research to major advances in the diagnosis and management of patients with cardiovascular diseases. Often a series of developments are required before scientific discoveries — theoretical or practical — can be applied to the care of patients through improvements in the diagnosis and treatment of disease. Most new developments in medicine, as in other sciences, are based on a series of discoveries, although this continuum is often overlooked not only by those who utilize the new technologies or therapies but even by the basic and clinical scientists who contribute to their development. New discoveries and new applications of old discoveries help us place the contributions of physicians and scientists of past generations in perspective. Recent developments in the management of patients with congestive heart failure and acute myocardial infarction are based on the clinical application of hemodynamic principles advanced or refined by Ernest Starling early in this century.

Ernest Henry Starling (1866–1927) is known to medical students and physicians for his “Law of the Heart.”2 Starling’s formulation of this important physiologic concept was an extension of the work of European physiologists such as Carl Ludwig and Otto Franck and American physiologists such as Henry Newell Martin and William Howell.3,4 Furthermore, Starling’s classic papers published between 1915 and 1919 on this subject represented the culmination of a quarter century of research in cardiovascular physiology.5 Starling was born in London in 1866 and entered Guy’s Hospital Medical School in 1882 at the age of 16.6,7 Here he came under the influence of Leonard Charles Wooldridge, nine years Starling’s senior, who had returned to Guy’s as assistant and subsequently demonstrator in physiology, having worked in Carl Ludwig’s Physiological Institute in Leipzig. From Ludwig’s laboratory Wooldridge published an article on the innervation of the mammalian heart, and upon his return to Britain his “predominant delight” was physiologic research.8 While continuing his medical training, Starling’s interest in experimental physiology was further heightened by a summer spent working in the Heidelberg laboratory of Willy Kühne, who had succeeded Helmholtz as professor of physiology in that institution. In 1887 Starling was appointed demonstrator in physiology at Guy’s Hospital. The premature death of Wooldridge at the age of 32 opened the position of lecturer in physiology, to which Starling was appointed in 1889.

Several factors are necessary to enhance the likelihood of success when one contemplates undertaking original research. Starling’s classmates and subsequent contemporaries generally agree that Starling possessed rare intellect and a deep commitment to the advancement of medical practice through fundamental research. Additional necessary requirements for a meaningful research effort included then, as now, time, funding, facilities, and the association with colleagues of similar or complimentary talents and interests. Physiology was barely emerging as a profession in Great Britain when Starling accepted his appointment at Guy’s. A small but increasing cadre of full-

Vol. 68, No. 5, November 1983
time physiologists was appearing, largely due to the recognition of the success of this approach in Germany, then the undisputed world leader in scientific medicine. In Britain the basic science movement was aided by the efforts of William Sharpey and his pupils, particularly Michael Foster, and by men such as Thomas H. Huxley, Walter Gaskell, and Thomas Lauder Brunton, who although trained in medicine chose careers in science. Funding for medical research in Great Britain (and America) in this era was virtually nonexistent and depended upon philanthropy, independent wealth, and a handful of modest prizes or scholarships competitively awarded by medical societies or private endowments. Starling’s ability to devote himself exclusively to teaching and research in physiology without having to depend upon medical practice for financial support was made possible by a combination of his modest salary as demonstrator, the fact that he won one of two scholarships awarded by the British Medical Association in 1892, and perhaps most importantly his marriage in 1891 to Florence Amelia Wooldridge, the widow of his teacher and the daughter of the prominent British physician and histologist Sir Edward Sieveking.

Inspired by Michael Foster’s *Textbook of Physiology*, his associate Wooldridge, and his own firsthand experience in a German physiologic laboratory, Starling published his first paper in 1890 with Frederick Gowland Hopkins, a classmate and subsequently Nobel laureate for his work in biochemistry. More adequate facilities for physiologic research were available at University College, where Michael Foster had organized the first modern physiologic laboratory in Great Britain in the late 1860s. Led to the laboratory at University College because he was “unable to obtain facilities for research at Guy’s,” Starling undertook the first of a long series of joint research projects with William Bayliss in the laboratory of Edward Schaefer. Starling now had access to adequate laboratory facilities in an institution with a heritage of research in cardiovascular physiology and anatomy. Starling’s second published paper was written with Bayliss and was based upon experiments undertaken at University College, extending observations made in the same laboratory by John Burdon-Sanderson a decade earlier when the first electrocardiogram was recorded in the intact animal (a frog). The Starling-Bayliss paper, “On the Electromotive Phenomena of the Mammalian Heart,” described the first successful attempt to record electrocardiograms from a mammal and demonstrated that contraction of the mammalian heart began at the base and proceeded to the apex. In addition to these important observations relating to electromechanical aspects of cardiac function, the collaborators developed an improved technique for the accurate measurement of intra-aortic and intraventricular pressures.

Having returned to Europe in 1892 to work in the Breslau laboratory of Rudolf Heidenhain, Starling’s research interests broadened to include such questions as the mechanism of lymph formation and the physiology of secretion and absorption in the cavities of the body. The dominant theme of Starling’s research remained the physiology of secretion and absorption through the first decade of the twentieth century. He was elected to membership in the Physiological Society in 1890 and received increasing recognition at home and abroad through his valuable publications. At Starling’s urging, Guy’s Hospital improved the laboratory facilities in 1897, but in the words of the school’s historian, “The School was slow to adjust its old-time arrangements and to reward him by appointment to a fitting position. When at length it proposed to do so, it was too late. He had been invited to become Professor of Physiology at University College.” Starling continued his research in the laboratory of University College, and in a series of studies on pancreatic secretion in 1902 he discovered secretin, which contributed to the development of our modern conception of internal secretions and endocrinology. Indeed, Starling proposed the term “hormone” in 1905 in his Croonian Lecture, “On the Chemical Correlation of the Functions of the Body.”

Although Starling had summarized his conceptualization of the mechanisms of adaptation of the heart to various physiologic and pathologic stresses in a lecture, “On the Compensatory Mechanisms of the Heart,” delivered in 1897, it would be nearly 15 years before the physiology of the heart would once again become the dominant theme of his research. There were assembled at University College in the early years of the present century an unusual group of physicians and clinical scientists who were especially interested in the physiology and pharmacology of the heart and circulation. This group, in addition to Bayliss and Starling, included Arthur Cushny, noted for his studies on digitalis, who joined the faculty in 1905 as the first to hold the new full-time chair of pharmacology, and Sidney Ringer, who had been associated with University College for half a century and had undertaken at this institution his classic experiments on the physiologic effects of electrolyte solutions on living tissues. Thomas Lewis, the great pioneer of electrocardiography, worked in Starling’s laboratory in 1907–1908,
the year after he received his M.D. from the London institution. Recognizing the increasing interest in circulatory physiology and pharmacology among the English speaking medical and scientific community and desiring a proper vehicle for the publication of his studies on electrocardiography, Lewis founded the journal *Heart* in 1909, which he edited from Starling’s laboratory at University College. Lewis was undoubtedly an especially stimulating associate, and the initiation of the journal *Heart* likely served as a catalyst for studies on the circulation in Starling’s laboratory.

C. A. L. Evans, a student in Starling’s laboratory beginning in 1911 and eventually Starling’s successor to the Jodrell chair at University College, claimed that ‘‘with increased staff, ample accommodation, new equipment and a rapidly-growing band of diligent helpers, his most earnest desire had been fulfilled.’’ The series of experiments that led to the comprehensive formulation of Starling’s law began in 1912 and concluded in 1920, when on the basis of his research on the isolated mammalian heart Starling claimed, ‘‘The heart, freed from all its nervous connexions, has the power of automatically adjusting the force and extent of its contractions to the task which is set it by the two factors determining its work, viz: the inflow into the heart from the veins, and the resistance offered to the outflow by the arterial pressure.’’ He studied these two physiologic variables separately in a series of elegant experiments, during which he varied the preload and afterload and further concluded:

The behaviour of the muscle tissue of the heart thus resembles that of muscular tissue generally, whether skeletal or unstriated, in which the contractile stress set up by each contraction is a function of the length of the fibre. The greater the length of the fibre, and therefore the greater amount of surface of its longitudinal contractile elements at the moment when it begins to contract, the greater will be the energy in the form of contractile stress set up in its contraction, and the more extensive will be the chemical changes involved. This relation between the length of the heart fibre and its power of contraction I have called ‘‘the law of the heart.’’

It was nearly a generation later that Tinsley Harrison first employed the basic physiologic concepts advanced by Starling to explain the clinical features of congestive heart failure. In recent years, through advances in our understanding of the physiology and biochemistry of muscular contraction, the fundamental principles underlying Starling’s observations and conclusions have been elucidated. Recent developments, including the introduction into clinical medicine of the flow-directed balloon-tipped catheter by Swan and Ganz, have greatly facilitated the ability of clinicians to obtain hemodynamic data from patients in a wide variety of clinical settings. The physiologic principles relating to the control of cardiac output described by Starling more than half a century ago took on new clinical relevance as the hemodynamic approach to the management of congestive heart failure and acute myocardial infarction was proposed by Forrester from Swan’s group in recent years. Therefore it required the development of cardiac catheterization techniques, and particularly the simplified method devised by Swan and Ganz, as well as advances in our understanding of the physiology and pharmacology of the heart in health and disease for us to fully appreciate the clinical significance of the fundamental hemodynamic principles outlined by Starling. Half a century ago Starling anticipated this occurrence, claiming:

For years the ‘‘muscle-nerve physiologist’’ was reproached by the so-called practical man with spending his time and attention on things which can have little importance in medicine, for the maintenance of health or the cure of disease. And yet it is in the researches on a subject, considered even by some physiologists as wearisome or trivial, that we have found the clue to the behaviour of the heart under all manner of conditions, and the explanation of phenomena which have long been a puzzle to the student of the healthy or diseased organism. . . . In physiology, as in all other sciences, no discovery is useless, no curiosity misplaced or too ambitious, and we may be certain that every advance achieved in the quest of pure knowledge will sooner or later play its part in the service of man.2

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1147


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