PRELUDES AND PROGRESS

Sydney Ringer, calcium, and cardiac function

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THE DISCOVERY of calcium-channel blockers in 1963 and the subsequent investigations of Fleckenstein and his colleagues signaled a major therapeutic advance in the management of patients with heart disease. The critical role of calcium in the function of the myocardium was recognized a century ago by Sydney Ringer, a British physician and physiologist. Until recently the clinical significance of Ringer’s observations related primarily to the use of physiologic saline solutions for intravascular volume expansion and to the employment of these solutions in the experimental study of tissues and organs. The observations of Ringer, which are a century old, have been extended by a number of workers and remain the subject of active investigation. Although the recent studies of calcium antagonists by Fleckenstein and colleagues were not a direct outgrowth of Ringer’s observations, they built upon several reports about the role of calcium and myocardial metabolism, which can be traced to Ringer’s experiments. Significant delays in the practical application of basic scientific discoveries are not infrequent. Following so soon after their recent discovery, the rapid acceptance of calcium-channel blockers as a major adjunct in management of patients with ischemic heart disease and cardiac arrhythmias attests to the efficacy of these drugs.

This article will consider the career of Ringer and will explore the intellectual context in which his important observations on the role of calcium in myocardial function were made. Both personal and institutional factors that guided and facilitated Ringer’s research will be considered.

Sydney Ringer was born in 1835 in Norwich, England. After receiving his preliminary education in Norwich, Ringer began his formal medical studies in London at University College in 1854. University College was founded in 1828, and its medical faculty placed greater emphasis on science than did its counterparts at Cambridge and Oxford or at the other London medical schools. Although Ringer displayed an unusual interest in science before enrolling at University College, it was undoubtedly there that he was most directly stimulated to pursue research. The staff of University College Medical School included a disproportionate number of physicians with a serious commitment to original scientific investigation. Among them were T. Wharton Jones, William Jenner, Edmund A. Parkes, and J. Russell Reynolds; in 1858 Reynolds claimed that, “... unless there is an advance of physiology or pathology there can be no real advance in practical medicine.” William Sharpey was appointed to the chair of anatomy and physiology in 1836 and for the ensuing four decades was a major force within the institution and a source of inspiration to pupils and colleagues interested in research. Sharpey undertook little original research. His impact was more through encouragement than by example. Joseph Lister, the innovator of antiseptic surgery, recalled, “As a Student at University College I was greatly attracted by Dr. Sharpey’s lectures, which inspired me with a love of physiology that has never left me.” Another of Sharpey’s pupils who went on to found the “Cambridge school of physiology” was Michael Foster, a contemporary of Ringer’s who received his degree from University College four years after Ringer.

Despite the emphasis placed upon physiology by Sharpey, there was no adequate laboratory or apparatus for undertaking original physiologic research at the school, until Foster returned to the institution after seven years of medical practice to begin a career as a full-time physiologist in 1867. By this time Ringer had completed his medical training and had been elected physician at University College Hospital, where he quickly gained a reputation as a superior clinician and respected teacher.

Ringer’s first publication appeared in 1859 when he was still a medical student. Over the next three years...
he published two additional articles relating to the urinary excretion of urea, sugar, and electrolytes. The research he reported was undoubtedly stimulated by Parkes (1819–1876), who had been appointed professor of clinical medicine at University College in 1849. Parkes made numerous contributions to the literature of the science and practice of medicine. Nearly a decade of investigation of the microscopic and chemical composition of the urine culminated in Parkes’ publication of a monograph on this subject in 1860. His influence was substantial. Ringer’s fellow student and colleague Jenner noted Parkes’ emphasis on basic research independent of the potential practical applications of such research. Jenner recalled, “‘He taught me, as a student, to desire knowledge for itself... and not for anything which might follow it.’” Parke’s scientific and clinical research was undertaken when he was a practicing physician and a medical school teacher. Full-time careers in medical research were essentially nonexistent in Great Britain and America in the middle nineteenth century. Ringer, in his career, would emulate his teacher, Parkes, by successfully combining commitments to medical practice, medical teaching, and original investigation. Therefore, Ringer’s scientific career began in an institution that placed more emphasis on the basic medical sciences than did any other medical school in Great Britain, and he began it under the tutelage of a professor who encouraged student participation in the laboratory and in research. Ringer’s investigations were undertaken in the context of a growing interest in the microscopic study and chemical analysis of body fluids. Improvements in the design and construction of microscopes and in chemical analysis by British and European scientists and physicians encouraged such work. A number of London physicians were actively studying the microscopic components of urine when Ringer initiated his investigations in this area. Among them were Golding Bird of Guy’s Hospital, Lionel Beale of King’s College, and H. Bence Jones of St. George’s Hospital.

During the 1870s, Ringer investigated the effects of saline, the compound from which salicylic acid is derived, on fever. He initiated a series of studies on the effects of atropine on the nervous system with William Murrell in 1877. Ringer and Murrell demonstrated that atropine had a direct paralyzing effect on the spinal cord and “...does not affect it through its depressing action on the circulation.” The genesis of Ringer’s interest in the effects of salts on the heart is revealed in their next paper. The authors noted:

As many drugs which paralyze the nervous system of frogs also powerfully depress or even arrest the heart’s action, we thought it possible that they might expend their force not immediately on the nervous system, but by arresting the circulation. Thus all potash salts produce paralysis, and they also arrest the heart’s action. We therefore commenced an investigation to ascertain if potash salts paralyze through their effects on the heart, or by their direct action on the nervous tissues, or by both means.22

Cyon, working in the Leipzig Physiological Institute directed by Carl Ludwig, had discovered in 1867 that the type of solution used to perfuse the isolated heart of the frog had a significant effect upon the stability of the preparation. This work was extended in Ludwig’s laboratory by Merunowicz in 1875. It seems likely that Ringer was aware of the focus on the circulatory system and neurophysiology in the Leipzig laboratory through Thomas Lauder Brunton, who studied with Ludwig in 1869 before returning to London, where he combined a successful clinical career with pioneering research in cardiovascular pharmacology at St. Bartholomew’s Hospital. Walter Gaskell, a pupil of Foster’s, worked in Ludwig’s laboratory in 1874 after two years of clinical training at University College Hospital London.25

Another stimulus to Ringer’s research with saline solutions was undoubtedly the lingering influence of Thomas Graham (1805–1869) upon University College London. Graham, a Scottish chemist, was appointed professor of chemistry at University College in 1837. Upon the death of John Dalton in 1844, Graham was generally acknowledged as the leading British chemist. Among Graham’s earliest research were studies on the physical and chemical characteristics of salt solutions. Graham developed the technique of dialysis and thereby was able to distinguish the colloid and crystalloidal constituents of animal fluids.27 Interest in this subject at University College persisted into the twentieth century, when Ernest Starling and William Bayliss published extensively in this area.

In an 1878 publication describing the effects of local application of salts on the nerves in frogs, Ringer acknowledged the studies of Guttmann and Podocaepow who had discovered that injection of potash salts in frogs produced arrest of the heart in diastole in addition to general paralysis. Ringer, Murrell, and Morshead extended these experiments. With the publication in 1882 of his paper “Concerning the influence exerted by each of the constituents of the blood on the contraction of the ventricle,” Ringer’s classic observations on the role of calcium and myocardial function began to appear. Ringer explained that the experiments were undertaken to “...ascertain the influence each constituent of the blood exercises on the contraction of the ventricle.” In an article published a few weeks later, Ringer revealed that the results described
in the former article were not because "I discovered, that the saline solution which I had used had not been prepared with distilled water, but with pipe water supplied by the New River Water Company. As this water contains minute traces of various inorganic substances, I at once tested the action of saline solution made with distilled water and I found that I did not get the effects described in the paper referred to. It is obvious therefore that the effects I had obtained are due to some of the inorganic constituents of the pipe water."30 In his original article Ringer was unaware that it was the calcium contained in the pipe water that was responsible for the prolongation of diastolic relaxation that he described. His thorough study of the components of the pipe water led to the recognition that it contained a significant amount of calcium. He now reported, "I find that calcium, in the form of lime water, or bicarbonate of lime or chloride of calcium, even in minute doses produces the changes in the ventricular beat described in my former paper. Each of these at first rounds the top, and also broadens the trace of the beat; next it greatly prolongs diastolic dilatation."30 Ringer continued, anticipating and providing the scientific basis for current approaches to the management of cardiac arrest when it is induced in the operating room by potassium cardioplegia or when attempts are made to reverse it by the administration of sodium bicarbonate and calcium chloride, writing,

When a ventricle supplied with saline has lost its contractility, it can be restored for a short time by adding to the 100 c.c. of saline solution 5 c.c. of sodium bicarbonate solution. On the addition of the potassium chloride solution the effects of the sodium bicarbonate are removed but the contractions quickly grow weak and soon stop. . . . Calcium chloride solution added to the saline, sodium bicarbonate and potassium chloride solution, after the ventricle has lost contractility, restores good spontaneous beats which will continue for a long time. . . . I conclude therefore that a lime salt is necessary for the maintenance of muscular contractility. But whilst calcium salts are necessary for the proper contraction of the heart, yet if unantagonized by potassium salts the beats would become so broad and the diastolic dilatation so prolonged that much fusion of the beats would occur and the ventricle would be thrown into a state of tetanus.30

Ringer extended these observations and investigated the antagonistic effects of potassium and calcium on myocardial function. Together with Harrington Sainsbury, Ringer studied the effects of various salts upon the refractory period. Working with Burdon-Sanderson, who had replaced Foster in 1875 as professor of physiology at University College and who had earlier undertaken extensive research into the electrical-mechanical relationships of the heart,31 Ringer concluded that potassium prolonged the refractory period of ventricular muscle. In 1885, Ringer extended his experi-

ments to include a study of the influence of the organic constituents of the blood on the contractility of the ventricle. Furthermore, he continued his investigations on the physiologic effects of inorganic components of the blood on cardiac muscle throughout the century. He demonstrated that his findings were not species specific, yet he identified substantial differences in the effects of saline solutions on skeletal muscle compared with cardiac muscle.32

Upon review of Ringer's numerous publications several observations emerge. His writings reveal his familiarity with the relevant scientific literature. For a decade (1878–1887) Ringer vigorously studied the physiologic effects of saline solutions on muscle, publishing 30 articles on this and related subjects in the newly founded Journal of Physiology edited by his former colleague, Foster. From his scientific output one might conclude that Ringer was devoting his time exclusively to original research. This was hardly the case, however. One of his biographers noted, "Clinical work absorbed a large portion of his time and energies. . . ."7 Another biographer described the conflicts confronting the energetic Ringer, noting

The work in the pharmacological laboratory went on unremittingly, and all those who shared his labours there will agree that these were an unalloyed joy to him, and absorbed the whole man, even to serious conflict with the demands of clinical work. Here lay an unquestionable danger, but somehow it was overcome, and he managed to satisfy the claims of an extensive practice, in addition to those of his hospital duties, and yet find time for his beloved pharmacology. How this was compassed is hard to understand, but the explanation lay partly in his exceptional power of rapid thinking, partly in his mode of life, which was planned for and wholly devoted to his work. Thus, he would rise early, dispatch a hasty breakfast at eight, and the next few minutes would see him on his way to hospital, always on foot . . . the hospital visit would generally, in pharmacological days, conclude with a quick-change appearance in the physiological laboratory — Ringer the physician transformed into Ringer the pharmacologist. Upon the patiently plodding laboratory assistant these visits came not unlike electric shocks, from which he would scarcely have recovered before he would find that it was all over . . . and off he was again on his way back to Cavendish Place and the morning's consulting work — gradually, very gradually the assistant's breath would revert to 15 per minute. The afternoon would next be filled with visits, consultations, the hospital round, a post-mortem examination, and again, when possible, and for as long as possible, a visit to the laboratory. His attraction to this workshop was quite wonderful. . . . The punctual dinner following upon the busy afternoon was itself followed by the post-prandial chat, and then the thinking would go on afresh, either in the armchair or at the table, the materials of a fresh paper spread out before him. At last came the early cough, Ringer showing great wisdom in allowing himself an ample rest; by ten, or soon after, he was generally in bed.6

This description gives a vivid picture of the hyperkinetic Ringer attending to his clinical responsibilities yet devoted to his research and writing. Acknowledg-
ing the emphasis placed upon clinical practice during the first half of Ringer’s career a colleague recalled, When his position as a physician was thoroughly established, his interest in physiological problems was awakened, and for a period of some 30 years he devoted every available moment spared from a busy professional life to continuous and unremitting work in the physiological laboratory of University College.6

An interesting appraisal of Ringer came from William Osler who had met him in 1872 when the young Canadian graduate spent a year working in Burdon-Sanderson’s physiology laboratory at University College. Osler recalled, “From Ringer, Bastian and Tilbury Fox, I learned how attractive out-patient teaching could be made. Ringer I always felt missed his generation, and suffered from living in advance of it.”33

Recognition of Ringer’s accomplishments led to his election as a Fellow of the Royal College of Physicians in 1870 and a Fellow of the prestigious Royal Society in 1885. Thus, the significance of his contributions was at least partially recognized during his lifetime. In his obituary published in Nature it was noted, “The solution of salts introduced by him and universally known by his name is to-day to be found in every biological laboratory, and its use has led to developments in many fields of research.”34 A theoretical matrix for Ringer’s observations was provided in the late 1880s by the formulation of the theory of electrolyte disassociation by the Swedish chemist Arrhenius.35 Ringer’s scientific and clinical interests were combined in his successful textbook of therapeutics that first appeared in 1869 and went through 13 revisions by 1897. His colleague Edward Schäfer claimed, “...no more thoroughly practical handbook of treatment has probably ever been written.”36

Among the critical factors in Ringer’s success as an investigator were his early exposure to scientifically oriented physicians and teachers in a university medical school that placed unusual emphasis on the scientific side of medicine and provided an institutional base for Ringer’s laboratory studies. Ringer’s intense dedication to his research explains how he was able to undertake an extensive series of experiments over many years leading to significant contributions, despite substantial clinical and teaching demands. Ringer represents one of the earliest examples of the successful integration of activities of a teacher, clinician, and biomedical scientist. For the ensuing century the model he epitomized was adopted increasingly by medical schools in Great Britain and America, although its validity has recently come under increased scrutiny.37-39 It is likely that Ringer would be among the few today who successfully make meaningful contributions to original research and who are recognized also as leading teachers and respected clinicians. Ringer’s research required not only a sophisticated understanding of chemistry, physiology, and related basic sciences but benefitted also from an atmosphere conducive to investigation and the availability of then-modern laboratory equipment and personnel. All of these existed at University College London in the 1870s. Similar opportunities were still uncommon in Great Britain and virtually nonexistent in America.

Ringer’s experiments extended a local tradition of research into the chemical composition of fluids that began with Graham and continued into the twentieth century. Ringer improved his chances for success as an original investigator by familiarizing himself thoroughly with the relevant literature, selecting a subject for research that lent itself to the expertise and equipment available to him within his own institution, and pursuing consistently a single theme over more than a decade. Unlike many current investigators, Ringer resisted the temptation to become too diffuse in his research or to shift from one “hot topic” to another. He did this despite the unprecedented growth of biomedical sciences in the closing decades of the nineteenth century. Many scientifically oriented physicians in the 1880s turned their attention to the exploding field of bacteriology. Ringer pursued a single theme and refined his important studies on the physiologic effects of saline solutions by making a series of fundamental observations that have been subsequently confirmed and extended.

With the recent introduction of calcium antagonists to clinical medicine, the relevance of calcium metabolism and its role in myocardial mechanics, cardiac electrophysiology, hemodynamics, and coronary blood flow has increased dramatically. Ringer, whose fellow clinical scientist and coauthor Murrell introduced nitroglycerin in the therapy of angina pectoris in 1879, would likely be pleased that his own efforts toward understanding the physiologic and pharmacologic effects of calcium and the heart underlay a major therapeutic advance in the management of an only recently recognized form of ischemic heart disease, coronary artery spasm.40, 41 Of further interest from the standpoint of the efficacy of calcium antagonists in the management of cardiac arrhythmias, several of Ringer’s associates at University College London made important observations on the normal and abnormal electrical activity of the heart and their graphic representation. These colleagues included at one time or another, Burdon-Sanderson, Gaskell, Bayliss, Starling, Thomas Lewis, and Arthur Cushny; it was
Cushny who first demonstrated in 1896 that digitalis produced varying degrees of heart block, a physiologic effect shared by the much more recently discovered calcium antagonists. References

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Sydney Ringer, calcium, and cardiac function.
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