T. Lauder Brunton and amyl nitrite: a Victorian vasodilator

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CARDIOVASCULAR PHARMACOLOGY owes much to Thomas Lauder Brunton (1844-1916), a Scottish physician and medical scientist whose career spanned half a century. He first suggested using vasodilators as a remedy for angina pectoris more than a century ago. In 1885, the pioneering physiologist H. Newell Martin emphasized the significance of the steps that had led to the introduction of amyl nitrite into clinical practice. Brunton's use of this substance in patients with angina was the culmination of the efforts of several individuals who worked in different fields. Martin explained, "The chemist has discovered it; the physiologist and pharmacologist have experimented with it; and now the practicing physician is testing it clinically. Whatever his ultimate decision be as to its greater or less value, its story serves well to illustrate how a new remedy is discovered, and how many sciences cooperate to add to the physician's armament." 1

Born in southeast Scotland, Brunton received his medical training at the University of Edinburgh. 2-4 While a medical student he began a series of experiments on the pharmacology and clinical use of digitalis, introduced into medical practice 75 years earlier by William Withering. Brunton's experiments were suggested by Andrew MacLagan, professor of medical jurisprudence and clinical medicine at Edinburgh. He was given access to MacLagan's laboratory and received help and encouragement from two other members of the Edinburgh faculty: Arthur Gamgee, MacLagan's assistant, and Robert Christison, professor of materia medica. For more than a quarter of a century, Christison had investigated the physiologic actions of a wide variety of medicines. He had published an important paper on digitaline, the active principle of foxglove, in 1855.

To these men Brunton owed his early interest in materia medica and experimentation. Late in life, Brunton's mentor Christison recalled, "At one time I had planned a wise and prolonged investigation into the Physiological Action of Remedies . . . as an important, indeed, essential, foundation for arriving at positive knowledge of the influence of many of them on disease. This inquiry had been almost entirely neglected for various reasons, and chiefly on account of its extent, its difficulty, and the long time required." 5 Brunton accepted this challenge and throughout his career sought to elevate therapeutics to a science through the application of the techniques of chemistry, physics, and physiology to the study of drugs. His talent was recognized early; Brunton was awarded a gold medal by the University of Edinburgh for his thesis on digitalis, which was written when he was 22. 6 His teachers appreciated Brunton's abilities and encouraged him to continue his experimental work. Christison believed Brunton "possessed remarkable powers for successful original inquiry in the several branches of therapeutic and physiologic research." 7 Brunton valued the support of his teachers and dedicated his monograph on digitalis to MacLagan, "at whose suggestion this investigation was begun, by whose assistance it was carried out, and to whose kindness the author will ever be deeply indebted." 8

While a medical student Brunton declared,

As we review the rapid progress made within late years by physiology, pathology, and other departments of medical science, and compare it with the slow advance of therapeutics, we experience a growing dissatisfaction with our present empirical method of treatment, which, consisting, as it does, in the mere tentative administration of drugs without a definite knowledge of their action, must necessarily retard progress, the same medicine being tried time after time by different physicians, and the panacea of one generation being discarded by the next, only to be again resorted to and trusted in by a third. Turning from this unsatisfactory method, we begin anxiously to look for one of a more rational character, which shall be based not only on a knowledge of the changes induced by disease, but on a minute and accurate acquaintance with the action of the remedies which we prescribe for its cure. 9
Brunton’s assessment was shared by Georgy Shrady, editor of the New York Medical Record, who complained in 1867, “Therapeutics is not at present, we must acknowledge, a very inviting study. It is so much behind its sister departments that a great amount of labor is required before we can make an even start. But this should not discourage us. Most of our works are made up of much that is useless; of too many remedies that are obsolete.”

Brunton’s thesis on digitalis, written in 1866 and published two years later, reveals his familiarity with the earlier literature on the subject. On the basis of self-experimentation and animal studies, Brunton concluded, “Digitalis causes contraction of the small arteries, and at the same time acts on the regulating apparatus of the heart, both directly, and to a much greater extent through the vagus, thus causing slowing of the heart without loss of tension; it stimulates the musculomotor apparatus, causing increased force of the cardiac contractions.” Brunton vividly described the gastrointestinal and ophthalmologic side effects of digitalis intoxication that he experienced during his experiments with the drug.

Brunton became aware of amyl nitrite while he was a medical student because faculty members at the University of Edinburgh were interested in the substance. Amyl nitrite was first synthesized in 1844 by Antoine Balard, a French chemist best known for his discovery of bromine. The chemical aspects of the substance had been studied by two leaders of contemporary chemistry: Frederick Guthrie, a British chemist who had studied under Thomas Graham at University College, London, and Robert Bunsen of Germany. Guthrie’s paper on amyl nitrite appeared in 1859, the year he became assistant in chemistry at the University of Edinburgh. In his report Guthrie noted, “One of the most prominent of its properties is the singular effect of its vapour, when inhaled, upon the action of the heart. If a piece of bibulous paper, moistened with two drops of the nitrite of amyl, be held to the nostrils, through which the breath is exclusively drawn, after the lapse of about fifty seconds, a sudden throbbing of the arteries of the neck is felt, immediately followed by a flushing of the neck, temples and forehead, and an acceleration in the action of the heart.” Guthrie claimed, “It is probable that this body may find an application in medicine as a resuscitative, as in cases of suffocation, drowning or prostrated fainting.”

The first significant investigation of the possible medical applications of amyl nitrite was undertaken by Benjamin Ward Richardson, who presented his findings at meetings of the British Association for the Advancement of Science between 1863 and 1865. Richardson, trained in Glasgow, was a practicing physician who also taught physiology at St. George’s Hospital in London. Richardson claimed that amyl nitrite, “when inhaled, produced an immediate action on the heart, increasing the action of the organ more powerfully than any other known agent.” To dramatize this effect, Richardson passed around samples of amyl nitrite so members of the audience could inhale it. Richardson declared amyl nitrite a “physiological curiosity” and did not recommend its use in medicine “because of the intensity of its action”, although he planned to study the agent further.

In 1864 Richardson reported the results of his continued experiments on amyl nitrite. On the basis of his studies and contemporary understanding of the vasomotor nerves, Richardson concluded, “It is possible that the action of the nitrite is exerted immediately upon the extreme filaments of the vasomotor nerves, and that the heart beats quickly, because the resistance to its force is taken off by the dilatation of the minute vessels it supplies with blood.” Richardson’s studies represented a new direction in pharmacologic research. He was one of the leaders in a movement to place therapeutics on a sound scientific basis by applying the principles of chemistry and physics to the study of organic compounds.

Richardson’s experiments were soon extended by Arthur Gamgee, a recent medical graduate of the University of Edinburgh, who “in an unpublished series of experiments, both with the sphygmograph and haemodynamometer, has found that (amyl nitrite) greatly lessens the arterial tension, both in animals and man.” Brunton, three years Gamgee’s junior and his colleague at the University of Edinburgh, witnessed some of Gamgee’s experiments with amyl nitrite and claimed that this led him to try the substance in subjects with angina pectoris. Brunton later acknowledged Gamgee’s influence on the development of his own scientific career. Writing in 1882, Brunton informed Gamgee,

A good many years have passed since you gave me the first lessons I ever received in experimental physiology. Yet it is still a pleasure to revert to that time and to recall the kindness with which you instructed me, utterly ignorant as I was of the methods of research. You seemed never to regard the sacrifice of your own time, nor heed the trouble it gave you to help me in some experiment which, but for you, would have failed. You taught me how to plan a research, how to devise and arrange experiments, how to draw conclusions, and how to avoid fallacies. Your enthusiasm helped to spur me on when I might have otherwise flagged, and your ready aid helped me over every difficulty. Your wide and accurate knowledge excited my admi-
ration, and your genius for research made me long to follow in your footsteps.15

Shortly after beginning his medical career as a house physician at the Edinburgh Royal Infirmary, Brunton became impressed with the inability of physicians to treat the pain of cardiac disease “in which angina pectoris forms at once the most prominent and the most painful and distressing symptom.”14 In December 1866 Brunton saw a patient on the wards of the Royal Infirmary with recurring nocturnal chest discomfort that he believed represented angina pectoris. He also saw several other patients “in whom the affection, though present, was less frequent and less severe.” A variety of agents, including digitalis,aconite, and brandy, had been administered without benefit. Although the popularity of therapeutic bleeding had declined in British medicine by the late 1860s, it was still advocated for the treatment of angina by some authors.16,17 Brunton employed blood-letting in the treatment of some patients with angina. He found that this procedure sometimes brought relief, but any benefit was quite transient. In his brief report on the use of amyl nitrite in the treatment of angina, published in the Lancet in 1867, Brunton revealed the origin of his interest in this subject. He explained, “As I believed the relief produced by the bleeding to be due to the diminution it occasioned in the arterial tension, it occurred to me that a substance which possesses the power of lessening it in such an eminent degree as nitrite of amyl would probably produce the same effect, and might be repeated as often as necessary without detriment to the patient’s health.”14

With the approval of the attending physician J. Hughes Bennett, Brunton studied the effects of amyl nitrite on patients in the Edinburgh Royal Infirmary. He observed the same systemic effects previously reported by Richardson. When amyl nitrite was administered to patients with chest pain thought to represent angina, the discomfort usually disappeared in less than a minute. This was accompanied by facial flushing, an outward sign of the effect of amyl nitrite on the vascular system. Brunton found that the pain would occasionally recur in a few minutes but the inhalation of more amyl nitrite would usually lead to complete relief.

Brunton’s description of the chest pain in his patients is too sketchy to conclude with certainty that they had coronary artery disease or typical angina pectoris. Indeed, the subject of his first case report was a 26-year-old toll keeper with a history of recurrent rheumatism since childhood who had findings consistent with aortic stenosis and insufficiency.18 This young man’s chest pain occurred at night while at rest and he did not have typical angina. Brunton’s interpretation of the pathophysiology of angina pectoris was incorrect; he attributed this symptom to hypertension caused by an increase in vascular tone due to a “derangement of the vaso-motor system.” The pathophysiology of angina pectoris was poorly understood in the 19th century, however, so Brunton should not be judged harshly in this regard.19

It is noteworthy that Brunton employed a new instrument to graphically record the pulse in an attempt to lend objectivity to his observations. The French physiologist Étienne Jules Marey had recently invented the sphygmograph to facilitate study of the circulatory system. In a comprehensive monograph on cardiovascular physiology published in 1863, Marey had described the use of his sphygmograph in the study of the physical characteristics of the circulation, including elasticity, resistance, and vascular tone.20 Brunton reported, “From observations during the attack, and from an examination of numerous sphygmographic tracings taken while the patients were free from pain, while it was coming on, at its height, passing off under the influence of amyl, and again completely gone, I find that when the attack comes on gradually the pulse becomes smaller and the arterial tension greater as the pain increases in severity. During the attack the breathing is quick, the pulse small and rapid, and the arterial tension high, owing, I believe, to contraction of the systemic capillaries. As the nitrite is inhaled the pulse becomes slower and fuller, the tension diminished, and the breathing less hurried.”14

Recalling his early experience with amyl nitrite, Brunton explained in 1877, “Some years ago, I was placed in exceptionally favourable circumstances for studying this disease. I was able to watch a patient at every hour of the day and night, and to observe every phase of the attack. By the aid of Marey’s sphygmograph, I discovered that, during the paroxysm, the blood-pressure rose and the pulse became quick. I might have imagined that the rise in pressure was due to the quickness of the heart’s pulsations; but the experiments of Marey and Chauveau enabled me to say, from the form of the tracing, what I could not have discovered by the finger, that the arterioles were excessively contracted.”21 “The pathology of the disease thus seemed clear,” Brunton asserted, “and the next question was how to treat it. The remedy wanted was on which would dilate the vessels, and this the researches of Richardson and Gamgee supplied. Nitrite of amyl they had shown to possess the very power
which I desired and thus their experiments on the pharmacology of the drug and my observations on the pathology of the disease, united, led to successful therapeutics."

Amyl nitrite was not always successful in relieving chest discomfort thought to represent angina, however. In some instances this was probably because the pain was noncardiac in origin, and in other cases it is likely that the patient was having an acute myocardial infarction, a condition that was not distinguished from angina in this era. Richardson used amyl nitrite to treat attacks of angina after Brunton’s publication and claimed, “I have seen myself the happiest results from this method.” An ardent believer in the new chemically oriented pharmacology, Richardson declared, “Gradually, the curer of bodies will learn from the chemist and the practical physiologist that his remedies, rapid in action, easy in administration, positive in result, must all come from the organic compounds.”

The innervation of blood vessels was a subject that interested many leading 19th century physiologists. Important contributions to this area were made by Claude Bernard, C.-É. Brown-Séquard, Carl Ludwig, and Augustus V. Waller, among others. The histologic aspects of this subject interested Joseph Lister when he was assistant surgeon at the Edinburgh Royal Infirmary in the mid 1850s. Thus there was a tradition of interest in the vasomotor system and the effects of agents on it at the University of Edinburgh when Brunton was a pupil there. This helps to explain why he became interested in amyl nitrate and its effect on the vasomotor system.

After graduating from the University of Edinburgh, Brunton went to Europe for postgraduate training. There, he worked with several leaders of physiology and pharmacology, including Ernst von Brücke in Vienna and Willy Kühne in Amsterdam. In 1869 Brunton became one of Carl Ludwig’s first pupils in the new Leipzig Physiological Institute. With his pupil Elie de Cyon, Ludwig had discovered the vasomotor reflexes three years earlier, so it is not surprising that the German physiologist encourage Brunton to investigate the contraction of denervated arterioles and capillaries. Although there was insufficient time for Brunton to conclude his research into this area under Ludwig’s direction, the recent Scottish graduate did complete a smaller project on the effect of amyl nitrite on denervated arterioles. Brunton had great respect for the German physiologist and declared, “More than to anyone else since the time of Harvey, do we owe our present knowledge of the circulation, to Carl Ludwig.” On the basis of experiments performed in Ludwig’s laboratory, Brunton concluded that the hypotension induced by the inhalation of amyl nitrite “is not due to weakening of the heart’s action, but to a dilatation of the vessels, and that this depends on the action of the nitrite on the walls of the vessels themselves. Whether this is due to its action on the muscular walls themselves, or the nerve-ends in them, cannot at present be with certainty said; and further experiments must be made to determine whether the walls of the arteries are the only structures consisting of unstriped muscle which are affected by it.”

The pioneering American pharmacologist, Horatio Wood, published the results of an extensive series of experiments on the physiologic action of amyl nitrate in 1871. Wood was attracted to this subject, in part, by the contradictory conclusions regarding the mechanism of action of the substance reached by earlier investigators as well as by the hope “that practical therapeutics may be benefitted by the inquiry.” Wood concluded that the mechanism of action of amyl nitrite was due “in the first place to a paralysis of the capillaries, and finally also to a direct action on the muscular structure of the heart, and is practically independent of the central nervous system.” In a subsequent paper on the therapeutic value of amyl nitrite, Wood pointed out the difficulty posed by the use of amyl nitrate in angina, a disease whose pathophysiology was poorly understood. He claimed, “The truth is, we have no positive knowledge of the real nature of the disease alluded to. How futile then to attempt to explain the physiological action of a medicine by its effect upon it. This attempting to study physiologically a not understood medicine by its influence upon a not understood pathological condition, is unfortunately not new in medical annals; to complete its absurdity is only needed the common practice of explaining also the disease by the influence of the medicine upon it. Surely, this reading the unknown by the unknown resembles the youthful gambols of a kitten in pursuit of its tail — a circle of useless labour.” Nevertheless, Wood acknowledged that “a considerable amount of clinical evidence shows the nitrite of Amyl to be of very great value” in the treatment of angina.

Shortly after his return from Europe, Brunton published the first of a series of papers in which he articulated his impressions of, and dedication to, the developing field of pharmacology. In outlining his concept of the proper approach to experimental pharmacology, Brunton addressed some of the issues raised by Wood. The Scottish physician asserted, “(We should) investigate the action of our remedies in circumstances and under conditions which we know and can vary at will,
marking the effect of each variation upon their action till we thoroughly and exactly understand what it is, before we proceed to give them in disease, when not only the conditions under which they operate are at present in a great measure unknown, but the effects they produce cannot be definitely ascertained from insufficient knowledge of what the result would have been had they been withheld."

After returning from Europe, Brunton continued his studies on amyl nitrite in the physiology laboratory of University College, London. Brunton was aware of the special circumstances that favored research at University College. Michael Foster, Britain’s leading experimental physiologist, had recently established the University College laboratory and had equipped it with sophisticated apparatus to study the circulation. Although Foster had recently left London to inaugurate a physiology program at Cambridge, several scientists and scientifically oriented physicians remained and worked in the University College laboratory. The new professor of physiology, John Burdon-Sanderson, as well as Sidney Ringer and Walter Gaskell were all working in the laboratory when Brunton used it after returning from Europe.

In addition to establishing himself in private practice, Brunton sought a teaching position at St. Bartholomew’s Hospital, a venerable London institution where William Harvey had taught 250 years earlier. Brunton hoped to become lecturer in materia medica and therapeutics as well as assistant physician at the institution. As was the custom, Brunton requested his former teachers and associates to provide him with testimonials to support his candidacy for the post. Nearly forty letters on Brunton’s behalf were received from leading physicians and medical scientists from Scotland, England, and the continent. In his testimonial, the Dutch physician and pathologist Barend Stokvis declared, “Undoubtedly the whole future of medical science depends on a true scientific elaboration of the clinical material at hand, and it is to be hoped that the number may daily increase of real scientific persons, who propose to themselves to reform medical practice through physiology.” Stokvis told Brunton, “I am aware that such a task has always been your ideal, and that you are just the man for it. . . . Your excellent physiological researches and studies make you the right man in the right place.”

Brunton was selected for the post and soon began lecturing on materia medica and therapeutics at St. Bartholomew’s. Shortly after commencing his career at the institution, he organized a small laboratory in which to continue his pharmacologic research. Brunton had seen some of the best experimental facilities on the continent but had to be content with a modest space, “about 12 feet by 6, and formerly . . . used only for washing dishes and jars in the museum.” However, there were few facilities for biomedical research outside of Germany in this era. This was particularly true for pharmacology, a new field. Writing 10 years after Brunton established his laboratory in London, the American physiologist H. Newell Martin, who had worked with Foster at University College and Cambridge before becoming professor of biology at Johns Hopkins, complained about the lack of facilities for pharmacology research: “There are at present a small number of laboratories devoted entirely to such work on the continent of Europe; not one, I think, in the United States. . . . I believe that as regards the advancement of medical art, there is nothing at present more desirable than an increase of well-equipped workshops, in which men already trained in chemistry, in physiology, in pathology, shall investigate the action of substances, with a view to discover whether they may be useful as medicines, and in what pathological conditions they may be rationally expected to prove of benefit.”

Despite the cramped conditions, Brunton invited interested and promising students to work with him in his laboratory at St. Bartholomew’s. One of these students was E. S. Tait, who, with Brunton, published a paper on the physiologic action of nitroglycerin in 1876. Brunton was aware of the observations of Constantine Hering, the homeopath who had introduced nitroglycerin into medical practice three decades earlier, and others who had studied the effects of this substance in man and animals. Brunton concluded, however, “Although many facts regarding its action have already been ascertained, it has not yet been made the subject of an elaborate investigation, and it therefore seemed to us advisable to ascertain its action more thoroughly than has yet been done.” Brunton’s studies were confined to animals, in part, because “the severity of the headache which nitro-glycerine induced in one of us [Brunton] was so great that it made us delay in trying it on patients, and before we had done this it was proposed by Dr. Murrell as a substitute for nitrite of amyl.” Although Brunton observed that nitroglycerin, like amyl nitrite, lowered the blood pressure of his experimental animals, he did not propose the substance as a remedy for angina.

The discovery by William Murrell in 1879 that nitroglycerin was effective in angina did not result in the abandonment of amyl nitrite as a remedy for this condition. In 1881 an editor of the Boston Medical and
Surgical Journal proclaimed amyl nitrite, “the remedy par excellence for angina pectoris,” and declared it was “inhuman to allow a patient to endure the agonizing pain and the sense of impending death which render angina pectoris so dire, when we can offer a form of relief, in the majority of cases, nearly instantaneous.” He concluded amyl nitrite was “a neglected drug” and chastised physicians for their “timidity” in using it. The introduction of amyl nitrite as a remedy for angina was heralded, along with the discovery of bacteria and the germ theory of disease, as an example of the benefits of research to practical medicine and therefore to mankind. An editor of the Medical News wrote in 1883, “In few maladies are the improvements in our therapeutical resources more conspicuous. In the use of the most effective remedy for the relief of the paroxysm, an admirable illustration is given of the remarkable value of the contributions made to therapeutics by physiological investigations. We refer to the use of amyl nitrite in this affection — an addition to scientific medicine which we owe to Dr. Lauder Brunton.”

Brunton believed that longer acting vasodilating agents would be useful in conditions other than angina pectoris:

There are several diseases in which it is very desirable to relax the blood vessels and relieve the tension within them; but the kind of relaxation required is not the same in all. In angina pectoris we wish a drug which will relax spasm of the vessels very quickly, but as a rule we do not require the relaxation to be prolonged. On the other hand, in cases of Bright’s disease, where there is a constant high tension within the blood vessels, or in cases of failing heart, where the enfeebled ventricle is barely able to overcome the elastic resistance of the arterial walls and force the blood onwards, we require a drug which will produce a prolonged dilatation of the vessels, less in extent perhaps, and less rapid than we require in angina pectoris, but so prolonged that by continued administration of the remedy we may practically keep the tension in the blood vessels down to the point we desire and thus prevent the risk of rupture of the vessels and apoplexy on the one hand, or a failure of the heart on the other. By further investigations into the various organic nitrates or allied bodies, we may hope ultimately to get exactly the remedies we want, and thus be certain of giving to our patients the relief they require.

Brunton’s understanding of the pathophysiology of congestive heart failure was advanced for his time. His suggestion that long acting vasodilators might be efficacious in preventing or treating congestive heart failure has been forgotten. Contemporary writers generally credit George Burch and John Johnson with advocating this approach; but their papers appeared in the 1950s, 70 years after Brunton made his claims about the potential value of vasodilators for the treatment of hypertension and left ventricular failure. Extraordinary advances in our understanding of the pathophysiology of congestive heart failure have occurred in recent decades as a result of intense investigation using sophisticated new instruments and innovative experimental approaches. As a result of this work by many physicians and scientists, Brunton’s proposal that vasodilators should be useful in the treatment of angina pectoris, hypertension, and congestive heart failure has been supported and agents of this class are now in widespread use for these clinical problems.

Brunton was a prolific author; during the first 20 years of his career he published nearly fifty papers, most based on his own research. He also published several books, including a classic textbook of pharmacology and therapeutics considered by one reviewer “the first to consider pharmacology as a scientific study of the physiological action of drugs.” Although he studied the pharmacology of anesthetics and poisons, the theme of much of Brunton’s research dealt with the cardiovascular system. He remained interested in the pathophysiology of angina, and a quarter of a century after he made his first observations on the use of amyl nitrite in this condition he summarized his current conception of the mechanism of this complaint. Attempting to correlate earlier postmortem evaluations of patients who suffered from angina, Brunton claimed, A fatty condition of the heart is naturally one of the most powerful causes of lessened contractile power, and fatty heart has been frequently noted as a post mortem appearance in cases of fatal angina pectoris; but an inelastic condition of the aorta, with calcification of the coronary arteries, has been noted much more frequently still. At first sight it is difficult to understand what connexion a calcified condition of the coronary arteries can have with pain in the heart itself, but when we remember that one of the concomitants of muscular action is dilatation of the vessels which supply the muscle with blood, we can understand that rigid arteries, rendering such an increased supply impractical, might naturally lead to weakened contractile power, and therefore to pain.

In time, Brunton became increasingly impressed with the role of coronary artery lesions in the genesis of angina pectoris. In 1897 he observed, “All the nitrates are, however, simply palliative measures — they relieve pain for the time being, but they do not relieve the condition of the heart and vessels upon which the pain depends. . . As a rule, it is found that the coronary arteries are involved in angina pectoris; so that the heart is unable to contract as it ought to do.”

Near the close of his long career, Brunton reflected on the development of pharmacology and identified several factors that had contributed to the relatively slow progress of that field, which he believed held great promise for physician and patient alike. Recall-
ing his early career, Brunton claimed in 1909, "When I was a student . . . pathology consisted almost entirely of morbid anatomy and general pathology was unknown. The efforts of medical men were chiefly directed towards bringing into relationship the symptoms observed during life and the appearance presented in the post-mortem theatre. The results have been of the utmost value. . . At the same time, the constant observation of post-mortem appearances tended to bring about therapeutic skepticism, for the pathologists could not readily see how the conditions observed at an autopsy could be greatly influenced by medicines given during life." He continued, "Nor was too close attention to morbid anatomy the only cause of therapeutic skepticism. We had no exact knowledge of the action of medicines, and the reproach was only too true that physic consisted in pouring drugs of which we knew little into bodies of which we knew less. But at that time pharmacological observations were just beginning. . . Between 1865 and 1875 medical research began to take a new direction, and to look more and more to the causes, rather than to the results of disease."43

Brunton was well aware of the skepticism of some practitioners toward medical science. He had asked rhetorically in 1889, "But some men may say, What does it matter to us whether a frog’s muscle dipped in caffeine, becomes longer or shorter? and, What possible connection with medicine can a discussion have on the question whether its fibres contract transversely as well as longitudinally? and yet it is a matter of vital importance to a patient with mitral disease whether the muscular fibres of his heart will shorten sufficiently to expel the blood from his ventricles or whether they will remain quiescent all together."44 Like many of his scientifically oriented medical colleagues, Brunton consistently spoke out in defense of experimentation in the laboratory and on the ward and emphasized the practical benefits that would ultimately, if somewhat unpredictably, result from basic research. Brunton was deeply concerned about the potential impact of the antivivisectionists on experimental medicine. The passage of the British Cruelty to Animals Act in 1876 had interrupted his studies with Joseph Fayrer on the toxicology of snake venom.45, 46 In 1898 Brunton wrote to William Welch, a leader of experimental medicine in America and pathologist at Johns Hopkins, “I regret extremely to hear that there is a movement in America to stop the progress of medicine by prohibiting experimenta- tion upon animals. . . . It is through experimentation on animals that medicine and surgery have made such enormous strides of recent years. . . . It is a want of conception of the importance of experimentation in increasing the power of the medical man to relieve pain and prevent death that causes sentimentalists to oppose it.”47

Brunton’s discovery of the efficacy of amyl nitrite in the treatment of angina was the result of a combination of deductive reasoning and empiricism. His original conception of the pathophysiology of angina was incorrect but was no less sophisticated than that of his peers. Brunton attempted to clarify the mechanism of action of amyl nitrite through experimentation. Some of his conclusions were erroneous because contemporary understanding of the vasomotor system was imperfect.48 But, who would claim that it is perfect today, more than a century later? Indeed, there in ongoing controversy regarding the relative importance of the various effects of the organic nitrates on the heart and vascular system.49, 50 During the past century many sophisticated methods for studying the physiology of the circulation and the mechanism of drugs have been developed.51 Newer techniques continue to be employed to study questions raised by Brunton more than 100 years ago.52

By the time of Brunton’s death in 1916, it was recognized that he had overestimated the significance of elevated blood pressure in causing angina. A writer in one of Brunton’s obituaries claimed, “His famous discovery has, therefore, been called the lucky shot, but such hits are made only by persons who have profoundly studied the conditions.”53 François-Franck first suggested that amyl nitrite was a coronary vasodilator in 1903. Brunton accepted the new evidence on the pathophysiology of angina and the proposal that organic nitrates acted directly on the coronary arteries. In 1914 he acknowledged the “dilating action of amyl nitrite and nitro-glycerine upon the coronary vessels would readily explain the relief they offer in angina pectoris, even in cases where the blood-pressure is normal.”54

Brunton was primarily a medical practitioner, an energetic man who successfully combined his clinical and research careers. He identified the problems, outlined the experimental approach, and, if he employed research assistants in a specific project, supervised the work. At times he would become intimately involved in the experiments, as he had been in his early years: “When some absorbing research was on foot, Brunton would leave his large practice, even for weeks, to work with his assistants.”54 Brunton’s friend and colleague David Ferrier recalled, “He lived laborious days, and sacrificed comfort, self-indulgence and pecuniary advantages when engaged in any research which took his

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fancy at the time. When experimenting on himself with Digitalis he lived a life of penance for six months; and he told me that one of the greatest pleasures he had ever experienced was when he felt at liberty to eat and drink without having to weigh and measure his ingesta and egesta. All throughout life, self-sacrifice was his dominant principle when he thought the occasion demanded it. Not unfrequently he gave up his lucrative practice for months in order to accomplish some work demanded it. These characteristics made it possible for Brunton to have such a profound effect on the young science of pharmacology. A long-time friend Mitchell Bruce succinctly summed up Brunton’s career: “It was the aim of Lauder Brunton’s life to leave therapeutics, if possible, as a science instead of merely an art, as he found it.”

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T. Lauder Brunton and amyl nitrite: a Victorian vasodilator.

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_Circulation_. 1986;74:222-229
doi: 10.1161/01.CIR.74.2.222

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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