

Nitroglycerin: a homeopathic remedy

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IN A 1905 address on nitroglycerin, a New York physician observed, "It is difficult to explain why certain drugs have come into such general use unless it is a question of fashion as in other things, nor are we right in assuming that their popularity assures their value, much less their permanency. The study of the physiological action of drugs, first upon animals and then upon man, furnishes of course the only scientific and reliable method we have, of predicting future usefulness in the treatment of disease; still it is before the result of clinical experience alone that a drug must take or lose its place in the world's pharmacopeia."¹ Arguments regarding the efficacy and mechanism of action of the organic nitrates date back more than a century. It is a little known fact that nitroglycerin would probably not be in the pharmacopeia were it not for the peculiar doctrine of homeopathy that first led to the purposeful ingestion of this chemical compound. This essay on the early history of nitroglycerin will address several issues relevant to current pharmacologic research and clinical therapeutics. The synthesis of nitroglycerin was immediately recognized as a valuable discovery; a new explosive had been invented. This discovery was noticed by a homeopathic physician whose therapeutic doctrine led him to investigate the potential medical value of organic and botanic compounds. Medical politics and economics enhanced the skepticism of 19th century "regular" or "allopathic" physicians for anything advocated by the homeopathic healers. This contributed to a delay of more than a quarter of a century before nitroglycerin was used by regular physicians. The homeopaths did not recognize the value of nitroglycerin in the treatment of angina pectoris in this interval. The early history of nitroglycerin illustrates the approach used by physicians in evaluating new

remedies a century ago. They had little understanding of the pathophysiology of ischemic heart disease and did not have access to physiologic instruments and techniques necessary to objectively evaluate the safety and efficacy of a potential remedy. Empiric observation was eventually supplemented by scientific study and nitroglycerin became a mainstay of therapy for angina pectoris.

Nitroglycerin was synthesized as a result of a systematic search for other explosives after Schonbein's discovery of "gun cotton," a powerful explosive formed by the action of nitric acid on cotton.² The Italian chemist Sobrero first synthesized nitroglycerin in 1846 by combining nitric and sulphuric acids with glycerin.^{3,4} Nitroglycerin's possible value as a therapeutic agent was first investigated by Constantin Hering, a homeopathic physician. Born in Germany in 1800, Hering studied medicine at the Universities of Leipzig and Würzburg and received his medical degree in 1826.⁵⁻⁷ Ironically, he was converted to homeopathy when he read Samuel Hahnemann's writings while preparing a refutation of homeopathy. After emigrating to America, Hering settled in Philadelphia and became "the most powerful factor in the growth of early American homeopathy." Hering asked the Philadelphia chemist Morris Davis to synthesize nitroglycerin and collaborated with several homeopathic physicians in a series of self-experiments with the substance in the late 1840s. Why, it may be asked, would these individuals ingest a substance known to be highly explosive? The answer lies in the nature of homeopathy; Hahnemann routinely employed self-experimentation to test the effects of various substances that might have therapeutic value.⁸

Before his development of homeopathy, Hahnemann had been a traditional medical practitioner. He had a particular interest in therapeutics but had become disillusioned with the unpredictability and inefficacy of drugs then in use. Voicing his frustration with the traditional materia medica, Hahnemann declared in 1798, "Nothing remains for us but experiment on the human body."⁹ An essential part of Hahnemann's new theory was that drugs should be "proved" by administering them to healthy individuals to identify their ef-

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fects. This novel approach, the “proving,” developed in the early 1800s, included elements that we would consider attempts to control the experimental conditions to increase the likelihood of significant results. Generally, Hahnemann and his family members ingested the agents first; then they were given to his students and physician-followers. Those who proved the substances carried notebooks to record the time and symptoms associated with their ingestion. If the initial dose did not produce symptoms, the dose was generally increased. Doses and effects were carefully recorded and compared among the participants who included healthy individuals of various ages and both sexes. Proving was always repeated to distinguish actual from perceived symptoms accompanying the ingestion of the agent. A prominent homeopath claimed in 1838,

The effects of drugs have to be observed in all possible conditions and circumstances. We know that, under certain circumstances, the action of the drug is increased, diminished, or neutralized. . . . The action of the drug must be as little as possible disturbed by heterogeneous influences. Provers must subject themselves to a rigorous diet, avoid coffee, tea, spirits, spices, asparagus, celery, parsley, onion, garlick, radishes, old cheese, acids, mineral waters, the use of tobacco in any shape, violent exertions and emotions, and they must always live in a pure air. Persons accustomed to stimulants of any kind, are unfit for the business of proving.¹⁰

The effects of drugs on specific organs were carefully noted. Although “human life should, of course, not be hazarded in proving . . . [the] drugs must be taken in sufficiently large doses to make their primary effects distinctly perceptible.”¹⁰

Hahnemann’s provings represented a new departure in therapeutics; they were the earliest attempt to systematically assess the effects of a wide variety of potential therapeutic agents in man. Leopold Reicke, a leading homeopath, claimed in 1833, “Nobody before Hahnemann completed the investigation of medicinal potencies by experiments on healthy subjects. The theory of medicinal diseases, research as to the duration of the effects of every single drug, the knowledge of the specifically varied primary and secondary effects of the medicines — all these are discoveries which are bound to metamorphose for the most part our whole materia medica.”⁸ The provings were observations, not formal experiments. In this era, however, most of the biomedical sciences were studied by observation and description rather than by experimentation. Nevertheless, then as now, intellectual curiosity was a driving force. There was an awareness among some of Hahnemann’s disciples that it was important “to investigate the mode in which medicines act dynamically.” One homeopath claimed, “Reason . . . is not content

with a merely mechanical exhibition of our remedies. Though we cannot explain everything, is it therefore improper that we should endeavor to perfect our understanding?”¹⁰ The approach taken by the homeopaths in their provings was actually quite sophisticated for the early 19th century and far exceeded anything attempted by their regular counterparts.

These provings were, in a sense, a precursor to the contemporary approach of screening newly synthesized compounds for toxic and potential therapeutic effects. Although botanical preparations were most frequently employed in Hahnemann’s early experiments, organic chemistry was developing rapidly during the first half of the 19th century and synthetic compounds were also tested. Hering, who became involved in provings under Hahnemann’s supervision in Germany, was largely responsible for introducing provings in America. The practice of proving medicines was assailed by contemporary regular physicians. A frequent criticism was that medications may have one effect in a healthy individual but a different effect in the ill patient.¹¹ A regular physician complained in 1843, “Experiments made on persons in health are by no means accurate tests of the powers or the virtues of medicinal substances in disease. . . . No really valuable information can be expected, therefore, from experiments upon the healthy.”¹²

Nitroglycerin was given the acronym “glonoin” by Hering, who claimed in 1849, “Sobrero, the discoverer of this substance . . . remarked it had a pungent taste and caused violent headache with every one who tasted it. With this remark, the new substance becomes an important one to physiologists, as there is nothing known which in such small quantities and with such precision causes headache. Every substance with such certainty of effect, ought also to be considered as important to the physician.”¹³ The doctrine of homeopathy taught that a drug that produced specific effects in the provers would be efficacious in diseases with symptoms similar to the effects caused by the drug; this is the homeopathic simile “like cures like.” Hering, on the basis of a year of provings of nitroglycerin, concluded, “This new substance has caused headache with all who tasted it: thus . . . it will cure such headaches and other complaints in the sick as are similar to the symptoms produced by it on the healthy.” He also observed, “The kind of headache, being in the highest degree a throbbing one, lead [sic] me to the examination of the pulse, and in all cases the pulse was altered.” Hering explained, “I urged that the pulse should be felt, and so made the important discovery, the glonoin, even in very small quantities, exercised a

more decided influence upon the activity of the heart than any other remedy had done before. The pulse was accelerated in almost every prover, and so soon after taking it, that the acceleration is sometimes already felt by the finger when the globules can scarcely have melted on the tongue."¹³

The interest of the regular profession in glonoine was minimal, in large part because of their skepticism of the entire homeopathic dogma and the threat this sect represented to their financial well-being. When a report of experiments with the substance appeared in a regular medical journal in 1849, Hering gloated, "Our Glonoine has even created a great sensation among members of the regular profession."¹³ Hering had provided William Jackson, a medical student at Jefferson Medical College, a regular medical school, with instructions for preparing nitroglycerin, and informed him of the results of the homeopathic provings of the substance. Jackson tested the effects of nitroglycerin on himself and also performed animal experiments. Jackson reported that nitroglycerin caused "laboured action of the heart with a peculiar sense of oppression," and noted the development of a severe throbbing headache and tachycardia a few seconds after the ingestion of a small amount of the substance. He declared, "How valuable it may prove as a therapeutical agent I am not prepared to say; but when we consider how many of our most valuable remedies are the most virulent poisons, we have a right to infer that this may not be without its uses." The concept of basic research was not ignored; Jackson continued, "Should it not prove valuable as a medicinal agent, it is certainly, in a physiological point of view, worthy of an extended and careful examination."¹⁴ Unlike Hering, whose homeopathic colleagues were willing to ingest potentially toxic substances, Jackson had difficulty finding volunteers on whom to test nitroglycerin "on account of the unpleasant effects which this substance produces . . . even medical students are not over anxious to gratify their curiosity." According to Hering, the prominent Jefferson physiologist Robley Dunglison "had such an idea of this awful substance, that he not only would not taste it, but would not even allow a bottle of it to be opened in his presence!"¹³ Dunglison made no mention of glonoine in his popular text on therapeutics.¹⁵

In 1851 Hering published the results of four years of experiments with nitroglycerin in which he had supervised the proving of this substance by one hundred homeopaths. This paper appeared in a German homeopathic journal and was not translated into English until 1874 when Hering republished his observations with additions.³ Hering's glonoine was dispensed as sugar

pellets containing an alcoholic solution of nitroglycerin, which were placed on the tongue. This standard homeopathic method of preparing and administering drugs was particularly well suited to the readily absorbed nitroglycerin. The most prominent side effect noted by the provers was a throbbing headache. In view of the importance of the simile in homeopathic theory, it is not surprising that nitroglycerin was advocated for the treatment of headache. Some homeopaths also suggested that it had a place in the treatment of palpitations. This claim resulted from the observation that nitroglycerin induced forceful pounding of the heart in many of the provers.

Although the most impressive side effects related to sensations in the head, a number of the provers recorded symptoms of "oppression in the chest," further characterized as "contraction of the whole chest, as if chains were being placed around it, and tightened more and more"; "as if the chest were being screwed together"; "indescribable sensation in the chest, as if some misfortune were impending"; and "sensation of numbness, upward in chest and down left arm." Other provers noted "undefined aching in the heart" and a "sensation of fullness about the heart."¹³ It may seem strange, in view of these reports of side effects from nitroglycerin that mimic the complaint we call angina pectoris, that Hering did not advocate glonoine for chest pain. It must be understood, however, that these chest sensations associated with placing nitroglycerin on the tongue were only a few of the several hundred observations made by Hering and several dozen provers. Many side effects were observed in addition to headache, chest sensations, and forceful heartbeat. Moreover, angina pectoris was seen infrequently in the practices of 19th century physicians. A homeopath claimed in 1882, "Angina pectoris is a rare disease, and there are not many physicians . . . who can truthfully say they have met with half a dozen cases in a lifetime."¹⁶ A prominent homeopath declared he had seen angina only once during 40 years of practice.¹⁷ One should not assume that the homeopaths were unique in their belief that angina pectoris was a rare disorder; William Osler came to the same conclusion late in the 19th century.¹⁸

It cannot be argued that nitroglycerin failed to become a homeopathic remedy; it was advocated throughout the 19th century for a variety of conditions.¹⁹ A thorough review of the standard homeopathic texts of the middle of the 19th century has failed to reveal any suggestion that the agent be used for angina pectoris, however. Although angina was an uncommon complaint, numerous remedies for it were included in the homeopathic pharmacopeia. An 1874 review

on the treatment of angina included a list of thirty-four drugs that homeopaths advocated for this symptom. Glonoine was not included despite the fact the list was derived from Hering's many contributions to drug provings.²⁰ Despite its dramatic side effect of headache and the homeopaths' enthusiasm for its use in patients with this complaint, glonoine was only one of dozens of remedies they advocated for headache.²¹

Although glonoine became a standard homeopathic remedy, it attracted little attention from regular practitioners. In 1858, however, the British regular physician Alfred Field published a study of the effects of nitroglycerin. He became interested in this substance after placing a small amount of it on his tongue upon the urging of a homeopath. Field described the dramatic side effects he experienced, including a sense of fullness in the neck, headache and persistent nausea, and explained, "My own personal experience of the very marked and peculiar effects produced by this drug made me anxious to test its qualities still further."²² Field obtained an additional supply of glonoine from a homeopathic chemist and began a series of studies on animals as well as experiments on himself, a friend, and a medical colleague. Field turned to human experimentation when his animal studies were inconclusive. He explained, "Disappointed in my endeavours to gain any information from experiments on animals, I still thought I had seen and felt enough of the physiological action of the medicine to justify my cautious employing it in the treatment of disease."²² His first patient was a 68-year-old woman who suffered frequent attacks of "intense pain in the epigastrium, extending up to the top of the chest, and then down the innerside of the left arm" beginning suddenly, usually lasting thirty minutes and subsiding without any sequelae. She was begun on the medication chronically and benefitted from it. The attacks occurred less frequently and were promptly aborted by the administration of glonoine to the tongue." Field had no understanding of the mechanism of action of this medication, nor did he attempt to discuss it. He felt it was primarily an antispasmodic.

Field's article prompted Henry Fuller and George Harley of University College, London, to undertake experiments on animals and themselves. Fuller claimed that glonoine "does not produce the effects which have been ascribed to it; and that . . . it may be taken with impunity in considerable quantity." He did note the development of tachycardia but was unsure whether this was a response to glonoine or some contaminant.²³ Upon placing the medication on his tongue, Harley noted tachycardia, fullness in the head and tightness of the throat, ". . . but as these effects gradu-

ally passed off in the course of a few minutes, I thought that they were most probably due to fear and imagination."²⁴ Scattered case reports were published in response to Field's observations. In the few instances nitroglycerin was prescribed by regular physicians, it was advocated for various forms of neuralgia involving the face or head. Responding to the controversy his report had stimulated, Field alluded to what we would call bioavailability and declared, "Absolute proof of the power of any medicine over disease is scarcely attainable. . . . I would strongly advise every one who intends to employ Nitro-Glycerin, first to test the power of the particular sample by taking a minute quantity himself."²⁵

During the second half of the 19th century a more scientific approach to biology and medicine arose in Europe. Laboratories were built and new instruments of precision were developed to facilitate scientific research. The older approaches of description and observation gave way to a new philosophy of science in which carefully planned experiments were employed to test hypotheses. The German physician Albers published a study of the physiologic and therapeutic effects of nitroglycerin in 1864, which included the results of experiments on the effects of this substance on the heart and circulation.²⁶ He believed the effects of nitroglycerin were mediated through the central nervous system rather than having any significant direct effect on the heart. The topic of vasomotor control of the heart and circulation had interested continental physiologists for decades.²⁷ Albers may have observed the vasodilator effects of the agent as well as the preferential shortening of diastole in tachycardia, since he claimed, "The heart action is changed in a way that the chambers receive less blood." Other German physicians, including Eulenberg and Husemann, studied the pharmacology and toxicology of nitroglycerin in the mid-1860s, but the remedy still did not achieve popularity among regular physicians. The New York neurologist Allan Hamilton studied the physiologic effects of nitroglycerin in 1875 and concluded, on the basis of animal and self-experimentation, that it had a direct effect on the nervous system but also caused paralysis of the vasomotor nerves. In view of the dramatic side effect of throbbing headache, Hamilton advocated nitroglycerin "in all spasms of the cerebral vessels."²⁸

The first individual to advocate nitroglycerin for angina pectoris was William Murrell, a British regular physician, who published a review on the subject in the *Lancet* in 1879.^{29, 30} Murrell had recently completed his medical studies at University College, London, where he served as demonstrator in physiology for one of

Britain's leading biomedical scientists, John Burdon-Sanderson. Here he also came under the influence of the pioneering pharmacologist Sydney Ringer.³¹ Despite widespread skepticism of homeopathy, some regular physicians with an interest in therapeutics familiarized themselves with the homeopathic pharmacopeia. A leading historian of homeopathy has claimed that Ringer's popular *Handbook of Therapeutics*, first published in 1870, "marked the first breakthrough, on a large scale, of homeopathic remedies into allopathic practice."^{11, 32} Glonoine was not included in Ringer's work, however. In the late 1870s, Ringer invited Murrell to collaborate with him in studies of the effects of atropine on the nervous system and various potash salts on the heart. Murrell was therefore involved in research that led him to think about the effects of various substances on the nerves and hearts of experimental animals. Murrell, like his colleague and teacher Ringer, was primarily a practitioner; when he published his review of nitroglycerin he was physician to the Royal Hospital for Diseases of the Chest.

Aware of the experiments on nitroglycerin undertaken at his alma mater 20 years previously by Harley and Fuller, Murrell opened his 1879 article with a review of the earlier debate over the efficacy and action of the substance. He explained, "Being greatly interested in this curious controversy, and being quite at a loss to reconcile the conflicting statements of the different observers, or arrive at any conclusion respecting the properties of the drug, I determined to try its action on myself." Murrell had unwittingly touched the moistened cork stopper of a vial of nitroglycerin to his tongue while seeing outpatients, "and a moment after, a patient coming in, I had forgotten all about it. Not for long, however, for I had not asked my patient half a dozen questions before I experienced a violent pulsation in my head, and Mr. Field's observations rose considerably in my estimation." Murrell also noted the development of tachycardia and a dramatic increase in the force of his heartbeat, which "seemed to shake my whole body. I regretted that I had not taken a more opportune moment of trying my experiments, and was afraid the patient would notice my distress, and think that I was either ill or intoxicated." Aware of the variability of response to nitroglycerin reported earlier, Murrell decided to investigate the response of others to the agent. Each of 35 individuals, 12 males and 23 females, ages 12 to 58, who took nitroglycerin experienced symptoms similar to those described by Murrell.²⁹

Murrell's interest in the organic nitrates can be traced, in part, to the observations of the Scottish phy-

sician and pharmacologist, T. Lauder Brunton,* who had advocated amyl nitrite for the treatment of angina pectoris a decade earlier.³³ The efficacy of amyl nitrite in angina pectoris had been rapidly acknowledged by regular and homeopathic physicians alike. In the last year of his life, Hering proclaimed the value of amyl nitrite in the treatment of angina. He described the medicine as "something similar to glonoine" and encouraged his homeopathic colleagues to use it despite its introduction by their competitors, the regular physicians.³⁴ Despite Hering's recognition of the similarity of glonoine and amyl nitrite, he did not suggest using the former agent for angina pectoris. In a contemporary homeopathic monograph on heart disease, Edwin Hale credited "allopathic" (regular) physicians with first advocating nitroglycerin, Hering's glonoine for angina.³⁵

Brunton had reported the results of his animal studies of the physiologic action of nitroglycerin in 1876 but later explained, "The severity of headache which nitroglycerine 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."³⁶ Murrell knew of Brunton's work on amyl nitrite and nitroglycerin. Murrell's familiarity with modern pharmacologic principles and his deductive mind led him to claim, "From a consideration of the physiological action of the drug and more especially from the similarity existing between its general action and that of nitrite of amyl, I concluded that it would probably prove of service in the treatment of angina pectoris, and I am happy to say that this anticipation has been realised."²⁹

The sphygmograph, an instrument recently invented for graphically recording the pulse, allowed Murrell to objectively document the effects of nitroglycerin on the pulse. He discovered that the pulse tracings were similar after the administration of amyl nitrite and nitroglycerin. Murrell also observed that amyl nitrite had its maximum effect in less than a minute, whereas it took several minutes for nitroglycerin to induce tachycardia and a change in the pulse contour. Moreover, although the effects of amyl nitrite lasted only a few seconds, the effects of nitroglycerin could be demonstrated for nearly an hour, and "the effect may be maintained for a much longer time by repeating the dose."²⁹

In the summer of 1878 Murrell began treating patients with angina with nitroglycerin. His first patient was a 64-year-old heavy smoker with symptoms con-

*Brunton will be the subject of a forthcoming essay in the *Preludes and Progress* series.

sistent with angina pectoris. Murrell considered the possibility of what we would call the placebo effect and first placed the patient on an infusion of quassia, a bitter tonic derived from the wood of a West Indian tree, “in order that he might be observed, and also to eliminate the effects of expectation. It need hardly be said that he derived no benefit from this treatment.” Murrell continued

He was then ordered drop-doses of the 1% nitro-glycerin solution in half an ounce of water three times a day. At the expiration of a week he reported that there had been a very great improvement. The attacks had been considerably reduced in frequency. . . . [and] when they did occur, were much less severe. He found, too, that a dose of medicine taken during an attack would cut it short. He had tried it several times, and it had always succeeded. It would not act instantly, but still very quickly. . . . He was thoroughly convinced that the medicine had done him good, and said he was better than he had been since first he had the attacks.

Murrell included other case reports in his paper, which he concluded with a note of appreciation to Sidney Ringer “for his kindness in having frequently examined these patients, and also for many valuable suggestions.”²⁹

An early testimonial to the value of nitroglycerin in the treatment of angina came from a British physician who suffered from this symptom. He declared, “I always found relief if I took the dose when I felt the first threatening of an attack, and the paroxysm was staved off. I continued to take the two-minim dose regularly every three to four hours for about four days; and, as the attacks did not trouble me so much, I began to diminish the frequency of the dose, and only took it when I felt an attack threatened. . . . It is a great boon to have a remedy in which you can have perfect confidence that the painful attacks can be controlled.”³⁷

The liquid preparation of nitroglycerin used by Murrell was inconvenient. As early as 1864 it was recognized that topical application of nitroglycerin in ointments and subcutaneous injections of the drug in solution were followed by the typical effects witnessed after oral administration.²⁶ Within a year of Murrell’s report on the value of nitroglycerin in angina, the British chemist William Martindale claimed, “Nitroglycerin having been in medicinal request during the last twelve months, more stable and portable preparations of it . . . have been called for.” In response to this he prepared a tablet form of the substance containing one one-hundredth of a grain of nitroglycerin, which dissolved readily in the mouth, but he made no mention of the homeopathic origins of this dosage form. Anticipating the logical concern about the explosive potential of his preparation, Martindale claimed it was “stable,

non-volatile . . . [and] perfectly inexplusive — it cannot be detonated.”³⁸

By 1882, when Murrell’s essay on nitroglycerin was republished as a monograph in Britain and America, the drug was available in pill form in five different strengths from Parke Davis & Company of Detroit. Murrell declared that these preparations were “perfectly active, and . . . taken without difficulty.”³⁹ Elsewhere, he protested the decision of those responsible for selecting drugs for the British Pharmacopoeia for including only one nitroglycerin preparation, citing the variable dosage requirements among different patients.⁴⁰ Important experiments on the chemical nature and physiologic action of nitroglycerin were performed by Matthew Hay of the University of Edinburgh. He discovered that nitroglycerin was not decomposed by the acid in the stomach so that “none of the latent power of the nitro-glycerin is therefore lost, previous to its absorption into the blood.”⁴¹ Thus it was recognized a century ago that oral, sublingual, subcutaneous, and topical administration of nitroglycerin was possible.

The introduction of nitroglycerin did not lead to the abandonment of amyl nitrite for angina pectoris. Moreover, other traditional remedies continued to be prescribed for angina, although their efficacy had not been demonstrated. Among the remedies advocated for angina in 1885 by Brunton, who first used amyl nitrite for angina nearly 20 years earlier, were aconite, arsenic, phosphorus, strychnia, and turpentine.⁴² Insight into the persistence of some of these remedies is provided by D. W. Cathell, whose popular guide to success in medical practice contained the admonition, “To set unused medicines aside and order others so as not to shake confidence, requires a great deal of clever management. In many cases where a remedy is ceasing to be useful, or indications for something different are appearing, it is better not to stop the old abruptly as though it were wrong or doing harm, but instead to instruct them to set it aside and begin the new at — o’clock.”⁴³

The value of nitroglycerin in angina was gaining recognition among the medical community, however. An editor proclaimed in 1882, “One of the most important additions recently made to practical therapeutics is nitro-glycerine. . . . The applications of nitro-glycerine to the treatment of disease are directly deducible from the physiological study — another proof, if more were needed, of the value of the physiological method.”⁴⁴ The practical value of scientific research was gradually being recognized by the medical community and the public in this era.^{45, 46}

There was no suggestion that nitroglycerin had any direct effect on the coronary arteries a century ago. A Michigan physician summarized contemporary opinion about angina pectoris in 1882 when he claimed, "This is a disease in which the exact pathological state in unknown, yet it seems quite likely that the coronary arteries are at fault — a condition of spasm existing whereby the nutrition of the heart is interfered with."⁴⁷ The primary action of nitroglycerin was thought to be on the vasomotor nerves and that it affected the balance of vasodilator and vasoconstrictor effects leading to a reduction of tone in the systemic arterial tree. The French physician Dujardin-Beaumez, reflecting the beliefs of Huchard, possessed rather unusual insight into the pathophysiology of ischemic heart disease for his time. He believed that angina pectoris was the result of "ischemia of the cardiac muscle" and declared, "Every medicament which energizes the capillary circulation of the heart . . . is then applicable to these cases, and this it is that explains the relief which vaso-dilator medicaments give."⁴⁸

Although the pathophysiology of left ventricular dysfunction was poorly understood, the beneficial effects of nitroglycerin in congestive heart failure were commented upon by some writers:

The application of nitro-glycerine to the treatment of certain cardiac diseases is a most important therapeutical expedient. When the walls of the heart are weakened by myocarditis, or by fatty degeneration, any cause suddenly increasing the vascular tension may arrest the movements of the organ. Great embarrassment of breathing, pulmonary congestion and oedema, and general dropsy may result from the weakness of the heart's walls, and these difficulties are enhanced by a condition of elevated tension of the arteries. In such cases nitro-glycerine is found to do much better than digitalis, which, on the other hand, is more efficient when the vascular tension is low.⁴⁴

In 1888 a Philadelphia physician reported two cases in which acute pulmonary edema had resolved in response to the hypodermic administration of nitroglycerin and concluded, "One who has seen cases of heart failure treated in the usual way can have no conception of the brilliant results which may be obtained by the hypodermic use of Nitroglycerin."⁴⁹

Murrell's work on nitroglycerin stimulated others to attempt to duplicate his findings. In reporting his experiments with the agent in healthy individuals and patients with a variety of ailments, the Polish physician Korczynski declared, "The views of Murrell were confirmed in every particular."⁵⁰ The special role of nitroglycerin in the treatment of angina was rapidly and widely acknowledged. The British physician William Green proclaimed in 1882, "I am not overstating [nitroglycerin's] merits when I say it deserves to rank

only second to digitalis in the treatment of disease of the heart."⁵¹

During the mid-1880s numerous papers were published reporting the beneficial effects of nitroglycerin in a wide range of ailments, including asthma, seasickness, whooping-cough, migraine, apoplexy, and Bright's disease. This reflects the enthusiasm of 19th century practitioners for new remedies, and their willingness to employ them in the absence of scientific proof of either mode of action or efficacy. Effective methods to address these issues were just beginning to be developed, however, so we should not be too harsh on the physicians of a century ago. They were, in some of these diseases, using nitroglycerin to reduce elevated arterial tension in conformity with contemporary teaching about the pathophysiology of the illnesses and nitroglycerin's presumed mechanism of action. One writer cautioned, speaking of new remedies in general, "There is always a rage with some of our profession for new medicines . . . but we must regret and condemn a wholesale and promiscuous laudation of any and all articles before they have been subjected to systematic and extended trials." Addressing a critical issue in an era when diagnosis rested on the history, physical findings, and microscopic examination of body fluids, the author warned, "Remember, too, that without accurate diagnosis, his [the pharmacologist's] investigations will afford results worse than useless." He closed with the admonition, "Be assured your agent is all it purports to be; be secure in your diagnosis, and well fortified in the pathology of the disease; have a definite idea as to what you are to accomplish; see that a sufficient quantity of the article is administered; when the patient has recovered, or you have achieved the desired end, consider well whether your remedy was the means of such achievement; then you may feel authorized to make further investigations, and, after that report progress."⁵²

Research has led to a sophisticated understanding of the pathophysiology of ischemic heart disease and methods have been developed to objectively evaluate the pharmacology and efficacy of remedies advocated for these conditions.⁵³ The empiric observations of Hering, and the early attempts of Brunton and Murrell to evaluate the hemodynamic effects of the organic nitrates were followed by a vast amount of research that has placed the therapeutics of nitroglycerin on a firm scientific footing. Early in the 20th century recently developed experimental techniques made it possible to study the effects of drugs on the coronary arteries. It was shown that nitroglycerin had a direct dilating effect on these vessels. Nevertheless, in 1939

Katz introduced one of his numerous papers on the physiology and pharmacology of the coronary circulation with the observation, "A great deal of confusion exists regarding the reactions of the coronary blood vessels to many products of metabolic origin and to numerous drugs."⁵⁴

The hemodynamic responses to nitroglycerin and the effects of this agent on the peripheral vasculature, the epicardial and intramural coronary arteries, and coronary anastomoses have been delineated to a significant degree.^{55, 56} It is becoming apparent, however, that there are effects at the cellular and biochemical level as well. This promising area of research is attracting increasing attention among biomedical scientists.⁵⁷ A recent reviewer has commented, "The clinical experience with the organic nitrates can now be interpreted and to a large extent accounted for in terms of pharmacological mechanisms and pharmacokinetics. Increasing knowledge about the pharmacological properties of these remarkable drugs can obviously still contribute to an even more proper practical use of them."⁵⁸

The contributions of Hering and his homeopathic followers in demonstrating that nitroglycerin, a powerful explosive, could be safely ingested by humans have been largely forgotten. Nevertheless, this was the critical step in introducing this agent into the regular pharmacopeia; Field and Murrell, regular practitioners, were encouraged to try the remedy by homeopathic physicians. Hering's acronym, glonoine, does live on as the origin of the term "glonoinism," which refers to the syndrome of nitroglycerin toxicity among individuals exposed to high concentration of the explosive during its manufacture or use. Another aspect of nitroglycerin should not be overlooked. The Swedish chemist Alfred Nobel developed a device that detonated the explosive, organized the first factory devoted to its manufacture, and, by inventing dynamite, prepared a solid form of nitroglycerin that was far safer to handle. Nobel was impressed by the advances in public health made possible by biomedical research during the second half of the 19th century. He left his considerable fortune, much of it derived from his various contributions to the technology of explosives, especially nitroglycerin, to found the Nobel Foundation, which awards prizes to individuals who "during the previous year, shall have conferred the greatest benefit on mankind." Three of the five prizes recognize scientific achievements, including physiology and medicine. Thus, nitroglycerin, initially a homeopathic remedy, in addition to its important role in the management of patients with ischemic heart disease, also indirectly led to the establishment of a major prize that

acknowledges the benefits of scientific research to mankind.

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