Nitroglycerin: The Explosive Drug

Throughout the history of medicine one idea seems evident—that man, if given enough time, can overcome almost any medical problem. Consider, for example, the case of angina pectoris. In 1768 when William Heberden first described and named this malady there was no known remedy for it. And yet today almost anyone suffering from angina can obtain prompt relief from a simple chemical compound known as nitroglycerin. But the use of this wonder drug in the treatment of angina was not discovered overnight by some ingenious scientist who knew exactly what he was looking for. Great scientific discoveries rarely occur that way. The importance of nitroglycerin to medicine was determined only after many years of experimentation by many scientists and physicians. And perhaps it is only now that we can fit together all the bits and pieces in order to see the entire story of nitroglycerin.

The story began early in the nineteenth century with an Italian scientist, Ascanio Sobrero, the discoverer of nitroglycerin. Born in Casale in 1812, Sobrero graduated from the University of Torino in 1832 with a degree in medicine. But circumstances forced him to abandon the profession for which he was trained, and in 1836 he began work in a private laboratory. This was the beginning of a distinguished career in chemistry which would culminate in the discovery of nitroglycerin.

In 1840, despite financial difficulties, Sobrero managed to visit Paris where the scientific revolution was in full swing. There he studied at several of the eminent schools of science and made numerous valuable contacts. Among them was Theophile Pelouse, a well-known French doctor and chemist, under whom Sobrero worked and studied. Pelouse was immediately impressed with Sobrero’s brilliance and enthusiasm. He said in a letter to Sobrero’s father, “I have never known of a young man more zealous, more industrious, more capable than he” (1). In 1843 Sobrero traveled to Germany to study under Liebig. He, too, was impressed with Sobrero’s capabilities. He said, “His pure love of science and his modesty, his profound and basic chemical knowledge and his great talent for observation immediately gained my predilection” (1).

In 1845 Sobrero returned to Torino where he was appointed to the second chair at the new school of applied chemistry and mechanics (1). He had learned a great deal during his years of association with such men as Pelouse and Liebig, and he was ripe with experience as the time was ripe with the spirit of scientific inquiry.

Other scientists, among them Pelouse, had previously noted that substances such as starch, cotton, hemp, and linen were converted to extremely combustible materials when treated with nitric acid. Sobrero, himself, had already discovered that with heat cellulose is transformed by nitric acid into a substance identical to that created by treating starch with nitric acid (1). Schoenbein discovered, and Knapp rediscovered, the importance of using a mixture of nitric and sulfuric acids (1). Following this lead, Sobrero turned to the study of sugar, rubber, dextrin, and lactose as they react with mixtures of these acids. By the end of 1846 he had obtained a series of highly explosive substances, among them nitroglycerin (1). Early in 1847 he announced his discovery to his old master Pelouse. An extract of this letter was printed in an 1847 issue of Comptes Rendus (2). In it he described the method of production and the characteristics of nitroglycerin. He let water-free glycerin run down into a cooled mixture of concentrated sulfuric and nitric acids. Sobrero described nitroglycerin as looking like olive oil with a slight yellow color, as being insoluble in water but soluble in ether and alcohol and as having no odor but a sweet, piquant, and aromatic flavor.

Also in his letter to Pelouse, Sobrero did not miss the opportunity to claim priority in producing explosive substances from sugars. It seems that Pelouse had just announced in Comptes Rendus thatMessrs. Flores Domete and Minard were experimenting with nitric acid and sugar. But Sobrero claimed priority even in conceiving the experiment (2). And certainly it was partly as the result of his communication with Pelouse that Sobrero is today universally accepted as the discoverer of nitroglycerin, but Pelouse seemed to have gotten more credit in the discovery of nitroglycerin than was due to the more recipient of correspondence. In fact, Sobrero frequently complained about the fact that he was alleged to have made his discovery while under Pelouse’s supervision. He in no way wanted to minimize a contribution made entirely by an Italian (1). He stressed over and over again that his work with nitroglycerin was done while he was a teacher at the school of applied chemistry at Torino, and said, “Nitroglycerin is the fruit of exclusively Italian labor” (3).

Shortly after he communicated his discovery to Pelouse in Paris, Sobrero made a presentation to the Academy of Science of Torino. He explained the properties of his new explosive compounds and even brought along a sample of nitroglycerin weighing 300 grams (1). This seems like sheer folly, for certainly, even from the very beginning, Sobrero was aware of how extremely dangerous the compound was. Early in his study he had heated a drop of it in a glass tube. It blew up sending splinters of glass in all directions and...
wounding his face and hands (4). At any rate, the Academy must have been favorably impressed for soon the Italian government was sponsoring experiments with Sobrero’s compounds to determine their worth to the military, but the danger of spontaneous explosions led the government to dismiss the compounds (3).

It was unfortunate for Sobrero, who was interested in the glory of Italy and the triumph of Italian science, that his government could not assess the real worth of those explosive compounds. For meanwhile, the Russian government was becoming very interested in Sobrero’s discovery. And here is where the renowned Alfred Nobel steps into the picture. He had heard of nitroglycerin from his tutor, Professor N. N. Zinin, who had studied the compound and worked on it with Vassillii Petrushevskii, an eminent chemist and artilleryman. Later Petrushevskii was to claim priority in the invention of dynamite (5).

But once Nobel had as powerful a chemical as nitroglycerin in his hands he was well on the way toward inventing what he called dynamite. By using a porous silica to absorb the unstable nitroglycerin, Nobel created an easily-handled explosive. This, of course, is part of a different story, the story of nitroglycerin in dynamite. But, there is a sidelight to this story that includes Sobrero. As Nobel became increasingly successful in the business of dynamite manufacture, he established factories all over Europe. But he never forgot Ascanio Sobrero to whom he was so indebted for discovering nitroglycerin, the vital ingredient in his success. In fact, he employed Sobrero as a consultant chemist in his Swiss-Italian firm in Avigliana, and in 1879 he erected a bust of Sobrero outside that plant. Later he further showed his indebtedness to the Italian by awarding his widow a life pension (4).

But, as far as Sobrero was concerned, the dynamite industry, Nobel’s brainchild, left much to be desired. Humanitarian that he was, Sobrero continually expressed deep sorrow for the disasters and loss of life that resulted from his discovery. And yet he felt that perhaps some day its use would be safer and more constructive (1). Sobrero, himself, was continually working with nitroglycerin with those specific goals in mind. In one of his papers on the manufacture of dynamite he said, “For my part, I would be happy if I had rendered, by this communication, a service to the manufacturers and to humanity in lessening the dangers that accompany so important an industry and one to which I have a certain right of paternity as inventor of nitroglycerin” (6).

The discovery of nitroglycerin was important in itself, and it was important to the dynamite industry. But in the realm of medicine Sobrero’s discovery was invaluable. From the very beginning Sobrero had noticed that nitroglycerin had a peculiar effect on the human body. He said in his letter to Pelouse, “One must be careful in performing this experiment, for it suffices to take a very small quantity of it (that which one can take by lightly wetting the tip of the little finger) on the tongue to experience a rather strong migraine for several hours. This action on the human body has been verified by several persons in my laboratory, and I experienced several times myself before I was certain that it has toxic properties” (2). By tasting his new compound, Sobrero triggered the series of events that ultimately led to the use of nitroglycerin in the treatment of angina pectoris!

The next step in the fascinating story of nitroglycerin as a drug, was taken by Constantin Hering, professor of materia medica at the Hahnemann Medical School in Philadelphia. It was he who organized the first significant and purely scientific study of the effects of nitroglycerin on the human body. Hering’s interest in the compound resulted from reading Sobrero’s letter to Pelouze. He immediately tried to repeat Sobrero’s process but without success; he was unable to maintain a cold enough temperature throughout the experiment. His colleague, Morris Davis, however, was able to duplicate Sobrero’s experiment exactly with the help of winter temperatures. He produced about twenty drops of nitroglycerin. And just as Sobrero had done several years earlier, Davis tasted the compound. Immediately he developed a severe headache. Hering and Davis were intrigued with this new compound and its peculiar effects. They took the remainder of the twenty drops to Dr. Jeanes. Ignoring all warnings, Dr. Jeanes tasted a rather large amount of the compound and immediately experienced a severe headache along with several other strange sensations. After a few minutes Jeanes gulped some coffee as an emergency antidote. Minutes later the peculiar sensations had disappeared (7).

One problem Hering and his friends had to overcome was obtaining a more definite dosage—one that could be easily regulated. To do this they dissolved the nitroglycerin in alcohol (one of the properties which Sobrero noted). Then they used sugar pellets to absorb the solution. Each pellet contained 1/300th to 1/500th of a drop, depending on its size and was administered sublingually (7). With this method of controlled dosages future experiments were more significant. For example, with 1/10 drop Morris Davis experienced a headache, pounding of blood in the head, and a trembling of the hand. Dr. Jeanes reported that 1/30th drop caused a headache, pain in the eyebrows, a stimulation of the nerves in the neck, and extreme thirst. In other cases there were pains in the chest that radiated down the left arm, sensations of warmth, and feelings of congestion in the region of the heart (7). Hering noticed that although there were differences in reactions among individuals, nitroglycerin had a very definite effect on the heart and pulse of all cases. He also observed that these particular effects occurred to a greater extent and more quickly than with any other substance. Regarding nitroglycerin’s action on the pulse, Hering stated, “I know of no experiment with any other drugs which produces similar effects.”

Hering was a homeopath and, as such, he worked according to the principle similia similibus curantur. He fought fire with fire. And since he knew that nitroglycerin causes a headache, he believed that it would cure a headache. He also proposed nitroglycerin as a remedy for sunstroke, encephalitis, edema of the brain, epilepsy, inflammation of the eyes and ears, inflammation of the heart, congestion of the breast, worms, cholera, and typhus (7).

About the same time that Hering was experimenting with the effects of nitroglycerin, A. G. Field was performing his own experiments with that compound.
Using himself and a friend as the only subjects, Field noticed the same symptoms as did Hering—headache, pressure in the throat, neck and temples, and congestion in the region of the heart. In addition, he experienced a definite feeling of sickness, pain in the bowels, and faintness. Furthermore, after the ingestion of two drops of nitroglycerin, he experienced a loud, rushing noise in his ears, nausea, frequent yawning, and a dull, heavy pain in the stomach. From these preliminary experiments he concluded that the drug acts directly as a sedative to the nervous system without being a permanent depressant. And because of its power to subdue muscular action, Field reasoned that nitroglycerin, could be used as a remedy for many nervous and spasmodic diseases.

Field’s experiments were obviously not performed with a scientific accuracy or objectivity. Nevertheless, he felt sufficiently justified in prescribing nitroglycerin as a drug. And so he began using it in cases of severe headache, toothache, and nervous spasms. He said, “I have frequently seen severe headache cured or relieved by nitroglycerin, though it must be confessed the malady is much more frequently aggravated by it” (8). He also noted the beneficial action of nitroglycerin in cases of neuralgia, and stated, “I have not yet met with one well-defined case of neuralgic or spasmodic disease in which this medicine has failed to afford relief” (8).

Nitroglycerin is definitely effective in the treatment of a spasmodic disease, namely, angina pectoris. But Field failed to recognize this. He was too busy prescribing it in cases of headache, toothache, and facial neuralgia to see its real value. His sloppy experimentation and his hasty conclusions show the status of nitroglycerin research at mid-century. The tendency to use the drug strictly in homeopathic medicine made further significant research almost impossible.

But if the progress of nitroglycerin from a wild chemical curiosity to a wonder drug was, for the moment, at a standstill, it was soon to take a giant leap forward with Sir Thomas Lauder Brunton. It was his work with amyl nitrite that directly resulted in the use of nitroglycerin, a compound similar to amyl nitrite, as a remedy for angina pectoris. Brunton, a clinical pharmacologist knighted by Queen Victoria, himself suffered from angina and like many others who had that disease, he was unable to find relief from the paroxysmal attacks of agonizing chest pain. At that time in medical history—in fact, ever since the time of Heberden—there were no “remedies” for angina other than brandy and opium. And their effects were too short-lived to be significant. Doctors at the time were even using ether and chloroform, two of the newest compounds, but with meager results.

As a resident physician in the clinical wards of the Royal Infirmary in Edinburgh, Lauder Brunton came across many cases of angina pectoris. From his own experience with that malady, he knew how its victims suffered. But his kinship with the clinic patients lay much deeper than the fact that both he and they were victims of the same disease. Lauder Brunton viewed his patients strictly from a human standpoint. He did not merely see an illness to be cured or a broken limb to be mended by the sheer magic of his art. He saw instead a suffering human being in need of his sympathy as well as his art. That was Lauder Brunton’s special gift—his capacity to feel. And it was exactly that which spurred him on to making his important contribution to heart research. In fact, he himself said, “Few things are more distressing to a physician than to stand beside a suffering patient who is anxiously looking to him for that relief from pain which he feels himself utterly unable to afford. His sympathy for the sufferer, and the regret he feels for the impotence of his art, engrave the picture indelibly in his search after the causes of the pain, the means by which it may be alleviated” (12). This, Lauder Brunton made his personal and professional goal.

In his treatment of angina pectoris, Lauder Brunton tried all the conventional remedies plus digitalis and chloroform—all without success. However, he did note that small bleedings of three to four ounces were always beneficial in alleviating the pain of angina pectoris. The bleeding, he surmised, produced a significant decrease in arterial tension. Amyl nitrite, he knew, had the same effect—his friend, Dr. Arthur Gamgee had just proven that. On the strength of Gamgee’s experiments, Lauder Brunton decided to use amyl nitrite in the treatment of angina. During his subject’s attack he noted that breathing was rapid, the pulse was small, and arterial tension was high. Thirty to sixty seconds after inhalation of amyl nitrite, however, the pulse rate decreased, arterial tension diminished, breathing became less hurried, and, most important of all, the pain disappeared. A major medical break-through had occurred! Man was now only a small step away from using nitroglycerin—a similar but more effective drug—in the treatment of angina pectoris!

It is difficult to over-estimate Lauder Brunton’s contribution to our knowledge about nitroglycerin. Without his work, effective treatment of angina pectoris might have been delayed another fifty years. Fortunately for mankind there was a Lauder Brunton—a very special man whose scientific curiosity was equaled by his human compassion. As was said of him one hundred years later, “Lauder Brunton was a man whose mind lay not in the laboratory or in the ward, but halfway between the two” (19).

It merely remained for William Murrell to establish the similarity between the effects of nitroglycerin and those of amyl nitrite. This he did in 1879 in his publication, “Nitroglycerin as a Remedy for Angina Pectoris.” He said, “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” (14).

It had been exactly thirty-three years before that Ascanio Sobrero had tasted his new explosive chemical and developed a severe headache from it. And in thirty-three years, with increasing knowledge of the compound, nitroglycerin changed from an uncontrollable chemical to a miracle drug. Actually the work done in the years between Sobrero and Murrell forms the major part of the story of nitroglycerin. But research continued in the latter part of the nineteenth century and the early part of the twentieth. Dr.
Mathew Hay in 1883 further described the effects of nitroglycerin on the body. He noted that the drug paralyzes the motor and sensory centers of the spinal cord and the voluntary muscles; it quickens the heart, then makes it go slower finally paralyzing it; it diminishes the blood pressure and it stimulates the respiratory centers, afterwards paralyzing them. He also made studies of what happens to nitroglycerin in the blood stream (15).

Later, in 1907, Albion Walter Hewlett conducted additional studies on the effects of both nitroglycerin and amyl nitrite on the blood pressure of man (16). And in 1912 Dr. Alfred Weinberg studied nitroglycerin as a drug and nitroglycerin poisoning (17).

Today, nitroglycerin, or glyceryl trinitrate as it is properly called, is widely accepted as the best remedy for angina pectoris. The drug is administered sublingually—in the manner of Hering’s sugar pellets. And despite the sophisticated experimentation of the last few decades nitroglycerin is still the fastest and surest-acting compound known to abort an attack of angina pectoris.

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