

# THE INTRODUCTION OF HYDROCYANIC ACID INTO MEDICINE

## A STUDY IN THE HISTORY OF CLINICAL PHARMACOLOGY

by

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IN the early years of the nineteenth century, advances in chemistry led to the isolation of active constituents from crude drugs. The isolation of the alkaloids in particular was an important event in the development of pharmacology. Their purity indicated the advances being made in the chemistry of organic materials, and the determination of doses and descriptions of their properties reflect the growing use of experiment to determine the action of substances on the animal body. In therapeutics, however, they were not new: morphine was used where opium had been used before; a dose of quinine replaced an infusion of cinchona. To examine developments in experimental pharmacology in relation to therapeutics and the thinking behind acceptance of a new remedy in this period, it is of greater value to study hydrocyanic acid, the pure, toxic, chemical substance which entered medicine at the same time as the alkaloids and, with them, formed the group designated by Magendie in 1821 as *nouveaux médicaments*.

Legends and stories of sudden death as a result of poisoning suggest that hydrocyanic acid has been available to assassins since earliest times, probably in the form of aromatic preparations of peach and almond. In the early materia medica there were a number of preparations containing hydrocyanic acid, amongst them cherry-laurel water prepared by distilling the leaves of *Prunus laurocerasus*, L., an evergreen shrub containing the glucoside *Prulaurasin* which decomposes on distillation to benzaldehyde and hydrocyanic acid (about 0.1 per cent). It was an investigation into the toxicity of this preparation that opened the modern history of the pharmacology of the acid.

In 1731, Thomas Maddern (died c. 1737), lecturer in anatomy and surgery in Trinity College, Dublin, published the results of an investigation into the effects of cherry-laurel water, which, used as a flavouring additive to brandy, had caused the death of two Dublin women.<sup>1</sup> Maddern's experiments were on dogs, and he showed that reaction varied with dose: small doses caused convulsions; larger doses brought about paralysis and rapid death. In one experiment, he described the blood as being of a 'very bright florid colour' and he was probably observing oxygenated venous blood. Maddern opposed the opinion that the substance caused inflammation of the stomach and intestines. The colour of these organs, resulting from the high colour of the blood, lent support to this common explanation of the action of poisons, but he observed that some of the animals recovered too quickly for stomach inflammation to be the cause of their condition. These experiments were repeated in 1731 by Cromwell Mortimer (d. 1752), acting Secretary to the Royal Society of London.<sup>2</sup> He also commented on the colour of the blood and, finding clots in the veins and ventricles

of the heart, suggested that the substance coagulated the blood so that it could not pass the lungs and brain. A further confirmation of the poisonous nature of cherry-laurel appeared in 1737 as a result of some experiments carried out under the direction of Abraham Vater (1684–1751).<sup>3</sup>

The next to take up the study was an English physician, Browne Langrish (d. 1759), who was less concerned with toxicity than with mode of action and possible therapeutic effects of small doses.<sup>4</sup> His studies, reported in 1746, are an early example of a quantitative approach to the elucidation of a pharmacological problem. He began by making a standard preparation using a method adopted by Mortimer. He took a peck of leaves, weighed them carefully ('lest I might be deceived by different measure in future Tryalls'), mixed them with three gallons of water, distilled and collected two quarts of the distillate. To confirm that this sample had the same strength (i.e. toxicity) as those of the earlier workers, he gave a dose of four fluid ounces to a large dog, which died in convulsions within seconds. This sudden effect was attributed to the action of the substance on the nerves and animal spirits, the action being too rapid to be explained in any other way.

Langrish found more to interest him when he began to observe the results of administering small doses. A daily dose was administered to a dog over a month, then doubled over a further period. During the course of the experiments the pulse rate increased, and at the end the blood was described as 'extremely florid and beautiful . . . the Coagululum . . . as vivid as possible'. The subject remained apparently healthy and even grew fat so that the author concluded the dose to be beneficial, explaining its action as being the result of its ability to thin the blood and so increase the circulation. In another experiment, increasing doses of fresh leaves were administered in food and an attempt made to assess the action of the substance by allowing a known volume of blood to coagulate, then weighing the separated serum. Over a period of four months, during which time the dose was increased to two ounces, an increase in the weight of separated serum was observed and this result confirmed Langrish in his opinion that the principles in the leaves 'thinned' the blood.

The supposed attenuation of the blood was attributed to alterations brought about in the cohesion of its particles and Langrish believed he could pursue the matter further by attempting to measure the resistance of the blood clot which is formed after the sample of blood is allowed to stand for twenty-four hours. The technique used was to take a glass tube, one-third of an inch in diameter, with a closed 'obtuse' point about the size of a pea. This was laid on the clot and the mercury poured into the tube until the point penetrated the mass; the height of the column of mercury was taken to be proportional to the resistance of the clot. In the experiment, which was carried out on a sick horse, he found that the resistance of the clot was reduced as the dose of cherry-laurel increased. This was taken as further confirmation of the attenuating effects of the preparation on the blood.

There are a number of interesting features in this investigation. First, Langrish appreciated the value of animal experiments at a time when such experiments were widely suspected as having little comparative value. Second, he realized that, in the investigation of a reported poison, the effects of small doses should be investigated as well as larger toxic doses. (Later in the century, Withering redeemed the therapeutic

### *The Introduction of Hydrocyanic Acid into Medicine*

reputation of digitalis by using small doses). Third, Langrish used quantitative techniques to study physiological changes. These features, however, are of interest only in relation to the history of experimental pharmacology; the work itself had nothing to contribute to therapeutics. The peculiar effects of cherry-laurel upon the blood, in particular the 'improved' colour, were misinterpreted by Langrish as being of a tonic and beneficial nature and led him to recommend the administration of the water in toxic and near-toxic doses. Little notice, however, was taken of these recommendations. At the time of the publication of Langrish's experiments, the evidence of toxicity of the preparation had already brought it into disrepute. Not only was cherry-laurel condemned, but also preparations of a similar nature. The revision committee of the London pharmacopoeia of 1746 refused to admit *Aqua cerasorum nigrorum* (black-cherry water), a common remedy for convulsive fits in children, because experiments on animals had shown it to have an effect similar to that of cherry-laurel. It was therefore considered too dangerous for children, especially in the hands of their unskilled nurses.<sup>5</sup> The Edinburgh College deleted the same preparation from its pharmacopoeia in 1756.

William Cullen in 1789 described the *Aqua laurocerasi* as a sedative of the most powerful kind but was critical of its use in medicine.<sup>6</sup> He rejected the opinions of Langrish and also the belief that it was useful in the cure of pulmonary conditions. At this time, a number of physicians in Europe were using it to treat chest complaints where its transitory sedative action had the effect of reducing persistent coughing. This had led to the claim, which Cullen rejected as having no reasonable basis, that the preparation cured *phthisis pulmonalis*. In view of the subsequent history of hydrocyanic acid, it is interesting to note that Cullen continued to regard cherry-laurel as a potential remedy: 'That a matter of such power in changing the state of the animal economy should, in certain circumstances, prove a medicine, we can have no doubt; but we have not yet learned to what circumstance of disease it is peculiarly adapted'.

Thus it was that a preparation having a distinct physiological action on the body was rejected from medicine, partly on the lack of a reasonable basis for its use in therapy, but more particularly for the very obvious hazards attendant upon its use. This was not merely because the water was toxic (there were many poisonous substances in the materia medica), but because it was a variable, and therefore a dangerous preparation. It is probable that the death of the two women which initiated the investigation of the preparation was caused by a sample accidentally more potent than that used before. Later, when hydrocyanic acid was introduced into medicine, although of greater toxicity than cherry-laurel water, the problem did not exist because it was a pure substance and the dose could be controlled by careful dilution.

When in 1779 the Italian scientist, Felice Fontana (1730–1805), began to study cherry-laurel water, it was not as a medicament but as a poison.<sup>7</sup> Fontana, who had extensively studied viper venom and the American (curare) arrow poisons, began by observing the effects of the water on rabbits and guinea pigs. His results were contradictory and no relation could be established between dose, route of administration and physiological action—another result of the variability of the preparation. Fontana, who, in his earlier studies, had been accustomed to working with small doses of pure, highly active poisons, resolved to attempt the isolation of the toxic principle in cherry-

laurel. To do this, he distilled the leaves with water and collected the distillate from which an oil separated; the aqueous portion was then redistilled to obtain another oil and an aqueous fraction which was distilled yet again. The residues, oils and aqueous fractions were each administered to animals to observe their effects and one hundred and thirty-nine tests were made using pigeons, guinea pigs, rabbits and frogs. All these preparations, however, proved to be toxic and there was no evidence that the toxic principle had been isolated or even concentrated. Fontana had failed in his attempt to isolate the toxic principle of cherry-laurel but, by a coincidence, the material he was seeking, was discovered shortly afterwards by the Swedish apothecary chemist, Carl Wilhelm Scheele (1742–1786).<sup>8</sup> In the course of his study of prussian blue, Scheele heated yellow prussiate of potash with sulphuric acid and obtained a dilute acid. The solution had a characteristic smell, and Scheele described it as having a slightly sweet taste—he was obviously unaware of the toxicity of the new substance and was fortunate that it had not been isolated in a more concentrated form. He called the substance the ‘colouring principle’, and shortly afterwards Guyton de Morveau gave it the more familiar name of prussic acid.<sup>9</sup> The relationship between this acid and known toxic vegetable materials was established about 1800 when a German pharmacist named Bohm, observing a similarity between the odour of the acid and distilled water of bitter almonds, used almond water to prepare prussian blue.<sup>10</sup> Two years later another pharmacist, Johann Christian Karl Schrader (1762–1826) of Berlin, demonstrated the presence of the acid, which he called ‘blausäure’, in cherry-laurel as well as in bitter almonds and peach.<sup>11</sup> In his experiments he treated the distillates with lime, added iron sulphate and then acidified the mixture to obtain prussian blue. He put small birds into containers with the acid and the manner of their death convinced him that it was the toxic principle of cherry-laurel and bitter almonds. Shortly after this the acid was discovered in other vegetable materials by Vauquelin and Bergeman.<sup>12</sup>

It was not long before the extreme toxicity of the newly discovered hydrocyanic acid was clearly and unequivocally demonstrated. In 1805, Carl Friedrich Emmert (d. 1834) published his experiments on dogs which showed it to be a rapid and dangerous poison.<sup>13</sup> In 1814, it was reported that the vapour killed rabbits, cats and dogs within seconds<sup>14</sup> and shortly afterwards François Magendie (1783–1855) described the pure acid as the quickest acting substance known: an animal injected with it died ‘*comme s’il eût été frappé d’un boulet ou de la foudre*’.<sup>15</sup>

The introduction of hydrocyanic acid in a diluted form into the materia medica was surprisingly rapid and quite undeterred by the proven toxicity of the concentrated acid. It began with the followers of *Brunonism* and, in their case, developed directly from the medicinal use of cherry-laurel water. The Brunonists, not averse to heroic treatments, were in the habit of prescribing cherry-laurel for cases of what they called ‘sthenic diseases’ or diseases of high excitement. One of them, Siro Borda (1761–1824), a professor at Pavia, recommended a dilution of pure hydrocyanic acid after Schrader discovered its presence in cherry-laurel. This fact was reported by Luigi Brugnatelli (1761–1818), who went on to describe the acid as an anti-excitant and anthelmintic.<sup>16</sup> The first recorded use of the acid for pulmonary complaints was by Valerino Luigi Brera (1772–1840), who, in 1809, administered it to a female patient suffering from

### *The Introduction of Hydrocyanic Acid into Medicine*

pneumonia.<sup>17</sup> The major influence, however, in the introduction of the acid into medicine for treatment of pulmonary conditions was that of François Magendie, who, in 1817, published a memoir on the subject under the title, *Mémoire sur l'emploi de l'acide prussique dans le traitement de plusieurs maladies de poitrine, et particulièrement dans la phthisie pulmonaire*.<sup>18</sup>

This memoir is of particular interest to the history of clinical pharmacology because it illustrates an early scientific approach to the therapeutic use of a new pure chemical substance. Magendie, in his experiments with strychnine arrow poisons in 1809<sup>19</sup> had clearly demonstrated the importance and scientific value of carefully planned systematic animal experiments to determine the mode of action and sites of action of poisons. In the paper on hydrocyanic acid, he expresses the belief that such experiments can advance therapy.

Physiological experiments, which are so important to the theory of medicine, are no less important to the practice and application of that science. They reveal the true value of substances whose long use in medicine has been based only upon hypothetical principles and yield more information on the mode of action of the really active substances so that it becomes easier to vary their effects and to remedy their disadvantages. Their greatest advantage is to assist the physician in the discovery of new medicaments either from amongst substances long known but not used in medicine or from the many simple and compound chemicals which are the daily discovery of modern chemistry and which, if subjected to the new methods of examination, may become particularly valuable to science and mankind.

The observation on which Magendie based his therapeutic measures was that hydrocyanic acid apparently destroyed the sensibility and contractility without affecting the respiration and circulation. These observations were substantially correct; the cyanide ion in low concentrations stimulates respiration and its effects are compared by some authors with a transient functional decerebration. Magendie's therapeutic deductions from these physiological observations were recorded as follows: 'This property of extinguishing the general sensibility without ostensible injury to the respiration and circulation . . . induced me first to believe that the prussic acid might be advantageously used in cases where the disease seemed to owe its origin to a vicious augmentation of sensibility.' Such a condition was persistent nervous and chronic cough, and Magendie records a number of cases where the diluted acid had been used with success. He extended treatment to cases with consumption and, in a case where the disease was in the incipient stage, he considered some improvement to have taken place. From the physiological observations and case histories, Magendie drew a number of conclusions which provided a guide to the use of the new medicament. He observed that the dilute acid is of benefit in cases of chronic or nervous cough. He recommended it as a useful palliative in tuberculosis and suggested that on further study it may prove to be curative for the disease in its early stages. He made it quite clear that on the evidence the pure acid was far too toxic for use in medicine and observed that in cases of tuberculosis where the disease was in an advanced stage even the dilute acid could be injurious. Obviously with so dangerous a substance careful standardization and dose was important. In the case studies for the 1817 memoir, Magendie had used Scheele's acid, but finding its strength to be variable, turned to a purer form prepared after the manner of Gay-

Lussac, who decomposed prussiate of mercury with hydrochloric acid. Later, in his widely read *Formulaire pour la Préparation et l'Emploi de Nouveaux Médicaments* (Paris, 1821), Magendie recommended a preparation which he called 'medicinal prussic acid' composed of one part of Gay-Lussac acid and six parts of water.

This carefully reasoned monograph with its precise conclusions was one of the first to include evidence of animal experiments in support of clinical findings and was directly responsible for the introduction of the acid into official French pharmacy and medicine. It was included in an appendix to the *Codex medicamentarius sive Pharmacopoeia Gallica*, published in 1818 and the first pharmacopoeia to be official for the whole of France. There it appeared under the title *Acidum Hydrocyanicum*, the latinized version of the new name given to it after Gay-Lussac's study of the radical *cyanogen*. There it was stated that it was necessary to include the acid because so many doctors, following Magendie's observations, were prescribing it for their patients. The admission of the acid into the French pharmacopoeia probably led to its inclusion in the first *United States Pharmacopoeia* in 1820.

Some time was to elapse before hydrocyanic acid was admitted into the official British pharmacopoeias. It was first brought to the notice of English physicians by the much-travelled Augustus Bozzi Granville (1783–1872), who had learned of the effects of laurel water and prussic acid when he studied under Borda and Brera in Pavia.<sup>20</sup> Little notice was taken of his first paper in 1815<sup>21</sup> so, in 1818, he published a translation of Magendie's memoir.<sup>22</sup> A year later, he produced his *An historical and practical treatise on the internal use of the hydrocyanic acid*, which reappeared in 1820 in a greatly enlarged second edition. In it, he reported on a number of case histories where the acid had been used for a variety of nervous and pulmonary conditions and gave a review of the methods of preparation. He took a proprietary attitude to the new medicament, claiming that his writings on the subject had so impressed doctors and laymen that he was embarrassed by the demands made upon his services.

The sale of the acid in London in 1820 provides evidence that it was being fairly extensively used there. It is reported by Granville that nine quarts of the preparation was sold at Apothecaries' Hall over a period of nine months, and another chemist recorded the disposal of forty pints over a similar period.<sup>23</sup> It was being prescribed at that time in St. Thomas's hospital, and it was there that John Elliotson (1791–1868) found a new use for it when a dose of the diluted acid, prescribed for a pulmonary case, was administered by mistake to a patient suffering from 'violent spasms and flatulence of the stomach'.<sup>24</sup> The patient derived temporary relief, and henceforth, on Elliotson's recommendation, the acid was prescribed for treatment of gastrodynia, dyspepsia and other stomach conditions where pain was experienced.

In spite of the use of the dilute acid in British practice, the compilers of the *Pharmacopoeia Londinensis*, who only accepted new substances receiving the approbation of a majority of the Committee, did not include the preparation in the 1824 edition. There were, of course, reasonable grounds for opposition to this substance. The toxic properties of cherry-laurel and similar preparations had led to their deletion from medicine, and British physicians had no reason to be greatly influenced in favour of a substance recommended by the followers of Brunonism. They were

### *The Introduction of Hydrocyanic Acid into Medicine*

aware that it had been included in the French pharmacopoeia (in an appendix which also included morphine), but the main text of that work was unlikely to impress them, including as it did such items as frogs, vipers and millipedes, all of which had long been deleted from the London pharmacopoeia. Caution was expressed by Thomas Cox in a commentary in his translation of the 1824 London pharmacopoeia: ' . . . since the first introduction of hydrocyanic acid, few diseases occur in which practitioners have not employed it. Although we are unable to decide the precise condition of the body, or states of disease fit for the remedy, we cannot doubt its activity, something further must be known before we prescribe it'.<sup>25</sup>

Caution in the official recognition of a new drug is to be recommended but when a drug is already in use and is of a highly active nature, it is in the interests of safety that standards of strength and dose be established as soon as possible. In this respect hydrocyanic acid can be said to have exposed a major problem facing compilers of pharmacopoeias in the days before pharmacological testing was developed and when judgement relied solely upon the habits and observations of general practice. The shortcomings of the London pharmacopoeia in this particular instance were compensated by commentaries and translations of the pharmacopoeia. Thomas Cox, in an appendix to his translation, gave information concerning preparation and usage and toxicity of the acid, although, as we have seen, he advised caution in its use and accused Granville of overrating its value. Samuel Frederick Gray, in his supplement to the new pharmacopoeia,<sup>26</sup> gave information concerning the preparations of the acid in the French formulary. In the preface, Gray criticized the methods of selection of the London College and commented that prussic acid and the like, even if only used by a minority of physicians, require 'an uniformity of preparation to be speedily instituted'. He forecast the institution of the modern pharmacopoeial *addenda* when he added that one should not wait for a new edition of the pharmacopoeia to regulate the strength and preparations of new drugs.

A preparation of hydrocyanic acid in the form of a two per cent dilution prepared from ferrocyanide of potash and sulphuric acid was eventually introduced into the *Pharmacopoeia Londinensis* in 1836. This led, in time, to the reintroduction of *Aqua laurocerasis*, which appeared in the first *British Pharmacopoeia* of 1864. Thomas Castle and Richard Phillips in their translations of the 1836 pharmacopoeia both describe the acid as a sedative and antispasmodic.<sup>27</sup> Pockets of resistance to the drug remained ('commonly used for suicide and is fit for little else', wrote Collier in 1837<sup>28</sup>), but in general it was accepted as a useful item of the materia medica. In the years that followed, distinguished teachers added their support for its use. A. T. Thomson in 1835 recommended it as a palliative in cough, and described it as a 'sheet anchor of the practitioner' in the treatment of 'hooping cough'.<sup>29</sup> R. Christison in 1842 labelled it as calmative, anodyne, antispasmodic and noted that in his own practice its effects in dyspepsia were unequivocal.<sup>30</sup> J. Pereira in 1850 expressed his doubts concerning the value of the acid as a cure for pulmonary conditions but recommended it as a sedative, particularly for gastrodynia.<sup>31</sup>

The importance of a medicinal substance must be measured against the other materials available at the time. The *sedantia* of the early nineteenth century included tobacco, aconite, hemlock, colchicum and blood-letting. Compared with these,

hydrocyanic acid, properly diluted and dispensed, was an effective remedy and by far the most efficient alternative to the narcotic opium. Its rapid sedative action, even though of a transitory nature, was a useful medicament to the physician. It was soon discovered that it lacked the curative powers claimed for it, but as a palliative giving relief to coughing and gastric pain it was welcome. Its decline began with the introduction of new, more efficient sedatives, e.g. the bromides and chloral, in the latter half of the nineteenth century, although it retained its place long after these substances were admitted to the pharmacopoeias. In time, its toxicity became once more a dominant idea in the minds of physicians and finally, with the advent of the barbiturates and other synthetics, its period of usefulness was over. In 1918, A. R. Cushny, in his *Textbook of Pharmacology and Therapeutics* (7th edition), commented that prussic acid might be eliminated from therapeutics without loss. The Americans deleted it from their pharmacopoeia in 1925 and the French followed in 1937. Because of delays in the publication of the pharmacopoeia, its official life was prolonged in Britain until 1948.

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## *News, Notes and Queries*

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### SIXTH HUNDREDTH ANNIVERSARY OF THE FOUNDATION OF THE FIRST UNIVERSITY OF HUNGARY

IN 1367 King Louis d'Anjou (1342–1382) founded at Pécs or Fünfkirchen (in Latin, *Quinque Ecclesiae*) the first University of Hungary. It was the first centre of higher education to be established in the south-east part of Europe, and its foundation was a sign of the cultural development of Hungary, then a great political power in Europe.

In 1345 King Louis wrote to Pope Clement VI, commenting on the difficulty of obtaining a sufficient number of counsellors trained in the humanities. Although talented students were sent to the Italian universities, especially to the universities of Bologna and Padua, the expense was great, and the time necessary for the completion of their studies too long. King Louis therefore decided to found a University in his own country where Hungarian, Croatian, and Dalmatian students could be educated together. In 1360 he wrote to the Duke of the Carrara family in whose territory the University of Padua was situated at that time, to ask him to send the Professor of Humanities, Bartolomeo Piacenti, to organize the school<sup>2</sup> on the model of the University of Padua. But Bartolomeo Piacenti could not come. After long discussions Galvano di Bologna (known also as Galvano de Bettini),<sup>3</sup> Professor of Roman Law and Saraceno di Padova (known also as Giovanni Saraceno), an apothecary and presumably a physician also, came in the year 1367 from Padua to Hungary, where, with the help of King Louis and Wilhelm von Bergzabern, Bishop of Pécs, the new humanistic university was organized. Bishop Wilhelm was a native of Pfalz, Germany, and was the son of Henrik of Bergzabern. He had had an excellent education, and by the year 1357 he was a high ecclesiastical dignitary and privy