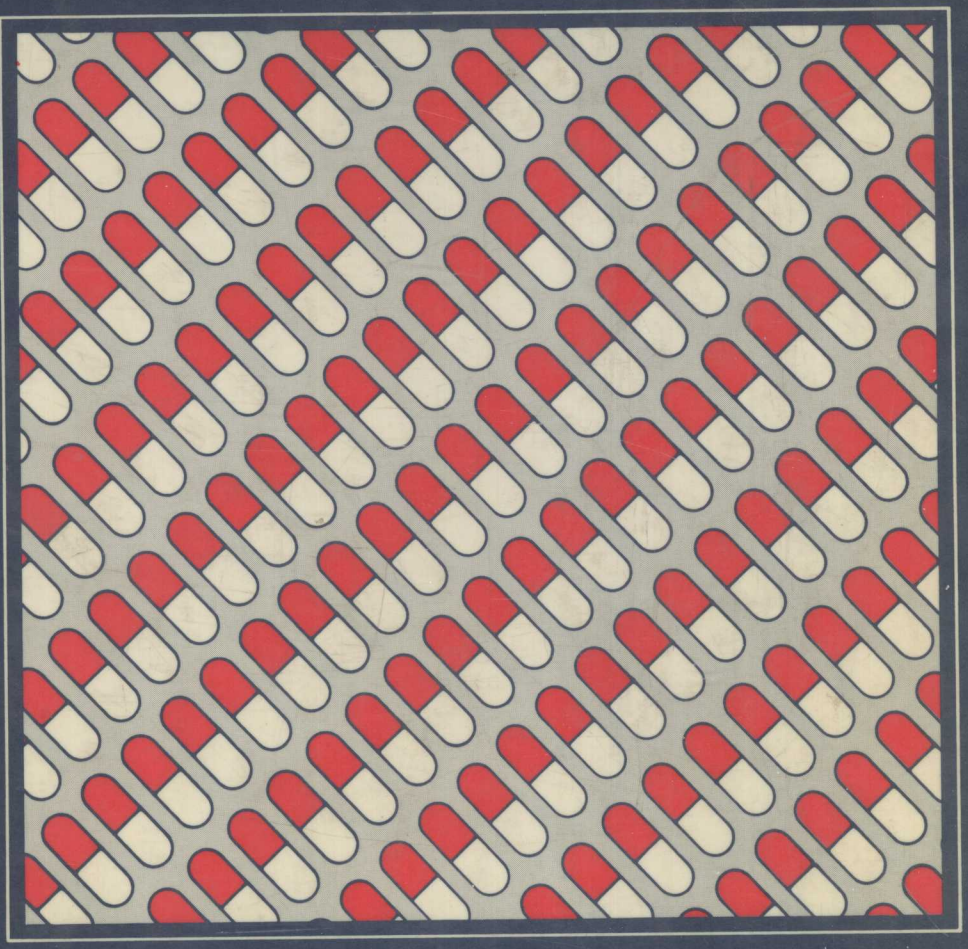
DRUG DISCOVERY: the evolution of modern medicines

Walter Sneader



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DRUG DISCOVERY: THE EVOLUTION OF MODERN MEDICINES

For Myrna

Preface

The past century has witnessed the realization of one of man's ancient dreams—the conquest of disease through the use of effective drugs. This book, which describes for the first time how this has transpired, attempts to convey some of the drama and excitement that must have been experienced by the doctors and scientists who were involved. Much of this drama arose from the opportunistic exploitation of unexpected observations, that combination of chance and sagacity known as serendipity. Recently, however, major new drugs have been developed through the application of rigorous scientific thought.

A major problem encountered in writing this book has been the acquisition of basic facts concerning the discovery of scores of drugs. This required many hours of painstaking searches amongst dusty volumes of old journals. Fortunately, this was to some extent offset by the availability of secondary literature dealing with the more celebrated drugs. Progress might have been faster, and the text more accurate in some details, had it been written by several hands, but it would have been difficult to communicate the overall integration and continuity of events in this manner. Hopefully, my readers will forgive the shortcomings that are inevitable in a single-author work attempting to cover so vast a field of knowledge; it might prove possible to rectify these in a future edition if readers will supply me with the relevant information.

The text is liberally interspersed with chemical formulae. Their presence should not deter either the general reader or the professional who harbours feelings of inadequacy so far as chemistry is concerned. These formulae supplement the information in the text so as to enable those with the appropriate knowledge to relate what appears in these pages to their existing understanding of the subject. Throughout this book the text should be comprehensible without reference to the chemical formulae.

It is my desire that this book should provide health-care workers in the medical, pharmaceutical, and nursing professions, as well as scientists whose work entails the handling of drugs, with an insight into how such a diverse range of chemical substances has been introduced into clinical practice. Many years

of teaching experience have convinced me that this can create greater confidence in coping with an otherwise overwhelming plethora of pharmaceutical products. There is, however, a further dimension to this book insofar as it outlines the rise of one of the first so-called high technology industries. This may furnish a useful background to the public debate concerning the nature and funding of research in the pharmaceutical industry.

For the benefit of those readers who may wish to pursue the subject matter further, an extensive bibliography relating to drug discovery has been included. In many cases it will be evident as to which part of the text a given reference relates, but where this might not be the case an indication of the particular drug concerned is given after the reference. This may seem a little unconventional, but it has been done to avoid disrupting the readability of the text through the insertion of embedded reference numbers, bearing in mind that the majority of readers will consult the bibliography only infrequently.

Walter Sneader

Glasgow,
January 1985.

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I

The Legacy of the Past

Before the advent of modern chemistry, physicians seeking drugs to treat their patients could only select natural products or inorganic materials. There was no shortage of the former. Herbals and pharmacopoeias filled with ancient plant lore were testimony to the effort that had been expended over thousands of years in the search for panaceas to cure all ills. The principles underlying the use of these herbal remedies were far from scientific, for primitive medicine had been firmly bound up with magic and religion. In a world where disease was held to be a result of either possession by demons or the wrath of the deity, it was the priesthood which was entrusted with the responsibility of discovering drugs. In Egypt, the priest-physicians concocted vile potions from dead flies, dried excreta, garlic, leek, onion, and bitter herbs, in heroic attempts to drive out the demons via any appropriate orifice in the body. They seem to have fought something of a losing battle, for the Ebers Papyrus, discovered by George Ebers in 1862, contained no less than 811 different formulae for fighting off disease. This was compiled around 1550 BC, but the legacy of the Egyptians remains with us, for many people still put their trust in herbal remedies or take purgatives regularly in the hope of maintaining good health! The influence of the Assyrians and Babylonians also persists amongst modern devotees of herbalism, but one wonders if they realize that the origins of many herbal remedies can be traced back to the astrologers of Chaldea who believed that each star could exert its influence upon a specific plant? With so many stars in the firmament, there was no shortage of plants that might cure the sick, provided a knowledgeable astrologer-priest was consulted.

Demonology was unacceptable to the Greeks, but they did not reject the herbs that were associated with it. Nor did they spurn the idea that the stars influenced the therapeutic qualities of plants. Indeed, so diverse was the range of herbs employed by Greek physicians that a corps of plant-gatherers emerged to satisfy the unremitting demand. Probably to protect their privileged position as much as out of devotion for the principles laid down by their predecessors, these forerunners of the apothecaries issued warnings that only by recitation of the correct incantation and due regard to the position of the heavenly bodies at the time of ingathering, could the therapeutic efficacy of herbs be guaranteed. Sometimes, even worse might happen if plants were gathered by those unauthorized to do so—as in the case of the mandrake, which could only be uprooted by a tethered dog as whomsoever wrested it from the ground died instantly!

The medical knowledge of the Greeks was enshrined in the writings of Galen (129–199), especially his voluminous *On the Art of Healing*. Born in Pergamum, he began his study of medicine at nearby Smyrna, and completed his

training twelve years later in Alexandria. During his lifetime he achieved considerable fame as a clinician, and his success enabled him to devote much time to writing. He possessed a sound understanding of philosophy, his work being imbued with Aristotelian concepts. Thus, he asserted that imbalance of the four humours (blood, phlegm, black bile, and yellow bile) was the cause of disease. As these humours corresponded to Aristotle's four qualities (moist, dry, cold, and warm), of which all substances were constituted, Galen held that it should be possible to administer herbs with opposing qualities in order to cure disease. He expressed this succinctly with the maxim *contraria contrariis curantur*. Invariably, this necessitated the compounding of several plants in complex formulations that later became known as 'galenicals'. To discover plants with the appropriate properties, the so-called simples, has exercised the minds of his followers ever since. Despite this apparent recognition of the importance of the empirical testing of drugs, there was much speculation in Galen's books, particularly with regard to how medicines acted. He even managed to justify the age-old use of excrement and amulets. Galen's influence did not wane after his death, for his writings were translated into many languages. They exerted a stultifying influence on therapeutic practice for more than 1500 years, particularly through their incorporation into Arabic medicine, which came to the fore when the Arabs conquered the lands around the southern shores of the Mediterranean and also Spain.

The revival of interest in Greek culture during the Renaissance, hastened by the introduction of the printing press, focused attention on Galen's original texts, with the compilers of pharmacopoeias and herbals drawing freely from them. One of the earliest printed herbals, *Liber de Proprietatibus Rerum*, was published in Basle in 1470; it was written by Bartholomeus Anglicus, an English professor of theology in Paris. The first pharmacopoeia was the *Nuovo Receptario Composito*, a slim volume compiled in Venice in 1498 by the College of Physicians at the request of the Guild of Pharmacists. The next century saw the appearance of botanists in Germany, the most eminent of whom, Valerius Cordus, wrote a four volume history of plants.

The first major challenge to Galen's teachings came from the Swiss physician, Paracelsus (1493–1541). Rejecting the use of herbs, he urged alchemists to desist from the quest for gold and the compounding of worthless elixirs, and instead apply their skill and knowledge to the needs of the sick by developing chemical medicine from mineral sources. He sought the *arcanum*, the healing essence within all effective pharmaceutical preparations, be they animal, vegetable, or mineral. In this, he was ahead of his time, for it was not until the beginning of the nineteenth century that the first active principle was successfully extracted from a plant.

Despite Paracelsus, herbal medicine reached its zenith in the seventeenth century. Its subsequent decline was due to the emergence of physicians who rejected authoritarianism in favour of the experimental method. Opposing the magic and superstition that had dominated medical thinking, these pioneers demanded evidence for the effectiveness of medicinal preparations, be these

the traditional galenicals or merely simples gathered from the hedgerow as domestic remedies for those who could not afford the expensive services of a physician. Gradually, other physicians came to share their views, with the result that towards the end of the eighteenth century, a mood of therapeutic nihilism developed amongst leading practitioners. Wise physicians came to the conclusion that, apart from cinchona bark for malaria and ipecacuanha for dysentery, both remedies having been introduced from the New World during the preceding century, opium and belladonna (the use of which had just been revived) were the only traditional drugs with any real value.

Desperate to find alternative therapeutic measures to satisfy their patients, physicians welcomed any new system that came into vogue, such as sea bathing, hydropathic spas, heliotherapy, electrotherapy, or diet therapy. It was against this background that English physicians began to take an interest in Joseph Priestley's experiments with 'fixed air', i.e. carbon dioxide, and 'dephlogisticated air', to which Lavoisier later gave the name oxygen. Patients were given carbonated drinks in the hope that any carbon dioxide that was absorbed would dissolve kidney stones. After Lavoisier had elucidated the role of oxygen in respiration, around 1785, this was administered by inhalation for emergency resuscitation.

In 1786, Lavoisier was visited by a young English doctor, Thomas Beddoes, who was keen to learn of the latest developments in pneumatic chemistry. After his appointment as reader in chemistry at Oxford two years later, Beddoes acquired the reputation of being the leading English exponent of pneumatic medicine. In an effort to establish a theoretical basis for the therapeutic inhalation of gases, Beddoes turned to the controversial Brunonian system of medicine which argued that patients were either asthenic, meaning their tissues required stimulation, or sthenic, being the opposite. As oxygen had undoubted stimulating properties, Beddoes administered air enriched with it to asthenic patients, whilst his sthenic patients were required to inhale air deficient in oxygen. Beddoes carried out his experiments at Oxford until 1792, when his outspoken views on the merits of the French Revolution finally forced him to resign his post. This turn of events persuaded Beddoes that it was time to open an institution where patients could be properly treated with specially manufactured 'factitious airs'.

Beddoes' father-in-law and several acquaintances were members of the elite Lunar Society, quaintly named because it met monthly in Birmingham when the moon was full, thus enabling its members to ride home by moonlight. When Priestley had lived in Birmingham during the 1780s, he greatly influenced the philosophical activities of this small group. Other distinguished members included Josiah Wedgewood, the pottery magnate, William Withering, the physician who introduced digitalis into medicine, his rival Erasmus Darwin, and the famous engineer James Watt, who had been persuaded by members of the Lunar Society to settle in Birmingham. It was to the Society, then, that Beddoes turned for patronage in 1793 after he published a pamphlet on the treatment of consumption (tuberculosis) by inhalation of factitious airs.

Whether Beddoes was aware of it or not at that time, several members of the Lunar Society had good cause to support his efforts, for members of their own families were dying of consumption. Not least amongst these was young Gregory Watt, the son of the engineer.

Intrigued by the imaginative nature of Beddoe's plans and their utility, the Society members backed him financially, Wedgewood contributing £1000 and others providing what they could afford. James Watt collaborated with Beddoes on the scientific side, the two men publishing the five volume *Considerations on the Medicinal Powers and the Production of Factitious Airs*, which appeared between 1794 and 1796. This marked the heyday of pneumatic medicine, and Beddoes forged ahead with his plans to open what was to become known as The Pneumatic Institution for Relieving Diseases by Medical Airs.

The Pneumatic Institution was established in Clifton, Bristol, in 1798. In the basement was a massive machine built by James Watt for the production of a variety of gases under the supervision of a young man who had been recruited from Cornwall, one Humphrey Davy. The latter was encouraged to experiment with new gases for the patients to inhale, and this led him to examine Priestley's nitrous oxide which an American, Samuel Mitchell, was claiming to be highly toxic. After establishing that small animals could be immersed in a jar of nitrous oxide without any apparent harm, Davy boldly inhaled the gas himself, only to experience what he later described as, '. . . the most vivid sensation of pleasure accompanied by a rapid succession of highly excited ideas.'

The reputation of nitrous oxide as a euphoriant spread quickly, earning it the popular name of 'laughing gas'. It was to remain as the most enduring product of the Pneumatic Institution, which itself soon developed into a mere nursing home as physicians and patients alike came to realize that factitious airs were not the panacea for all ills. Indeed, so rapid was the demise of pneumatic medicine that by the turn of the century only the inhalation of oxygen was considered to have any therapeutic merit. A few pioneers, however, did continue to experiment, including a general practitioner in Ludlow, England, who showed that animals could be rendered unconscious by carbon dioxide inhalation. In 1824, he published a pamphlet encouraging surgeons to experiment with this technique so that their patients might be spared the dreadful agonies of surgery. Despite pleading his case in London and Paris, Henry Hill Hickman died six years later at the age of thirty, without seeing the medical profession take up his proposals.

Richard Pearson, one of the Birmingham group of pneumatic physicians, discovered that when it was not practicable to use gases it was possible for patients to inhale ether as an alternative. He made no extravagant claims about the value of ether, but employed it for many years for respiratory disorders. In 1818, the *Journal of Science and the Arts*, published by the Royal Institution, carried a report that the effects of ether inhalation were similar to those of nitrous oxide. This report may well have been written by Humphrey Davy who

was by then the director of the Royal Institution. The veracity of this report was confirmed by the wave of 'ether frolics' which swept through both Great Britain and America, ultimately leading to the discovery of its value as an inhalational anaesthetic.

While physicians were coming to the conclusion that pneumatic chemistry had little to offer them, an important development had been taking place in Paris. Antoine Fourcroy, the son of an apothecary, had been supported financially by influential members of the Société Royale de Médecine while he pursued medical studies. Such was his talent for chemistry that the Société permitted him to participate in its work even before he graduated in 1780. The Société was required to assess the medicinal value of mineral waters, and Fourcroy was given the responsibility of analysing these. He rejected the existing system of merely evaporating the waters to dryness, and instituted the use of specific chemical reagents to determine which minerals were actually present. From this modest beginning, Fourcroy proceeded to devote much of his distinguished career to the application of chemistry to medicine. Although he was primarily interested in the examination of the solids and fluids of the human body, in 1791 he published an analysis of St. Lucia and St. Domingo barks, which had been recommended as substitutes for cinchona bark in the treatment of malaria. This was for many years considered to be a model of vegetable analysis, and it stimulated others to examine cinchona and opium, the two most important vegetable drugs then in common use.

Following the decision of the Convention, on 8th August 1793, to suppress academic and professional bodies that had enjoyed privilege under the monarchy, new institutions of higher learning were established throughout France. The responsibility for medicinal analysis eventually passed to the Société de Pharmacie and the Ecole Supérieure de Pharmacie, which opened in Paris in 1803. Its first director was Nicolas Vauquelin, a close associate of Fourcroy, who had now become an important political figure. Vauquelin, an outstanding analytical chemist, encouraged the close association of chemistry with pharmacy in the curriculum. His response to growing concern in medical circles over the variable quality of plant products was to encourage his faculty members and their students to try to extract pharmacologically active principles from plants so that reliable chemical assays could then be established. He was inspired to suggest this through the work of the Swedish pharmacist Carl Gustav Scheele who, during the 1780s had isolated no leas than a dozen plant acids in pure form, including tartaric, malic, citric, oxalic, lactic, and uric acids. The fact that none of these were active principles did not seem to have discouraged Vaquelin.

Opium (Gr. *opos* = juice), obtained by drying the latex that exudes from the capsule of the poppy, *Papaver somniferum*, is probably the most ancient effective drug of all. Remains of the garden poppy have been found in the stone-age lake dwellings of Switzerland. The Ebers Papyrus refers to a mixture of poppy pods and flies as a sedative for children. In the Iliad, Homer mentions the poppy growing in gardens, which confirms its cultivation had been estab-

lished by the eighth century BC. Whether the *nepenthe* that he wrote of in the Odyssey was opium is open to conjecture. The first accurate description of the poppy appeared in the *Historia Plantarum* written by Theophrastus (372–287 BC), the father of botany. Three centuries later, in his *De Universa Medicina*, Dioscorides, a Greek surgeon serving with Nero's army, explained how the poppy capsule should be incised in order to obtain its juice. Pliny the Elder (23–79) mentioned opium in his thirty-seven volume work on natural history. He shared some of his fellow citizens' contempt for the Greek physicians who monopolized medical practice in Rome, and did not lose the opportunity to warn of the dangers of opium. Nonetheless, its pain-relieving properties were by now clearly established, and its place in medicine was assured.

It was inevitable that opium should have been one of the first plant drugs to be investigated by means of the new system of plant analysis introduced by Fourcroy. Nevertheless, the French authorities had a long-standing interest in the constituents of the poppy. Wild rumours that poppy seeds and their oil, which were widely used for culinary purposes, had the same narcotic action as opium, forced the issuing of decrees, in 1718 and 1735, prohibiting their sale in France. Only after the matter was investigated by the Secretary of Agriculture in 1773 was the ban lifted.

In 1803, Jean-Francois Derosne, the owner of a fashionable Parisian pharmacy in the Rue St. Honoré, delivered a memoir to the Sociéte de Pharmacie, in which he reported that in the course of devising an assay for opium he had isolated a novel crystalline salt. A variety of tests revealed that this salt had alkaline properties, which Derosne attributed to contamination by the potash used to precipitate it from acid solution. He appreciated that he had been handling a peculiar substance that was certainly not a plant acid, and he described it as a salt because it crystallized readily. Nevertheless, he added the rider that this was a circumlocution to compensate for his inability to assign it to any known class of chemical compounds. In December 1804, Armand Séguin, formerly an assistant to Lavoisier and now the director of a highly successful tannery outside Paris, reported to the Institut de France that he had isolated a new plant acid and also a crystalline narcotic from opium. His findings were presented in a paper that he submitted to the Académie des Sciences, but it was laid aside. Séguin did not continue with his investigations, and by the time his paper finally appeared in the *Annales de Chimie* in 1814, similar observations had been reported elsewhere.

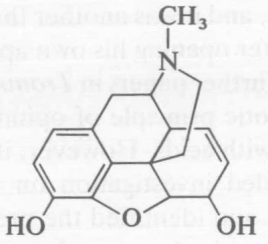
Friedrich Wilhelm Sertürner, the son of an Austrian engineer in the service of Prince Friedrich Wilhelm of Paderborn and Hildesheim, completed his apprenticeship with the court apothecary in 1803 when he was twenty years old. He remained at the Adlerapotheke in Paderborn for a further thirty months, during which period he was able to carry out a variety of chemical experiments. He turned to an examination of opium and was soon able to extract an organic acid that had not been reported in the literature. He named it meconic acid (Gr. *mekon* = poppy). When tested on dogs, it proved to be inactive. However, alkalinization of the mother liquors with ammonia caused precipita-

tion of a substance that he collected and crystallized from alcohol. This time, when he administered it to a dog, it proved to be a narcotic. He published a preliminary report of his findings in 1805 in *Johann Trommsdorff's Journal der Pharmazie*. A detailed account of his isolation of the *principium somniferum* was printed in the same journal the following year, but scant attention was paid to it, possibly because it appeared in a journal read mainly by practising apothecaries. Sertürner included in his paper a footnote stating that he had not learned of Derosne's work until after his own had been completed. That he wrote of the 'almost alkali-like character' of this principle from a plant source should itself have caught the attention of chemists, for all plant principles isolated prior to this were acidic in nature. Sertürner explained that his *principium somniferum* could neutralize free acid, but he failed to recognize the great significance of this aspect of his work, and it was another three years before he briefly renewed his investigations after opening his own apothecary in Einbeck, Westphalia. In 1811, he published further papers in *Trommsdorff's Journal*, in which he confirmed that the narcotic principle of opium was an alkaline substance, or base, that formed salts with acids. However, it was not until 1815 that he carried out a more detailed investigation on it in the Ratsapotheke. He refined his earlier methods and identified the presence of carbon, hydrogen, oxygen, and possibly nitrogen in the narcotic material. In 1817, he published another paper, but this time it appeared in a prominent scientific journal, *Gilbert's Annalen der Physik*. The paper was entitled, 'On Morphium, a Salt-like Base, and Meconic Acid as Chief Constituents of Opium'. In this, Sertürner drew attention to the particular ease with which morphium reacted with acids to form readily crystallizable salts. He also described how he and three companions swallowed does of about 100 mg of morphium and experienced the symptoms of severe opium poisoning for several days despite recourse to strong vinegar to induce vomiting when these symptoms first appeared! This time, Sertürner was not ignored, Joseph Gay-Lussac, the doyen of French chemists, read the paper and immediately had it translated and re-published in the prestigious *Annales de Chimie*, the journal founded by Lavoisier and which Gay-Lussac now edited.

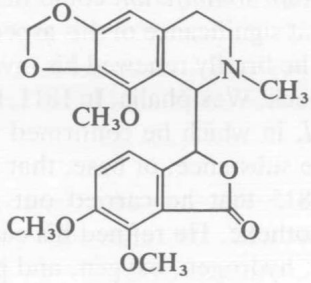
Gay-Lussac wrote an editorial to accompany the translation of Sertürner's paper. In this, he expressed surprise that Sertürner's work had been ignored for so many years, but not simply because the isolation of the active principle of opium was important. Of much greater significance, according to Gay-Lussac, was the discovery of a salt-forming organic plant alkali analogous to the familiar organic acids. He predicted that many other organic alkalis would be found in plants, for there was already some evidence to suggest that the few crude active principles isolated in the previous decade contained nitrogen and had alkaline properties. To ensure a degree of conformity in the naming of plant bases, Gay-Lussac proposed that their names should always end with the suffix '-ine'. This was the first time such standardization of nomenclature was introduced into organic chemistry. For this reason, Gay-Lussac altered Serturner's term 'morphium' to 'morphine'. In 1818 the German chemist Wilhelm

Meissner introduced the term 'alkaloid' to describe the plant alkalis, but several years passed before this was generally accepted.

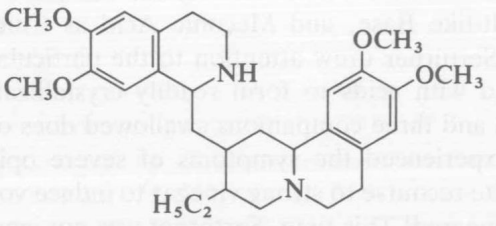
Gay-Lussac asked Professor Robiquet of the Ecole Supérieure de Pharmacie to check Sertürner's experimental work. Robiquet noted the differences in the properties of the salts isolated by Derosne and Sertürner, and he concluded that they were different plant alkalis. He purified the base isolated by Derosne and gave it the name 'narcotine'; this is now generally known as noscapine. It had no narcotic properties, although it was later found to retain the cough suppressant properties of morphine, and is still prescribed for this purpose.



Morphine



Noscapine

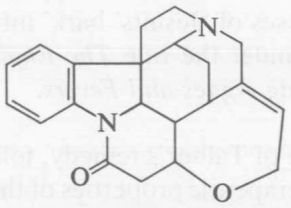


Emetine

Shortly before the publication of Sertürner's paper, Joseph Pelletier, the assistant professor in Robiquet's department at the Ecole Supérieure de Pharmacie, had collaborated with the brilliant physiologist François Magendie to isolate the emetic principle from ipecacuanha root. Early Portuguese settlers had found this root being used as an emetic by the natives of Brazil and Peru. An Amsterdam physician, Wilhelm Piso, who had spent several years in Brazil, described the root in his *Natural History of Brazil*, published in 1684. He stated that it was a specific remedy for dysentery. For some years the root was employed for this purpose in Spain and Portugal, but fell out of favour because it was thought to be too toxic. A few years later, a Parisian merchant who had imported the root, gave a sample of it to his physician, Afforty, as a sign of gratitude for treatment he had received. Afforty paid no attention to the merchant's claim that the root cured dysentery, but his assistant, Jean-Adrian Helvetius, tried the root and became convinced it was indeed a specific remedy

for dysentery. He then placed placards around Paris, extolling the virtues of his secret formula that could cure dysentery. This came to the attention of the Court, and he was summoned to treat the dauphin and several courtiers. Louis XIV then ordered the remedy to be tested at the Hôtel-Dieu, and he was so impressed with the outcome that he paid 1000 louis-d'or to Helvetius for publication of his secret formula. After this episode, ipecacuanha was in constant demand, but considerable confusion existed over the nature of the root until Bernardino Gomes, a Portuguese naval surgeon, published a dissertation on it after returning from Brazil in 1800. He identified the root as *Cephaelis ipecacuanha*. Pelletier and Magendie isolated its active principle in 1817, and named it emetine once they realized it was a plant alkali.

Pelletier acted on Gay-Lussac's suggestion that further plant alkalies would be found. He was assisted by Joseph Caventou, a student who had shown considerable flair for chemical research. They attempted to provide evidence in support of Linnaeus's belief that plants of the same genus would exhibit the same pharmacological properties. In 1818, they examined different species of the *Strychnos* family, the most potent plant poisons then known. In 1540, Valerius Cordus had described *Strychnos nux vomica*, the poisonous seeds of an Indian tree. The following century it was in use to kill pestilent animals. The related *Strychnos ignatii* (Saint Ignatius bean) was first described in 1699 by Camelli, a Jesuit missionary who served in Manilla. Pelletier and Caventou managed to isolate the same plant alkali from Saint Ignatius beans and *nux vomica*, as well as from snake wood (*S. colubrina*). Tests were conducted to confirm that the pharmacological activity of the new principle was identical, irrespective of its source. In honour of the director of their faculty, Pelletier and Caventou named the new plant base 'vauqueline', but this was deemed inappropriate by the commissioners of the Académie des Sciences, on the grounds that such a distinguished name ought not to be associated with a harmful principle. The name strychnine was then substituted. Pelletier and Caventou expected to find strychnine in the bitter bark of the false angostura (*Brucea anti-dysenterica*), but instead isolated another new base which they called brucine.



Strychnine

The work for which Pelletier and Caventou will always be best remembered was their isolation of quinine in 1820. The cinchona bark from which it was obtained had been introduced into Europe two centuries earlier. It was first mentioned in *The Chronicle of St Augustine*, written not later than 1633 by an