The evolution of chemistry and medicine in the 18th and 19th centuries

Michael Edmonds

Department of Applied Sciences and Allied Health, Christchurch Polytechnic Institute of Technology, PO Box 540, Christchurch 8140 (email: *michael.edmonds@cpit.ac.nz*)

Keywords: *chemistry, medicine, history, 18th Century, 19th Century*

Introduction

Throughout history there have always been close ties between chemistry and medicine. For millennia, healers, shamans and physicians have applied many essentially chemical techniques including distillation, smelting and soap-making in their search for new ways to treat disease. Much of this chemical experimentation was associated with various mystical, astrological and other pseudoscientific beliefs, and is, therefore, best described using the term 'alchemy' rather than 'chemistry'.

By the 18th century, the mysticism of alchemy was being replaced by rigorous quantitative experimentation and the new science of chemistry was emerging, although it was still often considered a subset of medicine. Consequently, most chemistry teaching and research was carried out in medical schools and apothecaries, and this would not change until the latter part of the 18th century when the applications of chemistry outside of medicine, for example in manufacturing and mining, became obvious.

However, researchers remained limited by their inability to accurately conceptualise the microscopic and atomic worlds. Physicians had not yet discovered the role microorganisms play in many diseases, while chemists were still debating flawed ideas such as phlogiston, and whether an element was a physical or philosophical concept.

As chemistry advanced into the 19th century a framework of core chemical concepts such as chemical affinity, valency and bonding began to emerge. At the same time medicine was freeing itself from the thrall of the "four humour" model of disease, a model which had been embraced since the time of the ancient Greeks. According to the four humour model, disease was caused by an imbalance of the four humours in the body: blood, phlegm, black or yellow bile. Attempts to rebalance a patient's humours included some potentially lethal practices, including the bleeding of patients and the use of toxins such as mercury (results in excessive salivation), antimony and arsenic as medicines. An unfortunate by product of these drastic treatments has been that they enabled non-effective, but essentially harmless pseudoscientific treatments, such as homeopathy, to establish themselves as viable medical therapies (at least in the eyes of the general public).

Airs and gases

At the turn of the 18th century, it was understood that air played a role in combustion and respiration and that it exerted pressure, but the idea that it might consist of different gases had not yet been conceptualised.

In 1727, botanist and chemist Reverend Stephen Hales developed a new piece of apparatus: the pneumatic trough. By passing gases into a trough of water over which was held an inverted vessel containing water, the gases could be collected and quantified. However, the potential application of this apparatus in the study of gases was not taken up by chemists until the 1770s, when there was surge of interest in gases by many prominent chemists including Antoine Lavoisier, Henry Cavendish and Joseph Priestley. By 1800, twenty different "airs" had been prepared and differentiated, including hydrogen, nitrogen, oxygen, hydrogen chloride and the various oxides of carbon.

The 1780s saw the development of 'pneumatic medicine': the use of gases to treat illness. A chemist and physician, Thomas Beddoes first used oxygen-enriched air to treat asthenic (weak) patients. In 1798, he established the Pneumatic Institution for Relieving Diseases by Medical Airs in Bristol, where patients could inhale gases produced in the basement by an enormous machine built by Gregory Watt, son of the engineer James Watt. Gas production was supervised by the young chemist, Humphrey Davy, who experimented with several gases including nitrous oxide. Upon taking nitrous oxide himself, he noted the pain-killing effects, but its potential use as an anaesthetic was not realised until 1844 when it was first used by dentist Horace Wells in Hertford, Connecticut to anaesthetise a patient before the removal of a troublesome molar tooth. Instead, prior to 1844, nitrous oxide was primarily used at "laughing gas" parties to entertain the upper classes.

Despite Wells' early success, a failed demonstration to surgeons at Massachusetts General Hospital that same year led to nitrous oxide being largely ignored for two more decades, in favour of the use of ether and chloroform. However, after dentist G. Q. Colton, demonstrated its safe use on thousands of patients without mishap in 1862, the use of nitrous oxide became common place in hospitals throughout Europe and the United States.

In addition to their medical applications, the study of gases and their reactions played a role in the development of many concepts vital to the further advancement of chemistry, including the various gas laws, the mole, molar ratios, and atomic theory.

Plant-derived medicines

Plants are an abundant source of bioactive compounds, and throughout history they have been pulped, dried, powdered, extracted and distilled in order to access the myriad of potentially beneficial compounds. However, even into the 19th century, the attribution of beneficial properties to certain plants was often based on myth rather than on science. Treatments were still described in relation to their effects on the four humours, or related to the Doctrine of Signatures (formulated in the 17th century by Jacob Bohme, a

follower of Paracelsus), whereby the curative properties of a plant were indicated by a "Divine signature" reflected in the colour, shape or other physical properties of a plant. For example, the yellow hued goldenrod was deemed to be a cure for jaundice, while the liver shaped leaves of liverwort were believed to hold the cure for liver diseases.

Astrology played a major role in the work of Nicolas Culpepper, arguably the author of one of the most famous English herbals. Published in 1653, *The Complete Herbal* incorporated many references to astrology. Culpepper's herbal remained influential throughout the 18th and 19th centuries and can still be found on bookshelves today, albeit with most of the astrological references removed.

The Doctrine of Signatures and the incorporation of astrology into herbalism reflected the religious beliefs of the time, which placed humankind at the centre of the universe. However, the Enlightenment movement of the 18th century provided an environment in which such beliefs could be challenged, particularly when scientific evidence disputed such beliefs. Chemists played a key role in challenging vitalism, the idea that living organisms possess some "vital force" that differentiates them from inorganic matter. The synthesis of urea by Wohler in 1828, acetic acid by Adoph Kolbe in 1845, and a range of organic compounds by Marcellin Berthelot in the 1850s soon removed the idea of vitalism from scientific discussion.

Prior to the 18th century a few effective treatments for disease were in use, e.g., quinine to treat malaria (first documented in 1663) and iron to treat anaemia (first described in the 1640's)), however; their discovery was largely serendipitous. In the 18th and19th centuries, a more scientific approach began to reveal many new treatments for a wide range of diseases.

The first clinical trial

In 1747, the Scottish naval surgeon, James Lind, carried out what is believed to be the first clinical trial to identify a cure for scurvy, a disease responsible for the deaths of thousands of British sailors. Taking 12 sailors suffering from the disease, he divided them into six groups, with five of the groups receiving a different daily supplement to their diet (oranges and a lemon, vinegar, dilute sulfuric acid, a herbal mix) while the sixth served as the control group. The results were clear: only the two sailors who consumed the citrus fruits responded rapidly, one of whom returned to duty after only six days. While it had previously been observed that citrus fruits had a beneficial effect in preventing scurvy, this belief was often extended to all acids. Lind's research was acted on by Captain James Cook in his second voyage, resulting in no scurvy deaths during the three years at sea.

Another physician who introduced a scientific approach to herbalism was Anton von Storck (1731 – 1803), a member of the Viennese aristocracy, and confidant to royalty, who had begun life poor and orphaned. Concerned that only the rich could afford the services of a physician, Storck sought to determine which folk remedies could be used to effectively treat disease. By testing samples on animals and then on himself, Storck studied plants such as hemlock, thorn apple, henbane, monkshood and colchicum corm. He identified monkshood as a diuretic and diaphoretic, and colchicum corm as a treatment for dropsy and pleural effusion. Later, colchicum corm would also be shown to be effective in the treatment of gout.

Folk remedies containing more than one herb could confound the search for effective herbal remedies. In 1775, physician and botanist William Withering was asked his opinion of an herbal tea which was being used to treat dropsy (fluid accumulation associated with heart failure). Examining the various herbs within the tea, Withering suspected that it was the foxglove which was causing an improvement in patients. Testing foxglove on himself, he standardised the doses to determine what would be a safe yet effective dose and then treated 158 patients, with around two thirds responding favourably.

Purification and isolation of therapeutic agents

One of the challenges of working with herbal remedies is their unreliability owing to their compositional complexity and variation. However, by the beginning of the 19th century purification methods, including acid/base extraction and crystallisation, allowed isolation of the active components of various plants with known therapeutic properties. In 1805, Friedrich Wilhelm Serturner published his isolation of an alkaline substance from opium which induced drowsiness when administered to a dog. Further research revealed that this new compound contained carbon, hydrogen, oxygen and nitrogen. When this new research was published in 1817 it drew the attention of prominent French chemist Joseph Gay Lussac who coined the term morphine to describe the new compound and predicted that similar compounds (named alkaloids in 1818) would soon be found. Improvements in purification methods would later reveal that the isolated compound was impure, and it was not until 1831 that morphine was completely purified by Professor William Gregory at the University of Edinburgh.

Other important natural products extracted at that time included emetine, which was purified enough by 1817 to demonstrate its effectiveness in treating amoebic dysentery; and quinine, in 1820. The more reliable (and more palatable) nature of quinine in treating malaria, compared to its parent natural product – powdered cinchona bark, led to great demand for this new product, and by 1826 a factory owned by Pelletier was producing 3600 kg per annum. The success of quinine in treating malaria appears to have been a pivotal point in the shift away from the use of natural products towards pure compounds to treat disease. Morphine also moved into bulk commercial production once the hypodermic syringe was invented in 1853. Thus by the mid 1850s a nascent pharmaceutical industry had been born.

Synthetic drugs

The introduction of coal gas as a source of lighting in the early 1800s provided chemists with an unwanted by-product, coal tar, to experiment with. By 1842, a German gas works chemist, Friedlieb Runge had extracted carbolic acid (phenol) and observed that this new substance could prevent the decay of organic material. This property was exploited by industrial chemist Frederick Calvert who used phenol as a disinfectant and for water purification in the

1850s. In France its use for disinfecting wounds was popularised by physician Jules Lemaire in 1862. However, its use was largely ignored by British surgeons until its use was championed by Joseph Lister, Professor of Surgery at the University of Glasgow.

The caustic nature of phenol led to the search for alternatives. A collaboration between Carl Thiersch, Professor of Surgery and Hermann Kolbe, Professor of Chemistry at Leipzig, resulted in the synthesis of salicylic acid (by the treatment of phenol with carbon dioxide in the presence of sodium) and its subsequent use as an antiseptic. This process was industrialised by 1874, and, thus, salicylic acid became the first drug to be synthesised for medical use.

A further use for salicylic acid was revealed when, on using salicylic acid as an "internal antiseptic" in the treatment of typhoid patients, Carl Buss discovered that it was an effective antipyretic. Salicyclic acid was soon being applied to other diseases, including rheumatic fever, rheumatoid arthritis and gout (owing to its anti-inflammatory properties).

Despite its myriad of applications many patients found salicylic acid irritated the stomach. In 1883, Polish physician and chemist, Marceli Nencki, attempted to solve this by reacting salicylic acid with phenol to form phenyl salicylate. Insoluble in the stomach, it was more soluble in the small intestine where it had a small therapeutic effect.

Further chemical modifications of salicylic acid, carried out by Arthur Eichengrun and Felix Hoffman at the Bayer company in Germany in 1896 resulted in the synthesis of acetylsalicylic acid (aspirin). Although initially rejected as a drug by the company pharmacologist, it eventually underwent clinical trials which demonstrated its impressive analgesic, anti-pyretic and anti-inflammatory properties. By 1899 it was being sold worldwide.

Inorganic compounds as medicines

Many inorganic compounds can either be found in relatively pure form in nature or readily extracted using physical methods. Consequently they have been applied to the treatment of disease throughout history. One prominent promoter of mineral-based treatments was Paracelsus (1493-1541), who rejected many of the herbal remedies of his time in favour of inorganic treatments. Treatments included the use of mercury, arsenic and antimony compounds. While many of these treatments had been discarded by the 18th century, some continued to be used into the 18th, 19th and even the 20th century. Some even proved successful in actually treating disease.

The treatment of iron deficient anaemia (historically described as chlorosis, "green sickness", or "love sickness") with iron compounds has been known since the 17th century; however, it was in 1832 that French physician Pierre Blaud first used ferrous sulphate to successfully treat 30 cases of chlorosis.

Mercury has had a chequered medical history. Believed to be too toxic for medical use by prominent Roman physician, Galen, it was brought into use again in the 15th century, when treatments of the day had proven ineffective against syphilis. In desperation, mercury (in pure and compound forms) was applied to the treatment of syphilis, and later to a wide range of other diseases. Indeed pharmacopoeias from the 1950s can still be found which list ointments containing 30% metallic mercury, and purgatives for children made from mercury and chalk. Various attempts have been made to find less toxic mercury-based cures. Mercurous salts were found to be less corrosive than mercuric salts, and in the late 1880s mercury benzoate, the first organomercurial compounds was developed.

Arsenic compounds have been used since the tenth century when arsenic trioxide was applied to the treatment of cancer of prominent Arab physician and alchemist, Ibn Sina. In 1786, Thomas Fowler developed an alcoholic solution of potassium arsenite for the treatment of malaria. Although the solution proved less reliable than quinine, its use was expanded to other applications, including the treatment of pernicious anaemia. Unfortunately, the rosy cheeks arising from its use were less to do with a cure and more to do with capillary damage resulting from arsenic poisoning. Its use in the treatment of leukaemia proved more interesting. In 1865, Heinrich Lissauer used Fowler's Solution (1% KH_2AsO_3) to successfully (albeit temporarily – she died five months after being discharged from hospital) treat a young women with acute leukaemia. The use of Fowler's Solution for the treatment of leukaemia persisted into the 20th century, and it was used in the 1990s in China to successfully treat acute promyelocytic leukaemia, an approach which was approved for use in the USA by the FDA in 2001.

In 1863, Antoine Bechamp prepared the sodium salt of the meta-anilide of phenylarsonic acid and this compound was initially used as a treatment for skin diseases. However, in 1905 it was discovered that this compound killed the trypanosomes which caused sleeping sickness, and although it proved to be too toxic for use, its effectiveness convinced immunologist Paul Ehrlich to research analogues as potential chemotherapeutics. One of the results would be arsphenamine (Salvarsan), a potent anti-syphilitic which entered production at the end of 1910.

The time which would elapse between the identification of a new substance and its incorporation into medicine was often fairly short. Many physicians would often experiment on themselves (unlike the ancient Greeks who would experiment and often poison hapless slaves). Bismuth had often been confused with tin, lead and antimony throughout history; however, in 1753, French nobleman, Claude Geoffrey the Younger, identified bismuth as a unique substance. Within a few years various salts of uncertain composition were being applied to medicine. In 1857, bismuth subcarbonate [$(BiO)_2(CO_3)$] was used as an antacid. Bismuth subsalicylate is one of the components of modern Pepto-Bismol antacid treatments.

Magnesium sulfate was a favoured purgative in England in the 18th and 19th century. Isolated from the mineral waters of Epsom, a spa town at the time, it became known as Epsom salts. Other salts soon entered the market as antacids and purgatives, including magnesium carbonate and magnesium oxide, as well as hydrated sodium sulfate (known as Glauber's salt after Johann Glauber who isolated it from a Viennese spring).

Iodine was isolated from seaweed by Bernard Courtois in 1811. Samples of his volatile purple crystals were passed on through friends to Joseph Louis Gay Lussac, and also to Humphrey Davy.[1] Both quickly realised that it was an element similar to chlorine and rushed to lay claim to the discovery, publishing their conclusions within one day of each other, which resulted in much argument over who had made the discovery first.

By 1820, iodine was being used by Francois Coindet as a treatment for goitre. Observing that one of the natural remedies for goitre was burnt sea sponge, Coindet concluded that the active ingredient was likely to be iodine. Unfortunately, overdosing of his patients led to toxicity, and this, as well as the treatment's limited ability to treat patients with chronic goitre, led to its initial abandonment as a treatment for goitre.

Iodine was also applied to the treatment of a range of other diseases including tuberculosis, often in the form of Lugol's iodine (a 2:1 aqueous solution of potassium iodine and iodine) developed by Jean Lugol in 1829. Iodoform, synthesised by G.S. Srullas in 1822, was also used for the treatment of goitre by physician Robert Glover in 1847.

Iodine solutions were used in 1839 by J. Davies, a Hertford physician, to disinfect wounds. Although such solutions were used in the American Civil War, they were not widely applied until research by French bacteriologist Casimir Davaine in the 1870s showed that iodine solutions could kill a wide range of organisms.

Potassium bromide was first introduced into the British Pharmacopoeia in 1836, after claims that it had been successfully used to treat enlargement of the spleen. In 1857, its use as a treatment for epilepsy was described by obstetrician Sir Charles Locock. At the time, the prevalent view was that epilepsy was due to masturbation. Having read that lithium bromide could suppress the libido, Locock supposed it would be an effective treatment for epilepsy. Despite the faulty reasoning, lithium bromide proved to be an effective treatment for epilepsy, as well as being used as a sedative.

Chemistry and microbes

Elemental chlorine was first prepared and studied in 1774 by Carl Wilhelm Scheele, who mistakenly identified it as an oxide rather than an element. Within 20 years, an aqueous solution was being used as a disinfectant and for purifying water, and by the middle of the 19th century hypochlorite solutions were in common use as disinfectants.

Despite the success of such solutions as disinfectants, the medical fraternity resisted suggestions that without these solutions, they were infecting their patients with some type of "putrid particle". Both Oliver Wendell Holmes in Boston (1843) and Ignaz Semmelweis in Vienna (1847) suffered the derision of their medical colleagues when they suggested that they should wash their hands with chloride of lime (calcium hypochorite) between post-mortem examinations and dealing with patients. At the time, it was believed that infection resulted from miasma, or exposure to "bad airs".

In the 1860s Louis Pasteur published his germ theory, observing that chemical solutions could kill the infectious agent. This was applied by Joseph Lister in his use of carbolic acid (phenol) solutions to spray surgical equipment, dressings and the patient. Rates of infection dropped dramatically.

While chemistry had provided the means to kill micro-organisms, it also proved important in better understanding the structure of micro-organisms. Stains and dyes, which were first utilised in the 1870s, revealed the complex structures of the cells of microorganisms. Paul Ehrlich played a key role in the development of staining and made many important discoveries, including the identification of mast cells and a urine test to identify typhoid. Later, at the beginning of the 20th century, Ehrlich also realised that some dyes possessed the ability to kill microorganisms, and began to study their use as chemotherapeutics. As mentioned previously, this research eventually led to the synthesis of salvarsan in 1910, the first effective drug for the treatment of syphilis.

Post-1900 chemistry and medicine

By the end of the 19th century many of the theoretical foundations of modern chemistry and medicine had been laid. Therapeutic agents had been isolated from various sources, purified, quantified, tested and applied to various diseases, and the first successful attempts at the synthesis of drugs had been made. Chemistry was no longer an offshoot of medicine but a fully developed science in its own right, and was already dividing into various specialities of its own (e.g., analytical, organic, inorganic, etc.).

In the 20th century, chemists would rapidly expand on the knowledge gained during the previous two centuries. More complex drug molecules would be synthesised and the pharmaceutical industry would grow into a multi-billion dollar enterprise. The development of chromatography, mass spectrometry, nuclear magnetic resonance and other analytical techniques would reveal and identify millions of new compounds, some of which were suitable for therapeutic use.

In medicine, the discovery of DNA would bring a better understanding of diseases we now know have a genetic cause, and following the Second World War, the United States would start another war, this time on cancer. The consequences of environmental contamination would also reveal new diseases resulting from careless disregard for the effect new compounds can have on our surroundings.

Afterword

This article includes information derived from various books on the history of chemistry.[1-4]

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