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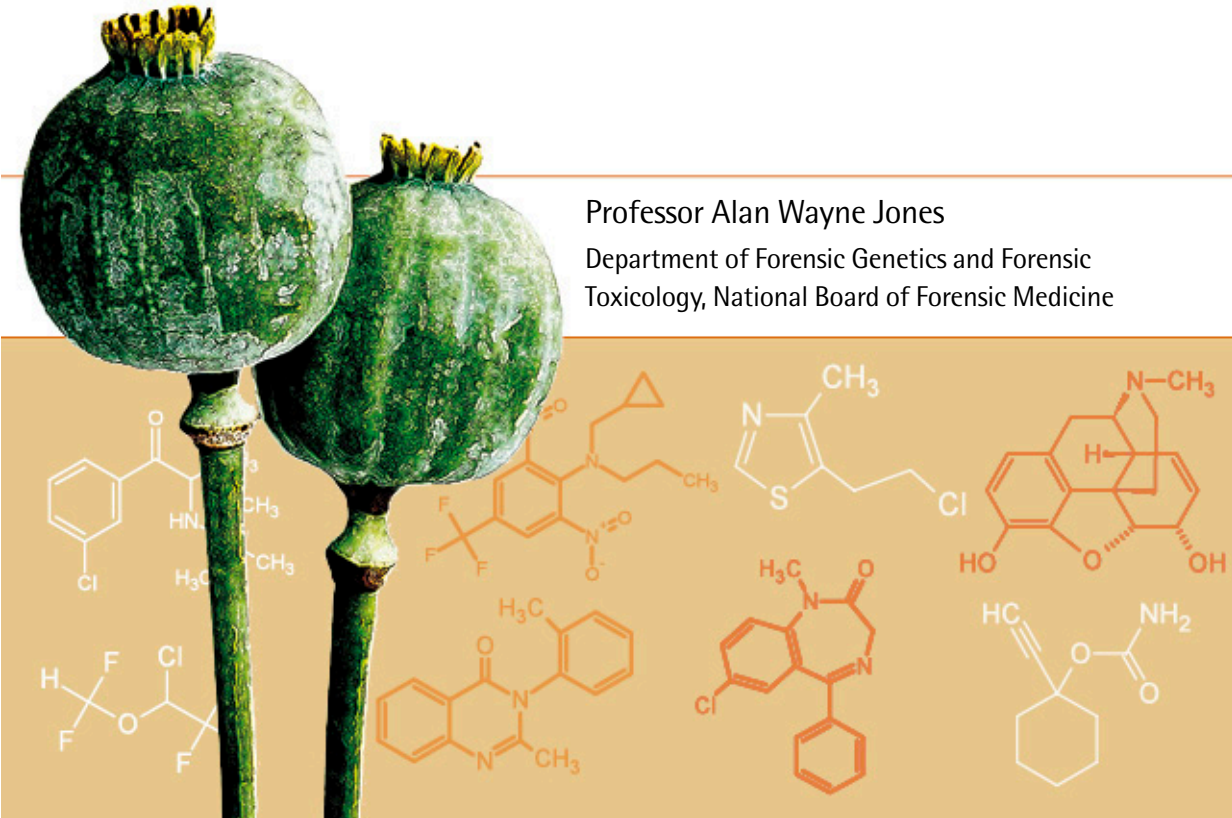
Perspectives in Drug Discovery

A Collection of Essays on the History and Development of Pharmaceutical Substances



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Preface

This collection of short essays deal with the history of drug discovery and covers a wide range of pharmaceutical substances, including prescription medication as well as illicit recreational drugs of abuse. Consideration was also given to the plethora of drugs encountered in routine forensic casework, especially in traffic crimes, such as driving under the influence of drugs (DUID) and in post-mortem toxicology when drug poisoning deaths are investigated. The essays were written over a number of years and reflect to a large extent my own interests and reading about the history of pharmacology and toxicology of drugs. Background information about the chemistry and pharmacology of many of the most commonly encountered drugs and poisons is presented and this should prove useful in the training of newly recruited staff as well as students starting their studies in pharmacology and toxicology. One aim of the essays was to highlight the human side of pharmacology in medicine by providing details about the scientists who are credited with making the crucial observation when a new therapeutic agent was discovered. Another aim was to highlight the role of serendipity in drug discovery. Abbreviated versions of the essays are scheduled to appear in consecutive issues of the bulletin of The International Association of Forensic Toxicologists (TIAFT).

For those who might be interested in a more in-depth coverage of this subject the book by Walter Sneader entitled *"Drug discovery – a history"* is highly recommended. Sneader's book has received excellent reviews and represents the best single reference source on the subject of drug discovery. It traces the development of drugs and medication from antiquity until the present day. Chemical structures are provided for most of the drugs discussed along with many interesting anecdotes about the individuals involved – chemists, physi-

cians and pharmacologists – and key events in their quest to discover new and improved therapeutic agents. Another excellent and highly recommended text is the book entitled *"Pharmaceutical achievers"* produced by the Chemical Heritage Foundation in Philadelphia. Of particular note to historians of science is the fact that this book also contains many photographs and biosketches of the men and women who made the discoveries.

The essays are collected together here to make them more easily available and are published in book-form thanks to support from the Swedish National Board of Forensic Medicine (Rättsmedicinalverket, RMV). Hopefully these essays will be of interest to colleagues within various branches of the RMV organisation who specialise in forensic psychiatry, forensic genetics, forensic medicine and especially forensic toxicology.

Linköping 2010-10-01
A.W. Jones
Perspectives in Drug Discovery

Introduction

The word drug is probably of Arabic origin and appeared in Old German as drög, which referred to a powder and, indeed, the first pharmaceuticals were obtained from the vegetable kingdom as the dried parts of plants, herbs and shrubs. According to Wikipedia etymology of the word drug is the Old French word drogue or the Dutch word droog, both of which refer to dry barrels that contained herbs.

Nature has provided a rich source of naturally occurring chemical substances, many of which are pharmacologically active and are contained in or produced by various plants, herbs, shrubs, fungi, insects and reptiles. The influence of these xenobiotics, both positive and negative, was no doubt experienced by early humans in their quest for food and survival. Many of the toxins produced by plants, insects and reptiles were the defence mechanism by which they avoided being eaten by predators and these substances have therefore been around since the dawn of history. Some such herbal medicines have proven useful to relieve man's suffering, to heal wounds, to alleviate pain and fever and to treat all types of maladies.

A host of mineral, plant and animal products were mentioned in the famous Egyptian Ebers papyrus, named after the German Egyptologist Georg Ebers, who acquired it in 1872. This remarkable 110-page scroll, which is about 20 meters long, presents a detailed record of remedies and cures used in Ancient Egypt, dating back to ~1500 B.C., to treat the medical complaints and suffering of that time. In all about 700 drugs and 800 prescriptions and purported cures are referenced, not only herbs and shrubs but also mineral and animal products, which were mixed together in various ways for treatment of a host of medical problems of the day. This early record obviously had

a strong influence on future civilisations when medical knowledge about herbal drugs became more organized. This is particularly evident among Greek, Roman, and Indian cultures, as well as traditional Chinese medicine.

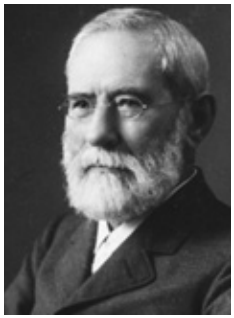
Examples of drugs derived from plants include morphine from the opium poppy, nicotine from the tobacco plant, cannabinoids from cannabis leaves, caffeine from tea, digitoxin from woolly foxglove, quinine from the cinchona tree and salicylates from the bark of the white willow tree. Early hunters learnt the trick of spiking their darts and arrows with plant toxins (poisons), such as curare to kill or stupefy wild animals. In fact the word toxicology derives from the Greek *toxikos*, which meant a bow for shooting arrows. Other psychoactive substances from the ancient world were popular in some cultures, such as cocaine from coca leaves, psilocybin from mushrooms, mescaline from the peyote cactus, to name just a few. However, the isolation and characterization of the active principles of medicinal plants had to await advances in chemistry and pharmacology during the 19th and 20th centuries, when methods for extraction and purification were refined so that the chemical substances were obtained in relatively pure form.

Page from the Ebers papyrus which dates from ~1500 BC.

Apothecaries probably represent the first pharmaceutical chemists, who among other things dispensed mixtures of herbal products and other concoctions in the hope of finding a cure for the ailments that inflicted their customers or the disease they were suffering from. Foremost among the early apothecaries was the Swede Carl Wilhelm Scheele (1742-1786), who is known and admired by all historians of chemistry as a veritable pioneer. Also from Sweden the physician and chemist Jöns Jacob Berzelius (1779-1848), born in the vicinity of Linköping, made immense contributions to analytical chemistry and also wrote the first book on animal (physiological) chemistry. In the mid-1800s Germany began to dominate in the field of organic chemistry with

such luminaries as Friedrich Wöhler (1800-1882), famed for the synthesis of urea *"without the help of a kidney"* simply by heating ammonium cyanate. A contemporary of Wöhler, close friend and sometimes scientific rival was Justus von Liebig (1803-1873), whose chemical discoveries became legend and he is considered by many as the founding father of organic chemistry.

Rudolf Buchheim (1820-1879).



Oswald Schmiedeberg (1838-1921).

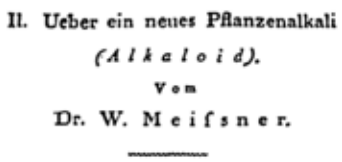
Louis Lewin (1850-1929).

The subject of pharmacology (Materia Medica) was established as a scientific discipline in the 19th century thanks to the efforts of scientists from German speaking countries, among others Rudolf Buchheim (1820-1879), Oswald Schmiedeberg (1838-1921), Paul Ehrlich (1854-1915) and the toxicologist Louis Lewin (1850-1929). Studies in the field of forensic pharmacology and toxicology would not be complete without some knowledge about the history of drug discovery, the various personalities involved and the events leading to the development and introduction of new therapeutic agents. Hopefully this series of perspectives in drug discovery will interest forensic toxicologists and, in this connection, it is perhaps worth paraphrasing the great French chemist and microbiologist Louis Pasteur (1822-1895):

> *"It is by reading what discoverers have done that*
> *we lift and maintain the sacred flame of discovery."*

The discovery of alkaloids, a word coined in 1819 by the German chemist Carl F Wilhelm Meissner (1792-1853) played a prominent role in the development of forensic toxicology as a scientific discipline. Many of these nitro-

gen-containing bitter-tasting (alkaline) substances produced by plants are deadly poisons when they exist in a pure state. These natural products were subsequently used to commit murder by poisoning in many well-publicised cases. The analysis and identification of alkaloids in body organs and tissues was a daunting challenge, owing to their complex chemical properties and the difficulties in extracting them from biological material. Without being able to identify a poison in the body it was not possible to prove its use in the crime of murder.



II. Ueber ein neues Pflanzenalkali
(Alkaloid).
Vom
Dr. W. Meissner.

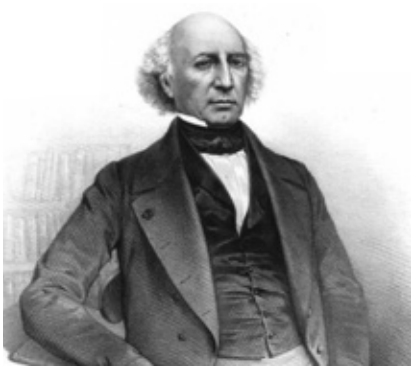
Journal für Chemie und Physik, vol. 25, pp. 377-381, 1819,

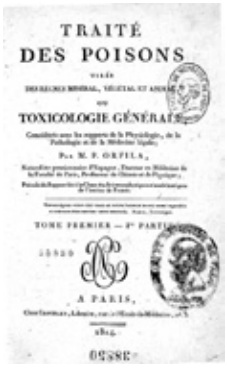
"In general, it seems appropriate to me to impose on the known plant substances not the name "alkalis" but "alkaloids", since they differ greatly in some properties from the alkalis; among the chapters of plant chemistry, they would therefore find their place before plant acids [since "Alkaloid" would precede "Säure" (acid)."

Many analytical chemists in the second half of the nineteenth century strived to develop methods permitting the analysis and identification of alkaloids in body organs and tissues. Some of these individuals became pioneers in forensic toxicology; Mathieu JB Orfila (1787-1853) in France, Jean-Servais Stas (1813-1881) in Belgium and Robert Christison (1797-1882) from Scotland and Alfred Swaine Taylor (1806-1880) from London, UK.

Examples of alkaloids and natural toxins and their botanical plant origin include morphine (papaver somniferum), LSD (ergot fungus), emetine (cephaelis ipecacuanha) strychnine (strychnos nux-vomica), physostigmine (calabar beans), scopolamine (scopolla camiolica), atropine (atropa belladona), ricinine (castor oil beans), and coniine (spotted hemlock).

This collection of short essays about drug discovery highlights the importance of pharmacologically active substances obtained from plants, roots, vines and barks and also the role of chance observation and serendipity. These accounts have been written as a general introduction to the chemistry and pharmacology of pharmaceutical substances. The essays are subdivided into various drug families and information is given about some of the pioneer workers in this field.





Mathieu JB Orfila and his seminal work on poisons from 1814.

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1 The First Sedative-hypnotics

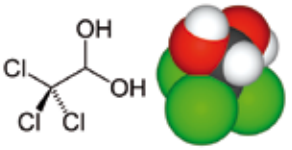
Sedative drugs slow activity in the central nervous system - apply brakes on the brain - and the first substance used by humans with this pharmacological effect was probably alcohol (ethanol), closely followed by opium. Alcohol is not a naturally occurring substance but is easily produced by fermentation of the carbohydrates contained in many fruits and berries when these come into contact with yeast or other micro-organism under appropriate conditions of temperature and time. However, the low solubility of ethanol in lipids and the high solubility in water meant that massive amounts must be ingested to bring about stupor and narcosis.

The modern era of drug discovery has its roots in the 1800s and coincided with major advances in knowledge about animal chemistry as evidenced by the research and writings by European chemists, such as Jöns Jacob Berzelius, Friedrich Wöhler and Justus von Liebeg. As a typical example, Liebig synthesized chloroform ($CHCl_3$) in 1831 and the anesthetic properties were discovered in 1847 when James Young Simpson (1811-1870) first used chloroform to deaden pain in obstetrics, such as during child birth. Liebig (1803-1872) also prepared chloral hydrate in 1832 and showed that in alkaline solution it was converted into chloroform and formic acid. This prompted the physician and pharmacologist Oscar Liebreich (1839-1908) to test whether the same reaction might work in-vivo, which would mean that chloral hydrate might also function as an anesthetic in the same way as chloroform. Administration of chloral hydrate to animals did indeed produce a deep sleep, but without the loss of pain sensation. Later experiments showed that chloral hydrate was a relatively safe sedative-hypnotic drug for use in humans and it became available for treatment in 1869 and remains in use today in some circumstances.

Later work showed that the sleep-producing properties of chloral hydrate had nothing to do with chloroform but instead depended on a metabolite trichloroethanol (CCl_3CH_2OH). After ingestion chloral hydrate is quickly

hydrolyzed in the stomach to trichloracetaldehyde (chloral), which is then reduced to trichlorethanol by the hepatic enzyme alcohol dehydrogenase (ADH). The trichlorethanol (half-life 6-10 h) forms two pharmacologically inactive metabolites, one produced by oxidation to trichloracetic acid and the other by conjugation with glucuronic acid to give urochloralic acid, which is the main urinary excretion product.

Chloral hydrate (Noctec®) was heralded as the first safe hypnotic drug and was taken in liquid form thus having an advantage for treatment of children or geriatric patients, who might have difficulties in swallowing tablets. Chloral hydrate is dangerous to use together with alcohol and other sedatives and a number of deaths have occurred, fairly recently in 2007 when the Playboy model Anna Nicole Smith (1967-2007) was found dead in the bedroom of her hotel in Florida after poly-pharmacy including a high concentration of trichlorethanol in blood. Furthermore, the Hollywood sex-symbol movie-star Marilyn Monroe (1926-1962) overdosed with a combination of alcohol, chloral hydrate and a barbiturate.



Structural formula and space filling model of chloral hydrate, synthesized by Justus von Liebig in 1832.


CHLORALHYDRAT

Title page from Oscar Liebreich's 1869 monograph on chloral hydrate.

Anna Nicole Smith (1967-2007) died of a mixed drug overdose, which included chloral hydrate.

In the quest to discover safer and more effective sedative drugs many derivatives of chloral hydrate were prepared but none proved better than chloral hydrate itself. The potency of chloral hydrate as a sedative is thought to be enhanced if taken together with ethanol. Such a mixture is commonly re-

ferred to as knock-out drops or a Mickey Finn, after a Chicago bar owner who drugged his customers before robbing them, hence the term slipping a Mickey. This example of a drug-alcohol interaction has interesting pharmacokinetic and pharmacodynamic mechanisms.

During oxidative metabolism of ethanol to acetaldehyde in the liver, the coenzyme NAD^+ is reduced to NADH and the elevated ratio of NADH to NAD^+ in the hepatocytes promotes reduction of chloral to trichlorethanol. Both ethanol and trichloroethanol are agonists for the $GABA_A$ receptor complex opening a chloride ion-channel to cause depression of the central nervous system, which accounts for the potential pharmacodynamic interaction between these drugs.

Examples of other early synthetic drugs used as sedatives were bromides, paraldehyde, urethane, chloral ammonia, sulphonal and diethylacetylurea although they offered no special advantage over chloral hydrate. At the turn of the century (1902) the first pharmacologically active barbiturate drug was synthesized (Veronal®) followed by a large number of congeners, which swiftly dominated the market as sleeping aids. Overdosing with barbiturates and interaction with other drugs, especially alcohol, became a major problem with many overdose deaths being recorded both accidental and with suicidal intent.

It took another 50 years before safer medication appeared on the market to compete with the barbiturates as sedative-hypnotics. Well-known examples include glutethimide (1952) trade name Doriden® followed in quick succession by methaqualone (Sopor® 1956), chlormethiazole (Heminevrin® 1957), ethchlorvynol (Placidyl® 1955) and not least the minor tranquilizer meprobamate (Miltown® 1955). The latter drug owes much to the efforts of Frank M Berger (1913-2008) and meprobamate combined both sedative and muscle relaxant properties, hence the drug company slogan *"relaxes both mind and body"*. Today's analytical toxicologists usually encounter meprobamate as a metabolite of carisoprodol (Soma®), a well-known skeletal muscle relaxant and a drug which is also subject to abuse. These older sedatives and tranquilizers became more or less redundant when Hoffmann-La Roche introduced the first benzodiazepines (Librium® and Valium®) in the early 1960s.

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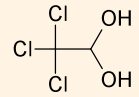
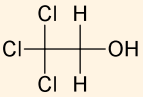
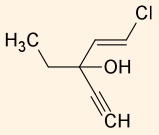
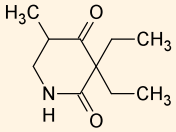
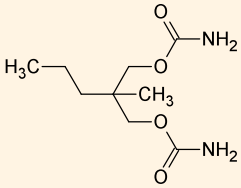
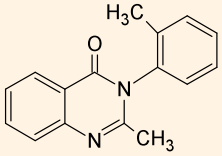
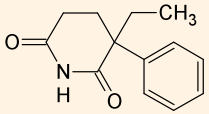
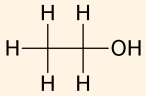
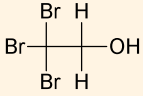
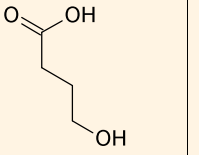
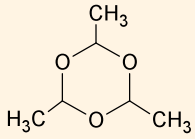
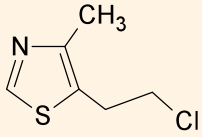
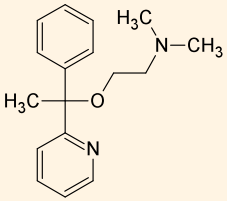
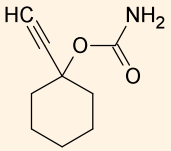
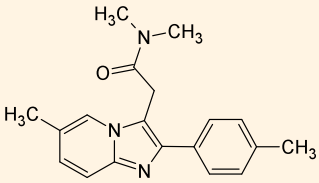
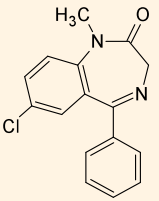
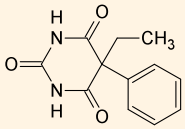
Diverse chemical structures of sedative-hypnotic drugs

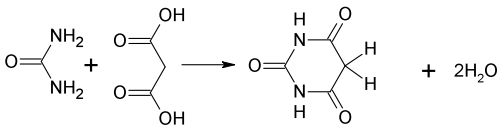
 Chloral Hydrate	 Trichlorethanol	 Ethchlorvynol	 Methyprylon
 Meprobamate		 Methaqualone	 Glutethimide
 Ethanol	 Tribromoethanol	 Gammahydroxybutyrate	 Paraldehyde
 Chlormethiazole		 Doxylamine	 Ethinamate
 Zolpidem		 Diazepam	 Phenobarbital

2 The Barbiturates

The pharmaceutical industry has its roots in the production of synthetic dyes based on the rich source of aromatic chemicals derived from distillation of coal and the coal-tar industry. A close collaboration developed between academic scientists working at the German universities and industrial organizations interested in chemicals and this led to the training and recruitment of a new breed of organic chemists. These individuals played a key role in the creation and successes of many of the first pharmaceutical companies, such as Hoechst and Bayer in Germany and Sandoz and Ciba in Switzerland. The discovery of barbiturates, a purely synthetic and highly versatile group of drugs, provides a good example of the collaboration between organic chemists, pharmacologists and funding from the pharmaceutical industry.

Soporifics (substances that cause or induce profound sleep) were limited to alcohol and opium until 1869 when chloral hydrate was discovered and used as the first sedative and hypnotic drug. Urethane, bromides, and sulphones came shortly afterwards, but these were made more or less obsolete when the barbiturates emerged in the first decade of the 1900s.

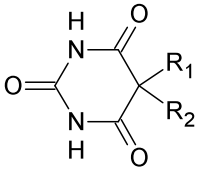
The parent compound of the barbiturates (barbituric acid) was synthesised in 1864 by Adolph von Baeyer (1835-1917), who, incidentally, was later awarded the Nobel Prize in chemistry (1905) for his many contributions to organic chemistry and particularly the chemistry of indigo dyes. During work for his thesis (Habilitation) aged just 28 years, von Baeyer prepared various derivatives of uric acid, a naturally occurring substance of considerable interest at the time. In a simple condensation reaction with urea (an animal waste product) and malonic acid (an acid derived from apples), von Baeyer synthesized malonylurea, which he christened barbituric acid.



There are several stories about the origin of the name barbituric acid. According to one version, von Baeyer and his associates visited a tavern on December 4th to celebrate the preparation of this new compound. That same day the town's artillery garrison was celebrating Saint Barbara, the patron saint of artillerists. During the festivities, von Baeyer socialized with some of the artillery officers and is allegedly said to have proposed a toast to St Barbara and announced that his new compound would be christened *"barbituric acid"* thus amalgamating barbara (after St. Barbara) and urea one of the starting compounds. However, a more romantic version claims that von Baeyer was dating a girl named Barbara at the time of his synthesis and to show his affections he named the new compound after her, thus combining Barbara with urea to give barbituric acid.

Later studies showed that barbituric acid (pKa = 4.12) was poorly absorbed from the gut and lacked any pharmacologically activity. However, 5,5-substitution of two hydrogen atoms in the pyrimidine ring with various alkyl, aryl or aromatic groups gave a series of compounds with higher pKa (less acid). The replacement of hydrogen atoms with alkyl groups in the ring made the molecule more lipid-soluble so that absorption from the gut was easier. The molecule was also less ionized at physiological pH (7.35) and more lipophilic making it easier to cross the blood-brain barrier.

At the turn of the century Josef von Mering (1849-1908), a German physician and pharmacologist, who is credited with many important discoveries, including demonstrating the role of the pancreas in controlling blood-sugar level was interested in finding an alternative sedative-hypnotic to chloral hydrate. From experience and knowledge of the chemistry of sulphonal it occurred to von Mering that a key structural feature for sedative properties was two ethyl groups joined to the same carbon atom. This led him to prepare diethyl acetylurea and soon afterwards 5,5-diethylbarbituric acid, which was pharmacologically active and produced sedation and sleep when tested on dogs.



General formula for a 5,5-substituted barbiturate.

Because Josef von Mering was a pharmacologist and medical doctor and not a trained chemist he considered it necessary to consult the doyen of German organic chemistry at the time, namely Emil Fisher (1852-1919). He asked Fisher to verify the correct structure of his new compound and to check its purity and chemical properties. Incidentally, Emil Fisher, who began his career as a student of von Baeyer also received a Nobel Prize in chemistry in 1902 for, among other things, his work in the field of carbohydrate chemistry. Fisher doubted the correctness of the proposed structure of the compound given to him by von Mering so together with his students he repeated the work and synthesised diethylmalonylurea. Results of pharmacological testing showed that Fisher's product was more potent than the compound given to him by von Mering.

In the article describing their work with the diethyl derivative of barbituric acid Fisher remarked *"the chemical name of the compound is cumbersome and we suggest for it the name Veronal"*. The name Veronal was said to come from the Latin word *verus*, which means true and implied that the synthesis by Fisher and his students was the true substance. Another account claims that Veronal was named after the Italian city of Verona where von Mering was visiting at the time of Fisher's synthesis. Verona was considered a very peaceful (tranquil) place, which prompted von Mering to suggest the name Veronal for the new sedative drug. Fisher went on to patent the name barbital in 1903, which constituted a landmark in drug discovery and pharmacotherapy for insomnia and other disorders.

Adolf von Baeyer (1835-1917).

Emil Fisher (1852-1919).

Josef von Mering (1849-1908).

Fisher and von Mering (1903) in their joint publication reached the following conclusions about the hypnotic properties of diethylmalonylurea (Veronal).

"Veronal administered in solution requires approximately 30 min to act, and it is best to dissolve the powdered compound by stirring it into a cup of hot tea. Most people are also quite willing to take Vernal in solid form with or without a wafer. The chemical observations made so far show no unwelcome side-effects. Whether the prolonged and extensive use of Veronal causes side-effects must be decided by further therapeutic investigations. The outcome of our experiments is such that we do not hesitate to offer Veronal to clinicians and physicians for therapy trials in cases of sleeplessness,"

Veronal represented the first of a large number of derivatives of barbituric acid many of which were registered and marketed as therapeutic agents with different inherent potency, elimination half-lives and with a short or long duration of action. These many derivatives of barbituric acid found usefulness as anticonvulsants, sedative-hypnotics and short-acting anesthetic agents. Long acting barbiturates were used for the treatment of convulsions (e.g. phenobarbital), short acting barbiturates for treatment of insomnia, as exemplified by pentobarbital and secobarbital and ultra-short acting barbiturate drugs as pre-operative intravenous anesthetics, such as thiopental.

Not long after barbiturate drugs became widely prescribed a number of problems arose when they were found to be both toxic in overdose and dependence producing. Moreover, the repeated administration of barbiturates led to the induction of cytochrome P450 enzymes in the liver increasing the rate of metabolism of the barbiturate and even co-administered drugs that shared the same microsomal oxidative enzymes. The barbiturate drugs had a strong abuse liability and after long-term use some people became dependent on their medication. Abrupt withdrawal led to dangerous physiological disturbances that sometimes proved fatal. When barbiturate-like drugs were used as sleeping-aids there was a narrow margin between a therapeutic dose and a lethal dose. Overdosing with barbiturates, either alone or mixed with alcohol, was a common method of suicide. The pop star Jimi Hendrix (1943-1970) died from asphyxia when he inhaled vomit after a night of heavy drinking and using a prescription sleeping aid (Vesparax®), which contains a

mixture of two barbiturates, namely brallobarbital and secobarbital as well as some hydroxyzine.

Jimi Hendrix (1943-1970).

Prescription sleeping aid taken by Hendrix.

The barbiturate family of drugs, without any shadow of doubt, represented a major advance in pharmacotherapy and some members of the group are still available today as anticonvulsants (phenobarbital) and as an induction anaesthetic agent (e.g. thiopental). Thiopental is also one of a cocktail of drugs used for capital punishment by lethal injection. The methods developed for the extraction, identification and quantitative analysis of barbiturates in blood and liver tissue belong to classic procedures in analytical and forensic toxicology.

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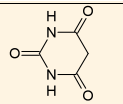
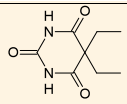
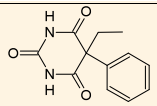
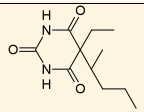
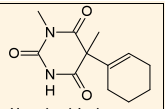
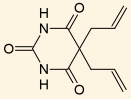
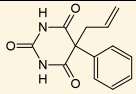
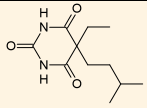
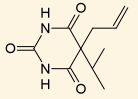
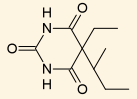
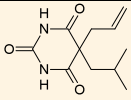
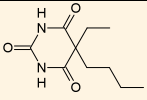
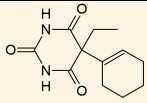
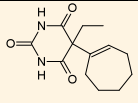
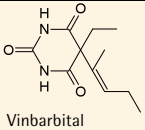
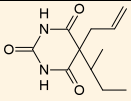
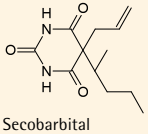
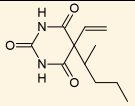
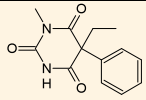
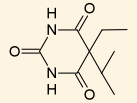
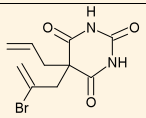
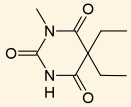
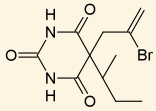
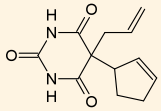
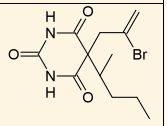
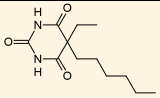
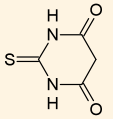
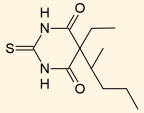
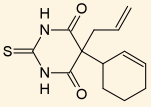
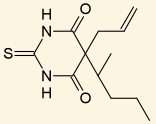
Chemical structure, generic and trade names of derivatives of barbituric acid

 Barbituric acid (malonylurea)	 Barbital Veronal®	 Phenobarbital Luminal®	 Pentobarbital Nembutal®	 Hexobarbital Hexanal ®
 Allobarbital Dial®	 Alpheal	 Amobarbital Amytal®	 Aprobarbital Alurate®	 Butabarbital Butisol ®
 Butalbital Sandoptal®	 Butethal Neonal®	 Cyclobarbital Phanodorn®	 Hepatabarbital Medomin®	 Vinbarbital Delvinal®
 Talbutal Lotusate®	 Secobarbital Seconal®	 Vinylbital	 Mephobarbital Mebaral®	 Probarbital Ipral®
 Brallobarbitall Ves parax®	 Methabarbital Gemonil®	 Butallylonal Pernoston®	 Cyclopentabarbital Cyclopal®	 Sigmodal Rectidon®
 Hexethal Ortal®	 Thiobarbituric acid	 Thiopental Pentothal®	 Thialbarbital Kemithal®	 Thiamylal Surital®

3 The Benzodiazepines

Few stories in the history of pharmaceutical chemistry can compare with the discovery of the benzodiazepine class of drugs, both in terms of usefulness as therapeutic agents and also worldwide sales and profits for the industry. The starting point was Nutley (New Jersey) in the early 1950s, where the Swiss pharmaceutical company Hoffmann-La Roche had its US subsidiary. The parent company, located in Basel, Switzerland, was concerned about the threat of a Nazi invasion during WW2 and in this connection decided to evacuate vulnerable employees, including the organic chemist Leo H Sternbach (1908-2005), to work in Nutley, New Jersey, USA.

Leo Sternbach had studied chemistry in Krakow, Poland where he first obtained his PhD in 1931 and then followed this with postdoctoral research working on the development of quinazoline dyes. The political unrest in Poland forced him to move to the neutral Switzerland arriving there in 1938. He obtained a job as an organic chemist first at the Technical High School in Zurich before joining the pharmaceutical company Hoffmann-La Roche. During his long career Sternbach helped to develop many successful therapeutic products and his name appears on 241 patents and 122 scientific publications.

In the mid-1950s many pharmaceutical companies, including Hoffmann-La Roche, were interested in the new discipline of psychopharmacology and the development of drugs to treat various psychiatric disorders, such as anxiety. This coincided with new knowledge about chemical neurotransmission and the behavioural effects of drugs on the brain and pharmaceutical companies were eager to find a lucrative new product. In 1954 Roche made a strategic decision to develop new tranquilizer drugs and Leo Sternbach was one of the chemists assigned to this project. He chose as starting material a compound having a fused heterocyclic ring structure, which he mistakenly thought was a heptoxdiazine but was later shown to contain a quinazoline

ring. From his time in Poland, Sternbach knew that these compounds could be prepared in good yield and that they gave nice derivatives in a suitable crystalline form.

With a combination of hard-work, trial and error, and serendipity, Sternbach and his team stumbled upon a completely new class of anxiolytic drugs, known as the benzodiazepines. The first compounds synthesised and sent for pharmacological testing proved to be disappointing and Dr. Lowell Randall (1911-2005), the company pharmacologist, reported that they lacked any biological activity or were no better than currently available tranquilizer drugs, such as meprobamate (Miltown®). Under pressure from senior management to embark on more promising work Sternbach began a clean-up of his laboratory and in the process an assistant prompted him to submit one last compound (RO 5-690) for pharmacological testing.

Leo H Sternbach (1908-2005).

Advert for Librium® from the word equi-LIBRIUM.

Mother's little helper an early advert for Valium.

Lead article from 2002 Time Magazine on anxiety.

The results from use of a battery of animal tests for anti-anxiety properties showed that RO 5-690 faired very well compared with meprobamate, chlorpromazine and phenobarbital. In particular, RO 5-690 had superior anticonvulsant properties and also possessed interesting sedative effects. More detailed work on the chemical structure of RO 5-690, including UV and IR spectra, showed that it did not match that expected for a quinazoline N-oxide. Seemingly, the molecule had undergone a ring expansion when treated with methyl amine as a stabilizing agent producing the corresponding 7-membered benzodiazepine N-oxide. The generic name given to RO 5-690 was chlordiazepoxide, better known throughout the world by its trade name Librium® derived from the second syllable in equi-LIBRIUM (in balance). Librium® was approved and registered as a prescription drug in 1960 repre-

senting the first member in a new family of benzodiazepine-type drugs many of which are still widely prescribed today, 50 years later.

Further tests with Librium® showed that it was relatively non-toxic, orally active and had an acceptable pharmacokinetic profile. The sales of Librium escalated and Sternbach and his team immediately began to synthesize a range of closely related benzodiazepine drugs. Within a few months Leo Sternbach and his fellow chemists produced an even greater success story when they synthesized the more potent anti-anxiety agent and blockbuster drug diazepam (Valium®). This was marketed by Hoffmann-La Roche in 1963 and even today represents one of the most prescribed medications for treatment of anxiety and other mood disorders.

Few if any drugs in the arsenal of therapeutics have made such an immediate and long-lasting impact on society as the benzodiazepines, which were widely prescribed as anti-anxiety agents, sedative-hypnotics and anticonvulsants. The major advantage over barbiturates was the much lower risk of toxicity in overdose, although prolonged use of benzodiazepines led to abuse and dependence in some pre-disposed individuals.

The site and mechanism of action of sedative-hypnotic drugs, including benzodiazepines and barbiturates, is the brain's major inhibitory neurotransmitter, namely gamma-aminobutyric acid, especially the $GABA_A$ receptor subtype. When an agonist drug binds to the receptor, this promotes the opening of a chloride ion-channel and negatively charged Cl^- ions flow into the adjacent neuron. The chloride ion lowers the resting potential (hyperpolarization) in the cell and decreases overall neuronal functioning thereby slowing-down or applying brakes on the brain.

Skillful marketing by Hoffmann-La Roche, much aided by the news media, propelled Valium® (derived from the Latin word for healthy) to became the most widely prescribed drug lasting for two decades (1962-1982). TV programs, talk-show hosts as well as film personalities openly admitted taking tranquilizers and many magazines wrote about the *"age of anxiety"* and popular music songs contained reference to Valium as *"mother's little helper"*. Today benzodiazepine drugs still hold a prominent place in the pharmacopeia as anxiolytics (diazepam), for panic attacks (alprazolam), insomnia (temazepam

or flunitrazepam) and as anticonvulsants (clonazepam). Benzodiazepines, such as diazepam or lorazepam, are also administered to alcoholics during withdrawal to relieve dangerous seizures that might prove life-threatening. Indeed, Valium® is sometimes referred to as dry alcohol, which gives a hint to the similarity in pharmacological effects and mode of action at the GABA inhibitory receptor.

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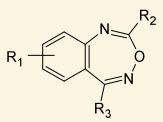
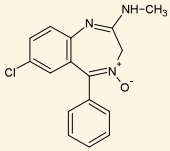
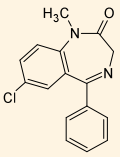
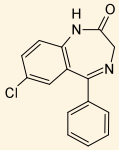
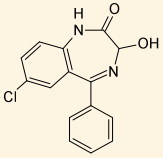
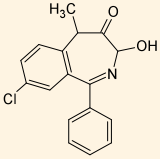
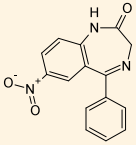
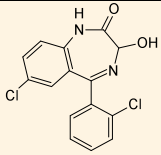
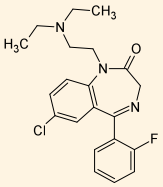
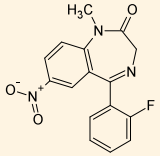
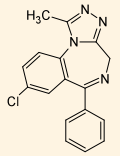
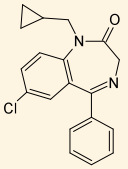
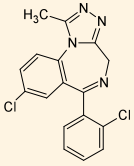
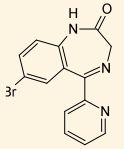
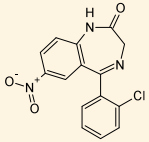
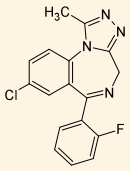
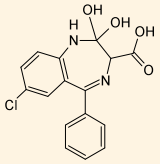
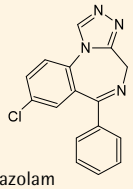
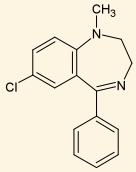
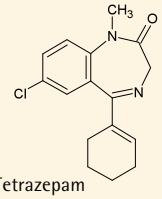
Generic name, trade name, chemical structure
and date of introduction of some benzodiazepine drugs

 1,4-benzo-heptoxdiazines	 Chlordiazepoxide (Librium®) 1960	 Diazepam (Valium®) 1963	 Nordiazepam (Madar®) 1973
 Oxazepam (Serax® or Sobril®)1965	 Temazepam (Restoril®) 1970	 Nitrazepam (Mogadon®) 1965	 Lorazepam (Ativan®) 1977
 Flurazepam (Dalmane®) 1970	 Flunitrazepam (Rohypnol®) 1975	 Alprazalam (Xanax®) 1981	 Parazepam (Centrax®) 1977
 Triazolam (Halcoin®)1977	 Bromazepam (Lexotanil®) 1974	 Clonazepam (Clonopin®) 1975	 Midazolam (Veresd®) 1976
 Chlorazepate (Tranxene®) 1972	 Estazolam (Eurodin®) 1975	 Medazepam (Nobrium®) 1968	 Tetrazepam (Myalastam®) 1974

4 Narcotic Analgesics

From poppies to peptides would be an appropriate sub-title for this particular perspective in drug discovery, which traces the history and development of pain-killing drugs dating from ~3000 BC with papaver somniferum (poppies) to the endorphins (peptides), which were discovered in the 1970s. The opium poppy is mentioned in the famous Eber's papyrus, which dates from ~1500 BC according to which Egyptian mothers (~3000 BC) used the *"poppy juice"* as a way to stop their children's excessive crying.

Since pre-historic times relief of pain and suffering and the alleviation of hunger and fatigue have been paramount for survival of the human race. The juice extracted from the unripe seed-pod of the opium poppy (papaver somniferum) furnishes a pain-killing drug of immense value to mankind and still today its active constituent morphine is a mainstay of the pharmacopeia. When the unripe seed capsule of the poppy plant is cut with a sharp knife a milky extract emerges. When this is allowed to dry it turns into a brownish gummy mass, which is crude opium (the word opium comes from *opos*, the Greek word for juice). Depending on the method of cultivation and the geographic region where the plant grows opium consists of a mixture of several alkaloids; morphine (~10%) codeine (~0.5%) thebaine (~0.5%), papaverin (~1%) and noscapine (~6%). Papaver somniferum grows primarily in Southeast and Southwest Asia and much of today's illicit opium reaching the West comes from Afghanistan.

The importance of opium as a medicinal drug was appreciated already by the Swiss physician Paracelsus (1493-1541), who introduced laudanum (a word from Latin meaning *"something to be praised"*). Consisting of a mixture of opium and wine, laudanum was touted and prescribed for relief of all kinds of medical ailments. Another early advocate of the use of opium in medicine was the British physician Thomas Sydenham (1624-1689), who is reported to have written *"Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and as efficacious as opium."*

The pharmacologically active principle in poppy juice (raw opium) was

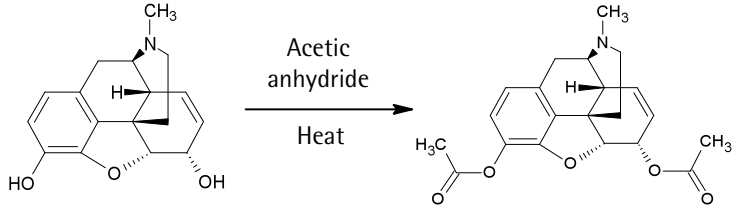
discovered in 1805 by a 21 year old German apothecary named Friedrich Wilhelm Adam Sertürner (1783-1841). He extracted the alkaloid by mixing raw opium with hot water and after making the mixture basic by adding ammonia he obtained a precipitate that eventually yielded colorless crystals that were poorly soluble in water but readily dissolved in acids. As was customary at the time newly prepared drugs were tested by self-administration often in dangerously large amounts. Together with three young volunteers Sertürner administered an unusually large dose of morphine, actually 1½ grains in three divided doses (~100 mg) and felt the respiratory depressant effects and deep sedation bordering on acute opiate poisoning that might have proven fatal.

Although a short report of this work was published in 1805-1806 a detailed account, including a description of the pharmacological effects, did not appear until 1817. The new compound was christened morphine after *Morpheus* the Greek god of dreams. Sertürner received a prestigious award from the French Academy of Sciences for discovering the first plant alkaloid. Not long afterwards other alkaloids were extracted from opium including codeine (1832), thebaine (1833) and papaverine (1848) and later on also others.

The pleasurable effects of opium were known for centuries and smoking of the drug became a popular pastime in some cultures. However, the potential for addiction and dependence on opiates and the risk of dying from an overdose was exacerbated after morphine, its active constituent, was isolated by Sertürner. Another key event in this connection was invention of the hypodermic syringe and needle in 1853 by the Scottish physician Dr. Alexander Wood (1817-1884). This device made it a lot easier to administer morphine parenterally and this route of administration increases the bioavailability of the dose resulting in higher concentrations in blood and brain.

Morphine has a complex chemical structure (see below), which was first elucidated by two British organic chemists in 1925 (Gulland and Robinson) after a long series of degradation reactions. However, final confirmation of the structure of morphine by total synthesis took another 20 years, owing to the molecule's complex stereochemistry (5 chiral carbon atoms). Only the *l*-form or (-)-isomer of morphine is pharmacologically active, which happens to be the enantiomer produced by nature.

Heroin (diacetylmorphine or diamorphine) was discovered at St. Mary's Hospital, London in 1874 by Charles Alder Wright (1844-1894). Very simply, he took anhydrous morphine and boiled it for a few hours with acetic anhydride converting the two hydroxyl groups at the 3- and 6-positions into acetyl groups (see below). Although Wright tested the effects of this new morphine derivative on rodents he apparently did not consider it was any better than morphine as an analgesic. In 1900 the pharmaceutical division of the Friedrich Bayer Company showed an interest in developing an opiate drug that was more effective than morphine or codeine as an anti-tussive agent. They turned their attention to heroin, which they began to produce and market on a large scale (~1 ton per year), which was sold for the relief of coughs and toothache in the form of lozenges.



Acetylation of morphine to heroin, first reported in 1874.

The name heroin is said to have originated from the German word *"heroische"* which means large, powerful or extreme. Heroin was heralded by some as a wonder drug and as a cure for many respiratory ailments, and also as a sleeping aid before its potential for abuse and dependence was fully appreciated. This forced the Bayer Company to stop over-the-counter sales of heroin as a cough suppressant.

Hundreds of chemical derivatives of morphine have been synthesized in the quest to find an equipotent analgesic but with less respiratory depressant side-effects and potential for abuse. This search has not been successful and morphine is still widely prescribed as a strong analgesic drug and is the first choice for use in palliative care.

Raw opium emerging from cuts made in the seed capsule.

Friedrich WA Sertürner (1783-1841).

Heroin originally marketed by the Bayer company for relief of coughs.

Heroin, the most dangerous recreational drug.

Methadone is a synthetic opioid analgesic drug with a long elimination half-life (~24 h), which was first prepared by chemists in Germany in 1939 working at I.G. Farbenkonzern (later Hoechst). The detailed pharmacologically testing of this new drug was delayed until 1942 and the generic name methadone was suggested in 1947. Methadone entered the media spotlight in 1965 when clinical trials were reported by Dole and Nyswander showing its usefulness for the treatment of heroin addiction. The first methadone maintenance clinic was opened in New York City and substitution therapy for heroin addicts was established. Methadone maintenance as a treatment for heroin addiction spread around the world as more and more young people experimented with drugs during the hippy culture and in the wake of the Vietnam War in the 1960s.

The substitution of an opioid (methadone) for an opiate (heroin) has undoubtedly saved the lives of many thousands of drug addicts but methadone itself is also a dangerous drug subject to abuse and has been responsible for many overdose deaths. More recently buprenorphine, a highly potent opiate partial agonist has been approved for use in substitution treatment of heroin addiction. Time will tell whether buprenorphine holds any advantage over methadone in the rehabilitation of heroin addicts but both drugs are frequently encountered in post-mortem toxicology routine casework.

Replacement of the N-methyl group in morphine with N-allyl gives nalorphine, which functions as an antagonist at the opiate receptor. An even more potent antagonist is naloxone, which is the drug of choice for use in emer-

gency medicine to reverse the life-threatening respiratory depressant effects in people who overdose with heroin or morphine. Naltrexone is yet another pure opiate antagonist and the fact that this substance is orally active has resulted in a medication (ReVia®) developed for the treatment of alcoholics during abstinence. The combination of naltrexone and psychological counseling seems an effective way to reduce craving for alcohol and helps to prolong the time before relapse to drinking in recovering alcoholic patients.

Research into the mechanism of action of morphine and other narcotic analgesics received a boost in the 1970s when the opiate receptors (μ, kappa and delta) were identified in various animal tissues. Shortly afterwards the endogenous ligands (endorphins) for these brain receptors were discovered and identified as penta-peptides, named met- and leu-enkephalin (from the Greek meaning *"in the head"*). Later on more potent and much larger opioid peptides were isolated including dynorphin (from the Greek word for *"power"*). These research breakthroughs in opiate pharmacology came from Aberdeen in Scotland (Kosterlitz and Hughes), Uppsala in Sweden (Terenius) and USA (Goldstein, Snyder, Simon and Pert). These scientists helped spawn a new domain in psychopharmacology pertaining to the mode of action of opioid peptides and their role as neurotransmitters. However, the quest for a non-addictive opiate analgesic, peptide or otherwise, still continues.

Further reading

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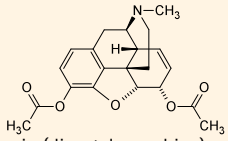
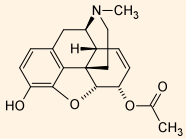
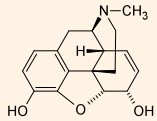
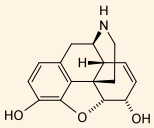
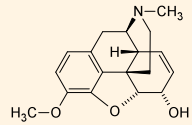
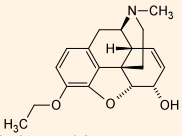
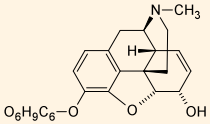
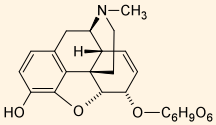
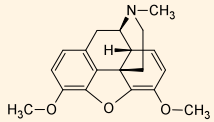
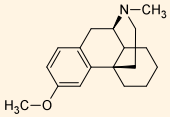
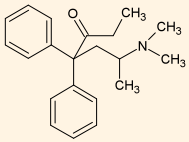
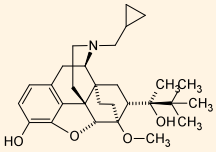
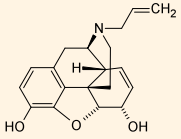
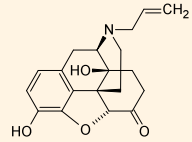
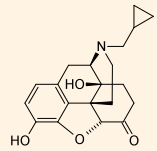
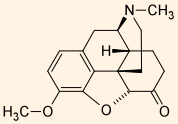
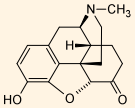
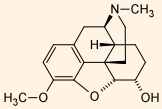
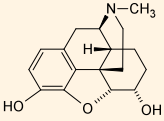
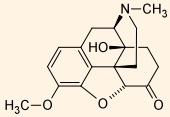
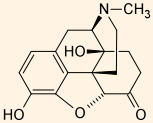
Chemical structure and generic names of major opiates and opioids

 Heroin (diacetyl morphine)	 6 Acetyl-morphine	 Morphine
 Normorphine	 Codeine	 Ethyl morphine
 Morphine-3-glucuronide	 Morphine-6-glucuronide	 Thebaine
 Dextromethorphan	 Methadone	 Buprenorphine
 Nalorphine	 Naloxone	 Naltrexone
 Hydrocodone	 Hydromorphone	 Dihydrocodeine
 Dihydromorphine	 Oxycodone	 Oxymorphone

5 Central Stimulant Amines

If depressants apply the brakes on the brain then central stimulants are the accelerators – hence the slang or street name *"speed"* for amphetamine and methamphetamine. The prototype central stimulant amine is amphetamine (1-phenyl-2-aminopropane or ß-phenylisopropylamine), which according to the MERCK index was synthesized in 1887 by organic chemists in Berlin as a spin-off from their work on the preparation of structural analogues of the naturally occurring amine ephedrine (Ephedra). However, the first well documented pharmacological testing of amphetamine in humans and animals was done much later in the 1930s by Gordon Alles (1901-1963) working at University of California in San Francisco.

Human subject tests showed that amphetamine possessed vasoconstrictor properties resulting in a marked rise in blood pressure and causing dilatation of the bronchial tubes of the lungs. An unexpected side-effect was that the volunteers participating in the clinical trials showed a marked elevation in mood; they became more talkative, seemed to have increased energy and a higher working capacity. These stimulant properties of amphetamine prompted a consideration of its use as a psycho-stimulant for possible use in treatment of depression.

The results of Gorden Alles's experiments were communicated to the pharmaceutical company Smith Kline & French (SKF) and they developed and marketed the drug as a nasal decongestant. In the form of its volatile free base amphetamine was patented in 1933 by SKF under the trade name Benzedrine® a mixture of *d*- and *l*-amphetamine isomers. This product was administered by sniffing into each nostril a treatment that proved highly effective for relief of nasal congestion. The marketing department at SKF was keen to investigate the use of amphetamine as an antidepressant, because people using it often experienced mood elevation and exhilaration. They evidently foresaw sales of amphetamine in one form or another as a pick-me-up,

but as more and more people were taking Benzedrine the potential for abuse and dependence soon became evident.

During WW2, allied soldiers were issued with amphetamine tablets to counteract fatigue and to increase alertness and hopefully boost their battle morale. Even today amphetamine-like drugs (10-20 mg) are available for air-force pilots to help them remain awake and heighten their concentration on long-distance flights. Most research on amphetamine has focused on its psycho-stimulant properties because this is the principal reason for widespread recreational use and abuse of the drug, which escalated during the hippy and student revolts of the 1960s.

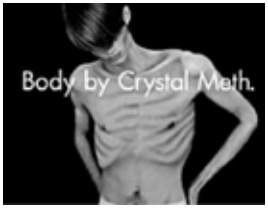
Another widely abused stimulant is the closely related secondary amine (methamphetamine), which was synthesized in 1919 in Japan. Also this stimulant found military applications during WW2 to reduce battle fatigue, to boost morale and as an appetite suppressant. An epidemic of central stimulant abuse arose in Japan after the war and spread to other countries, including Sweden. The dependence liability increased appreciably after the intravenous route of administration became popular. This way of taking the drug leads to an increased tolerance, and escalating doses are necessary to achieve the same euphoric effect while attacks of paranoia and delusions are unwanted side-effects. The abuse potential of amphetamine and methamphetamine has limited their usefulness as therapeutic agents and in most nations they are listed as controlled substances (class II).

Besides the ability to relieve nasal congestion, amphetamine and its derivatives were tested as anti-obesity drugs (anorexic), for treatment of narcolepsy (falling asleep), to treat adolescents suffering from attention deficit hyperactivity disorder (ADHD) and as cognitive enhancers. Taking amphetamines boosts stamina and increases endurance, which gave advantages in some sports as a way to improve performance. Amphetamine was once used as a doping agent in professional cycling with some tragic consequences. The untoward cardiovascular effects of the stimulant, along with dehydration resulted in extreme exhaustion and the death of some athletes.

A single methyl group in the side chain distinguishes amphetamine from phenylethylamine, which is a naturally occurring amine contained in various

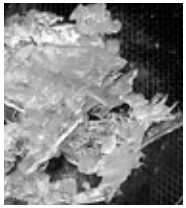
foodstuffs (e.g. chocolate). However, this amine lacks pharmacological activity, owing to an effective first-pass metabolism by monoamine oxidase (MAO) in the gut and liver. The alpha methyl group protects amphetamine from degradation by the MAO enzyme, increasing bioavailability after oral ingestion and making it easier to cross the blood-brain barrier. Amphetamine is a racemate with a single asymmetric carbon atom that renders optical activity. The *d*-form or (+)-amphetamine is the more pharmacologically active enantiomer, another discovery credited to Gordon Alles. This led SKF to manufacture and sell Dexedrine® (containing essentially the *d*-isomer) as an alternative product to Benzedrine®.

Amphetamine inhaler Benzedrine®.



Appetite suppressants and anorectic drug.


Ecstasy (MDMA) a designer drug of abuse.


Methamphetamine hydrochloride (ice).

The chemical structure of amphetamine resembles in some respects the chemical messengers dopamine, adrenaline and norepinephrine (noradrenaline) that play such a fundamental role in communication between nerve cells. This gives a clue to the mechanism of amphetamine's central nervous action, namely as a so-called false transmitter amine. When amphetamine enters a synapse it releases dopamine and noradrenaline from the nerve endings facilitating contact with receptors on postsynaptic neurons. Because of its ability to stimulate body functions controlled by the sympathetic nervous system, amphetamine and its analogues are often referred to as sympathomimetic amines, a term coined by the British pharmacologist Sir Henry Dale (1875-1968).

Scientific and media interest in central stimulant amines escalated in the 1990s with the advent of designer drugs and their popularity with adolescents belonging to the rave culture. Ecstasy (MDMA) tablets gave people more drive and energy and heightened sexual arousal during all-night rave parties

and dance events. Ecstasy combines both stimulant (amphetamine-like) and hallucinogenic (mescaline-like) properties by interacting with receptors for both dopamine and serotonin.

The German pharmaceutical company Merck (Darmstadt) synthesized MDMA in 1912 in a research project aimed at developing drugs to prevent blood clotting. The date of the first human studies with MDMA is obscure, although its stimulant properties became well known through the writings of Alexander Shulgin (born 1925) especially his book PIHKAL. The popularity of MDMA as a recreational drug meant that it soon attracted media attention and became implicated in drug-related deaths, as a result of physical exhaustion, hypertension and dehydration. The lack of any therapeutic uses for MDMA and its popularity as a recreational drug led to it being classified as a scheduled substance (class 1) in many countries.

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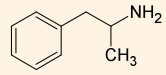
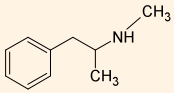
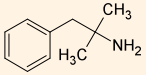
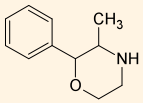
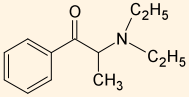
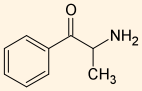
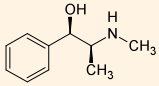
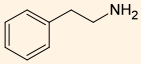
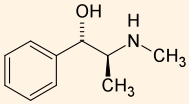
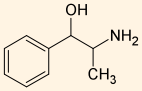
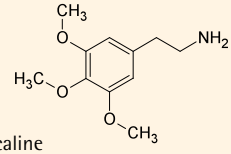
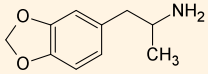
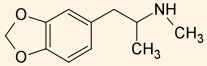
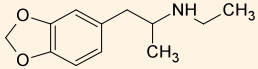
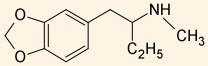
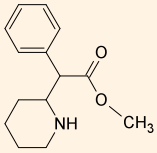
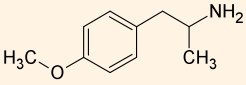
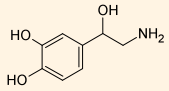
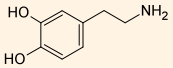
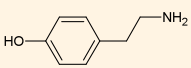
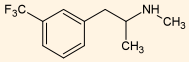
Chemical structures of amphetamines and other central stimulant amines

 Amphetamine	 Methamphetamine	 Phentermine	 Phenmetrazine
 Diethylpropion	 Cathinone	 Ephedrine	 Phenethylamine
 Pseudoephedrine	 Norephedrine	 Mescaline	
 MDA	 MDMA	 MDEA	
 MBDB	 Methylphenidate	 p-Methoxyamphetamine	
 Noradrenaline (norepinephrine)	 Dopamine	 Tyramine	 Fenfluramine

6 The First Antidepressants

Major depression is a particularly common psychiatric disorder in today's society resulting from an imbalance in certain brain chemicals, especially the biogenic amines serotonin and noradrenaline. Typical symptoms of depression include an altered mood, difficulties in rational thinking and decision making, pre-occupation with painful thoughts, the loss of interest and energy and a failure to take initiative. Psychoanalysis and electroconvulsive therapy were the traditional medical treatments for depressed patients and these approaches are still widely used today. The first pharmacotherapy for depression was to prescribe a central nervous stimulant, such as amphetamine (Dexedrine), which often led to other problems including addiction and dependence. Many depressed patients often self-medicated with alcohol as a way to relieve their inhibitions making them more sociable, but this often led to over-consumption, liver damage and the development of alcoholism.

Four separate events in the early 1950s are deemed important for discovery of drugs to treat depression and other mood disorders. First, an effective antipsychotic medication (chlorpromazine) had already been introduced and drug companies attempted to modify its chemical structure in the hope of finding more useful therapeutic agents. Second, the importance of certain endogenous amines, dopamine, noradrenaline and serotonin and their functioning as chemical messengers in the brain was starting to be recognized. Third, sensitive methods were development (spectrophotofluorimetry) for the analysis of trace amounts of biogenic amines and their metabolites in brain tissue and cerebrospinal fluid. Fourth, animal models (rats and mice) were used to test the effects of psychoactive drugs on spontaneous motor activity, cataleptic immobility, conditional avoidance and working to obtain a reward (food). The fruits of all these research efforts and activity led to the development of the *"catecholamine hypothesis"* of mental illness.

For many centuries it was known in parts of India that a crude extract from

the plant *Rauwolfia serpentina* (snakeroot) was useful in the treatment of, among other things, anxiety, high blood pressure and senility. In 1950, the Swiss pharmaceutical company Ciba decided to investigate this natural product and to search for the active chemical principle in *Rauwolfia*. They succeeded in isolating a plant alkaloid reserpine, which had a dramatic effect on blood pressure and also an unexpected side-effect, namely people taking the drug complained of feeling depressed.

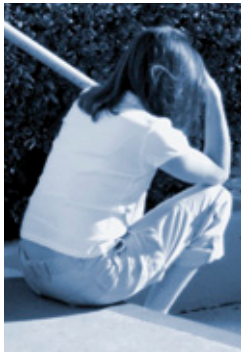
Clinical trials with reserpine were conducted by an American psychiatrist Dr. Nathan Kline (1916-1982), who used it to treat patients suffering from schizophrenia. These agitated and disturbed patients calmed down, became less suspicious and were more co-operative after the treatment. Other workers showed that after administration of reserpine the concentrations of noradrenaline and serotonin in rat brain decreased appreciably thus creating a link between the turnover of these amines and mental disorder. The chemical structure and stereochemistry of reserpine was far too complicated to permit making molecular modifications in the hope of finding a closely-related psychoactive substance.

In the mid-1950s another accidental discovery led to the development of antidepressant drugs when observations were made of people undergoing chemotherapy for tuberculosis. Two drugs found to be useful in treating this lung disorder were isoniazid and iproniazid (derivatives of hydrazine). Besides healing the tuberculosis legions this treatment also enhanced the mood of the patients even though they were suffering from a serious pulmonary condition. Many of those receiving iproniazid became euphoric and exhibited overactive behaviour. This led to studies of the behavioural effects of iproniazid in healthy volunteers and depressed patients and shortly thereafter the anti-depressive properties were confirmed in controlled patient trials, although what was causing this effect on mood was not known at the time.

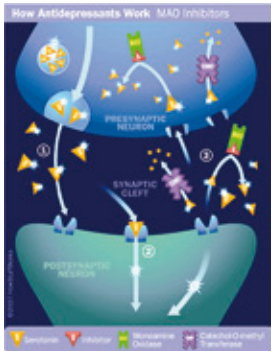
Before iproniazid was used in the treatment of tuberculosis, research done at several UK laboratories discovered a liver enzyme capable of oxidative deamination of biogenic amines, such as tyramine (4-hydroxyphenylethylamine). This enzyme was isolated, purified and given the name monoamine oxidize (MAO) and also shown to oxidise other biogenic amines such as adrenaline. Later work verified that the MAO enzyme was widely distributed

in organs and tissue including the gut, liver and brain. In animals treated with iproniazid the levels of serotonin and noradrenaline in the brain were higher compared with a control treatment thus giving a clue as to how the drug worked, namely by the inhibition of MAO.

Animal models have played an important role in testing the action of psychoactive drugs, such as conditioned avoidance.



Depression, a major public health problem in today's society.



How antidepressant drugs work at receptors at the synaptic cleft.

Experiments done at the Northwestern University Medical School in Chicago, USA showed that iproniazid blocked the action of the MAO enzyme in-vitro so it was not long before this inhibitory effect was tested in-vivo. These studies showed that the concentration of serotonin and noradrenaline in brain regions was dependent on the activity of the MAO enzyme. Also known at the time was that treatment of animals with reserpine lowered the levels of these same amines in brain tissue, which were subsequently restored after administration of iproniazid. Putting all these observations together various investigators proposed the biogenic amine hypothesis of depression and the search for drugs that modulated the turnover of noradrenaline, dopamine and serotonin began in earnest.

Prompted by the success story of chlorpromazine, chemists at the Swiss drug company Geigy began to synthesise a series of chemical derivatives of antihistamine drugs with the iminodibenzyl nucleus to test their usefulness as sedatives or antipsychotics. One of these was coded G 22,355 and was tested clinically on psychotic patients by the psychiatrist Dr. Roland Kuhn (1912-2005) who reported that it had no beneficial effects for this condition.

Almost by chance Kuhn decided to test the same drug on a patient with endogenous depression and to his surprise this female patient showed a remarkable improvement. The result with this single-patient was confirmed in tests with others having the same depressive disorder all of whom responded to treatment and when the drug was withheld the depression returned. The results of these studies were published in 1957 in the Swiss Medical Journal (87:1135-40) and the drug was named imipramine, the first tricyclic antidepressant (TCA) used in therapy.

Although both MAO inhibitors and TCAs are effective treatments for depression like most medication there are unwanted side-effects and toxicity in overdose. Many deaths have been reported, both accidental and by suicide, after use of TCAs. People taking MAO inhibitors often complained of insomnia and headaches and there was also a risk of dangerous interactions with other coingested drugs. Moreover, a person taking a MAO inhibitor should refrain from eating foods that contain the biogenic amine tyramine, such as cheese, smoked meats or red wines. MAO enzymes located in the intestine are blocked by treatment with MAO inhibitors, which means that tyramine contained in food products is more easily absorbed into the blood where it exert its pressor effects causing dangerous hypertension. More recently, a reversible inhibitor of monoamine oxidase-A moclobemide was marketed and this drug has only minimal anticholinergic side-effects and also fewer dietary restrictions are needed for patients prescribed this medication.

Other unpleasant side-effects of TCAs included dry mouth, sexual dysfunction, blurred vision, constipation, sedation, dizziness and hypotension. The effectiveness of TCAs also varies greatly from patient to patient in part as a result of polymorphism in the hepatic CYP450 enzyme, such as CYP2D6, which converts imipramine into the more pharmacologically active metabolite desipramine. In the late 1980s TCAs and MAO inhibitors were joined by a new class of antidepressants, namely the selective serotonin reuptake inhibitors (SSRI), as exemplified by fluoxetine (Prozac®) and others, which is the subject of a later essay (Chapter 10).

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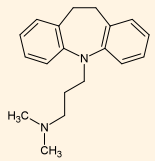
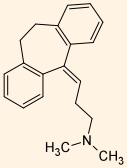
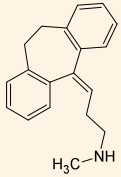
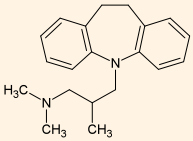
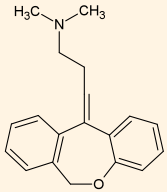
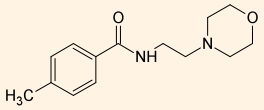
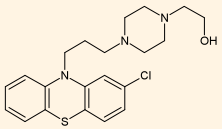
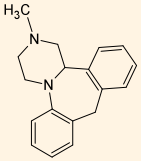
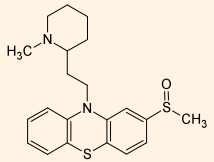
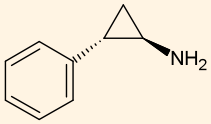
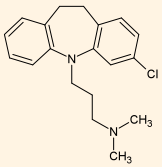
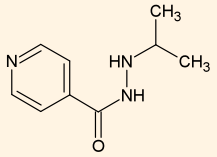
Chemical structures and generic names of some of the first antidepressants

 Imipramine (Tofranil®)	 Amitriptyline (Elavil®)	 Nortriptyline (Pamelor®)
 Trimipramine (Surmontil®)	 Doxepin (Adapin®)	 Moclobemide (Aurorix®)
 Perphenazine	 Mianserin (Bolvidon®)	 Mesoridazine
 Tranylcypromine	 Clomipramine (Anafranil®)	 Iproniazid

7 Antipsychotic Medication

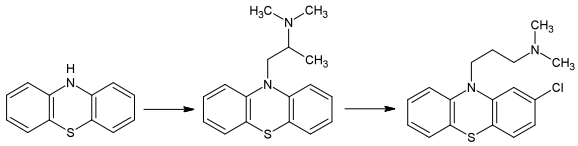
Seriously ill psychotic patients, once ridiculed by society and locked away in lunatic asylums or prisons, suddenly became treatable in the early 1950s. This coincided with the introduction into psychiatry of chlorpromazine and new research about the chemistry of the brain, especially the mode of action of neurotransmitter amines dopamine, noradrenaline and serotonin. Over the centuries people suffering from paranoid psychoses underwent barbaric treatment, including physical restraint with manacles, use of straitjackets and even flogging. During the last century, deep sedation with barbiturates, drug-induced epileptic seizures, electric (convulsive) shock treatment and lobotomy were examples of the other dubious treatments. An effective drug therapy for people suffering from schizophrenia (derived from two Greek words to split and mind) did not appear on the market until the early 1950s.

In the late 1940s an Australian psychiatrist John Cade (1912-1980), published a short report about the usefulness of lithium salts for treating people suffering from bipolar disorder, manic highs followed by a deep depression. During the analysis of urine samples collected from manic patients Cade found that they contained an abnormally high content of the waste product urea. This led him to hypothesize that toxicity of urea might have something to do with the medical condition of his patients. He decided to experiment with guinea pigs and wanted to give them large doses of uric acid. However, this acid was not very soluble so Cade instead administered the more soluble lithium ureate salt. One thing led to another and Cade observed that the guinea pigs became lethargic and unresponsive for several hours after treatment. When lithium carbonate was given to manic patients, this treatment seemed to calm them down for several hours and a short report of the results of this first clinical trial was published in the Medical Journal of Australia (2:349-352, 1949).

The worldwide acceptance of lithium carbonate in the treatment of mania

is attributed in large part to the efforts of a Danish psychiatrist Mogens Schou (1918-2005) at the University of Aarhus. Schou designed and evaluated randomized double blind clinical trials of lithium therapy and showed its effectiveness for patients suffering form bipolar disorder. Even today lithium carbonate remains the prophylactic treatment of choice for mania, but exactly how this small alkali metal ion alleviates the symptoms of bipolar disorder is still not definitely established.

When the Swiss pharmaceutical company Ciba was in the process of investigating the properties of reserpine, other scientists turned their attention to antihistamine drugs from the phenothiazine group, particularly promethazine which had *"unwanted"* sedative effects. A close link exists between antihistamines and antipsychotics in terms of their chemical structure. A chemist (Paul Charpentier) who worked for a French drug company Rhône-Poulenc (later Aventis) was tasked with making a number of derivatives of promethazine and, among other things, he added a chloride atom to one of the benzene rings to give chlorpromazine.



Phenothiazine Promethazine Chlorpromazine

Discovery of the antipsychotic properties of chlorpromazine and its use in psychiatry owes much to a French naval surgeon Dr. Henri Laborit (1914-1995). As often happens in drug discovery, the antipsychotic property of chlorpromazine was a chance finding thanks to the persistence of Dr. Laborit. He was concerned about the dangerous drop in blood pressure associated with surgical shock in his patients after the operation. Among other drugs Laborit's patients were pre-medicated with promethazine and he asked the drug company Rhône-Poulenc to prepare more potent derivatives. One of the drugs sent to him was chlorpromazine and Laborit noticed that his patients became sleepy and less apprehensive. He suggested further testing of this substance and the possibility of clinical applications of chlorpromazine as a sedative, because of the calming effect it had on his patients.

In 1952 Jean Delay (1907-1987) and Pierre Deniker (1917-1998) two psychiatrist working at Hospital Sainte Anne in Paris followed the suggestion of Laborit had tested the effect of chlorpromazine in psychiatric patients with various forms of schizophrenia. They gave a glowing report of its effects in relieving symptoms of delusion and hallucination in hitherto untreatable patients. Chlorpromazine was later developed and approved as the first major tranquilizer or neuroleptic drug (a word coined by Delay coming from Greek to take hold of the nerves).

The first scientific papers describing clinical results with chlorpromazine were all written in French and appeared in 1952. The drug was given the trade name in France of Largactil® (literally meaning large activity). For the development of chlorpromazine several of the pioneers, including Laborit, Deniker and Lehmann shared the prestigious Albert Lasker award for their contribution to drug treatment of a major psychiatric disorder.

In 1952 the Philadelphia-based pharmaceutical company Smith-Kline & French (SKF) purchased the marketing rights to chlorpromazine in the US. The initial intention was to market the substance as another antihistamine, despite the fact it possessed strong sedative properties and was also a powerful antiemetic and lowered body temperature. The drug was administered to patients scheduled for cardiovascular surgery to increase the time available for the surgeons to operate by a drug-induced surgical hypothermia. SKF received FDA approval for chlorpromazine as an antiemetic agent and only later when the work from France was widely accepted did off-label prescribing as an antipsychotic begin. Chlorpromazine was given the trade name Thorazine® the first major tranquilizer (neuroleptic).

Within a short time Thorazine had revolutionized the way in which many psychotic patients were treated. The year 1952 witnessed the birth of new scientific disciplines, that of biological psychiatry and psychopharmacology. Without exaggeration, chlorpromazine was a milestone in drug therapy for seriously disturbed patients, previously institutionalized because of schizophrenia. Indeed, the Hollywood movie *"Awakenings"* staring Robin Williams and Robert De Nero, which was based on a book by Oliver Sachs, described the introduction of Thorazine® into psychiatry.

Julius Axelrod, Nobel prize winner who discovered the re-uptake mechanism of TCA drugs.

"The Scream" by Edvard Munch (1893).

Artists view of the targets of psychoactive drugs in the brain.

Early advert for the first antipsychotic drug chlorpromazine.

In 1958 a small Belgium drug company discovered a more potent antipsychotic, which was given the generic name haloperidol, but is perhaps better known by its trade name Haldol®. Much of the credit for this discovery belongs to Dr. Paul Janssen (1926-2003) a physician and pharmacologist and the man who founded Janssen Laboratories (now a part of Johnson & Johnson).

Dr. Paul Janssen was a remarkably successful scientist and entrepreneur and over his long career he was responsible for putting on the market several useful pharmaceutical products, including fentanyl (1963) and risperidone (1993). Janssen noticed the similarity between the symptoms of chronic use of amphetamine and paranoid schizophrenia and wanted to find an antagonist to the effects of amphetamine that might be useful as an antipsychotic drug. Paul Janssen held over 100 patents and co-authored more than 850 scientific papers. Many consider that Janssen's overall body of work in drug discovery was worthy of a Nobel Prize. He died suddenly in 2003 aged 77 years while attending a psychopharmacology conference in Rome.

The haloperidol story is yet another example when the search for one class of drugs (narcotic analgesics) results in the discovery of another with unexpected therapeutic properties. After discussion with Professor Arnold Beckett (1920-2010) at the Pharmacy Department of Chelsea College in London, Janssen began to make derivatives of the analgesic pethidine (meperidine®). The original idea was to produce a more powerful narcotic analgesic and ini-

tial animal experiments gave promising results. However, structurally the new compounds resembled those already in existence, which would have caused infringement of patent rights so the chemists at Janssen laboratories began to modify the molecular structures by extending the lateral side chain.

One of the derivatives of pethidine (R 1625) was tested in animals and instead of deadening pain, which was the expected result, it had cataleptic properties. When administered to mice R 1625 put them into a cataleptic and sedated state resembling the effects seen after treatment with the antipsychotic drug chlorpromazine. This prompted tests in patients and when haloperidol was given to psychotic patients their delusions and hallucinations were immediately less pronounced and they became calmer and more manageable. Haldol® was quickly approved and marketed in Europe as a new antipsychotic medication. However, it took until 1969 before haloperidol was eventually approved for sale in the United States. This longer time for approval by the FDA seems to have been a consequence of the aftermath of the thalidomide disaster. This teratogenic drug was sold in Europe but not the US thanks to over-caution and requests for more information from Francis Oldham Kelsey (1914-2009) an employee of the FDA.

After long term use haloperidol caused extrapyramidal side-effects, such as tradive dyskinesia (late occurring abnormal involuntary and repetitive movements) not unlike the clinical signs in Parkinson's disease e.g. shuffling of the feet, slow movements and shaking of the hands. Haloperidol (Haldol®) became the prototype of a new class of antipsychotic drugs, known as the butyrophenones and worked by blocking the dopamine receptor.

Following the discovery of multiple dopamine receptors (D_1 to D_5) in the 1970s considerable efforts were made to find a second generation of antipsychotic drugs with fewer side-effects and that bind more selectively to certain dopamine receptors. Often referred to as atypical anti-psychotics, because extrapyramidal side-effects are minimal or lacking; these medicines have become big-sellers and they include, sulpride, clozapine, olanzapine and risperidone (see structures).

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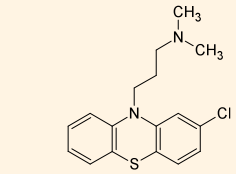
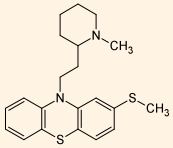
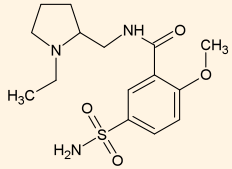
Chemical Structures of Some Antipsychotic Drugs



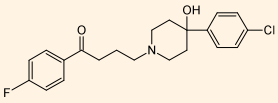
Chlorpromazine (Thorazine)



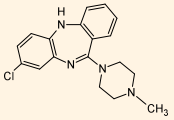
Thioridazine (Mellaril®)



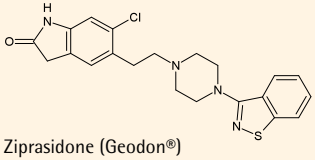
Sulpiride (Meresa®)



Haloperidol (Haldol)



Clozapine (Clozaril®)



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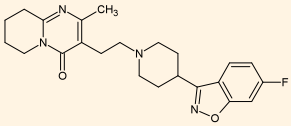
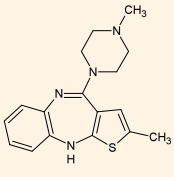
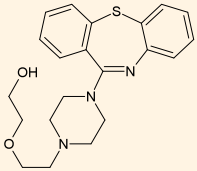


Risperidone (Risperdal®)



Olanzapine (Xyprexa®)



Quetiapine (Seroquel®)

8 Aspirin and Other NSAID

The discovery of the first synthetic drugs is closely linked with the burgeoning textiles and synthetic dye industry, which developed in the mid-1800s, particularly in Germany. Industrial chemistry had also taken root in England and was spearheaded into a major commercial enterprise by the young William Henry Perkin (1838-1907). Already as an 18 year old chemistry student Perkin attempted to synthesize quinine from the aromatic chemicals derived from coal tar, a distillation product of coke. This experiment failed but when he discarded the reaction mixture it resulted in a bright purple color (mauve), which he further developed into the first aniline-based synthetic dye. William Perkin exploited this accidental discovery and went on to make a fortune producing synthetic dyes for the clothing industry. The color mauve or mauveine became highly fashionable when it was shown to be a favourite for the clothes worn by Queen Victoria of England.

The black mass (tar) condensate after coal is burnt in a furnace under vacuum provides a rich source of organic chemicals, including phenol, benzene and aniline. The Friedrich Bayer Company (founded in 1863) was also interested in the manufacture of dyes derived from coal tar and during this work they stumbled upon a substance that possessed useful antipyretic effects. A waste product from the dye-works was p-nitrophenol and after acetylation was converted into the first synthetic analgesic and antipyretic drug phenacetin® which was marketed in 1888.

Plants from nature have always provided a rich source of medicinal cures as exemplified by extracts from the bark of the willow tree, which grows close to rivers and marches. Extracts from the bark were effective in the treatment of various maladies such as rheumatism and fevers. The Reverend Edward Stone (1702-1768) published a detailed account in 1763 of the curative properties of extracts of the willow tree (*Salix alba*). Salicylic acid was synthesized in the 1820s by German and French chemists, who also demonstrated its anti-in-

flammatory properties. However, salicylic acid had a very bitter taste and was not easy to take because it irritated the gastric mucosa. A chemical derivative, acetylsalicylic acid better known as Aspirin® was first synthesized in 1897 by Felix Hoffmann (1868-1946), who worked as a chemist in the pharmaceutical division of the Bayer Company.

Legend has it that Hoffmann's father suffered from chronic rheumatism and used salicylic acid to relieve his pains but complained about its bitter taste and the irritation it caused to the mucous surfaces of the stomach. This prompted Hoffmann to investigate whether a simple derivative of salicylic acid might be more palatable. Reaction with acetic anhydride converted the phenolic group into an acetyl group and hence acetylsalicylic acid. This substance retained the medicinal properties of salicylic acid but was much more palatable and caused less gastrointestinal problems. In fact acetylsalicylic acid had actually been synthesized years earlier but was now given the trade name Aspirin® and marketed in 1897. The A denotes Acetyl and spirin comes from spiraea the genus name for the plant source (*Spiraea ulmaria*) of salicylic acid, a pain reliever well known as a herbal cure.

The mechanism of action of aspirin was not discovered until the 1960s when a British pharmacologist, working at the Royal College of Surgeons (Sir John Vane 1927-2004), showed that aspirin worked by inhibiting cyclooxygenase (COX), a key enzyme in the biosynthesis of prostaglandins.


Felix Hoffmann (1868-1946).


Early bottle of aspirin.


A weeping willow the bark of which contains salicylic acid.

Insignia of the Bayer pharmaceutical company founded 1863.


Sir John Vane Nobel Laureate 1982.

Accordingly, the Bayer Company quickly and profitably expanded its interests from manufacture of dyes to pharmaceuticals, as exemplified by phenacetin, heroin and aspirin. Meanwhile, other German chemists were busy synthesizing new compounds from the waste-products of coal tar and the

Hoechst dye works bought the rights to manufacture the drug antipyrine, which had been synthesized in 1884 by Ludwig Knorr (1859-1921) a former student of the Doyen of German Organic Chemistry Emil Fisher (1852-1919). Antipyrine was a derivative of pyrazolone and possessed antipyretic and analgesic properties and was marketed under the trade name phenazone® becoming a best seller until aspirin appeared at the turn of the century (1900).

Another chance discovery of a useful drug was the antipyretic-analgesic agent acetanilide. Naphthalene, yet another product of the distillation of coal, had been prescribed for the treatment of patients suffering form intestinal worms. However, by mistake a pharmacist had dispensed acetanilide instead of naphthalene. This drug did not help the problem of worms but had the unexpected effect of alleviating the fever (antipyretic) that some of the patients were suffering from at the time. Further investigations showed that acetanilide lowered body temperature and had no immediate side-effect. However, long term use of acetanilide caused a condition known as methemoglobinemia, whereby methyl groups bind to hemoglobin molecules and prevent the red-blood cells from transporting oxygen.

Bernard B Brodie (1907-1989) and Julius Axelrod (1912-2004) two veritable pioneers in neurochemistry and drug metabolism were given the task of investigating this problem. Brodie suggested that the acetanilide might be converted in the body into aniline, which was known to cause methemoglobinemia. A detailed study of the metabolism of acetanilide showed that it was indeed converted in part to aniline and a pharmacologically active p-hydroxy metabolite. This retained the fever-lowering properties of the parent drug but without the side-effects causing methemoglobinemia. The p-hydroxy metabolite was later synthesized and marketed as acetaminophen (USA) and paracetamol (Europe), becoming a blockbuster drug available over-the-counter and used daily by infants, children and adults worldwide.

The ubiquitous availability of paracetamol in bathroom cabinets is not without risk because this drug is commonly encountered in poisoning deaths both accidental overdose and with intent on suicide. The major pathway in metabolism of paracetamol is by formation of glucuronide and sulfate conjugates, which are then excreted in the urine. However, there is also a minor oxidative metabolite called N-acetyl-p-benzoquinoneimine (NAPQI), which

is chemically highly reactive and binds to endogenous molecules. This metabolite is produced in the liver by the microsomal enzyme CYP2E1, which is also involved in the metabolism of ethanol.

After therapeutic doses of paracetamol the small amounts of the NAPQI metabolite are rendered harmless by the free-radical scavenger glutathione. But massive doses of paracetamol tend to saturate the enzyme systems and NAPQI is then produced in excess binding covalently with cellular proteins to cause hepatic necrosis and cell death. Thousands of people die each year as a result of overdosing with paracetamol, which causes liver failure.

Paracetamol is not a recommended drug for use by alcohol-dependent patients who might have an induced CYP2E1 enzyme owing to their continuous heavy drinking making them more susceptible to liver damage caused by the effects of NAPQI. In the poisoned patient, an important antidote is N-acetylcystine, which serves as precursor to the short-chain peptide and antioxidant glutathione. However, this treatment needs to be administered as soon as possible after admission to be effective. In those presenting too late in worst case scenarios a liver transplant is the only thing that saves lives.

One of the newer generation of NSAIDs, namely refecoxib (Vioxx®), hit the headlines a few years ago when new research studies suggested that long-term use of the drug by people suffering from arthritis led to an increased risk of a myocardial infarction. The media frenzy that erupted eventually forced the pharmaceutical giant Merck to withdraw Vioxx® from the market. Vioxx® was launched in 1999 and looked like becoming a blockbuster drug until controversy about its cardiovascular side effects broke. The recall of Vioxx® had enormous financial consequences for Merck and its share price dropped precipitously and has not yet recovered. Moreover, hundreds of lawsuits were filed against Merck, some still on-going, about the lack of transparency and failure to divulge information linking use of the drug to a heightened risk of heart attack and stroke. Vioxx® worked by specifically blocking a so-called COX-2 enzyme, which meant fewer gastrointestinal problems (bleeding) compared with aspirin, which inhibits both COX-1 and COX-2 enzymes.

Another second-generation NSAID, also a specific inhibitor of COX-2

enzyme, is celecoxib (Celebrex®), manufactured by the pharmaceutical company Pfizer. This drug is still on the market and is widely used as a painkiller for people with arthritis on the basis that the benefits outweigh the risks.

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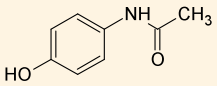
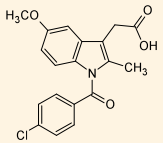
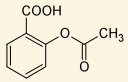
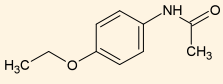
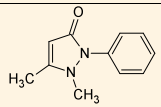
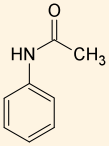
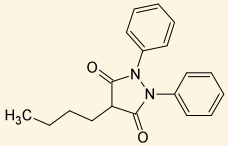
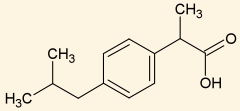
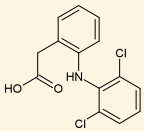
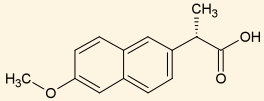
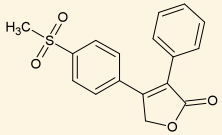
Structure of aspirin and other anti-inflammatory mild analgesics

 Salicylic acid	 Acetaminophen (Paracetamol)	 Indomethacin
 Acetylsalicylic acid	 Phenacetin	 Antipyrine (Phenazone)
 Acetanilide	 Phenylbutazone	 Ibuprofen
 Diclofenac	 Naproxen	 Refecoxib (Vioxx®)

9 General Anesthetics

The discovery of general anesthetics and their subsequent entry into medicine as a way to deaden pain and relieve suffering during surgical operations probably ranks as one of the greatest benefits to mankind. The word anesthesia was coined in 1846 by Oliver Wendell Holmes (1809-1894) and means loss of or without sensation, stress or pain. Until the nineteenth century, the drugs used to induce sleep and relieve suffering when amputations were performed were alcohol and opium, both available for centuries to dull the senses when battle wounds were treated.

Joseph Priestley (1733-1804) is credited with the discovery of the gas nitrous oxide (N_2O) in 1776 not long after he had isolated oxygen and demonstrated its chemical properties. Sir Humphry Davy (1778-1829) self-experimented with N_2O, inhaling the gas and experiencing its physiological effects. Indeed, the inhalation of N_2O became a popular pastime in some circles as a way to induce euphoria, excitement and exhilaration, hence the name laughing gas. N_2O can therefore be considered as one of the first recreational drugs. When the gas was inhaled, Davy noted that the pain he had been suffering from a wisdom tooth disappeared, which prompted him to suggest the application of N_2O in minor surgery already in 1800.

> *"As nitrous oxide in its extensive operation appears capable of destroying physical pain, it may probably be used with advantage during surgical operations in which no great effusion of blood takes place."*

Unfortunately, it took another 40 years (1843) before nitrous oxide was introduced into clinical practice as an anesthetic gas in dental surgery. The credit for this goes to an American Horace Wells (1815-1848) who worked as a dentist in the town of Hartford in Connecticut. The idea came after a visit he made to a traveling show or fairground when a man named Quincy Colton demonstrated the effects of inhaling laughing gas. After inhalation of the gas a volunteer from the audience fell and suffered a deep cut on his leg

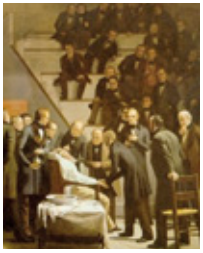
but claimed he felt no pain from the wound, which prompted Horace Wells, who witnessed the event, to consider testing N_2O gas in dentistry. He demonstrated its usefulness as an anesthetic agent for extracting teeth in some of his patients and subsequently agreed to perform the same operation before surgeons at the Boston General Hospital, the Mecca of US medicine at the time.

Unfortunately, the first public demonstration of the anesthetic properties of N_2O failed miserably because the patient awoke too early screaming in pain, probably a consequence of an insufficient dose or a leakage in the equipment used. The ridicule of this botched attempt to use N_2O in dentistry had serious effects on Wells who suffered from depression and his physical and mental state deteriorated. This was compounded by other problems including addiction to chloroform and he suffered a nervous breakdown. He was arrested by the police for throwing acid at two prostitutes and when sent to prison awaiting trial he committed suicide by cutting his femoral artery dying at the age of just 33 years. It would take another 20 years before N_2O was again introduced into medicine as a safe general anesthetic and is used worldwide even to the present day.

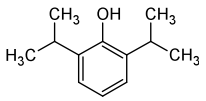
Sir Humphry Davy a British chemist, who first suggested that laughing gas N_2O might have value in surgery.


UNITED STATES PATENT OFFICE.

US patent 1842 given to Morton et al. for use of ether in general anesthesia.



Painting of the first use of ether in surgical anesthesia *"ether day"* at the General Hospital in Boston Massachusetts.



Chemical structure of propofol, an intravenous induction anesthetic and the drug that allegedly killed Michael Jackson (1958-2009).

Diethyl ether had been known as a chemical substance since 1540, although it took several hundred years before it was used as a general anesthetic

during surgery. Interestingly, it was Michael Faraday (1791-1867), a younger colleague and successor to Davy at the Royal Institution, who suggested the use of ether as an anesthetic agent when he described his feelings after breathing the vapors himself. In 1818 he wrote;

> *"When the vapor of ether mixed with common air is inhaled, it produces effects similar to those occasioned by nitrous oxide."*

The first use of diethyl ether as a surgical anesthetic is credited to an American dental surgeon William TG Morton (1819-1868) who had witnessed the failed attempt by Wells to use N_2O to deaden the pain of tooth extraction. Morton turned his attention to other gases and volatile chemicals for use in anesthesia, among others diethyl ether, which had been suggested by Faraday. Morton was also much interested in business and profiting from his discovery and was an early American entrepreneur. After many tests inhaling the ether vapors himself, using desolate people and also his wife's dog Morton felt he had discovered the perfect anesthetic. Use of ether as a general anesthetic was successfully demonstrated in 1846 before a critical audience at the Massachusetts General Hospital (now Harvard Medical School). Morton administered the vapors when a surgeon removed a vascular tumor form a man's face without any pain or ill-effects. The successful use of ether vapors in this operation was the starting point for *"painless"* surgery and prompted an intensive search for better and less inflammable liquids for this same purpose. Lack of care in use of ether in surgery resulted in many fires and explosions and today other volatile anesthetics are used instead.

The next major advance in use of general anesthesia came with chloroform in obstetrics by Sir James Young Simpson (1811-1870) who worked at the infirmary in Edinburgh, Scotland in 1847. Among his patients was none other than Queen Victoria to whom he administered chloroform to lessen the pain during birth of two of her children. This famous patient helped to increase public awareness and acceptance of general anesthetics in surgical operations. However, chloroform was not without its problems and sudden cardiac arrest and death was reported in some patients during surgery. Such a problem was not experienced with N_2O which led to a renaissance for its use in surgery.

Many volatile liquids and gases with diverse chemical structures and physico-chemical properties have been developed and tested for use as inhalation or intravenous anesthetics, including hydrocarbons (ethylene, cyclopropane, n-pentane), halocarbons (chloroform, halothane, trichloroethylene) as well as miscellaneous agents (propofol, fentanyl, ketamine and sodium thiopental) and even inert gases, such as xenon and argon.

Most anesthetic gases and volatile solvents are highly lipid-soluble and their low blood/gas partition coefficients mean they easily cross the alveolar-capillary membrane of the lungs and enter the pulmonary blood after inhalation. The high solubility in fat also means that these compounds pass the blood-brain barrier with ease and penetrate cell membranes to interact with various receptors and ion-channels, including the chloride ion channel of the $GABA_A$ receptor. The mechanism of action of structurally diverse general and intravenous anesthetic agents is still not completely agreed upon but the pioneers of this medical revolution were Wells, Morton and Simpson.

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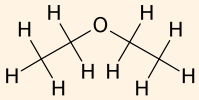
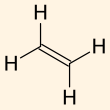
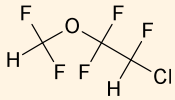
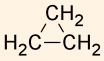
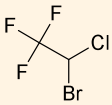
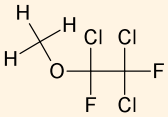
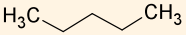
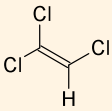
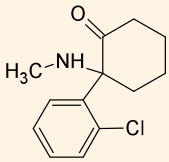
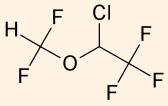
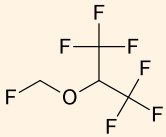
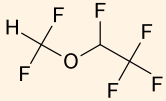
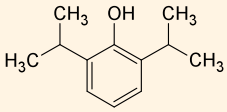
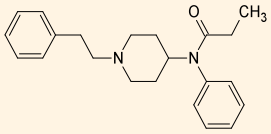
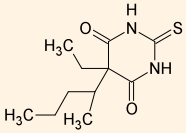
Diverse chemical structures of drugs used in general anesthesia

Ethers	Hydrocarbons	Halocarbons	Miscellaneous agents
 Diethylether	 Ethylene	 Chloroform	Xe Ar Xenon Argon
 Enflurane	 Cyclopropane	 Halothane	 Nitrous oxide
 Methoxyflurane	 n-Pentane	 Trichlorethylene	 Ketamine
 Isoflurane	 Servoflurane	 Desflurane	Nitrogen
 Propofol	 Fentanyl		 Thiopental

10 SSRI Antidepressants

The subject of biological psychiatry emerged as a scientific discipline in the 1950s coinciding with new research discoveries about the way nerve cells communicate, especially the fact that this is chemical-based rather than electrical-based. The individual response to stress, fear, anxiety and depression rank among the commonest forms of chemical imbalance in the brain. Depression is characterized by prolonged feelings of sadness and a sense of uselessness often accompanied by anxiety and panic attacks. In today's society millions of people worldwide suffer from depression in one form or another as evidenced by the exponential rise in prescriptions and sales of many antidepressant drugs.

Today the first-choice medication for people with depression is one or other of the SSRI drugs, an acronym for **S**elective **S**erotonin **R**euptake **I**nhibitor. Serotonin or 5-hydroxytryptamine (5-HT) is synthesized from the dietary amino acid precursor tryptophan. Endogenous 5-HT is widely distributed in the body, being mostly located in the small intestines (enterochromaffin cells), the blood platelets and the brain. After trytophan passes through the blood-brain barrier it undergoes ring hydroxylation followed by decarboxylation to the active 5-HT neurotransmitter.

The name SSRI refers to the mechanism of action of this class of drugs, namely by blocking the re-uptake pump that sends serotonin molecules back into the pre-synaptic neuron. Treatment with SSRIs lead to an increase in the extra-cellular concentration of serotonin facilitating more intimate contact with brain receptors and thereby enhancing serotonergic neurotransmission. The brand name for the prototype SSRI is Prozac® known chemically as fluoxetine in the form of its hydrochloride salt. This drug was approved by the US Food and Drug Administration (FDA) in 1987 and much aided by the news-media the subsequent sales of Prozac® rocketed giving it the status of a blockbuster drug. This led other companies to prepare drugs with a

similar mechanism of action and clinical profile and not long afterwards citalopram (Cipramil®), paroxetine (Paxil®) and sertraline (Zoltoft®) as well as others entered the market.

Depression has become an increasingly common psychiatric disorder with first symptoms often appearing during adolescence and then continuing off and on throughout adult life. Even after treatment feelings of depression often return with negative consequences for the individual's personal and professional life. The mechanism of action of drugs used in the treatment of psychiatric disorders is closely related to the way recreational drugs of abuse work, that is, by influencing the biosynthesis, release and degradation of biogenic amine neurotransmitter molecules.

The first successful drug-treatment for depression was iproniazid, a substance that blocked the action of an enzyme known as monoamine oxidase (MAO) and thus preventing the breakdown (deamination) of newly synthesized neurotransmitter amines. The next type of medication for depression was discovered in the search for a new antipsychotic drug related to chlorpromazine introduced a few years earlier. This led to the emergence of tricyclic antidepressants (TCAs), which worked by blocking the re-uptake of serotonin and noradrenaline after their release into the synaptic cleft. The main problem with TCA medication was a lack of specificity and acute toxicity when taken in overdose.

Side-effects of MAO inhibitors included splitting headaches and insomnia and dangerous hypertension when the medication was used with certain foodstuffs rich in tyramine, hence the so-called *"cheese effect."* Other foodstuffs rich in tyramine included smoked meats and red wine and these should be avoided by those taking MAO inhibitors. Side-effects with TCAs included a dry mouth, blurred vision, constipation, confusion and sedation. Moreover TCAs were more dangerous in overdose and many adverse drug interactions were reported.

The discovery of selective serotonin reuptake inhibitors (SSRI) as a new class of antidepressant drug has its roots in the 1950s and pioneer work by, among others, the Swedish pharmacologist and Nobel Prize winner Arvid Carlsson (born 1923). Carlsson shared the Nobel Prize in Medicine or

Physiology in 2000 with Paul Greengard (born 1925) and Eric R. Kandel (born 1929) *"for their discoveries concerning signal transduction in the nervous system."* The joint work of these scientists was pivotal in developments in the field of neuropsychopharmacology and the monoamine hypothesis of depression. It was increasingly becoming evident that depression was caused by functional disturbances in central noradrenergic and/or serotonergic systems. A drug-induced depletion of the neurotransmitter amines noradrenaline and serotonin after treatment with reserpine was counteracted by giving iproniazid or a TCA.

In 1958, Roland Kuhn (1912-2005) published his findings demonstrating the clinical effectiveness of the first tricyclic antidepressant (TCA), namely imipramine and its metabolite desipramine. Later work showed that TCAs prolonged the effects of the neurotransmitters noradrenaline (NA) and serotonin (5-HT) increasing the concentrations of these amines in the synaptic cleft thus facilitating a longer contact with post-synaptic receptors. During propagation of a nerve signal a neurotransmitter, such as serotonin, leaves the pre-synaptic neuron, crosses the synaptic cleft and then interacts (binds) to a post-synaptic receptor. When this happens the receptor on the adjacent neuron causes transmission of the nerve signal to elicit a physiological response.

After binding to post-synaptic receptors, the neurotransmitters are inactivated by a re-uptake mechanism a type of *"pump"* which returns the amine into the pre-synaptic neuron. SSRI drugs prevent or slow the re-uptake mechanism and thereby enhance contact between serotonin and its post-synaptic receptors. Because depression and other psychological disorders are associated with a decreased level of serotonin in these brain regions the SSRI drugs are effective antidepressants.

Owing to the undesirable side-effects and toxicity of TCAs when used as antidepressant medication, including their cardiotoxicity and anticholinergic effects, there was a definite need to develop improved pharmaceutical agents for this ailment. In consultation with Arvid Carlsson the Swedish drug company Astra (now AstraZeneca) began a research programme aimed at developing a new class of antidepressant drug. It was found that some antihistamine drugs also functioned as 5-HT reuptake inhibitors and that it was the tricyclic part of the TCA molecule that was mainly responsible for the adverse effects.

This research culminated in the development of zimelidine, which was patented in 1972 as the first SSRI. The specific mechanism of action entailed blocking the reuptake pump that removed serotonin from the synaptic cleft. Unfortunately, not long after this medication was approved and widely prescribed a serious side-effect was reported in some patients; Guillain-Barré syndrome, a rare and incurable form of paralysis that could be fatal. Astra management decided to withdraw zimelidine from the market and end their quest for a new antidepressant drug, a premature and highly regrettable decision.

In the meantime, other pharmaceutical companies, such as Indianapolis-based Eli Lilly were also in the hunt for a new antidepressant drug. Eli Lilly's team of chemists and pharmacologists (David Wong, biochemist, Bryan Molloy, organic chemist and Ray Fuller, pharmacologist) began to work with another antihistamine drug diphenhydramine (Benadryl®). They were aware that this drug caused sedation and some of its effects on the central nervous system involved altering serotonin neurotransmission. With diphenhydramine as their lead compound they followed the classic approach and began to synthesize a large number of chemical derivatives.

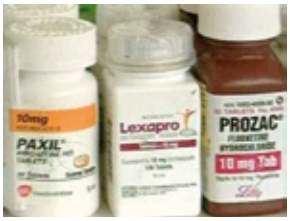
Also available at the time was a highly sensitive and specific receptor binding assay using rat brain synaptosomes so that the effect of drugs on serotonin binding could be more easily investigated. One of the compounds tested by Lilly was coded LY 4514081 and in-vitro tests showed it prevented the deactivation of serotonin at receptor sites thereby prolonging its effects on neurotransmission. This new inhibitor of the reuptake of serotonin was given the generic name fluoxetine and entered clinical trials with depressed patients.

Fluoxetine hydrochloride (trade name Prozac®) improved the quality of life and more importantly had fewer anticholinergic and cardiotoxic side-effects than other antidepressant drugs available at the time, such as TCAs or MAO inhibitors. A patent was approved in 1974 and Prozac® was marketed as an antidepressant in Belgium in 1986 and the following year in the USA. Much aided by attention from the media, Prozac® became a blockbuster drug and first choice medication for treating depression being referred to as *"happy pills"* bringing large profits for the industry.

The dream of pharmaceutical companies is an orally active medication with low toxicity in overdose and the ability to pass the blood-brain barrier. These features were achieved with Prozac and *"big pharma"* were quick to capitalize on the immediate success. Within a relatively short period of time other SSRIs were synthesized, subjected to clinical trials and registered as medicines including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline.

Professor Arvid Carlsson, pharmacologist (Nobel Prize in medicine or physiology 2000).

Early advert for Prozac® as *"happy pills"*.



Prozac® a block-buster drug alongside other SSRI medications.

Besides their use in the treatment of depression, SSRIs are increasingly being advocated for other psychological or psychiatric disorder, such as obsessive-compulsive behaviour and panic attacks. The aggressive marketing of antidepressants, especially for teenagers, and the liberal prescribing by many physicians has been linked to a rise in suicidal thoughts and actions. Taking drugs to help people cope with stresses and strains of daily life is controversial and has attracted a lot of negative publicity.

The off-label prescribing of SSRI drugs for people suffering from various social phobias, such as overt shyness and panic disorder as well as ADHD has been much criticized. Numerous reports mention that the over-prescribing of SSRIs is likely to change a person's personality and increase propensity for self-destructive behaviour including suicide attempts. Another area of concern with SSRI agents, especially when combined with other medication and recreational drugs, is the potential for toxicity as exemplified by the serotonin syndrome.

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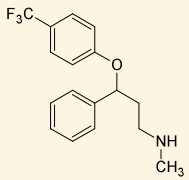
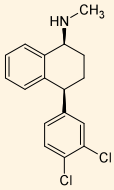
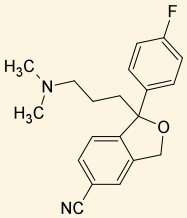
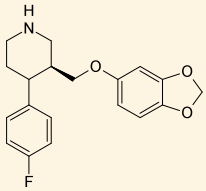
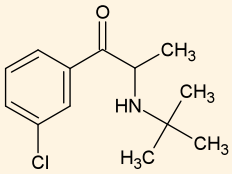
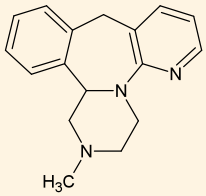
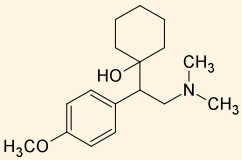
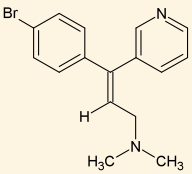
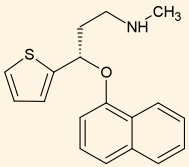
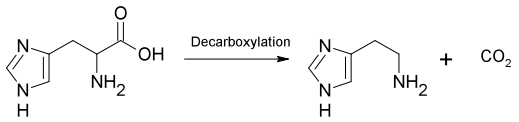
Generic names, trade name and chemical structure of SSRI and SNRI antidepressants

 Fluoxetine (Prozac®)	 Sertraline (Zoloft®)	 Citalopram (Celexa®)
 Paroxetine (Paxil®)	 Bupropion (Wellbutrin®)	 Mirtazapine (Avanza®)
 Venlafaxine (Effexor®)	 Zimelidine (Zelmide®)	 Duloxetine (Cymbalta®)

11 Histamine Antagonists

Allergic or hypersensitivity reactions typified by sneezing, red and itchy-eyes and runny nose are unpleasant daily experiences for millions of people worldwide. The term allergy was introduced in 1906 by Clemens von Pirquet (1874-1929) and is derived from Greek *allos* meaning other and *ergon* meaning reaction. Large inter-individual differences exist in the frequency and severity of allergic symptoms caused by an excessive immune response, sometimes proving life-threatening, as in the case of anaphylactic shock and the ensuing cardiovascular and respiratory collapse. The mediator of this hypersensitivity is the small bio-amine molecule histamine (ß-aminoethylimidazole), which is released from its endogenous stores (mast cells) after cellular injury, such as when the skin comes into contact with injurious stimuli, e.g. from an insect bite, a nettle sting, excessive heat or cold or other irritation.

Histamine ranks as one of the first bioactive amines to be extracted from mammalian tissue by Sir Henry Dale (1875-1968) and his co-workers during the first decades of the 20th century. Histamine is produced in the body by decarboxylation of the dietary amino-acid histidine (see reaction below). Extensive chemical and pharmacological testing of this endogenous amine confirmed its role as a transmitter molecule both in the peripheral and later in the central nervous system. Histamine is widely distributed in the gut, the lungs and the vascular system (mast cells and basophils). During an immune response, IgE antibodies cause mast cells to release histamine into the blood stream, which binds to receptors resulting in difficulties breathing (bronchoconstriction), dilatation of blood vessels (fall in blood pressure) and increased permeability of blood vessel walls as well as stimulation of gastric acid secretion.

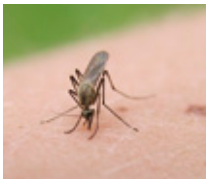


Histidine

Histamine
(ß-aminoethylimidazole)

The physiology of histamine and the discovery of antihistamines owes much to an investigative technique unique to pharmacology, namely the biological assay or bioassay for short. Bioassay methods have proven indispensable to test for biological activity of new drugs and tissue extracts and also for the standardization and purity testing of pharmaceutical products, such as vitamins and hormones. The ability of a certain substance, usually extracted from tissue, to block the contraction of smooth muscle - guinea pig ileum, cat's utreus or the mouse vas deferens – was crucial in the discovery of substances such as prostaglandins and endogenous opiates.

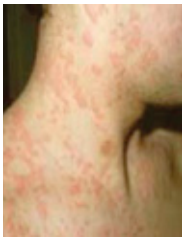
Histamine elicits a typical allergic inflammatory reaction when injected under the skin characterized first by a localized red spot followed by a larger flush and thirdly the formation of a wheal or oedema with itching. Drugs that compete with histamine for binding to peripheral receptor sites (H_1-antagonists) help to relieve these unpleasant allergic reactions. The everyday symptoms of sneezing, running nose (rhinorrhea), itching of the eyes and nose and allergic rhinitis (hay fever) meant a lucrative market for an effective drug therapy.



People show large differences in sensitivity and reaction to insect bites.

Benadryl® generic name for diphenhydramine, a widely used antihistamine.

Daniel Bovet, 1957 Nobel Prize winner.



Example of an allergic skin reaction.

The first antihistamine drug was discovered by a Swiss-born Italian physiologist Daniel Bovet (1907-1992), who also published seminal papers dealing with chemical neurotransmission and received the Nobel Prize in Physiology or Medicine in 1957. The pharmacological activity of a large number of chemical compounds was screened for their ability to counteract the physiological effects of histamine on guinea pig ileum. Success was achieved with a derivative of phenoxyethylamine, but this compound was too toxic for use in humans and no clinical trials were made. Thereafter a French pharmaceu-

tical company Rhône-Poulenc (later Aventis) continued the search for antihistamine-type drugs in the usual way by making chemical derivatives and minor structural modifications. In 1939 a substance was found that protected guinea-pigs from histamine-induced anaphylaxis, namely a phenylethylenediamine, which received the generic name phenbenzamine and was registered for treatment of allergies (Antergan®) becoming the first practically useful antihistamine.

Further structural modifications produced compounds with less sedating effects, such as mepyramine (neo-Antergan®). Many other antihistamine drugs were developed and some were judged suitable for purchase without a prescription for symptomatic treatment of allergic reactions, such as the popular ethanolamine Benadryl®. Antihistamines interact with a variety of receptors including muscarinic, adrenergic, serotonergic and dopaminergic, which accounts for many side-effects, some good some bad. Besides the peripheral anticholingeric actions of this class of drugs, they also interact with a number of neurotransmitter systems in the CNS leading to sedation, fatigue and dizziness. Indeed, the sedative effect of promethazine was exploited in the discovery of the highly successful antipsychotic chlorpromazine. Antihistamines were also the starting substance in the discovery of SSRI antidepressants (see chapter 9).

Antihistamine drugs are usually classified as H_1 or H_2 antagonists depending on their pharmacological profiles and site of action. The H_1 antagonists are further sub-classified as belonging to first generation classical antihistamines or second generation non-sedating antihistamines, although the latter were not developed until the 1980s. Research on antihistamines has focused on the search for drugs having a higher selectivity for binding to specific histamine receptors, both in peripheral tissues and the central nervous system. The aim of many pharmaceutical companies was to find an antihistamine that did not penetrate the blood-brain barrier thus ameliorating the unwanted sedative properties. Relative differences in lipid solubility and plasma protein binding are thought to account for the differences in sedative properties of first and second generation antihistamines.

Some of the first generation H_1-antihistamines, such as the phenothiazines, had the useful side-effect in that they were anti-emetic and therefore useful in

treatment of nausea and vomiting associated with motion sickness. Other first-generation antihistamines found off-label usefulness as non-prescription sleeping aids, sometimes with fatal consequences in overdose. H_1-antagonists also display a variety of drug interactions when co-administered with other therapeutic agents, such as monoamine oxidase inhibitors, which enhance or prolong the anticholinergic effects of antihistamines. The sedative effects of antihistamines are especially dangerous when combined with barbiturates, alcohol or narcotic analgesics. Even some of the second generation antihistamines produce life-threatening arrhythmias when co-administered with drugs that inhibit their metabolism.

Another physiological target for the action of histamine is located in the gastrointestinal track and, among other things, controls the increased production of gastric acid by binding to H_2-receptors located on parietal cells. This action of histamine was not prevented by any of the first-generation of antihistamine drugs, because these bind preferentially to H_1-receptors. This led to the notion of the existence of a second subtype of histamine (H_2) receptor and sparked a search for drugs that blocked the action of histamine on gastric acid secretion at the H_2-receptor site.

Sir James Black (1924-2010).

A British drug firm Smith Kline & French embarked on a systematic search for a drug that competitively inhibited the action of histamine at the H_2-receptor. This research programme was led by a Scottish physician and pharmacologist James W. Black (1924-2010) and culminated in the discovery of the first successful histamine-2-antagonist cimetidine, a block buster drug with annual sales of over $1 billion. Traditionally, the development of new drugs began with chemists making a large number of chemical modifications and derivatives of some naturally occurring substance, whereas Black introduced a more rational approach. This entailed a deeper understanding of the basic physiological processes of drug action at receptor sites.

James Black had already made a name for himself in drug discovery while working at the Pharmaceutical division of Britain's Imperial Chemical Industries (ICI), later Zeneca and now Astra-Zeneca. James Black was an

early proponent of the sub-classification of receptors to explain the action of adrenergic drugs. He was the team leader and the driving force behind the synthesis and clinical testing of the first beta-blocker drug (propranolol), which proved so important in the treatment of coronary heart disease (angina), control of high blood pressure and heart failure. Black pioneered the concept of receptor theory and rational drug design, that is, the synthesis of new molecules that interact with receptors associated with a particular disease or medical condition. For his overall body of work in the design of new pharmaceuticals James Black shared the Nobel Prize in Physiology or Medicine in 1988 together with Gertrude Elion (1918-1999) and George Hitchings (1905-1998).

Much thought is given when deciding on the proprietary name of a new pharmaceutical product and the name of the first H_2-antagonist (TAGAMET®) was derived by combining letters taken from the word anTAGonist and the drug's generic name ciMETidine. Sales of Tagamet® skyrocketed to reach blockbuster status and in the process generating enormous profiles for the pharmaceutical industry. More recently H_3 and H_4 receptors have been identified in some body organs and tissues and the search is on for drugs that preferentially bind and compete with histamine for these receptor subtypes.

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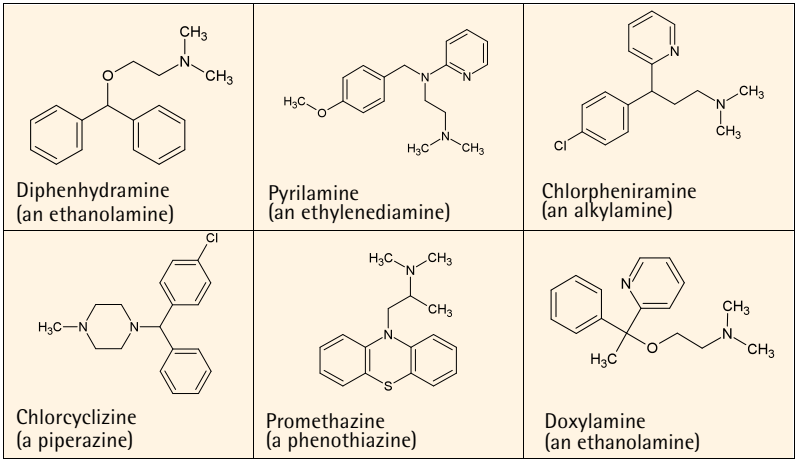
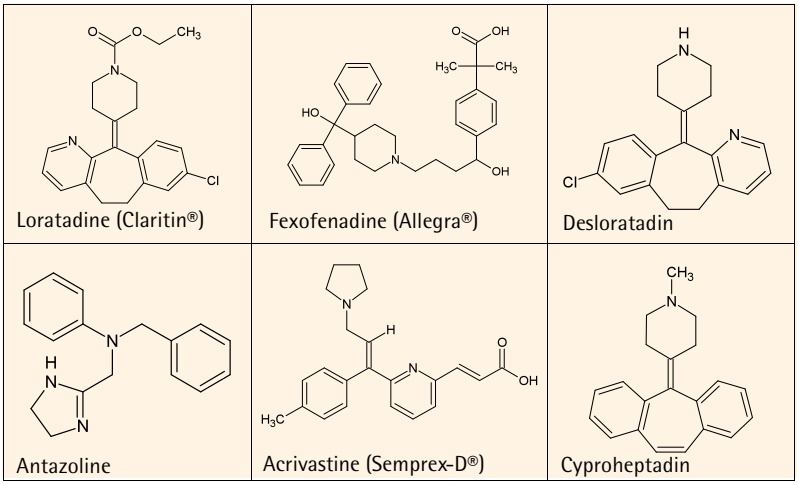
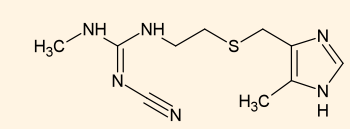
Structural formulae of some of the classic first generation antihistamines



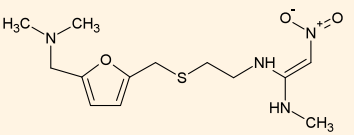
Structural formulae of some second generation (non-sedating) antihistamines



Structural formulae of well-known histamine-H_2-antagonists



Cimetidine (Tagamet®)



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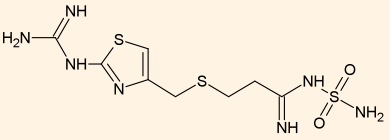
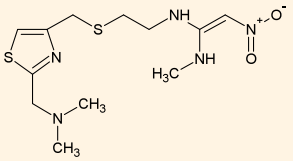


Famotidine (Pepcidine®)



Nizatidine (Tazac®)

12 Anti-convulsants

Epilepsy is a common neurological (brain) disorder, which inflicts millions of people worldwide, especially in third world developing nations where appropriate medication is not widely available. Attacks of epilepsy can strike at all ages when the processes that control normal neuronal activity are in some way disturbed. This results in abnormal firing of nerve cells and those inflicted experience unusual sensations, emotions, body movements and altered behaviour. Epileptic attacks have been recognized and described since ancient times. The clinical manifestations include lapses in attention to muscle spasm and severe and prolonged life-threatening convulsions. The name epilepsy first appeared in the English language in 1570 and comes from two Greek words epilepsia, which means *"taking hold of or seizing"* hence epi (upon) + lepsis (seizure). This one word encompasses the cardinal signs of an epileptic attack, namely spontaneous and recurrent seizures.

Notable people, such as Julius Caesar, Napoleon Bonaparte and Vincent Van Gogh were reputed to have suffered from epilepsy in one form or another. During an attack a person's arms and legs might jerk violently and the individual sometimes suffers a loss of consciousness. Seizures in which the whole body reacts violently are referred to as tonic-clonic (earlier known as grand mal seizures). Absence seizures (once known as petit mal) are generalized seizures that often develop in childhood and are characterized by a sudden loss of activity, muscle jerks and the person might stare into space for a few moments. The scary nature of an epileptic attack meant that in some cultures sufferers were thought to be possessed with *"evil spirits"* and only a few hundred years ago these individuals were discriminated against and locked away in asylums together with the insane.

A wide range of drugs with diverse chemical structures have been tested and approved as supportive or prophylactic treatment for epileptic fits. In some cases treatment for epilepsy might involve electric shock therapy or neurosurgery, but in the main this aliment is handled by pharmacotherapy.

The neurological targets for anticonvulsant drugs involve several neurotransmitter systems or some combination of them, including the following.

- Voltage gated ion channels (Na^+, K^+ and Ca^{2+})
- Non-specific cation channels
- Ligand gated ion channels, mainly GABA receptors
- Receptors and metabolizing enzymes for the neurotransmitter glutamate

The first pharmacological treatment for epilepsy dates from 1853 and involved treatment with bromide salts (KBr), which introduced other problems besides seemingly controlling epileptic seizures in some patients. Treatment with bromide salts is credited to Sir Charles Locock (1799-1875) who advocated their use to treat *"hysterical epilepsy"* in women, which he thought was related to their heightened sexual excitement during the menstrual cycle. In males an old explanation for epilepsy was an excessive masturbation and long-term treatment with bromide salts made the patients impotent. The use of bromide salts did seem to reduce the incidence of epileptic attacks but on the whole this treatment was highly questionable, not least because of the risk of bromide toxicity. Increasing doses of KBr caused overt sleepiness, diminished mental function, and a staggering gait as well as other negative side-effects, such as sexual dysfunction.

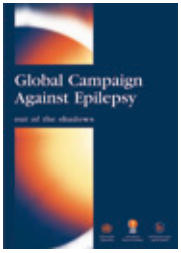
In 1912 a newly synthesized barbiturate drug was used to treat epilepsy. The hypnotic properties of phenobarbital were exploited to help epileptic patients get a better night's sleep and this treatment was also found to reduce the prevalence of epileptic fits during the day. Phenobarbital is still prescribed today as an anticonvulsant drug for treatment of seizures. The success of phenobarbital prompted the drug firm Parke-Davis to search for improved antiepileptic medication with similar chemical structure but with fewer sedative effects.

This research led to the discovery in 1938 of phenytoin, structurally related to the barbiturates but without the sedative properties. This represented a major advance in pharmacotherapy when phenytoin, an orally active drug, was marketed in the form of its sodium salt, which was given the proprietary name sodium dilantin. This medication controlled and prevented seizures with less undesirable side-effects compared with other antiepileptic drugs.

Another widely used antiepileptic medication carbamazepine was approved in 1965 and is still in use today. Also in the 1960s the anticonvulsant properties of several benzodiazepine drugs, especially diazepam and clonazepam was utilized to treat epileptic seizures, such as status epilepticus, the more dangerous type of prolonged seizure (~30 min). The benzodiazepines bind to the brain's major inhibitory receptor (GABA) and this action increases the flow of negatively charged chloride ions into the adjacent neuron. This makes the cell less excitable, fewer impulses are produced and there is an overall dampening of neuronal activity. The well-known alcohol-induced withdrawal seizures often seen in alcoholics after a long drinking binge are also treated with benzodiazepine drugs.

Epilepsy, a common brain disorder that inflicts millions of people.

Topimarate one of several newer drugs used in the treatment of epilepsy.



Front page from WHO campaign to de-stigmatize epilepsy in the third world.

Depiction of chemical signalling *"firing"* between neurons.

In recent years a wide range of drugs with diverse chemical structure have been tested and used as pharmacotherapy for epilepsy to suppress the rapid and excessive firing of neurons. These drugs act via various molecular targets at synapses and receptors involving the excitatory amino acid glutamate and the inhibitory amino acid GABA. Other medication targets are voltage-gated sodium or chloride ion channels. Another type of drug is designed to block the voltage gated calcium ion channels and some work to enhance GABA activity. In children suffering from epilepsy the use of a ketogenic diet (low carbohydrate and high fat) has had some success in preventing seizures.

Treatment with anticonvulsants or antiepileptic drugs (AEDs) is an effective way to control seizures but this medication is not a cure for this neurological disorder, the cause of which is still unknown. With some of the newer

antiepileptic drugs a concern has been raised about the risk for abuse and dependence (e.g. topiramate and pregabalin). There are also several clinically important drug interactions to consider when prescribing some antiepileptic drugs. Studies have shown that suicide risk increases by a factor of two with some of the newer AED medication and a *"black box warning"* has been issued by the FDA on these substances.

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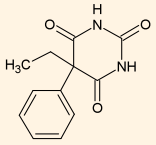
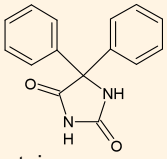
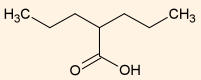
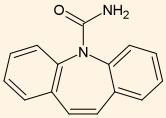
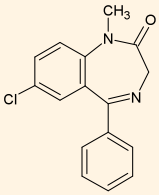
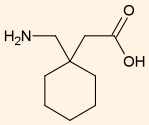
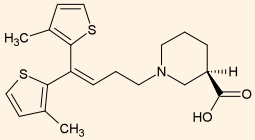
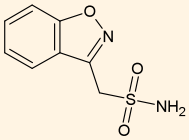
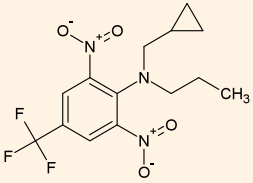
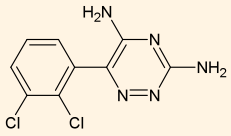
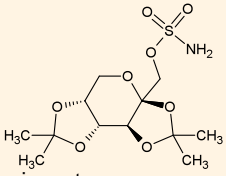
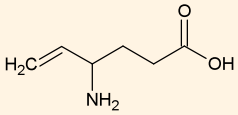
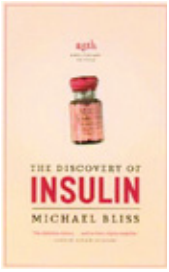
Diverse structures of some old and newer anticonvulsant drugs for epilepsy

 Phenobarbital	 Phenytoin	 Valporic acid
 Carbamazepine	 Diazepam	 Gabapentin
 Tiagabine	 Zonisamide	 Pregabalin
 Lamotrigine	 Topiramate	 Vigabatrin

13 Life-Saving Drugs Insulin and Penicillin

Much has been written about life-saving drugs but none can compare with the discovery of insulin and penicillin in the early 1920s and 1940s, respectively. The scientific backgrounds to these discoveries and the role of serendipity have been described in several publications. Some of the scientists involved in development of these wonder drugs have become household names.

Insulin



Cover of a book by Michael Bliss about the drama and discovery of diabetes.

Until the 1920s diabetes mellitus killed indiscriminately and when a diagnosis was made emaciation was already underway and little could be done to save the person's life. Switching to a low carbohydrate or high fat diet was a common practice but in the long-run this treatment did little to prolong life of the person diagnosed with diabetes. Diabetes often occurred in childhood, hence the term juvenile or type I diabetes, and the victims simply wasted away and death was more or less a certainty. The cardinal signs and symptoms of diabetes included weakness, weight loss, constant thirst and excessive urination and this malady was known and documented since ancient times. The word diabetes comes from the Greek word meaning a siphon or pipe-like, hence referring to a wasting away of the flesh and its conversion into urine. The word mellitus was added much later and comes from the Latin word for honey-sweet referring to the copious production of sweet tasting urine.

A Hollywood film captured the drama of the discovery of insulin, which told the story of an unknown country doctor (Frederick Banting) from Western Ontario, who had the self-confidence to search for a cure for diabetes. To test his hypothesis Banting needed the financial support, laboratory space and encouragement from the Department of Physiology at the

University of Toronto, which was headed by Professor John Macleod. Even before Banting started his research, it was already known that diabetes was related to the functioning of the pancreas because when this organ was removed from experimental animals (dogs) they developed the cardinal signs; an enormous thirst, production of copious amounts of sweet-tasting urine, weight-loss and eventually death.

In the summer of 1921 and with the support of Professor Macleod, who provided laboratory space, a technical assistant and a limited supply of dogs, Frederick Banting began his quest to find the endogenous factor in the pancreas that protected people from becoming diabetic. A medical student named Charles Best served as a laboratory assistant whose main job was to determine the sugar-content of blood and urine in the animals after various treatments. In terms of personality and enthusiasm Banting and Best made a good research team. When obvious signs of diabetes had developed in the animals extracts from the pancreas, after various stages of purification, were injected to see the effect on blood-sugar level. The tentative name given to the pancreatic extract was *"isletin"* because it came from the *"Islets of Langerhans"* named after Paul Langerhans (1847-1888) who, in 1869, first observed the special cells in the pancreas where the hormone (from Greek *hormao*, I excite) was produced. This name was later changed to insulin after the Latin insula (island).

Four scientists working at the University of Toronto were involved in the discovery of insulin, namely Frederick Banting (1891-1941, physician and team leader), Charles Best (1899-1978, assistant and medical student), John Macleod (1876-1935, professor of physiology) and James Collip (1892-1965, a biochemist and visiting scientist). Together they eventually obtained an extract that showed great promise in lowering blood sugar in a depancreatized dog close to death. In one account of this experiment it mentions that after the injection, the dog stood up and began to wag its tail. The next step was to test the extract on a patient suffering from diabetes and this first clinical trial was done on a boy named Leonard Thompson.

The first pancreatic extracts, although seemingly effective in lowering blood sugar in animals, contained a lot of impurities and large volumes were necessary. James Collip's main contribution to the discovery of insulin was refining

the methods used to extract and purify the hormone using alcohol as a solvent and careful acidification, because protein solubility is sensitive to pH. When Collip's extract was tested on Leonard Thompson, the boy's blood sugar concentration dropped immediately and after a few days he was considered fit enough to leave the hospital, although insulin injections were needed for the rest of his life. When news broke of this success the demand for insulin became overwhelming, although the quantities available were initially very small. With help from the pharmaceutical industry, especially the Eli Lilly Company in Indianapolis, large-scale production of the life-saving insulin hormone began in earnest. Insulin treatment proved a miracle cure for a hitherto deadly disease and the rest, as they say, is history. Countless millions of people (type 1 diabetics) have been able to live fairly normal lives, albeit with daily injections of insulin.

For the discovery of insulin two of the team members Banting and Macleod shared the Nobel Prize in Physiology or Medicine in 1923, although some felt that Charles Best should also have been included in the award. Frederick Banting, who by all accounts was a rather volatile character, was unhappy about the omission of Best and reacted by sharing half the prize money with him. Macleod felt he should reciprocate so he shared half of his prize money with Collip. There was certainly no love lost between Banting and Macleod neither before nor after the Nobel awards were made. The relationship between them deteriorated over the allocation of credit for making this major medical discovery of a life-saving drug. The news media placed the laurels firmly on Banting's head, who, after all, was a son of Canada whereas Macleod was an immigrant to the country. The idea to embark on the project was unquestionably that of Frederick Banting but Macleod provided the necessary support and he was also a recognized expert in carbohydrate metabolism. The conflict between the two men escalated in the years after the Nobel award, which some believe prompted Macleod to leave Toronto and return to his native Scotland. He took-up a position as Professor of Physiology at the University of Aberdeen where he died in 1935 aged just 59 years.

Sadly, Frederick Banting also met an early death aged 50 years. He was engaged in the war effort and when en route to England in a military aircraft the plane crashed in Newfoundland with no survivors. Both Best and Collip

went on to enjoy successful careers in academia as professors of physiology and biochemistry, respectively.

Penicillin

An equally famous story in drug discovery is that of penicillin and its subsequent development into a life-saving antibiotic, a word meaning *"destructive of life."* The story starts with Dr. Alexander Fleming (1881-1955) working as a bacteriologist at St. Mary's Hospital in London in 1928. Before leaving on a two-week summer vacation Fleming left a number of bacterial culture plates unattended on a laboratory bench.

Alexander Fleming receiving his Nobel Prize from the hands of King Gustav V Adolf of Sweden with Ernst Chain (moustache) behind him.

The petri dishes contained staphylococcal bacteria, the pathogens responsible for boils, abscesses, pneumonia and septicaemia. Instead of being discarded the culture plates were left in the open air while Fleming was away. On his return from vacation Fleming noticed that one of the culture plates was contaminated with a mould and that the bacteria colonies close to the fungus had been destroyed. They had undergone lysis (dissolving), whereas more distant from the mould the bacteria colonies were still intact. As the Pasteur saying goes *"chance favors the prepared mind"* Fleming decided to cultivate the responsible mould and he showed that it belonged to the genus *Penicillium notatum*, so he named it penicillin. The results of this work were published in British Journal of Experimental Pathology, but the article at the time did not attract much attention.

Fleming showed that the mould had a low inherent toxicity but it was difficult to prepare and its antibiotic properties were not investigated in mice or rats infected with staphylococci bacteria. This oversight meant that it took another 15 years before the antibacterial power of penicillin was re-discovered and developed into a life-saving drug. The initiative for this later work came from the Sir William Dunne School of Pathology at Oxford University, which was headed by an Australian Howard Florey (1898-1968). Together with a biochemist refugee from Nazi Germany Ernst Chain (1906-1979) an inves-

tigation was made of the chemotherapeutic properties of Fleming's penicillin.

The crucial experiment involved injecting a purified form of penicillin into mice infected with deadly staphylococci bacteria. The animals not treated all died whereas those receiving penicillin all survived. A short report of the experiment was published in the Lancet in 1940 in a paper entitled *"Penicillin as a chemotherapeutic agent"* and the co-authors were Chain, Florey, Gardner, Heatley, Jennings, Ore-Ewing and Sanders (note the alphabetical ordering).

The first patient to receive penicillin was a 43-year old policeman who was dying of septicaemia and he received the drug in February 1941. The man had scratched the side of his face on a rose bush when gardening and contracted a staphylococcal infection, which entered the blood stream and spread throughout the body resulting in multiple abscesses on the skin and the lungs and the loss of an eye. The man's condition improved after the administration of penicillin but the supply was limited and much too dilute and even had to be extracted from the man's urine for re-use. The bacterial infection was far too advanced for the amount of antibiotic available and the man's condition deteriorated and he died a month later.

Further experiments showed that penicillin was not an easy substance to purify and the yields were low and unpredictable. Moreover, the chemical structure of penicillin was complex containing the ß-lactam ring so synthesis from simple chemicals was not an option and the mould had to be produced by fermentation. In this connection, an important member of the Oxford team was Norman Heatley (1911-2004) who made major contributions when he improved considerably the production techniques for penicillin by use of deep-tank fermentation. In the mass production of penicillin much help was obtained from pharmaceutical companies located in the USA. This collaboration was crucial during the war years because the required facilities were not available at pharmaceutical companies in the UK.

When the antibiotic power of this *"magic bullet"* was fully appreciated, massive amounts of penicillin were needed to treat wounded allied soldiers during WW2. Bacterial infections were a common cause of death after gun-shot wounds and without penicillin to fight bacteria the wound became septic resulting in a certain death. By 1944 penicillin was available in large quantities and its use must have saved tens of thousands of lives.

In 1945 the Nobel Prize in Physiology or Medicine was awarded jointly to Fleming, Florey and Chain for their work on penicillin, a discovery that ranks alongside that of insulin as one of the twentieth century's greatest benefits to mankind. As often happens after such a major discovery relationships between those involved can become strained and there arose differences of opinion about the respective roles and contributions of Fleming at St. Mary's compared with the Oxford researchers (Florey and Chain). Funding for much of the research done at Oxford came from the Medical Research Council (British taxpayers) and ironically at the time it was not considered *"gentlemanly"* to take out a patent on the discovery of this life-saving drug. This meant that Britain had to pay royalties to American companies for the manufacture and sale of penicillin, much to the animosity of Ernst Chain, who was a rather flamboyant individual and an early scientific entrepreneur.

Alexander Fleming was a man of few words, he was humble, soft-spoken and his introverted personality made him a popular target for newspaper reporters. After the Nobel awards Fleming became in great demand by the news media to give interviews and speak on the radio to relate the circumstances of his chance discovery of such a wonder drug. The story of an air-borne fungus, which just happened to enter an open laboratory window during the summer months in London, giving rise to a life-saving drug was hard to resist by the media and the general public.

Fleming was showered with awards and honorary doctorates and he became a world traveller with invitations to give plenary lectures at conferences until the time of his death after a sudden heart attack in 1955. His first wife had died in 1949 and at 72-years of age Fleming married a Greek scientific colleague and co-worker 28 years his junior. Howard Florey achieved a distinguished career in the UK and in his native Australia, among other things he was awarded a life peerage in 1965 (Baron Florey of Adelaide and Marston) and was also elected to the Presidency of the Royal Society of London in 1960. After the Nobel award Ernst Chain moved to live in Italy serving as the head of a large research institute devoted to basic research in bacteriology and biochemistry. Much later he returned to work in the UK when he was appointed Professor of Biochemistry at Imperial College London.

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Acknowledgment

The illustrations and photographs included in these essays about the discovery of drugs were collected over several years from various sources, such as medical libraries, books, scientific journals and more recently the Internet and Wikipedia. The covers of some books, magazines and journal articles were scanned from the originals in my own archives. Several pharmaceutical companies, including Hofmann-La Roche and Bayer AG., were generous in providing information about the discovery of benzodiazepines and aspirin, respectively. Other images and chemical symbols included in the text are already in the public domain including the portraits of some of the pioneers in pharmacology and toxicology, which were taken from the internet (Google photos). The photographs of a few celebrities, alleged victims of drug-related poisonings, were obtained from magazines or web-sites devoted to the deceased.

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APPENDIX 1

List of Chemical Structures of the Drugs Included

The First Sedative Hypnotics

Chloral Hydrate
Trichlorethanol
Ethchlorvynol
Methyprylon
Meprobamate
Methaqualone
Glutethimide
Ethanol
Tribromoethanol
Gammahydroxybutyrate
Paraldehyde
Chlormethiazole
Doxylamine
Ethinamate
Zolpidem
Diazepam
Phenobarbital

The Barbiturates

Barbituric acid
Barbital
Phenobarbital
Pentobarbital
Hexobarbital
Allobarbital
Alpheal
Amobarbital
Aprobarbital
Butabarbital
Butalbital
Butethal
Cyclobarbital
Hepatabarbital
Vinbarbital
Talbutal
Secobarbital
Vinylbital
Mephobarbital
Probarbital
Brallobarbitall
Methabarbital
Butallylonal
Cyclopentabarbital
Sigmodal
Hexethal
Thiobarbituric acid
Thiopental
Thialbarbital
Thiamylal

The Benzodiazepines

Chlordiazepoxide
Diazepam
Nordiazepam
Oxazepam
Temazepam
Nitrazepam
Lorazepam
Flurazepam
Flunitrazepam
Alprazalam
Parazepam
Triazolam
Bromazepam
Clonazepam
Midazolam
Chlorazepate
Estazolam
Medazepam
Tetrazepam

APPENDIX 1

List of Chemical Structures of the Drugs Included

Narcotic Analgesics

Heroin (diacetyl morphine)
6-acetyl morphine
Morphine
Normorphine
Codeine
Ethyl morphine
Morphine-3-glucuronide
Morphine-6-glucuronide
Thebaine
Dextromethorphan
Methadone
Buprenorphine
Nalorphine
Naloxone
Naltrexone
Hydrocodone
Hydromorphone
Dihydrocodeine
Dihydromorphine
Oxycodone
Oxymorphone

Central Stimulant Amines

Amphetamine
Methamphetamine
Phentermine
Phenmetrazine
Diethylpropion
Cathinone
Ephedrine
Phenethylamine
Pseudoephedrine
Norephedrine
Mescaline
MDA
MDMA (ecstasy)
MDEA
MBDB
Methylphenidate
p-Methoxyamphetamine
Noradrenaline (norepinephrine)
Dopamine
Tyramine
Fenfluramine

The First Antidepressants

Imipramine
Amitriptyline
Nortriptyline
Trimipramine
Doxepin
Moclobemide
Perphenazine
Mianserin
Mesoridazine
Tranylcypromine
Clomipramine
Iproniazid

APPENDIX 1

List of Chemical Structures of the Drugs Included

Antipsychotic Medication

Phenothiazine
Promethazine
Chlorpromazine
Thioridazine
Haloperidol
Clozapine
Risperidone
Olanzapine
Ziprasidone
Sulpiride
Quetiapine

Aspirin and Other NSAID

Salicylic acid
Acetylsalicylic acid
Acetaminophen
Indomethacin
Phenacetin
Antipyrine
Acetanilide
Phenylbutazone
Ibuprofen
Diclofenac
Naproxen
Refecoxib

General Anesthetics

Diethylether
Ethylene
Chloroform
Xenon
Argon
Enflurane
Cyclopropane
Halothane
Nitrous oxide
Methoxyflurane
n-Pentane
Trichlorethylene
Ketamine
Isoflurane
Servoflurane
Desflurane
Nitrogen
Propofol
Fentanyl
Thiopental

APPENDIX 1

List of Chemical Structures of the Drugs Included

SSRI Antidepressants

Fluoxetine
Sertraline
Citalopram
Paroxetine
Bupropion
Mirtazapine
Venlafaxine
Zimelidine
Duloxetine

Histamine Antagonists

Histidine
Histamine
Diphenhydramine
Pyrilamine
Chlorpheniramine
Chlorcyclizine
Promethazine
Doxylamine
Loratadine
Fexofenadine
Desloratadin
Antazoline
Acrivastine
Cyproheptadin
Cimetidine
Ranitidine
Famotidine
Nizatidine

Anticonvulsants

Phenobarbital
Phenytoin
Valporic acid
Carbamazepine
Diazepam
Gabapentin
Tiagabine
Zonisamide
Pregabalin
Lamotrigine
Topiramate
Vigabatrin

APPENDIX 2

Scientists mentioned in the text

[1] Nobel Laureates.

Alles, Gordon (1901-1963)
Axelrod, Julius (1912-2004)[1]
Baeyer von, Adolf (1835-1917) [1]
Banting, Frederick (1891-1941) [1]
Beckett, Arnold (1920-2010)
Berger, Frank (1913-2008)
Berzelius, Jöns Jacob (1779-1848)
Best, Charles (1899-1978)
Black, James (1924-2010) [1]
Bovet, Daniel (1907-1992) [1]
Brodie, Bernard (1907-1989)
Buchheim, Rudolf (1820-1879)
Cade, John (1912-1980)
Carlsson, Arvid (1923-) [1]
Chain, Ernst (1906-1979) [1]
Christison, Robert (1797-1882)
Collip, James (1892-1965)
Dalay, Jean (1907-1987)
Dale, Henry (1875-1968) [1]
Davy, Humphry (1778-1829)
Deniker, Pierre (1917-1998)
Ehrlich, Paul (1854-1915) [1]
Elion, Gertrude (1918-1999) [1]
Faraday, Michael (1791-1867)
Fisher, Emil (1852-1919) [1]
Fleming, Alexander (1881-1955) [1]
Florey, Howard (1898-1968) [1]
Greengard, Paul (1925-) [1]
Heatley, Norman (1911-2006)
Hitchings, George (1905-1998) [1]
Hoffmann, Felix (1868-1946)
Holmes, Wendell Oliver (1809-1894)
Janssen, Paul (1926-2003)
Kandel, Eric (1929-) [1]
Kelsey, Oldham Francis (1914-2009)
Kline, Nathan (1916-1982)
Knorr, Ludwig (1859-1921)
Kuhn, Roland (1912-2005)
Laborit, Henri (1914-1995)
Lewin, Louis (1850-1929)
Liebig von, Justus (1803-1873)
Liebreich, Oscar (1839-1908)
Locock, Charles (1799-1875)
Macleod, John (1876-1935) [1]
Meissner, Carl (1792-1853)
Mering von, Josef (1849-1908)
Morton, William (1819-1868)
Orfila, Mathieu (1787-1853)
Paracelsus (1493-1541)
Pasteur, Louis (1822-1895)
Perkin, William Henry (1838-1907)
Pirquet von, Clemens (1874-1929)
Priestley, Joseph (1733-1804)
Randall, Lowell (1911-2005)
Scheele, Carl Wilhelm (1742-1786)
Schmiedeberg, Oswald (1838-1921)
Schou, Mogens (1918-2005)
Sertürner, Freidrich (1783-1841)
Shulgin, Alexander (1925-)
Simpson, James Young (1811-1870)
Stas, Jean Servais (1813-1881)
Sternbach, Leo (1908-2005)
Stone, Edward (1702-1768)
Swaine-Taylor, Alfred (1806-1880)
Sydenham, Thomas (1624-1689)
Vane, John (1927-2004) [1]
Wells, Horace (1815-1848)
Wöhler, Friedrich (1800-1882)
Wood, Alexander (1817-1884)
Wright, Charles Alder (1844-1894)

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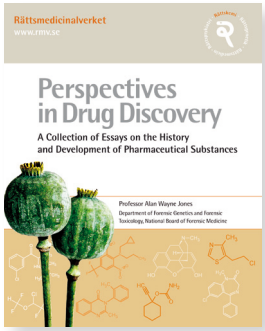
Perspectives in Drug Discovery

A Collection of Essays on the History and Development of Pharmaceutical Substances

Alan Wayne Jones



This RMV report deals with the history and development of medicinal drugs with a major focus on substances encountered in routine forensic casework, especially in traffic crimes, such as driving under the influence of drugs (DUID) and in post-mortem toxicology when drug poisoning deaths are investigated. Most people, at one time or another, find it necessary to take medication especially the elderly, who might be prescribed several different drugs at the same time (poly-pharmacy). This report should be of special interest to newly recruited staff within the RMV organization as well as those with a general interest in medicinal chemistry and pharmacology. One aim of the essays was to highlight the human side of pharmacology in medicine by including details about the scientists involved and their quest to discover new therapeutic agents.