

# INTRODUCTION TO MEDICINAL CHEMISTRY

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**Introduction:** The subject of medicinal chemistry explains the design and synthesis of compounds that can be used for the prevention, treatment or cure of human and animal diseases. Medicinal chemistry includes the study of already existing drugs, of their biological properties and their structure activity relationships.

Medicinal chemistry was defined by an IUPAC specified commission as “it concerns with the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level”.

Medicinal chemistry covers the following stages:

- (i) In the first stage new active substances or drugs are identified and prepared from natural sources, organic chemical reactions or biotechnological processes. They are known as lead molecules.
- (ii) The second stage is optimization of lead structure to improve potency, selectivity and lessen toxicity.
- (iii) Third stage is development stage which involves optimization of synthetic route for bulk production and modification of pharmacokinetic and pharmaceutical properties of active substance to render it chemically useful.

Medicinal chemistry is the application of chemical research techniques for the synthesis of pharmaceuticals. During the early stages of medicinal chemistry development, scientists were primarily concerned with the isolation of medicinal agents found in plants. Today, scientists in this field are also equally concerned with the creation of new synthetic drug compounds. Medicinal chemistry is almost always geared toward drug discovery and development.

Medicinal chemists apply their chemistry training to the process of synthesizing new pharmaceuticals. They also work on improving the process by which other pharmaceuticals are made. Most chemists work with a team of scientists from different disciplines, including biologists, toxicologists, pharmacologists, theoretical chemists, microbiologists, and biopharmacists. Together this team uses sophisticated analytical techniques to synthesize and test new drug products and to develop the most cost-effective and environmental friendly means of production.

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The focus on development of new synthetic drug compounds has resulted in the incorporation of many other disciplines, such as biochemistry and molecular biology into medicinal chemistry. These areas include biology, computer-aided design, X-ray crystallography, metabolism and pharmacokinetics, legal and regulatory affairs, clinical, franchise management, pharmaceuticals, and process research chemistry.

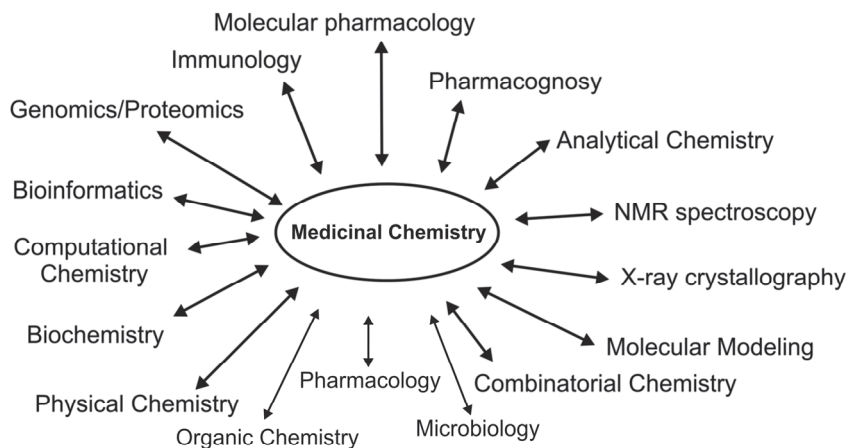


Fig. 1.1. Modern Medicinal Chemistry

### History of medicinal chemistry:

#### Chronology of drug introductions

##### 8000 BC: Prehistoric medicine

It is difficult to imagine anything other than modern medical treatments but for thousands of years humans have become ill and for the same amount of time people have tried to cure them. Our ideas about medicines in prehistoric times come from archaeologists who have excavated and explored ancient sites. Their findings reveal a very different world to the one we experience today.

Cave paintings and symbolic artefacts found by archaeologists suggest the earliest humans believed in spirits and supernatural forces. One form of primitive surgery seems quite shocking. Ancient skulls have been found with a hole bored into them. This appears to have been a deliberate operation and carried out whilst the person was still alive. We can only speculate as to the reason for this operation, called trepanning, but it may have been to allow the evil spirits to leave a sick person.



Fig. 1.2. Trepanning: an ancient human skull viewed from above. Note the large hole

### 2000 BC : Egyptian medicines

The ancient Egyptians built pyramids to bury their Pharaohs and worshipped gods who ruled every aspect of their lives. The goddess Sekhmet was believed to cause or cure diseases and priests played a large part in Egyptian medicine. Archaeologists have found documents, written on a type of paper called papyrus, that describe medical techniques similar to those used today. The Egyptians used compression on a wound to stop bleeding and had specialists in obstetrics and gynaecology who were the forerunners of modern midwives.

Their pharmacists prepared prescriptions of ointments, lotions, inhalers and pills by processing plant materials that were used to treat specific illnesses. Records show that they used many preparations including opium, cannabis, linseed oil and senna. Many modern drugs have originated from the study and isolation of active ingredients from plants with healing properties.



**Fig. 1.3. Egyptian hieroglyphs:** like this one, show medical procedures. *Wellcome Library, London*

### 450 BC to 300 AD: Greeks and Romans

Greece was home to one of the earliest civilisations. Writing, mathematics, philosophy and the arts all flourished. The Greeks believed in many different gods but they also tried to understand their world in a much more scientific way.

Possibly the most famous name in medicine belongs to the Greek philosopher Hippocrates. He is seen as the father of modern medicine and gives his name to the Hippocratic oath that doctors take.

The Romans realised that there was a link between dirt and disease. To improve public health, they built aqueducts to supply clean drinking water and sewers to remove wastes safely. Improved personal hygiene helped to reduce disease and Roman baths were places to socialise as well as stay clean.



**Fig. 1.4. Hippocrates:** famed for the Hippocratic oath

### 500 - 1400 AD: The Middle Ages

The fall of the Roman Empire meant that many of their public hygiene practices were soon lost. The middle ages in Europe saw most people without access to clean drinking water, regular bathing or a sewage system. This meant that health conditions were often worse than during the Roman occupation of earlier centuries. Most people were farmers and food was not as plentiful as today. Starvation and disease were common.

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Medicine in the Middle Ages was dominated by religion. Sickness was believed to be a punishment from God for sins committed and the only way to cure someone was to pray for their forgiveness. Doctors in the middle ages were usually priests or other religious scholars. Hospitals often sprang up in monasteries and other religious establishments. The patients were given food and comforted by religious nursing staff but little else was done to cure their illness.

Traditional cures, using herbal remedies and potions were seen as witchcraft and outlawed by the church. Laws stated that only trained and registered people could practice medicine. Schools and universities began to educate wealthy individuals in religion, the arts, law and medicine. Generally, men, and occasionally a few women, were trained and allowed to become physicians. As universities developed, more and more came from a non-religious background and eventually it was not necessary to be a cleric to practice medicine.

Surgery was a crude practice during the Middle Ages but operations such as amputations, setting broken bones, replacing dislocations and binding wounds were relatively common. Opium was sometimes used as an anesthetic while wounds were cleaned with wine to prevent infections.

During the Middle Ages, the only treatments were superstitious remedies, prayer, herbal medicines and recipes for clearing the air of miasma or poison. The plague was considered to be a punishment from God and so public health was not considered to be important.

#### 700 - 1500 AD: Arabic medicines

For many centuries after the fall of the Roman Empire, the Arabic world was the centre of scientific and medical knowledge. Texts from Greece and Rome were translated into Arabic and studied by Islamic scholars. They developed and refined Hippocrates's theories and Islamic physicians began to use the regulation of diet, exercise and the prescription of medicinal herbs in the treatment of their patients. Arabic pharmacists became skilled in the formulation of medicines from plants and minerals. Even though they did not know about microbes, they used alcohol to clean wounds which healed better and did not become infected.

Records show that Arabic doctors performed many different surgical operations including the removal of varicose veins, kidney stones and the replacement of dislocated limbs.



**Fig. 1.5. A medieval hospital:** Patients were given food and cared for by monks and nuns. *Wellcome Library, London*



**Fig. 1.6. The Arab Physician and scholar Ibn Sina (or Avicenna).** *Wellcome Library, London*

They used sponges soaked in narcotic drugs which were placed over the patient's nose as early anaesthetics.

### 1700 - 1900: 18<sup>th</sup> and 19<sup>th</sup> centuries

The industrial revolution of the eighteenth and nineteenth centuries saw a massive change in the way, people lived and how this affected their health. People moved from small villages and an agricultural lifestyle to live in towns and cities that sprang up around the new factories, where they could work. People lived in dirty, overcrowded conditions with poor sanitation and dirty drinking water. Many died from diseases such as cholera, tuberculosis, measles and



**Fig. 1.7. Operating theatres:** In 1900 were not the sterile environments

pneumonia infections that could spread quickly and easily in these conditions. Two of the big medical advances of this time were: vaccinations, X-rays.

Edward Jenner pioneered the earliest vaccinations and discoveries by Louis Pasteur and Robert Koch led to the understanding that infections were caused by certain bacteria or germs. The study of microbes, or microbiology, was born and the increased knowledge of pathogenic microbes led to the development of new medicines to tackle infectious diseases. The pharmaceutical industry was born.

The ideas of an earlier physician, Thomas Sydenham, were applied and this led to a great advance in the treatment of patients. He recognised the importance of detailed observation, record-keeping and the influence of the environment on the health of the patient.

### 1900 - 2000: The 20<sup>th</sup> century

In 1901, the average life expectancy in the United Kingdom was 47 years. By the year 2000 it had risen to 77 years. New medicines, improved air quality and better public hygiene has contributed to this 64% increase in the life-expectancy. The twentieth century has seen some major advances in healthcare. These have included the development of:

- Penicillin: The discovery and development of antibiotics by Fleming, Florey and Chain.
- Insulin: Banting and Best's work to show that insulin can be used to treat diabetes.
- Other medicines: Pharmaceutical laboratories around the world are constantly producing new treatments for diseases.

## Development of various classes of drugs

### Anesthetics

In the first century AD the Greek physician Pedanius Dioscorides (40-90 AD) described the use of wine of mandragora to produce sleep. Early Arab writings also mention anesthesia by inhalation. Guy de Chauliac (1300-1368) employed compression of the nerve trunk in the 1300s, and Ambroise Pare did the same in the 1500s. Priestly discovered nitrous oxide in 1772, and in 1800 Humphrey Davy discovered the gas's anesthetic properties when inhaled. Davy's student, Michael Faraday, showed in 1818 that inhalation of ether had the same effect. Henry Hill Hickman (1800-1830) experimented with both carbon dioxide and nitrous oxide on animals to carry out painless surgery in the early 1820s. Boston dentist William T.G. Morton arranged the first public demonstration of ether-anesthetized surgery in 1846. In 1842, Crawford W. Long, a physician of Georgia, flashed with the possibility of using ether as an agent to relieve pain. Queen Victoria's use of chloroform for her own labors in 1853 and 1857 firmly established the procedure as standard in childbirth. In 1922 ethylene was added to the list of general anesthetics. In 1929 at the university of Toronto, Lucas and Henderson used cyclopropane as general anesthetics. This gas gives deep surgical anesthesia in concentrations of 15 percent compared with 90 percent with nitrous oxide or 80 to 90 percent of ethylene.

Carl Koller demonstrated the use of cocaine as a local anesthetic in 1884. The addictive cocaine was replaced by synthetics beginning with Novocaine in 1904. The German doctor August Bier refined the technique in 1898, and Rudolph Matas of New Orleans introduced it to the United States in 1899. By the 1920s the use of spinal anesthesia was widespread in the United States. Robert Boyle first attempted intravenous anesthesia and the renowned architect. The idea, however, was abandoned until about 1874, when Pierre Ore used chloral hydrate intravenously on a dog and then, in 1875, on a human patient. Once barbiturates were discovered in the early 1900s, and especially after improved substances were developed in the 1920s, the use of intravenous anesthetics became firmly established.

### Non-Steroidal Anti-Inflammatory agents

In 1874 Thomas John Maclagan introduced salicylic acid as an antiseptic tablet for internal use. In 1876 he observed antirheumatic activity for salicylic acid. In 1886, Eahn and Hepp reported acetanilide as an antipyretic. Shortly after the introduction of acetanilide, Hinsberg introduced phenacetin (somewhat less toxic). In 1893 paracetamol (a metabolite of phenacetin) was introduced but its superiority over phenacetin was recognized after 60 years. In 1837 Charles Gergardt synthesized acetylsalicylic acid. Twenty-one non-steroidal anti-inflammatory drugs (NSAIDs) approved in 1990.

### Cardiovascular Drugs

In 1775 William Withering reported foxglove as medicine. Oswald Schmiedberg managed to produce digitoxin (1882-1911). Albert Arnaud (1853-1915) extracted Ouabain from *Acokanthera* roots and bark and strophanthin from *strophanthus*. Amylnitrate had been synthesized in 1844 by Balard at the Sorbonne. Jerome Balard discovered bromine in 1826 and Amyl nitrate in 1844. In 1846, Ascanio Sobrero discovered nitroglycerine.

The use of quinidine as antiarrhythmic agent was established in 1920. In 1936 Frederick Mantz of Cleveland proved procaine as superior antiarrhythmic agent than cocaine or piperocaine.

### Antibiotics

Gramicidin, the first natural antibiotic extracted from soil bacteria in 1939. It arrests the growth of staphylococcus but highly toxic. The modern history of antibiotics began with the observation in 1928 by British bacteriologist Alexander Flemming. He found that *Penicillium notatum* produced a substance which has bacteriostatic. In mid-1950s, Penicillin is available orally to the public without prescription. Penicillin was first obtained as pure crystals by Wintersteiner in 1943. In 1957, Sheeran synthesized phenoxymethyl penicillin or penicillin V. In 1940, Selman Waksman isolated and purified actinomycin from *Actinomyces griseus* (Later named *streptomyces griseus*). In 1942 Walksman introduced streptomycin. In 1952, Walksman was awarded the Noble prize in Physiology or medicine for his discovery of streptomycin. During the following years, a succession of antitubercular drugs appeared. These were important because with streptomycin monotherapy, resistant mutants began to appear within few years, P-aminosalicylic acid (1949), isoniazid (1952), pyrazinamide (1954), cycloserine (1955), ethambutol (1962) were introduced as antitubercular drugs. The discovery of rifampicin in 1967 was considered one of the greatest achievements in the history of chemotherapy against tuberculosis. Chloramphenicol was first isolated from cultures of *streptomyces venezuelae* an organism from a soil sample collected from Venezuela (1948). During the immediate past war years, microbiologists conducted an extensive global search for novel antibiotic producing organisms. In 1945 G. Brotzu cultivated *cephalosporin acremonium* from sea water near a sewage outlet on the coast of sardinia. Cephalosporin C was structurally related to penicillins, but exhibited resistance to penicillinase. In 1964, cephalothin and cephaloridine were marketed as broad spectrum injectable antibiotics. Cyclosporin was one of several antifungal antibiotics isolated from certain varieties of fungi imperfecti in 1969.

### Antitubercular Drugs

Tuberculosis was one of the major causes of death until the beginning of the 20<sup>th</sup> century. Half of the patients with active pulmonary tuberculosis died within two years, a quarter recovered and a quarter became chronic positive cases. In 1943 the Swedish researcher Lehmann discovered the anti-tubercular action of para-aminosalicylic acid (PAS). In 1946 the development of streptomycin led to a true revolution in treatment (Selman Waksman, Nobel Prize 1952). In 1952 isoniazid (INH) was discovered as a tuberculostatic. Rifampicin then followed in 1970.

### Antiseptics

The concept of antiseptics was introduced in 1750 by Sir John Pringle. In 1815 the antiseptic properties of coal tar were recognized. Mercury benzoate, carboxylate and salicylate were introduced in the late 1880s. These were water insoluble and later water soluble compounds were introduced one after the other.

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### Antihistaminic drugs

In 1910, it was shown that histamine was formed by putrefaction of proteins containing the amino acid histidine. In 1942 Boret and Stanb introduced *phenbenzamine*. Boret introduced mepyramine in 1944 followed by tripelemnamine, diphenhydramine, triprolidine and cyclizine. The early antihistamines were unable to antagonize the release of gastric acid caused by the action of histamine. In 1976 cimetidine was introduced into clinical practice. Ten years later cimetidine and the closely related ranitidine had become the two best selling drugs in the world. In April 2020, the Food and Drug Administration (FDA), in 2022, India has removed ranitidine (found to have low-level N-Nitrosodimethylamine (NDMA), which according to the NIH, is marked as human carcinogens, associated with cancers of the stomach, esophagus, nasopharynx, and bladder). from essential drug list.

### Antiepileptic drugs

The original first generation antiepileptic drug, a bromide salt appeared in 1857. In 1912 phenobarbitone came into use for epilepsy. Tracy J. Putnam and Houston H. Merritt introduced phenytoin as an antiepileptic drug in 1938. In early 1960s, carbamazepine, valproic acid and its derivatives were introduced to treat epilepsy. In mid-1990s a series of novel antiepileptic drugs were approved (felbamate, lamotrigine, gabapentin etc.).

### Diuretics

In 1925 chlorothiazide (diuril), a thiazide diuretic was introduced. In 1962 Mersalyl and ethacrynic acid were identified. Potassium sparing diuretic – triamterene was found in 1963.

### Anticancer agents

Many anticancer drugs are extracted from plants. More than 1600 genera have been examined in recent decades (Vincristine, Vinblastine, Taxol etc.). Taxol introduced into the market in January 1993 by Bristol-Myers. Besides natural products, synthetic anticancer drugs flourished in various directions. The first agents were nitrogen mustards, among which 2-2'-2''-trichloro triethylamine was the prototype first studied by Louis Goodman and Alfred Gitroan. Antimetabolites in cancer treatment were discovered by George Hitchings and Gertrude Elion (6-mercaptopurine, azathioprine, allopurinol etc). Daunorubicin was isolated from *S.pencautius* in 1962. In 1972 the National Cancer Institute introduced cisplatin into clinical trials.