Origins of Medicinal Chemistry

3500 BC - Sumerians report use of opium
3000 BC - Chinese report use of ma huang (ephedra)

Greek culture:
Hippocrates- followed the teachings of Aristotle; focus is on the soul.
Galen- followed the teachings of Plato; focus is on experiment- believed the whole could be explained by the parts

Renaissance period:
Doctors were humanists- followers of Hippocrates- treat the soul and the body will heal. Initially, there were no relationships with alchemy.

Paracelsus (1493-1541)- adopted teachings of Galen; urged alchemists to discover the chemical essence of herbal drugs and to develop chemical medicines- particularly those composed of inorganic compounds (mercury, lead, antimony)

France (1560)- courts forbid the use of chemistry in medicines even though paracelsians are gaining in popularity - much controversy.

"The innumerable dissentions amongst the learned concerning the Arabick and Chymicke remedies at this day infinitely, and with opposite and contradictorie writings, and invectives, burthen the whole world."

John Cotta (1612)

In 1658, Louis XIV is cured of chronic digestive problems with an antimony purge- by 1666 the use of antimony and other chemical medicines is approved by the courts.....
In 1793, Faureroy & Vauquehin split from the monarchy-controlled bodies and establish the Ecole Supérieure de Pharmacie—1st to incorporate chemistry into the pharmacy curriculum. Develop research to find the active principles in plant-based drugs.

1803 - Derosse isolates a crystalline salt from opium

1817 - Sertürner publishes work demonstrating that the narcotic principle of opium is basic (alkaline) and, thus, it will form salts with acids—names the principle "morphius"

\[ \text{N:} + \text{H-X} \xrightarrow{\downarrow} \text{N}^+ \text{H}^\text{X}^- \]

Gay-Lussac predicts that other alkaline plant extracts will have useful medical properties—changes name of morphius to morphine

1818 - Meissner proposes the general term alkaloids

1853 - Henry How proposes that there are "functional groups" that can be chemically modified to alter reactivities…

Fraser and Brown make quaternary salts of many different alkaloids (i.e., morphine, strychnine, nicotine) and find that all exhibit curare-paralyzing activities—propose that quaternary salts have curariform activity

Stimulated by Fraser and Brown’s results, Alder and Wright treat morphine with various organic acids—synthesize diacetylmorphine.

1898 - E. Merck of Darmstadt markets Dionin (ethyl ether of morphine) as a cough sedative
Pierce tests diacetylmorphine and finds it be much more potent than morphine—thus, smaller doses can be given, which lowers toxicity.

1898 - F. Bayer & Co. markets diacetyl morphine as a safer alternative to morphine—described as a “heroic drug” and given the name “heroin”. Within 4 years the use of heroin was highly restricted.

In 1820 Pelletier isolated quinine from cinchona bark—by 1826 his group is producing 3600 kg/yr of pure quinine, which is used instead of cinchona extracts to treat malaria—birth of the pharmaceutical industry.

1840's - ether, chloroform, and nitrous oxide move from being party drugs to anesthetics - begins the search for other hypnotics.

1869 - Bucheim develops chloral hydrate, an oral compound that exhibits hypnotic properties—he argues that it produces chloroform in the blood while von Mering correctly postulates that it produces trichloroethanol.

F. Bayer & Co. markets its first successful pharmaceutical, sulphonal, a hypnotic produced from acetone.

Based on sulphonal, von Mering suggests that a carbon with two ethyl groups should be a good hypnotic—makes diethyl acetyl urea and then diethylbarbituric acid.
1875- Carl Buss isolates salicylic acid from *Spirea ulmaria* and shows that it is an effective antipyretic- however, it is unpalatable and causes gastric distress.

1883- von Nencki makes a salicylate ester with phenol, salol- it has very poor solubility but it is better tolerated. It is hydrolyzed slowly in the small intestine to give salicylic acid- the first sustained release drug

1890s - Hoffman at Bayer tests acetyl salicylic acid and finds it to be better tolerated- names it aspirin as in “a” for acetyl and “spirin” for *Spirea*. It is rapidly hydrolyzed in the gut to give active salicylic acid- it is a “pro-drug”

Phenazone was synthesized in 1884 and was the most popular drug world-wide until it was taken over by aspirin in the early 1900s- in addition to being an antipyretic, it also cured headaches- a new market was born...

1880s- Kussmaul’s lab in Strasbourg is trying to eliminate intestinal worms with naphthalene- they are mistakenly given acetanilide, which proves to be an effective antipyretic

Bayer & Co. makes ethoxyacetanilide and markets it as phenacetin

1893- Von Mering shows that para-hydroxyacetanilide (paracetamol) is an effective antipyretic and analgesic- it is later confirmed that paracetamol is the active metabolite of phenacetin and acetanilide. Sterling-Winthrop markets it as Panadol (acetaminophen), which is now marketed as Tylenol

1884- Carl Koller- an ophthamologist- at the advice of his friend, Sigmund Freud, evaluates the use of cocaine as a topical anesthetic. Within a month of publishing his results it is being used world-wide. By 1887 problems are widespread- stimulating the search for new anesthetics.
Braun adds a polar amino group from adrenaline to give procaine (novocaine)-addition of a butyl group gives tetracaine with greatly extended duration. In 1935 isogramine is isolated and found to be a very potent local anesthetic. In 1946 Löfgren synthesizes lidocaine modeled after isogramine-coin the concept of an "isostere". This remains the most commonly used local anesthetic. Addition of a butyl group gives the long lasting (~8 hours) bupivacaine, which is used for epidural anesthesia during childbirth.

Questions to ponder...

Why do these two alcohols differ in reactivity?

Why does this OH group react with phenol to form an ester? While the other reacts with acetic acid to give an ester?

Why is it that only this nitrogen is charged?

Why does this amine react with CH$_3$I?

Why do CYP450 enzymes put an OH group only at this position?