

Brief Description: Critical review of global historical landmark developments of drugs. Associated pharmacological sciences, scientists, institutions that were key to the drug discovery will be included.

Introduction

In the book, *The Common Sense of Science*, the author Jacob Bronowski wrote... "The purpose of science is to describe the world in an orderly scheme or language which will help us to look ahead". An orderly scheme means history which must connect with the sequential logical events. The current cumulative knowledge about drugs is vast and appears fragmentary. The study of the history of drugs and chemicals is essential for the proper utility of these substances by the population at large. Since the 1950s, our knowledge of medicine and pesticides increased greatly. Students in general are not familiar with the fascinating historical events and scientific stories associated with natural or synthetic substances. It is important to note that plants containing morphine, THC, hyoscyamine, physostigmine, pilocarpine, tubocurarine, digoxin, ephedrine and reserpine were used by various cultures for centuries before pure active therapeutic constituents were isolated and chemically characterized. Template molecules were synthesized. Parallel to these developments, the science of anatomy, physiology, biochemistry and pharmacology advanced. Better testing methods developed. Causes of many diseases were better understood. Drug laws were instituted. Pharmaceutical industry flourished. Class presentations should include the panoramic view of when, where, who, how and why drugs were developed.

Syllabus

- I Human migration and botanical legacy from ancient cultures, Drugs and Diseases, exchange by Globetrotters. Discovery of circulation of blood- Harvey, 1628 A.D.
- II The Discovery of Natural Therapeutic Agents (~1600-1800)
- III Hypnosis, Hypnotics & Anesthetics For Surgery.
- IV Foundations of Experimental Pharmacology by Fontana, Magendie and his students, Christison, et al. (1700-1850)
- V Neuro-Functional outline of the Nervous System, Langley, et al.
- VI First half of Twentieth Century: Landmark Developments. Abel, Chemical transmission, Aspirin, Chen, Psychedelics, WWII – Fractionation of Plasma, Sulfa Drugs, Antibiotics, Insulin, Easson-Stedman Theory, Drug receptors, Quantitative Pharmacology, Nobel prizes in Chemistry, Medicine or Physiology.
- VII Second Half of the Twentieth Century: Contributions of Ariens, Stephenson, Gaddum, Schild, Axelrod, Furchgott, Trendelenburg. Discovery of action of reserpine, chlorpromazine, catecholamines, DCl and adrenoceptors.
- VIII Golden Age of Pharmacology and Drug Industry.
- IX Structure and Function of receptors, Gilman, Lefkowitz, Changeux.
- X Pesticides and hidden problems. Role of FDA and EPA.
- XI Biotechnology and Anticancer Therapy.
- XII Rise of nutraceuticals, back to nature, ethics, advertising, information overload and sensible healing medicine.

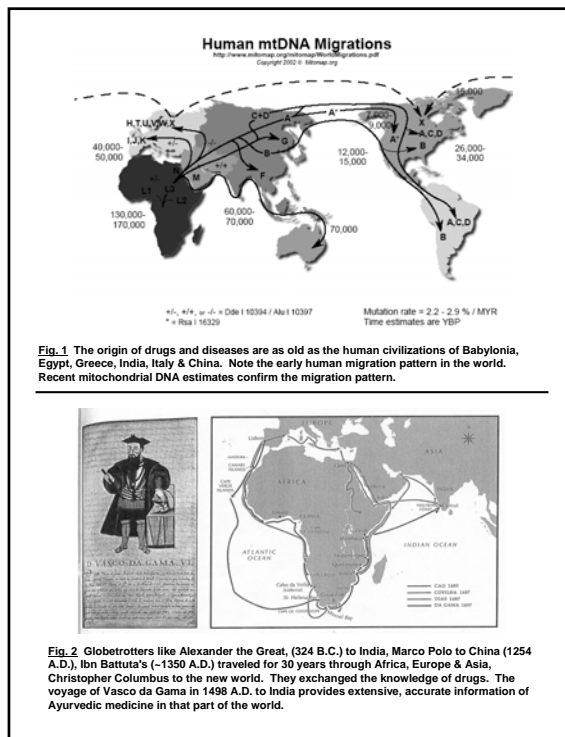
Comments: On Section I and II

It is said that history needs distance and perspective. Ancient remedies developed in different parts of the world, written in different scripts, are difficult to decipher. Our understanding is based mainly on translation of old documents through current perspectives. Books on ancient Egyptian, Greek and European history provide some unique illustrations, artifacts and pharmaceutical antiques for the preparation of the lecture. But details of oriental drugs, translated into English from Sanskrit literature or Chinese medicine are scant. Since the time of Alexander-the-Great and others, the exchange of diseases and drugs occurred. Gaitonde wrote some impressive drug history during the time of Portuguese explorer Vasco da Gama in India. Then Unani system found its way through Muslim invaders.

Between 1500 AD to late 1600, many important personalities like Andreas Vesalius, Antony van Leeuwenhoek and William Harvey provided foundations for the future of medical sciences and drug discovery.

Isolation of pure active substance from poppy capsules by the German Pharmacist, F. Serturner, in 1805 paved the way for the isolation of many alkaloids from medicinal plants. By the 1820's industrial production of drugs was initiated. The stories are unique!¹⁻⁹

There is plenty of information on scurvy and its cure, spread of plague and the flu pandemic.



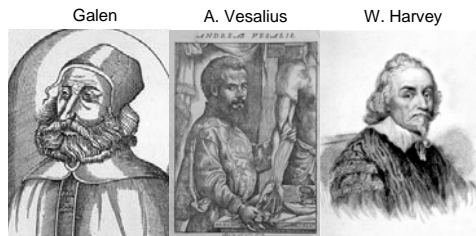


Fig. 3 **Galen** (130-200 A.D.) dominated the early medicine in Europe for nearly 1500 years until **Andreas Vesalius** created "Fabrica", 1543, the foundation of anatomy and the discovery of circulation by **William Harvey**, in 1628. Soon microbes and the microcirculation was viewed under the microscope built by **Louwenhoek** ~1670 A.D.



Fig. 4 **Friedrich Sertürner**, the Pharmacist in Germany, perfected isolation of pure morphine (morphine) alkaloid from poppy capsules in 1805. The alkaloid was tested for the narcotic action on laboratory animals and on his associates.

Comments: On Section III

In the Pharmacology Textbook, Peter J. Cohen wrote an interesting history of anesthesia.¹⁰

Chronology of the introduction of medical gases and related substances: Nitrous oxide (1840s-1860) by Wells & Colton; Chloroform (1950s) by Simpson; Ether (1842-1847) by Jackson, Long, Morton, Squibb; Ethylene (1922) by Luckhardt; then Cyclopropane (1930s), Halothane (1956) like agents were introduced.

Morton obtained a patent in 1846, but it was protested by chemists Jackson, Long and Wells because of proprietary claims. Nobody was a winner of the complicated case. Dr. Edward Robinson Squibb, MD 1845, was an assistant surgeon in the US Navy. He noticed problems, impurities and causes of variations in ether anesthesia. He was the first person to produce pure ether of uniform potency. He invented the mask that replaced the inhaler of Dr. Morton. O.W. Holmes coined the words anesthesia, anesthetic and anesthetist. After World War I, fluorinated chemicals were synthesized as refrigerants. In 1946, Robbins at Vanderbilt University and McBee at Purdue University produced over 40 compounds and examined their activity. John C. Krantz, Jr. introduced trifluoroethyl vinyl ether into clinical anesthesia in humans. In 1953, Fluoromar showed excellent anesthetic activity without fire hazard. Halothane was also introduced. Dr. Max Sadove, anesthesiologist at the University of Illinois, tested the effect in a clinical setting (1953). Ethrane was safely marketed.

H. Behrend used potassium bromide in patients to induce sleep (Lancet, 1:607, 1864). Its anti-epileptic properties were discovered later. Oscar Liebreich (1839-1908), MD from Berlin, Professor of Pharmacology at Berlin, demonstrated the anesthetic properties of chloral hydrate and its usefulness as a hypnotic (~1869). Josef von Mering taught forensic medicine at Strassburg. He worked with Schmiedeberg and Ludwig. In 1903, with Emil Fischer, they conducted the most comprehensive SAR work on hypnotics, anesthetics and antiepileptics. Barbitol, propional and diphenylhydantoin were introduced in medicine.

Carl Köller (1858-1944) used cocaine drops in 1884 to produce corneal anesthesia in animals and patients (J. Amer. Med. Assoc., 90 1742, 1928). Walter Sneader well outlined the story of the development of xylocaine.¹¹⁻¹³

Comments: On Sections IV and V

According to the dissertation of the historian, M.P. Earles, Felice Fontana (1730-1805) conducted about 6000 well designed experiments on Viper venom. His investigations were inspired by the well known physiologist, Haller. Fontana was a keen unbiased observer who used the 'control' experiments in scientific investigations. Studies were repeated across the animal species and the implication to humans was extended. For the century earlier the remedy for snake bites included viper fat, olive oil, oil of amber, ammonia, and the application of 'spongy-stone'. The investigative mind of Fontana questioned these claims where over 3000 vipers were utilized. The outcome was a noteworthy contribution in pharmacology and toxicology.

Francois Magendie (1783-1855) who provided experimental physiology as the foundation for pharmacology. He was a rational experimental scientist at heart; a free, motivated explorer who, between 1808-1822, contributed to localization of the effect of nux vomica on the spinal cord and the value of 'controls' in medicine. In animal experiments, he discovered (with collaborators P.J. Pelletier Caventou and P.J. Robiquet) the potential pharmacotherapeutic effects of emetine, strychnine, brucine, veratrine, colchicine and quinine, all documented in "Formulaire" (1821). He described decerebrate rigidity and found foramen in the roof of the fourth ventricle. Magendie discovered the dorsal spinal nerves are sensory and ventral outflows are motor nerves (1822).

His famous students include Claude Bernard, Rudolf Buchheim, James Blake, Hyacinthe Laennec who invented stethoscopes and Philippe Pinel who initiated the humane treatment of patients and started modern psychiatry.^{1, 13}

Robert Christison (1797-1882), a Scottish pharmacologist, received medical education in Edinburgh. He studied chemistry with the well-known toxicologist, MJB Orfila, in Paris and wrote an authoritative book titled, "Treatise on Poisons" (1829). He worked on oxalic acid, arsenic, lead and hemlock. Self-medication with Calabar Bean is described in a monthly Journal of Medical Science, London and Edinburgh, 20, 193, 1855.

Comments: On Sections IV and V (continued...)

Thomas Richard Fraser (1841-1920) He was a student of Christison who studied cholinomimetic actions of extract of Calabar bean. His dissertation won a gold medal at the University of Edinburgh. Physostigmine was introduced in ophthalmology. He succeeded Christison as Professor of Materia Medica and Therapeutics. During 1868-1869, in collaboration with the chemist A. Crum Brown, Fraser published an important finding that quaternization of tertiary alkaloids produces neuromuscular paralyzing action in animals. He also studied antagonism between physostigmine and atropine in rabbits. The results were presented by 'Isobol' graphic method.¹³

J.N. Langley and the group of Physiologist from England together with students of J. Müller (1801-1858) and C. Ludwig (1816-1885) from Germany had a great impact in achievements in Physiology that is essential in drug research. Students must have this understanding of functional neuronal outline of the sensory and autonomic receptors.^{1, 13, 14}

F. Fontana



F. Magendie



Fig. 5 Felice Fontana (1730-1805) and Francois Magendie (1783-1855) be considered founders of experimental pharmacology and toxicology.

J. Müller



J.N. Langley



C. Ludwig



Fig. 6 Functional physiologic and pharmacologic studies of J.N. Langley (1852-1926) including J. Müller (1801-1858) and C. Ludwig (1816-1885) outlined the sensory and autonomic nervous system.

L. Pasteur



J.H. van't Hoff



Fig. 7 The remarkable achievements of Louis Pasteur (~1848) and J.H. van't Hoff (~1874) provides current understanding of stereochemistry and biological selectivity of the molecules.

Comments: On Sections VI and VII

In Germany, Oswald Schmiedeberg (1838-1921) mentored over 100 pharmacologists from 20 different countries. This accelerated drug research and education. John J. Abel spent 7 years in Europe and is considered the founder of American Pharmacology. Specific contributions of J.J. Abel include studies on electrical potentials in basic physiology, molecular weights of some bile constituents and composition of melanins. He discovered carbamic acid in alkaline horse urine and isolated ethyl-sulfide from dog urine and examined the long duration of action of anesthetic chloretone. In 1897 Abel and Crawford isolated the active principal of adrenal medulla. J. Takamine and J.J. Abel published the correct structure of epinephrine in 1901. With D.I. Match, Abel isolated cardiotoxic substances like adrenaline and bufagin from parotid gland of the toad *Bufo Agua*. After 1917, Abel and co-workers studied active principles of the posterior pituitary gland. E.M.K. Geiling and Abel isolated crystalline insulin in 1926. Toxins of *Amanita phalloids* were investigated. Abel and co-workers established the basic principles of artificial kidney dialysis, i.e., removal of toxic chemicals from plasma (1913). The information on the other subtopics in this section are easily available in literature.¹⁵⁻¹⁷

History of basic quantitative receptor pharmacology is vital for the drug research. It is well reviewed by David Colquhoun (2006) in TIPS, v. 27, P. 149.

J. J. Abel



Jokichi Takamine



Fig. 8 John J. Abel (1857-1938) The towering figure in American Pharmacology. J. Takamine and Abel proved the correct structure of epinephrine.

Comments: On Sections VIII – X

After 1950, rapid growth of the medical research occurred. Reserpine provided the valuable tool to understand the role of biogenic amines in the central nervous systems. Adrenergic mechanisms were elucidated. The number of pages in pharmacology textbooks increased. Chronic diseases, such as hypertension, arrhythmia, diabetes, asthma, glaucoma, Parkinson's syndrome, epilepsy and other neurological diseases are managed better by drugs than ever before. Effective antibiotics and antifungal drugs were developed. The Golden Age of pharmacology began and the tremendous growth of the pharmaceutical industry occurred. Many Nobel Prizes were awarded for basic or applied aspects of the therapeutic achievements. The information is exciting for the presentation.¹⁸⁻²⁴

Comments: On Sections XI and XII

These sections are lengthy, complicated and the difficult part of healthcare history. Willy Lange, a chemist at the University of Berlin and his student Gerda von Kreuger synthesized organophosphates in 1932. Vapours during synthesis produced cholinomimetic effects in the researchers. Subsequently, Gerhard Shrader of Leverkusen, Div. Of I.G. Farbenindustrie, synthesized additional chemicals, so that less toxic parathion was marketed in 1947.

Comments: On Sections XI and XII (continued...)

Organophosphate nerve gases, Sarin-like agents, produce cumulative effects. Pesticides pose major chronic health problems in the world. Better alternatives to irreversible inhibitors of acetylcholinesterase are needed.

In 1939, Paul Müller (1899-1965), a Swiss scientist, discovered DDT. He obtained a degree in chemistry from the University of Basel (1925). His achievements were recognized with a Nobel Prize, 1948. Currently, the use of DDT is curtailed, because it produces cumulative toxicity.

By law, the Environmental Protection Agency (EPA) must determine which substances used in the USA are dangerous and might be carefully released into the environment. Strict International Laws and enforcement is essential.

Superimposed on these hidden environmental contaminants, the iatrogenic diseases have increased significantly. Due to slow development of the disease, the specific toxicant is difficult to detect. Neurodegenerative diseases or cancer is treated with irregular success. Prevention is advocated.

As early as 1906 in the USA, the Pure Food and Drug Act was enacted. A physician-chemist, H. Wiley, was the chief architect who promoted such an act. Several revisions and amendments of these laws have occurred, including the Clean Air Act of 1972.

In 1957, Thalidomide was marketed in Europe. Many pregnant ladies who took the medicine gave birth to malformed babies. Dr. Frances O. Kelsey of US Food and Drug Administration blocked the entry of Thalidomide into the American market on the grounds that drugs were not fully tested in pregnant laboratory animals. Recently, a research physician, J. Folkman, graduate of The Ohio State University, reinvestigated the antiangiogenic effects of Thalidomide in male cancer patients with multiple myeloma. Along with other anticancer agents, the drug provides a beneficial effect in some patients. The ethical pros and cons of medicines continue. Barbara Seaman has carefully traced the use and abuse of diethylstilbesterol-like drugs prescribed to ladies for the management of menopause. Major side effects include a breast and/or cervical cancer, stroke and acceleration of osteoporosis. The ethical issues command greater and better attention of the health professionals.^{25, 26}

F. Kelsey



J. Folkman



Fig. 9 Dr. Frances Kelsey, then at the FDA, blocked the entry of hypnotic thalidomide, a teratogen, in the U.S. Market. (Courtesy of the American Society of Pharmacology and Experimental Therapeutics.) Judah Folkman, who found the new use of thalidomide in the treatment of cancer.

Some Thoughts on Implementation of the Course

The reasons for the initiation of the course are already presented in the introduction. The broad outline of topics is presented. The information is vast and class presentations in 15 or 50 lectures may present a challenge. Student participation in class discussion is essential to assimilate the history. Many events are connected with fascinating stories of drug discoveries and pharmacotherapeutics. The reading assignment should include multiple books along with reviews or chapters. The text by Holmstedt and Liljestrand is a concise document and may be assigned as a primary reference that is easy to read. In addition to the reading assignments, films are recommended.

Class presentations must include sketches, paintings, photographs, laboratories and their mapped locations in relation to the topic of interest. Every teacher has a different style for the take-home message that students must have. Class size and the examination grading system provide additional demands in the effective implementation of the course. Always it should be left with the instructor to make these adjustments to maintain the objectivity of the course. Internet distribution may be used but it has some limitations.

**Please provide your comments at patil.1@osu.edu
It will be greatly appreciated!**

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