History of Pharmacology: From the Origins to Modern Era

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What is Pharmacology?

Etymology:

*Pharmakon*: medicine, drug - *Logos*: science

William Paton (1986)

“If physiology is concerned with the function, anatomy with the structure, and biochemistry with the chemistry of the living body, then pharmacology is concerned with the changes in function, structure, and chemical properties of the body brought about by chemical substances”

Kenakin, A pharmacology primer, Chap.1, 3rd Ed., 2009

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... and in a modern perspective

Box 1 | **Various attempts to define Pharmacology**

- The scientific study of medicines and drugs.
- The branch of science relating to drugs and medicines.
- The study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes.
- The science studying the interactions between chemicals and living beings directed to prevent, ameliorate or cure the deleterious consequences of their diseases.
- The study of the manner in which the function of living systems is affected by chemical agents.
- The science that deals with the mechanism of action, uses and adverse effects of drugs.
- The scientific discipline that deals with the interaction between chemical agents and the living organism.
- Pharmacology is what pharmacologists do.

A journey through space and time
Sumerian medical clay tablet
Nippur
circa 2,225 BC
Antiquity

Ebers Papyrus (1,550 B.C.)
Antiquity

Shen-nung pen ts’ao ching (I and II B.C.)

Pen ts’ao kang mu
Li Shih-chen (1518-1593 A.D.)
Ayurveda (“Science of Life”)

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Hippocrates (460-377, B.C.)

“Father of Medicine”

Medicine v.s. superstition

Roman “portrait” bust (19th-century engraving)

Hippocratic oath

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Greece and Occidental Medicine

Theophrastus (372-287, A.D.)

“Father of Botany”

“Historia Plantarum”

Development of Pharmacy

1549

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Greece and Occidental Medicine

Dioscorides (40-90, A.D.)

“Father of Pharmacognosy”

De Materia Medica
Claudius Galenus (131-201, A.D.)

A pioneer of experimental physiology

Pharmacy: "galenic" preparations of plant active principles
Medieval Period (5-15th centuries)

First pharmacies (Bagdad, 754 A.D.)

Al-Biruni (973-1050, A.D.)

Kitab al-Saydalah ("The book of drugs")
Renaissance period (16th century)

**Nuovo Receptario Composito**
(Florence, 1498)

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Renaissance period (16th century)

Paracelsus (1493-1541)

“Father of Toxicology”
& “Grandfather of Pharmacology”

“sola dosis facit venenum”
Renaissance period (16th century)

Codex Badianus (1552)

Martin de la Cruz (Nahua)

Colegio de Santa Cruz de Tlatelolco
Until the end of the 18th century

Medicinal plants continued to be used without definition of their active principles

Examples:
- Opium (poppy latex, *Papaver somniferum*)
- Belladonna fruit extract (*Atropa belladonna*)
- Quinquina peel powder (*Cinchona officinalis*)
- Tea of coca leaves (*Erythroxylon coca*)
- Tea of Ephedra Branches (*Ephedra sinica*)
- Tea with foxglove leaves (*Digitalis lanata*)
17-19th centuries: Advances in Physiology and Chemistry

William Harvey (1578-1657)

“De Motu Cordis” (1628)
17-19th centuries: Advances in Physiology and Chemistry

The French vivisectionists

François Magendie (1783-1855)

“Formulaire” (1822)

pure alkaloids

Claude Bernard (1813-1878)
17-19th centuries: Advances in Physiology and Chemistry

Robert Boyle (1627-1691)

Frederick W. A. Sertürner (1783-1841)

Journal Der Pharmacie Fur Aerzte, Apotheker Und Chemisten
13: 229, 1805

Annalen der Physik
55: 56–89, 1817
17-19th centuries: Advances in Physiology and Chemistry

1826:
Pierre Joseph Pelletier & Joseph Caventou

Production of 1800 kg of pure and crystalline quinine sulphate from 150 tonnes of quinquina peel, the first commercial natural product to be produced in a process which may be considered as the embryo of a pharmaceutical company.
17-19th centuries: Advances in Physiology and Chemistry

Heinrich Emanuel Merck (1794-1855)

Engel’s pharmacy in Darmstadt (Friedrich Jacob Merck-1668)

alkaloids

1827 – (Heinrich Emanuel Merck)

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James Blake (1815-1893)

Concept of Structure-Activity Relationship

“there exists some intimate connection between the chemical properties of substances and their physiological action”

(Edinburgh Medical and Surgical Journal, 56:124, 1841)
19th century: Pharmacology as a new discipline and profession

Rudolf Buchheim (1820-1879)

1849: first professor of Pharmacology
1st Institute of Pharmacology

1860: University of Dorpat
Estonia

Book (1849)
Contributions to the study of medicines (bioassays)
19th century: Pharmacology as a new discipline and profession

Oswald Schmiedeberg (1838-1921)
“Father of modern Pharmacology

Birthday meeting for its 70 years
Strasbourg (1872): Institute of Pharmacology

Teaching and world influence

- Paul Ehrlich, Otto Loewi
- John Jacob Abel (1857-1938)

1908: founded the American Society for Pharmacology and Experimental Therapeutics and its journal (1909)
End of 19th century-beginning of 20th century:
- first synthetic drugs
- birth of the German pharmaceutical industry

1863: Friedrich Bayer dye factory

1881: Department of Pharmaceutical Research

1899: Aspirin® ("The wonder drug")
End of 19th century-beginning of 20th century:

Paul Ehrlich (1814-1915)

“Father of Chemotherapy”

“Corpora non agunt nisi fixata”

Ehrlich, Proc. R. Soc. Lond. 66:424-448, 1900

1909: Arsphenamine

“Magic bullet”
Torsten Teorell (1905-1992)

“Father of Pharmacokinetics”

Kinetics of distribution of substances administered to the body. I. The extravascular modes of administration.


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First period of Drug Discovery (1820-1930)
“classic” period of Pharmacology

- **First generation**: essentially alkaloids, isolated and purified from natural products

- **Second generation**: synthetic substances
  - (analgesics, hypnotics and chemotherapeutic agents)

- Techniques used: essentially isolated organs and *in vivo* assays.

- Receptor concept (*Langley, 1878*)

- Beginning of quantitative pharmacology (*Clark, 1930*)
Modern era (1935-present): the golden years of drugs

- **Third generation (1935-1960):** sulfonamides, other antibiotics and hormones

- **Fourth generation (1960-1980):** semi-synthetic antibiotics, psychopharmaceuticals (antipsychotics, antidepressants) and drugs that work on the CVS (β-blockers, antihypertensives, diuretics)

- **Fifth generation (1980-present):** enzymatic inhibitors (ECA, COX, $H^+/K^+$ -ATPase, virus enzymes (HIV) and tumor cells) and biopharmaceuticals
The Pendulum of History

Back to Natural Products
NOBEL PRIZE (2015): Ivermectin & Artemisinin

Satoshi Ōmura: *S. avermitilis*

William C. Campbell: Ivermectin

Youyou Tu: Artemisinin

Microfilaria

Malaria

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Modern era (1935-present): concepts and techniques used

- **Biochemical phase (1948-1970):**
  Techniques - purification of receptors
  Concepts - intrinsic activity, spare receptors, desensitization & allosteryism

- **Molecular phase (1970-1986):**
  Techniques – *binding* & recombinant systems
  Concepts – GPCRs and ternary complex model, oligomerization and internalization of receptors
Modern era (1935-present): concepts and techniques used

- **Genomic phase** (1987-present):
  Techniques – FRET or BRET, electrophysiology, imaging, X-ray crystallography, genetically modified animals
  Concepts – constitutive activity, allosteric modulators & residence time

- **Systems pharmacology phase** (2003-present):
  Techniques – “omics” (proteomics, metabolomics, epigenomics), molecular networks & DREADDs
  Concepts – multidimensional efficacy & functional selectivity
Pharmacology of the future

- Biopharmaceuticals
- Nano-drugs
- Individualized therapy based on pharmacogenetics
- RNA interference-based therapies (RNAi)
- Cell therapy, with stem cells or cells producing "drugs"
- Gene therapy
Drugs that made history

- 1827: Aspirin
- 1899: Insulin
- 1922: Penicillin
- 1928: Largactil
- 1952: Inderal
- 1964: Gleevec
- 1981: Zidovudine (the first authorized antiretroviral AIDS drug)
- 1997: Rituximab
- 1998: Viagra
- 1999: Viagra
- 2001: Viagra

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Pharmacologists who made history

Emil Fischer (1852-1919)
Henry H. Dale (1875-1968)
John R. Vane (1927-2004)
James W. Black (1924-2010)

Alfred J. Clark (1885-1941)
Daniel Bovet (1907-1992)

Alfred G. Gilman (1942-2015)

Solomon H. Snyder (1938-presente)

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Robert F. Furchgott (1916-2009)

Robert J. Lefkowitz (1943-presente)
Let’s have a look on Brazilian Pharmacology
History of Pharmacology in Brazil

Álvaro (1882-1952) & Miguel (1890-1953) de Almeida

They began their scientific work in the area of physiology in a laboratory installed in the basement of their residence (1910 - Rio de Janeiro)
Maurício Rocha e Silva (1910-1983)

“Father of Brazilian Pharmacology”

- Disseminated the use of bioassays
- 1949: He discovered that the enzymes of the snake venom Bothrops jararaca act on blood proteins, releasing a substance called bradykinin

BRADYKININ, A HYPOTENSIVE AND SMOOTH MUSCLE STIMULATING FACTOR RELEASED FROM PLASMA GLOBULIN BY SNAKE VENOMS AND BY TRYPsin

M. ROCHA E SILVA, WILSON T. BERALDO¹ AND G. ROSENFELD²
From the Department of Biochemistry and Pharmacodynamics, Instituto Biologico
SÃO PAULO, BRAZIL

Am. J. Physiol. 156(2):261-73, 1949
José Ribeiro do Valle (1908-2000)

- First Professor of Pharmacology
- Graduated many successful pharmacologists
- Scientific contributions: Endocrinology

Lauro Sollero (1916-1982)

- "Matrix of Masters in Pharmacology"
Sergio Henrique Ferreira (1934 – 2016)

1961: He discovered that the venom of Bothrops Jararaca, besides generating bradykinin, was also able to potentiate its pharmacological effects.

His studies led to the development of new innovative antihypertensive agents, such as Captopril (Bristol-Myers Squibb), the first ACE inhibitor.


A BRADYKININ-POTENTIATING FACTOR (BPF) PRESENT IN THE VENOM OF BOTHROPS JARARACA

BY

S. H. FERREIRA

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1969-1975: postdoctoral fellowship with John R. Vane (UK)

responsible for the elucidation of
- the mechanism of action of aspirin
- the participation of prostaglandins
in the inflammatory response

Brazil: Work in the area of pain: demonstration of a peripheral component in morphine analgesia

Teleantagonism: A pharmacodynamic property of the primary nociceptive neuron

Mani I. Funez, Luiz F. Ferrari, Dian B. Duarte, Daniela Sachs, Fernando Q. Cunha, Berenice B. Lorenzetti, Carlos A. Parada, and Sérgio H. Ferreira

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The first "Book" of Brazilian Pharmacology?

Jovelino (Armínio de Souza) Mineiro

1st Edition - 1911

2nd Edition - 1925

Escola de Farmácia de Ouro Preto (1839)

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Bibliography


SBFTE – Iniciativas Educacionais
(SBFTE – Education Initiatives)

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