



History of Pharmacology: *From the Origins to Modern Era*

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ICB - UFRJ



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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

... 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.

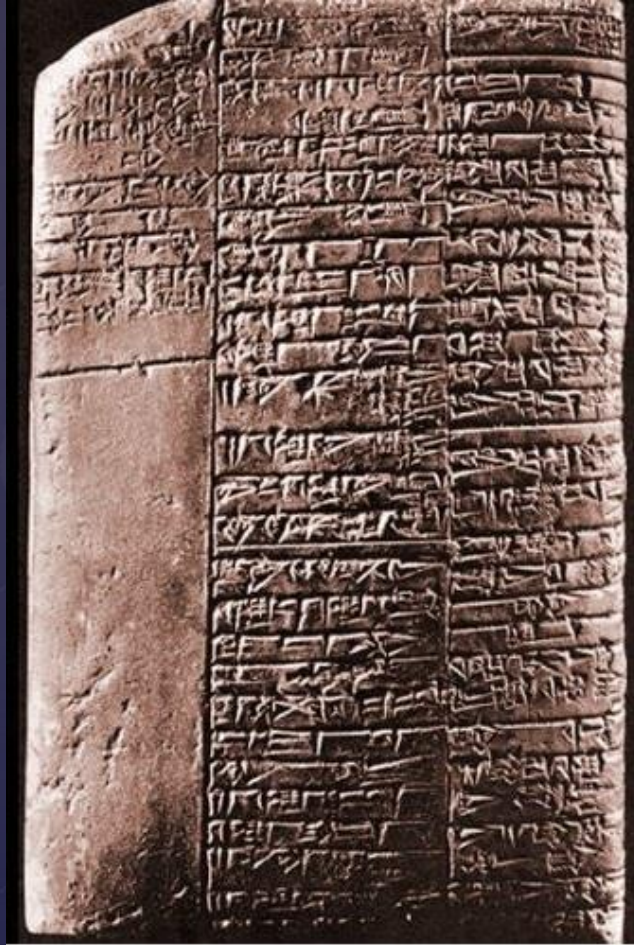


Fredholm et al. Nat. Rev Drug Discov. 1:237-8, 2002

A journey through space and time

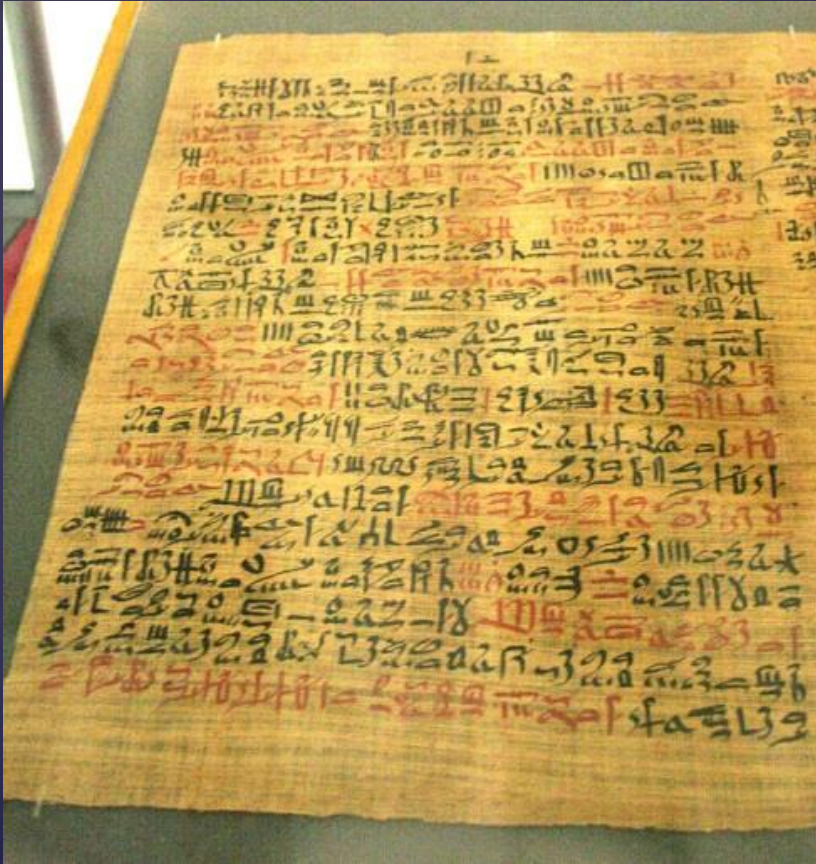


Antiquity



Sumerian medical clay tablet
Nippur
circa 2,225 BC

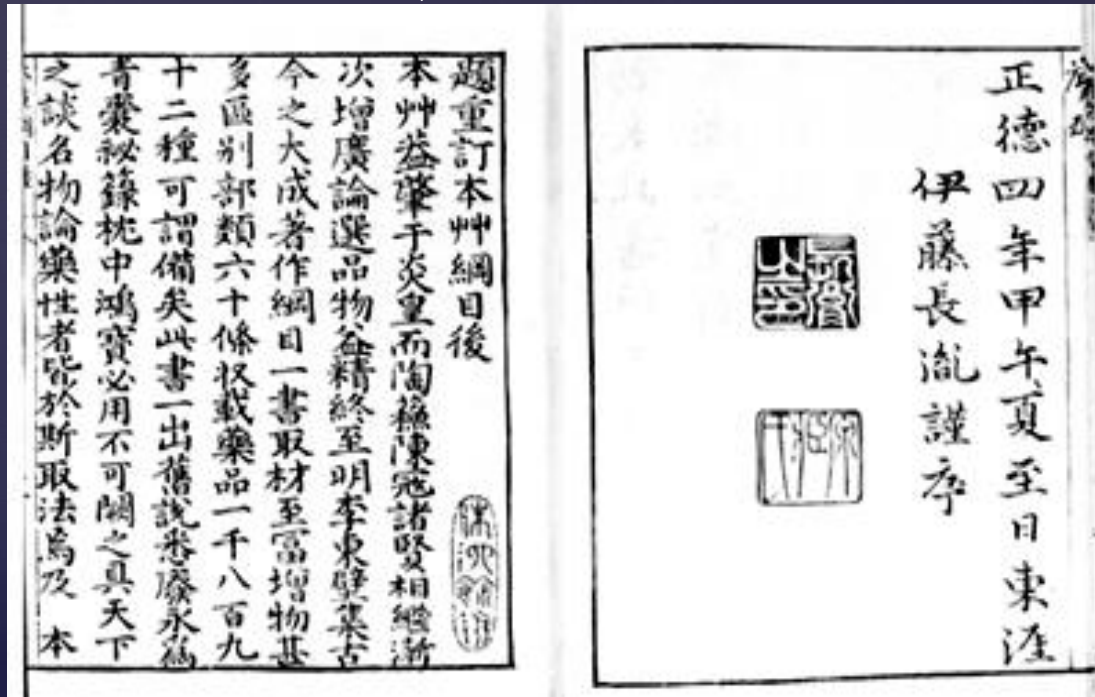
Antiquity



Ebers Papyrus (1,550 B.C.)

Antiquity

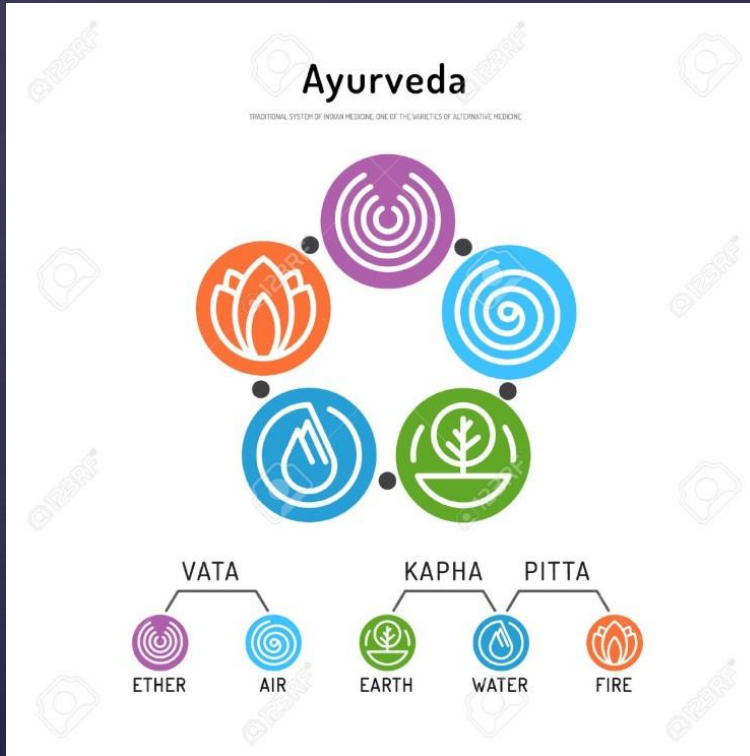
Shen-nung pen ts'ao ching
(I and II B.C.)



Pen ts'ao kang mu
Li Shih-chen
(1518-1593 A.D.)

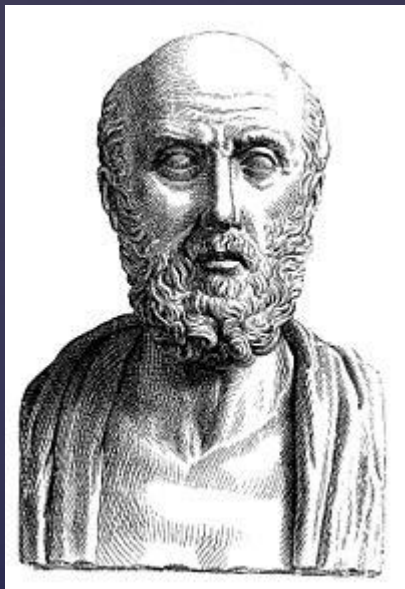
Antiquity

Ayurveda (“Science of Life”)



Greece and Occidental Medicine

Hippocrates (460-377, B.C.)

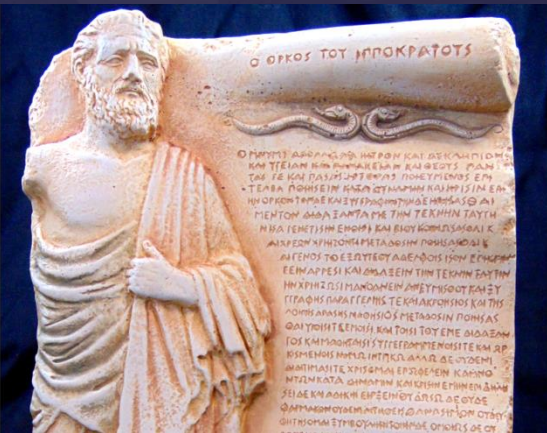


Roman “portrait” bust
(19th-century engraving)

“Father of Medicine”



Medicine *v.s.* superstition

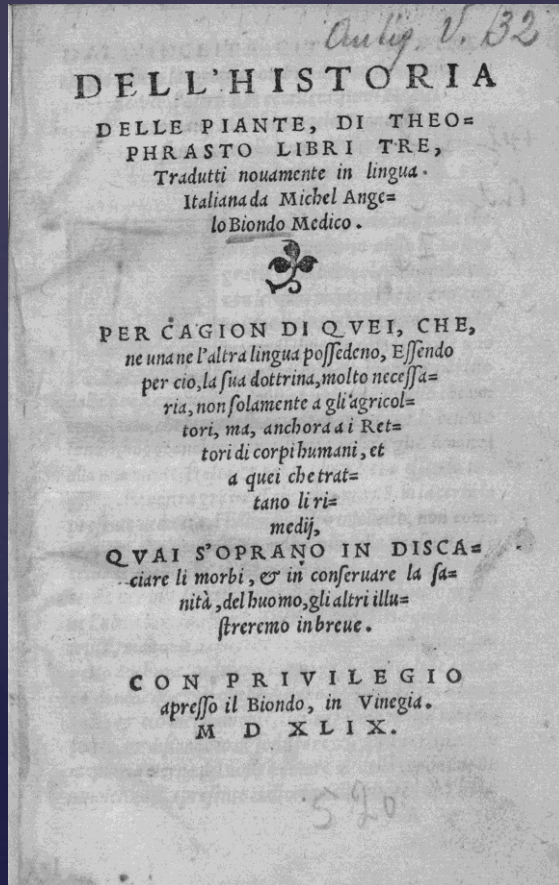


Hippocratic
oath



Greece and Occidental Medicine

Theophrastus (372-287, A.D.)



“Father of Botany”



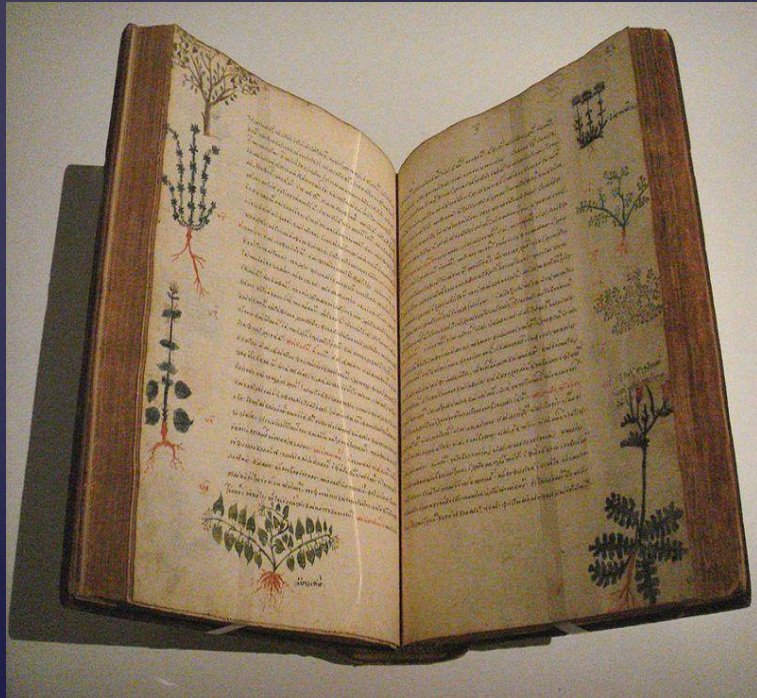
“*Historia Plantarum*”

Development of Pharmacy

Greece and Occidental Medicine

Dioscorides (40-90, A.D.)

“Father of Pharmacognosy”



De Materia Medica

Greece and Occidental Medicine

Claudius Galenus (131-201, A.D.)



A pioneer of experimental physiology

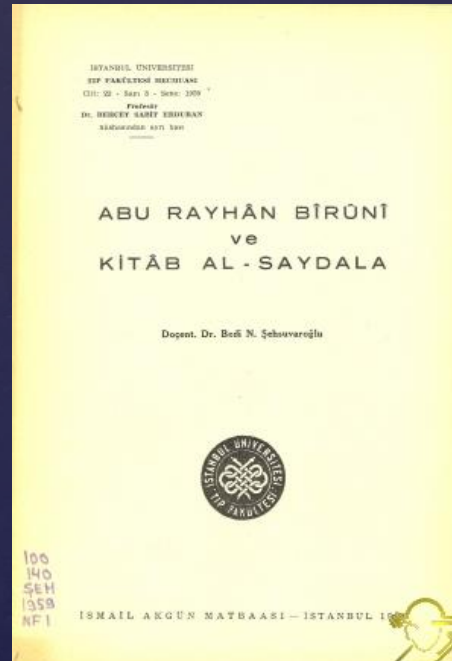
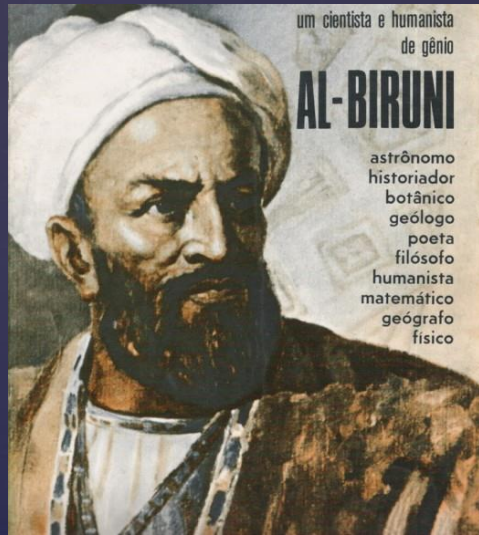
Pharmacy: "galenic" preparations of plant active principles

Medieval Period (5-15th centuries)

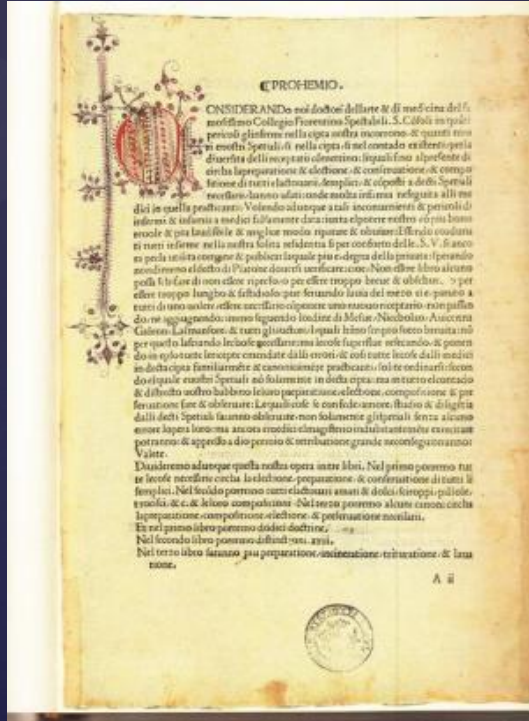
First pharmacies (Bagdad, 754 A.D.)



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



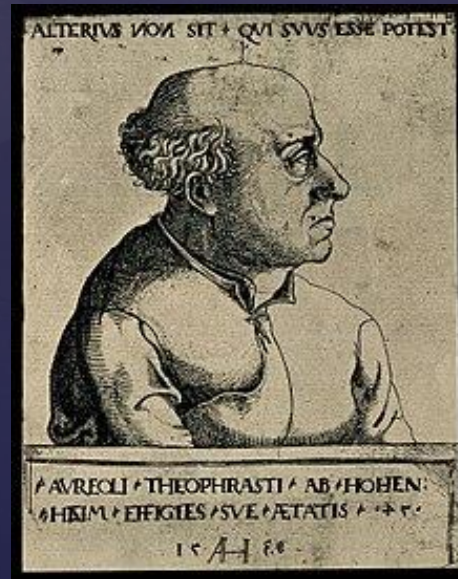
Kitab al-Saydalah
("The book of drugs")



Renaissance period (16th century)

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*)



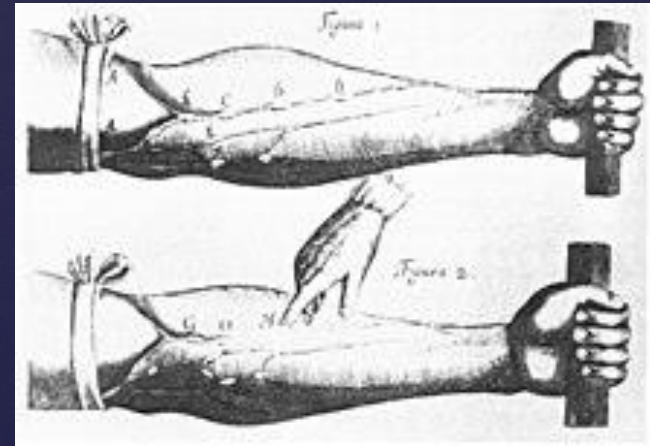
17-19th centuries:

Advances in Physiology and Chemistry

William Harvey (1578-1657)



"De Motu Cordis"
(1628)



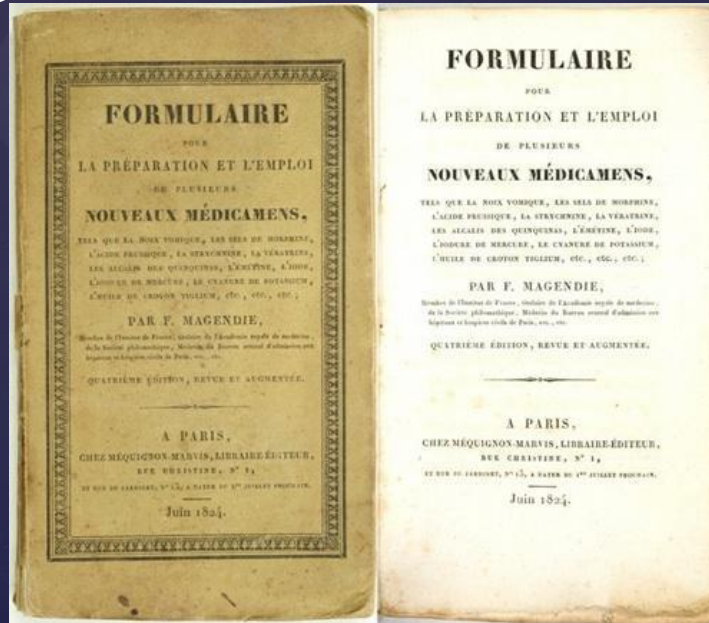
17-19th centuries:

Advances in Physiology and Chemistry



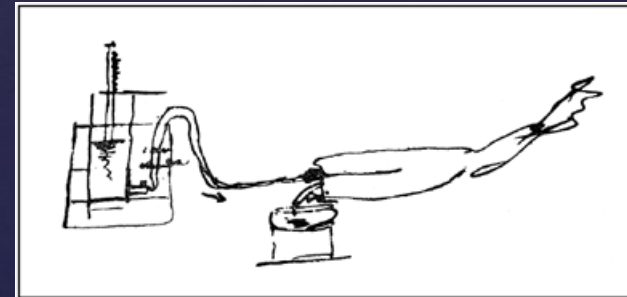
The French vivisectionists

François Magendie
(1783-1855)



“Formulaire”
(1822)
pure alkaloids

Claude Bernard
(1813-1878)



Extrait du Cahier de notes de Claude Bernard. Il s'agit d'un appareil pour injecter le sang dans un organe isolé. A gauche, un réservoir de sang immergé dans l'eau chaude et muni d'un piston. A droite, le sang est injecté dans l'artère d'une patte de grenouille.

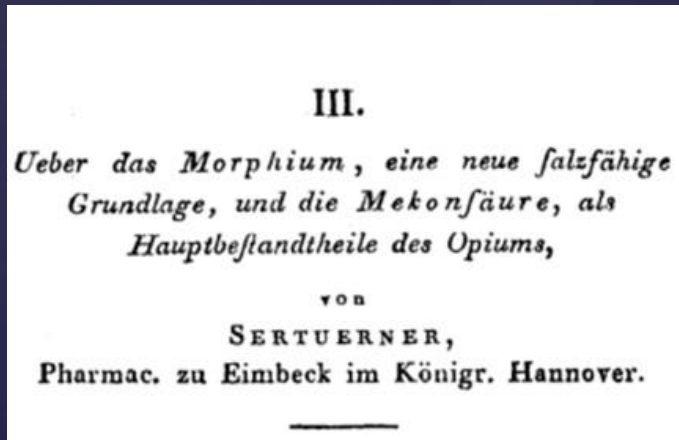
17-19th centuries:

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



17-19th centuries:

Advances in Physiology and Chemistry



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

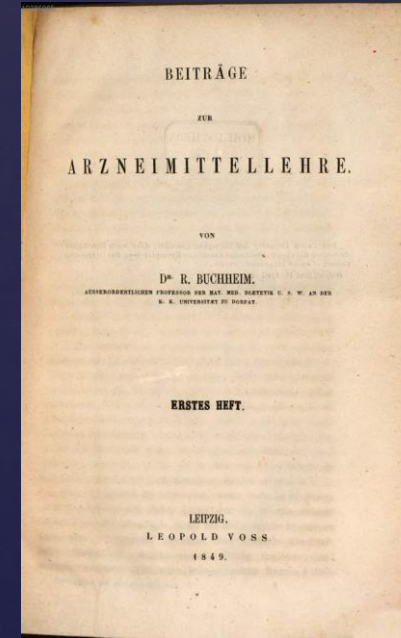


Rudolf Buchheim (1820-1879)

1849: first professor of Pharmacology
1st Institute of Pharmacology



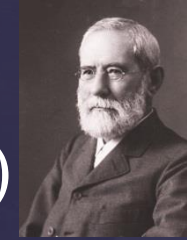
1860: University of Dorpat
Estonia



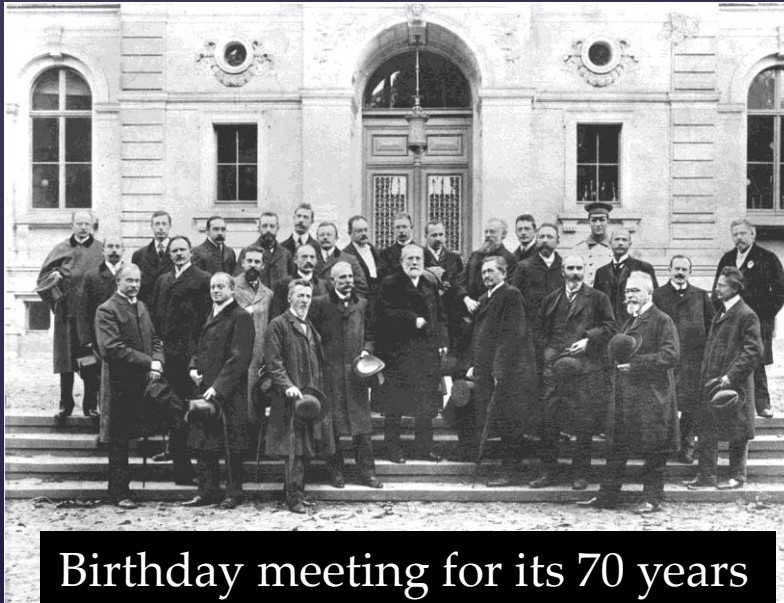
Book (1849)

Contributions
to the study
of medicines
(*bioassays*)

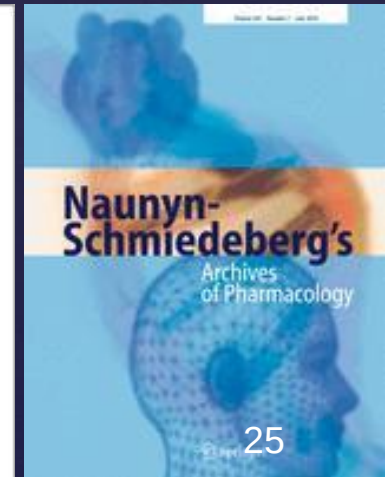
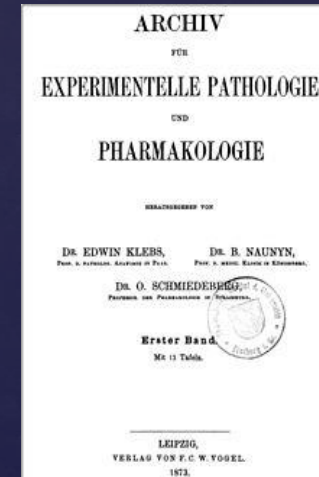
19th century: Pharmacology as a new discipline and profession



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



Birthday meeting for its 70 years



Strasbourg (1872): Institute of Pharmacology

Teaching and world influence

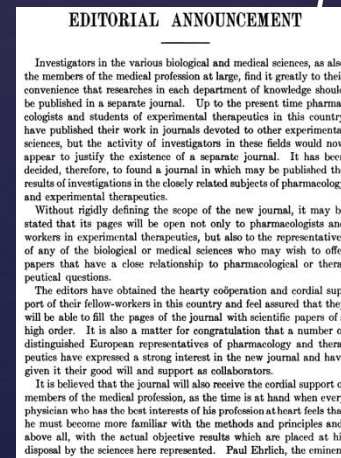
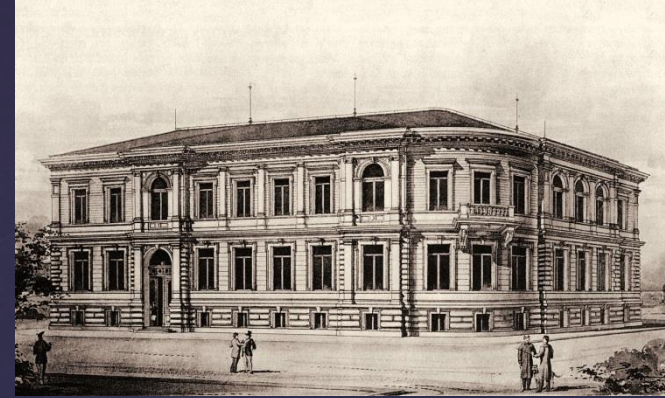
- Paul Ehrlich, Otto Loewi
- John Jacob Abel (1857-1938)

1908: founded the *American Society for Pharmacology and Experimental Therapeutics*



- and its journal (1909)

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End of 19th century-beginning of 20th century:

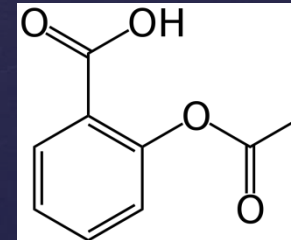
- first synthetic drugs
- birth of the German pharmaceutical industry



1863: Friedrich Bayer
dye factory



1881: Department of Pharmaceutical Research



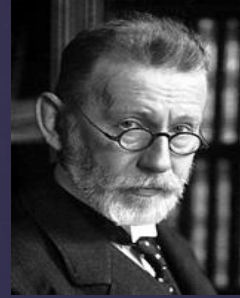
1899: Aspirin® ("The wonder drug")



End of 19th century-beginning of 20th century:

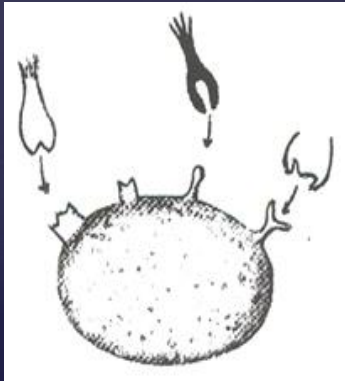
Paul Ehrlich (1814-1915)

“Father of Chemotherapy”



1909:
Arsphenamine

“*Corpora non agunt nisi fixata*”



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

Copyright_SBFTE_2020 “Magic bullet”



Torsten Teorell (1905-1992)

“Father of Pharmacokinetics”

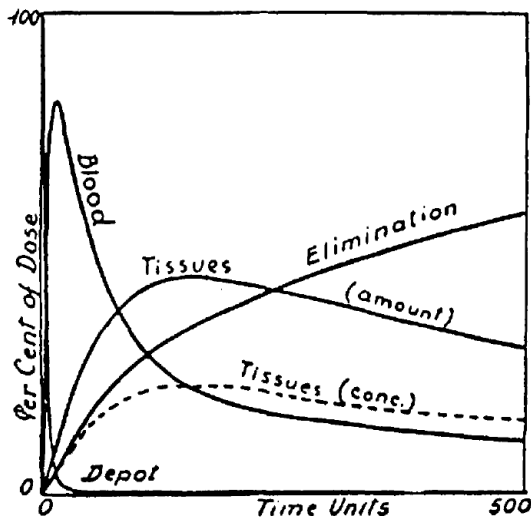


FIG. 3

Typical Case of Extravascular Administration in the absence of tissue inactivation.

($k_1 = 0.2$; $k_2 = 0.01$; $k_3 = 0.005$; i.e. “blood” volume/“tissue” volume is 1:2; $k_4 = 0.005$; $k_5 = 0$).

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

Teorell, *Arch. Int. Pharmacodyn. Ther.* 57: 205-225, 1937

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

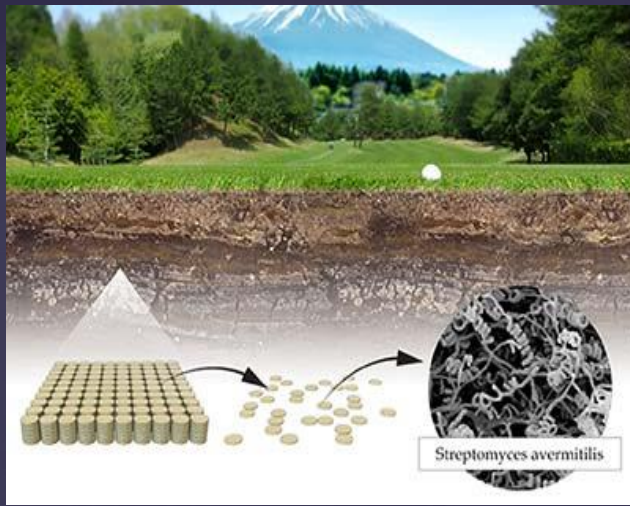
- **Third generation (1935-1960):** sulfonamides, other antibiotics and hormones
- **Fourth generation (1960-1980):** semi-synthetic antibiotics, psychopharmaceuticals (antipsychotics, antidepressants) and drugs that work on the CVS (β -blockers, antihypertensives, diuretics)
- **Fifth generation (1980-present):** enzymatic inhibitors (*ECA, COX, H^+/K^+ -ATPase, virus enzymes (HIV) and tumor cells*) and biopharmaceuticals



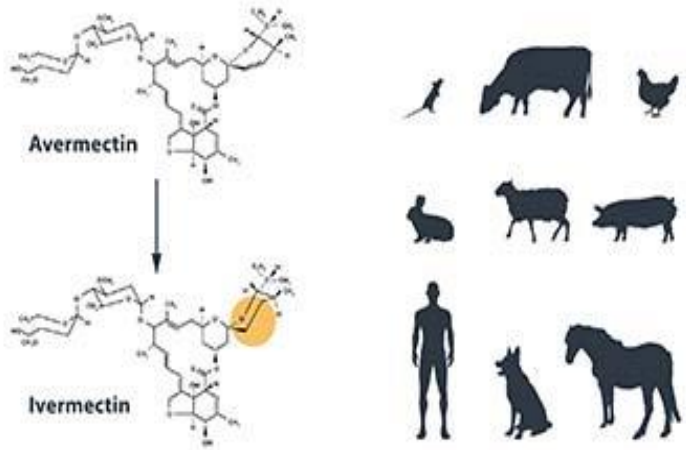
The Pendulum of History

Back to Natural Products

NOBEL PRIZE (2015): Ivermectin & Artemisinin

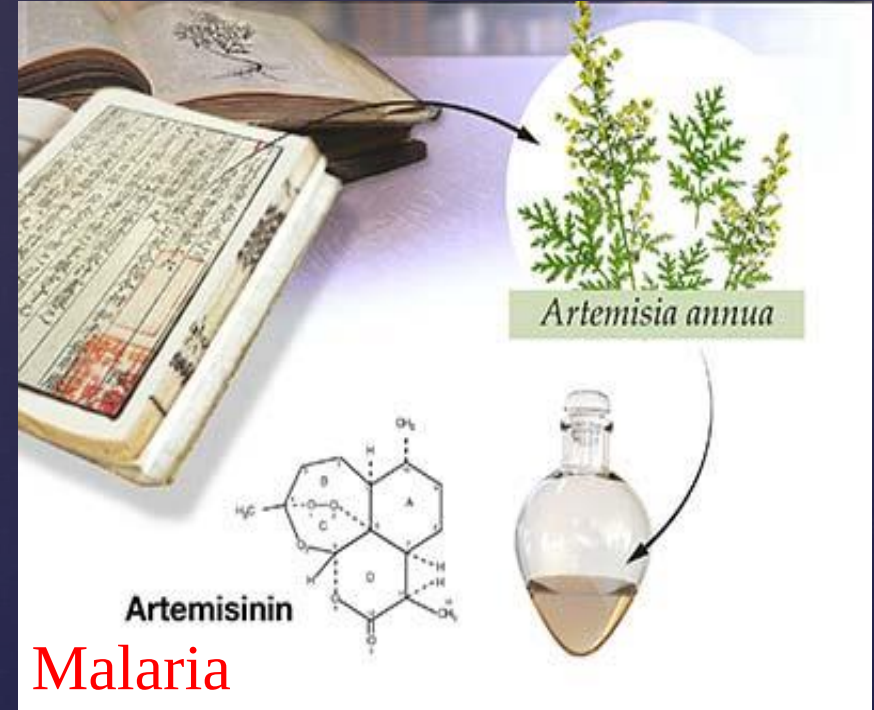


Satoshi Ōmura: *S. avermitilis*



Microfilaria

William C. Campbell: Ivermectin



Malaria

Youyou Tu: Artemisinin

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

- *Biochemical phase (1948-1970):*

Techniques - purification of receptors

Concepts - intrinsic activity, spare receptors, desensitization & allosterism

- *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):*

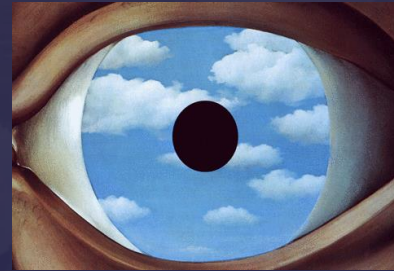
Techniques – “omics” (proteomics, metabolomics, epigenomics), molecular networks & DREADDs

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

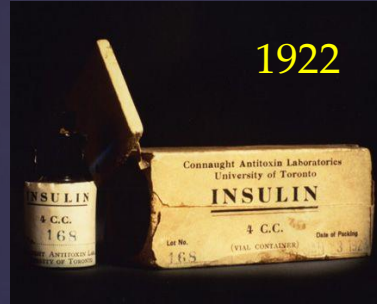
Drugs that made history



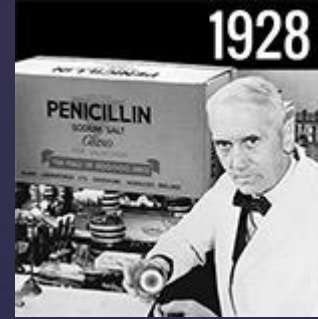
1827



1899



1922



1928



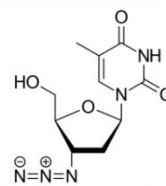
1952



1964



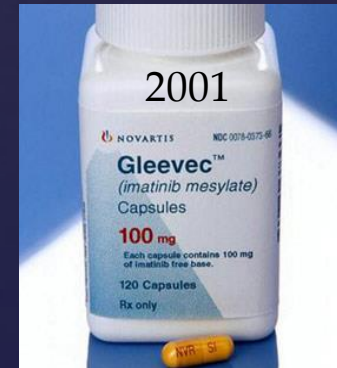
1981



1997



1998



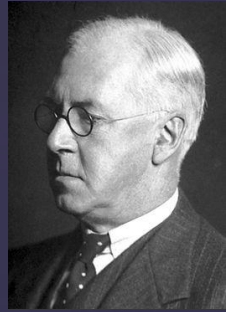
2001

March 20

In 1987, the FDA approved the sale of Zidovudine the first authorized antiretroviral AIDS drug

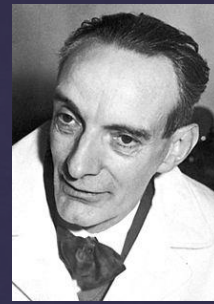
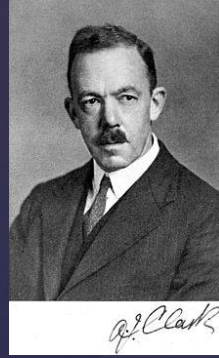
Pharmacologists who made history

Emil Fischer
(1852-1919)



Henry H. Dale
(1875-1968)

Alfred J. Clark
(1885-1941)



Daniel Bovet
(1907-1992)

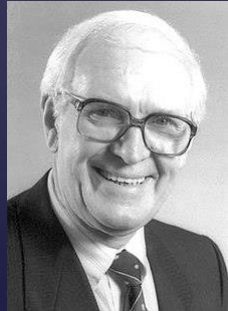
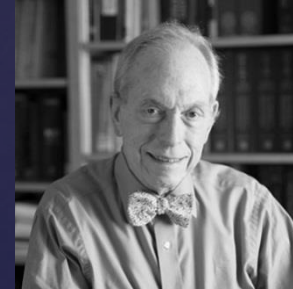
Robert F. Furchgott
(1916-2009)



John R. Vane
(1927-2004)



Solomon H. Snyder
(1938-presente)



James W. Black
(1924-2010)

Alfred G. Gilman
(1942-2015)



Robert J. Lefkowitz
(1943-presente)

Let's have a look on Brazilian Pharmacology



History of Pharmacology in Brazil

Álvaro (1882-1952)
Osório



& 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”



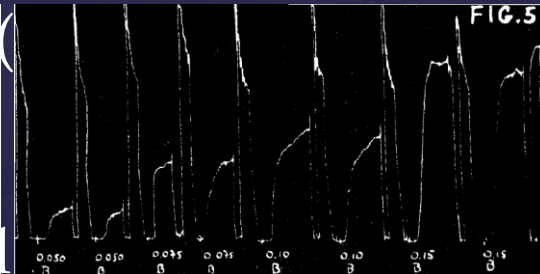
- Disseminated the use of bioassays
- **1949**: He discovered that the enzymes of the snake venom *Bothrops jararaca* act on blood proteins, releasing a substance called **bradykinin**

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

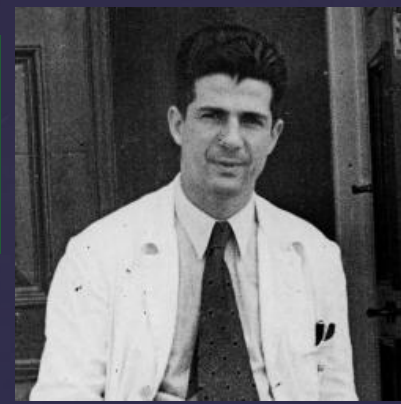
From the Department of Biochemistry and Pharmacodynamics, Instituto Biológico

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)



“Você só começa a gostar de Ciência fazendo. É uma atividade artesanal que você aprende com os seus mestres.”

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



***Brit. J. Pharmacol.* (1965), 24, 163–169.**

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

BY

S. H. FERREIRA

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

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

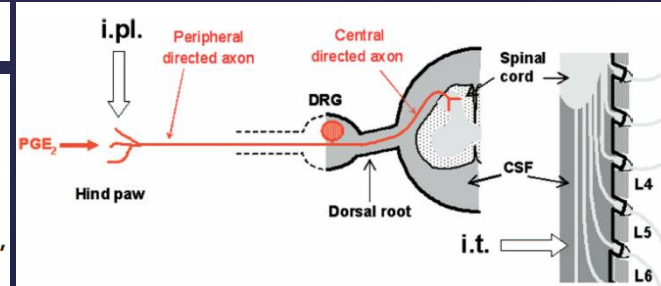


Brazil: Work in the area of pain: demonstration of a peripheral component in morphine analgesia

19038-19043 | PNAS | December 9, 2008 | vol. 105 | no. 49

Teleantagonism: A pharmacodynamic property of the primary nociceptive neuron

Mani I. Funez, Luiz F. Ferrari, Djane B. Duarte, Daniela Sachs, Fernando Q. Cunha, Berenice B. Lorenzetti, Carlos A. Parada, and Sérgio H. Ferreira¹

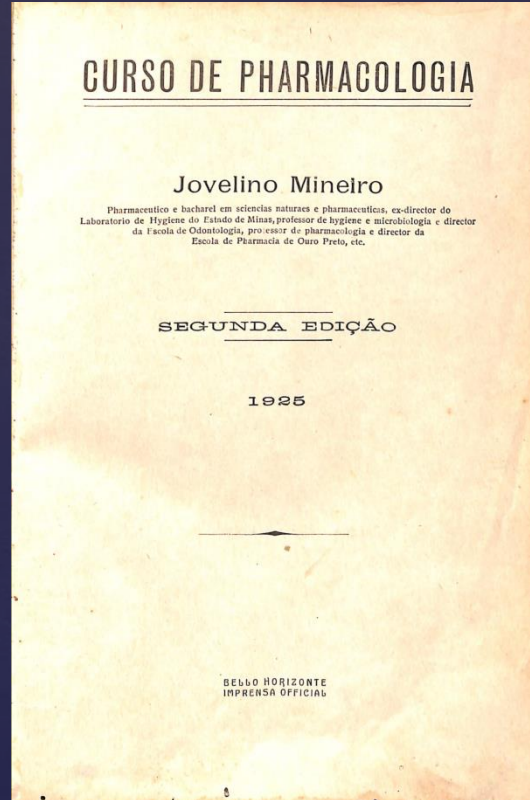


The first "Book" of Brazilian Pharmacology ?

Jovelino (Armínio de Souza) Mineiro



1st Edition - 1911



2st Edition - 1925

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Escola de Farmácia
de Ouro Preto
(1839)



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- Winkquist RJ, Mullane K, Williams M. The fall and rise of pharmacology – (Re)defining the discipline? *Biochem Pharmacol* 2014; 87:4-24.

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(SBFTE – Education Initiatives)



Construindo Divulgação e Educação Científica
em Farmacologia e Terapêutica Experimental

(Building on Scientific Information and Education
in Pharmacology and Experimental Therapeutics)

Informações e contato para envio de
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