N E W L A Y O U T

1,000,000,000 *CHF investment*

7,000,874 *hours of work*

6,587 *experiments*

423 *researchers*

1 *medicine*

With Prof Susan M Gasser
and Prof Olivier Michielin

THE MAKING OF AN INNOVATIVE MEDICINE

Introductory workshops on translational biomedical research and drug discovery and development

BIO-698 resumes Thursday September 21. 2023
4:15 PM @ AAC 108

EPFL

Sciences de la Vie -SV

Prof Roger G. Clerc

The Making Of An Innovative Medicine – course schedule

Thursday's @ 4-6 PM except 14.12/21.12.23 @2-6 PM

Session 1: **Scope of the course _ general organization _ case study**
21.09.23 *Embracing a career at the heart of biomedical research !?*

Session 2: **Historical perspective: the modern pharmacy**
28.09.23 *Advent of modern medicines - placebo controlled drug development*

Session 3: **Introduction to translational research: crossing the bridge**
05.10.23 *A chasm has opened wide between biomedical research and patients in need*

Session 4: **Therapeutic target identification I & II**
12-19.10.23 *"me too" vs a wealth of innovative targets _ small MW cpds vs biologicals*
Early front loading of biomarker identification for cohort stratification

Session 5: **Structure based drug design _medicinal chemistry_low/high throughtput**
26.10.23 **screening assays_ multiple parallel parameters optimization MDO**
Setting up screening assays, the robotics, the million cpds librairies

Session 6: **Therapeutic mpdalities peptides and biologicals: today's -**
02.11.23 **tomorrow's pharmacy NBEs**
Challengies (cost of goods - healthcare payers) and opportunities

WORKSHOP LISTING - THE MAKING OF AN INNOVATIVE MEDICINE BIO698			
! NON EXHAUSTIVE LISTING - SUGGESTIONS WELCOME !			
sessions	no	workshops	speaker/s
S02 (28-09-23) ! AAC108 !			
historical medicines	1	vaccine discovery : E. Jenner and smallpox	Danica M
with Nobel laureates while	2	penicilin: impact, whose invention ?	
hopping on giant shoulders	3	prozac at the core of psychiatry	
	4	lipitor/statins at last a blockbuster	
	5	artemisinin and malaria	Umair
	6	cyclosporin from soil sample to blockbuster	Umair
S03 (5-10-23) ! AAC014 !			
translational research	7	expanding the scope of targeted therapies	
an emerging field	8	chronotherapy	Pitt
S04 (12-10-23) ! AAC014 !			
therapeutic target identification	9	rare diseases repurposing medicines	Adrien
S04b (19-10-23) ! AAC108 !	10	nocosomial inf/MRSA/phage antibacterials	Georges
therapeutic target identification	11	Crispr/Cas9 gene editing huntington disease	Pitt
	12	AI in drug discovery	Simon
S05 (26-10-23) ! AAC108 !			
structure based drug design	13	macrocycles and non druggable targets	Masota
	14	chemoproteomics - NMEs	Nico G
S06 (02-11-23) ! AAC108 !			
therapeutic modalities - NBEs	15	Biologicals/biotech production/**incretins**	Tim F
	16	armed monoclonal AB medicines	Nico G
	16	RNA therapeutics, antisense medicines	
S07 (9-11-23) ! AAC108 !			
PHC personalized healthcare	17	BRCA1 preventive surgery/tumor board	Nikita
Human genomics	18	SOPHiA Genetics - GWAS	
	19	disease enabling biomarkers/micro RNAs	Isika
S08 (16-11-23) ! AAC014 !			
pharmacogenetic polymorphism	20	NextGenSequencing - precision medicine	Hien
	21	deCODE Inc pharmgenomic/iceland genealogy	
S09 (23-11-23) ! AAC108 !			
in vivo pharmacology	22	organoids come of age	Nathalie B
toxicology	23	thalidomide repurposing	Ekaterina
S10 (30-11-23) ! AAC108 !			
clinical research	24	AI medicine 2.0	Simon
	25	most common genetic defect : cystic fibrosis	.
	26	sex bias in preclicnial and clinical research	Weilin
	27	placebo/nocibo effects	Tim ?
S11 (07-12-23) ! AAC108 !			
intellectual property/integrity	28	SMA gene therapy - pay for performance	Abtin
	29	biopatents - 23 and Me - my genome	khosiyat
S12 (14-12-23) starts @ 2PM		Hacking medicine	all + invitees
! MED21522!			
S13 (21-12-23) start @ 2 PM		Hacking medicine	all + invitees
! AAC231 !			

Workshops _ The Making Of An Innovative Medicine

(non exhaustive listing)

- Historical perspectives : the early days of modern pharmacy : *Hopping on giant shoulders*

Sunday afternoon expt: a visit of the Pharmacy Museum of the University of Basel Switzerland

Historical perspective _ chinese medicinal plants_ Hippocrates

Ginseng root extracts (Panax q.) : evidence shows that taking **ginseng root** extracts daily for 12 weeks improves concentration and cognitive activities.
(cf pharmacognosy)

460-370 BC

- The works of Hippocrates (460-370 BC) contain 300 medicinal plants classified by physiological action: Wormwood and common centaury (*Centaurium umbellatum Gilib*) were applied against fever; garlic against intestine parasites; opium, henbane, deadly nightshade, and mandrake were used as narcotics; fragrant hellebore and haselwort as emetics; sea onion, celery, parsley, asparagus, and garlic as diuretics; oak and pomegranate as adstringents

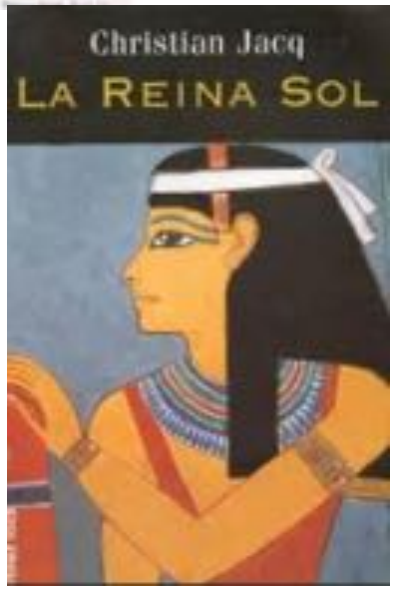
Historical perspective _ Key medical papyri

The Georg Ebers Papyrus.

Found in Egypt in the 1870s, the Ebers Papyrus contains prescriptions written in hieroglyphics for more than 700 remedies, including this one for an **acute asthma attack**.

From: University of Leipzig

- **The Kahun (1825 B.C)**
  - **-gynecology**
- **The Ebers (1534 B.C?)**
  - **-internal medicine**
- **The Edwin Smith Surgical Papyrus (1600 B.C)**
  - **-surgical wounds and fractures**



Historical perspective _ medicinal plant extracts

eg. Papaver somniferum (poppy seeds) known in the oldest civilisations as sleeping medicine

early past

recent past

morphine binds opiate receptors (3 subtypes) which in turn mediate the opioid receptor signaling, and highlight advances in opioid molecular and behavioural pharmacology, widely used as analgesics in the clinic.

Historical perspective : Paracelsius : „sola dosis facit venenum”

1493-1541

Paracelsus studied medicine in Basel Switzerland

“solely the dose determines that a thing is not a poison”

History of medicine by J. Starobinski : a philosophical perspective

Serendipity in medicne discovery

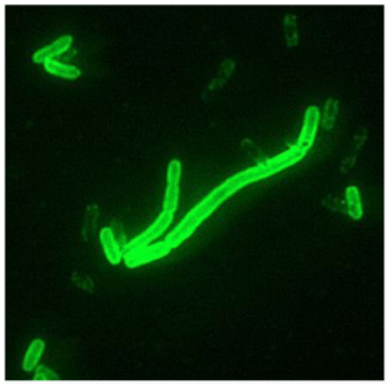
By C. Bohuon & Monneret : a sobering survey of the pre placebo era

Sommaire

Historical phobias and societal threats of infective agents

Marketplace of Napoli during plague near 1656
(Yersinia pestis)

Infectious diseases before the antibacterial era



Yersinia pestis seen at 200× magnification with a fluorescent label.

Yersinia pestis

A scanning electron micrograph depicting a mass of *Yersinia pestis* bacteria in the foregut of an infected flea

Plague in ancient times

(now known as Yersinia pestis)

A Yersin : 1863-1943

Historical perspective : the future is the past only better ?

130 YEARS AGO : Montreal 1885

Small Pox Victim: God's punishment ?

Edward Jenner invented patient "vaccination" by scarification of cow pox viruses and laid down the foundation of immunology

TODAY's : Sierra Leone 2015

EBOLA victims: all patients passed away

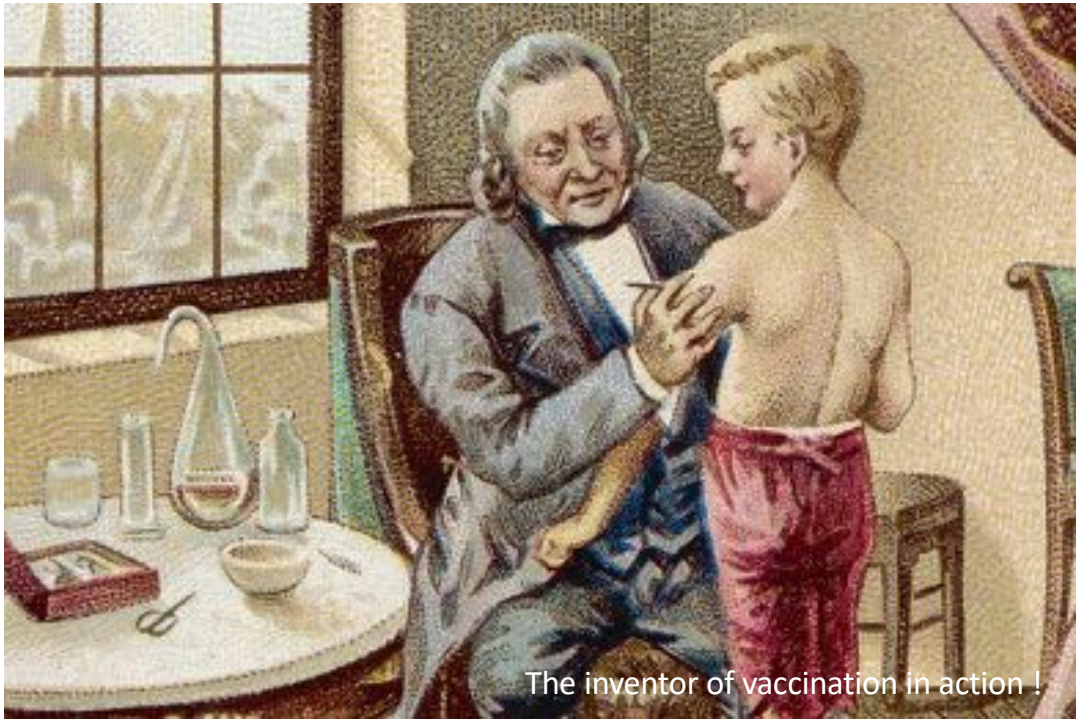
COVID 2019 world wide !

EBOLA'S LOST WARD

Two hundred years later we are still striving at a number of viruses pandemia and lots of unmet medical needs !

Historical true medical breakthroughs : the patient need

The first steps in the development of a modern medicine !
Centuries before the advent of therapeutic targets elucidation !
No knowledge what so ever of the underlying molecular mechanism (MOA)

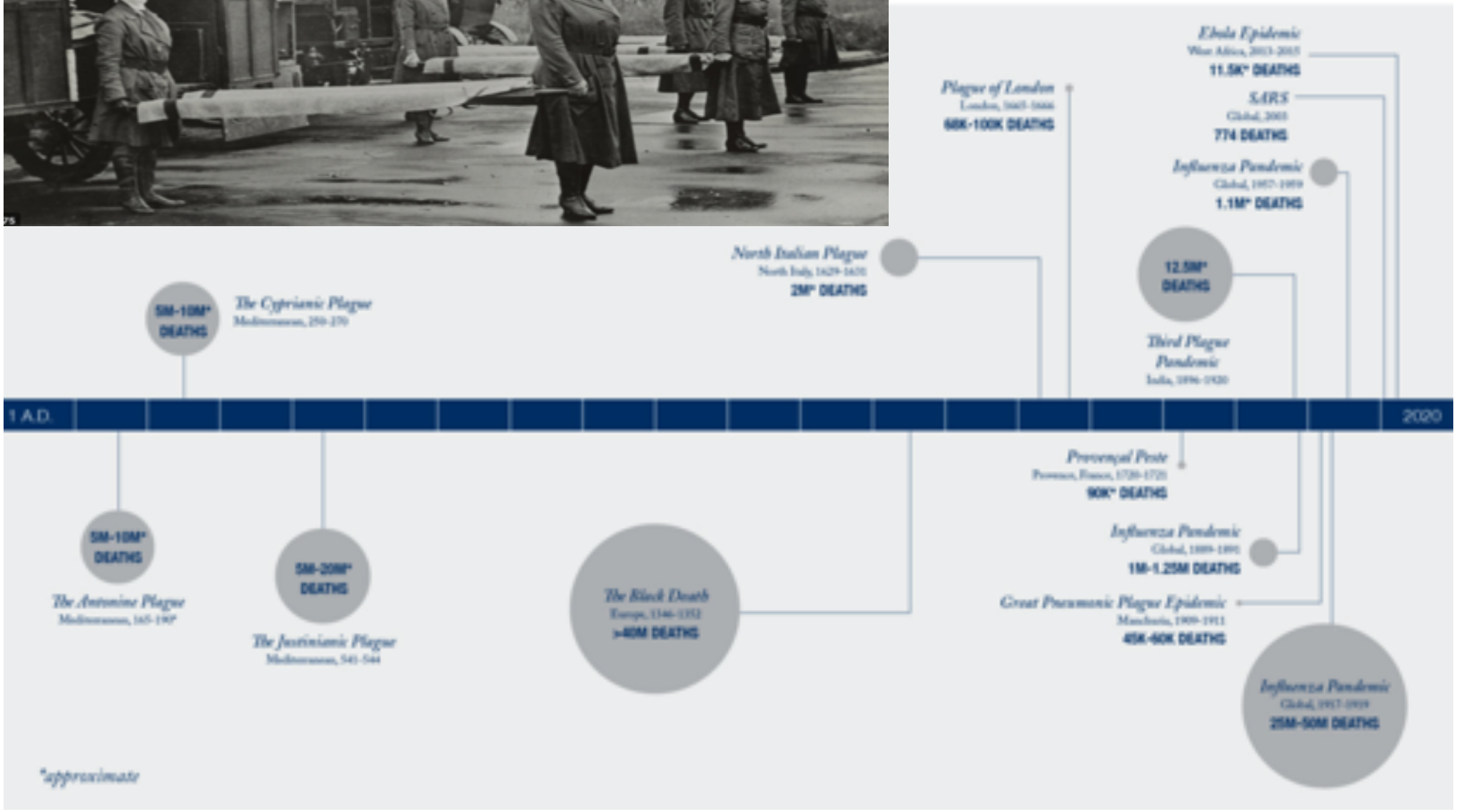


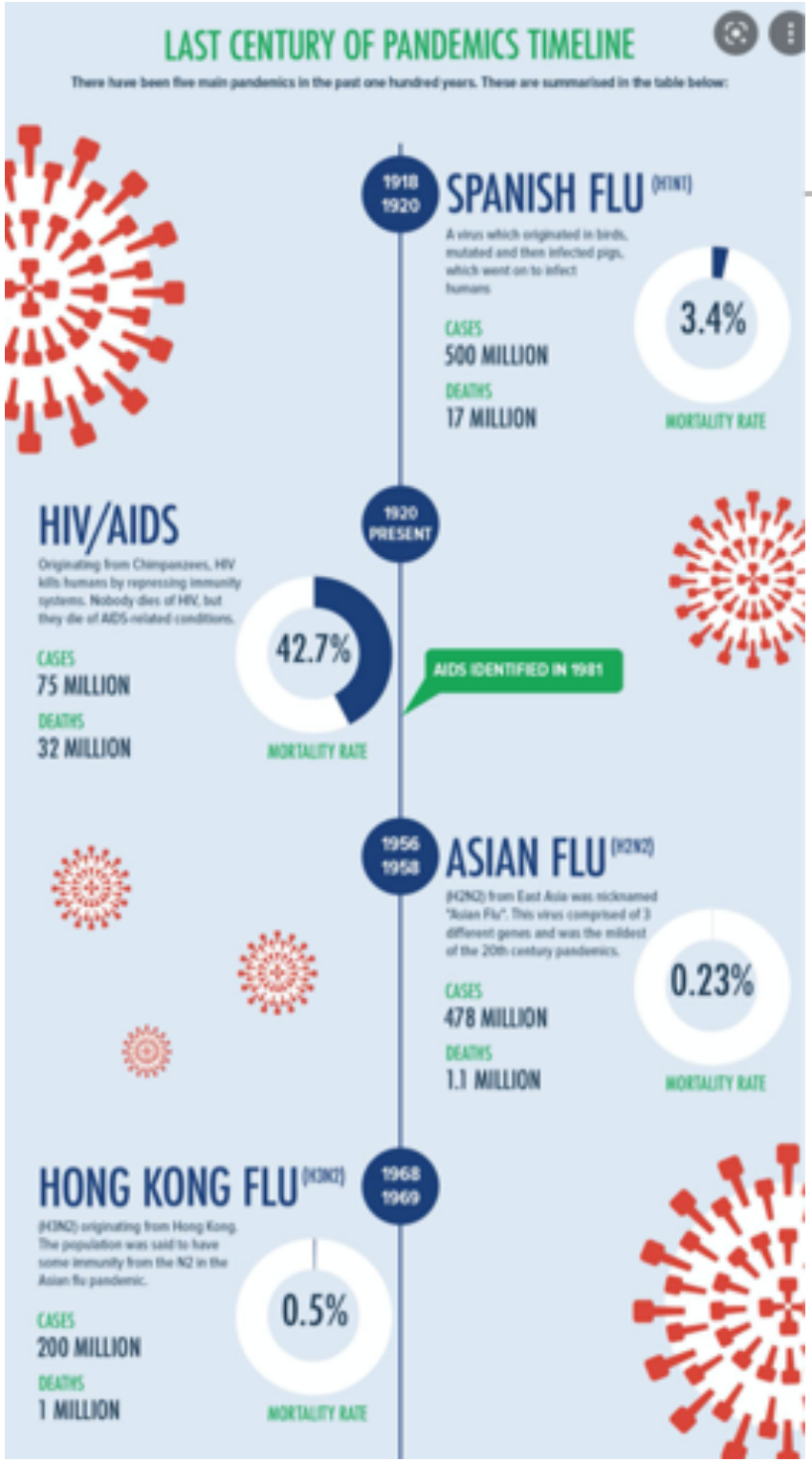
The inventor of vaccination in action !

WORKSHOP !

Would Edward Jenner's smallpox experiment pass a research ethics committee today ?
How can we go about discovering innovative medicine in the highly regulatory context of today ? Is a single fatality in clinical setting entitled to stop 10 years of research ?
How do we innovate healthcare today ? How much is 3 months life extension worth ?

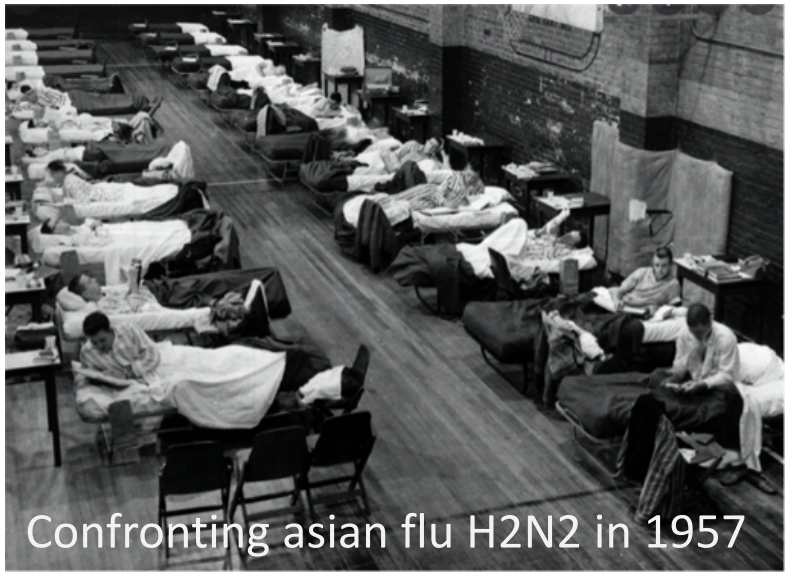
Throughout history, the pandemia has been a constant compagnion



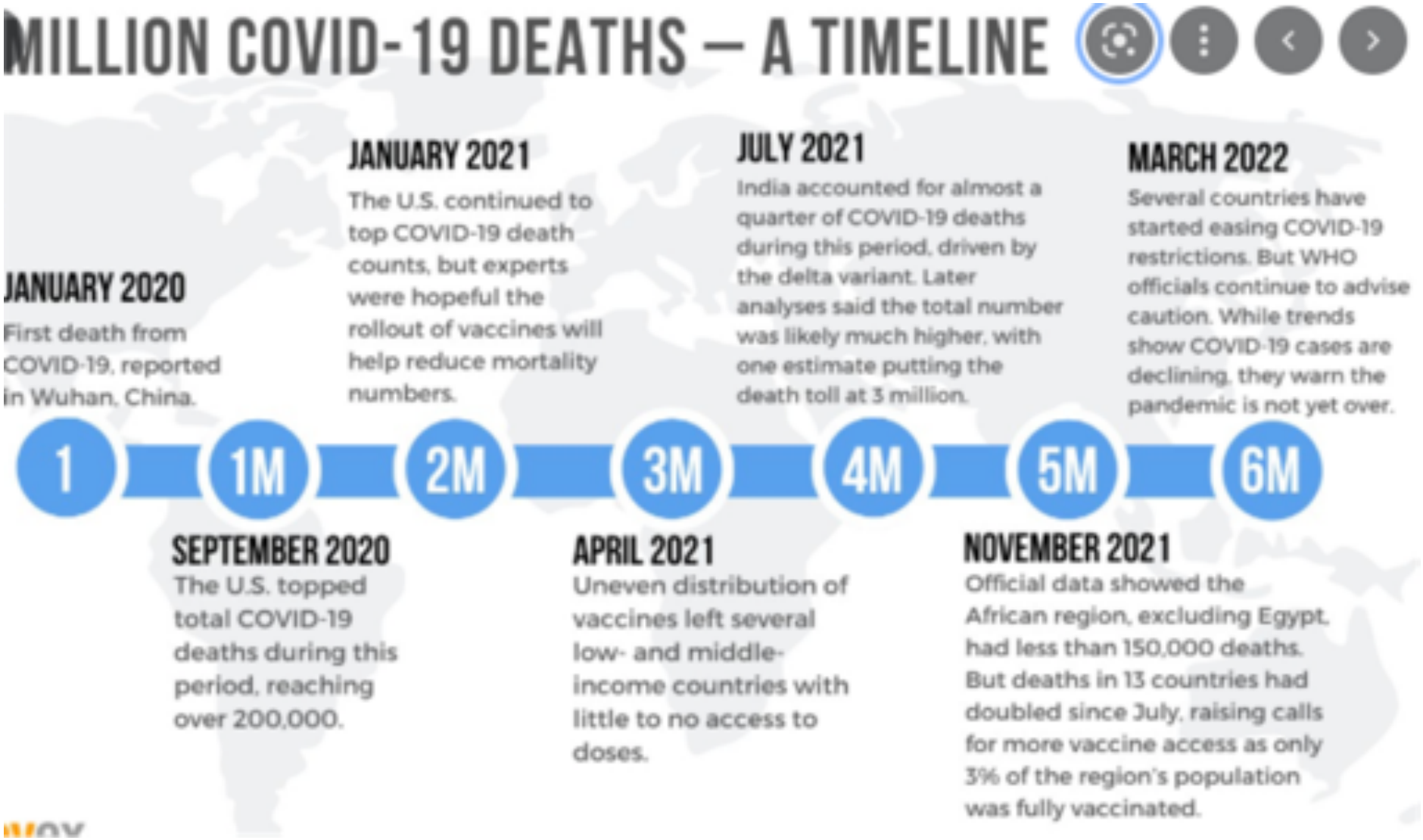


The future is the past : more pandemics, more zoonoses … when, how massive ?

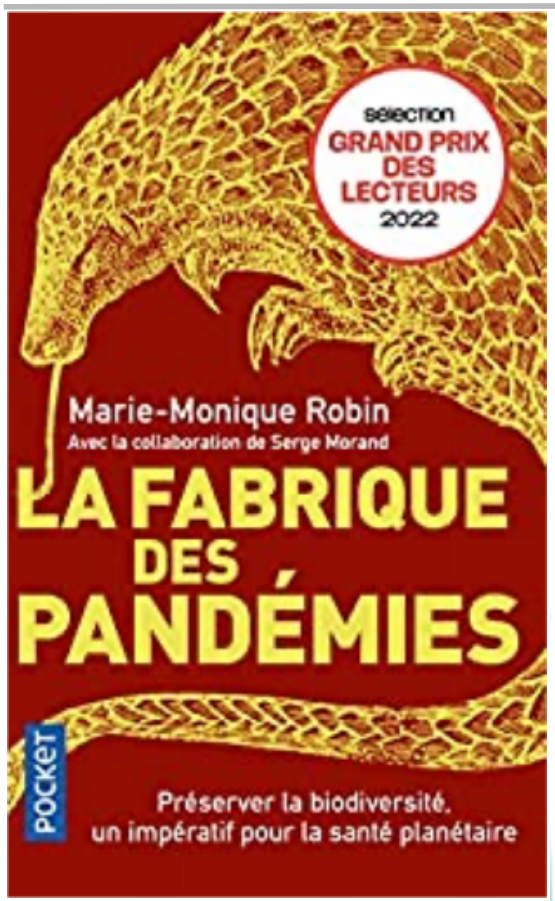
AIDS (HIV) pandemia (Kaposi sarcoma of bucal cavity)
1980's - today

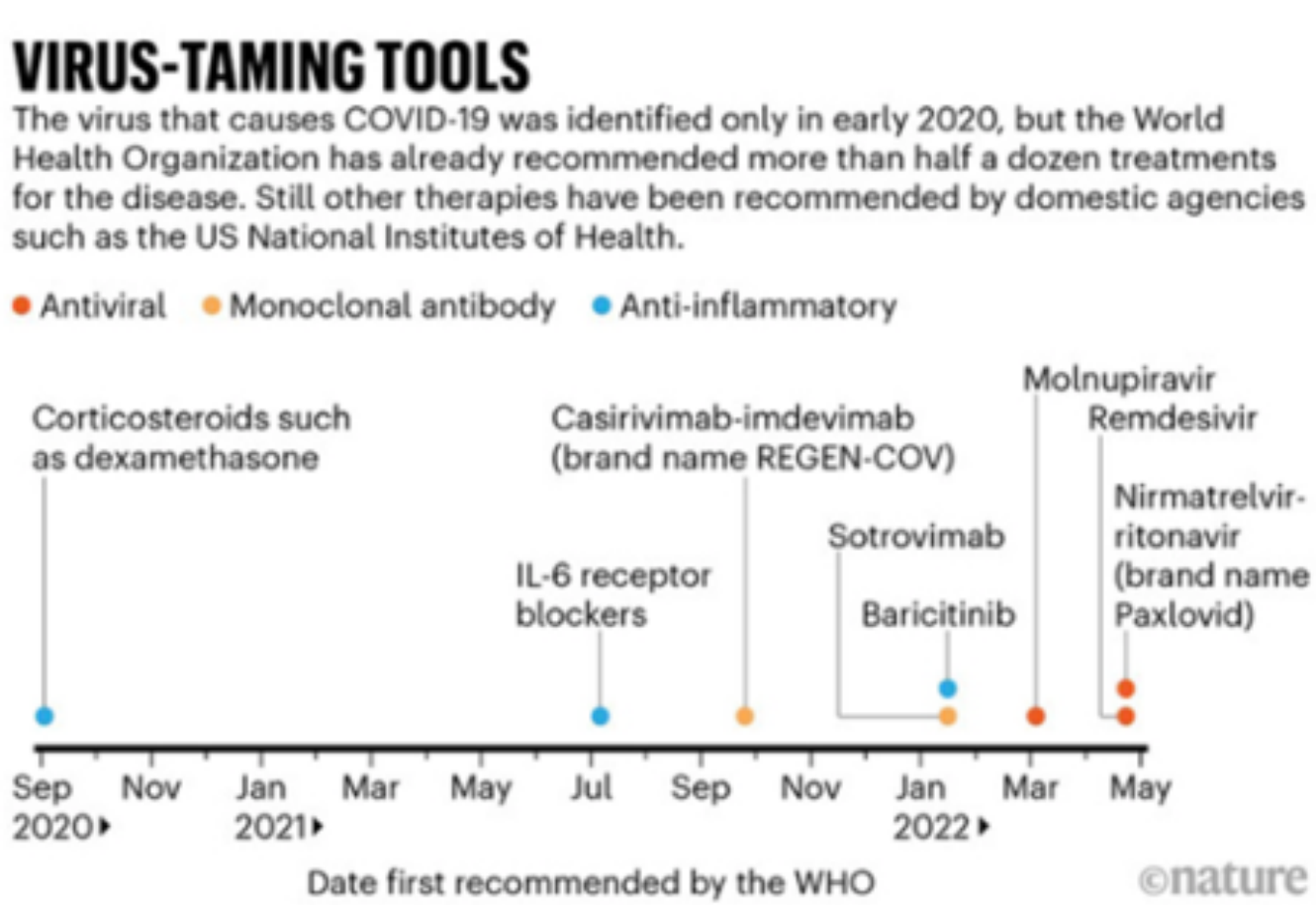


Throughout history a pandemic burst (of bacterial, viral or of zoonoses origin) is a constant threatful compagnion of healthcare

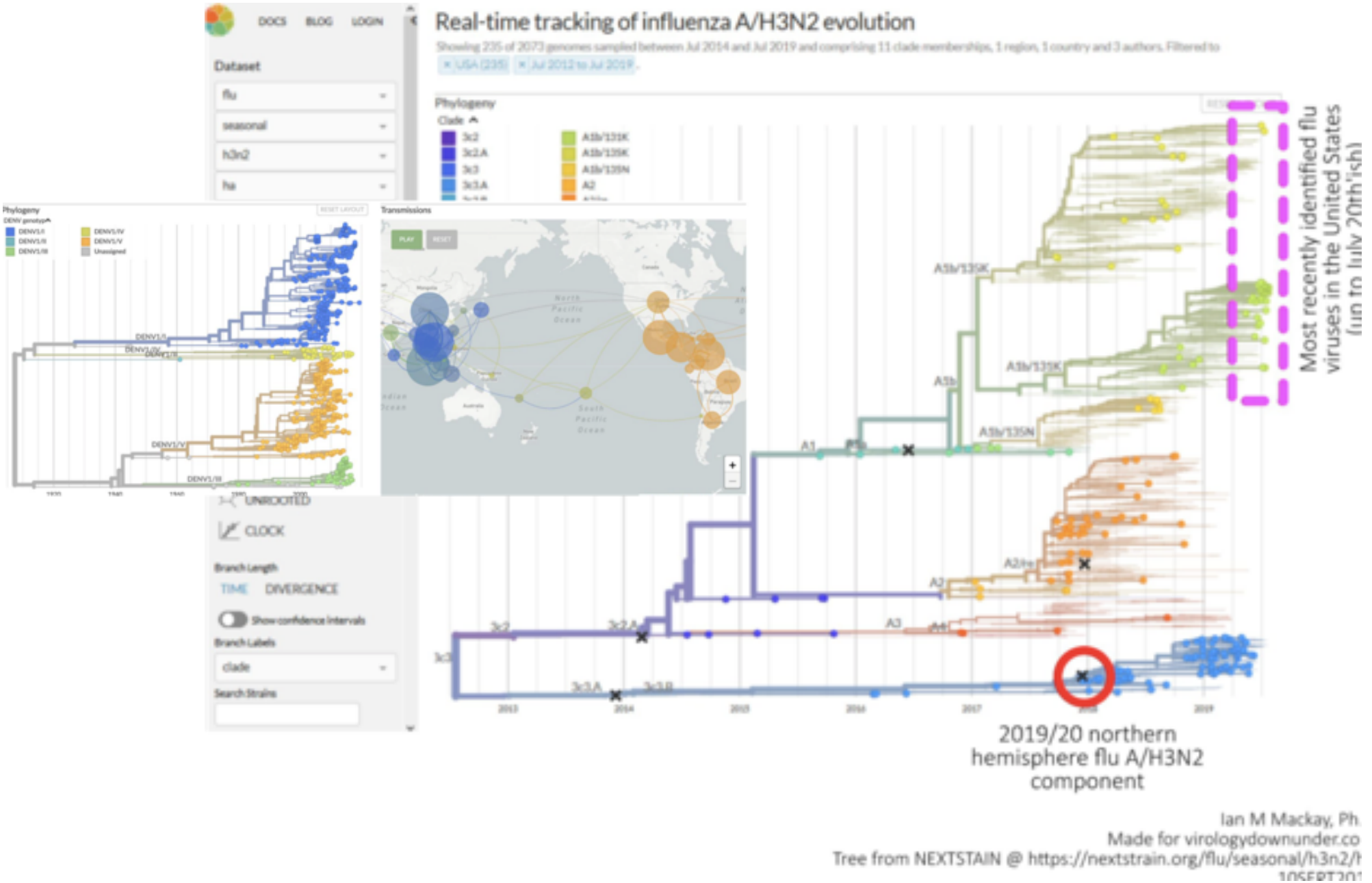


Throughout history Pandemias have been a constant compagnion today's SarsCoV2 pandemia from zoonoses origin

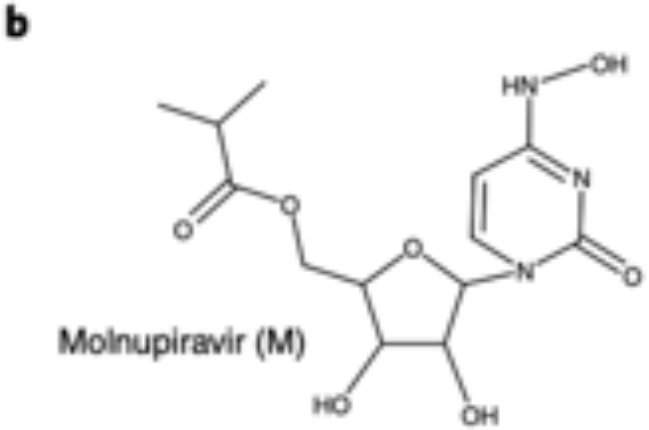


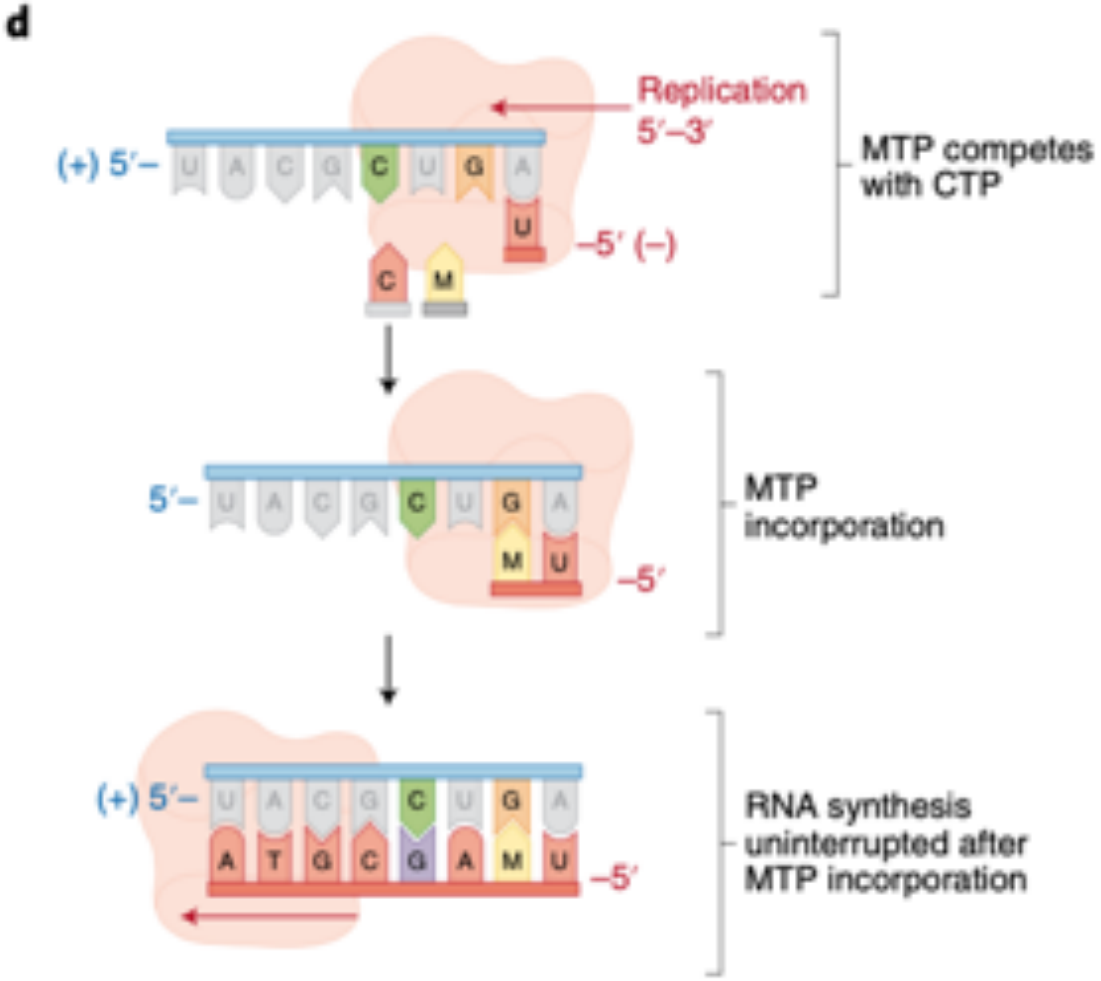


Today's Nextstrain® : real time tracking of viral pandemia



Today's medicinal chemistry therapeutic armamentarium towards pandemias is on a steap learing curve





MTP directs the incorporation at either Gs or As with a high rate of mutagenesis leading to mutated SarsCoV2 RNA products

HADLEY LEGGETT 08.31.09 12:00 AM

AUG. 31, 1909: FIRST CHEMOTHERAPY DRUG TREATS SYPHILIS

Ehrlich coins the term „chemotherapy“

DOCTORS HAVE FAITH IN EHRLICH'S '606'

Danger, All Admit, Attends Faulty Technique in Using the Blood Cure.

IT MUST ENTER THE VEINS

Fatalities Have Resulted Only Where Salvarsan Has Been Introduced Into Muscular Tissues.

__1909: __After searching through hundreds of potential chemicals, a German immunologist discovers a compound that can selectively kill the parasitic spirochete that causes

HADLEY LEGGETT 08.31.09 12:00 AM

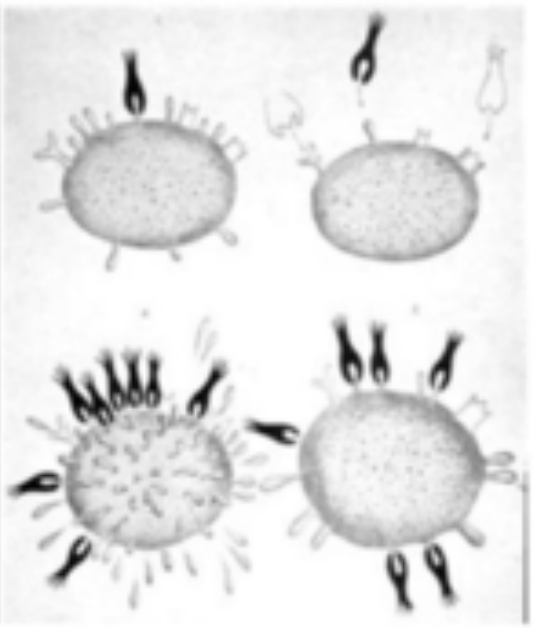
AUG. 31, 1909: FIRST CHEMOTHERAPY DRUG TREATS SYPHILIS

Ehrlich coins the term „chemotherapy“

Ehrlich reasoned that by screening many cpds, he could discover anti microbials that do not kill the patient !

__1909: __After searching through hu
chemicals, a German immunologist discovers a compound
that can selectively kill the parasitic spirochete that causes

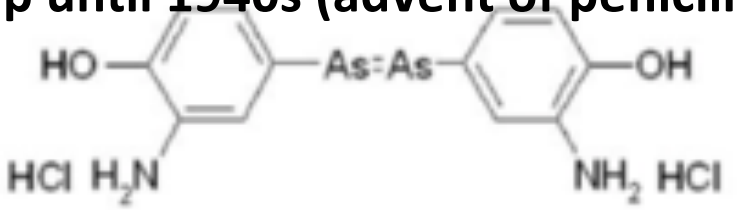
Paul Ehrlich and the "Magic Bullet"

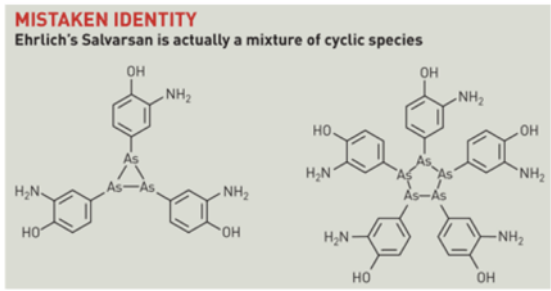


Up until 1940s (advent of penicillin)

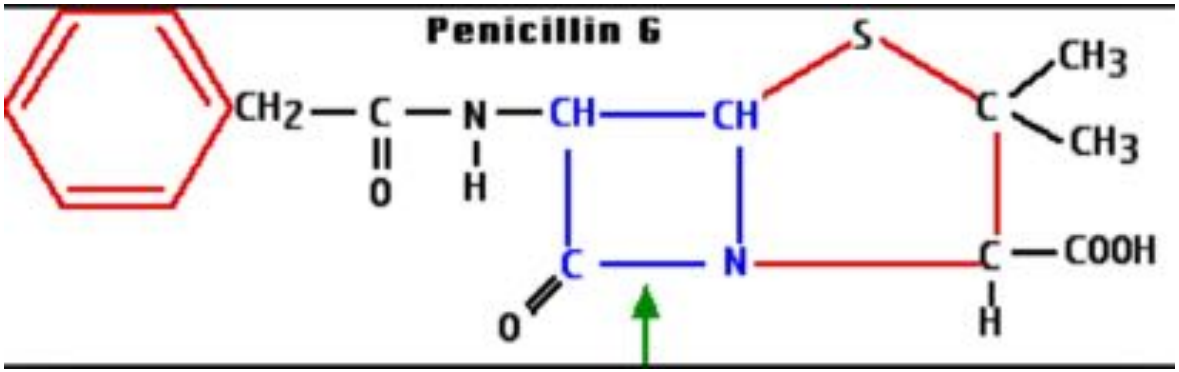
Salvarsan-Compound 606
Early antimicrobial chemical
Introduced in 1910s
Not 100% effective
Long treatment: 1-2 years

Arsenical cpd Arsphenamine

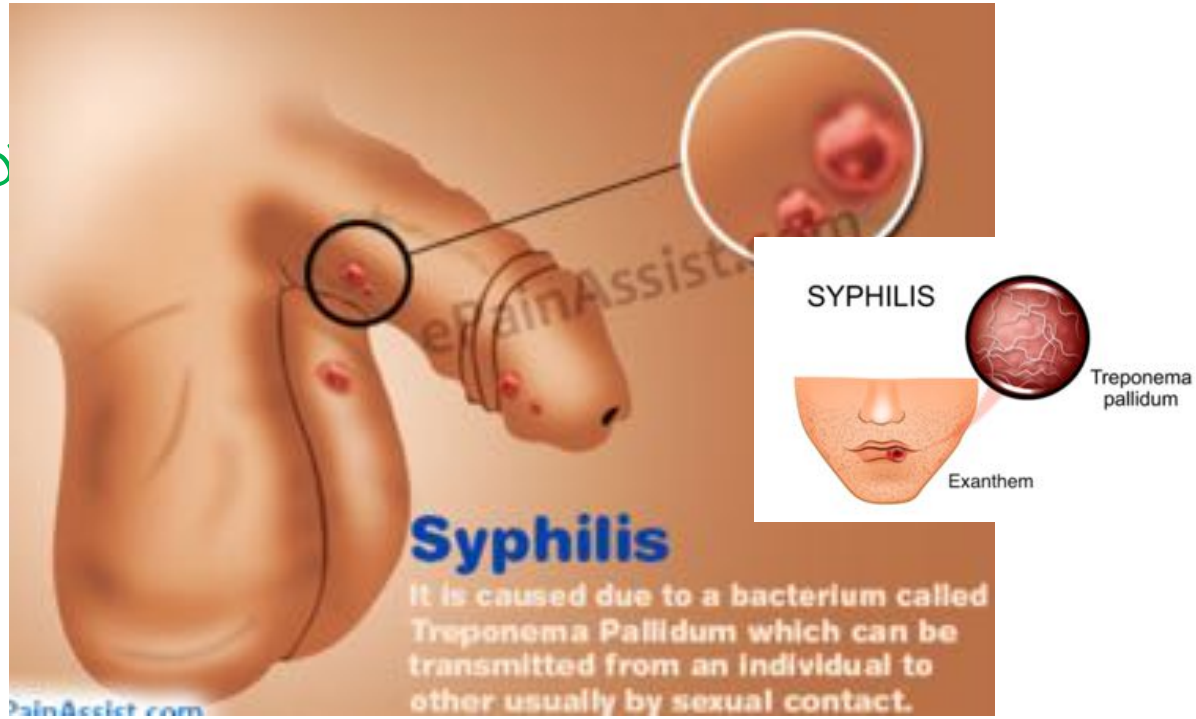




Historical medical breakthrough with impactful clinical value: debate : to whom penicilin‘s discovery?

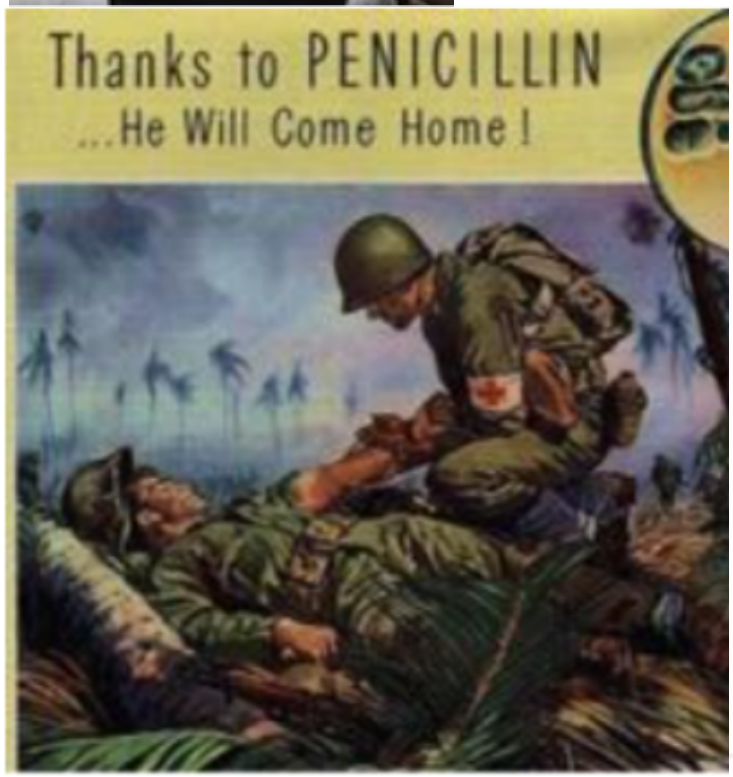


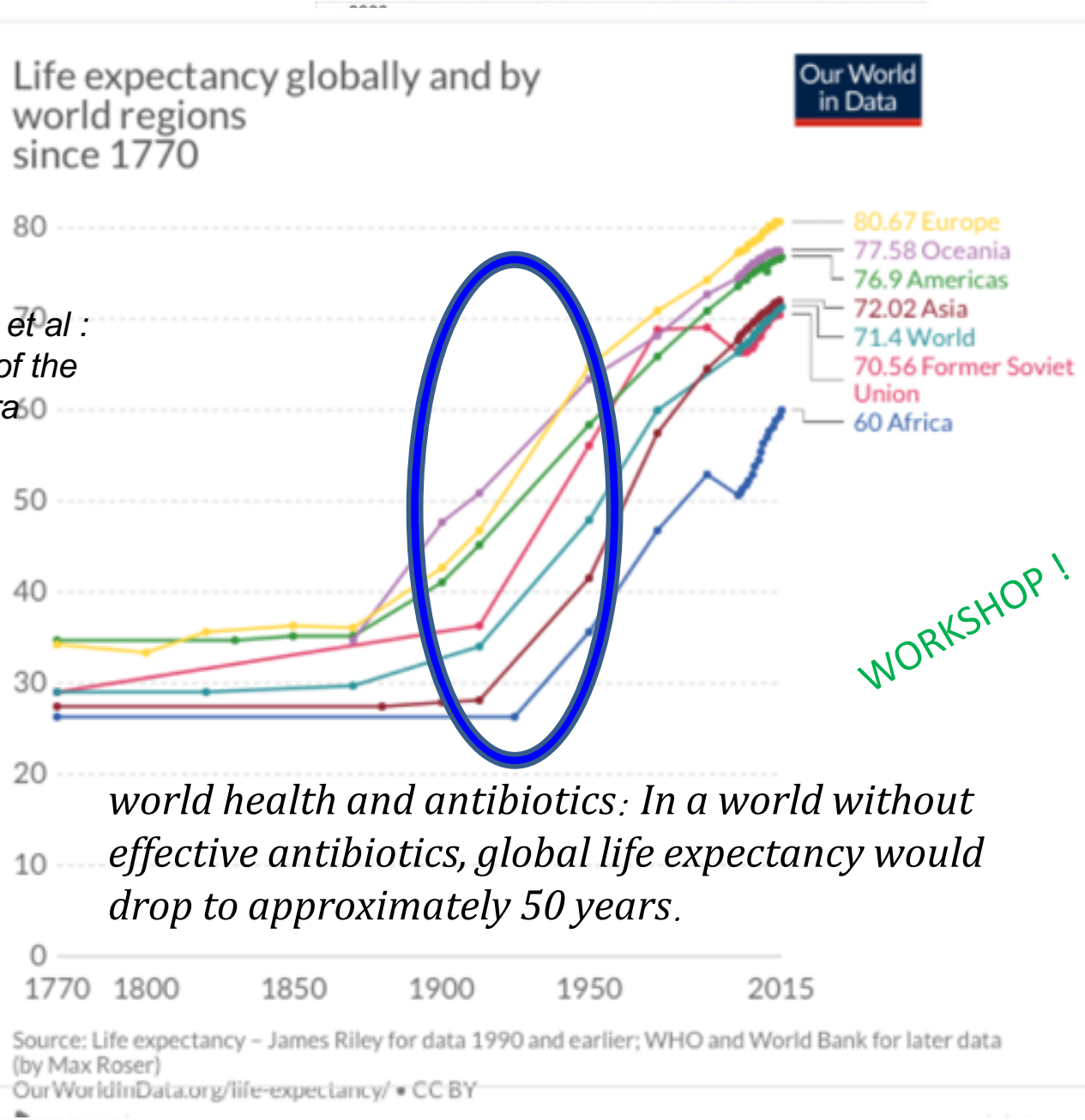
“THE OLD WONDER” IS STILL FIRST LINE TREATMENT FOR SEXUALLY TRANSMITTED DISEASES SUCH AS SYPHILIS ! (45 x 10<6 cases in 2015)



Historical medical breakthrough with impactful clinical value : 1940‘s and the New Wonder Drug From Mold

Sir A. Flemming et al : the foundation of the antibiotic era





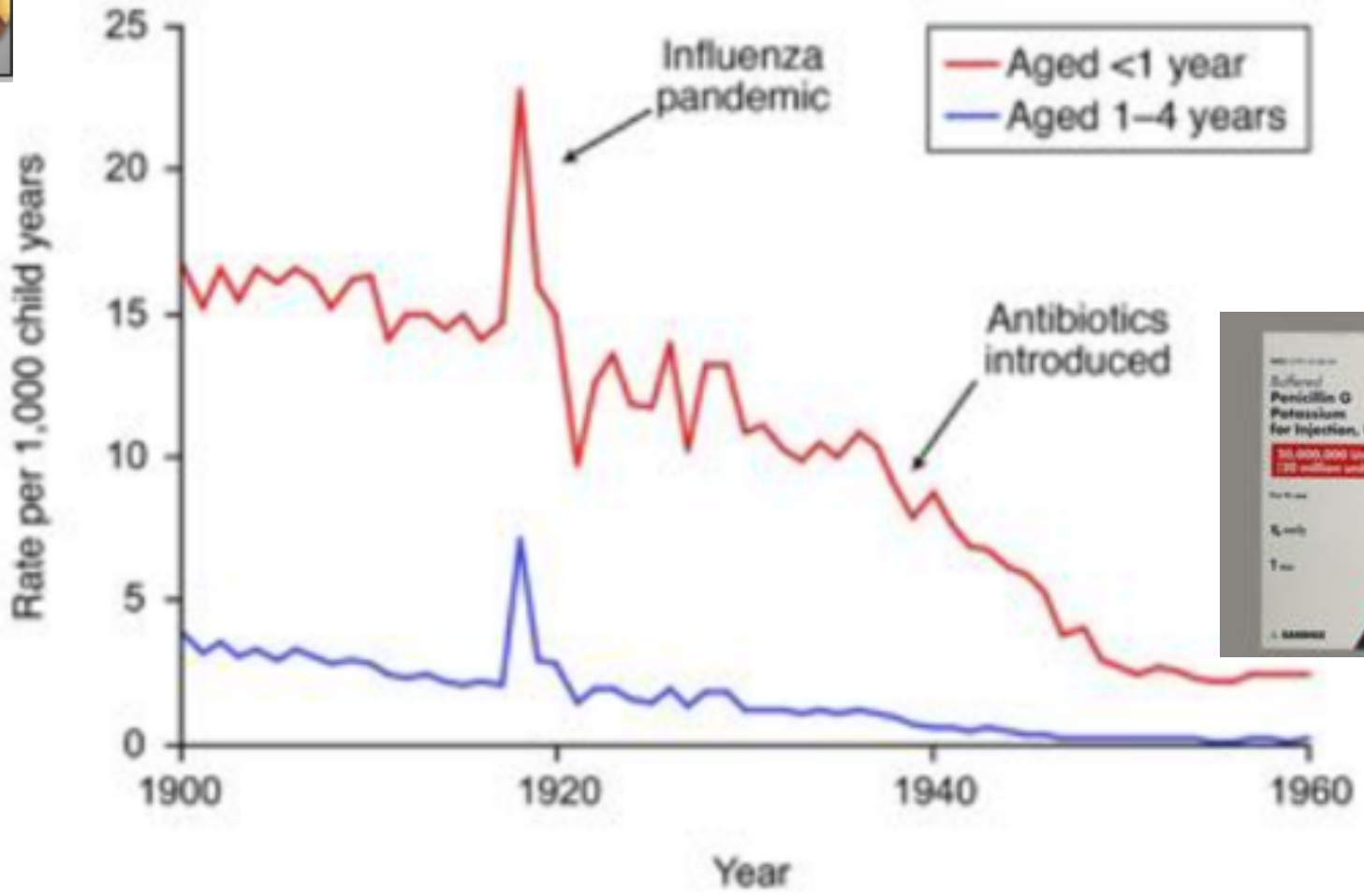
world health and antibiotics: In a world without effective antibiotics, global life expectancy would drop to approximately 50 years.

WORKSHOP !

Antibscterials : ever true medical breakthroughs

THE ADVENT OF ANTIBIOTICS CHANGED OUR MEDICAL STATUS AND LIFE EXPECTANCY IN THE MID OF 20TH CENTURY !

1945 NL Flemming, Florey and Chain

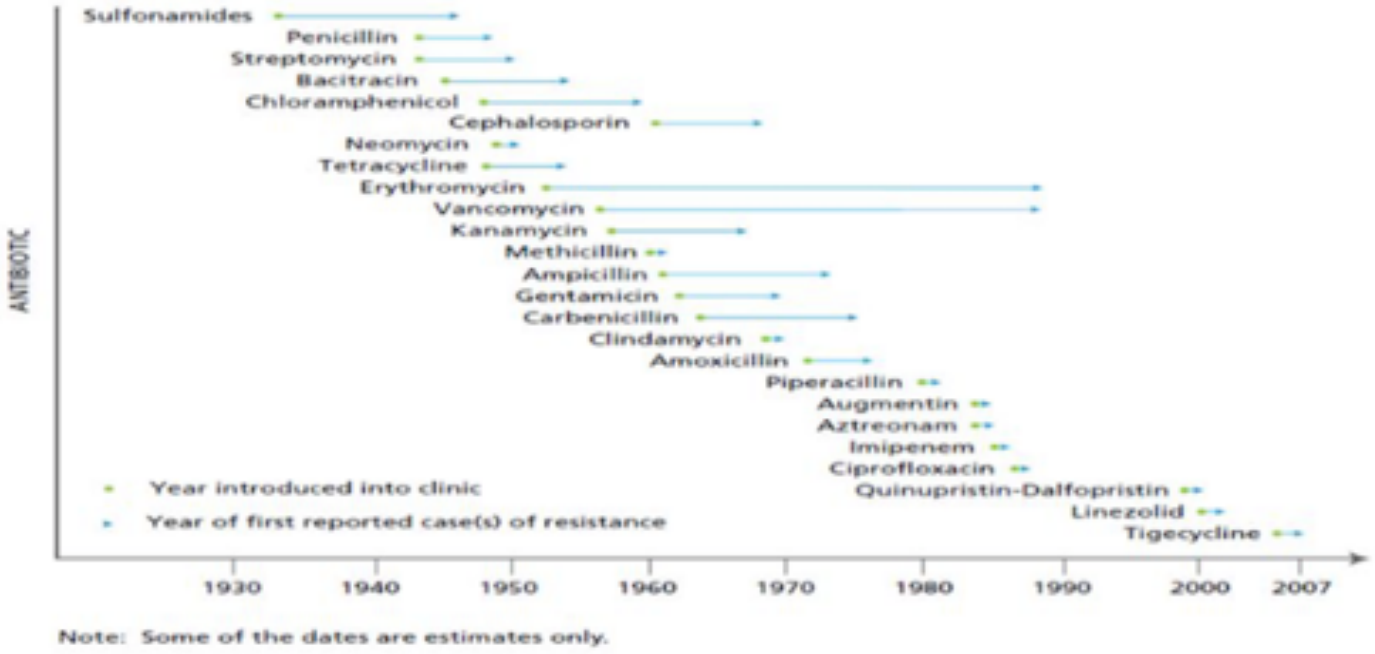


today 3000 types of resistant beta lactamase to antibiotics (ampicilin, methicillin, etc…)

Today's threat and challengies of a postantibacterials era – stay tuned !

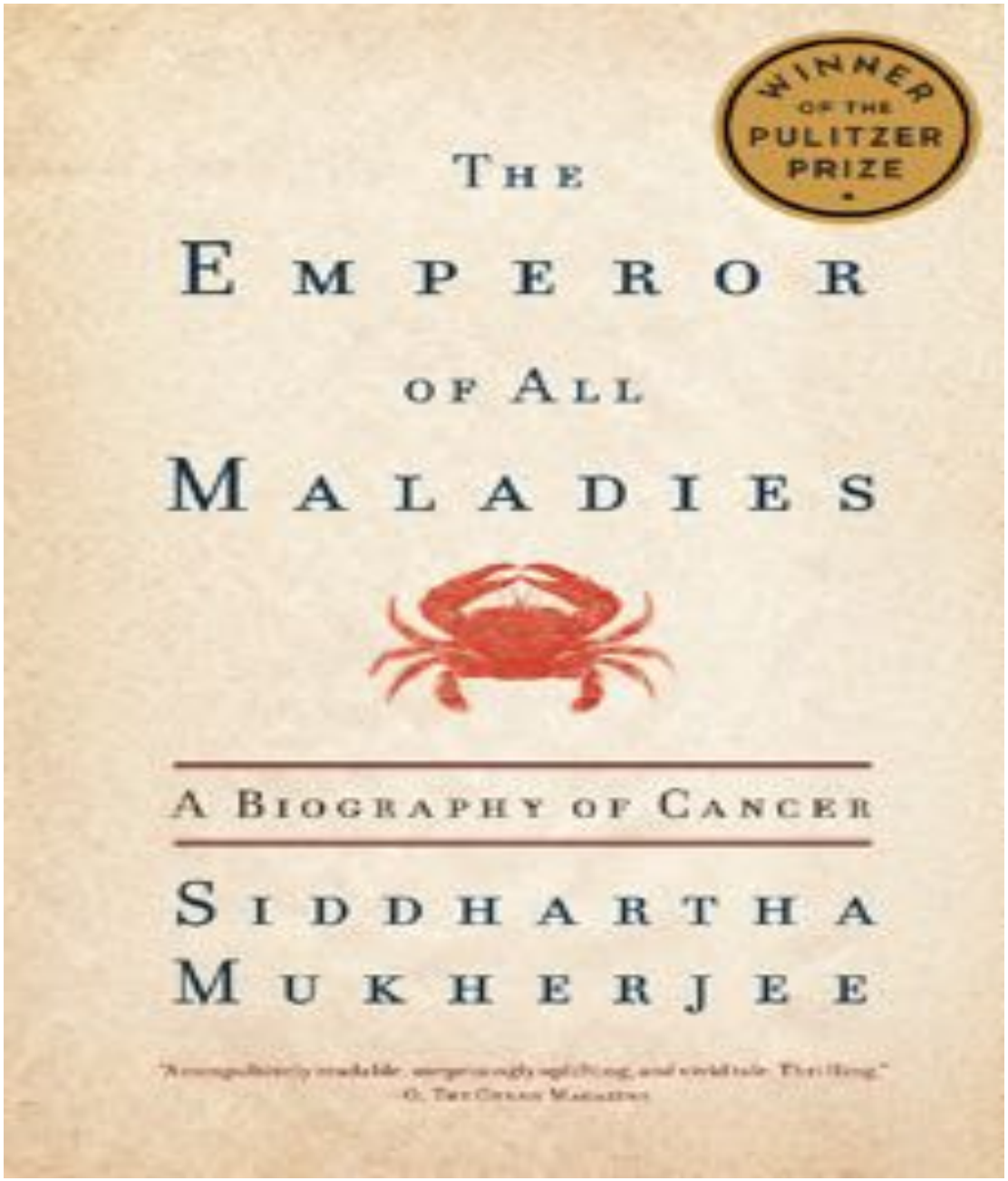
Emergence of antibiotic resistance

Antibiotic resistance threatens ability to control infection

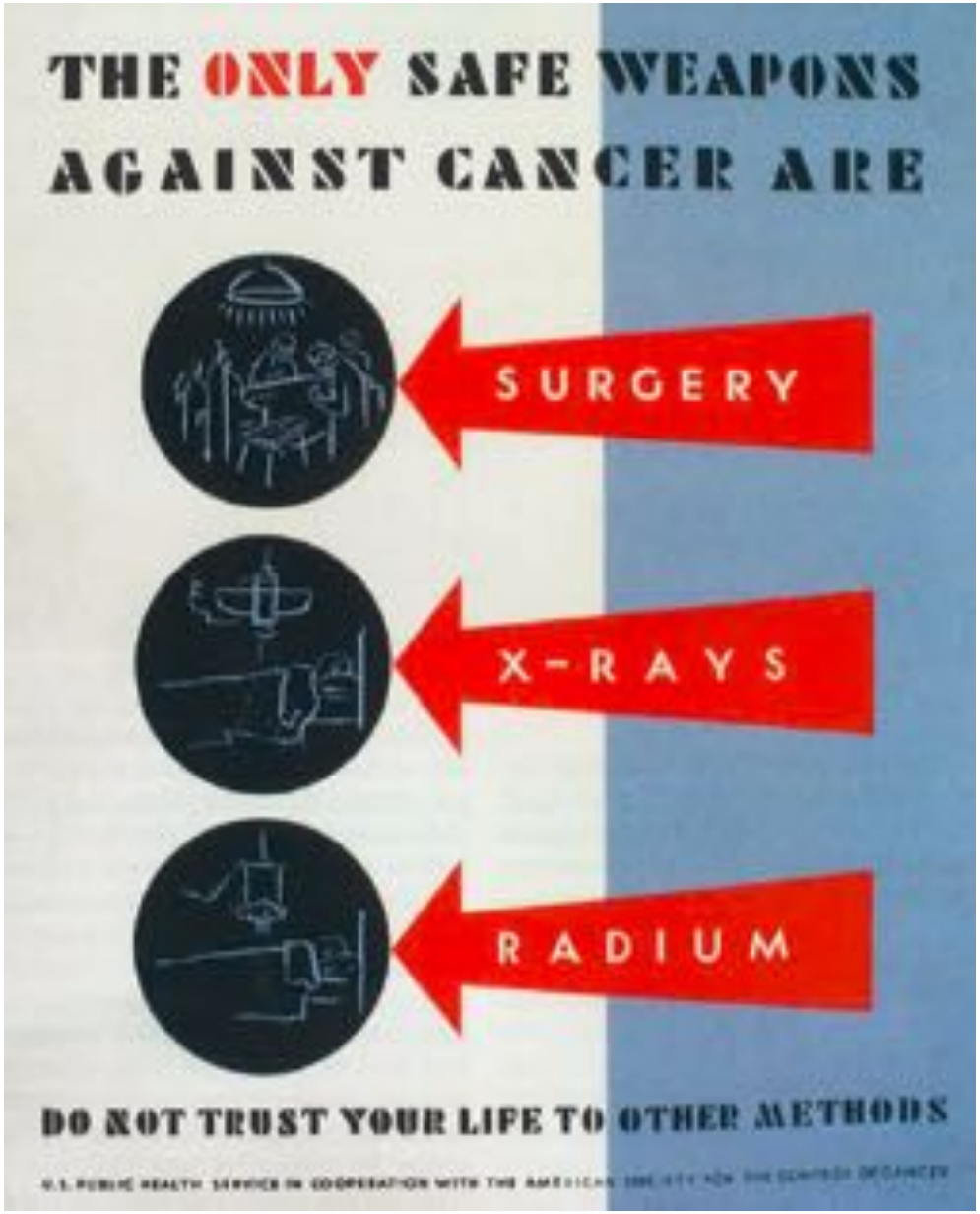


Note: Some of the dates are estimates only.

An oncologist view of patients facing their ordeal : historical perspective



Tumor biology therapy : 1938 – what is missing as of today ?



Tumor biology therapy : 1898 - discovery of Radium


Huit pages : CINQ centimes

Le Petit Parisien

SUPPLÉMENT LITTÉRAIRE ILLUSTRÉ

DIRECTION: 18, rue d'Enghien (10e), PARIS

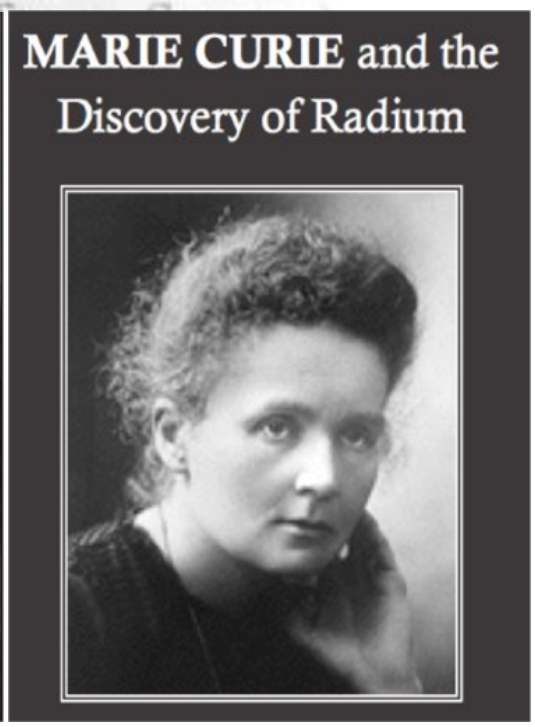
UNE NOUVELLE DÉCOUVERTE. — LE RADIUM

M. ET Mme CURIE DANS LEUR LABORATOIRE


THE PHYSIOLOGICAL ACTION OF RADIO-ACTIVE SUBS

Fig. 51.

Professor Curie's arm, showing a scar resulting from a



Radiotherapy : 1930‘s aftermath – the „radium girls“

blue bowl glowing: Marie Curie Sklodowska and Radium

Radiotherapy : 1917‘s aftermath – „les petites curies“

blue bowl glowing: Marie Curie Skolkova

Xray radiology ambulances for war surgery

Neglected tropical diseases – largely unmet medical needs !

MALARIA, LESHMANIASIS, FILARIASIS etc.

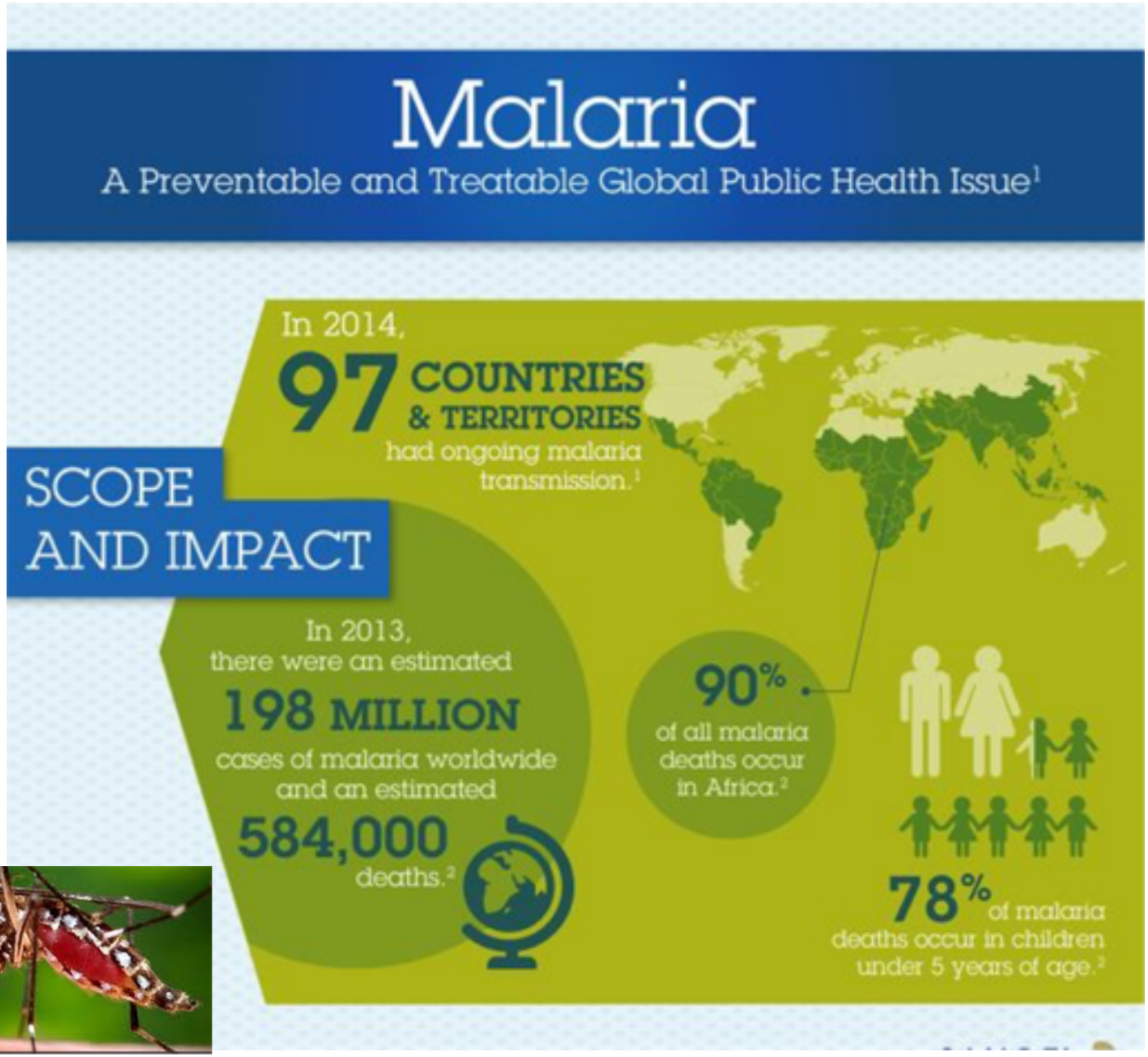
OLD NEGLECTED MEDICAL NEED

PUBLIC HEALTH ISSUE !

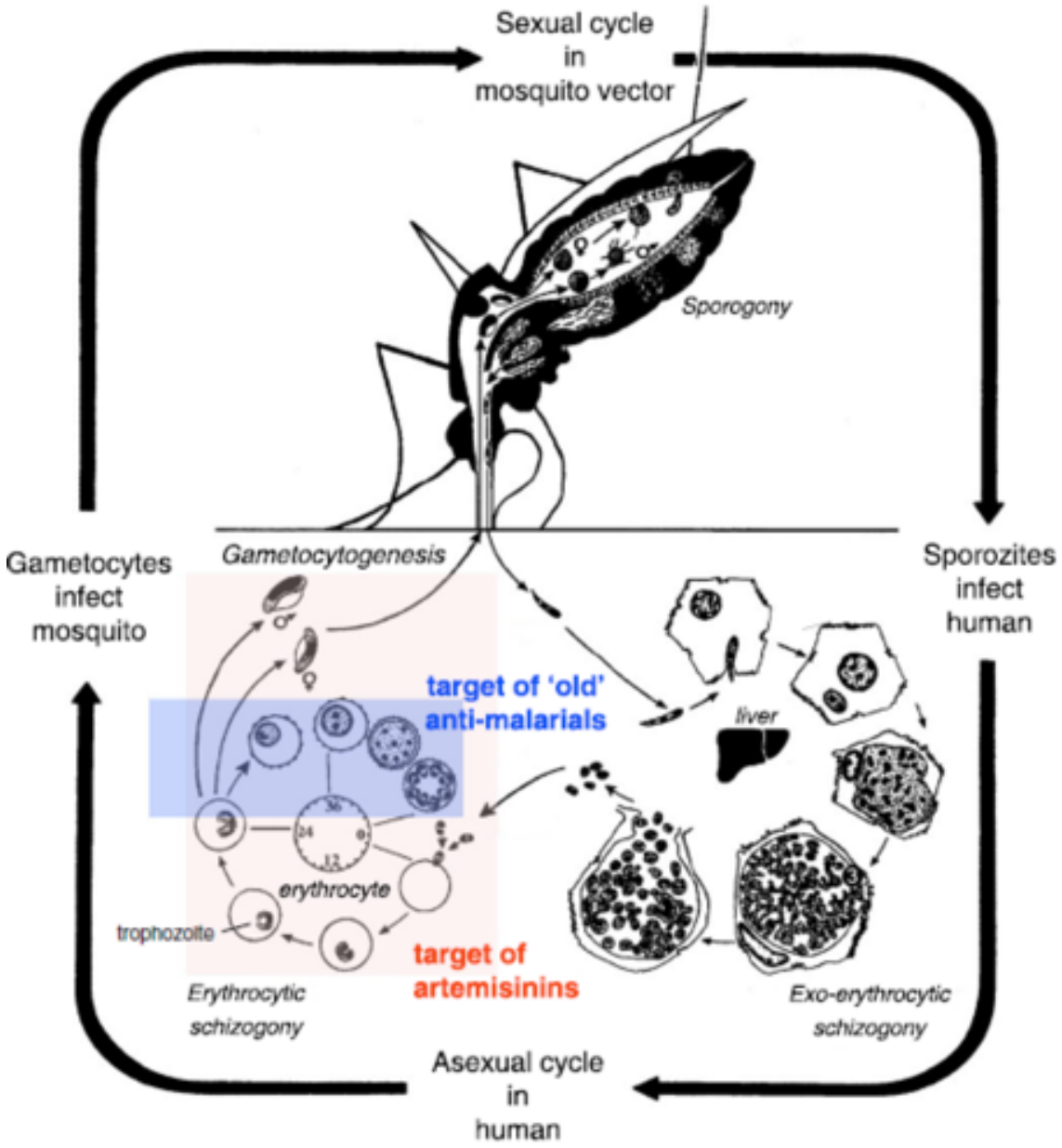
WORKSHOP !

SHORTAGE OF EFFICACIOUS MEDICINES (eg ARTEMISIN) !

The Making Of An Innovative Medicine: historical perspective
Artemisinin



The Making Of An Innovative Medicine: historical perspective
Artemisinin



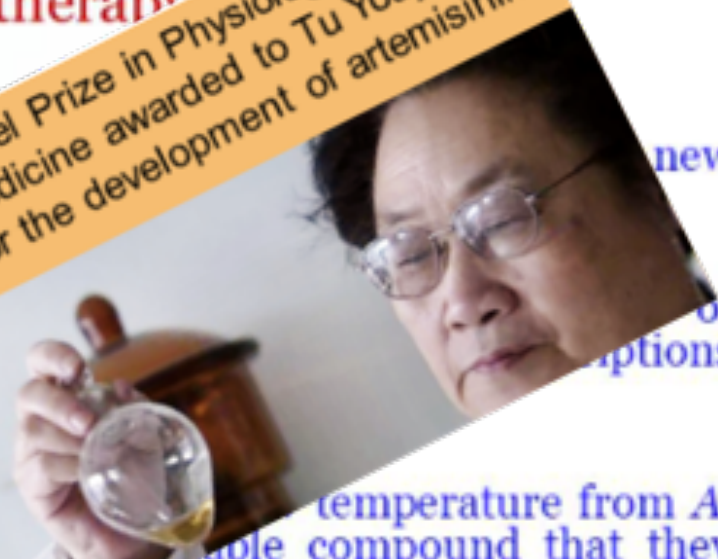
The Making Of An Innovative Medicine: historical perspective artemisinin

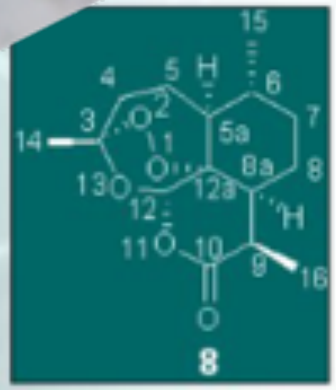
Artemisinin: A major breakthrough in malaria chemotherapy

- In 1967, the Chinese government ... new antimalarial drugs from indigenou...
- The first written rec... of *Artemisia annua* ... for Emergency ... ptions
- In 197... temperature from *A. annua* ... able compound that they named Q... 8.

Plants in the News
October 9 2015

Nobel Prize in Physiology or Medicine awarded to Tu Youyou for the development of artemisinin



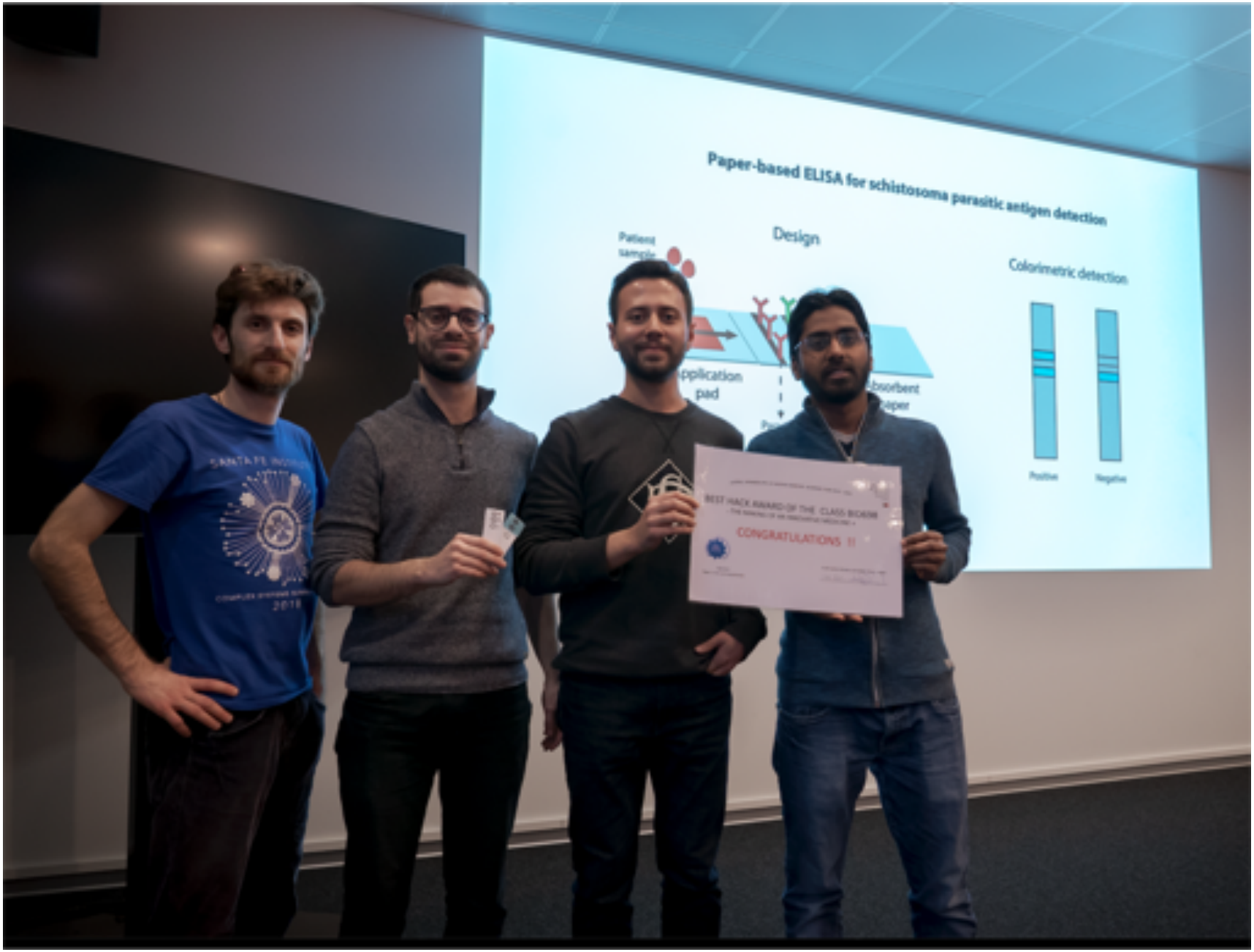


The Making Of An Innovative Medicine: historical perspective
A visit to the TPH in Basel website !

Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut

https://www.swisstph.ch/de/reisemedizin/

Tropical diseases unmet medical need : health hackathon 2021 winners!



Fabulous discovery – first ever biological therapeutic

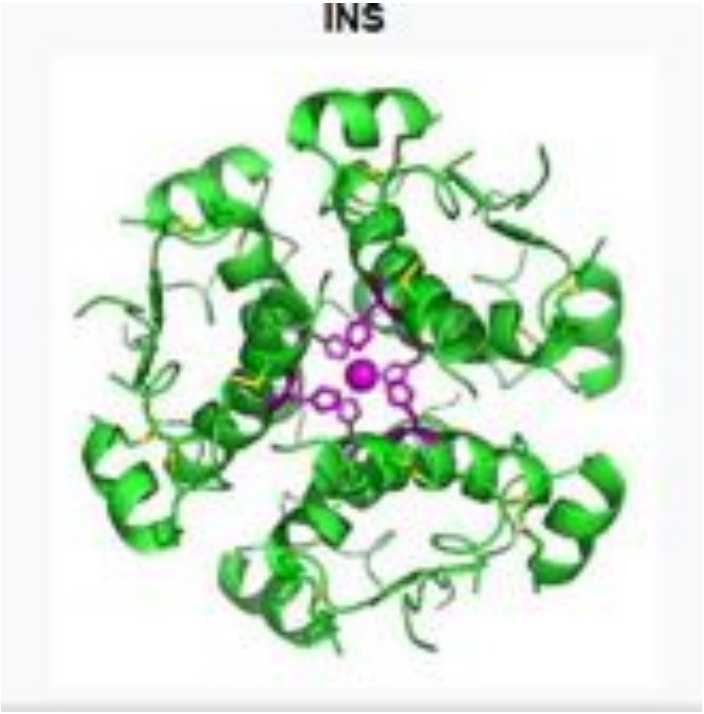
1920 : life expectancy of diabetes children is about 10-15 years !

Frederick Banting became as a GP interested in diabetes mellitus: he became aware of the scientific reports on stenosis of pancreas leaving the Langerhans islets intact and killing the trypsin producing cells. He left aside all his clinical duties to prove his hypothesis and received help from C Best to isolate upon 10 days ligature beagle dog pancreas islets: kids receiving those extracts however experienced no real benefit from this extract injection (5g/L to 4g/L and severe side effects ! Geat disappointment ; F. Banting went on and reasoned that the extracts contained impurities such as bacteria. He decided to further purify.

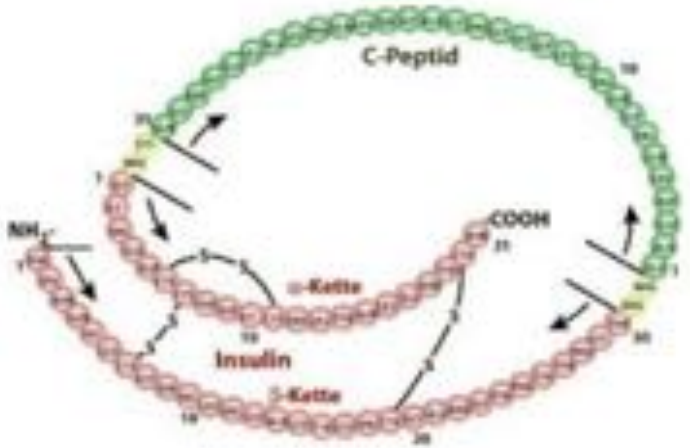
Frederick Banting then turned to a medical doctor biochemist James Collip who worked on an almost pure pyrogene free pancreatic insulin injectable.
The efficacy was closed to the miracle! glycemia droped from 5g/L to 1g/L !! The kids came out of coma and were starting a new life !
Frederick Banting eventually received a well deserved Nobel Prize in 1923.
Sofar millions of diabetic patient's life has been safed thanks to Frederick Banting resilience and perseverance and benefited from this breakthrough !
F Banting coined the name «insulin» from «insula» in latin (for islet/island of Langerhans) and became one of the most successful drug hunter ever in biomedical history.
Very few life threatening diseases have been cured sofar to such a extend of efficacy in modern medicine.

1920 : life expectancy of diabetes children is about 10-15 years !
Today diabetic patients live almost like healthy subjects !

Historical breakthrough medicines



Frederick Banting became as a GP interested «by accident» to help many kids in life threatening conditions purified extracts from dog ligatured pancreas : kids experienced no real benefit up until the dog pancreas extracts got purified. Later insulin has been extracted from porcine pancreas and provided by Eli Lilly USA



1960s : shortage of porcine insulin: bacterial recombinant insulin came to the rescue (first «biological» ever) Axel Ullrich et al. 1970s !

FROM AN HISTORICAL PERSPECTIVE THESE MEDICINE WERE TRUE INNOVATIONS ! TODAY'S REGULATORY AUTHORITIES WOULD PROBABLY NOT LET THEM PASS THROUGH THE REGISTRATION

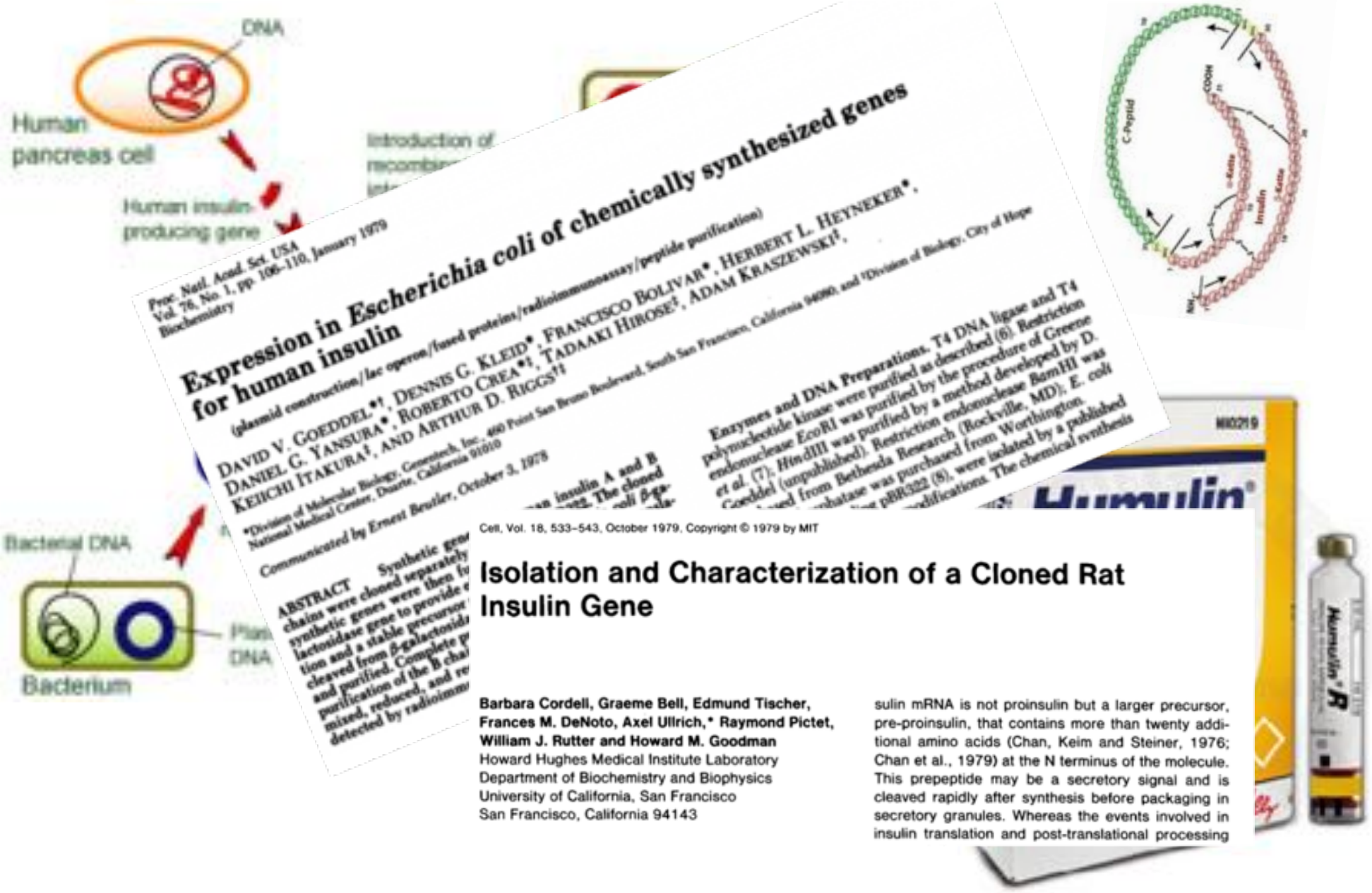
Science. 1977 Jun 17;196(4296):1313-9.

Rat insulin genes: construction of plasmids containing the coding sequences.

Ullrich A, Shine J, Chirgwin J, Pictet R, Tischer E, Rutter WJ, Goodman HM.

Abstract

Recombinant bacterial plasmids have been constructed that contain complementary DNA prepared from rat islets of Langerhans



Historical breakthrough medicine : Eli Lilly insulin

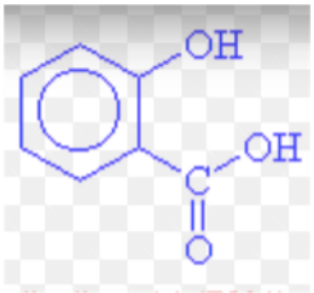
1960s : shortage of porcine insulin: bacterial recombinant insulin came to the rescue (first «biological» ever) Eli Lily Pharmaceuticals

Historical breakthrough medicines
The advent of placebo controled clinical trials

The advent of modern medicinal chemistry in drug development

Salicilic acid

Pain, antiinflamatory, cardio portective

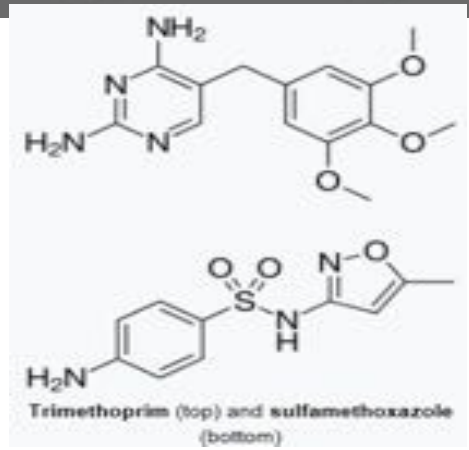


Isotretinoin

Severe acne, ichthyosis, birth defects

Bactrim

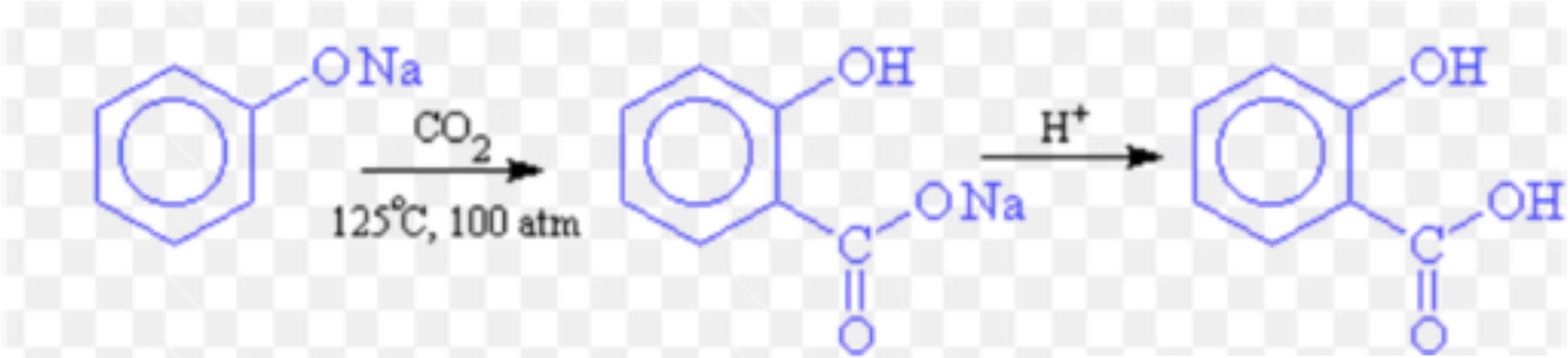
Antimicrobial sulfamethoxasol and trymethoprime



FROM AN HISTORICAL PERSPECTIVE THESE MEDICINE WERE TRUE INNOVATIONS ! TODAY'S REGULATORY AUTHORITIES WOULD PROBABLY NOT LET THEM PASS THROUGH THE REGISTRATION

Historical breakthrough medicines and the german medicinal chemistry

The advent of modern medicinal chemistry in drug development



Salicilic acid

Pain, antiinflamatory, cardio portective

The kolbe schmitt reaction has been invented in the 1930's for the preparation of aromatic hydroxy acids. Usually the substitution occurs ortho to the phenolic hydroxy group

FROM AN HISTORICAL PERSPECTIVE THESE MEDICINE WERE TRUE INNOVATIONS ! TODAY'S REGULATORY AUTHORITIES WOULD PROBABLY NOT LET THEM PASS THROUGH THE REGISTRATION

Aspirin - from tree bark to modern medicine

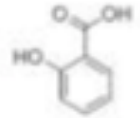
Aspirin

百年名藥-阿斯匹靈

Analgesic-止痛
relieve minor aches and pains
Antipyretic-解熱
reduce fever
Anti-inflammatory-消炎

Hippocrates

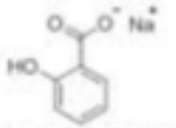
460 B.C and 377 B.C



Salicylic acid

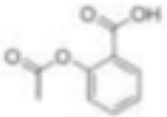
Hermann Kolbe

1853



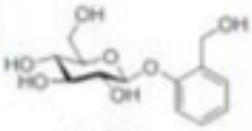
sodium salicylate

1859



Acetylsalicylic acid

1897 1897
1899



Salicin

Felix Hoffmann
In Bayer AG

1974

prevention of strokes
and heart attacks

Historical breakthrough medicines

The advent of modern medicinal chemistry in drug development

The salicin in willow bark converts to salicylic acid

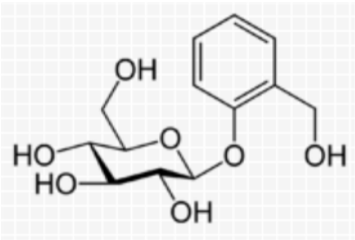
Known in chinese medicine

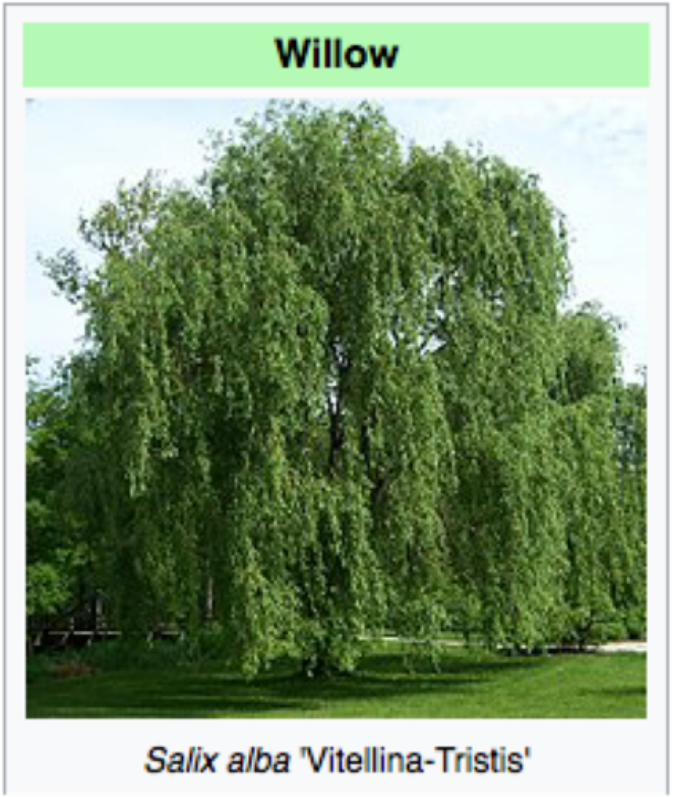
Extracts from white willow bark in 1821

Isolation of salicilic acid from **SALICILIN** in white willow bark in 1838

Salicilic acid

Pain, antiinflamatory, cardio portective





FROM AN HISTORICAL PERSPECTIVE THESE MEDICINE WERE TRUE INNOVATIONS ! TODAY'S REGULATORY AUTHORITIES WOULD PROBABLY NOT LET THEM PASS THROUGH THE REGISTRATION

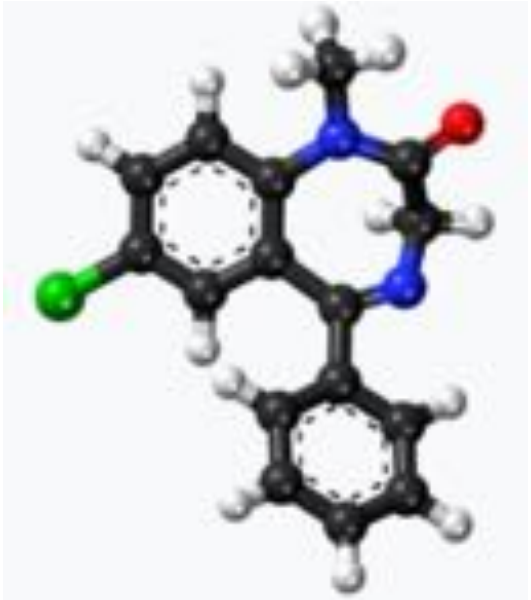
More historical breakthrough of modern medicinal chemistry

The advent of modern medicinal chemistry in drug development

BENZODIAZEPINES

1960 Valium® (diazepam)
Tranquilizer
(GABA receptor agonist)

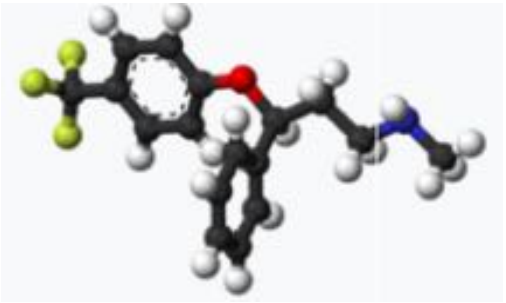
Leo Sternbach
Roche Ltd



SSRI selective serotonin reuptake inhibitors

1972 Prozac® (fluoxetine)
Antidepressant
(serotonin receptor)

Eli Lily Inc

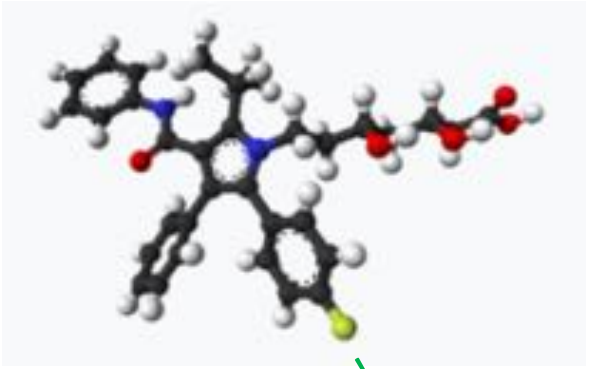


WORKSHOP !

STATINS

1985 Lipitor® (atorvastatin)
Lipid lowering, CVD
(HMGCoA reductase inhibitor)

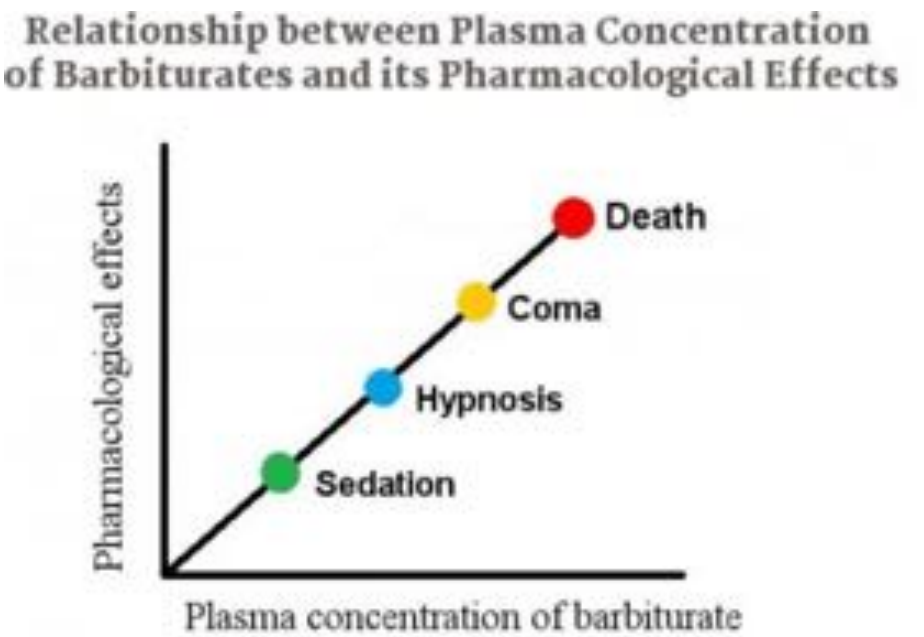
Akira Endo (Lasker Award)
@ Sankyo/Warner-Lambert
Pfizer



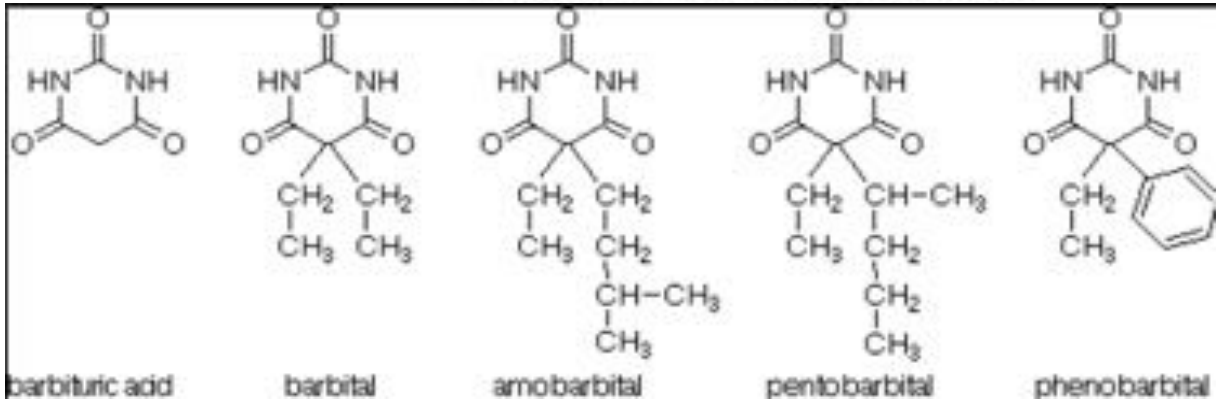
WORKSHOP !

Historical medical breakthroughs and pitfalls in psychiatry

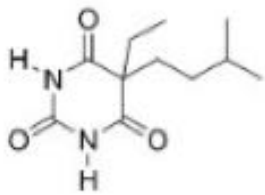
Before the Benzodiazepine Story: a number of celebrities died from ***barbiturates***



Chemist A. von Baeyer : 1864 tested a derivative of urea and malonic acid on himself ! the first hypnotic sleep drug with fatal adverse effects (NL 1905)



Historical psychiatric care -electroshocks

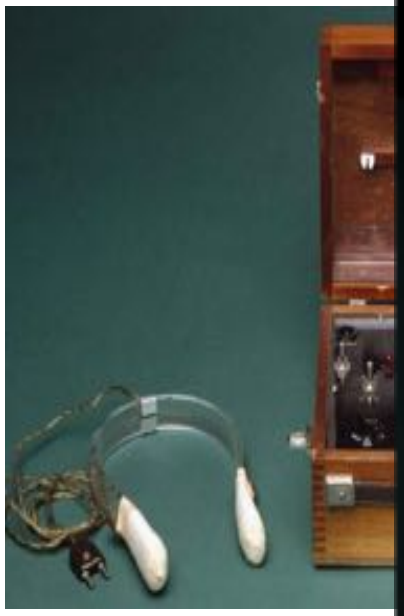


amobarbital
(hypnotic)

Psychiatry 1940's: ***electroconvulsive therapies, electroshocks, lobotomy***
see eg. Angelina Jolie starring "Changeling"

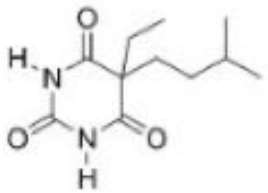
Note: barbiturates act by hyperpolarization and opening of GABA receptor associated ion Cl channels leading to inhibition of neural activity, MOA unknown up until 1980's

Historical psychiatric care-lobotomy



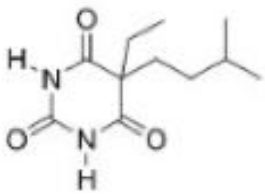
therapies, electroshocks, lobotomy

see eg. Angelina Jolie starring "Changeling"



Note: barbiturates act by hyperpolarization and opening of $GABA_A$ receptor associated ion Cl^- channels leading to inhibition of neural activity, MOA unknown up until 1980's

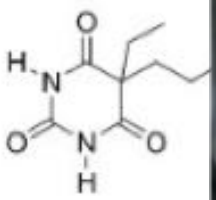
Historical psychiatric care– electroconvulsive therapies



Psychiatry 1940's: ***electroconvulsive therapies, electroshocks, lobotomy***

see eg. Jack Nicholson starring One flew over the cuckoo's nest "

Historical psychiatric clinic – reloaded by Jack Nicholson



amobarbital
(hypnotic)

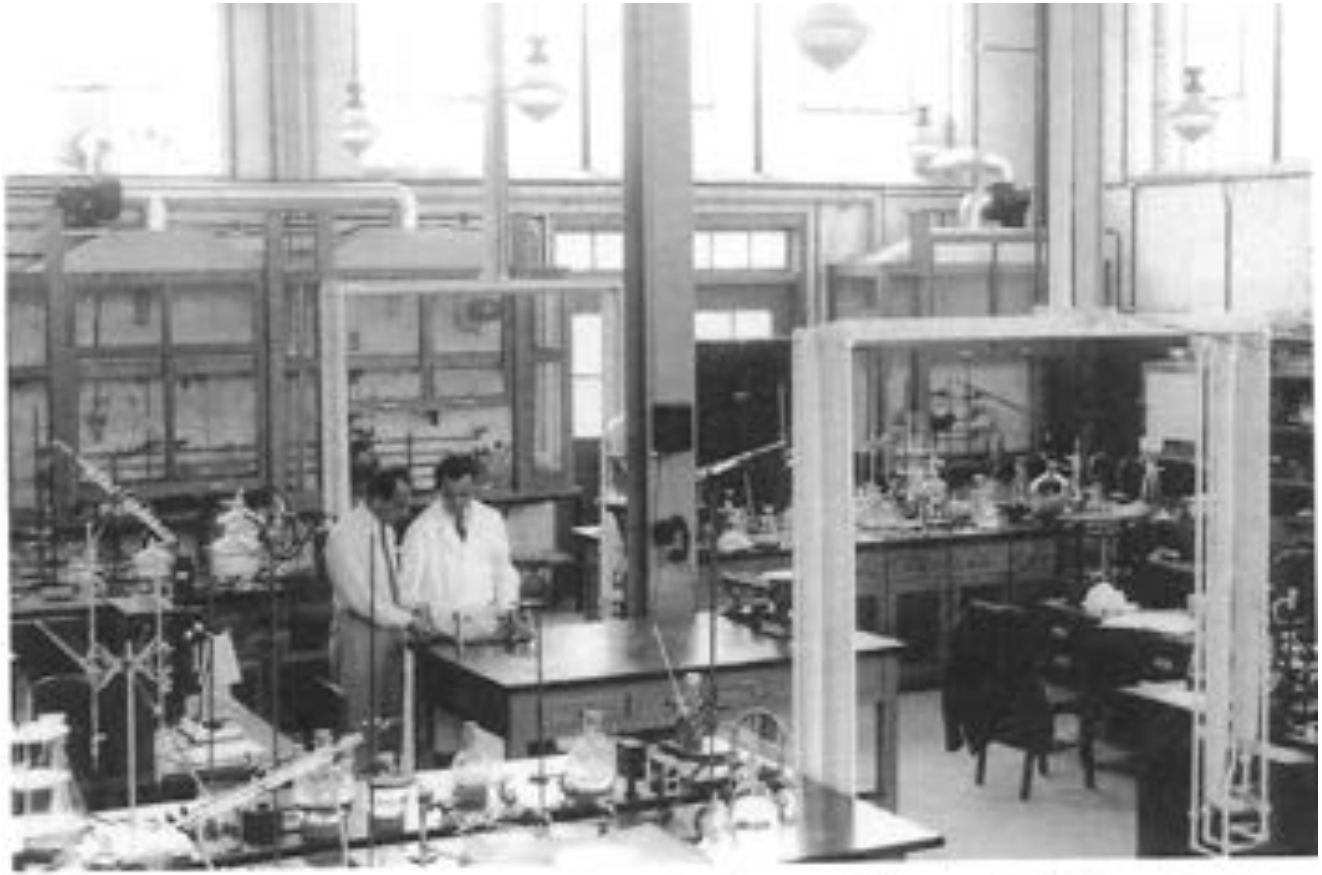
The advent of modern medicinal chemistry

The Benzodiazepine Story: towards Leo Sternbach life time achievement

- **1940's**
- **WW II time**
- **ROCHE Inc hires Nazi refugee polnish chemist L. Sternbach**
- **primitive tranquilizers anxiolytics: barbiturates with severe adverse effects and little therapeutic value**

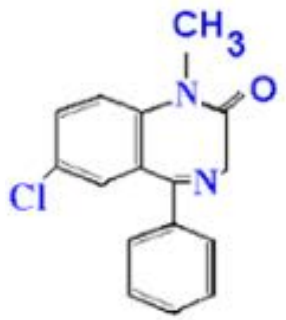
- **NO CELLULAR SIGNAL PATHWAY DECIPHERED !**
- **NO GENOME PROJECT**
- **TRIAL AN ERRORS NO HTS !**

- **Secondary screens *in vivo:* how to monitor a depressed anhedonic rodent in animal pharmacology ?**

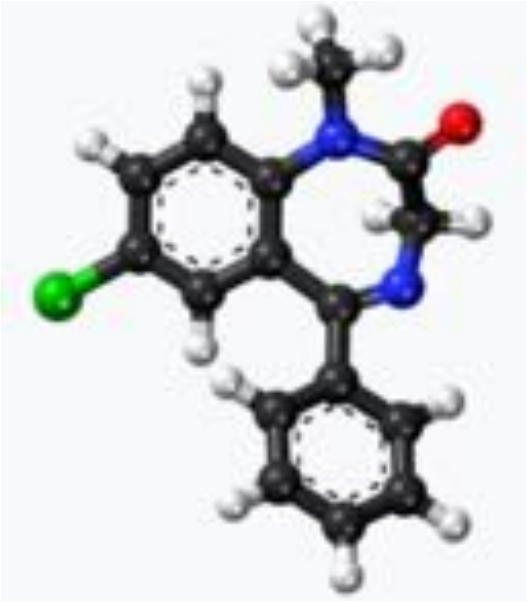


Leo Henryk Sternbach and Dr. Max Hoffer in the chemistry laboratory, building 25, Roche Nutley, 1941

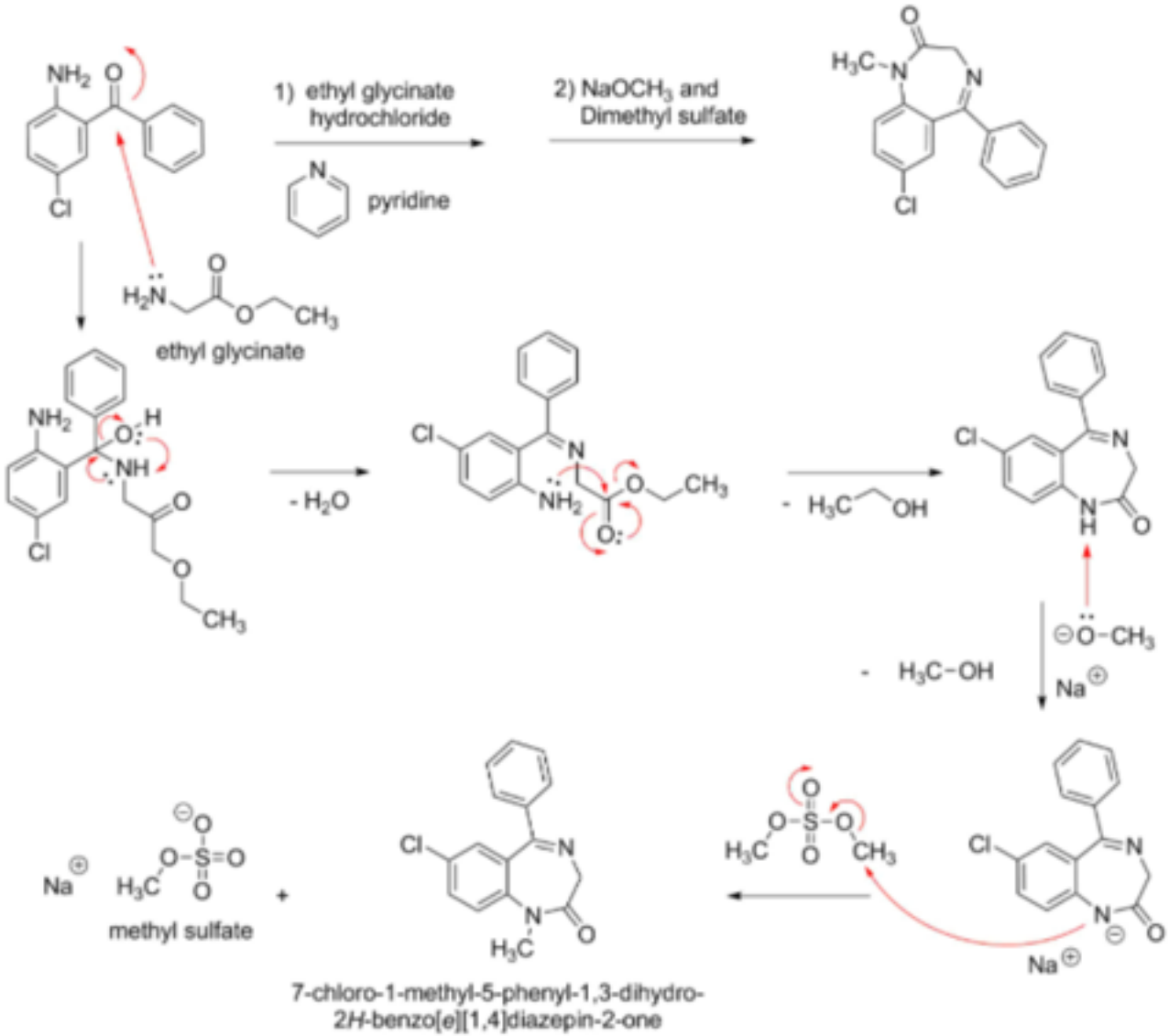
The Benzodiazepine Story of Valium: Leo Sternbach life time achievement



Diazepam
(Valium)



Synthesis of Diazepam with (2-amino-5-chlorophenyl)(phenyl)methanone



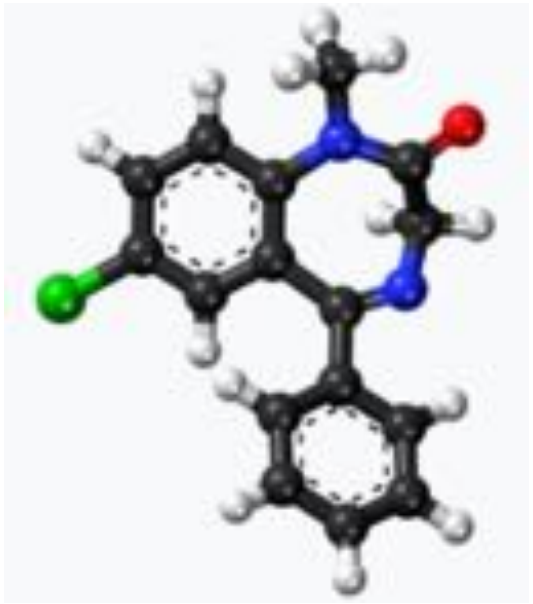
7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-one

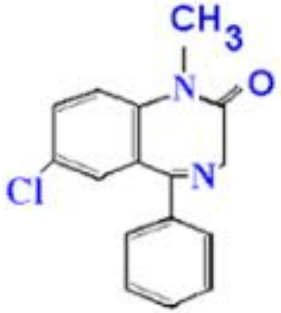
organic-chemistry | reaction-mechanism | synthesis

Historical medical breakthrough – the benzodiazepines

The Benzodiazepine Story of Valium®: Leo Sternbach life time achievement

1960's discovery of Valium®
(Diazepam) safe tranquilizer, anxiolytic





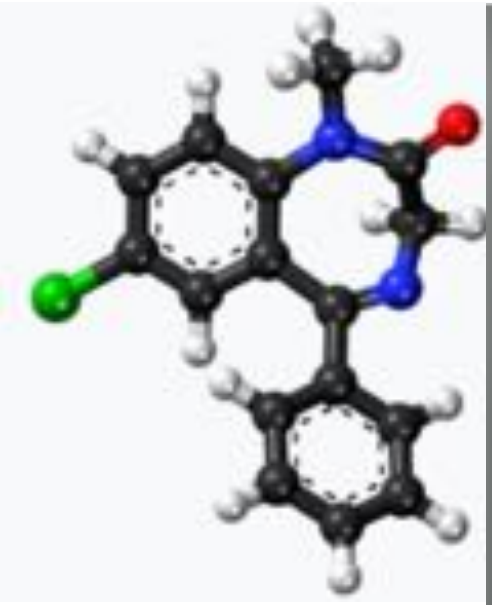
Diazepam
(Valium)

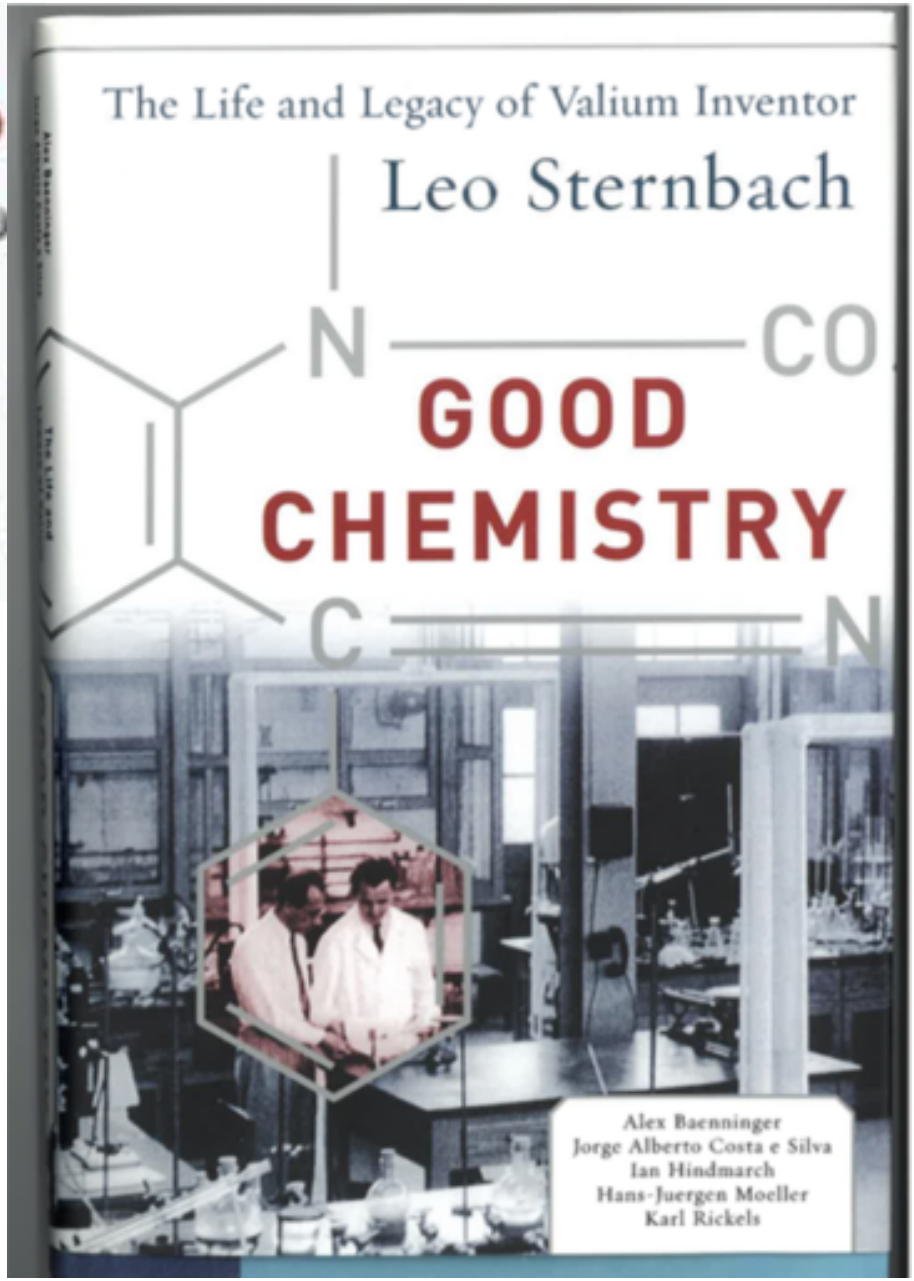
Leo Henryk Sternbach accepting award for Valium from Mr. Lindner on behalf of Roche, 1970

Historical medical breakthrough – the legacy of Leo Sternbach

1960‘s discovery of Valium®
(Diazepam) safe tranquilizer, anxiolytic.

Today’s “benzo” addiction syndrome still a major threat in psychiatric care





20 years later – Diazepam (Valium®)
The advent of the underlying molecular therapeutic target

20 YEARS AFTER THE DIAZEPAM DISCOVERY :

THERAPEUTIC TARGET IDENTIFIED !! A VERY SPECIFIC NEUROTRANSMITTER GABA RECEPTOR AGONIST

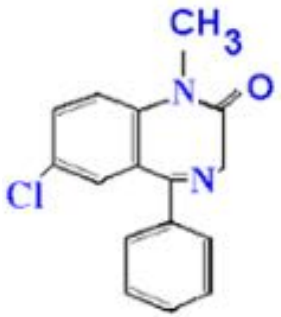
MARGINAL SIDE EFFECTS (ADDICTION), STILL IN CLINICAL USE TODAY AS VALIUM eg POST OP RELAXANT

Seeburg PH Barnard EA Lab at Genentech. Nature (1987) 328:221-227

The Benzodiazepine Story – Valium®: 20 years later !

$GABA_A$ receptor ($GABA_A R$)

- pentameric **ligand-gated Cl^- channel** (endogenous: GABA)
- Clinically relevant **allosteric binding** sites for: BZD, Z drugs, barbiturates, **ethanol**
- Neuronal hyperpolarisation
- anxiety, fear, consciousness, seizures



Diazepam
(Valium)

THANK YOU.....

DO YOU HAVE ANY QUESTİONS ?

IT IS NOT BECAUSE THINGS ARE DIFFICULT THAT WE DO NOT DARE, IT IS BECAUSE WE DO NOT DARE THAT THEY ARE DIFFICULT

LUCIUS ANNAEUS SENECA