

Return of the microbe



Four Horsemen of the Apocalypse:
Pestilence, War, Famine, and Death: 1887 Victor Vasnetsov

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Gresham College
Jan 2014

Viral infections of the eye

Adenovirus: 90nm: ds DNA non-enveloped humans, 57 serotypes cause variety of illnesses. transmitted by direct contact, faeco-oral; waterborne

respiratory system; Ad14 can be lethal

Gastroenteritis,

conjunctivitis,

Cystitis,

Rash

Pharyngo conjunctival fever

5-18yrs. It is often found in summer camps and during the spring and fall in schools. In Japan, the illness is commonly referred to as "pool fever"

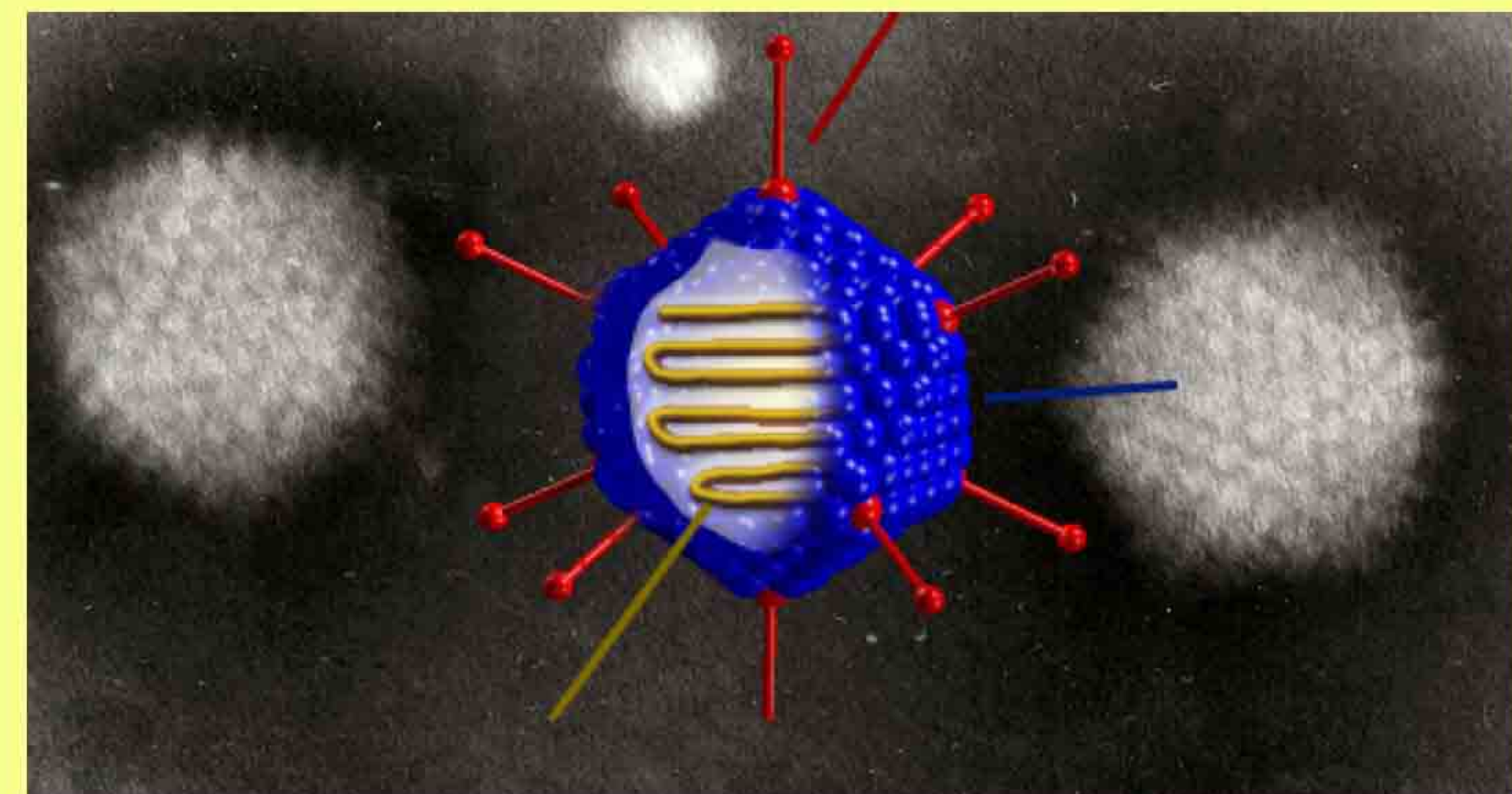
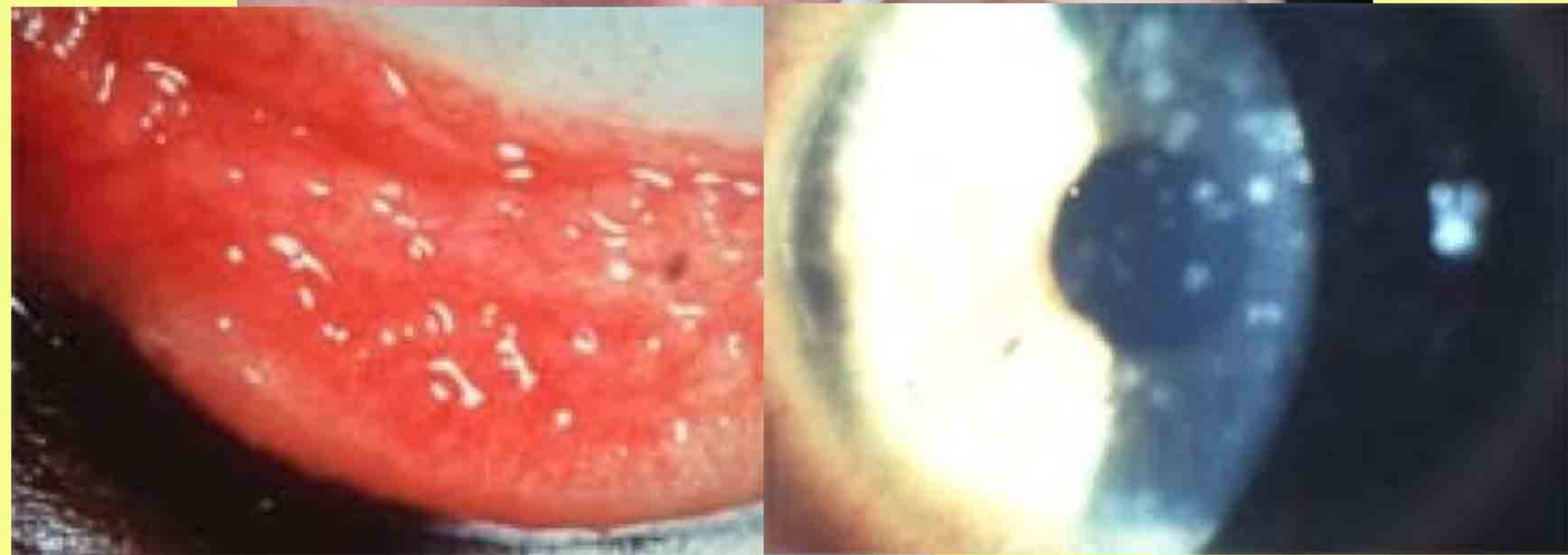
Epidemic Keratoconjunctivitis

Different serotypes

20% corneal spots

Link to Obesity:

USA: 30% of the obese individuals vs 5% of non-obese individuals have antibodies to Ad-36



Herpes

ἕρπης *herpēs*, "creeping"

HSV is an enveloped virus of approximately 200 μm

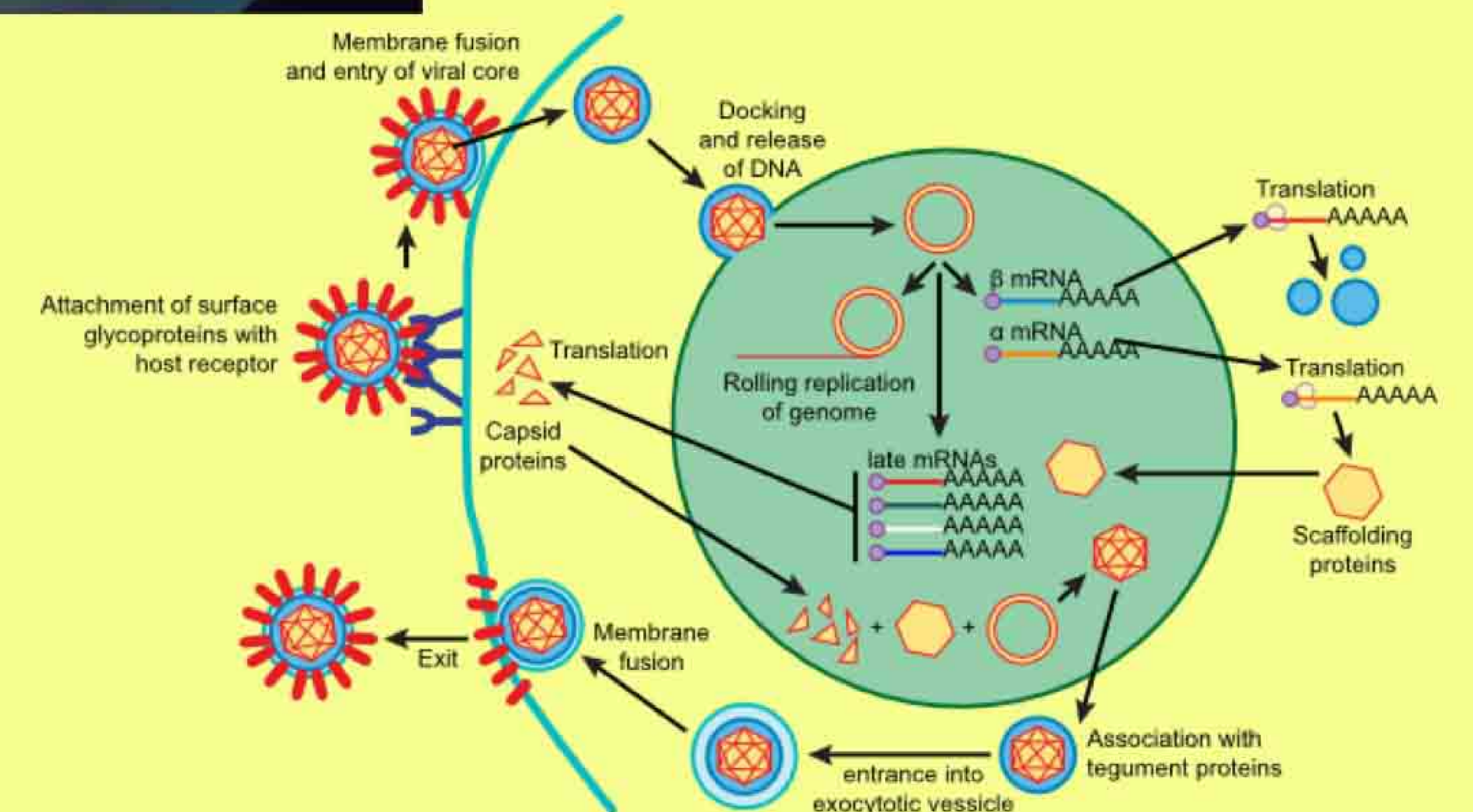
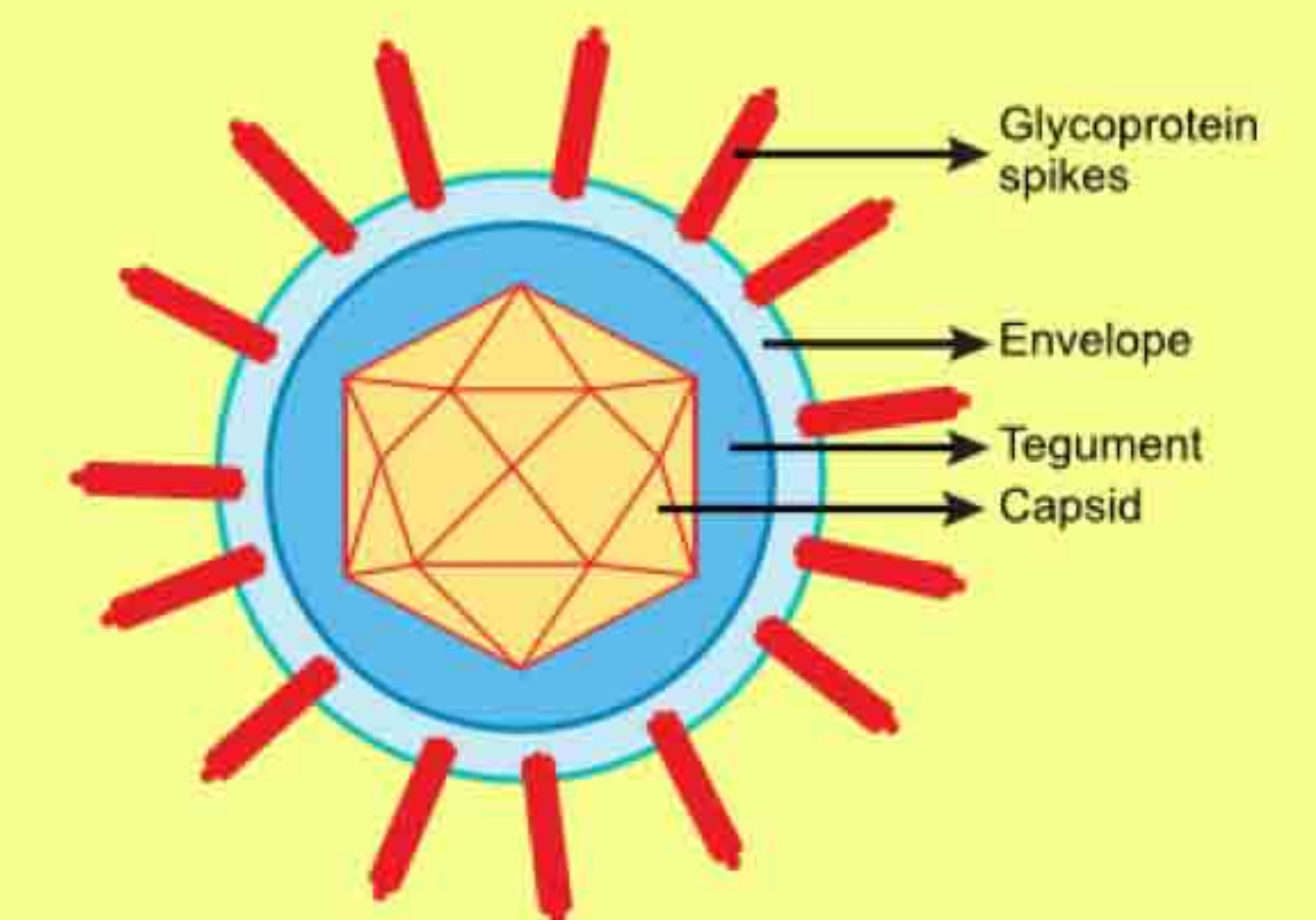
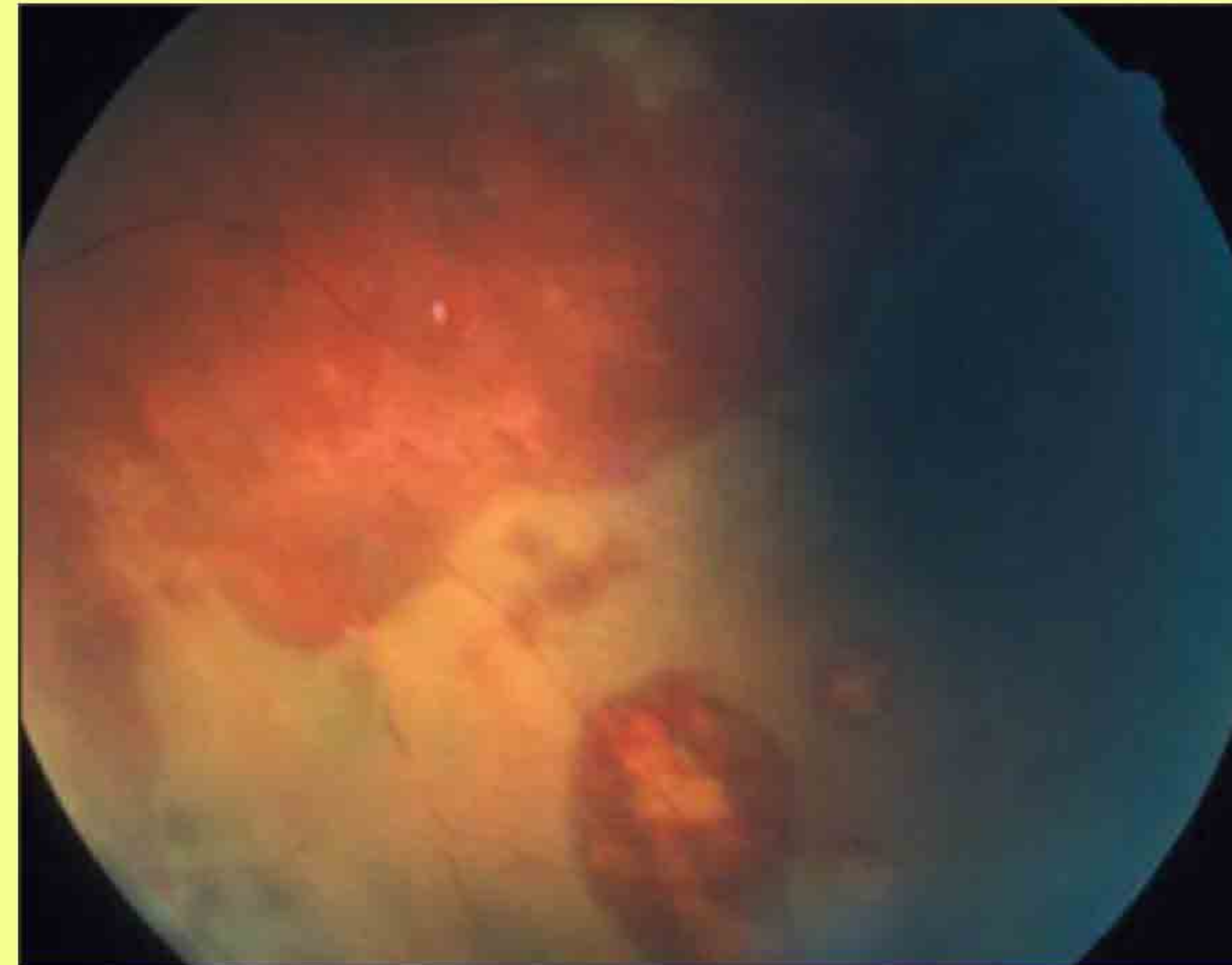
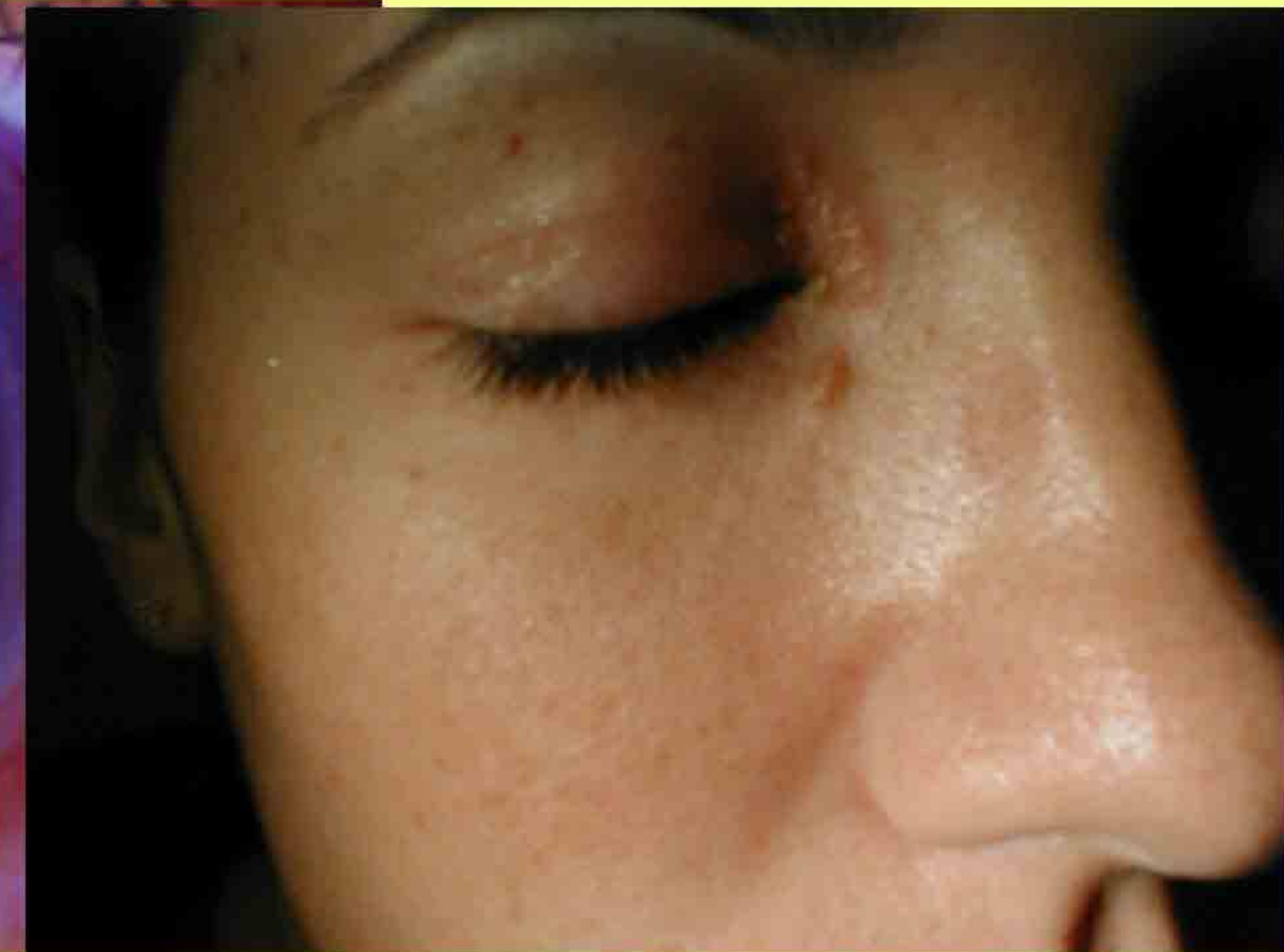
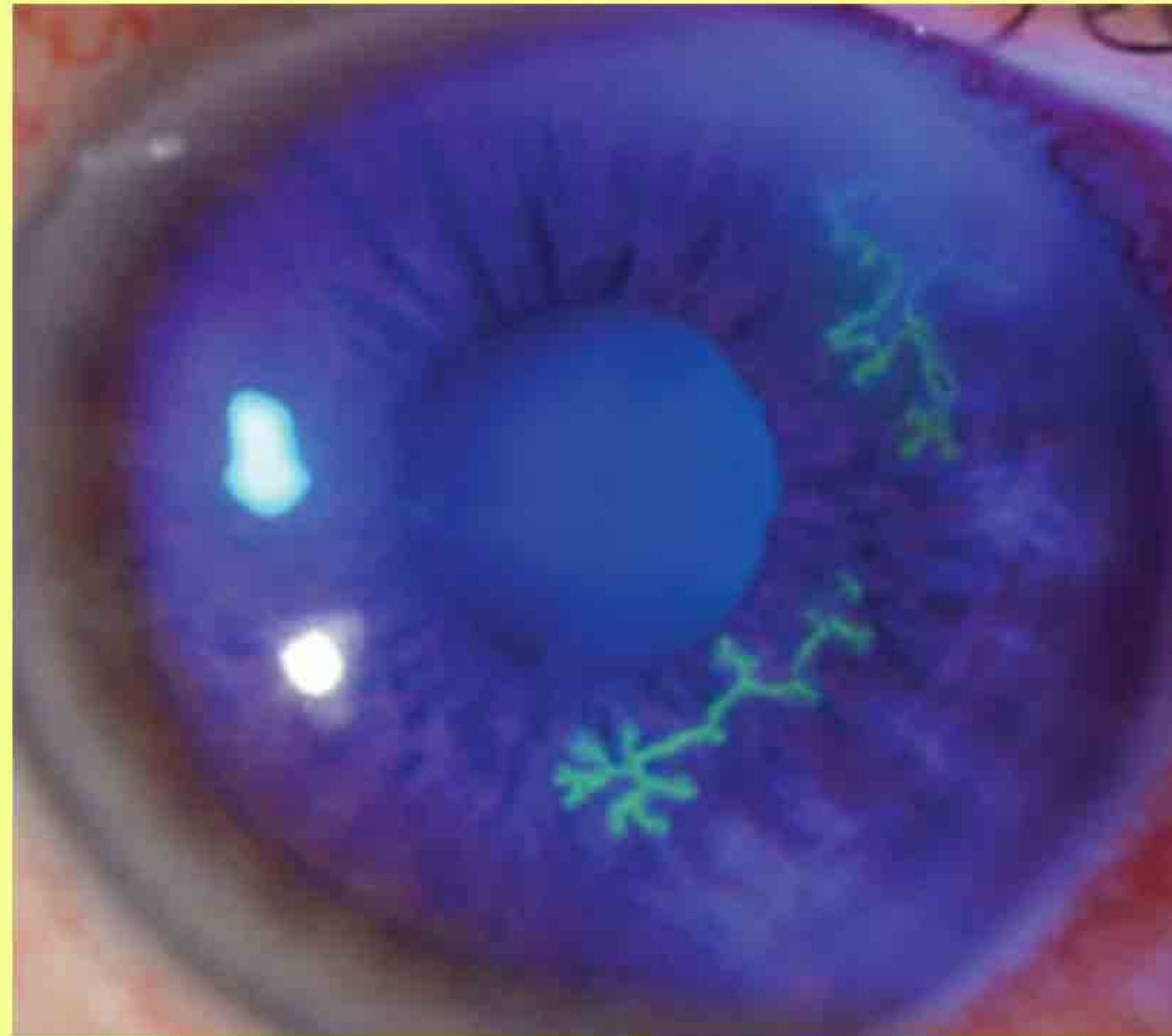
complex double-stranded DNA virus surrounded by icosahedral capsid and an envelope.

Latent infection by HSV occurs primarily in neurons

Aciclovir

Valaciclovir

Ganciclovir



Herpes Zoster Shingles

Chickenpox first recorded 1684,

Old English "cicen," "young fowl."

? designation *chicken* for a child ('child pox')

?Derived from *chickpeas*, based on resemblance of the vesicles to chickpeas, ? rash resembling chicken pecks.

?corruption of the Old English word, "giccin", which meant "itching" *itching-pox*,

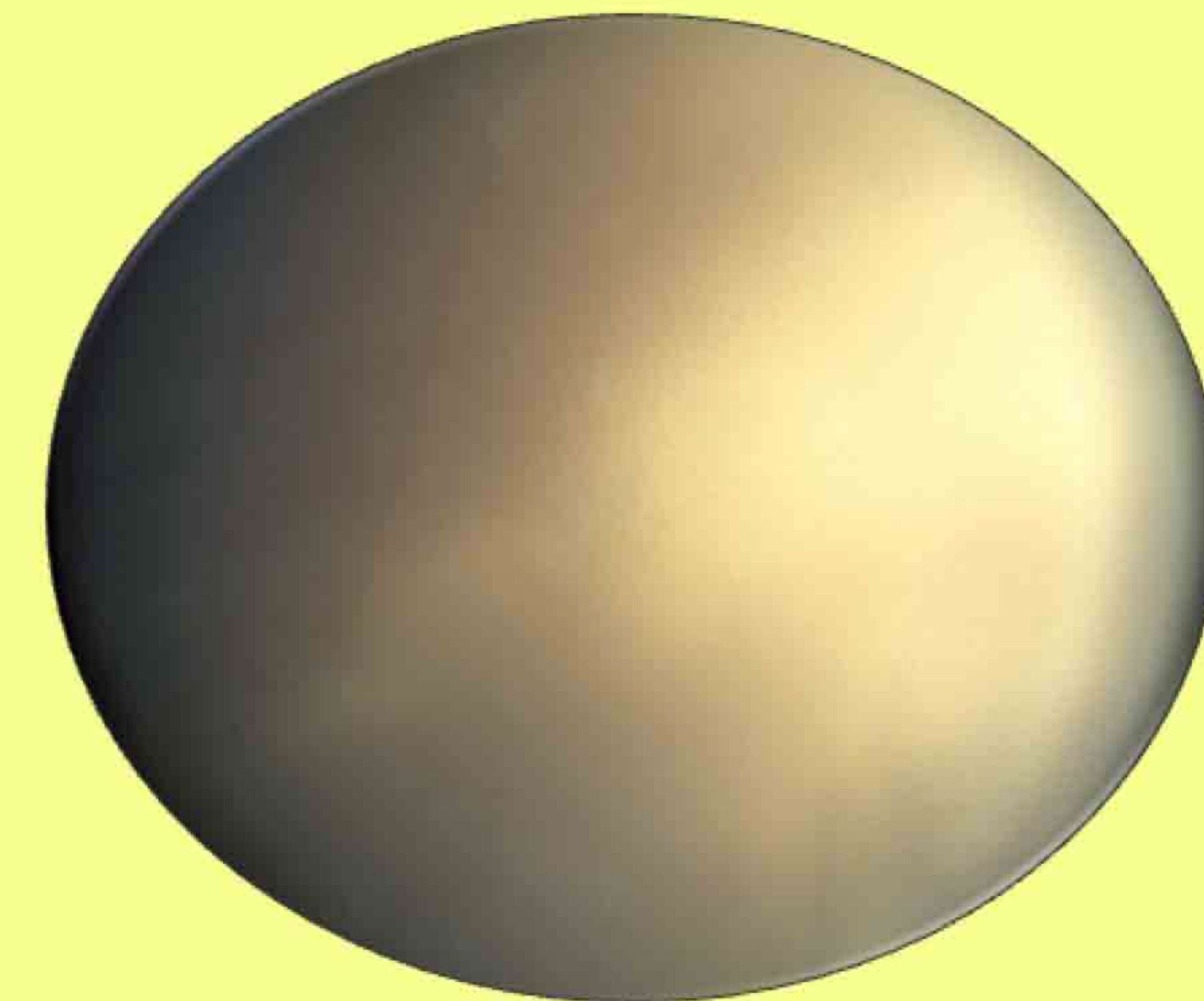
Samuel Johnson "from its being of no very great danger

USA death rate 0.4/m to 0.05/m

varicella declined 82% from 2000 to 2010.

3.5 million cases of varicella, 9,000 hospitalizations, and 100 deaths are prevented by varicella vaccination in the United States.

Varicella can be lethal to adults with impaired immunity. The number of people in this high-risk group has increased, due to the HIV epidemic and the increased use of immunosuppressive therapies



Muhammad ibn Zakariya ar-Razi (865-925) Persian physician, no attempt to distinguish chicken pox from small pox in *Al-Judari wa al-Hasbah* (On Smallpox and Measles) explained both ailments as small pox.

HIV

human immunodeficiency virus (HIV) is a lentivirus (slowly replicating retrovirus)

Infects cells of immune system

Infections and tumours not repressed

2012 WHO Global estimates: approximately 35.3 million people have HIV worldwide

Adult & child deaths due to AIDS 1.6 million

About 6,300 new HIV infections a day

95% are in low- and middle-income countries

66% with HIV or AIDS develop eye problems.

retina, bleeding

infection of the retina

Retina detachment

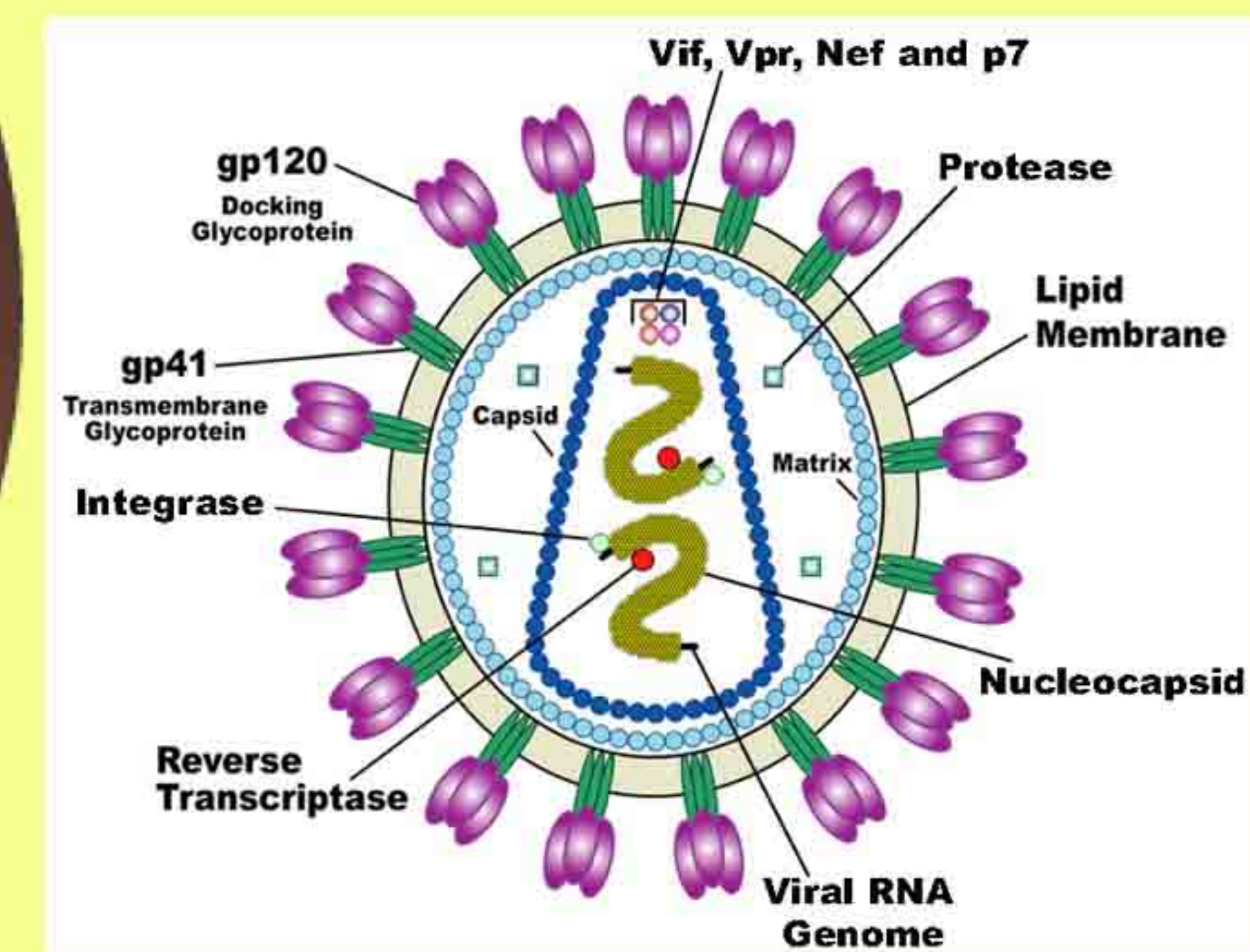
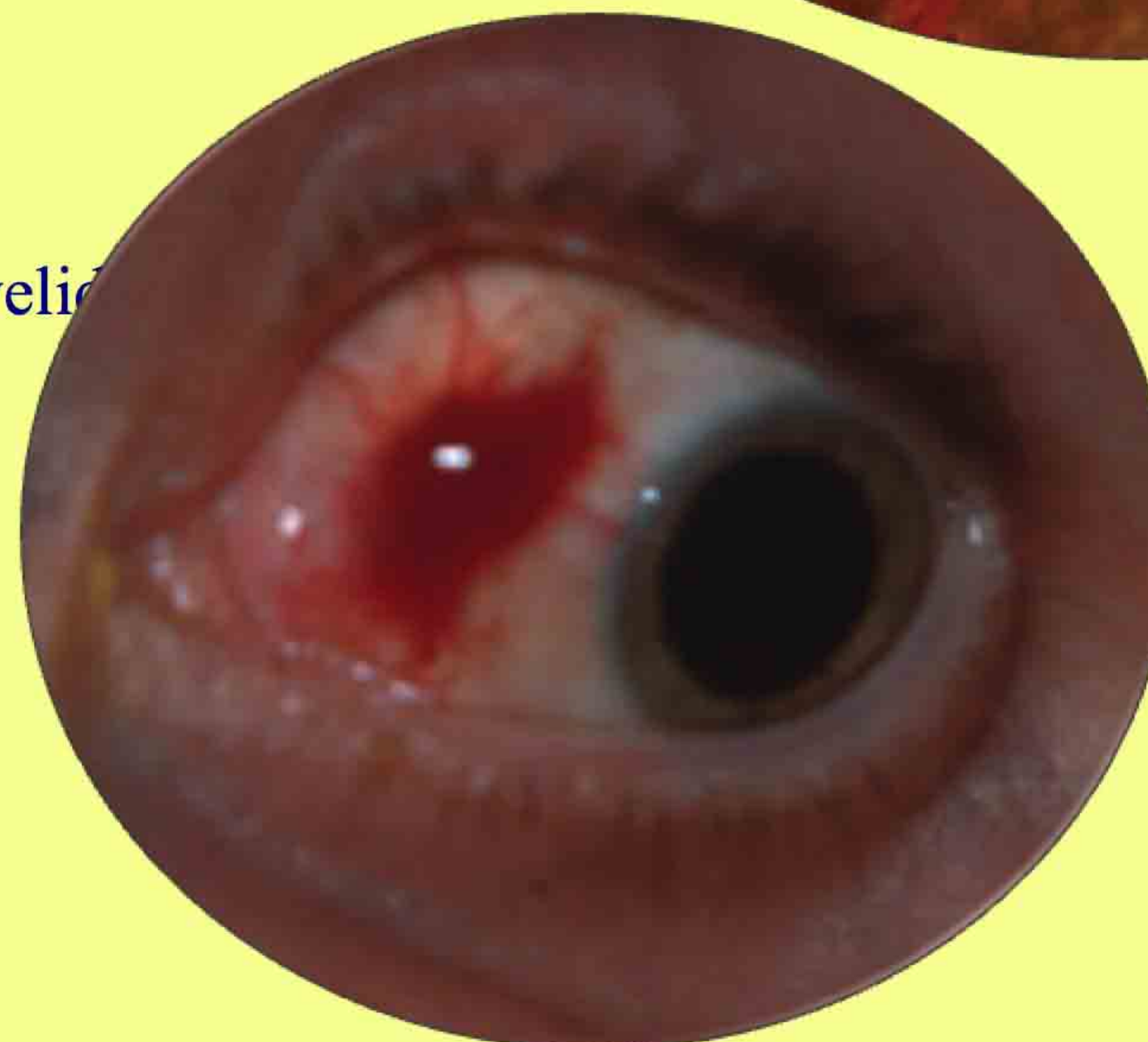
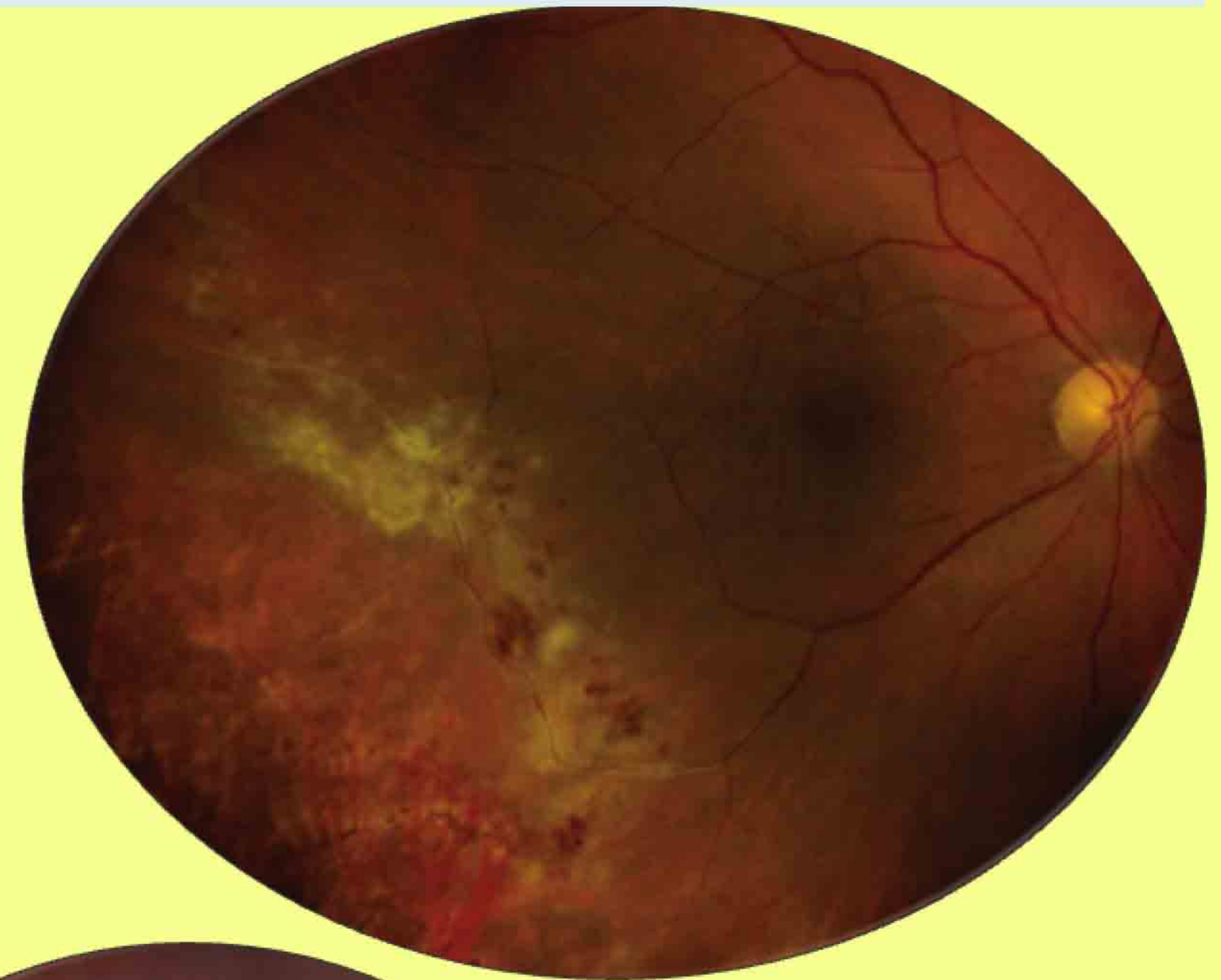
Kaposi's sarcoma. purple mass on the eye or eyelid

Herpes zoster ophthalmicus.

AIDS affects the brain.

problems with eye movement

Untreated CMV lesions usually enlarge rapidly, with the entire retina being destroyed within 6 months



Bacteria: Streptococci

1874: Biltroth association between streptococci and disease in patients with wound infections. coined the name *Streptococcus*. Στρεπτός, twisted, like a chain

1883: first cultured by surgeon Friedrich Fehleisen

Streptococcus pyogenes (Group A streptococcus)

Gram-+ve, ovoid cocci, chains or in pairs of cells.

5-15% of normal individuals colonised usually respiratory tract, without signs of disease

Infections: pharyngitis (strep throat), scarlet fever (rash), impetigo (infection of the skin) cellulitis (deep layers of the skin).

Invasive, toxigenic infections necrotizing fasciitis, myositis and streptococcal toxic shock syndrome.

Immune-mediated post-streptococcal sequelae, acute rheumatic fever and acute glomerulonephritis

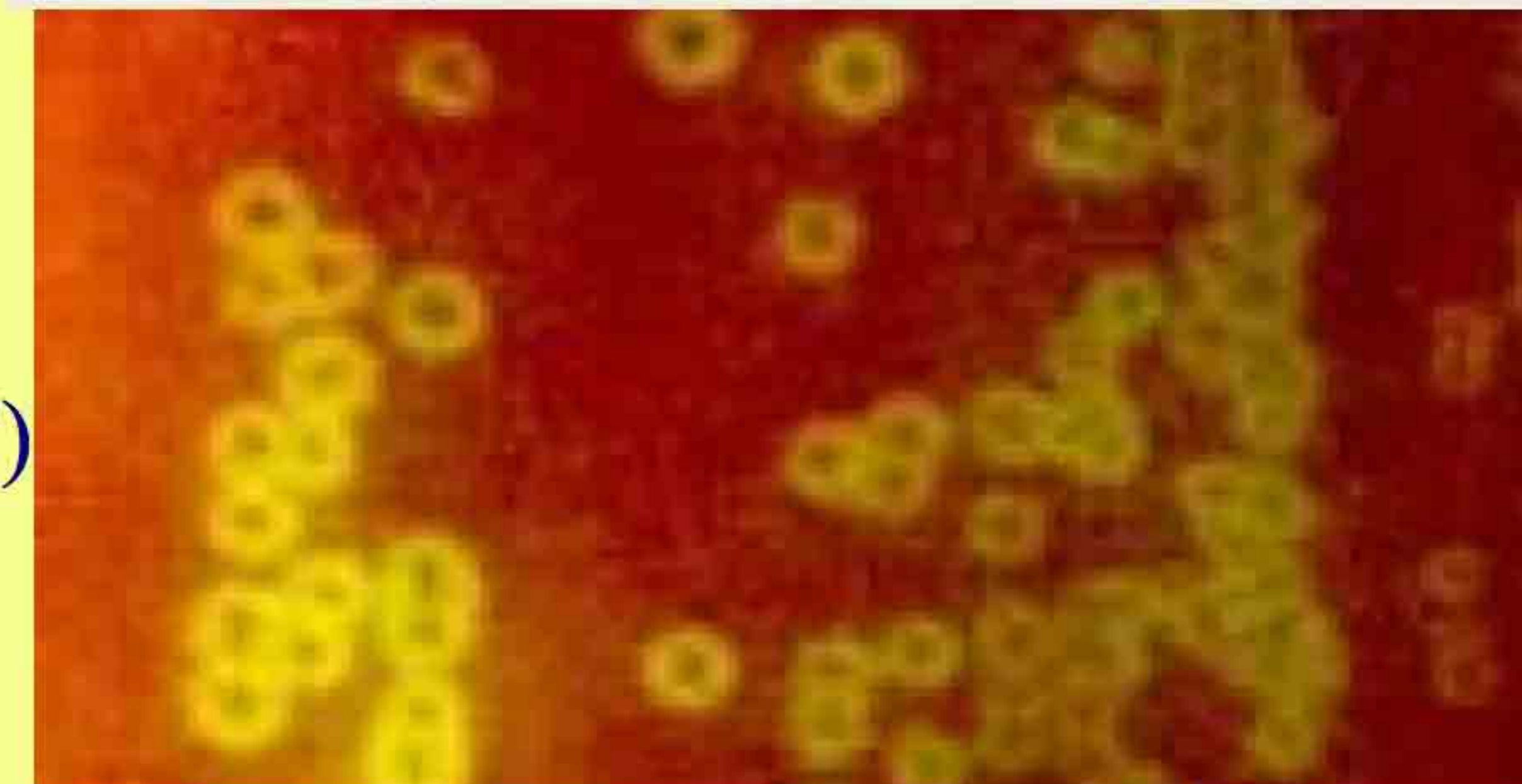
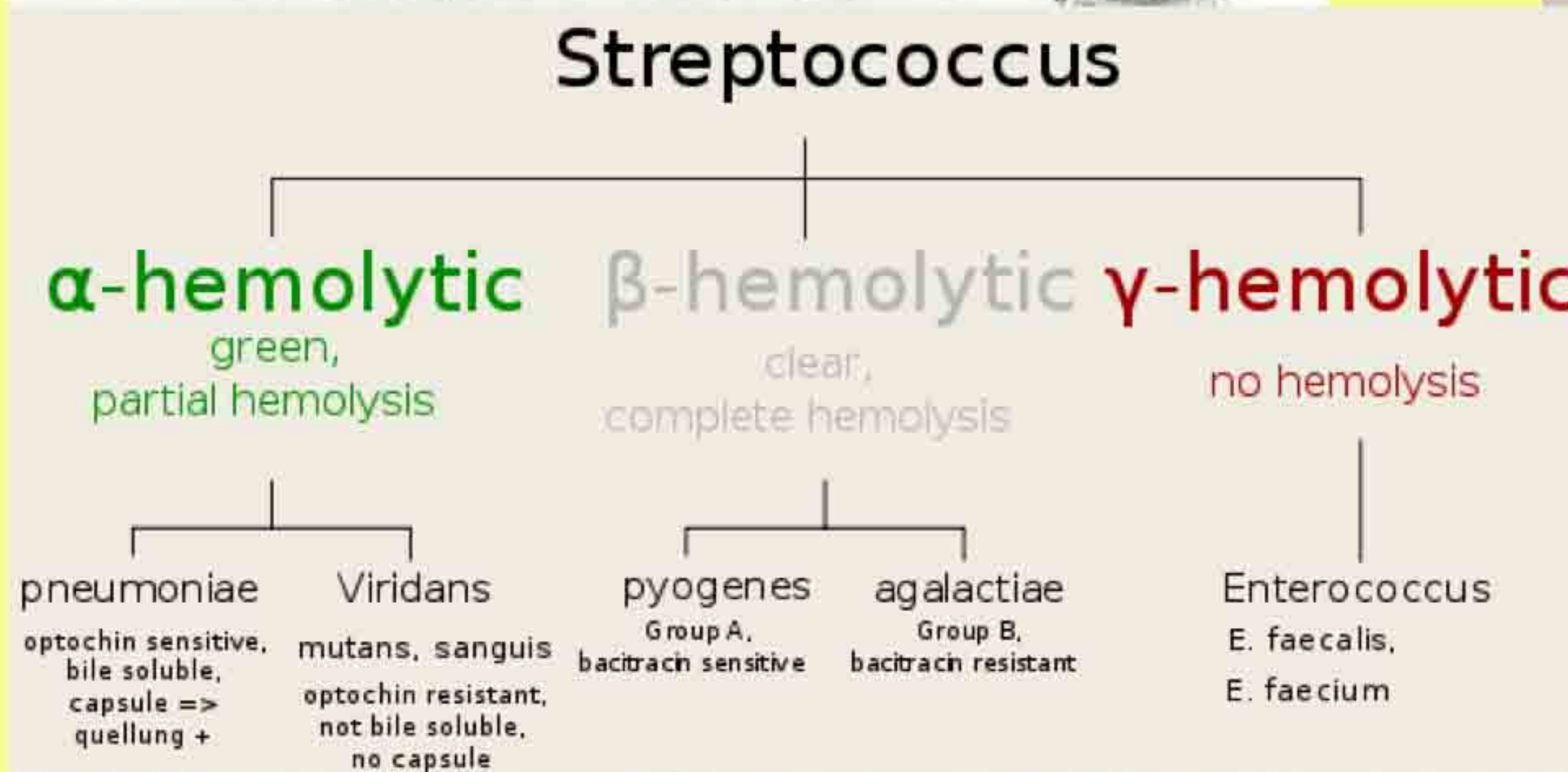
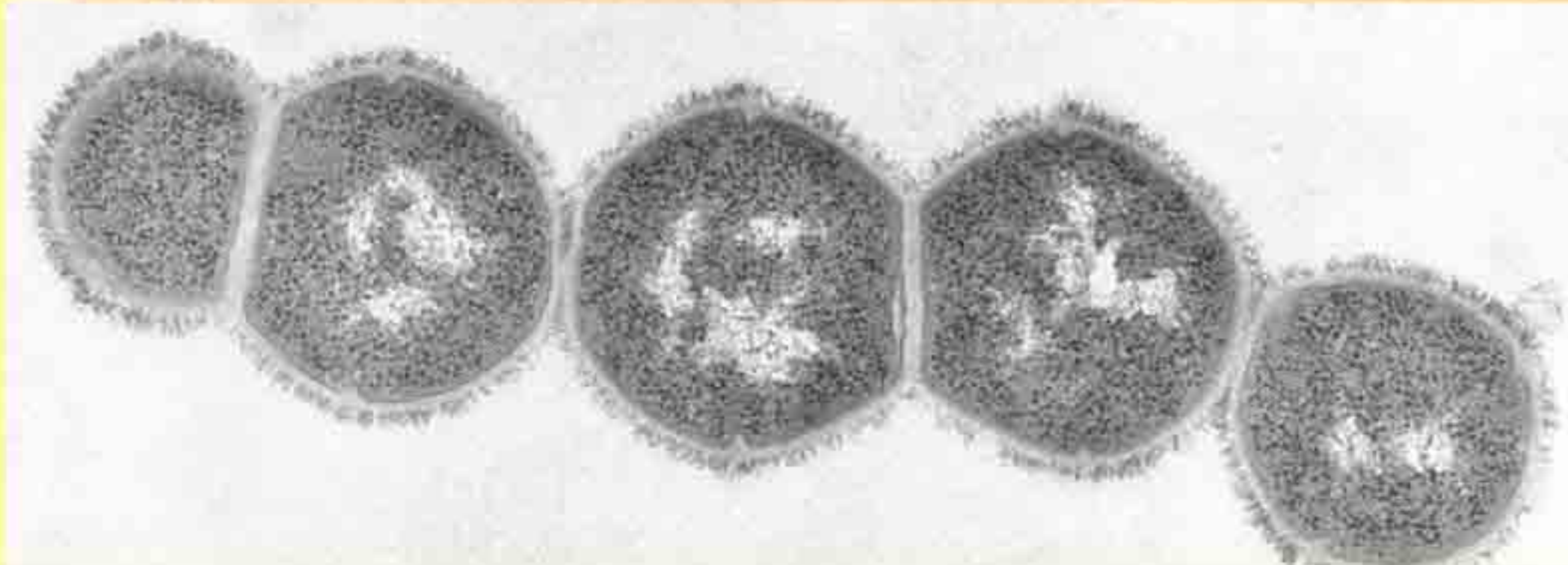
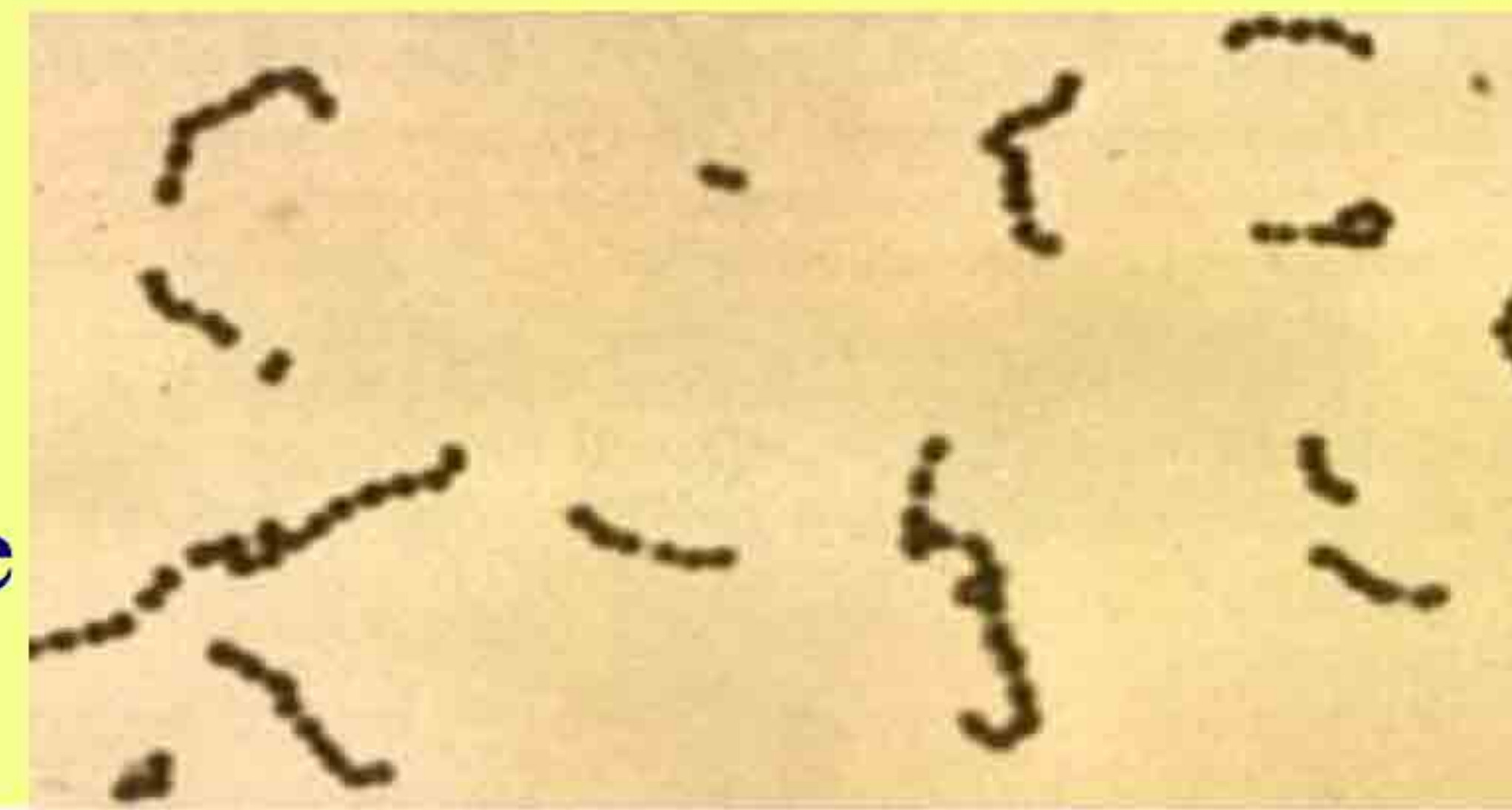
Produces a wide array of virulence factors

1: M protein, fibronectin-binding protein (Protein F) and lipoteichoic acid for adherence;

2: hyaluronic acid capsule immunological disguise M-protein to inhibit phagocytosis

3: invasins such as streptokinase, streptodornase (DNase B), hyaluronidase, and streptolysins;

4: exotoxins, pyrogenic (erythrogenic) toxin causes rash of scarlet fever and systemic toxic shock syndrome.



Three types of bacteria are used in Emmentaler: *Streptococcus thermophilus*, *Lactobacillus*, and *Propionibacterium freudenreichii*. *P. freudenreichii* consumes the lactic acid excreted by the other bacteria, and releases CO₂ bubbles

Puerperal fever

Alexander Gordon pioneer of handwashing

C19th childbed fever commonest cause of maternal mortality, second only to TB in killing women
 250,000–500,000 died C18th and 19th in E & Wales.
2005 14% of UK maternal deaths.

Maternity institutions: set up to address infanticide of illegitimate children. Care of poor married women.

Free attractive to poor, training doctors & midwives

1795: Alexander Gordon ex-naval surgeon, Aberdeen
Treatise on the Epidemic of Puerperal Fever
 observations on 1789 epidemic in Aberdeen.

Proposed transmitted by midwives and doctors Recommended hand washing and fumigated clothes

Recalled to Navy dies of TB age 47

1847: Ignaz Semmelweis: Vienna: Mortality 5-30% in First clinic (training medical students) only 4% in Second Clinic. students carried material from autopsy studies into the ward. After washing in lime to reduce the smell, cases dropped 90%.

1848, work presented before the Royal Medical and Surgical Society in London published in *The Lancet*

Unrest in Vienna, Uprising in his native Hungary suppressed by 70,000 Hapsburg troops.

Takes over Obstetric ward at St Rochus in Pest.

1858: "The Etiology of Childbed Fever"

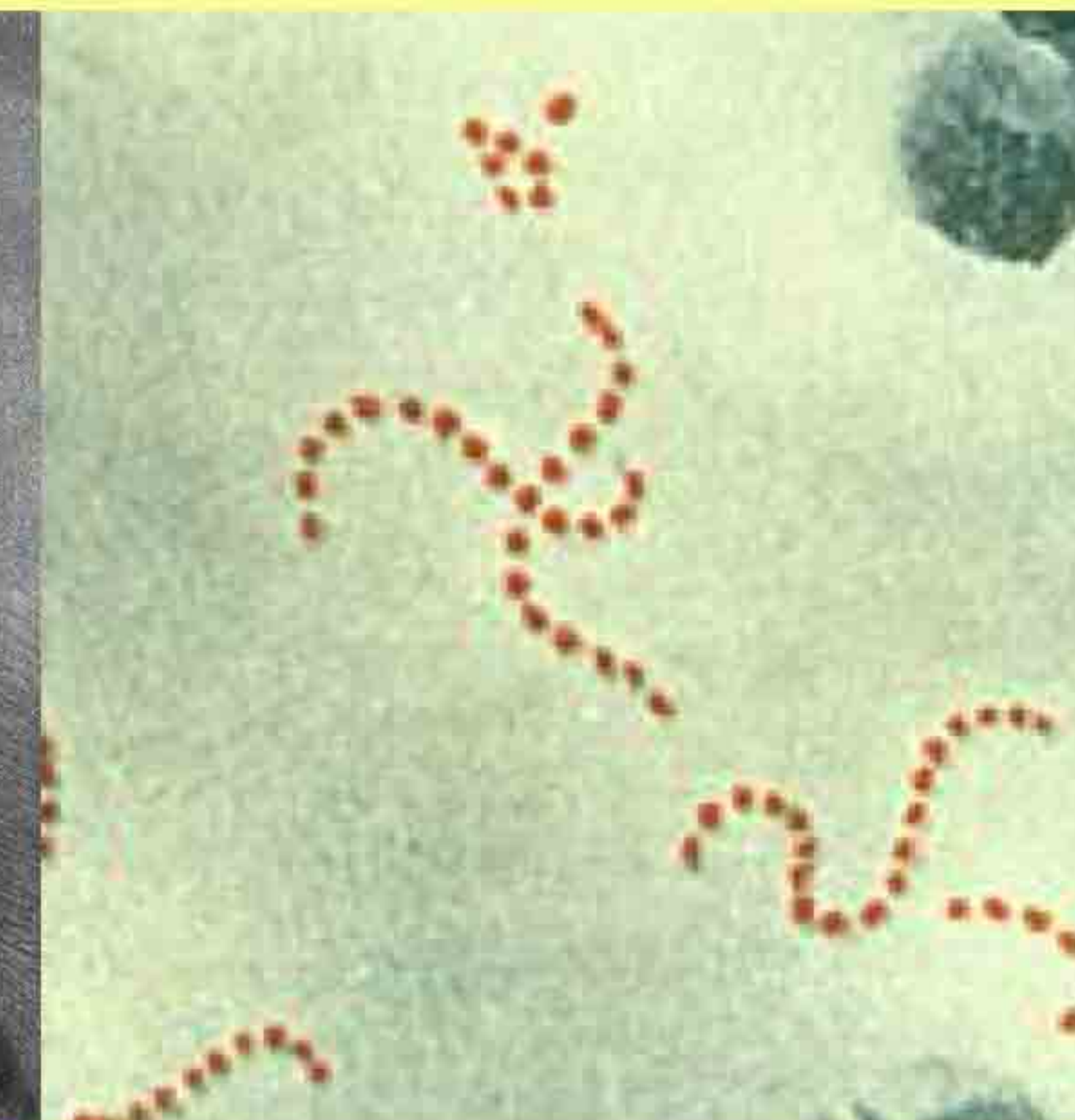
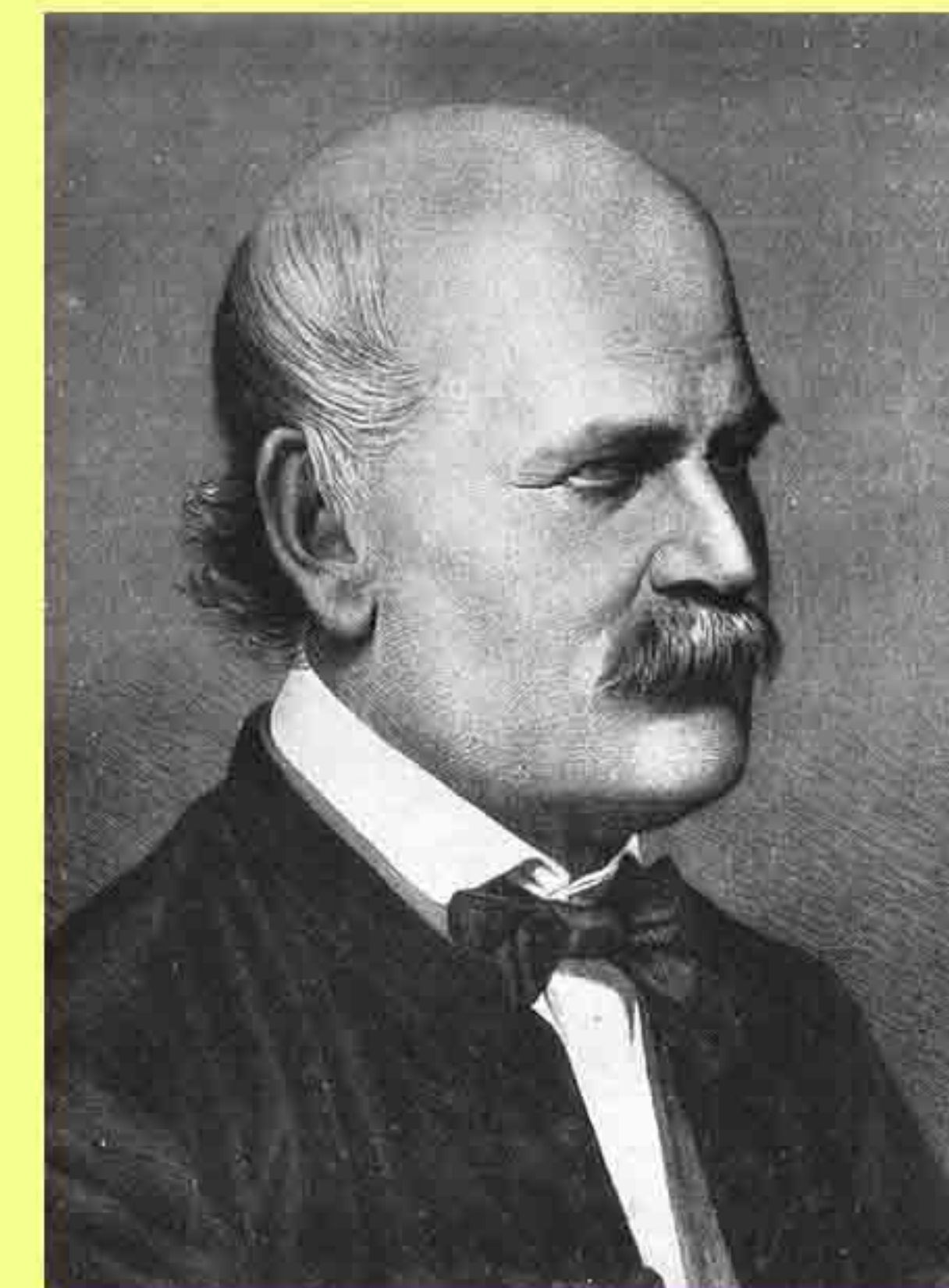
incensed by being ignored, overlooked for jobs, calling his colleagues murderers. Behavioural change

1865, died age 47 beaten by guards at asylum

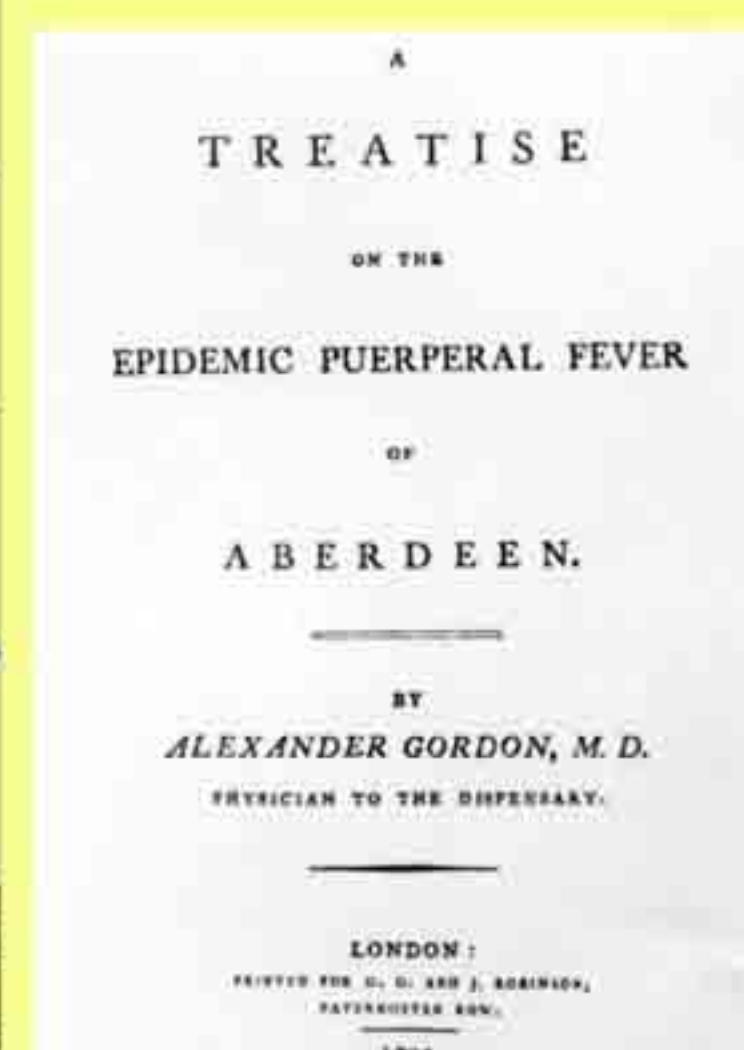
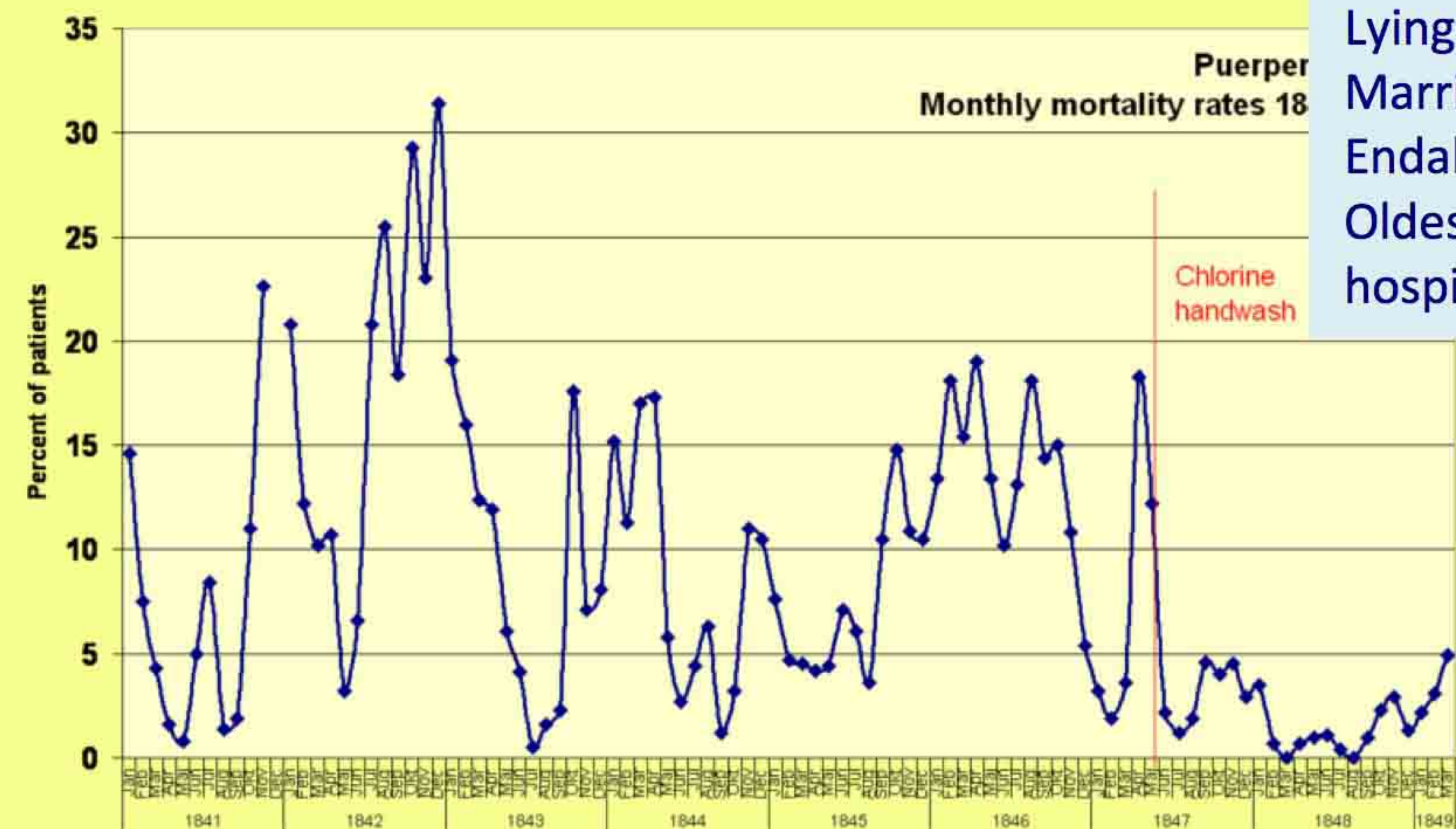


A T A B L E
 Containing an Account of those Patients affected with the PUERPERAL FEVER, who were attended by
 Dr. GORDON, from December 1789 to October 1791.

When taken ill.	No.	Name.	Age.	Residence.	Cured.	Dead.	By whom delivered.
1789.							
December	1	James Garrow's wife	27	Woolman-hill		5th day	Mrs. Blake
Ditto	2	James Smith's wife	30	Ditto		23 —	Ditto
Ditto	3	John Smith's wife	34	Green		11 —	Mrs. Elgin
Ditto	4	Al. Memmie's wife	25	Harrogate		11 —	Ditto
1790.							
January	5	John Anthony's wife	25	North-street		3 —	Dr. Gordon
February	6	Christian Durward	36	Rottenholes		3 —	Ditto
April	7	M. Stuart's wife	30	Denburn			Mrs. Philp
May	8	William Elrick's wife	34	Exchequer-wynd	1		Mrs. Blake
Ditto	9	Elizabeth Murray	28	North-street		7 —	Ditto
Ditto	10	Helen Mitchell	30	Ditto			Ditto
Ditto	11	Janet Wier	34	Denburn			Mrs. Elgin
August	12	Mrs. Johnston	36	Littlejohn's street	4		Mrs. Smith
Ditto	13	Geo. Webster's wife	38	Fowler's-wynd	6		Mrs. Blake



1749-1913: The Lying-In Hospital for Married Women, Endall St
 Oldest maternity hospital in London



Hungarian proverb "Tell the truth, and people will bash in your head."

Staphylococci

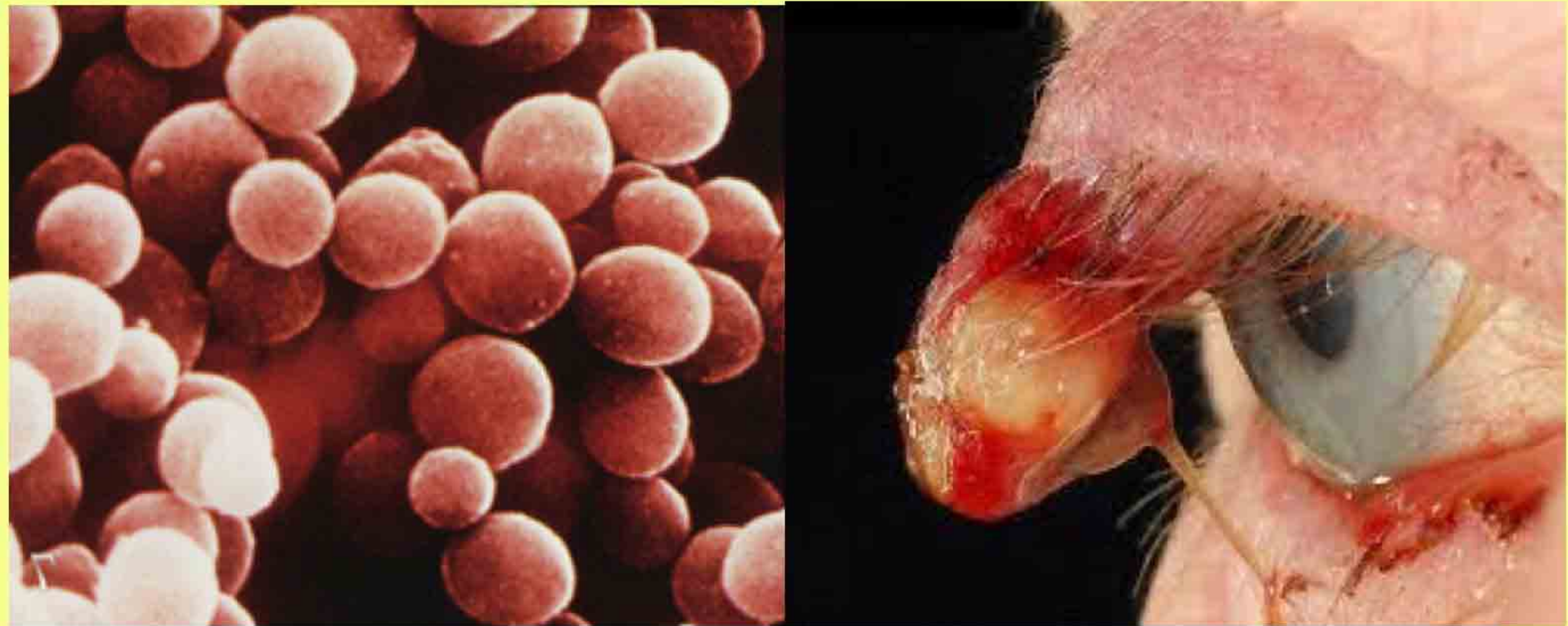
1884, Rosenbach: Two pigmented colony types of *Staphylococcus aureus* (yellow) and *Staphylococcus albus* (white) (*epidermis*).

S. aureus: suppurative (pus-forming) infections and toxinoses in humans.
superficial skin lesions **boils, styes**

Pneumonia, mastitis, phlebitis, meningitis, and urinary tract infections; osteomyelitis and endocarditis.

Major cause of **hospital acquired (nosocomial “disease whilst under care”) infection** of surgical wounds and infections associated with indwelling medical devices.

Food poisoning enterotoxins in food
toxic shock syndrome by release of superantigens into the blood stream.



PATHOGENICITY:

boils and pimples (folliculitis)

Colonization: cell-bound (protein) adhesins

Invasion: Invasins: staphylokinase; proteases, lipases, nucleases, collagenase, elastase. Etc.

Resistance to phagocytosis: coagulase, leukocidin

Resistance to immune responses: coagulase

Toxigenesis: cytotoxic toxins (hemolysins and leukocidin)

surgical wound infections

Colonization: cell-bound (protein) adhesins

Invasion: Invasins: staphylokinase, hyaluronidase proteases, lipases, nucleases, collagenase, elastase. etc.

Resistance to phagocytosis: coagulase, protein A, leukocidin, hemolysins, carotenoids, superoxide dismutase, catalase, growth at low pH

Resistance to immune responses: coagulase, protein A, antigenic variation

Toxigenesis: cytotoxic toxins (hemolysins and leukocidin)

food poisoning (emesis or vomiting)

Toxigenesis: Enterotoxins A-G

G-ve bacteria

Salmonella: pigs C19th vet pathologist, **Daniel Salmon**
Environment, animals; cold and warm-blooded.

food poisoning: fever, stomach pain, diarrhoea, nausea or vomiting. Most recover in a week but it can be deadly

Salmonella typhi: Subsp. **typhoid fever**, maybe fatal.

Contracted by direct contact with infected faecal matter

Affect 21.5m people each year

Mary Mallon (1869 –1938), Typhoid Mary,
asymptomatic carrier Working as cook she infected 50 people, 3 died,

forcibly isolated twice by public health authorities

Escherichia. Coli: G-ve, rod; 0.1% of gut flora

Facultative anaerobic, aerobic respiration if oxygen is present, but capable of switching to fermentation

Most strains harmless, some cause serious food poisoning

Pathogenic strains: virulence factors, exotoxins

Shiga-like toxin (verotoxin) major foodborne illness

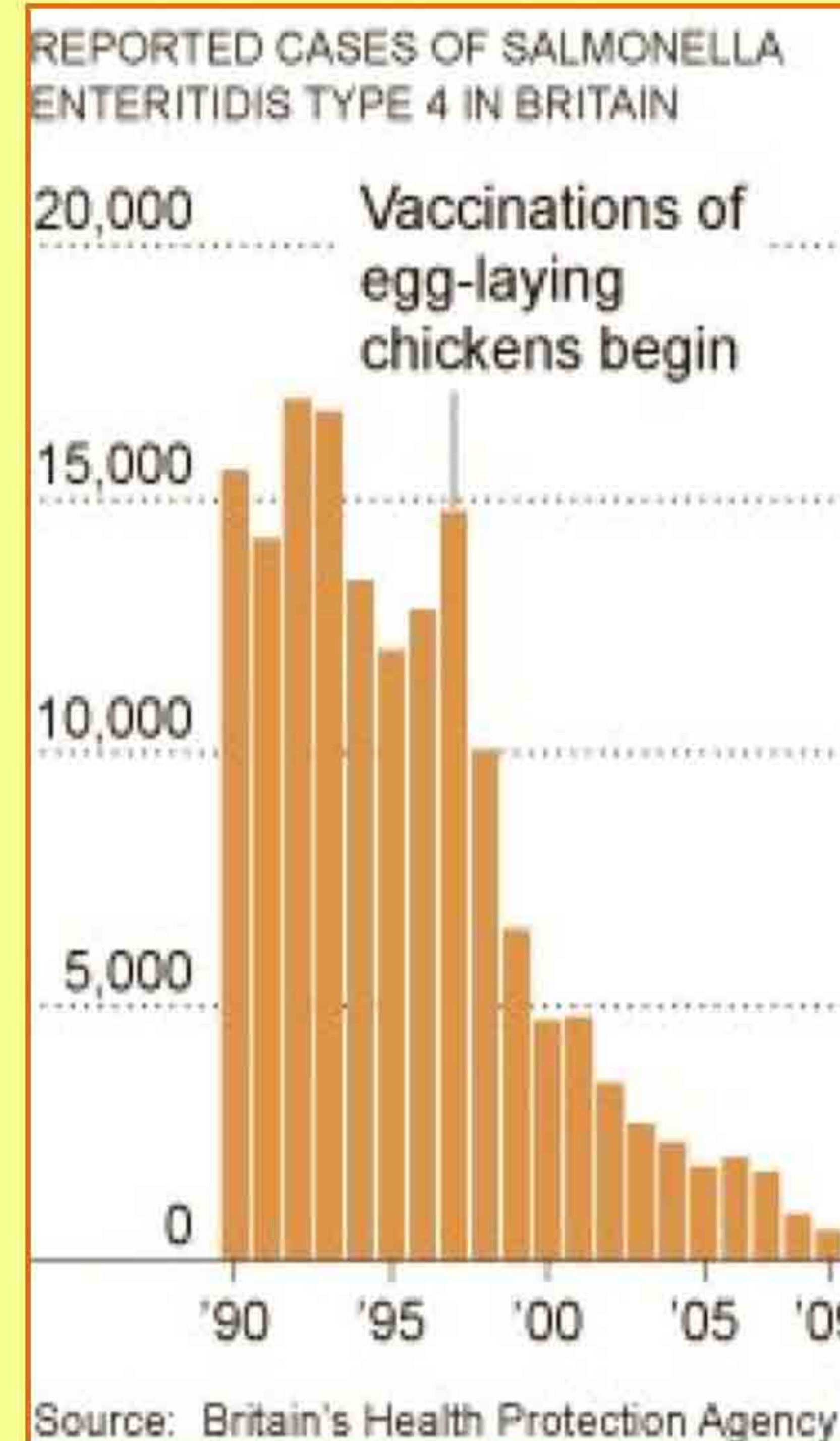
Enterohemorrhagic E. coli: VTEC possessing additional virulence factors, Bloody diarrhoea and hemolytic uremic syndrome in 10% of cases.

renal failure, hemolytic anemia, low platelets.

Famous **O157:H7**, non-O157 strains also cause 36,000 illnesses, 1,000 hospitalizations and 30 deaths in US yearly

E. coli O157:H7 intestine of some cattle.

Cattle lack the shiga toxin receptor,
Globotriaosylceramide, asymptomatic carriers



Eggwina: resigns Dec 1988. "most of the egg production in this country, sadly, is now affected with salmonella"

Angered egg producers, sales decline by 60%. Four million hens slaughtered.

Salmonella in flocks giving too many people food poisoning.

1998: vaccination of hens British Lion mark. reduced human cases of Salmonella enteritidis.

1997: 22,254 cases.

2005: 6,677.

2010: 581

2013: Salmonella in British eggs (11.9%) lower than France (17), Germany (29), Spain (77%)

USA decided not to vaccinate: 2010 recall 550 million eggs from two Iowa producers, after a nationwide outbreak of thousands of cases of salmonella was traced to contaminated eggs

(WHO) infected eggs 40% of reported food poisoning cases in Europe. uncooked and semi-cooked eggs and products containing raw eggs –desserts, tiramisu, mayonnaise and salad dressings

Cholera

Individuals dominated by hot, dry yellow bile – *cholera* – choleric temperament, hot-tempered; easily angered.

Natural purging in hot climates: If excessive pathological – *cholera morbus*, ‘bile sickness’.

First Pandemic: 1816-20: Kills >100,000 Indians & soldiers

1817: Asiatic cholera moves out of Bengal

1829-51: Second Pandemic Reaches UK:

22th Oct 1831: Sunderland: **William Sproat** keelman, dined on a mutton chop. After a stroll struck with a fever, stomach cramps, and explosive diarrhoea

JB Kell surgeon 82nd Regiment, seen cholera in Mauritius, treated with brandy, opium and calomel – HgCl_2

Dies at noon Wednesday

London houses cesspits in the basement, emptied regularly ‘night-soil men’.

1848 Nuisances Removal and Contagious Diseases Prevention Act banned cesspools and required all existing buildings to have sewer connections.

Thames changed from clean river to cesspool.

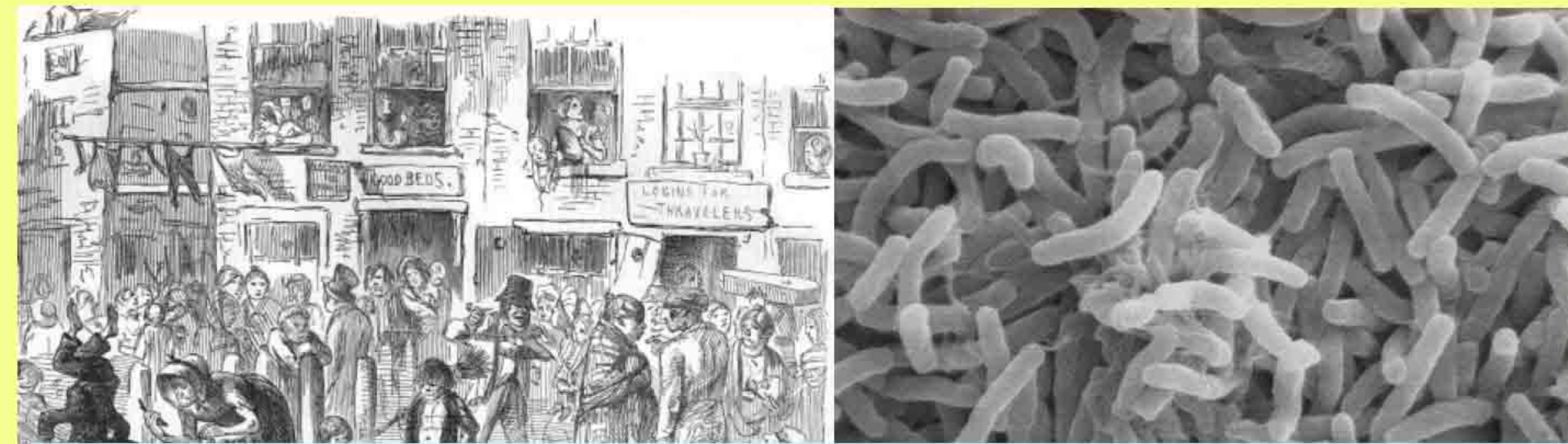
1853-4: Third Pandemic: Russia:

1834: Overnight 31 Aug, **cholera** struck Soho. 200 people around Broad Street died. fastest most deadly outbreak ever seen in Britain.

Whole families were carried off together.

Continues 10days, confined locally, peters out: 616 died

Over two years 10,738 Londoners die



infection of small intestine by bacterium *Vibrio cholerae*.
3-5 gallons of turbid grey fishy fluid/day



1831 engraving: 23yr old Venetian woman, before and hours after contracting cholera

Water borne: Faeco-oral

Poor district of Soho could not afford piped water:

John Snow, local GP: Vegetarian; teetotal “crank” linked outbreak to contaminated water,

Source was the pump: Handle removed (symbolic)

Brewers; drank only beer, brewed themselves. Safe

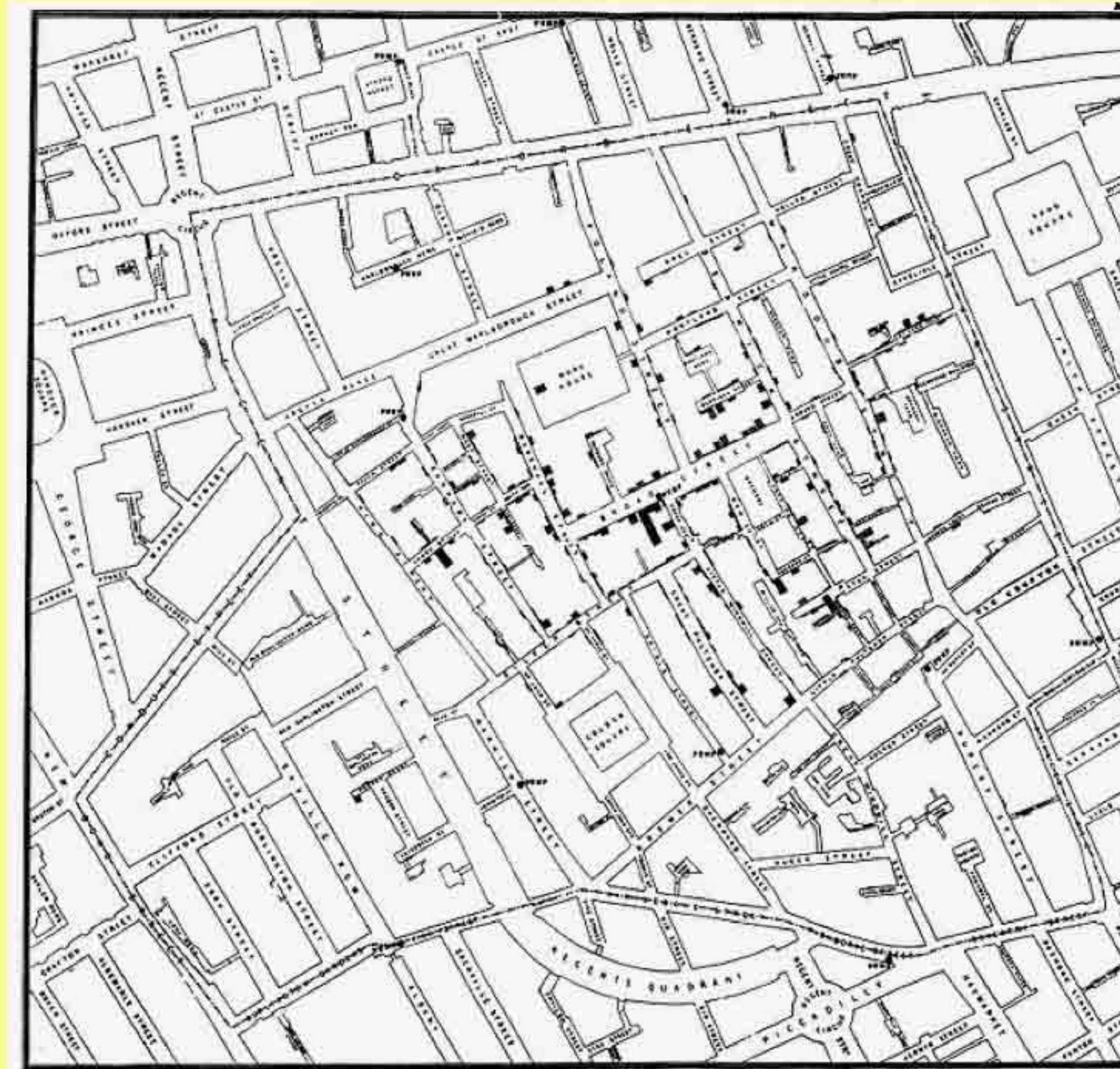
Susannah Eley: Widow drank Soho water died 22 Sep

Origin of infection: 2nd Sep 1854: baby died of diarrhoea in the house closest to the pump. Mother, Sarah Lewis, had rinsed soiled nappies and emptied the water into a cesspit in the cellar.

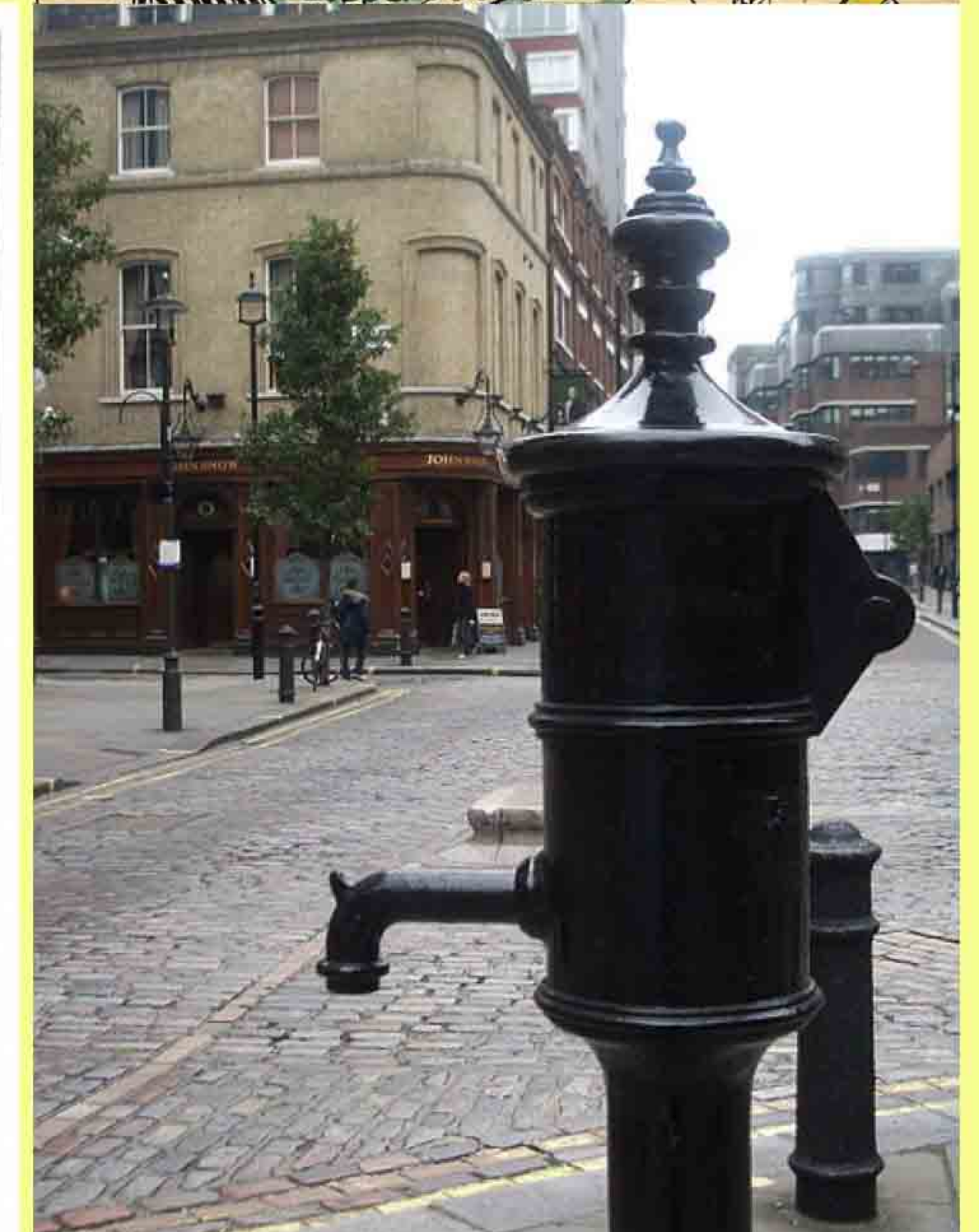
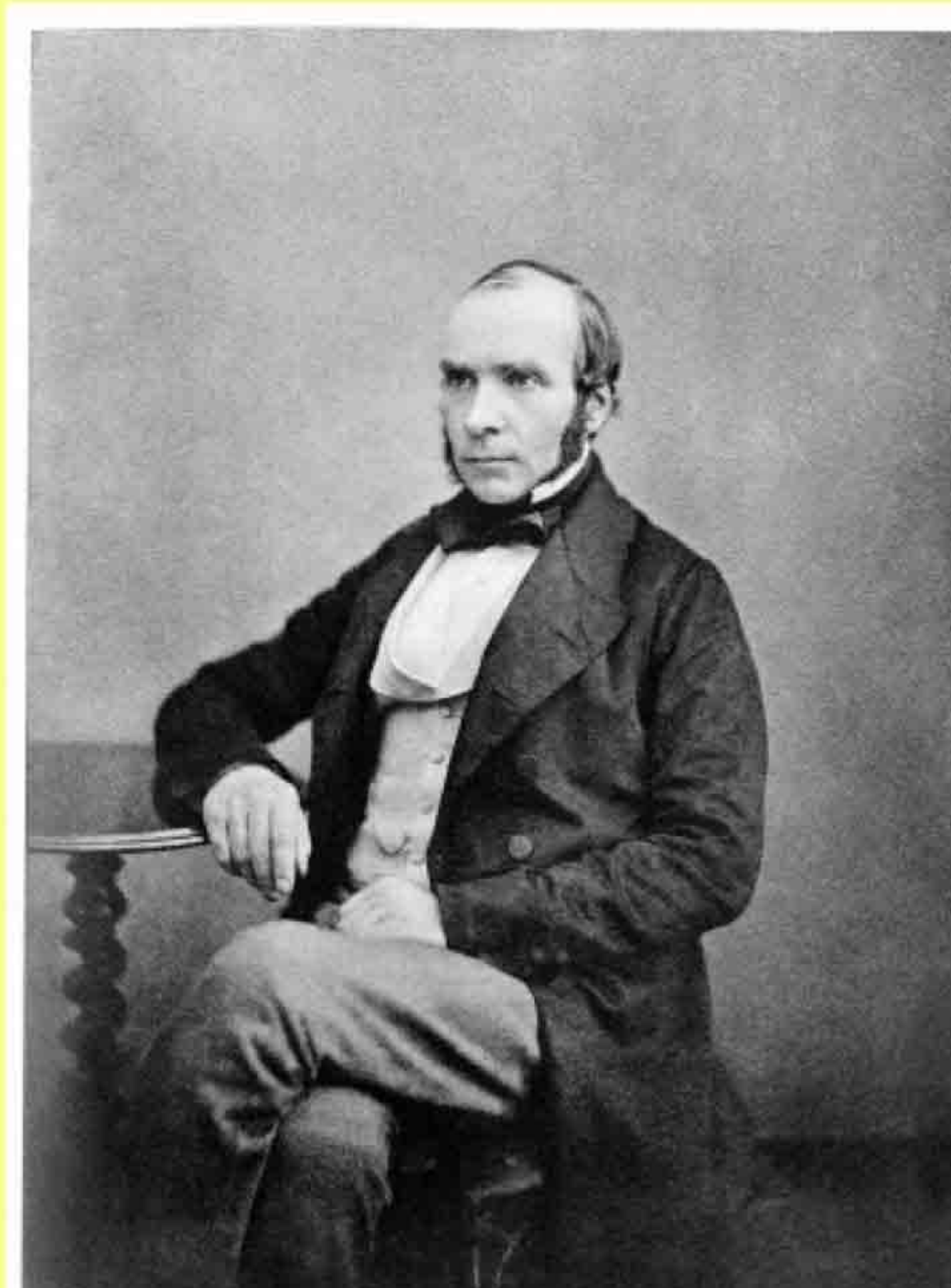
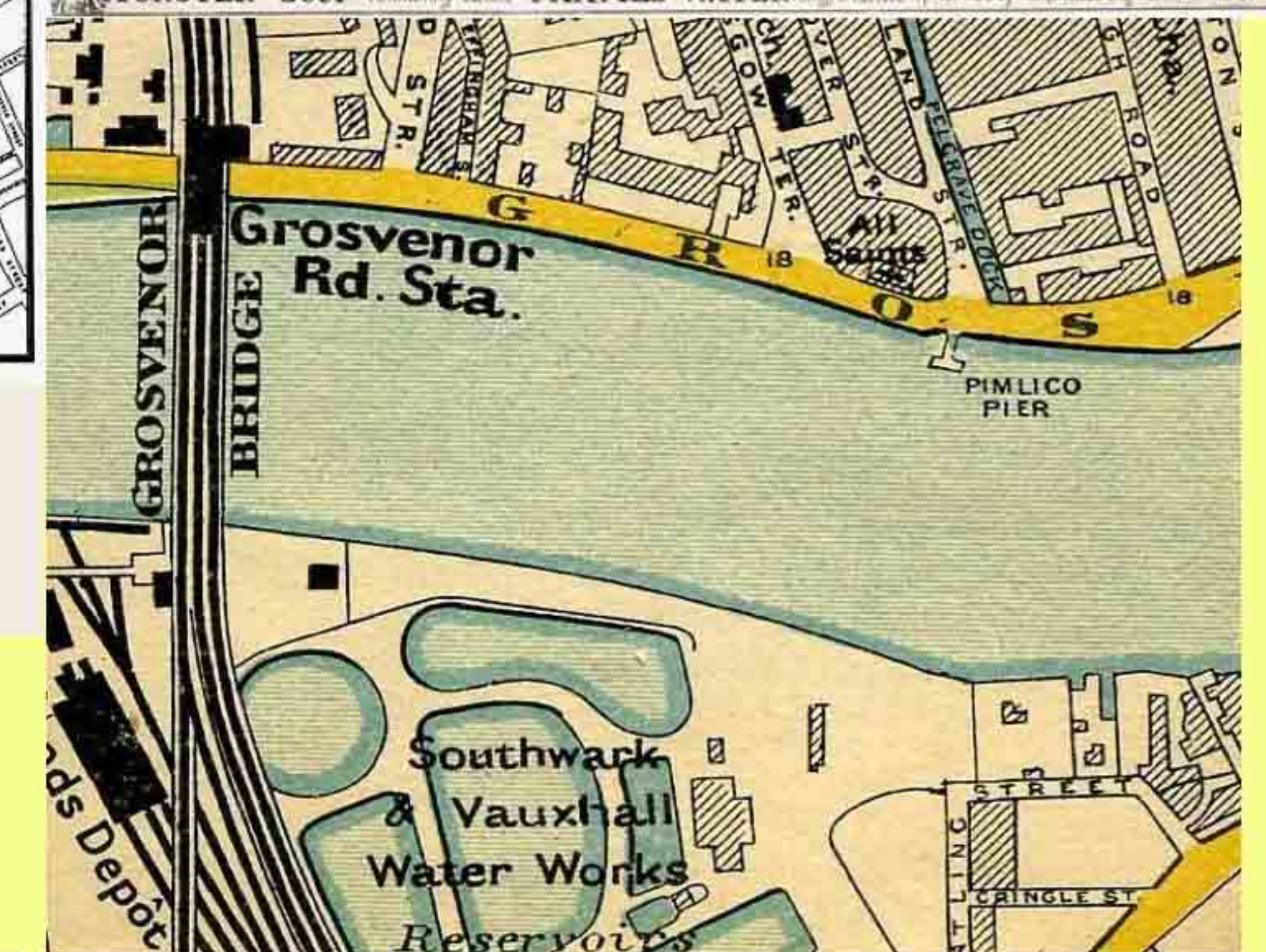
brickwork of this cesspit was decayed;

1849: *On the Mode of Communication of Cholera* printed privately: local infection of the bowels, caused by *materies morbi* – ‘disease-causing particles’. spread by water contaminated with faeces of cholera victims.

Also showed that the Southwark and Vauxhall Waterworks Company was taking water from sewage-polluted sections of the Thames and had 14X higher deaths than the Lambeth Company



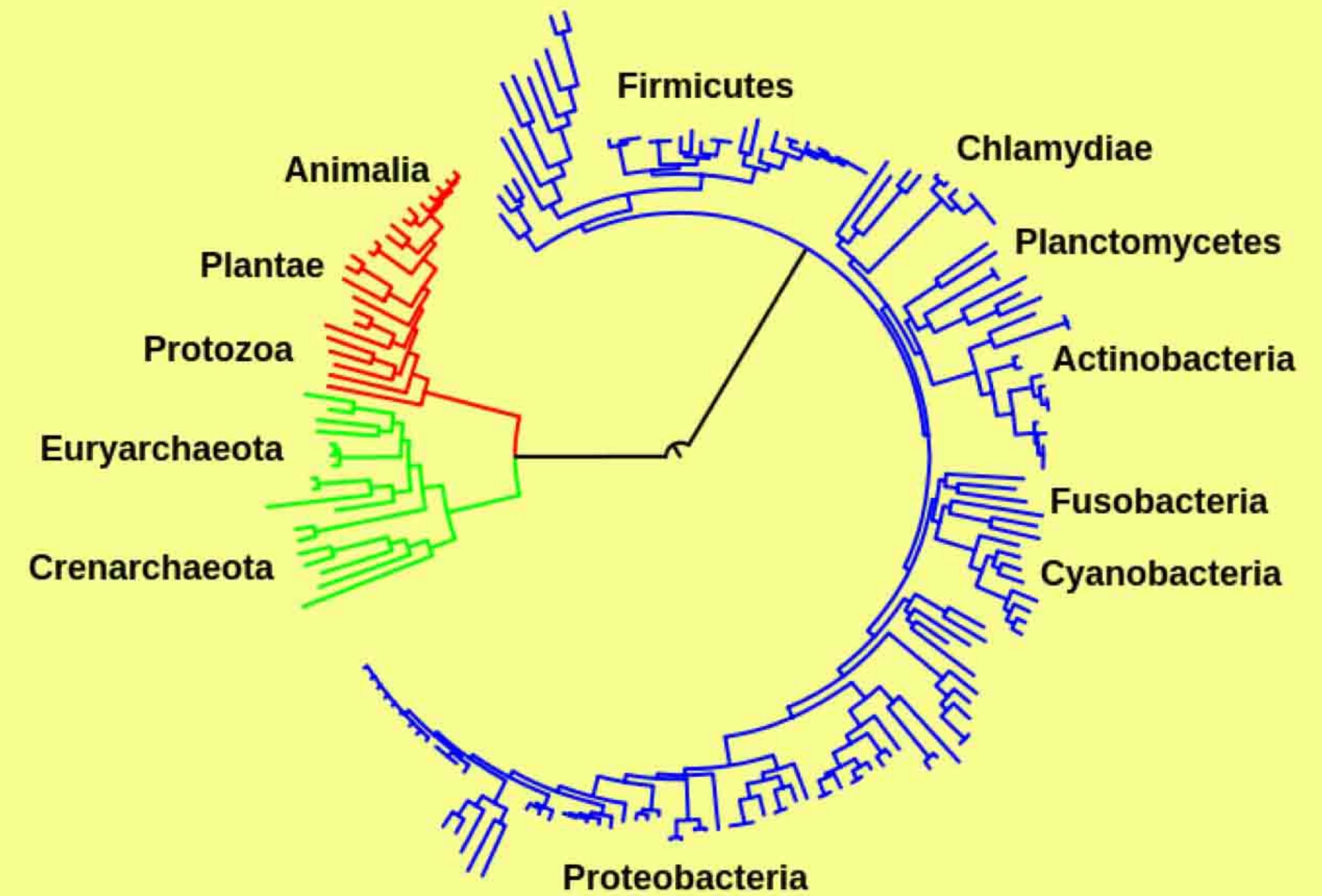
map: cases of cholera centered on the pump in Broad(wick) St



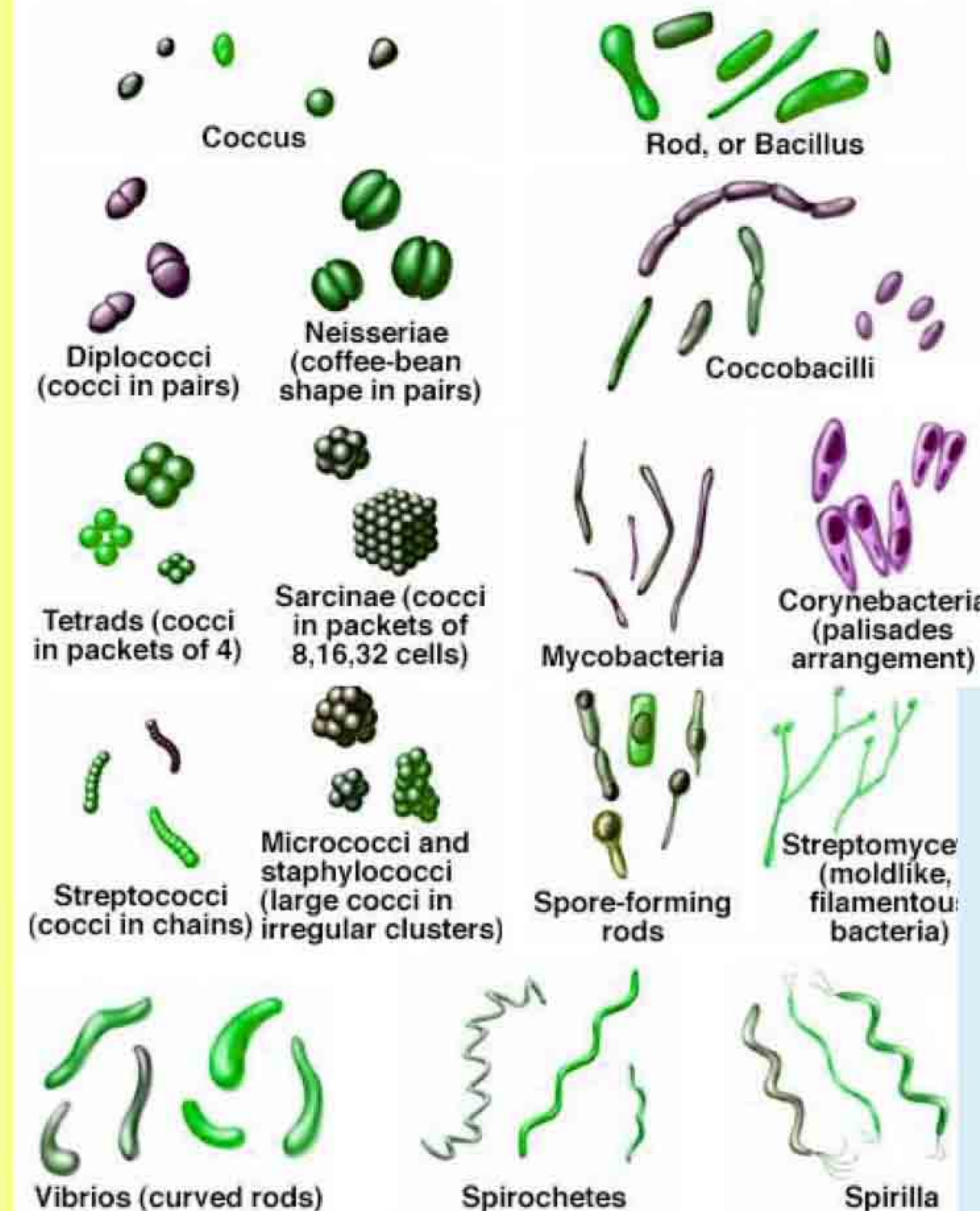
Microbes

Microbes: single-cell organisms oldest form of life.
 Fossils 3.5 billion yrs Earth covered with oceans boiling
Precambrian eon: For 3b yrs, all organisms microscopic
 Fast rate of evolution.
 Genetic variation: Horizontal gene transfer, high mutation
 Survival in new environments

Virus: Smallest microbe: small collection of genetic material (DNA or RNA) encased in protein capsid.
Prokaryotes: Bacteria, Archea (methanogens)
Eukaryotes (nucleus): Protists: Algae, protozoans
Multicellular



Shapes of bacteria



The Papal Belvedere Lucas Cranach the Elder 1545: Luther's *Depiction of the Papacy*. a papal bull with fire and brimstone, from Pope Paul III written in Vatican Room Belvedere: greeted by German peasants with farts, fresh from their own "Beautiful view"

Virus

Bacteria:

Archea:

Chlamydia:

Protists

Microfilaria

Drug resistance

21st century threats

Intra-cellular bacteria: Egyptian Ophthalmia

Sadaqa ash-Shadili C14th Egyptian oculist "the inhabitants of Egypt are more frequently attacked by ophthalmia than other people due to the abundance of dust and sand in their land."

Prospero Alpino, physician to the Venetian Consul in Cairo from 1580 to 1584, **De Medicina Aegyptiorum** (1591) seasonal occurrence of Ophthalmia in Cairo.

Standard of the medical profession low; anyone could buy a license on applying Turkish chief-physician (Hekimbashy).

Harant of Poljic: Bohemian nobleman. Notes masses of flies on eyes of children, attributes prevalence of eye disease to this

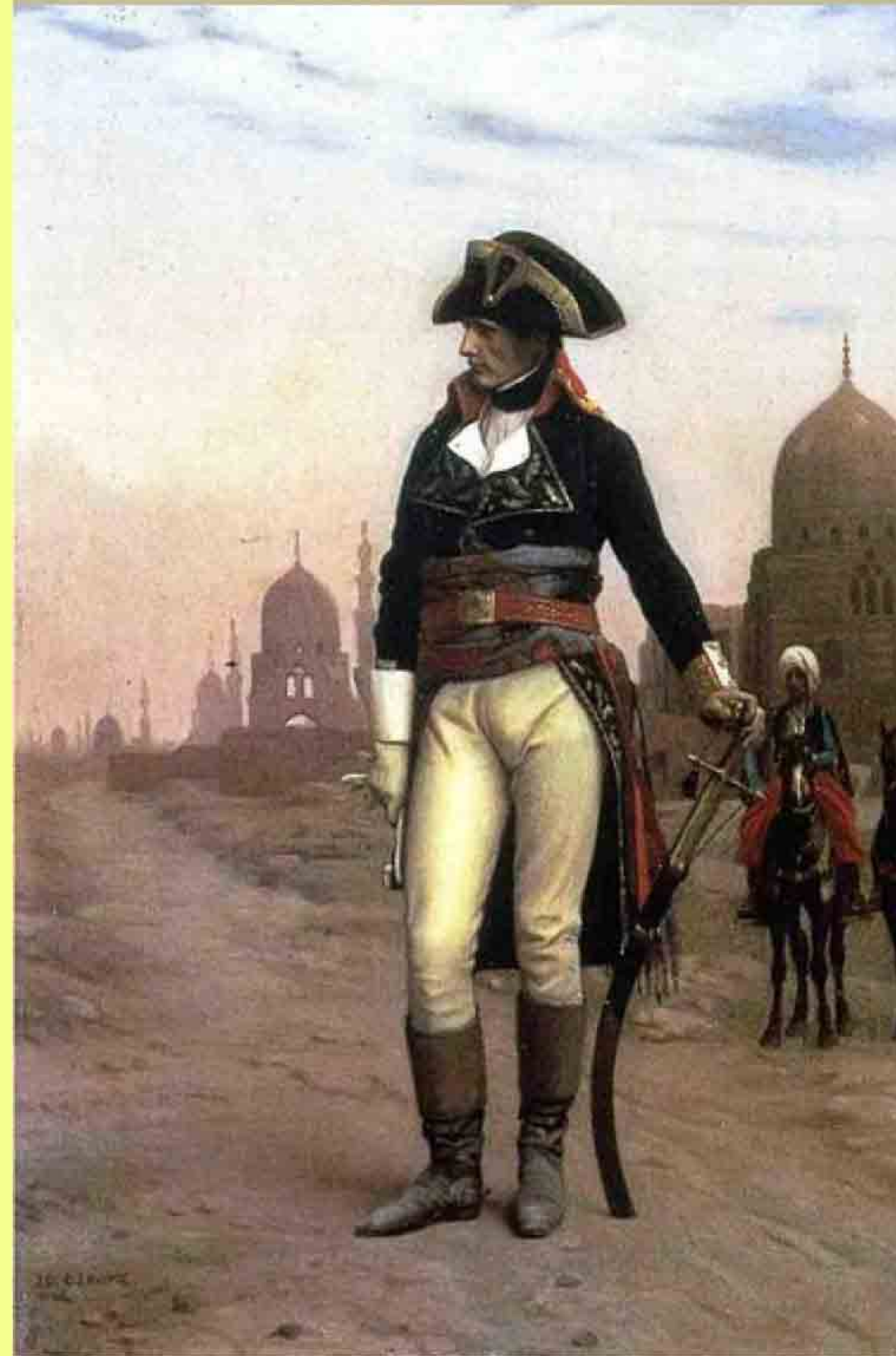
1735: a section for blind students was founded in the Theological College of the Azhar Mosque; it had some 80 to 150 inmates

1745: Tourtechot-Granger French physician Egypt "the land of the blind"

July 1, 1798: Napoleon Bonaparte, landed near Alexandria army of 40,000 men, march on Cairo



The **Battle of the Pyramids**, July 21, 1798: **Louis-François, Baron Lejeune** (1775-1848) French general, painter, and lithographer.



Napoleon in Egypt
1867 **Jean-Léon Gérôme**
(1824–1904) Princetown
University

Battle of the Pyramids (July 21)
3:30 pm: the Mamluk cavalry charged the French without warning.

The divisional "squares" of Desaix, Reynier and Dugua held firm and repelled the horsemen with point-blank musket and artillery fire.

Occupation of Cairo,
Immediately organize a large military hospital at Giza (S-western suburb opposite Cairo)
Wounded, dysenteric and ophthalmic soldiers

Egyptian Ophthalmia

John Butter (1791-1877)

1814 surgeon to the South Devon Militia, providing the guard at the Napoleonic War Prison at Princetown

1821: founded the Plymouth Eye Dispensary

lost the sight in one eye through ophthalmic rheumatism contracted Millbay Barracks while examining recruits for Crimean War.

In 1856 he became totally blind forced to retire.

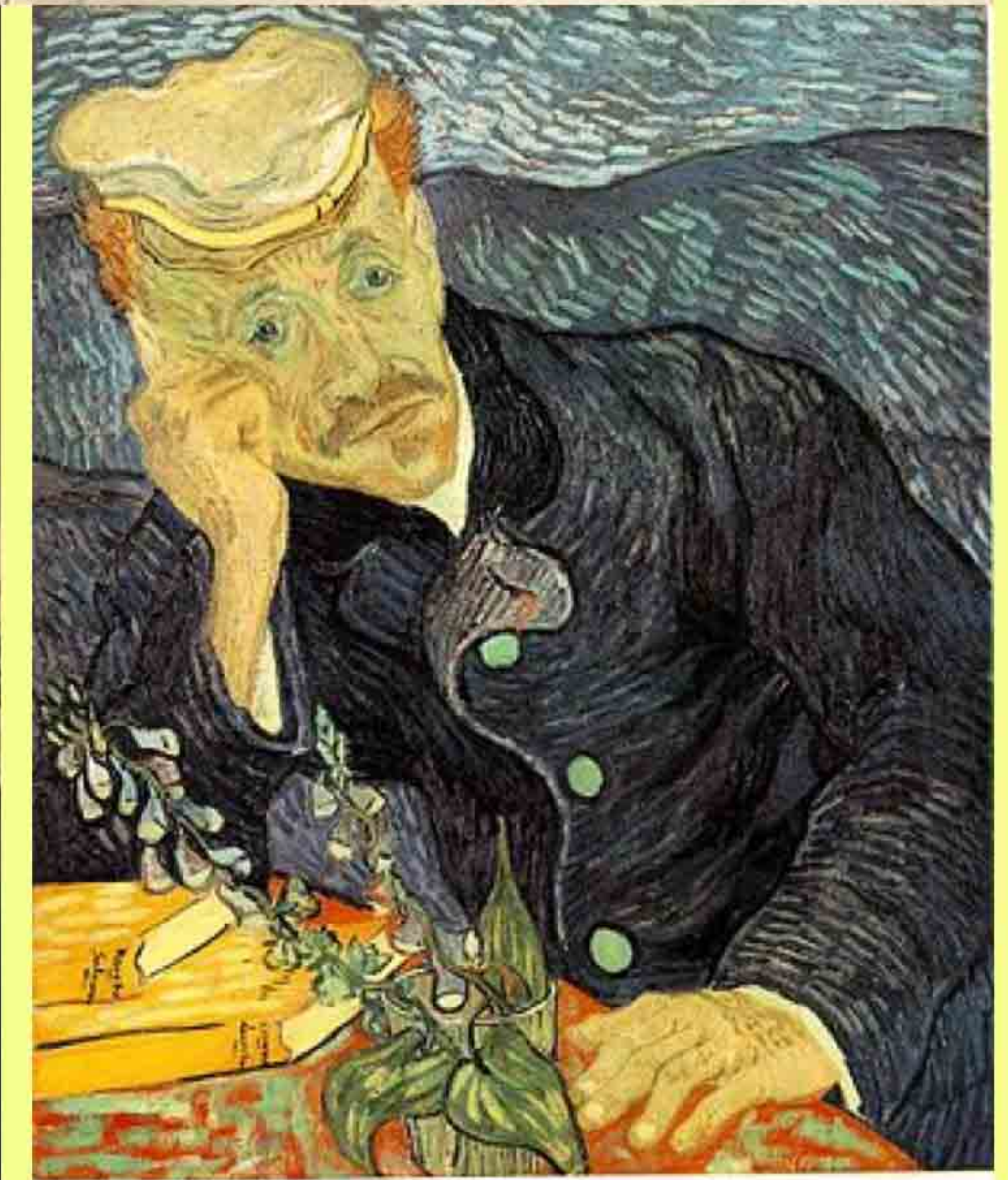
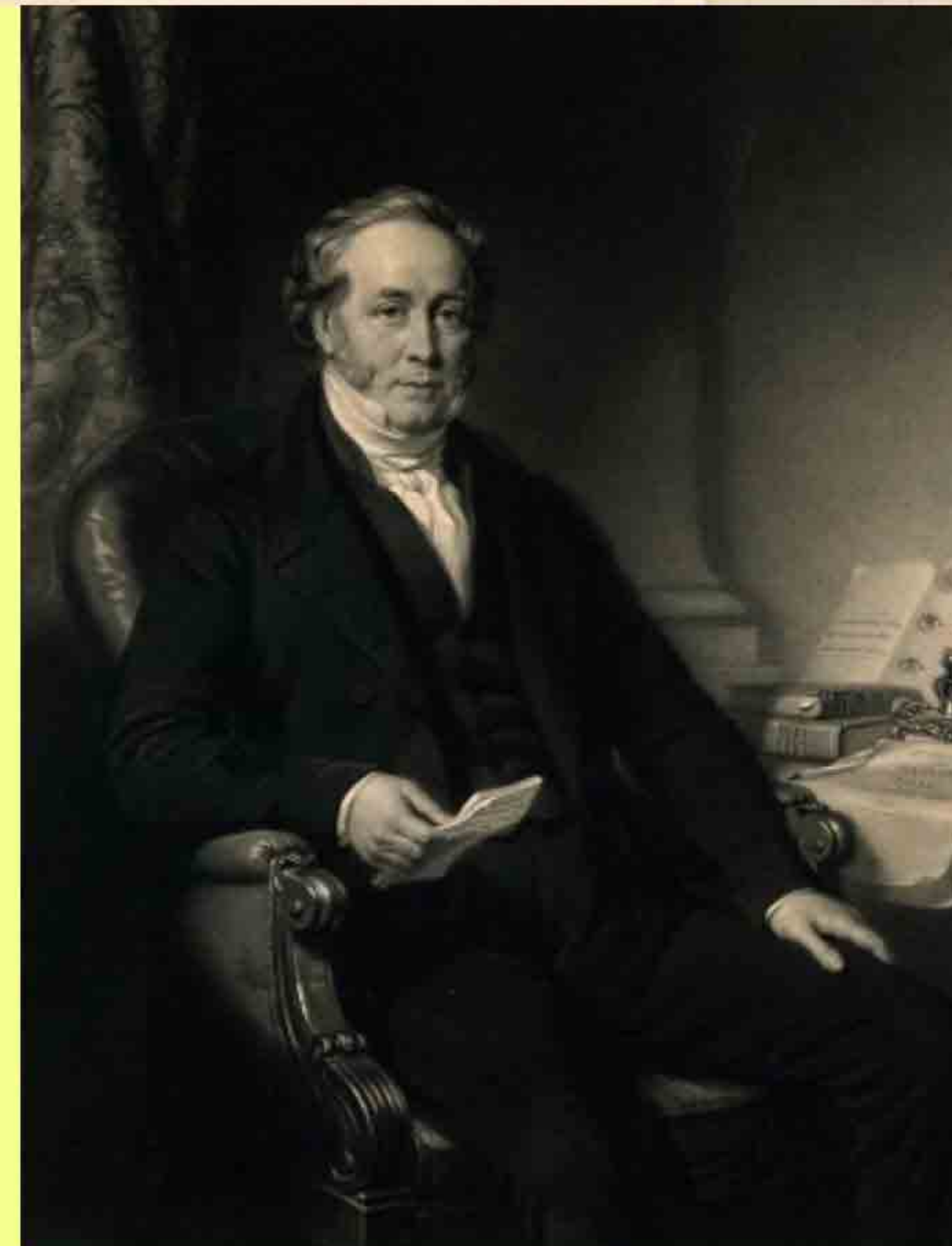
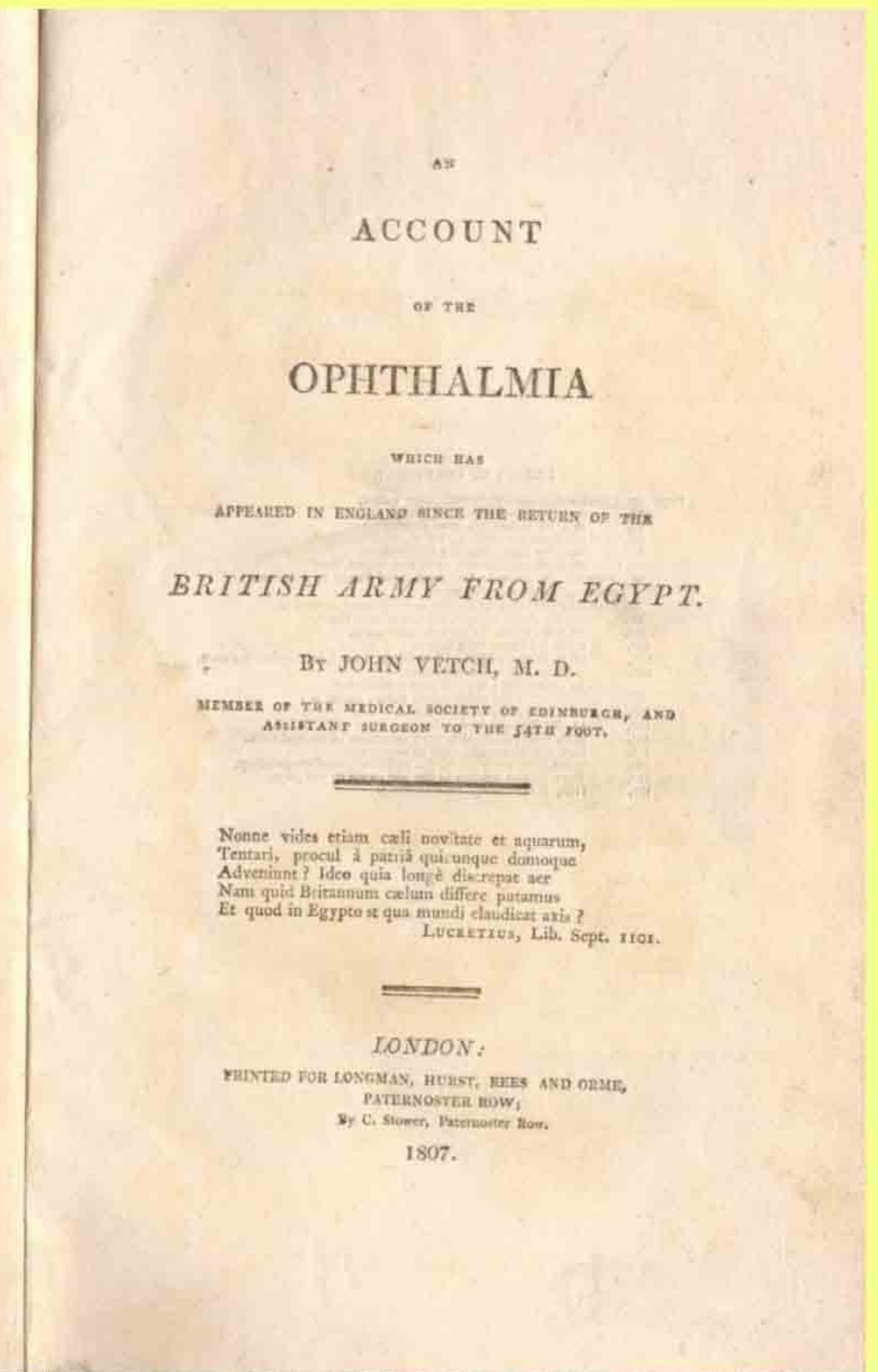
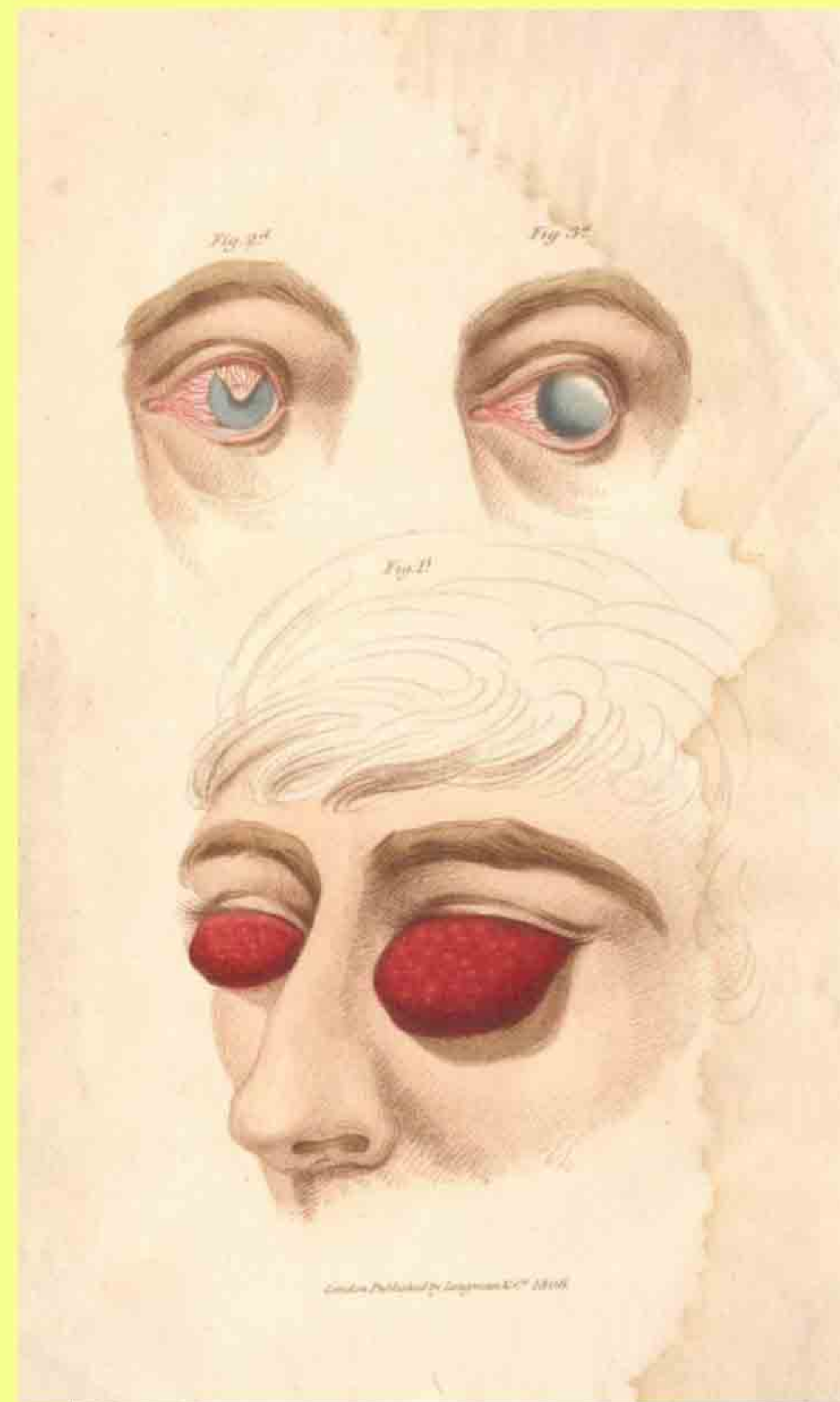
Baron Dominique Jean Larrey

Claimed success with his management and no cases of blindness were reported in the French army.

Nine years later 2,500 men suffering with trachoma and blindness in the army.

Memoirs of Military Surgery, and Campaigns of the French Armies ..., Volume 1

Paul-Ferdinand Gachet physician of many famous artists who lived in France toward the end of the 19th century. He was van Gogh's last physician, manuscript on the subject of military ophthalmia never published. Only one copy is known to exist.



Trachoma

The most blinding diseases in history. until the late 1930s, no effective cure destroy diseased tissue, making disease inactive. cure rates of approximately 20%.

Therapy same measures used by the ancient Egyptian, Greek, and Roman physicians.

1912: US Public Health survey identifies trachoma as the most rampant disease in Indian Country, 24%. Native Americans population infected, 72,000 33% of Indians on reservations in Nevada, Utah, and Wyoming, and 50% of Indian students in boarding schools.

Untreated, trachoma will progress to blindness.

1927: Commissioner of Indian Affairs Charles Burke orders eradication by surgical removal of infected lid tissue. Disaster abandoned

Dr. Procter personally founds a research institute at Fort Apache leading to discovery of the organism.

1938 Fred Loe, MD, self taught ophthalmology American Indian reservation, Sulfanilamide: 90% cure rate.



A grandfather and two of his grandchildren infected with trachoma, Rincon Reservation, California, 1912



Pupils at Carlisle Indian school Pennsylvania (c. 1900)

From 1879 hundreds of thousands of American Indian children attended Indian boarding schools.



simplified grading system.

Evert upper eyelid

Grade findings in defined area

Active trachoma

follicular inflammation (TF)

and/or

trachomatous inflammation intense (TI) in either eye.

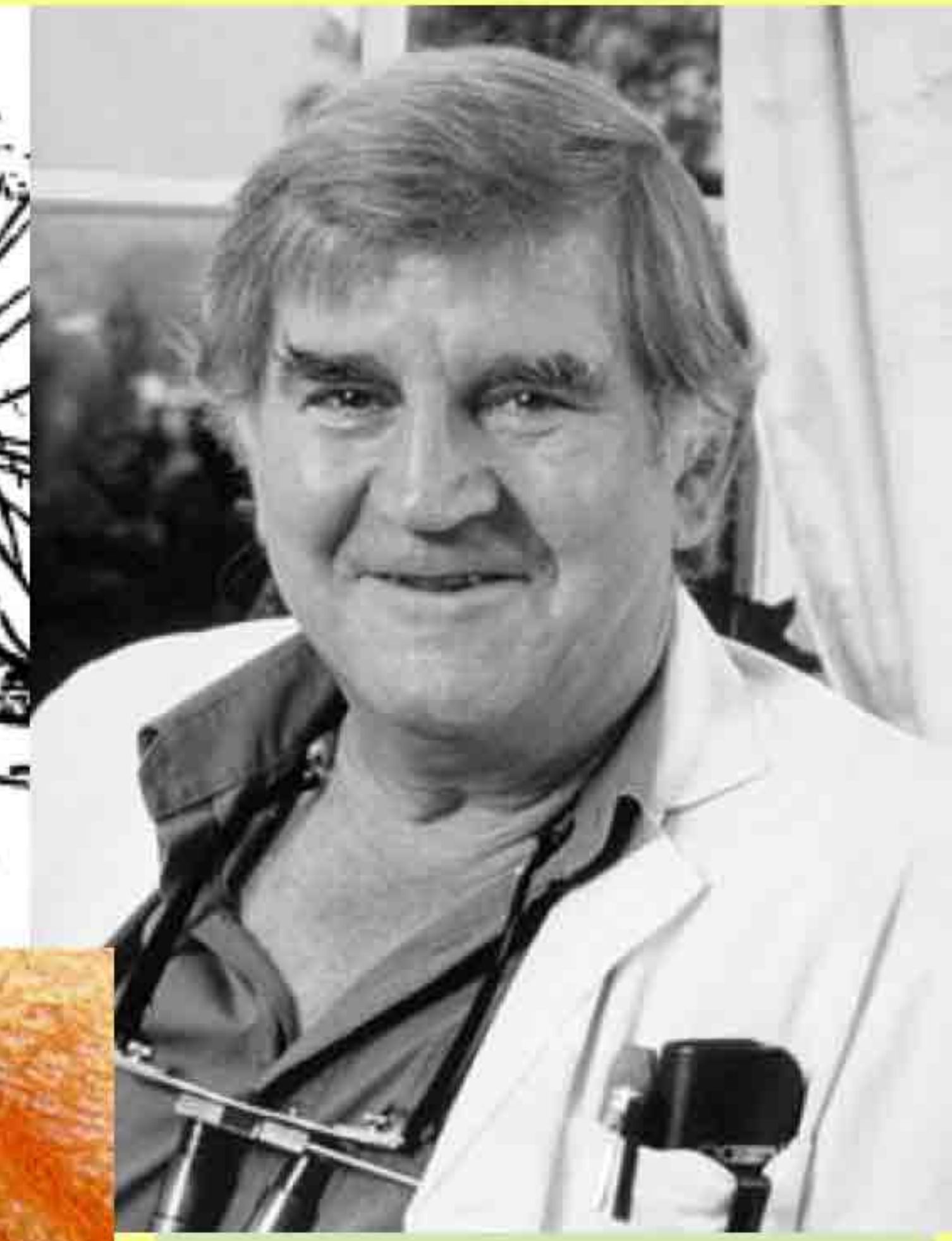
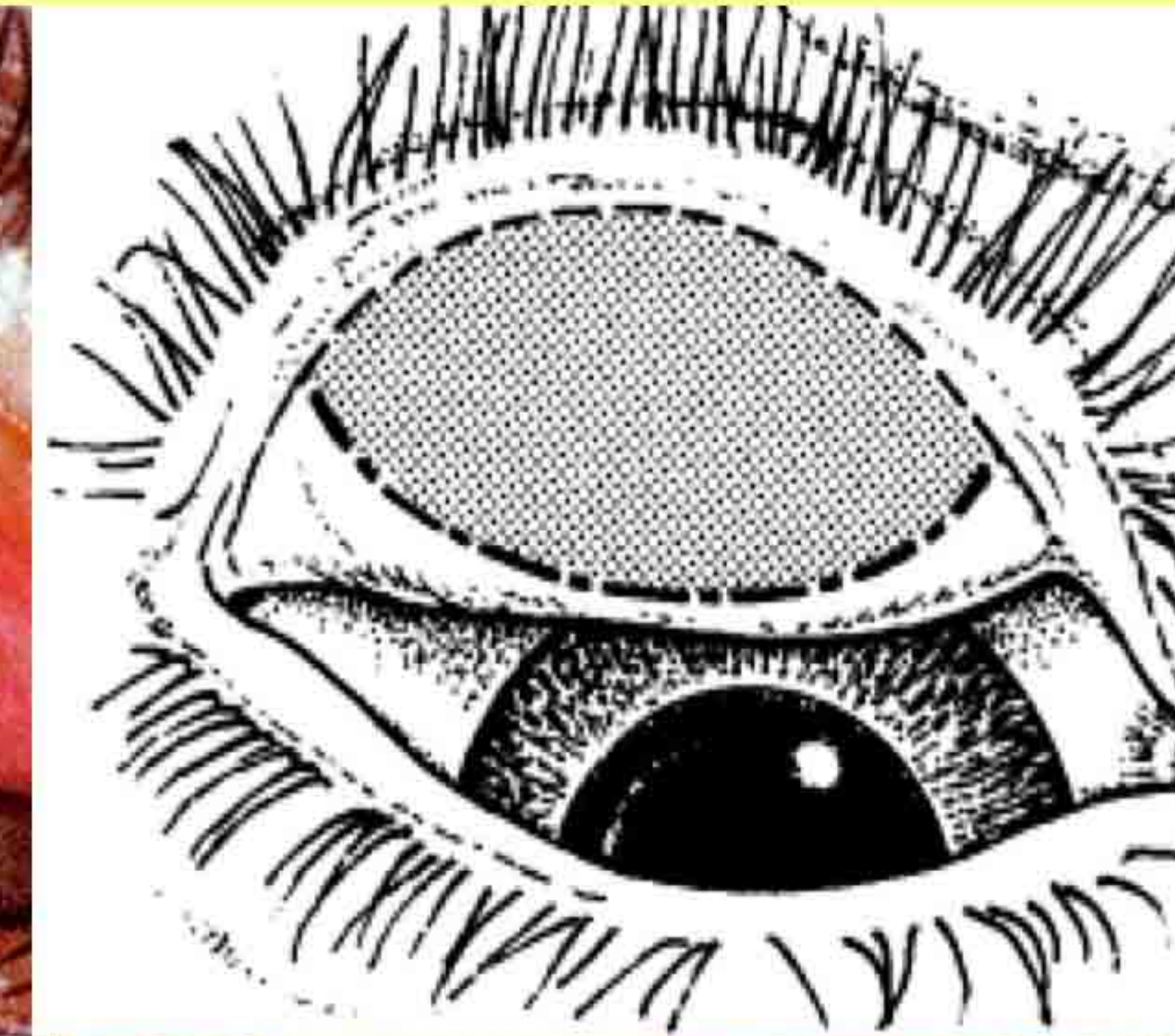
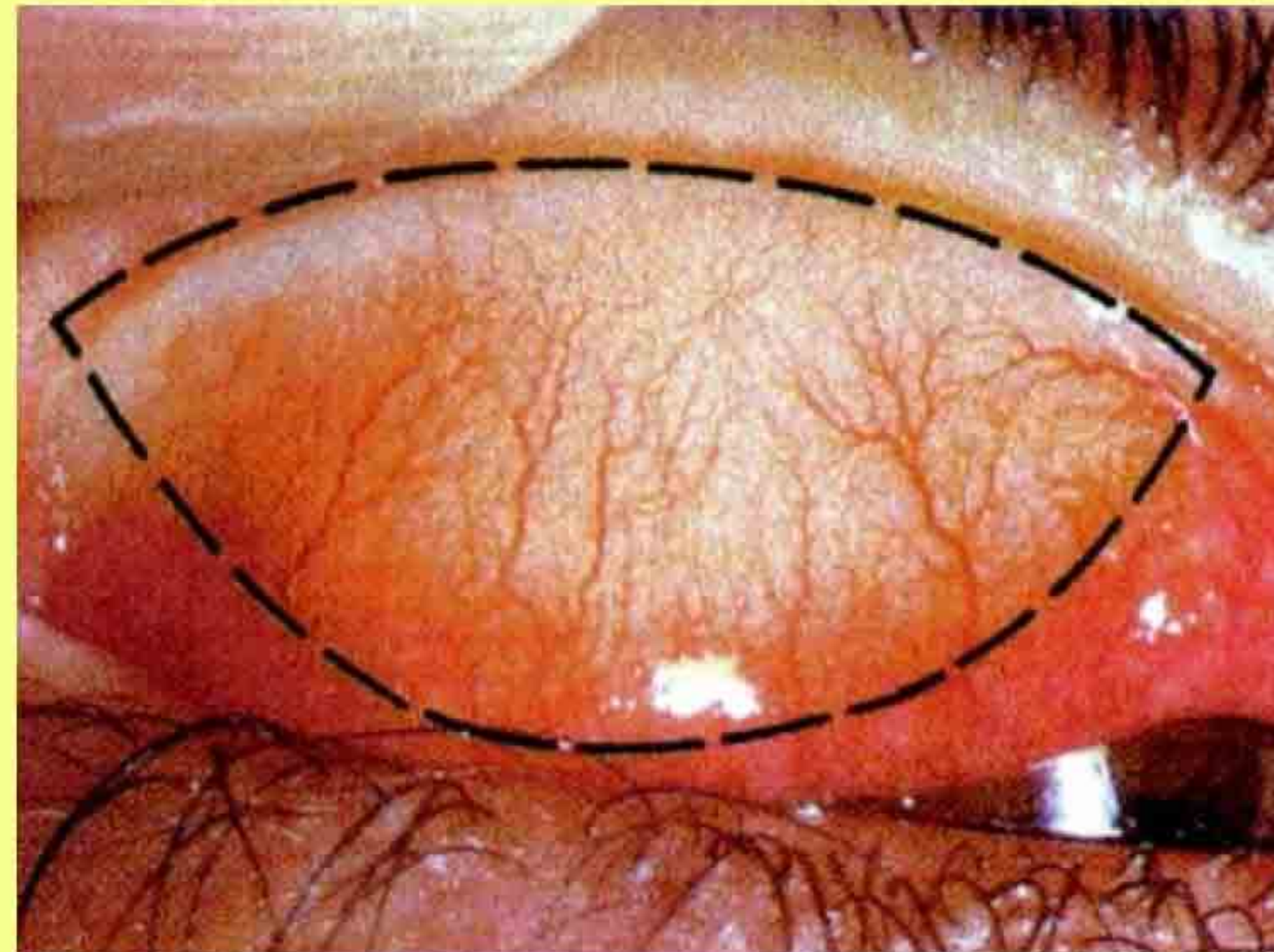
Scarring trachoma

trachomatous scarring (TS),
trachomatous trichiasis (TT)

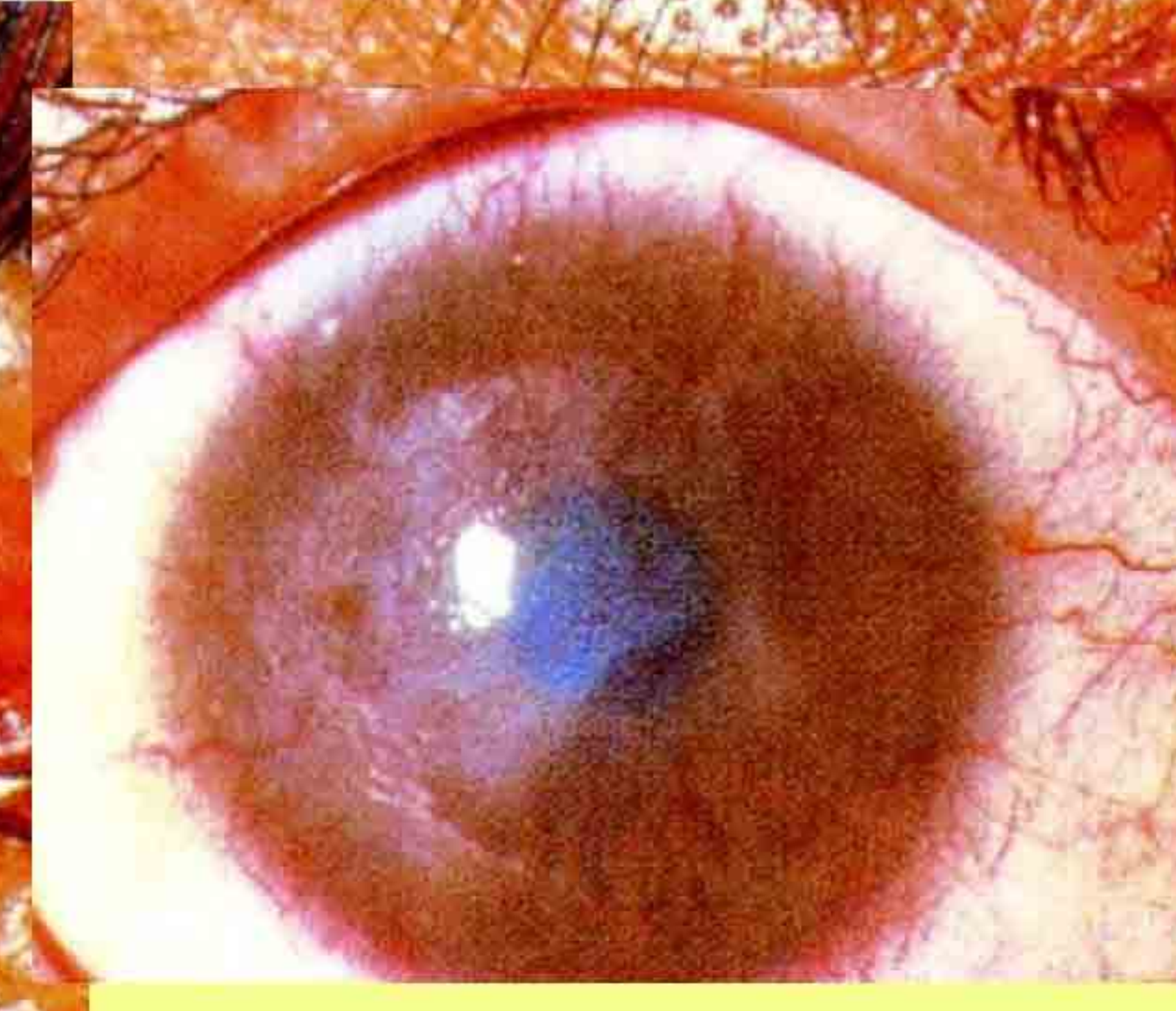
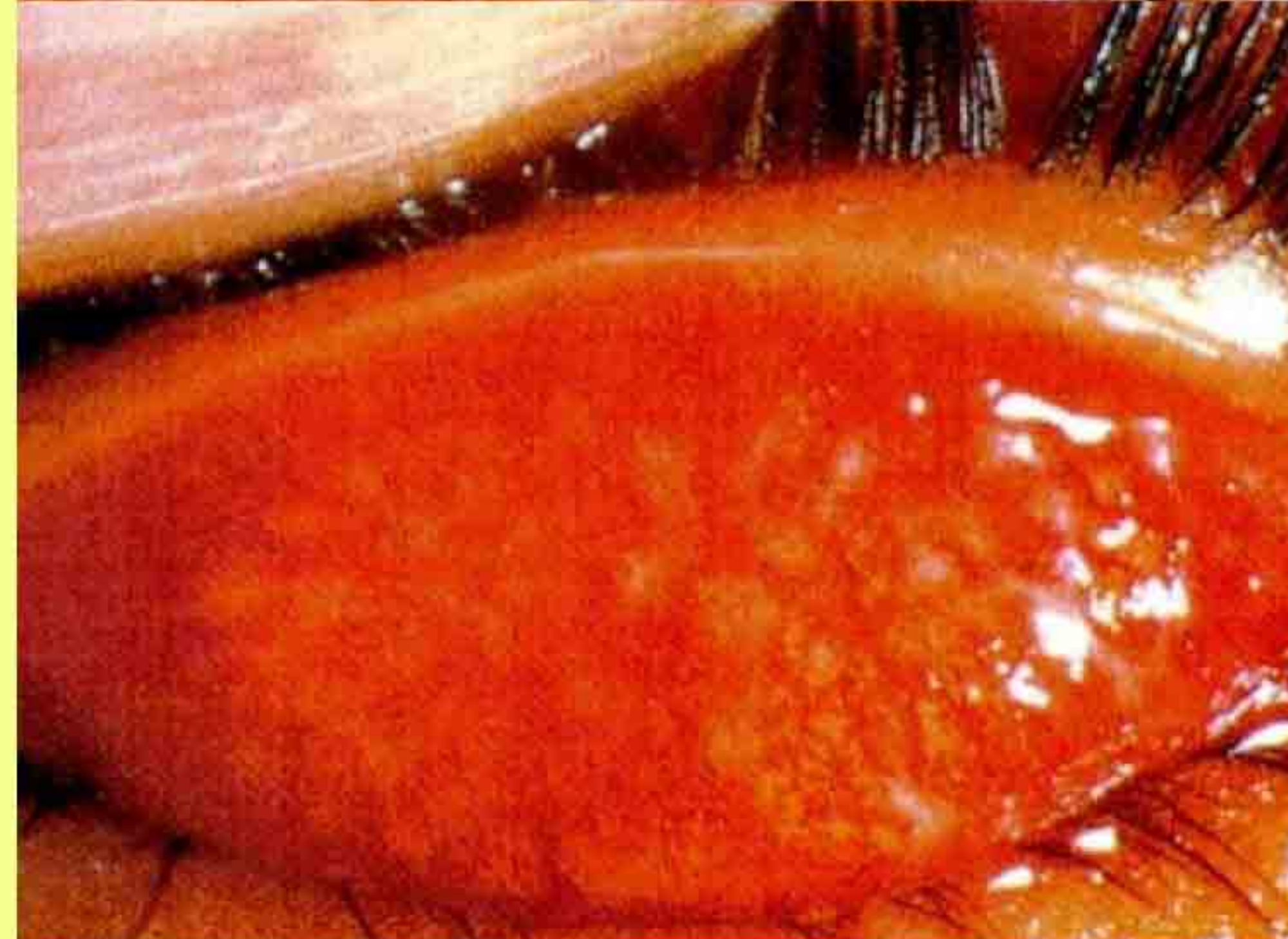
and/or

corneal opacity (CO) in either eye.

TT was defined as at least one eyelash rubbing the eyeball or evidence of recent removal of in-turned eyelashes.



Fred Hollows:
(1929 –93)
Dunedin NZ
Moorfields to
Australia.
Shocked by
incidence of
Trachoma, sets
up system for Rx



Flies

Most likely vector of trachoma is the bazaar fly, *Musca sorbens*

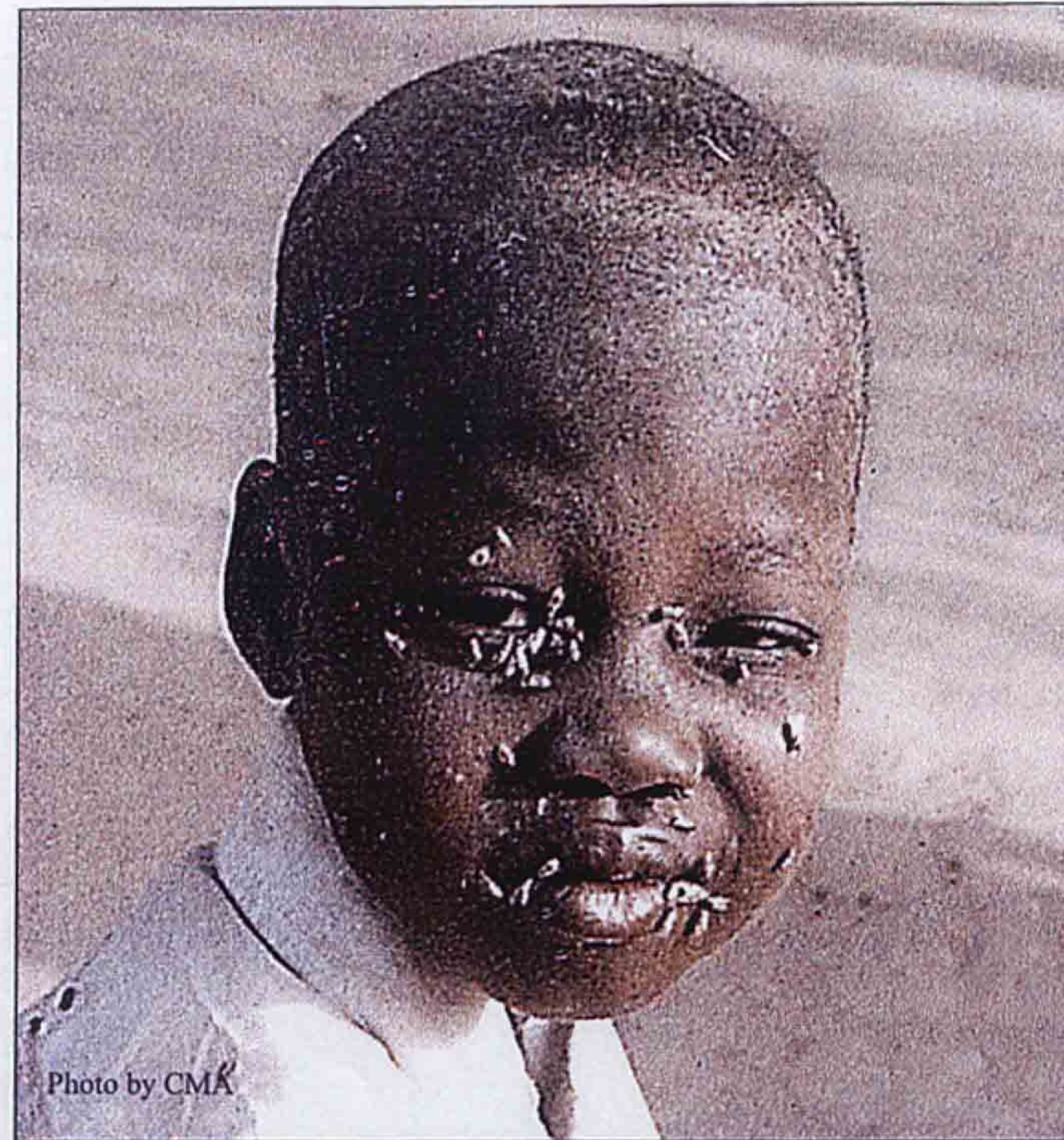
breeds in solid faeces lying on the ground, but does not breed in latrines, where the contents liquefy rapidly

After three months of fly control the prevalence of active trachoma was significantly lower in the intervention villages compared to the controls, in both seasons.

Overall there was a reduction in the community prevalence of active trachoma associated with fly control of 61%

Moreover, the number of new cases was significantly lower in the intervention villages than controls with an overall reduction of 75% in villages where fly control was practised

DIRTY FACES AND FLIES CAUSE TRACHOMA



FIGHT TRACHOMA BY WASHING YOUR FACE

Sudan Trachoma Control Program

Strategies for elimination

Trachoma, the leading cause of infectious blindness globally endemic in 57 countries of the world

1959–63 India: public health problem

active trachoma rates **79%** children <10yrs in four states

1976: National Programme for Control of Blindness (NPCB)

2006: 5.8% of children aged 1–9 years demonstrated clinical signs of active trachoma, trichiasis (0.15%).

WHO: Global Elimination of Trachoma (GET) by 2020

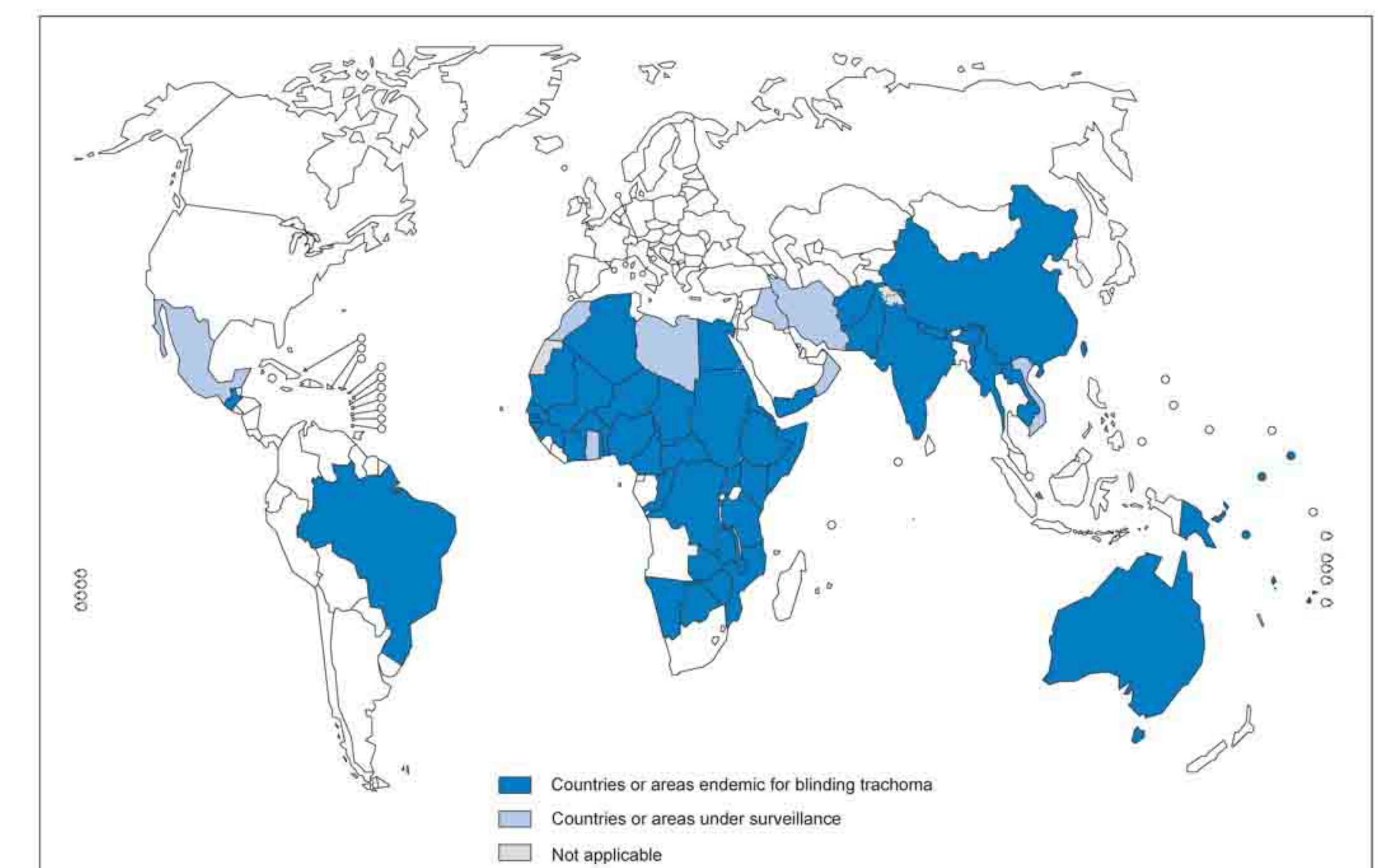
The SAFE strategy – Surgery, Antibiotics, face-washing, Environmental change

WHO 2010: reported estimates of the number of cases of trachoma world-wide down to 40 million, and number of cases of trichiasis at 8.2 million.

Trachoma, formerly the second leading cause of blindness, Now 6th leading cause (although still the leading infectious cause of blindness)



Distribution of trachoma, worldwide, 2010



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2011. All rights reserved.

Data Source: World Health Organization
Map Production: Control of Neglected
Tropical Diseases (NTD)
World Health Organization

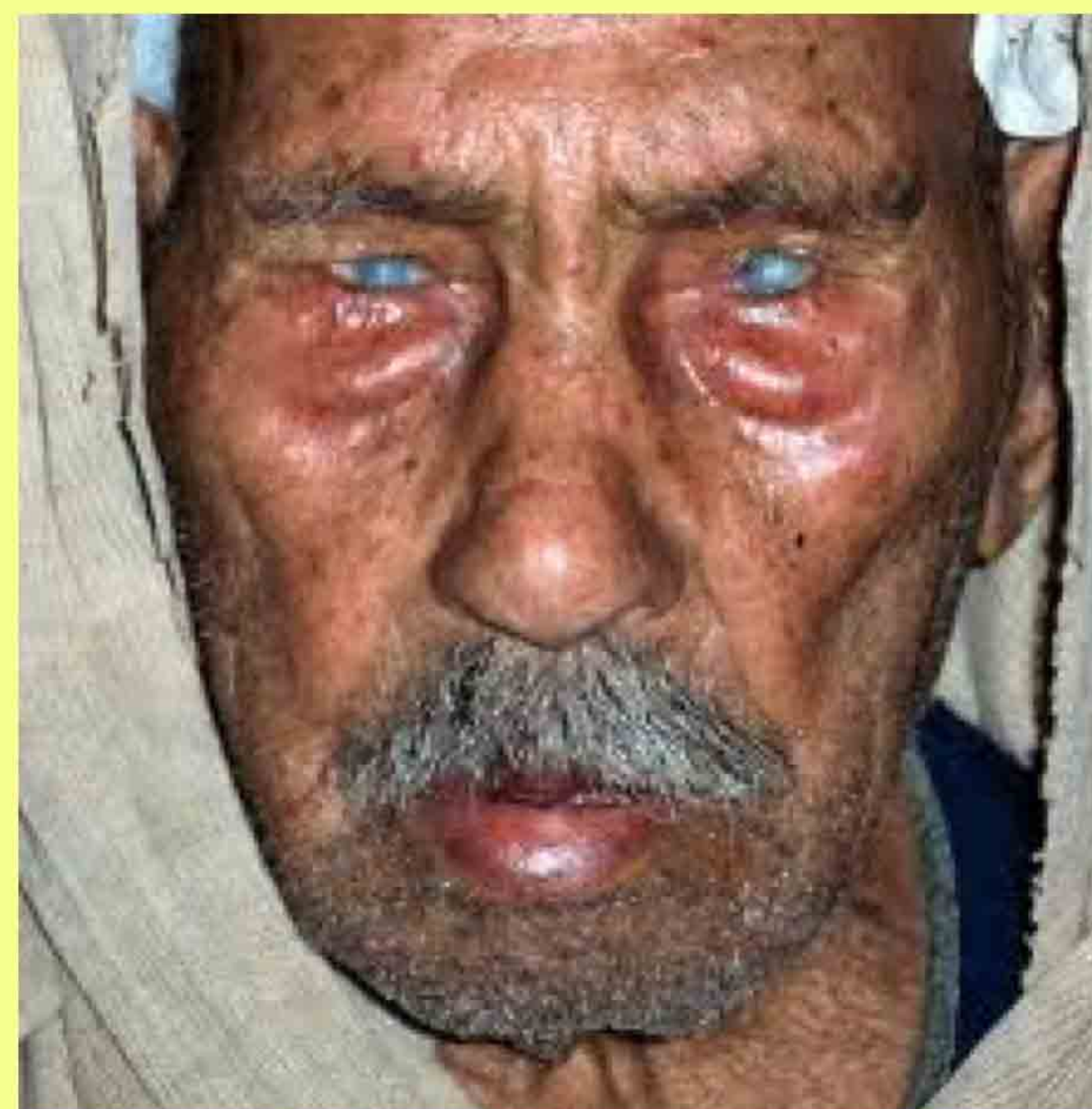


SURGERY afe

Surgery is the component of the SAFE strategy which has been shown to contribute significantly to prevention of blindness.

It also usually results in immediate and dramatic relief of discomfort for the patient.

The operation is quick and is widely performed by non-medical health workers under local anaesthetic as a day-case procedure.



s ANTIBIOTICS fe

– is currently being implemented for five pilot countries

donation programme by Pfizer, Inc.

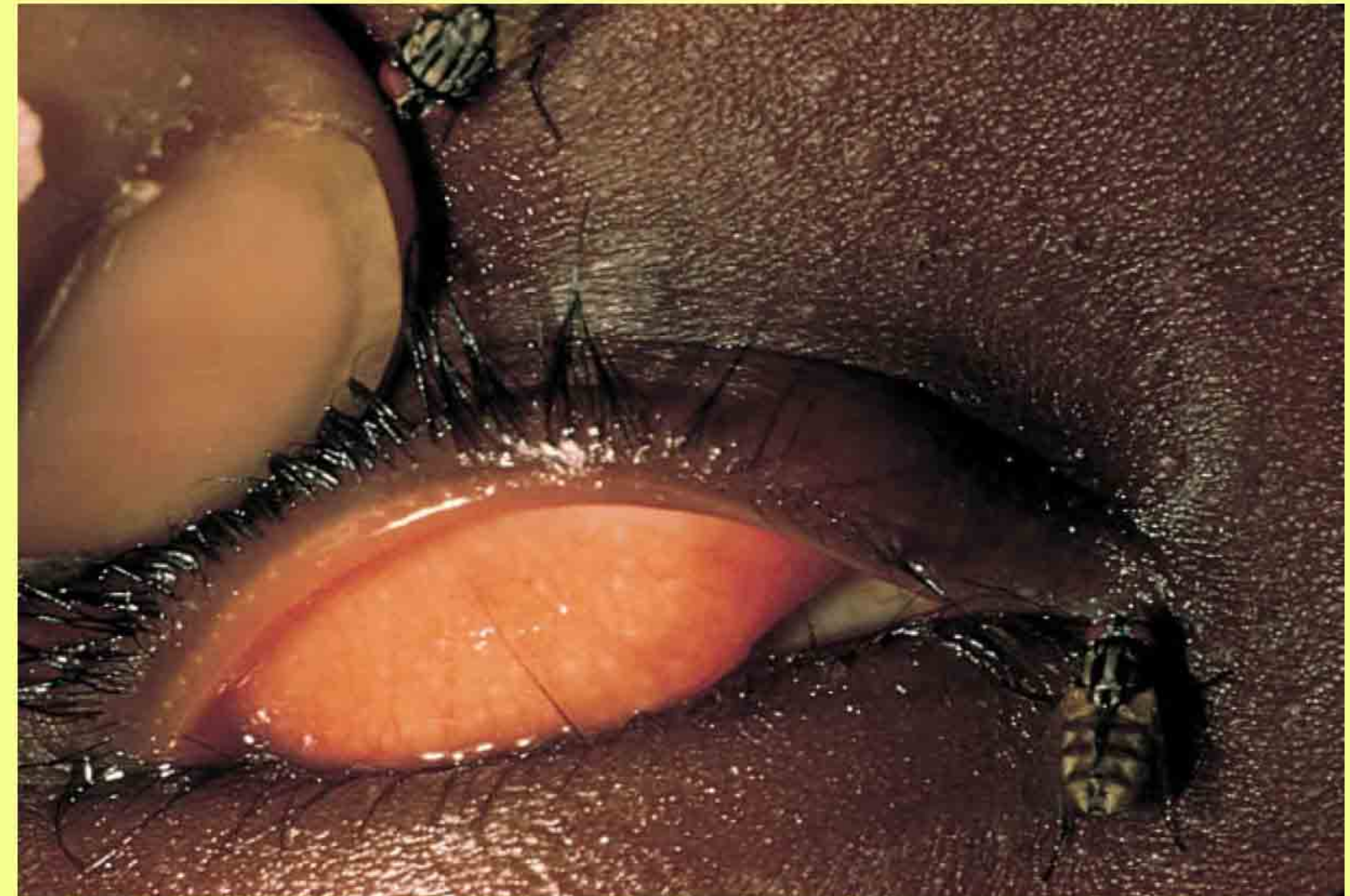
topical tetracycline must be used every day for four to six weeks to be effective. stings, is messy to use, and results in blurred vision because of its oily base

Azithromycin: azalide class of antibiotics.

ideal for treating trachoma; good oral bioavailability and distribution to tissues, sustained high tissue levels

sa **FACE WASHING** e

saf **ENVIRONMENTAL CONTROL**

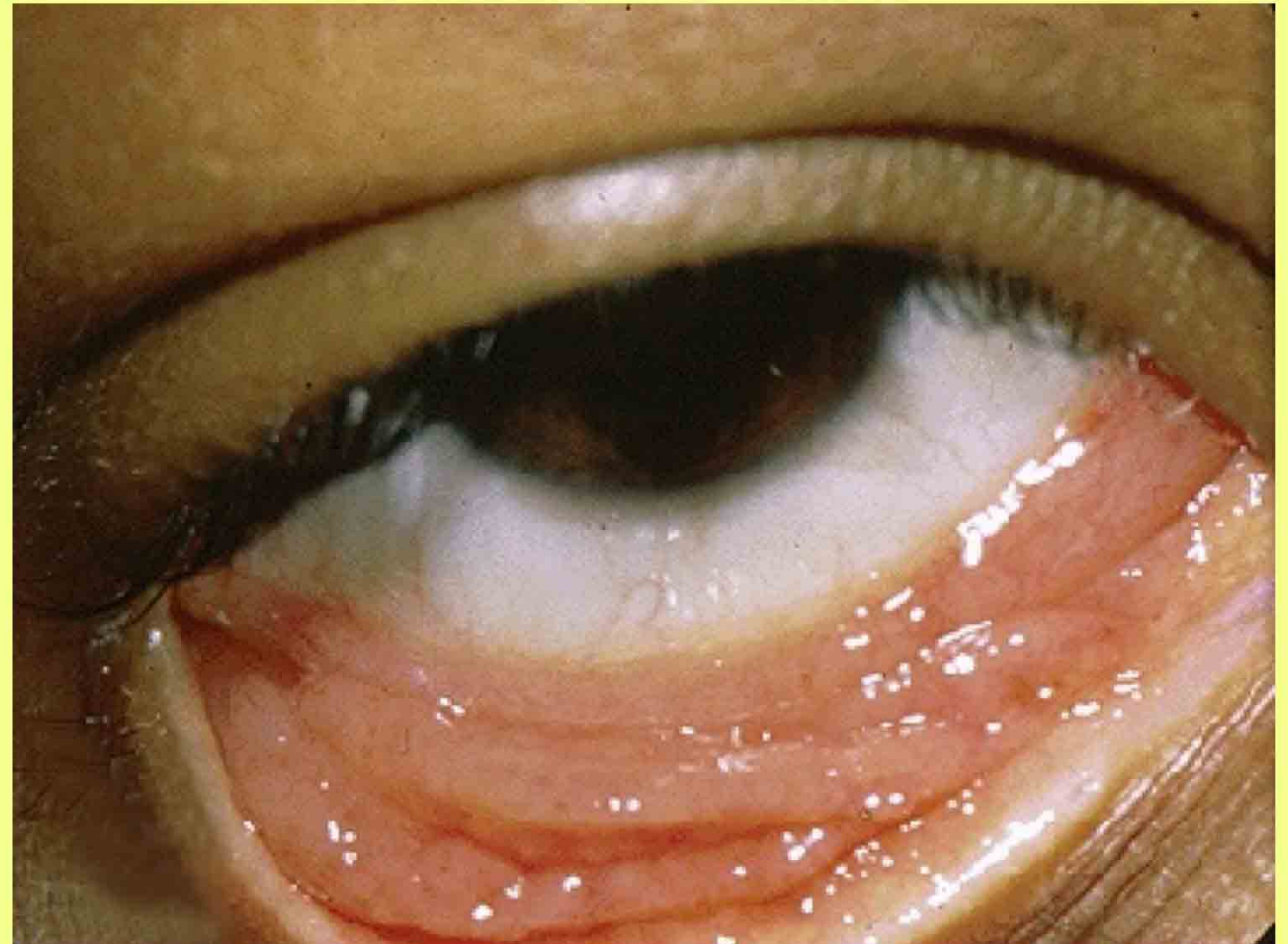


Venereal Chlamydia

Local and systemic treatment

Contact tracing

STD clinic



Fungi

Keratitis

Hot countries, hyderabad

Contact lens wear

Candidal chorioretinitis

Candida albicans,

Predisposing factors for candidemia

recent major surgery, bacterial sepsis,

indwelling intravenous catheters and

iv drug abuse

Aspergillus fumigatus retinitis is seen

mostly among intravenous drug

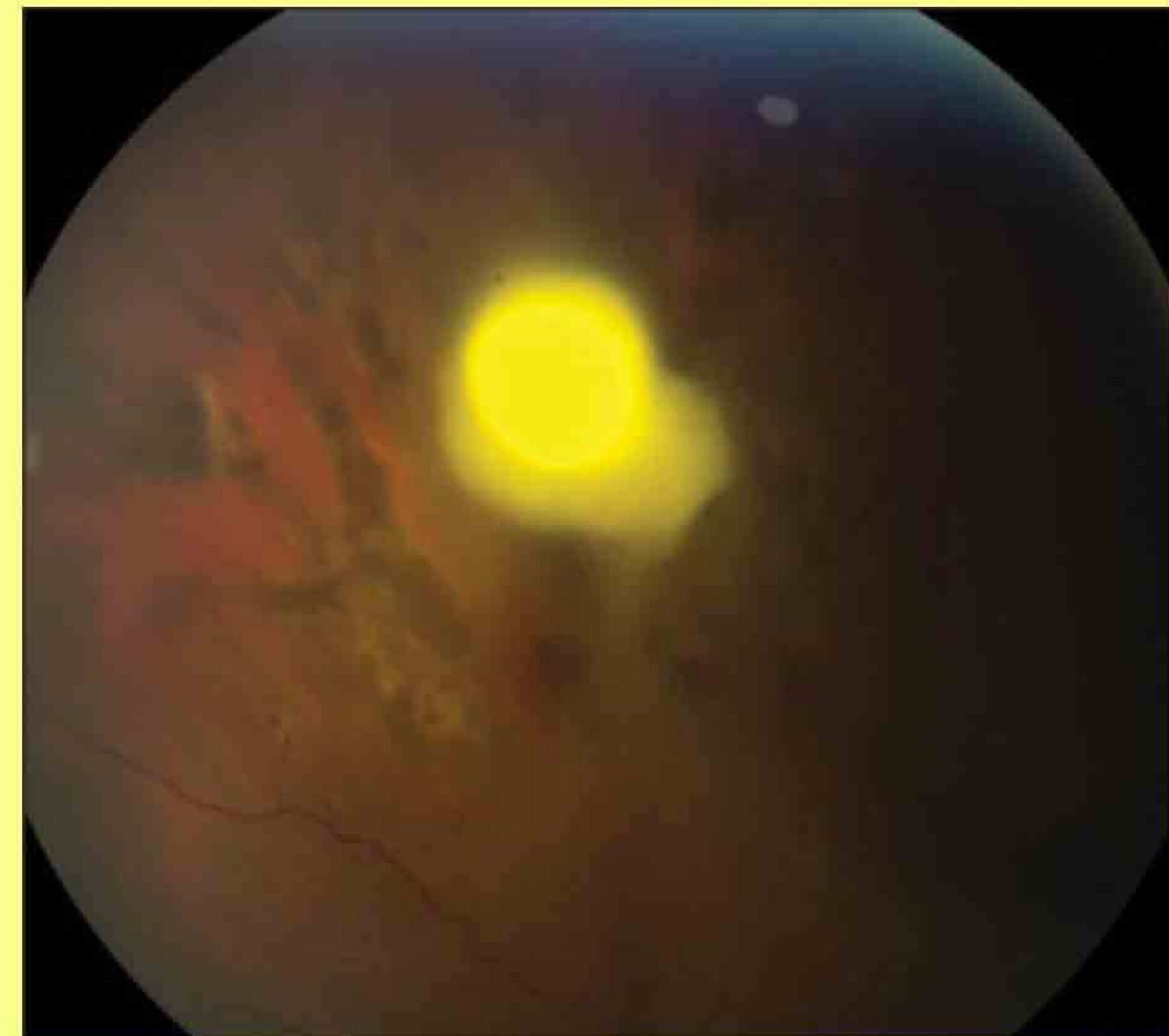
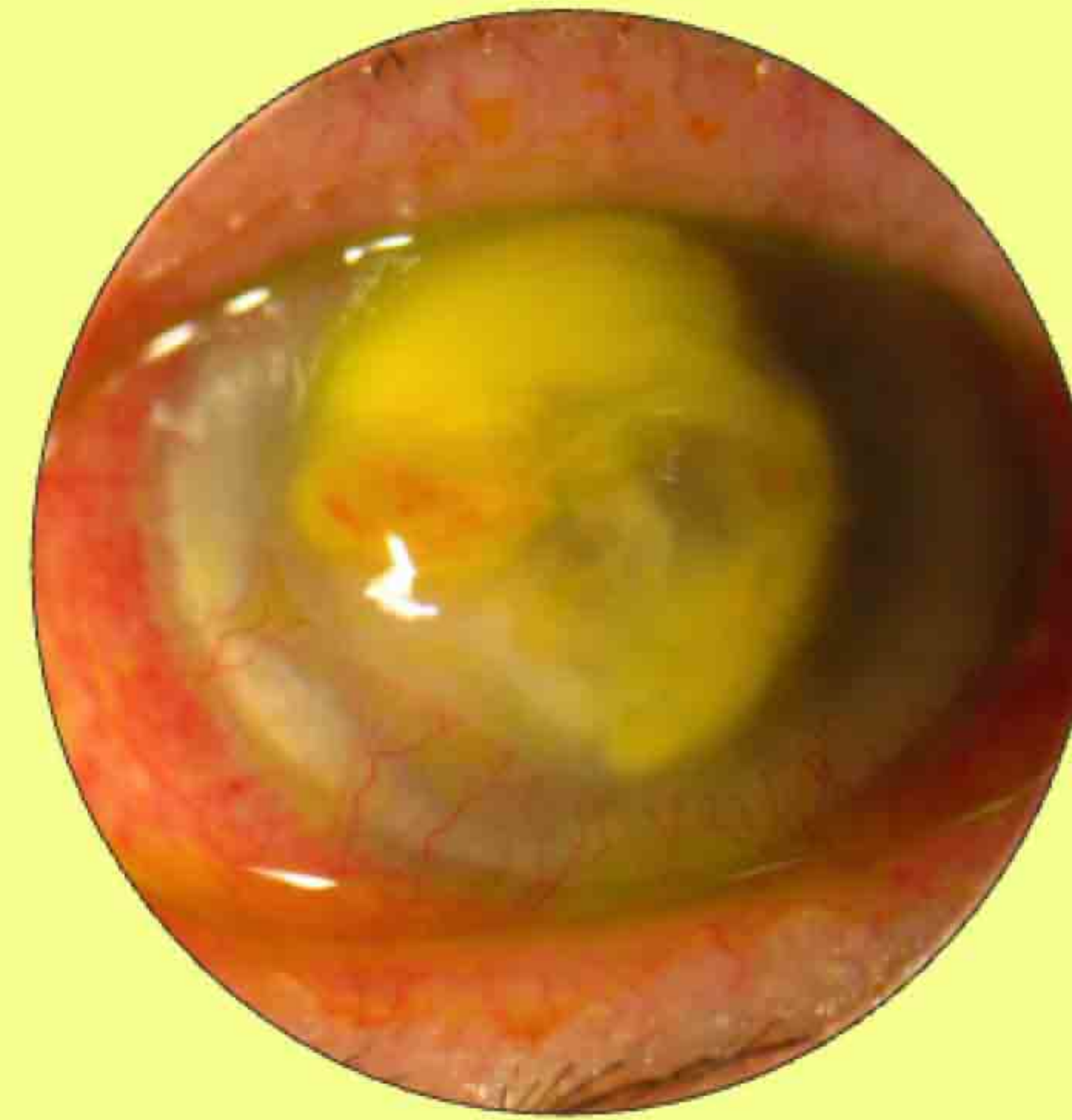
abusers, patients who have received

transplants, and malignancy and

chronic lung diseases

Retinal vessels invaded, thrombosis,

infarction, and retinal necrosis



Discovery of Microbes

Antonie van Leeuwenhoek:

mags $\times 30$ - $\times 270$ resolving power up to $1.4 \mu\text{m}$

1683: letter to Royal Society

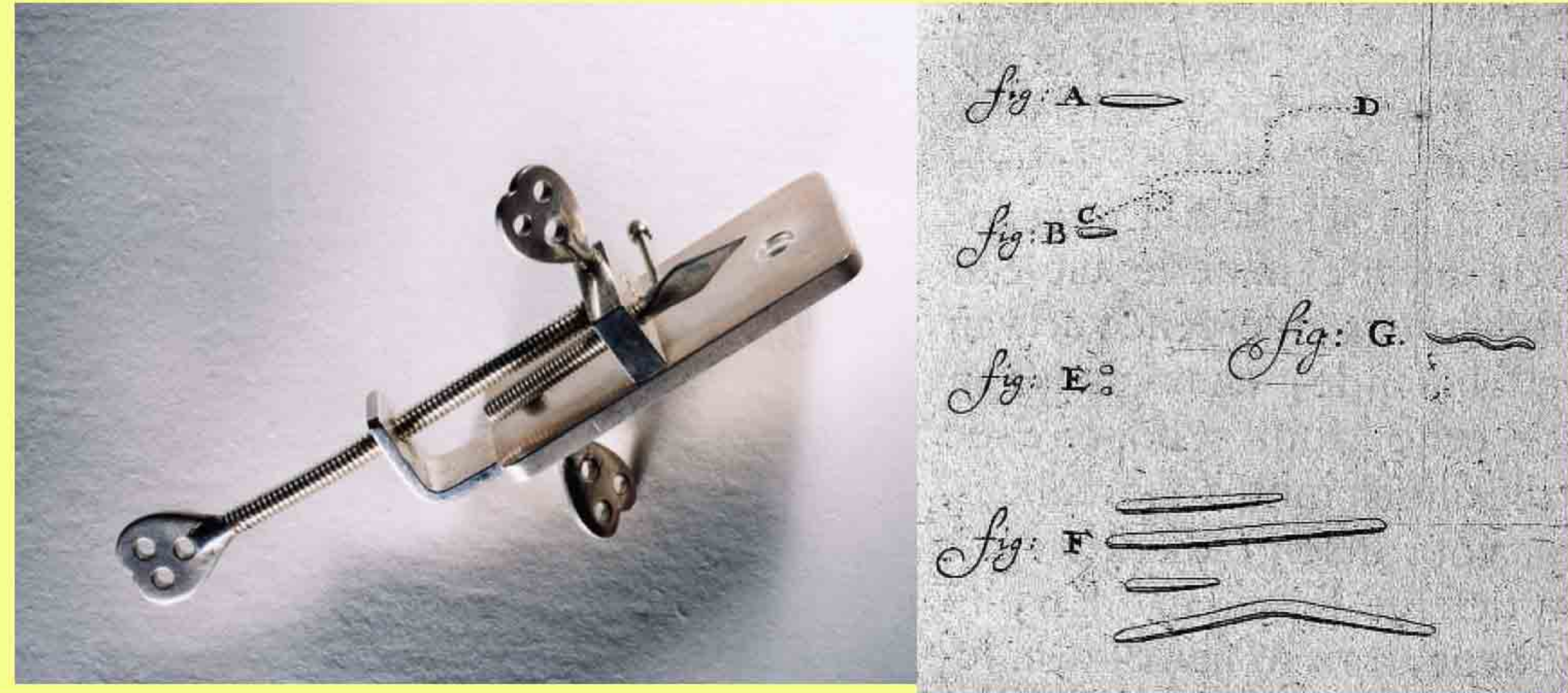
Observations on tooth plaque

“A little white matter, which is as thick as if ’twere batter.”

“I then most always saw, with great wonder, that in the said matter there were many very little living animalcules, very prettily a-moving. The biggest sort. . . had a very strong and swift motion, and shot through the water (or spittle) like a pike does through the water. The second sort. . . oft-times spun round like a top. . . and these were far more in number.”

In mouth of a man who had never cleaned his teeth;

“an unbelievably great company of living animalcules



Oral bacteria observed by Anton van Leeuwenhoek

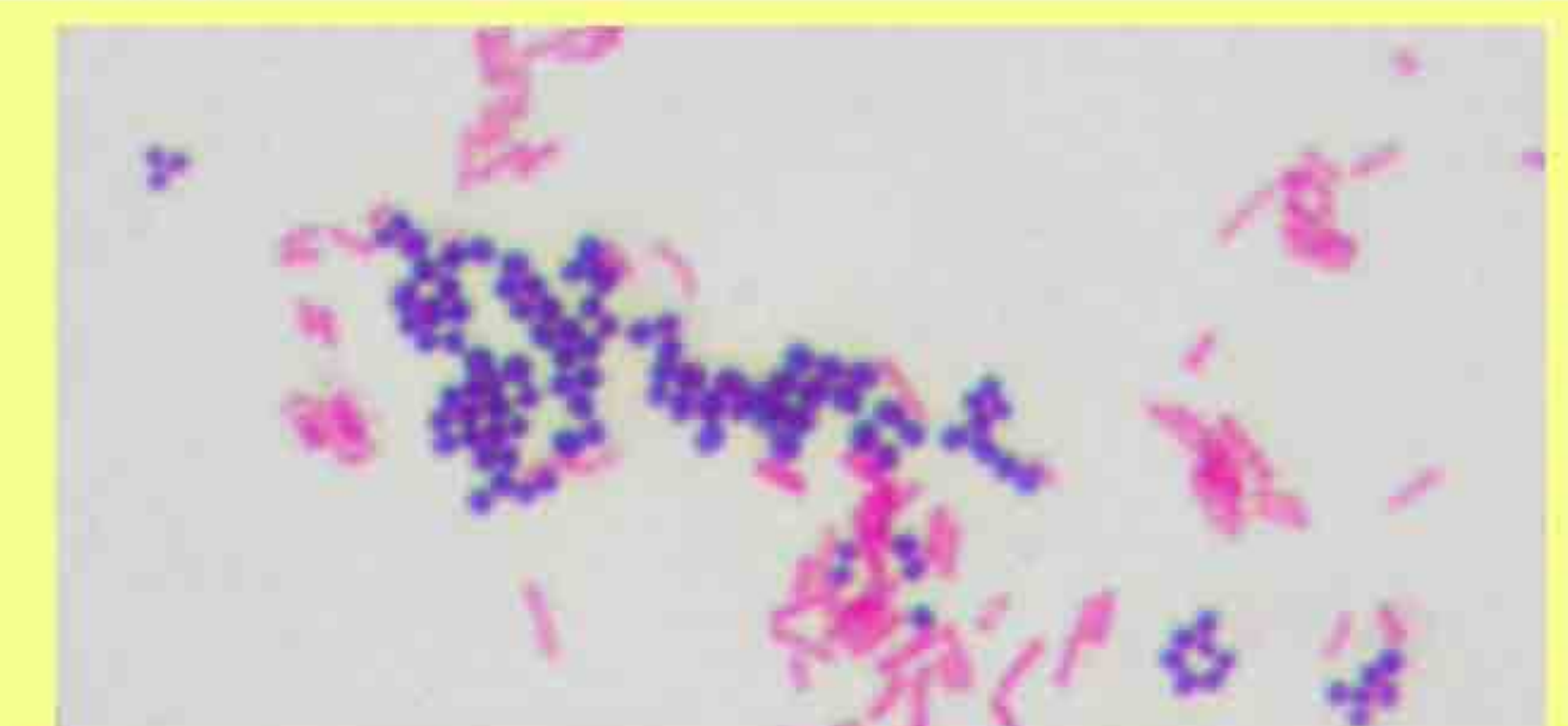
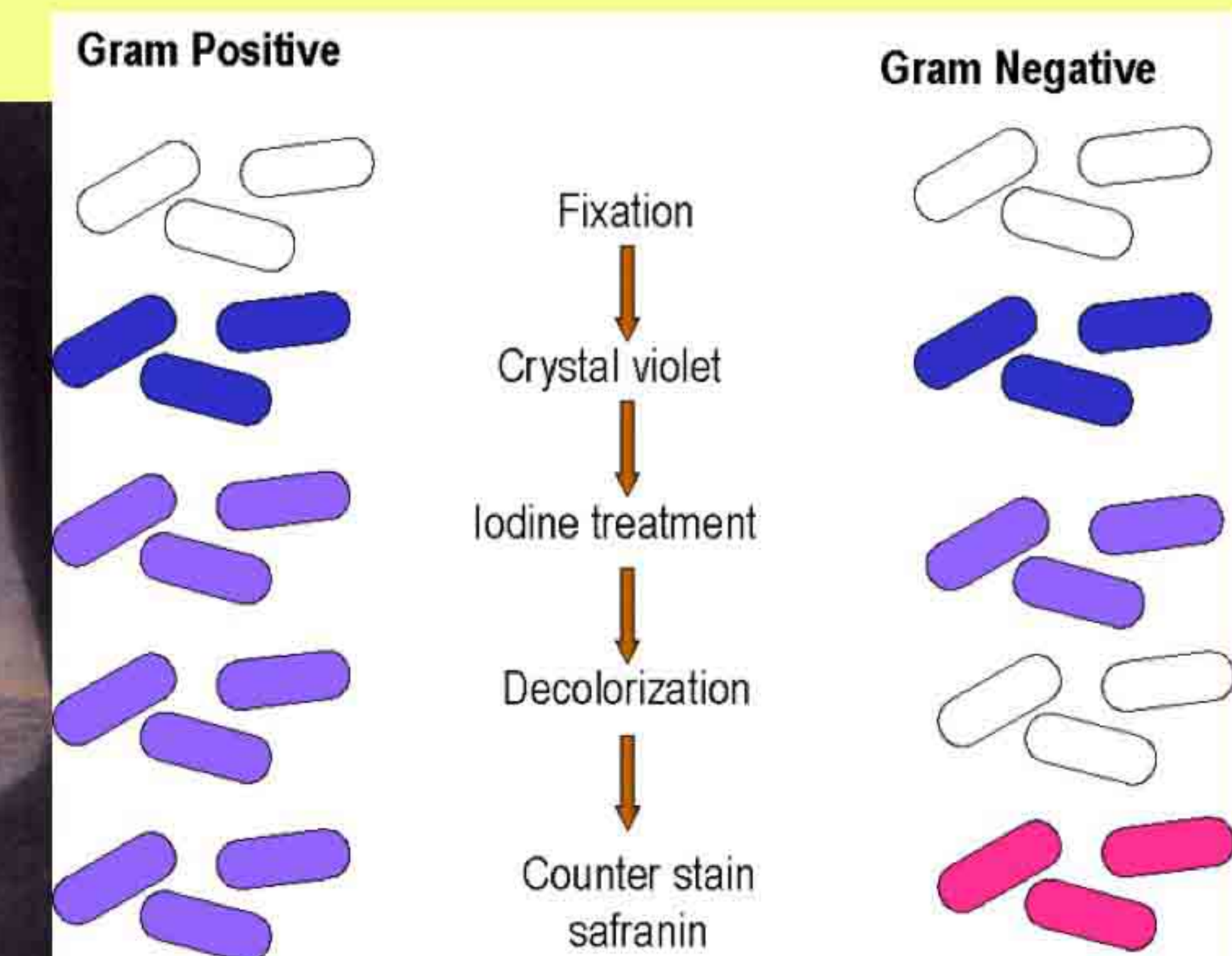
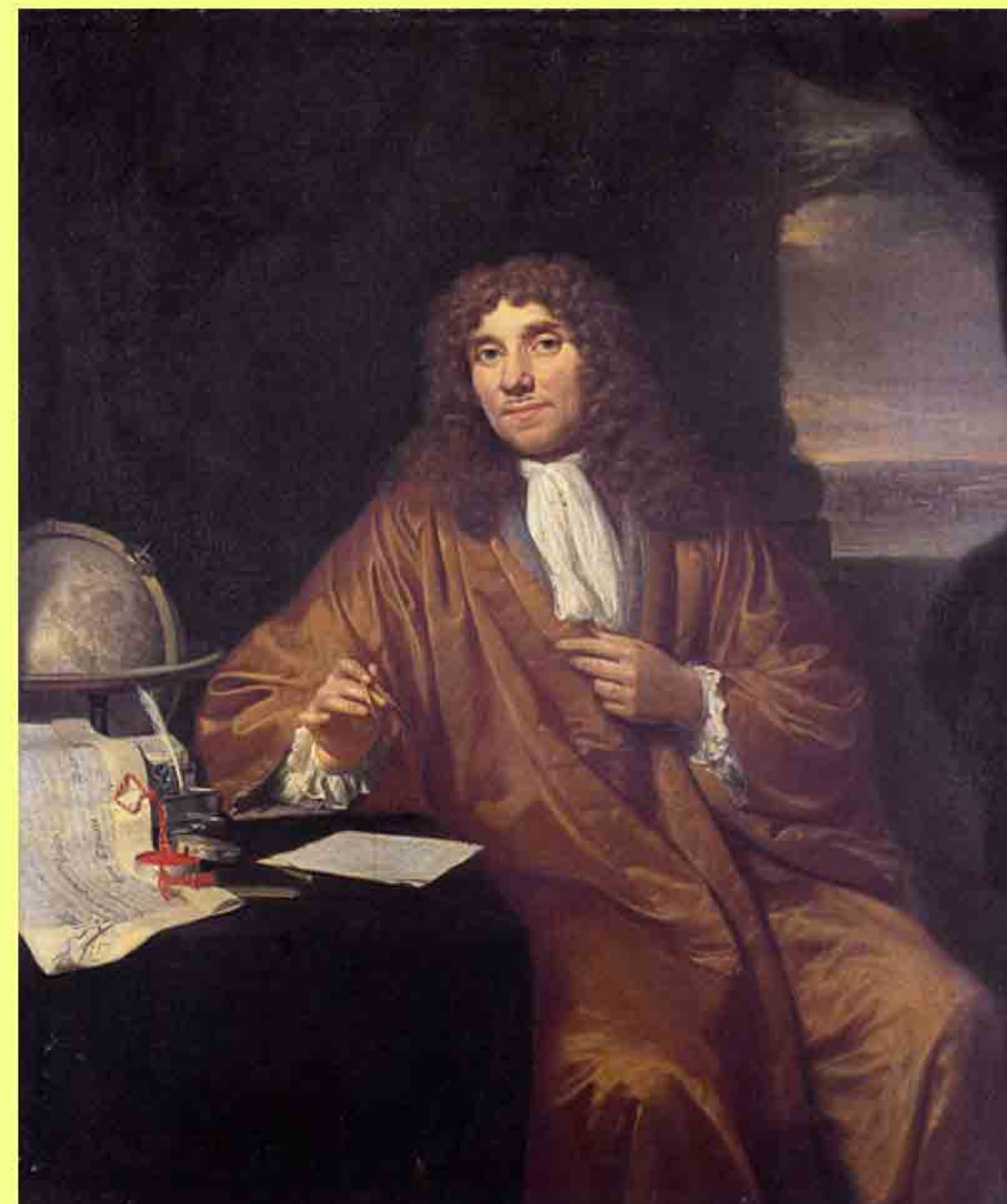
A: rod-shaped motile bacterium such as *Campylobacter rectus*

B: Motile moving from C to D likely *Selenomonas*

E: was proposed to be oral cocci

G: either a *Spirillum* sp. Or spirochete such as *Treponema denticola*

F: long fusiform species *Leptotrichia* (*Leptotrix*) *buccalis*



Hans Christian Gram (1853 - 1938) Danish bacteriologist.

Protozoa

“First animals.” behave like tiny 5-500 μm animals
 principal hunters and grazers of the microbial world
 Some protozoa absorb food through their cell membranes.
 Amoebas, surround food and engulf it.
 Some have mouth pores into which they sweep food.
 Digest food in vacuoles. give off nitrogen,
 Also themselves basis of many food chains.

Three patterns of life cycle

Flagellates: Asexual fission. Some use cysts which pass on trophozoites, others use insect vector

Amoebas: live in the lumen of the gut and multiply by binary fission. Trophozoites encyst and undergo nuclear division. The cyst is ingested by another host.

Apicomplexa alternate between asexual and sexual stages. Multiple asexual fission: produces **merozoite** daughters and **gametes:** unite and divide to produce **sporozoites** infect new host. Some complete cycle in vertebrate host, transmit via cysts, containing sporozoites

Other spp use **two hosts**, vertebrate for schizogony and gametogony, and invertebrate vector in which gametes unite in the gut (Ross 1895) and sporogony occurs in tissues.

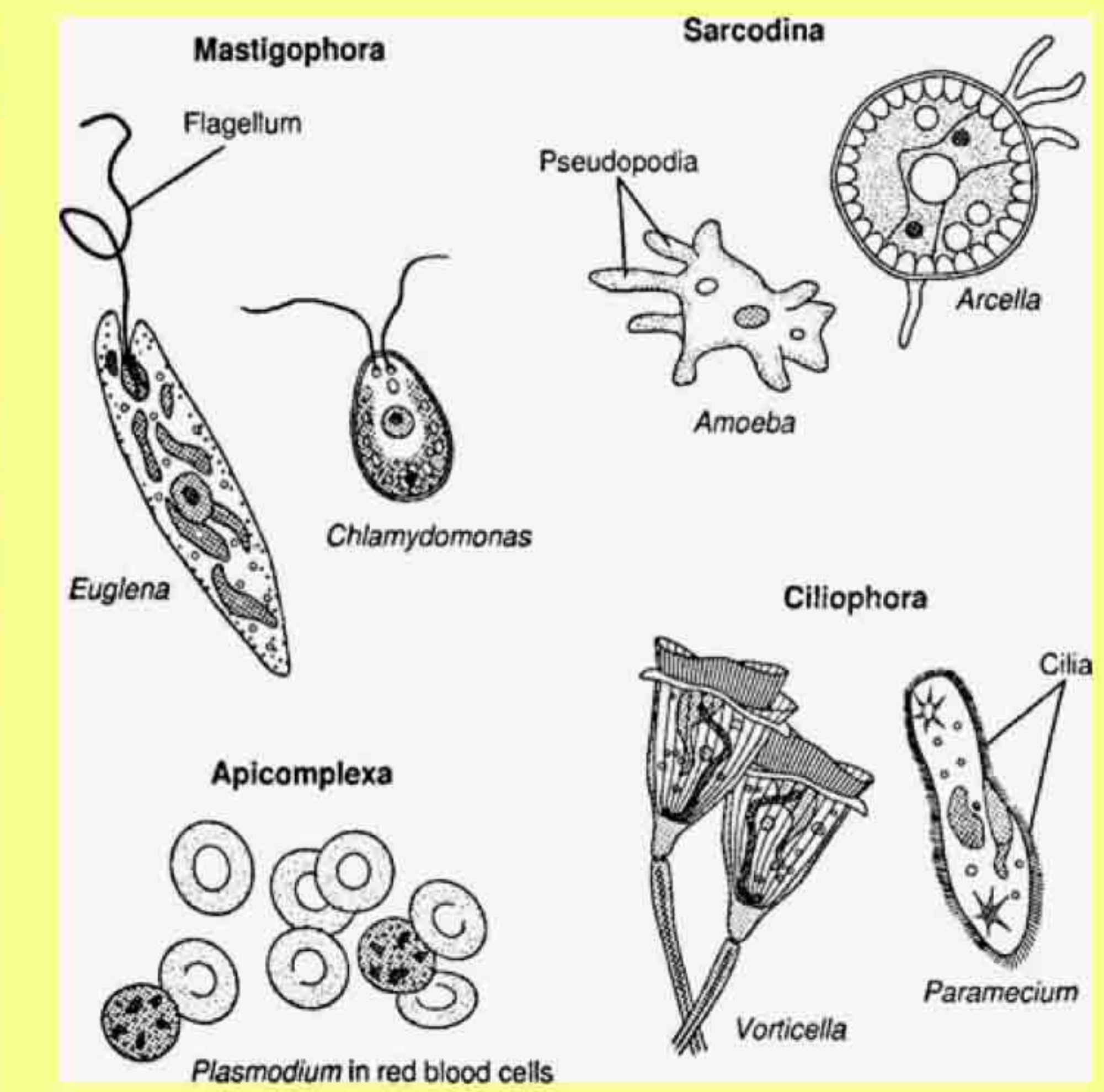
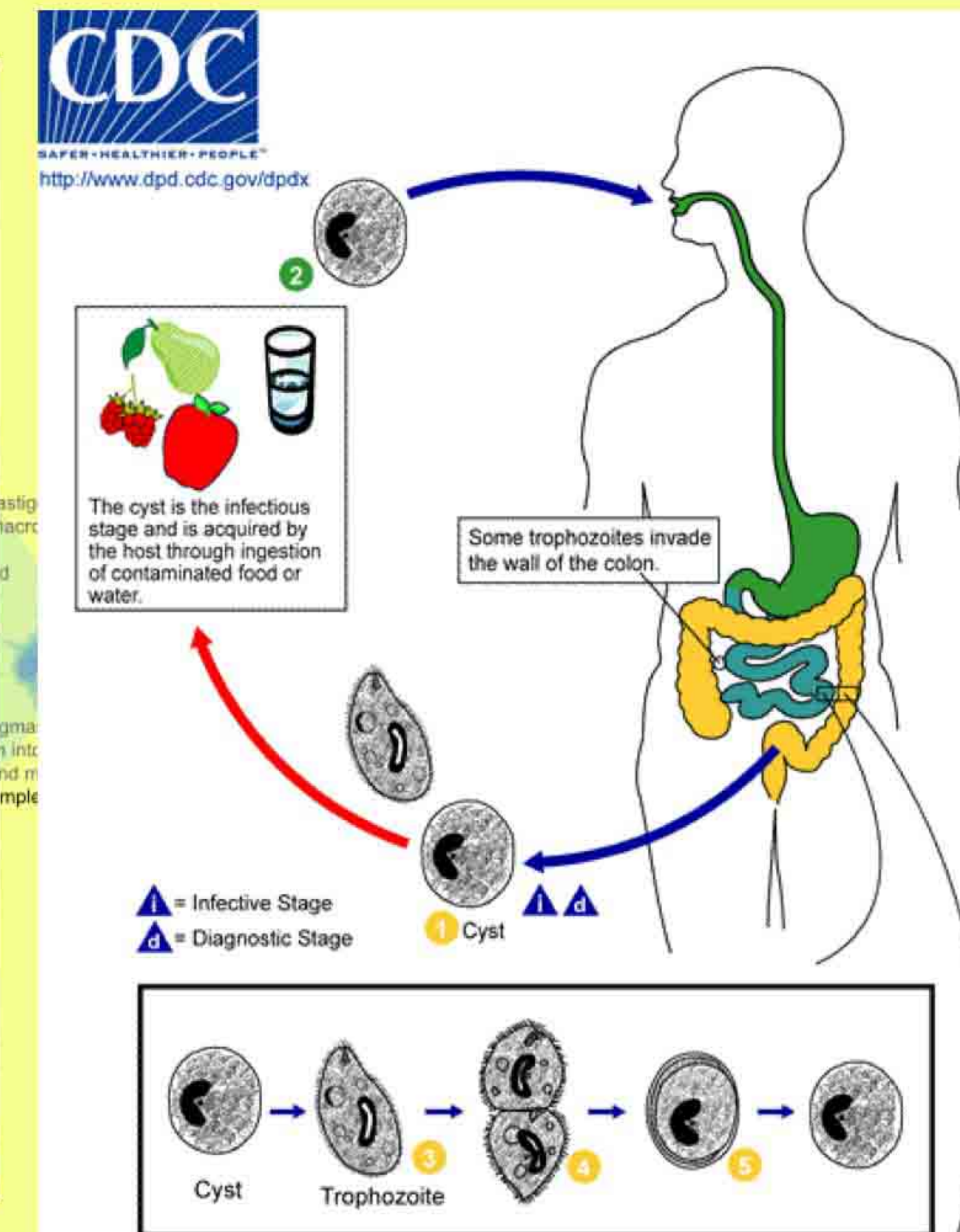
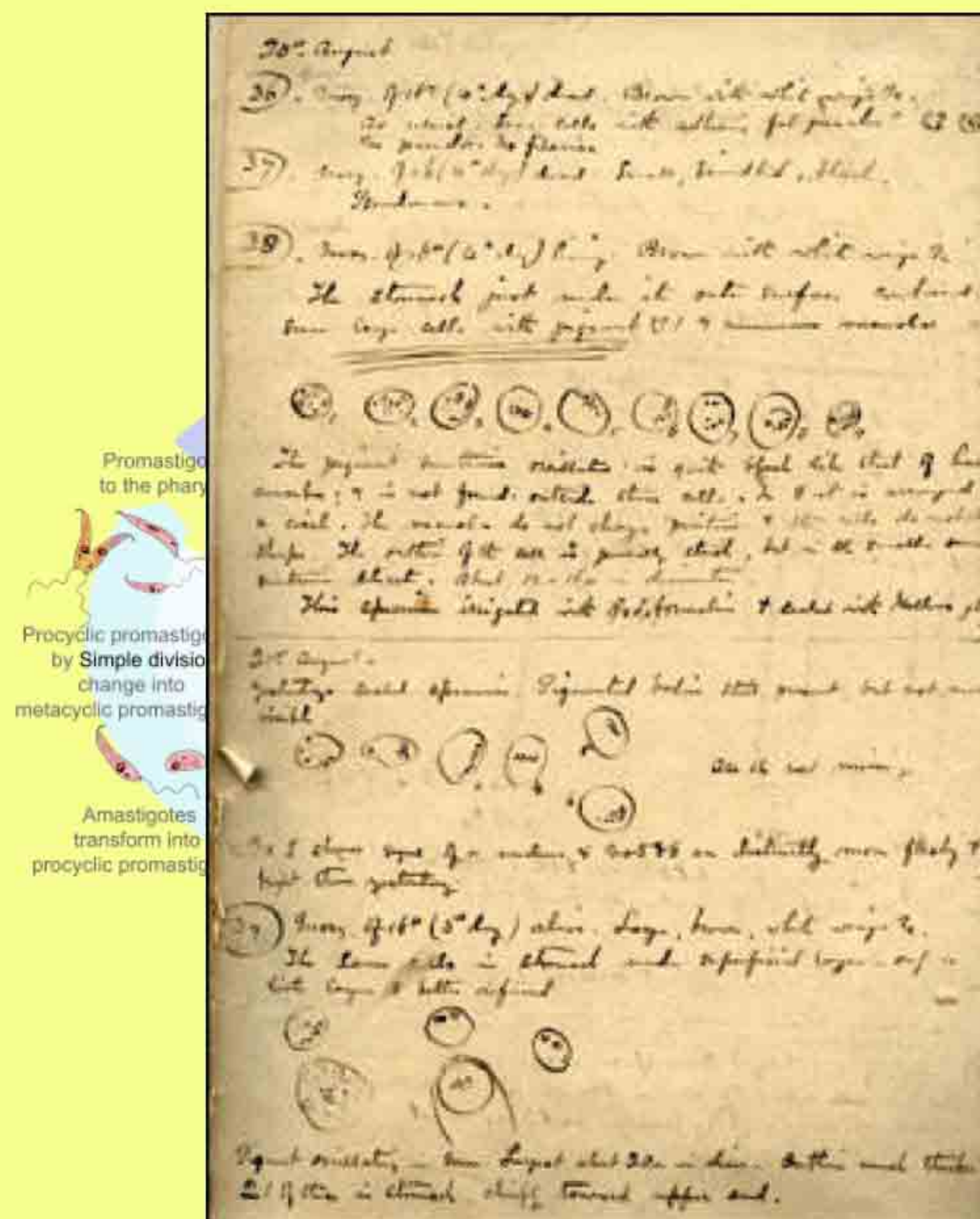
Plasmodium vivax, malaria.

Toxoplasma gondii

Cryptosporidium parvum: 1993: 400,000 people in Milwaukee tap water.

Entamoeba histolytica: Dysentary, liver abscess

Balantidium coli is the only ciliate which infects humans



Mastigophora	flagella	leishmania, trichomonas Giardia
Sarcodina	pseudopodia	Entamoeba, acanthamoeba
Apicomplexa	apical complex	Plasmodium, cryptosporidia, Coccidia (toxo)
Ciliophora	cilia	Balantidium

Protozoa: Malaria

1590: John Norden, cartographer: English marshlands

2010: 660,000 killed, most African children.

Infected 247 million worldwide, mainly in Africa

Female *Anopheles* bite acquires parasite **gametocytes**.

Fuse mature to **oocyst**: ruptures releasing **sporozoites**.

A week later mosquito takes its next blood meal.

sporozoites in saliva passed to host infect liver form

merozoites multiply in rbc feed off Hb

Burst out 7-18d later: fever and flu-like symptoms.

Some form **gametes** enter mosquito completing life cycle.

WHO: DDT used to kill *Anopheles* successful until the **1970s**, DDT-resistant mosquitoes

1982: United States ban following campaign

1658: Jesuit Bark: Quinine: countess of Chinchon, wife of Peruvian viceroy cured of fever

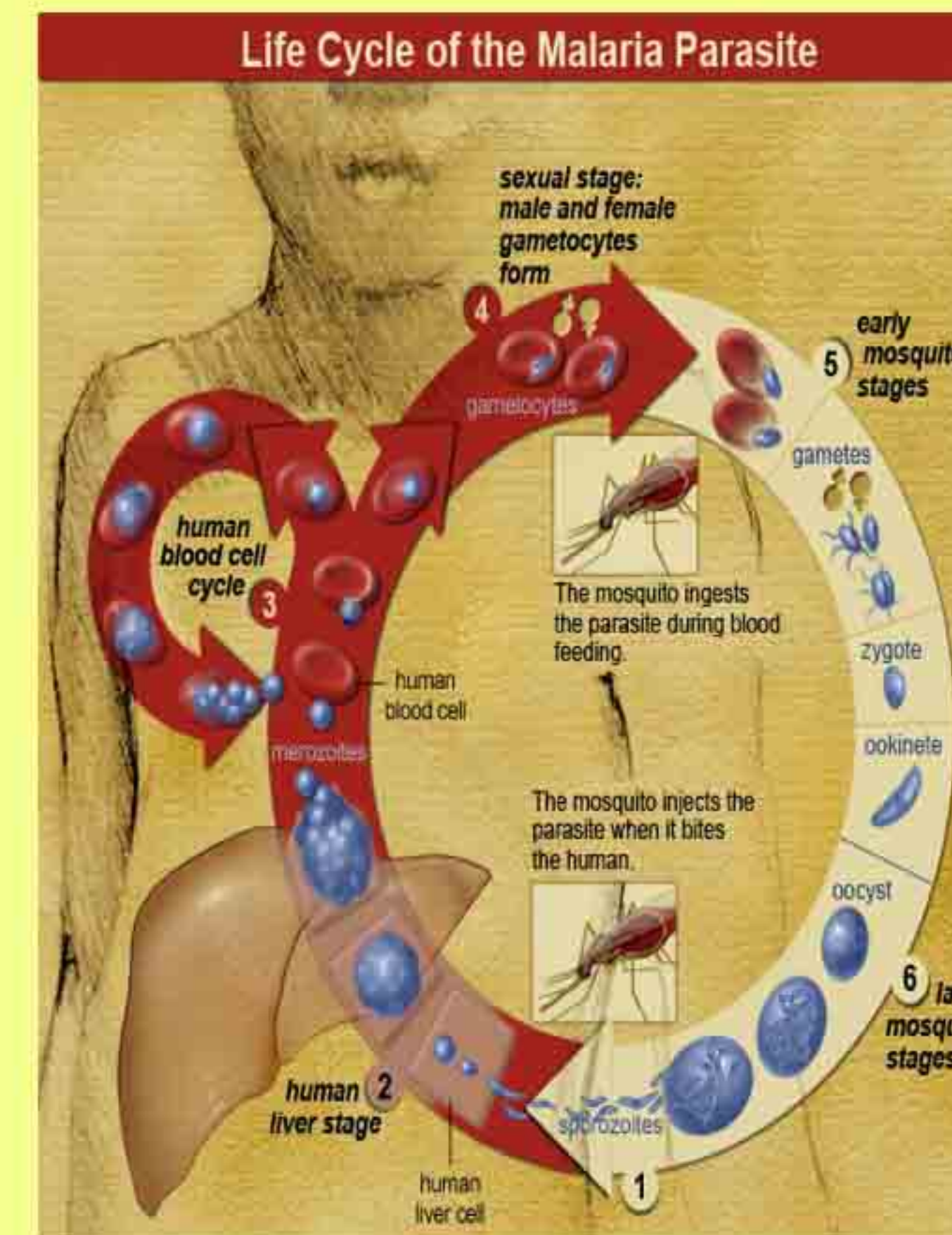
Derivatives after WW2 resistance

Artemether: derivative of artemisinin extracted from the sweet wormwood plant *Artemisia annua*,

Lumefantrine combined with Art kills residual parasites highly-effective 3d treatment with a cure rate of over 95%

2013: Cambodia New strains of *P. falciparum* resistant to artemisinin: The key drug against Malaria

Fake drugs: 40% in some areas



The moory soil. The watry atmosphere
With damp unhealthy moisture chills the air
Thick stinking fogs, and noxious vapours
fall,
Agues and coughs are epidemical;



Labourers sorting out cinchona bark on the Cinchona estate Tjinjiroean, West-Java



Plasmodium falciparum
Plasmodium vivax
Plasmodium ovale
Plasmodium malariae



Protozoa: Cerebral Malaria

Cerebral Malaria is often fatal, despite treatment.

These patients become comatose

Retina is the only part of the CNS in which the microvascular bed is visible to direct inspection.

Retinal changes in African Children with CM suggest that the cause is due to clogging of small vessels with clumps of red blood cells.

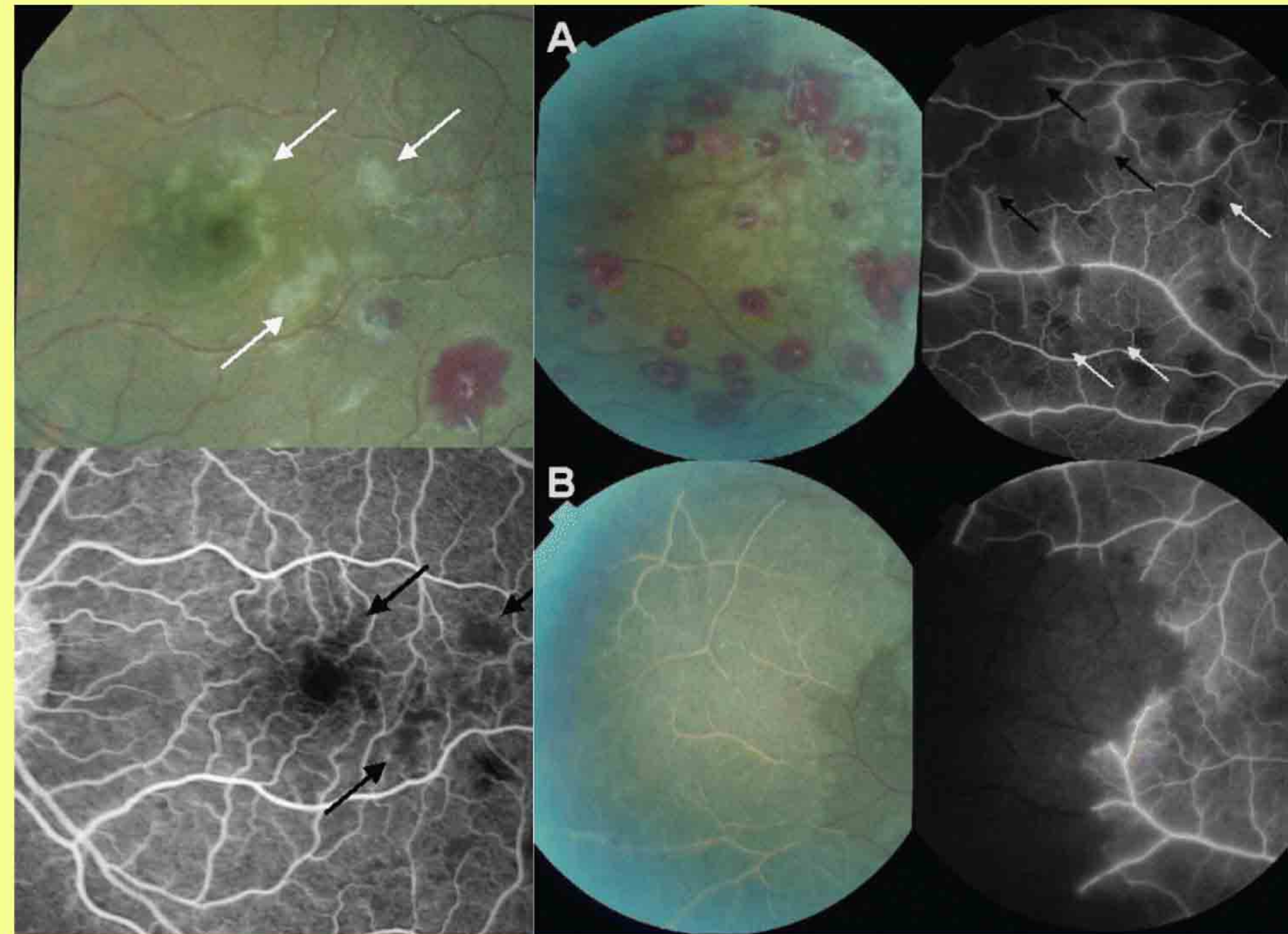
In endemic areas 1/3 of children with coma do not have malaria as the cause and the retinopathy may help distinguish them

Nick Beare: St Paul's Eye Unit Liverpool retinas of 45 children admitted to hospital in Malawi.

White opaque patches and whitened blood vessels unique signs of cerebral malaria.

Other signs include bleeding of the retina and swelling of the optic nerve.

Richard Maude: Trans R Soc Trop Med Hyg. 2009



Protozoa

Toxoplasmosis

1908: *Toxoplasma gondii* found in tissues of Comb rat in Pasteur Institute Tunis by Nicolle and Manceaux

toxo= bow or arc; plasma=creature

1923, Janku parasitic cysts in retina of infant hydrocephalus, seizures, and unilateral microphthalmia.

ubiquitous protozoan parasite infects many animals and one-third human population

Devastating ocular and CNS disease.

1 billion people seropositive for *T. gondii*,

11% USA population

80% developing economies

Cats primary source to human hosts.

Eating raw meat,

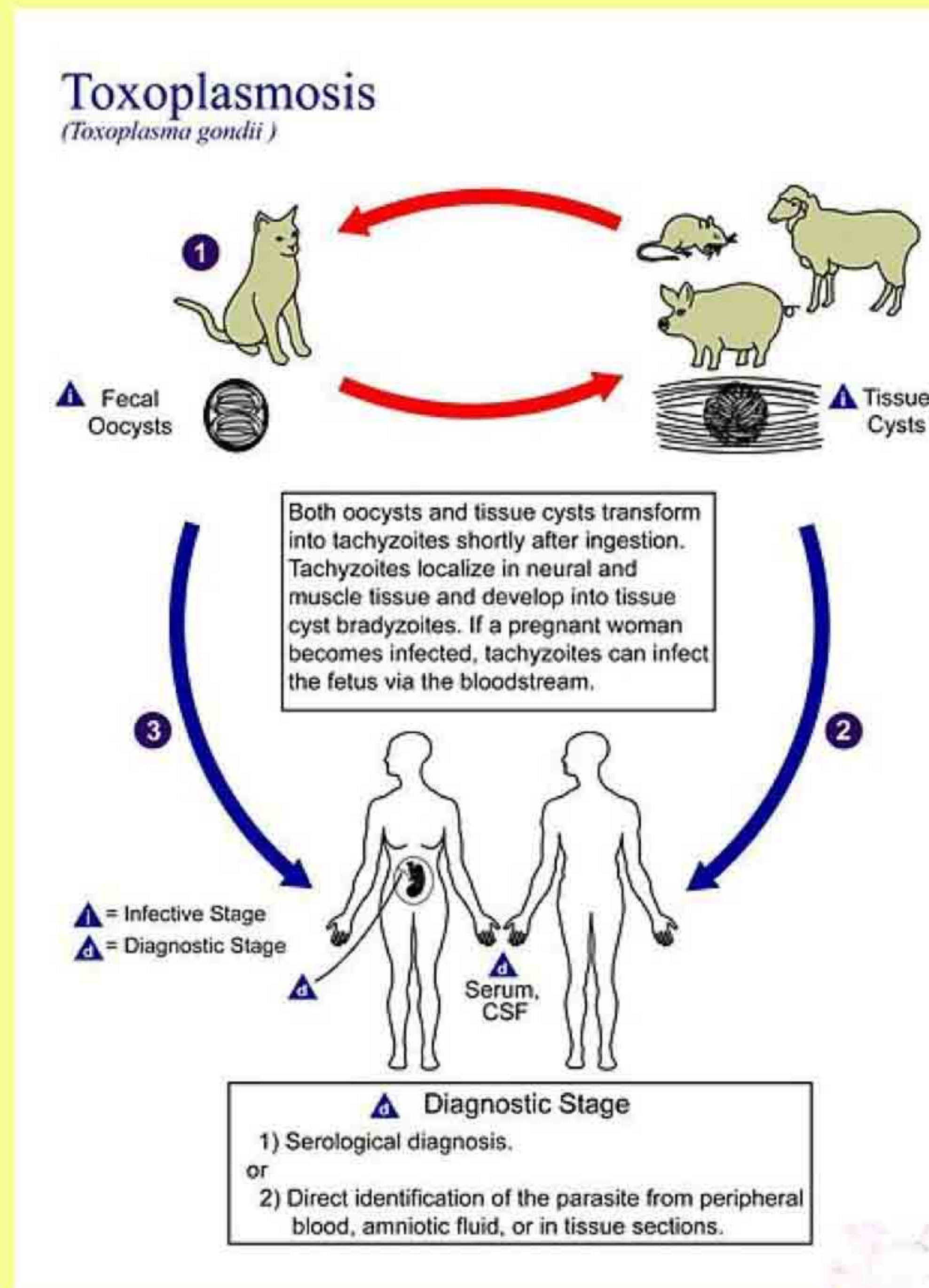
After ingestion, tissue cysts or oocysts invade host cells and differentiate into tachyzoites which divide rapidly within host cells.

Only 5% infections symptomatic: Lymphadenopathy

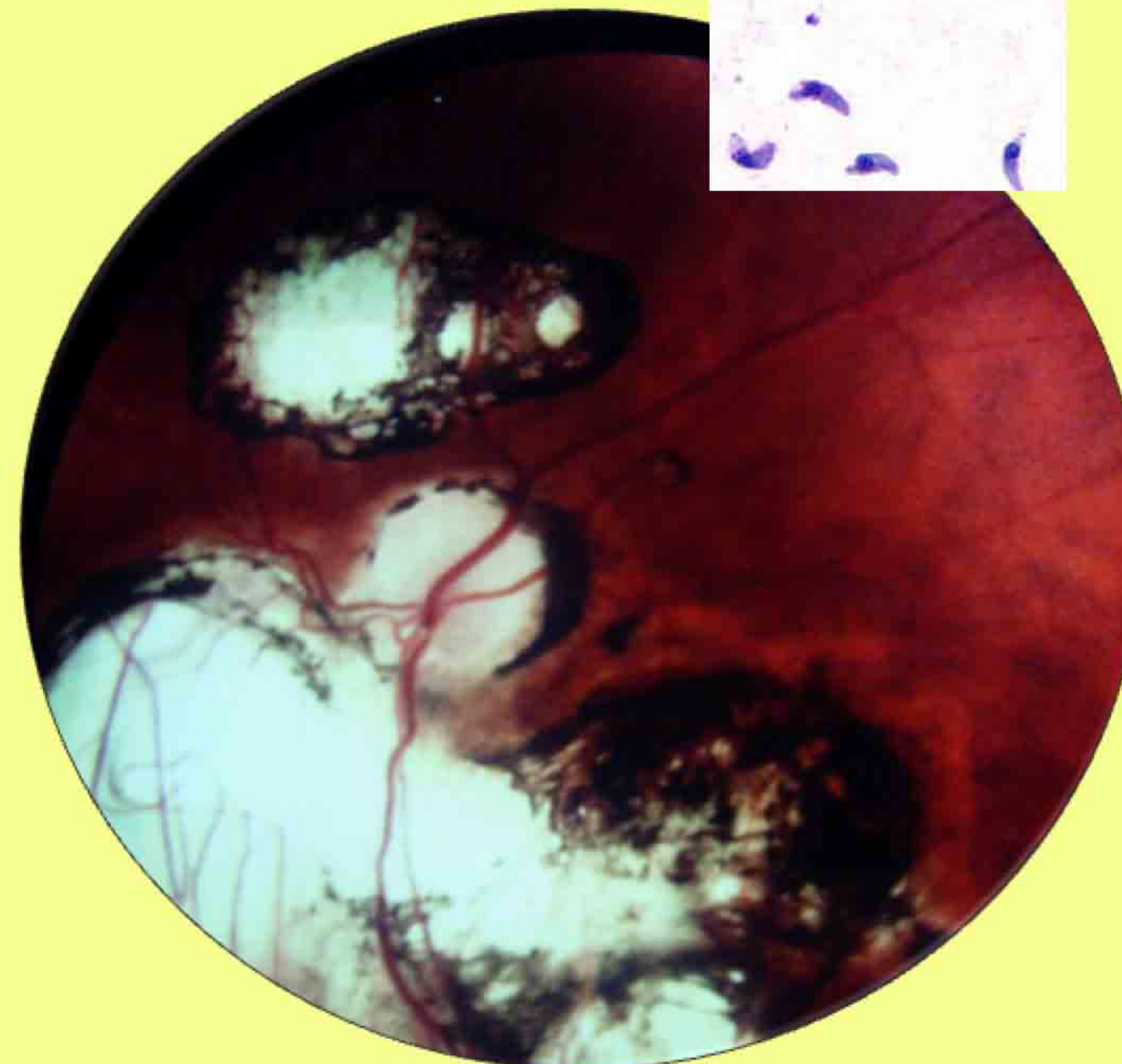
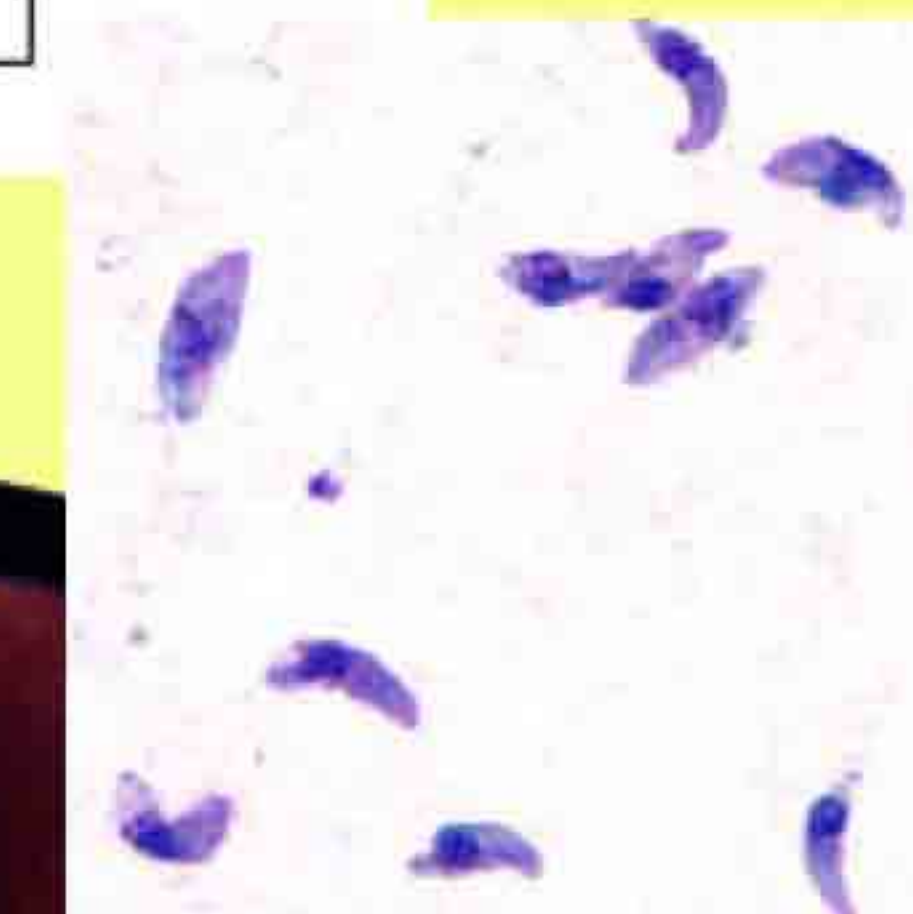
Immune reaction: tachyzoites become latent bradyzoites forming cysts in nerve and muscle tissue.

2–25% of people infected with *T. gondii* develop ocular lesions, making *T. gondii* the leading cause of blindness in South America

Main cause of posterior uveitis worldwide



Ctenodactylus gundi
Comb rat: comb like back paws
N. Africa
Used for Leishmaniasis research



Rx: oral pyrimethamine and sulfadiazine, plus systemic corticosteroid: TOXIC
trimethoprim/sulfamet
hoxazole/prednisone is an acceptable alternative
Endochin-like
quinolone effective against acute and latent toxoplasmosis in mice

Nematodes

νήμα thread

Roundworms

28,000 spp.

6,000 parasitic

Widely distributed and common

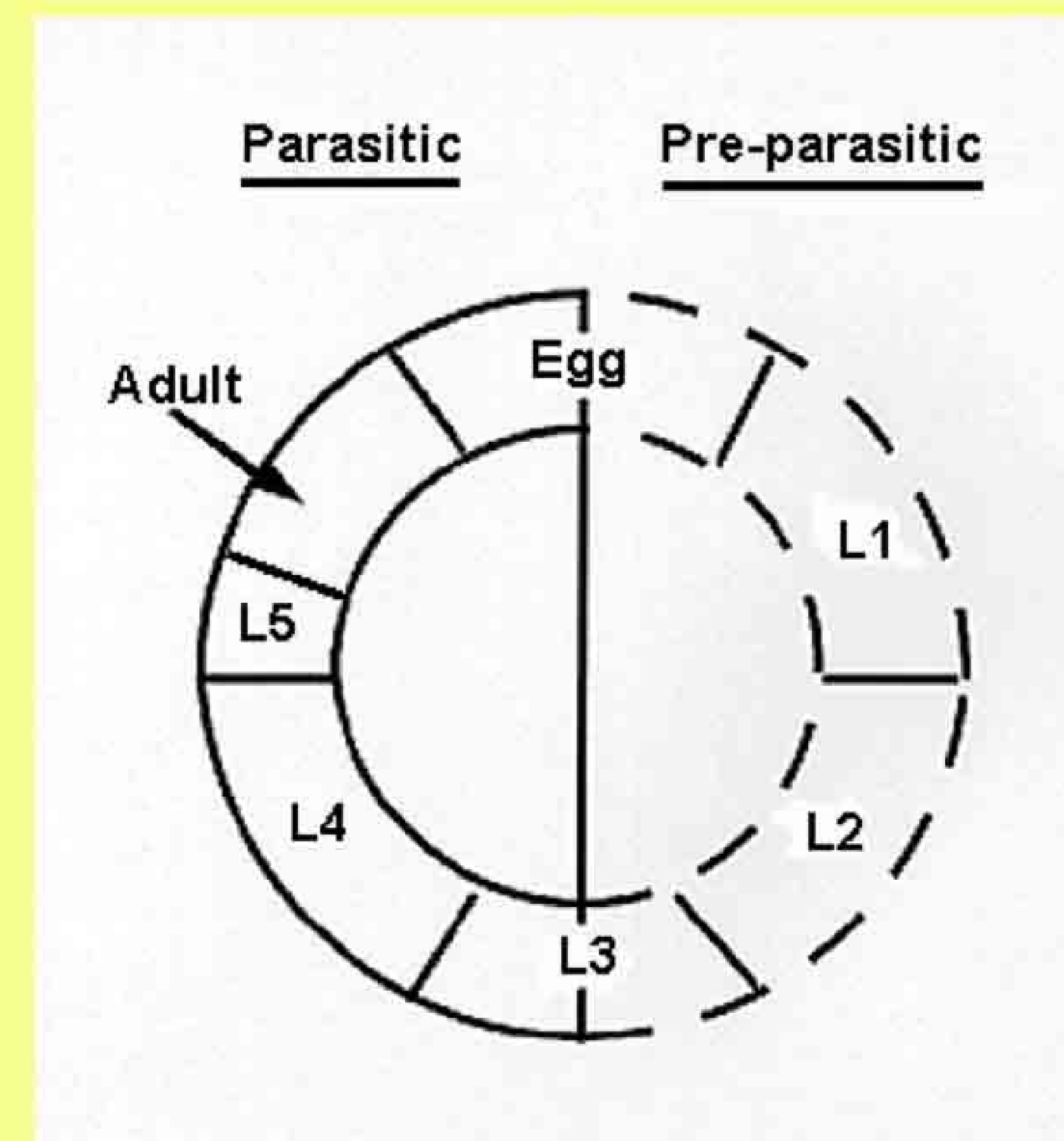
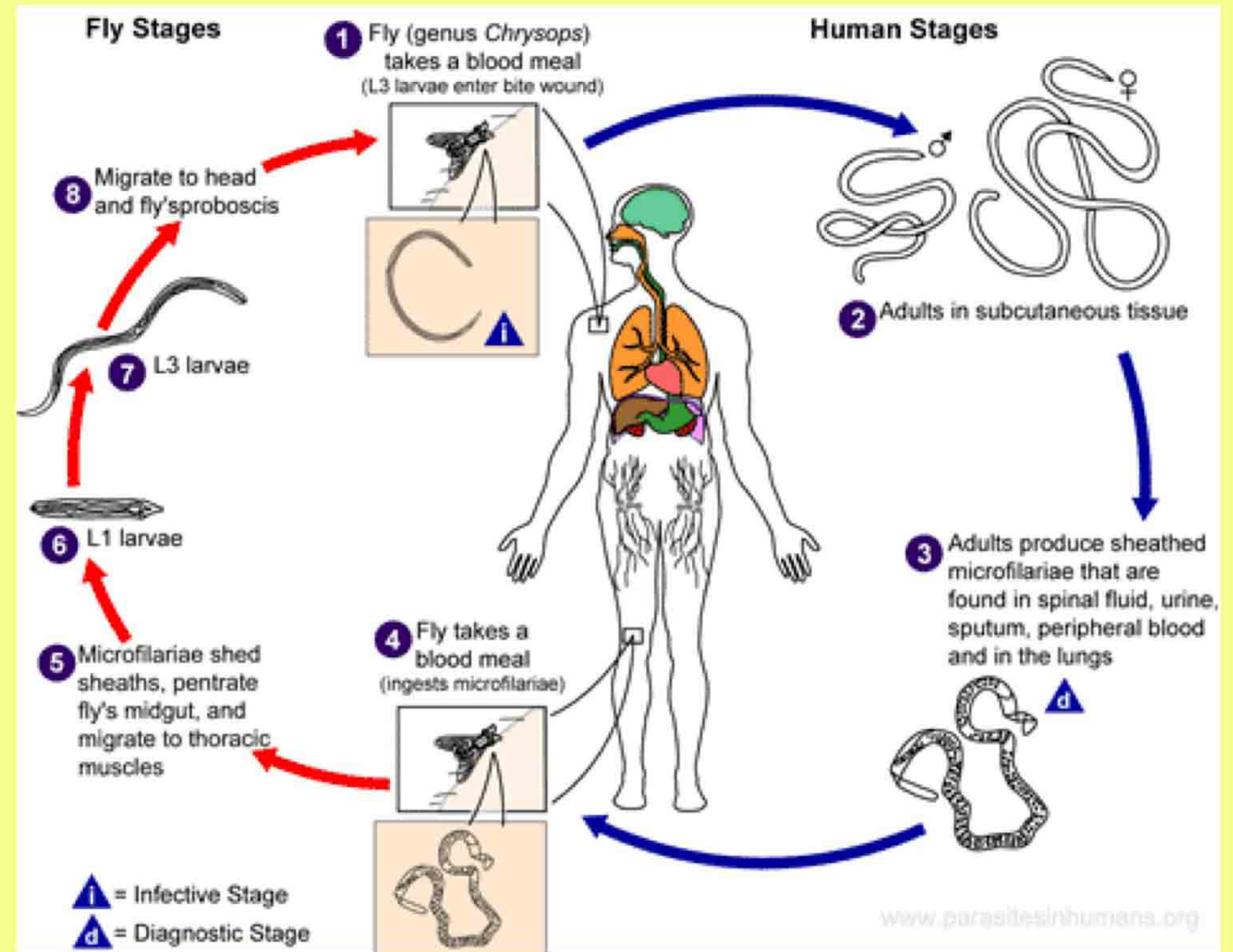
two phases, parasitic and pre-parasitic.

The parasitic phase takes place inside the definitive host

pre-parasitic phase occurs either

free-living phase in the external environment

inside a second intermediate host.



Toxocariasis

Caused by larvae (immature worms) of dog roundworm (*Toxocara canis*), or cat roundworm (*Toxocara cati*)

In most adult animals, full lifecycle does not occur, second stage larvae encyst after migration through the body

common in puppies

Larvae reactivated in pregnancy cross placental barrier to infect the pups

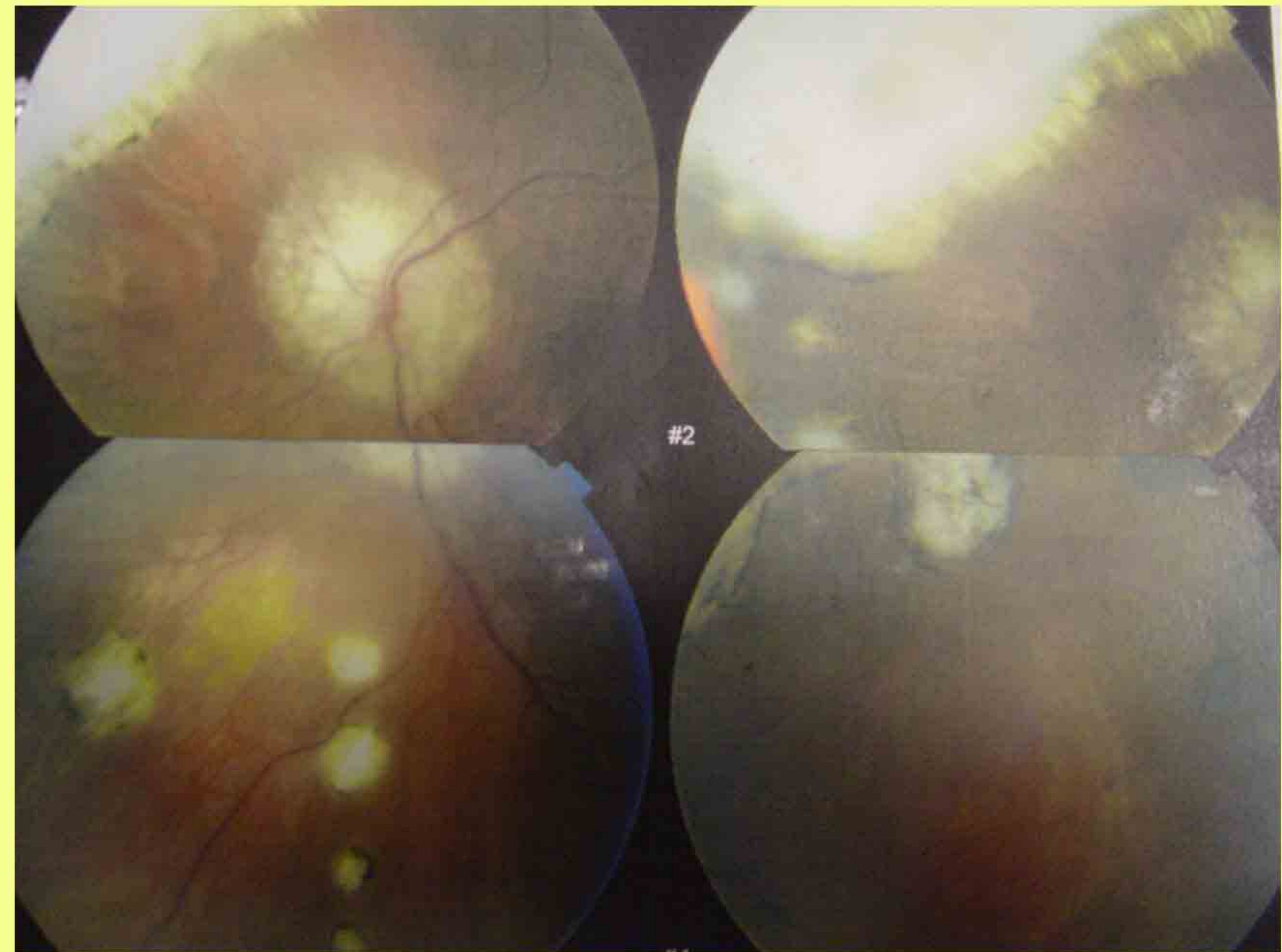
Infectious mothers, and puppies under five weeks old, pass eggs in their faeces
lay around 200,000 eggs per day

Humans accidental host:

larva can infect but not mature in humans.
migrate through the intestinal wall, travels in blood stream to various organs

Eosinophilic granuloma mass develops trapping larva, contain its migration.

public health importance as a cause of visceral larva migrans in man.



A cluster of nematodes, roundworm of dogs, *T canis*.

African eye worm

Loa loa: thread-like worm lives under the skin

1778, **Francois Guyot**: removed worms in eyes of West African slaves

1890: Ophthalmologist **Stephen McKenzie** identifies microfilariae

Bitten by infected *chrysops* deer and mango fly, painful: Lives in forested and swampy areas equatorial Africa but bites in open during daytime.

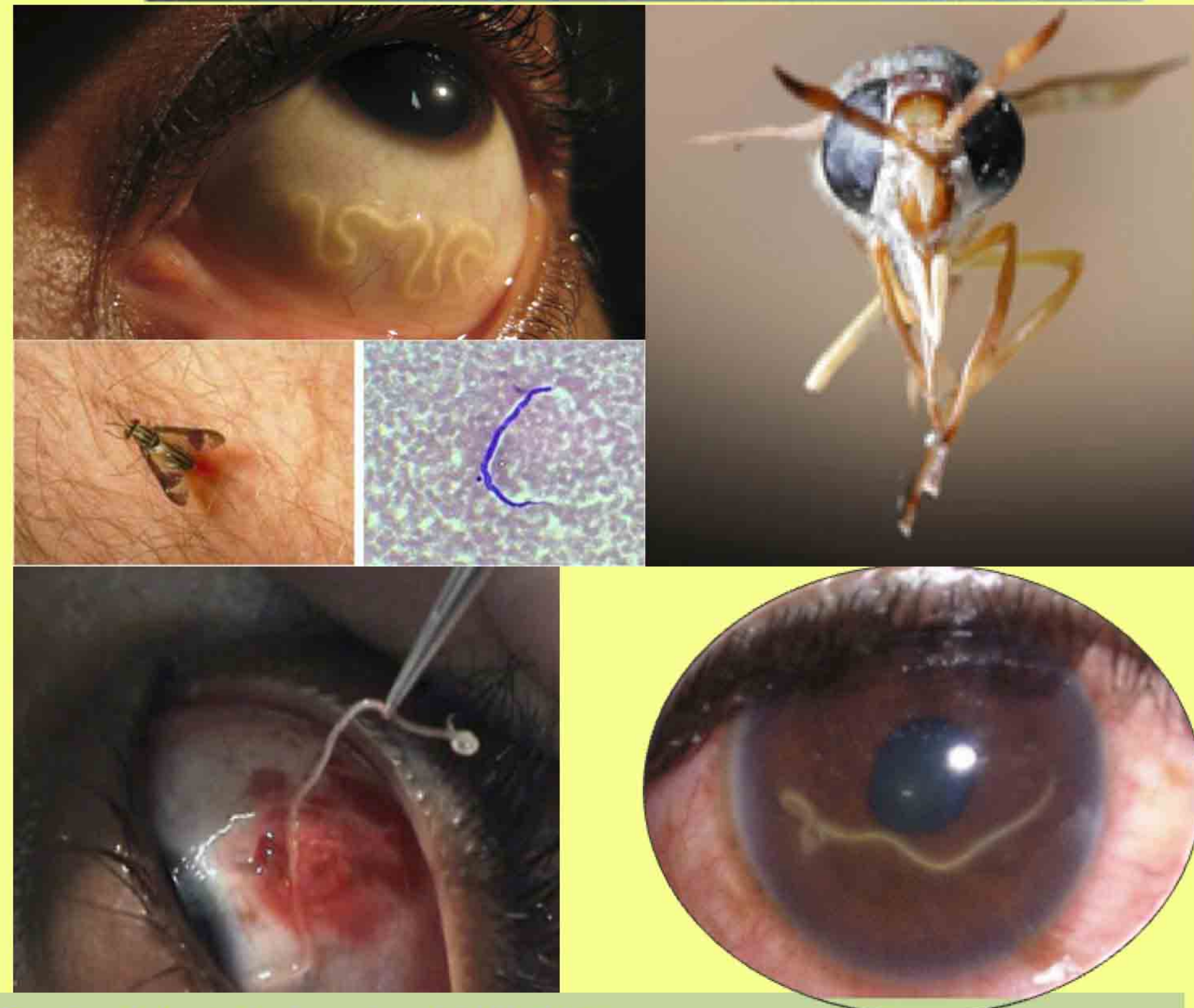
13m people infected

Over 4 years, larvae mature into adult worms, live for 17 years in a human, migrate up to 1cm/min subcutaneous tissues.

unnoticed until it enters the eye.

localized temporary allergic reactions (Calabar swellings)

Diethylcarbamazine: 6 mg/kg/d tds for 12 days kills the immature microfilaria in the bloodstream
surgical removal of adult worms from the eye



Ocular loiasis in London 2008–2009: a case series
G S Bowler, A N Shah, L A Bye and M Saldana

Onchocerciasis

Parasitic worm *Onchocerca volvulus*,
Transmitted by blackfly (Simulium). Breeds and
lives near fast-flowing rivers **river blindness**.

People living along these rivers receive about
10,000 bites per year

Itching skin and eye lesions.

Eye lesions occur after years not present in
young: "Lion's Stare".

Inflammation caused by death of larvae in the
eye 35% small opaque spots on the cornea.

Eventually becomes permanently cloudy

20% chorioretinitis

25% optic nerve atrophy

socioeconomic consequences

1970s, up to half of all adults in some
communities blind

Many abandon their ancestral homes; the
economic losses were estimated at US\$30
million.

Second leading infectious cause of blindness,
after trachoma.

2008: WHO ~ 26 million people infected

265,000 were blind

746,000 were visually impaired.



Nigeri: led through her village by
great granddaughter. Blind after
contracting onchocerciasis early in
life.

CREDIT: KATE
HOLT/SIGHTSAVERS



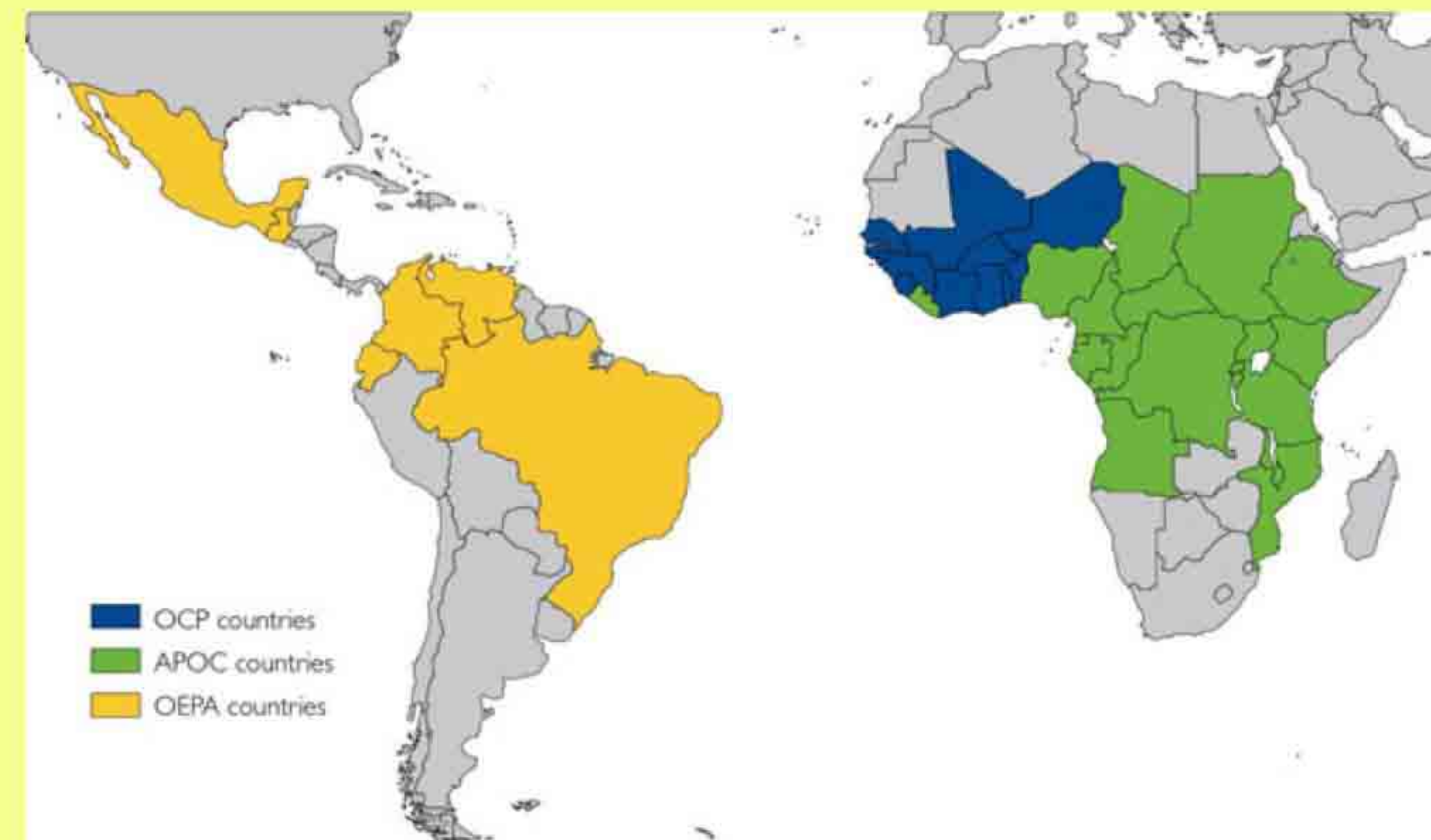
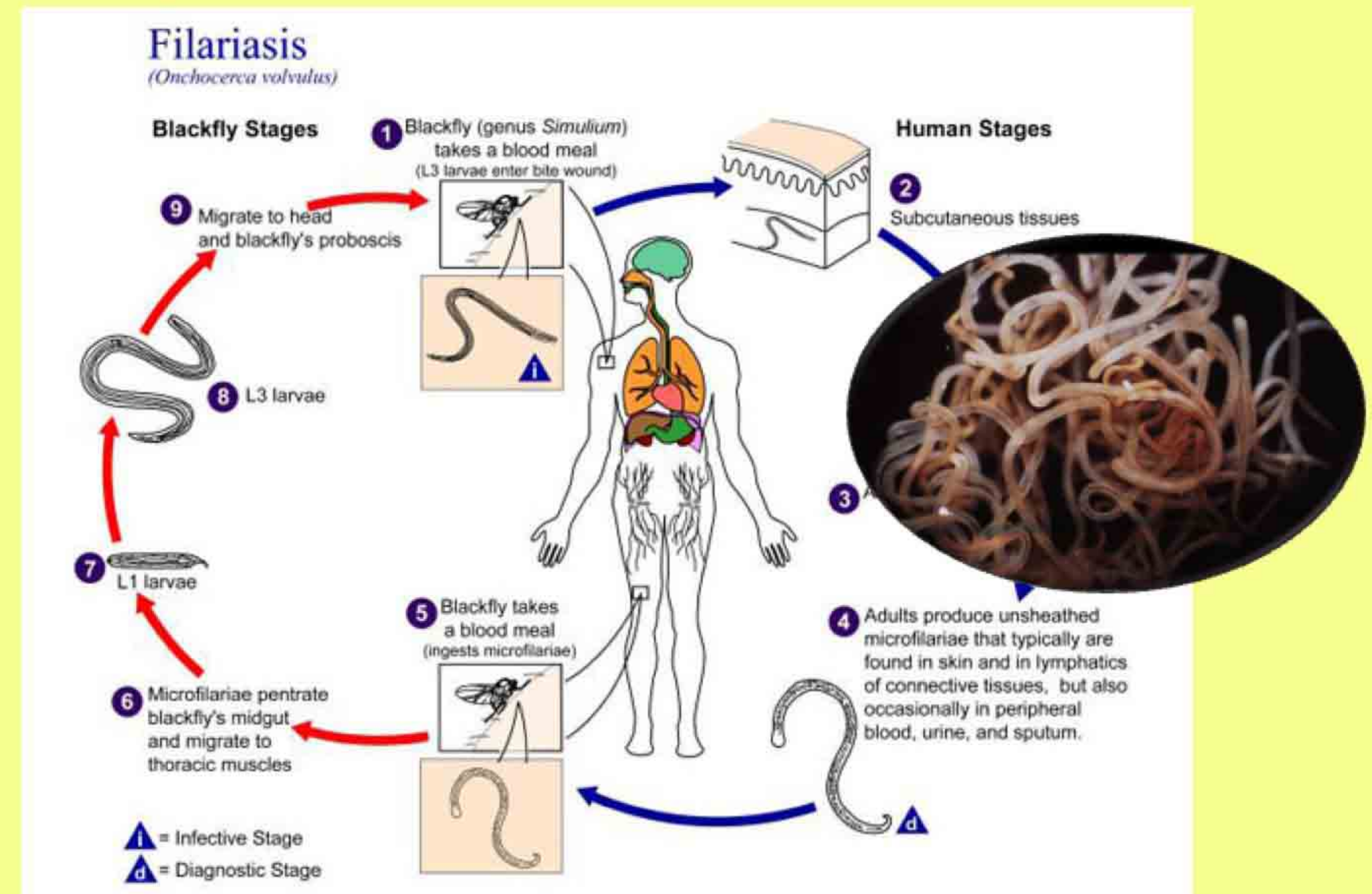
Control of River Blindness

Lifecycle: blackfly introduces larvae into human host
 Develop into adult worms 50” long. Reside in nodules in subcutaneous connective tissues, live for 15 years.
 Produce 1,600 larvae, (microfilariae)/day.
 Live for 2 yrs Migrate through body.
 Most destined to die, produce local inflammatory reaction
 Blackfly ingests microfilariae migrate from midgut to the thoracic muscles develop into third-stage infective larvae migrate to the blackfly’s proboscis

Onchocerciasis Control Programme

spraying insecticide preventing transmission of the parasite. Multimillion \$ contracts to US helicopter and insecticide companies.
 35,000 miles sprayed weekly for 14 years.
 OCP officially closed in Dec 2002 after stopping the transmission of the disease in all the participating countries except Sierra Leone, decade-long civil war.
 larviciding using environmentally safe insecticides, is **not** feasible or cost-effective.

1995: WHO & World Bank in 1995, program expanded **African Programme for Onchocerciasis Control (APOC)**. control the worms in humans through community-directed treatment with Ivermectin in 19 countries.



Ivermectin: Wonder drug

Drugs to eradicate adult worms too toxic

Diethylcarbamazine microfilaria death inflamed eye

Suramin: 50 yr old anti-sleeping sickness drug

Ivermectin: Derived from Japanese soil bacterium *Streptomyces avermitilis*;

Kills circulating microfilariae & those still in adult female worms;

Merck. Mectizan Donation Program, free drugs to any organization that capable to distribute ivermectin.

Blockbuster drug \$1b vets

Standard treatment is once a year, but infected people can be treated up to three times in one year.

APOC: aims to eliminate clinical onchocerciasis and interrupt transmission using biannual ivermectin treatment to cover 85% communities.

Since adult worms are not killed and will continue to reproduce, treatment must continue for 10 to 15 years.

Danger people who are co-infected with both *Onchocerca* and *Loa loa* receive **ivermectin** treatment.

The drug kills the immature worms of both species in the host's bloodstream, severe reactions including encephalopathy, leading to coma or even death



Microbiome

Life on Man

The body composed of **100 trillion human cells**.

10-20 X that number of bacteria.

large intestine: trillion bacteria per ml of fluid.

10 billion organisms on lining ($10^{10}/\text{cm}^2$)

Human skin: 50 million ($5 \times 10^7/\text{cm}^2$)

Entire microbiome only weighs 7.1 oz to 3 Lb.

Hundreds of different species. 80 in the mouth alone

NORMAL FLORA ECOSYSTEM

Indigenous microbiota

Synthesize and excrete vitamins,

Vitamin K; B12, Germ-free animals deficient dietary supplementation.

Prevent colonization by pathogens

Germ-free animals infected by only 10 *Salmonella* cells: Normal dose 10^6 cells.

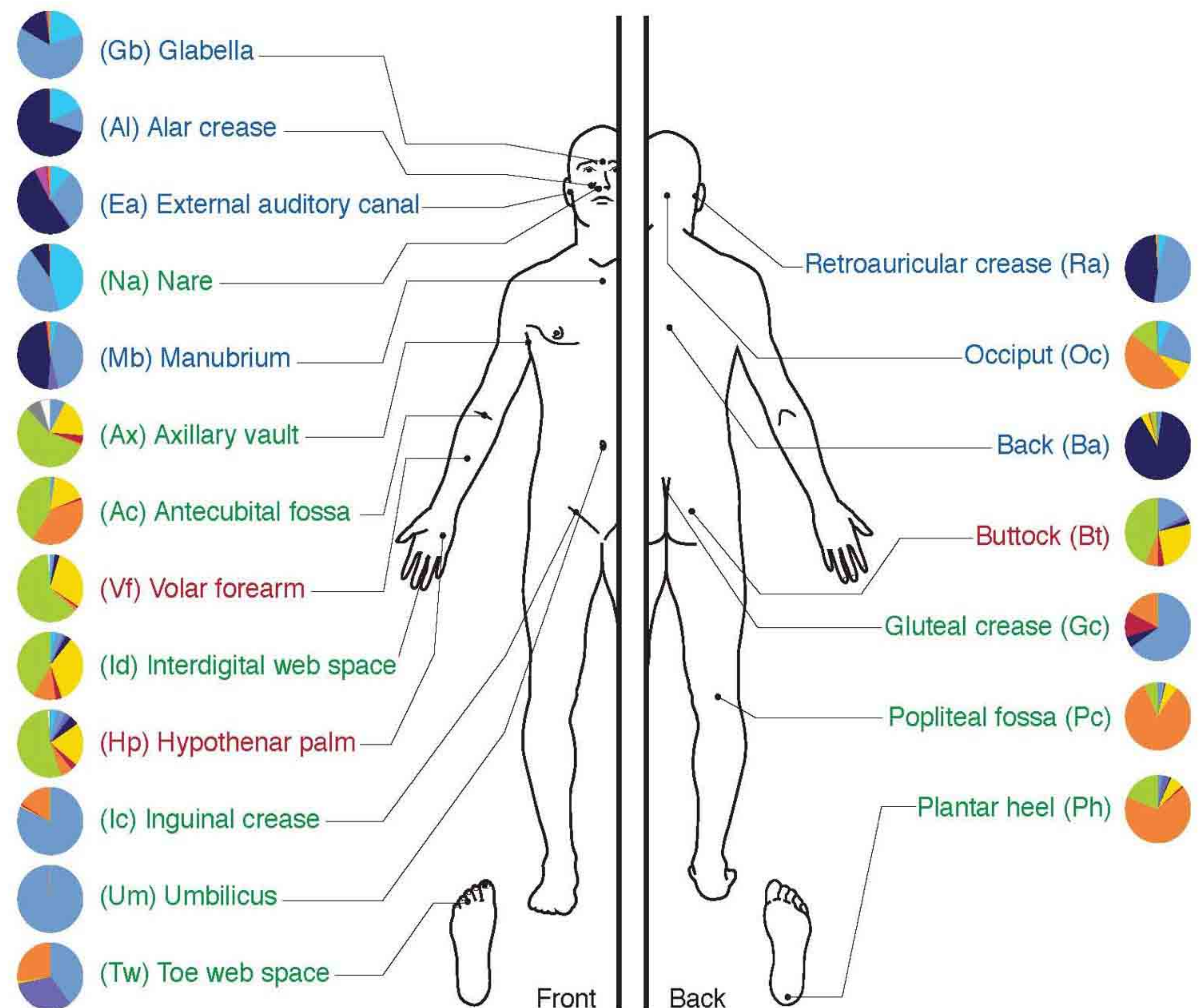
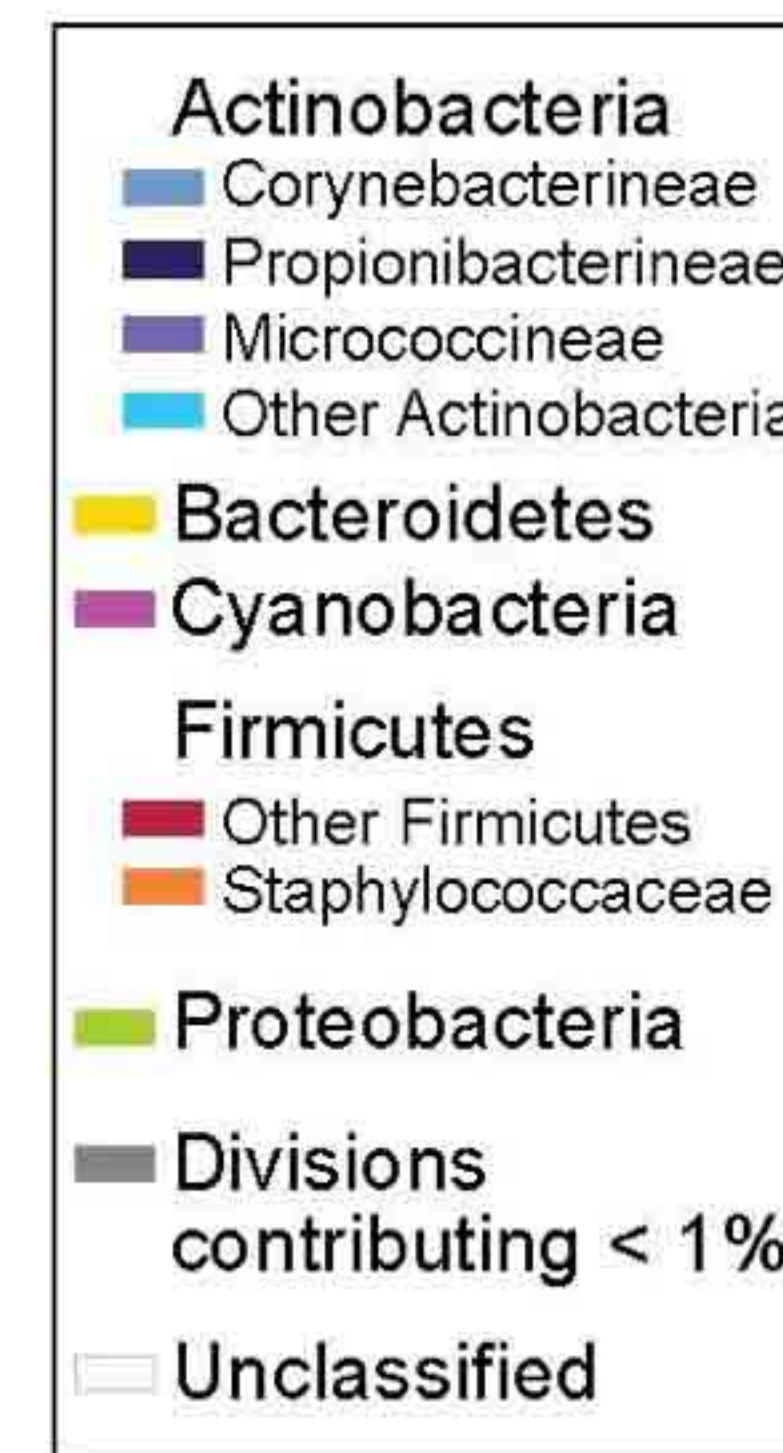
Intestinal bacteria produce nonspecific fatty acids peroxides, bacteriocins, inhibit or kill other bacteria.

Stimulate the development tissues: lymphatic tissue in GI tract. Caecum of germ-free animals is enlarged, thin-walled, and fluid-filled

Stimulate the production of natural antibodies

Also lot of viruses

Mites, lice, protozoa, worms.



Antimicrobials:

Inorganic Arsenic As

Gk: 'arsenikon' 'potent' 20th most abundant element in earth's crust.

55AD: **Nero** poisoned Britannicus to secure throne

White arsenic acquired a reputation, 'poudre de succession'

Hippocrates (460-370 BC)

realgar As_4S_4

orpiment: As_2S_3

Paracelsus: All substances are poisons right dose differentiates a poison and a remedy

1781: Thomas Wilson: London Ague drops

1786: Thomas Fowler's solution 1% potassium arsenite (KAsO_2), substitute for a patent "tasteless ague drop".

1845: Fowler's solution was a leukemia treatment.

1950s, Fowler's solution; *Kali arseniatum*, US for malaria, and syphilis

Joseph-Noël Sylvestre: Locusta testing in Nero's presence the poison prepared for Britannicus



Bronze of **Claudius**
River Alde near
Saxmundham, Suffolk
(BM).



Messalina holding her son
Britannicus, Louvre



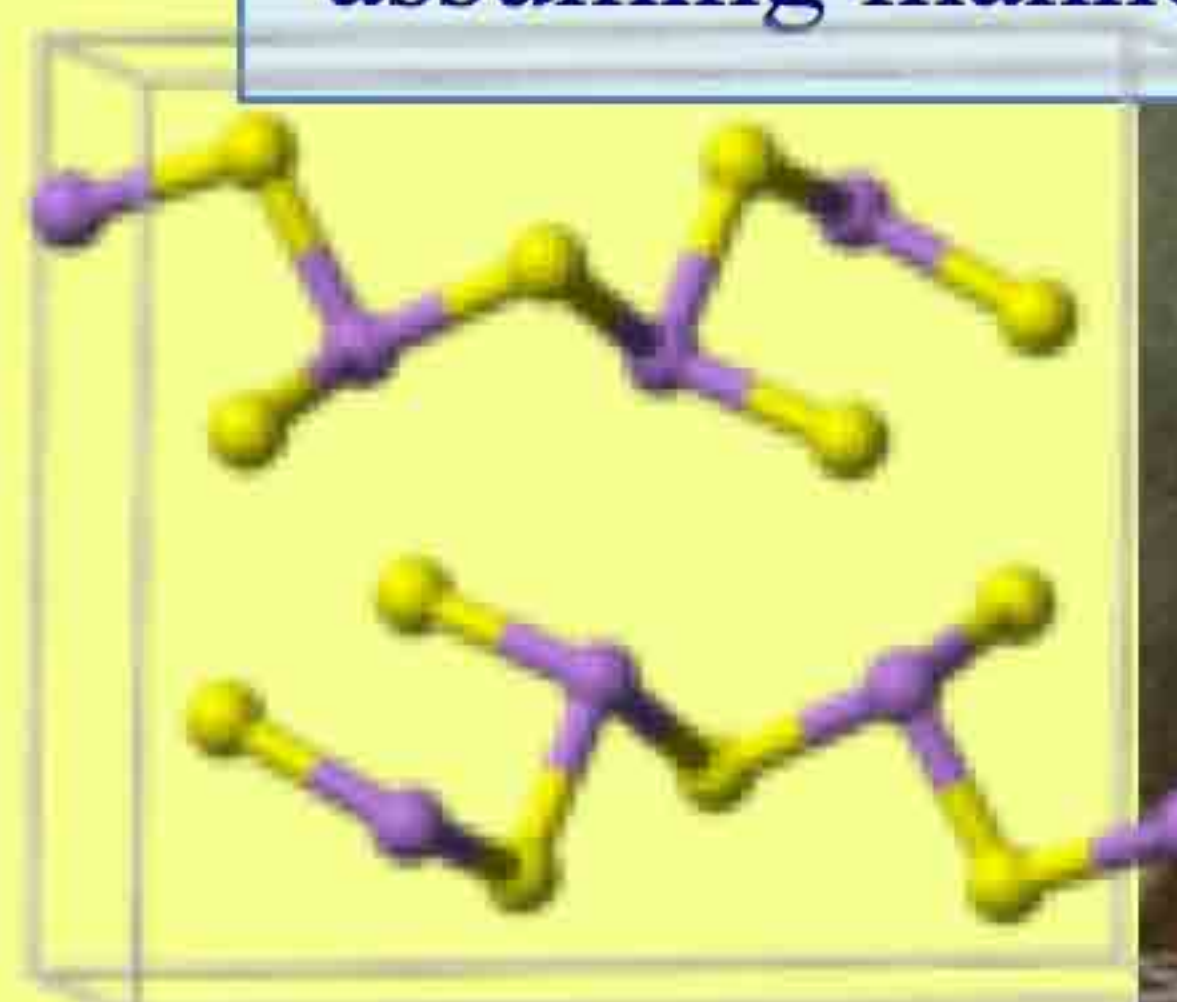
Agrippina, mother
of **Nero**, National
Museum, Warsaw

Britannicus: son of **Emperor Claudius** 3rd wife **Valeria Messalina**; notorious nymphomaniac disguised by an ash-blond wig stage name Lycisca ("Wolf Girl") plotted against husband, executed.

4th wife Agrippina, adopting her older son **Nero**.

54 AD: **Locusta** hired by **Agrippina** to supply poisoned mushrooms to murder **Claudius**. Convicted, Nero rescued her from execution requesting she supply poison to murder **Britannicus**.

Britannicus asked for his wine to be cooled, poison in cold water bypassing the taster: fatal, fell to the floor foaming at the mouth. He died, one day before his 14th birthday, less than a month before assuming manhood, and 4m after his father's death



Organic Arsenic

Breinl and Thomas Liverpool School of Tropical Medicine used Pierre Béchamp's aniline-Arsenical **Atoxyl** for experimental sleeping sickness

50x less toxic than Arsenic; blindness optic atrophy

Paul Ehrlich theorized a drug could be discovered with antimicrobial activity without killing the human **Magic Bullet**

1910: Arsphenamine, (Salvarsan) the arsenic that saves first effective treatment for syphilis, & for trypanosomiasis

Neosalvarsan: Easier to use

Phenylarsonic acid: closely related to Salvarsan

stimulates angiogenesis, improves the colour of chicken meat! became the major additive to chicken feed.

2006, 70% of the 9 billion broiler chickens produced annually in the US fed **roxarsone**.

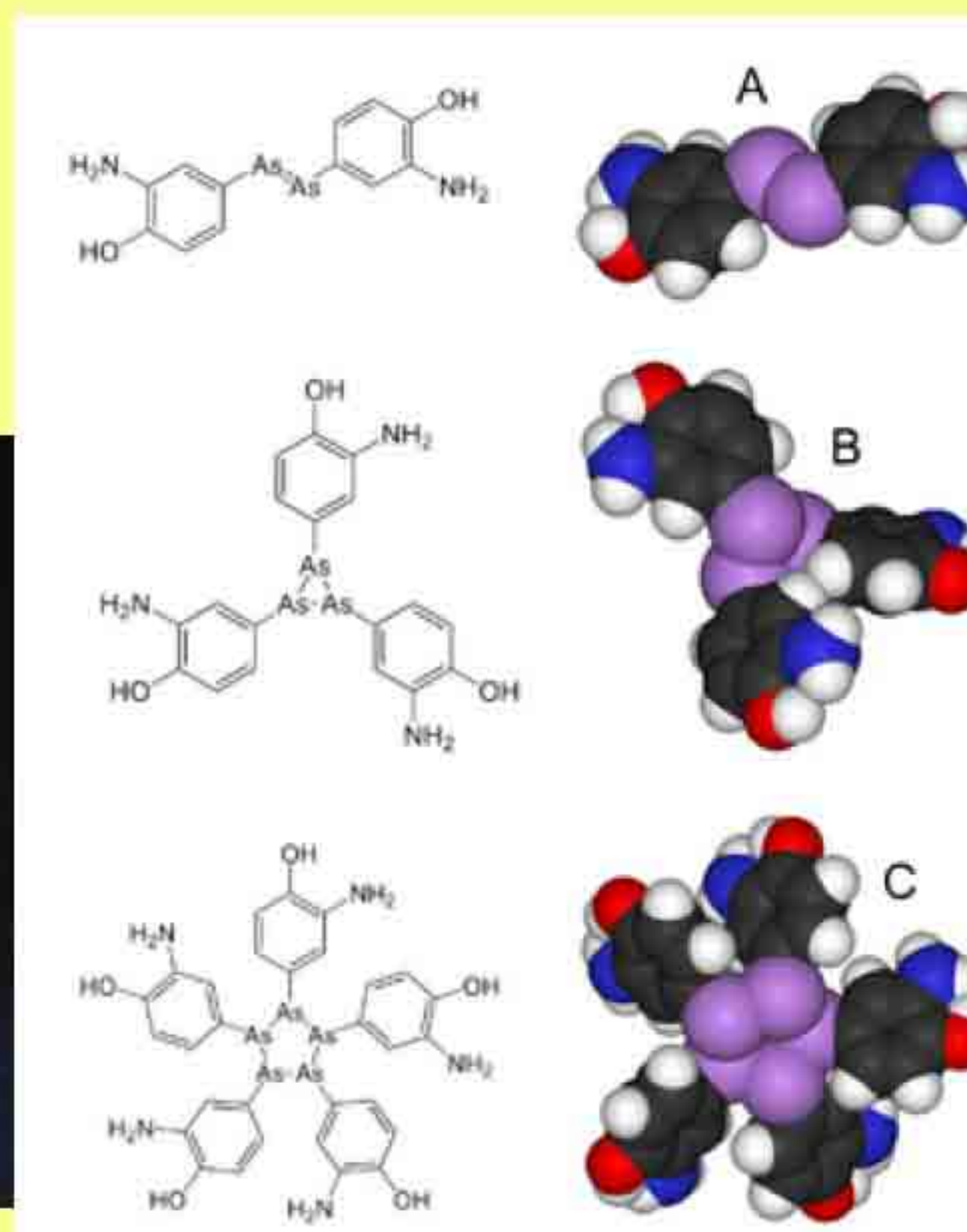
Breast meat from conventionally produced chickens x3 more inorganic arsenic than meat from organic chickens

Organic → Inorganic in gut. Pellets from faeces used as fertilizer. Potential threat to groundwater. Potential carcinogenesis

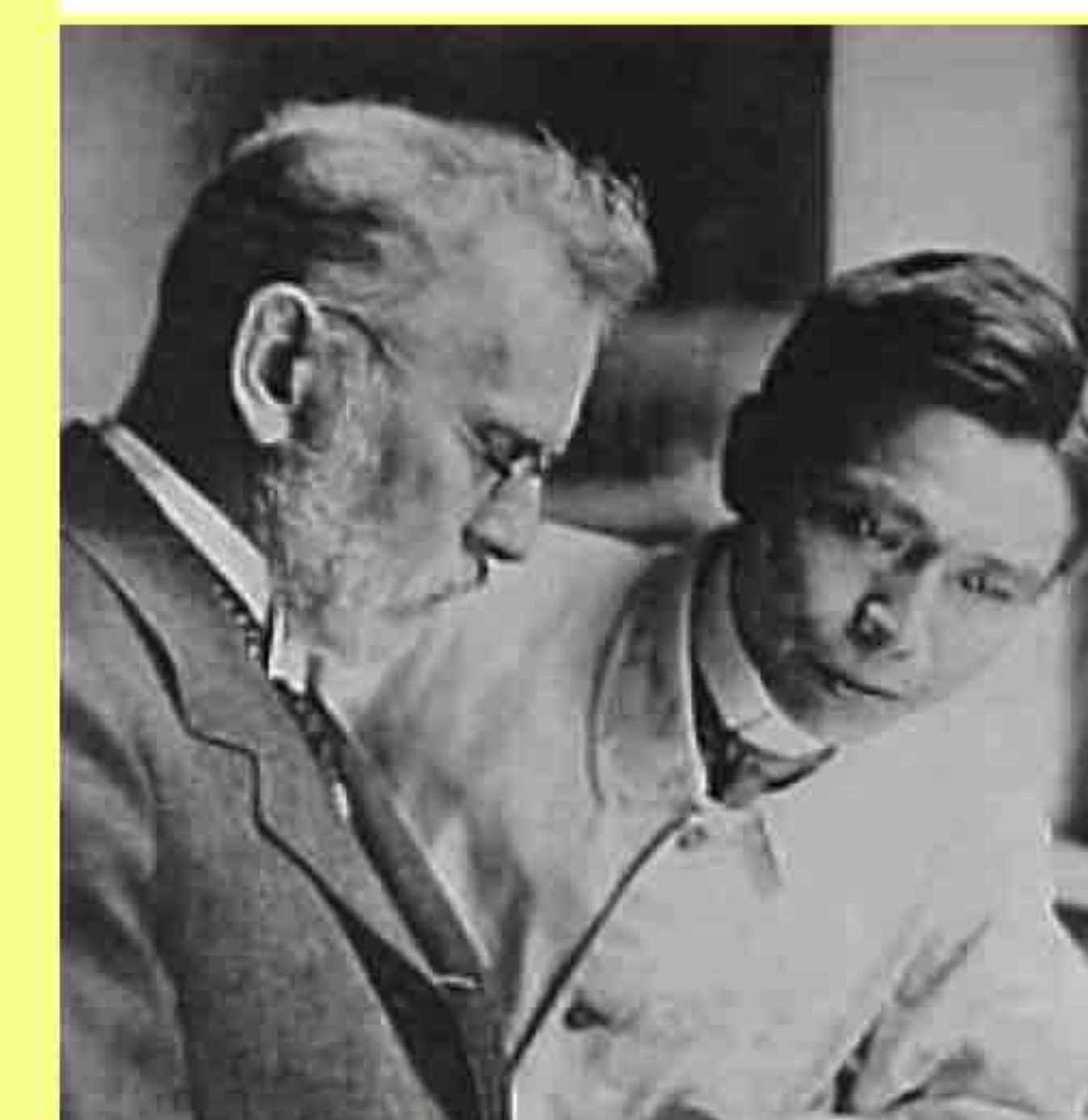
2011: Pfizer stops manufacture.

Still allowed and available

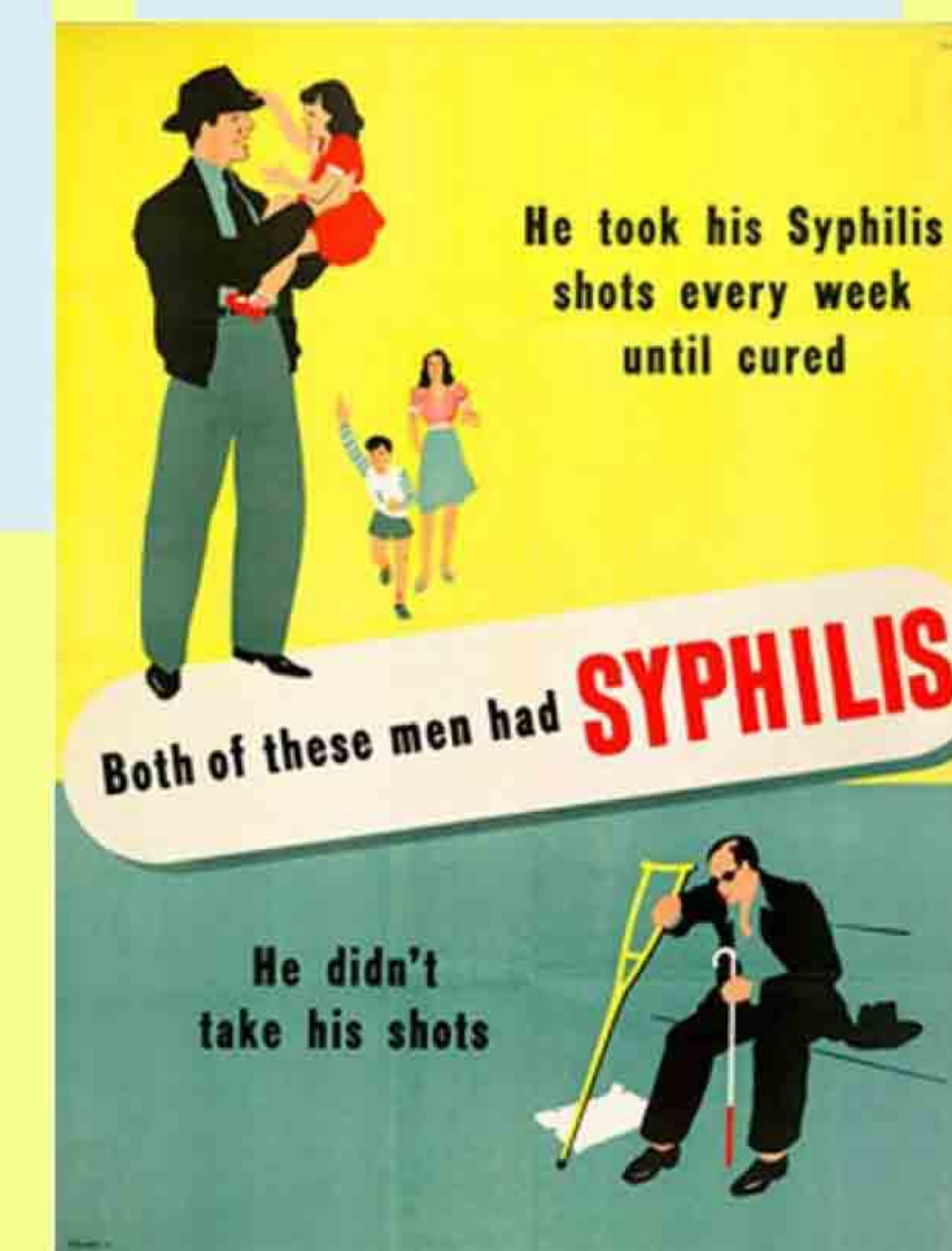
Banned in EU.



There is not a drug used in the treatment of syphilis that is not a rank poison. Such technique is required that, if results are not favorable — the disease is not cured — it is because of 'faulty technique.' The sun, moon and stars may vary in their courses, but Paul Ehrlich's remedies cannot fail, unless the technique is blunderingly carried out! **And the great medical profession** falls for this palpable fraud — this Germanic medical camouflage!" Dr. Tilden



Paul Ehrlich
Dr. Sahachiro Hata



Sulphonamides

Synthetic antimicrobials contain the sulfonamide group

Bayer AG-IG Farben. Coal-tar dyes bind to bacteria and parasites might target harmful organisms

1932: Gerhard Domagk Fought at Ypres, finally found one that worked: A red dye synthesized by Josef Klarer inhibited mouse bacterial infections

Prontosil: dyed skin red

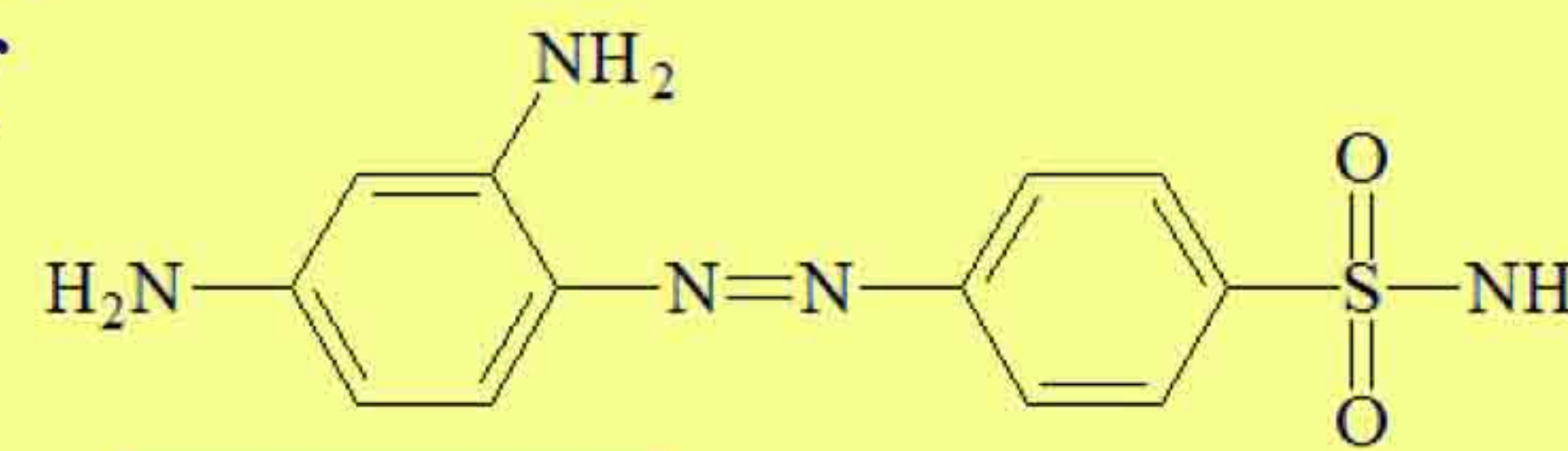
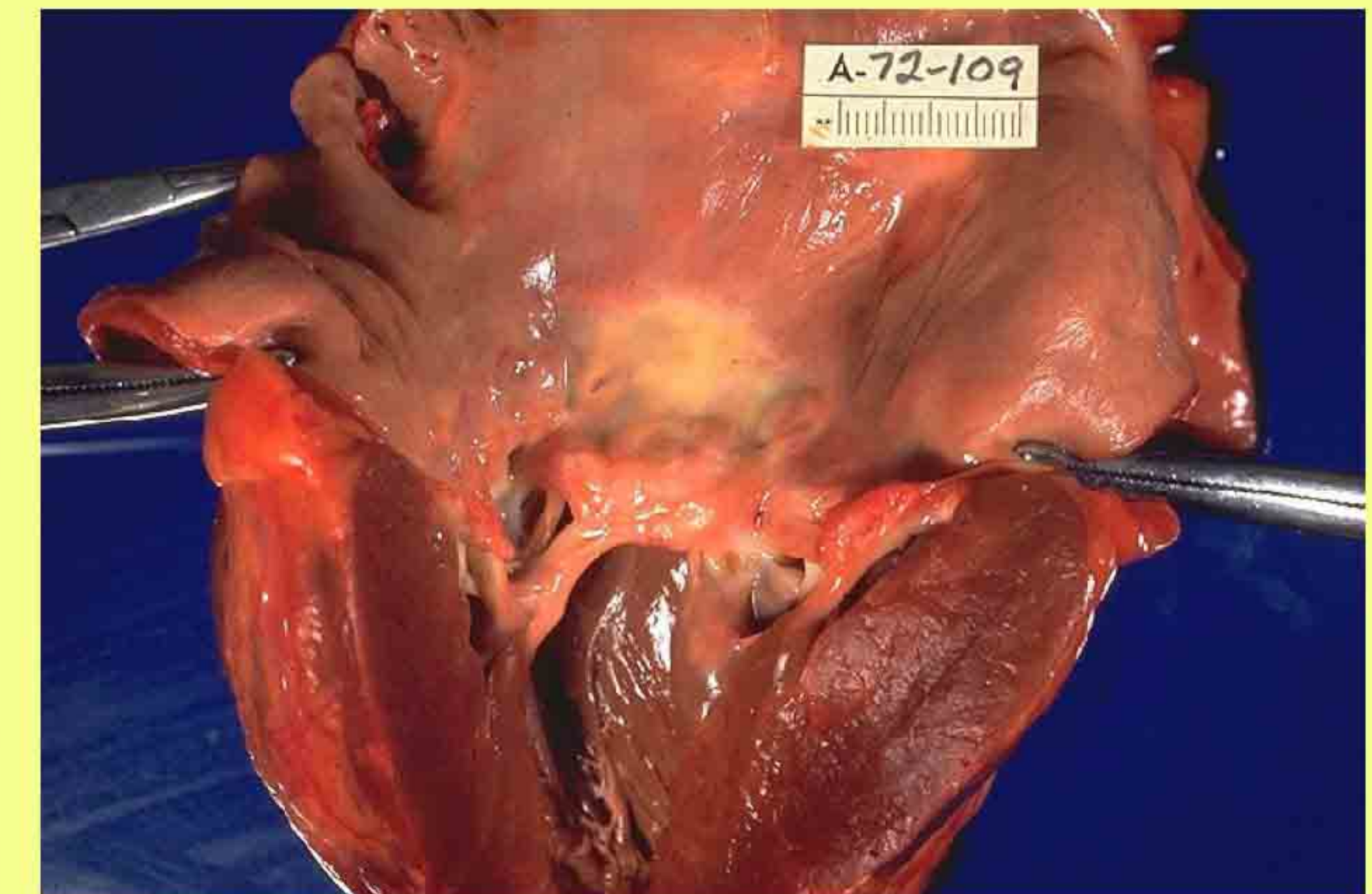
1939: Accepts Nobel Prize only to be arrested by Gestapo. (pacifist Carl von Ossietzky 1936 Peace prize, now in concentration camp)

1935 Leonard Colebrook Student of Almroth Wright at Mary's. Cure for puerperal fever. 38 pts

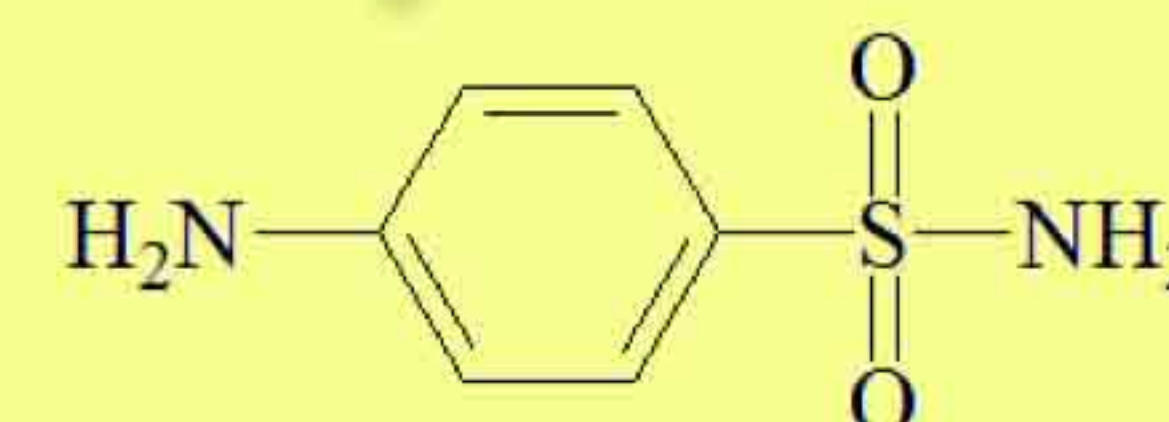
Isolation of burns patients reduced Strep contamination from 83% to 5%

Pro-drug of already known **sulfanilimide** off-patent rush of me-to drugs; **elixir sulfanilimide** disaster of 1937; 100 child deaths from ethylene glycol

1936: Franklin Delano Roosevelt, Jr: strep throat life-threatening complications. Saved with Prontosil Treatment prevents **rheumatic fever** Occurring 20d later and cardiac complications 5% mortality. 2010 globally: 345,000 deaths, down from 463,000 in 1990 due to antibiotic use.



Prontosil



sulfanilimide

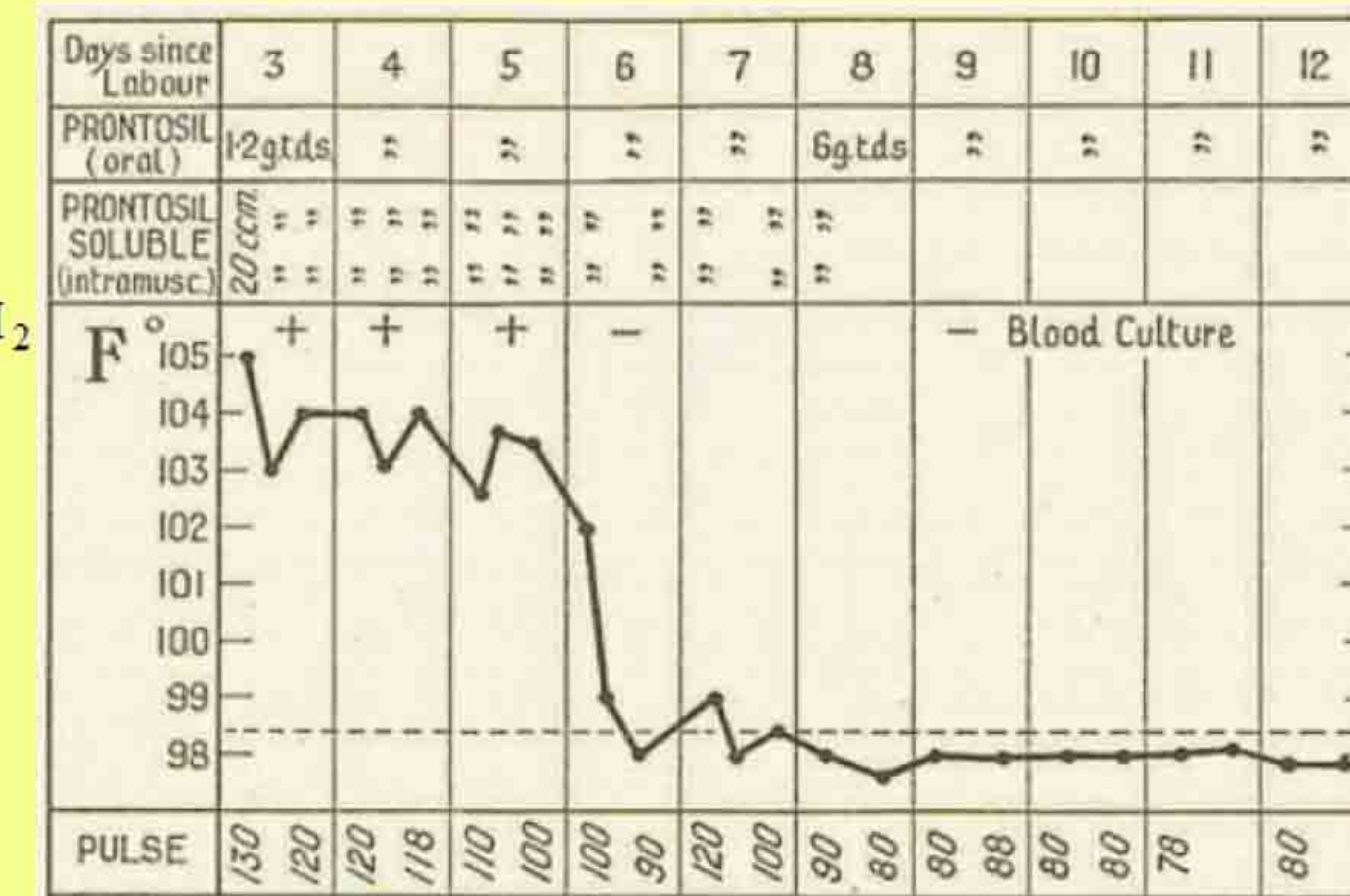


Chart showing a typical scheme of dosage in a case of puerperal septicemia.



Sulphonamides: New versions

M&B 693 (**sulfapyridine**), made at the Dagenham lab of May and Baker

G.M. Evans: Birmingham, 100 patients lobar pneumonia mortality rate 78% to 8%.

Oct 1938, May and Baker licensed Merck USA. preferred treatment for pneumonia, saving 33,000 a year in the US alone.

1943: Winston Churchill: Pneumonia. "This admirable 'M+B' (**Sulphapyridine**) from which I did not suffer any inconvenience, was used at the earliest moment and after a week's fever the intruders were repulsed."

WWII, each G.I. carried a first-aid pouch containing 5g sulfa powder and a dressing bandage. Whenever anyone was wounded, the sulfa powder was sprinkled into the wound. Medics carried sulfa pills too.

Use today limited: Resistance and side effects

Malaria and Toxoplasmosis: sulfadoxime and pyrimethamine (*Fansidar*)

Co-trimoxazole UTI

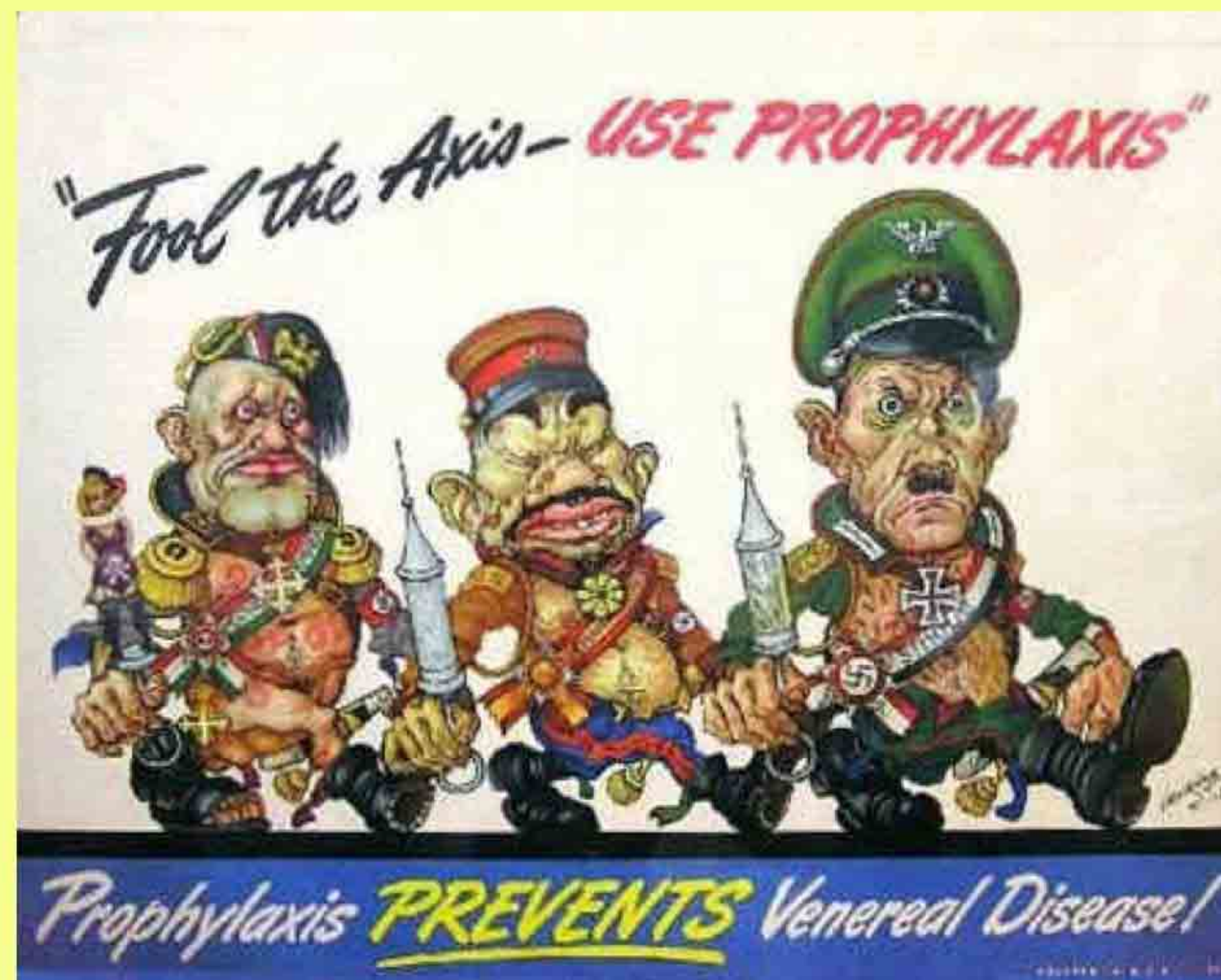
NSAID, Diamox, Azopt,



allowed to drink only weak whisky and soda and not to smoke at all. No cigars. He is quoted as saying: "Dear Nurse, pray remember that man cannot live by M & B alone."



US Army adopted two Sulfa Drugs; **Crystalline Sulfanilamide** and **Sulfadiazine Tablets**.



Arthur Szyk caricature:



Every G.I. was issued with an **Individual Chemical Prophylactic Packet** 1 Tube containing 5 Grams of Ointment (30% Calomel + 15% Sulfathiazole) Direction Sheet Soap Impregnated Cloth Cleansing Tissue

Penicillin

Sir Alexander Fleming, 1881- 1955 Q St Mary's
WW1 battlefront experience bacteria main killer
1923: discoveries enzyme lysozyme

1928: more than 650 penicillium moulds, few make penicillin. *Penicillium notatum*

WW2 concerted research at Oxford to purify the mould juice and extract the penicillin from it.

1939: **Ernst Boris Chain**: discover penicillin's therapeutic action and its chemical composition. Theorized the structure of penicillin

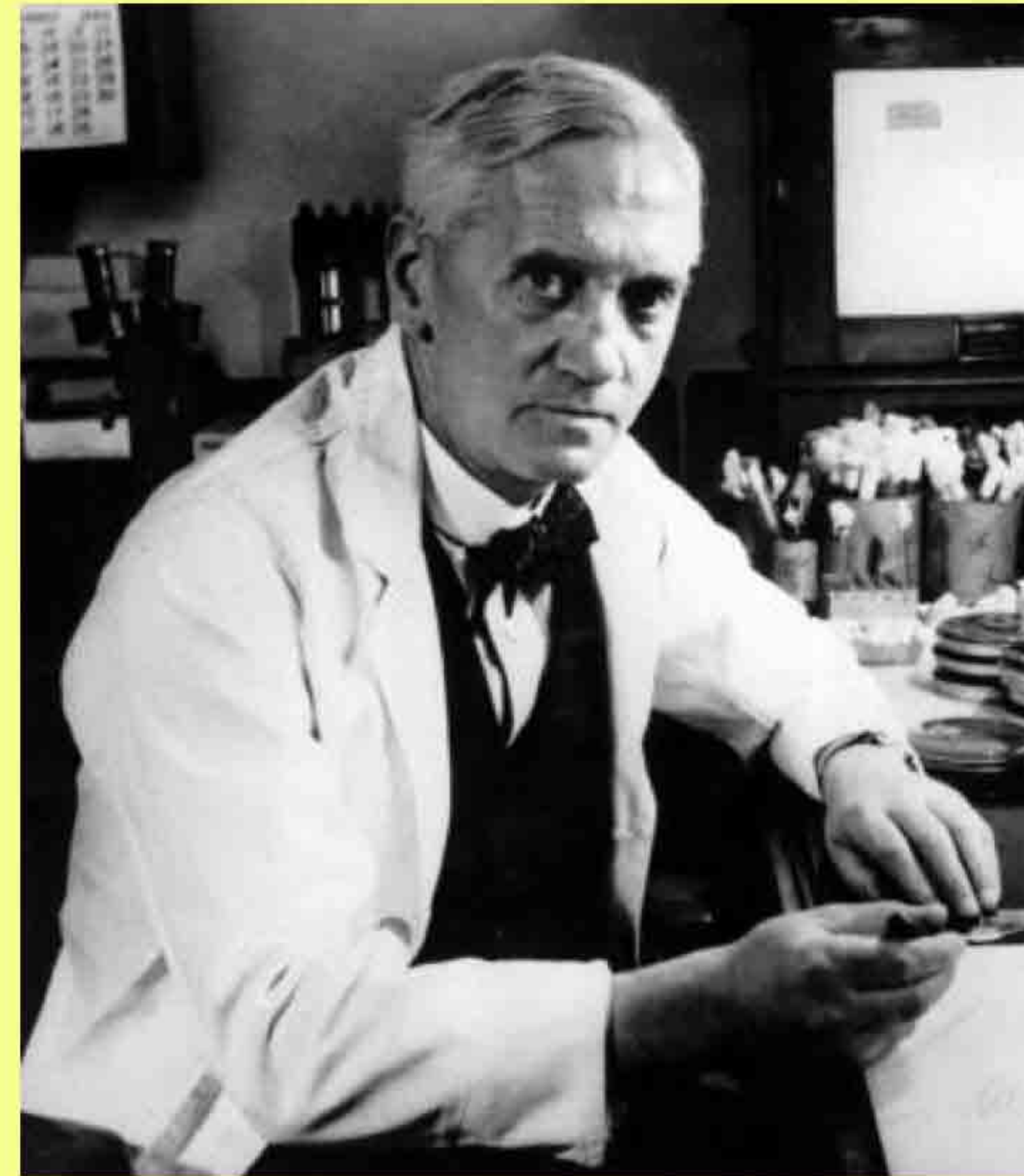
Florey: first clinical trials in 1941

First patient, **Albert Alexander**, policeman scratched by a rose thorn severe facial infections. eye removed to relieve some of the pain. Within a day started recovering. Not enough penicillin for full recovery, died. 20 gallons of mould juice needed to treat infection

1941: **Heatley & Florey** visit Department of Agriculture's Northern Regional Research Lab Peoria, Illinois larger scale prodⁿ.

A. J. Moyer. addition of corn-steep liquor to the fermentation produced a ten-fold increase in yield. Ironically, the most productive strain came from a moldy cantaloupe from a Peoria fruit market

Outrage: Between 1947 and 1949, Moyer filled for four patents regarding his work on Penicillin.



A night with venus a lifetime with mercury

August 1494, Army of King Charles VIII of France Conquered Kingdom of Naples from Alphonso II. While occupying Naples soldiers indulged in a long bout of celebration and debauchery

Genital sores, followed by foul abscesses and ulcers over the rest of the body and severe pains.

Main treatment **guaiacum**, or *holy wood*, Maipurean, language of Bahamian Taínos adopted into English into 1533, the first word of American origin

Paracelsus (1493-1541) derided guaiacum as useless and expensive and promoted **mercury** ‘*unguentum Saracenicum*’, or Saracen’s ointment, this had been a staple of Arab medicine for the treatment of scabs, psoriasis, leprosy and other skin diseases

Survived as Calomel

Neuropathies, kidney failure, mouth ulcers tooth loss, many patients died of mercurial poisoning

Mercury used for syphilis until 1910 when Ehrlich developed **Salvarsan**



Preparation and Use of Guayaco for Treating Syphilis Jan van der Straet 1580



Theodericus Ulsenius, Dirk van Ulsen, c. 1460-1508: Nürnberg : *Vaticinium in epidemicam scabiem*. **Morbus Gallicus**: Albrecht Dürer (1496). Earliest depiction of the disease: Wears clothes of *Landsknechten* Nov 1484 Saturn and Jupiter met in Scorpio: disease caused by unfavourable planetary alignment



WW1 Military problem

VD rates of British x7 than the Germans, refusing to acknowledge any problem

1915: British medical officers Le Havre, counted 171,000 visits to brothels in one street

1916: Defence of the Realm Act, crime to approach men in uniform. No longer allowed to solicit openly
Cheapest prostitutes in France 3 F private in an infantry battalion 10F/week. After, egg & chips, 1F a bottle 'ving blong' (vin blanc), beer, tobacco,
"Poverty, not prophylaxis or pharmacology, was probably the British soldier's best defence:

ANZAC & Canadians paid x5, suffered unintended consequences of generosity" 22% vs 3.5% British
Canadian and NZ prime ministers forced chiefs of staff to issue condoms

137 Maisons de Tolérance: in 35 towns: Général Sarrail to improve morale opened an establishment offering Tues & Thurs to British. "Unacceptable".

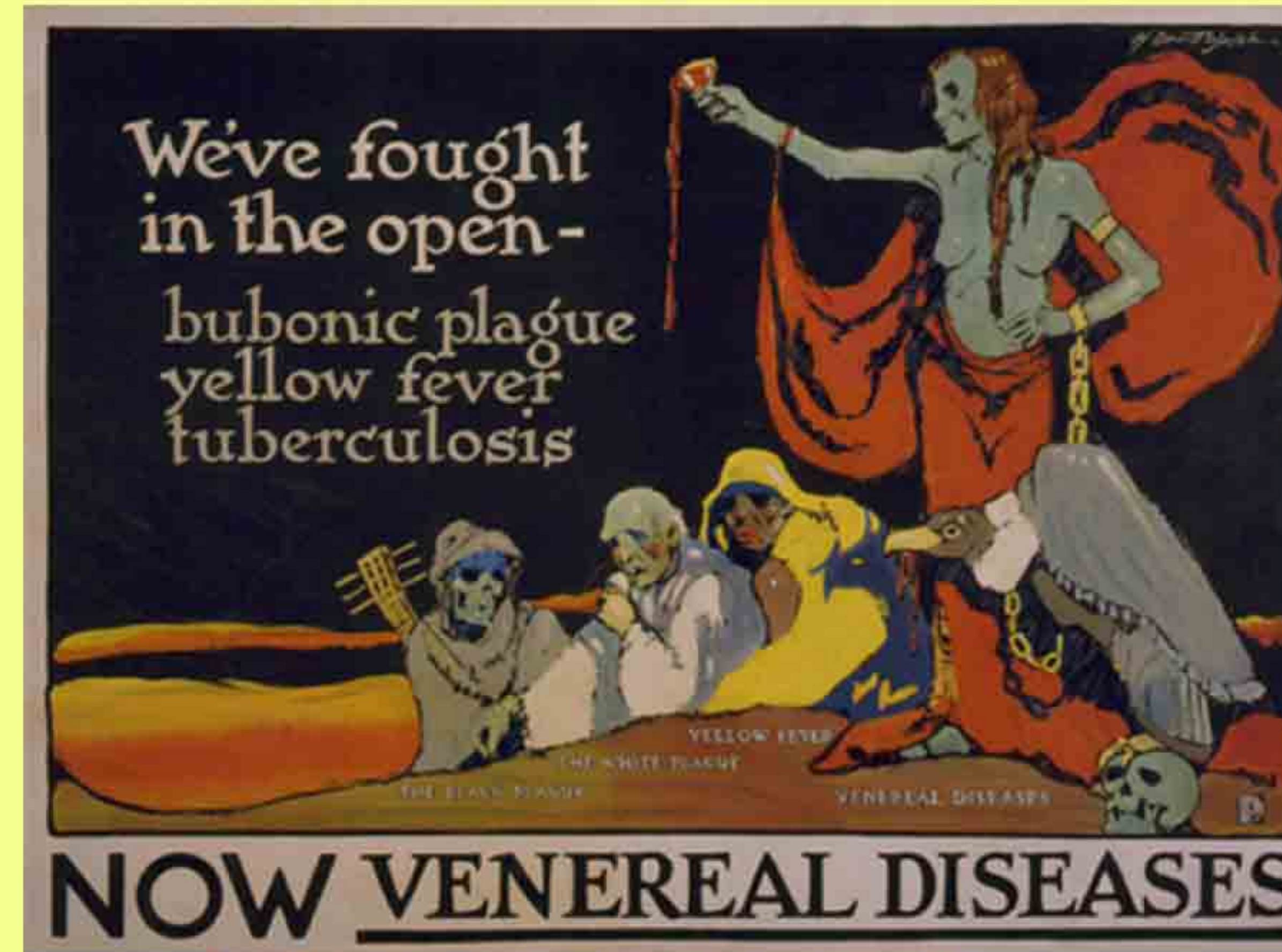
1918: 60,099 in France, more than trench foot and frost bite in entire war. Half contracted at home

VD caused **416,891** hospital admissions among British and Dominion troops: **1million** French

US Army lost use of 18,000 servicemen per day.

STD 2nd commonest reason for absence from duty, 7 million lost person-days and discharge of 10,000

Only Spanish influenza 1918-19 worse



H. Dewitt Welsh WWI

Ettie Rout NZ nurse in Egypt, VD a medical issue, not a moral. **1917** designed prophylactic kits on her own initiative. Letter *NZ Times* advocating condoms and clean brothels outrage her name forbidden in print £100 fine. NZ authorities issue her kits carefully kept secret
Decorated by the French
Established hygienic brothel for NZ troops in Paris
John Frith J of Military & Veterans' Health vol 20



The use of Penicillin

1941 and 1945 STD's in US Army: 43/1,000/yr.

Vietnam War 1963 to 70: 262/1,000/yr,

continental US-based army personnel: 30/1,000/yr

90% gonorrhoea and 1% were due to syphilis

US War Production Board controlled the disposition of all penicillin produced. Aim to have adequate for D-Day

1943: John Mahoney: Public Health Service: Efficacy of Penicillin in Gon and syph.

Penicillin: VD Soldiers available for combat quickly.

Emphasis on gonorrhea reflected priority of the military with respect to the supply of penicillin

1943 gonorrhea required a hospital treatment of 30d

Curing syphilis remained a 6m ordeal.

Winston Churchill & General Poole: 'this valuable drug must on no account be wasted. It must be used to the best military advantage'. Used for those wounded in Brothels

Florey wanted it to conduct trials on burns and gangrene

British medical officers in Sicily, treating 40,000 VD cases a month, x20 than number treated in England.

1944: VD reduced 30-fold, still 600 incapacitated every day.

Sickness reduced to 5days, patient remained on duty status while being treated.

June 44: US Army adopted penicillin for wounds. Supply of penicillin had increased. British soon followed

Allocation of penicillin within the Military controversial:

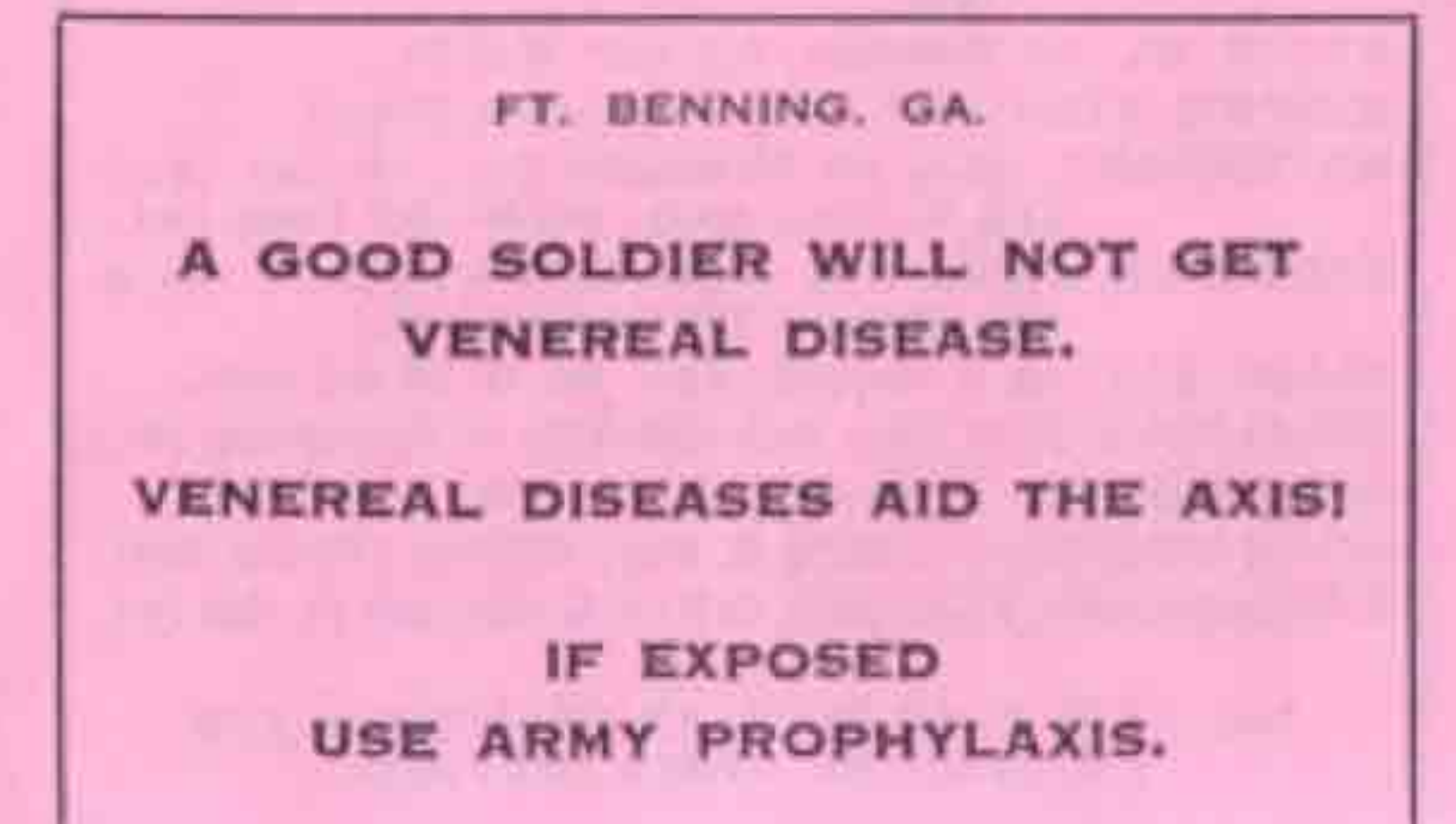
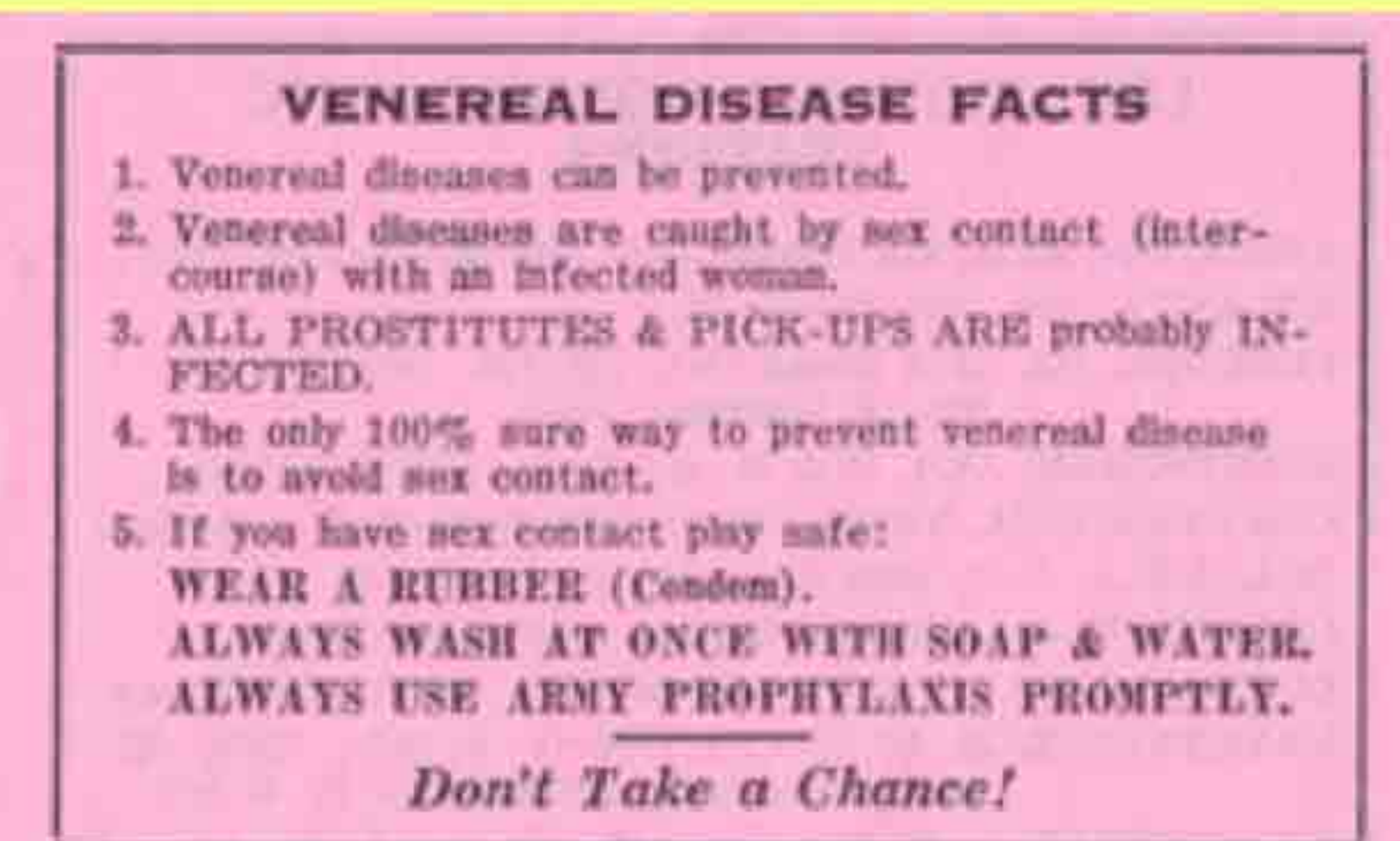
1943: first shipment arrived

North African Theatre, decision between using it for 'sulfa fast' gonorrhea or infected wounds.

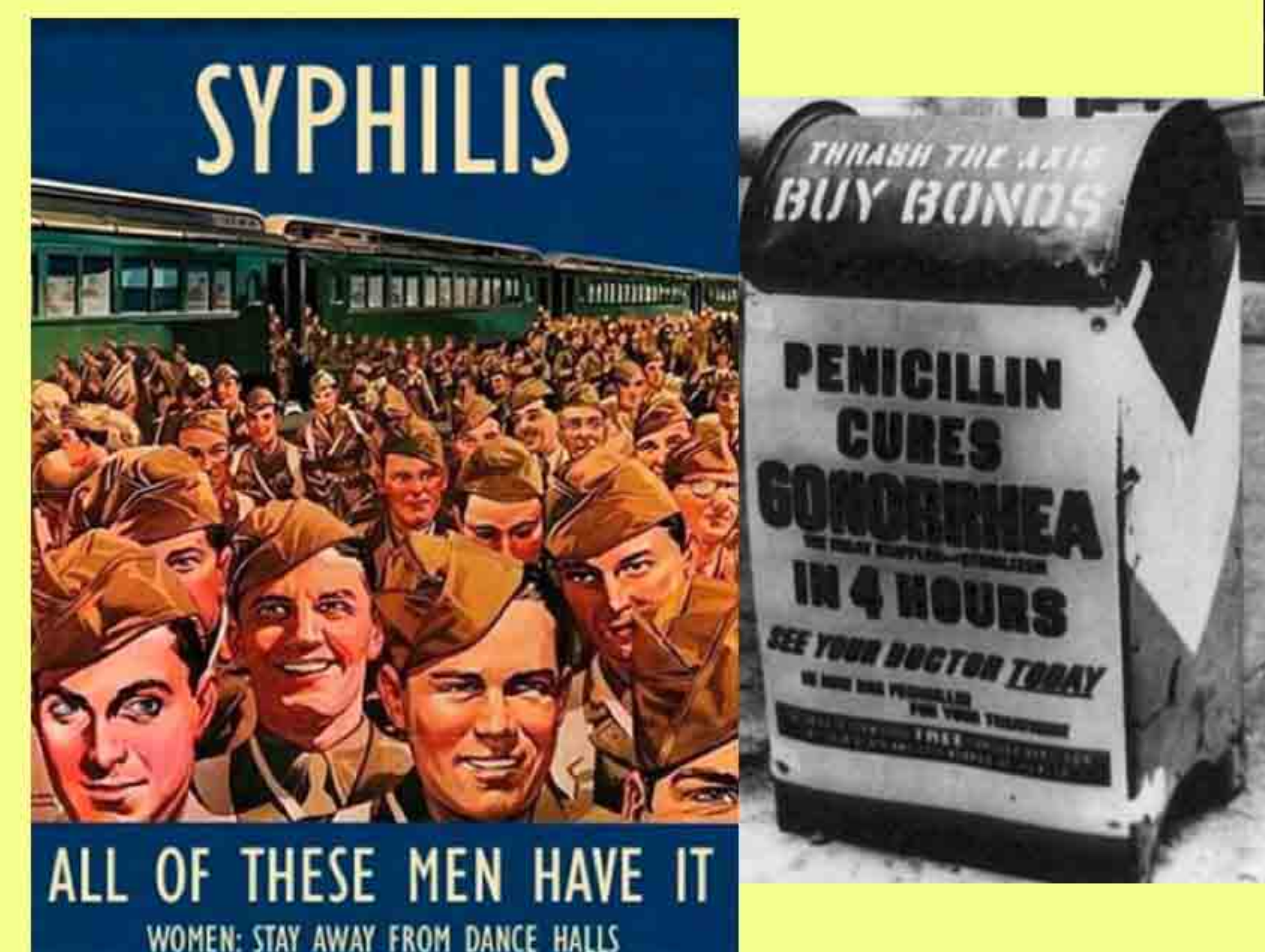
Col Edward D. Churchill, Chief Surgical Consultant, opted for use in those wounded in battle.

The Theatre Surgeon made the decision to use the available penicillin for those 'wounded' in brothels.

Military manpower shortage. In less than a week, those overfilling military hospitals with VD returned to battle line.



1943: Reginald Mount



Antibiotics in nature

50m yrs ago in Amazon: Ants cultivate fungus for food

Leaf-cutter ants, dominant herbivore of the Neotropics.

use fresh leaf substrate for their fungal partner

Symbiosis evolved to 230 spp of ants and diverse fungal strains.

fungal crop is attacked by a parasitic fungus, *Escovopsis*.

To prevent infections, the ants have adopted special defenses against the parasite, including fungus grooming, in which they run their mouthparts over their crops and lap up the parasite's spores

Some ants have a second mutualism with (actinomycetes *Pseudonocardia spp*) that produce many antibiotics

Ants with antibiotic-producing *Actinomycetes* protect their fungal gardens from microbial disease.

Queens carry fungal crop in their mouths and the bacteria on their exoskeletons to their new colony.

The ant–fungus–bacteria mutualism ancient system, special anatomical adaptations to house and nourish the actinomyces



New Antibiotic discovery

1941: Selman Waksman Ukranian born American soil scientist Rutgers Agricultural College.

Antibiotic small molecule made by a microbe that antagonizes the growth of other microbes (not a good definition, includes CO₂)

1943: Albert Schatz: Waksman's lab, search antibiotic effective against TB and Gram-negative bacteria – responsible for penicillin-resistant diseases.

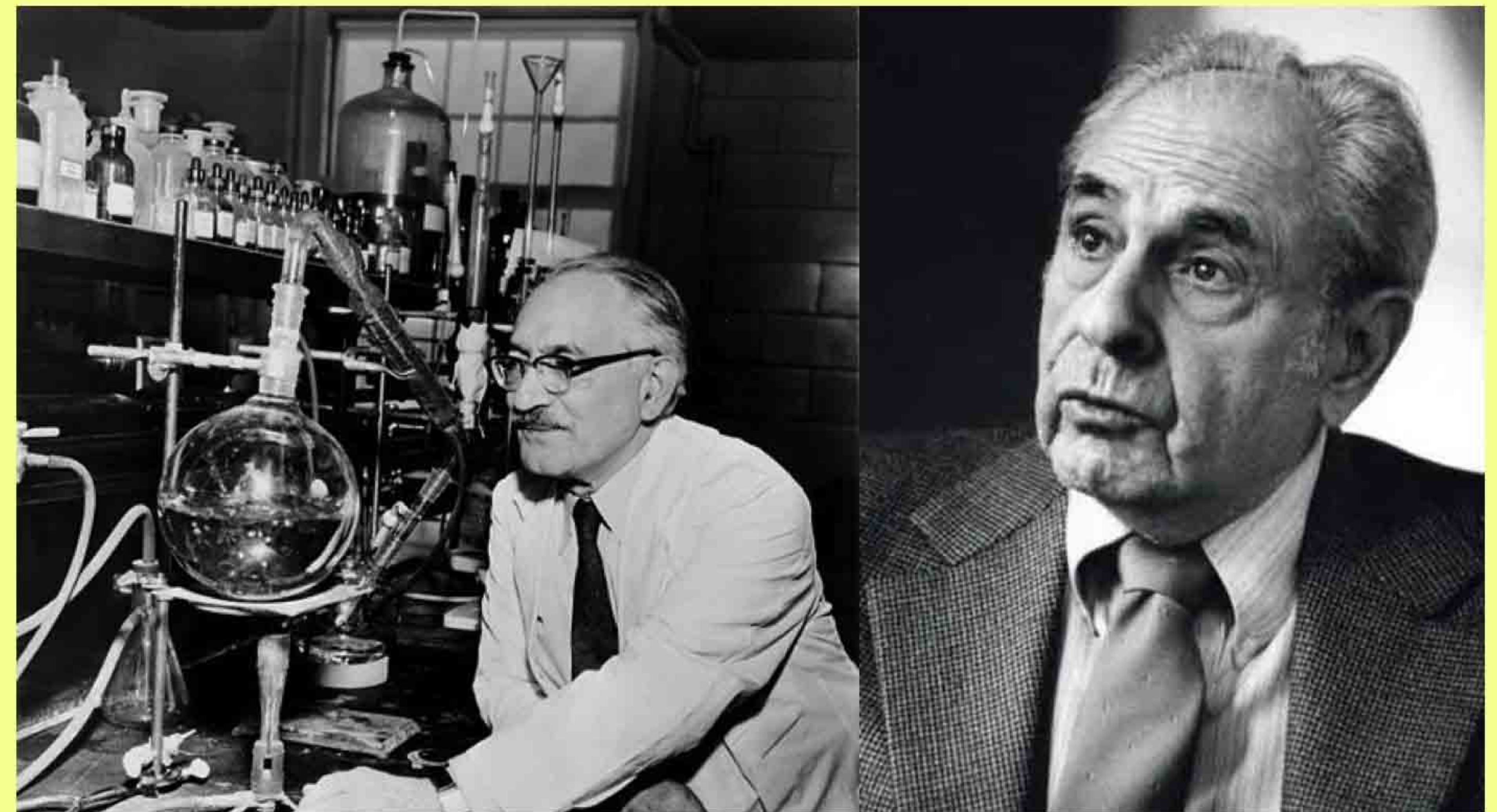
Two related strains of Actinomycetes inhibited tubercle bacillus and several Gram-negative bacteria. antibiotic named **STREPTOMYCIN**.

Controversy over Waksman's Nobel Prize and Royalties

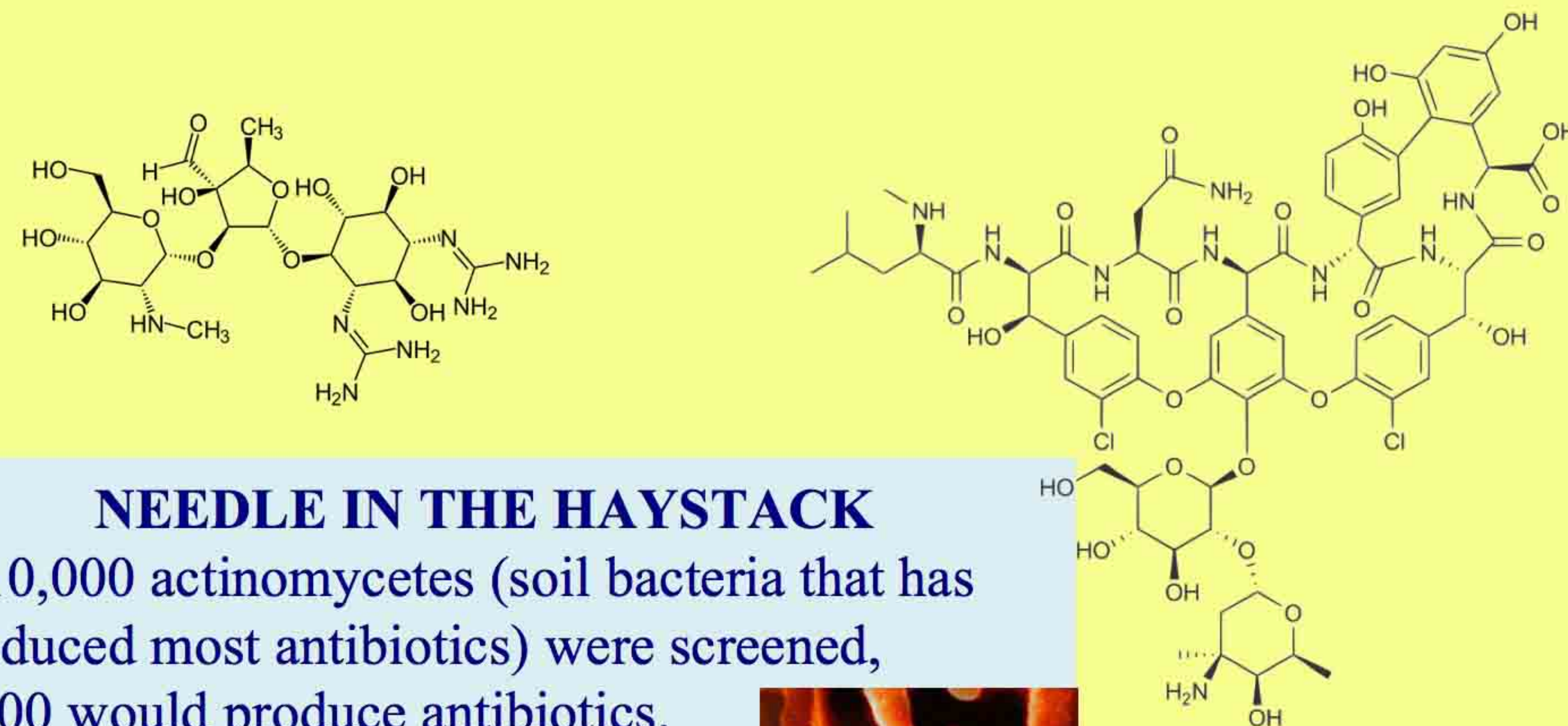
1945–1955: **penicillin**, produced by a fungus, **streptomycin**, **chloramphenicol**, and **tetracycline**, produced by soil bacteria,

1953: Vancomycin Edmund Kornfeld (Eli Lilly); soil sample from jungles of Borneo by a missionary. *Amycolatopsis orientalis*.

Treatment of penicillin-resistant *Staph aureus*

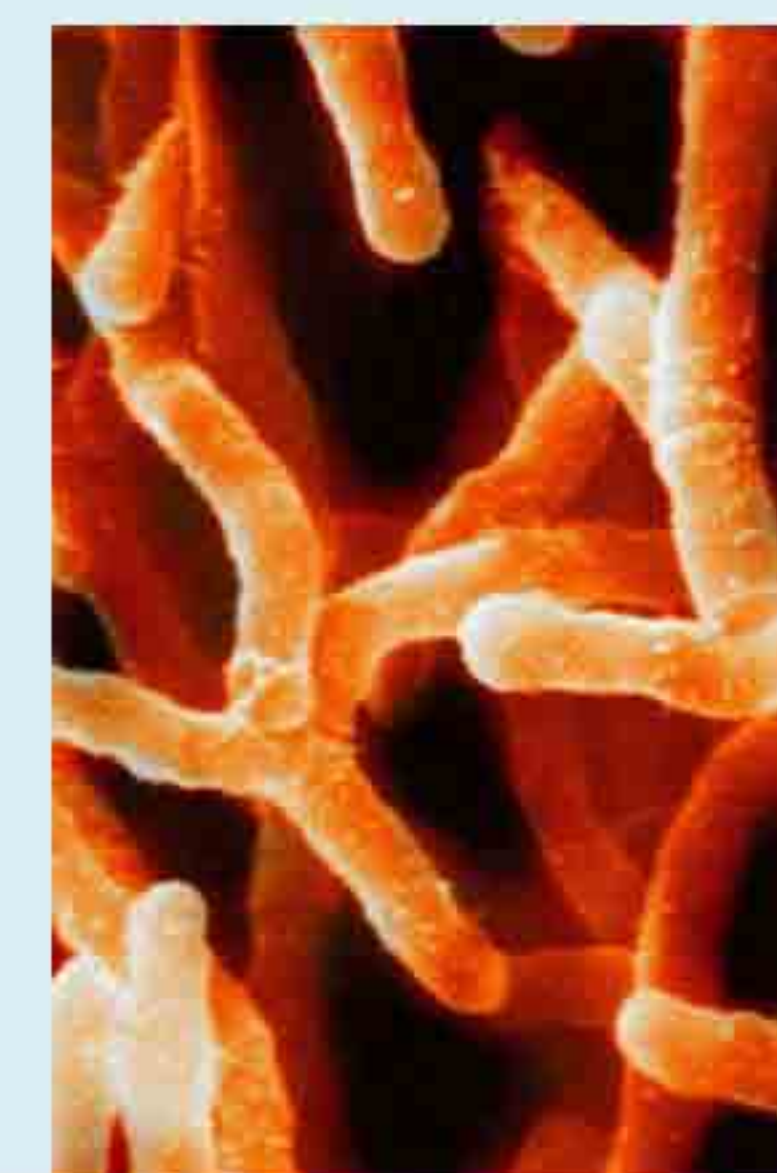


Albert Schatz (1920 –2005: two related strains Actinomycetes stopped the growth of tubercle bacillus and several Gram-negative bacteria. One strain mouth swab from a duck, the other from soil. Antibiotic derived from these bacteria "**streptomycin**".



NEEDLE IN THE HAYSTACK

If 10,000 actinomycetes (soil bacteria that has produced most antibiotics) were screened,
2,500 would produce antibiotics.
2,250 would make streptothricins
125 streptomycin
40 tetracycline.
1:100,000 Vancomycin
1:1 million erythromycin
1: 10 million daptomycin



Pre-antibiotic world

Such is the Old Town of Manchester.. and the frightful condition of this Hell upon Earth.

Everything here arouses horror and indignation.

Friedrich Engels, The Condition of the Working Class in England, 1844

The Poor Relief Act 1601: No longer fit for purpose in rapidly expanding towns

1834 Poor Law: provision of poor relief so unpleasant put off all but the most desperate

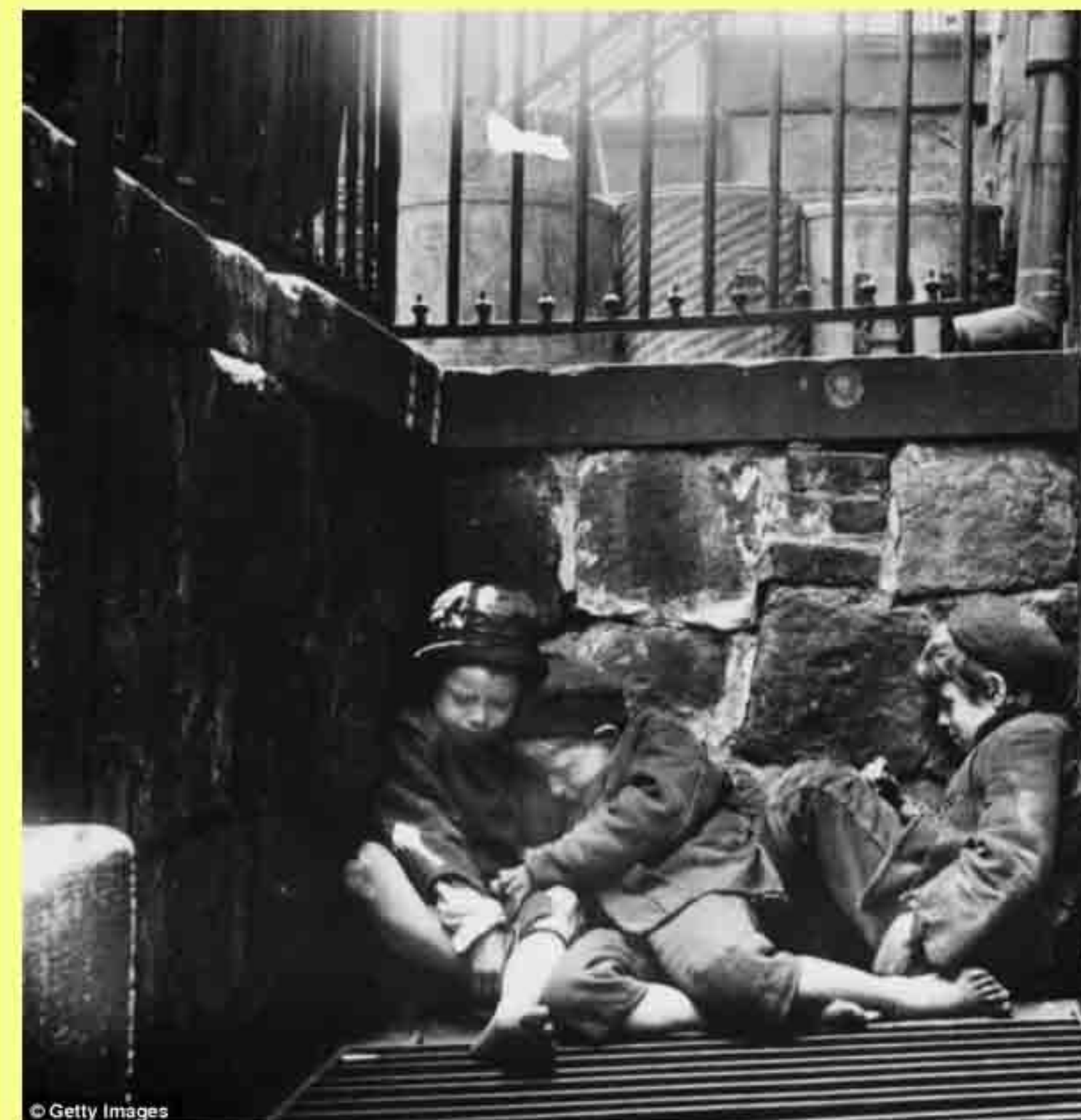
1842: Edwin Chadwick: b Manchester 1800 mother died before he was named. Humourless secretary to (new) Poor Law Board, *Report on the Sanitary Condition of the Labouring Population of Great Britain:* urban poverty not caused by individual immorality but by sickness caused by filth diseases

Quantitative methods: direct link poor living conditions and disease and life expectancy.

Much poor relief families of men who had died from infectious diseases. Money spent on improving public health was therefore cost effective

Poisoned by surroundings: sewage, refuse, graveyards, poisonous smelly vapours, ‘**miasmas**’

Letter to Times: ' We prefer to take our chance with cholera than be bullied into health. There is nothing a man hates so much as being cleansed against his will. It is a fact that many people have died from a good washing.'



Average life expectancy	professional tradesmen	labourers
Rutland	52	38
Leeds	44	19
Liverpool	35	15
Manchester	38	17
Bolton	34	18

1848 Public Health Act: promote the public's health and to ensure “more effective provision ... for improving sanitary conditions of towns

Bacterial biochemistry

A primer

Nucleic Acid synthesis
DNA-gyrase
RNA Polymerase

Folate synthesis

Cell wall Synthesis

Transpeptidase crosslinks the peptidoglycan net in the cell wall of Gram-positive bacteria.

Folic acid synthesis:

PABA used by bacteria to make DHF, needed for purine component of DNA,

Nucleic acid metabolism

Circular Double stranded DNA

No nuclear compartment

Unwinds for transcribing

RNA Polymerase binds to promotor region makes a complementary copy

Protein synthesis: Translation

Messenger is **mRNA**

Binds machinery for peptide construction
RIBOSOME

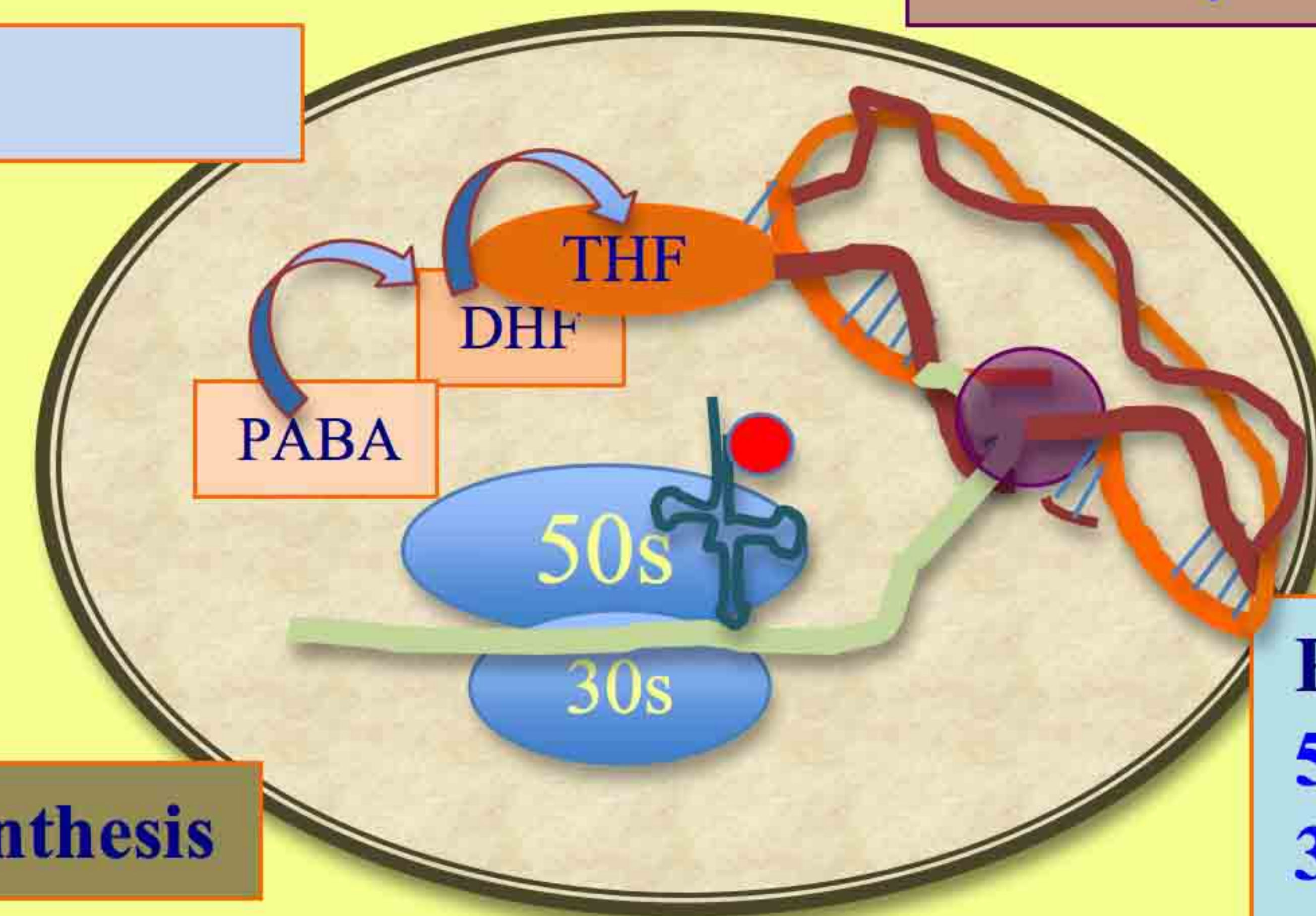
50s/30s subunits

Different to humans

Amino acids brought to ribosome

Transporter tRNA has anticodon

Fits into slot

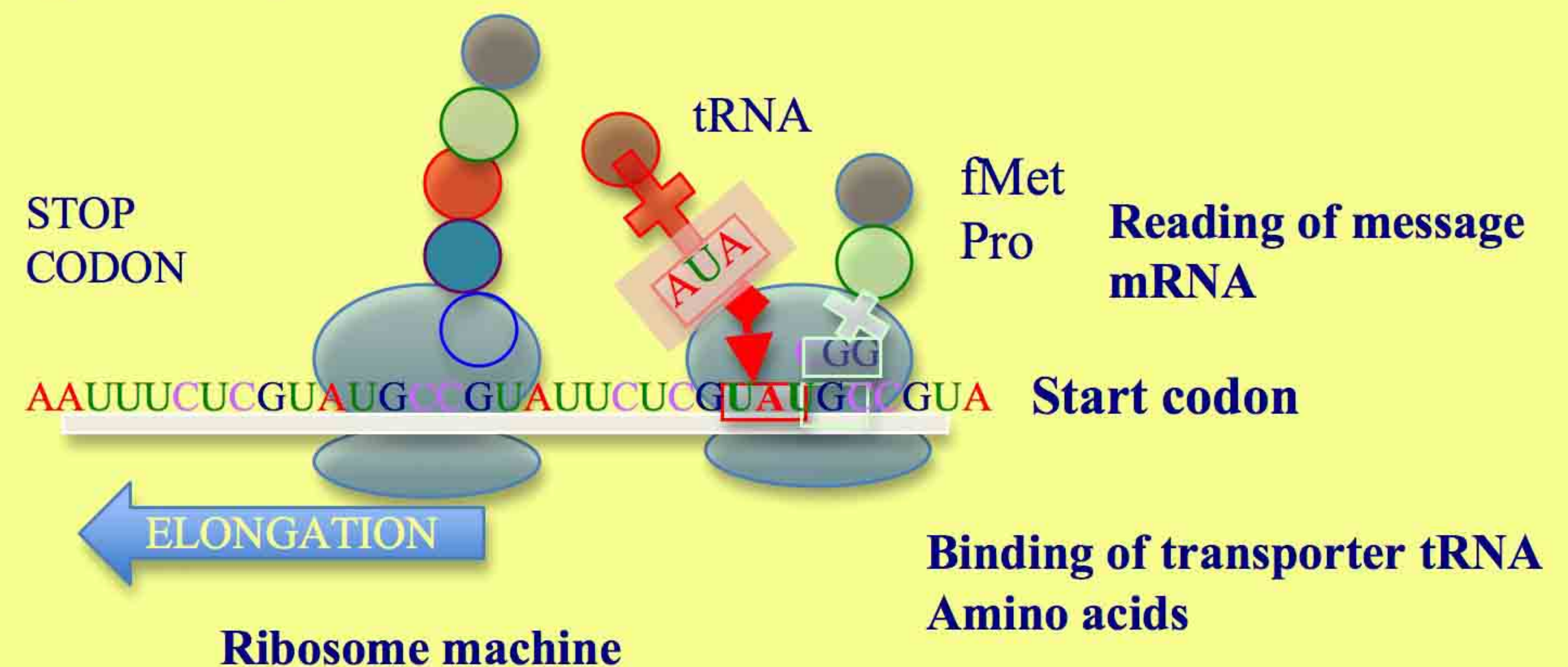


Cell wall Synthesis

Cell membrane

Protein synthesis
50s subunit
30s subunit

Peptide elongation



Mechanism of antibiotics

Cell wall

β-lactam ring mimics binding site of **transpeptidase**

Penicillin: (rupture) weak cell wall cannot contain growth.

Disrupters of nucleic acid synthesis

Rifampin inhibits prokaryotic RNA

Fluoroquinolones inhibit DNA gyrase, a bacterial enzyme that unwinds DNA in preparation for replication and transcription.

Disrupters of protein synthesis

Aminoglycosides inhibit nucleic acid or protein synthesis

shaped molecules fit in pockets of bacterial ribosomal RNA.

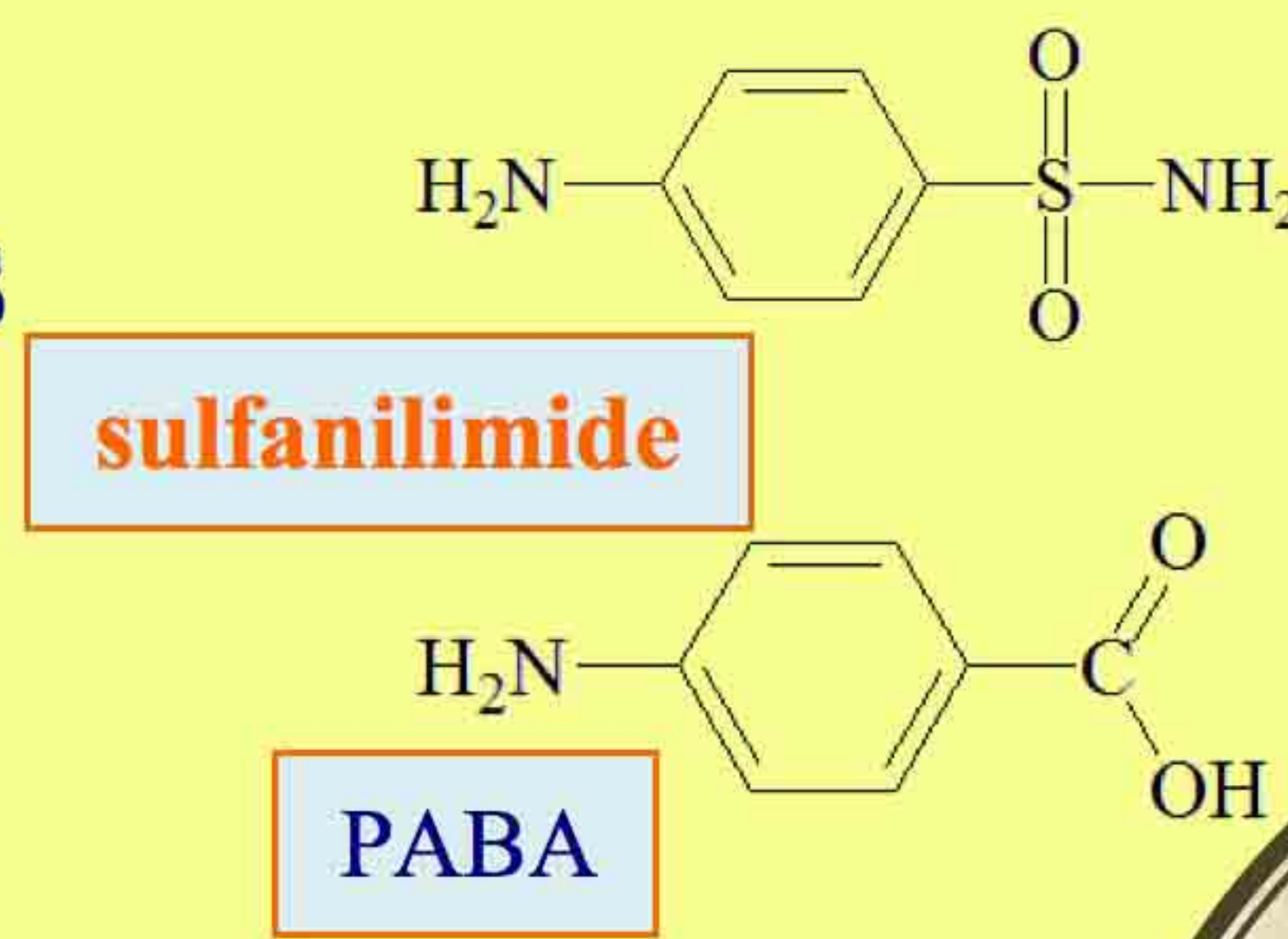
disrupt ribosomal structure.

specific to bacteria. No effect on human L-shaped pocket

Inhibitors of metabolism

Inhibit synthesis of purine and thymidylate precursors folic acid or tetrahydrofolate.

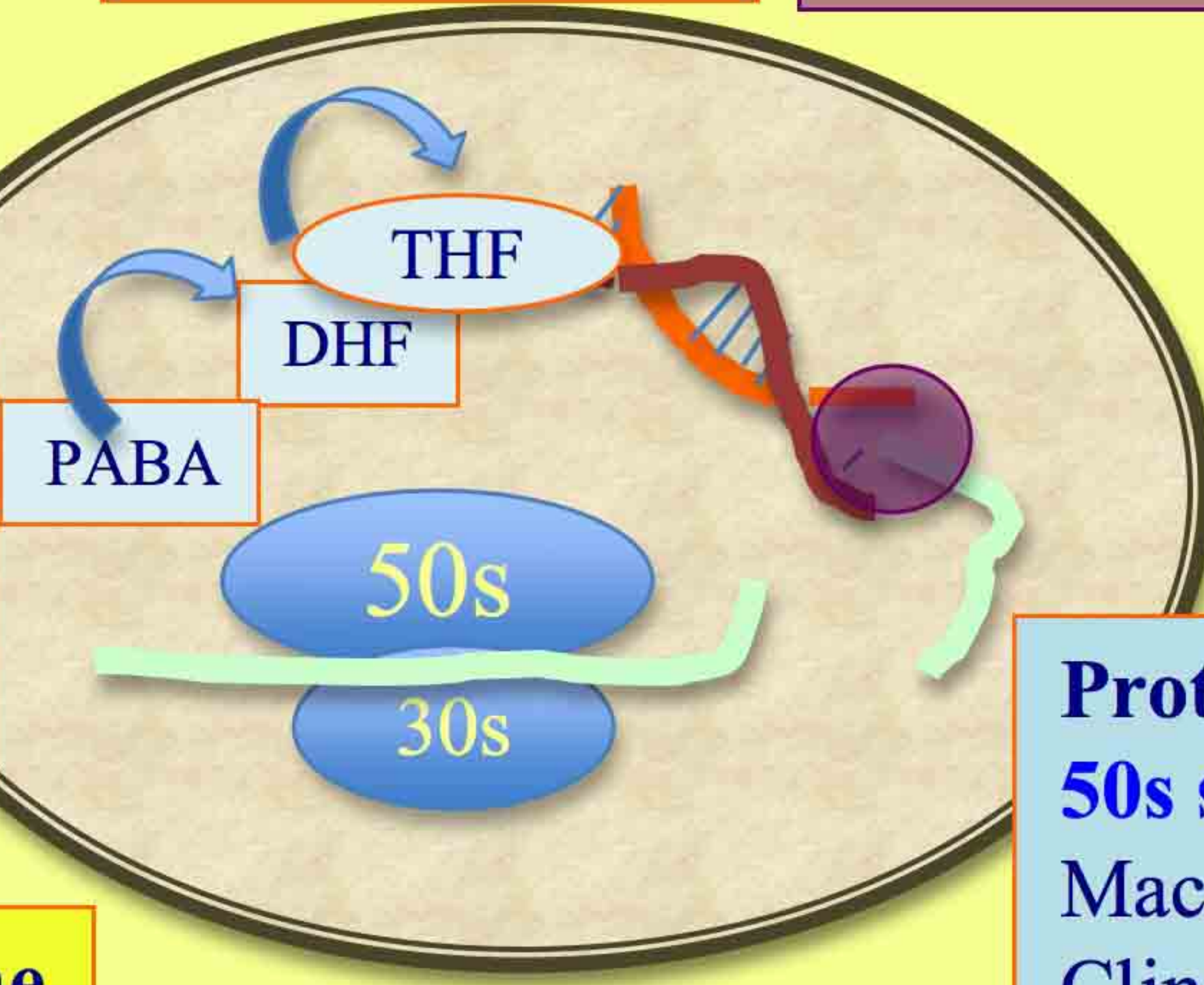
Sulfonamides inhibit bacteria-specific reaction.



Folate synthesis
Sulfonamide
Trimethoprim

Nucleic Acid synthesis
DNA-gyrase Quinolones
RNA Polymerase Rifampicin

Cell wall Synthesis
B-lactams (penicillin)
Vancomycin
Bacitracin



Cell membrane
Polymyxins
Colistin

30s subunit
Tetracyclines
Aminglycoside

Protein synthesis
50s subunit
Macrolides
Clindamycin
Linezolid
Chloramphenicol

Chloramphenicol

Binds to 50s
Inhibits formation
Of peptide bond



Erythromycin

Binds 50s rRNA
Blocks exit of peptide

Streptomycin
Changes shape of 30s
mRNA read incorrectly

Tetracyclines
Interfere with t-RNA
Anti-codon reading

Antibiotic resistance

1950s, bacterial diseases no longer public health threat!

1943: Abraham & Chain reported strains that could hydrolyse and inactivate B-lactam before use as an antibiotic.

Organisms either produce resistance factors to stop themselves being killed by their products or do not use that metabolic pathway

Many microbes also carry resistance genes for antibiotics that they themselves cannot produce,

B-lactamases found in remote Alaskan soils

Pathogens with multiple mutations and combinations of r genes evolve and survive successfully.

Naturally occurring antibiotic resistance is common

Environmental resistome.

Comprises all of the antibiotic resistance genes.

Includes cryptic resistance genes (not necessarily expressed) present in bacterial chromosomes.

20,000 potential resistance genes (r genes) of 400 types, predicted from bacterial genome sequences



Antibiotic resistance

ANTIMICROBIAL RESISTANCE IS GENETICALLY BASED

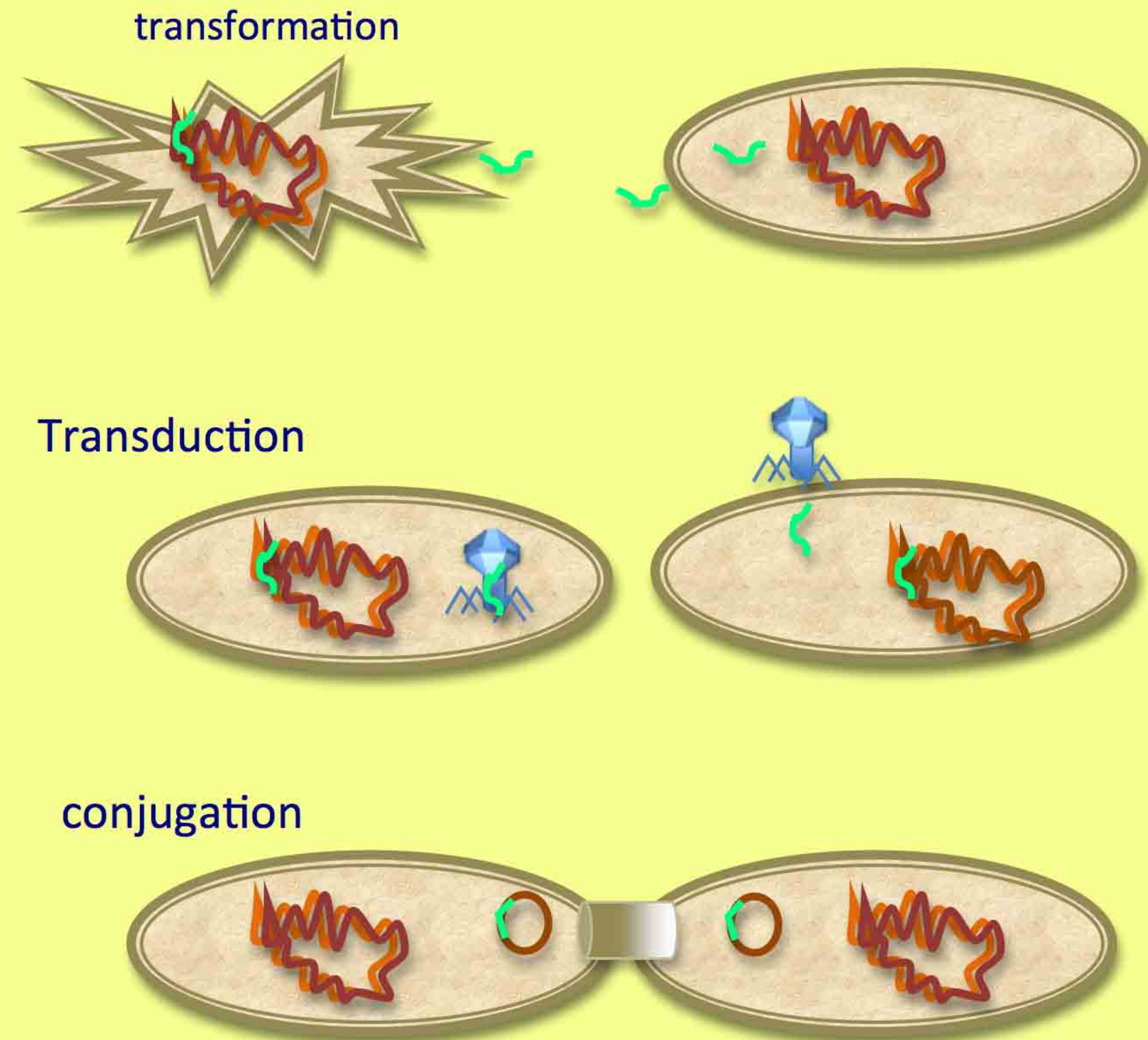
Mediated by acquisition of genetic elements containing resistance genes.

Horizontal gene transfer is common among bacteria, even distantly related ones.

Significant cause of increased drug resistance
resistance genes are transferred to other species

plasmids, transposable genetic elements, and genomic islands, which are transferred between bacteria via horizontal gene transfer

Resistance gene, *mecA*, stops β -lactam antibiotics from inactivating the enzymes (transpeptidases) that are critical for cell wall synthesis.



a) Transformation: naked DNA is released on lysis of an organism and is taken up by another organism. The antibiotic-resistance gene can be integrated into the recipient cell.

b) Transduction: antibiotic-resistance genes are transferred by bacteriophages integrated into the chromosome of the recipient (lysogeny).

c) Conjugation plasmids form a mating bridge across the bacteria and DNA is exchanged, which can result in acquisition of antibiotic-resistance genes by the recipient cell.

Mechanisms of resistance

Drug inactivation or modification:

β -lactamases: enzymatic deactivation of penicillin

chloramphenicol acetyl transferase: transfers an acetyl group; modified antibiotic no longer binds to ribosomes.

Alteration of target site:

Resist antibiotics by changing genetic code for binding proteins: **PBP_{2a}**

The ribosome can be methylated so that an antibiotic cannot bind to it.

Random mutations in the bacterial DNA may alter the gyrase and make it unrecognizable to antibiotics while still leaving it functional.

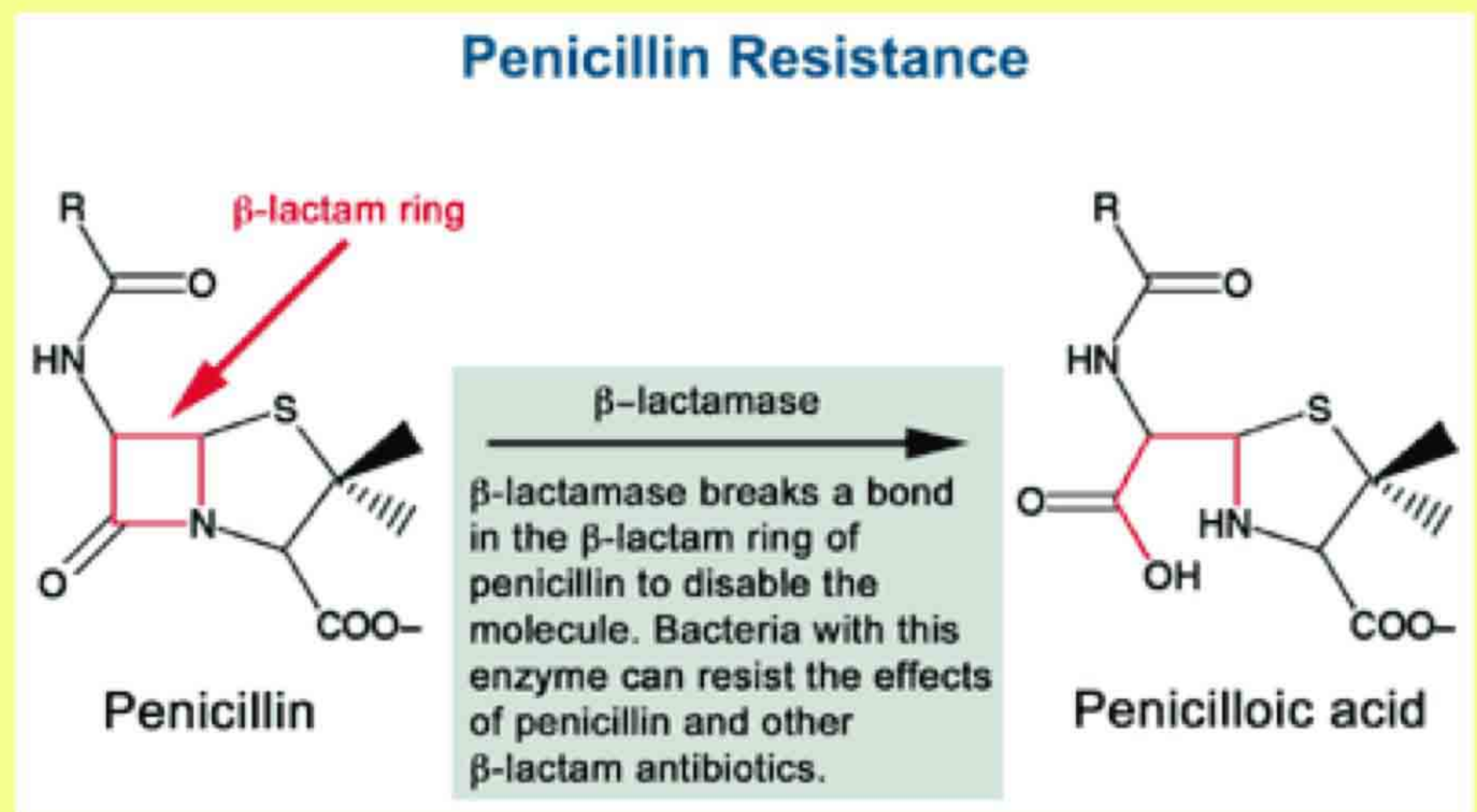
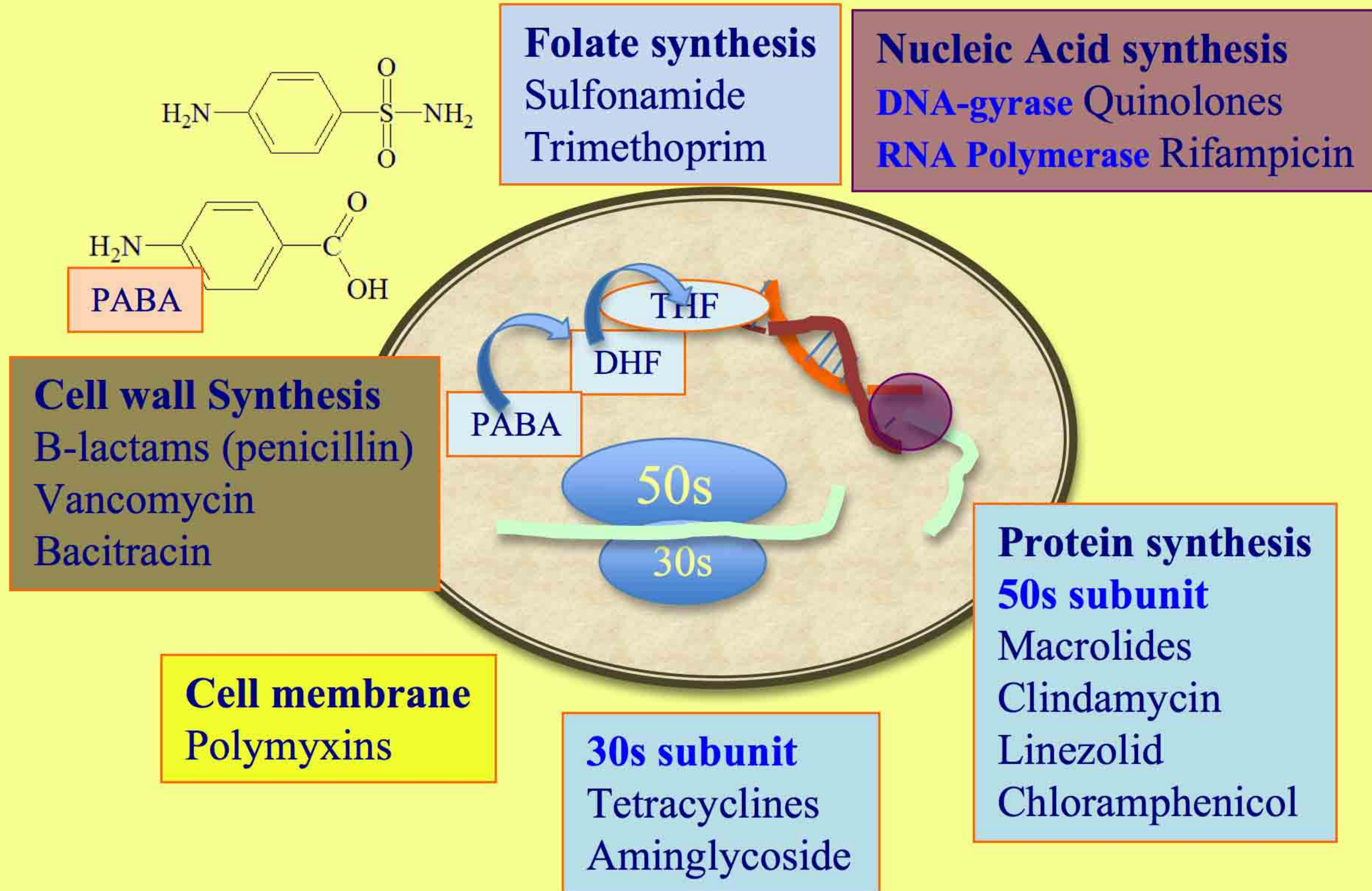
Alteration of metabolic pathway:

some sulfonamide-resistant bacteria do not require (PABA), use preformed folic acid.

Reduced drug accumulation:

Decreasing drug permeability or increasing active pumping out

Carbapenem resistance in *E.coli*



Methicillin Resistant SA

S. Aureus discovered by Sir Alexander Ogston in 1880, nasal commensal in 30% of the population, skin infections such as boils: Deadly if enters body

Soon hospital bacteria acquired enzymes that hydrolysed the B-lactam ring **Phage type 80/81** caused pandemic infections in the community.

1950's: Erythromycin introduced as an alternative to penicillin for the treatment of S. aureus in Boston City Hospital, withdrawn <year because 70% of all the S. aureus isolates were found to have become resistant.

1959 methicillin first designer antiresistance antibiotic

1961: 80/81 evolves into Methicillin-resistant:

This was not an enzyme but a low affinity binding pr for penicillin **PBP_{2a}** coded by gene *mecA*.

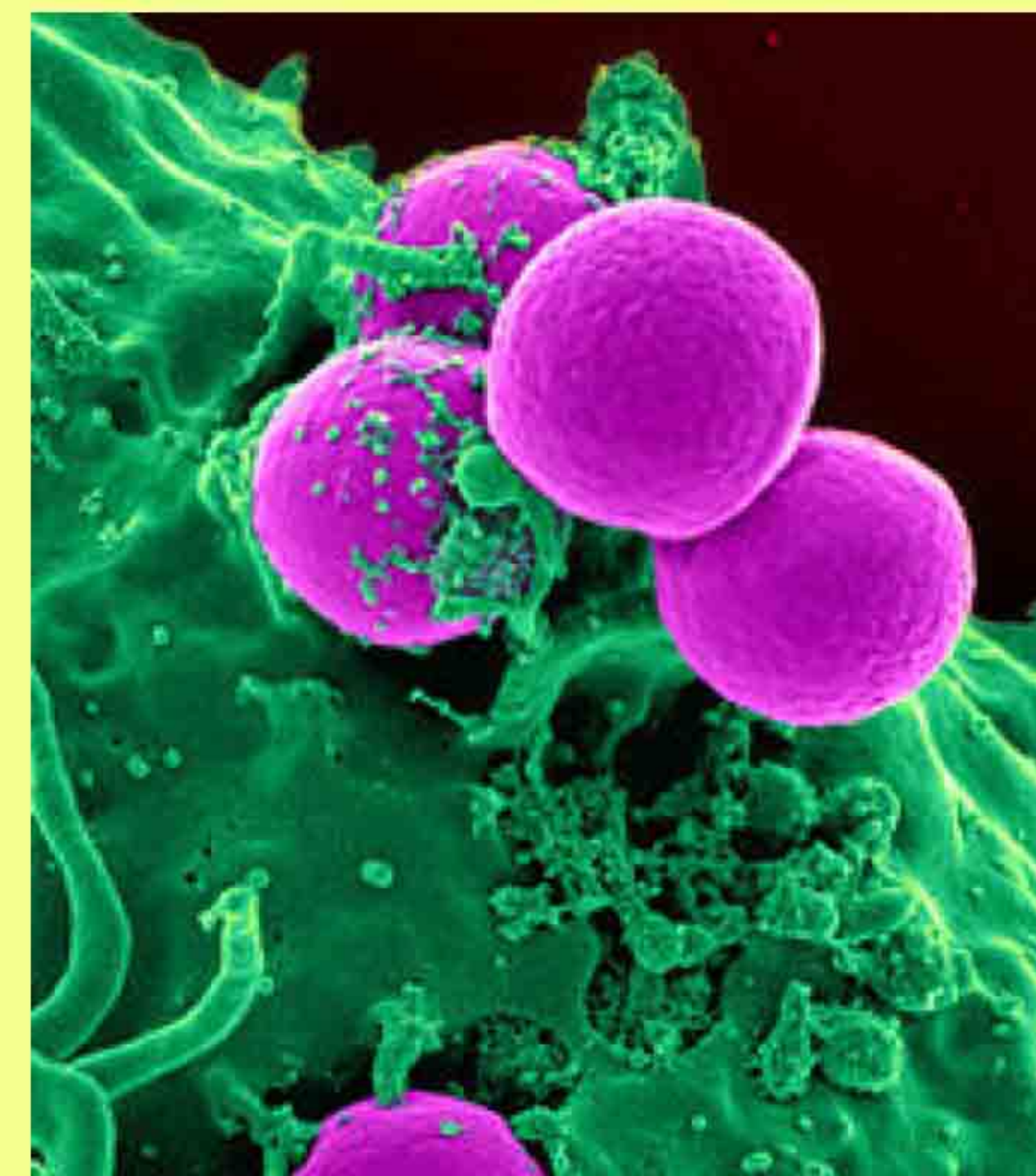
1997: new MRSA, emerged as community-acquired pathogen, with enhanced virulence. USA₄₀₀ clone

Killed healthy children. Displaced by USA₃₀₀ clone.

CA-MRSA has most of the properties of MRSA, but different *mec* gene clusters, and has acquired new pathogenicity genes, cytotoxic **Panton-Valentine leukocidin** for abscess formation in skin and lungs

Hospital MRSA has become Multi-resistant

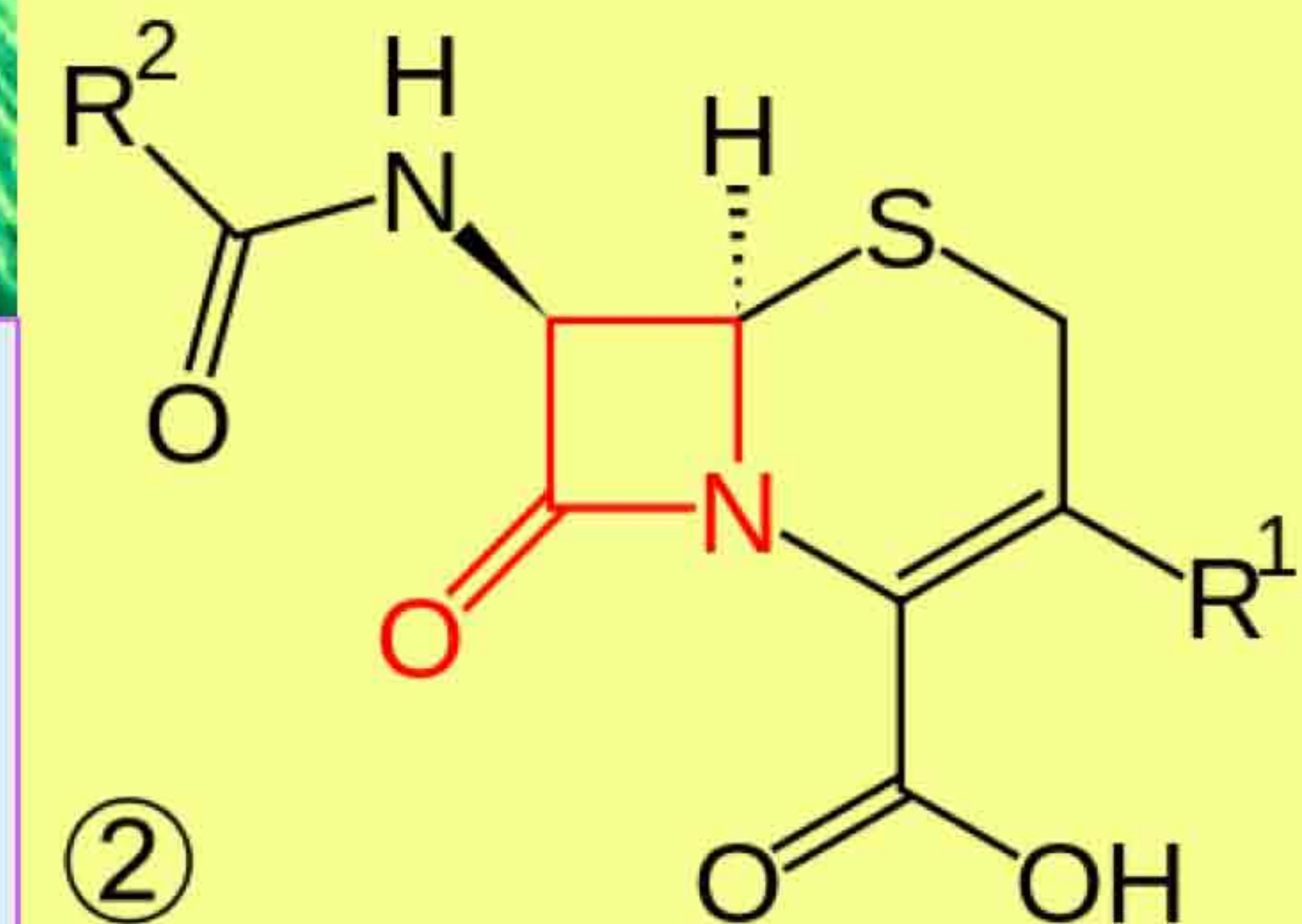
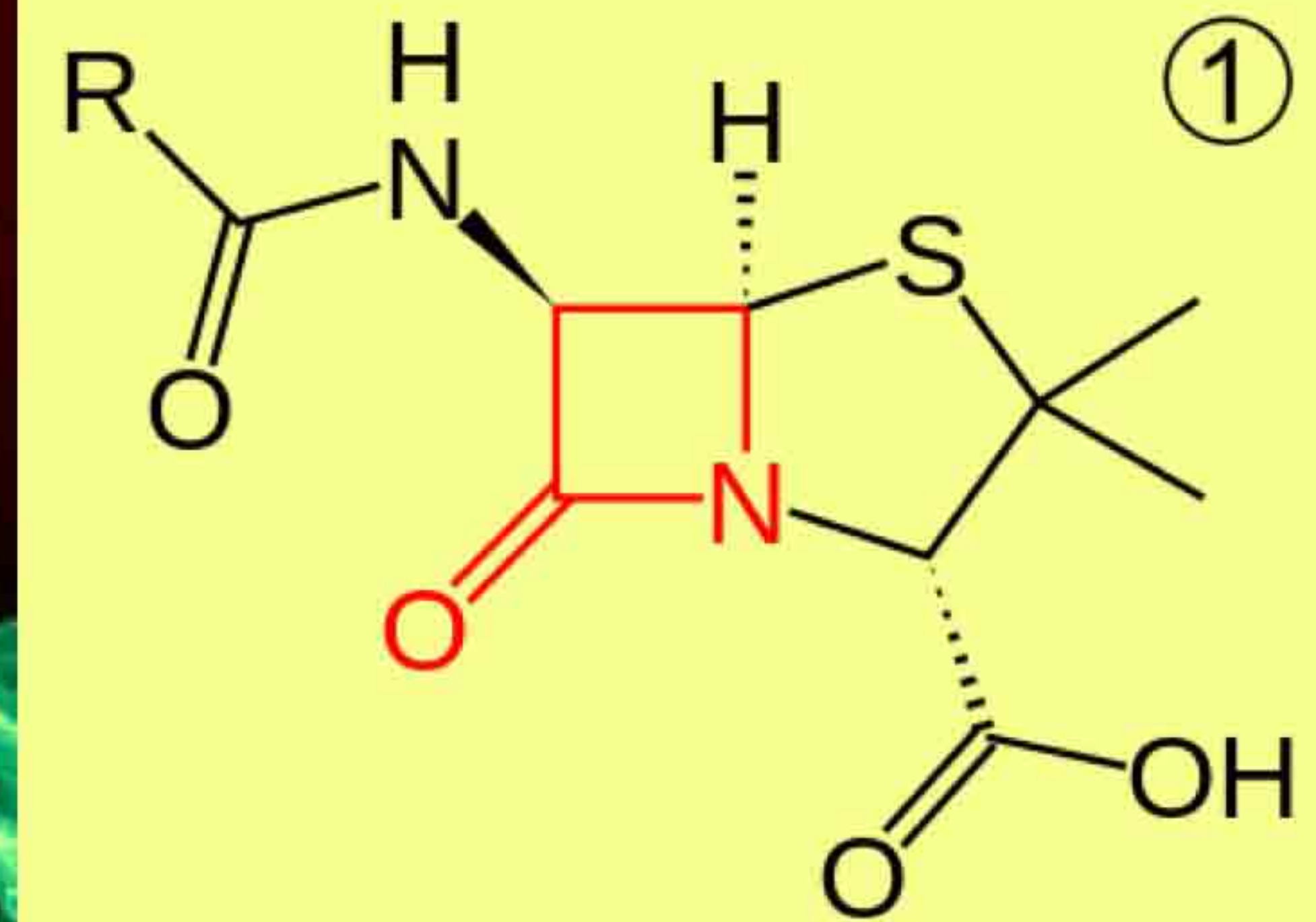
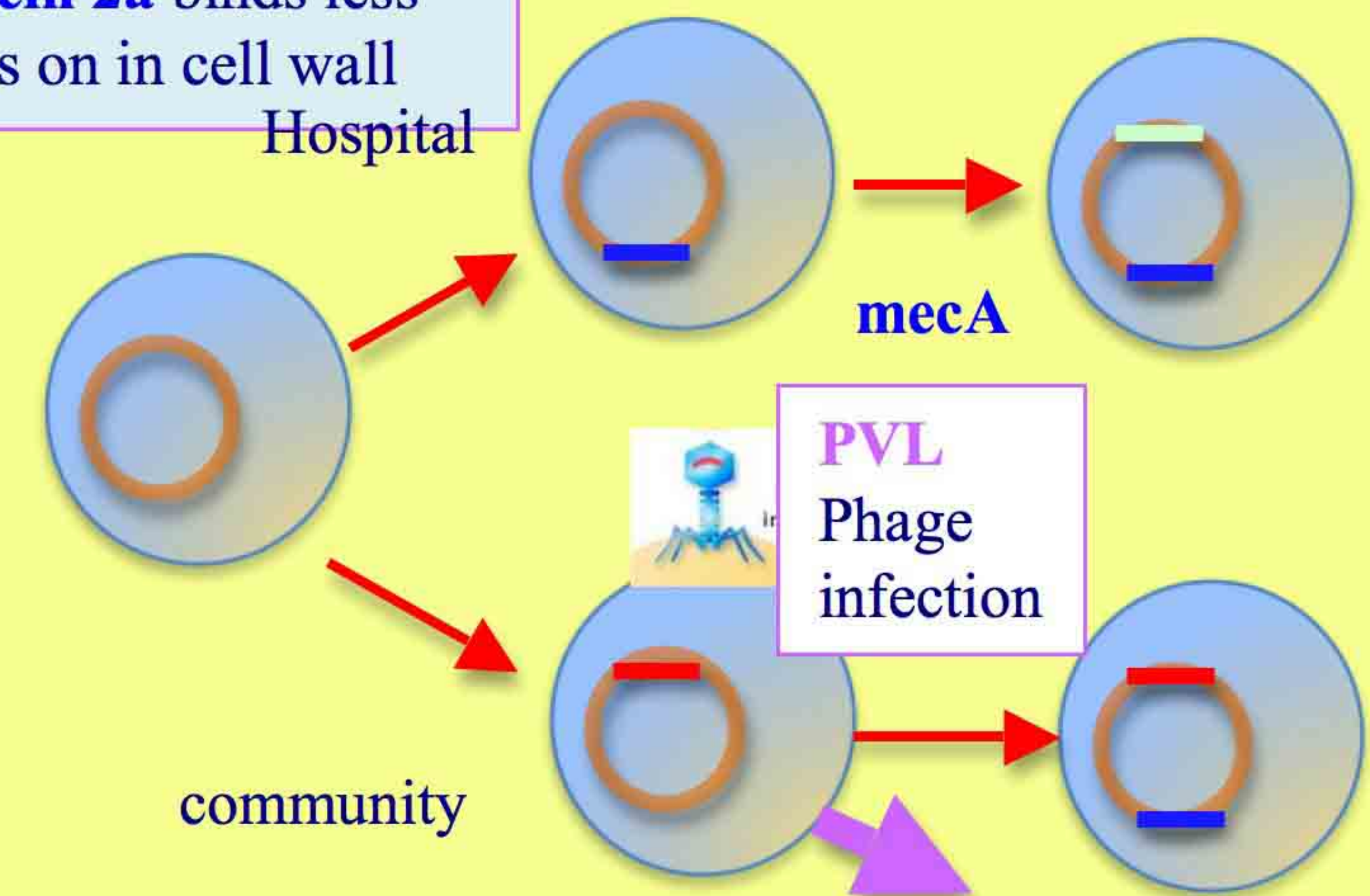
Mayday



MOBILE GENETIC ELEMENTS

Resistance to methicillin and β -lactam antibiotics encoded by the methicillin resistance gene *mecA* carried on the **staphylococcal cassette chromosome mec (SCCmec)**. Numerous variants (alleles) Make additional **penicillin binding protein 2a** binds less well so carries on in cell wall

Hospital



structure of **penicillins 1** and **cephalosporins 2**. **β -lactam ring**

Antibiotic-resistance

2013 CDC: antibiotic-resistant infections cost \$20bn US:
2m infected with resistant organisms a year
untreatable superbugs kill 23,000 of them

TB drug resistance development was rapid. Cocktails of anti-TB drugs essential multidrug resistance

2005: HIV in KwaZulu-Natal TB: lethal descendant: extensively drug-resistant (**XDR-TB**) resistant to both the first-line antibiotics and at least 3 of the 6 remaining second-line drugs.

Between HIV and TB : Africa India and China so many deaths that it will change societies,

TDR strains, which are totally drug resistant

carbapenem-resistant Enterobacteriaceae (CREs).

Carbapenems are one of the antibiotics of last resort for (*E. coli*) and *Klebsiella*.

N. Carolina *Klebsiella pneumoniae* gene that encoded **Carbapenemase** enzyme on a **plasmid**, # DNA move easily from one bacterium to another

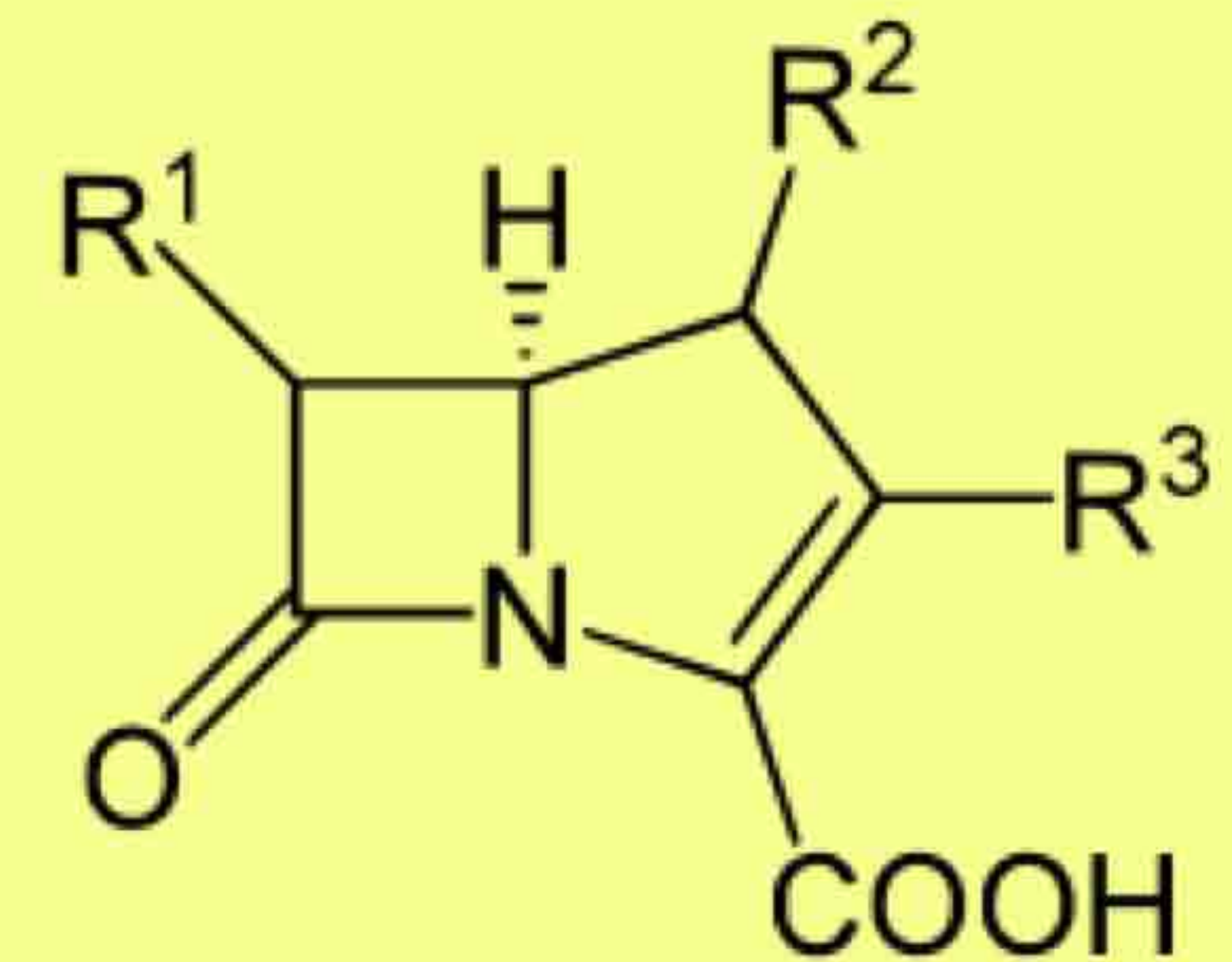
Jan 2008: 59yr-old Swede man *K. pneumoniae* resistant to carbapenems. dismantled the antibiotics with a different enzyme, a **metallo- β -lactamase**

Link to clinics in India, through medical tourism new enzyme **New Delhi metallo- β -lactamase (NDM)**,

16 December 2013: NDM-1 in two wastewater treatment plants in northern China.

Dame Sally Davies, the UK chief medical officer, **CREs as a risk as serious as terrorism**

Carbapenems broad spectrum β -lactam antibiotics structure resistant to most β -lactamases



Louise Slaughter: Democratic Representative for New York. "Every year, more than 100,000 Americans die from bacterial infections acquired in hospitals, 70% of these infections are resistant to drugs. This abuse and overuse must stop."



Reducing antibiotic resistance

Who's Hogging the pills?

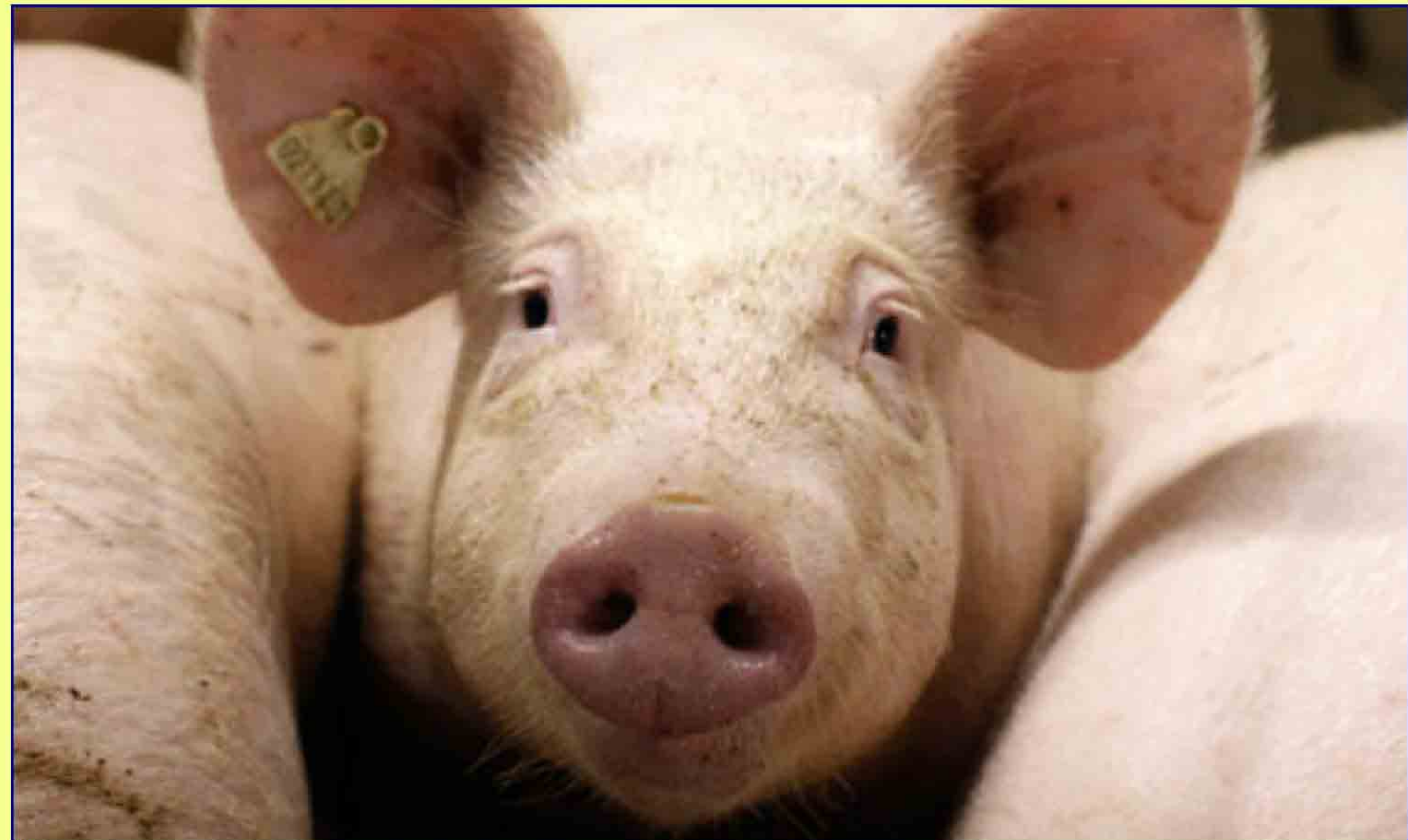
- (i) growth promotion/prophylactic use in animals;
- (ii) therapeutic/prophylactic use in humans;
- (iii) therapeutic/prophylactic use in aquaculture;
- (iv) therapeutic/prophylactic use in household pets;
- (v) pest control/cloning for plants and agriculture;
- (vi) use as biocides in toiletries and in hand care and household cleaning products; and
- (vii) culture sterility, cloning, and selection in research and industry.

therapeutic use in humans accounts for less than half of all applications of antibiotics produced commercially.

dumping of ciprofloxacin into rivers at levels in excess of 50 kg a day by pharmaceutical manufacturers in Hyderabad

many millions of metric tons of antibiotic compounds have been released into the biosphere over the last half-century

antibiotic resistance is a multifaceted global issue, and a coordinated **international effort will be needed**



Farms use double amount of antibiotics than humans
Small doses in feed curb low-grade infections
Antibiotics increase pigs' growth rate by 2.5%, the difference for farmers between profit and loss.
US\$1 per pound for a pig that costs about \$0.94 per pound to produce.
300mg of antibiotics to produce 1Kg meat and eggs
2009: 13,600 tonnes 80% of the antibiotics sold in US used on on animals that aren't sick. fatten up faster and prevent health problems in animals kept in extreme confinement (often filthy) conditions



Antibiotics in Farming

which antibiotic with your bacon sir?

2004: Holland, girl awaiting heart op screened +ve for MRSA. So did her family and their pigs!

swine have their own varieties of staph, and shouldn't get *S. aureus*, the human strain.

Sequence Type 398 *S. Aureus*: strain of resistant staph different from hospital and community variety; also resistant to tetracycline, routinely used in factory farming

spread widely across world. found on retail meat;

2012: Price et al: genetic analysis of **ST398** strains Originated humans; crossed into livestock, acquired the SCCmec cassette resistance genes then back to humans

Germany: 24% of farmers poultry and pigs were colonized with the animal MRSA strain **ST398**

Meat in 5 US cities, 47% contained *S. aureus*, 96% resistant to at least one antibiotic. 52% resistant to at least three antibiotics **ST1** in pigs, **ST5** in chickens and **ST398** in turkey.

2013: livestock-associated MRSA, drug-resistant staph, in UK poultry (Xmas Turkey's) for the first time

Risk is not food poisoning but transfer to skin

Resistant bacteria from farms are escaping

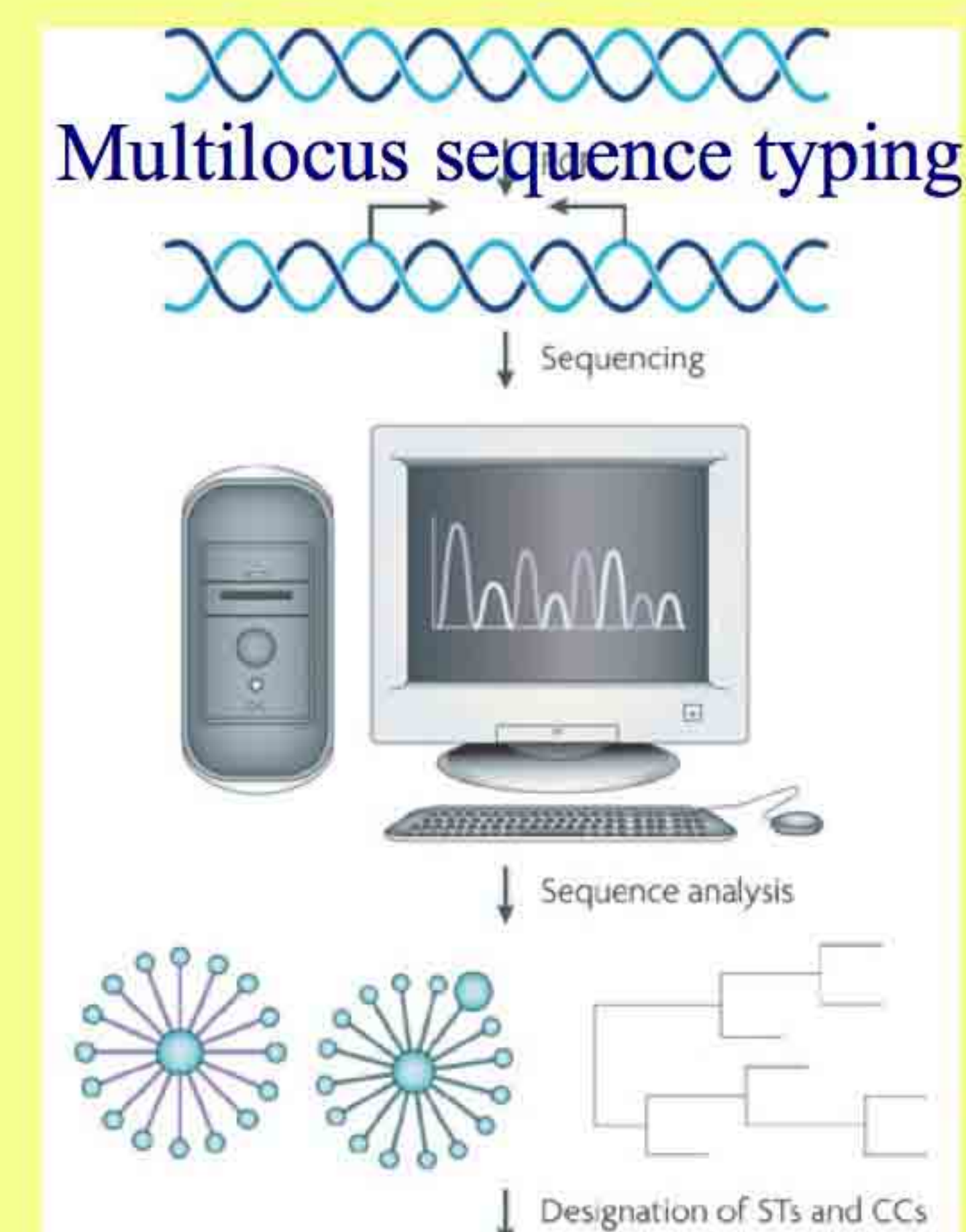
2006: EU banned antimicrobials to promote growth

Still able to be prescribed by a vet.

Tetracyclines, previously used as a growth promoter 50% of antimicrobial sales to farmers in the UK

2009: 350 tonnes of antibiotics used on UK farm animals

Dec 2013, FDA's new guidelines simply ask that industry voluntarily eliminate the routine use of antibiotics



Chromosomal genes and allelic designation	ST	CC
<i>arcC</i> <i>aroE</i> <i>glpF</i> <i>gmk</i> <i>pta</i> <i>tpiA</i> <i>yqiL</i>		
1 1 1 1 1 1 1	1	1
1 4 1 4 12 1 10	5	5
3 3 1 1 4 4 3	8	8
3 3 1 1 4 4 16	250	8
3 3 1 12 4 4 16	247	8

Nature Reviews | Microbiology

E.coli, new highly resistant type found on a large number of dairy, pig and poultry farms in England and Wales.

Post antibiotic world

After 90 years, antibiotics less effective.

1945: Nobel Address Fleming

“It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them... There is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.”

1924: 16-year-old **Calvin Coolidge Jr.**, son of the President blister on the toe playing tennis. Septicaemia dead in a week.

November 1930, **W.W. ("Dodger") Whysall**, Nottinghamshire cricketer, slipped on a dance floor, grazed his elbow, and died of septicaemia a fortnight later toured Australia as a member of the 1924-25 side, playing in three Test matches. He scored 75 at Adelaide and 76 at Melbourne.

Wisden cricketer of the year 1925

1:9 people with skin infection

3:10 pneumonia

5:1000 deliveries

Sore throats: kidney and chronic heart disease



Post antibiotic World

Sophie on her deathbed accompanied by her aunt Karen

A moment before the death of his older sister Johanne Sophie (1862–1877) from tuberculosis aged 15.

six completed oil paintings and many studies in various media, over a period of more than 40 years.

Nov 2013: Brian Poole operated on in Vietnam, returns to NZ dies of an infection totally resistant to everything!

A world where infection is so dangerous that even minor symptoms locked in confinement until they recover or die.

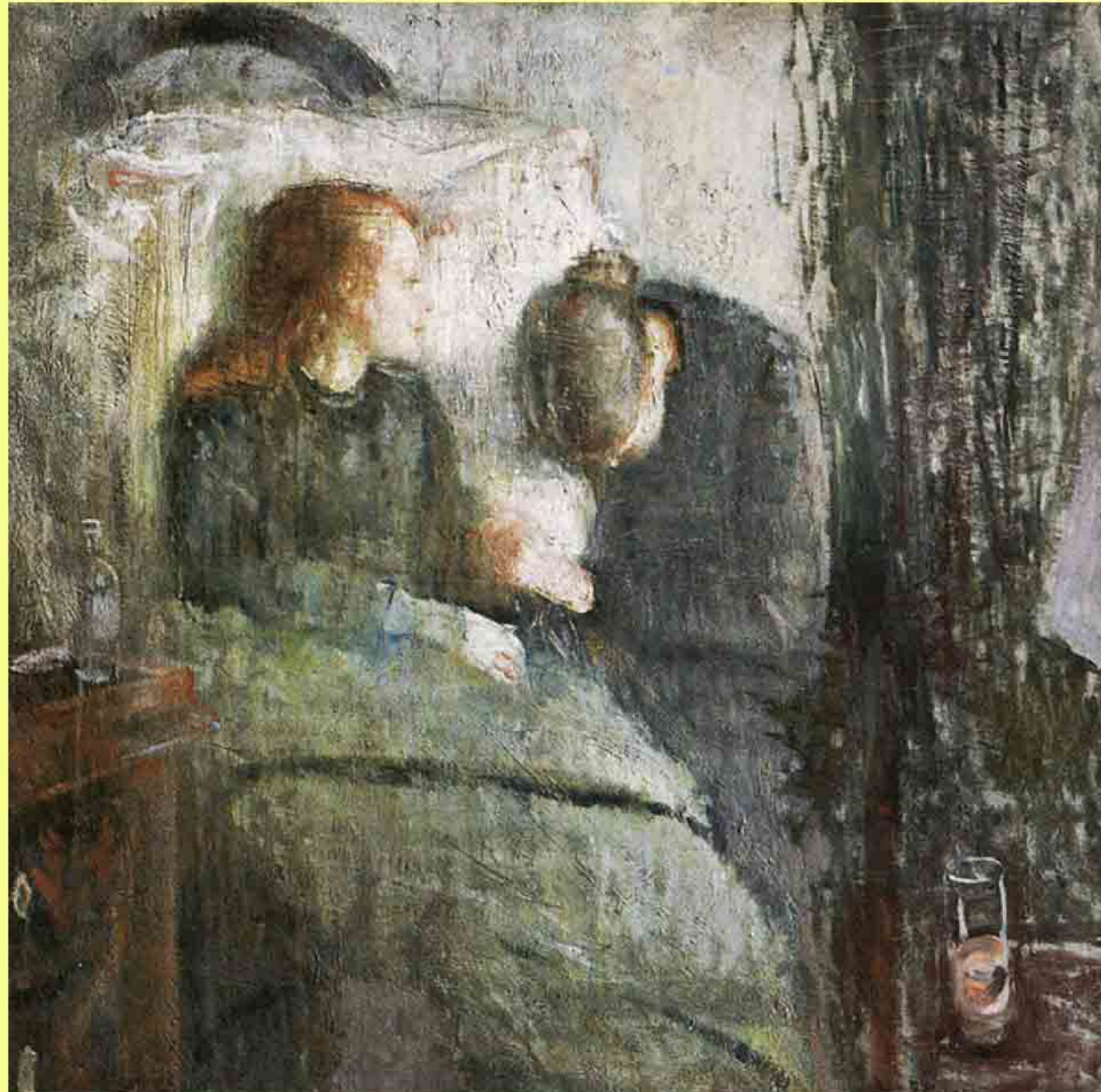
No routine surgery, no prosthetics (1:6 hip ops will die)

Childbirth becomes dangerous

Animal and fish protein prohibitively expensive

Unprotected sex resistant Gonorrhoea and Syphilis

Streptomycin-resistant fire blight, destroyed Michigan's orchards, now in upstate New York



Edvard Munch, *The Sick Child*, 1885–86



Christian Krohg, *The Sick Girl*

Pestilence, War, Famine, and Death

Four Horsemen of the Apocalypse are described by John of Patmos in his Book of Revelations, the last book of the New Testament.

A 'scroll', in God's right hand that is sealed with seven seals".

The Lamb of God, opens the first four of the seven seals, four beings ride out on white, red, black, and pale horses.

Interpretations differ

Conquest/Pestilence (infectious disease) War, Famine, and Death

First horseman conquering king **happens to sit on white horse**

"The horseman on the white horse was clad in a showy and barbarous attire. While his horse continued galloping, he was bending his bow in order to spread pestilence abroad.

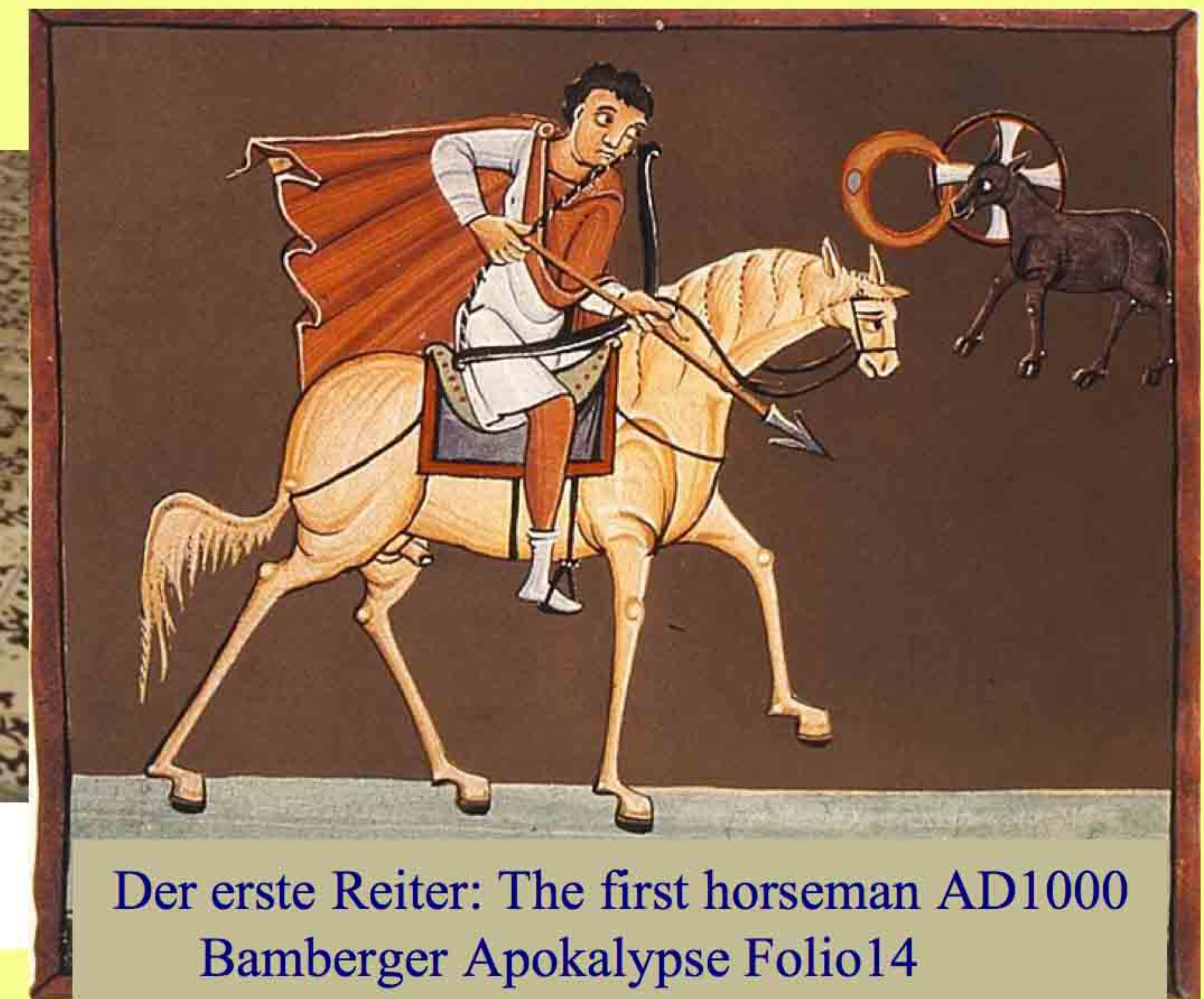
At his back swung the brass quiver filled with poisoned arrows, containing the germs of all diseases

Vicente Blasco Ibañez: 1916.

The vision is that the four horsemen are to set a divine apocalypse upon the world as harbingers of the Last Judgment.



Matthew 24:4-5, 11, 24	Religious deception	Revelation 6:1-2
Matthew 24:6-7	War	Revelation 6:3-4
Matthew 24:7	Famine	Revelation 6:4-5
Matthew 24:7	Pestilence	Revelation 6:7-8



Der erste Reiter: The first horseman AD1000
Bamberger Apokalypse Folio14

I watched as the Lamb opened the first of the seven seals. Then I heard one of the four living creatures say in a voice like thunder, "Come and see!" I looked, and there before me was a white horse! Its rider held a bow, and he was given a crown, and he rode out as a conqueror bent on conquest.

— **Revelation 6...1-2**

27-year-old Dürer published the text of the Book of Revelation with 15 woodcut illustrations compressed eight verses describing St John's visions (Revelation 6:1-8) into one scene. The first rider with a bow represents pestilence. The second, with a raised sword, represents war. The third, with the empty scales, represents famine. In front rides Death, sweeping citizens and a king into the jaws of Hades.



Four Horsemen of the Apocalypse
ca. 1497-98 Albrecht Dürer

THANK YOU

Patients

Teachers

Colleagues



Pieter Bruegel's "The Triumph of Death" Prado 1562

Death and diet in Victorian England

In C18th France half the children did not reach age 2

C19th: 1/3 children died before 1 year. Most of these deaths due to infectious disease

English death rate

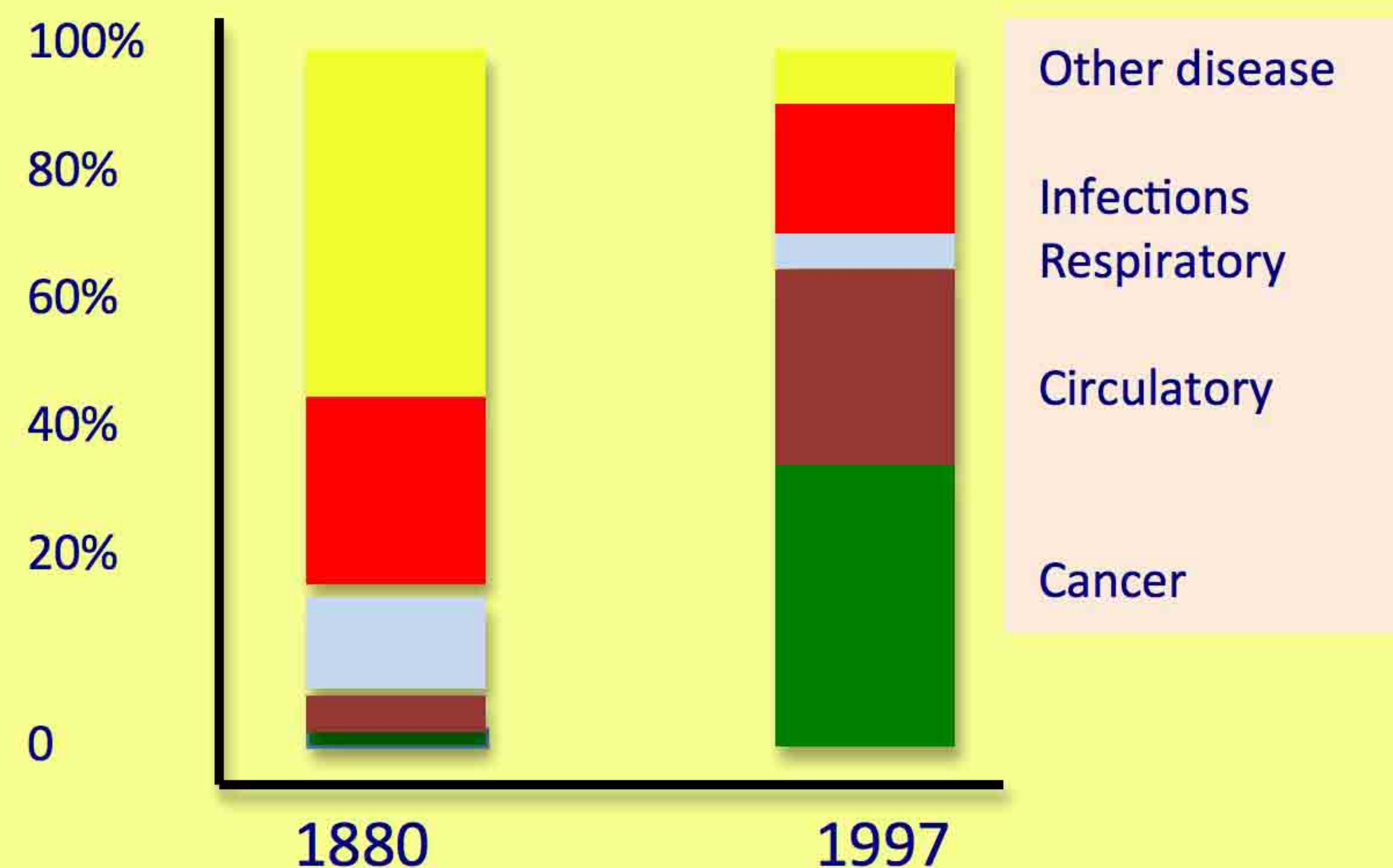
1740: 80 per 1,000.

1840: 23 per 1,000

2014: S. Leone worst death rate in the world: 22.1 per 1,000.

1. Infection: TB pneumonia; epidemics (scarlet fever, smallpox, influenza, typhoid, cholera etc), poor sanitation:.
2. Accidents/trauma burns open hearth cooking and fashions
3. Infant / mother mortality. infection, maternal haemorrhage
4. Heart failure. Valves rheumatic fever, not degeneration Angina appears in registrar general's records: 1857 a disease of old age
5. Cancer rare. Now common. Infectious causes known for many cancers

Causes of death England and Wales 1880 and 1997
Infection, trauma and infant / mother mortality
non-communicable degenerative disease insignificant.



We still die: Just of different things
Life is STD 100% mortality.

Improving survival and morbidity: Reducing burden of infectious disease?

By 1850's better: If survived 5yrs; adult life expectancy was 75 M; 73 F; remained in good health until their last few weeks of life.

2011: Blackpool: life expectancy 73.8: ONS data

UK Age 5 now 78

Clayton & Rowbotham: 1850's to 1880: Removing childhood mortality, the mid Victorian lived as long as we do and consumed 200% more calories non-sedentary

1.5% deaths malnutrition (similar today!)

Better diet, nutrient full organic fruit and veg

Better food production; Viscount Charles 'Turnip' Townshend

Repeal of Corn Laws: ends the hungry 40's

Fish, eggs nuts

Weaker alcohol beer 2%

Canning/bottles: Legislation: Less adulteration:

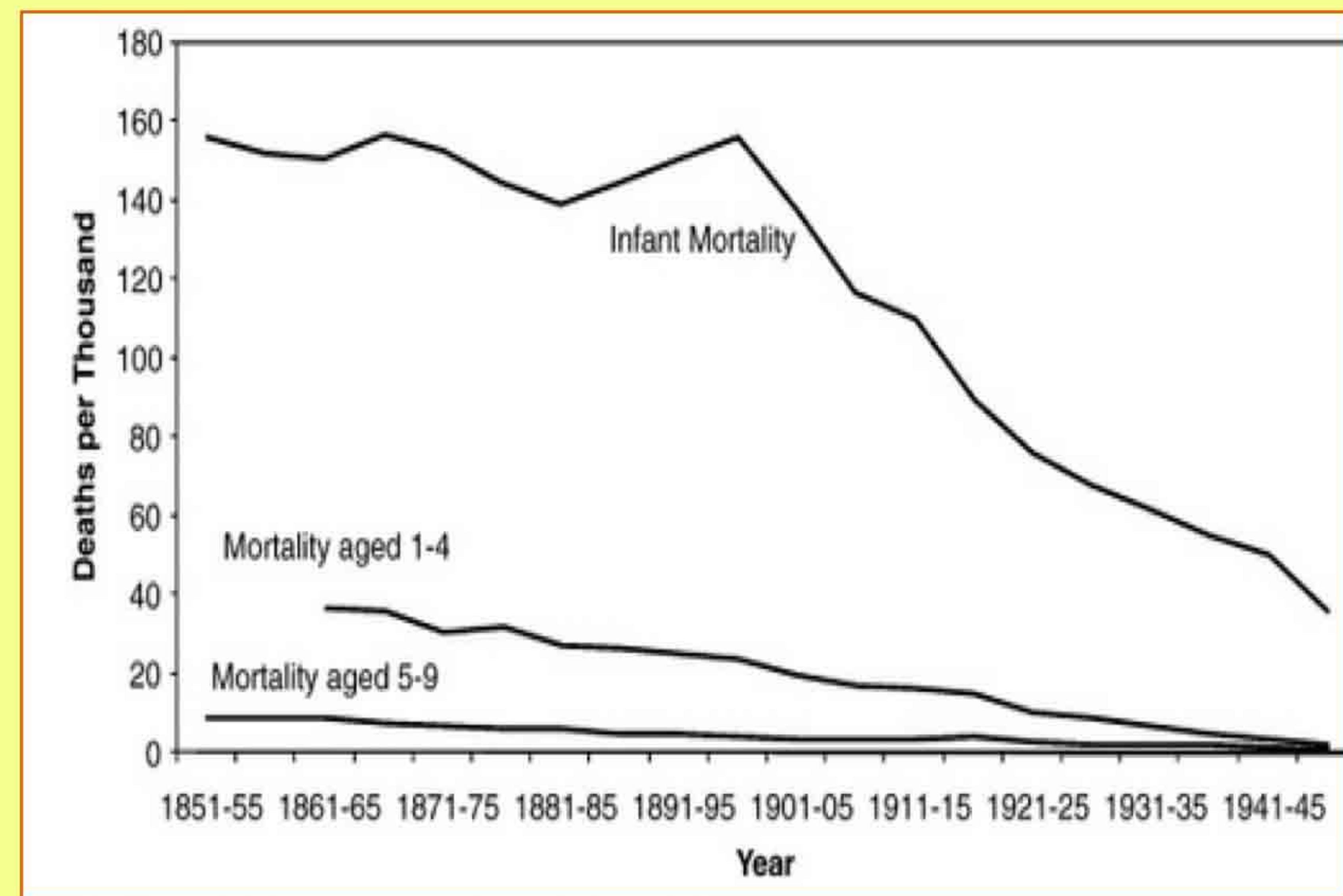
Squandered by high sugar, margarine and tobacco

By 1901 Army has to reduce height requirement

STATISTICAL NOTE

hypothetical country
50% child mortality,
rest die exactly 70 yrs,
life expectancy ~37 years,

However life expectancy at age 5 would be another 64 years.



Virus

Bacteria:

Archea:

Chlamydia:

Protists

Microfilaria

Drug resistance

21st century threats

Virus infections

Different strains of flu viruses adapt to specific hosts.

Influenza C: Humans and pigs

Influenza B: Humans and Seals

Influenza A: Influenza in birds (and some mammals, pigs)

A Subtypes: **H** (haemagglutinin) **N** (neuraminidase),

To release virus from the cell, **N** cleaves sialic acid groups from host glycoproteins

H1, H2, and H3: human flu viruses. **H18:** Peruvian fruit bat
1997: Avian flu virus H5N1 mutates to infects humans at a low rate. Bird Flu: single a/a change provided ability to bind to human receptors. Kills 50%!

2009 swine flu-pig origin: H1N1 influenza A epidemic

Spanish Flu: subtype of avian strain **H1N1**

First wave: Mar 1918: Fort Riley, Kansas, recruiting camp

Over 5 weeks 1,127 infected 46 died

Second wave: August. France; Mildly ill stayed in trenches.

Sicker soldiers hospitalised together selecting deadly strains.

Mortality 10-20% (normally 0.1%) H1N1 or 2⁰ pneumonia

Third Wave: Armistice November

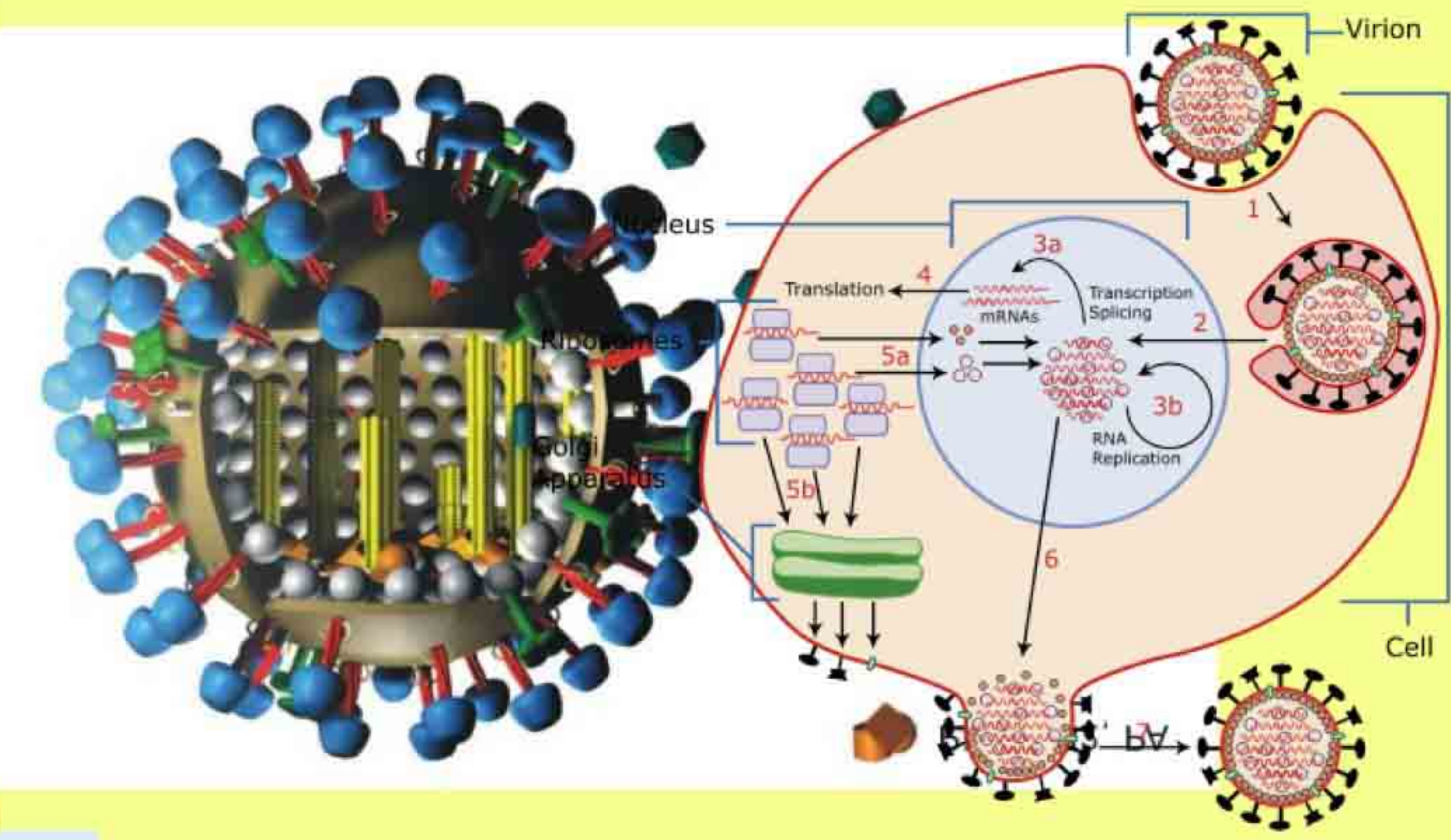
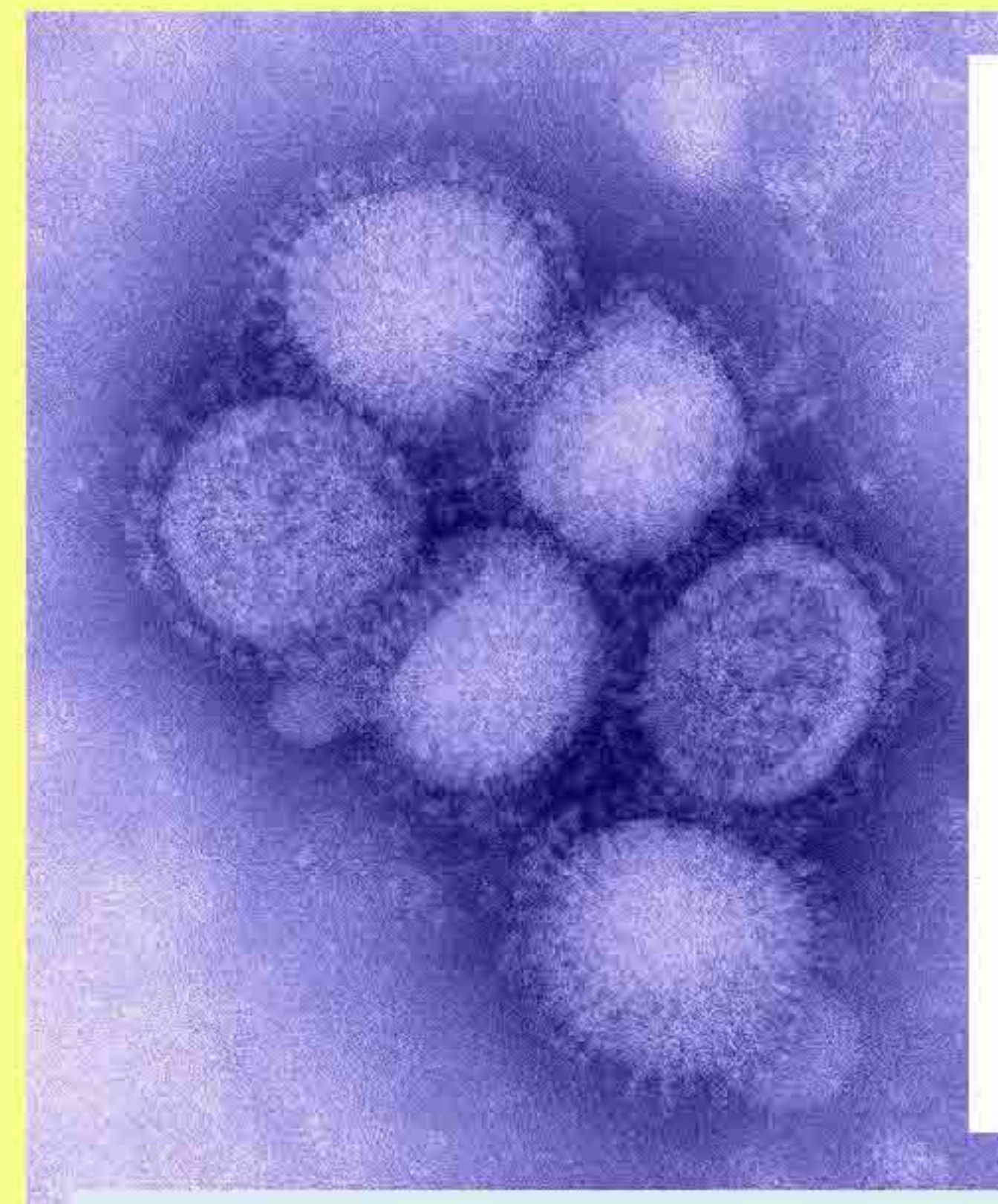
More people died in 1 year than in Black Death of 1347-51

3-6% World's Population 50-100m deaths

War censorship not applied in Spain. SPANISH FLU

Birds to pigs to soldiers.

Originated in mammal 1882-1913. ancestor virus diverged 1913-15 two groups, swine and human Pigs more readily infected with avian flu, passing virus to humans 1913-1918.



Orthomyxoviridae ssRNA
lipid membrane derived from host cell.

Glycoproteins, stud surface: **HA** and **NA**. determine virus subtype AB against glycopr protect against infection.

NA protein target Tamiflu.

Major changes in A HA "**antigenic shift**" reassortment from different A subtypes, between animal and human subtypes, shifted strains capable of causing global pandemic outbreaks

