

**The discovery of “*Clostridium*” and its
clinical impact:
An insight into the history of medicine**

**Conference on New Frontiers
in
Microbiology and Infectious Diseases**

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*Those who cannot remember the
past are condemned to repeat it*

George Santanyana

(1863 - 1952)

The Life of Reason

The discovery of “*Clostridium*” and its clinical impact: An insight into the history of medicine

Desire of man “to make sense out of illness”

Hippocrates of Cos (460 to 377 B.C.):

Imbalance of four humours associated with four elements
causes disease:

blood and fire	:	hot and dry
yellow bile and air	:	hot and wet
black bile and earth	:	cold and dry
phlegm and water	:	cold and wet



Separation of practice of medicine from superstition and religion.

**The discovery of “*Clostridium*” and its clinical impact:
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Desire of man “to make sense out of illness”

Claudius Galen (A.D. 129 – A.D. 216)

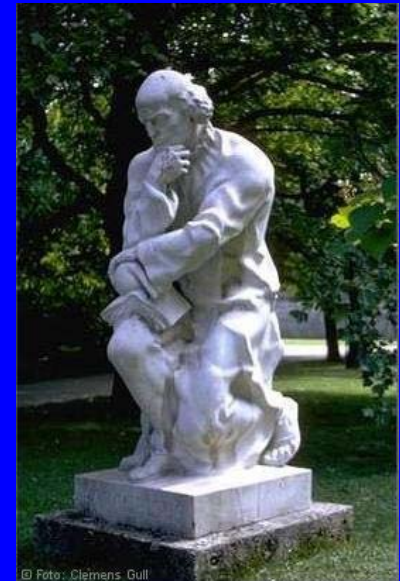
Anatomical and physiological studies: interpretation of findings within Hippocrates’ concept of imbalance of four humours. He influenced practice of medicine into 17th century.

The discovery of “*Clostridium*” and its clinical impact: An insight into the history of medicine

Desire of man “to make sense out of illness”

Paracelsus (1493-1541)

“...the profound understanding of nature and its secrets are expected from a doctor.”



Time line of microbiology

- 1546 - Girolamo Fracastoro: “De contagione seminaria morbi et seminaria contagium”
- 1674 – Antony van Leeuwenhook: “Animalcules minimissime”
- 1749 – Carolus Linnaeus: system of binominal nomenclature and classification of plants
- 1835 – Agostino M Bassi: muscardine of silkworm is caused by a fungus

Time line of microbiology

1838 – Christian G Ehrenberg: “Infusionstierchen”:
Bacterium, Spirillum, Vibrio, Spirochaeta

1840 - Friedrich GJ Henle: “Pathologische Untersuchungen”
“Germ theory of disease”

1849 – Ferdinand Cohn: carmine and haematoxylin for
staining of histological sections

Time line of microbiology

1858 – Rudolph Virchow: “Cellularpathologie”:

1861 – Louis Pasteur: “anaërobies”: butyric acid fermentation by bacteria in the absence of oxygen

1865 – Jean A Villemin: demonstrates that TB is caused by a specific infectious cause

1865 – Julius F Cohnheim: confirms Villemin’s findings

Time line of microbiology

1872 – Ferdinand Cohn: “Untersuchungen über Bakterien”:
establishes “Bacteriology” as a separate science

1876 – John Tyndall: “Tyndalization”:
basis for final move from “doctrine of spontaneous generation of micro-organisms in nutrient fluids”

Carl Weigert: methylene blue for microscopy in aqueous suspension

Robert Koch: “Die Aetiologie der Milzbrandkrankheit”
Confirmation of “Germ Theory of Disease”

Time line of microbiology

- 1878 – Ernst Abbé: numerical aperture and oil immersion microscopy
- 1880 – Adam Prazmowski: “*Clostridium*” term for anaerobic bacterium that forms spindle-shaped endospores
- 1884 – Robert Koch: “*Die Aetiologie der Tuberculose*”
“Koch-Henle Postulates”

Time line of “immunology”

500 – China: “*smallpox immunization*” by blowing dried scabs into nostrils

1715 – Giacommo Pylarini: description of “*vaccination*” of children against smallpox in 1701 in Constantinople

1717 – Mary M Montagu: “*ingrafting*” of children in Constantinople

Time line of “immunology”

1721 – Cotton Mather and Zabdiel Boylston “*smallpox inoculation*” during an epidemic in Boston

– Hans Sloane: experimental small pox “*variolation*” on condemned prisoners at Newgate prison as permitted by King George I

1764 – Angelo Gatti: publishes inoculation against smallpox using pus from infected persons

Time line of “immunology”

- 1774 – Benjamin Jesty: use of material from cowpox lesions for vaccination against smallpox
- 1776 – George Washington: inoculation of whole army against smallpox using material from infected patients
- 1778- Edward Jenner: *“An inquiry into the causes and effects of the variolae vaccine, a disease discovered in some of the western countries of England, particularly Gloucestershire, and known by the name of Cow Pox”*

Time line of “immunology”

1881 – Louis Pasteur: *“Sur les virus-vaccins du choléra des poules et du charbons”*

1884 – Elias Metschnikoff: *“Über eine Sproßpilzerkrankung der Daphnien. Beitrag der Lehre über den Kampf der Phagozyten gegen Krankheitserreger”*

1890 – Behring and Kitasato *“Über das Zustandekommen der Diphtherie-Immunität und der Tetanus- Immunität bei Thieren”*

Discovery of C.tetani

The discovery of *C.tetani* is the perfect success story of the newly established sciences of bacteriology and immunology.

Discovery of C.tetani

- 400 B.C: Hippocrates: Description of a clinical condition compatible with tetanus
- 1884: Confirmation of transmissibility: Carle and Rattone inject pus obtained from patient with tetanus into test animals.
- 1884: A. Nicolaier produces tetanus by inoculating soil into animals
- 1886: J.Rosenbaum describes “Clostridia” in human wound secretions

Discovery of C.tetani

1889: Kitasato isolates *C.tetani* from a human victim and confirms its pathogenic role by applying Koch's postulates.

1890: Kitasato demonstrates in addition:

- that tetanus toxin causes clinical picture of tetanus
- that “antiserum” can prevent tetanus
- that “antiserum” is highly specific

Discovery of C.tetani

1891: Availability of “*Tetanus antiserum*” for therapeutic purposes



Discovery of C.botulinum

The discovery of *C.botulinum* is the perfect success story of the newly established sciences of bacteriology and epidemiology.

Discovery of C.botulinum

900: The Byzantine Emperor Leo VI bans consumption of blood sausages because of association with fatal food poisoning compatible with botulism

1820: Justinus Kerner: complete description of clinical condition of “Wurßtvergiftung” or “Botulismus” as associated with consumption of sausages:

- comparative epidemiology
- intoxication of animals
- “self intoxication” with diluted extract from suspected sausage

Discovery of C.botulinum

1897: Emile van Ermengen: “*Ueber einen neuen anaëroben Bacillus und seine Beziehungen zum Botulismus.*”

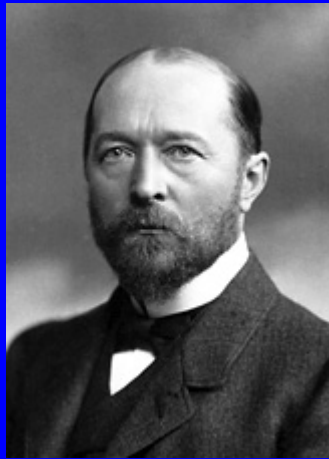
- Formulation of a case definition
- Confirmation of epidemiological association with consumption of suspicious bacon
- Fulfilment of Koch’s postulates

Late 20th century: Exploration of botulinum toxin for pain therapy

Management of infection

Controversy about the treatment of infectious diseases:

1. Immune therapy



Emil von Behring
1845-1917

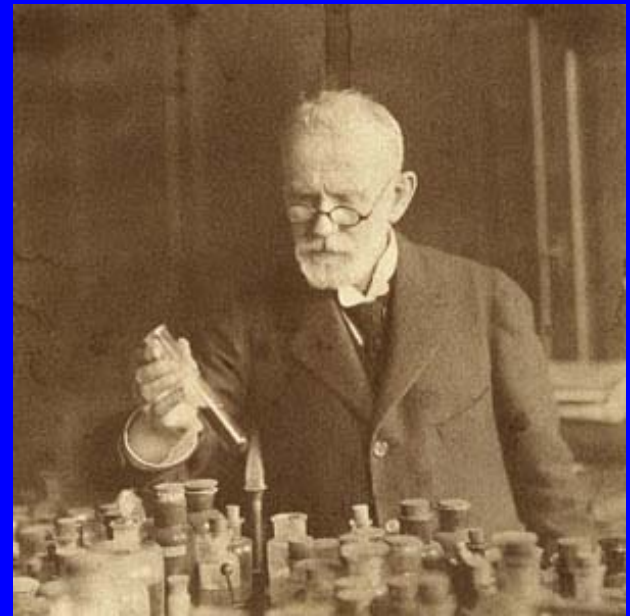


Kitasato Shibasaburo
1853-1931

Management of infection

Controversy about the treatment of infectious diseases:

1. Immune therapy
2. Chemotherapy “Magic bullet”



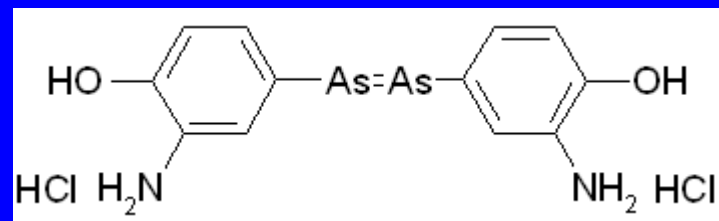
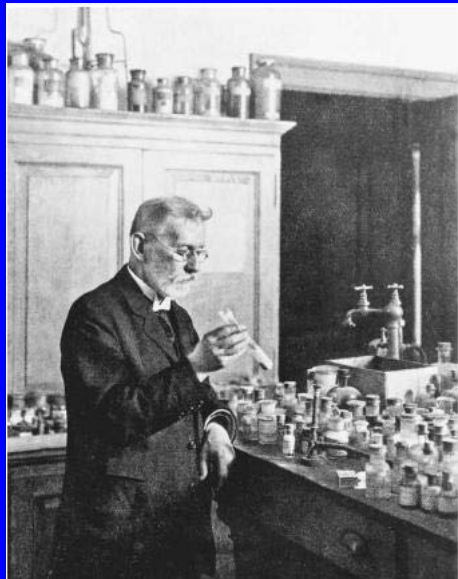
Paul Ehrlich
1854-1915

Management of infection

Paul Ehrlich:

1909: Introduction of Salvarsan for the treatment of syphilis

1912: Introduction of Neo-Salvarsan for the treatment of syphilis



Management of infection

Gerhard Domagk:

1935: Introduction of the first sulphonamide **Prontosil**



Management of infection

Controversy about the treatment of infectious diseases:

1. Immune therapy
2. Magic bullet
3. Surgery



Discovery of C.perfringens

The discovery of *C.perfringens* is the
perfect success story of the
newly established science
of
Bacteriology

however its treatment is controversial !

Discovery of C.perfringens

400 BC: Hippocrates: Description of a clinical condition compatible with gas gangrene

25 AD: Celsus provides similar evidence

1854-1856 Crimean War: N.I. Pirogoff describes classical clinical presentation, also known as “hospital gangrene”



Discovery of C.perfringens

1892: Welch and Nuttall: *Bacillus aerogenes capsulatus*

Welch WH, Nuttall GHF. A gas-producing bacillus (*Bacillus aerogenes capsulatus*, Nov. Spec.) capable of rapid development in the body after death. Bull Johns Hopkins Hosp Baltimore.1892;3:81–91.

1893: E Fraenkel: *Bacillus. phlegmonis emphysematosae*

E Fraenkel: Ueber die Aetiologie der Gasphlegmonen (Phlegmone emphytematosa) Zentralblatt für Bakteriologie und Parasitenkunde, 1893, Vol 13, 13-16

1893: E Fraenkel: Ueber Gasphlegmonen

Detailed study about various clinical presentations

1896: Welch and Flexner confirm that both isolates are in fact the same species

Discovery of C.perfringens

1914-1918: World War I

“Epidemic of Gas Gangrene”

What happened ?

History of wound management

1513 – Giovanni da Viga “*Practica copiosa in chirugica*”

1536 – Ambroise Paré: Ligation of blood vessels and improved “wound balsam”

17xx – Hunter: inflammation leads to wound healing

James Cook: Application of tea tree leafs onto wounds

1801 – John Rollo: banning of “wound sponges”

*“the (combat) wound must
forthwith be enlarged . . . so that
there may be free passage for
both the puss or matter . . .
obtained therein”*



Ambroise Paré
(1510-1590)

French Army Surgeon

...establish the making of a deep incision to explore a wound, remove dead tissue, and provide drainage - credited with coining the term “debridement”

Pierre Joseph Desault

(1744-1795)

French Military Surgeon

Dominique Jean Larrey (1766-1842)

Napoleon's Surgeon

Debridement for:

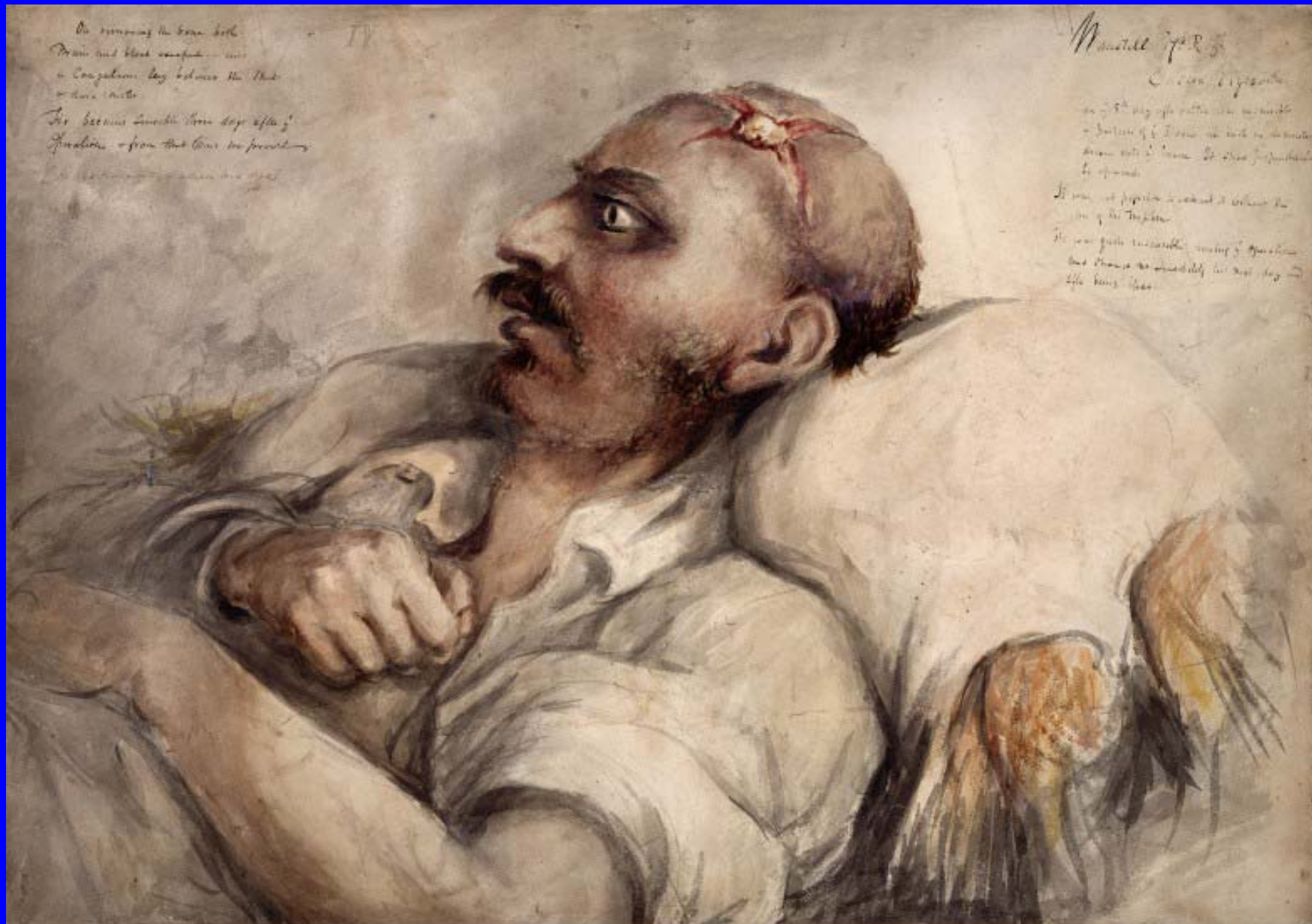
- the release of ecchymotic wounds
- removal of foreign bodies
- uncover and ligate arteries
- “freshen up” skin edges

Amputation

- if debridement unlikely to succeed







History of wound management

19th Century:

Ongoing controversy:

Aggressive surgical intervention

versus

Careful conservative approach

The American Civil War (1861 – 1865)

- Only 3% of “shot” wounds to the extremities were incised (debrided)
- Debridement was thought to hasten inflammation and gas gangrene
- Amputation was the Orthopedic Surgery of Choice
- Mini ball (.50 cal) missile
 - Low velocity
 - Highly inaccurate
 - Little damage outside the missile tract



Discovery of C.perfringens

1914-1918: World War I

“Epidemic of Gas Gangrene”

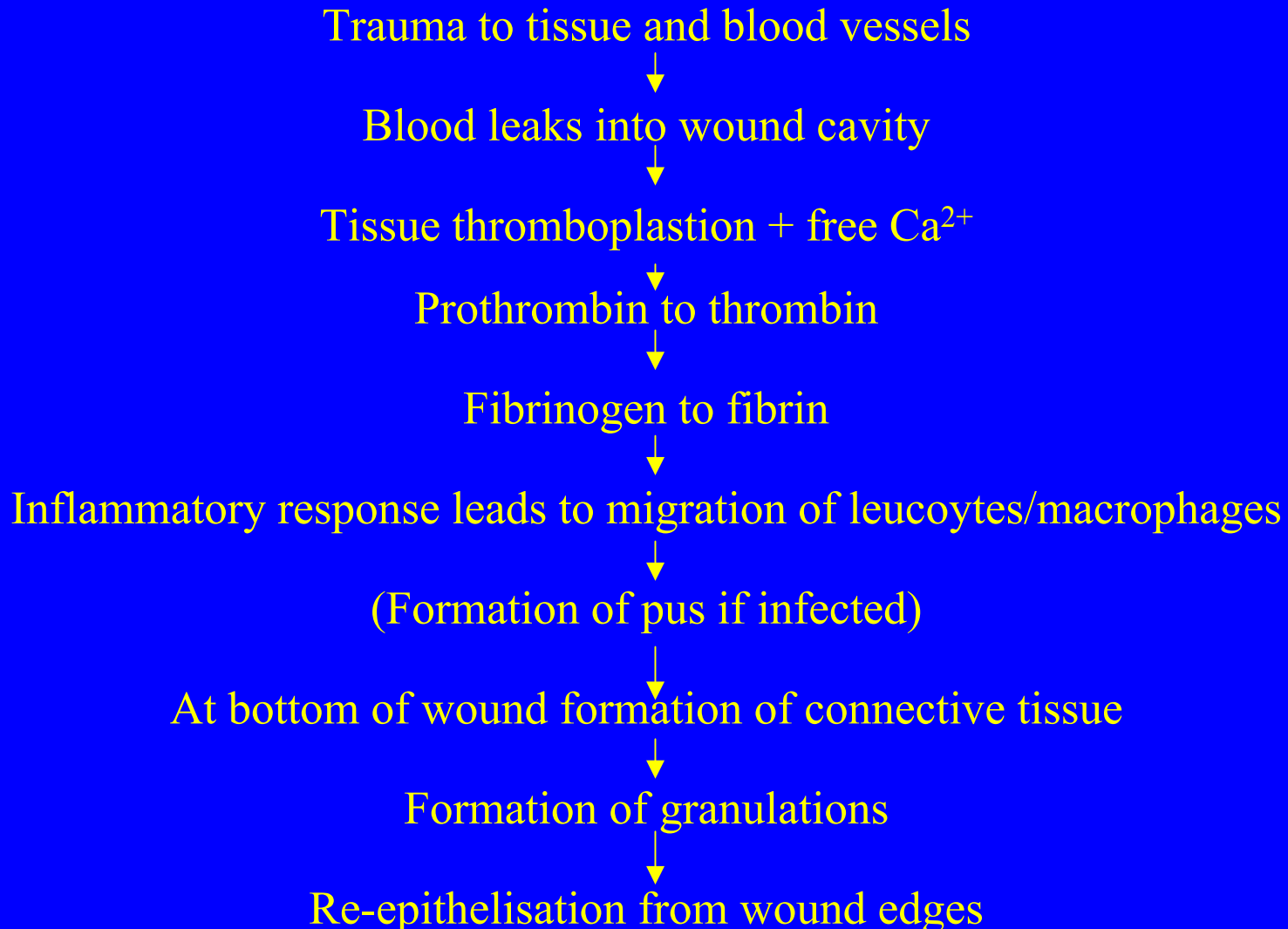
What happened ?

World War I

- Debridement was a technique that belonged to antiquity.
- Debridement was felt to be too invasive and of doubtful benefit.

W h y ?

Understanding of physiology of wound healing (at about 1900)



... Physiology of wound healing

Trauma to tissue and blood vessels



Blood leaks into wound cavity



Tissue thromboplastin + free Ca^{2+}



Prothrombin to thrombin



Fibrinogen to fibrin



Inflammatory response leads to migration of leucocytes/macrophages



Formation of pus



At bottom of wound formation of connective tissue



Formation of granulations



Re-epithelisation from wound edges



Reconstitutio ad defectum

Contamination:
environment, hands,
surgical instruments



Bacteria enter wounds



Wound infection



abscess
gangrene
etc



World War I

- Soldiers on both sides lived under atrocious conditions
- Battle fields were farmland fertilized with manure:

Bacterial epidemiology (Zeissler 1928):

<i>C.perfringens</i>	100%
<i>C.novyi</i>	64%
<i>C.tetani</i>	27%
<i>C.septicum</i>	8%
<i>C.septicum</i>	2%

Zeissler, Raßfeld: Die anaerobe Sporenflora der europäischen Kriegsschauplätze 1917. (1928) Kriegs. U. Konst. Path; 5, p 2ff

World War I

- Soldiers on both sides lived under atrocious conditions
- Battle fields were farmland fertilized with manure
- Penetrating injuries were always associated with deep inoculation of fragments of uniform tissue contaminated with bacterial spores into severely damaged tissue

World War I

- The energy of “projectiles” increased dramatically:
 - Explosive artillery shells (shrapnel)
 - Mass production of machine guns
 - High velocity, high accuracy rifles



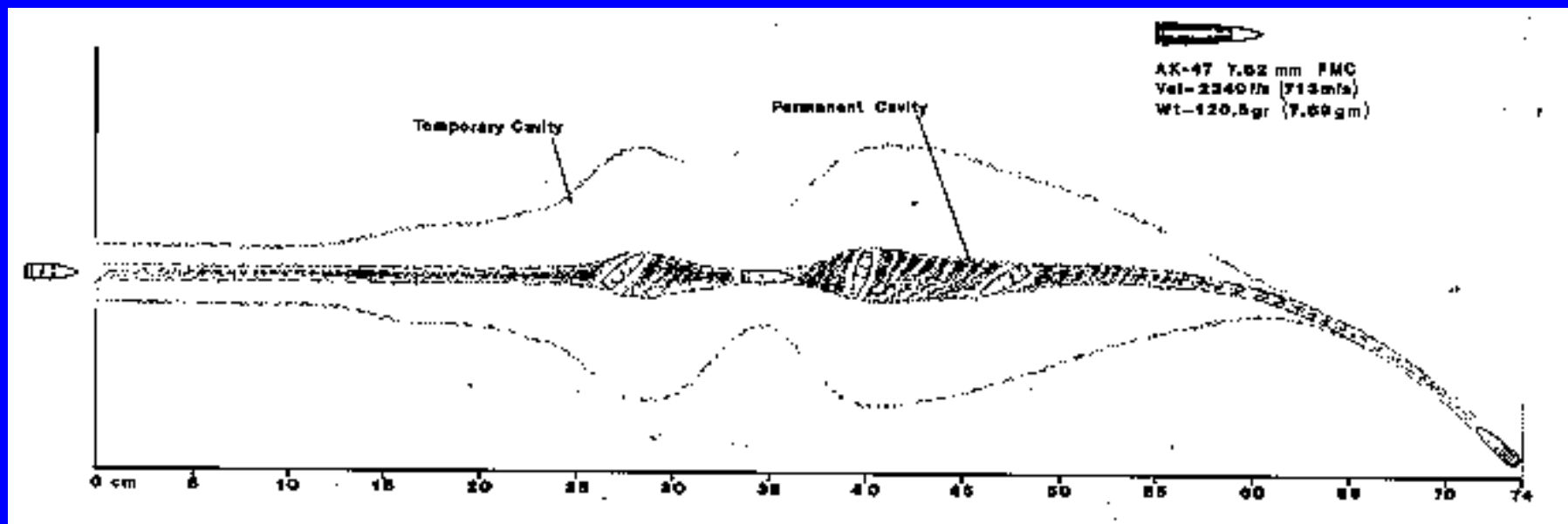
Progress in warfare technology



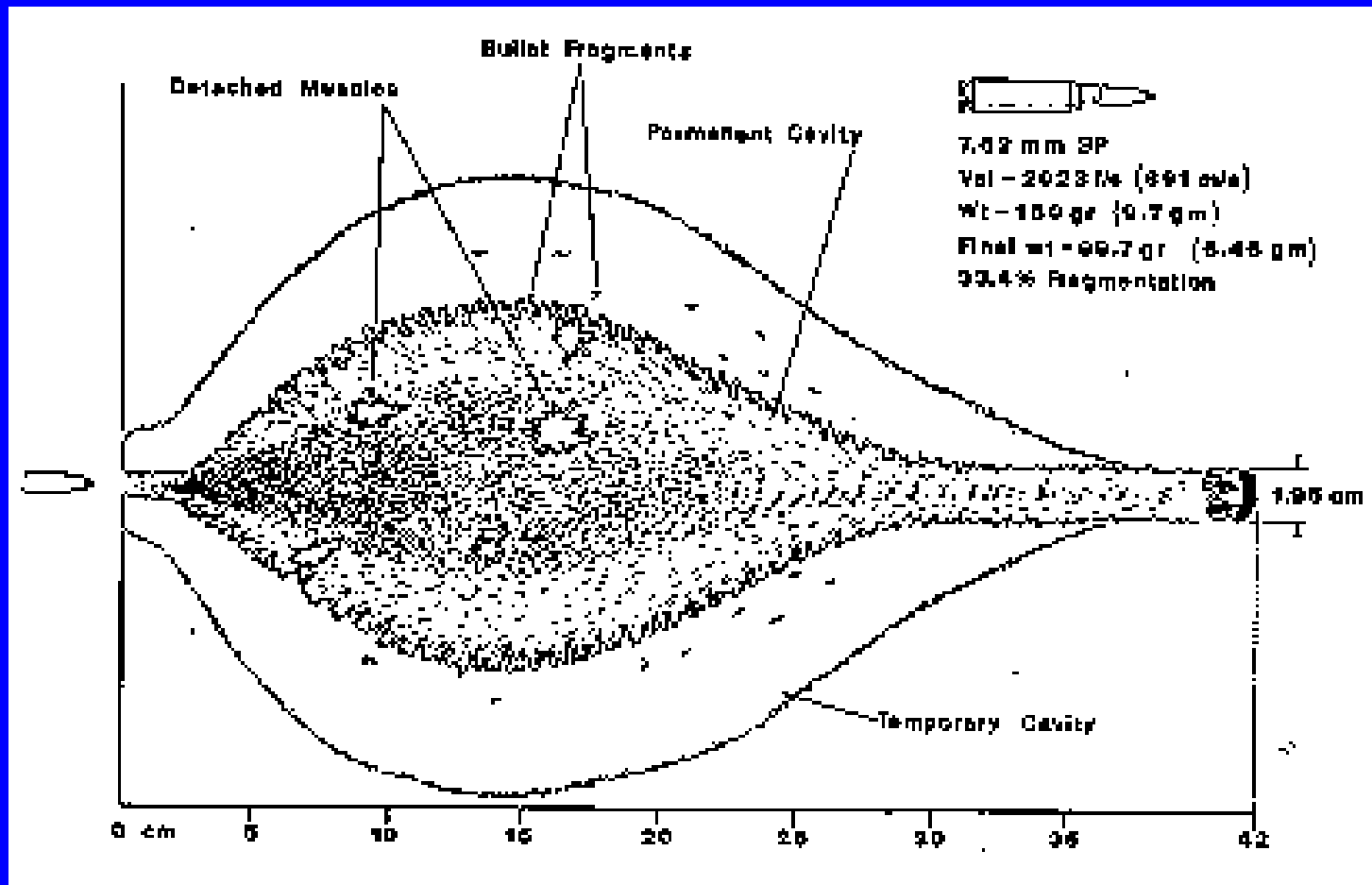
Progress in warfare technology



Full metal jacket 7.62mm Russian AK-47 / Chinese SKS



Soft point lead missile



Belgium 1914



*“Gentlemen
Surgeons,
do not abuse
injured
soldiers with
frivolous and
unnecessary
surgeries”*



World War I

What lessons were learned?





Antoine Depage



Ambulance de l'Ocean
La Panne, Belgium
12 miles from the front

Depage's Principles of War Surgery

- Treat all penetrating wounds as contaminated
- Resurrected the Napoleonic War practice of deep incisional wound exploration
- Advocated the excision of non-viable tissue

DePage formally described:

Primary Closure (suture immediate)

invites suppuration and gangrene... of little use in combatant's wounds

Delayed Primary Closure (suture primitive retardé)

Secondary Closure (suture secondaire)

Epidemiology of gas gangrene in WW I

Varies, depending on sources:

British data: 120/1000 \Rightarrow 25% mortality

German data: approx 150,000 deaths 2nd to gas gangrene

US data (Middle east): 3.6 in 1000

Management of gas gangrene

1. Immune therapy
2. Surgery

Management of infection after 1918

1. Immune therapy
2. Surgery

Concept of antimicrobial chemotherapy: Penicillin

- 1887: Louis Pasteur and Jules F Joubert observed inhibition of anthrax cultures by moulds
- 1928: Alexander Fleming observed anti-staphylococcal activity of *P.notatum*
- 1938: Howard Walter Florey initiated research to produce stable penicillin
- 1944: Pfizer (USA) produces penicillin G at industrial scale

Concept of antimicrobial chemotherapy: sulphonamides

Gerhard Domagk:

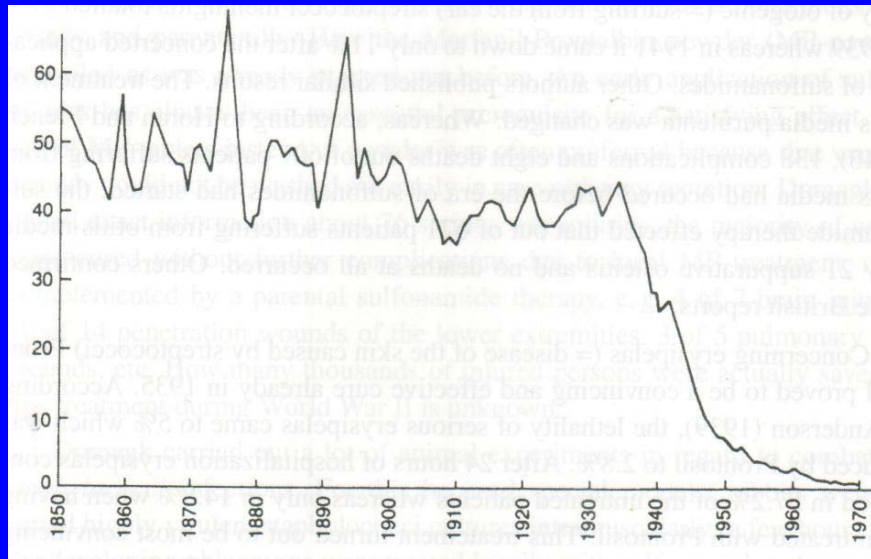
1935: Introduction of the first sulphonamide **Prontosil**



Concept of antimicrobial chemotherapy: sulphonamides

Gerhard Domagk:

1935: Introduction of the first sulphonamide **Prontosil**



Mortality secondary to puerperal fever in England and Wales per 10,000
Bynum WF, Porter R (1993) Companion Encyclopedia of the History of Medicine

Discovery of C.perfringens

Controversy about the treatment of gas gangrene

Immune therapy

versus

Chemotherapy

Concept of antimicrobial chemotherapy: sulphonamides

Gerhard Domagk:

1935: Introduction of the first sulphonamide **Prontosil**



Concept of antimicrobial chemotherapy: Treatment of gas gangrene

Gerhard Domagk:

1941: Introduction of Marfanil



benzyl-amine-4-sulphon-amide

Concept of antimicrobial chemotherapy: Treatment of gas gangrene

Gerhard Domagk:

1941: Introduction of Marfanil



benzyl-amine-4-sulphon-amide

Pfaff, Gasbrand und Gasbrandprophylaxe. D. Dtsch Mil.arzt (1944), 9, 315ff

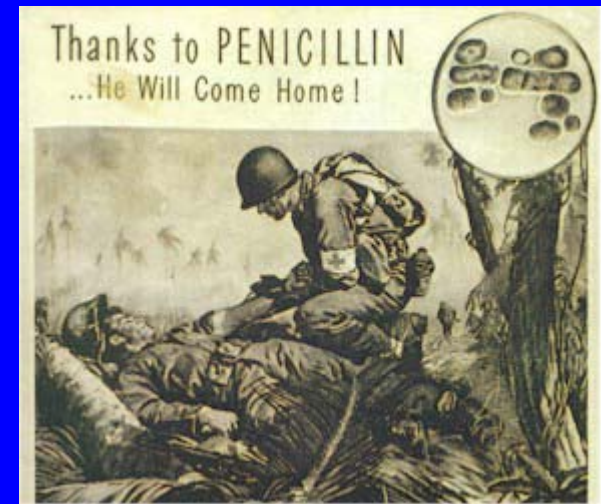
Mitchell GAG, Ress WS, Robinson CN, Lancet 635, May 13, 1944

Concept of antimicrobial chemotherapy: Treatment of gas gangrene

TABLE 8
Penicillin and Mortality Rate
(From McFarlane (46))

	PENICILLIN			NO PENICILLIN			DIFFERENCE ± S.E.
	Cases	Deaths	Rate	Cases	Deaths	Rate	
Gas Gangrene of Arm or Leg							
Group I.....	23	6	26.1	11	1	9.1	-17 ± 15
Group II.....	8	2	25	30	16	53.3	28 ± 20
Group III.....	1	1	100	11	10	90.9	-9 ± 29
Gas Gangrene of Thigh, Buttock or Shoulder							
Group I.....	13	5	38.5	11	6	54.5	16 ± 20
Group II.....	8	6	75	32	26	81.3	6 ± 16
Group III.....	6	6	100	31	31	100	

Group I—Treatment within 6 hours of diagnosis, including surgery and antitoxin.
Group II—Treatment later than 6 hours or less than 50,000 units of antitoxin.
Group III—No surgery, no antitoxin.



Treatment of gas gangrene at end of WW II

1. Antibiotics: Marfanil or penicillin
2. Polyvalente gas gangrene antiserum
3. Surgery

Current Principle of Debridement

(some things never change)

- Explore the wound
 - Define the damage, follow the trajectory of the missile
 - Radiographs are key to finding metal/foreign bodies & fractures
 - Always incise parallel to the axis of the extremity
 - Release all compartment's fascia
- Excise nonviable tissue and debris

Modern Surgical Management: cABC's +

- All non-viable tissue is excised in hours of wounding
 - Muscle excision (4C's)
 - Colour
 - Consistency
 - Contractility
 - Circulation
- All debris is removed
- Involved compartments are released
- Dressing change in the OR in 2 – 3 days
- DPC if the wound is clean
- Appropriate antibiotic coverage

*Those who cannot remember the
past are condemned to repeat it*

George Santanyana

(1863 - 1952)

The Life of Reason

The discovery of “*Clostridium*” and its clinical impact:

An insight into the history of medicine

In conclusion:

The discovery of *Clostridium spp* contributed to the development of essential principles of microbiology and the subsequent advancement of therapeutic approaches provided the basis for future cures and preventive strategies in health care:

- *C.botulinum*: preservation of food and using the toxin as a therapeutic agent
- *C.tetani*: passive and active immunisation
- *C.perfringens*: combination of different (“ancient”) therapeutic approaches leads ultimately to improved outcome

Acknowledgement

I would like to thank my colleague

Lieutenant Colonel
Ben Banerjee
Consultant Surgeon
Clin Senior Lecturer
Sunderland Royal Hospital

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material presented.