Chapter 0

Introduction to immunology - a historical perspective
免疫學的發展歷史

陳炳宏副教授

生物科技學系

第一教學大樓N1020/1023 (分機: 2676)

bhchen@kmu.edu.tw

http://allergy.kmu.edu.tw

Immunology: to understand the resistance to re-infections

- As early as 2000 BC, disease, pestilence, and epidemics were recorded in Egypt.
- Until recent centuries, diseases were regarded as a punishment from God in various religions.

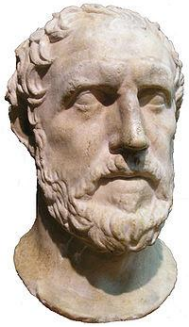
Immunology: to understand the resistance to re-infections

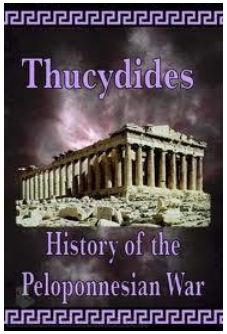
- BUT: Individuals having survived a disease might often be spared further involvement on the RETURN of the same disease, a phenomenon known as **IMMUNITY**.

- This was recorded at least 25 centuries ago.

- In 430 BC, a plague (the true pathogen is unknown) swept through Athens. Historian **Thucydides** documented in "**History of the Peloponnesian war**" that those who survived an attack did not experience the plague again.

Pre-historical Event in Immunology





Thucydides (修斯提底斯), B.C. 460-395

- Greek historian
- Author of "History of the Peloponnesian War" 【伯羅奔尼撒戰爭史】
  - Ancient war between Sparta and Athens
- Showed an interest in developing an understanding of human nature to explain behavior in such crisis as **plague**.
  - Patients contracted and recovered from plague are *immune* from re-contracting plague

Immunity

- ***Law***. Exemption from a service, obligation, or duty; Freedom from liability to taxation, jurisdiction, etc.; Privilege granted to an individual or a corporation conferring exemption from certain taxes, burdens, or duties.

- ***Health*****.** Nonsusceptibility (resistance) to the invasive or pathogenic effects of foreign microorganisms or to the toxic effect of antigenic substances

- The term "**immunity**" was first used in 1775 by Van Sweiten, a Dutch physician, as "immunitas" to describe the effects induced by an early attempt at variolization.

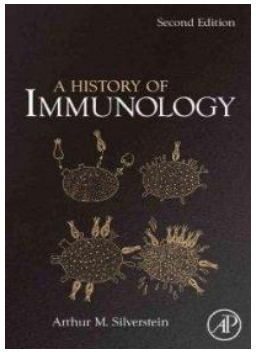
Development of Immunology as a Modern Discipline

I. Experiential immunology period (~ A.D. 1600-1850)

II. Experimental immunology period (~A.D. 1850-1950)

III. Modern immunology period (A.D. 1950 – present)

- Immunology acts as an independent subject:
  - In 1971, by International Conference of Immunology (USA)



A History of Immunology
(by Arthur M. Silverstein)

I. Experiential Immunology period
(經驗免疫學時期)

I. Experiential Immunology period

(the 17th – mid-19th century)

- In ancient times, many serious infection diseases, such as smallpox, plague and cholera …etc, caused innumerable people dead.

Descriptive Early Period

- Plagues & their pandemics
  - Especially small pox & bubonic plague
    - (old: *Pasteurella pestis*; new: *Yersinia pestis*)
- Causes of disease unknown until 19th C.
- Thought to be caused by poisons = "virus" (Latin).

Do you know Plague ??!!

--- *Black Death Disease*

“The triumph of death”

(1562 by Pieter Bruegel)

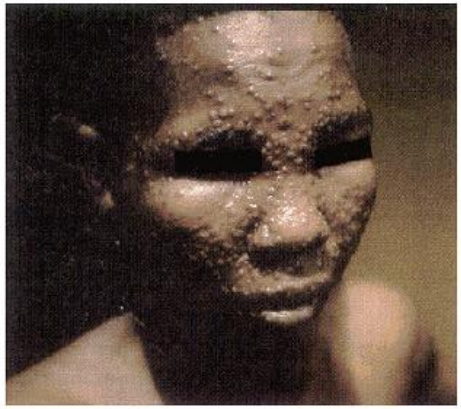
Smallpox has a long history of existence

Ramses V (~1000 BC)

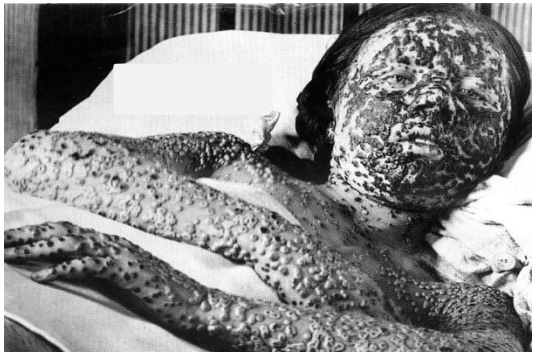
Spots on mummified remains of face believed to be smallpox.

Watch out for the graphical content of the next slide !!!

What disease do these patients have?



Smallpox



Watch out for the graphical content of this slide !!!

Quiz: Smallpox vs Great pox

- **Smallpox** (天花)
  - (Latin name) Variola or Variola vera
    - Latin derivatives ‘varius‘ (spotted) or ‘varus’ (pimple)
  - Unique to humans
  - Caused by two virus variants
    - *Variola major*, *Variola minor*
  - Name 1st used in Europe in the 15th C. to distinguish from the “great pox”
- **Great pox**
  - Syphilis (梅毒) (俗稱: 花柳病, 霉瘡)

Early Attempts at Immunization

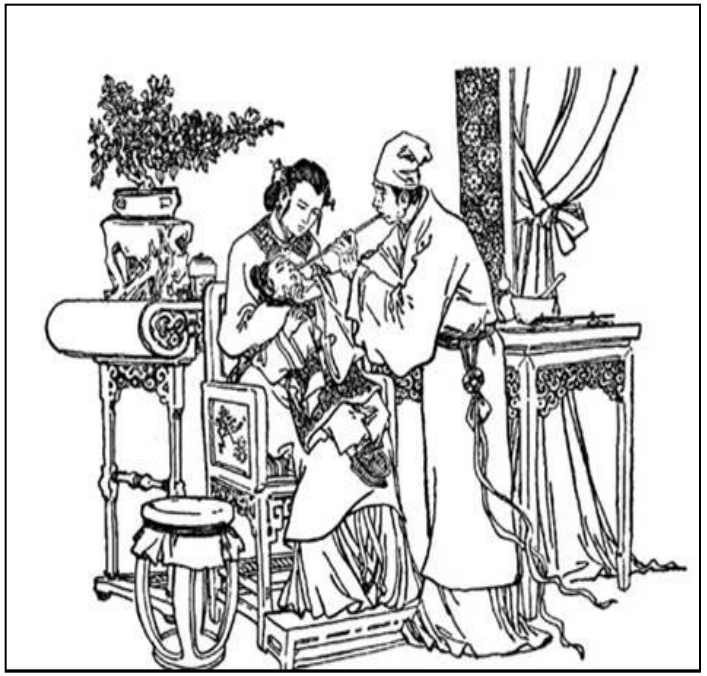
- Mithridates VI (King of Pontus; B.C. 100) took increasing daily doses of poisons.
  - 根據史書記載，密特裡達提六世據說有一食譜，日日佐以鹽巴食之（微毒），久而久之可以抗他人下毒。所以後世以此義瞭解 Mithridates。
  - 為英文片語 “a grain of salt” 之典故:
    - “對…半信半疑” or “對…持保留態度”
      - Skeptical, Conservative
    - The CEO’s marketing strategy is to be taken with a grain of salt.

Immunization against smallpox in the East

Variolation (痘毒接種法) was recorded as early as in the 10th century in China

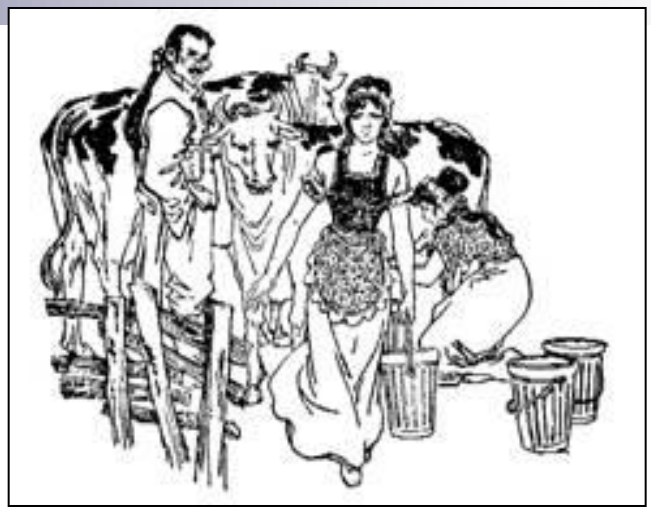
In 1670 (清,康熙)

- Chinese medical practitioners used dried crust (乾痂) from smallpox pustules to be inserted in nostrils of healthy individuals.



Definition of Variolation:

- Inoculation as a method of purposefully infecting a person with live smallpox (Variola) in a controlled manner.
- So as to minimize the severity of the infection,
- and also to induce immunity against further infection.



- **Edward Jenner** **(1749-1823)** - an English physician
- He discovered that cowpox vaccination protected against smallpox in 1796

Definition

Vaccine: A preparation of microbial antigen, often combined with adjuvants (佐劑), that is administered to individuals to induce protective immunity against microbial infections (an "active immunity").

Vaccination: A general term for immunization against infectious diseases, originally derived from immunization against smallpox which uses the Vaccinia virus (牛痘病毒).

A: Why do they NOT want to play with my kids?

B: Your kids should be VACCINATED first!!

Immunization against Smallpox
(1) Variolation

- **Early 18th C.**: **Lady Mary W. Montagu (1689-1762)**(wife of British Ambassador, Constantinople) inoculated her own children for protection against smallpox.
- **"The Royal Experiment"**

  George I (1660-1727) pardoned 7 criminals in Newgate Prison (1721): inoculated and all recovered subsequently. Repeated with 6 more criminals plus 5 orphans.

  Then, the 2 daughters of Prince & Princess of Wales were inoculated, hence became popular.

Immunization against Smallpox
(2) Vaccination

- End of 18th C.: **Edward Jenner**
- Inoculated 7 subjects with cowpox. 2 challenged with smallpox. All O.K.
- Cowpox = Vaccinia virus, hence vaccination became a general term.

Figure 1-1 Immunobiology, 6/e. (© Garland Science 2005)

Father of Immunology

II. Experimental Immunology period
(實驗免疫學時期)

(the middle 19th – the middle 20th century)

19th C.: Bacteria cause disease

- **Robert Koch & Louis Pasteur**
  - Established bacteria as cause of diseases.
  - Infectious diseases were caused by pathogens
- **Louis Pasteur**: Injected animals with live attenuated mico-organisms
  - immunity against chicken cholera, anthrax, rabies.

(I) Active Immunity

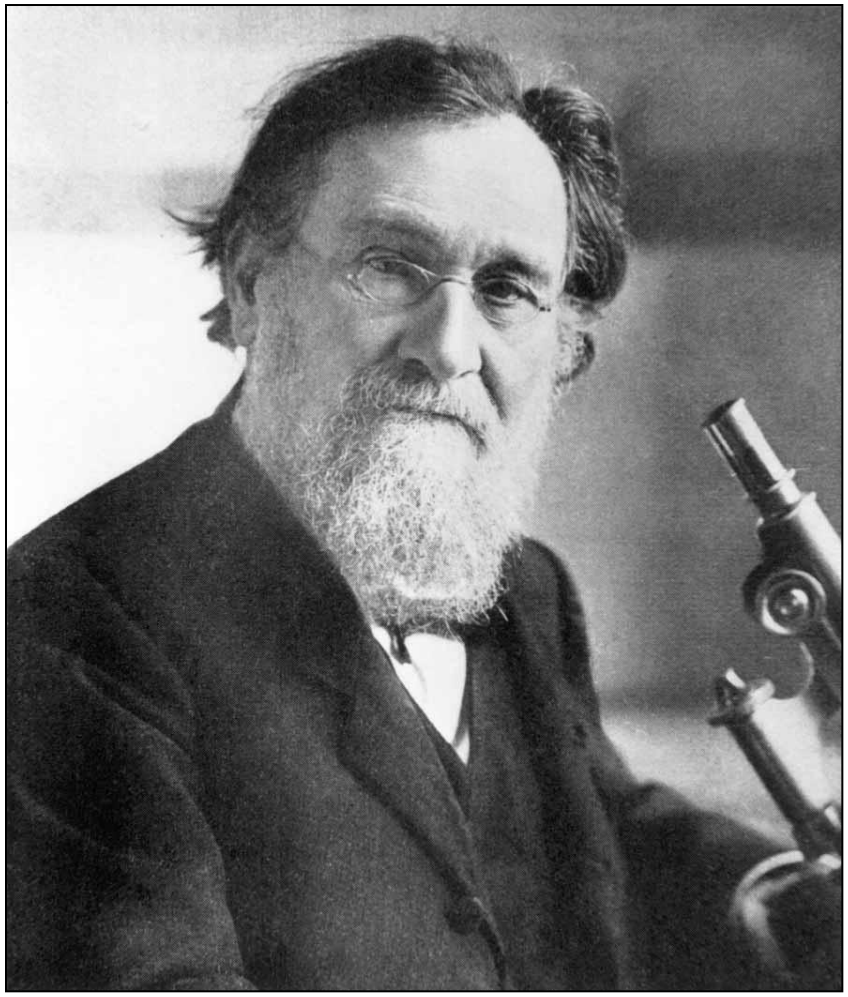
Louis Pasteur
(1822-1895)

Robert Koch
（1843-1910）

Wars of The Cells and Antibodies

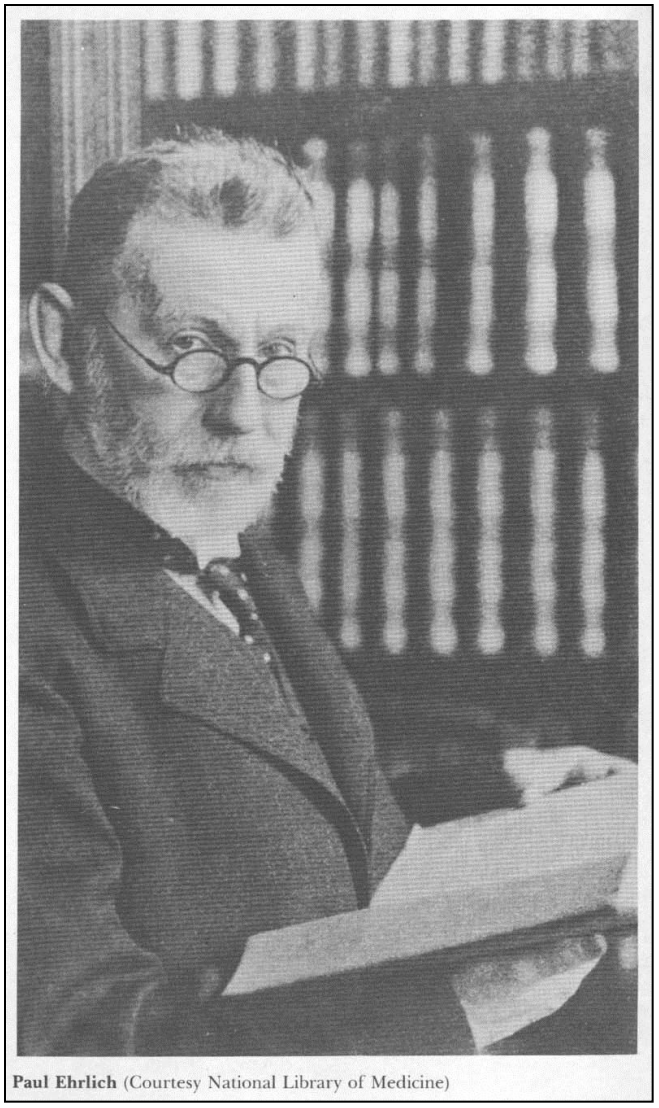
- **Cellular Theory: Elie Metchnikoff** (1845-1916)
  - Phagocytes in starfish larvae surround a splinter; phagocytosis & digestion of bacteria by MΦs & polymorphonuclear cells (PMNs)
  - **Phagocytic Theory** (innate immunity).

- **Humoral Theory: Koch, Paul Ehrlich** et al. (Berlin)
  - Showed serum from immunized animals kills bacteria.
  - (~1890) The "**Side-chain theory**" of Ab generation was proposed by Ehrlich
    - See later slide for details



Elie Metchnikoff

(1845-1916)



Paul Ehrlich (Courtesy National Library of Medicine)

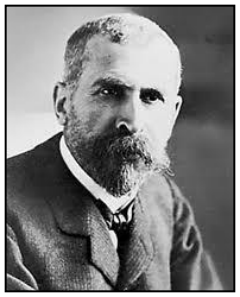
Paul Ehrlich

(1854-1915)

Late 19th C.: The battles continue

- **Emile Roux** and **Alexandre Yersin**
  - Diphtheria was caused by exotoxin
  - produced by *Clostridium diphtheriae*
- The discovery of diphtheriae antitoxin
  - Antitoxin – antibody (Ab)
  - Exotoxin – antigen (Ag)
- The study of Ab-Ag interaction *in vitro*
  - **Serology** 血清學

(II) Passive Immunity



Emile Roux

Alexandre Yersin

Passive Immunity

- Initiates the concept of "**Humoral Immunity**"
  - Immunity mediated by cellular factors other than cells
    - Antibodies, complements, …etc.
- **Jules Bordet** discovered complements in the serum.
  - Worked in Metchnikoff's lab, and
  - Was the 1st to discover phagocytosis of bacteria by WBCs (1894)

(II) Passive Immunity

Jules Bordet
(1870-1961)

Passive Immunity

- **Emil von Behring** & **Shibasaburo Kitasato**
  - discovered immunity to diphtheria & tetanus was due to Abs against exotoxins
    - Source of Abs was **serum** from pre-immunized animals
  - Passive transfer of immune serum conveys protection → 1st immunotherapy documented !!!

Emil von Behring

Shibasaburo Kitasato
北里 柴三郎

Figure 1 | **Pioneer: Shibasaburo Kitasato.** Pictured during his stay at Robert Koch's laboratory (Image courtesy of the Kitasato Institute).

Passive Immunity

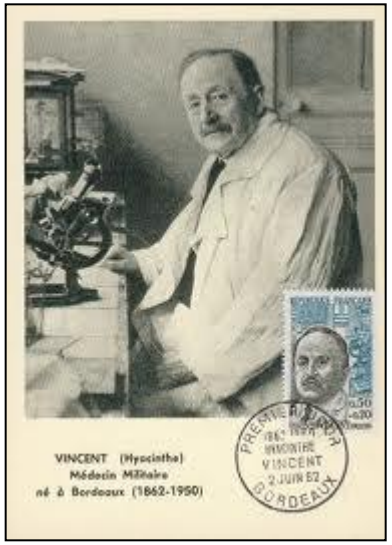
- Emil von Behring discovered that active component from immune **serum** could neutralize toxins.
- In 1891, Behring cured a **diphtheria** patient with serum from animals previously immunized to diphtheria.

It was the first cure case by **artificial passive immunization**.

So, he earned The Nobel prize in medicine in 1901.

Wars of The Cells and Antibodies: Truce

- **Sir Almroth Wright** & **Captain Douglas**
  - Opsonization (調理) of bacteria by Abs.
  - Attempted to fuse Cellular and Humoral Theories → nick-named "Sir Almost Right".
- Little progress in cellular immunology for 50 years (unfashionable).



Sir Almroth Wright (1861-1947)

20th C: How are Abs. made? Selective vs. Instructive Theories

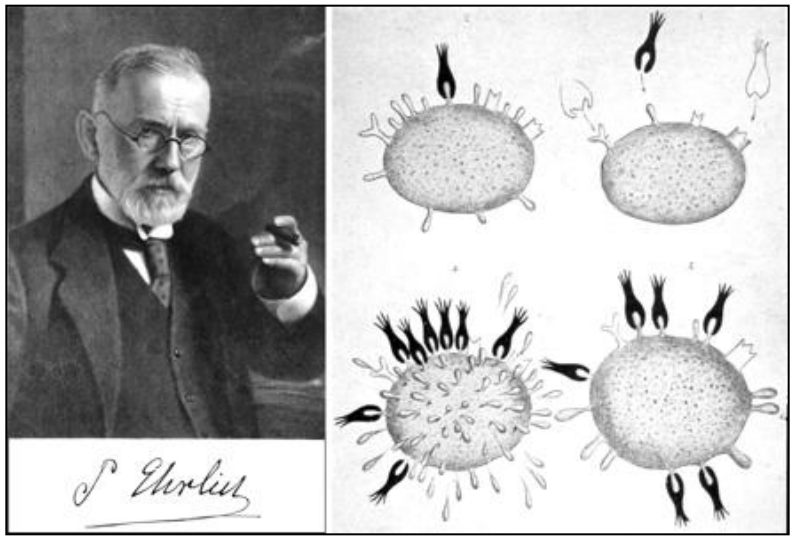
- Are Abs pre-made (selective) or "molded"塑造 by Ag (instructional)?
  - **Paul Ehrlich**(1854-1915)→ Selection theory
  - **Linus Pauling** (1901-1994)→ Instructional theory
- **Sir MacFarlane Burnet**
  - 1950s, refined the selection theory and proposed the "**Clonal selection theory**".
  - 1960 Nobel prize (med./physio.)

Sir MacFarlane Burnet (1899-1985)

Paul Erlich's side-chain theory of Ab

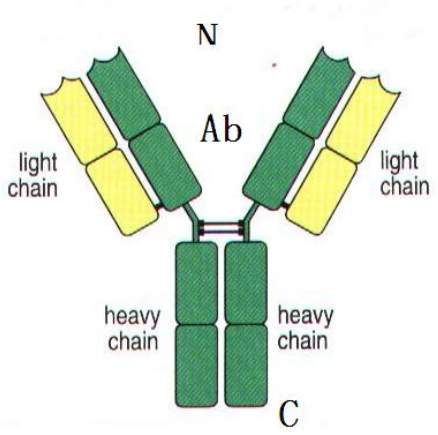
(proposed in ~ 1890)

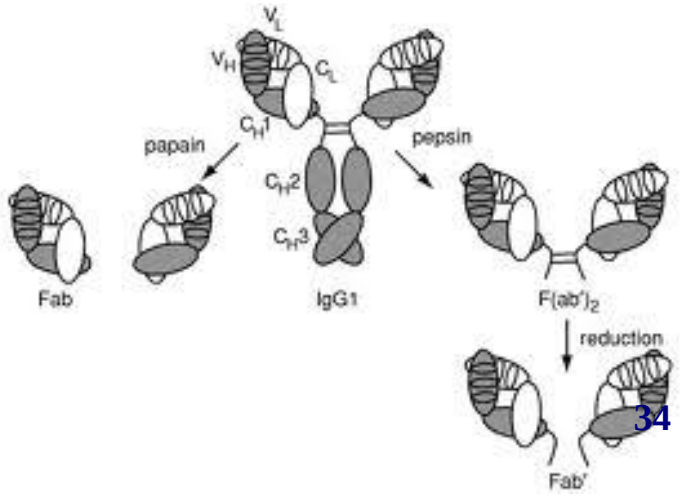
1. **Living cells have side-chains** in the same way chemical dyes have side-chains which are related to their coloring properties.
2. These side chains **can link with a particular toxin**.
3. **A cell under threat grew additional side-chains** to bind the toxin.
4. These additional side chains broke off to become the **antibodies (Abs)** that are circulated through the body.
5. These Abs that Ehrlich first described are as "**magic bullets**" in search of toxins.



Chemical Approach to Ab & Ag

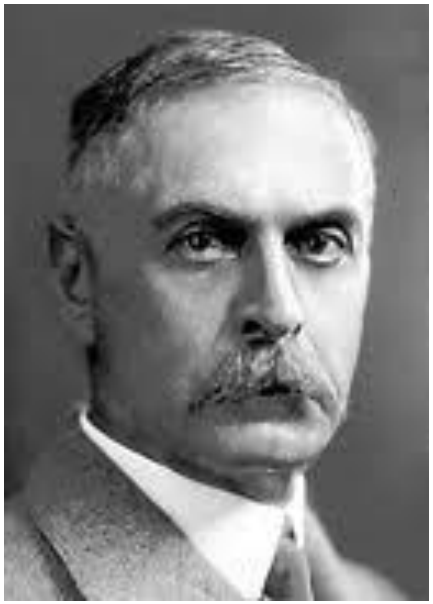
- **Karl Landsteiner** (1868-1943):
  - Specificity & diversity; blood group Ags (A/B/O/AB types).
- Abs as proteins, more accurately, glycoproteins
- **Rodney Porter & Gerald Edelman:**
  - 1st description of structure of IgG



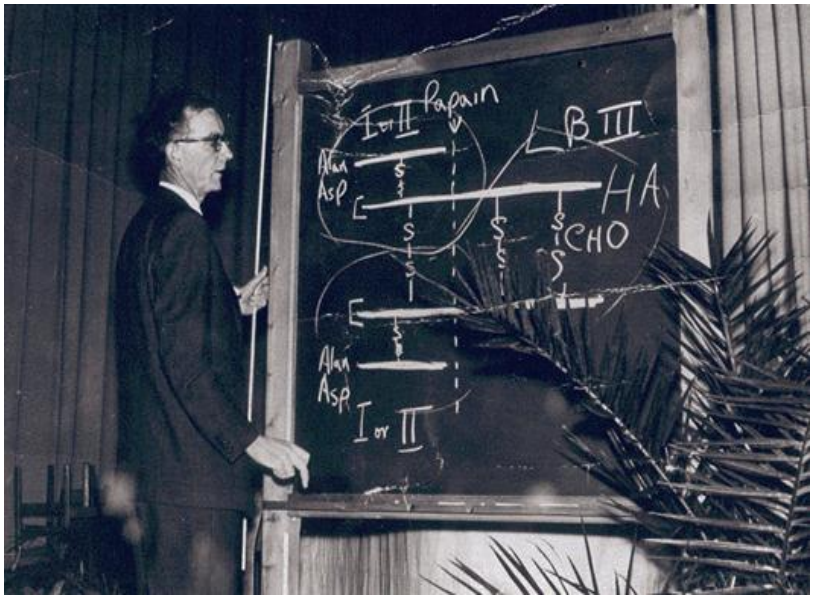


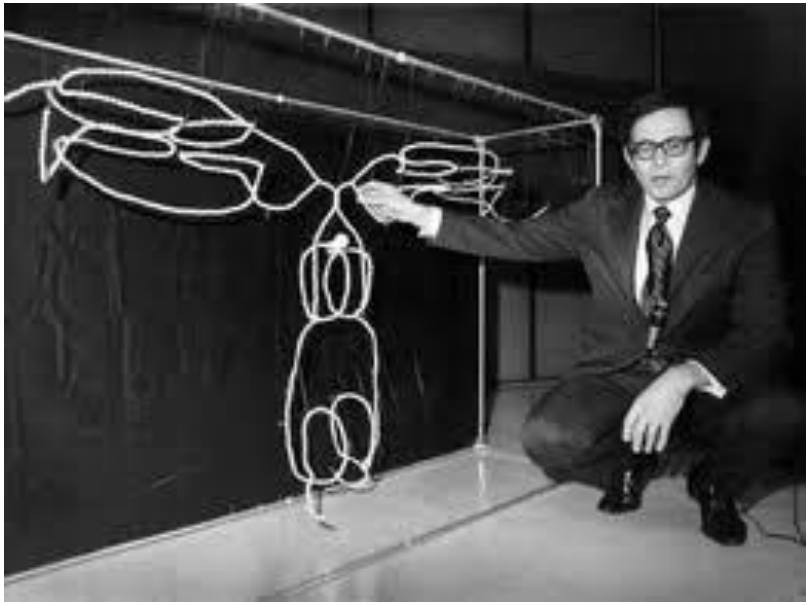
Karl Landsteiner

(1868-1943)



Rodney Porter (1917-1985)





Return to Cellular Theories

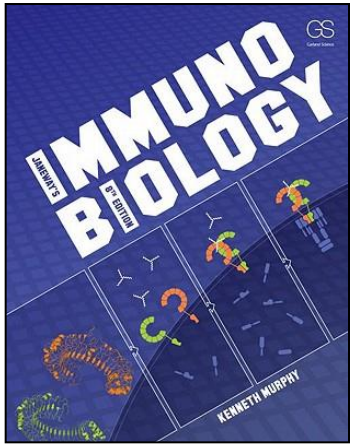
(In parallel with studies of Abs.)

- Humoral immunity cannot explain
  - graft rejection, tolerance, immunity to viruses.
- **Peter Medawar** (1915-1987)
  - tolerance to skin allografts

- Role of T-cells (2 types; helper & cytotoxic):
  - Th cells (T-B cell cooperation),
  - Tc cells (kill virus infected cells).
- **Rolf Zinkernagel** & **Peter Doherty**
  - Cytotoxic T (Tc) cells recognize Ag bound to MHC molecule - shared Nobel prize (1996)

III. Modern Immunology period (現代免疫學時期)

Most of the development will be covered in our lectures & textbook (Janeway's Immunobiology, 8th Ed.)



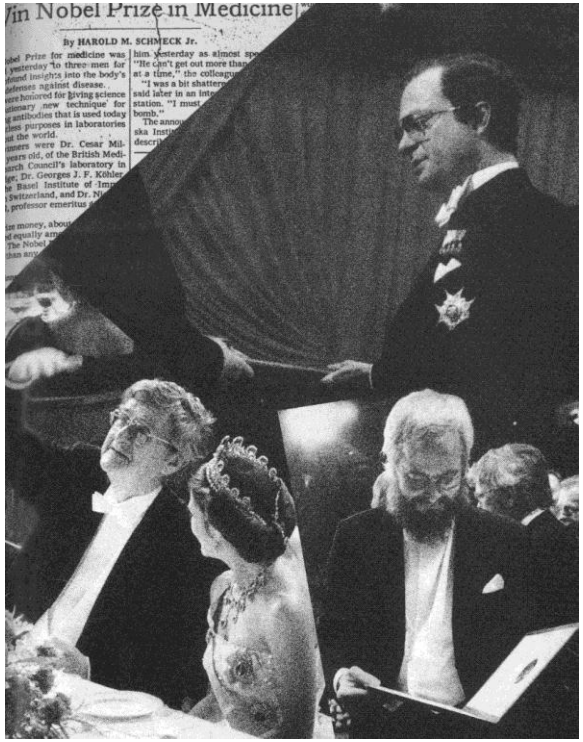
1975 – present: The Molecular Revolution (1)

George Köhler & Cesar Milstein :

Monoclonal Abs (mAbs)

Nobel Prize

1984

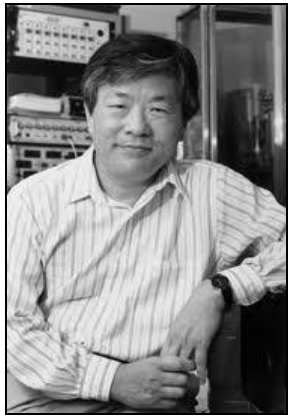


(1946 – 1995)

(1927 – 2002)

1975 – present: The Molecular Revolution (2)

- **Susumu Tonegawa** – genetic basis of Ab variability (1976)
- PCR, gene cloning techniques, mAb
  - Allow identification, structure & function of Ig & TCR genes, cell surface Ags. & cytokines.



利根川進

1975 – present: The Molecular Revolution (3)

- Genetic manipulation:
  - Gene knock-outs and transgenic mice enable study of effects of molecular components of immune system, signalling pathways, ..etc.
- Applications to Disease:
  - mAbs for diagnosis & immunotherapy;
  - recombinant & DNA vaccines;
  - gene therapy

End of Chapter