Understanding, Harnessing & Controlling Immunity

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What is immunity?

Immunity – from the Latin *immunitas*

Legal: exemption from a service, obligation, or duty; freedom from liability to taxes, burdens or duties

Medical: the state of being insusceptible or resistant to a noxious agent or process, especially a pathogen or infectious disease.

Immunology – the branch of science that studies immunity.

(Oxford English Dictionary)

Why is immunity important?

Immune “system” distributed & operating throughout the body

Natural protection against deadly bacterial, viral & parasitic diseases

Involved in normal physiological functions such as wound healing

Can be harnessed to detect, prevent & treat many infections and other important diseases including cancer

Understanding how it works gives important insights into otherwise unrelated disorders

The history of immunity

A little “pre-history” – origins of vaccination

The “Golden Age” of bacteriology – new vaccines, antitoxins & tests

Failure of theory to explain critical phenomena of immunity

New biological thinking about immunity and disease

Implications of our modern understanding

A little “pre-history”

Plague of Athens (430 BCE) – resistance after recovery from disease

India/China (early CE?) – inoculation with matter from smallpox pustules

Montagu (1721) – smallpox inoculation (“variolation”) introduced to Britain

Jenner (1798) – inoculation with less dangerous cowpox (“vaccination”)

Calf-lymph vaccine (late 1800s) – avoiding “arm-to-arm” inoculation

The birth of immunology
(1870s-1910s)

Role of microbes/bacteriology

Growth of laboratory science & animal experimentation

Professionalisation of research: universities, journals, congresses

Pharmaceutical research & development companies

Franco-Prussian antagonism & competition

Louis Pasteur (1822-1895)

French chemist

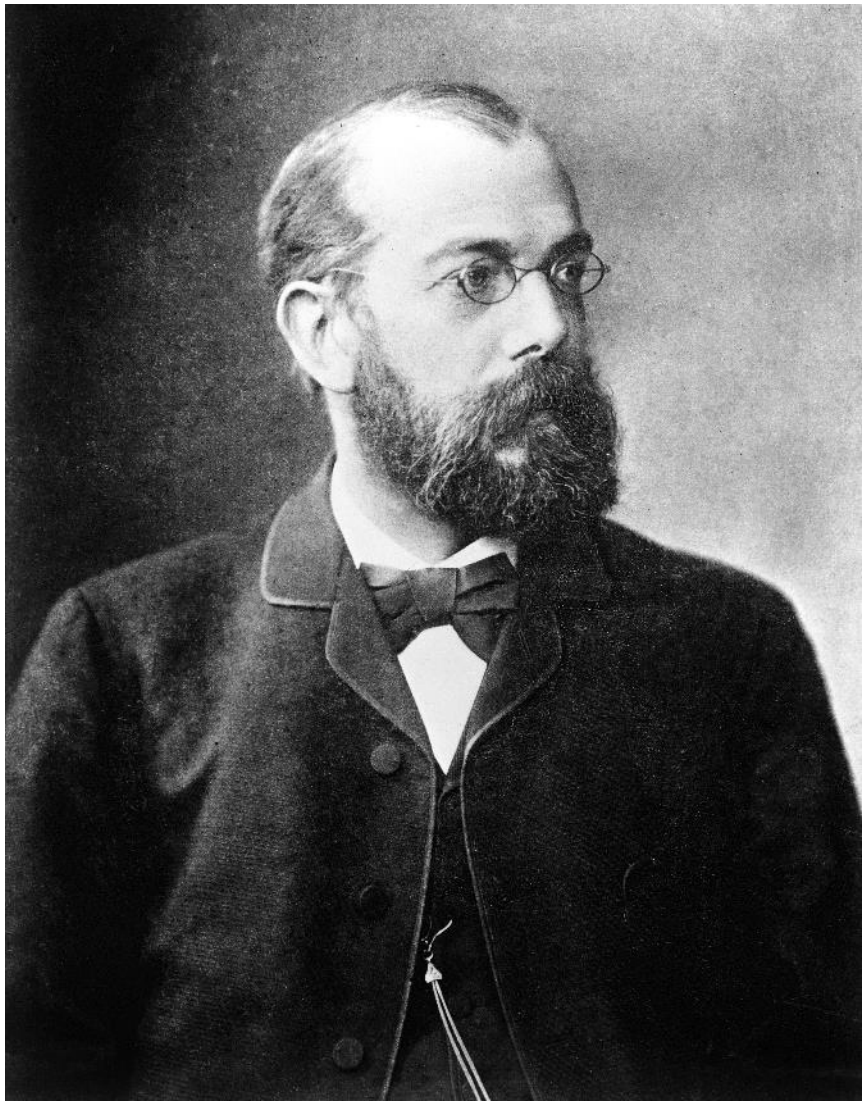
Role of microbes in fermentation
Disease of silkworms
Pasteurization
Antisepsis

Live “attenuated” vaccines:
Chicken cholera (1880), anthrax (1881),
swine erysipelas (1883) & rabies (1885)

Pasteur Institute, Paris (1888)

Subsequent vaccines: cholera, plague, typhoid

Robert Koch (1843-1910)



German doctor

Life cycle of anthrax bacillus (1876)
Tubercle bacillus (1882), cholera (1883), diphtheria (1884), tetanus (1884)

Agar media, Petri dishes, dye staining of bacterial cells, photo-microscopy

“Tuberculin” (1890)

Institute for Infectious Diseases, Berlin (1891)

Nobel Prize (1905)

Ideas about how immunity works (1880s)

How do vaccines work?

Live vaccines – do they deplete the body of specific nutrients?

Killed vaccines work – must be an active process in the body

What happens in the body?

The blood of some animals is naturally immune to bacterial growth

Cell-free blood serum can sometimes kill bacteria directly

Evidence favouring "humoral immunity"

The discovery of antitoxins (1890)

Some types of bacteria release lethal toxins

An animal inoculated with toxin develops immunity

Antitoxic property is found in blood serum

Antitoxin is transferable by serum

Protects non-immune animal

"Passive" immunity vs. "active" immunity (vaccination)

Shibasaburo Kitasato (1853-1931)

Japanese doctor

Visitor to Koch's Institute (1885)
Growth of tetanus in pure culture (1889)
Proof of toxic action (1889)

Discovery of "antitoxins" (1890)
"Tetanus antitoxin" (1890)

Director, Institute for Study of Infectious Diseases, Tokyo (1892)
Co-discoverer of plague bacillus (1894)

Kitasato Institute, Tokyo (1914)

Emil (von) Behring (1854-1917)

German military doctor

Assistant, Institute of Hygiene, Berlin (1889)
Interest in sepsis and disinfection
Focus on treating diphtheria

Discovery of “antitoxins” (1890)
“Tetanus and diphtheria antitoxins” (1890)

Professor, University of Marburg (1895)

Nobel Prize (1901)

Founded *Behringwerke* (1904)

Diphtheria

First described in antiquity

1500s– “*el garrotillo*” strikes Spain

1820s – Brettoneau describes “*la diphthérite*”

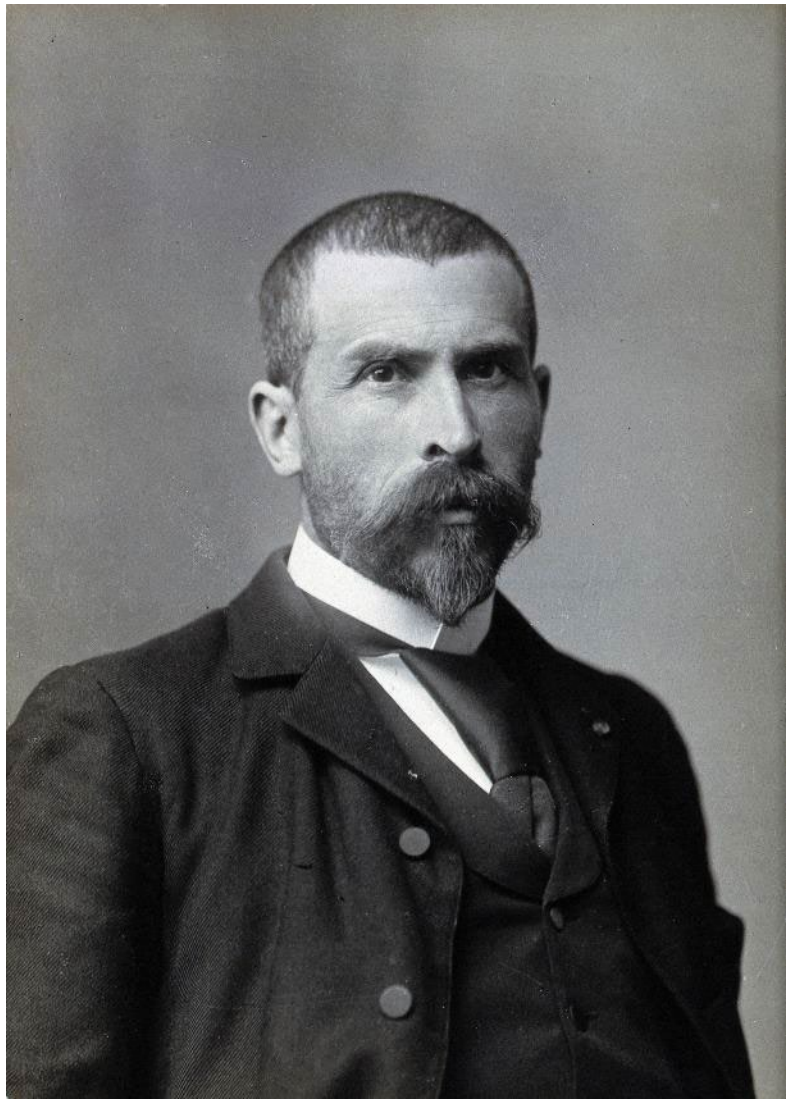
1830s – introduction of tracheotomy

1850s – major European epidemic spreads globally

1880s – intra-laryngeal intubation

1890s – diphtheria antitoxin

Emile Roux (1853-1933)



French doctor

Assistant to Louis Pasteur
Collaborator on attenuated vaccines

Isolated diphtheria toxin (1888)
Production of diphtheria antitoxin in horses

Diphtheria antitoxin trials (1894)
Reduced mortality in children by half

General Director, Pasteur Institute (1904)

Production of diphtheria antitoxin in horses

“Serum straight from the horse”

Diphtheria antitoxin

Reduction of child deaths in hospitals

Controversies: mild cases, late treatment, dosing, quality, deaths

Anti-vaccinators, antitoxin from horses, use of guinea pigs

Prophylaxis in juvenile hospitals, asylums and orphanages

Serum treatments
(from 1890s)

Antitoxins:

diphtheria, tetanus, anthrax, snake venoms

– relatively rare intoxications

Antibacterial serums:

streptococcus/scarlet fever, pneumonia, meningococcus & dysentery

– batch variability, high doses, strain variation

1940s: *antibiotics* & *penicillin*

– cheaper to make, easier to administer, broad spectrum

Therapeutic antibodies
(from 1940s)

Human gamma globulin

IVIG – intravenous immunoglobulin for multiple disorders

Hyperimmune immunoglobulins

Concentrated human antibodies to treat infectious diseases

Monoclonal and engineered antibodies

Highly potent human antibodies with a wide range of therapeutic applications

Antibody conjugates

Antibodies carrying cytotoxic drugs or radioisotopes

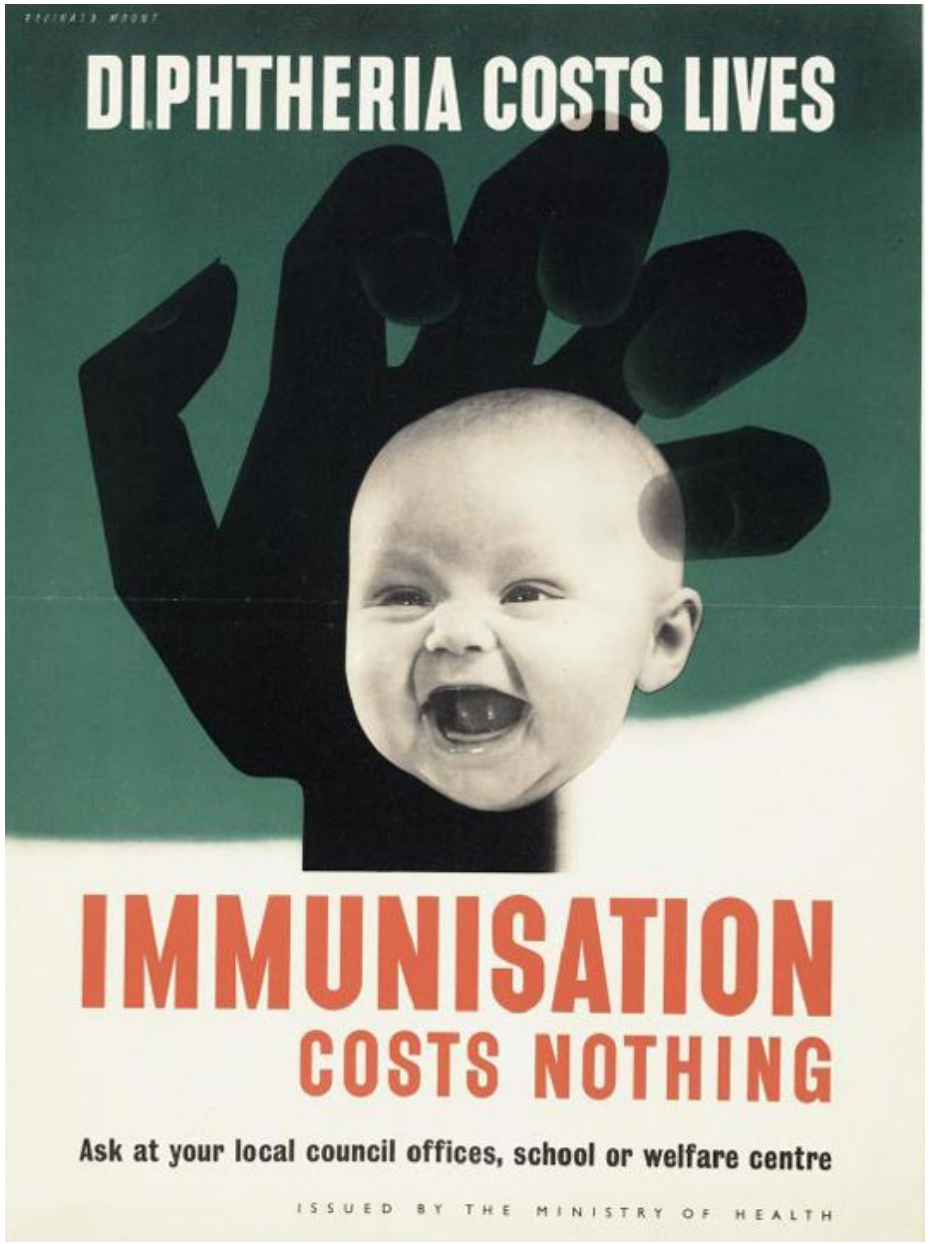
Diphtheria – the need for vaccines

Limitation of passive immunity
Problem of asymptomatic carriers

Mass child vaccination programmes in 1920s (New York City)

Campaigns of school vaccination
Poor, immigrants, tenements,
sweatshops, access to healthcare
Public health vs medical practitioners

Toxin-antitoxin vaccine
Toxoid (inactivated toxin)
Diphtheria-tetanus-pertussis (DTP)



Diphtheria – UK

40,000-80,000 cases per annum

Concerted vaccination drive during 1940s

Zero deaths in 1959 (in England & Wales)

Cases due to travel to endemic areas, contact with farm animals & incomplete vaccination

Vaccine developments

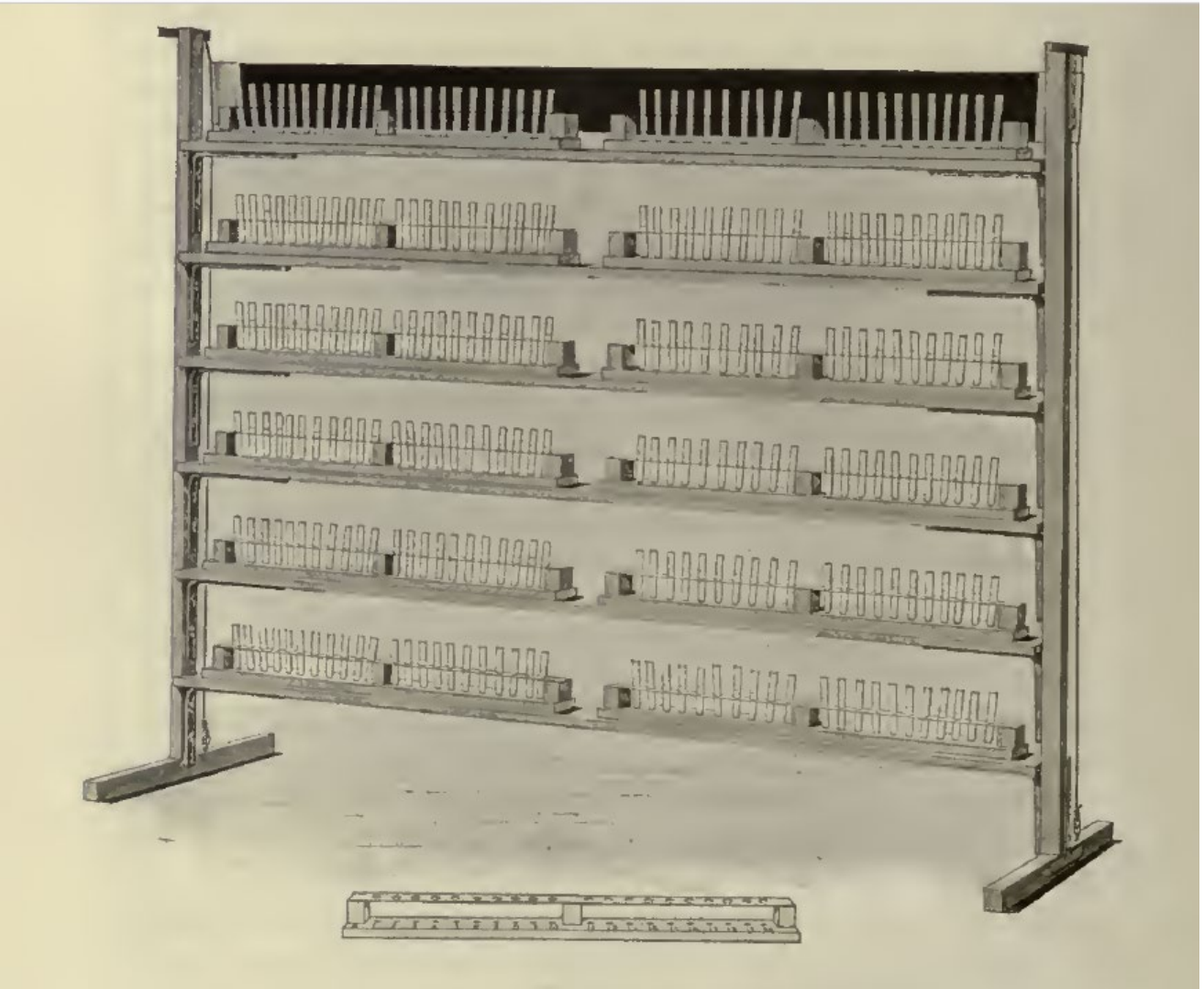
Technologies

Live attenuated – smallpox (1798)
Killed whole organism – typhoid (1896)
Toxoid – diphtheria (1923)
Subunit – anthrax (1970)
Virus-like particle – hepatitis B (1986)
Membrane vesicle – group B meningo (1987)
Conjugate – H. influenza type B (1987)
Viral vectored – Ebola virus (2019)
Nucleic acid – SARS-CoV-2 (2020)

Infection targets

Tuberculosis
Influenza
Yellow fever
Poliomyelitis
Measles
Mumps
Rubella
Hepatitis B
Rotavirus

Serological tests



Methods of visualisation

Agglutination (clumping)
Precipitation (depositing)
Lysis (breakdown)

Detecting infectious agents

Widal test – typhoid (1896)
Wassermann test – syphilis (1906)

Antibody-based tests

Typing tests

ABO, Rhesus and other blood cell groups

Bacterial and viral antigen typing, e.g., influenza variants

Immunoassays

Immunofluorescent assays of cells & tissues

Radio- and enzyme-immunoassays of drugs, hormones, proteins

Blood cell analysis

Distinguishing different white blood cells

FACS – fluorescence-activated cell sorting to separate cells

Diagnostics

Diagnostic tests for cancer biomarkers, e.g., HCG, PSA

Lateral-flow antibody test kits: pregnancy, fertility, HIV, COVID-19

Paul Ehrlich (1854-1915)

German Jewish doctor

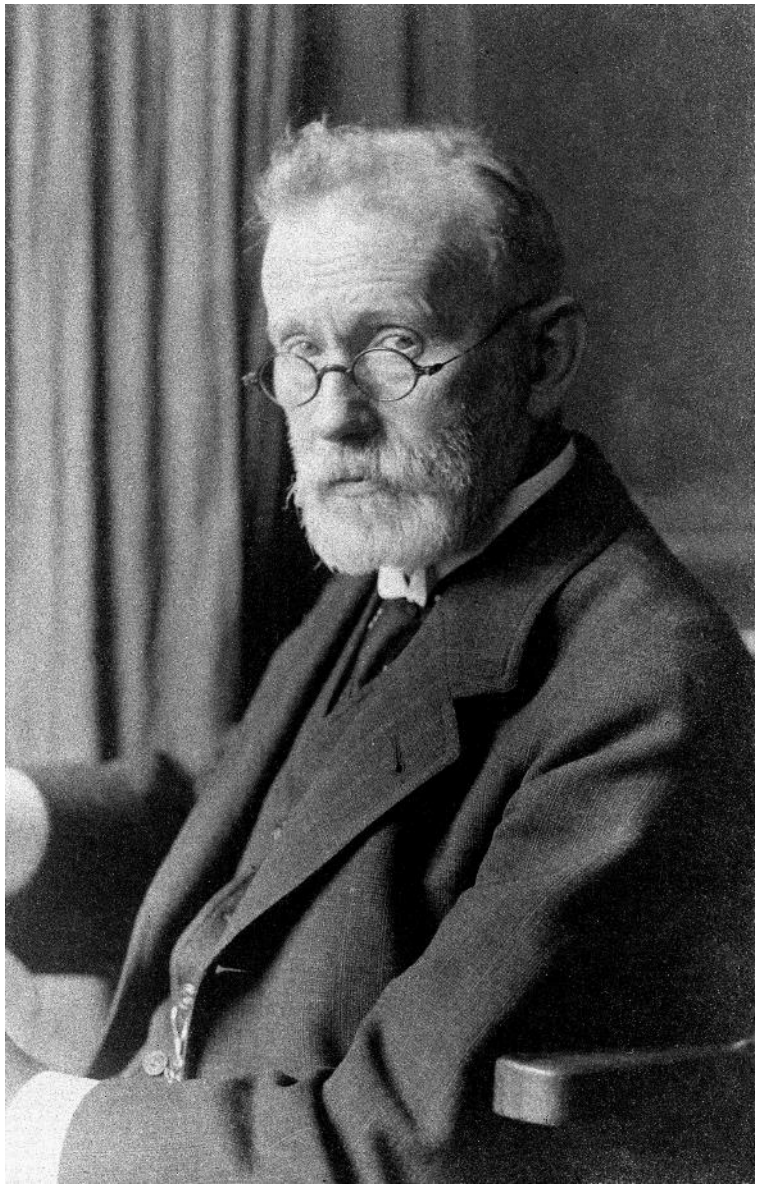
Dye-staining of cells, tissues & bacteria
Identification of different white blood cells

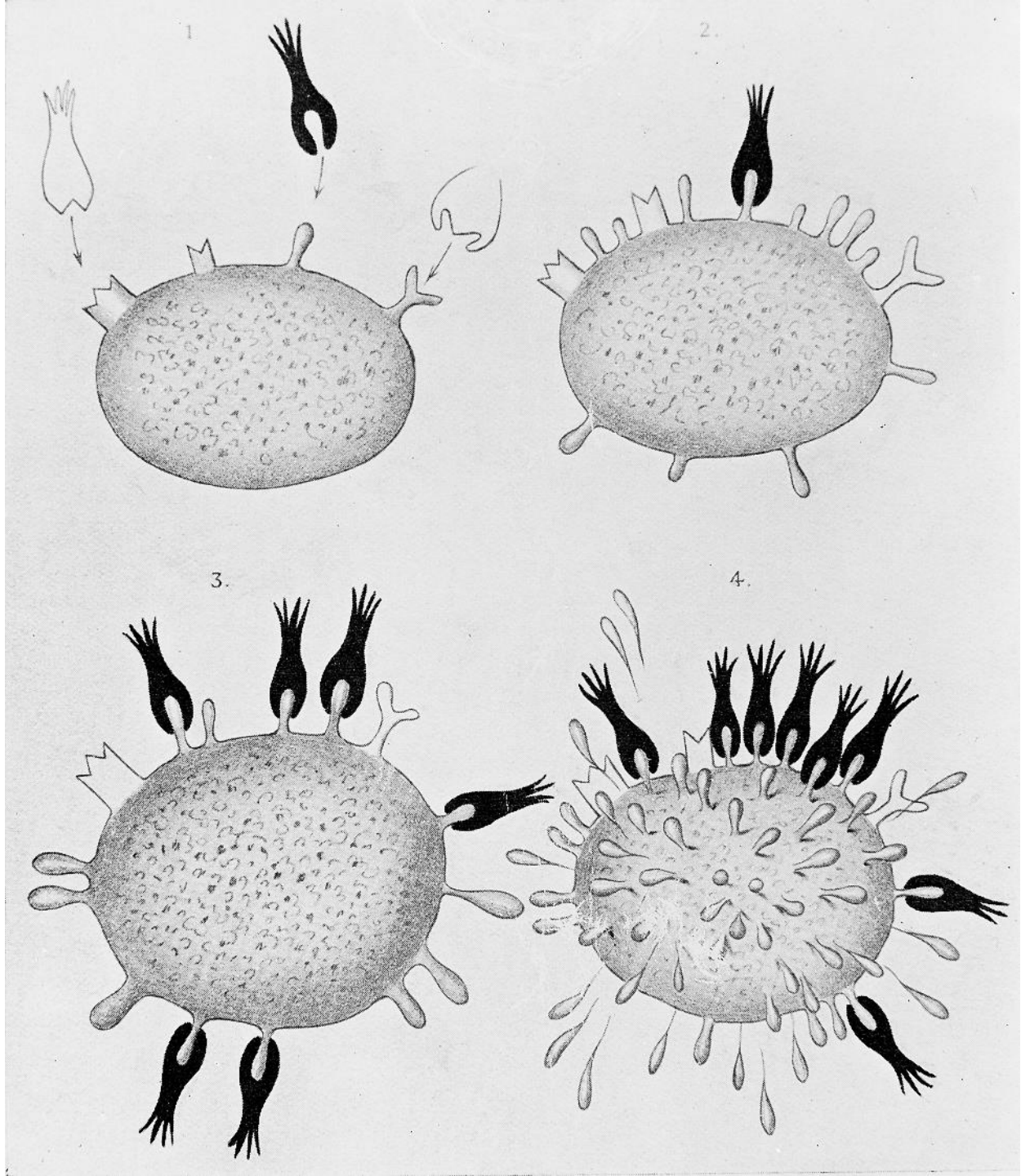
Specificity of antitoxins for their toxins &
transmission via maternal milk (1891)

Coined the word "antibody" ("*Antikörper*")

Institute for Serum Research & Testing, Berlin (1896)
Standardisation of diphtheria antitoxin (1897)
"Side-chain" theory (1897)

Institute of Experimental Therapy, Frankfurt (1899)
Nobel Prize (1908)
Magic bullets – "Salvarsan" for syphilis (1909)



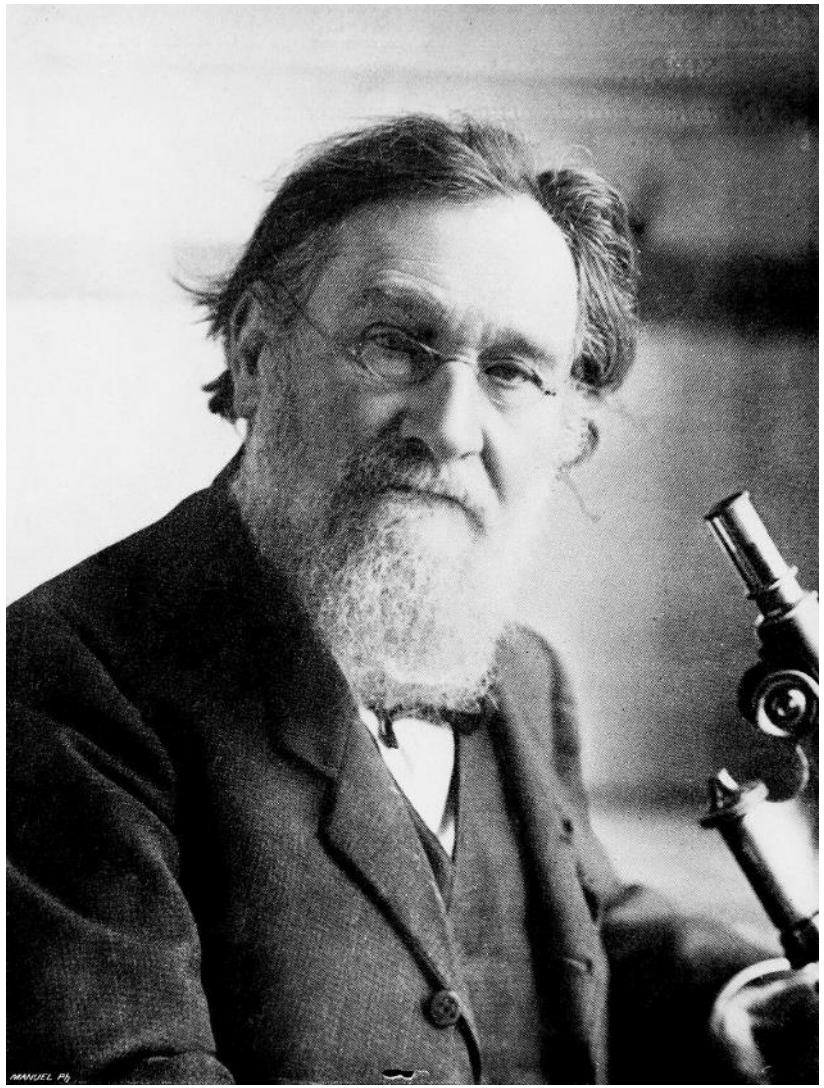


The "side-chain" theory of humoral immunity

antibodies
&
antigens

Ehrlich (1900)

Ilya (Elie) Metchnikoff (1845-1916)



Russian zoologist

The “thorn in the starfish” (1882)
Intracellular digestion in invertebrates

Mobile cells as first line of defence (1883)

Pasteur Institute (1888)

Inflammatory response protecting organism
Comparative Pathology of Inflammation (1893)

Interest in longevity and aging – advocated consumption of yoghurt

Nobel Prize (1908)

Inflammation and cellular immunity

Celsus (1st century CE)
– redness, swelling, heat & pain – signs of inflammation

William Addison (1802-1881)
– “colourless corpuscles” in inflammatory exudate (1843)

Julius Cohnheim (1839-1884)
– migration of white cells from blood vessel to exudate (1867)

Metchnikoff
– active engulfment of foreign bodies by “phagocytic” cells (1883)

Argument for “cellular” immunity … but difficult to explain specificity

(Sir) Almroth Wright (1861-1947)

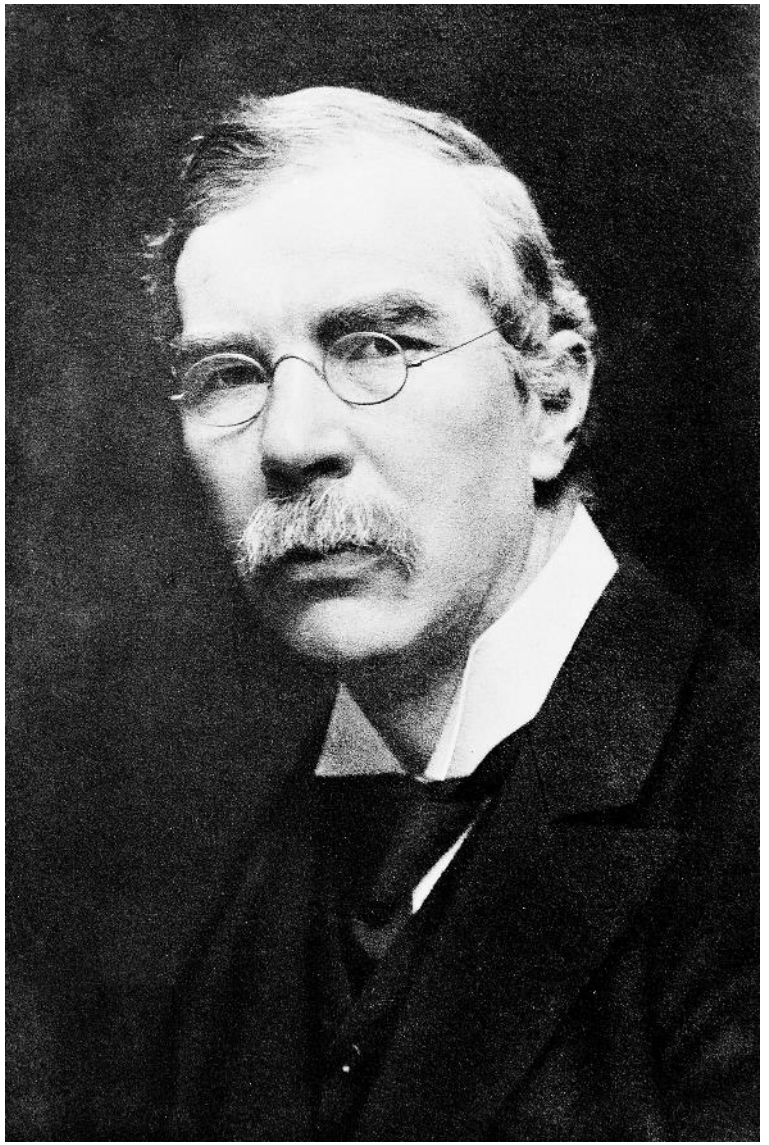
British physician & bacteriologist

Professor of Pathology, Army Medical School, Netley (1892)
Typhoid vaccine (1896)

St Mary's Hospital Medical School (1902)
Discovery of "opsonins" (1903)

Proponent of immunisation
Therapeutic vaccines & autovaccines

The "British Pasteur"/Sir "Almost Right"



“Opsonins”

Substances which have the power of combining with bacteria, thereby rendering them more easily taken up by phagocytic cells

Type of antibody found in immune serum which has a specific affinity for a bacterium

This notion supposed that invading bacteria first had to undergo sensitisation by opsonin before phagocytosis would occur

Link between the humoral and cellular theories of immunity

SUMMARY I

Practical developments

- New vaccines
- Antitoxins/serum therapy
- Serology/diagnostics

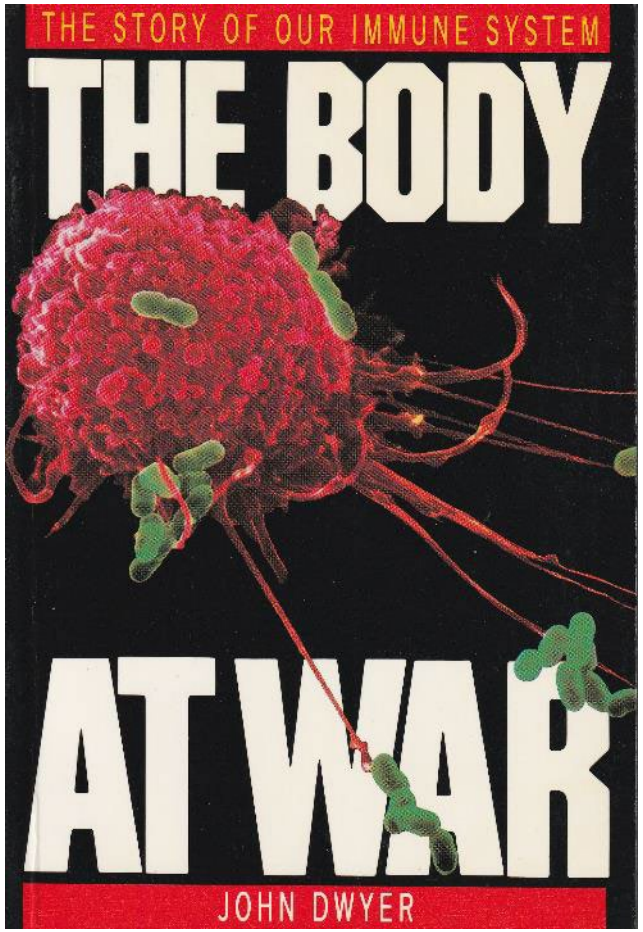
Medical advances

- Prevention of diphtheria, typhoid fever
- Treatment of bacterial infections
- Blood transfusion

Novel theories

- Mechanism of immunity
- Specificity of antibodies

War metaphors: “battle against foreign invaders”



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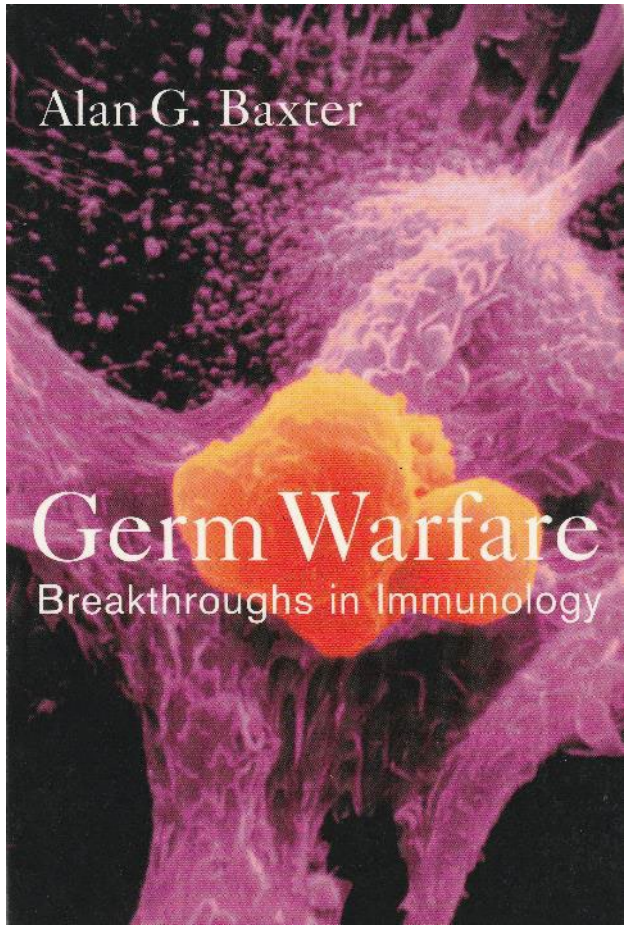

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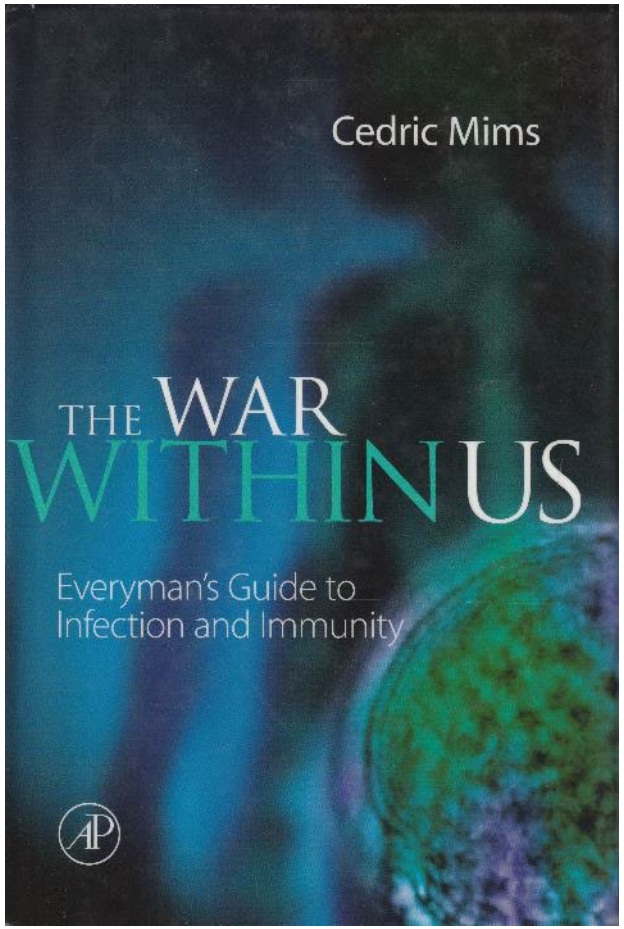

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Characteristics of acquired immunity
(1910s-1940s)

Active – reaction to presence of a substance

Specific – distinct antitoxins to different toxins

Memory-forming – greater secondary response

Long-lasting – persists long after antigen removed

Universal – microbes, animal cells, proteins, chemicals

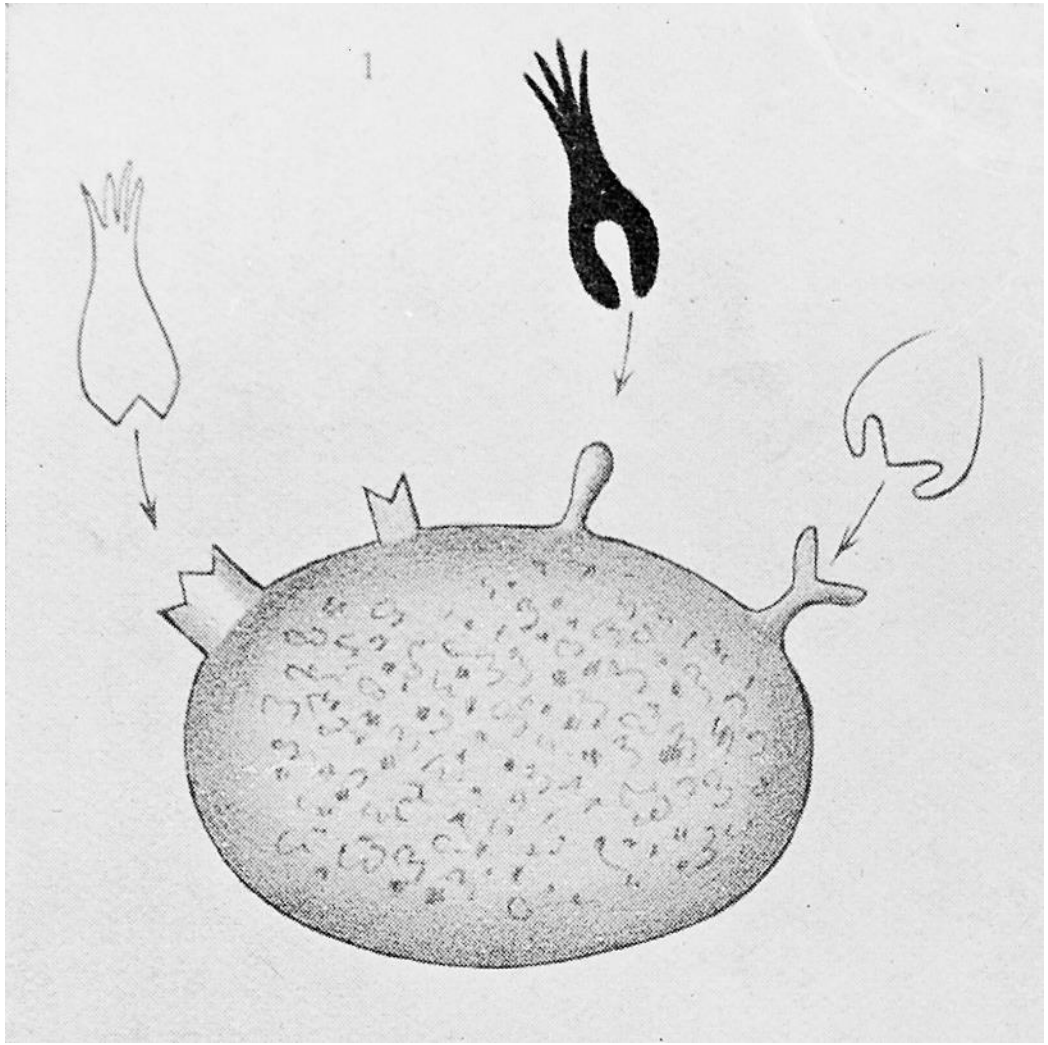
Hypersensitivity reactions
(1910s-1940s)

Anaphylaxis – acute reaction to small amounts of substances
Serum sickness – reaction to horse protein in serum products
Hay fever – reaction on exposure to pollen
Asthma – lung inflammation stimulated by certain antigens

"Allergy" – altered reactivity, antigen-specific & memory-forming,
passively transferred by serum

Tuberculin reaction – delayed type of inflammation
not transferable by serum

How are antibodies made?



Specificity of antibody for antigen determined by complementarity between structures

New biological thinking
(1940s-1960s)

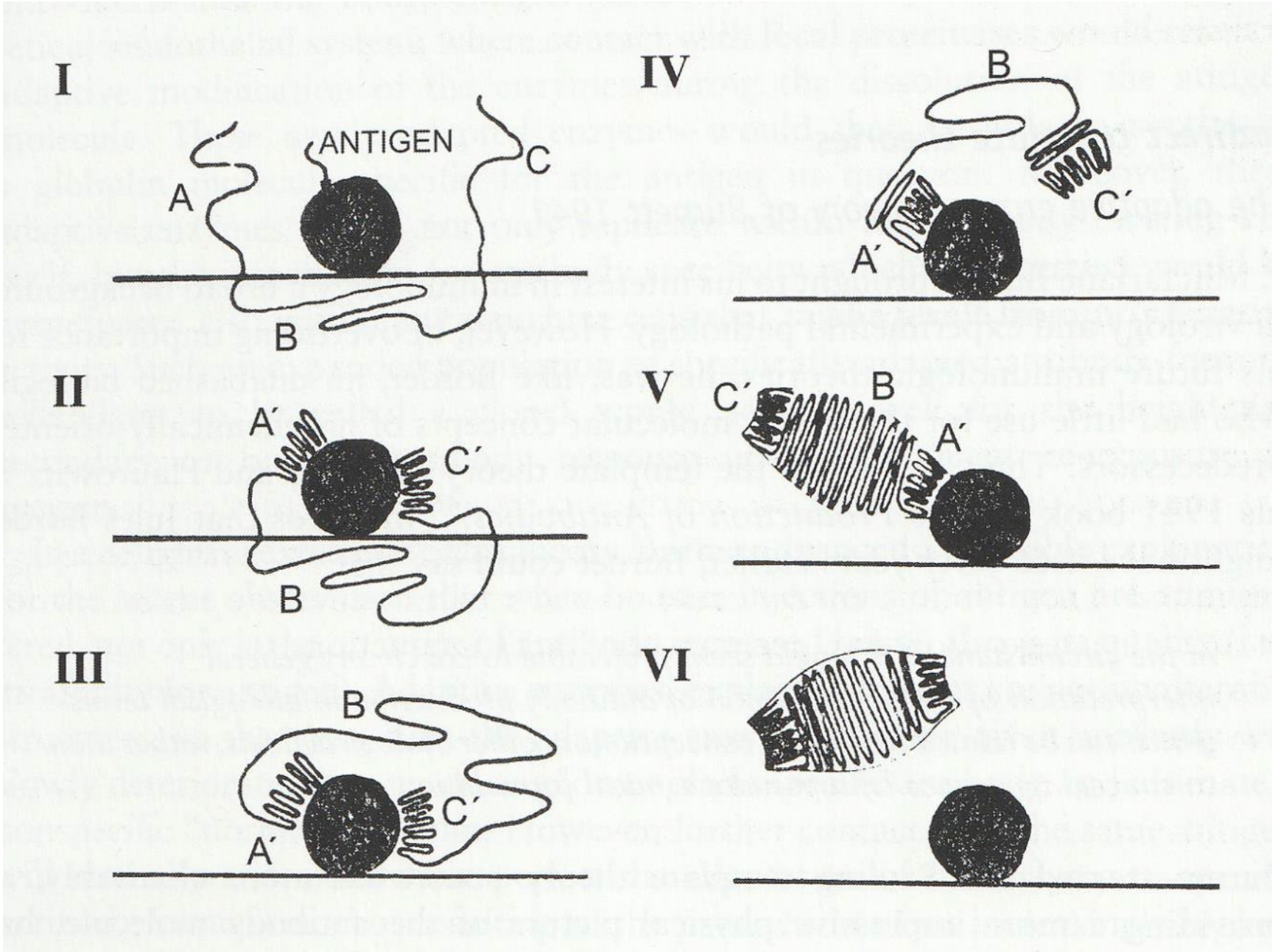
Instruction theory

The structure of the antigen acts as a template which “instructs” a cell to make antibody with complementary structure

vs.

Selection theory

From many cells, each making a single type of antibody, the antigen “selects” the cell with complementary structure



Instruction theory

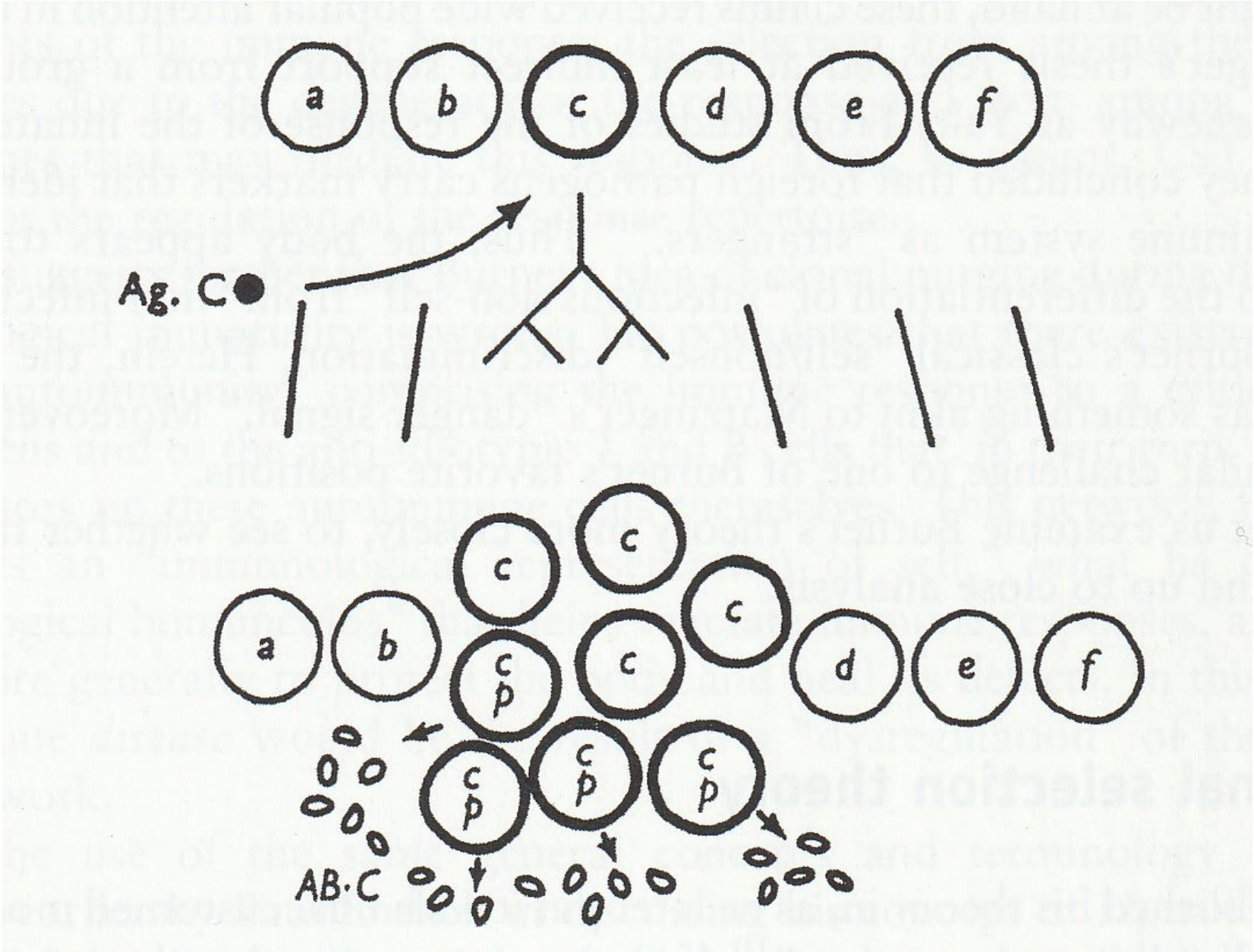
Pauling (1940)

lymphocytes

The "clonal selection" theory

Burnet (1957)

plasma cells making antibody



(Sir) Macfarlane Burnet (1899-1985)

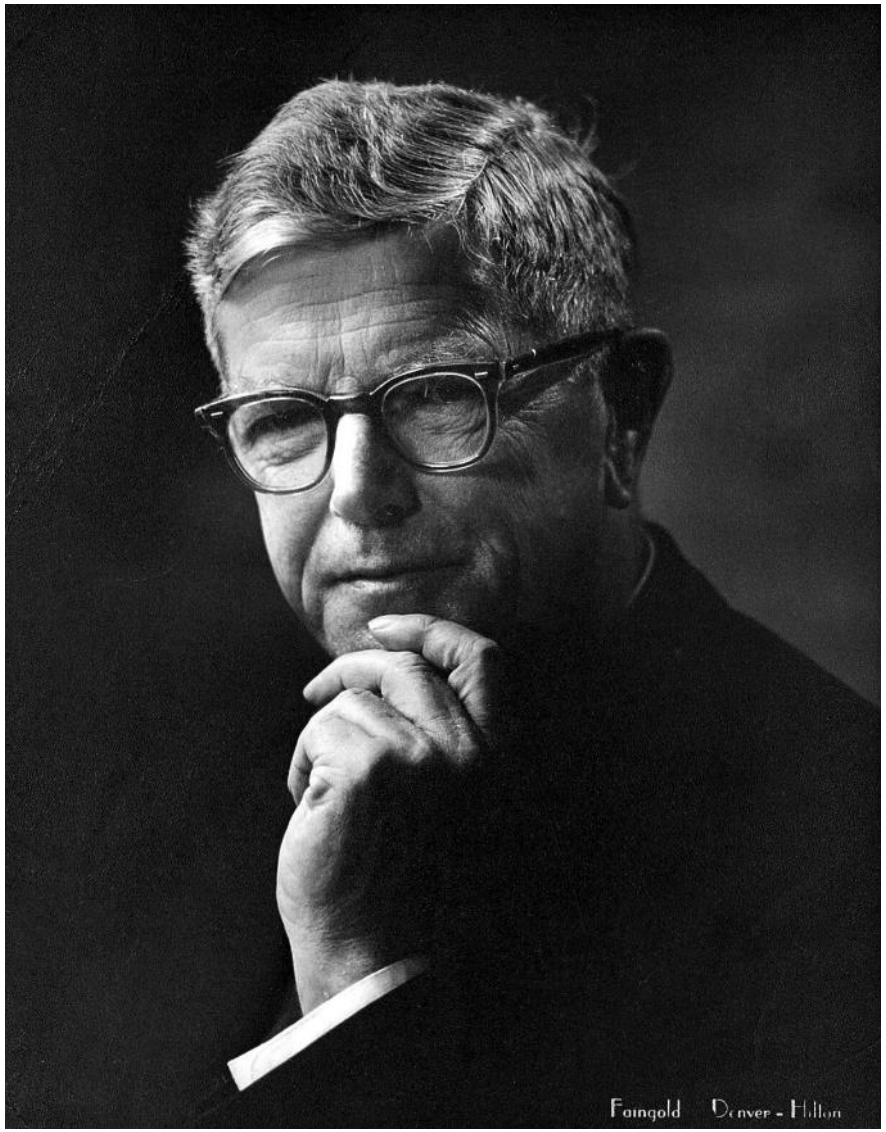
Australian virologist

Walter & Eliza Hall Institute, Melbourne (1944)

The Production of Antibodies, 2nd Ed. (1949)
Concept of “self” and “non-self”

The clonal selection theory (1957)
The Clonal Selection Theory of Acquired Immunity (1959)

Nobel Prize (1960)



“Self” vs. “Non-self”

Burnet’s hypothesis

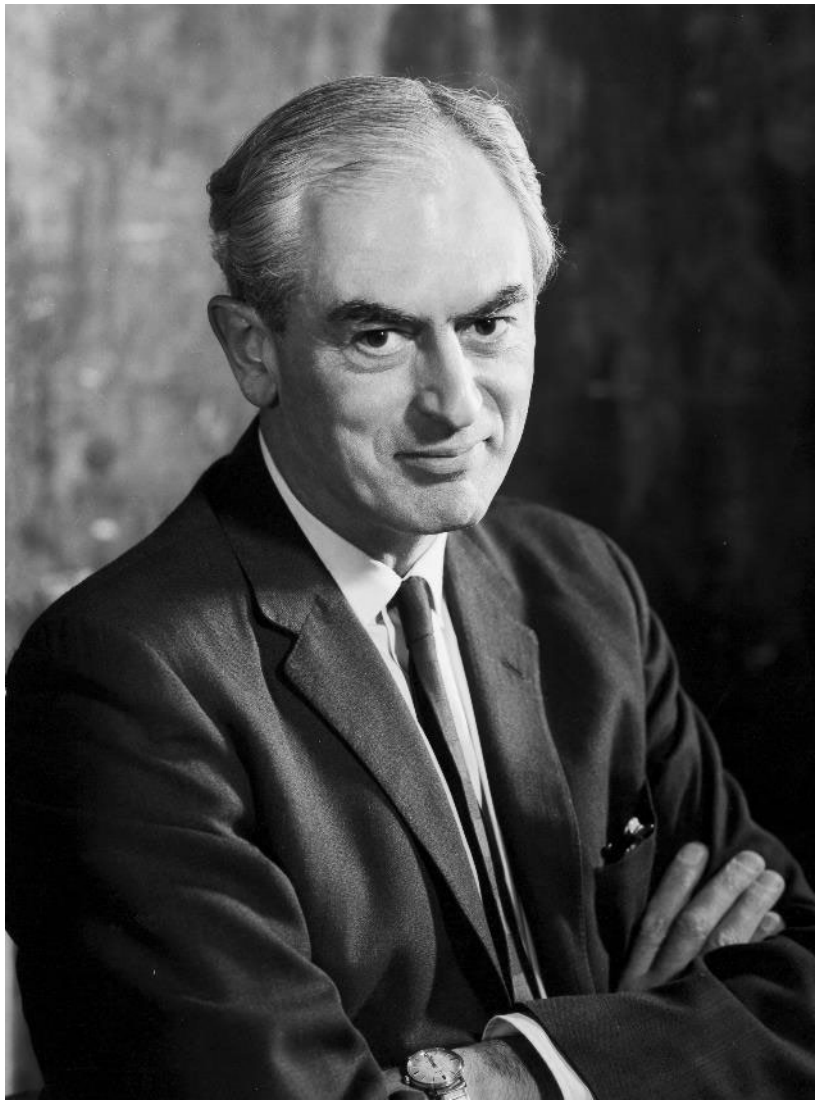
Set of “self” markers on every cell of the body
Immune system cells recognising “self” are deleted
Only “non-self” antigens would invoke immune response

Immunological “tolerance” established in utero

Ehrlich’s “horror autotoxicus”

Autoreactive antibodies, having no defensive role, should not exist

(Sir) Peter Medawar (1915-1987)



British zoologist

Professor, University of Birmingham (1947)
Professor, University College London (1951)
The Uniqueness of the Individual (1957)

Nobel Prize (1960)

Director, National Institute for Medical Research, London (1962)

The Art of the Soluble (1967)
Advice to a Young Scientist (1979)
The Limits of Science (1986)

The mechanism of skin-graft rejection

Study of a patient *(1943)*

Skin transplantation of a single patient with burns
“Autograft” (from self) succeeded
“Allograft” (from donor) initially took, then failed
A second allograft rejected more quickly

Animal experiments *(1950s)*

Actively acquired tolerance induced experimentally
Graft rejection caused by cellular reaction to foreign antigen

Tissue/organ transplantation

Transplantation in patients

- Success of transplants between identical twins
- Failure of transplants from unrelated individuals

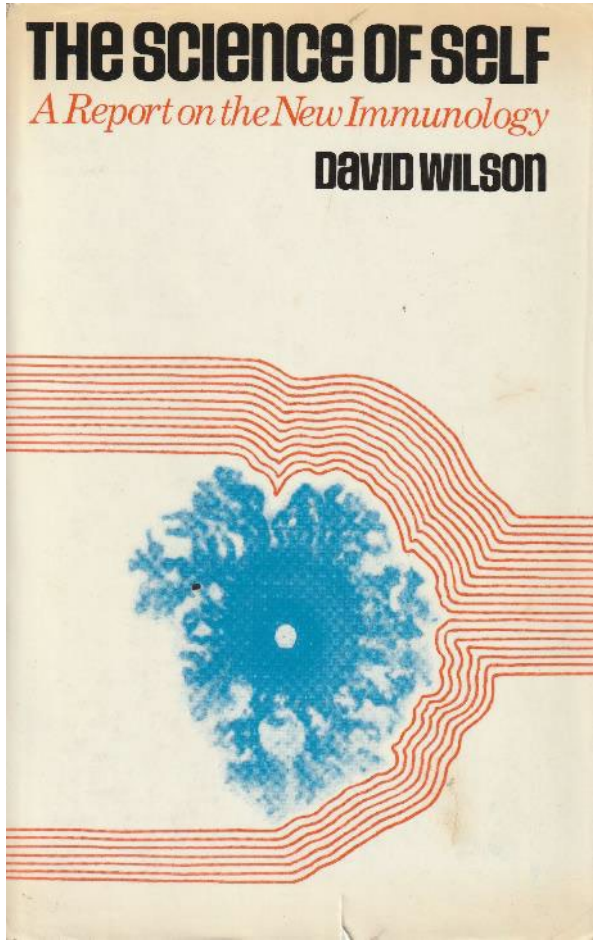
Studies in animal models

- Evidence for role of genetic likeness/foreignness
- Defined by antigens present on cell surface

Controlling transplant rejection

- Matching “histocompatibility” antigens
- Suppress immune responses with drugs

The new immunology: the “science of self”



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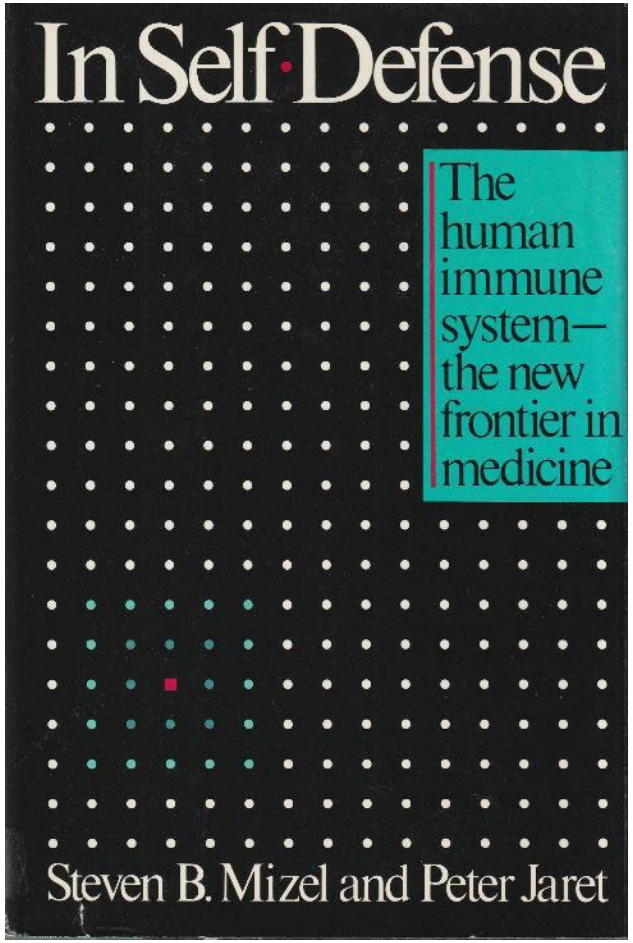

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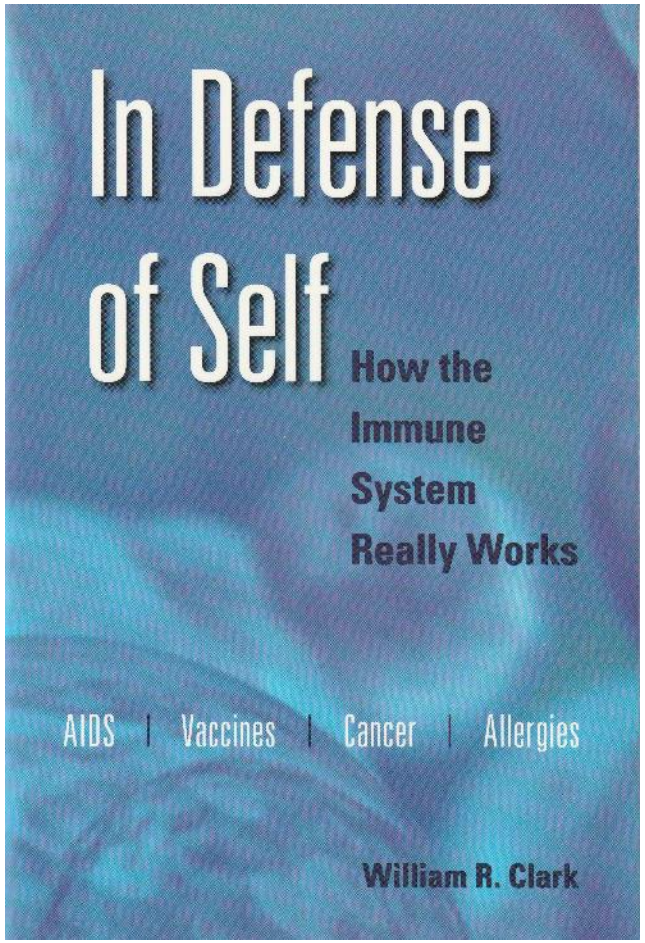

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“Autoimmunity”

Autoimmune diseases

Disparate group of disorders; new concept of pathogenesis

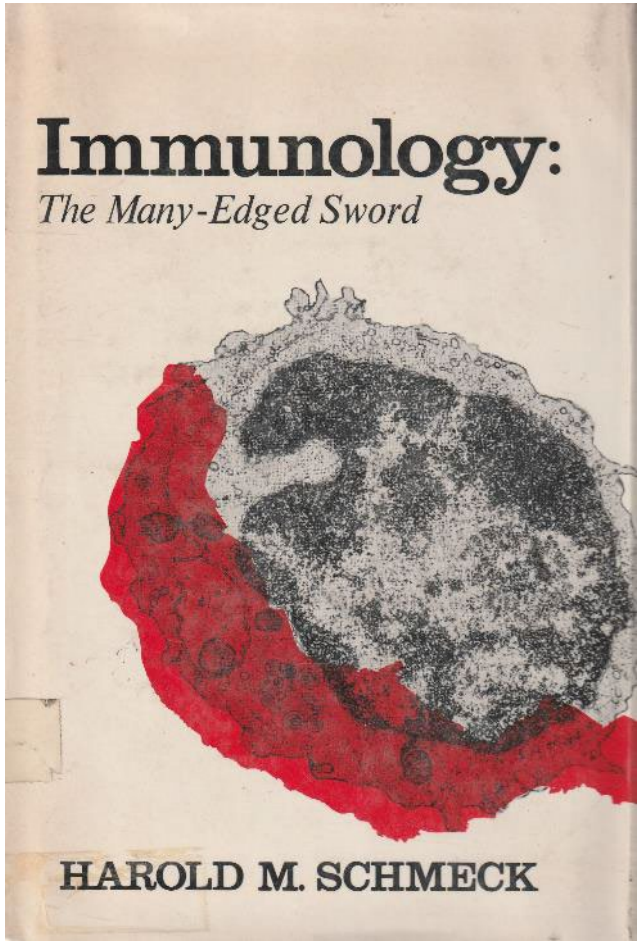
Autoantibodies

Haemolytic anaemias
Rheumatoid arthritis
Systemic lupus erythematosus
Autoimmune thyroiditis

Pathology

Chronic inflammatory attack on specific body tissues

Immunity: the “double-edged sword”



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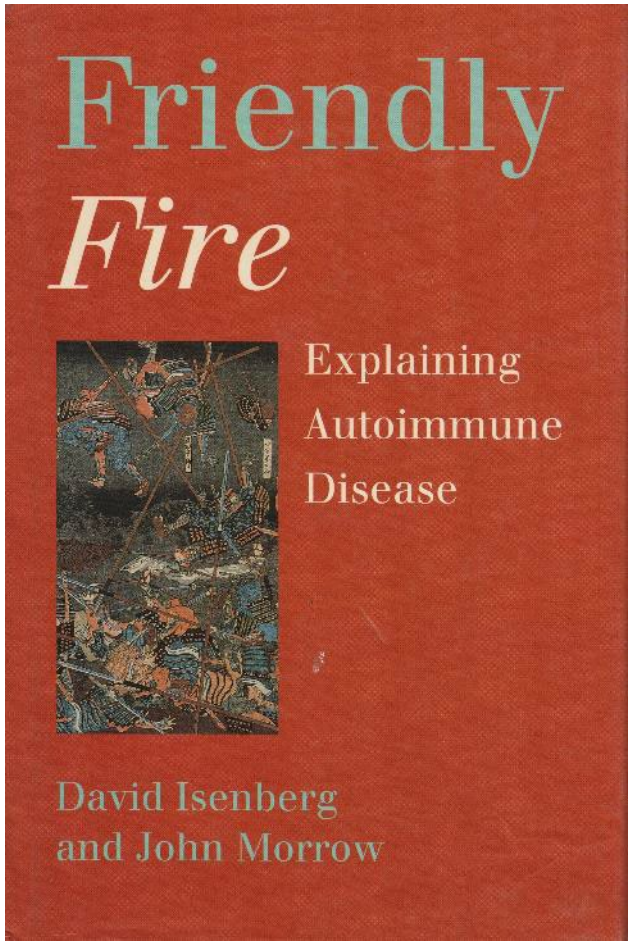

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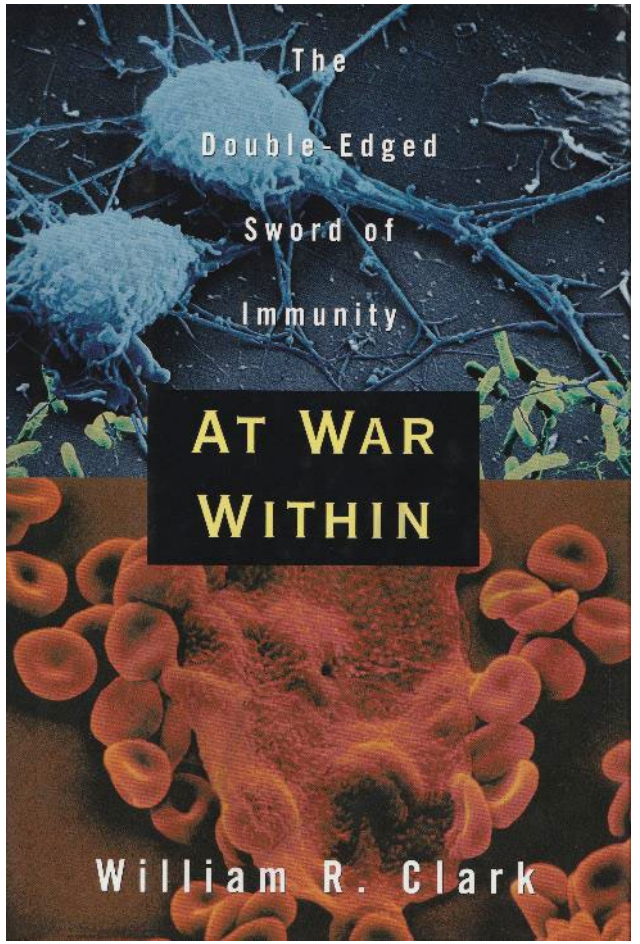

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“Immunodeficiency”

Congenital agammaglobulinaemia (antibody deficiency)

Plasma cells absent

B lymphocytes (from bone marrow) non-functional

DiGeorge syndrome (thymus deficiency)

Plasma and B cells present

T lymphocytes (thymus-derived) absent

SCID – Severe Combined Immunodeficiency (“bubble boy” syndrome)

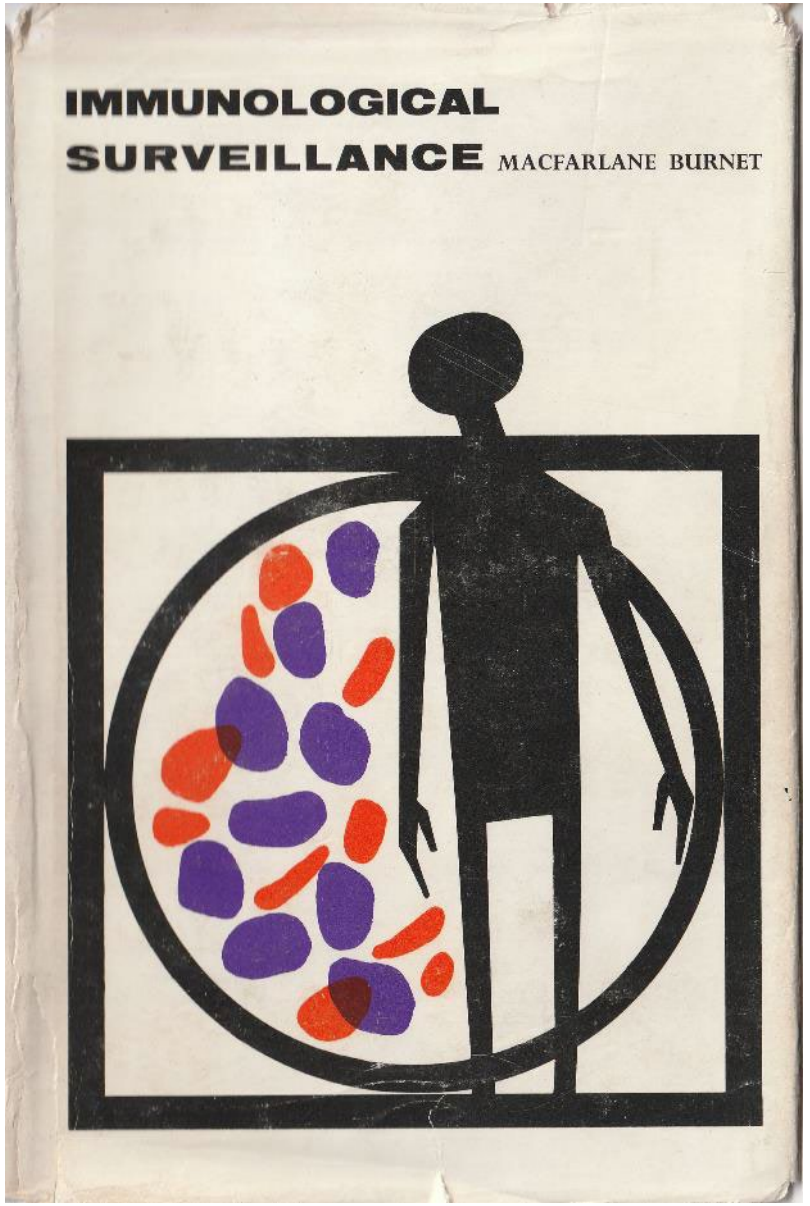
Lack of T cells

B cells non-functional

“Immunological surveillance”

“In essence, immunological surveillance is the concept that the major function of the immunological mechanisms in mammals is to recognise and eliminate foreign patterns arising in [the] body by somatic mutation or some equivalent process.”

Burnet (1970)



Cancer “immunotherapy”

Immune system recognises and destroys aberrant cells

Over time, however, a cancer that acquires additional mutations may eventually escape immune surveillance

Aim of immunotherapy is to generate effective anti-tumour activity

Immunomodulatory agents: cytokine therapy, checkpoint inhibitors

Cancer vaccines: both therapeutic & preventive approaches

Adoptive cell therapy: tumour-infiltrating lymphocytes and engineered T cell therapy

SUMMARY II

Novel mechanisms

- Clonal selection – self/non-self – tolerance
- Key roles of lymphocytes and co-operation

Medical advances

- Immunodeficiency
- Organ transplantation
- Autoimmune diseases
- Cancer surveillance

Practical developments

- Cellular therapies
- New antibodies/vaccines
- Novel markers of disease

The “immune system” today

Innate immunity

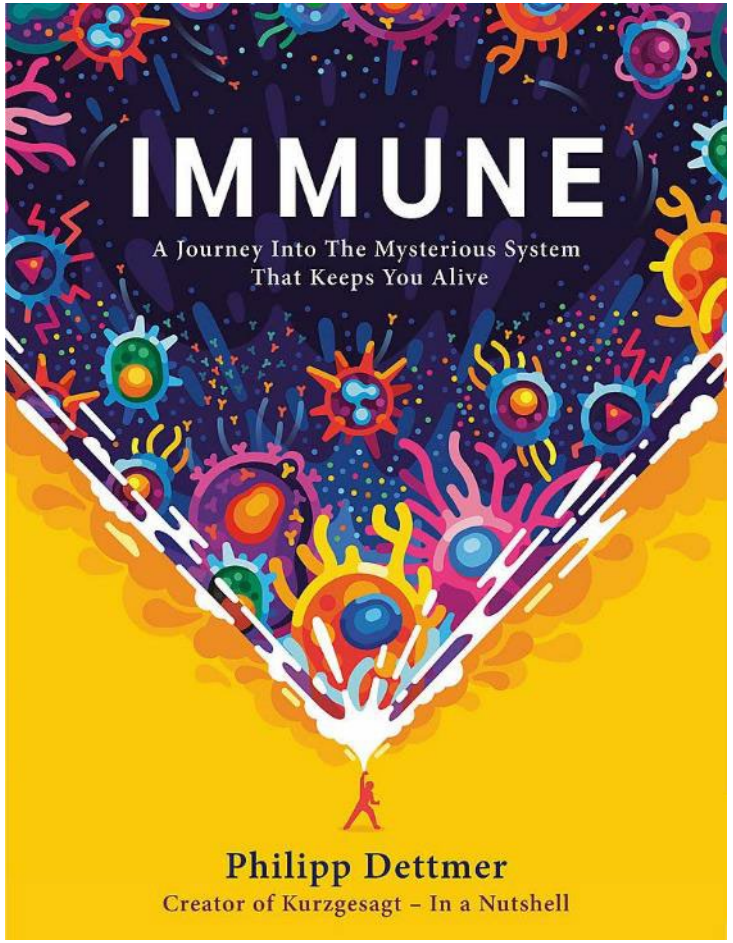
Cells recognise microbial components
Release of inflammatory mediators
Activate phagocytic cells

and triggers

Adaptive immunity

Acquired immunity via T and B cell co-operation
Antibody-mediated action against bacteria
Cell-mediated killing of virus-infected cells

“System that keeps you alive”



(2021)

Complex self-regulating network
Part of body’s homeostatic mechanisms
Maintain health of body & microbiome

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