


## Immuno-Parasitology

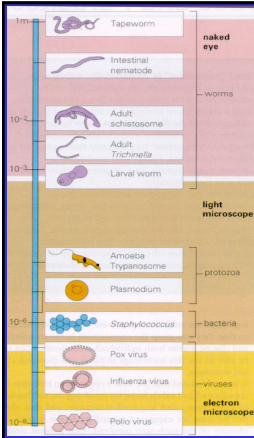
---



Professor Peter O'Donoghue

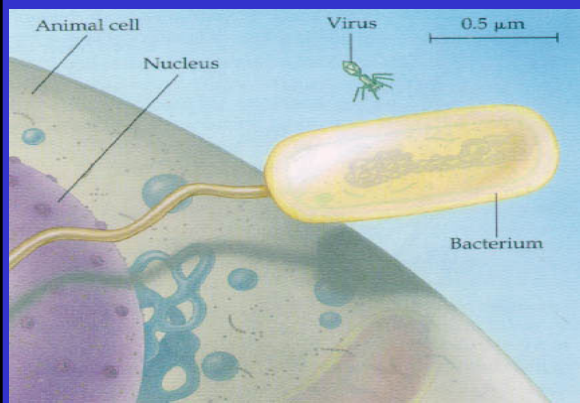
1

## ORGANISMS

	<table border="0" style="width: 100%;"> <tr> <td style="width: 50%;"><u>pathogens</u></td> <td style="width: 50%;"><u>hosts</u></td> </tr> <tr> <td>arthropods</td> <td>humans</td> </tr> <tr> <td>helminths</td> <td>animals</td> </tr> <tr> <td>protozoa</td> <td rowspan="4" style="font-size: 3em; vertical-align: middle;">}</td> </tr> <tr> <td>fungi</td> <td rowspan="4" style="vertical-align: middle;">microbiology</td> </tr> <tr> <td>bacteria</td> </tr> <tr> <td>viruses</td> </tr> </table>	<u>pathogens</u>	<u>hosts</u>	arthropods	humans	helminths	animals	protozoa	}	fungi	microbiology	bacteria	viruses
<u>pathogens</u>	<u>hosts</u>												
arthropods	humans												
helminths	animals												
protozoa	}												
fungi		microbiology											
bacteria													
viruses													

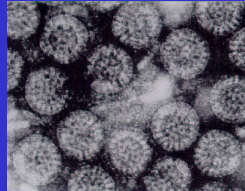

2

## Eukaryote - Prokaryote Domains



3

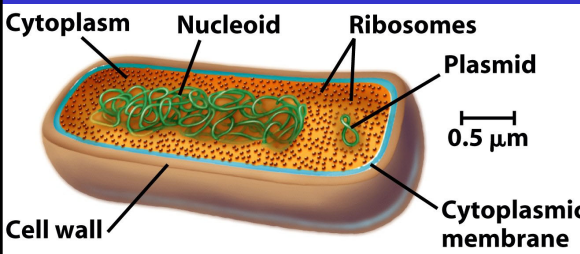
## VIRUSES (acellular)

- extremely small genomic fragments
- infect prokaryotic/eukaryotic cells and reproduce
- disease caused by cell dysfunction or lysis

4

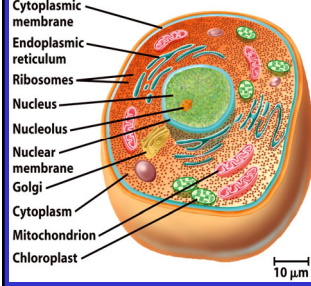
## BACTERIA (pro-karyotes)



- no endomembrane system
- nuclei in cytoplasm (high mutability)

5

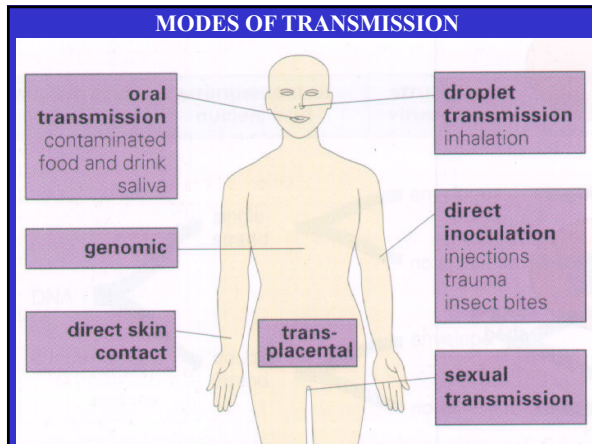
## PARASITES (eu-karyotes)



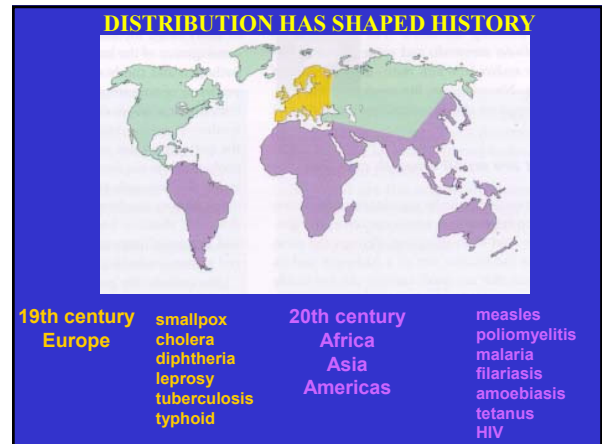
- Protozoa (uni-cellular)**
  - small, microscopic
  - solitary/colonial
- Metazoa (multi-cellular)**
  - larger, macroscopic
  - cellular specialization (tissues & organs)

- endomembrane systems
- genome and protein checking

6



7



8

### PREVAILING TAKE HOME MESSAGE

A staggering variety of micro-organisms cause infectious diseases in humans

Many micro-organisms are ubiquitous and have tremendous proliferative potential

How do hosts defend themselves against this microbiological onslaught?

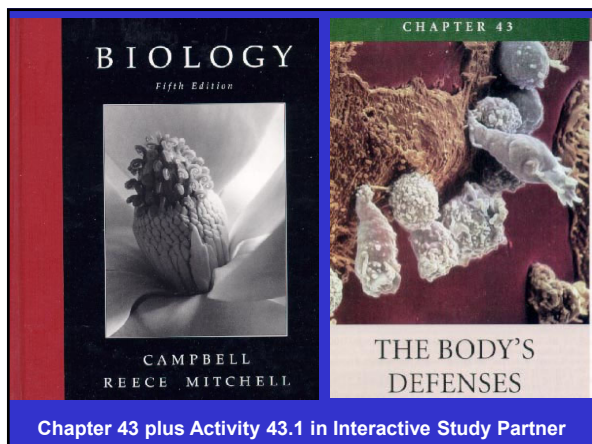
⇒ Thank heavens for immune systems!

9

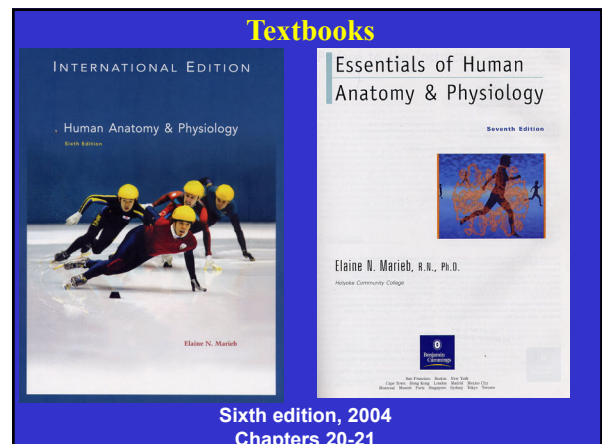
### ROLE OF IMMUNE SYSTEM IN HEALTH AND DISEASE

AGENT	NORMAL response	DEFICIENT response
infectious organism	protection	persistent/recurrent infection
tumour	immunity	cancer
grafted organ/tissue	rejection	acceptance
innocuous substance	allergy	no response

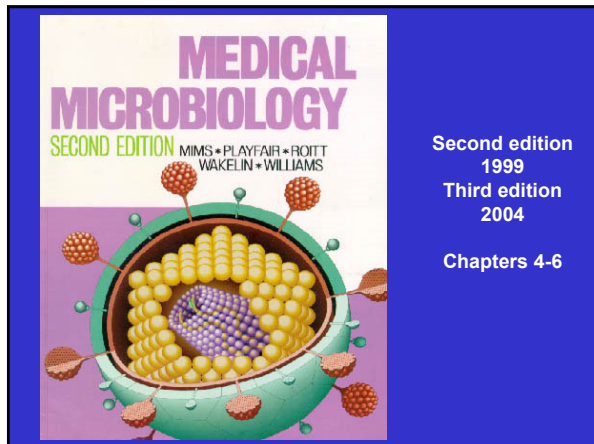
10



11

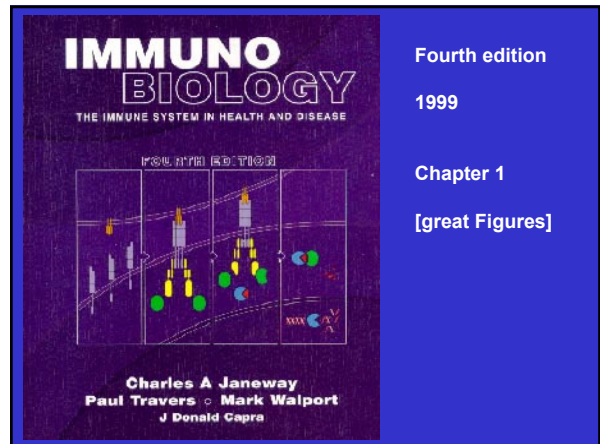


12



Second edition  
1999  
Third edition  
2004  
Chapters 4-6

13



Fourth edition  
1999  
Chapter 1  
[great Figures]

14

## IMMUNE SYSTEM

Structures	Function
<ul style="list-style-type: none"> <li>organs (bone marrow, thymus, spleen)</li> <li>tissues (lymphatic system)</li> <li>cells (phagocytes, lymphocytes)</li> <li>molecules (cytokines, lymphokines)</li> </ul>	<ul style="list-style-type: none"> <li>factory</li> <li>transit system</li> <li>effectors</li> <li>signals</li> </ul>

All function to provide:

- nonspecific immunity (innate) => no memory
- specific immunity (adaptive/acquired) => memory

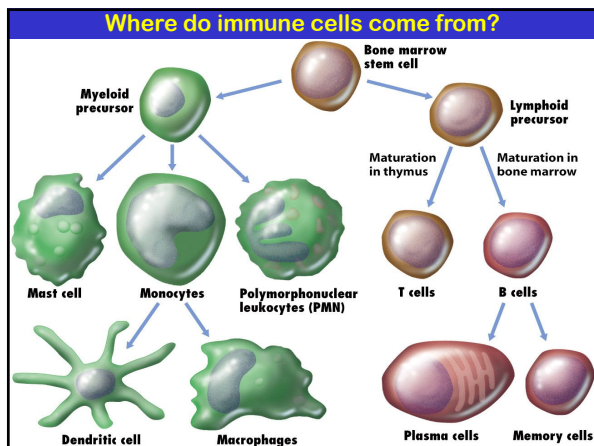
15

## BLOOD CELLS

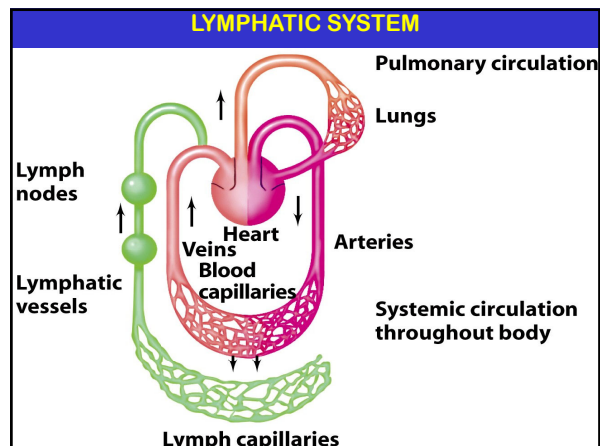
circulating cells divided into:

- erythrocytes (red blood cells)**
- leucocytes (white blood cells)**
  - granular
    - eosinophils
    - basophils
    - neutrophils
  - agranular
    - lymphocytes
    - monocytes

16



17



18

### Lymphatic filtration system

Lymph fluid collected by lymphatic vessels throughout body

Lymph nodes filled with macrophages, dendritic cells & lymphocytes filter out microbes and foreign particles

19

### Lymph organ THYMUS

- bilobed organ
- in inferior neck
- lobules & corpuscles
- causes lymphocytes (T cells) to become immunocompetent
- secretes hormones (thymosin & thymopoietin)

20

### THREE LINES OF IMMUNE DEFENSE

 first line <b>BARRIER</b>	 second line <b>INNATE</b>	 third line <b>ADAPTIVE (ACQUIRED)</b>
external coverings & secretions	phagocytes & inflammation	cell-mediated & humoral responses
nonspecific	nonspecific	specific

21

first line of defense

### NONSPECIFIC EXTERNAL BARRIERS

PHYSICAL (coverings)

intact skin  
mucous membranes  
cilia in respiratory tract  
flow through tubular organs

objective is to prevent entry of pathogens

22

first line of defense

### NONSPECIFIC EXTERNAL BARRIERS

CHEMICAL (secretions)

mucus  
lysozyme  
gastric juices  
saliva  
urine  
milk  
sweat

objective is to flush out or degrade pathogens

23

second line of defense



### NONSPECIFIC INNATE IMMUNITY

phagocytes	- ingest pathogens
natural killer cells	- lyse infected cells
antimicrobial proteins	
complement (C')	- lyse microbes
interferon (IFN)	- inhibit viral spread
inflammation	- deliver phagocytes to injured tissues

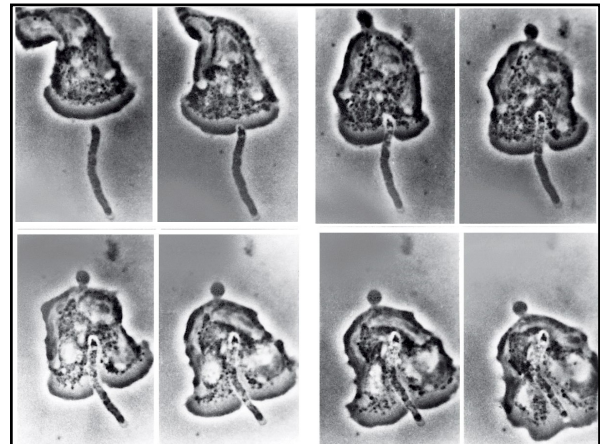
objective is to mop up microbes that have entered

24

**PHAGOCYTES**

tissue macrophages	circulating neutrophils
	
fixed or migratory long-lived	60-70% of leucocytes short-lived
chemotaxis - chemokines attract phagocytes	

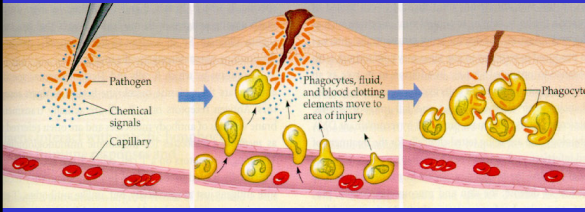
25



26

**INFLAMMATION**

"setting on fire" = rubor (redness), calor (heat), tumor (swelling), dolor (pain)



tissue injury release of chemical signals	dilation and increased permeability of blood vessels	phagocytosis of pathogens
--	---	------------------------------

27

**Reactive intermediates**

ROI (reactive oxygen intermediates) oxidative burst

$$\begin{array}{ccccccc}
 \text{O}_2 & \longrightarrow & \text{O}_2^- & \longrightarrow & \text{H}_2\text{O}_2 & \longrightarrow & \text{OH}^- \\
 \text{molecular} & & \text{superoxide} & & \text{hydrogen} & & \text{hydroxyl} \\
 \text{oxygen} & & \text{anion} & & \text{peroxide} & & \text{radicals}
 \end{array}$$

RNI (reactive nitrogen intermediates) nitric oxide

catalysed by eNOS/iNOS

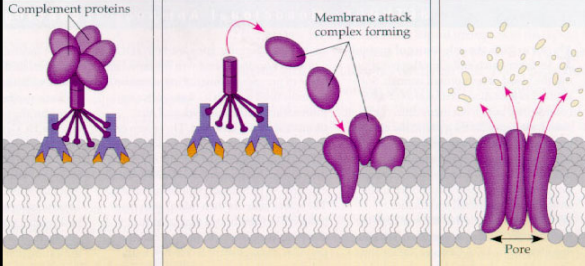
$$\text{L-arginine} \longrightarrow \text{L-citrulline}$$

generates NO

28

**COMPLEMENT CASCADE**

activation of serum proteins  
in presence or absence of antibody  
(classical and alternative pathways)



pathogen lysis by membrane disruption

29

third line of defense

**SPECIFIC ADAPTIVE (ACQUIRED) IMMUNITY**

reliant on lymphocytes

provide specificity, diversity, memory, self tolerance

develop from pluripotent stem cells in bone marrow

<p>T cells mature in thymus</p> <p>cell-mediated immunity</p>	<p>B cells mature in marrow</p> <p>humoral immunity</p>
---	---

objective is to target and destroy "nonself"

30

Triggered by exposure to **ANTIGENS**

Molecules provoking immune responses (non-self = foreign)

**Complete antigens**

- large molecules (proteins, nucleic acids, lipids, polysaccharides)
- reactive by themselves
- immunogenic (**antibody generating**)

**Incomplete antigens (haptens)**

- small molecules (peptides, nucleotides)
- only reactive when linked with other proteins
- not immunogenic (not protective)

31

**Recognition of 'self' versus 'nonself'**

governed by cell surface glycoproteins encoded by family of genes known as

**Major Histocompatibility Complex (MHC)**

<b>Class I MHC</b>	<b>Class II MHC</b>
present on all nucleated cells	present on all macrophages, dendritic cells and lymphocytes

32

**Class I MHC**      **Class II MHC**

MHC (self) cradles antigen (nonself) and presents it to effector cells

33

**Infected cells (class I MHC + Ag)**

**APC (macrophage) (class II MHC + antigen)**

34

Having been activated, the lymphocytes grow and proliferate - process known as **clonal selection**

Two types of clones formed:

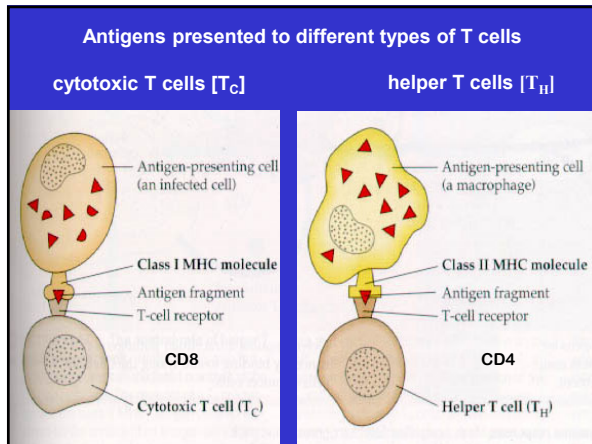
- short-lived effector cells
- long-lived memory cells

35

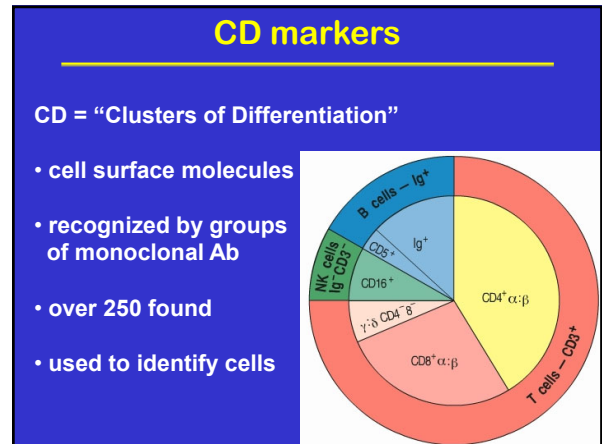
**Immunological Memory**

secondary response to same antigen faster and heightened

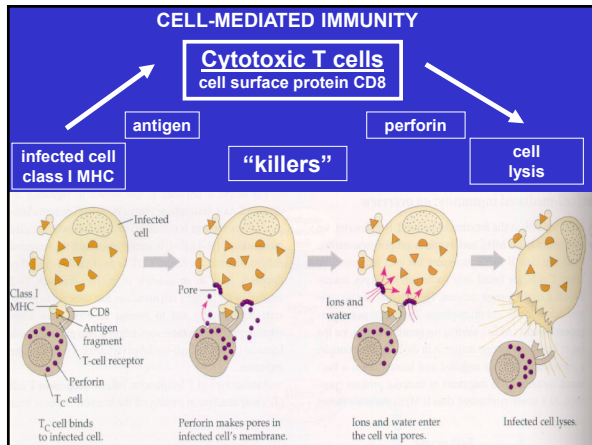
36



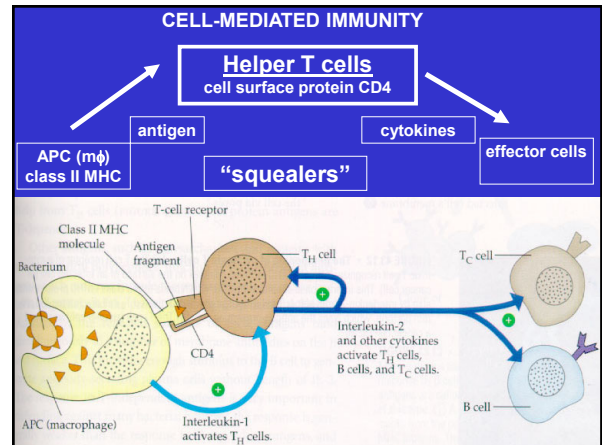
37



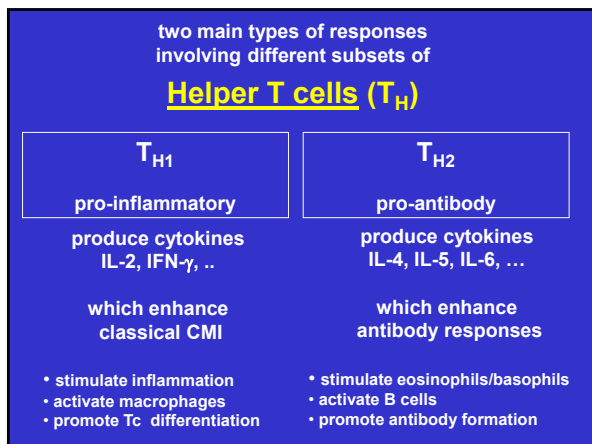
38



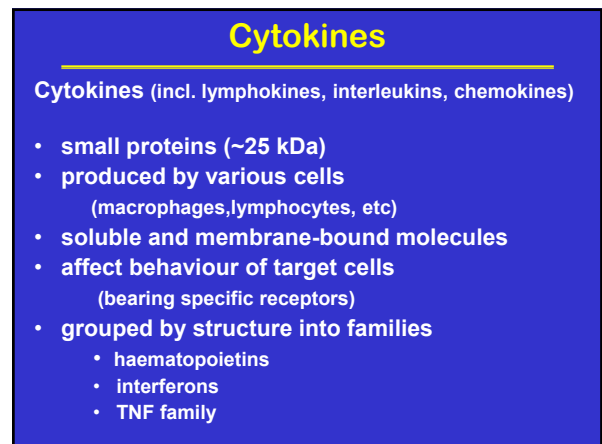
39



40



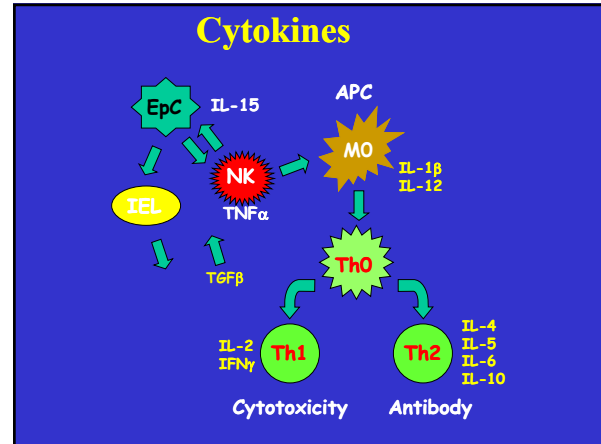
41



42

Cytokine	T-cell source	Effects on					Effect of gene knock-out
		B cells	T cells	Macrophages	Hematopoietic cells	Other somatic cells	
Interleukin-2 (IL-2)	T <sub>H0</sub> , T <sub>H1</sub> , some CTL	Stimulates growth and $\beta$ -chain synthesis	Growth	-	Stimulates NK cell growth	-	$\uparrow$ T cell responses (BC)
Interferon- $\gamma$ (IFN- $\gamma$ )	T <sub>H1</sub> , CTL	Differentiation IgG <sub>2c</sub> synthesis	Inhibits T <sub>H2</sub> cell growth	Activation $\uparrow$ MHC class II	Activates NK cells	Antiviral $\uparrow$ MHC class I and class II	Susceptible to mycobacteria
Lymphotoxin (LT, TNF- $\beta$ )	T <sub>H1</sub> , some CTL	Inhibits	Kills	Activates, induces NO production	Activates neutrophils	Kills fibroblasts and tumor cells	Absence of lymph nodes Disorganized spleen
Interleukin-4 (IL-4)	T <sub>H2</sub>	Activation growth $\uparrow$ CD1, $\uparrow$ MHC class II induction	Growth survival	Inhibits macrophage activation	$\uparrow$ Growth of mast cells	-	No T <sub>H2</sub>
Interleukin-5 (IL-5)	T <sub>H2</sub>	Differentiation IgA synthesis	-	-	$\uparrow$ Eosinophil growth and differentiation	-	-
Interleukin-10 (IL-10)	T <sub>H2</sub>	$\uparrow$ MHC class II	Inhibits T <sub>H1</sub>	Inhibits cytokine release	Co-stimulates mast cell growth	-	IBD
Interleukin-3 (IL-3)	T <sub>H1</sub> , T <sub>H2</sub> , some CTL	-	-	-	Growth factor for progenitor hematopoietic cells (multi-CSF)	-	-
Tumor necrosis factor- $\alpha$ (TNF- $\alpha$ )	T <sub>H1</sub> , some T <sub>H2</sub> , some CTL	-	-	Activates, induces NO production	-	Activates microvascular endothelium	Resistance to Gram- $\nu$ sepsis
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	T <sub>H1</sub> , some T <sub>H2</sub> , some CTL	Differentiation	Inhibits growth	Activation Differentiation to dendritic cells	$\uparrow$ Production of granulocytes and macrophages (myelopoiesis) and dendritic cells	-	-
Transforming growth factor- $\beta$ (TGF- $\beta$ )	CD4 T cells	Inhibits growth IgA secret factor	-	Inhibits activation	Activates neutrophils	Inhibits/stimulates cell growth	Death at $\sim$ 10 weeks

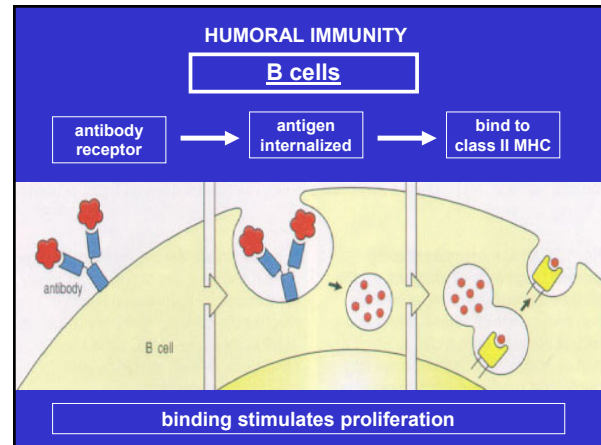
43



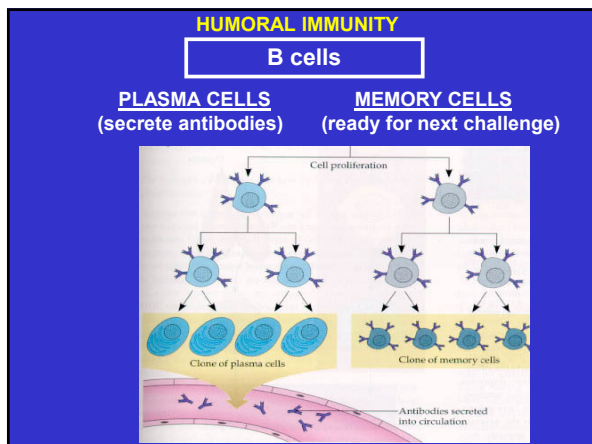
44

Interferon IFN $\gamma$	Interleukin IL-15	Transforming growth factor TGF $\beta$
<ul style="list-style-type: none"> <li>vital for resolution</li> <li>limits spread</li> <li>shortened infections</li> </ul>	<ul style="list-style-type: none"> <li>required for protection</li> <li>activates CD8, NK cells</li> <li>enhances CD8 <math>\gamma\delta</math> T-cell (IEL) activity</li> </ul>	<ul style="list-style-type: none"> <li>stimulates IgA</li> <li>involved in repair</li> </ul>

45



46



47

**ANTIBODY**

= immunoglobulin = gamma-globulin

Y-shaped glycoprotein formed by four polypeptide chains

- two light (L)
- two heavy (H)

Each chain has:


- constant (C) region
- variable (V) region (antigen-binding sites)

48



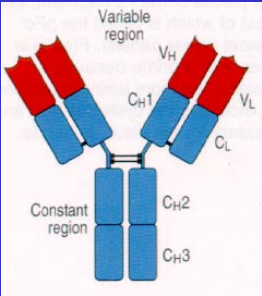
### ANTIBODY

= immunoglobulin = gamma-globulin



pinchers = Fab  
(antigen binding)

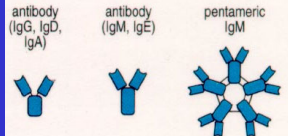
tail = Fc  
(constant for  $m\phi$   
opsonization)



49

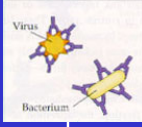
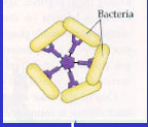
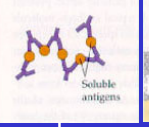
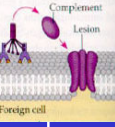

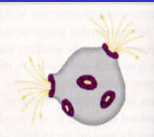
### FIVE ANTIBODY CLASSES ('MADGE')

IgM	serum	pentamer	early responder, fix C'
IgA	mucosae	dimer	secretory antibody
IgD	B cells	monomer	antigen receptor
IgG	serum	monomer	fix C', cross placenta
IgE	membranes	monomer	allergenic antibody



50

### ANTIBODY ACTION

neutralization	agglutination	precipitation	C' fixation
			
<p>phagocytosis</p>  <p>opsonization</p>			<p>cell lysis</p> 

51

### Immunoserology

Provides presumptive evidence of infection by demonstration of:

- host antibodies
- parasite antigens

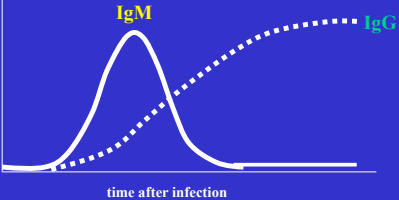
Useful for:

- antemortem diagnosis
- detecting carriers (asymptomatic)
- differentiating acute and chronic infections

52

### Antibody kinetics and dynamics

- early transient **IgM** response  
(coincident with **acute** phase)
- late persistent **IgG** response  
(coincident with **chronic** phase)

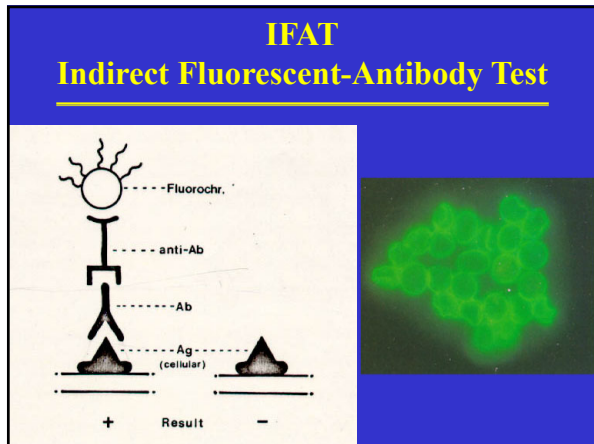


53

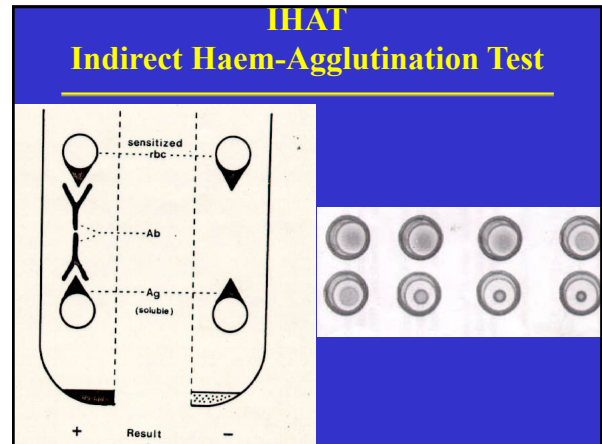
### SEROLOGICAL TESTS

- precipitin tests
- immunodiffusion
- immunoelectrophoresis
- complement fixation
- agglutination tests
- immunofluorescence
- enzyme immunoassays
- radio immunoassays

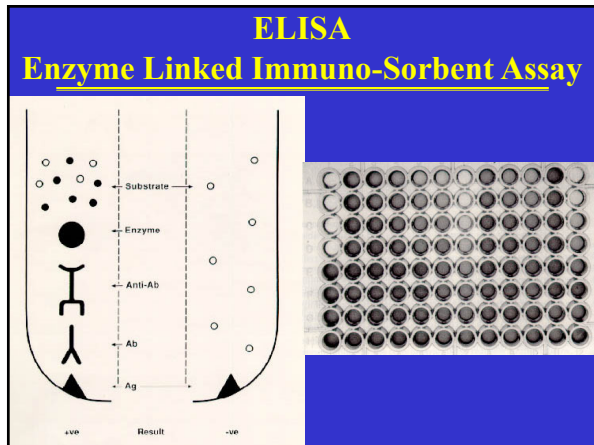
54



55



56

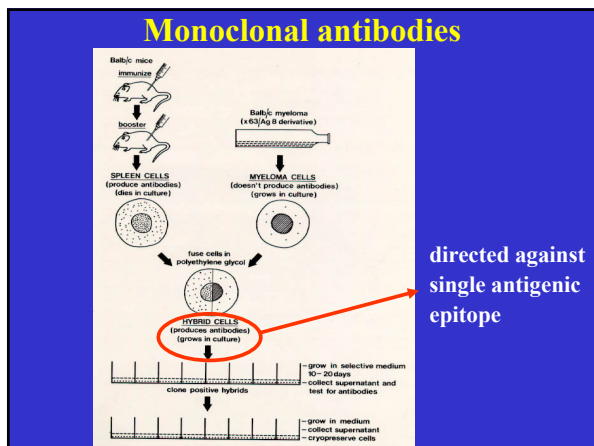


57

### Recent improvements in probes

- Improved antibody labels/probes
- most polyclonal antisera cross-react
- need antibody probes of defined specificity
- hybridomas producing monoclonal antibodies

58

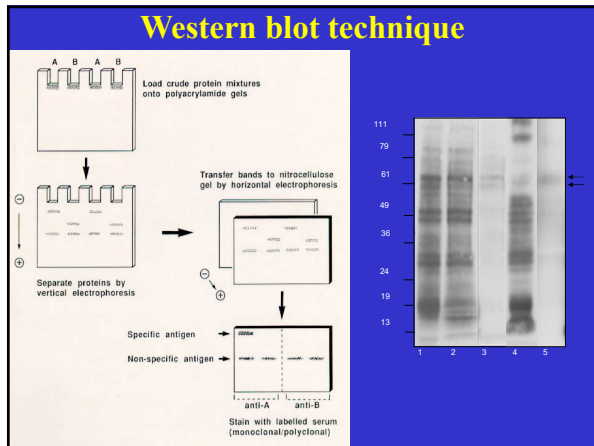


59

### Recent improvements

- Improved antigenic preparations
- most crude antigens are weak or cross-react
- need to identify immunodominant antigens
- Western blot technique defines antigens

60



61

- ### Ideal characteristics of diagnostic test
- safety consideration
  - cost efficient
  - time efficient
  - long-lived reagents
  - ease of performance
  - reproducibility
  - **specificity**
  - **sensitivity**
  - **accuracy**

62

### EFFICACY OF TEST

		INFECTION STATUS		
		infected	not infected	
SEROLOGY	positive	A	B	A+B
	negative	C	D	C+D
		A+C	B+D	N
ACCURACY		=		A+D/N
SENSITIVITY		=		A/A+C
SPECIFICITY		=		D/B+D

63

- ### Consequences of misdiagnosis
- Poor sensitivity  
unacceptable number of false negatives
- no treatment → disease progression → death
- Poor specificity  
unacceptable number of false positives
- unnecessary treatment → side effects → cost

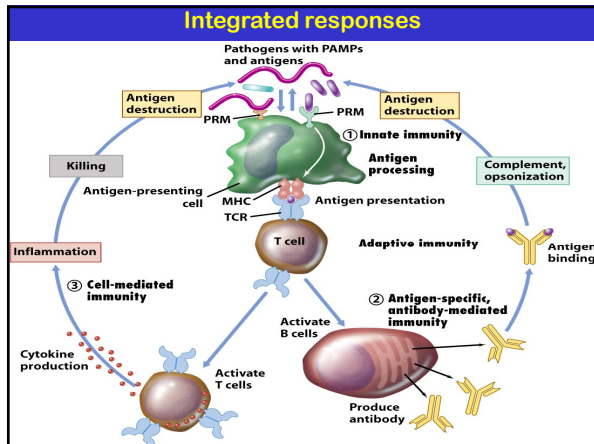
64

- ### The FUTURE
- Molecular biological techniques used to:**
- produce defined antigens for Ab assays
  - detect parasite molecules in host material (PCR-RFLP/RAPD, RNA/HSP, FISH)
- Advantages**
- species-specificity
  - high sensitivity
- Disadvantages**
- cost (equipment, reagents)
  - limited field potential

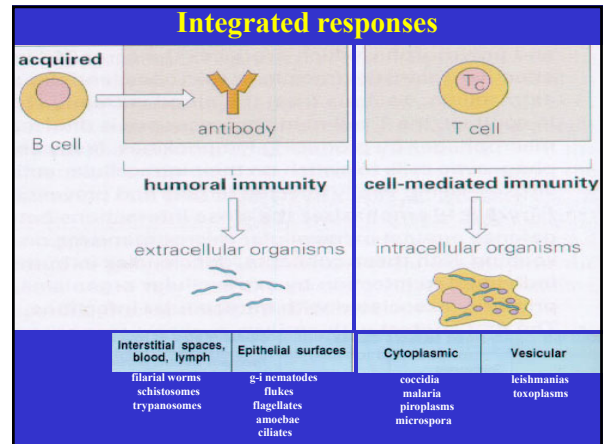
65

- ### RECAP
- IMMUNITY
- barrier (nonspecific) - physical
  - chemical
  - innate (nonspecific) - phagocytosis
  - inflammation
  - adaptive (specific) - humoral (B cells) - antibodies
  - cell-mediated (T cells) - helper
  - cytotoxic

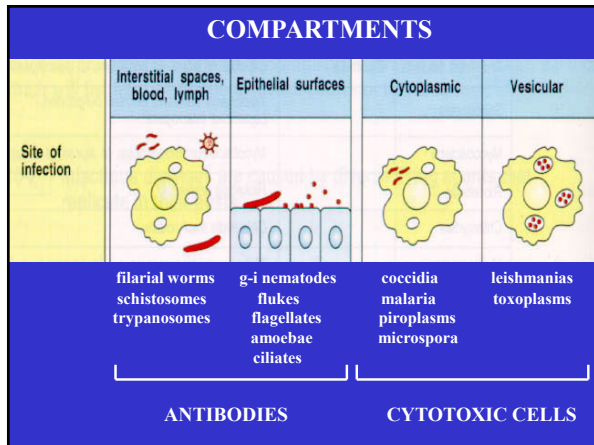
66



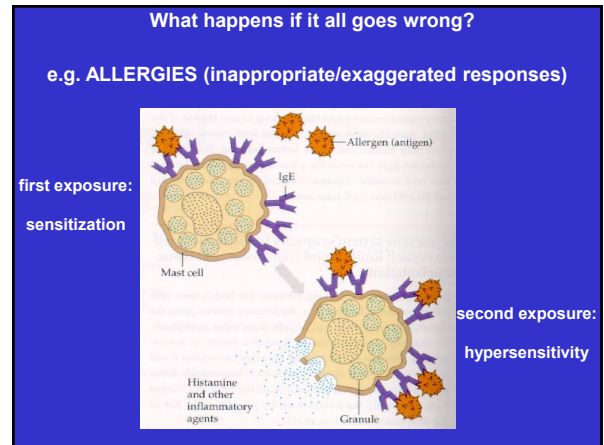
67



68



69



70



71

### FOUR TYPES OF HYPERSENSITIVITY

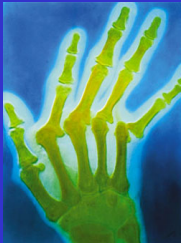
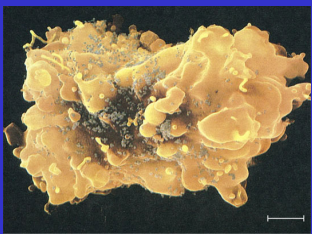
type I	immediate (minutes)	allergens	anaphylaxis, asthma, hives	IgE, mast cells
type II	cytotoxic (hours)	Ab-dep	haemolytic anaemia	IgG, IgM, C'
type III	immune complex (hours)	Ag-Ab deposits	serum sickness	IgG, Ag, C'
type IV	delayed type (days)	skin reactions	contact dermatitis	T cells, mØ

72

**IMMUNE SYSTEM PROBLEMS**



autoimmune diseases	- auto-antibodies (SLE, RA) - T cell intolerance (MS, diabetes)
immunodeficiencies	- congenital (SCID) - acquired (HIV-AIDS) - pathological (Hodgkins cancer)
immunosuppression	- chemotherapy (cancer treatment) - concomitant infections (measles)
incompatibility	- blood transfusion (groups) - tissue grafts (rejection) - organ transplantation (rejection)

73

<b>RA</b> rheumatoid arthritis	<b>HIV</b> human immuno- deficiency virus
	
autoimmune disease inflammation of joints	acquired immunodeficiency loss of T <sub>H</sub> cells

74

**INTERACTIONS**

<b><u>PATHOGEN</u></b>	<b><u>HOST</u></b>
- needs food supply	- resist infection
- place to develop	- moderate disease
- place to propagate	- develop protection
	

75

**How are hosts protected?**

- natural resistance (survival of fittest)  
(evolutionary arms-race, Red Queen hypothesis)
  - genetically determined
  - inherited (basis of animal breeding programs)
- acquired immunity  
(tolerance/amelioration/protection)
  - humoral responses (extracellular parasites)
  - cell-mediated responses (intracellular parasites)

76

**Control of infectious diseases**

**Treatment** (intervention)  
[demands knowledge of biochemistry/physiology]

- chemotherapy (treat pathogens)
- supportive therapy (treat symptoms)

**Prophylaxis** (prevention)  
[demands knowledge of biology/immunology]

- management (disrupt transmission)
- vaccination (induce protection)

77

**Current problems**

- Rapid emergence of drug resistance  
(variations on a theme)
- Complexity of immune interactions  
(humoral + cell-mediated responses)
- Few candidate vaccines  
(many antigens - few immunogens)
- Diminished immunocompetency
  - congenital immunodeficiencies
  - acquired immunodeficiencies
  - immunosuppressive chemotherapy

78

## Host susceptibility/resistance

---

Age-related

- clinical infections most common in neonates
- rapid development of resistance in animals

Acquisition of mature intestinal flora

- severe infections in germ-free/gnotobiotic animals

Malnutrition

- depleted iron status, low protein diet

Immunological competency

- immature - senescent
- immunodeficiencies (congenital + acquired)
- immunosuppression (iatrogenic + concomitant)

79

## Protective immunity

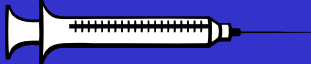
---

Active (self-generated)

- natural infection (subclinical)
- vaccination (stimulate immunity)

Passive (inter-host transfer)

- natural (transplacental, colostral)
- artificial (cells/antibodies) - immunotherapy



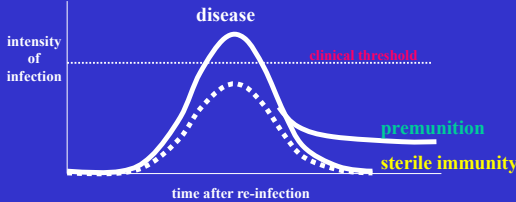
80

## Three types of immunity

---

Previous exposure confers:

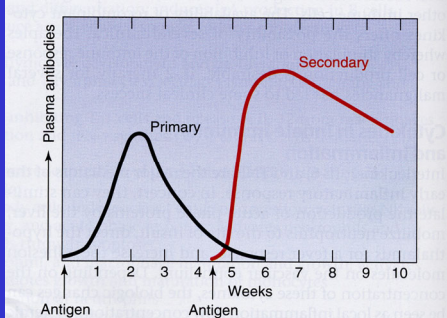
- **clinical immunity** (disease prevented)
- **sterile immunity** (parasites eradicated)
- **concomitant immunity** (some parasites persist)



81

## Can immune system be manipulated?

**YES!**  
invoke/heighten immunological memory through **VACCINATION**



82

## History

---

- ancient Middle Eastern practice of “leishmanization”  
deliberately infect children at inconspicuous site (buttocks) with *L. tropica* from mild cases resulting in self-healing lesion (Oriental sore)
- 10th century China - “variolation” infect children with mild cases of smallpox




83

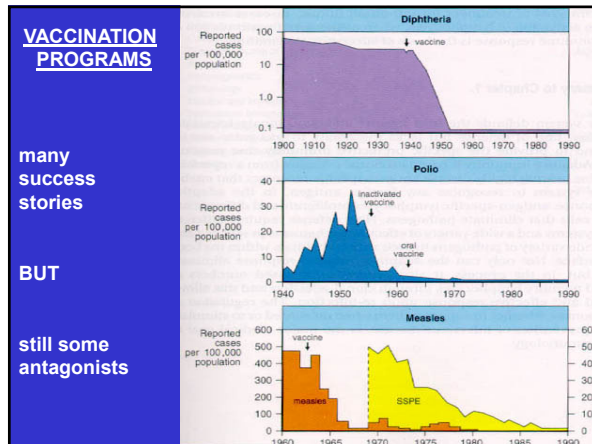
## Vaccination

---

Jenner 1796-98 used cowpox (vaccinia) to protect against smallpox (variola)



84



85

**Best vaccines**

- native/natural antigens
- contain multiple epitopes
- contain both T and B cell epitopes
- contribute to cooperative cell-mediated and humoral immunity (MHC class II needed for T cell responses)

86

**Objectives**

Resultant immunity acts to:

- prevent infection (block transmission)
- prevent disease (limit pathogenicity)
- eradicate infection (affect cure)

Various success stories

- most against bacterial or viral diseases
- few against parasites

87

**Vaccination**

Vaccine type:	Problems:
• live attenuated organisms 	• reversion
• killed organisms 	• allergy
• subcellular vaccines 	• contamination

88

**Live attenuated vaccines**

Selection of induced mutants (genetic roulette)

- avirulent species/strains/clones
- precocious strains
- serial passage in animal models
- serial passage in tissue culture
- adaptation to low temperature
- chemical mutagenesis
- irradiation

89

**Killed vaccines**

Inactivated through:

- chemical treatment
  - formaldehyde
  - phenol/acetone
  - $\beta$ -propiolactone/ethylenimines/psoralens
- heat/cold
- irradiation
  - microwave
  - ultra-violet

90



## Subcellular vaccines

- surface coats
- membrane determinants
- cytosol fractions
- organelle extracts
- cytoskeletal elements
- secretory/excretory metabolic products
- inactivated toxins (toxoids)
- anti-idiotypic vaccines (surrogate antigens)

91

## Vaccine production

Direct from parasites  
(poor quantity, good quality)

- culture parasites
- harvest antigens
- purify immunogens



Via molecular biology  
(good quantity, poor quality)

- recombinant vaccines
- DNA vaccines



92

## Recombinant vaccines

Expression vector used for bulk production but recombinant antigen often less immunogenic

- lacking glycosylation sites
- inappropriate presentation
- loss of epitopes during expression
- often stimulate B cell responses (not T cell)
- best presented as MAP (multiple antigenic peptides) - structure with branching lysine core large enough to eliminate need for carrier

93

## DNA vaccines

- cloned genes via microbial vectors (virus/bacteria)
- immunize with plasmid DNA encoding antigens
- use plasmids with promoters for high expression
- expression library immunization (single antigens often ineffective)
- application
  - injected (i/m, s/c)
  - needle-free (Biojector using CO<sub>2</sub>)
  - particle bombardment (gene gun)



94

## Vaccine optimization

Small antigens cleared rapidly from host  
Need to prolong exposure to achieve response

- use carrier molecules
- use adjuvants
- use delivery systems
- use slow release depots



95

## Adjuvants

Immunostimulants (additive/synergistic)

- inorganic salts (flocos)
  - aluminium hydroxide, beryllium hydroxide
  - aluminium phosphate, calcium phosphate
- saponins
- bacterial products
  - BCG (bacille Calmette-Guerin) tubercle bacillus
  - Freund's complete (bovine tuberculosis)
  - MDP (muramyl dipeptide)
- natural mediators
  - IL-1, IL-2, IFN- $\gamma$

96



## Delivery systems

- liposomes (phospholipid vesicles)
- proteosomes
- iscoms (immune stimulating complexes)
  - cage-like micelles of saponin derivative QuilA, cholesterol, phospholipids and antigen
- block polymers
  - polyoxyethylene
  - polyoxypropylene
- slow release formulations (bolus)



97

## Vaccine failure

- incomplete immunity (partial protection, disease in immunocompromised)
- short-term immunity (loss of protection)
- inappropriate responses (polyclonal activation)
- exaggerated responses (immunopathology)
- no clinical immunity (host disease)
- complete failure (host death)



98

## Vaccine pathology

- contamination (esp. with viruses)
- allergy/hypersensitivity (to egg proteins, horse serum)
- autoimmunity (arthritis)
- neurological side-effects (convulsions) (meningitis/encephalitis)



99

## The great debate

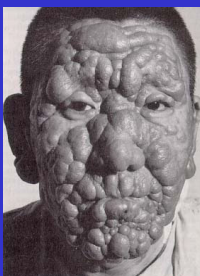
Chemotherapy versus Vaccination

- |   |                                      |
|---|--------------------------------------|
| • broad spectrum (targets whole groups) | • narrow activity (species specific) |
| • short-acting                          | • long-lasting                       |
| • re-infection possible                 | • re-infection prevented             |
| • drug resistance                       | • reversion of virulence             |
| • drug residues                         | • hypersensitivity                   |
| • environmental toxins                  | • contamination                      |

100

## Take home message

Prevention is better than cure!



101

## Immunotherapy

### Endogenous

- constitutive (modulate existing function)
- restitutive (restore absent function)
- delimiting (splenectomy)

### Exogenous

- immune cells (lymphopheresis)
- immunoglobulins (antibody transfer)
- soluble factors (cytokine therapy)
- immunostimulants

102

### Humoral immunity

---

Serum antibodies (acute-convalescent)

- transient IgM, IgA, IgE (weeks)
- prolonged IgG (months)

Secretory antibodies

- local/secretory IgA, IgM, IgG

B cell deficiencies

- hypo-, a-gammaglobulinaemia
- selective immunodeficiencies

Antibodies alone not strongly protective

103

### Cell-mediated immunity

---

Knowledge from *in situ* and *in vivo* situations

- tissue pathology (inflammation/infiltration)
- histopathology (neutrophils, macrophages, lymphocytes, plasma cells)
- clinical immunology (esp. patients with selective immunodeficiencies)
  - low CD4 (helper)/AIDS patients - chronic infections
  - CD4 modulation (depletion/restitution)
  - CD8 (cytotoxic) modulation
  - NK (natural killer cell) modulation
- experimental models
  - SCID mice (combined immunodeficiencies)
  - nude mice/rats (athymic)

104

### Cytokine immunotherapy

---

Improve Th1 cytokine levels

- IFN $\gamma$ : limit spread

Improve macrophage activation

- IL-12: better antigen presentation

BUT, therapy cost-prohibitive

AND adverse effects unknown

105

### Lactogenic immunity


---

Observations from surveys of neonates

- fewer infections in breast-fed children than in bottle-fed children
- more severe infections in colostrum-deprived calves, lambs

Passive transfer studies

- colostrum neutralizes pathogens
- colostrum protects against severe disease
- colostrum helps resolve symptoms



106

### Colostrum

---

- maternal milk produced post-partum
- nutritionally-rich (protein/fat)
- immunologically-rich (antibodies)
- plentiful source (dairy industry)

Source

- uninfected cows - low titre (1:100)
- infected cows - medium titre (1:1000)
- devise immunization schedule to improve titre

107

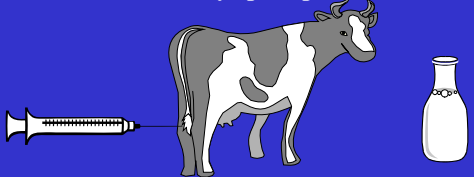
### Immunization

---

Route - intramammary infusion

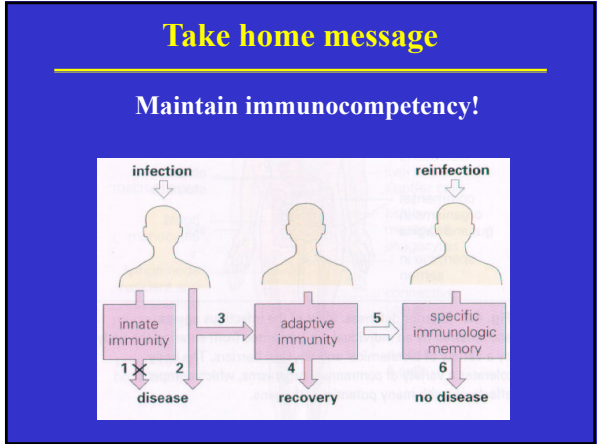
Dose - soluble extracts weekly pre-partum

Collection - two days post-partum

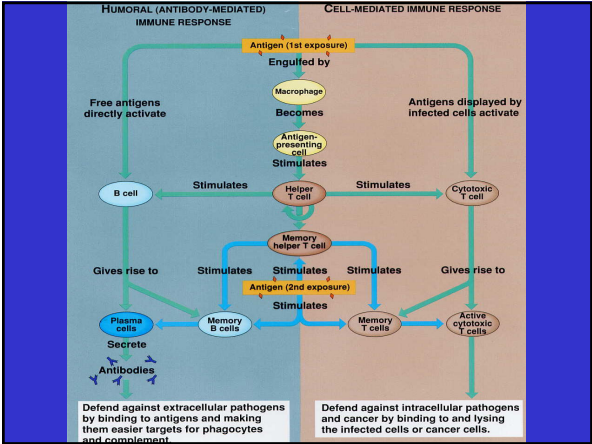


HIBC = hyper immune bovine colostrum antibody titres 1:1,000,000 esp. IgA

108



109



110