โครงการหนึ่งอาจารย์หนึ่งผลงาน ประจำปี พ.ศ. 2555

เอกสารประกอบการสอน

108303 ภูมิคุ้มกันวิทยาทางการแพทย์

(MEDICAL IMMUNOLOGY)

เรื่อง ภูมิคุ้มกันบกพร่อง

หลักสูตรแพทยศาสตร์

โดย

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สำนักวิชาวิทยาศาสตร์

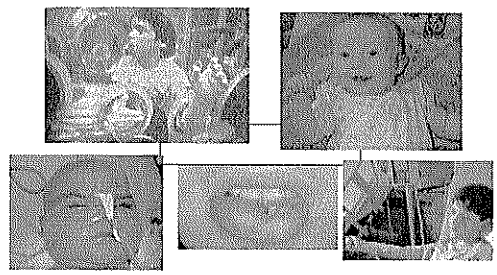
มหาวิทยาลัยเทคโนโลยีสุรนารี

Congenital and Acquired Immunodeficiencies Part A

(Diseases caused by defective immune responses)

By Asst. Prof. Dr. Wilairat Leeanansaksiri

What's Happen to Them ?



Can you help them ?

Immunodeficiency

Outline

1. Concise summarization of normal immune response
2. Concise summarization of normal immunity to infection
3. innate immunodeficiency and primary immunodeficiency diseases Adaptive Immunodeficiency
4. adaptive immunodeficiency and secondary immunodeficiency diseases

Immunodeficiency

Objectives

1. Understand and can explain normal immune response both innate and adaptive immunities
2. Understand and can explain capability of microbes to escape immune response
3. Understand and can explain innate immunodeficiency and primary immunodeficiency diseases
4. Understand and can explain adaptive immunodeficiency and secondary immunodeficiency diseases

Immunodeficiency

1. Primary Immunodeficiency
- Adaptive (Part A)
- Innate (Part B)

2. Secondary Immunodeficiency
- Adaptive (Part A)
- Innate (Part B)

1. Primary Immunodeficiency

- congenital Immunodeficiency (usually abnormal since birth)
- due to **genetic defect** leads to blocks in the maturation or functions of different components of the immune system
  - Innate immunity components defect e.g. phagocytosis, complement
  - Adaptive immunity components defect e.g. T- cells, B- cells

2. Secondary Immunodeficiency

- Acquired Immunodeficiency
- **No genetic defect**
- **due to other defects** including infections, nutritional abnormalities, or treatment that cause loss or inadequate function of various components of the immune system e.g. immune suppressive drugs, HIV infection.

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2. Secondary Immunodeficiency

- Drug related
- Disease related
  - –Cancer
  - –AIDS
    - HIV
    - T helper cell as target

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Loss or reduction of:

- Cell type
- Cell numbers
- Cell function

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Loss of Cell Function

- Receptors
- Cell signaling
- Cytokine production
- Ig production
- Co stimulation impairment
- Intracellular killing
- Extravasation impairment

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Part A : Adaptive immunity components defect e.g. T- cells, B- cells

Many diseases: SCID, CVID, etc.

2. Secondary Immunodeficiency

- Drug related
- Disease related
  - – Cancer , AIDS

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Part B : Innate immunity components defect e.g. Macrophage…

- Chronic granulomatous disease
- Congenital agranulocytosis
- Leukocyte-adhesion deficiency
- Chediak-Higashi syndrome

2. Secondary Immunodeficiency

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Part A
1. Primary Immunodeficiency

Defect in T and B cells

- **Severe combined immunodeficiency (SCID)**
- **B cells**
  - **Agammaglobulinemia**
  - **Hypogammaglobulinemia**
  - **Specific Ig Deficiencies**
- **T cells**
  - **DiGeorge Syndrome**
  - **Wiskott Aldrich Syndrome**

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Review T and B cell in immune response

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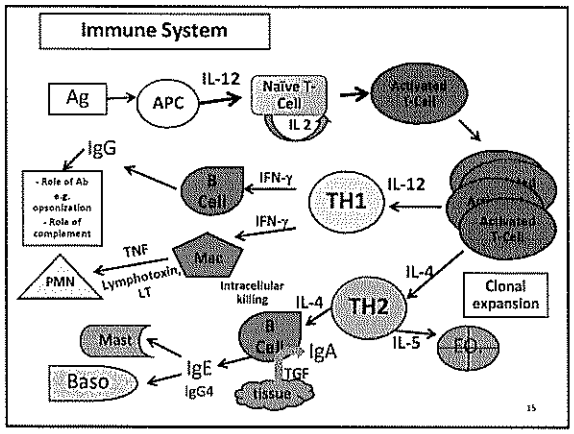

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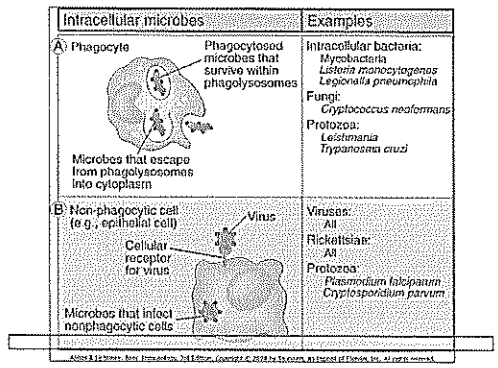

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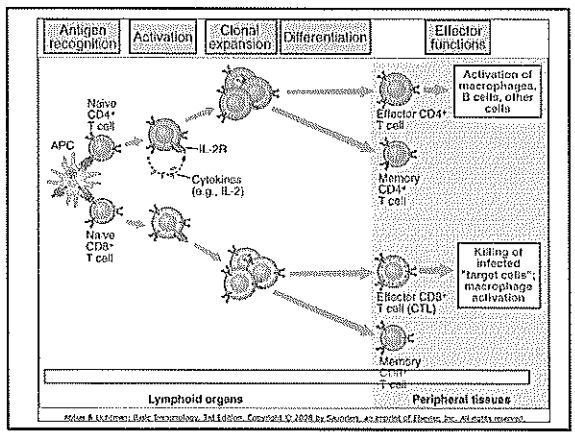

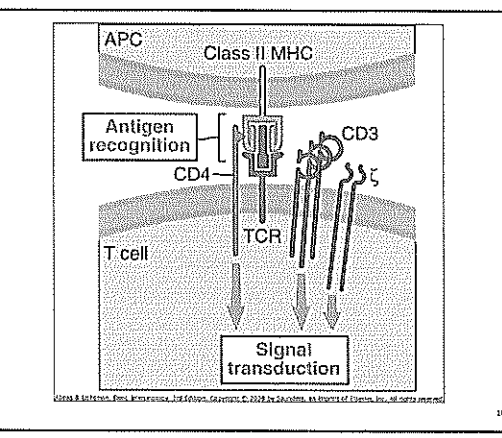

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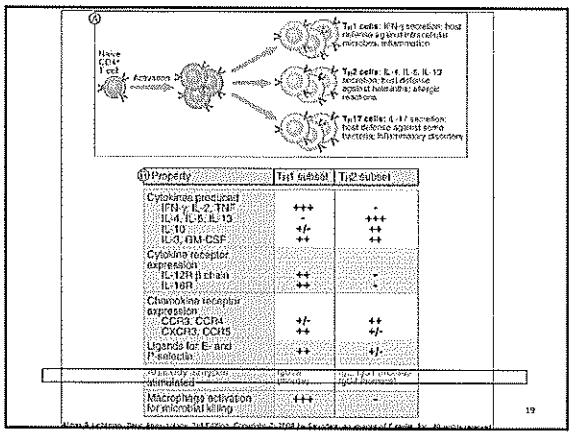

Property	$T_{H}1$ subset	$T_{H}2$ subset
Cytokines produced		
IFN-γ, IL-2, TNF	+++	-
IL-4, IL-5, IL-13	-	+++
IL-10	+/-	++
IL-3, GM-CSF	++	++
Cytokine receptor expression		
IL-12R β chain	++	-
IL-18R	++	-
Chemokine receptor expression		
CCR3, CCR4	+/-	++
CXCR3, CCR5	++	+/-
Ligands for E- and P-selectin	++	+/-
[illegible]	[illegible]	[illegible]
Macrophage activation for microbicidal killing	+++	-

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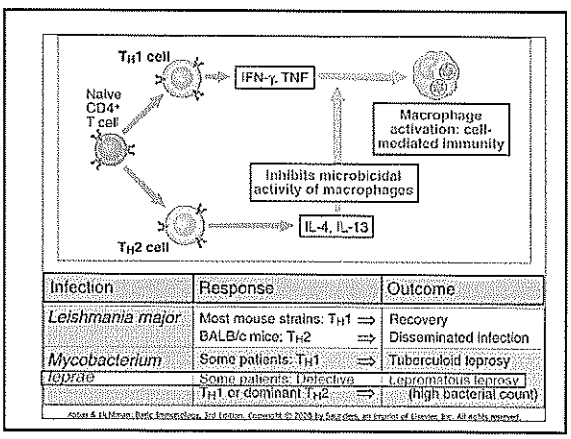

Infection	Response	Outcome
Leishmania major	Most mouse strains: $T_{H}1$ ⟹	Recovery
	BALB/c mice: $T_{H}2$ ⟹	Disseminated infection
Mycobacterium leprae	Some patients: $T_{H}1$ ⟹	Tuberculoid leprosy
	Some patients: $T_{H}2$ ⟹	Lepromatous leprosy
	$T_{H}1$ or dominant $T_{H}2$ ⟹	(high bacterial count)

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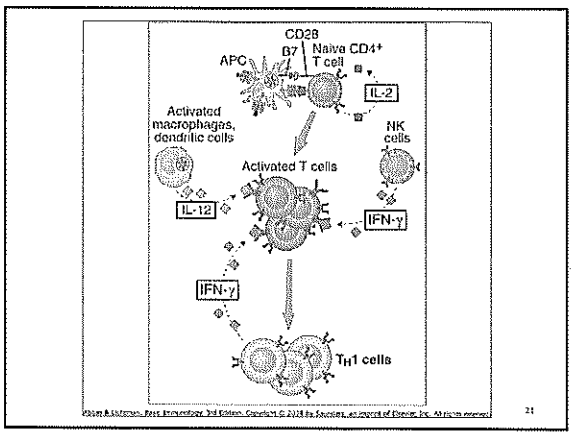

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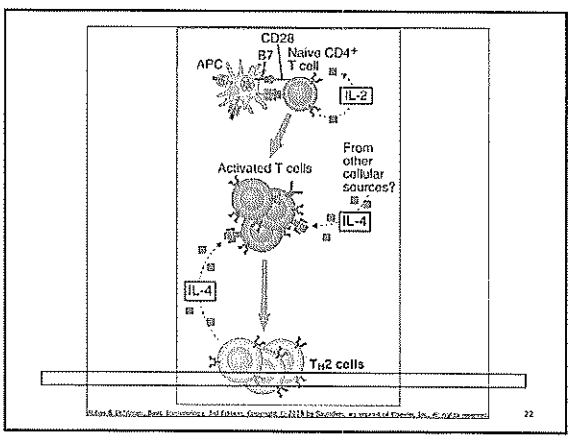

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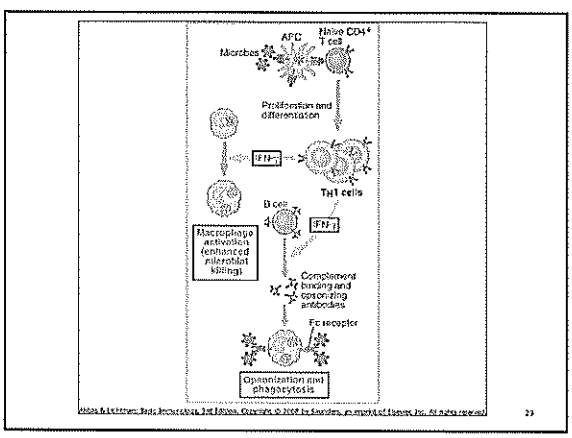

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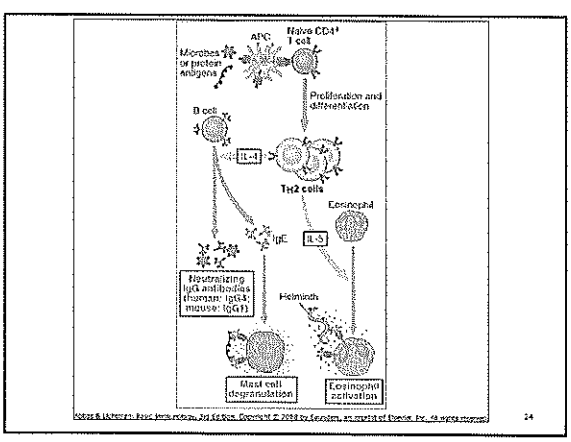

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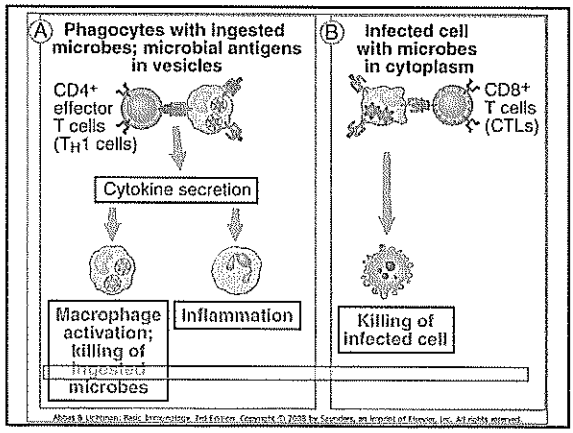
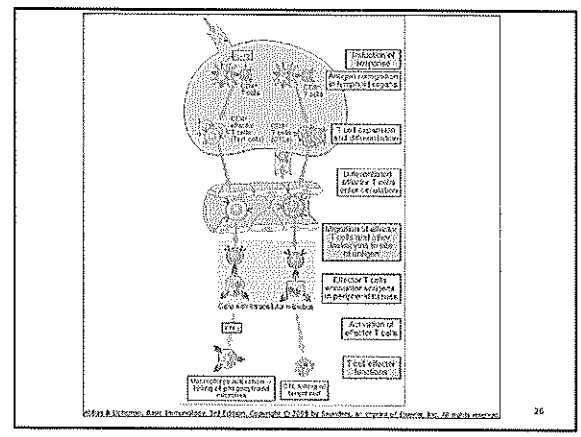
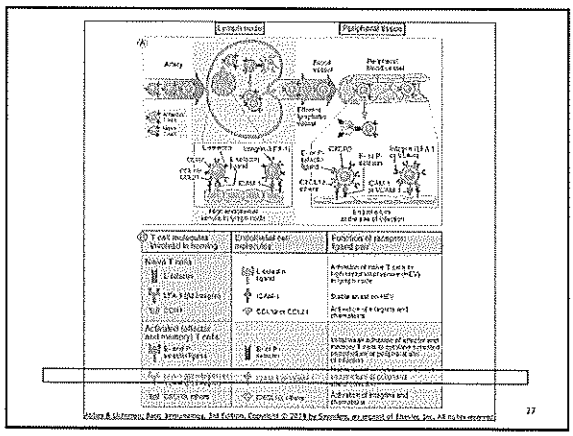
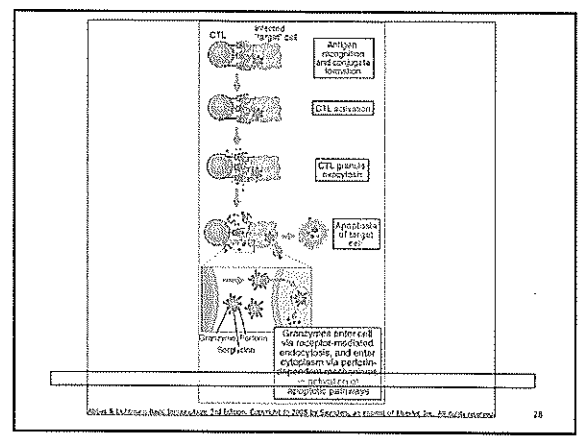
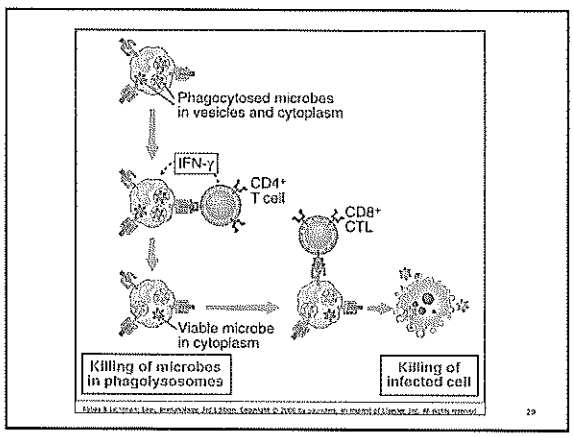
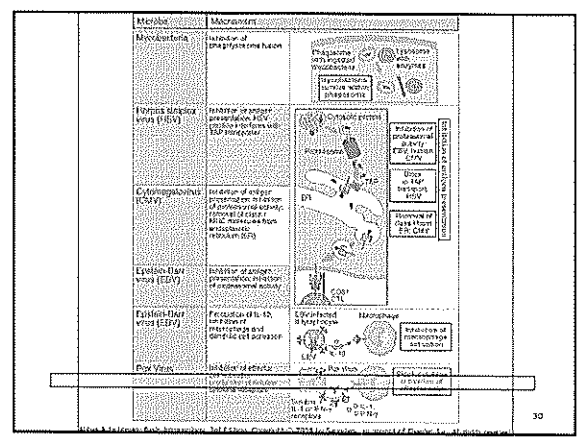

A Phagocytes with ingested microbes; microbial antigens in vesicles
CD4+ effector T cells (T_H1 cells)
Cytokine secretion
Macrophage activation; killing of ingested microbes
Inflammation
B Infected cell with microbes in cytoplasm
CD8+ T cells (CTLs)
Killing of infected cell

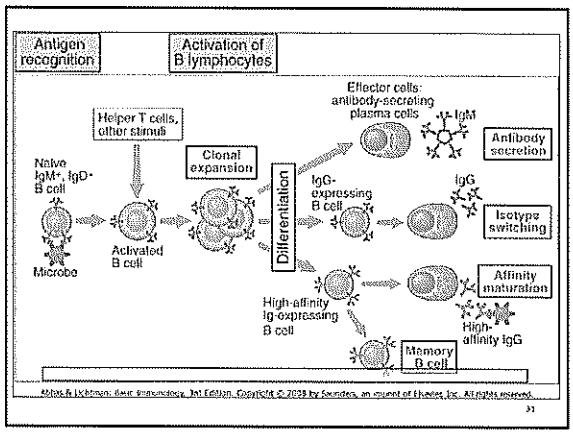





CTL
Infected target cell
Antigen recognition and conjugate formation
CTL activation
CTL granule exocytosis
Apoptosis of target cell
Granzymes enter cell via receptor-mediated endocytosis, and enter cytoplasm via perforin-dependent pore
Granzymes activate apoptotic pathways


Phagocytosed microbes in vesicles and cytoplasm
IFN-γ
CD4+ T cell
CD8+ CTL
Viable microbe in cytoplasm
Killing of microbes in phagolysosomes
Killing of infected cell




Antigen recognition
Activation of B lymphocytes
Helper T cells, other stimuli
Effector cells: antibody-secreting plasma cells
IgM
Antibody secretion
Clonal expansion
Naive IgM+, IgD+ B cell
Activated B cell
Microbe
Differentiation
IgG-expressing B cell
IgG
Isotype switching
Affinity maturation
High-affinity Ig-expressing B cell
High-affinity IgG
Memory B cell
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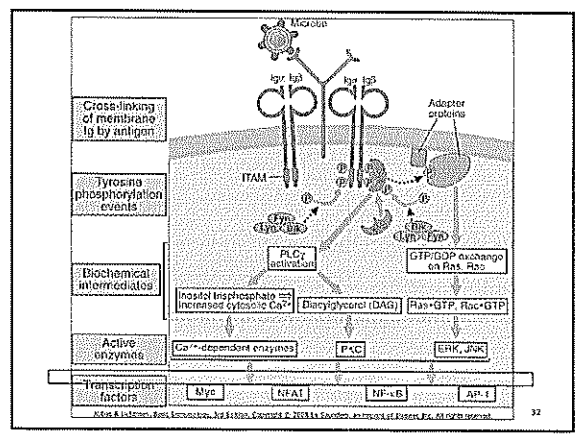
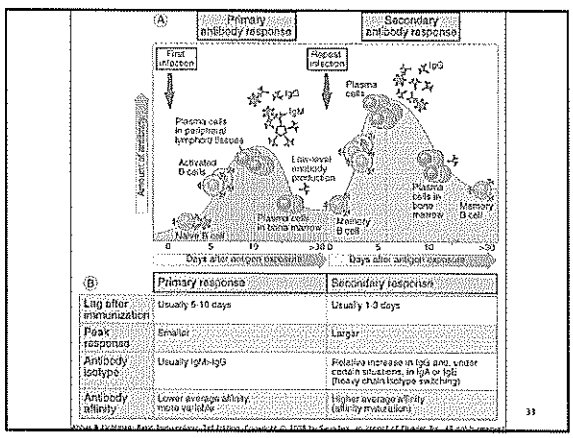

Microbe
IgG IgG
IgG IgG
Cross-linking of membrane Ig by antigen
Adapter proteins
Tyrosine phosphorylation events
ITAM
Syk
Lyn
Fyn
Lyn
Syk
PLCγ activation
GTP/GDP exchange on Ras, Rac
Biochemical intermediates
Inositol trisphosphate → increased cytosolic Ca2+
Diacylglycerol (DAG)
Ras•GTP, Rac•GTP
Active enzymes
Ca2+-dependent enzymes
PKC
ERK, JNK
Transcription factors
Myc
NFAT
NF-κB
AP-1
32


A
Primary antibody response
Secondary antibody response
First infection
Repeat infection
IgG
IgM
Plasma cells
Plasma cells in peripheral lymphoid tissues
Activated B cells
Early-level antibody production
Plasma cells in bone marrow
Memory B cell
Naive B cell
0 5 10 >300 5 10 >50
Days after antigen exposure
Days after antigen exposure
B
Primary response
Secondary response
Lag after immunization
Usually 5-10 days
Usually 1-3 days
Peak response
Smaller
Larger
Antibody isotype
Usually IgM-IgG
Relative increase in IgG and, under certain situations, in IgA or IgE (heavy chain isotype switching)
Antibody affinity
Lower average affinity; more variable
Higher average affinity (affinity maturation)
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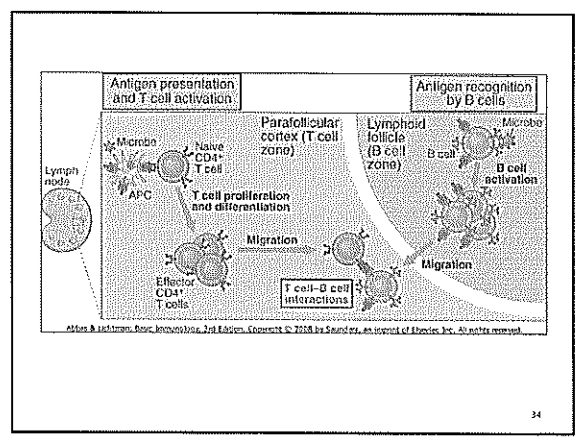
Antigen presentation and T cell activation
Antigen recognition by B cells
Lymph node
Microbe
Naive CD4+ T cell
APC
Parafollicular cortex (T cell zone)
T cell proliferation and differentiation
Migration
Effector CD4+ T cells
T cell–B cell interactions
Lymphoid follicle (B cell zone)
Microbe
B cell
B cell activation
Migration
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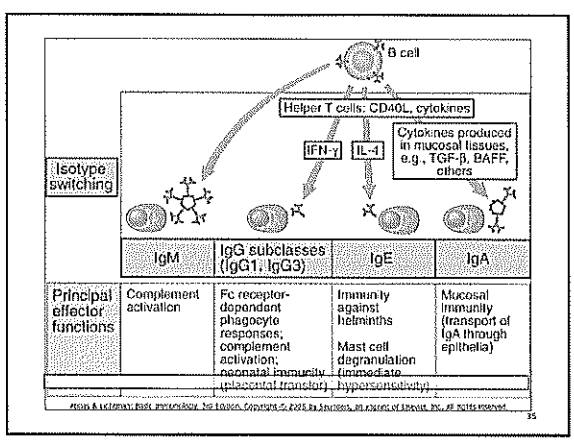
B cell
Helper T cells: CD40L, cytokines
IFN-γ
IL-4
Cytokines produced in mucosal tissues, e.g., TGF-β, BAFF, others
Isotype switching
IgM
IgG subclasses (IgG1, IgG3)
IgE
IgA
Principal effector functions
Complement activation
Fc receptor-dependent phagocyte responses; complement activation; neonatal immunity (placental transfer)
Immunity against helminths
Mast cell degranulation (immediate hypersensitivity)
Mucosal immunity (transport of IgA through epithelia)
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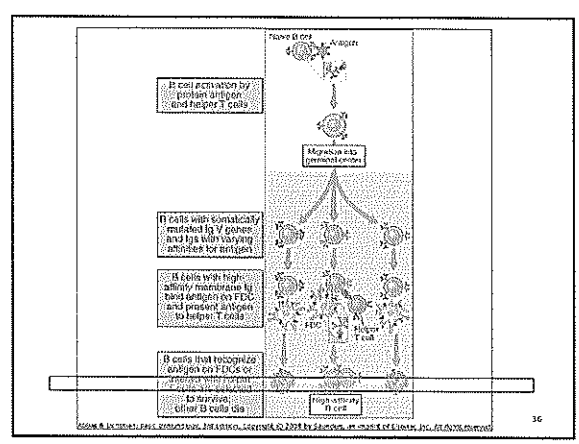
Naive B cell
Antigen
B cell activation by protein antigen and helper T cells
Migration into germinal centers
B cells with somatically mutated Ig V genes and Ig with varying affinities for antigen
B cells with high-affinity membrane Ig bind antigen on FDC and present antigen to helper T cells
FDC
Helper T cell
B cells that recognize antigen on FDCs or helper T cells survive
Memory B cell
High-affinity B cell
to survive; other B cells die
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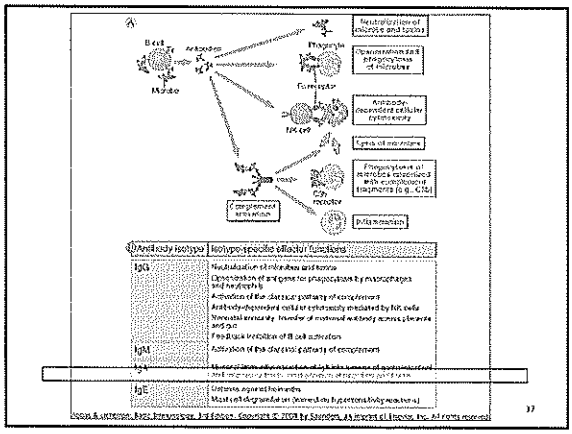

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Mechanism of immune evasion	Example(s)
Antigenic variation	Many viruses, *e.g.*, influenza, HIV *Neisseria gonorrhoeae*, *E. coli*, *Salmonella typhimurium*
Inhibition of complement activation	Many bacteria
Resistance to phagocytosis	Pneumococcus

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Type of vaccine	Examples	Form of protection
Live attenuated, or killed, bacteria	BCG, cholera	Antibody response
Live attenuated viruses	Polio, rabies	Antibody response; cell-mediated immune response
Subunit (antigen) vaccines	Tetanus toxoid, diphtheria toxoid	Antibody response
Conjugate vaccines	*Haemophilus influenzae* infection	Helper T cell–dependent antibody response
Synthetic vaccines	Hepatitis (recombinant proteins)	Antibody response
Viral vectors	Clinical trials of HIV antigens in canary pox vector	Cell-mediated and humoral immune responses
DNA vaccines	Clinical trials ongoing for several infections	Cell mediated and humoral immune responses

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Primary Immunodeficiency

T- cells and B-cells Deficiency

1. Defects in Lymphocyte Maturation
2. Defects in Lymphocyte activation and Function

B cell most common (IgA def is #1)
T cells

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Type of immunodeficiency	Histopathologic and laboratory abnormalities	Common infectious consequences
B cell deficiencies	Absent or reduced follicles and germinal centers in lymphoid organs Reduced serum Ig levels	Pyogenic bacterial infections
T cell deficiencies	May be reduced T cell zones in lymphoid organs Reduced DTH reactions to common antigens Defective T cell proliferative responses to mitogens *in vitro*	Viral and other intracellular microbial infections (e.g., *Pneumocystis jiroveci*, atypical mycobacteria, fungi) Virus-associated malignancies (e.g., EBV-associated lymphomas)
Innate immune deficiencies	Variable, depending on which component of innate immunity is defective	Variable, pyogenic bacterial infections

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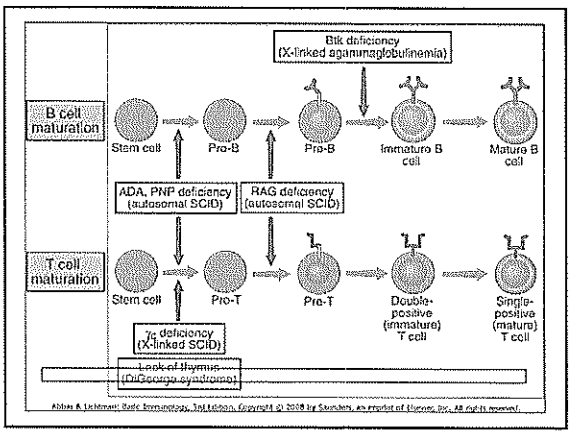

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Severe combined immunodeficiency (SCID)		
Disease	Functional deficiencies	Mechanism of defect
X-linked SCID	Markedly decreased T cells; normal or increased B cells; reduced serum Ig	Cytokine receptor common γ chain gene mutations; defective T cell maturation due to lack of IL-7 signals
Autosomal recessive SCID due to ADA, PNP deficiency	Progressive decrease in T and B cells (mostly T); reduced serum Ig in ADA deficiency; normal B cells and serum Ig in PNP deficiency	ADA or PNP deficiency leads to accumulation of toxic metabolites in lymphocytes
Autosomal recessive SCID due to other causes	Decreased T and B cells; reduced serum Ig	Defective maturation of T and B cells; genetic basis unknown in most cases; may be mutations in *RAG* genes
B cell immunodeficiencies		
Disease	Functional deficiencies	Mechanism of defect
X-linked agammaglobulinemia	Decrease in all serum Ig isotypes; reduced B cell numbers	Block in maturation beyond pre-B cells, because of mutation in B cell tyrosine kinase
Ig heavy chain deletions	IgG1, IgG3, or IgG4 absent; sometimes associated with absent IgA or IgE	Chromosomal deletion at 14q32 (Ig heavy chain locus)
T cell immunodeficiencies		
Disease	Functional deficiencies	Mechanism of defect
DiGeorge syndrome	Decreased T cells; normal serum Ig	Arrested development of 3rd and 4th pharyngeal pouches, leading to thymic hypoplasia

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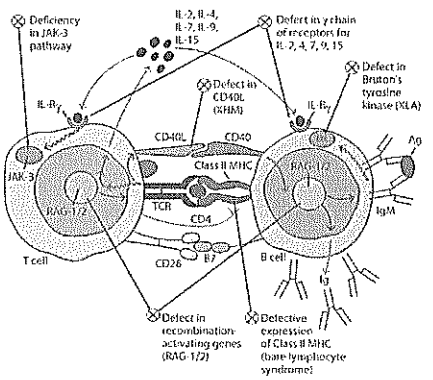
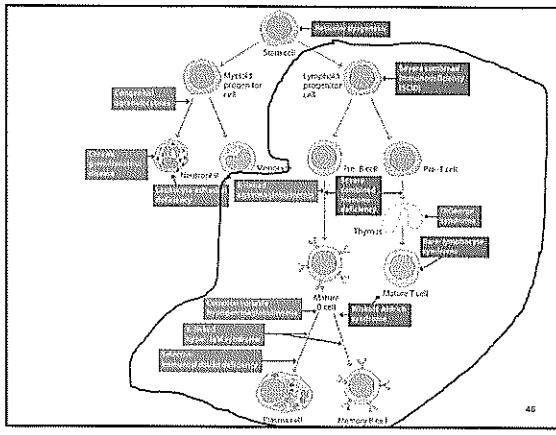
Primary Immunodeficiency

T- cells and B-cells Deficiency





Defects in lymphocyte Maturation

Both T and B-Cell Deficiency

SCID

SCID

- Various genetic defects
- No TCR or defective TCR
- Defective cell signaling
- Defective IL 2

- Recurrent infections
- Death at early age

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SCID

- Stem cells defective or absent
- OR T helpers defective or absent
- OR thymus defective or absent (no T cell maturation
- B cells are affected because there's no T help
- ADA def: no T or B cells
- PNP (purine nucleoside phosphorolase): much more T cell
- Invasive infections and really serious viral infections; PCP

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SCID

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B-Cell Deficiency

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(Selective) IgA deficiency

- Most common: 1 in 500?
- Related to CVID – can run in sibs
- Can evolve to normal or become increasingly deficient over years
- Have B cells, but they don't go on to form plasma cells.
- Allergy-type sxs and chronic mucosal infx

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Common Variable Immune Deficiency (CVID)

Common Variable Immune Deficiency (CVID) is a disorder characterized by low levels of serum immunoglobulins (antibodies) and an increased susceptibility to infections. The exact cause of the low levels of serum immunoglobulins is usually not known. It is a relatively common form of immunodeficiency, hence, the word "common." The degree and type of deficiency of serum immunoglobulins, and the clinical course, varies from patient to patient, hence, the word "variable." In some patients, there is a decrease in both IgG and IgA; in others, all three major types (IgG, IgA and IgM) of immunoglobulins may be decreased. The clinical signs and symptoms also vary from severe to mild. Frequent and unusual infections may first occur during early childhood, adolescence or adult life. In the majority of patients, the diagnosis is not made until the 3rd or 4th decade of life. However, about 20% of patients have symptoms of disease or are found to be immunodeficient under the age of 16.

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CVID

- Wastebasket dx for B cell + Ig deficient pt's
- Some have decreased total B cells,
  some decreased T-helpers,
  some increased T-suppressors.
- Low Ig's in any combination that includes "G." (G, G+A, G+A+M)
- Recurrent bacterial infections;
  - onset in infancy, at puberty, or even later.
  - Ears, nose, sinuses, bronchi, lungs.
  - Can have chronic lung dz.
- Enlarged neck and chest LN's;
  can have increased incidence of mycoplasma and/or chlamydia

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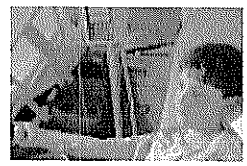
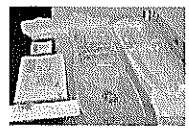
CVID





Infusion Supplies: Intravenous immune globulin (IVIG) is the standard treatment for CVID.

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Bruton's Agammaglobulinemia

X-Linked Agammaglobulinemia (XLA) was first described in 1952 by Dr. Ogden Bruton. This disease, sometimes called Bruton's Agammaglobulinemia or Congenital Agammaglobulinemia, was one of the first immunodeficiency diseases to be identified. XLA is an inherited immunodeficiency disease in which patients lack the ability to produce antibodies, proteins that make up the gamma globulin or immunoglobulin fraction of blood plasma.

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Bruton's Agammaglobulinemia

- Recurrent pyogenic infections from infancy/early childhood: mucous membranes.
- Ears, sinuses, lungs, GI tract, bacteremias; also increased viral infections.
- Family history of affected lateral (maternal) male relatives
- No tonsils or palpable lymph nodes (they have nodes, but no B cell centers, so non-palpable.)
- Few mature B cells (unlike CVID)
  [Have pre-B's]

58

Bruton's Agammaglobulinemia

- Low levels of IgG
- B cell signal transduction affected
  - usually undetectable B cells in peripheral blood because B cell development is arrested at per-B cell stage
- Defective BCR

- Recurrent bacterial diseases starting at end of first year of life
- Short life span

59

XL Agammaglob, cont.

- Mutation in B cell specific protein (a tyrosine kinase – "BTK") in the proto-oncogenic src family (X q 22): abnormal kinase activity in B and pre-B
- Over 300 different mutations in BTK can result in this disease phenotype.
  - The most typical form has a mutation in the area of the protein for catalytic function.
  - Atypical forms have protein-protein interaction problems and are more subtle clinically.
  - Mouse model XID: N-terminal mutation (function unknown)

60

B cell (-) [AR] Agammaglob's

- μ heavy chain gene mutation
- λ 5/14.1 (surrogate light chain) mutation
- Ig α (B cell α Ag receptor) mutation
- B cell linker protein (BLNK) mutation

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T Cell Immunodeficiencies

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DiGeorge Syndrome

- Poorly developed or functioning thymus
- Associated with other developmental conditions
- Depression of T cell numbers
- Absence of T cell response
- Humoral response to T independent antigens only

63

DiGeorge Syndrome

- Associated abnormalities of face, brain, thymus, parathyroid, heart/aorta (and platelets!)
- FISH for 11q22
- Hypocalcemia, seizures
- Extremely variable phenotype

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DiGeorge Syndrome





Defects in lymphocyte Activation and Function

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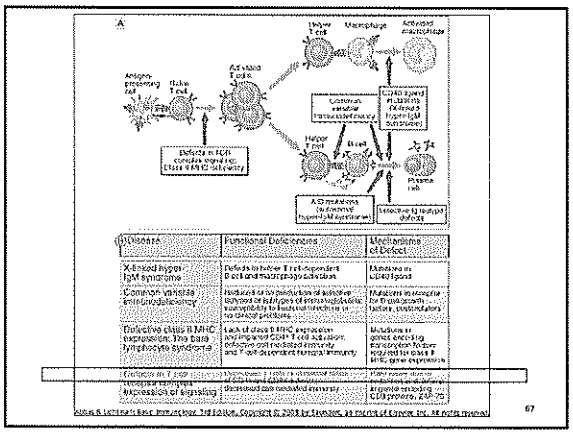

Disease	Functional Deficiencies	Mechanisms of Defect
X-linked hyper-IgM syndrome	Defects in helper T cell-dependent B cell and macrophage activation	Mutations in CD40 ligand
Common variable immunodeficiency	Reduced or no production of antibody isotypes of multiple types; susceptibility to bacterial infections in childhood	Mutations in receptor for B cell growth factors; unknown factors
Defective class II MHC expression; the bare lymphocyte syndrome	Lack of class II MHC expression; impaired CD4+ T cell activation; defective cell-mediated immunity and T cell-dependent humoral immunity	Mutations in genes encoding transcription factors required for class II MHC gene expression
Defects in T cell [illegible]	[illegible]	[illegible]
Impaired signaling and expression of signaling [illegible]	Decreased cell-mediated immunity	Unknown; encoding CD3 proteins, ZAP-70

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XL HyperIgM

- *in vivo*, no IgG, A, or E
- Can have the "no tonsils, no LN's" presentation
- B cells can make IgE with IL-4 and anti-CD40 *in vitro*
- Gene mutation at CD40L (it can't "hear from" the T cell)
- See also AR form

68

Hyper IgE

- Abscesses (staph), esp skin (boils) but also lung
- Lung abscesses progressing to giant cysts/pneumatocoeles.
- No diagnostic test; markedly elevated levels of IgE are even seen in atopic dermatitis

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Lymphocyte Abnormalities Associated with Other Diseases

70

Wiskott-Aldrich Syndrome

- X linked disorder
- Affects platelet numbers/function
  - thrombocytopenia is one of crucial clue
- Affects T cell function
- Cytoskeleton of lymphocytes affected

- Lower amounts of IgM
- Increased susceptibility to certain bacterial infections

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Wiskott-Aldrich Syndrome

- Eczema, thrombocytopenia; infections of ears, lungs, meninges. Opportunistic infections and bugs with capsular polysaccharide Ag's
- Poor response to polysaccharide antigens but normal IgG_2
  (So look for Ab's, not IgG subclasses)
- Xp11.22-11.23
- WASP gene binds lots of signaling molecules

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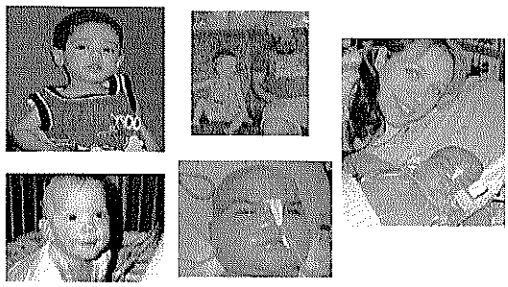
Wiskott-Aldrich Syndrome



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From the CBC

- Normal Absolute Lymphocyte Count (ALC):
  - excludes T cell defects, AIDS
  - excludes congenital and acquired neutropenias and LAD (increased ANC)
- Normal platelets:
  - excludes Wiscott Aldrich Syndrome (WAS)
- No Howell-Jolly bodies: no asplenia

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Screening for B cell defects

- IgA: most common
- IgG and IgM: agammaglobulinemia
- Isohemaglutinins:
  - IgM to blood group(s): get if Ig's are low to see if production failure vs. loss
- Antibody titers to immunizations
- AGE NORM'S: IgG and A are not at adult levels until age 7
- Check flow: if no B cells, usually = Bruton

75

IgG subclasses

- No good age norm's
- Lows can be transient
- Poorly correlated with disease
- BUT, can be a harbinger of CVID
- Best test: immunize with protein then polysaccharide vaccines; check serum before and after. If they respond, they're okay.

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T cell defects

- Mucocutaneous candida, chronic diarrhea, PCP, FTT, disseminated CMV/VZV/HSV
- Examples: SCID, CVID, AIDS
- ALC usually low, though can be normal in DiGeorge
  - (NOTE: Adult ALC > 1000; NB ALC $\geq$ 4000)
- Candida skin test: kids should respond by age 9 mos; a normal response virtually rules out T cell problems.
- Can also check flow, do mitogen/antigen stim, assay cytokines

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Part A
2. Secondary Immunodeficiency

- Acquired Immunodeficiency
- **No genetic defect**
- **due to other defects** including infections, nutritional abnormalities, or treatment that cause loss or inadequate function of various components of the immune system e.g. immune suppressive drugs, HIV infection.

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Part A
2. Secondary Immunodeficiency

- Drug related
- Disease related
  - –Cancer
  - –AIDS
    - HIV
    - T helper cell as target

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Cause	Mechanism
Human immunodeficiency virus infection	Depletion of $CD4^+$ helper T cells
Irradiation and chemotherapy treatments for cancer	Decreased bone marrow precursors for all leukocytes
Involvement of bone marrow by cancers (metastases, leukemias)	Reduced site of leukocyte development
Protein-calorie malnutrition	Metabolic derangements inhibit lymphocyte maturation and function
Removal of spleen	Decreased phagocytosis of microbes

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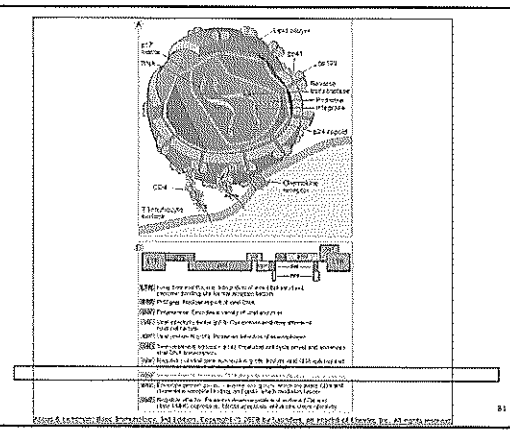

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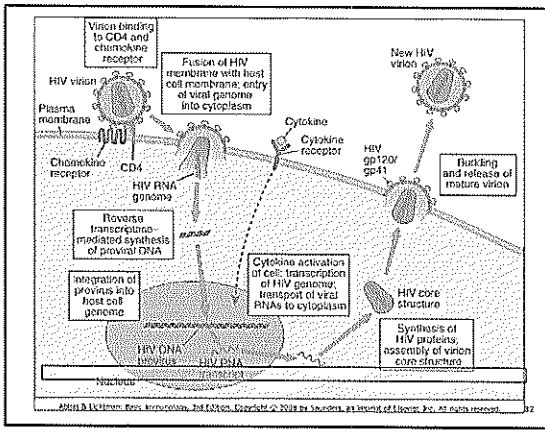

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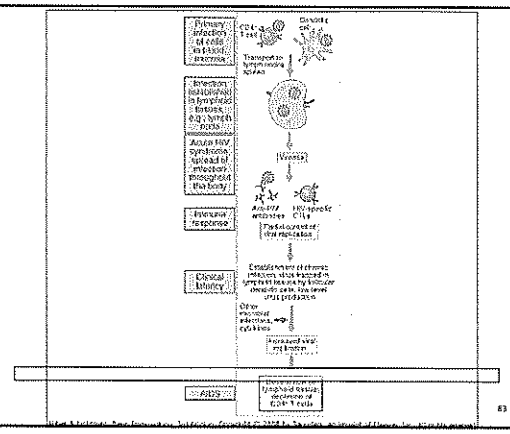

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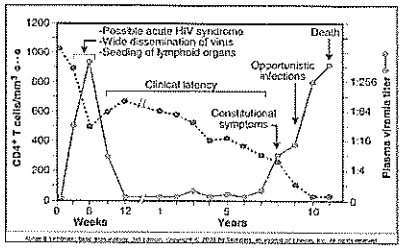

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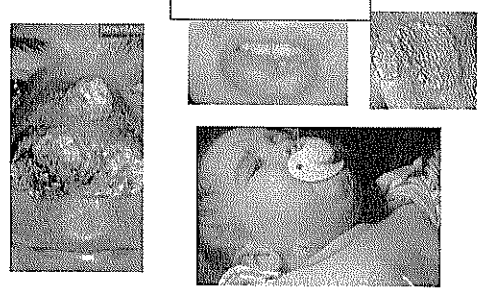
Congenital and Acquired Immunodeficiencies
Part B
(Diseases caused by defective immune responses)

By Asst. Prof. Dr. Wilairat Leeanansaksiri

What's Happen to Them ?



Can you help them ?

Immunodefeiciency

Outline

1. Concise summarization of normal immune response
2. Concise summarization of normal immunity to infection
3. innate immunodeficiency and primary immunodeficiency diseases Adaptive Immunodeficiency

Immunodeficiency

Objectives

1. Understand and can explain normal immune response both innate and adaptive immunities
2. Understand and can explain capability of microbes to escape immune response
3. Understand and can explain innate immunodeficiency and primary immunodeficiency diseases

Immunodeficiency

1. Primary Immunodeficiency
- Adaptive (Part A)
- Innate (Part B)

2. Secondary Immunodeficiency
- Adaptive (Part A)
- Innate (Part B)

Part B : Innate immunity components defect e.g. Macrophage…

1. Primary Immunodeficiency

- Chronic granulomatous disease
- Congenital agranulocytosis
- Leukocyte-adhesion deficiency
- Chediak-Higashi syndrome

2. Secondary Immunodeficiency

1. Primary Immunodeficiency

- congenital Immunodeficiency (usually abnormal since birth)
- due to **genetic defect** leads to blocks in the maturation or functions of different components of the immune system
  - Innate immunity components defect e.g. phagocytosis, complement
  - Adaptive immunity components defect e.g. T- cells, B- cells

[illegible]

Loss or reduction of:

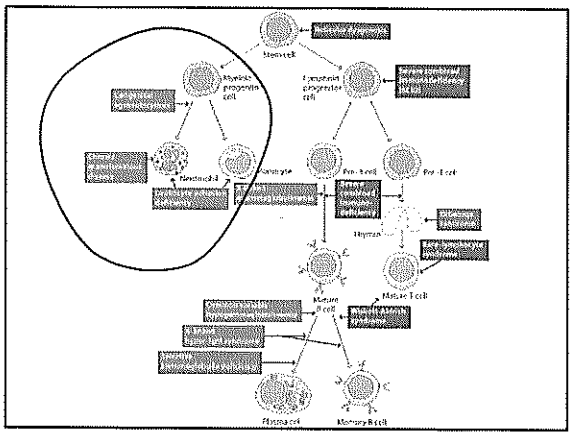
- Cell type
- Cell numbers
- Cell function

Loss of Cell Function

- Receptors
- Cell signaling
- Cytokine production
- Ig production
- Co stimulation impairment
- Intracellular killing
- Extravasation impairment

1. Primary Immunodeficiency

- **Defect in innate immunity**
  - **Chronic granulomatous disease**
  - **Congenital agranulocytosis**
  - **Leukocyte-adhesion deficiency**
  - **Chediak-Higashi syndrome**
- **Defect in T and B cells**
  - **Severe combined immunodeficiency (SCID)**
  - **B cells**
    - **Agammaglobulinemia**
    - **Hypogammaglobuliaemia**
    - **Specific Ig Deficiencies**
  - **T cells**
    - **DiGeorge Syndrome**
    - **Wiskott Aldrich Syndrome**



Primary Immunodeficiency
Pathogens

- Humoral defects
  - Capsulated bacteria
    - *S. pneumoniae*
    - *H. influenzae*
    - *N. meningilidis*
    - *S. aureus*
  - Enteroviruses
  - mycoplasma
- Neutrophil defects
  - *S. aureus, Candida, Aspergillus*
- Cell-mediated
  - intracellular bacteria
    - *Mycobacteria, Salmonella, Listeria, Legionella*
  - Viruses
    - Herpes, Respiratory & Enteric viruses
  - Fungi & protozoa
    - *Candida, Aspergillus, Pneumocystis, Cryptococcus, Cryptosporidium, Toxoplasma*

Congenital Infections

- Toxoplasmosis
- Rubella
- CMV
- HSV
- Hepatitis B, HIV
- Parvovirus B19
- Syphilis
- Ophthalmia neonatorum

- Seek expert advice on management & diagnosis
- Prevention
  - Vaccination
    - rubella, hep B
  - Treatment
    - Antimicrobial (anti-retrovirals, syphilis, acyclovir, spiramycin for toxo, silver nitrate eye drops etc.)
    - Other (intra-uterine blood transfusion for B19)
  - Screening (syphilis, HIV, hep B), Vigilance , Avoidance (e.g. of slapped cheek syndrome)

Primary Immunodeficiency
Management

- Correct defect
  - Immunoglobulin, cytokines
  - BMT
  - Gene therapy?
- Early aggressive antibiotic treatment
- Prophylaxis
  - Daily co-trimoxazole
  - Penicillin if complement deficiency
  - Flucloxacillin in some neutrophil disorders

2. Secondary Immunodeficiency

- Acquired Immunodeficiency
- **No genetic defect**
- **due to other defects** including infections, nutritional abnormalities, or treatment that cause loss or inadequate function of various components of the immune system e.g. immune suppressive drugs, HIV infection.

Secondary Immunodeficiency

- Drug related
- Disease related
  - Cancer
  - AIDS
    - HIV
    - T helper cell as target

CORE

A. Laboratory tests to assess immune function

(1) T cell: Enumeration (flow cytometry), functional assays (mitogen response, MLR, DTH skin tests)

(2) B cell: Enumeration, circulating antibody levels

(3) Macrophage: Enumeration, functional assays (nitroblue tetrazolium)

(4) Complement: Direct measurement of complement components, complement hemolysis assay

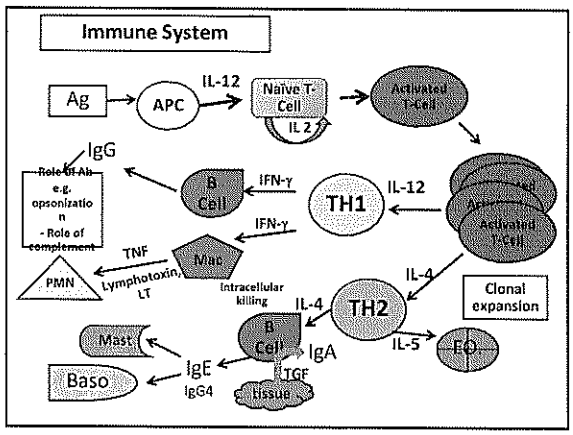
1. Innate Immunodeficiency

- **Chronic granulomatous disease**
- **Congenital agranulocytosis**
- **Leukocyte-adhesion deficiency**
- **Chediak-Higashi syndrome**
- **Phagocyte Defect**
- **Complement Defect**

Normal and Abnormal of Innate Immunity

Outline

1. Normal innate immunity
2. Role of immunity in infectious diseases
3. How microbes escape immune response ?
4. Diseases associates with immunodeficiency in innate immunity



Role of the immune system	Implications
Defense against infections	Deficient immunity results in increased susceptibility to infections; exemplified by AIDS Vaccination boosts immune defenses and protects against infections
The immune system recognizes and responds to tissue grafts and newly introduced proteins	Immune responses are barriers to transplantation and gene therapy
Defense against tumors	Potential for immunotherapy of cancer

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Disease	Maximum number of cases (year)	Number of cases in 2004	Percent change
Diphtheria	206,939 (1921)	0	-99.99
Measles	894,134 (1941)	37	-99.99
Mumps	152,209 (1968)	236	-99.90
Pertussis	265,269 (1934)	18,957	-96.84
Polio (paralytic)	21,269 (1952)	0	-100.0
Rubella	57,686 (1969)	12	-99.98
Tetanus	1,560 (1923)	26	-98.33
Haemophilus influenzae type b infection	~20,000 (1984)	16	-99.92
Hepatitis B	26,611 (1985)	6,632	-75.08

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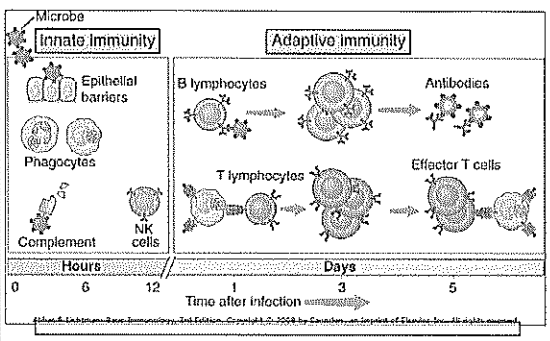

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Third line of DEFENSE

Specific Defense Mechanisms

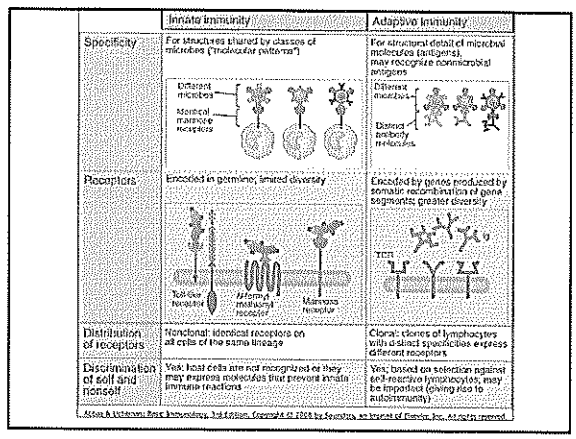
How to deal with specific & recurring invasion?

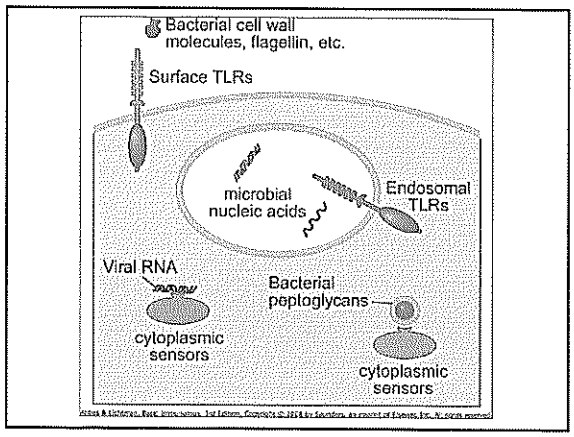
MEMORY

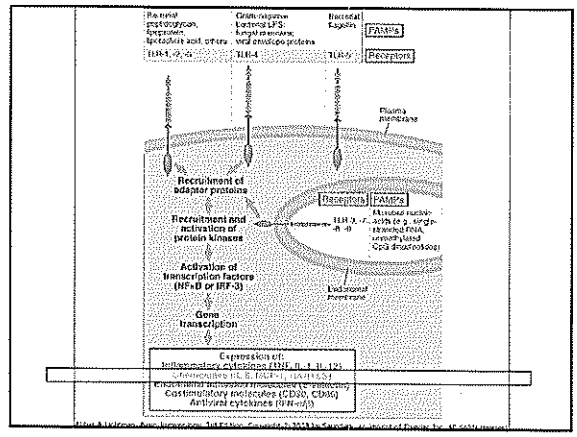
3rd line of defense
ACQUIRED IMMUNITY
Slower responses to specific microbes

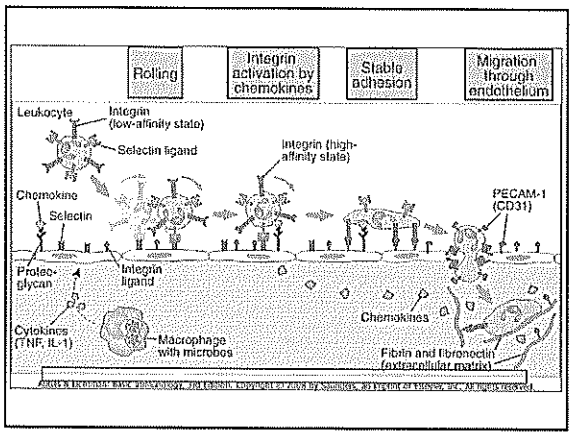
- Humoral response (antibodies; B-lymphocytes)
- Cell-mediated response (cytotoxic T-lymphocytes)

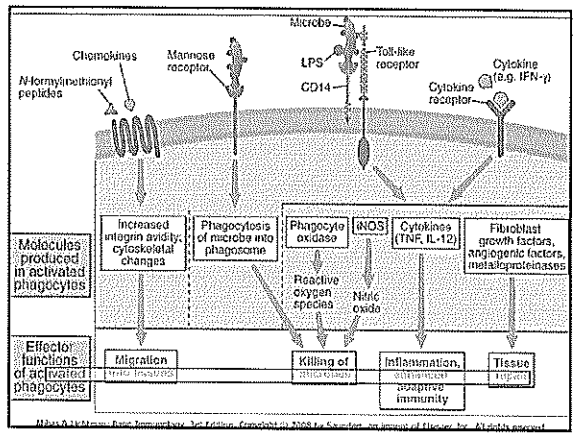
	Innate	Adaptive
Characteristics		
Specificity	For structures shared by groups of related microbes	For antigens of microbes and for nonmicrobial antigens
Diversity	Limited; germline-encoded	Very large; receptors are produced by somatic recombination of gene segments
Memory	None	Yes
Nonreactivity to self	Yes	Yes
Components		
Cellular and chemical barriers	Skin, mucosal epithelia; antimicrobial chemicals	Lymphocytes in epithelia; antibodies secreted at epithelial surfaces
Blood proteins	Complement, others	Antibodies
Cells	Phagocytes (macrophages, neutrophils), natural killer cells	Lymphocytes

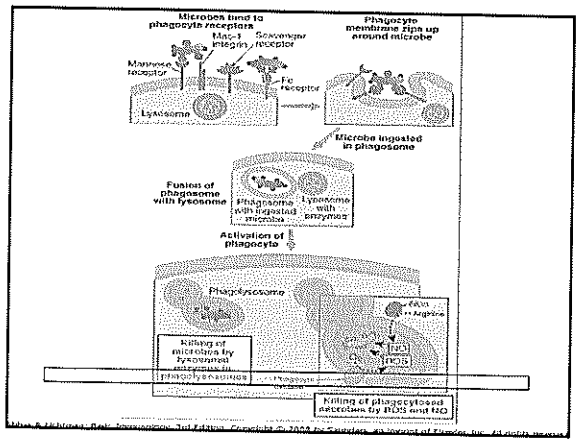


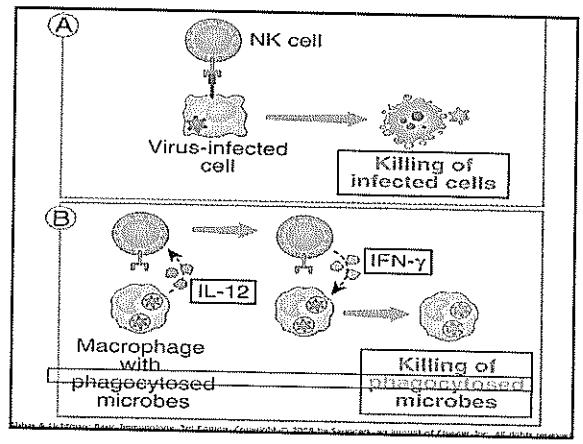


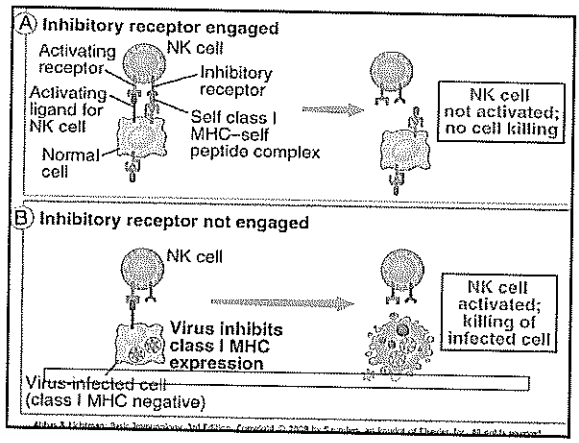


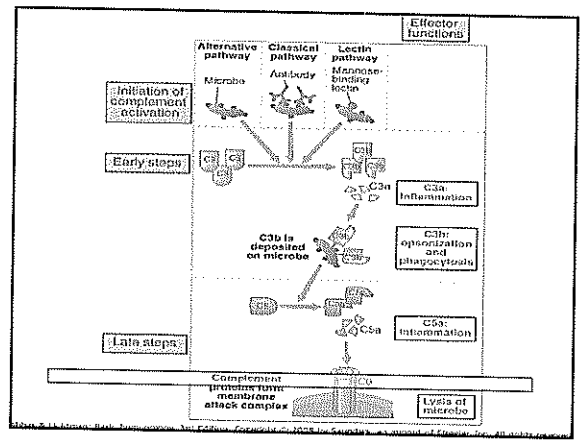


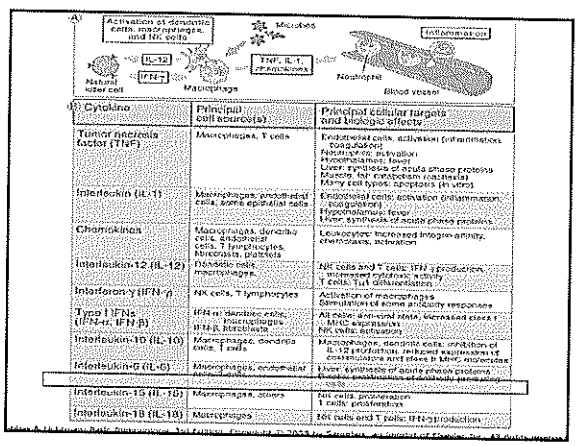












Mechanism of immune evasion	Organism (example)	Mechanism
Resistance to phagocytosis	Pneumococci	Capsular polysaccharide inhibits phagocytosis
Resistance to reactive oxygen species in phagocytes	Staphylococci	Production of catalase, which breaks down reactive oxygen intermediates
Resistance to complement activation (alternative pathway)	*Neisseria meningitidis*	Sialic acid expression inhibits C3 and C5 convertases
	Streptococci	M protein blocks C3 binding to organism, and C3b binding to complement receptors
Resistance to antimicrobial peptide antibiotics	*Pseudomonas*	Synthesis of modified LPS that resists action of peptide antibiotics

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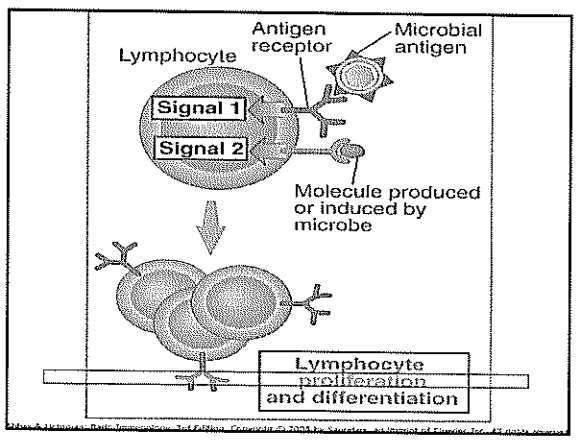
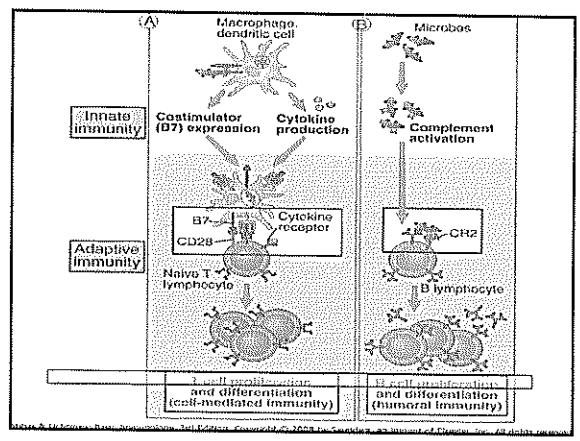
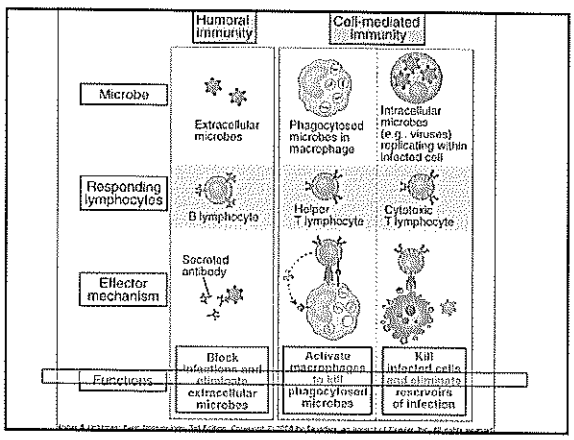
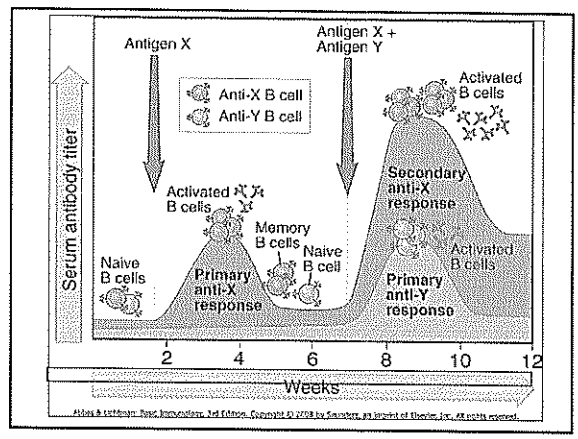








Disease	Functional Deficiencies	Mechanisms of Defect
Chronic granulomatous disease	Defective production of reactive oxygen species by phagocytes	Mutations in genes encoding components of the phagocyte oxidase enzyme, most often cytochrome b558
Leukocyte adhesion deficiency-1	Absent or deficient expression of β2 integrins causing defective leukocyte adhesion–dependent functions	Mutations in gene encoding the β chain (CD18) of β2 integrins
Leukocyte adhesion deficiency-2	Absent or deficient expression of leukocyte ligands for endothelial E- and P-selectins, causing failure of leukocyte migration into tissues	Mutations in gene encoding a protein required for synthesis of the sialyl-Lewis X component of E- and P-selectin ligands
Complement C3 deficiency	Defect in complement cascade activation	Mutations in the C3 gene
Complement C2, C4 deficiency	Deficient activation of classical pathway of complement leading to failure to clear immune complexes and development of lupus-like disease	Mutations in C2 or C4 genes
Chédiak-Higashi syndrome	Defective lysosomal function in neutrophils, macrophages, and dendritic cells; and defective granule function in natural killer cells	Mutation in a gene encoding a lysosomal trafficking regulatory protein

Defects in phagocytic cells

Type of defect/name of syndrome	Associated infectious or other diseases
Leukocyte adhesion deficiency	Widespread pyogenic bacterial infections
Chronic granulomatous disease	Intracellular and extracellular infection, granulomas
G6PD deficiency	Defective respiratory burst, chronic infection
Myeloperoxidase deficiency	Defective intracellular killing, chronic infection
Chediak–Higashi syndrome	Intracellular and extracellular infection, granulomas

Figure 11-16 Immunobiology, 6/e © Garland Science 2005

Primary phagocyte deficiencies (symptoms, description of defect, current therapy)

- (1) Neutropenia
- (2) Chronic Granulomatous Disease
- (3) Leukocyte Adhesion Deficiency

Phagocyte deficiencies:

QUANTITATIVE OR QUALITATIVE .

Quantitative defects:

1. Congenital agranulocytosis ;
   Kostmann syndrome .
   Defect in the gene inducing G-CSF (granulocyte colony stimulating factor).

Features: pneumonia ,otitis media, gingivostomatitis perineal abscesses.

Management:
Respond to G-CSF therapy.

Qualitative defects :

1.Defect in response to chemotactic agents.
2.Defect in intracellular killing.

A . Defect in chemotaxis:
Leukocyte adhesion deficiency (LAD.)
2 types.
*LAD type 1: defect in gene encoding CD18. (B integrin .)

B.Defect in intracellular killing:

1.Chronic granulomatous disease:
X-LINKED. (75%)
AUTOSOMAL RECESSIVE .(25%).

DEFECT: in the oxidative complex .
(responsible for producing superoxide radicals .)

FEATURES:
Extreme susceptibility to infections.
Granulomatous inflammation.
(chronic T-cell stimulation.)

2. Glucose -6- phosphate dehydrogenase deficiency . (G6-P-D). (no resp.burst.)

3. myeloperoxidase deficiency .
(no resp. burst).

4. Chediak - Higashi syndrome: defect in formation of phagolysosome .
Associated with:
abnormal platelet function.
partial albinism .

Chronic Granulomatous Disease

Defect in mutation in enzyme phagocyte oxidase, which catalyzes the production of microbicidal reactive oxygen intermediates in lysosome

↓

Result:
Neutrophils and macrophages that phagocytose microbes unable to kill the microbes

Immune events:

Immune try to compensate

↓

Try to get more phargocytes to the site of infection by activate more T-cells

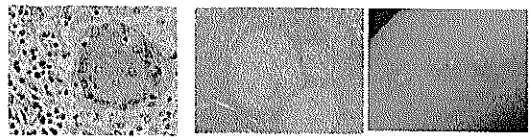
↓

Accumulation of phagocytes
Resembles granulomas

↓

Disease : chronic granulomatous disease

CGD



These defects leave patients vulnerable to severe recurrent bacterial and fungal infections and chronic inflammatory conditions such as gingivitis (swollen inflamed gums), enlarged lymph glands, or tumor-like masses called granulomas. While not malignant, granulomas can cause serious problems by obstructing passage of food through the esophagus, stomach, and intestines as well as blocking urine flow from the kidneys and bladder.

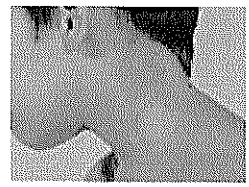
Rhinoscleroma

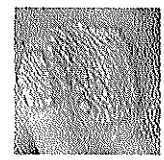
Rhinoscleroma is a chronic granulomatous disease of the upper respiratory tract caused by a gram-negative organism, Klebsiella rhinoscleromatis. It is uncommon in the US, but is endemic in parts of Central and South America, Egypt, Africa, and Eastern Europe. Mucopurulent discharge characterizes the rhinitic stage, followed by mucosal thickening during florid stage The disease resolves with marked fibrosis.

Rhinoscleroma is rare in the US, but occurs in regions of poor living conditions that foster the spread of the bacteria. Three clinical stages define the disease: 1) rhinitic 2) florid, and 3) fibrotic. Symptoms vary with the location of the infection. Nasal cavity (septum) is the most common site, but other sites of infection include: paranasal sinuses, orbit, larynx, tracheobronchial tree, and middle ear. Tetracycline is the treatment of choice with excellent prognosis. However, significant airway obstruction requires surgical excision.

Suppurative lymphadenitis in chronic granulomatous disease

CGD

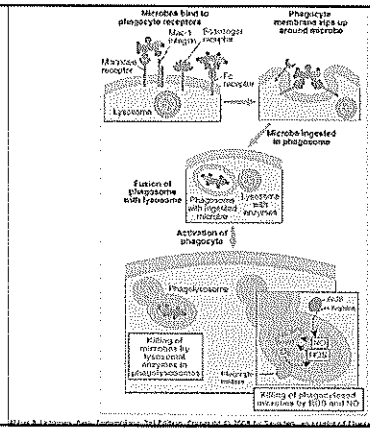




Suppurative lymphadenitis is a common feature of CGD,

CGD occur in many

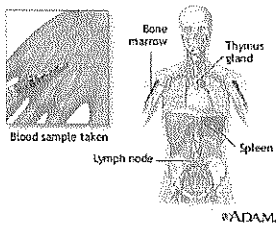
organs in response to chronic inflammation. which develop in many organs in response to chronic inflammation. organ



Chronic Granulomatous Disease

- Short arm of the X chromosome
- NBT (nitro blue tetrazoleum):
  - feed to PMN's with a particle (bacteria, latex).
    If the hexose monophosphate path is nl, the dye is reduced (turns purple).
    Heparin interferes. High false (-) rate.
- Respiratory burst assay:
  - non-fluorescing dye to PMN's; addition of particle makes it fluoresce. A quantitative test – can pick up carriers.
- Poor phagocytosis; poor peroxidase production
- Infections with non-peroxidase-producing org's: staph, serratia
- Abscesses of lung, LN; also infx of skin, liver, bone

Nitroblue tetrazolium test

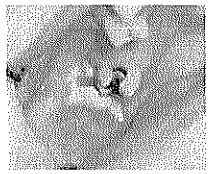


Nitroblue tetrazolium test is a blood test that measures the ability of the immune system to convert the colorless nitroblue tetrazolium (NBT) to a deep blue. This test is performed as a screen for chronic granulomatous disease (CGD). If an individual has CGD, the white cells in their blood will not turn blue when exposed to the NBT

Agranulocytosis

a severe reduction in the number of leukocytes (basophils, eosinophils, and neutrophils). Neutropenia results, whereby the body is severely depleted in its ability to defend itself. Fever, prostration, and bleeding ulcers of the rectum, mouth, and vagina may be present. The acute disease may be an adverse reaction to a medication or the result of the effect of radiation therapy or chemotherapy on bone marrow.

Agranulocytosis



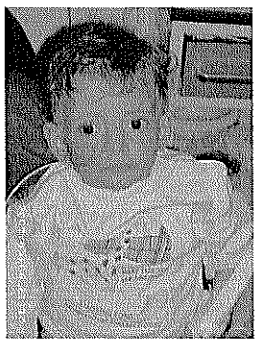
Oral lesions are ulceronecrotic, involving the gingivae, tongue, buccal mucosa, or lips. Regional lymphadenopathy and lymphadenitis are prevalent.

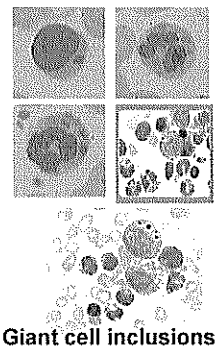
Chediak-Higashi syndrome

Defect lysosomal function in neutrophils,Macrophages, and dendritic cells, and defective granule function in NK cells

Molecular defect
mutation in gene encoding a lysosomal trafficking regulatory protein

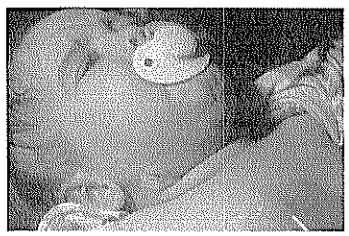
Chediak-Higashi syndrome





Giant cell inclusions

Leukocyte-adhesion deficiency



This 10-month-old patient with severe leukocyte adhesion deficiency type I (LAD I) developed a cervical adenitis caused by *Klebsiella pneumoniae*. Following incision and drainage, wound healing took 4 months.

LAD type 1:

- 3.TYPES:

*CD18+CD11a- leukocyte function associated molecule (LFA-1).

CD18+CD11b- complement receptor (CR3).

CD18+CD11c- complement receptor (CR4).

LFA-1 mediate tight adhesion of leukocytes to the endothelium .

WITH DEFECT IN LFA-1:

- Leukocytes are trapped in the circulation.
- Leukocyte count can reach 100,000 cells per mm3.
- Abscesses do not suppurate.

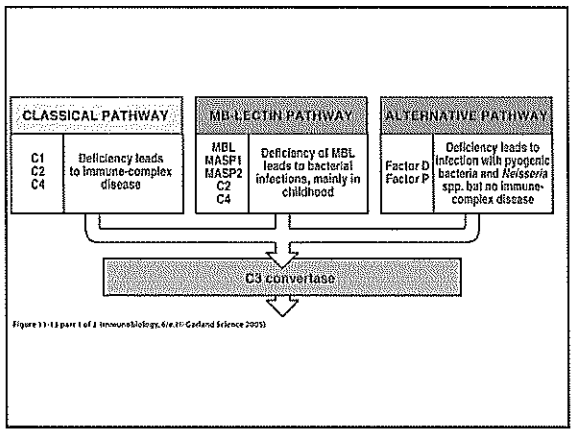
LAD type 2:

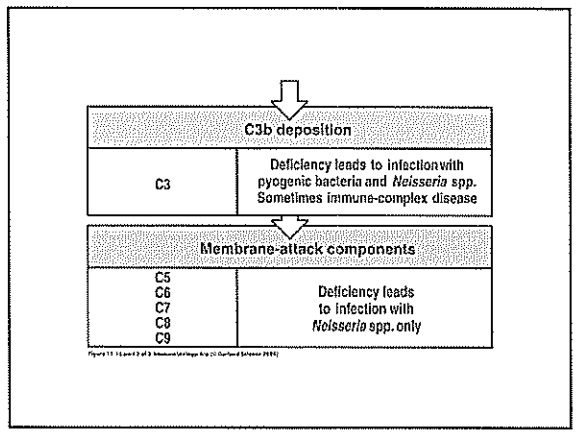
- Defect in Sialyl lewis protein (ligand for E- selectin).

Leukocytes cannot attach to endothelium.

Defective chemotaxis .

Name of deficiency syndrome	Specific abnormality	Immune defect	Susceptibility
Phagocyte deficiencies	Many different	Loss of phagocyte function	Extracellular bacteria and fungi
Complement deficiencies	Many different	Loss of specific complement components	Extracellular bacteria especially *Neisseria* spp.





Deficiencies in the pathways of complement activation

Complement protein	Effects of deficiency	
C1, C2, C4	Immune-complex disease	Clearance of immune (Ab-Ag) complex
C3	Susceptibility to capsulated bacteria	Opsonin
C5–C9	Only effect is susceptibility to *Neisseria*	Membrane attack
Factor D, properdin (factor P)	Susceptibility to capsulated bacteria and *Neisseria* but no immune-complex disease	Enhances alternative path
Factor I	Similar effects to deficiency of C3	Supplies C3
DAF, CD59	Autoimmune-like conditions including paroxysmal nocturnal hemoglobinuria	Prevent host cell destruction

Complement deficiencies :

Deficiency of all complement components have been described C1-C9.

1. Deficiency of C1, C2 & C4.
(classical pathway)
lead to immune-complex diseases which can cause significant pathology in autoimmune diseases.

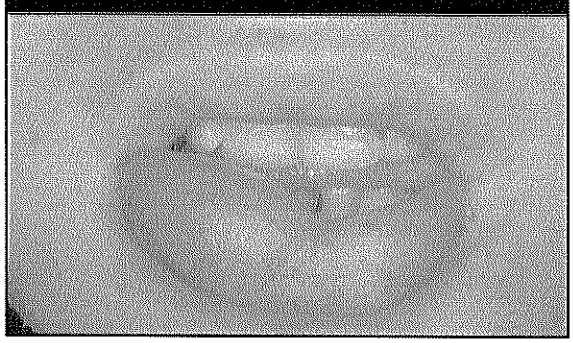
Complement Deficiencies and Disease Classical Pathway

Pathway Component	Disease	Mechanism
C1INH	Hereditary Angioedema	Overproduction of C2b (prokinin)
C1, C2, C4	Predisposition to SLE	Opsonization of immune complexes help keep them soluble, deficiency results in increased precipitation in tissues and inflammation

4. Deficiency of membrane - attack complex.
(C5 - C9)
Lead to infection with N.meningitides and N.gonorrhea .

5. Deficiency of C3.
Lead to infections with pyogenic bacteria.
impaired clearance of immune-complexes. .

C1 - inhibitor deficiency: hereditary angioedema



Complement Deficiencies and Disease. Lectin Pathway

Pathway Component	Disease	Mechanism
MBL	Susceptibility to bacterial infections in infants or immunosuppressed	Inability to initiate lectin pathway

2. Deficiency of mannose - binding lectin. (lectin pathway)

*MBL , C2, & C4.
Lead to bacterial infections mainly in Early childhood .

3. Deficiency of Factor D & Factor P. (alternative pathway).
Lead to infection with pyogenic bacteria .

Complement Deficiencies and Disease. Alternative Pathway cont.

Pathway Component	Disease	Mechanism
Properdin (X-linked)	Susceptibility meningococcal meningitis	Lack of opsonization of bacteria
Factors H or I	C3 deficiency and susceptibility to bacterial infections	Uncontrolled activation of C3 via alternative pathway resulting in depletion of C3

Complement Deficiencies and Disease. Alternative Pathway

Pathway/Component	Disease	Mechanism
Factors B or D	Susceptibility to pyogenic (pus-forming) bacterial infections	Lack of sufficient opsonization of bacteria
C3	Susceptibility to bacterial infections	Lack of opsonization and inability to utilize the membrane attack pathway
C5, C6, C7 C8, or C9	Susceptibility to Gram-negative infections	Inability to attack the outer membrane of Gram-negative bacteria

Diseases (other than I.D.) , caused by complement defects.

1.Loss of control proteins.
(decay accelerating factor, DAF, & CD59.)
Lead to destruction of R.B.C., which result in paroxysmal nocturnal hemoglobinuria .

2.C1 esterase inhibitor deficiency (C1 inhibitor.) result in excess of vasoactive mediators (kinins).
Causes : **Hereditary angioneurotic edema.**
*Recurrent attacks of subepithelial swellings involving the larynx & intestinal mucosa.
(may be fatal)

Clinical approach to suspected immunodeficiency.

1.History.
* **Infections of unusual frequency, chronicity or severity .**

* **Family history of infectious problems.**

Consanguinity should be investigated (inter-family marriages).

2.Physical examination.

* Absence of tonsils.
* Partial albinism.
* Telangiectasia .(bleeding capillaries).

3.Radiologic evaluation .

* Absence of thymic shadow .
* Pneumatocele (hyper IgE syndrome)

4.Laboratory evaluation.

1. Complete blood count .(total & differential).

2. Evaluation of antibody responses.
   A. determination of serum immunglobulins.

   B. measure specific antibody responses:

   -To polysaccharide antigens.
   (measure isohemagglutinins.)

   - To protein antigens .
   (measure antibodies to tetanus .)

3. Determination of T & B cell counts.
(by flow cytometry)

4. Determination of the complement components. C3, C4 .
- assess functional activity by CH50.

5. Assess phagocyte function.
- phagocytosis & respiratory burst.

6. Carrier detection & prenatal diagnosis . (important for genetic counseling .)

Analysis of lymphocytes in umbilical cord blood during gestation

* Help to diagnose immunodeficiency In pregnancies at risk .

* Bone marrow or stem cell transplantation may be applied before birth .

Laboratory tests to assess immune function

- Macrophage: Enumeration, functional assays (nitroblue tetrazolium)
- Complement: Direct measurement of complement components, complement hemolysis assay

Determination of the complement components. C3, C4 .
- assess functional activity by CH50.

Assess phagocyte function.
- phagocytosis & respiratory burst.

Phagocytic cell defects

- Skin infections without underlying skin disease
- Abscesses of skin, liver, lung, nodes
- Examples: CGD, LAD
- Check flow (NK cells, CD11/CD18 [LAD-1], CD15 [LAD-2, aka Sialyl Lewis X – VERY rare)

Complement problems

- CH50 assay is the screen; need all the other levels to be normal for it to be normal
- Complement spontaneously activates
  - blood that has been sitting around is inappropriate for testing
- CH50 levels should turn up VERY low – like 11

Therapy of immunodeficiency.

1. IVIG .(IV infusion of immunoglobulin.)
   For : a. agammaglbulinaemia .
   b. CVI. c. WAS.

2. Periodic antibiotic treatment.

3. Bone marrow transplantation .
   For : a. SCID . b. WAS.

4. Enzyme replacement .
   For : a. ADA deficiency.

5. G-CSF.(colony stimulating factor)
   For : neutropenia .

6. Thymus transplantation .
   For : DiGeorge syndrome.

7. IFN – gamma .
   For : CGD.