

Congenital and Acquired Immunodeficiency Diseases (not HIV)

May 6, 2009

IMMUNODEFICIENCY DISEASES

Defects in one or more components of the immune system can lead to serious and often fatal disorders collectively known as immunodeficiency diseases.

Primary immunodeficiency diseases - defects in genes for components of the immune system.

Secondary immunodeficiency diseases - due to factors that have an adverse impact on the immune system.

If primary immune deficiency diseases are genetic, why are some of these diseases first diagnosed in adults?

- **Compensating immune functions** keep serious problems from developing earlier.

OR

- **Slowly deteriorating immune function**, genetically determined, that does not become significant until later in life.

Patients with immunodeficiency diseases are most often recognized because of an **increased susceptibility to infections**.

1. Chronic/recurrent infections w/o other explanations.
2. Infections with organisms of low virulence.
3. Infections of unusual severity.

Immunodeficiency diseases may also present with non-infectious manifestations such as autoimmune diseases.

THERAPY

- **Gamma globulin** - fraction of blood that contains Igs. Pooled from 2,000 - 10,000 donors. Contains abs to many different ags.
- **Bone marrow transplantation** - requires a good match (sibling) - removed from pelvic bones
- **Antibiotics** - supportive
- **Cytokines**
- **Gene therapy**

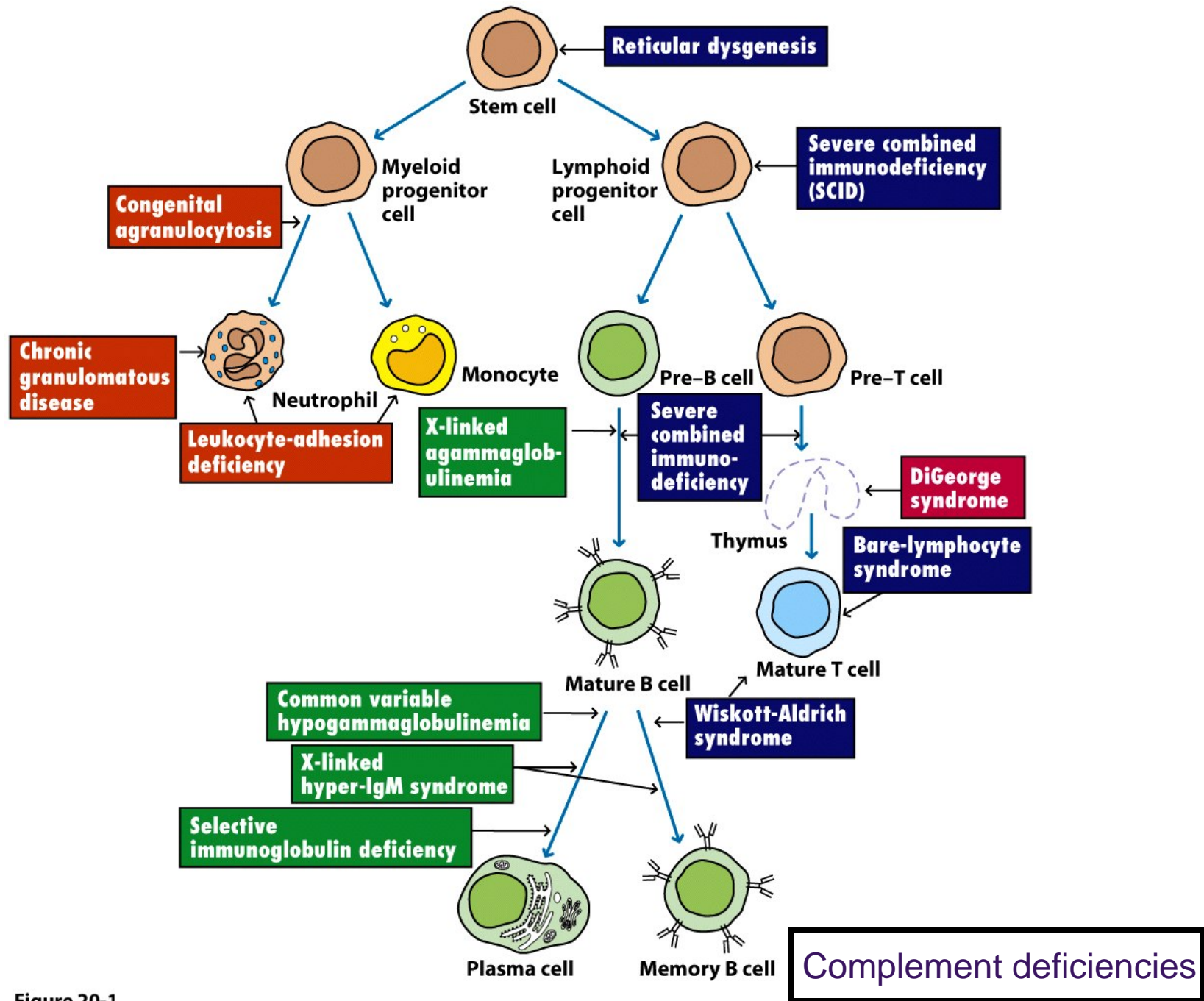


Figure 20-1
 Kuby IMMUNOLOGY, Sixth Edition
 © 2007 W.H. Freeman and Company

Evaluation of the Components of the Human Immune System

- Differential cell counts/FACS analysis
- B cell function
 - *In vivo*: serum Ig levels, specific ab levels
 - *In vitro*: mitogen-induced ab production
- T cell function
 - *In vivo*: skin test
 - *In vitro*: T cell proliferation in response to mitogens
- Phagocytes: NBT test, intracellular killing of bacteria
- Complement: dilution of serum required to lyse 50% of antibody-coated rbc or ELISA

SCID (Severe Combined Immunodeficiency Disease)/Defects in T Cell Function

- Defects in lymphoid development affecting T cells alone or with B cells & NK cells.
- Thymus does not develop. Few circulating T cells. Defective T cell function - may extend to B cells & NK cells.
- Usually presents in infancy.
 - Failure to thrive
 - Fungal or viral infections - skin, mouth, and throat lesions - pneumonia
 - Chronic diarrhea
- ~50% of cases are due to deficiency of the common gamma chain of the IL-2 receptor (“boy in the bubble”)

David Vetter (9/21/71-2/22/84)

- Lived in a plastic bubble - sterile environment - began 20 seconds after birth
- 1977 - NASA developed the Mobile Biological Isolation System - allowed David to venture outside the bubble
- 1983 - given bone marrow from sister - less than perfect match but expected to work with new methods using unmatched marrow
- Transplant seemed to work at first.
- Transplant harbored EB virus - David died of Burkitt's lymphoma

1976 made-for-television movie starred John Travolta



BAYLOR COLLEGE OF MEDICINE ARCHIVES

Photo: European Press Agency



👤 **LOOKING FOR AN END TO THE BUBBLE** Child with severe, hereditary immune deficiency at Debrousse Hospital in Lyon, France.

IL-2 receptor subfamily (common γ subunit)

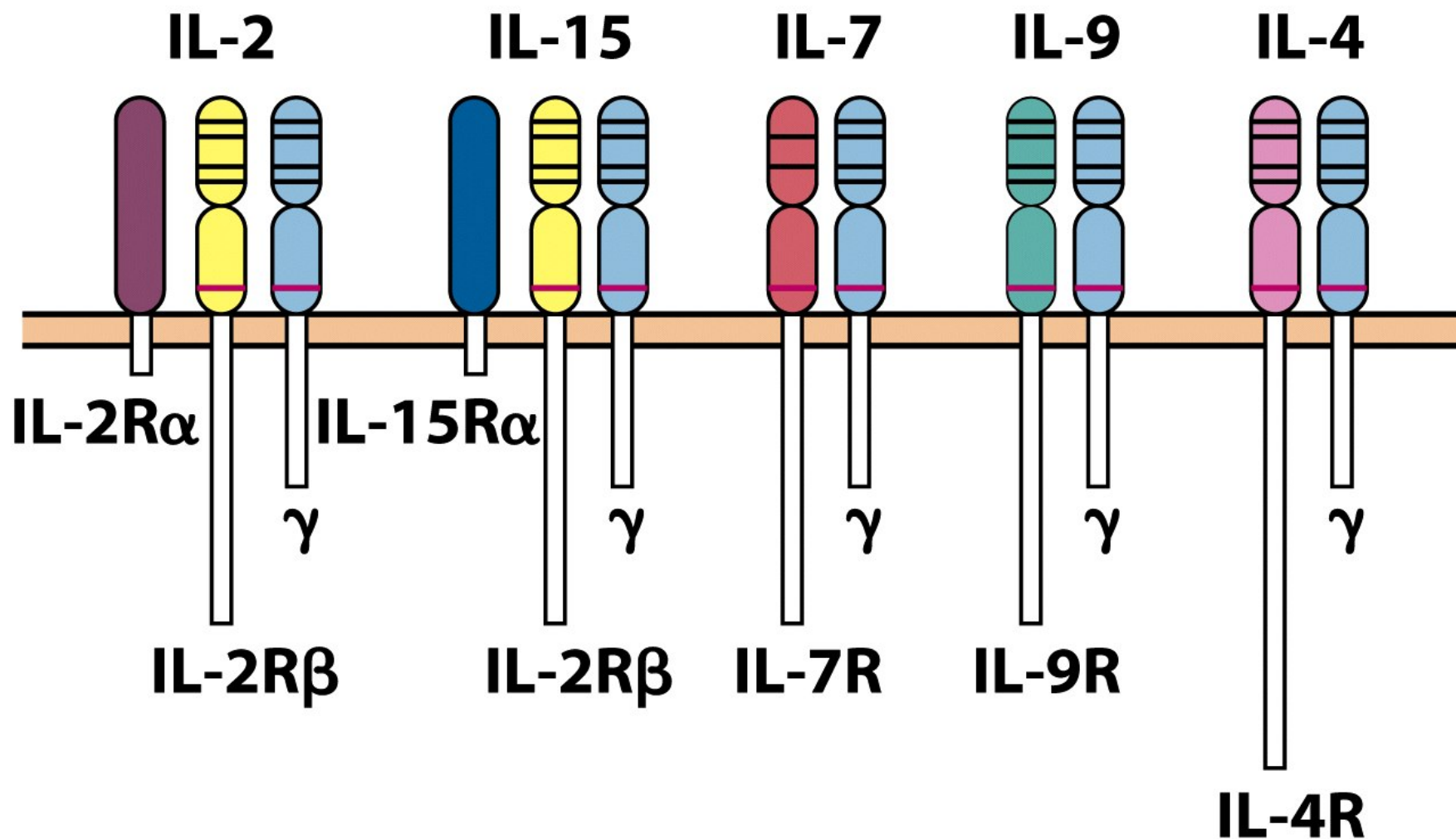


Figure 12-7c
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W. H. Freeman and Company

NK cells are present

ADA = adenosine
deaminase
T, B, NK cells
are affected
accumulation
of adenosine

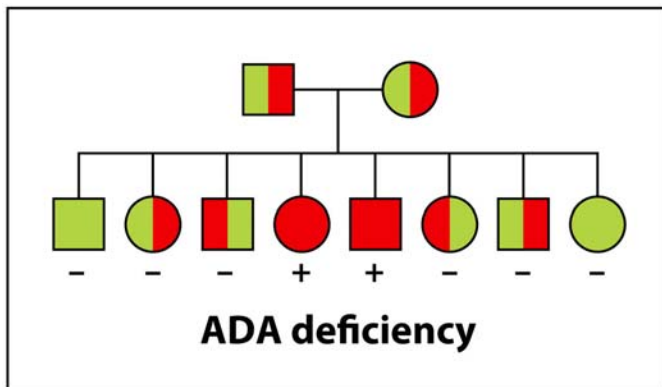
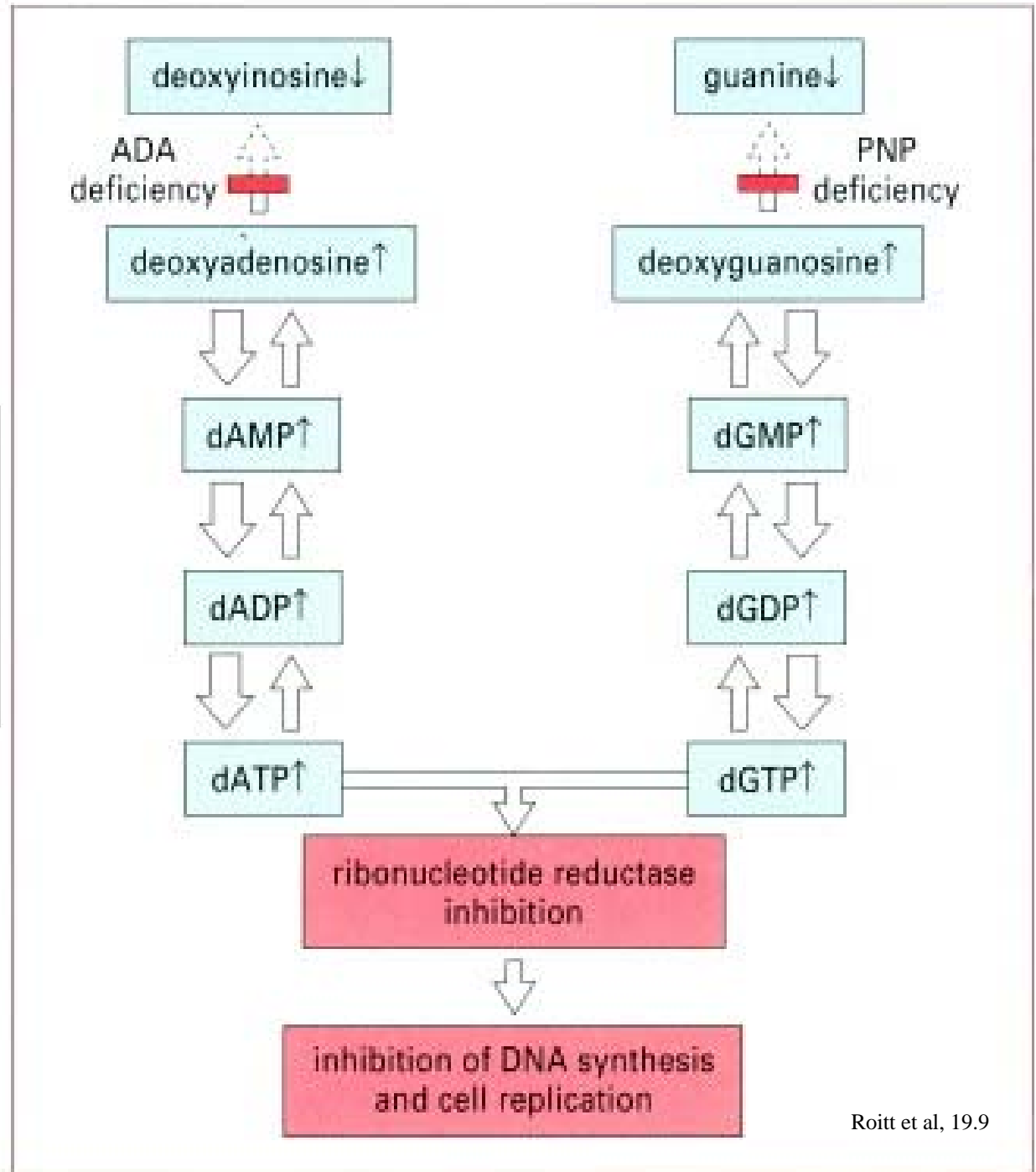


Figure 11.15 The Immune System, 3ed. © Garland Science 2009

Treatment : bm transplant,
PEG-ADA, gene therapy
(retrovirus vectors)

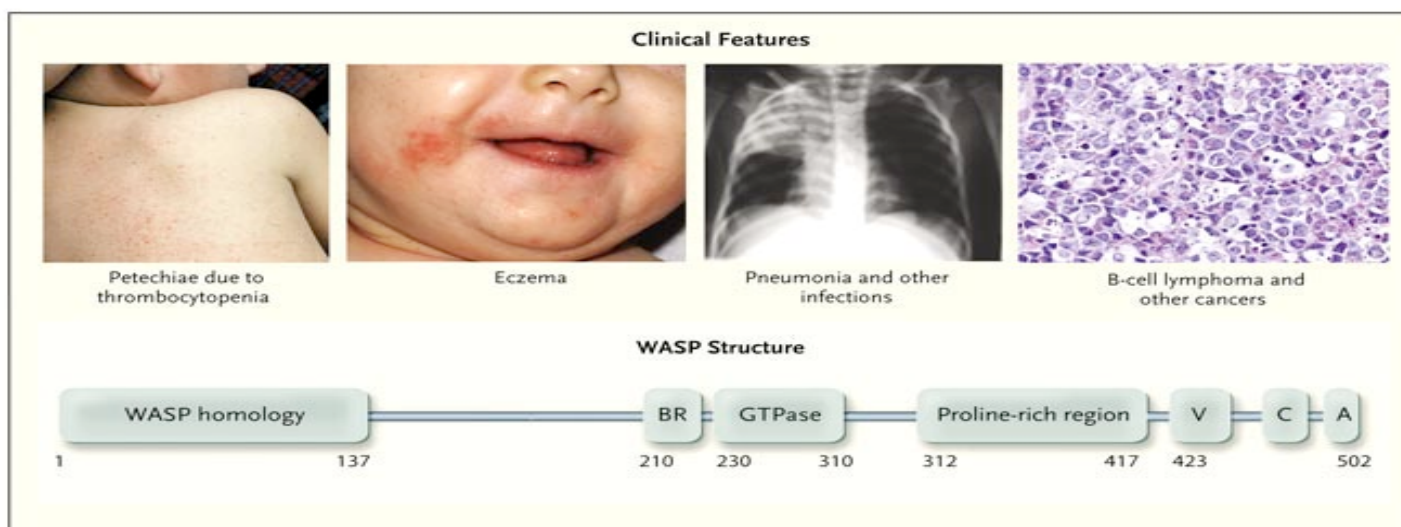
PNP = purine nucleoside
phosphorylase



- **Wiskott -Aldrich syndrome (WAS)**
- Bare lymphocyte syndrome (MHC class II)
- Bare lymphocyte syndrome (MHC class I)
- ZAP-70 (signal transduction defect)
- *RAG* mutations (cell development defect)

Wiskott Aldrich Syndrome

- X-linked disease characterized by:



www.uv.es

- Defective gene encodes for CD43 (sialophorin) required for cytoskeletal reorganization - needed for T cells to deliver cytokines & signals - cell counts are normal
- Poor antibody response - gradual loss of humoral and CMI responses

- Wiskott -Aldrich syndrome (WAS)
- Bare lymphocyte syndrome (MHC class II)
- Bare lymphocyte syndrome (MHC class I)
- ZAP-70 (signal transduction defect)
- *RAG* mutations (cell development defect)

Bare lymphocyte syndrome - defects in MHC expression

- MHC class II
 - Impairment of MHC gene transcription
 - CD4 cells fail to develop
 - Treatment - bone marrow transplant
- MHC class I
 - Mutation in TAP genes - necessary for antigen processing in CD8+-mediated immunity
 - Treatment - antibiotics and IVIG

- Wiskott -Aldrich syndrome (WAS)
- Bare lymphocyte syndrome (MHC class II)
- Bare lymphocyte syndrome (MHC class I)
- ZAP-70 (T cell signal transduction defect)
- JAK3 (signal transduction defect)
- *RAG* mutations (cell development defect) - both T and B cells
- Artemis - X-linked SCIDs with radiation sensitivity

QuickTime™ and a
decompressor
are needed to see this picture.

DiGeorge Syndrome

(aka congenital thymic aplasia or third and fourth pharyngeal pouch syndrome)

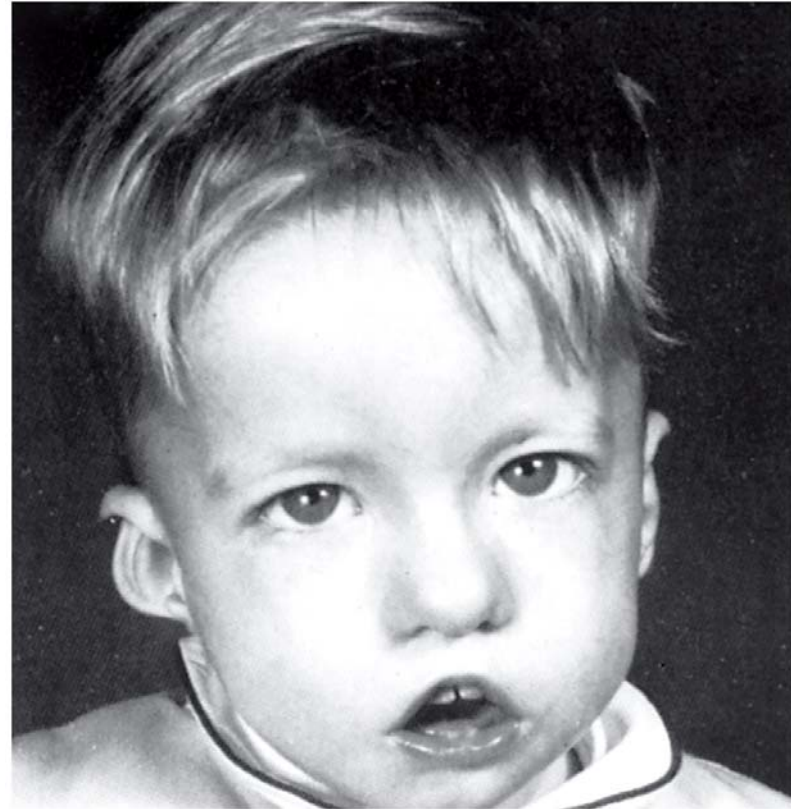


Figure 20-5
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W. H. Freeman and Company

Congenital malformation that results in **defective development of the thymus and the parathyroid glands**. **Deficient T cell maturation**. Absent parathyroids cause **abnormal calcium homeostasis and muscle twitching (tetany)**. Abnormal development of the heart. Facial deformities. Peripheral T cells are absent or reduced in number and do not respond to polyclonal T cell activators. B cells may be normal but antibody levels may be reduced in severely affected patients. Patients are susceptible to mycobacterial, viral, and fungal infections - failure to thrive.

Humoral Deficiencies

X-linked agammaglobulinemia

X-linked hyper IgM syndrome

Selective Ig deficiencies

CVID

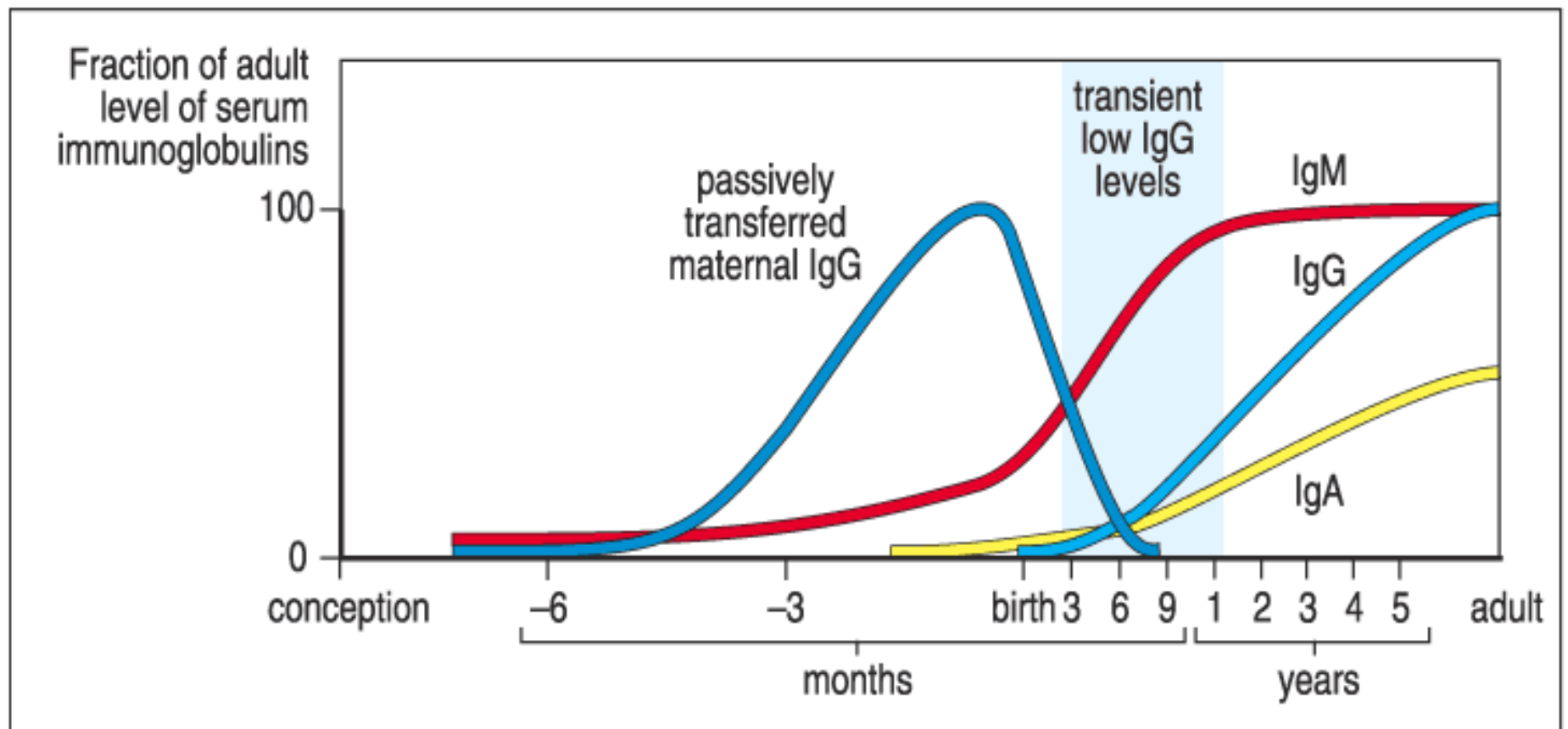


Fig 11.12 © 2001 Garland Science

X-linked agammaglobulinemia (aka Bruton's agammaglobulinemia)

- Characterized by:
 - Low levels or absence of gamma globulin in the blood
 - Reduced or absent B cells in the peripheral blood and lymphoid tissues
 - No germinal centers in lymph nodes
 - No plasma cells
 - Maturation, numbers and functions of T cells are usually normal
 - Autoimmune diseases develop in ~20% of patients - reason(s) unknown
- Failure of B cells to mature beyond the pre-B cell stage in the bone marrow because of mutations or deletions in the gene encoding B cell tyrosine kinase (Btk).

X-linked hyper-IgM syndrome (XHM)

- Deficiency of IgG, IgA, and IgE - elevated levels of IgM
- Normal numbers of B cells
- Both X-linked & acquired
- Autoantibodies to PMNs, platelets, & rbc
- Failure to produce germinal centers
- Defect is in gene encoding CD40L (CD154) required for B cell responses to T-dependent antigens. Class switching and memory B cells are not formed.

Selective Ig deficiencies

- IgA deficiency is most common
 - Symptoms range from unnoticed to various problems including recurrent respiratory and urogenital tract infections
 - Other problems: intestinal malabsorption, allergic disease, autoimmune disorders
 - Some pts can substitute IgM for IgA as a mucosal antibody
- IgM deficiency rare autosomal recessive - severe infections, malignancies, autoimmune diseases
- IgG deficiency - rare - may be unnoticed till adulthood - treatment is Ig administration

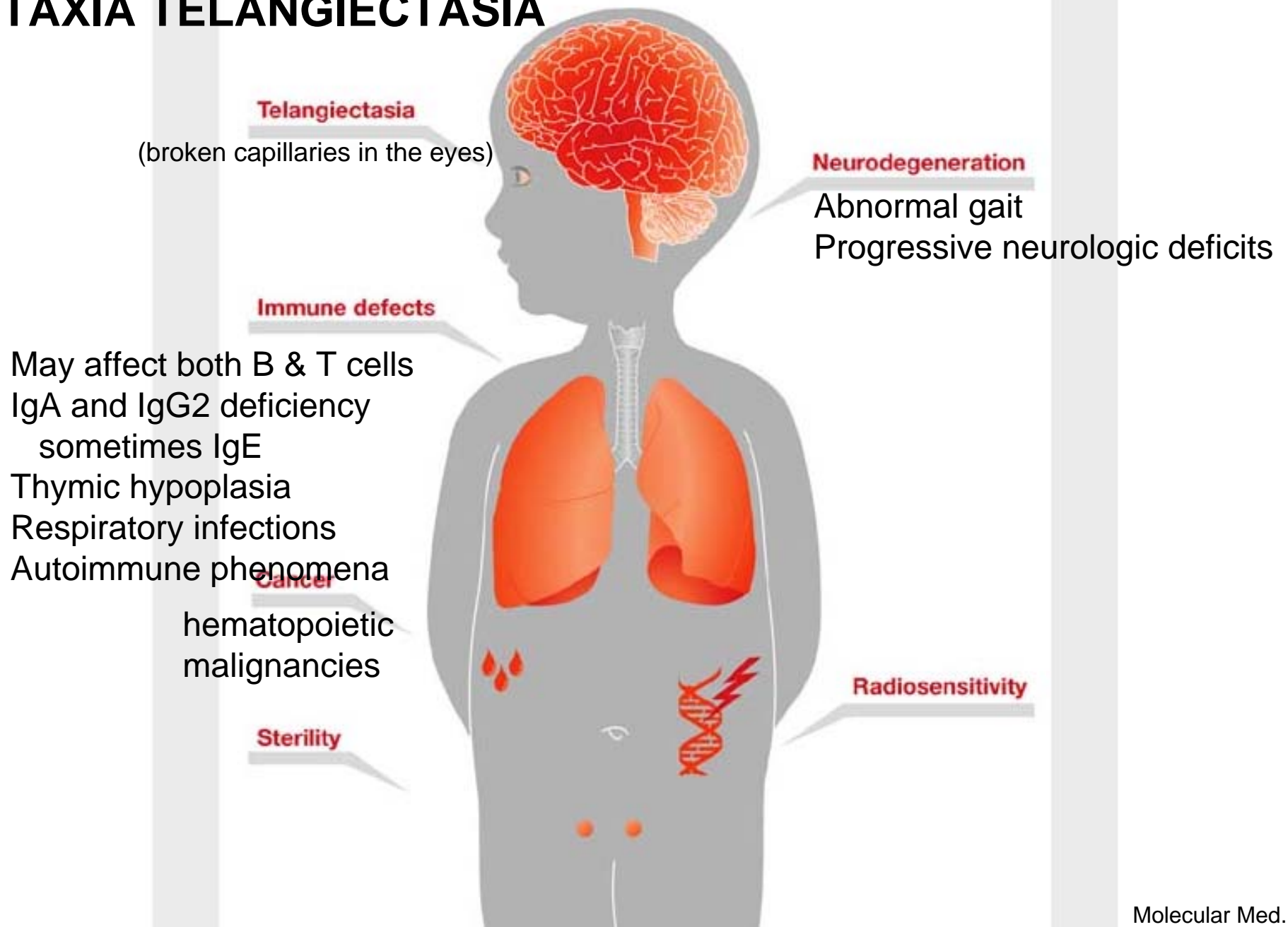
Combined variable immunodeficiency disease (CVID)

- Often shows up later in life
- Decrease in numbers of plasma cells - therefore reduced serum levels of IgG, IgA, and often IgM - recurrent infections
- Diagnosis is made by exclusion of other causes for ab deficiency
- Some cases are sporadic but some are familial - may be due to genuine B cell defects presumably at the stage where B cells become plasma cells - mutations in TAC1, a member of the TNFR family have been identified

Combined Deficiencies

(defects of more than one lineage)

ATAXIA TELANGIECTASIA



Mutation in *ATM* - kinase involved in cell cycle regulation
Chromosome 11

Disorders of Myeloid Cells

Syndrome	Cellular abnormality	Immune defect	Associated infections and other diseases
Leukocyte adhesion deficiency	Defective CD18 (cell adhesion molecule)	Defective migration of phagocytes into infected tissues	Widespread infections with capsulated bacteria
Chronic granulomatous disease (CGD)	Defective NADPH oxidase. Phagocytes cannot produce O_2^-	Impaired killing of phagocytosed bacteria	Chronic bacterial and fungal infections. Granulomas
Glucose-6-phosphate dehydrogenase (G6PD) deficiency	Deficiency of glucose-6-phosphate dehydrogenase. Defective respiratory burst	Impaired killing of phagocytosed bacteria	Chronic bacterial and fungal infections. Anemia is induced by certain agents
Myeloperoxidase deficiency	Deficiency of myeloperoxidase in neutrophil granules and macrophage lysosomes and impaired production of toxic oxygen species	Impaired killing of phagocytosed bacteria	Chronic bacterial and fungal infections
Chédiak–Higashi syndrome	Defect in vesicle fusion	Impaired phagocytosis due to inability of endosomes to fuse with lysosomes	Recurrent and persistent bacterial infections. Granulomas. Effects on many organs

Figure 11.14 The Immune System, 3ed. (© Garland Science 2009)

Chronic granulomatous disease (CGD)

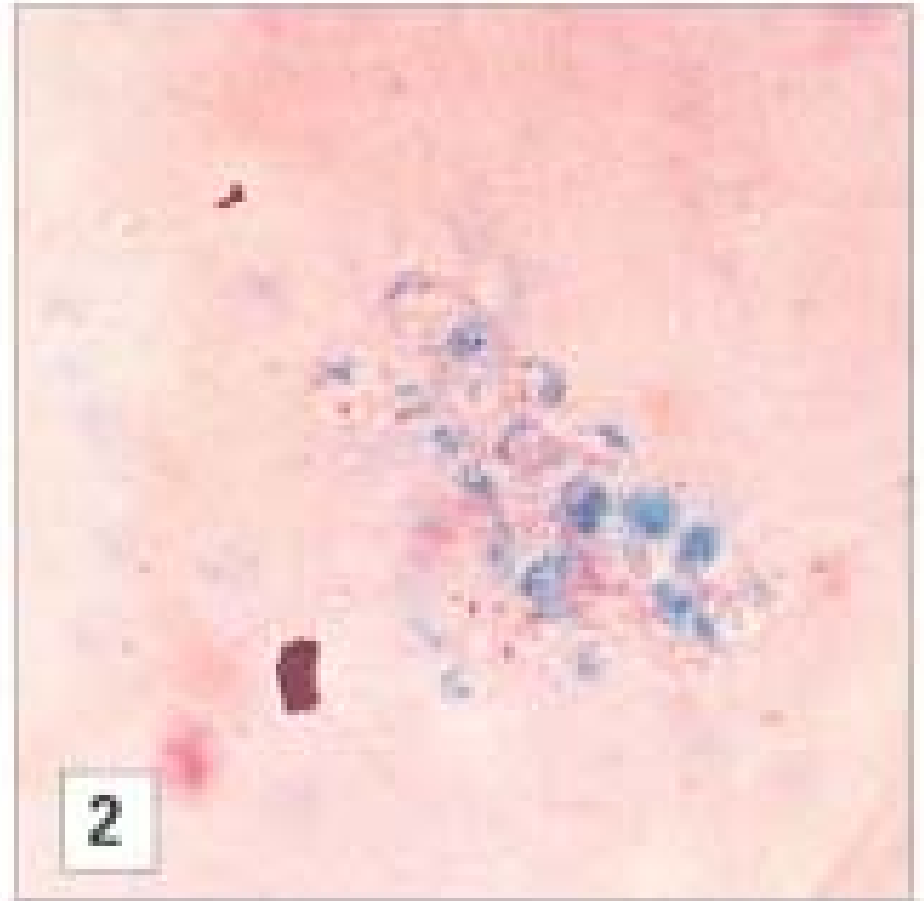
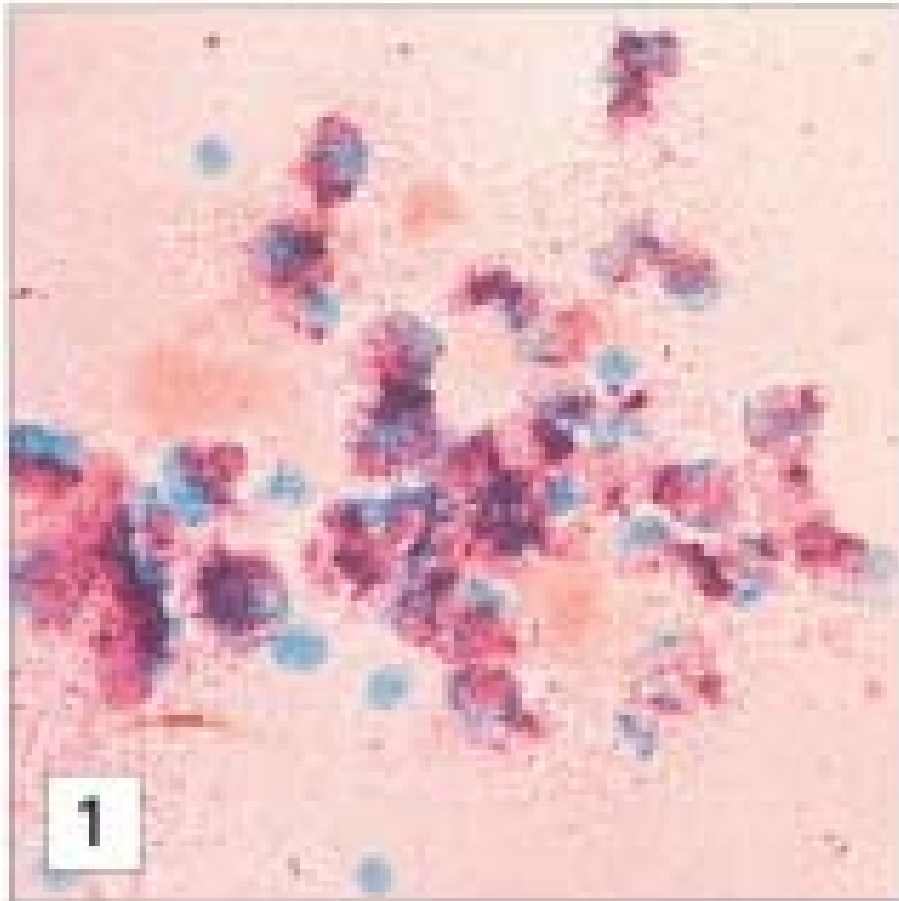
- X-linked (70%) and AR (30%) forms
- Defect in pathway that produces hydrogen peroxide and reactive products that kill phagocytosed bacteria (missing or defective cytochrome b558) - also decrease in mononuclear cell ability to process & present antigen
- Excessive inflammatory reactions leading to gingivitis, swollen lymph nodes, and nonmalignant granulomas - also bacterial and fungal infections
- IFN- γ treatment has been successful - gene therapy is also promising



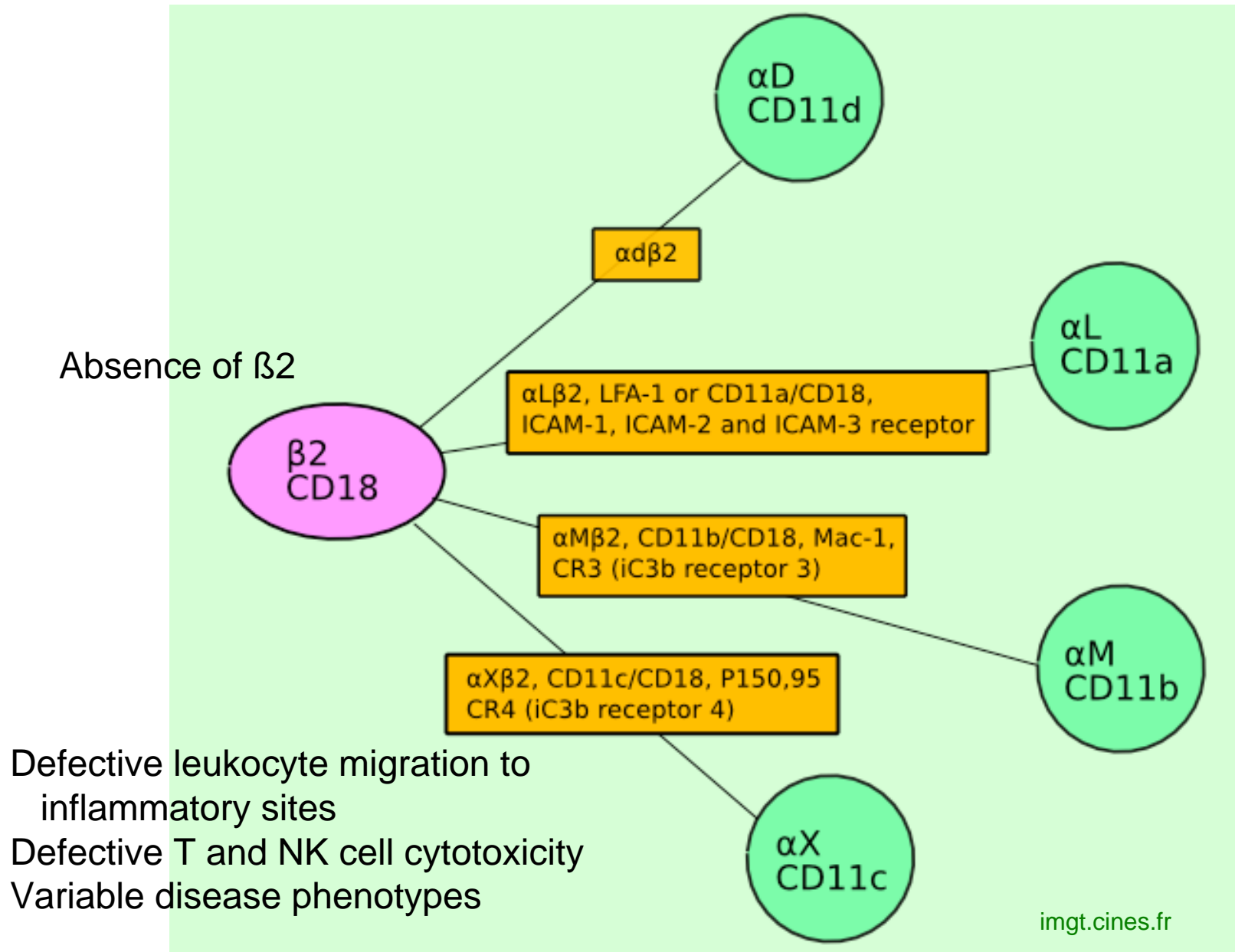
Unnumbered figure pg 213
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W. H. Freeman and Company

Necrotizing granulomatous
lesions

NBT Test

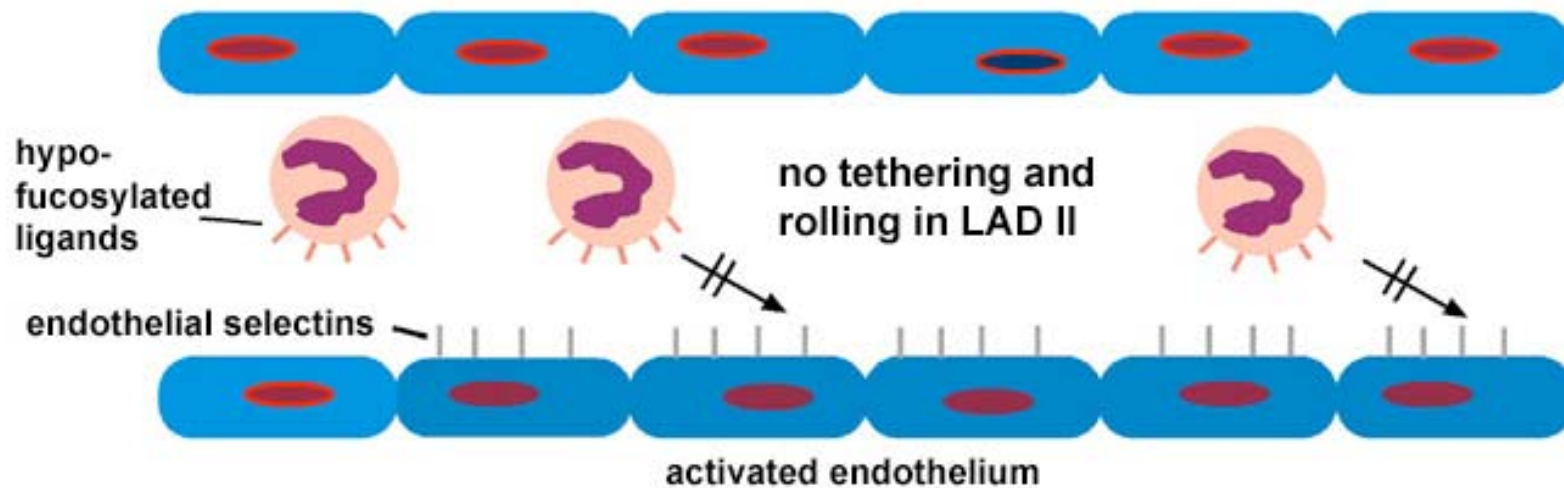


Leukocyte Adhesion Deficiency -LAD1



Leukocyte Adhesion Deficiency - LAD 2

Failure to convert GDP mannose to fucose - missing surface Sialyl Lewis^x which binds to P- and E-selectin on endothelium
Characterized by delayed wound healing, chronic skin ulcers, periodontitis, mental retardation



Chediak-Higashi Syndrome

Autosomal recessive

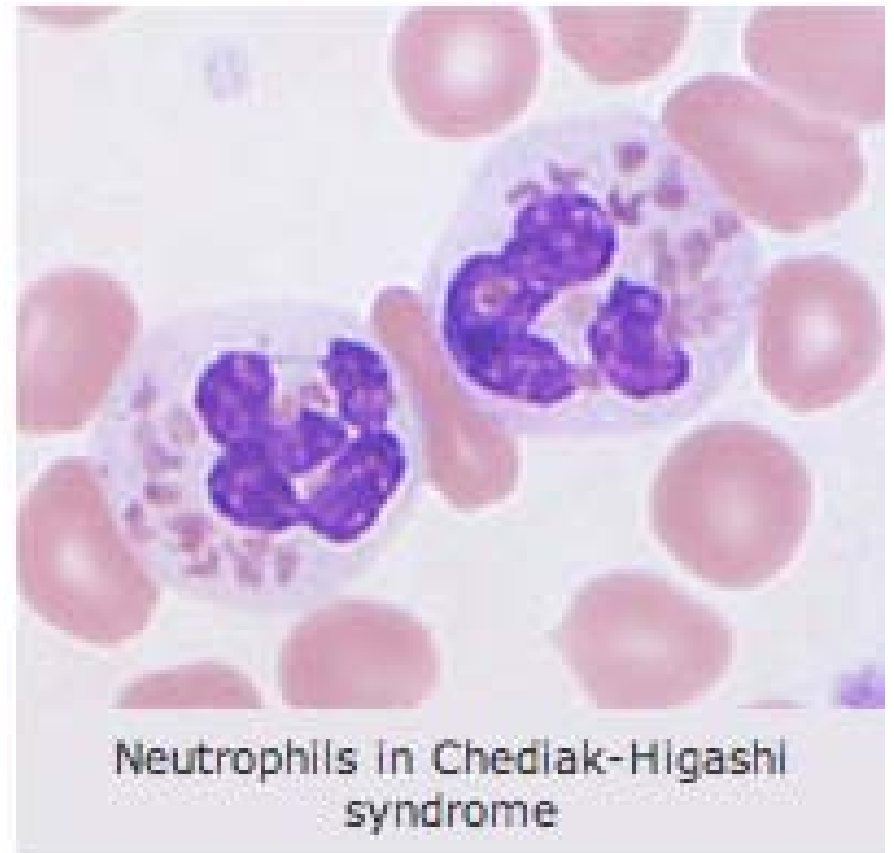
Recurrent bacterial infections, lack of skin & eye pigment

Phagocytes contain giant granules - cannot kill bacteria

Mutation in LYST - protein

involved in the regulation of
intracellular trafficking

Impaired targeting of proteins to
secretory lysosomes, which
makes them unable to kill
bacteria



Complement protein	Effects of deficiency
C1, C2, C4	Immune-complex disease
C3	Susceptibility to capsulated bacteria
C5–C9	Susceptibility to <i>Neisseria</i>
Factor D, properdin (factor P)	Susceptibility to capsulated bacteria and <i>Neisseria</i> but no immune-complex disease
Factor I	Similar effects to deficiency of C3
DAF, CD59	Autoimmune-like conditions including paroxysmal nocturnal hemoglobinuria
C1INH	Hereditary angioneurotic edema (HANE)

Figure 11.12 The Immune System, 3ed. (© Garland Science 2009)

Hereditary angioneurotic edema



Roitt et al, 19.12

Recently discovered immunodeficiency diseases:

- **UNC-93B** - essential for the normal response to signaling through TLRs that respond to viral infection (TLR3, TLR7, TLR8, and TLR9). Deficiency results in reduced production of IFN α , IFN β , IFN λ , TNF α , IL-1 β , and IL-6 in response to stimulation.
- **IFN γ R** - persistent mycobacterial infections
- **IPEX Syndrome** - development of systemic autoimmunity in first year of life - most common symptoms are watery diarrhea, eczema, insulin-dependent diabetes. *FOXP3* is the only gene associated with the IPEX so far (~60%). Elevated IgE (other Igs are normal), autoantibodies to pancreatic islet ags, thyroid ags, small bowel mucosa. Autoimmune anemia, low platelets &/or PMNs



Secondary (acquired) immunodeficiency diseases

Protein-calorie malnutrition

Irradiation and chemotherapy for cancer

Cancer metastases to bone

Immunosuppressive drugs

Removal of spleen

Infection with HIV

Protein-calorie malnutrition

- **Increases susceptibility to infectious disease - decreases all aspects of immune protection**
 - Reduced production of IL-2 and IFN- γ and an increased production of IL-4 and IL-10. Decrease in activation antigens (CD69 and CD25)
- Minerals and cofactors - transcriptional regulation of immune maturation
- Specific protein, vitamin and lipid needs
- Increased demand for antioxidant protection and tissue repair

Irradiation and chemotherapy

- **Cytotoxic drugs** enhance the **susceptibility to infection**
 - leukopenia (opportunistic infections) and thrombocytopenia
 - decreased cell-mediated immunity
- **Neutropenia** (leukemia, immunosuppression or irradiation) - patients **develop gram-negative bacteremia** from infections acquired through the mucous membranes or secondary to pneumonia
- **Severely immunosuppressed patients, patients with Hodgkin's disease and HIV** - depressed cellular immune mechanisms - serious infections with mycobacteria, *Aspergillus*, *Candida*, *Cryptococcus*, *Histoplasma*, *Mucor*, *Nocardia*, or *Staphylococcus* are frequent. Also *Herpes zoster*, cytomegalovirus, *Pneumocystis*, and *Toxoplasma* infections

Cancer metastases to bone

- Competes with development of progenitor cells in the bone marrow.

Immunosuppressive drugs

- Immunosuppressive drugs - autoimmune diseases, prevent transplant rejection - interfere with lymphocytes function - **not specific and suppress all of the immune system - leave the patient vulnerable to a variety of opportunistic infections** and complications
- Example: **corticosteroids** inhibit the movement of neutrophils, monocytes, and lymphocytes into inflammatory sites - patients have increased susceptibility to infection from both usual and unusual bacteria.

Removal of spleen

- Functions of the spleen:
 - Removal of unwanted elements from the blood
 - Major secondary organ of the immune system (DCs trap antigens and present them to T cells).
 - Source of hematopoietic cells in cases of severe anemia.
 - Can serve as a sequestering organ for blood elements
- **Single major clinical manifestation: increased susceptibility to disseminated infection with encapsulated bacteria** (pneumococcus, meningococcus, *Haemophilus influenzae*) - probably due to the reduced filtering and antibody production