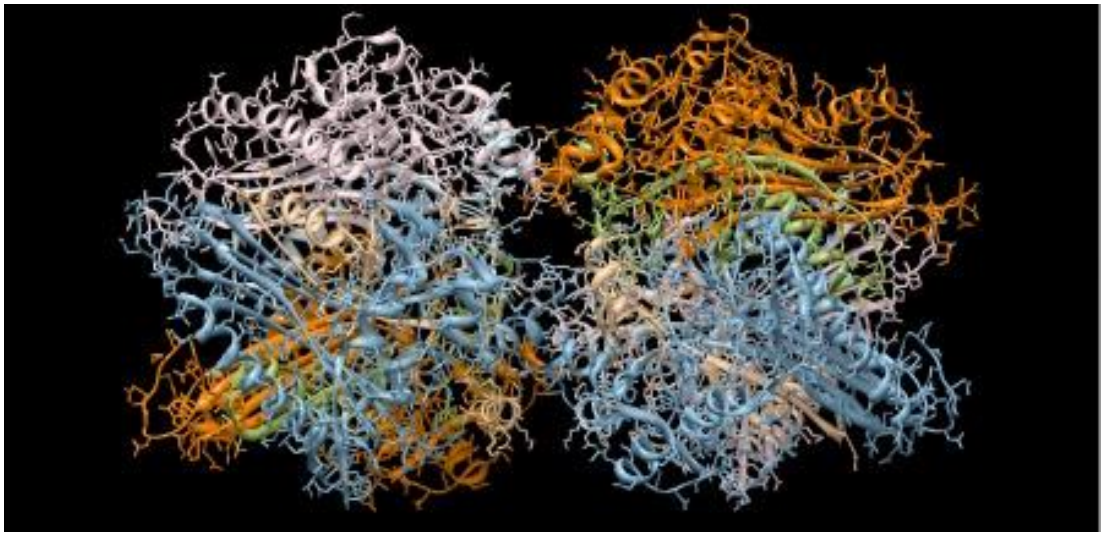
Immune deficiency



Neelika Malavige

Learning objectives

You should know:

- The mechanisms that lead to immune deficiency.
- Causes of primary and secondary immune deficiency.
- Effects of immune deficiency.
- The diagnosis of immune deficiency.
- The principals of management.

Sachin was born healthy baby boy until at the age of 3 months he developed otitis media. He developed repeated attacks of otitis media at 6 and 11 months of age. At 9 months he developed a pneumonia due to H. influenzae.

When he was seen at 15 months of age with another episode of otitis media, he was <3rd centile for his height and weight. His immunizations have been up to date.

1. What do you think is wrong with this baby?
2. What investigations would you do and why?

IgG	0.17	(5.5-10)
IgA	not detected	(0.3-0.8)
IgM	0.07	(0.4-1.8)

Immunuzation responses

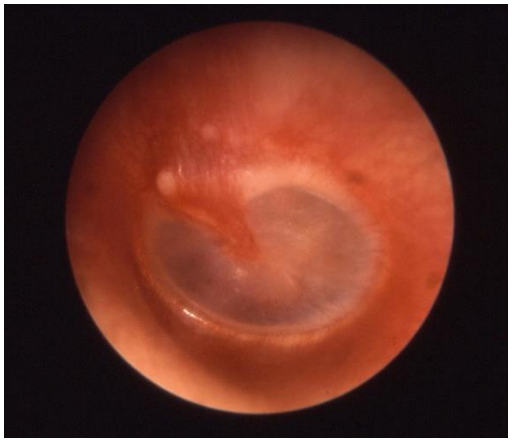
IgG to tetanus: not detected

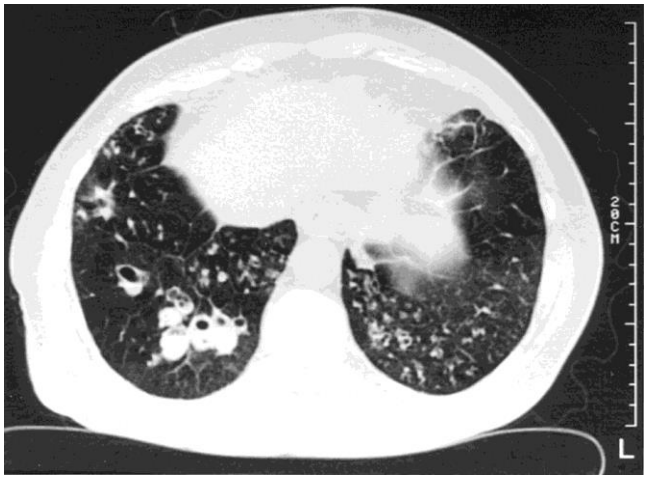
IgG to measles: not detected

IgG to polio: not detected

Immune deficiency

- **S**erious infection
- **P**rolonged infection
- **U**nusual infecting micro-organisms
- **R**ecurrent infection





Immune deficiency

Primary

Occurs when certain cells or a part of the immune system does not work properly due to a genetic defect of the immune system

Secondary

The immune system works properly but the function is compromised due to external factors

Types of immune deficiencies

Abnormalities in the innate immune system

Defects in phagocytes

Complement deficiencies

Abnormalities in the adaptive immune system

Absence of T and B cells

Functional defects in T and B cells

Secondary immune deficiency

Causes of secondary immune deficiencies

- Under nutrition: Protein energy malnutrition, vitamin deficiencies
- HIV
- Immune suppressive drugs: cyclosporin, methotrexate, steroids
- Malignancy: especially haematological
- Chronic illness: chronic liver and renal disease, poorly controlled diabetes mellitus
- Infections: measles (effect is usually transient)

Malnutrition leads to immune deficiency and initiates a viscous cycle

Primary immune deficiency

- Usually rare. Occur in 1:2000 to 1: 10,000 live births.
- Many are associated with single gene defects.
- Usually present in the first few years of life but can present later.

Primary antibody deficiencies

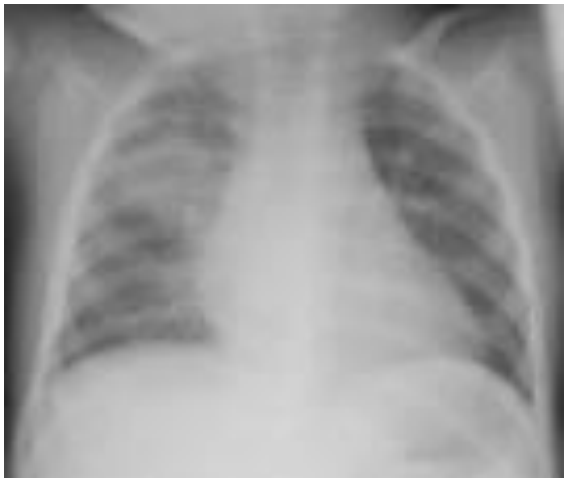
- Commonest form of primary immune deficiency.

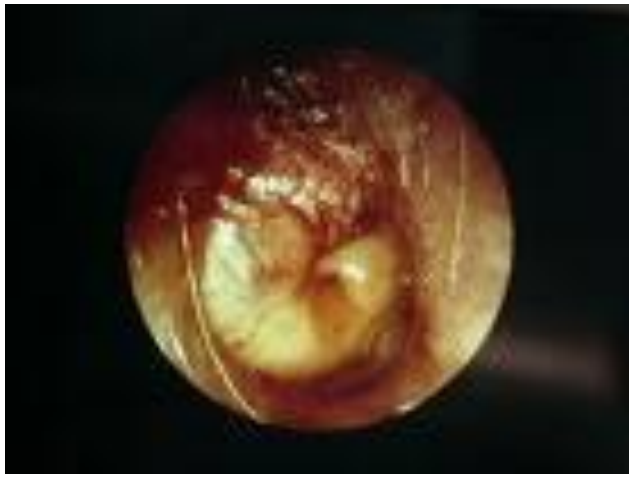
Types:

- Transient agammaglobulinaemia of infancy
- X linked and autosomal recessive agammaglobulinaemia
- Common variable immune deficiency (CVID)
- IgA deficiency
- IgG subclass deficiency
- Hyper IgM syndromes

Clinical presentation of antibody deficiencies

- May present in early childhood or in some types may present later in life.
- > 90% who fail to produce Abs present after 10 years of age.
- May present with autoimmune diseases. E.g. vitiligo, type I diabetes, thyroiditis





Clues from the history that are important to find out Abs deficiency

Repeated sinus or chest infections

- Repeated pneumonia
- Otitis media
- Early bronchiectasis

Other system involvement

- Skin sepsis
- Menigitis
- GIT infections

Repeated infections due to common bacteria

- Strep. Pneumoniae
- H. Influenzae

Non infectious features

- Autoimmune thyroid disease
- ITP
- Arthritis

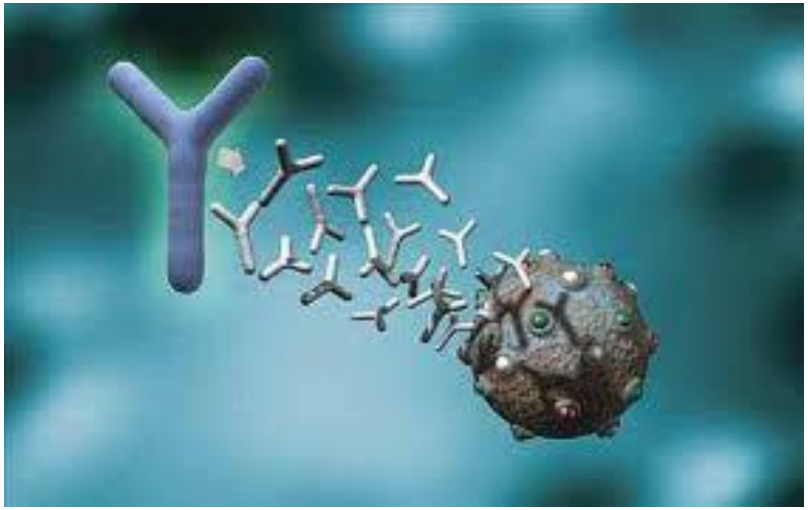
Common variable immune deficiency

- >90% are not diagnosed until adulthood
- Most have low serum levels of IgA or IgG or both
- may be associated autoimmunity, allergy, malignancy

Selective IgA deficiency

- Have low IgA levels, but normal IgG and IgM levels
- Incidence 1:700 to 1: 2000. commonest primary Ab disorder
- Most individuals are healthy
- Can have serious or recurrent bacterial infections
- Prone to transfusion reactions due to presence of anti IgA antibodies

Primary antibody deficiency or B cell defects usually do not manifest at birth



Why?

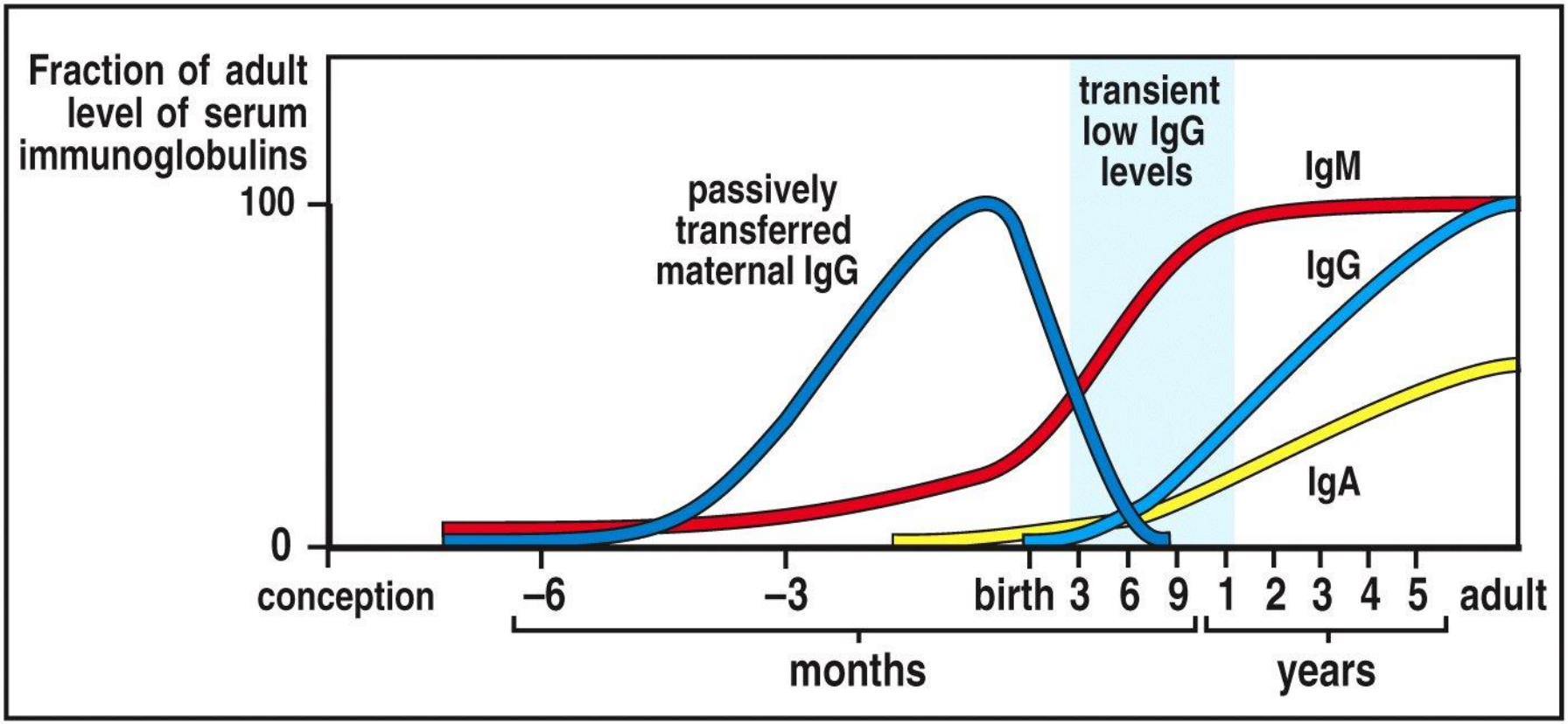


Figure 11-11 Immunobiology, 6/e. (© Garland Science 2005)

Secondary antibody deficiency

- Much more commoner than primary Ab deficiencies.

Causes

- Prematurity not enough maternal IgG, transient problem

- Antibody loss: extensive burns, nephrotic syndrome, protein-losing enteropathy

- Decreased production: Malignancy of B-cells, CLL /lymphoma,myeloma, Drugs such as gold, anticonvulsants

Q: In which of the following situation should you think about a primary ID?

a) A 15 year old child with 3 episodes of pneumonia

b) A 35 year old female with 5 lower UTIs

c) A 35 year old man with a past history of pneumonia, chronic otitis media, who now presents with bronchiectasis

d) A 23 year old medical student with 4 episodes of sore throats/year

e) A 45 year old female, who has had asthma for the past 5 years, which is getting worse. 2 episodes of pneuminia and now bronchiectasis

Q: which of the following patients do you think could be having a secondary antibody deficiency?

a) A 3 year old child with minimal change nephrotic syndrome
b) A 40 year old patient with 50% burns
c) A patient with poorly controlled DM

Evaluation of possible B cell/Ab deficiency

Initial evaluation: WBC with differential

Specific tests of antibodies and B lymphocytes

- IgG, IgA, IgM concentrations
- Specific antibody analysis e.g. antibodies to pneumococcus, haemophilus, tetanus
- Response to immunisation
- Quantify B-cells (also T-cells) using flow cytometry

Management of primary antibody deficiencies

Replacement of antibodies

- Intravenous immunoglobulins
- Should be given every 3-4 weeks
- Expensive

Prevention and aggressive treatment of infections

T cell defects

Infections

- Viruses: CMV, HSV, VZV
- Fungi: candida
- Protozoa: pneumocystis, cryptosporidia
- Intracellular bacteria:mycobacteria, listeria

Abnormal antibody production due to defects in B-cell regulation, thus may also have

- infections with pyogenic bacteria e.g. pneumococcus

Loss of delayed hypersensitivity and loss of ability to reject foreign tissue

Abnormal immune regulation associated with allergy, autoimmunity

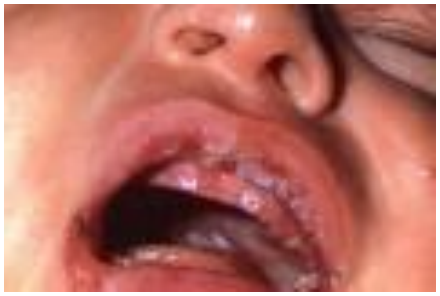
Malignancy e.g. lymphoma, squamous carcinoma skin, Kaposi's sarcoma

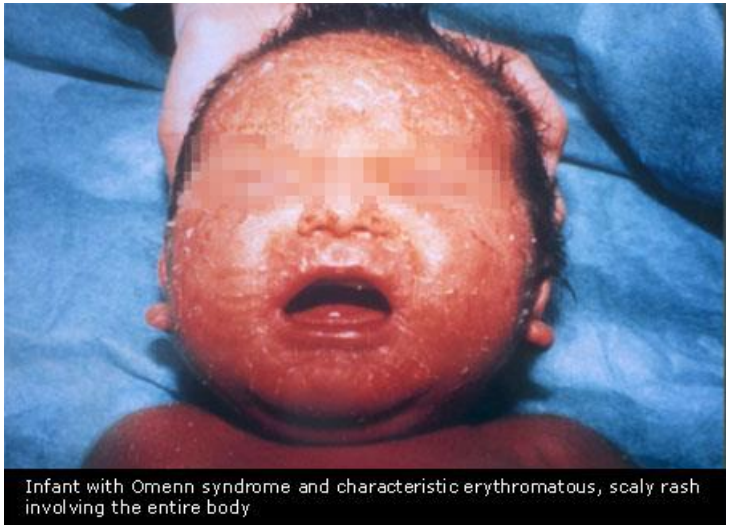
Combined primary T and B cell immune deficiencies

- Impaired T cell immunity is usually associated with some degree of B cell defects (as T cells are needed for B cells to function properly).
- Known as SCID (severe combined immune deficiency)
- Associated with severe infections very early in life.
- Treatment: bone marrow transplantation, aggressive treatment and prevention of infections.

Clinical presentation of SCID

- Early onset of bacterial, viral, fungal and opportunistic infections.
- Persistent oral candidiasis
- Failure to thrive
- Diarrhoea
- Skeletal abnormalities





Infant with Omenn syndrome and characteristic erythromatous, scaly rash involving the entire body

Treatment: bone marrow transplantation, prevention of infection and aggressive detection and treatment of infections.

Causes of secondary T cell defects

- Infection transient: measles
- Progressive infection: HIV infection
- Malnutrition
- Iatrogenic e.g. fractionated radiation, drugs e.g. corticosteroids
- Autoimmunity e.g. SLE
- Malignancy
- Aging

Investigation of T cell numbers and function

- WBC with differential: will give total lymphocyte number.

- Flow cytometry: to detect the absolute CD4+ and CD8+ T cell numbers.

Functional assessment of T cells:

- T cell proliferative capacity when stimulated with antigen: by flow cytometry
- T cell cytokine responses to antigens: by ELISpot and flow cytometry
- T cell surface markers: by flow cytometry
- Delayed type hypersensitivity reactions

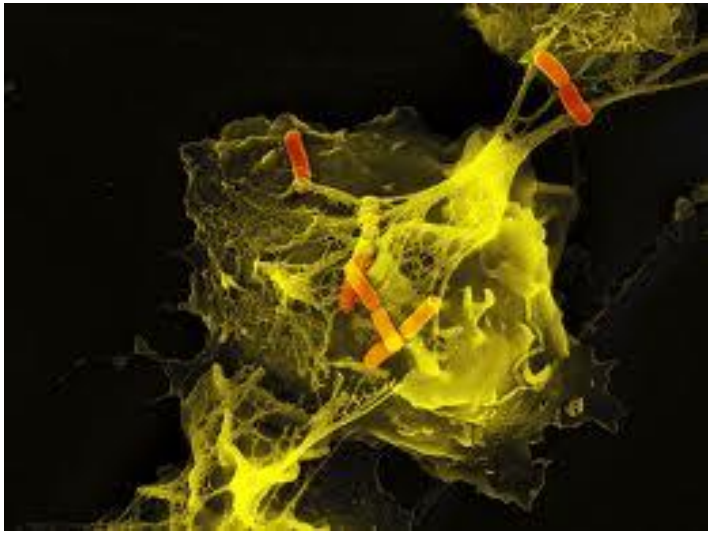
Immune deficiency due to abnormalities of neutrophils

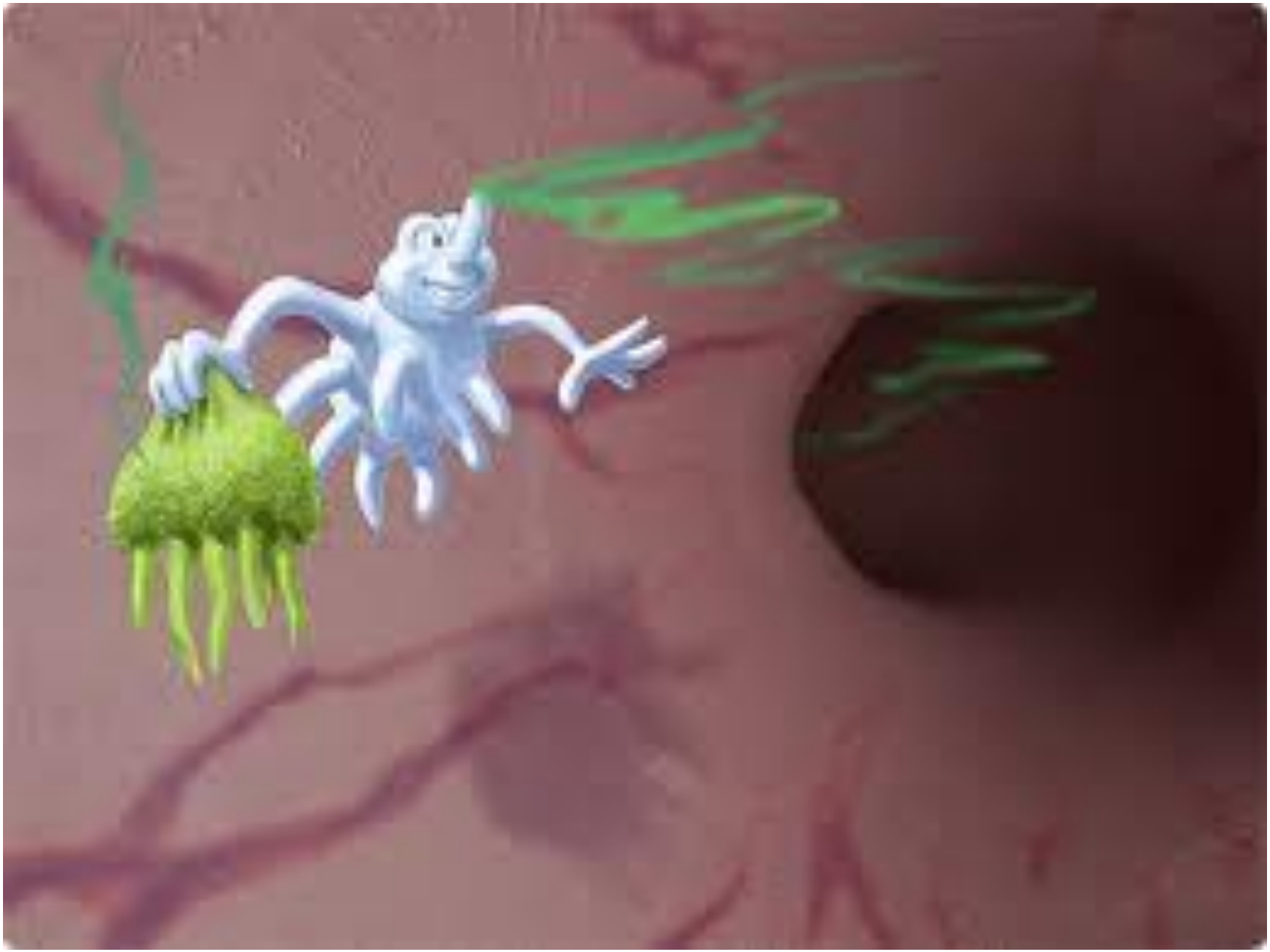
Infections due to

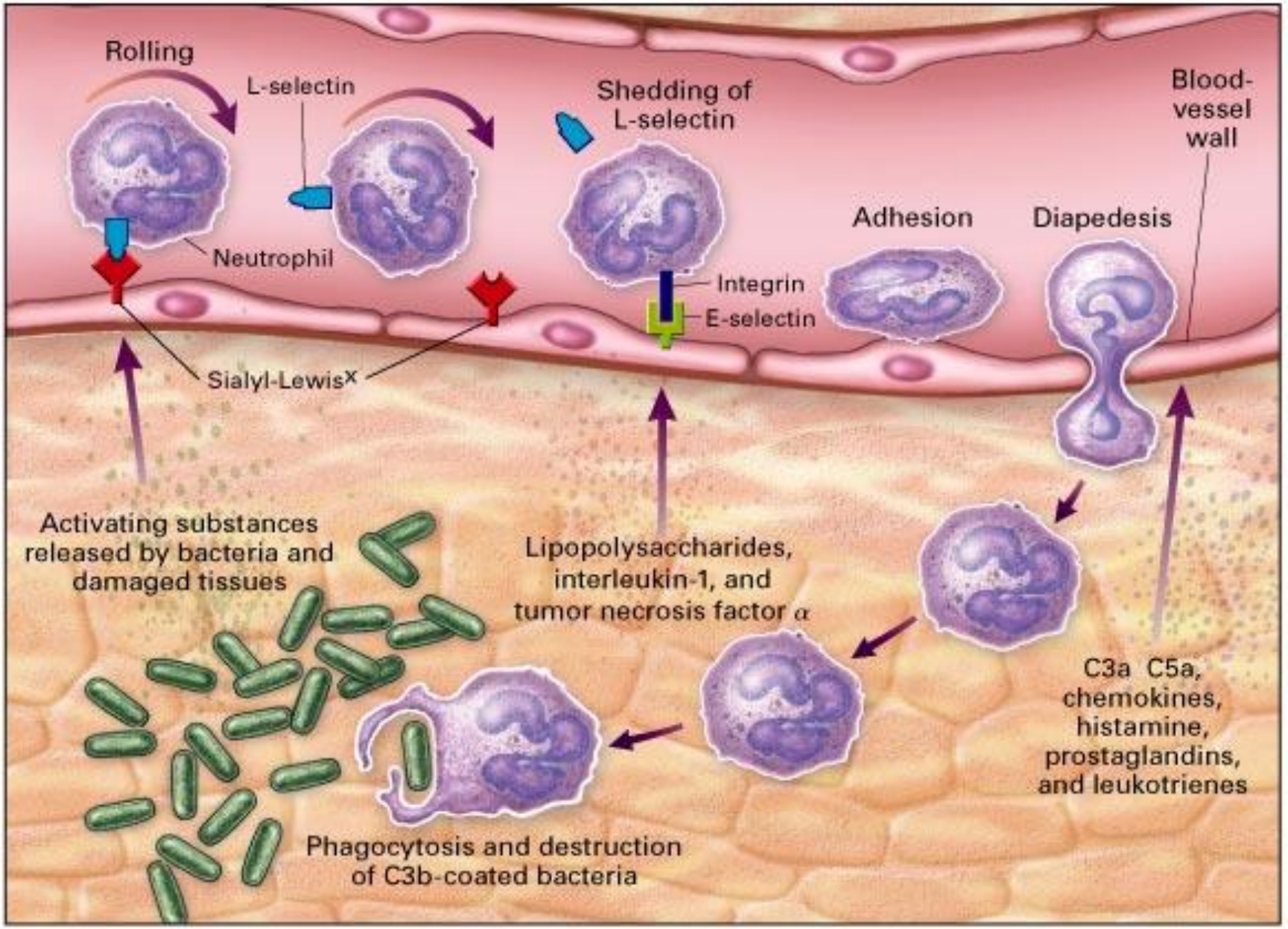
- extra-cellular bacteria e.g. staphylococcus, *E coli*
- fungi e.g. aspergillus

sites: skin, mucous membranes, bone, lung and liver

Impaired wound healing






Rolling
L-selectin
Shedding of L-selectin
Blood-vessel wall
Neutrophil
Integrin
E-selectin
Adhesion
Diapedesis
Sialyl-Lewis^x
Activating substances released by bacteria and damaged tissues
Lipopolysaccharides, interleukin-1, and tumor necrosis factor α
C3a C5a, chemokines, histamine, prostaglandins, and leukotrienes
Phagocytosis and destruction of C3b-coated bacteria

SOME NEUTROPHIL / PHAGOCYTE DISORDERS

	PRIMARY	SECONDARY
NEUTROPENIA	Chronic hereditary neutropenia	Cytotoxic drugs
	Cyclic neutropenia	Bone marrow metastases
		Auto-immune
ADHESION	Leucocyte adhesion deficiency (LAD)	Corticosteroids
MOVEMENT	LAD	Viral infection
PHAGOCYTOSIS	LAD	Diabetes mellitus
KILLING DEFECTS	Chronic Granulomatous Disease*	Diabetes mellitus
MORPHOLOGICAL	Chediak-Higashi syndrome	

Investigation of neutrophil defects

- WBC with differential: Is there neutropenia?
- Nitroblue tetrazolium reduction assay: do the neutrophils function properly?
- Assessment of chemotaxsis:

Exclude other immune defect with similar range of infections

- Serum IgG, IgA, IgM and IgE
- C3, C4, CH100 (haemolytic complement function)

Complement deficiency

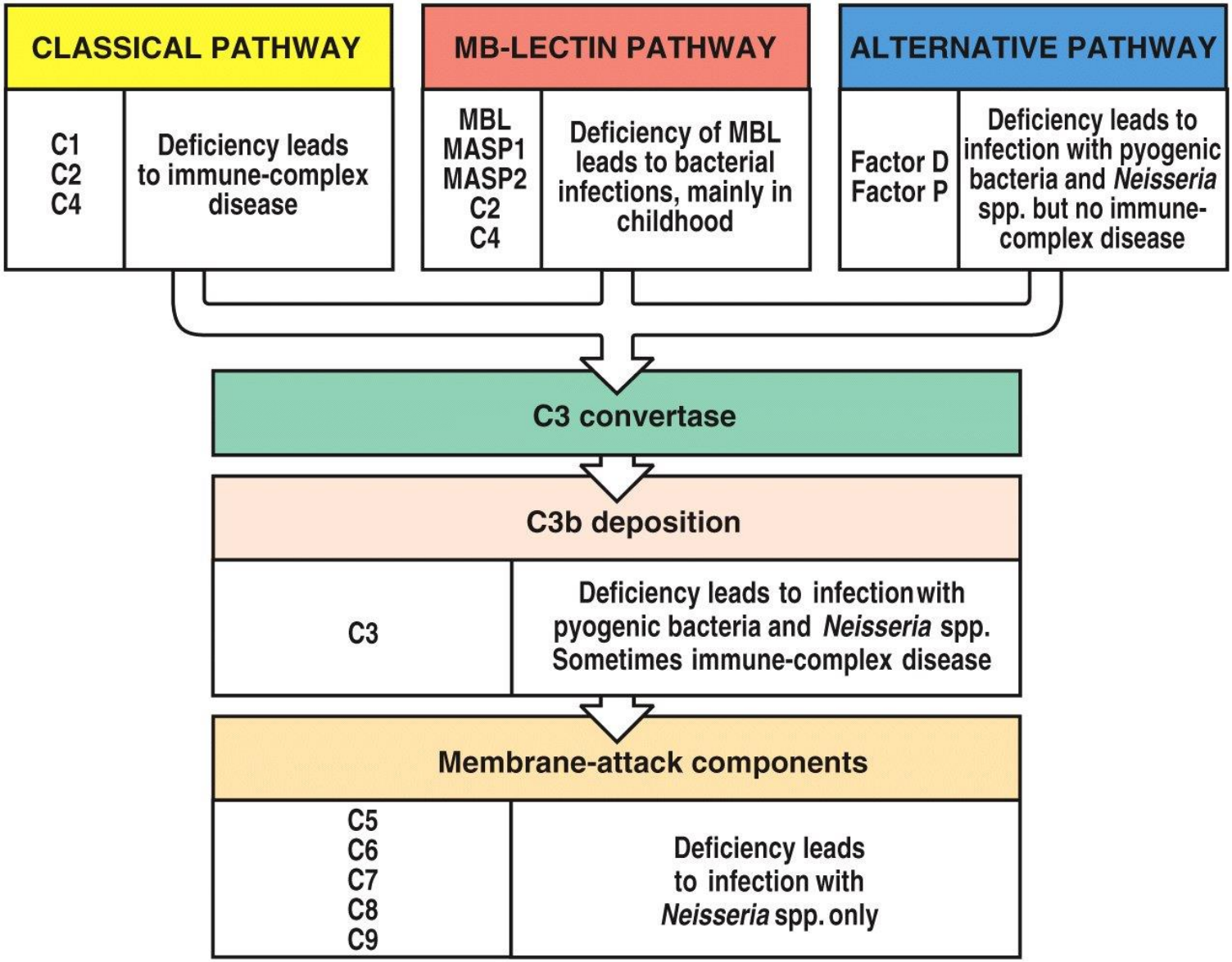


Figure 11-13 Immunobiology, 6/e. (© Garland Science 2005)

Abnormalities of complement

Elevated: Part of the acute phase reaction

Reduced

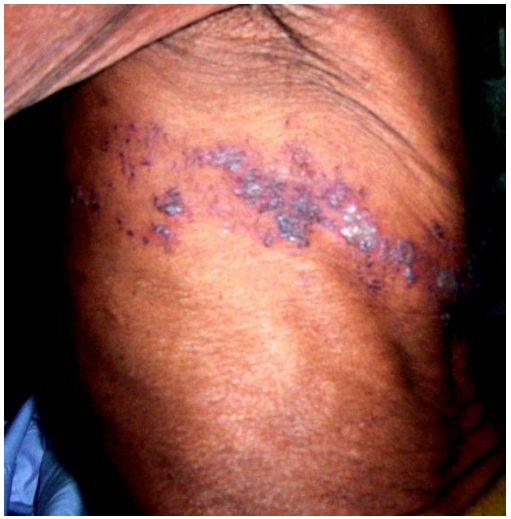
- Reduced production - fulminating liver failure
- Consumption - infection, immune complex disease
- Inherited deficiencies

Inherited complement deficiencies

- Deficiency of ***C1,4,2,3: immune complex disease*** similar to SLE
- Deficiency of ***C3, H,I, C5 : pyogenic bacterial infection***
- Deficiency of ***C1 inhibitor: angioedema***
- Deficiency of ***C5,6,7,8,9: neisserial infections***

A 51-year-old male presented with shingles for the second time in a year. About 5 years ago he was found to have Hodgkin's disease for which he had received fractionated radiotherapy as part of his treatment. The Hodgkin's disease had not recurred.

Analysis of his lymphocytes revealed the following:
Total lymphocyte count 1.1x109/L (ref range 1.0-3.2)
CD3 T lymphocytes 0.90x109/L (reference range 0.7-2.1)
CD4 T lymphocytes 0.25x109/L (reference range 0.3-1.4)
CD8 T lymphocytes 0.64 x109/L (reference range 0.2-0.9)



a) What is the cause for repeated attacks of herpes zoster?

b) What is the most likely mechanism for the findings on analysis of her lymphocytes?

c) What precautions should be taken when managing this patient?

Management:

Avoid additional immune suppressants

Antimicrobial prophylaxis

Treat infections aggressively

No live vaccines

Transfusions - use CMV-negative

Summary

- Secondary immune deficiencies are far commoner than primary immune deficiencies.
- Severe, recurrent, unusual infection should raise the suspicion.
- Most primary antibody deficiencies don’t present till >10 years of age.