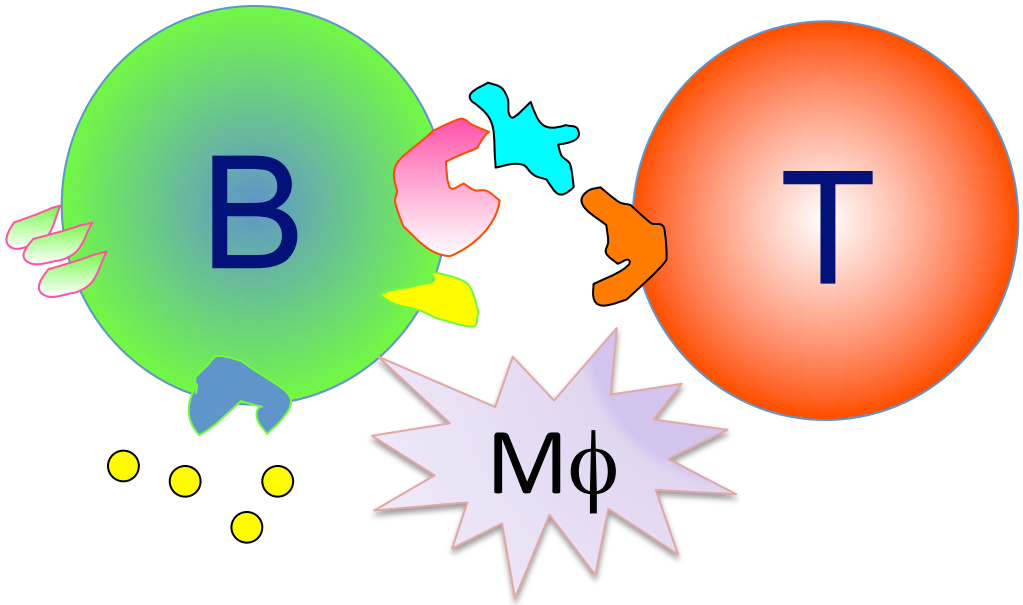
Primary Immune Deficiency

Charlotte Cunningham-Rundles MD PhD
Mount Sinai School of Medicine



Conflicts of Interest

1. Talecris/Grifols Medical Advisory Board
2. Baxter Heathcare: research funding for project on the Statewide Planning and Research Cooperative System (SPARCS) data base seeking use of IDC codes in primary immune deficiency in NYS.
3. Octapharma: research grant to dissect antibody deficiencies to guide Ig therapy

Congenital defects of the immune system produce a number of different clinical syndromes:

- Most of the human immune deficiency diseases have been identified in the last 40 years.
- Recognition of the disease or syndrome preceded knowledge of the genes or mechanisms involved.
- In most cases there are frequent and severe infections, propensity to inflammation, autoimmune diseases and/ or development of cancers.
- These defects are found in infants, children and adults.
- First recognized were in infants; those with X-linked inheritance, slowly other syndromes and phenotypes identified

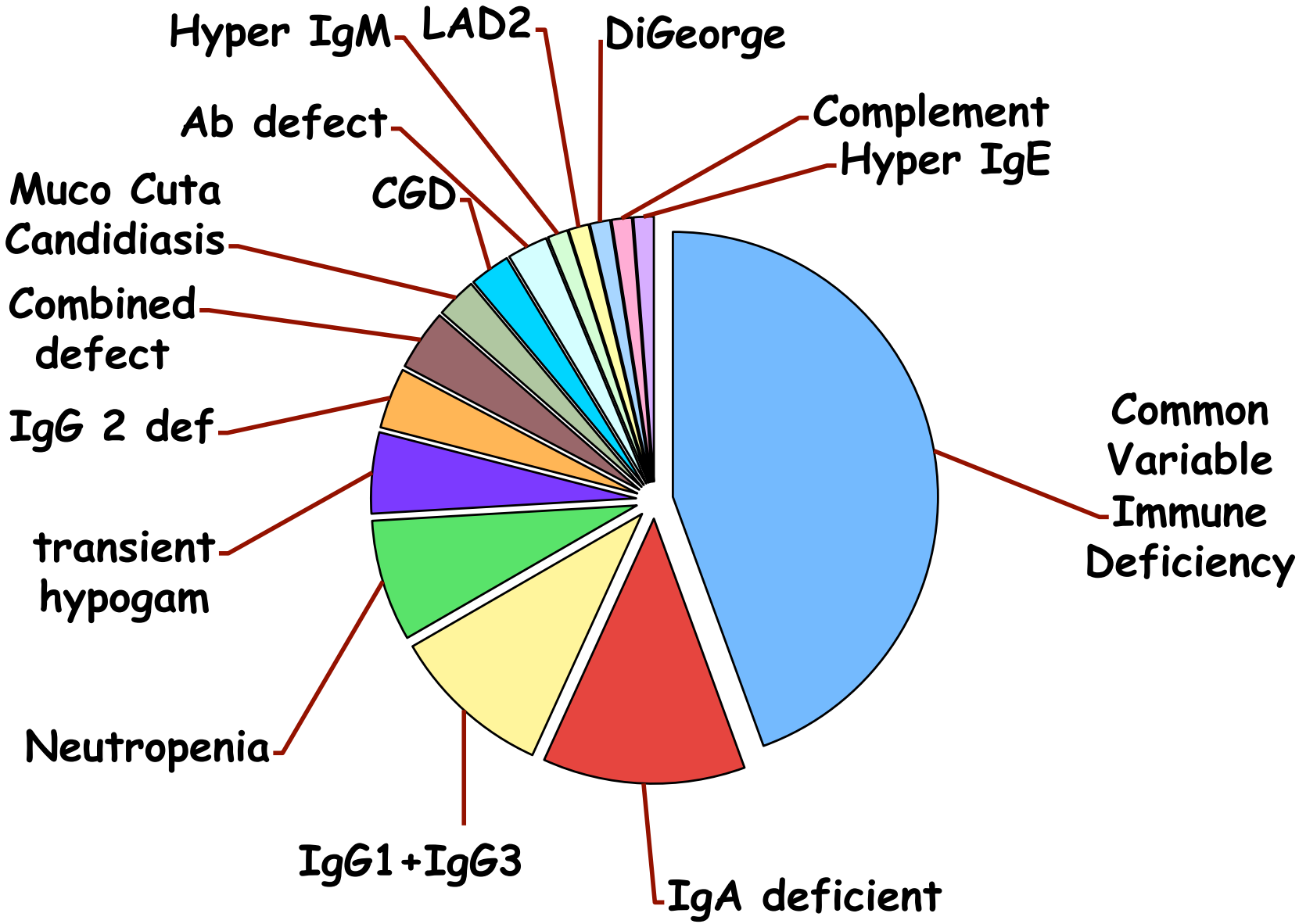
Immune defects: time lines

- Wiskott Aldrich Syndrome, 1937
- Severe combined immune deficiency; "Swiss type" 1950
- X-linked agammaglobulinemia, 1952
- Common variable immune deficiency, 1954
- Kostmann : agranulocytosis, 1956
- Chronic granulomatous disease, 1957
- X linked hyper IgM syndrome, 1961
- DiGeorge syndrome, 1965
- X linked lymphoproliferative disease, 1969
- Adenosine deaminase type SCID, 1972

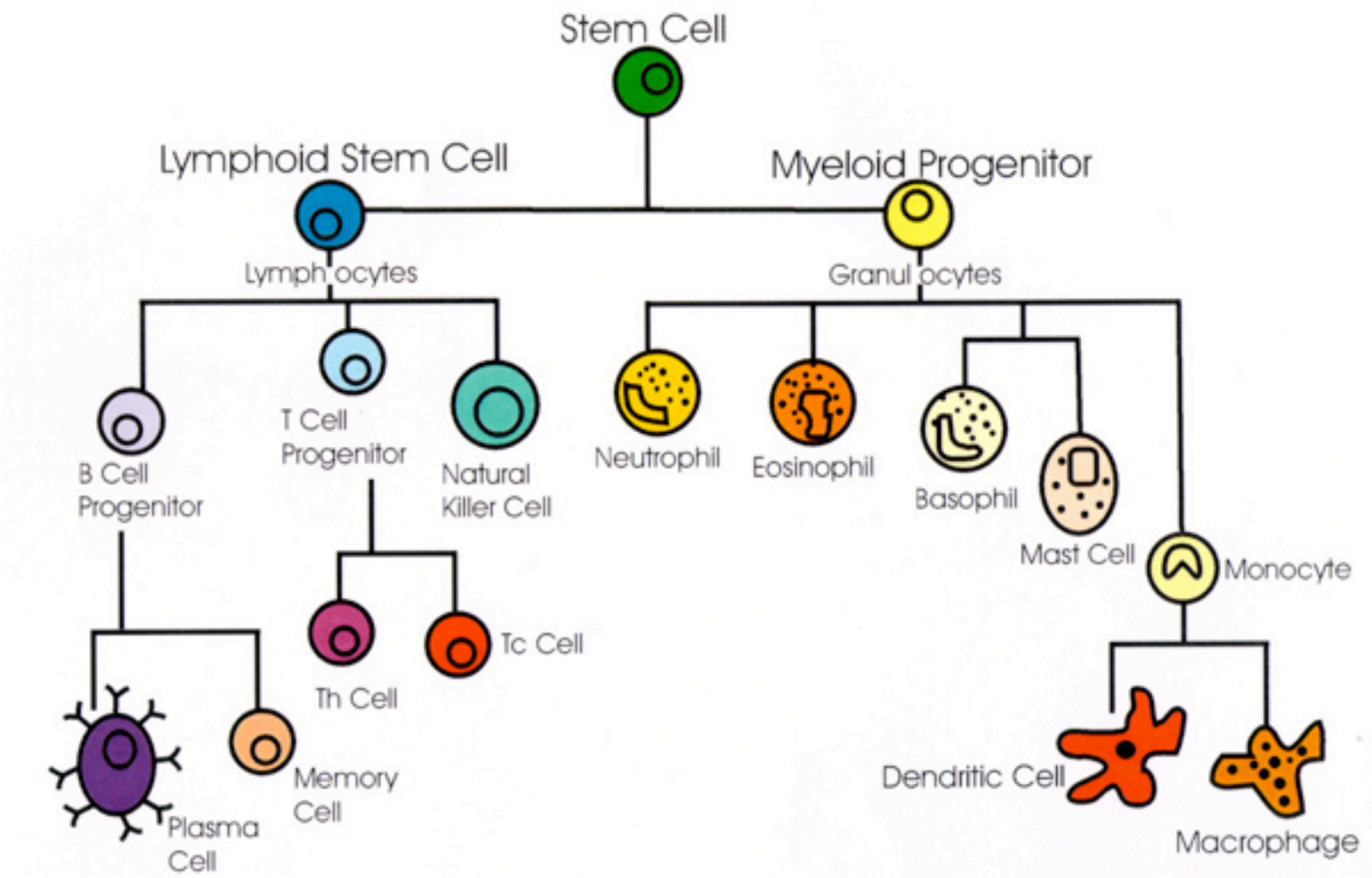
Text Book Incidence of Selected Primary Immunodeficiency States -- about 1:10,000 overall

Disease	Estimated frequencies	Number of Patients in United States
CVID	1:30,000	8666
Di George	1:66,000	3939
SCID (all forms)	1:50,000-1:100,000	3135
XLA	1:103,000	2524
Mucocutaneous Candiasis	1:103,000	2524
CGD	1:181,000	1436
XLP	1:500,000 ?	520
Wiskott Aldrich	1:500,000 ?	520

200 patients with primary immune deficiency



Usual way to define these by an outline of the hematopoietic system



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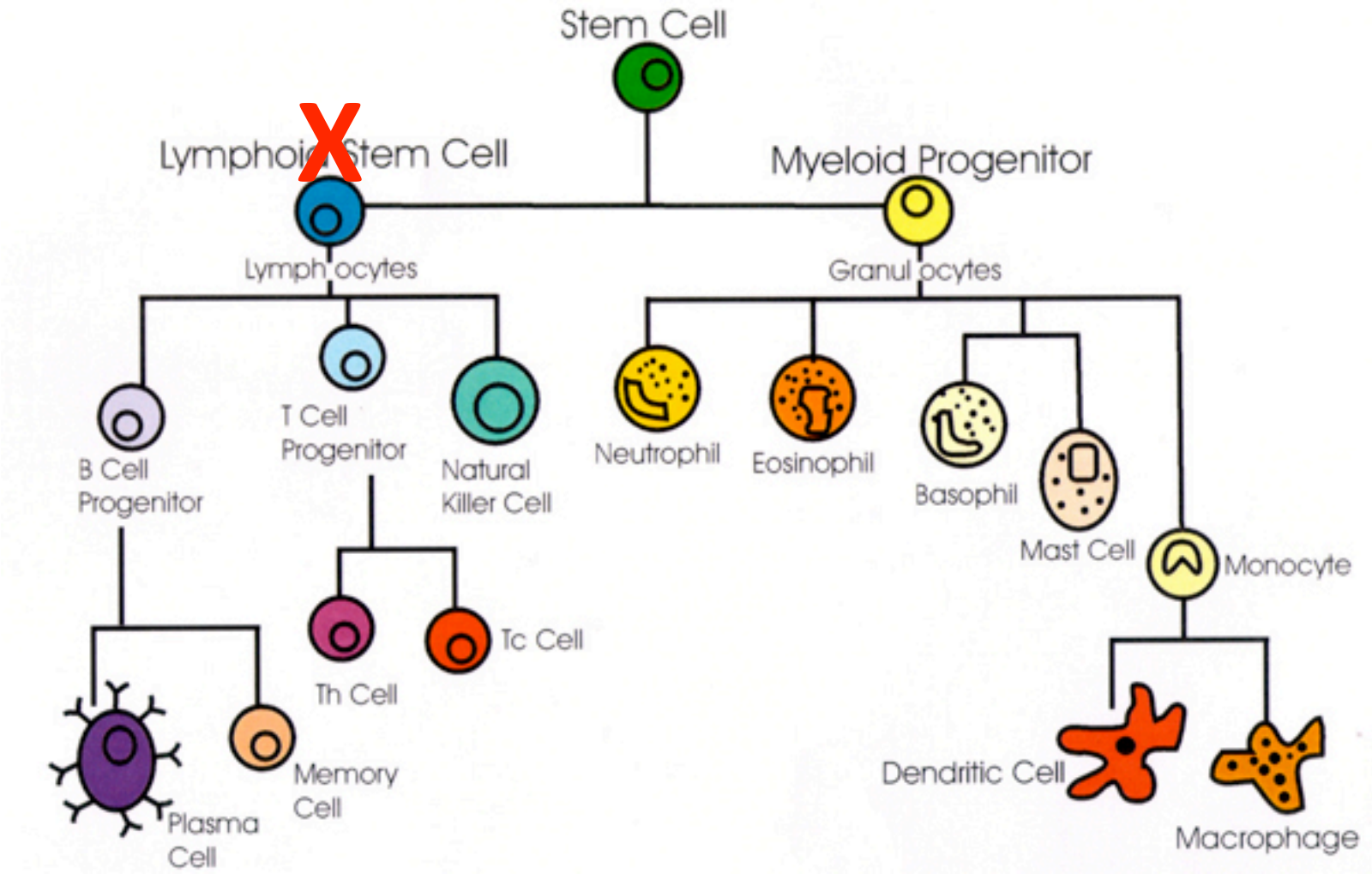
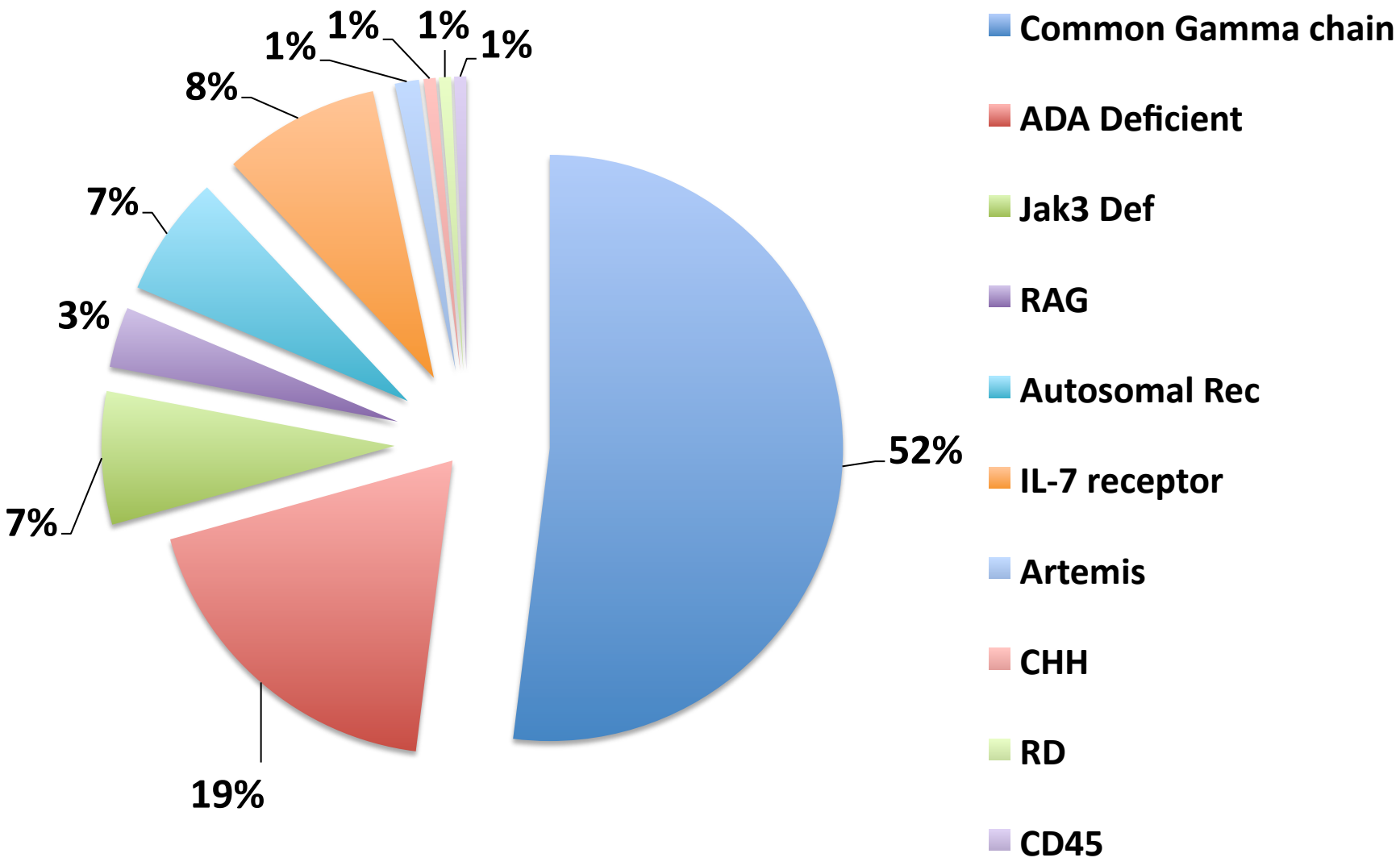
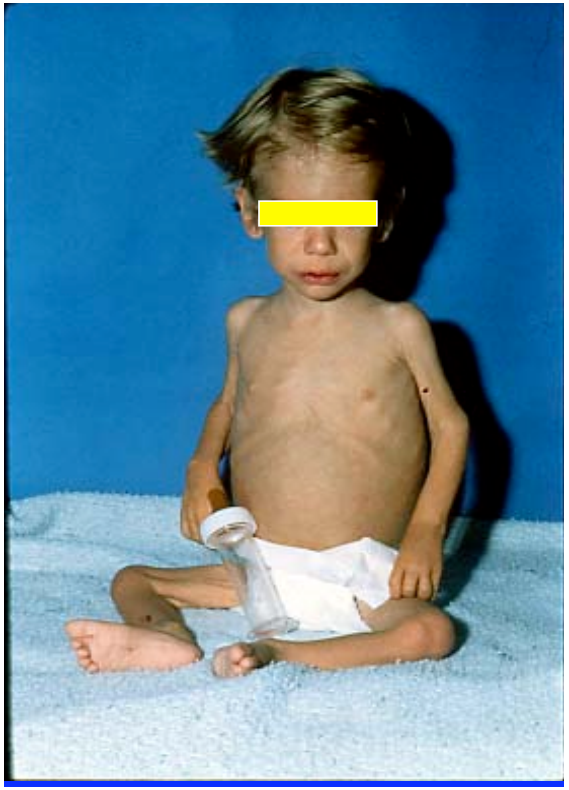
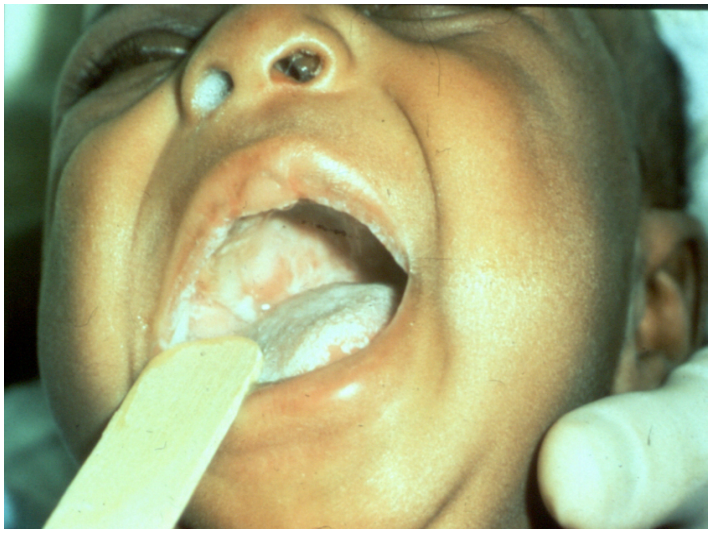
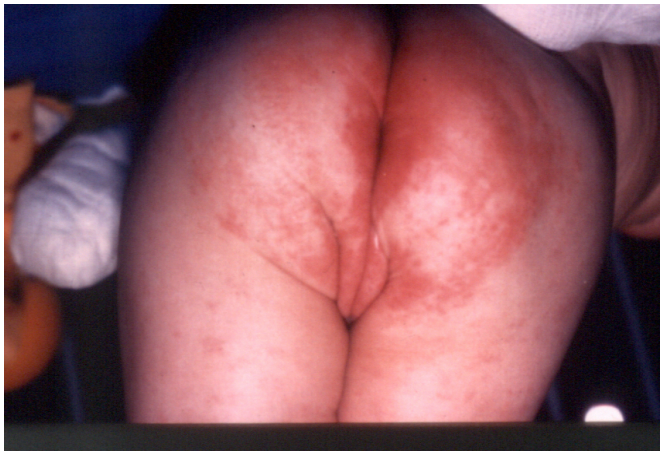


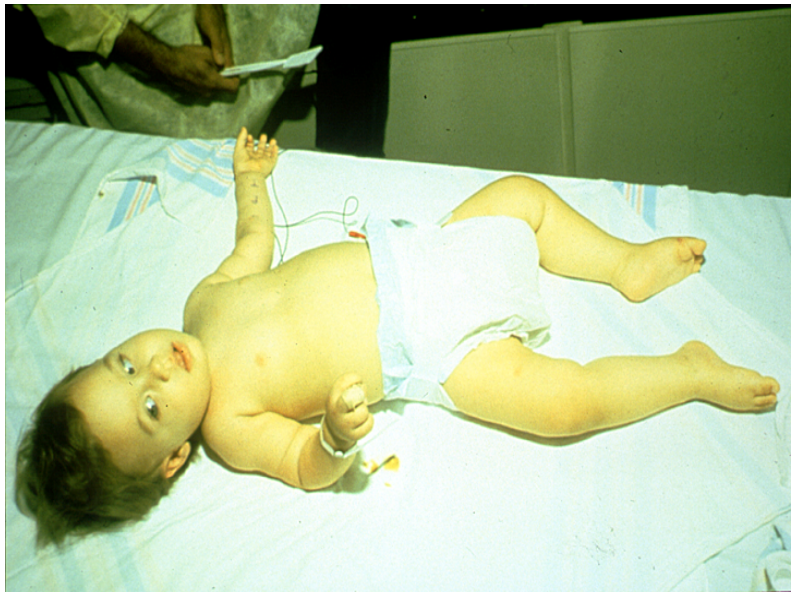
Severe Combined Immune Deficiency (13 genes)





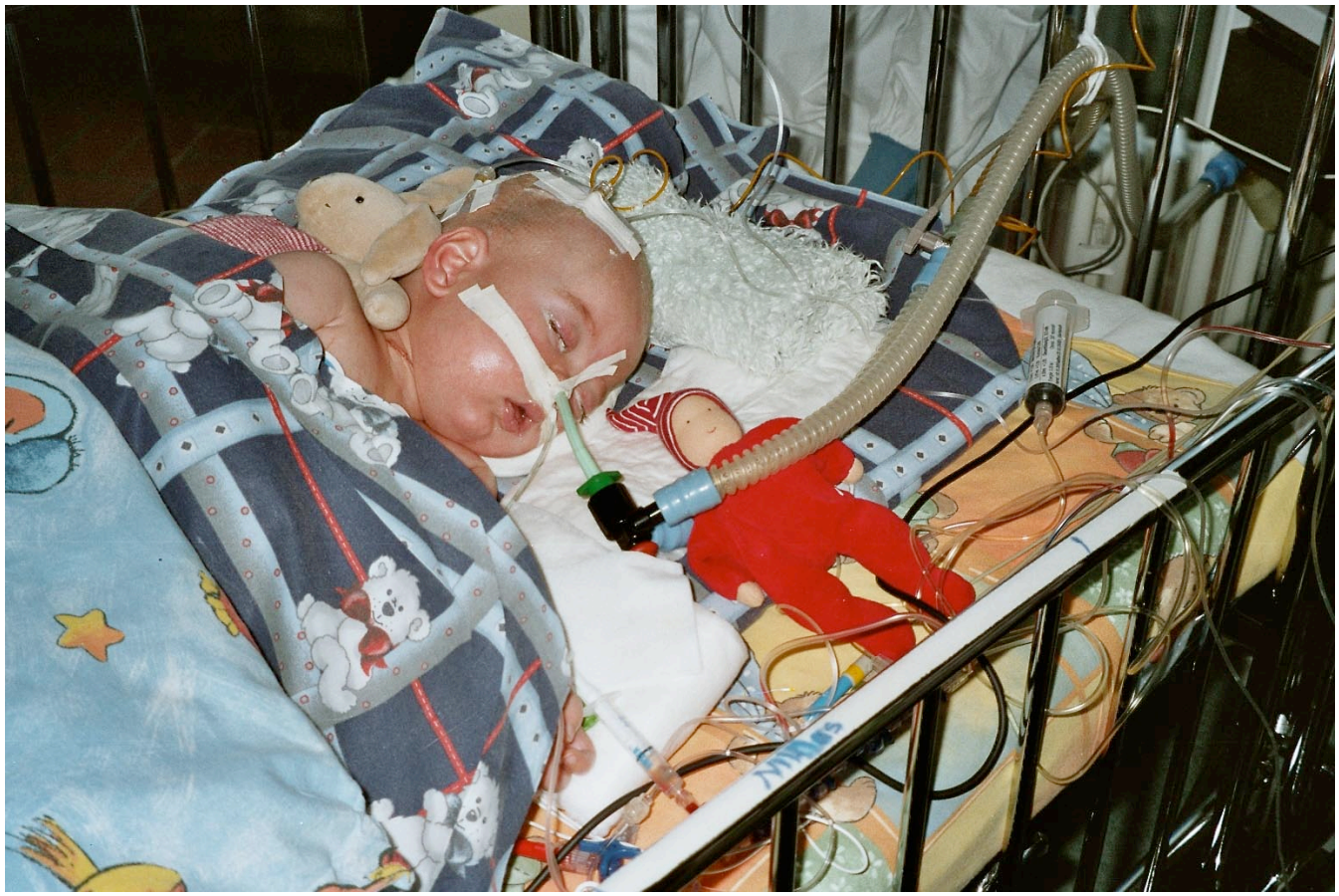






Healthy looking 6 month old, boy swimming at the beach,

PCP pneumonia

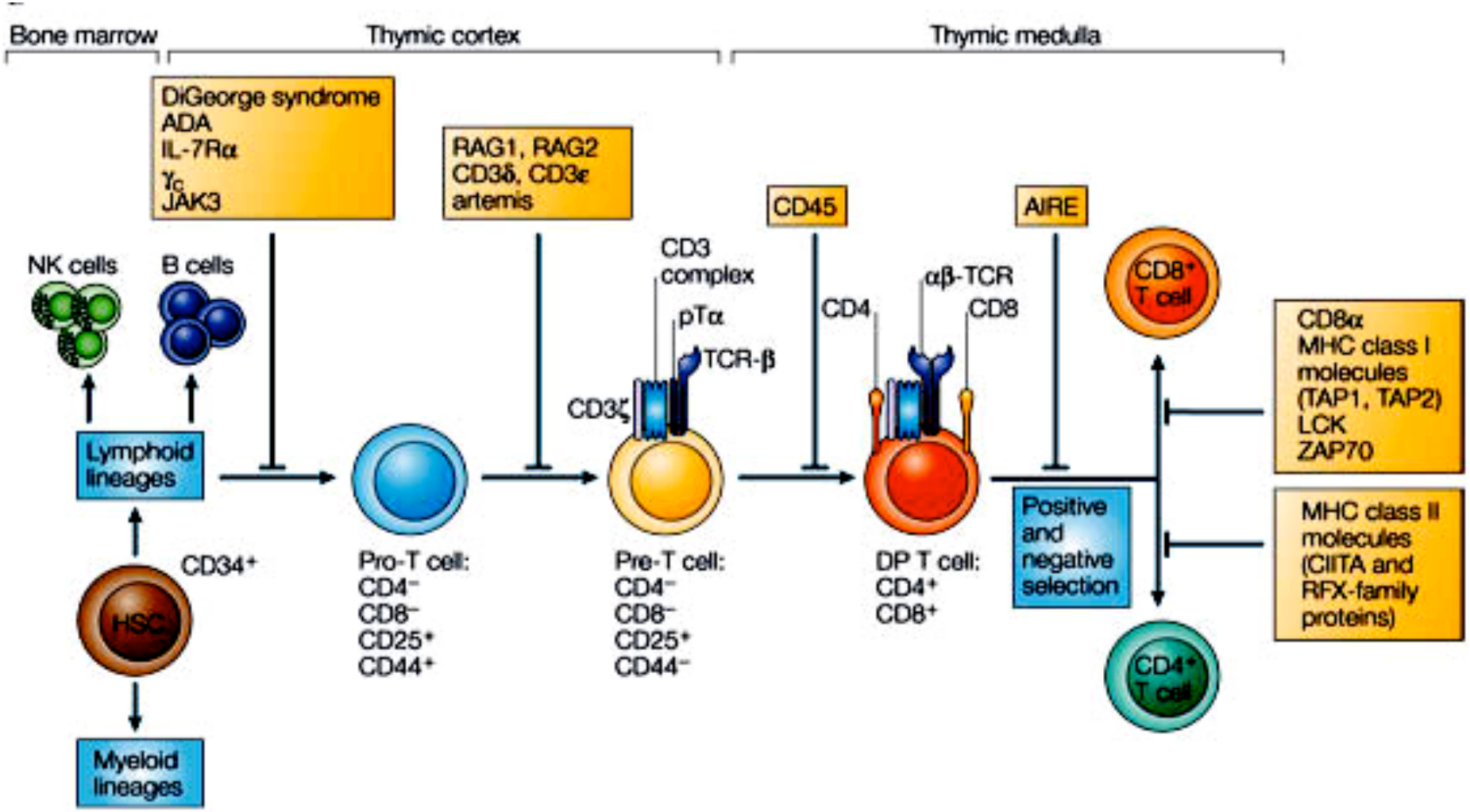


10- 13 stem cell transplantation (CD34+), donor: father without conditioning

11- 11 appearance of T cells (>20%), but HLA = maternal

12- 30 2nd stem cell transplantation, donor: mother without conditioning

T cell defects



Ponda and Cunningham-Rundles Nat Rev Immun 2005

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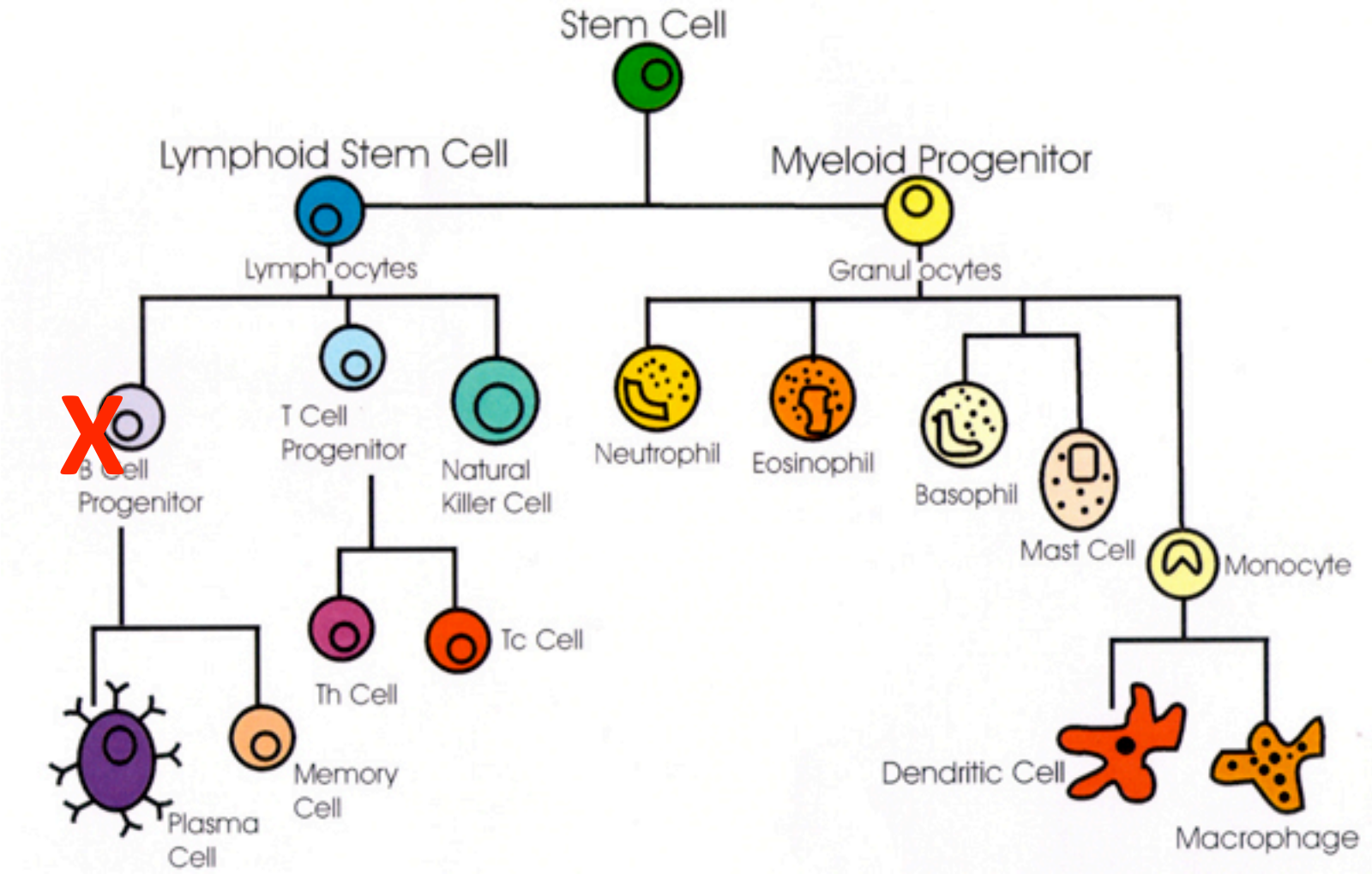
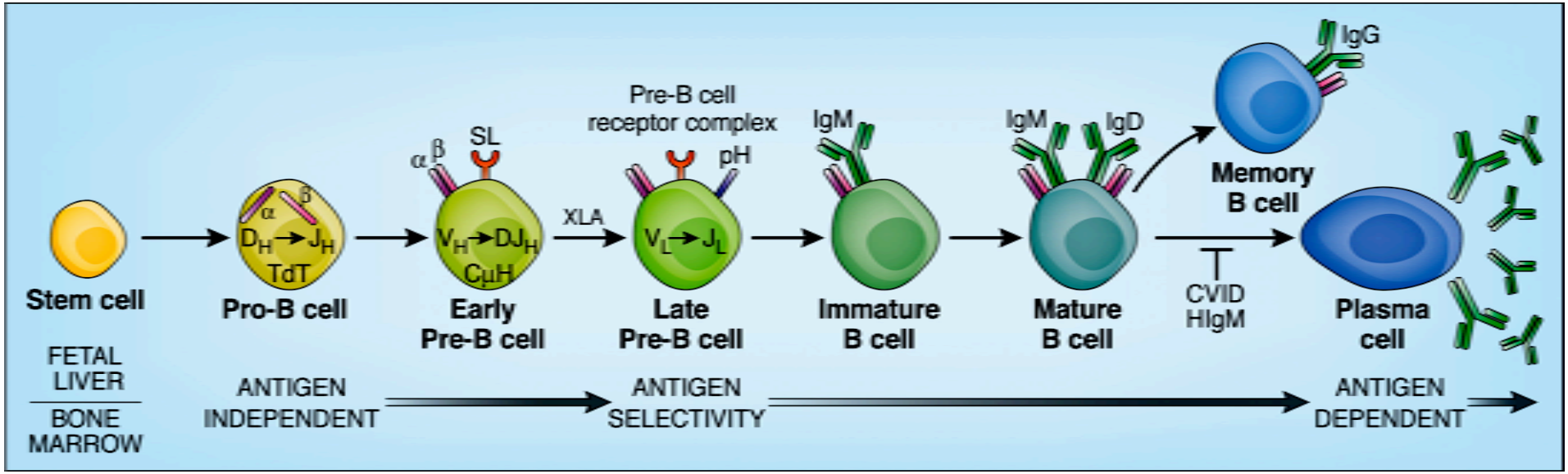


Antibody defects



XLA

Hyper IgM

CVID

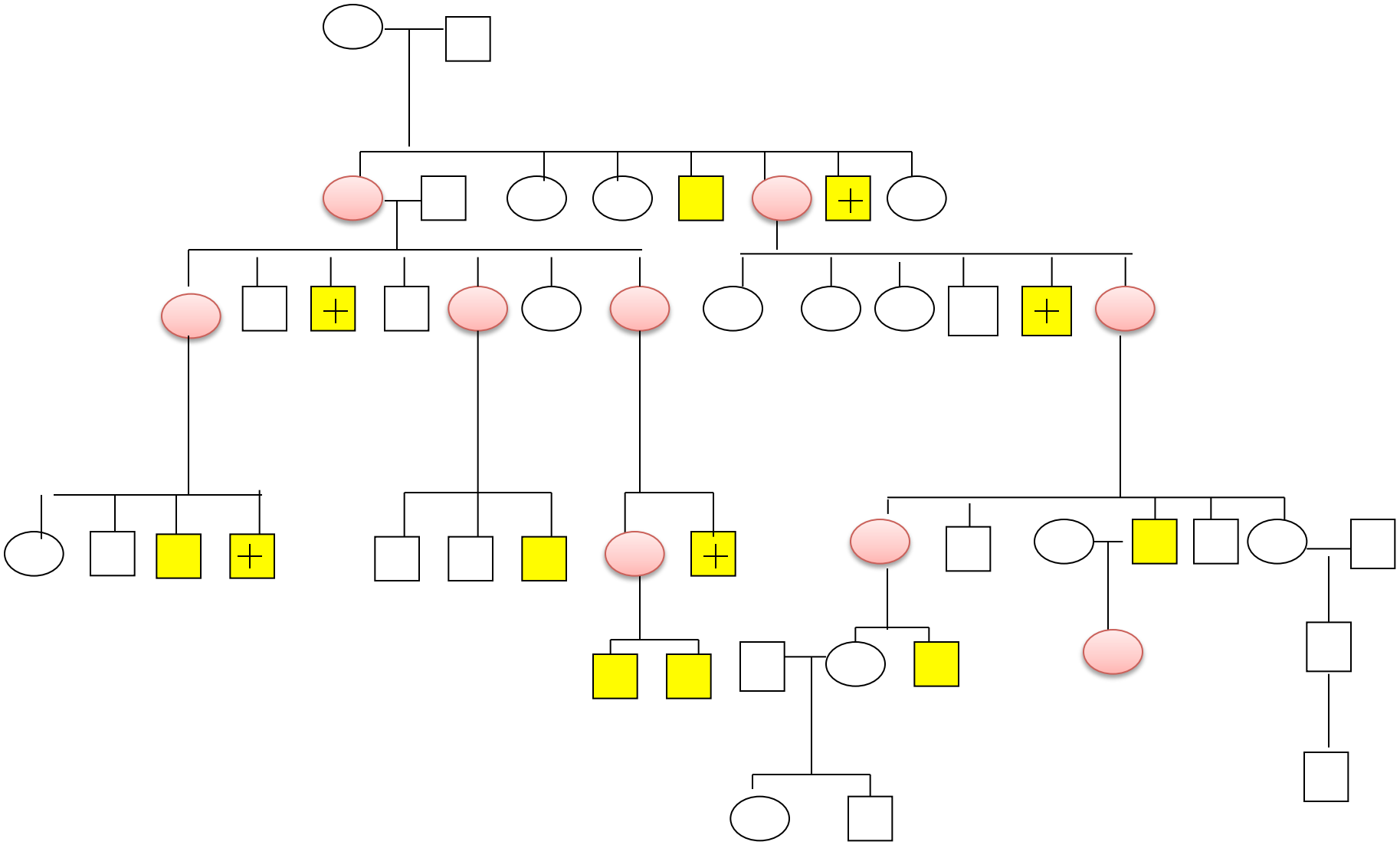
Others!

X linked agammaglobulinemia

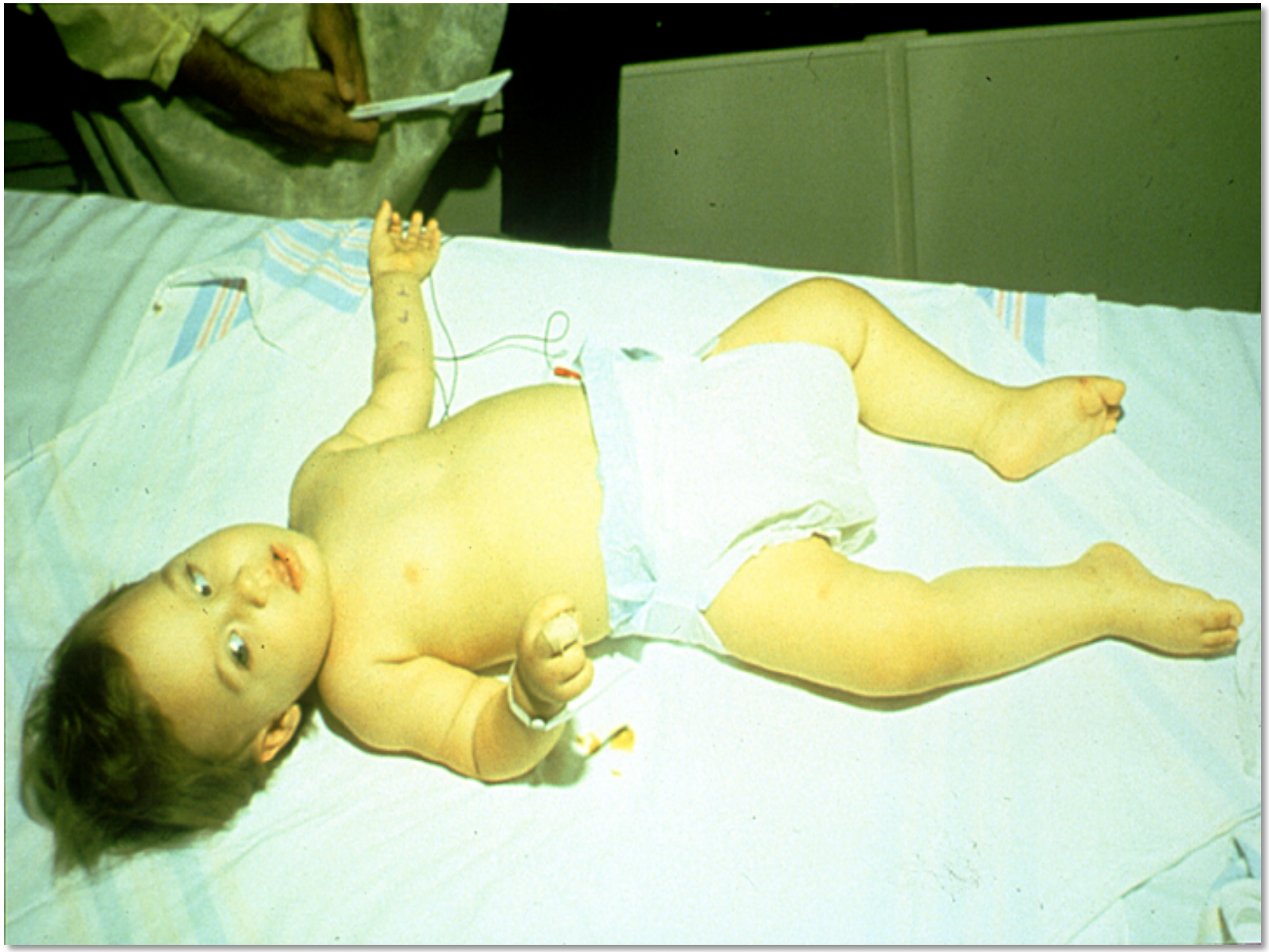
- **Affects males, severe infections usually starting in the first year of life.**
- **Serum IgG, IgA IgM are very low or undetectable.**
- **No antibody production.**
- **Tiny tonsils, lack of normal germinal centers in nodes.**
- **Lymphocyte numbers are normal; few or no B cells.**
- **Chronic sino-pulmonary infections, respiratory failure**
- **Molecular defects of Btk, a B cell cytoplasmic tyrosine kinase, in honor of Dr. Bruton.**

"Agammaglobulinemia," *Pediatrics*, 9, 722-728, 1952

X-Linked Agammaglobulinemia



Polio resulting from live polio vaccine



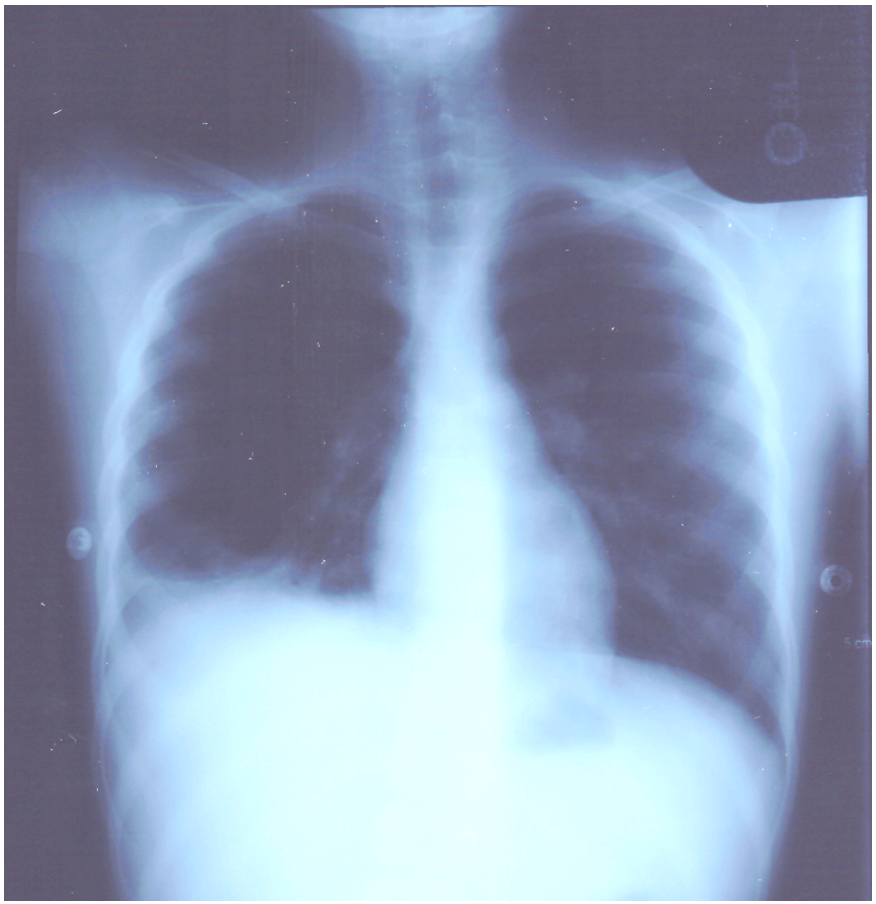
XLA diagnosed in a 10 year old boy with RLL pneumonia

10 year old Mexican American boy admitted to Mount Sinai with cough and RUQ pain.

Past history of conjunctivitis, cellulitis, buttock abscess, frequent URI, otitis media.

No family history of infections or significant illnesses in males.

Mom and sister are carriers



ICD-9 Code	Ab Immune Defects
279.0	Hypogammaglobulinemia
279.01	Selective IgA immunodeficiency
279.02	Selective IgM immunodeficiency
279.03	Selective IgG deficiency
279.04	Congenital agammaglobulinemia
279.05	Immunodeficiency with increased IgM
279.06	Common variable immunodeficiency
279.09	Transient hypogammaglobulinemia

CVID: A Basic Definition

1. Four years of age or older.

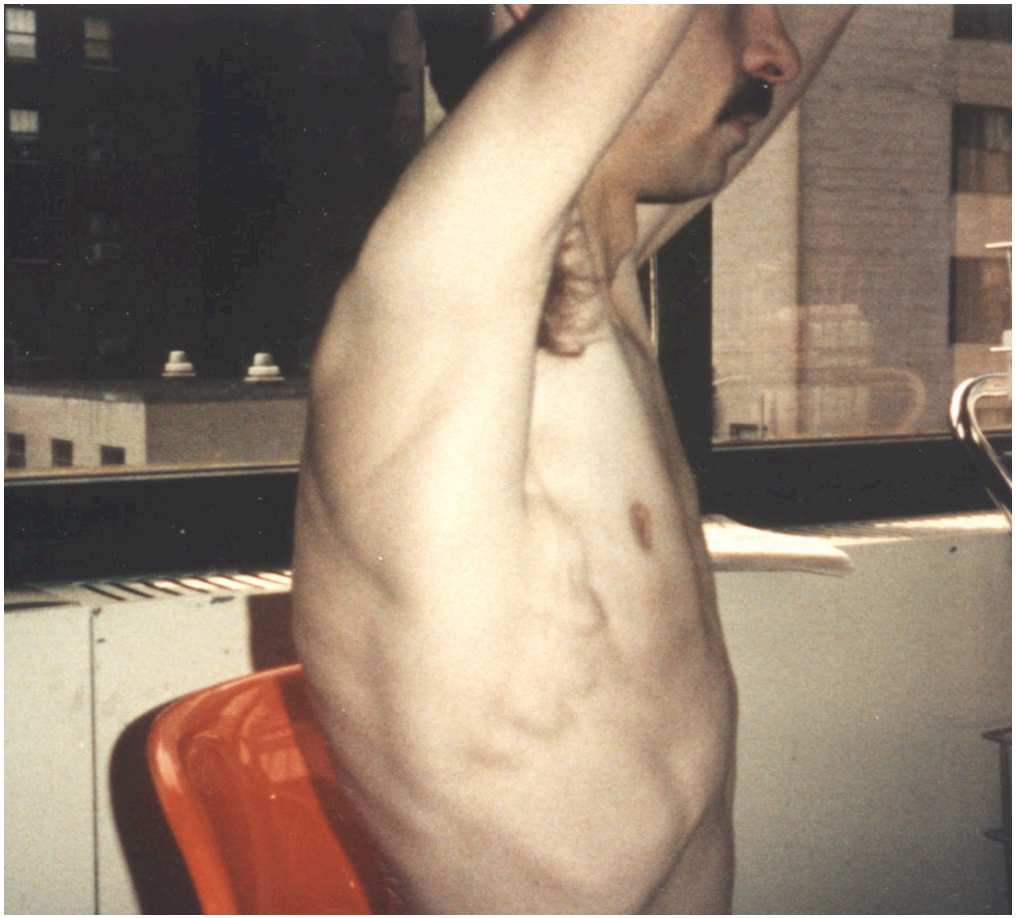
2. Serum IgG levels <4·5 g/l for adults or the 2.5th percentile for age, with levels of serum IgA and/or IgM below the lower limit of normal for age.

3. Lack of antibody responses to protein antigens following immunization or exposure antigens in at least two assays.

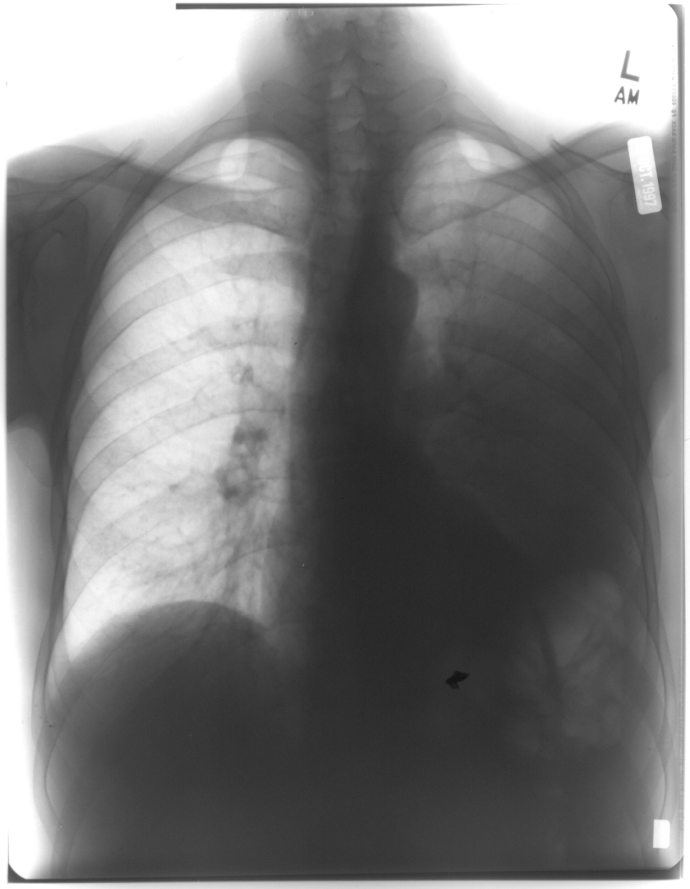
4. Exclusion of all other known causes of failure of immunoglobulin production.

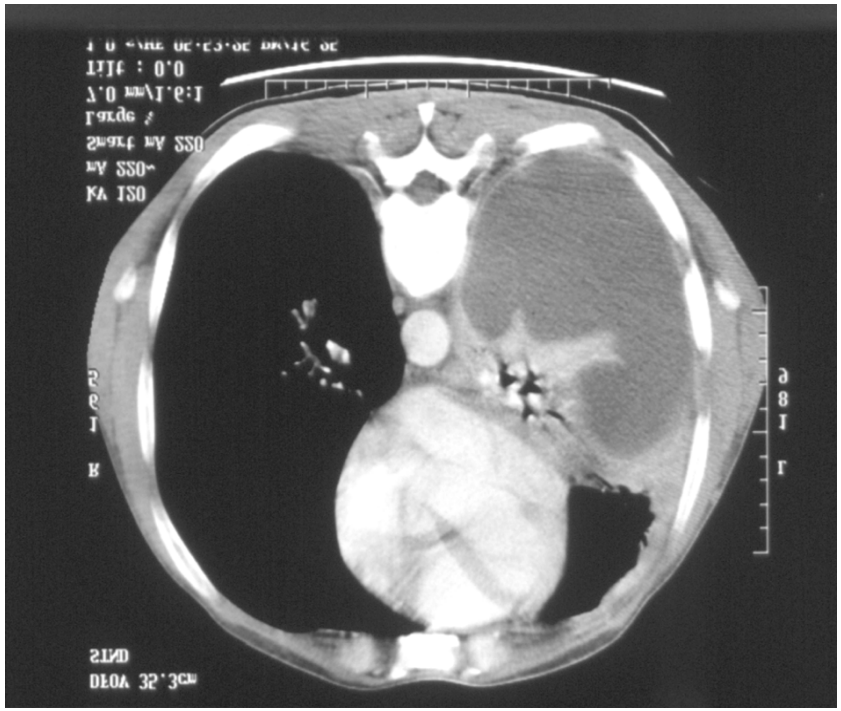
Chapel H, Cunningham-Rundles C. Br J Haematol. 2009.

24 year old man who had a history of lung infections, evaluated for cystic fibrosis on several occasions.
Immune globulins: IgG=30, IgA=3, IgM= 29



Empyema with bacterial pneumonia: usually S. pneumoniae



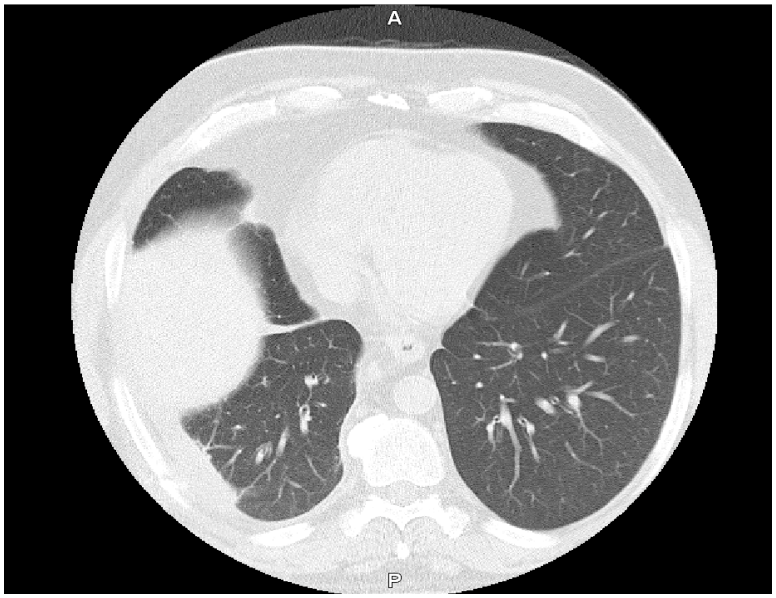


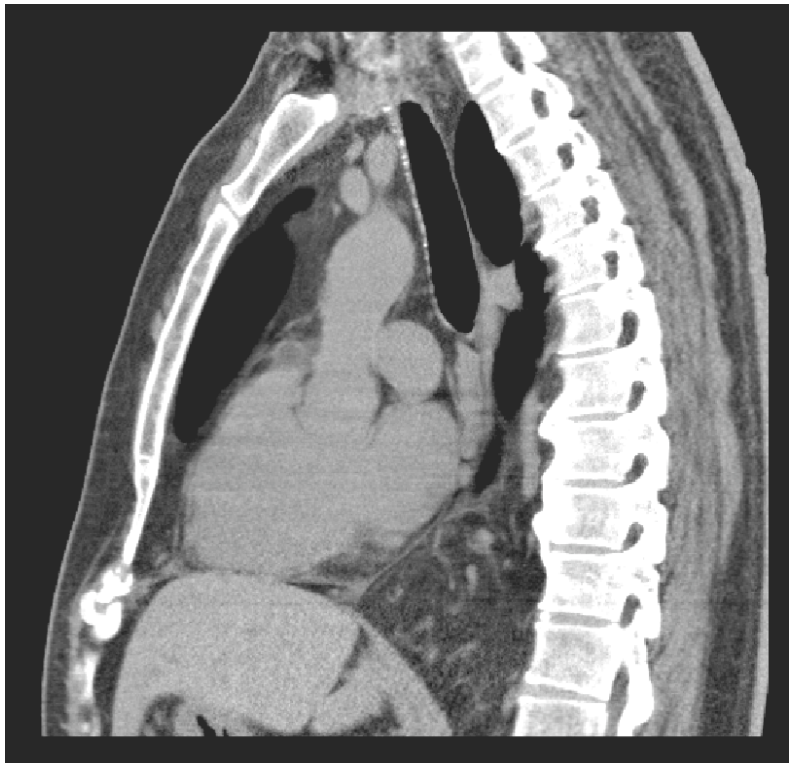
47 year old man with second episode of pneumonia in 2 years; developed empyema. *S pneumonia* was cultured.

Autoimmunity and then a late diagnosis:

46 year old man with autoimmune hemolytic anemia x3
Last episode 2006: clot in aorta; thrombosis to kidney; splenic infarct, Splenectomy
October 2006: pneumonia, collapsed lung, empyema
Streptococcus pneumoniae

IgG=71; IgA=6; IgM=15





Gastrointestinal Infections in Antibody Deficiency

Bacteria:

- Campylobacter
- Salmonella
- Bacterial overgrowth

Parasites:

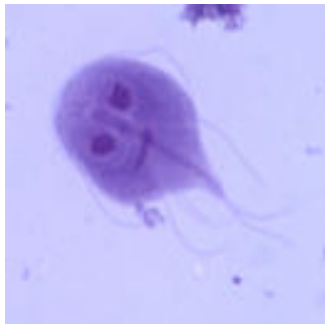
- Giardia
- Cyptosporidia

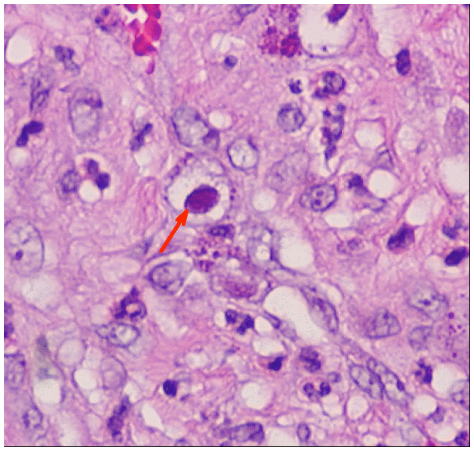
Virus:

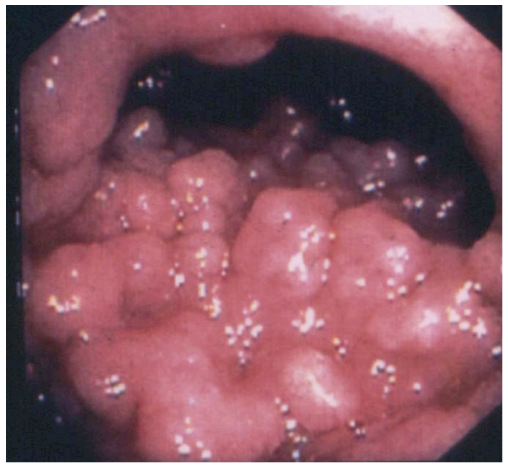
- CMV
- Enteroviruses
- Herpes simplex

Results in:

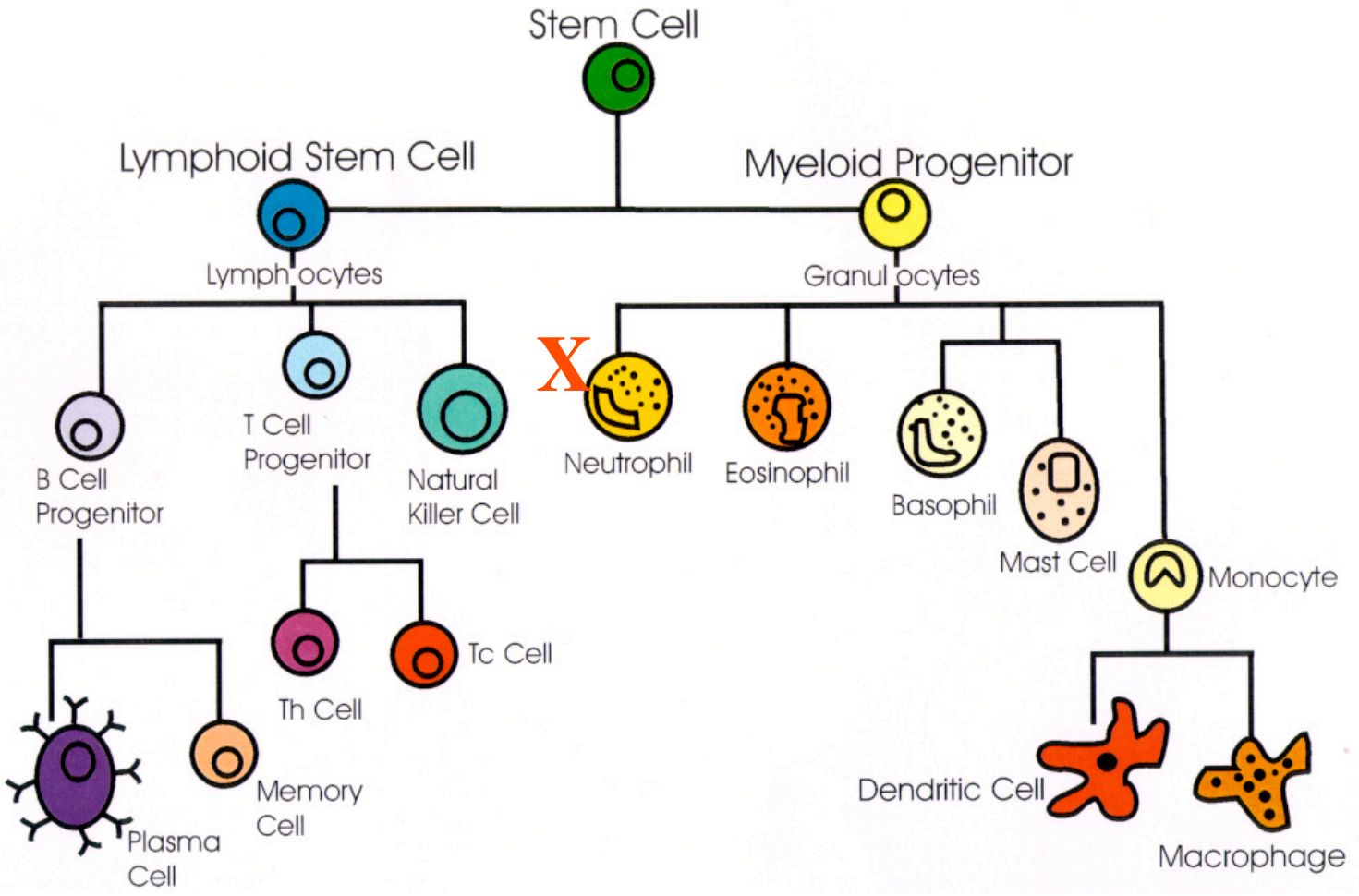
- Chronic diarrhea
- Nodular hyperplasia
- Malabsorption







Cells of the Immune System

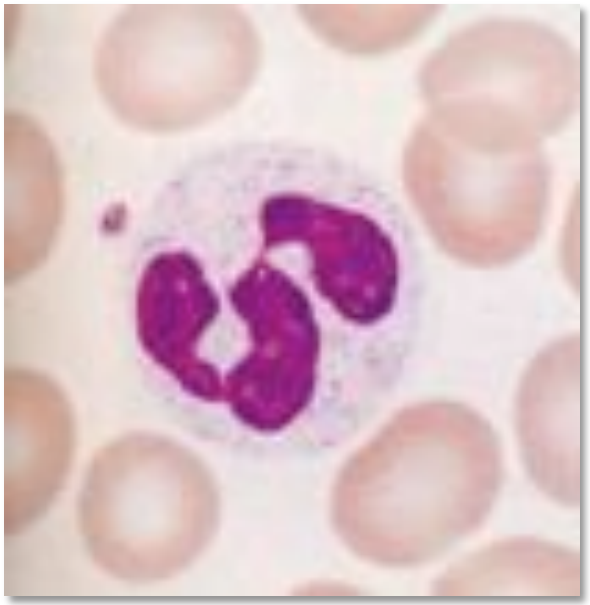


Neutrophils and Disorders

54-75% of the total white blood cell count.

3,000-7,500 neutrophils/mm3 of blood.

Called neutrophils because their granules stain poorly - they have a neutral color - with the mixture of dyes used in staining leukocytes.



- Neutropenia (too few neutrophils)
- Defects in Function:
  1. Adhesion
  2. Locomotion
  3. Killing
  4. Abnormal structure

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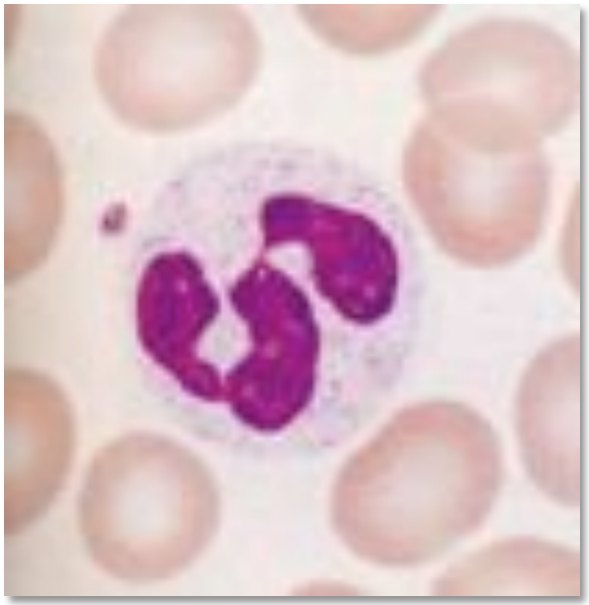

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- Defects in Function:
  1. Adhesion
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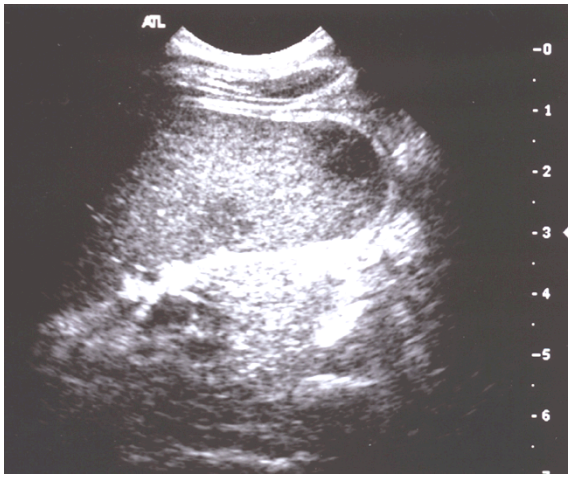
Typical Chronic Granulomatous Disease cases

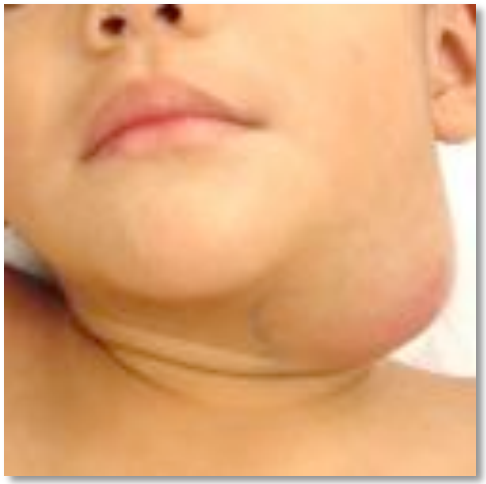
18 month old male with rectal abscess at 2 months

Admitted to hospital, increased abdo size + fever

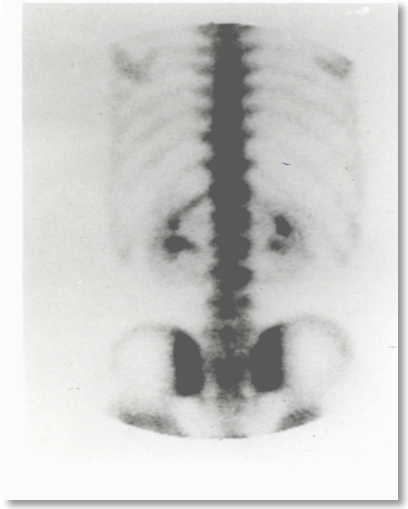
Sonogram - fluid in the abdomen and lesions in spleen



3 year old with enlarged lymph node in the neck



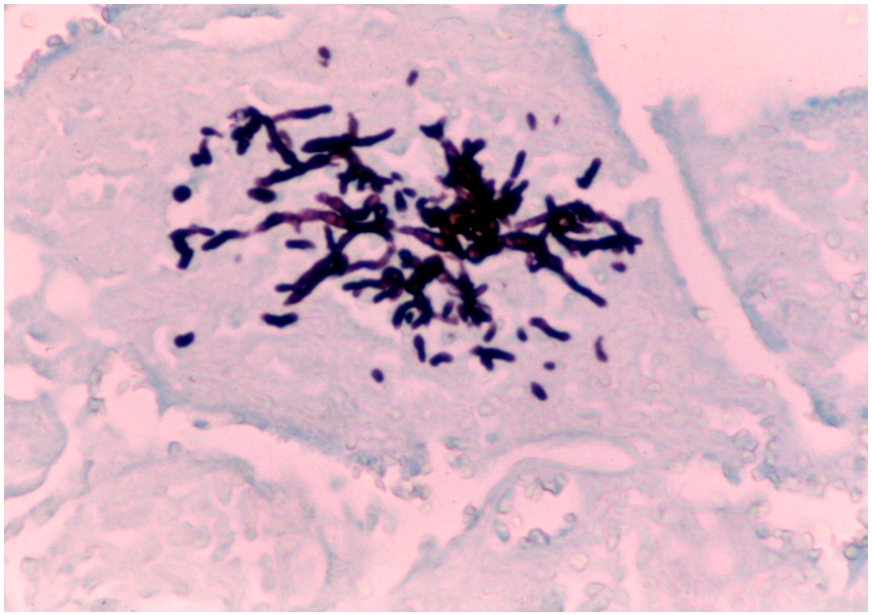
21 year old graduate student with long standing CGD with back pain



Sudden Pulmonary Disease Treated as ABPA

- 25 year old medical student was exposed to compost while gardening.
- She developed fever, cough and pulmonary infiltrates. No bacteria were isolated; antibodies to aspergillous (IgG and IgE) were found and she was given oral corticosteroids.
- As a child, she had recurrent skin infections and elevated IgE; the diagnosis of Hyper IgE syndrome was considered and she was given prophylactic dicloxacillin: stopped in high school.
- One month after exposure, she had not improved, and a lung biopsy was suggested, but she refused. The dose of corticosteroids was increased.
- Two months later, a lung biopsy was done. showed hyphae and necrotizing granulomata; amphotericin was started but she died of respiratory failure two days later.

Lung biopsy: necrotizing granuloma with hyphae and other fungal elements, *Aspergillous niger* . Amphotericin was started but she died of respiratory failure two days later.



frontiers in
IMMUNOLOGY

CLASSIFICATION ARTICLE
published: 08 November 2011
doi: 10.3389/fimmu.2011.00054

Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency

1. Combined defects severe and otherwise
2. Well-defined Defects
3. Antibody defects
4. Immune Dysregulation
5. Phagocyte defects
6. Defects of Innate Immunity
7. Auto inflammatory defects
8. Complement

- But the syndromes overlap too much to segregate neatly
- Lymphocytes/granulocytes are not the only players
- Predicting defects based on phenotypes is becoming outmoded
- New themes:
  - Using selected infections to dissect immunity
  - Using whole genome sequencing to investigate syndromes

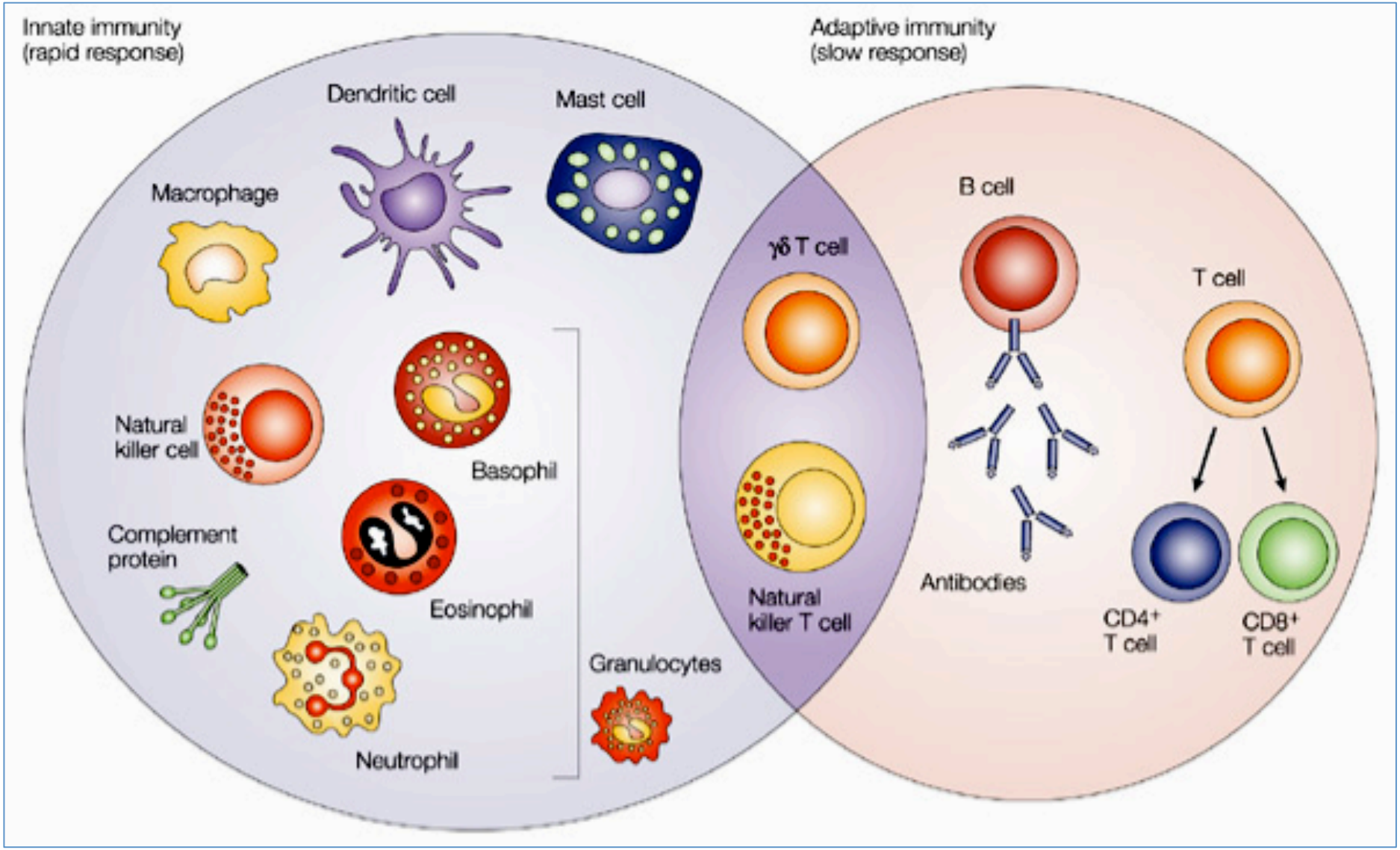
1. Combined defects
   - Severe combined immune deficiencies (13)
   - DNA damage syndromes
   - CD3 defects
   - CD8 defect
   - ZAP-70
   - Calcium channel defects
   - MCH 1 and II defects
   - Cartilage hair hyperplasia
   - IKAROS
   - ITK
   - STAT-5b
   - MAGT-1
2. Well-defined Defects:
   - Wiskott Aldrich
   - Ataxia Telangiectasia
   - Other breakage syndromes
   - ICF syndrome
   - PMS2 class switch
   - Hyper IgE ; Stat3
   - TYK -2
   - DOCK8
   - DiGeorge syndrome
   - Dykaratosus congenita
3. Antibody defects
   - BTK
   - B cell receptor defects
   - BLNK
   - Thymoma
   - CVID
   - ICOS
   - CD19, 20, 21, 27, CD81,
   - TACI
   - BAFFr
   - CD40 and CD40-L
   - AID
   - UNG
   - IgG and subclass
   - IgA
   - Specific antibody defects
   - Transient hypogammaglobulinemia
4. Immune Dysregulation
   - Hypopigmention defects
   - Familial hemophagcytosis
   - Lymphoproliferation
   - Syndromes with autoimmunity

5. Phagocyte defects
   - Differentiation
   - Motility
   - Respiratory burst
   - Mycobacterial/Salmonella
   - Other
     - IRF-8
     - GATA2

6. Defects of Innate Immunity
   - NEMO
   - IRAK4
   - MyD88
   - WHIM
   - Epidermal dysplasia verucciformis
   - Herpes simplex encephalitis
     - TLR3
     - UNC93B
     - TRAF3
   - Chronic mucocutaneous candidiasis
     - Dectin 1
     - CARD9
     - Stat-1

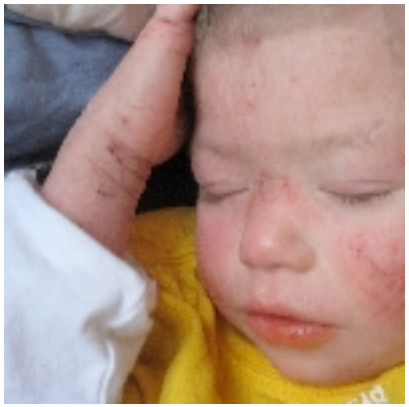
7. Auto inflammatory defects
   - Defects of the inflamasome
     - FMF
     - Hyper IgD
     - Muckel Wells
     - Cold inflammatory syndromes
     - NOMID
   - Non inflamasome
   - TNF receptor syndrome
   - IL-10/ IL-10r
   - Blau
   - Recurrent osteomyelitis
   - DIRA

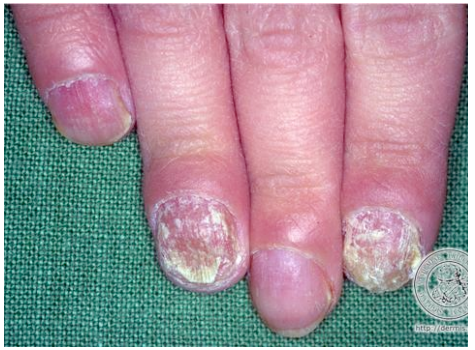
8. Complement
   - Classical
   - Alternative
   - Regulatory

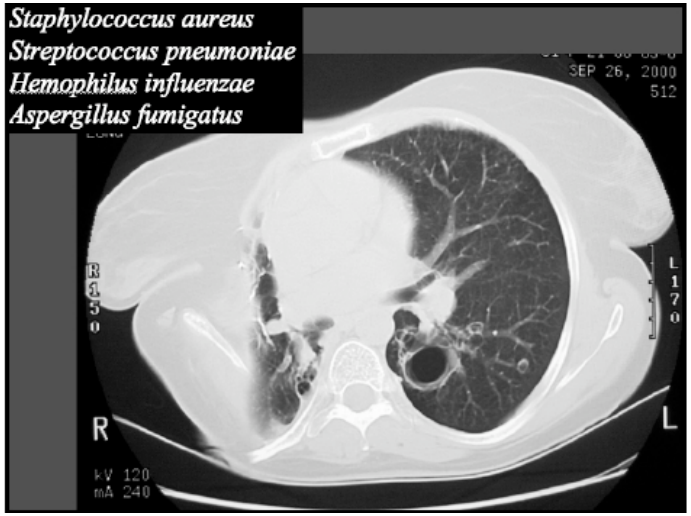

Innate immunity
(rapid response)
Adaptive immunity
(slow response)
Dendritic cell
Mast cell
Macrophage
γδ T cell
B cell
T cell
Natural
killer cell
Basophil
Complement
protein
Eosinophil
Natural
killer T cell
Antibodies
CD4+
T cell
CD8+
T cell
Granulocytes
Neutrophil

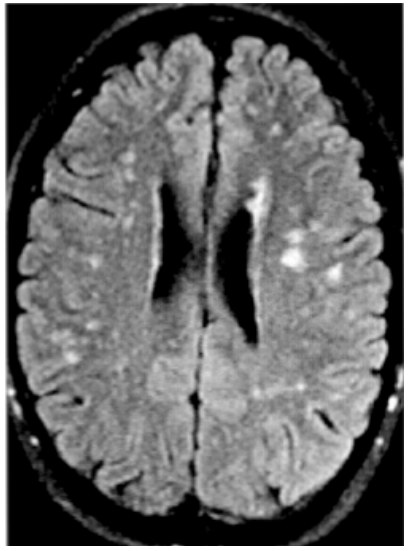
Job's syndrome (hyper IgE)

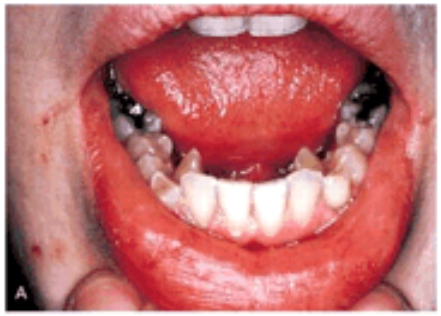
Eczema	100%
Characteristic facies (>16y)	100%
Skin boils	87%
Pneumonias	87%
Lung cysts	77%
Mucocutaneous candidiasis	83%
Scoliosis (>16y)	76%
Delayed dental deciduation	72%
Brain T2 hyperintensities	70%
Coronary artery aneurysms	65%
Pathologic fractures	57%
Chiari I malformation	18%





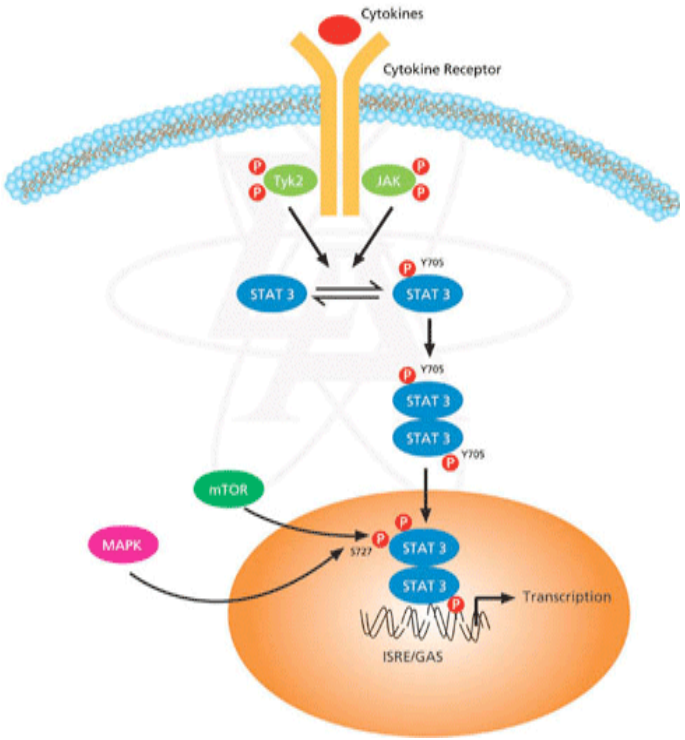


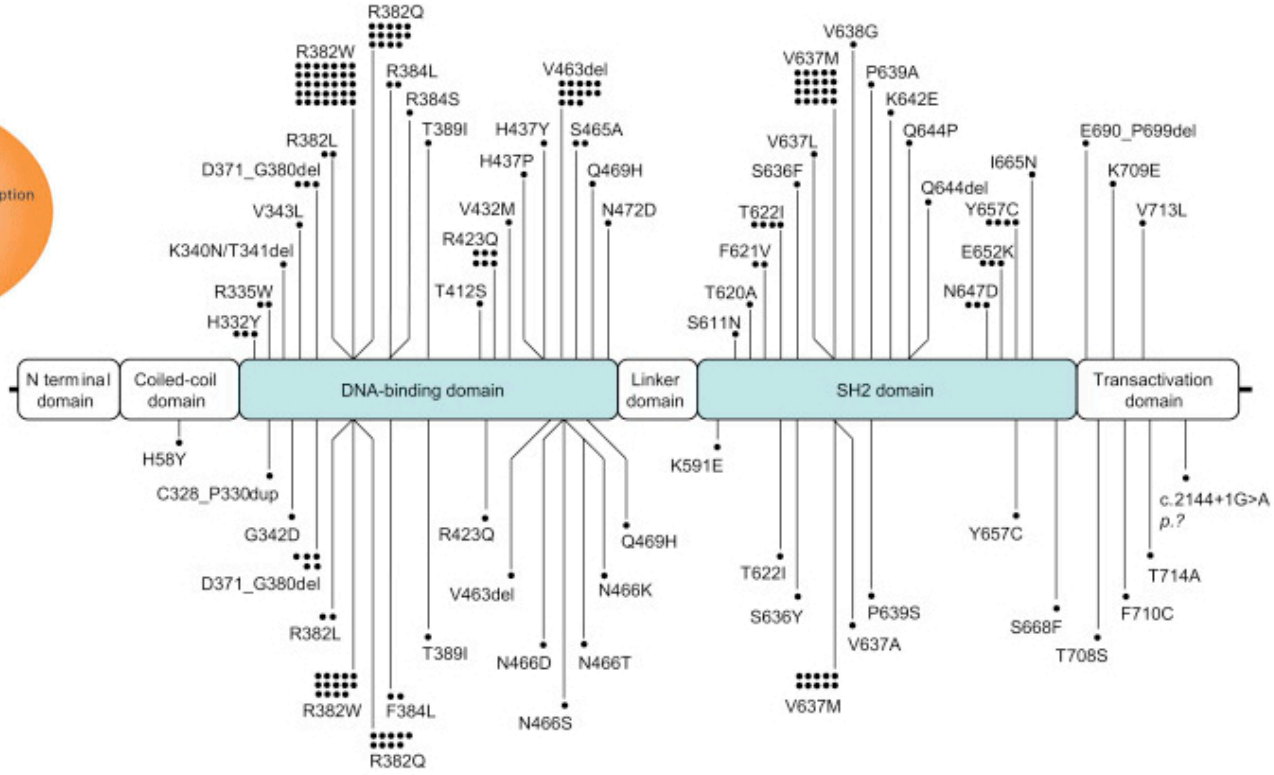




Clearly many organ systems are involved

Stat 3 signaling and mutations





Using Infections to guide studies:

Defects of Innate Immunity

Type	Genes
Invasive pneumococcal disease	IRAK4 MyD88 others
Warts:	WHIM Epidermal veruciformis
Herpes simplex encephalitis	TLR3 UNC93B TRAF3
Candidiasis	Stat-3 Dectin 1 CARD9 Stat-1
Mycobacterial disease	IL-12 IL-23 INF-g receptor STAT1 Macrophage gp91 IRF8

Newer methods

- Targeting genes that seem likely
- Family studies; especially consanguineous large families with multiple affected family members
- Whole genome sequencing

Conclusions