INTRODUCTION TO MEDICAL

# IMMUNOLOGY

SLIDE SHEET

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|---|---|
| NUMBER | 3 (Lec #25) |
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*Salam everyone ♥, we finally reached the last sheet in ID material, it was my pleasure to have you studying these sheets, and I always pray they would benefit you in the future. May your day be blessed with Allah's guidance, and always remember that there's no greater virtue than the virtue of giving ♥*

In the previous Lecture we started talking about Primary immunodeficiency (refer to Page5; sheet2), and probably the most important thing you're required to know is "How to suspect existence of underlying immunodeficiency in a certain patient?" and "How to efficiently build your suspicion of an underlying ID upon the patient's signs and symptoms?"

In order to do that, you'll have to be a skilled clinician, who can **spot special signs of immunodeficiency** (e.g. opportunistic infections; increased severity of infections by common pathogens; increased frequency of infections; positive family history in case of PID, You can refer to page 6 in sheet 2 and page 3 in sheet 1 to remember).

We have +200 Primary immunodeficiency disorders, we took some as cases before Midterm: **Chronic granulomatous disease** (Defected NADPH oxidase in phagocytes), **Hereditary Angioedema** (C1INH deficiency; C1INH acts to inhibit assembly of C1qr2s2 in classical complement pathway), **Activation-induced Cytidine deaminase deficiency** (AID enzyme deficient in B cells and so class switching is impaired resulting in a form of Hyper IgM syndrome), **Severe combined immune deficiency** (multiple genetic deficiencies), DiGeorge syndrome (Hypoplasia in thymus gland so T cells are affected, with other congenital anomalies; CATCH 22).

## Primary Immunodeficiency Disorders :Selected Examples

We'll discuss selected examples of PID disorders, highlighting the main required things:

1. Names of PID disorders

2. Which component of immune system is deficient (innate component, humoral immunity, cellular immunity)?

3. Underlying genetic cause

4. What kind of infections (and opportunistic pathogens) will take place?

** A table will be at the end will be summarizing all of them.

## 1. Defects of the B-Cell System

### A. X-Linked Bruton's Agammaglobulinemia (XLA)

Bruton's agammaglobulinemia was first described in 1952; it was named after the pediatrician who described it (Dr.Ogden Carr Bruton). It is an X chromosome-linked, **so it affects males almost exclusively (male predominance)**, yet, the chance of females being affected is linked to carrier state of their mother **plus** father being affected. Patients with XLA **lack circulating mature B cells (CD19+),** and exhibit a deficiency of immunoglobulins of all classes (Humoral immunity affected).

Remember: When we talked about severity of PID disorder (page 12; sheet 2), we said that if the defect was in early stages of lymphocyte development, it would be more severe (because many cells and cellular components will be defected) than if it was in late stages or after the cell is fully mature, so we should guess that XLA is of the low-severity disorders.

XLA is caused by arrested differentiation at the pre-B cell stage, which will lead to a complete absence of CD19+ B cells and plasma cells. The underlying genetic mechanism is a deficiency of an enzyme called the Bruton tyrosine kinase (Btk) in B-cell progenitor cells. Lack of the enzyme apparently causes a failure of VH (variable domain of the heavy chain) gene rearrangement.

The patients also lack the plasma cells in their lymphoid tissues, but they do have pre-B cells in their bone marrow (level of affected B cells is in-between pre B cells and plasma cells). Because of the lack of B cells, the tonsils and adenoids are small or entirely absent (because most of the bulk of tonsils and lymph nodes is made up of B-lymphocytes), and lymph nodes lack normal germinal centers (where mature B cells proliferate, and differentiate through somatic hypermutation and class switching during a normal immune response to an infection).

T cells are normal in number and function.

FOR YOUR INFO: XLA is a complete absence of Abs while Hypogammaglobulinemia (discussed later in this sheet; common variable ID) is another PID disorder referring to not having enough Abs (Abs number is lower than normal range).

**General Q: How do we normally decide normal ranges of molecules in human body? By biologic variation.**

**E.g. we'd like to measure normal levels of K+ in our body (which is 3.5 – 5), we take 100 apparently healthy individuals, we take the results and place them on normal distribution curve, then we exclude the extremes on both sides (2.5% of the area under the curve on both sides), the remaining 95% area is where normal range lies). Same applies to how we get normal Igs range.**

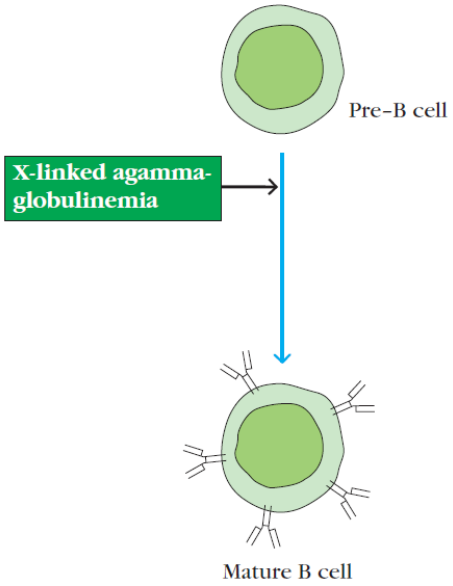



**Figure 1: inhibition of B cell maturation**

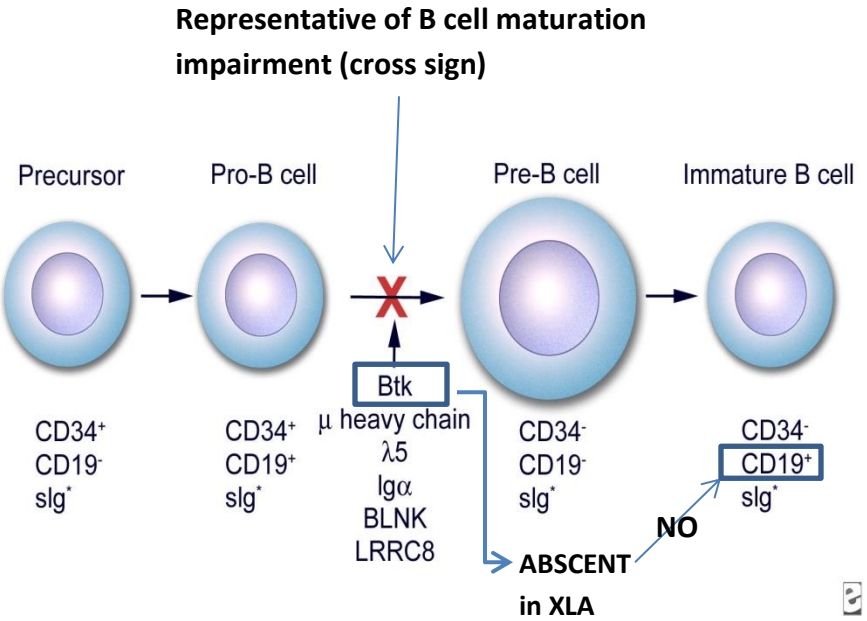



**Figure 2: Normal Job of BTK in B cell maturation**

Since humoral immunity defends at its best level against encapsulated bacterial pathogens that mostly attack sinuses and pulmonary part of respiratory tract, **Patients most commonly develop sino-pulmonary infections caused by encapsulated organisms** such as *Streptococci, meningococci (Nisseria meningitidis),* and *Haemophilus influenzae*. Other infections seen include bacterial otitis media, bronchitis, pneumonia and meningitis.

**Please note for the sake of exam:** You'll have to link disorders with their clinical manifestations and infections that accompany the disorder since exam Qs will be indirect.

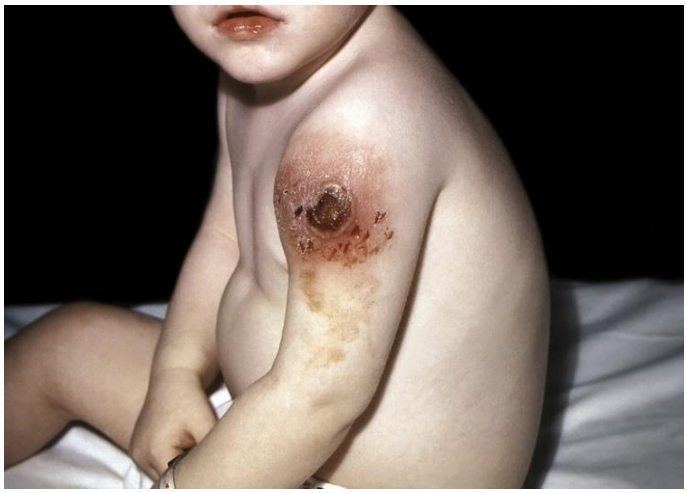
E.g. a 2 year old child came to you WITH RECCURENT SINUSITIS by *Nisseria meningitides* (or mostly it'll be *Strep.pneumonia*), what's the most likely underlying cause of this immunodefiency? **Humoral component deficiency**.

How are these patients managed?? The use of antibiotics and replacement therapy by IVIG (Intravenous immunoglobulin) can make X-linked agammaglobulinemia a quite manageable disorder.

* The following part on PG is not part of the exam **(OPTIONAL):**

The picture here shows a complication of XLA, called **Pyoderma gangrenosum (PG)**. PG is an uncommon, ulcerating, neutrophilic dermatosis.

A small article published in Aug. 2017 (where they reported PG in an 8-year-old patient with XLA) for further info:



https://synapse.koreamed.org/Synapse/Data/PDFData/0140AD/ad-29-476.pdf

**Figure 3: Pyoderma gangrenosum**

0.00 min- 12.50 min

**B. Selective IgA Deficiency**

Remember where did we hear about it? What was special about it?? Refer to page5, sheet1 and page 13, sheet 2.

Selective IgA deficiency is the most common congenital immunodeficiency; occurring in about 1 in 300 to 1 in 1500 person globally, meaning that it's the most common PID disorder. Also, we mentioned that it's mostly ASYMPTOMATIC which means that the person can reach adulthood and still not know he has it, and may be discovered incidentally upon a visit to the hospital for another reason.

Individuals with selective IgA deficiency typically exhibit normal levels of other antibody isotypes; they'll live a normal life span, but their life would be troubled only by a greater-than-normal susceptibility to infections of the respiratory and genitourinary tracts which are the primary sites of IgA secretion.

**To remember…** Handout 5+6: "IgA is the Ab that protects mucosal surfaces; IgA molecule looks like 2 IgG clipped together. This clip is important for the IgA function; it allows its movement through intestinal wall and protects it from the intestinal acidity and enzymes.

In the intestinal lumen IgA coat the invading pathogen preventing it from attacking the intestinal cells. Because IgA has four Fab regions it can attach to bacteria and produce a large enough particle to pass through mucus or stool. IgA is secreted in mothers' milk and taken by

the baby during breast feeding; they coat the baby's intestine and protect it. IgA cannot fix complement, which is good because if they do our mucosal membranes will be always attacked by complement in response to bacteria that is always there in the mucosal membranes."

Although the genetic defect has not been established, it is hypothesized that lack of IgA is caused by impaired differentiation of lymphocytes to become IgA-producing plasma cells, meaning that impaired class switching from IgM to IgA might be involved.

C. **Common Variable Immunodeficiencies (CVIDs)**

CVIDs encompass the largest group of symptomatic primary immunodeficiency disorders, with an estimated incidence between 1 in 10,000 and 1 in 50,000. Since it's called "deficiencie**s**" we would expect that it's a heterogeneous group of disorders that lie under the name "common variable ID", so you won't find a single underlying cause of CVID but rather multiple genetic defects that are **diagnosed by <u>exclusion</u>.**

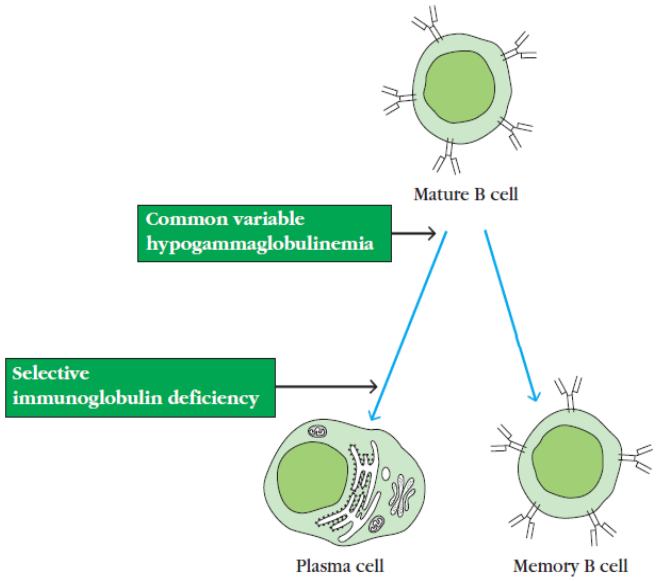



**Figure 4: CVID**

**Please, what does this suppose to mean??**

If we tested patients immunity, and we observed a deficiency in his humoral immunity

We place a list with certain possible diagnoses

a. X- linked agamma globulinemia: excluded if Btk was normal.

b. Selective IgA deficiency: excluded if not only IgA was deficient.

c. Common variable immunodeficiency: left in the list; affirmed if it also fit **diagnostic criteria** of having VERY LOW IgG **plus** having **either** IgM or IgA in Low levels.

Patients usually begin to have symptoms in their 20s and 30s (most common age of CVID diagnosis), but age at onset ranges from 7 to 70 years of age.

As we mentioned a moment ago, there's a diagnostic criteria for CVID; Also, falling into this criteria is the patient's age upon diagnosis with CVID; the patient **<u>must not be less than 4 years old</u>**, why? Because at age of infancy and early childhood, we have other PID disorders that'll cause same manifestations.

What are these OTHER PID disorders??

E.g. **Transient** hypogammaglobulinemia of infancy.

This disorder is physiological. Neonates dependency of on their mothers IgGs, and since these Abs have a half-life and soon they'll reduce in number, so these babies will have to start depending on themselves to build their humoral immunity response once they encounter infections since their immune system is not well developed yet. Nevertheless, some babies when they encounter infections, they'll develop their humoral immunity **slowly** thus will be diagnosed with Transient hypogammaglobulinemia of infancy.

Respiratory tract infection by common bacterial pathogens is the most common symptom.

VERY IMPORTANT: Always always remember that once you see that humoral immunity is affected, directly think of **ENCAPSULATED bacteria** and their MAIN TARGET which is **respiratory tract**.

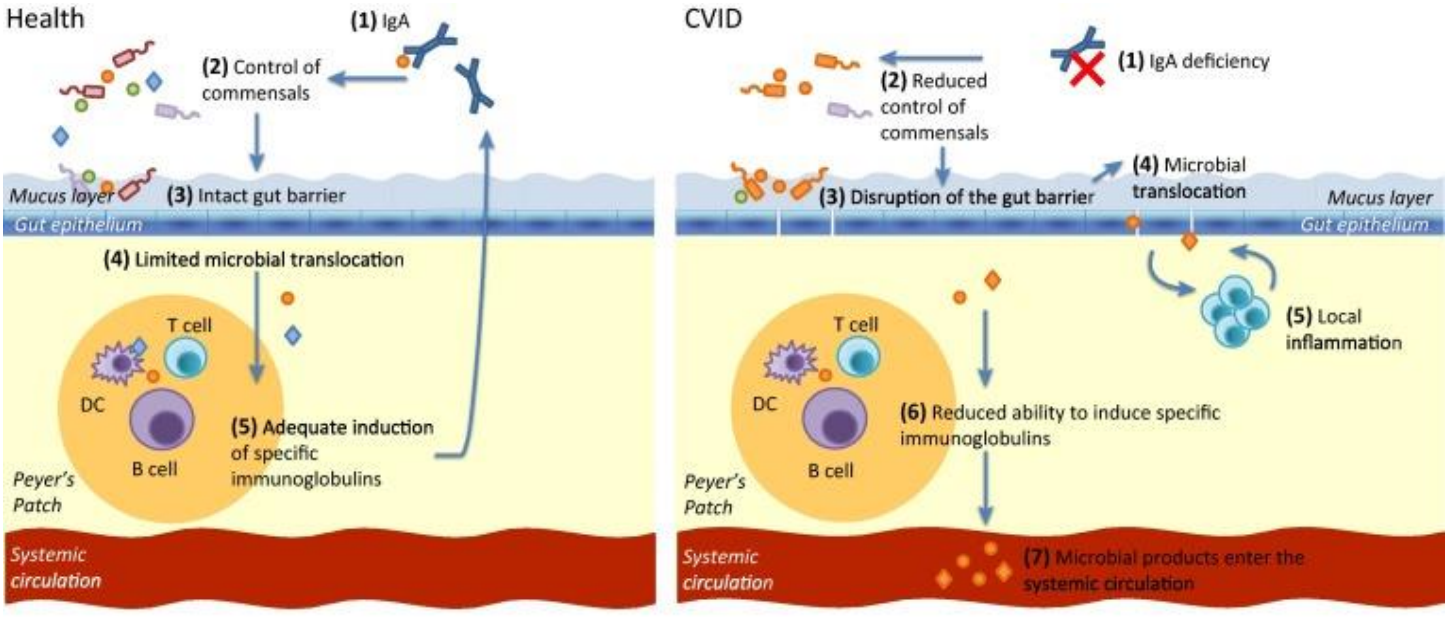



**Figure 5: CVID postulated pathogenesis**

** The lack of a real comprehensive and combined analysis of all cases of CVIDs hindered (impaired) the definitive description of all immunopathogenic pathways leading to such diseases.

12.50min - 21.05min

## 2. Defects of the T-Cell or T-cell/B-cell Systems

A. **DiGeorge Anomaly**

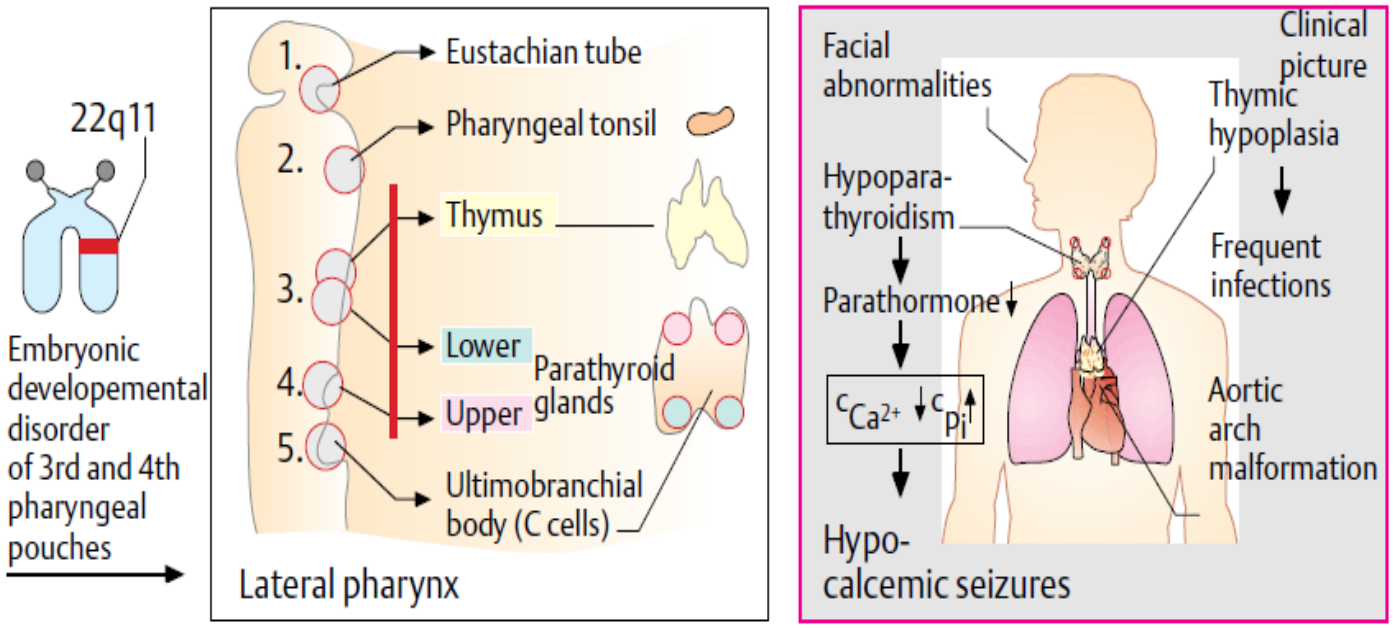
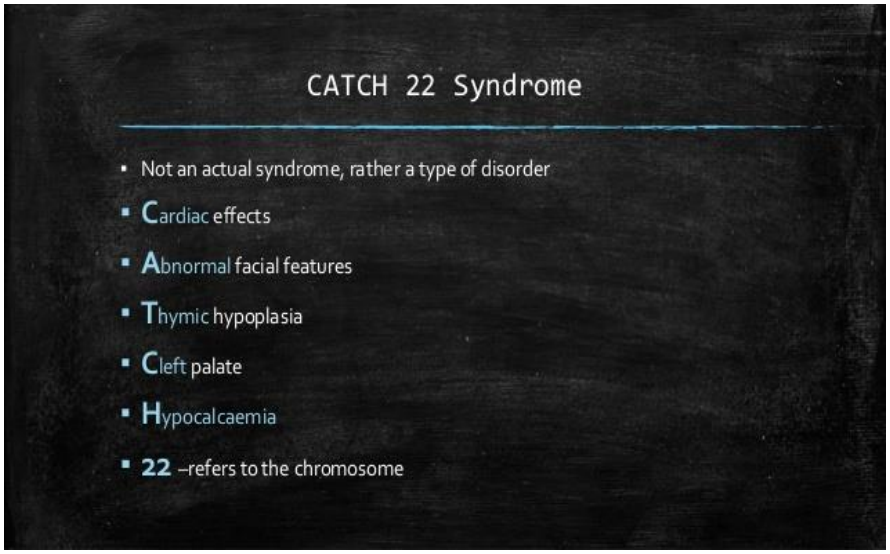



**Figure 6: DiGeorge Syndrome**

Developmental abnormality of the third and fourth pharyngeal pouches that affects thymic development.




Specifically, most patients show a deletion in chromosome 22, region q11 (recall: q is the long arm; p (petit) is the short arm of the chromosome)

"Catch 22" describes the most famous clinical outcomes in DiGeorge patients.

Handout 13: "DiGeorge syndrome has a broad range of clinical features, but most infants present with a congenital cardiac defect, mild to moderate immunodeficiency, facial dysmorphisms, developmental delay, palatal dysfunction, feeding difficulties, and hypocalcemia due to absent or low function of the parathyroid glands. Neurobehavioral and psychiatric abnormalities (schizophrenia) may be observed in a significant fraction of patients, especially during adolescence or adulthood."

The severity and extent of the developmental defect can be quite variable; The MOST COMMON clinical presentation (how would they look like when they come to the hospital?) in infants with DiGeorge syndrome is **TETANY**.

Refresh your memory: 'Low ionized calcium levels in the extracellular fluid increase the permeability of neuronal membranes to sodium ion, causing a progressive depolarization, which increases the possibility of action potentials. This occurs because calcium ions interact with the exterior surface of sodium channels in the plasma membrane of nerve cells. When calcium ions are absent, the voltage level required to open voltage gated sodium channels is significantly altered (less excitation is required). If the plasma Ca2+ decreases to less than 50% of the normal value of 9.4 mg/dl, action potentials may be spontaneously generated, causing contraction of peripheral skeletal muscles.' – Wikipedia

Many patients with a partial DiGeorge anomaly have only a minimal thymic defect, and are thus near normal immune function. However, about 20% of children with a defect of the third and fourth pharyngeal pouches have a severe and persistent decrease in **T-cell** numbers due to thymic atrophy; cardiac defects are also expected to be seen; these children tend to have severe, recurrent viral and fungal infections (Recall: B cells were related to bacterial infections MOSTLY in respiratory tract ). HIV which is related to 2ndary ID and cause CD4+ **T cells** depletion was also related as you remember with CMV (virus) and *Pneumocystis* (fungus) infections.

Severely affected children usually present in the neonatal period with tetany (caused by hypocalcemia resulting from hypoparathyroidism) or manifestations of cardiac defects.

**B. Severe combined immunodeficiencies (SCID)**

The most serious of the congenital immune deficiencies is severe combined immunodeficiency (SCID). It is a group of related diseases that all affect T- and B-cell function but with differing causes, this means that both humoral and cellular adaptive immunity are affected. X-linked SCID is the most common form of the disease, accounting for approximately 50% of the cases in the US, the rest are autosomal.

The abnormal gene involved in X-linked SCID codes for a protein chain called the **common gamma chain**, which is common to **receptors** for interleukins- 2, 4, 7, 9, 15, and 21. The gene is referred to as the IL2RG gene and is located on the X chromosome. Normal signaling cannot occur in cells with defective receptors, thus halting (ceasing, arresting; إيقاف،قطع) natural maturation.

Although this chain was first identified as a part of the IL-2 receptor, impaired IL-7 signaling is likely the source of both T-and B-cell developmental defects, while lack of IL-15 signaling is believed to account for the block to NK cells.

Handout 11: "Defects in the receptors for IL-2 (which was first identified to have common gamma chain), IL-4, IL-9, IL-15, and IL-21 **do not seem relevant to the early block in T-cell development seen in X -linked SCID**, because all of them activate mature lymphocytes or other effector cells. However, the receptor for **IL-7** is thought to be important for pre-T-cell growth. A loss of IL-7 receptor function is therefore likely to be the most important loss of function responsible for X-linked SCID."

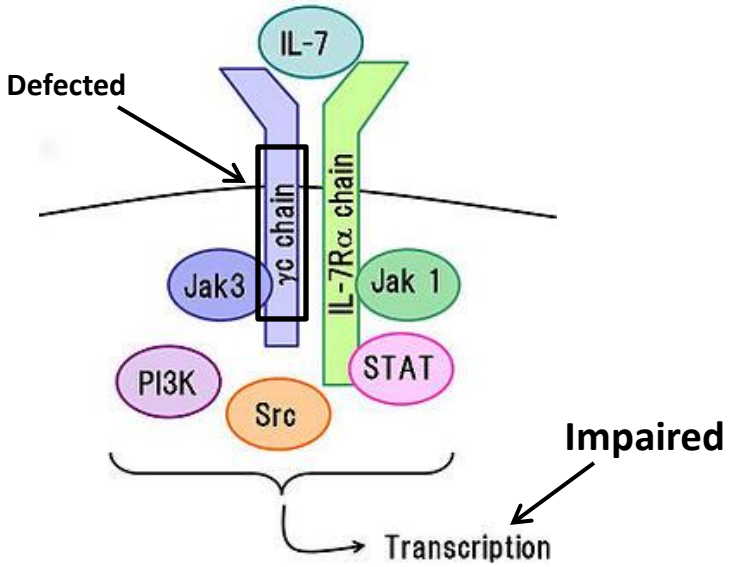



**Figure 7: IL-7 receptor and cell signaling**

Autosomal defects can be many:

1. A JAK3 deficiency may be found without the common gamma chain deletion. This results in an autosomal recessive form of SCID, affecting both males and females.
2. A single defect involving RAGs: Defects in the pathways involved in the recombination events that produce immunoglobulin and T-cell receptors highlight the importance of early signaling through these receptors for lymphocyte survival. Mutations in the recombinase activating genes (RAG1 and RAG2) and genes encoding proteins involved in the DNA excision-repair pathways employed during gene rearrangement can also lead to SCID.
3. Adenosine deaminase (ADA) deficiency; another relatively common defect resulting in SCID. Adenosine deaminase catalyzes conversion of adenosine or deoxyadenosine to

inosine or deoxyinosine, respectively. Its deficiency results in the intracellular accumulation of toxic adenosine metabolites, which interferes with purine metabolism and DNA synthesis. This housekeeping enzyme " housekeeping is like being essential to exist in each house " is found in all cells in the body, so these toxic compounds also produce neurologic and metabolic symptoms, including deafness صمم, behavioral problems, and liver damage.

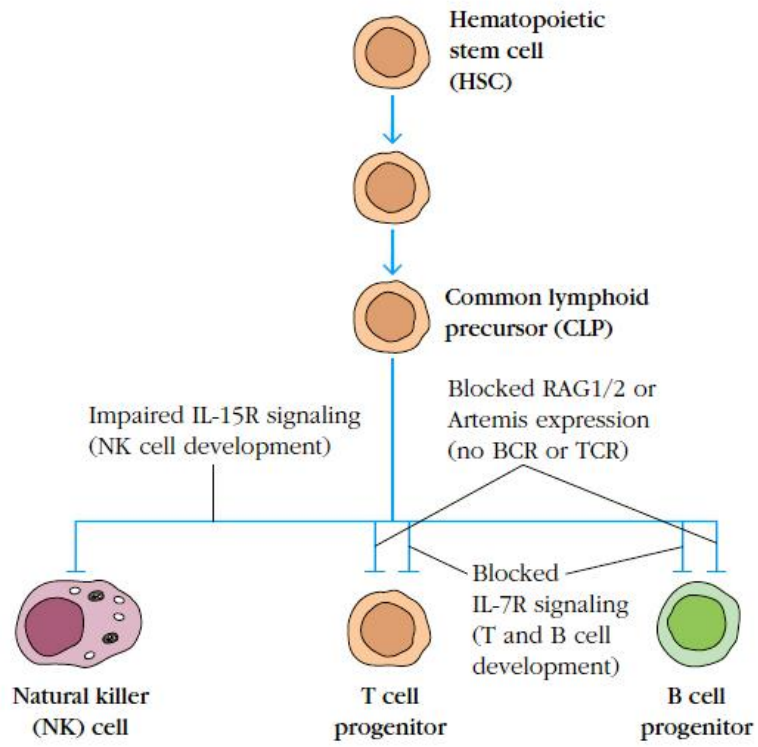



**Figure 8: SCID types and involved immune system components**

***** The following part is just to broaden your knowledge with SCID (optional)**

David … **The boy in the bubble,** who New York Times wrote about: "the boy in the bubble who moved a world he couldn't touch."

This picture was taken in July 1972 - About 10 months old.

Immune deficiency foundation writes: "For 12 years, David captured the world's attention as he lived in protected environments to maintain relatively germ-free surroundings

at Texas Children's Hospital. Speaking for her family, including David's father and sister, his mother Carol Ann Demaret explains, "As parents of an afflicted child, the only thing we had in our control was to see that David received the best possible care. We trusted our doctors. We were grateful for the bubble; the bubble was the only treatment option available for David at the time. If it hadn't been for the bubble, we would not have had him for 12 years. Our goals were to keep David safe, bring the outside in and make sure he felt loved."

Sadly in 1984, four months after receiving a bone marrow transfusion, David died from lymphoma—a cancer later determined to have been introduced into his system by the Epstein-Barr virus.

Carol Ann carries on David's legacy today through her work with IDF as a long-time member of the Foundation's Board of Trustees.

Carol Ann believes, and science has stated, that because of what was learned from David's gallant life and death, many children with SCID have since been diagnosed early, received bone marrow transplants and now lead healthy lives. In her words, "David was a great blessing to our family and to the world.""

** To know more about David: https://primaryimmune.org/living-pi-explaining-pi-others/story-david

**C. Hyper IgM Syndrome**

An inherited deficiency in CD40 ligand (CD40L or CD154) leads to impaired communication between T cells and APCs (B cells, Dendritic cells, Macrophages), highlighting the role of this surface molecule in this costimulatory process. In this X-linked disorder, TH cells fail to express functional CD40L on their plasma membrane, which typically interacts with the CD40 molecule present on B cells and dendritic cells.

The B-cell response to T-independent antigens (antigens that don't need co- stimulation of Th cells to activate B cells), however, is unaffected, accounting for the presence of IgM antibodies in these patients, which range from normal to high levels and give the disorder its common name, hyper IgM syndrome.

Remember in Handout 5+6: "B cells can change their class by changing their Fc region. They also change their binding capacity (affinity) by hyper mutation of the fab region .These two processes need T helper signaling, that's why B cells which are co-stimulated without T helper (T helper independent stimulation) don't undergo these change ( they don't have class switching

or hypermutation).” That’s why TH cell independent activation of B cells upon encountering T-cell independent Ags **will NEVER initiate class switching to Ab other than IgM**.

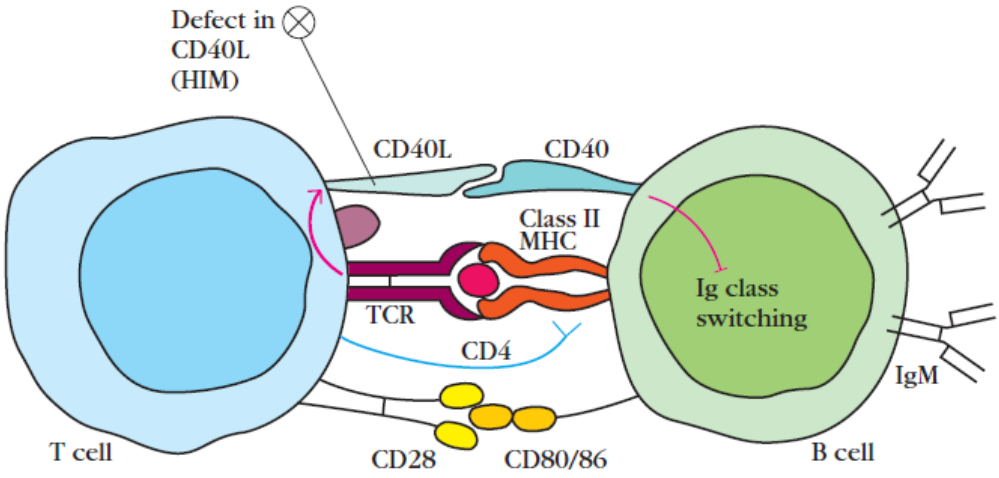



**Figure 9: X-Linked hyper IgM syndrome**

## 3. Defects of Neutrophil Function – innate immunity

### A. Chronic Granulomatous Disease (CGD)

CGD is caused by an inherited defect in the NADPH oxidase enzyme complex (also called phox: **ph**agocyte **ox**idase), present in a variety of cells including phagocytes. The NADPH oxidase enzyme **complex** consists of two membrane-spanning subunits, gp91phox and p22phox as well as three cytosolic components p47phox, p67phox, and p40phox. Approximately, **66%** (2 thirds) of all CGD cases result from mutations within the **X-linked** gp91phox gene (one of membrane spanning subunits), followed by the autosomal recessive forms of CGD, with defects in the gene coding for p47phox (one of cytosolic components), accounting for 33% (one third) of all CGD cases.

NADPH oxidase is required for the respiratory burst and has a critical role in microbial killing. It reduces molecular oxygen to superoxide, which subsequently reacts to form reactive oxygen species (ROS) such as hydrogen peroxide, hypochlorous acid, and hydroxyl radicals. Patients are particularly susceptible to fungal infection, typically from *Aspergillus* species, but also catalase positive bacteria including *Staphylococcus aureus*, *Serratia marcescens* and *Burkholderia cepacia*. Most patients present with infections, typically lymph node abscesses, but also recurrent respiratory infection, deep-seated abscesses and septicaemia.

Making the diagnosis of CGD is not technically difficult, and historically is based on the use of the “gold standard” nitroblue tetrazolium (NBT) assay (refer to page 11, sheet 2).

Normal non-immunodeficient people (in Fig.10 referred to as control) will have positive results because they have active NADPH Oxidase so the color will turn into purple and they’ll have purple deposits inside their cells, while CGD patient cells will remain the same.

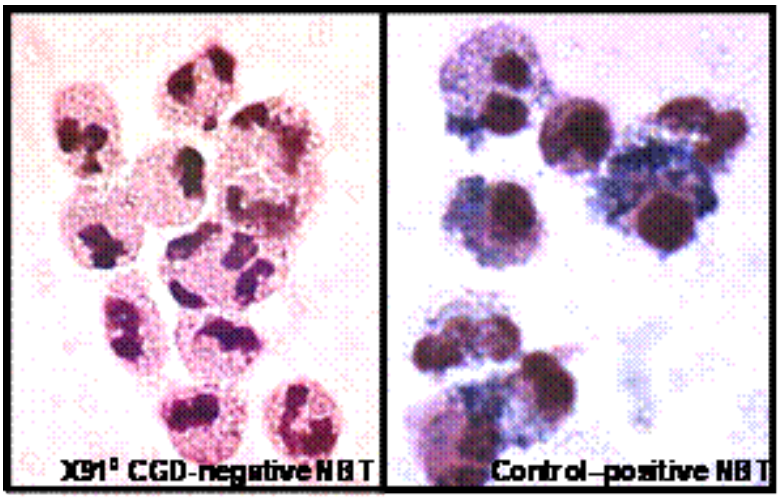



**Figure 10: Nitroblue tetrazolium assay**

A Recent assay (test; فحص) is flow cytometry based on the reduction of dihydrorhodamine-123 (DHR) by phorbal myristate acetate stimulated phagocytic cells.

**B. Leukocyte Adhesion Deficiency**

Leukocyte adhesion deficiency (LAD) syndromes are rare genetic immunodeficiency disorders that are caused by defects in adhesion and signaling of leukocytes and platelets. Defects include:

(1) Absent or reduced expression of β2 integrins (which is a critical subset of integrins that are restricted to leukocytes).

(2) Mutations resulting in impaired fucosylation (the process of adding fucose sugar units to a molecule which is a type of glycosylation) of ligands that are recognized by selectins and mediate leukocyte adhesion and signaling.

(3) Impaired inside-out signaling of β1, β2, and β3 integrins, resulting in defective leukocyte adhesion and signaling and a Glanzmann-like bleeding tendency.

** **For your info**: Glanzmann thrombasthenia (GT) (asthenia ضعف) is a rare genetic platelet disorder in which the platelets have qualitative or quantitative deficiencies of the fibrinogen receptor αIIbβ3; Signs and symptoms include the following: Mucosal bleeding, Gingival bleeding, Petechiae and ecchymoses, Mennorhagia, Gastrointestinal bleeding.

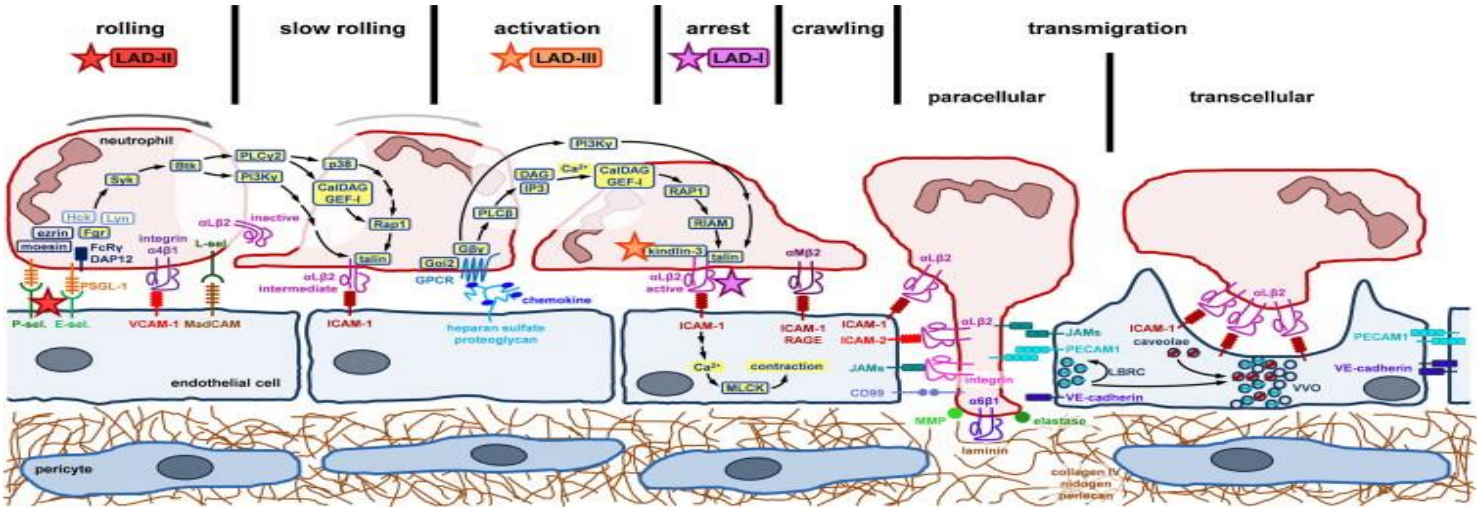



**Figure 11: Neutrophil Recruitment stages**

## 4. Complement Deficiencies – innate immunity

Deficiencies in the early complement components, C1q, 4, and 2, are usually associated with a lupus-like syndrome. Deficiency of C2 is believed to be the most common complement component deficiency (refer to page 11, sheet 2). A C3 deficiency may also have a lupus-like clinical presentation but is more likely to involve recurrent encapsulated organism infection. Deficiencies of the late components of complement (MAC: C5 through C9) are often associated with recurrent *Neisseria* infections. A deficiency of C1 esterase inhibitor has been found in patients with hereditary angioedema. Most complement deficiencies appear to be inherited in an autosomal recessive manner.

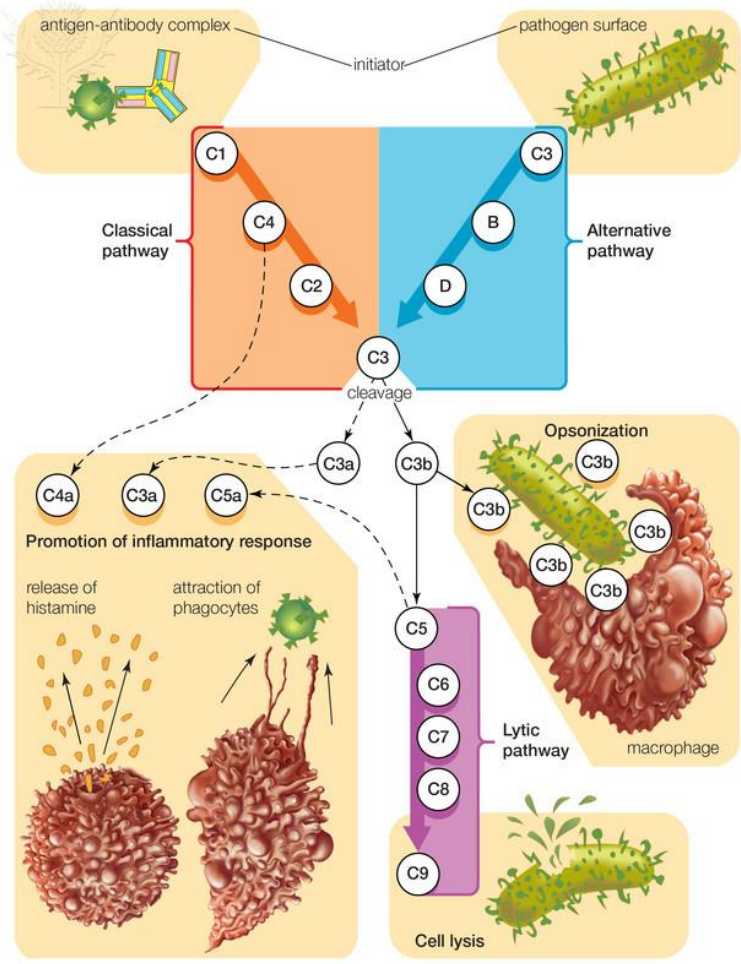



**Figure 12: Complement system roles in immunity**

21.05 min - 37.50 min

**By this we finally can say that we finished Immune deficiency material.** Following is a table that summarizes what is mostly required from you in this lecture, plus after it is Test- your-self questions + key ways to solve Immune deficiency MCQs.

**NOTE: THE WHOLE FOLLOWING PART** (The summary table, how to solve MCQs, the 6 questions) was thought of and written by me and the doctor liked to note that "he can't take the responsibility for such information". I'd like to assure to you, however, that the table is copied carefully to help you sum up most important info; the Keyway to solve MCQs was how I found myself solving them and I told myself that it might help someone; and lastly the questions were to break the ice between you and ID material, so I hope you'd benefit to the MAX!

| **Primary Immune deficiency name** | **Affected immune system component** | **Genetic defect** | **Infections taking place** |
|---|---|---|---|
| **X-Linked Bruton's Agammaglobulinemia** | B cells (humoral immunity) | Bruton tyrosine kinase (Btk) in B-cell progenitor cells | Sino-pulmonary infections caused by encapsulated organisms ( Bacteria) |
| **Selective IgA Deficiency** | B cells (humoral immunity) | the genetic defect has not been established, it is hypothesized that lack of IgA is caused by impaired differentiation of lymphocytes to become IgA-producing plasma cells. | Susceptibility to infections of the respiratory and genitourinary tracts which are the primary sites of IgA secretion. |
| **Common Variable Immunodeficiencies (CVIDs)** | B cells (humoral immunity) | multiple genetic defects | Respiratory tract infection by common bacterial pathogens is the most common symptom. |
| **DiGeorge Anomaly** | Defects of the T-Cell System (cellular immunity) | deletion in chromosome 22, region q11 | severe, recurrent viral and fungal infections |
| **Severe combined immunodeficiencies (SCID)** | Defects of the T-Cell/B-Cell Systems | **X-linked** : The abnormal gene coding for a protein chain called the common gamma chain (IL2RG gene), which is common to receptors for interleukins- 2, 4, **7**, 9, 15, and 21. | *Pneumocystis*, *Candida*, viruses |

| | | | |
|---|---|---|---|
| | | **Autosomal**: 1. JAK3 deficiency may be found without the common gamma chain deletion (Autosomal recessive), 2.Mutations in the recombinase activating genes (RAG1 and RAG2) and genes encoding proteins involved in the DNA excision-repair pathways employed during gene rearrangement.<br>**** Please refer to the original page for these points.** | *Pneumocystis*, *Candida*, viruses |
| **Severe combined immunodeficiencies (SCID) … Cont.** | Defects of the T-Cell/B-Cell Systems + other cells | **Autosomal:** Adenosine deaminase (ADA) deficiency | The intracellular accumulation of toxic adenosine metabolites, which interfere with purine metabolism and DNA synthesis. Also, they produce neurologic and metabolic symptoms, including deafness, behavioral problems, and liver damage. |
| **Hyper IgM Syndrome** | Defects of the T-Cell/B-Cell Systems | X-Linked: inherited deficiency in CD40 ligand (CD40L or CD154) | *Pneumocystis*, viruses |
| **Chronic Granulomatous Disease (CGD)** | Defects of Neutrophil Function (innate immunity) | an inherited defect in the NADPH oxidase enzyme complex | Particularly susceptible to fungal infection, typically from Aspergillus species, but also catalase positive bacteria including Staphylococcus aureus, Serratia marcescens and Burkholderia cepacia. |

| | | | |
|---|---|---|---|
| **Leukocyte Adhesion Deficiency** | Defects of Neutrophil Function (innate immunity) | (1)Defects include absent or reduced expression of β2 integrins<br>(2) Mutations resulting in impaired fucosylation of ligands that are recognized by selectins and mediate leukocyte adhesion and signaling,<br>(3) Impaired inside-out signaling of β1, β2, and β3 integrins, resulting in defective leukocyte adhesion and signaling and a Glanzmann-like bleeding tendency. | Bacterial infections |
| **Complement Deficiencies** | Innate immunity | Early and late components could be deficient ( C2 as most common) | Deficiencies of the later components of complement (MAC: C5 through C9) are often associated with recurrent Neisseria infections |

**read the question carefully and look for certain keywords that relate to immunodeficiency**

**Q: do I have recurrent infections? opportunistic infections? increased severity of common infections?**

Differentiate between secondary and primary immunodeficiency depending on existance of genetic (PID) or underlying cause (SID)

**Yes ; Q: is there a genetic defect or not ?**

**No**

**A topic-specific question; look for details related**

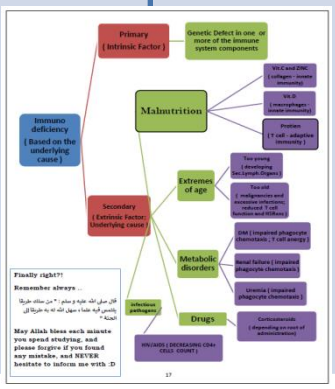
**YES (Primary); Q: what is the underlying genetic defect or whhich immune system component got affected**

**NO (secondary); Q: Old or young? or What underlying cause do I have?**

Look for special features that remind you of the disease

**Bacterial infection ( most likely B cell defect"humoral immunity" + COULD BE PHAGOCYTES)**

**Viral or fungal (T cell defect; cellular immunity)**




Refer to this diagram in last page of sheet 1

**Table in this sheet**

## How to Think of ID Qs?!

# Test your self

**** These are some questions wrote in multiple ways to guarantee you would be able to interpret info from any Q given to you! Best wishes :D**

1. Which of the following combinations is right regarding immune deficiency disorder and **corresponding genetic defect**?
   a. HIV …. CD4 cell deficiency
   b. SCID… 22q11.2 deletion
   c. DiGeorge … Btk enzyme deficiency
   d. CGD … IL-7 receptor common gamma chain deficiency
   e. Hyper IgM syndrome … deficiency in CD40L gene
2. : 4-year-old baby came to the hospital with his mother; upon taking medical history he was found to have recurrent bacterial infections with staph. Aureus. Nitroblue tertrazolium test was Negative. Choose the correct involved immune system component:
   a. B cell system
   b. T-cell + B cell system
   c. Innate immunity – complement system
   d. Innate system – phagocytes
   e. T cell system
3. Upon immunophenotyping of cells of a patient suspected to be immune deficient, CD4+ cells were found to be very low; the patient was then diagnosed with HIV. If this patient was in a poor country and couldn't afford antiretroviral therapy, which infections would complicate his case?
   a. Pneumocystis jirovecii
   b. Histoplasma
   c. Coccidioidomycosis "valley fever"
   d. Candida
   e. All of the above.
4. Upon a trip to the South Pole, a family took with them food needed to make the journey as amusing as possible. 2 days after the ship started sailing, a storm hit the ship and almost all their food was lost and for almost 8 days they

were living only on mashed potato بطاطا مهروسة; the mother noticed that her and her son's skin started to get weaker. Choose the correct statement:

a. Taking supplementary Vitmain D would reduce the problem
b. Taking supplementary Vitmain C would reduce the problem
c. Taking supplementary Zinc would reduce the problem
d. Nothing can reduce their problem.
e. b+c

5. A 50 year old male with clinical history of prostate cancer and Diabetes with A1C of 12 (very high) came to your clinic with dyspnea as chief compliant. After doing the work up needed, he was diagnosed with TB. After knowing that he took TB vaccine (BCG) and DPT vaccine when he was young, which of the following **will not be found** in this patient?
   a. IgGs for recent diphtheria infection
   b. –ve delayed hypersensitivity (HSRxn type 4)
   c. –ve mitogen test
   d. No response from neutrophils to chemotactic agents
   e. None of the above
6. A 25 year old HIV patient was diagnosed 3 weeks ago with HIV. His CD4+ cells count was 800. Upon immunophenotyping, his CCR5 levels where very low while CD4 and CXCR4 were normal, choose the right statement:
   a. This HIV patient will never progress to AIDS stage.
   b. CCR5 low levels are expected to be due to a mutation in CCR5 gene.
   c. The most common lymphoid tissue to be affected at this stage of the disease is the GALT.
   d. At this stage , this patient is prone to be infected by Pneumocystis jirovecii
   e. a+d

Answers: 1e, 2d, 3e, 4e, 5a, 6c

**DONE at last :D**

**Congrats brave future Doctor!!**

**Please if you found anything that needs enhancement don't hesitate! Generously remember me in your prayers ... Wishing you the best in your finals, and now leaving you with this Holy Hadith…**

**قال النبي - صلى الله عليه وسلم - : يقول الله تعالى : ( أنا عند ظن عبدي بي ، وأنا معه إذا ذكرني، فإن ذكرني في نفسه ذكرته في نفسي ... )**