INTRODUCTION TO MEDICAL

IMMUNOLOGY

SLIDE SHEET

NUMBER	1 (Lec #22)
DONE BY	Mariam Hassouneh
CORRECTION	Dr.Malik Sallam
DOCTOR	Dr.Malik Sallam

Salam everybody ♥ … hope you're all good and having a blessed day :D

As you start studying I'll be on the other side always praying this would be an easy going sheet, and I hope you'll find it useful as you're getting closer and closer to the day you'll meet your first patient in your fancy clinic ^.^

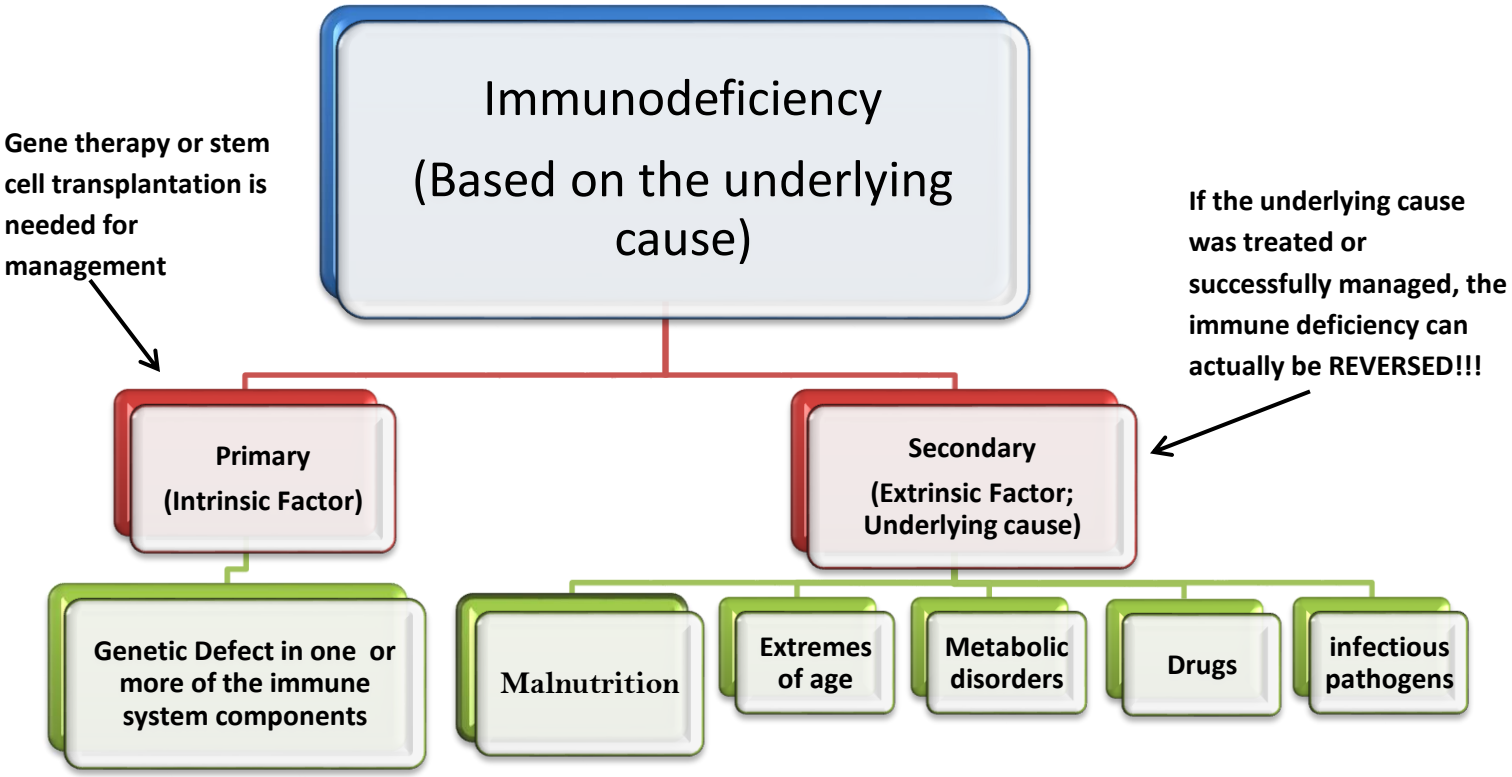
Immunodeficiency

Immunodeficiency can be simply defined as failure of the immune system to protect the body.

Our immune system operates as a:

1. Protector against infections (Protection from pathogens).
2. Defender whenever abnormal alterations in the body happen (e.g : Tumors)

So failure to do so will result in immunodeficiency!!



** Highlighted sentences found through the sheet are info the doctor focused on its importance :D !

- How would we suspect that a certain person is immune deficient??

1. Frequency of infections is unusual

   Mum said: “We went 3 times to the hospital this month”!!

   This child is having **Recurrent** infections.

   Normal people might have few respiratory infections per year, but with these people, several times might be the case.

2. Microbiologic result is not commonly encountered.

   Common cold and flu viruses are considered to be common infectious pathogens between all people, but an infection with unusual microorganisms (or **opportunistic** infections) may drag attention to the possible presence of an underlying immune deficiency.

   ** Recurrent + Opportunistic are thus the key words.

- Type of infection can give us clues for which type of organism is the cause as well as the degree of immune deficiency, how?

Examples are the best to explain; Yet, Take a look at this table first as it sums everything.

**Note: The whole table is required.

Type of infections associated with major categories of PIDs

Organism	Antibody deficiencies	CIDs	Phagocytic defects	Complement deficiencies
Viruses	Enteroviruses	All, especially: CMV, respiratory syncytial virus, EBV, parainfluenza type 3	No	No
Bacteria	*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus, Neisseria meningitidis, Mycoplasma pneumoniae*	As for antibody deficiencies, also: *Salmonella typhi, Listeria monocytogenes*, enteric flora	*S aureus, P aeruginosa, Nocardia asteroides, S typhi*	As for antibody deficiencies: especially *N meningitidis* in deficiency of late components
Mycobacteria	No	Nontuberculous, including BCG	Nontuberculous, including BCG	No
Fungi	No	*Candida* species, *Aspergillus* species, *Cryptococcus neoformans, Histoplasmosis capsulatum*	*Candida* species, *Aspergillus* species	No
Protozoa	*Giardia lamblia*	*Pneumocystis jiroveci, Toxoplasma gondii, Cryptosporidium parvum*	No	No

Ex.1: If we had a defect in humoral immunity (Remember B cells and **Abs**), Individuals will be mostly susceptible to bacterial infections usually involving respiratory tract (upper and lower) like *Streptococcus pneumoniae, H. Influenzae, Moraxella, Staph. aureus, Mycoplasma pneumoniae*

Ex.2 : (possible Exam Q) If we had a defect in Late complement component (components acting after formation of C3 convertase like Membrane attack complex MAC which is formed by assembly of complement proteins from C5 to C9 –mainly of C9-), the patient will be mostly **susceptible to recurrent invasive *Neisseria* infections**.

Ex.3 : previously taken as 1st case ; deficiency in C1INH (also called C1 esterase) which inhibits the successful assembly of $C1qr^2s^2$ to activate C4 and C2 in the classical pathway will result in **Hereditary Angioedema**

Ex.4 : *Salmonella Typhi*, an intracellular organism with increased susceptibility to infection by it upon defects in phagocytes.

Ex.5 : *Candida* infection is related to SCID (severe combined immunodeficiency; Main defect in T cells that'll affect B cells and other immune system components' functions). Recurrent Candida infections can also result from defects in innate immune components.

** Other examples are in the table.

Getting back to our subject, we'll today mainly focus on secondary type of immunodeficiency because it's Important, more common, and includes a wide range of underlying causes; Also, Primary type Immunodeficiencies – excluding selective IgA deficiency - are **RARE** to be encountered throughout our medical career except in pediatrics, immunology or allergy departments.

** The most Famous type of 2ndary immunodeficiency is HIV/ AIDS.

Secondary immunodeficiency

Since this type is due to an underlying cause that affects the host, the management of it will reverse and may restore the immune function.

As a quick teaser, variety of underlying causes are present:

1. Infectious agents like HIV and some other viruses
2. Drugs like steroids, chemotherapeutic agents that primarily work as immunosuppressants
3. Metabolic diseases like DM (Diabetes) and renal failure may be also involved.
4. Life style like Alcoholism

BUT, the **most common cause of secondary immunodeficiency** is MALNUTRITION!

1) Malnutrition

It isn't just "not eating enough" but it's all about "not eating enough of **what my body needs** to stay healthy" , so it's defined literally as Low **nutrients** intake.

An obese person can suffer malnutrition if he's fast–food dependent, so a meal deprived of essential metals, vitamins is an inadequate meal to meet body nutritional demands!

Malnutrition can result from limited access to food resources or from chronic diseases associated for example with Cachexia.

Cachexia الهزال : A state of muscle weakness and loss of weight.

A cytokine named Cachexin (also known as TNF alpha) is the most involved molecule in producing Cachexia, so we can conclude that cachexia can also be seen in cancer patients (we took this in neoplasia if you remember) as well as in people having limited food access .

HOW does malnutrition affect our immunity??

Let's take a look at **types of Malnutrition**:

1. **Protein Malnutrition**: (Globally it's The most common cause of malnutrition; Very important to be familiar with it being the most common)
   It'll impair normal T cell function and production, and this impairment will be directly proportional to the severity of malnutrition (Specially in hypoproteinemia), and you might be thinking the other way round … Since we have low protein doesn't that mean it'll affect immunoglobulin synthesis so it'll affect B cells ???
   Well, apparently it was found that cellular manifestations mainly in T cells are observed in this state.

2. **Micronutrients malnutrition** (Zinc, Ascorbic acid A.K.A Vit.C)

Deficiency in these micronutrients will result in increased susceptibility to infections.

a. Vit.C deficiency

** Remember: Vit.C deficiency is also known as scurvy الاسقربوط.

Let's figure out how together:

Vit.C deficiency for example affects collagen --> Vit C is IMPORTANT in collagen synthesis and cross linking --> Deficiency will result in deformed dermis of the skin --> Skin integrity is affected (the Dam is falling apart) --> easy access for pathogens through skin whenever they wish! --> And then?? Increased susceptibility to infections by innate immunity being deficient plus weakness of mucosal barrier as in Gums which will facilitate pathogens invasiveness!!

b. Vit D deficiency

Vit.D deficiency will mainly affect macrophages activity, which is important in fighting intracellular organisms like *Mycobacterium tuberculosis* (For your info : *M. tuberculosis* is phagocytosed by alveolar (lung alveoli) macrophages, but they are unable to kill and digest the bacterium, so Protective granulomas are formed due to the production of cytokines and upregulation of proteins involved in recruitment. Granulomatous lesions are important in both regulating the immune response and minimizing tissue damage. Moreover, T cells help maintain *Mycobacterium* within the granulomas).

c. Zinc deficiency

Also related to collagen synthesis , which tells us that it'd deficiency is related to innate immunity deficiency 0.00 min – 13.48 min

So as a quick Recap: Protein malnutrition affects T cells and so adaptive immunity, while Zinc and Vit.C deficiency affects skin and so innate immunity, and Vit.D deficiency affect macrophages activity and so innate immunity.

2) Extremes Of Age (Too Old or too Young)

- Too young

You can clearly observe that in neonates - though partially protected by maternal IgG - the frequency of infection is greater than toddlers (12 – 36 months), or children in adolescence age or children older than that.

These babies are more prone to get both common and opportunistic infections, as well as sepsis, due to the fact that in early life they have less marginal zone B cells (in spleen marginal zone) , and a decreased expression of CD 21 on B cells (remember that this is the receptor for opsonins on Bacteria and it acts as co stimulatory receptor for B cells) , which will contribute to limitation of their ability to develop specific immune response which is in this case the **HUMORAL** response.

Although fetuses in Utero are in sterile environment, if they ever encountered a foreign antigen, they can develop humoral immunity against it due to their dependency on their mothers immune system which will be already fighting the pathogen, so the fetus secondary lymphoid organs will be actually **not yet developed**. But after the baby is born, he will sure then encounter all types of pathogens (commensal, common, or opportunistic organisms) so his secondary lymphoid organs will start developing more in response to that all over his body (especially the Lymphoid associated tissue in bronchi A.K.A the BALT and in the gut

A.K.A the GALT). In neonates, secondary lymphoid organs will still be immature due to the absence of memory cells since they are about to encounter pathogens for **their first time**, but as the baby grows, he'll encounter more pathogens so more foreign antigens, thus his Sec.Lymph. Organs (unless he had an immune-related genetic defect) will develop more as B cells proliferate and produce Abs and make memory B cells, and that's why as he grows, the frequency of infections will become less!

- Too old

Some elderly people experience malignancies and excessive number of infections caused by viruses or bacteria or else, which will reflect a decrease in immune function, particularly a decrease in the CELLULAR part of immunity (especially T cells), which will be first manifested in decreased hypersensitivity Rxns, and decreased lymphocytic proliferative responses in response to mitogens (explained in metabolic disorders). Then, innate immunity will become compromised with **increased skin breakdown**.

Metabolic and endocrine changes (Like in DM) associated with aging will affect innate immune system by having a diminished production -with aging- of hematopoietic cells which are the source of neutrophils and macrophages, and so decreased ability to upregulate proliferation and function of Neutrophils and macrophages in response to invaders! 13.48min - 18.45min

3) Metabolic Disorders

Like In DM, renal failure or uremia

1. Diabetes and uremia, which are common metabolic disorders, have deleterious effects on immunity so the optimal control of these disorders like controlling blood sugar as much as possible in DM and managing renal failure in its early stages will result in improved and may be restored-to-normal immune function (that's the main idea behind secondary immune deficiency cause management).

2. In DM, the main deficiencies would be in :

a. Phagocytosis and macrophage chemotaxis (innate).

This was noticed in vitro (outside the body) but it was not affirmed in vivo.

Impairment in neutrophils and macrophages chemotaxis was seen in vitro in DM patient.

b. T cells activity (Adaptive)

T cell Anergy (inactivation) demonstrated by delayed hypersensitivity skin tests (the test may be –ve in DM patients because Type 4 HSR is cell-mediated Rxn which depends on T cells).

c. Proliferative response of T cells to mitogens which will be relatively poor response due to chronic exposure to sugar (Hyperglycemia), but the exact relation between hyperglycemia and impaired T cell proliferative response is quite unclear.

*** Mitogens are non-specific activators for T cells, and they are used to measure functionality of T cells and their ability to proliferate by giving these mitogens, and since T cells upon seeing these non-specific agents are supposed to proliferate, mitogens test result will best reflect T cell functionality.

d. Capacity to generate memory Ab responses which will be diminished **REGARDLESS** of repeated vaccination.

3. In Uremia and renal failure, the main deficiencies would be :

a. Defective phagocyte chemotaxis.

b. Defective antimicrobial activity.

4) Drugs

The use of drugs to control undesired immune responses is common in clinical practice, as a consequence of increased in prevalence of inflammatory and autoimmune conditions, as well as the increased number of individuals with transplantation that require immunosuppressive therapy.

We previously discussed " Hygiene hypothesis" and how it resulted in increase in Autoimmune diseases prevalence and decrease in infectious diseases prevalence, which lead to the subsequent increase in usage of immunosuppressants and so a higher number of people prone to 2ndary type of immunodeficiency due to the exposure to these drugs.

As we can predict, immunosuppressants and anti-inflammatory drugs are used in treating autoimmune disorders, allergic disorders, transplant rejection, and Graft Vs. Host disease.

**** Azathioprine; Imurane ©**

We discussed before the usage of this drug as a treatment of Myasthenia gravis.

**** Overall results of using these drugs would be:**

1. Decreased Cytokine production (↓ IL-1, IL-6, TNF α)

2. Impaired leukocyte chemotaxis
3. Impaired cell adhesion (Neutrophil firm adhesion –after rolling- to Endothelium)
4. Impaired phagocytosis
5. Lymphocyte Anergy
6. Lymphopenia: This can occur as a result due to proapoptotic activity (not being stimulated to mature will upregulate expression of proapoptotic proteins inside the cell), and inhibition to IL-2 mediated proliferative response (remember that the most important growth factor T cell proliferation is IL-2) by some drugs like Cyclosporine (immunosuppressant; mainly affect T cells).

So again we can conclude that drugs affect both innate and adaptive immunity!!

- The wide range of immune defects (as seen above) resulting from usage of immunosuppressants and Anti-Inflammatory drugs will render the patient susceptible to bacterial, viral and fungal infections, according to the degree of immune suppression.

In easier words: Different **Roots of administration** for the same drug can be associated with inactivation of different immune responses and so susceptibility to certain type of infectious microorganisms for each root.

Famous Ex. Administration of **Inhaled** Corticosteroids is associated with susceptibility to *Candida* infections (like oral Candidaisis), while **Systemic** use of Corticosteroids is associated with (POSSIBLE Exam Q.) reactivation of *Human Herpes virus Type 3 HHV3 (Varicella-Zoster)* which upon reactivation in cases of immunosupression gets back from latency as Shingles الحزام الناري.

18.45min - 26.23 min

5) Infectious Diseases

Transient Periods of immune suppression had been associated with viral infections such as measles; CMV (Cytomegalo virus *HHV5*); Flu sometimes, but they are all less severe and reversible!

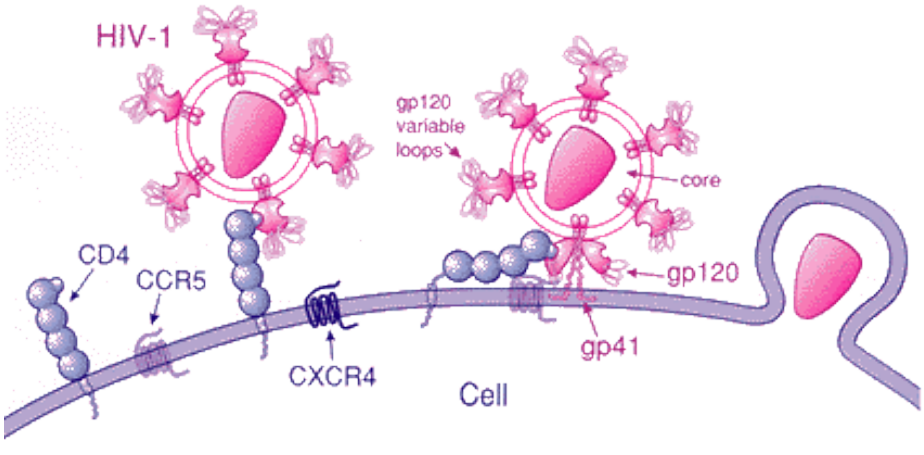
Yet, THE MOST COMMON CAUSE of secondary immunodeficiency caused by infectious diseases is ***Human Immunodeficiency virus (HIV)***

- HIV has 2 types (both of them cause AIDS):

1. HIV Type 1
2. HIV Type 2 which is confined to West Africa mainly (Guinea Bissau and it's neighboring countries, plus Portugal which colonized Guinea thus it was found that cases of HIV Type 2 where reported there).
   Usually progression to AIDS in type 2 is slower than type 1.

** Both types will infect T cells expressing CD4 on their surface (Th cells) , and Co-receptors which are **CCR5** and (in advanced stage of the disease) **CXCR4.**

* CCR5: Also On macrophages, plus in CNS on Microglial cells (Macrophage derived, can be also targeted by HIV!!)



The picture above illustrates what is seen in HIV infection.

1. HIV infection will begin by HIV **binding** through surface **glycoprotein 120 (gp120)** found in HIV envelope **to** Th cell receptor **CD4**, **and** to the Co-receptor **CCR5** on target cells (Macrophages initially).
2. Infected cells will migrate to the lymph nodes, where initial replication of infected cells plus infecting neighboring CD4+ Th cells will occur

** Very Imp. : We know that there are populations of T cells everywhere, in Lymph nodes, in associated lymphoid tissue, Circulating T cells in blood, and so on.

In acute HIV infection**, The most affected secondary lymphoid organ is the Gut associated lymphoid tissue (GALT)**, considering the fact that 90% of **Th-cell population** will be affected once GALT is infected by HIV, so it'll be severely damaged and will never get back to its normal state!!

** **Imp. Note** : When measuring Th cells number, for example CD4+/ CD8+ ratio in **acute** HIV infection, we'll notice that it's reduced too much **MAINLY due to the decreased number of Th cells in GALT.**

In acute HIV infection which lasts several months: We have severely depleted GALT, with predominant loss of CD4+ memory T cells, High Viremia, and immune activation

- For your info: There's a thing called the natural history of the disease which is a description of "How would the disease progress if the patient was **kept without management or treatment**? "

For example in SLE, remissions and relapses will happen (without taking immunosuppressants), the kidney and CNS will be involved and will deteriorate (That's why management is crucial!).

Now after acute HIV infection, even if there was no management for the patient, the patient will remain **ASYMPTOMATIC** , and if there were any signs even though they'll be few, **lymphadenopathy** will be one of them.

* New guidelines in treatment recommend that once a person is diagnosed with HIV, he must start taking Antiretroviral therapy.

* Viral load at the **viral set point** which is the nadir "lowest level" of viral load following acute HIV infection is inversely related to patient prognosis; the Higher the viral load at the set point the worse the prognosis.

* **T cell Lymphopenia (**CD4+ cells being lost) occurs through several mechanisms:

a. HIV inducing apoptosis of cells it infects (HIV cytopathogenic nature).

b. Apoptosis happening due to Cytotoxic immunity activation (not directly related to the virus), and so Cytotoxic T cells will act on infected CD4+ cells (Through the action of perforin-granzyme which will enter the cytoplasm of the target cell; trigger the caspase cascade; and eventually lead to apoptosis).

c. Innate immunity : Due to the setting of an infection, innate immunity will act as well by the action of NK cells killing CD4+ T cells by apoptosis.

** It was previously thought that the loss was due to aggregation of CD4+ T cells to form a syncytium but apparently it turned out to be not true.

HIV to AIDS :

It is said to be HIV state upon infection and along the way of progressive decreasing of CD4+ cells count, BUT, once the **CD4+ count reaches 200**, we now say that the patient **entered AIDS state.**

AIDS state has a thing called AIDS defining conditions, which are very common in AIDS patient. These conditions are the infections that the patient is susceptible to suffer from as the CD4+ cells count gets below 200.

In this case, the patient is prone to many infections , most typical organism to infect is *Pneumocystis jirovecii* (fungus that was previously classified as protozoan) and can be typically observed in these patients. A patient for example in late stage that has a CD4+ count of 150 is seen to have lung infiltrates clearly shown on X- Ray. Upon doing Bronchoalveolar lavage "bronchoalveolar washing" (a medical procedure in which a bronchoscope is passed through the mouth or nose into the lungs and fluid is injected into a small part of the lung and then collected for examination. It is typically performed to diagnose lung disease) that is then observed in Cytology to show cysts typical for pneumocystis.

** For your info: *Pneumocystis jirovecii* was previously named *P. carinii .*

** Other organisms might be: *Histoplasma* and *Toxoplasma* in CNS, *Coccidioidomyces* " Valley fever", Kaposi's sarcoma associated virus (*HHV8*).

- Small portion of HIV patients remain asymptomatic and doesn't have AIDS, these patients are called " long term non progressors" or " Elite controllers".

- You must know that progression to AIDS depend on both viral and host factors.

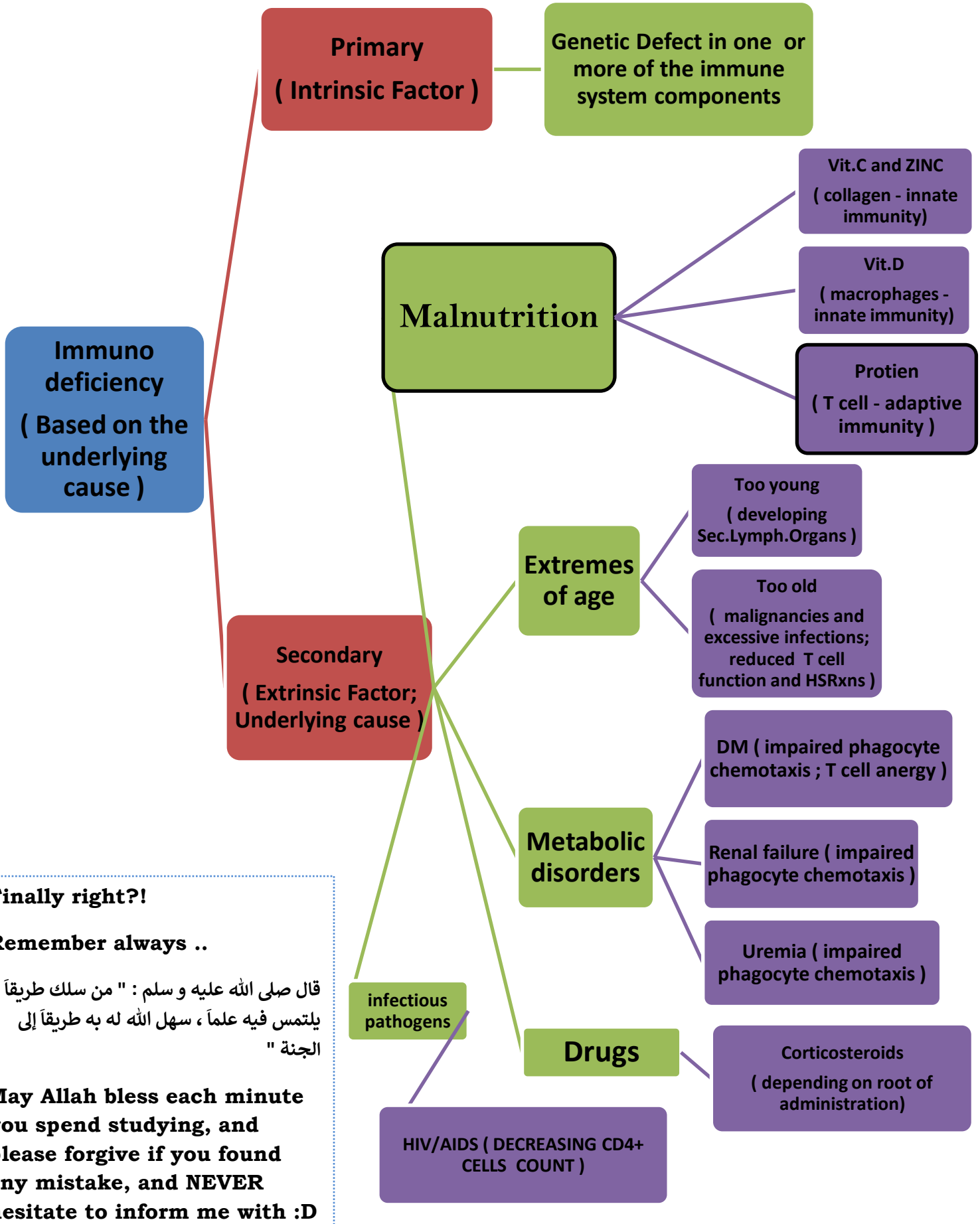
A Host factor indicating a defect in co-receptor CCR5 (CCR5- Δ 32 , meaning there is a deletion of 32 base pairs in CCR5 gene) , this co- receptor will be non-functional, and so HIV particles that **depend on this co-receptor for their entry** will simply NOT ENTER the cell and so will not be able to infect these cells having a deficient CCR5, and so these patients will have the infection Because the virus might utilize other co-receptors like CXCR4 but it'll slowly or might not progress to AIDS.

- Conclusions

Take the clinical history; uncover the conditions affecting the immune system like infection, malnutrition, metabolic disorders if uncontrolled, and use of drugs.

26.23min- 44.22min

** A figure below contains key info to remember :D



Finally right?!

Remember always ..

قال صلى الله عليه و سلم : " من سلك طريقاً يلتمس فيه علماً ، سهل الله له به طريقاً إلى الجنة "

May Allah bless each minute you spend studying, and please forgive if you found any mistake, and NEVER hesitate to inform me with :D