# Hematology

## *pathology*

☑ Sheet ☐ Slide ☐ Handout

Number: **6**

Subject: **Non neoplastic Disorders of WBC**

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# Non neoplastic disorders of White Blood Cells

- This sheet was written according to the recording of section 2
- This sheet discuss (Non neoplastic disorders of WBCs ):
    1. introduction
    2. Leukopenia :
        a. Neutropenia
        b. lymphopenia
    3. leukocytosis

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## Introduction:

- Non-neoplastic WBCs disorders are quantitative diseased ( we have a problem in the number of white blood cells )
- Normal range of white blood cells that we use in clinical practice between 4,000-10,000 cells per milliliter (4,000-10,000 / mL) or in another unit 4 – 10 trillion cells per liter ( 4.0-10.0 * $10^{12}$ / L )

**(But we have an exception for infants as they have a higher number of WBCs than the normal range.)**

- (4,000-10,000/ mL) is the total count of WBCs
- WBCs contain many cell types and each type of these cells has a normal range / percentage :

**1) Neutrophils**: most common cells (40- 75%) of the total count

**2)Lymphocytes** : second most common (20-45%) , lymphocytes in children are normally higher in range and sometimes they are more common than neutrophils and this is normal , because children are building their immune systems and they need lymphocytes more than neutrophils .

**3) Monocytes**: third most common (2-10%)

**4) Eosinophiles**: (1-6%)

**5) Basophiles**: the last one (0-1%)

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## Leukopenia

- Leukopenia: the decrease in WBC total count below average levels (<4,000 cells), and the most common cause of leucopenia is a decrease in neutrophils. Why??
  Because Neutrophils are the bulk of the WBC count, so if they decrease or increase they would result in leucopenia or leukocytosis.
- In this lecture we're going to talk about two types of leukopenia ( neutropenia and lymphopenia )

### ***first: neutropenia***

- **When do we have neutropenia?**
  We depend on something that's more accurate than the percentage, which is ANC (absolute neutrophils count), it's calculates by multiplying the percentage with the total WBC count.

**ANC = (%neutrophils) * (total webs count)**

- If ANC is below 1500, then the patient has neutropenia. (ANC < 1500 cell/ micro liter )

- If a patient has the total WBC count (15,000) and the neutrophils percentage is (20%), when you multiply them you would get (ANC = 3,000 cells/micro liter) which is higher than 1500. so, although the patient had a low percentage of neutrophils than normal (20 %< 40-75%) he still has a normal number of neutrophils. So this is how we know if the patient has real neutropenia.

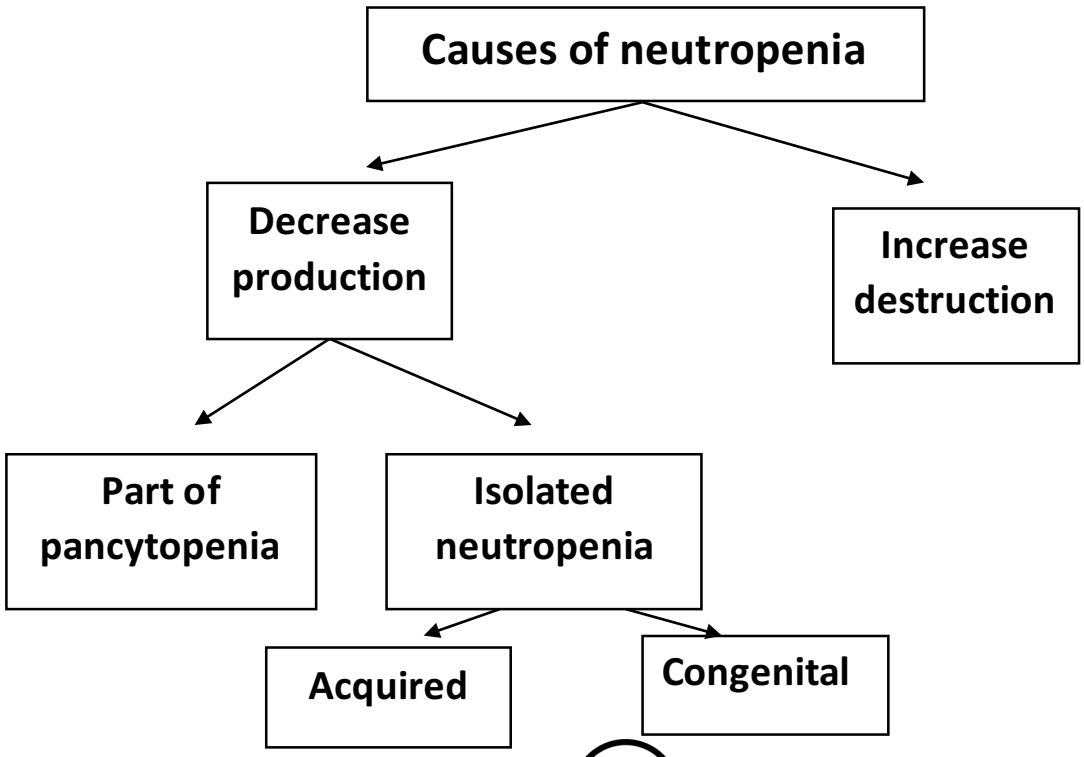
  We have stages of neutropenia that depends on the ANC, when the patients reaches ANC < 500 cells /micro liter then the patient has severe neutropenia (the most severe part or stage and is fatal if not treated), and the patient would start to develop spontaneous infections.

- **Causes of neutropenia :**

In general

1) Decrease production

2) Increase destruction



**A. Decreased production:**

**1**) Part of pancytopenia: here we have a problem in the bone marrow that affects the hematopoietic process , so the patient would have anemia, thrombocytopenia besides neutropenia, and this is the most common cause.

Causes:

- Bone marrow failure as occurs in aplastic anemia.
- myelophthisic anemia (physical destruction in the bone marrow most commonly by a tumor , tumors accumulate in the bone marrow and they destroy everything , similar to aplastic anemia but in aplastic anemia we have total failure in the bone marrow ,where stem cells fail to divide , and if we look at the bone marrow in aplastic anemia we will see fat and won't find any hematopoietic cells ) .
  That's why it's called myelophthisic, (phthisis) means physical infiltrations most commonly by cancer (metastasis or even by leukemia) and the patient won't have hematopoisis.
- Megaloblastic anemia : causes low production of RBCs ,WBCs ,and platelets
- Myelodysplastic syndrome : type of neoplasia where there is increased proliferation of myeloid progenitor cells that has the ability to become red cells ,granulocytes ,and platelets but in a manner that is ineffective ;so the cells produced are useless.
- Chemotherapy : affects the bone marrow

(To make it easier to memorize, they're combined in the word (MAC)

( 3M, 1A, 1C)

2) Isolated neutropenia: less common, the patient has only a problem in the neutrophils count; he doesn't have anemia or thrombocytopenia. This could be acquired or congenital.

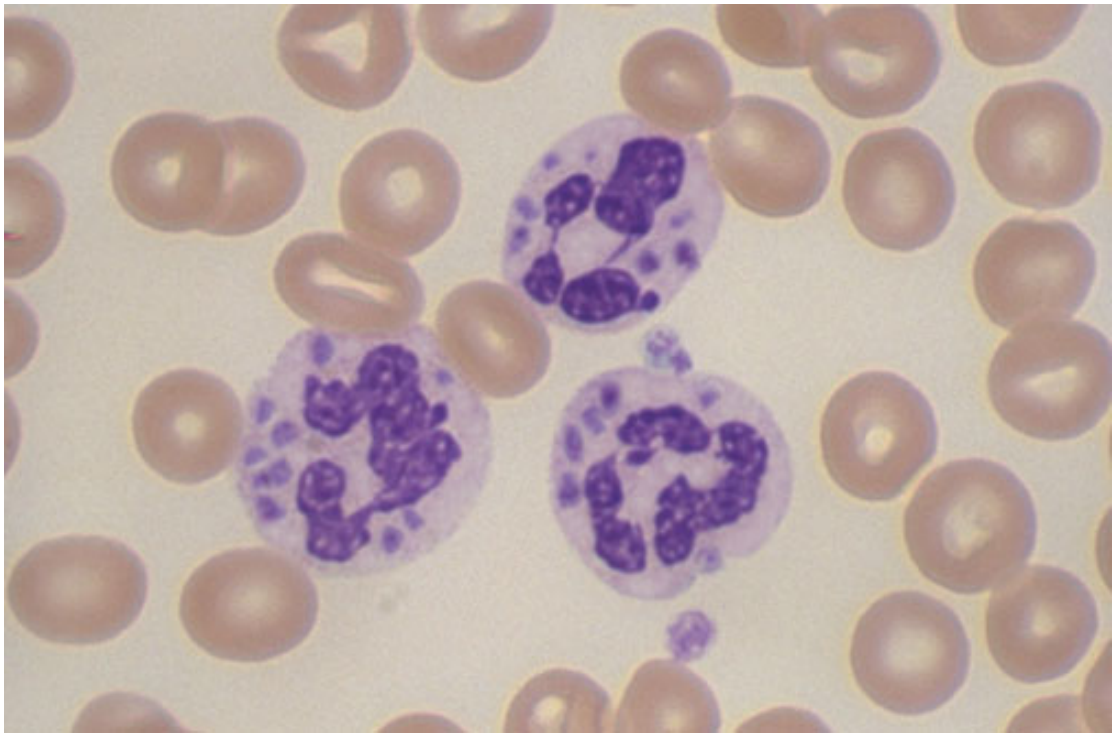
Acquired : isolated neutropenia is most commonly a side effect of drugs , some drugs can suppress the myelogenesis in the bone marrow , the most common are (anti epileptic, anti psychotic, anti-hyperthyroidism ) drugs , so remember whenever these drugs are administered , you have to always check the patient's WBCs count , cause if it severely decreased , the patient might have severe neutropenia , and die from spontaneous infections

Congenital: this means it would appear in pediatric patients, we have two syndromes:

1. Schwachman-Diamond Syndrome : autosomal recessive, there is a mutation in the gene SBDS , the normal function of this gene is to stabilize the RNA , so these patients don't have normal stability of RNA so they have a problem in the metabolism in the cells of the entire body , that why the patient comes with a group of diseases (multiple systemic defects) , such as : problem in the skeletal system and they don't grow properly , the pancreas doesn't function well so they have malabsorbtion cause they don't secret the normal enzymes , neutrophils are also affected, so the patient has a decrease in the count of neutrophils .

2. Chediak- Higashi syndrome : it's part of the immune deficiency syndromes , but this one is specialized in neutrophils , its autosomal recessive , a mutation in a gene called LYST , (LYS for lysosome , and T for trafficking ) , so we have a problem in the lysosomes , the normal function of lysosomes is to fuse with the phagosome to destroy its contents , here we have a problem in the lysosomes trafficking , as the lysosomes can't join the phagosomes , and instead they aggregate together , that’s why these patients have a morphology in their neutrophils , their neutrophils contains large lysosomes that can be seen by normal stain .

These neutrophils have abnormality in function, and the pathogens that enter are not being destroyed and they kill the neutrophils, that's why the patient develop a decrease in the count of neutrophils and they have common infections. We diagnose this syndrome by the morphology of cells.



Note: (Bone marrow morphology) in general in the neutropenia that's caused by a decrease in production we have a distinctive morphology in the bone marrow, which is, decreased myeloid cells in both (pancytopenia or isolated neutropenia) but the only exception is myelodysplastic syndrome and megaloblastic anemia.

**B. Increased destruction:**

This means that the BM is functioning well, neutrophils are present in the BM but when they go to the peripheral blood they get destructed and die quickly, neutrophils have a normal lifespan of 5 days, so these patients have neutrophils that live for less than 5 days.

**Causes:**

1) Special overwhelming infections**:** normal infection would cause an increase in the neutrophils, but in this case the neutrophils count decrease, this happens in severe overwhelming infection, when bacteria overcome the immune system, and they destroy the neutrophils. This happens in terminal cases, when a patient has an infection and his neutrophils count is decreasing then you know that he's going to die. In this special setting infection we have (severe sepsis) also we have special type of bacteria that are known to dominate the neutrophils which are (salmonella and brucella), and usually in this case we have lymphocytosis along with neutropenia.

2) Immune mediated: patients would have destruction of the neutrophils by abnormal antibodies such as in (Rheumatoid arthritis).

3) Cyclic neutropenia :inherited disease manifests at early ages (children) , caused by a mutation in a gene called ELANE (ELA for elastase and NE for neutrophils ) , here we have a mutation in elastase whish a protease that cuts the protein elastin , elastin is used to shape the cell , in this disease we have a mutation in elastase that makes it resistant to destruction and it (elastase) stays in the cell to destroy more elastin , the cell's skeleton becomes weak and they die , so these neutrophils die quickly and prematurely by apoptosis . This case clinically comes in periods / cycles, the patient is normal and suddenly he has neutropenia then normal then again neutropenia and so it comes in cycles. this case is seen in children

4) Hypersplenism: increased function of the spleen ,resulting in destruction of blood cells. It causes: anemia ,neutropenia, and thrombocytopenia.

5) PNH (Paroxysmal nocturnal hemoglobinuria): acquired somatic mutations in myeloid stem cells. In this case we have acquired mutations in gene PIGA which is required for the synthesis of membrane anchors which are required for anchoring surface proteins (specifically CD 55 / CD 59 ) ,what is the function of CD55 and CD59 ?

They protect the cell from the complement system. ( note : complement system works as a part of the innate immune system and can kill cell be drilling a whole in the cell membrane by building MAC complex ) so our cells protect themselves from the complement system by using these surface proteins , they neutralize and stop the complement system .so a mutation happens and the cells don't have these proteins anymore , if these proteins are not there , then the complement system will destroy the normal cells in the blood , which are RBCS , WBCs and platelets .

Note: (bone marrow morphology) in general in the increased destruction if we took a biopsy from the BM, we see normal production or even an increase because it's trying to compensate, so the myeloid cells are present normally in the BM but the patient has neutropenia, so we know that the disease is outside the BM, either in the blood or in the spleen.

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## ***second: lymphopenia***

**Lymphopenia**: mush less common than neutropenia

Caused by a decrease in lymphocytes count (like ANC, we calculate lymphocytes count by multiplying the lymphocytes percentage with the total WBCs count)

- **causes :**

1) **Acquired :**
**HIV**: most common, destroys the normal T cells

**Steroid treatment (corticosteroids therapy)**: doesn't cause a true lymphopenia but it inhibits the migration so lymphocytes can't go to the blood, so it causes a relative lymphopenia

These two causes are the only acquired causes of lymphopenia . (For older / adult patients two possible causes only)

2) **Congenital** : the cause for lymphopenia in children/ pediatric
**Congenital immunodeficiency:** too many diseases, but they cause a decreased production in either T cells or B cells. For example, some disease includes absent thymus gland which results in decreased production of T cells.

## *Leukocytosis :*

Leukocytosis is classified according to the :

Cause : reactive leukocytosis / leukemia

***leukemia:*** is a group of cancers that usually begin in the bone marrow and result in high numbers of abnormal white blood cells

note: leukemia will be discussed thoroughly in the next lectures .

## *Reactive leukocytosis:*

- Causes: inflammation caused by:
  a. Microbial causative agents
  b. Non microbial causative agents (sterile agents) : Physical destruction of the tissue ;like burns / ischemia or hypoxia .so the tissue dies and becomes necrotic, and wherever there's necrosis we have inflammation, , so any damage to the tissue causes inflammation. (This is the opposite of what happens in apoptosis)
- Luekicytosis can happen in **any type of cells** but it's most common in neutrophils.

- ✓ In reactive leukocytosis the white blood cell count will be higher reaching up to 12 thousands and in some cases 20 thousands /microlitter
- ✓ In rare cases reactive leukocytosis may mimic leukemia ; such “leukemoid” reactions must be distinguished from true white cell malignancies specifically chronic myelogenous leukemia
- ✓ Leukemoid reaction: markedly increase in the count of leukocytes, usually above 20,000 cells/ micro liter In this case, if we look under the microscope, we will find a lot of neutrophils and also some immature cells like myelocytes and metamyelocytes because we have an increased production (left shift)

  - Causes:

I. severe infection or sever stress like trauma or after major surgeries .

II. usually patients in the ICU ( intensive care unit ) commonly have this reaction

III. secondary to paraneoplastic syndrome , here we have cancer , and cancer secretes cytokines that stimulates the bone marrow to produce more myeloid cells .

- Now how to differentiate between leukemoid reaction and leukemia?

Both have high count if WBCs , but

1) in the leukemoid reaction you have an obvious cause for this case , like a major surgery or a trauma or cancer ,but leukemia patient come with little symptoms and with no obvious reason you find that they have a markedly increased WBCs
2) another thing that we can do is a genetic mutation test where leukemoid reaction patients don't have any mutations
3) the leukemoid reaction is reversible , but leukemia results in a permenant change in cells .

These are the differences between leukemia and leukemoid reaction .

**classification of reactive leukocytosis according to the type of cell causing it:**

1) Neutrophilia : most common cause of leukocytosis
    a) Causes:
        I. True Neutrophilia: bacterial infection (most common cause) / sterile or aseptic inflammation (burns / tissue necrosis myocardial infarction )
        II. Apparent Neutrophilia: steroid treatment (steroids increase the production of neutrophils) / drugs like adrenaline ( it shifts the equilibrium between circulating

and marginating neutrophils and increases the number of circulating neutrophils

b) In all these cases , we have an increase in the function of neutrophils which to fight bacteria , neutrophils :

I. show more granules , and become full of granules , this is called Toxic granulation

II. also the vacuoles in the cytoplasm become more prominent.

so in Neutrophilia , neutrophils show toxic granulation and cytoplasmic vacuoles = toxic change

c) This toxic change is considered another difference between leukemoid reaction and leukemia , as leukemia contain normal morphology of neutrophils but with an increase in number . but in leukemoid reaction we have a reaction and you can see the toxic changes in neutrophils morphology .

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2) Eosinophilia : they only increase in number in special cases :

a) Allergic reactions : the most common cause

b) Parasitic infections

c) Drug reaction : it includes an allergic reaction toward a drug or as a side effect of the drug

d) In association with Some cancers / malignancies : the most famous one is Hodgkin Lymphoma , as this type of cancer activates eosinophils .note that the increase in eosinophils is a result of malignancy not a malignancy itself

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*3)* Monocytosis : monocytes can increase in both acute or *chronic inflammations*

a) Chronic infections (e.g. tuberculosis)

b) Inflammatory bowel disease (e.g. ulcerative colitis)

c) Rheumatologic diseases ( chronic inflammation ) : in any chronic inflammation , the monocytes increase

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4) Lymphocytosis :

a) Causes: it's also common in chronic diseases

I. Accompanies monocytosis in many chronic inflammations: e.ge Rheumatologic diseases ( a chronic disease )

II. Viral infections : viruses are always attacked by lymphocytes instead of neutrophils , wether it was acute or chronic infection

III. Tuberculosis (chronic inflammation ) ; caused by bacterial infection , but this type of bacteria behave like viruses that's why it's attacked by lymphocytes , so in TB we have an increase in Lymphocytes as well as Monocytes and not neutrophils .

b) All of these causes caused an increased lymphocytes in the blood , so what about lymph nodes ?

I. Lymph nodes are full of lymphocytes , and sometimes these lymphocytes increase (lymphocyte hyperplasia) even in the lymph nodes , so the lymph node eventually become enlarged with and this is called **reactive lymphadenitis .**

Note: Reactive means it's non-neoplastic, because when a lymph node gets bigger it could be lymphoma or reactive lymphadenitis, here it's non-neoplastic because it results from a response to antigen (this antigen could be from an infection or from autoimmune disease)

So The lymph node becomes enlarged , and in clinical practice this is called **(lymphadenopathy)** , adeno means gland , and this means lymph node enlargement

II. The infections causing reactive lymphadenitis may be acute or chronic:

1) **In the acute setting** of the reactive lymphadenitis , the lymph node becomes painful ; because of the rapid enlargement it stretches in the capsule of the lymph node which contain nerves , so they are painful .

always when it's painful this means it's acute . this is the opposite of lymphomas , they enlarge slowly , which means that they are painless . ( this is how you can differentiate between lymphomas and acute reactive lymphadenitis )

**2) Chronic reactive lymphadenitis**

There are 3 patterns of chronic reactive lymphadenitis:

a. Follicular hyperplasia: caused by B cell hyperplasia.

Now B cells histologically in the lymph nodes are located in the follicles, so when there is a proliferation in B cells we have Follicular hyperplasia.

Normally , follicles in lymph nodes are far from each other ( not touching other follicles ) and arranges neatly , but if we took a sample from a patient, and found an increased follicles and they were touching and infusing with each other , then this is not normal and the patient has follicular hyperplasia .

Certain diseases activate the proliferation of B cells only and you have to know them:

- HIV ( because HIV virus destroys T lymphocytes )

- Toxoplasmosis
- Rheumatologic diseases in general

b. Paracortical hyperplasia: T cells hyperplasia

T cells are normally present between the in the paracortix and when they proliferate they will cover the follicles( تغطي عليها) and this is called diffused hyperplasia or paracortical hyperplasia .

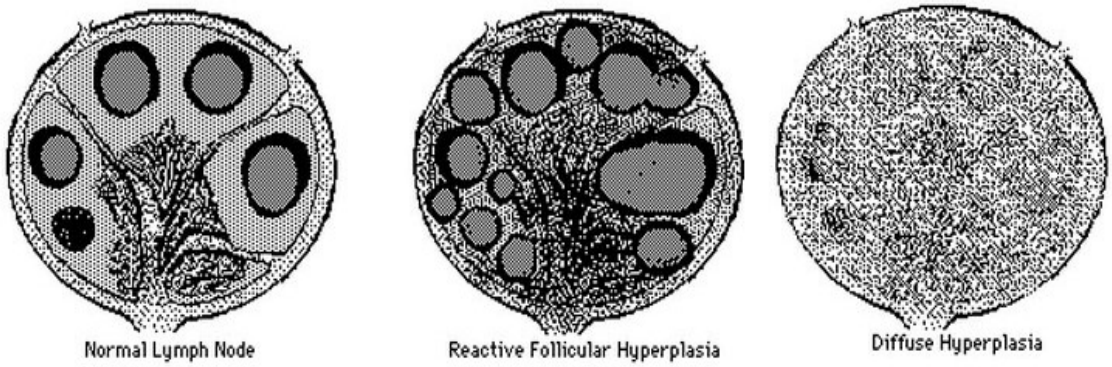
Certain diseases activate the proliferation of T cells:

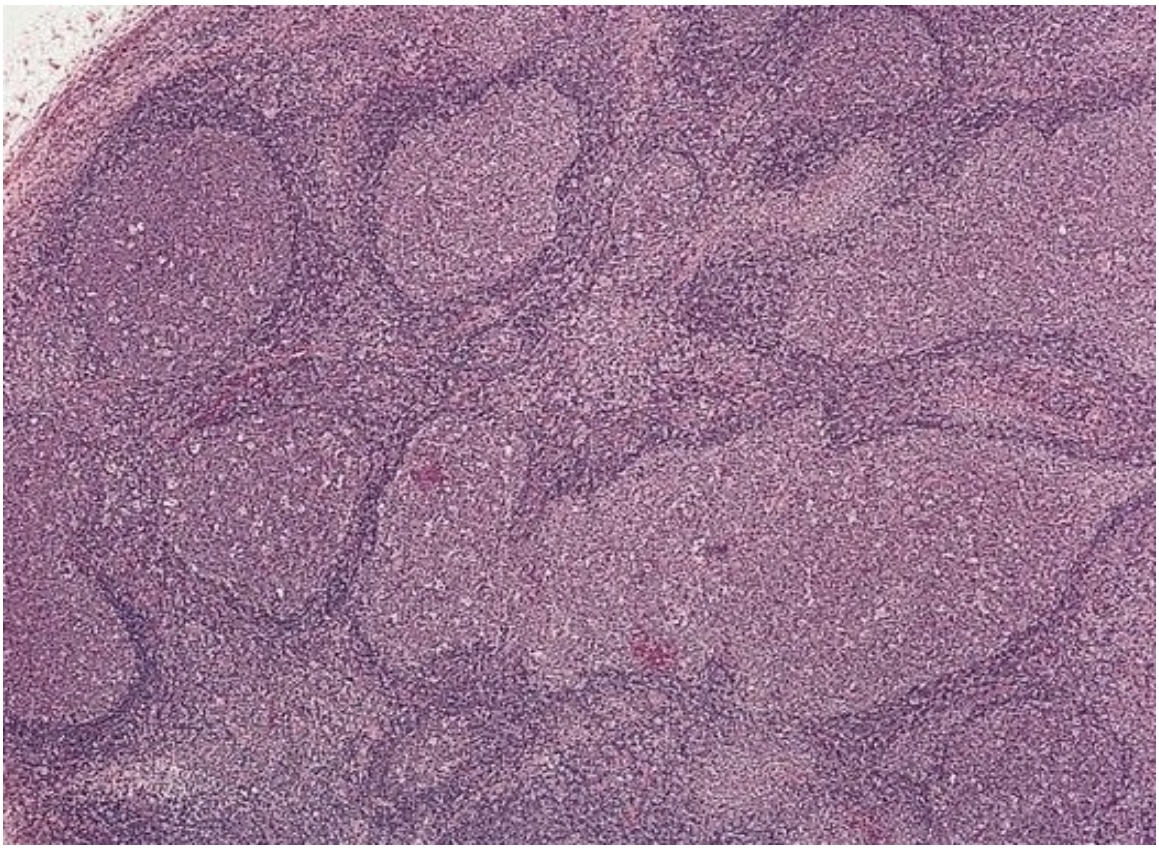
- Viral infection : the most common ( except HIV )
- Drugs reaction : drugs sometimes could activate the proliferation of T lymphocytes , as well as Eosinophils like we said before .
- Post vaccination : vaccination could result in an enlargement in lymph nodes , and in this case it a diffuse hyperplasia caused be proliferation of T cells .

c. Sinus histiocytosis: hypertrophy of lining endothelial cells and dense infiltration of macrophages (histiocytes) causes distention of lymphatic sinusoids.

This pattern is found in : lymph nodes draining cancers

Note : the Dr did not discuss the last pattern.



Reactive follicular hyperplasia: note the enlarged follicles, variable sizes and shapes