Hematology

Medical Committee
The University of Jorda

- Histology
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- lecture number : 5
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POLYCYTHEMIA

- It is defined as an increase in RBC **mass** above the normal level when hemoglobin is above 16 g/dl in women and 18 g/dl in men.
  Note: erythrocytosis is the increased **production** of RBCs above the normal count, it can occur in polycythemia and some hemolytic anemias (for example in thalassemia where you have ineffective erythropoiesis).
  So erythrocytosis does NOT equal polycythemia.

- There are two types of polycythemia:

Primary Polycythemia (polycythemia vera): there is no obvious cause, this is neoplastic, the bone marrow is abnormal, it produces excess amount of RBCs without any obvious reason. So, it is a neoplastic disease of the RBC line.

It is characterized by low erythropoietin (which is secondarily suppressed by the high number of RBCs) and patients have splenomegaly, Plethora (redness of the skin due to congestion of RBCs in superficial veins), cyanosis (blue color due to hypoxia) and itching (due to an increase in WBCs that secrete interleukins).

Also, the circulation becomes slow/sluggish due to increased number of erythrocytes, and they tend to thrombose secondary to the high number and slow movement of the RBCs.
In any organ of the body (one of them is the bone marrow), the increased number of cells causes gout due to increased production of uric acid by lysis of cells.

Secondary polycythemia: (more common) there is an obvious cause that increases blood production of RBCs or polycythemia.

Chronic hypoxia for any reason causes secondary polycythemia, and this might be due to:

1. Chronic lung disease.

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2. Chronic heart disease: like in septal defect in which the heart does not work well, so there will be systemic hypoxia (which induces high levels of erythropoietin that will increase the bone marrow production of RBCs and result in secondary polycythemia).
3. Alcoholism: there are many mechanisms in which alcohol causes erythrocytosis, in one of them alcohol suppresses ADH secretion, so patients who drink a lot of alcohol tend to urinate more and therefore lose more fluids, so RBCs become more concentrated. Also, alcohol suppresses breathing (specially at night), and it causes acidosis, hyperkalemia and increases CO2 concentration, and this causes hypoxia, so the body responds by producing erythropoietin.
4. Smoking: causes hypoxia in the lung.
5. High altitude.

Another cause of secondary polycythemia is renal cell carcinoma, which increases the production of erythropoietin.

Surreptitious, which is the voluntary intake of erythropoietin or RBCs, is common in athletes who try to enhance their performance by bringing more oxygen to their tissues. This causes polycythemia.

- What's the difference between Primary and secondary polycythemia?
  In secondary polycythemia, if you eliminate the underlying cause, patients will no longer have polycythemia (i.e. it is reversible). Also, in secondary polycythemia, you have high levels of erythropoietin and NO splenomegaly.

Note: In polycythemia vera, RBCs are abnormal, so one of its manifestations might be cyanosis due to hypoxia. However in surreptitious intake, athletes use RBCs that are normal, and can readily deliver oxygen.

Now, we're done with the RBC disorders.

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WHITE BLOOD CELL DISORDERS

Normally in the peripheral blood, the WBC count is between 4,000-10,000 cell/microliter, and this is for both men and women.

Most of the cells are neutrophils, and the normal range in an adult is 40-75%. The second most common cell is the lymphocyte and the normal range is 20-45% (however in children lymphocytes are more abundant than neutrophils). Then monocytes 2-10%, eosinophils 1-6% and the least common are the basophils 0-1%. And if you want to calculate the absolute number of each cell (neutrophils for example) you multiply the total number of WBCs by the percentage of that cell.

We could have Leukocytosis (an increase in the total number of WBCs above 10,000 cell/microliter) or leukopenia (a decrease in the total number of WBCs below 4,000 cell/microliter). At the same time, each cell type could be decreased or increased in number regardless of the total number of cells, and that's why we should also study the differential count. So we should care about both the total count and differential count for each cell.

Note: most RBC disorders are anemias (benign) except for polycythemia, whereas most WBC disorders are malignant and very few are benign (not neoplastic).

A. Leukopenia

It is a decrease in the total number of WBCs. Neutropenia is the most common cause of leukopenia. In contrast, lymphopenia is much less common than neutropenia. Lymphopenia is most commonly congenital (babies are born with defects in the production of lymphocytes and they are vulnerable for infections), however; lymphopenia is acquired in cases of HIV infection which leads to AIDS or in high doses of corticosteroids.

Neutropenia

- We calculate the absolute neutrophil count (ANC) by multiplying the total WBC count by the percentage of neutrophils. If it is below 1,500 cell/microliter, this is absolute neutropenia, and with progression of the decrease in neutrophil count it might reach below 500 cell/microliter and this is called severe neutropenia, and these patients suffer from spontaneous infections (caused by the normal flora).

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- Causes of Neutropenia; decreased production or increased destruction.

Decreased production: and it could be:

Part of pancytopenia (more common): there is a reduction of RBC, WBC and thrombocytes as well mainly due to bone marrow failure. Like in Aplastic anemia, Myelophthesic anemia (bone marrow destruction), megaloblastic anemia (cells are prone to apoptosis due to abnormal DNA), myelodysplastic syndrome (failure of differentiation of the cells) and chemotherapy (similar to aplastic anemia but it's reversible).

Isolated Neutopenia: only the Neutrophil count is decreasing (RBC and platelets are still normal). Usually it's acquired secondary to drugs (anti-epileptics, anti-psychotics and anti-hyperthyroidism drugs).

Congenital Neutropenia (less common) is due to 2 syndromes:

1. Schwachman-diamond Syndrome: autosomal recessive, there is a mutation in the gene *SBDS*, these patients have multiple systemic defects (skeletal abnormalities and pancreatic failure) early in life during infancy, and bone marrow is not producing neutrophils.
2. Chediak-Higashi syndrome: autosomal recessive, the mutant gene is called *LYST*, Neutrophils are not produced in sufficient amounts and they cannot function well (the problem is both quantitative and qualitative). These patients have abnormal lysosomal aggregation so they have bacterial infections early in life, they also have platelet dysfunction (so they have a bleeding tendency) and are Albinos (no melanosis of the skin and the hair, and the iris of the eye is blue).

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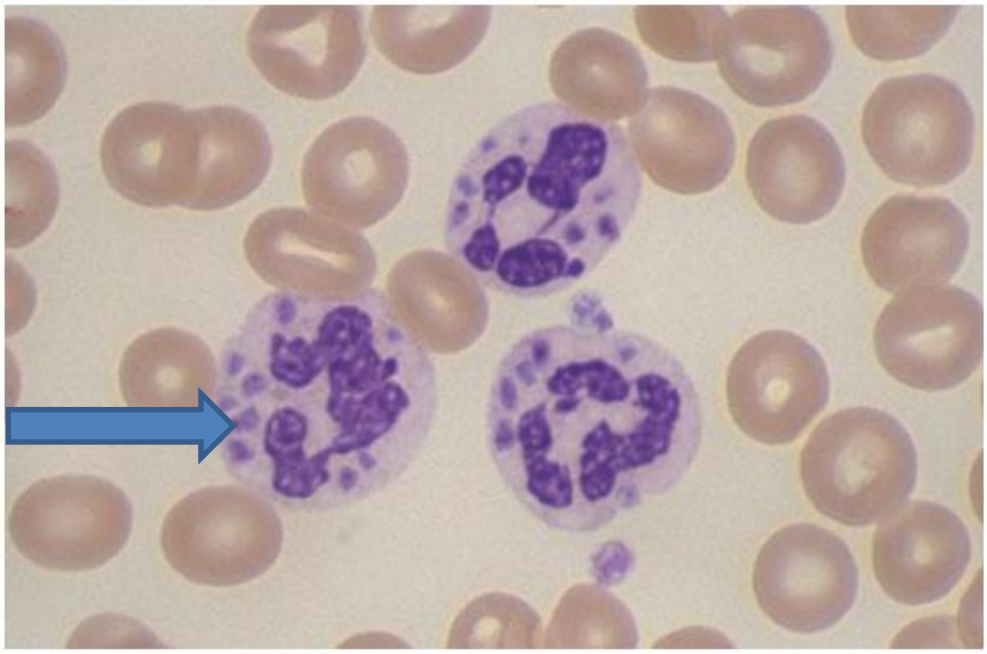

This is an image from a person with Chediak-Higashi, you can notice there are big granules (arrow) in the cytoplasm which are aggregates of lysosomes (this is abnormal).

Increased Destruction: and the causes are:

Severe infections and sepsis: when the bacteria overcome the neutrophils and destroy them, so the patient develops neutropenia, and this might result in death. Salmonella and Brucella are well-known for causing neutropenia. So not every bacterial infection causes neutrophilia.

Immune-mediated: patients would have destruction of the neutrophils by abnormal antibodies and it is common in auto-immune diseases (ex. Rheumatoid arthritis).

Cyclic neutropenia: autosomal dominant, occurs in children early in life, there is a mutation in *ELANE* gene which causes abnormal elastase quantity (elastase: metalloproteinase which causes destruction of the materials in the cells), so due to the increased number of elastase, and neutrophils would die prematurely. It occurs in cycles (neutropenia occurs in episodes) and this manifests clinically.

Hypersplinism: increased function of the spleen, resulting in destruction of cells which causes anemia, neutropenia and thrombocytopenia.

Paroxysmal Nocturnal Hematuria: if you remember it causes destruction and lysis of all three cell lineages.

B. Leukocytosis

When we discussed the RBC disorders, we said that most of them are benign (anemias), while polycythemia vera (cancer) is very rare and simple. In WBC disorders, it is the contrary. Reactive disorders are benign and there is an obvious cause that increases bone marrow activity, these disorders are small in number. In contrast, neoplastic disorders are much more common, and much more complicated.

Reactive Leukocytosis

It is an increase in the number of WBCs in the blood. The most common cause is infections. We have another non-microbial stimuli which we will later talk about. So, we notice an increase in number above 10,000 cell/microliter, and we have to look at the differential count of each cell type (neutrophils, lymphocytes …).

A special condition of leukocytosis is called **Leukemoid Reaction** where there is a marked increase in WBC count. The normal count is up to 10,000 cell/microliter, in this condition it might reach up to 50,000 or 100,000 cell/microliter or more. It is similar to leukemia, however there is an obvious cause in leukemoid reaction that causes the increase in number. Usually, there is a left-shifted granulopoiesis, which means that immatures WBCs go into the circulation and normally these cells are not present (metamyelocytes, myelocytes and promyelocytes are usually limited to the bone marrow), these cells go into the peripheral blood and this mimics leukemia. It occurs in very severe stress (patients in ICU) and in paraneoplastic syndrome in which patients have cancer and this cancer is functioning, and the cancer cells produce leukotrienes and all the inflammatory mediators which stimulate the bone marrow to produce a large number of neutrophils.

Neutrophilia

- It is an increase in the count of neutrophils above the normal level.
- Most common form of leukocytosis
- The most common cause is bacterial infections.
- Other causes are burns, tissue necrosis (ex. Myocardial infarction) and steroids (activate myelogenesis in the bone marrow).

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- In Reactive (non-neoplastic) neutrophilia, neutrophils are very active with prominent granules that are increased in number, and this is called toxic granulation.

Eosinophila

- It is an increase in eosinophils in the peripheral blood due to allergic diseases, parasitic infections, drug reactions (sensitivity to drugs) and in some cancers/malignancies (ex. Hodgkin lymphoma).

Monocytosis

- It occurs in chronic infections (ex. Tuberculosis), inflammatory bowel disease (there is a chronic inflammation in the GI system) and in rheumatologic diseases.

Lymphocytosis

- In case of a viral infection, the body responds by increasing the number of lymphocytes.
- Also, tuberculosis and rheumatologic diseases cause lymphocytosis.

Reactive Lymphadenitis

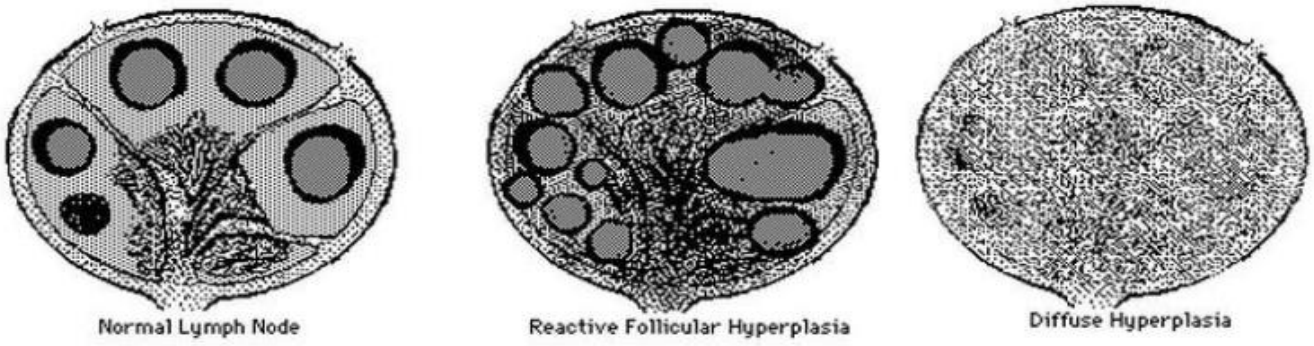
- All the previous disorders were related to blood while this is related to the lymph nodes. It is the increase in the size of lymph nodes secondary to the increase in the number of lymphocytes for a reactive purpose.
- Lymphocytes respond to antigenic stimuli in the body, which could be due to infections like viral infections and tuberculosis, or it could be autoimmune like Rheumatoid arthritis in which patients have enlarged lymph nodes.
- So it leads to enlargement of the Lymph nodes which is clinically referred to as Lymphadenopathy, where you can palpate these lymph nodes.
- In acute settings, the lymph nodes are painful; the rapid increase in size will compress the nerves around it, so patients will feel

pain. Most commonly it is benign due to bacterial or viral infections.

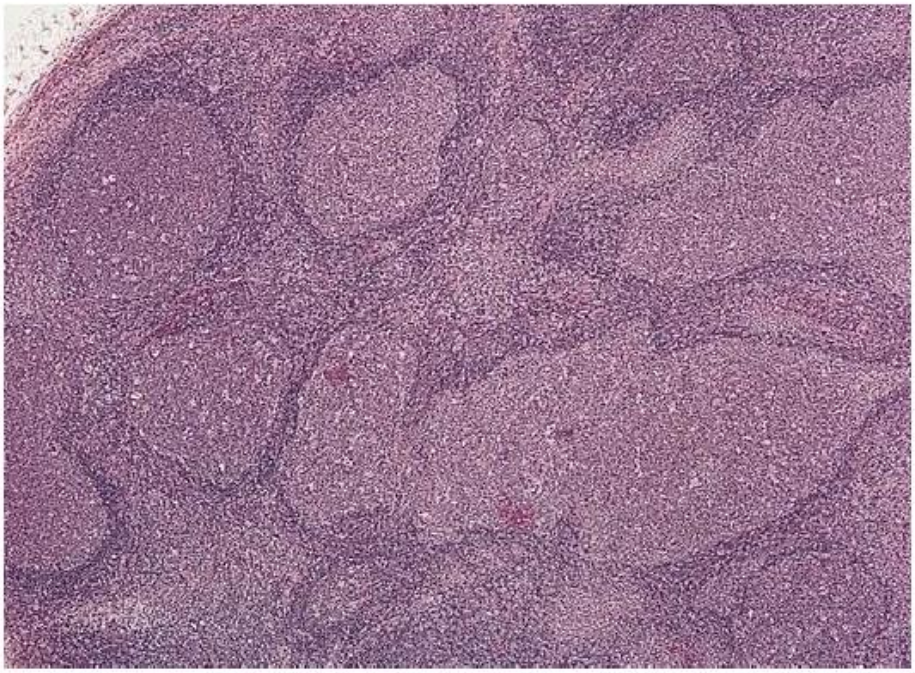
- However if it was chronic, it would be painless. It is common in rheumatoid arthritis and in cancer like lymphoma (it occurs over a long period of time so patients will have no pain).
  We will only talk about the benign causes of chronic reactive lymphadenitis, and they are many causes, however according to the response of the lymphocytes we classify them between B and T cells:

Follicular hyperplasia: when B lymphocytes proliferate they form germinal centers, and with increased proliferation of B lymphocytes, there will be an increased number of germinal centers and follicles inside the lymph node, so the lymph node will be enlarged. This occurs in HIV infection, toxoplasmosis (a parasite which causes increased number of B cells), in rheumatoid arthritis and other rheumatologic diseases. These patients will have chronic lymphadenopathy, increased number of B cells and a lot of germinal centers are seen under the microscope.

Paracortical (diffuse) hyperplasia: it is due to T cell proliferation, T cells are present in an area between follicles, so when they proliferate this area will expand and the lymph node will appear as if it has less germinal centers and it results in a diffused sheet-like appearance. It occurs in viral infections, drug reactions (sensitivity) and post-vaccination.



You can notice that in Reactive follicular hyperplasia, the follicles are in contact with each other. While in Diffuse Hyperplasia, you cannot clearly see the germinal centers due to the proliferation of T cells.



This is a Histologic specimen from a patient with B cell lymohcytosis, as you see there are a lot of germinal centers. So this is reactive follicular hyperplasia (Note the enlarged follicles, variable sizes and shapes).

C. Hematopoietic Malignancies

They are classified according to the cell of origin into: myeloid (the diseases is arising from the myeloblast), lymphoid (from the lymphocyte) and histiocytic (from the histiocyte).

Myeloid Neoplasms

We sub-classify them into three main categories:

(1) Myeloproliferative neoplasms.

(2) Myelodysplastic syndromes.

(3) Acute myeloid leukemia.

We will talk about the differences between them, but you have to know that there are genetic abnormalities in the three diseases; there are mutations in the stem cells which cause neoplasms. In all of them, there is an increased number of cells in the bone marrow (like any cancer). Also, both myeloproliferative neoplasms and myelodysplastic syndromes tend to progress to acute myeloid leukemia (the most severe one), so they are neoplastic conditions but they have slow progression (patients

may have the disease for a long period of time, then these stem cells can acquire mutations which transform them into blasts = acute myeloid leukemia).

Risk Factors for myeloid tumors:

In most cases there is no known risk factor, however some of the studied and proven risk factor are:

1. Chemicals: benzene which is used in chemical industry as a solvent, and pesticides (cause leukemia and myeloid neoplasms in cases of long exposure).
2. Radiation.
3. Some congenital disease: the most common one is fanconi anemia (seen in congenital aplastic anemia).
4. Smoking
5. Paroxysmal Nocturnal Hematuria: in which patients tend to accumulate more mutations.

Normal Cellularity of the Bone Marrow : normally in the bone marrow, each cell has a certain range, it does not exceed it or go below it. (You have to know these numbers)

The earliest cell is the **blast** (it could be a myeloblast, lymphoblast or monoblast), in normal people these blasts do not exceed 5% of the total cells in the bone marrow. If they exceed 5% this could be an indication of a neoplasm.

Promyelocytes: normally, they're up to 8%. If they are increased in number we have a disease.

Monocytes: do not exceed 5%.

Lymphcytes: do not exceed 17%.

Plasma cells: do not exceed 3%.

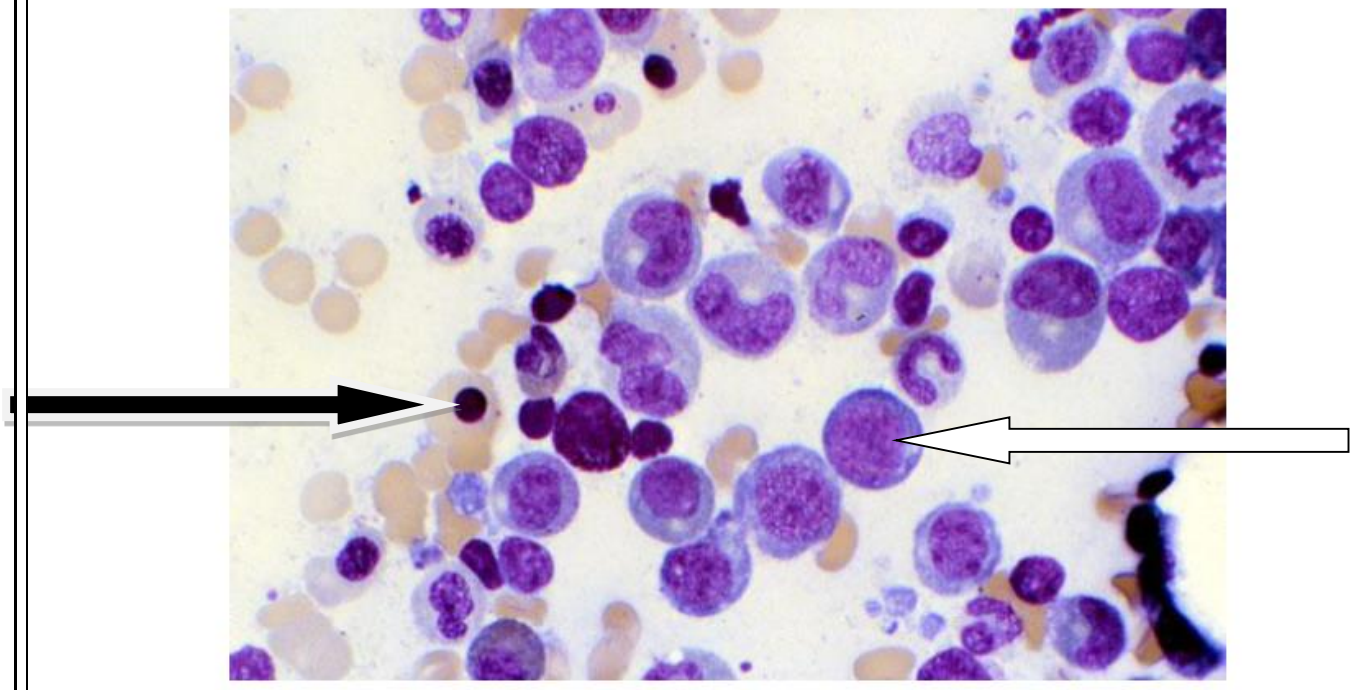
In practice, pathologists count the number of each cell in the bone marrow in order to know what is going on. Then we examine the myeloid to erythroid ratio (M:E). In the normal bone marrow, we have excess of the myeloid cells (they are more common than the nucleated normoblasts= developing RBCs). So we calculate the myeloid cells starting from the Promyelocytes till we reach basophils, neutrophils and eosinophils (this includes metamyelocytes and myelocytes), the same for erythroid cells; we start counting from the pronormoblasts to the metachromatic normoblasts, then we divide the number of myeloid cells over the number of erythroid cells and we get a ratio. This ratio should fall between 3-4

(i.e. the number of myeloid cells is 3-4 times the number of erythroid cells).

Now imagine a person having a M:E ratio of 10, this means that this patient has a marked increase in the production of myeloid cells (could be reactive or leukemic) or a marked decrease in RBC production. In another patient, you count the M:E ratio and you find that it's 0.5, this means either there is a decrease in the production of WBCs or there is a true increase in the number of RBCs (like polycythemia vera for example). So this is how you approach diseases in bone marrow examinations.

In addition to quantitation, we perform morphologic examinations. When we examine bone marrow specimens, there are two types of specimens:

1. Aspirate smear: you swipe blood on a slide and examine it under the microscope, and you can visualize the cells individually (how each cell looks like).



This is a smear from a patient, you can see myeloid cells which include the round myelocytes (white arrow), metamyelocytes (kidney-shaped nucleus) and some band cells and neutrophils. Also, you can notice the normoblasts (black arrow) which appear as nucleated RBCs. What is important is for you to notice that this smear contains <u>all stages of maturation</u>. If it only had myeloblasts, it would be an indication of leukemia. Also, if it had a lot of mature neutrophils, this could be an

indication of CML for example. You might see a smear without any normoblasts, it would be either decreased production of RBCs (ex. In parvovirus infection or pure red cell aplasia) or markedly increased myeloid cells (ex. Leukemoid reaction). To calculate the M:E ratio, you count each cell type by itself and then you add them together (like previously explained). So this is a normal bone marrow smear.

2. Bone Marrow Biopsy: using lower magnification you try to see how the tissue and its cells look like. Cellularity of the tissue in the normal bone marrow is variable. In early life the bone marrow is very active and the cellularity can reach 100%. The bone marrow's components are hematopoietic cells and fat. In Babies and during infancy there is no fat in the bone marrow (you have only hematopoietic cells). With age, atrophy occurs in the bone marrow, and it appears as a decrease in hematopoietic cells and an increase in the fat content, so hematopoiesis decreases with age.
   To calculate normal cellularity of the bone marrow, we subtract the age from 100%.

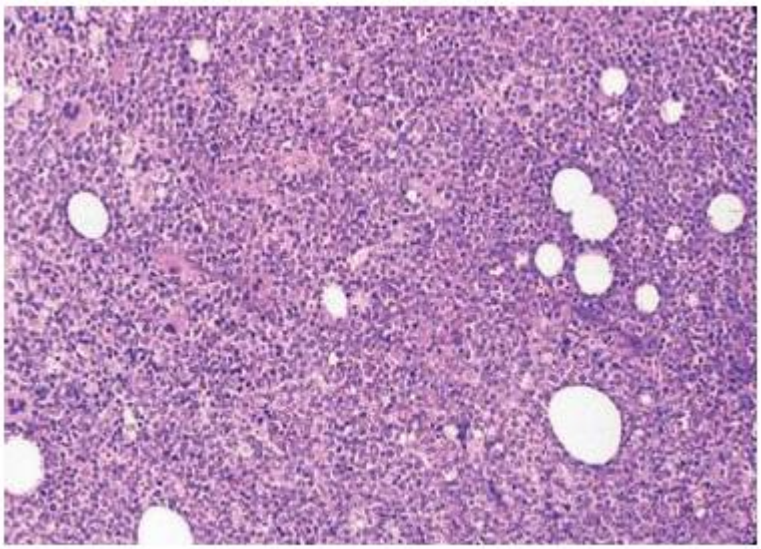
Q: Let's say we have a patient, who is 20 years old, what is the expected cellularity of the bone marrow?

A: normal cellularity = 100% - 20 = 80% (if you look at the bone marrow you should see 80% hematopoietic cells and 20% fat).

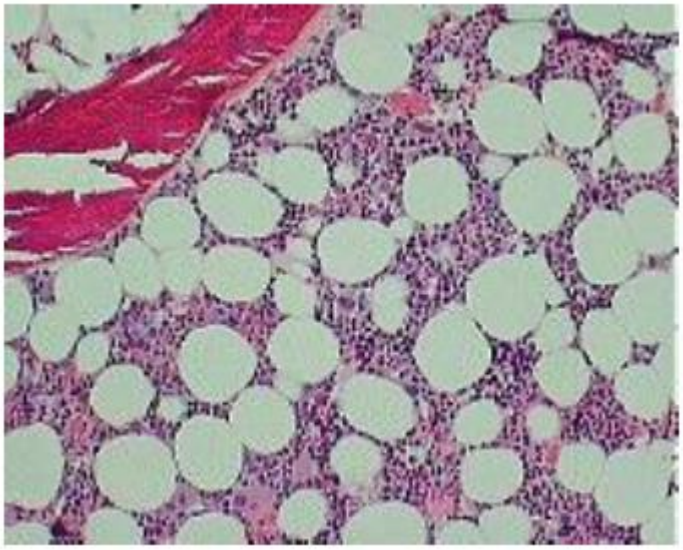
Q: let's say you took a bone marrow biopsy from a patient who is 30 years old, and you found out that he has 90% fat. Is this normal?

A: It is abnormal, you diagnose him with aplastic anemia, the bone marrow is failing and there is no hematopoiesis.

Conclusion: In the aspirate we count the cells, and in the bone marrow biopsy we observe the cellularity.



In this patient (previous image) the percentage of hematopoietic cells is around 90% and you estimate the percentage of fat to be 10%. We assume that this patient is a child (due to high cellularity).



However in this patient, the cellularity is about 50%, so we expect him to be almost 50 years old.

This is the end of this lecture.
Shout out to A.K. ♥