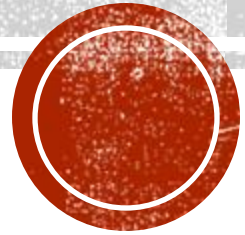
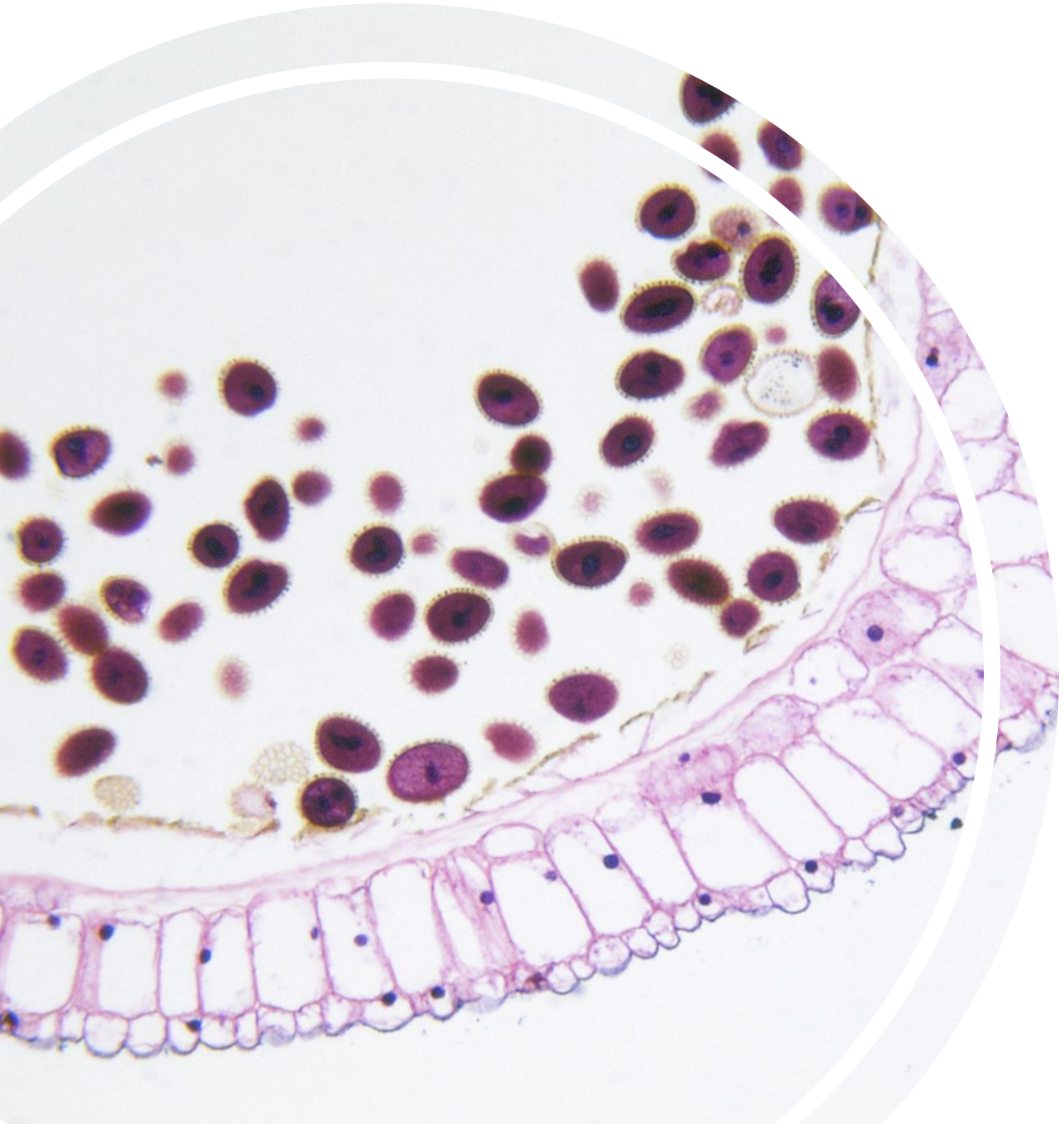
MEGALOBLASTIC ANEMIA

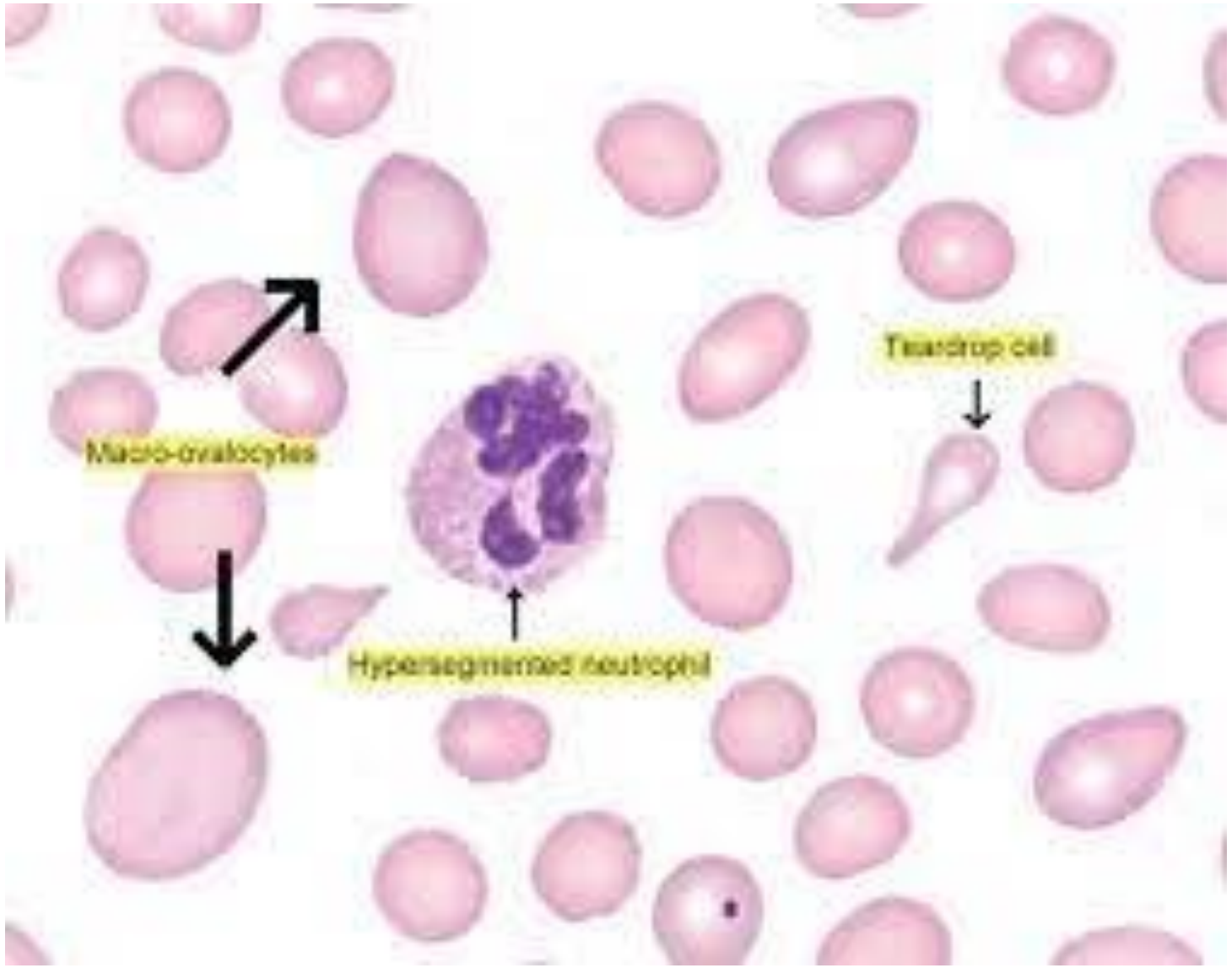




OVERVIEW

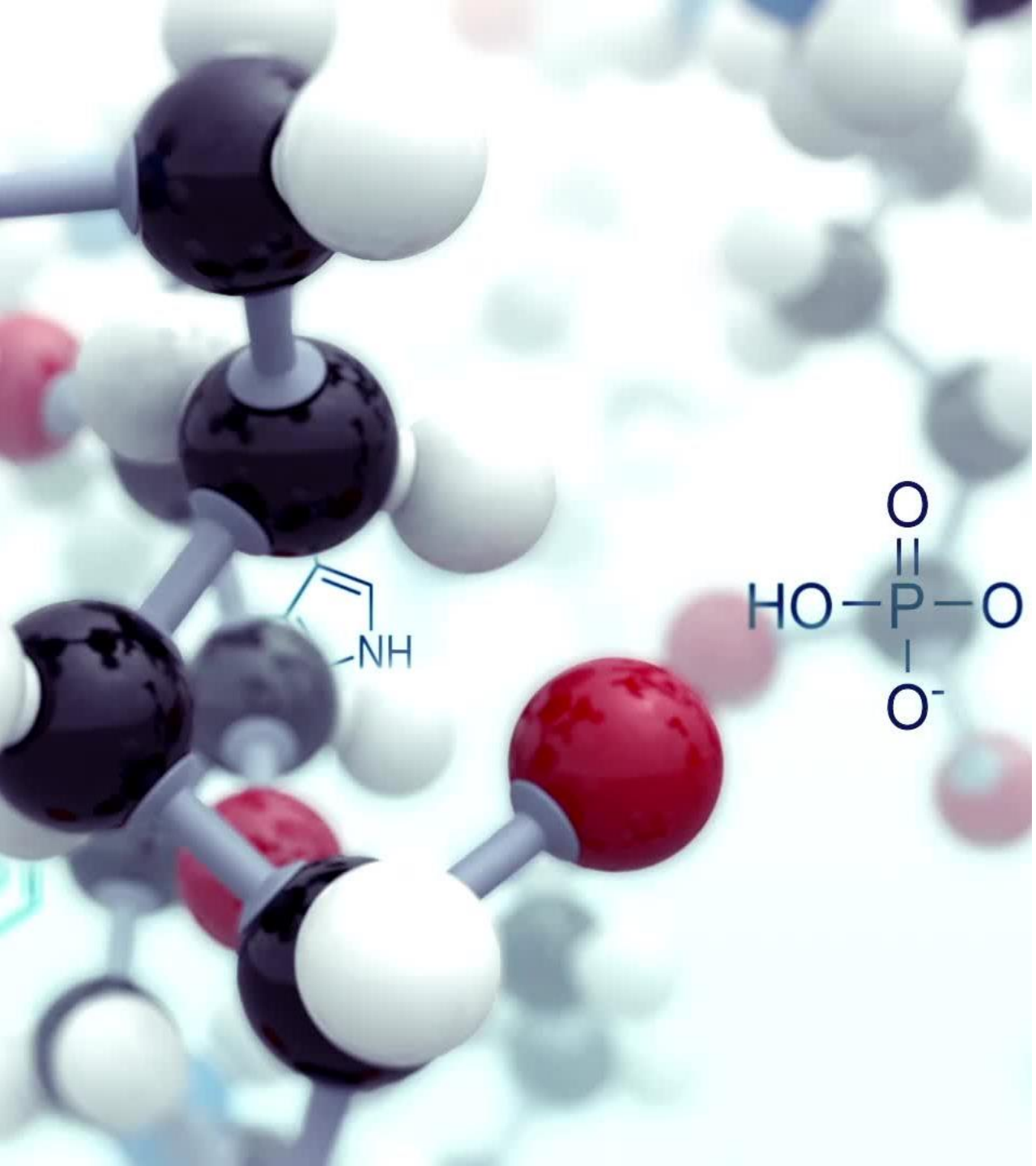
- Megaloblastic anemia (MA) encompasses a heterogeneous group of anemias characterized by the presence of large red blood cell precursors called **megaloblasts** in the bone marrow. This condition is due to impaired DNA synthesis, which inhibits nuclear division. Cytoplasmic maturation, mainly dependent on RNA and protein synthesis, is less impaired. This leads to an asynchronous maturation between the nucleus and cytoplasm of erythroblasts, explaining the large size of the megaloblasts

- **Megaloblastic Anemia:**
- Macro-ovalocytes
- Hypersegmented neutrophils
- Tear drop cell



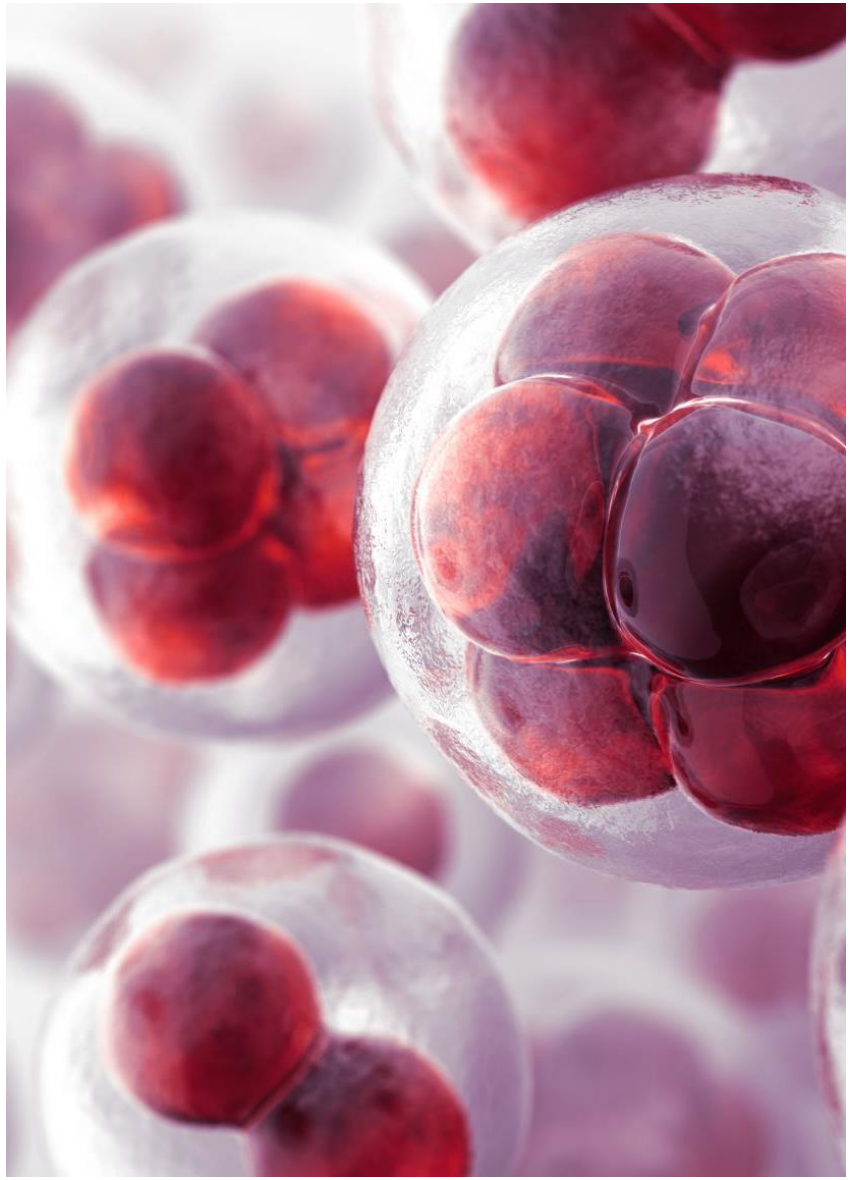
OBJECTIVES:

- Identify the etiology of megaloblastic anemia.
- Describe the diagnostic approach towards the evaluation of patients with megaloblastic anemia.
- Summarize the complications of megaloblastic anemia.
- Review the importance of improving care coordination among interprofessional team members to improve outcomes for patients affected by megaloblastic anemia.



ETIOLOGY

- Megaloblastic anemia is most often due to hypovitaminosis, specifically vitamin B12 (cobalamin) and folate deficiencies, which are necessary for the synthesis of DNA. Copper deficiency and adverse drug reactions (due to drug interference with DNA synthesis) are other well-known causes of megaloblastic anemia. A rare hereditary disorder known as thiamine-responsive megaloblastic anemia syndrome (TRMA) is also identified as a cause of megaloblastic anemia.

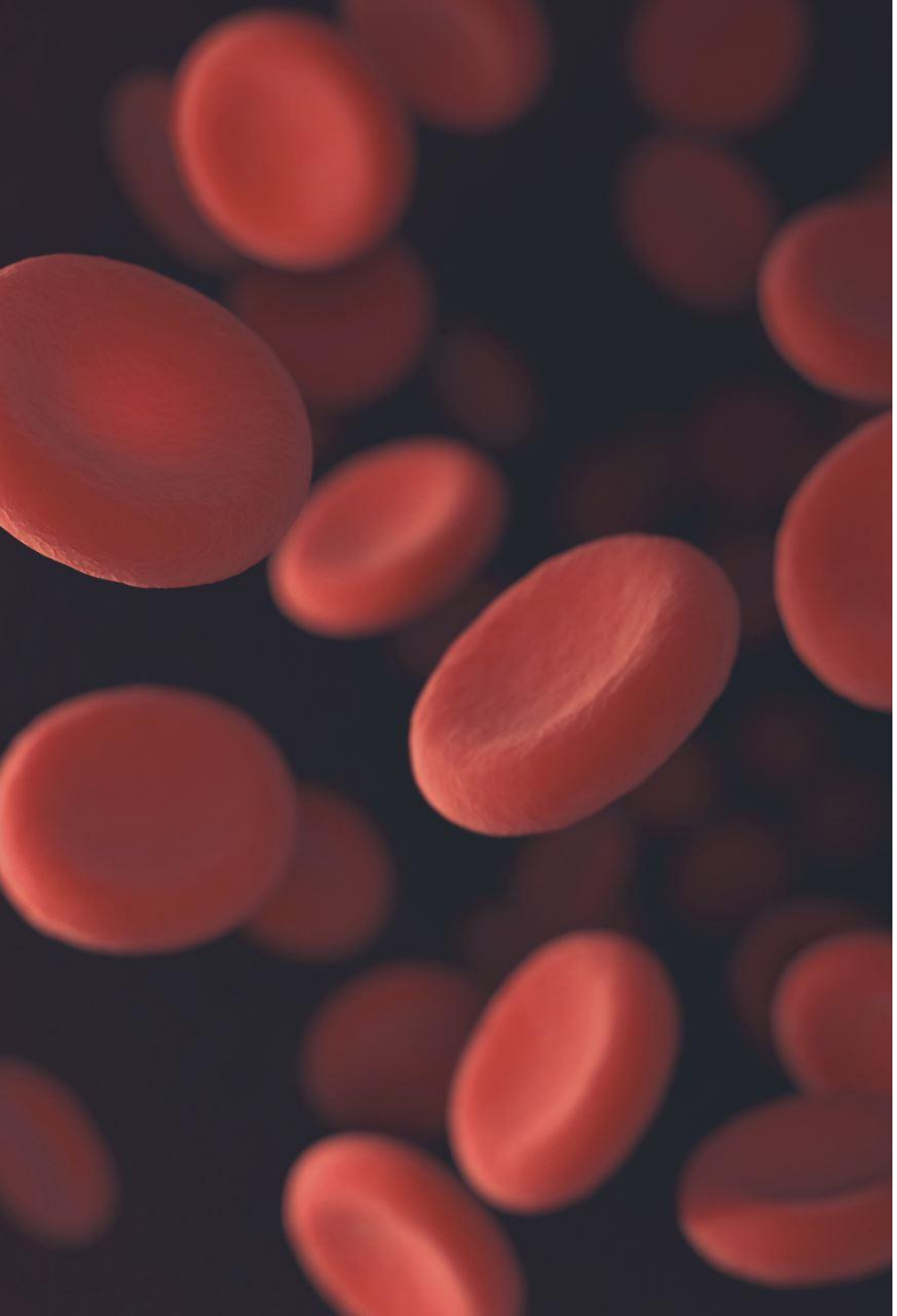


VITAMIN B12 DEFICIENCY

- The primary dietary sources of cobalamin are meats, fish, eggs, and dairy products.
- Vitamin B12 is first bound within the duodenum and jejunum to the intrinsic factor (IF) produced by gastric parietal cells and is then absorbed in the terminal ileum. The body stores 2 to 3 mg of vitamin B12 in the liver (sufficient for 2 to 4 years).
- The most frequent cause of vitamin B12 deficiency is pernicious anemia caused by autoimmune gastric atrophy, leading to decreased intrinsic factor production.Vitamin B12 deficiency may also develop following gastrectomy, ileal resection, or ileitis of any cause. Other causes of impaired vitamin B12 absorption include Zollinger-Ellison syndrome, blind loop syndrome, fish tapeworm infestation, and pancreatic insufficiency.

FOLIC ACID DEFICIENCY

- Folic acid is present in food such as green vegetables, fruits, meat, and liver. Daily adult needs range from 50 to 100 mcg. The recommended dietary allowance is 400 mcg in adults and 600 mcg in pregnant women.
- Folic acid is mainly absorbed in the jejunum and the body stores around 5 mg of folate in the liver, which is enough for 3 to 4 months.
- Folic acid deficiency may be related to decreased intake in the case of alcohol use disorder or malnutrition (elderly patients, institutionalized patients, poverty, special diets, etc.), increased demand particularly in case of pregnancy, hemolysis, hemodialysis, and malabsorption (tropical sprue, celiac disease, jejunal resection, Crohn disease, etc.). In some cases, medications like anticonvulsants and anticancer agents cause megaloblastic anemia related to folate deficiency by affecting folate metabolism.



COPPER DEFICIENCY

Clinical copper deficiency can cause microcytic, normocytic, or macrocytic anemia and neutropenia.

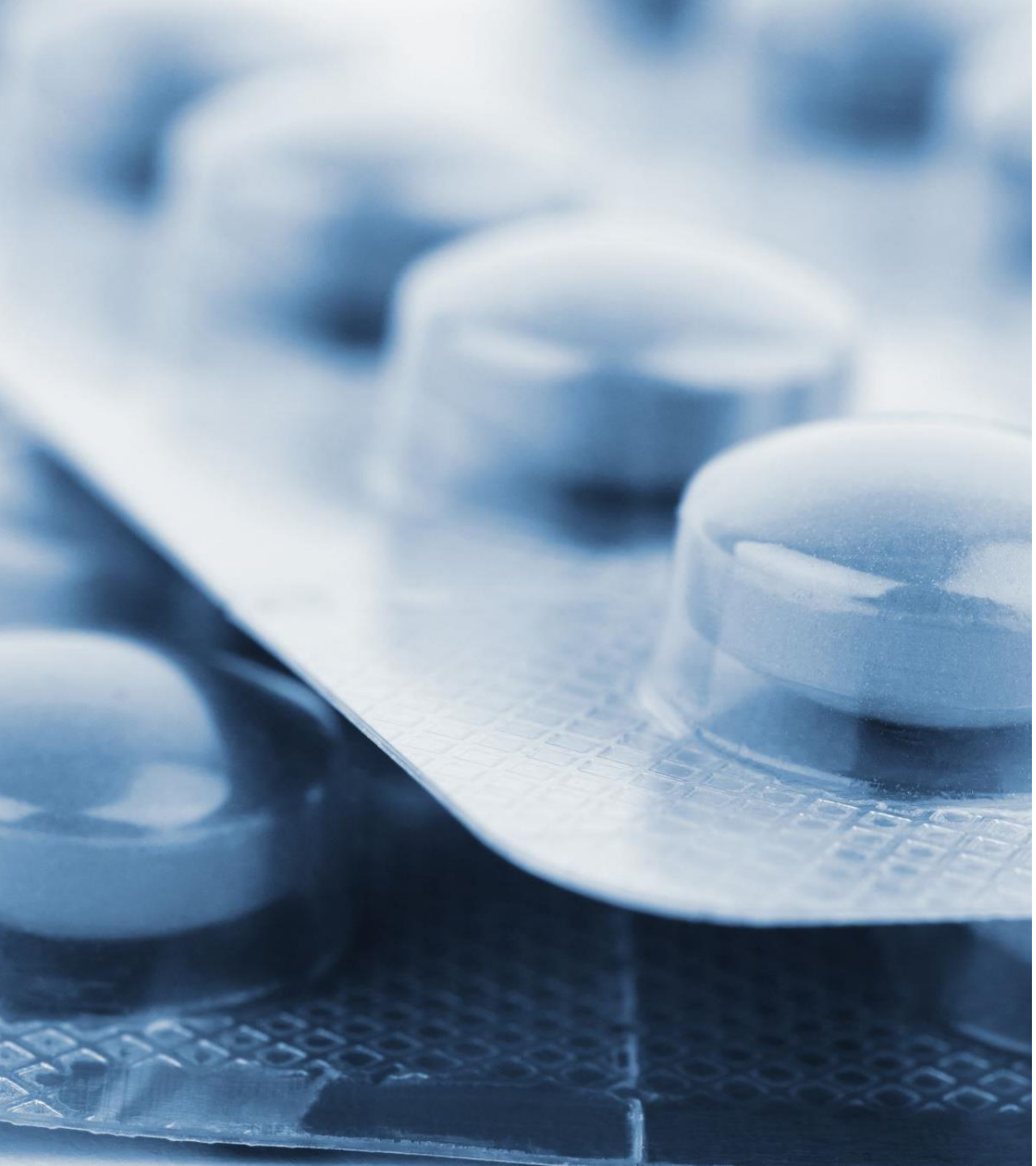
Copper deficiency also causes myelopathy and peripheral neuropathy.

Bone marrow evaluation can reveal myelodysplasia and megaloblastic anemia.

Treatment with copper replacement promptly reverses hematologic manifestations of the disease, although neurologic manifestation may take longer.

RARELY, MA IS DUE TO INHERITED PROBLEMS:

- Thiamine-responsive megaloblastic anemia syndrome: An autosomal recessive disease characterized by megaloblastic anemia associated with diabetes mellitus and early-onset sensorineural hearing loss. Mutations in the gene encoding a thiamine transporter (SLC19A2) are thought to be the cause of this disorder. The disease manifests in early infancy and is treated with high-dose thiamine.
- Inherited deficiency of intrinsic factor or the receptor in the intestines: Imerslund-Grasbeck syndrome or juvenile megaloblastic anemia is caused by biallelic mutations affecting the ileal receptor for the vitamin B12-IF complex. These patients also have proteinuria and abnormal vitamin D metabolism.
- Some infants have congenital folate malabsorption syndrome.



DRUG-INDUCED MEGALOBLASTIC ANEMIA

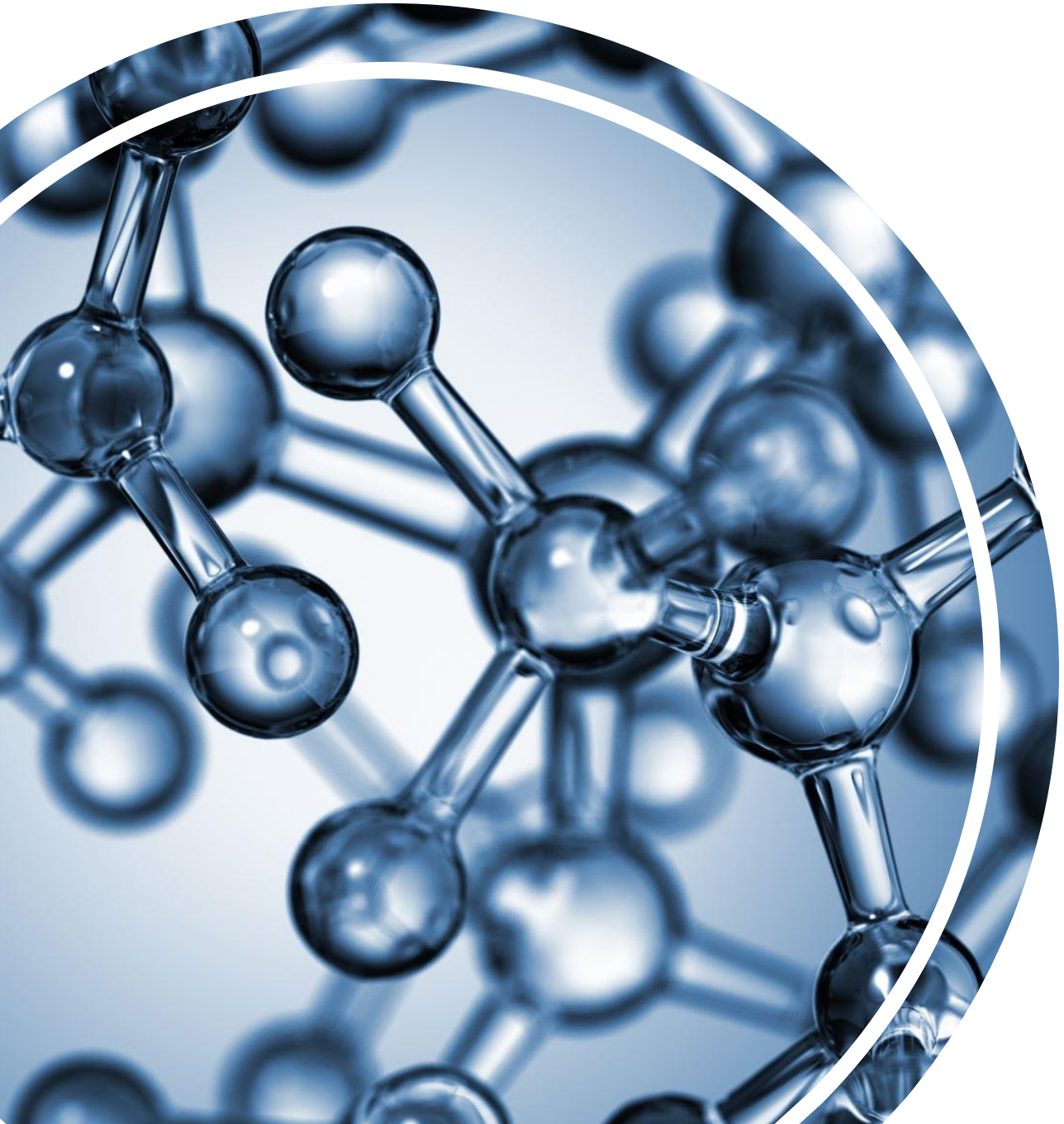
- Bone Marrow Effect (DNA Synthesis):
- Allopurinol, Azathioprine, Capecitabine, Cladribine, Fludarabine, Fluorouracil, Gadolinium, Gemcitabine, Hydroxyurea, Lamivudine, Leflunomide, Mercaptopurine, Methotrexate, Mycophenolate mofetil, Trimethoprim, Zidovudine.
- Reduce the intestinal absorption or metabolism of these vitamins:
- Aminosalicylic acid, Antacids and proton pump inhibitors, Penicillin antibiotics, Chloramphenicol, Erythromycin, Oral contraceptives, Metformin, Phenytoin, Tetracyclines, Valproic acid.

EPIDEMIOLOGY

The incidence of megaloblastic anemia increases with elderly, (> 60 years of age) Especially those living in retirement facilities.

Pernicious anemia is the most frequent cause of anemia related to cobalamin deficiency and usually occurs in individuals older than 40 years.

The incidence of folate deficiency is low, especially in countries with universal supplementation of folate in dietary products, but increases with alcohol use disorder, malabsorption syndromes, and decreased oral intake due to mental health diagnoses as the identified causes.

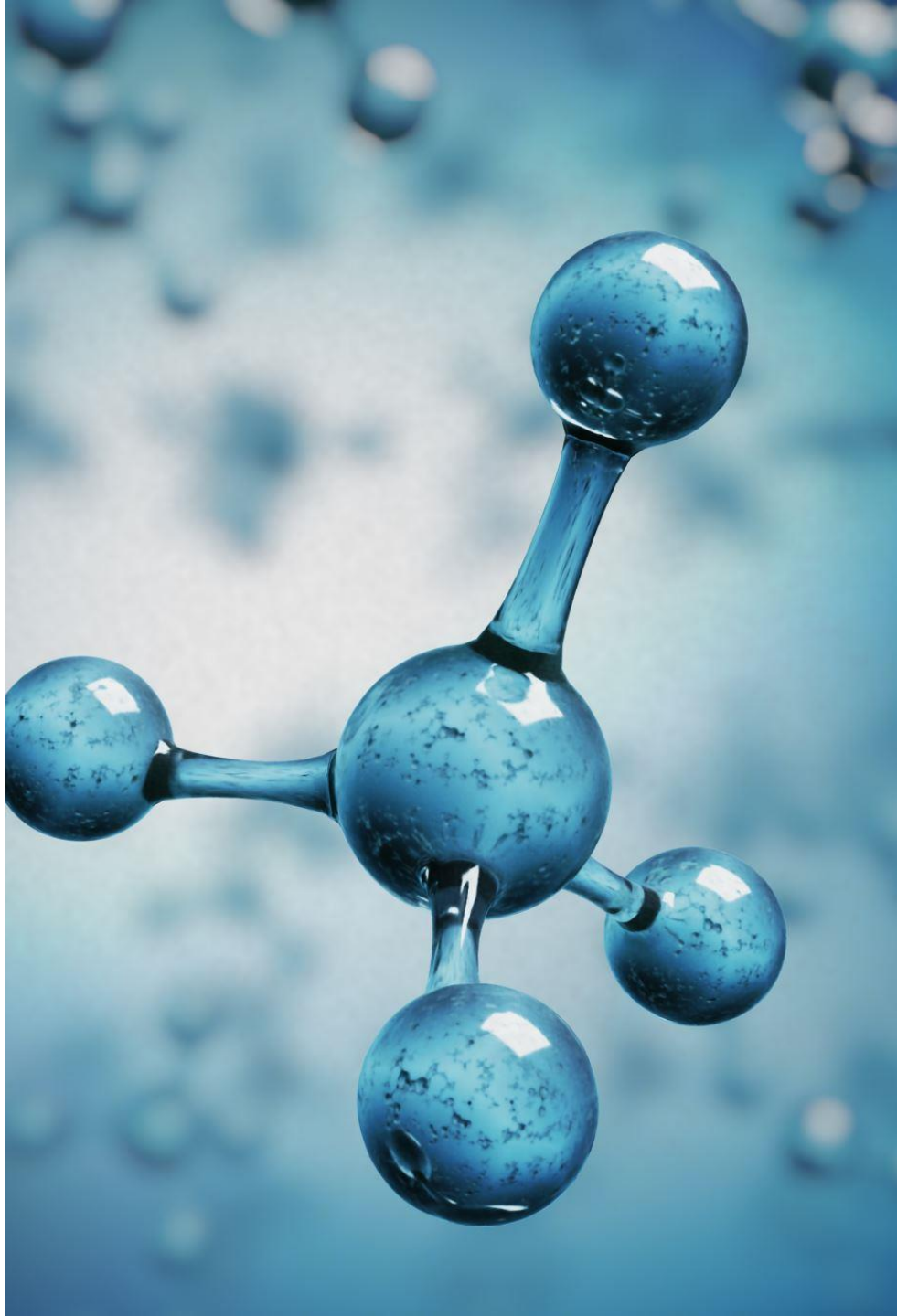


PATHOPHYSIOLOGY

- Ineffective erythropoiesis secondary to intramedullary apoptosis of hematopoietic cell precursors, which results from DNA synthesis abnormalities.
- Both vitamin B12 and folate deficiencies may cause defective DNA synthesis. Subsequently, the nucleus and cytoplasm do not mature simultaneously. The cytoplasm (in which hemoglobin synthesis is unaltered) mature at the normal rate, and the nucleus (with impaired DNA synthesis) is not fully mature.
- The cells arrest in the DNA synthesis (S) phase and make DNA replication errors, which eventually leads to apoptotic cell death

PATHOPHYSIOLOGY

- The primary role of folate is to donate methyl groups in DNA synthesis. Vitamin B12 is a cofactor in the reaction that recycles 5-methyl-tetrahydrofolate back to tetrahydrofolate (THF).
- The generation of THF is coupled to the conversion of homocysteine to methionine.
- Lack of vitamin B12 causes folate to become trapped in the 5-methyl-THF form, and it also leads to a deficiency of methionine.
- The donation of a methyl group or the "one-carbon metabolism" pathway is crucial for DNA synthesis



- Nucleated precursor cells in the develop immature or morphologically abnormal nuclei and giant metamyelocytes, with macrocytic red blood cells and hypersegmented neutrophils on the peripheral blood smear.
- Prolonged deficiency leads to intramedullary hemolysis of the developing erythropoietic precursor cells in the bone marrow.
- Laboratory evaluation during this phase reveals bone marrow hypercellularity and peripheral evidence of hemolysis with a low reticulocyte count.
- The pathophysiology behind neuronal dysfunction associated with megaloblastic anemia is unclear.
- The pathophysiology behind pernicious anemia involves autoantibodies against the intrinsic factor or gastric parietal cell antigens. These antibodies are not sensitive or specific for pernicious anemia and cannot be used in isolation to make the diagnosis.

PATHOPHYSIOLOGY

CLINICAL PRESENTATION

The most common presentation of megaloblastic anemia is an asymptomatic incidental finding on routine laboratory testing. Usually, anemia develops gradually, and symptoms are present only in severely anemic patients.

Common symptoms include weakness, shortness of breath (primarily with exertion), palpitation, and lightheadedness. Physical examination may reveal pallor, tachycardia, functional heart murmur, Hunter glossitis, and splenomegaly. Jaundice can occur from intramedullary hemolysis.

CLINICAL PRESENTATION

There are some minor differences between the clinical manifestations caused by cobalamin deficiency and folic acid deficiency.

In vitamin B12 deficiency, neurological manifestations are observable. The main symptoms are paresthesia and balance disorders. Lancinating pains caused by peripheral neuropathy.

Less frequently, there may be a development of visual disturbances caused by optic atrophy.

The clinical exam usually shows a loss of **vibratory sense** and **proprioception** with a **positive Romberg test**. **Babinski reflex**, hyporeflexia, and clonus are less frequent. Moreover, there are psychological disturbances that include a form of **dementia**. These neurological disorders may not be completely reversible after replacement therapy.

EVALUATION

- Clinical suspicion for megaloblastic anemia should be high in patients with unexplained macrocytic (mean corpuscular volume [MCV] greater than 100 fL) anemia or hypersegmented neutrophils on a peripheral smear.
- An MCV of greater than 115 fL is more specific for vitamin B12 deficiency or folate deficiency than other causes of macrocytosis, however, a normal MCV does not rule out megaloblastic anemia.
- A reticulocyte count is also indicated in the workup of this disease.

EVALUATION

- A B12 level above 300 pg/mL (above 221 pmol/L) is considered normal. A level between 200 to 300 pg/mL (148 to 221 pmol/L) is considered borderline and additional testing should be obtained to verify the diagnosis and elucidate the cause. A level below 200 pg/mL (below 148 pmol/L) is consistent with deficiency and further testing is only indicated if the route of administration of B12 supplementation needs clarification.
- A folate level of 2 to 4 ng/mL (from 4.5 to 9.1 nmol/L) is considered borderline. A level below 2 ng/mL (below 4.5 nmol/L) is consistent with folate deficiency.
- It is important to note that this assay is not accurate in patients with IF autoantibodies and will give false-negative results.

EVALUATION

- Spuriously low serum vitamin B12 levels can occur in patients with multiple myeloma, HIV infection, pregnancy, oral contraceptive use, and diphenylhydantoin administration.
- Falsely elevated B12 levels may be seen in patients with myeloproliferative neoplasm, alcoholic liver disease, and renal disease.
- Homocysteine is elevated in both vitamin B12 and folate deficiencies.
- Methylmalonic acid can also help differentiate between vitamin B12 and folate deficiency as it is elevated in vitamin B12 deficiency but not in folate deficiency.

EVALUATION

- It is imperative to remember that vitamin B12 and folate deficiency testing should be done simultaneously to ensure both deficiencies are diagnosed if present. In cases where folate is replaced without vitamin B12 supplementation and underlying B12 deficiency, the neurologic manifestations of vitamin B12 deficiency will not be treated and may potentially get worse.

TREATMENT

- If there is no evidence of malabsorption, the generally preferred route for supplementation is oral.
- In asymptomatic cases, oral supplementation is sufficient. In patients with neurologic symptoms or those with increased demand such as pregnancy and in infancy, vitamin B12 and folic acid supplementation should be initiated parenterally.
- Patients with symptomatic anemia may require a blood transfusion to relieve symptoms, as vitamin B12 and folic acid supplementation do not correct anemia rapidly.
- Vitamin B12 is also available in a sublingual formulation, which may be appropriate for patients with intestinal malabsorption syndromes.

TREATMENT

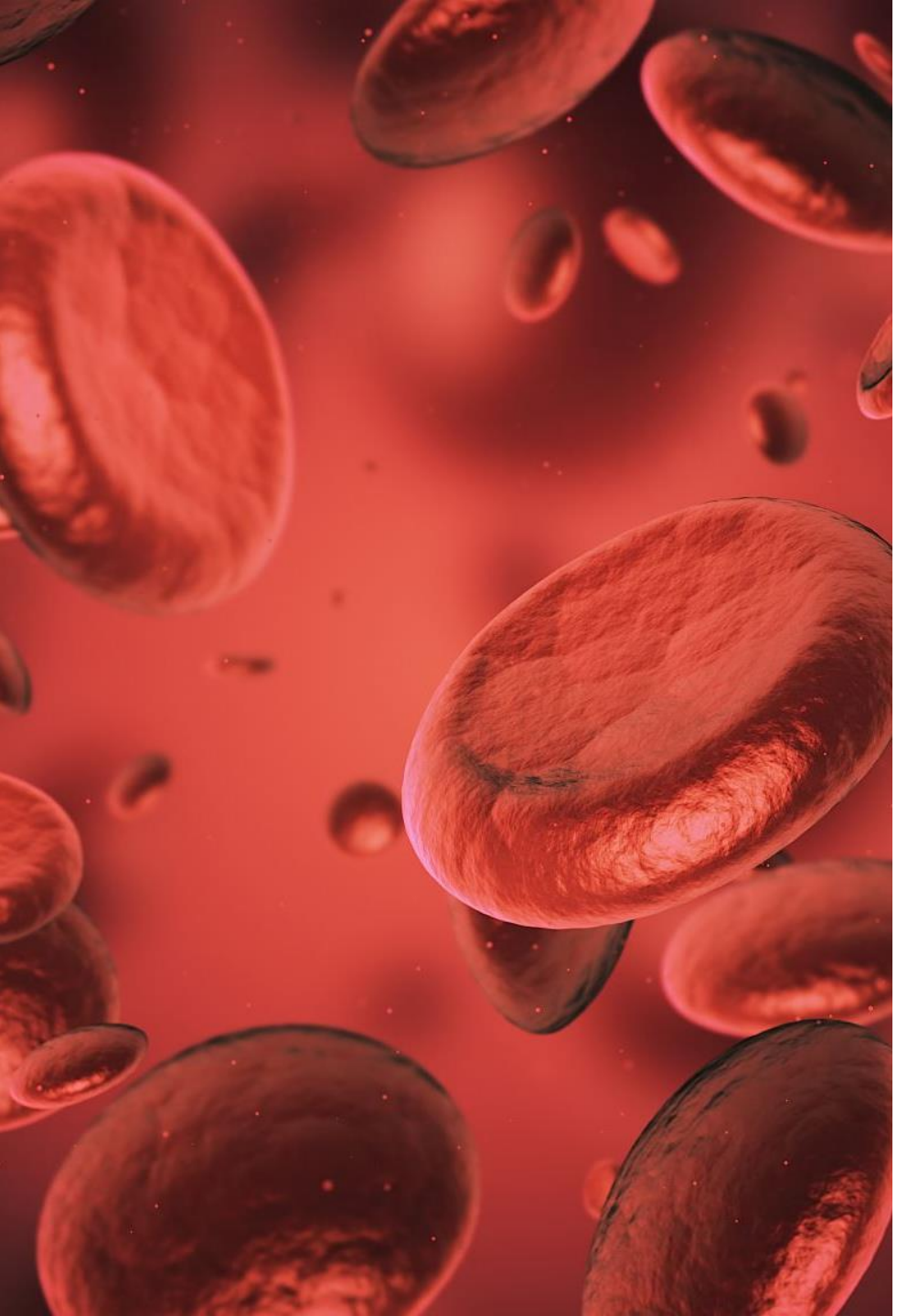
- In adults, the recommended dose is 1000 mcg parenterally once a week until the deficiency is corrected, followed by supplemental doses every month or every other month. An oral vitamin B12 dose of 1000 mcg daily is equally effective as the above parenteral regimen, provided that there is no intestinal malabsorption issue.The duration of treatment is dependent on the cause of the deficiency. If the root cause is correctable, supplementation can be stopped after serum B12 levels normalize. However, in cases with expected life-long deficiency (gastric bypass surgery patients, pernicious anemia, etc.) indefinite supplementation is warranted.

TREATMENT

- The recommended dose for folic acid supplementation is 1 mg orally once a day until the deficiency is corrected. If the cause of this deficiency is correctable, supplementation can be stopped after repletion. However, in cases with nonreversible causes, indefinite supplementation is recommended.

TREATMENT

- With adequate supplementation and bone marrow response, hemolytic markers (if intramedullary hemolysis is present) will improve within 1 week and serum hemoglobin/hematocrit levels will completely normalize within 1 to 2 months.However, the neuropsychiatric symptoms take a longer period of time to recover (from 3 to 12 months) and according to some reports, there is transient clinical worsening of the neurological symptoms. In some cases, the neurological symptoms may be irreversible.



DIFFERENTIAL DIAGNOSIS

- The complete blood count may show macrocytosis in non-megaloblastic macrocytic anemias. Reticulocyte count will help distinguish between two primary conditions. If reticulocytosis is present, hemolytic anemia and acute hemorrhage are the two main conditions for which the clinician must look. If a reticulocytopenia is present, the underlying conditions may be evident in some cases, such as hypothyroidism, alcoholism, liver dysfunction, and certain drugs. In other cases, one should perform bone marrow aspiration provided that the investigations to exclude vitamin B12 or folate deficiency are carried out. Indeed, myelodysplastic disorders and sideroblastic anemia can manifest as refractory megaloblastic anemia.

DIFFERENTIAL DIAGNOSIS

- Common clinical conditions to consider in patients who present with megaloblastic anemia include conditions that present with macrocytosis such as:
- Alcoholic hepatitis
- Atrophic gastritis
- Gastric cancer
- Celiac sprue
- Tropical sprue
- Myelodysplastic syndrome
- Aplastic anemia
- Acquired sideroblastic anemia
- Homocystinuria

PROGNOSIS

- The prognosis for megaloblastic anemia is favorable with proper identification of the precise etiology and the institution of appropriate treatment. Hematologic abnormalities recover with adequate supplementation although neurologic manifestations show some delay in improvement. Timely recognition and supplementation improve the prognosis of this disease, which may have little to no morbidity or mortality associated with it. There are some complications of the disease that can lead to poor outcomes in patients, such as gastric malignancy in patients with pernicious anemia as the cause of megaloblastic anemia.

COMPLICATIONS

- The most concerning complication of patients with megaloblastic anemia secondary to pernicious anemia are gastric malignancy. The incidence of gastric malignancy in patients with pernicious anemia was reported as 0.27% per patient-year and a sevenfold relative risk of gastric cancer in patients with pernicious anemia
- Folate deficiency is associated with neural tube defects in the fetus. This is a highly preventable complication with potentially devastating consequences, that can be eliminated with adequate supplementation during pregnancy.

PATIENTS' EDUCATION

- Patient education centers on resolving potential dietary deficiencies, working on other modifiable risk factors such as alcohol intake and medication regimens. Patients following a strictly vegan diet are at high risk for vitamin B12 deficiency and should take oral supplementation on a regular basis.
- In patients with gastrointestinal alterations, patient education on the cause of megaloblastic anemia and the importance of medication compliance is of the utmost importance. Patients need to be educated on the potentially irreversible neurologic complications of B12 deficiency and counseled on treatment compliance to prevent this outcome.
- Patients diagnosed with pernicious anemia, need counseling on self-monitoring of gastrointestinal symptoms, as they may be an early sign of gastric malignancy that will need urgent evaluation.
- Patients taking medications that can potentially cause megaloblastic anemia, need to be counseled regarding vitamin supplementation while taking these medications to prevent megaloblastic anemia.

THANK YOU

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