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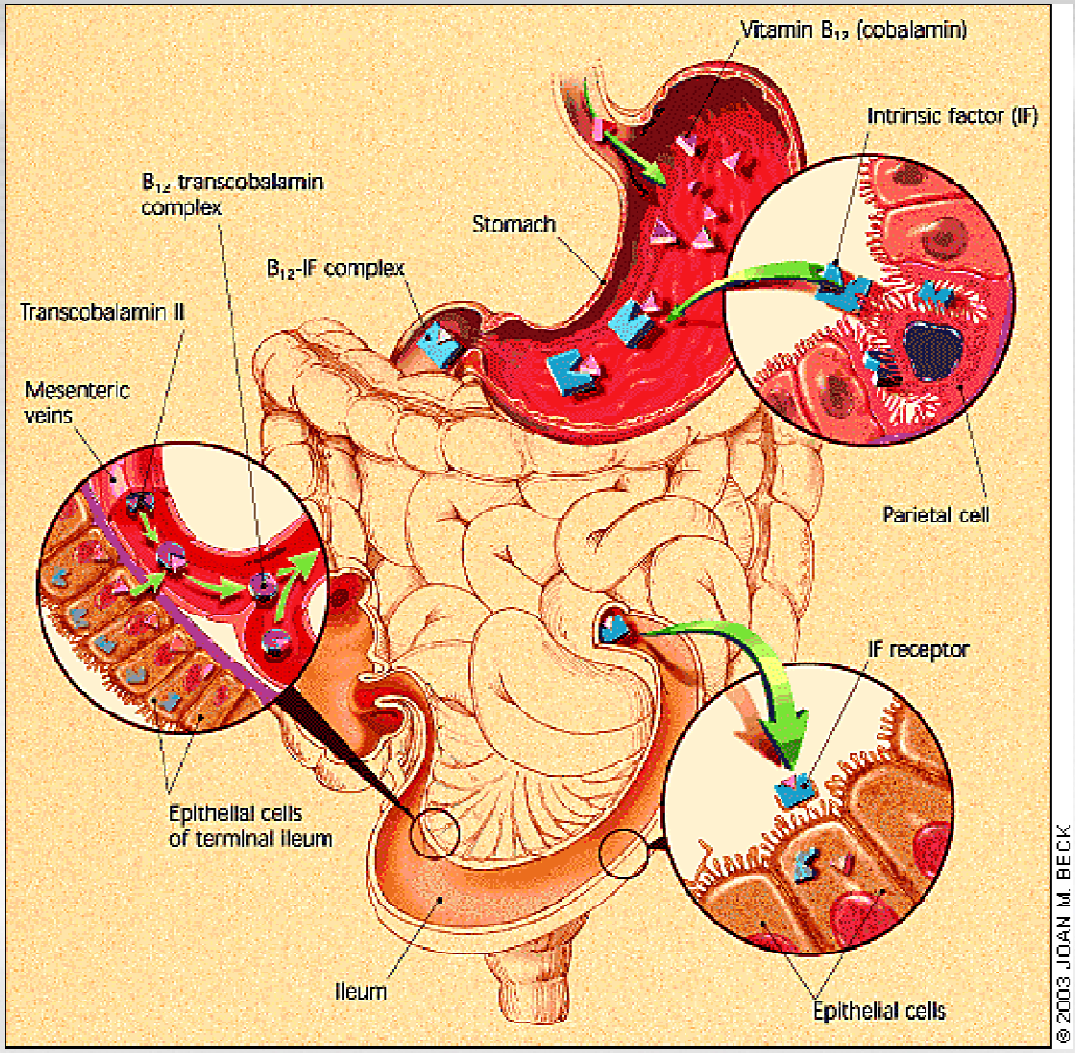
VITAMIN B_{12} DEFICIENCY ANEMIA
FOLIC ACID DEFICIENCY ANEMIA
APLASTIC ANEMIAS

CHISINAU - 2020

SCHEME OF VITAMIN B_{12} ABSORPTION



SCHEME OF VITAMIN B_{12} ABSORPTION

Pernicious Anemia.mp4

ETIOLOGIC FACTORS IN VITAMIN B_{12} DEFICIENCY ANEMIA

I. Decreased dietary intake

1. Vegetarianism
2. Long-term severe malnutrition
3. Newborns from the mothers with vitamin B_{12} deficiency anemia

II. Inadecuate dissociation of vitamin B_{12} from digested proteins

1. Atrophic gastritis
2. Partial gastrectomy with hypochlorhydria

III. Deficiency or abnormality of the intrinsic factor

1. Deficiency of the intrinsic factor
   a) Hereditary deficiency
   b) Atrophy or loss of mucosa sector which produces the intrinsic factor:
      Partial gastrectomy
      Total gastrectomy
      Autoimmune destruction:
         Pernicious anemia in adults
         Juvenile pernicious anemia
      Destruction by chemical agents (burns): ethanol, etc.
2. Abnormal intrinsic factor
   a) Intrinsic factor hypersensitive to acid, pepsin, trypsin
   b) Intrinsic factor with the reduced affinity to the absorption receptors of the ilium

ETIOLOGIC FACTORS IN VITAMIN B_{12} DEFICIENCY ANEMIA

IV. Pathologic conditions of the small intestine

1. Inadecuate pancreatic proteases

a) Deficiency of pancreatic proteases – pancreatic failure

b) Inactivation of pancreatic proteases by gastric hypersecretion (Zollinger-Ellison syndrome)

2. Consumption of vitamin B_{12} in the intestine (inadecuate conjugation of vitamin B_{12} with the intrinsic factor)

a) By bacteria:

stasis syndrome (diverticulosis, strictures, fistula, anastomoses)

peristalsis disturbances of the small intestine (scleroderma, pseudoobstruction)

b) Invasion with bothriocephaliasis (fish tapeworm)

V. Disorders of the ilium mucosa / abnormalities of the intrinsic factor binding receptors

1. Lack or absence of the intrinsic factor binding receptors – surgical interventions

2. Morpho-functional pathologies of the mucosa (sprue, Crohn's disease, tuberculosis ileitis, non-Hodgkin lymphoma)

3. Disorders of the intrinsic factor binding receptors or intrinsic post-factor receptors:

a) Immerslund-Grasbeck syndrome

b) Transcobalamin II deficiency

VI. Disorders of the plasmatic transportation

1. Genetic deficiency of transcobalamin II

2. Abnormal transcobalamin II

CLINICAL FEATURES OF VITAMIN B_{12} DEFICIENCY ANEMIA:

1. Anemic syndrome

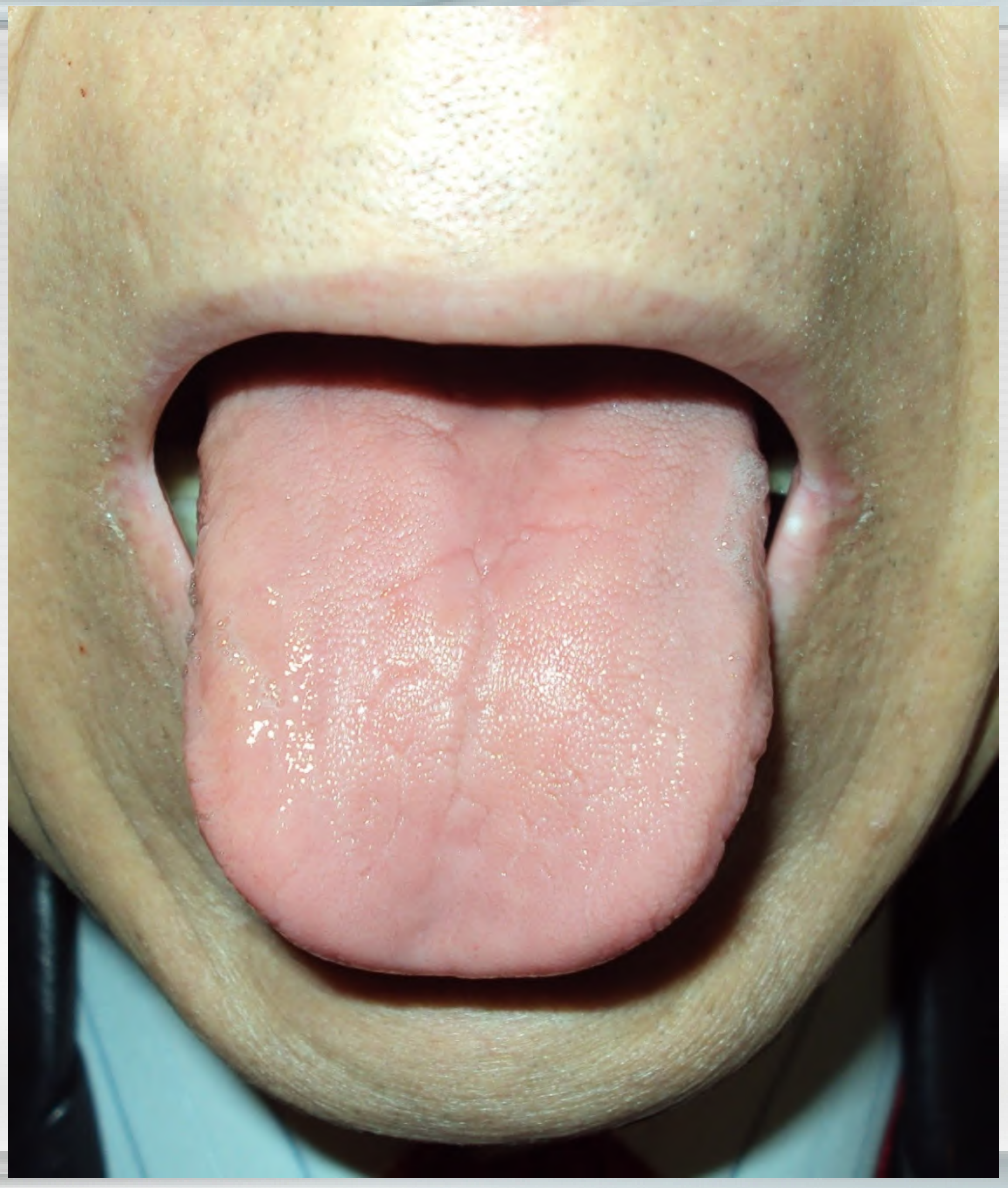
2. Gastrointestinal syndrome:

An abnormal tongue is found in about 25% of patients with vitamin B_{12} deficiency anemia. When glossitis is at its height, the tongue is painful, glazed and “beefy” red. The frequent complaints are loss of appetite, diarrhea, or constipation, a sense of fullness and epigastric discomfort, nausea, and irregular abdominal pain. The pain may be symptomatic of changes in spinal cord. The liver and the spleen may be insignificantly enlarged.

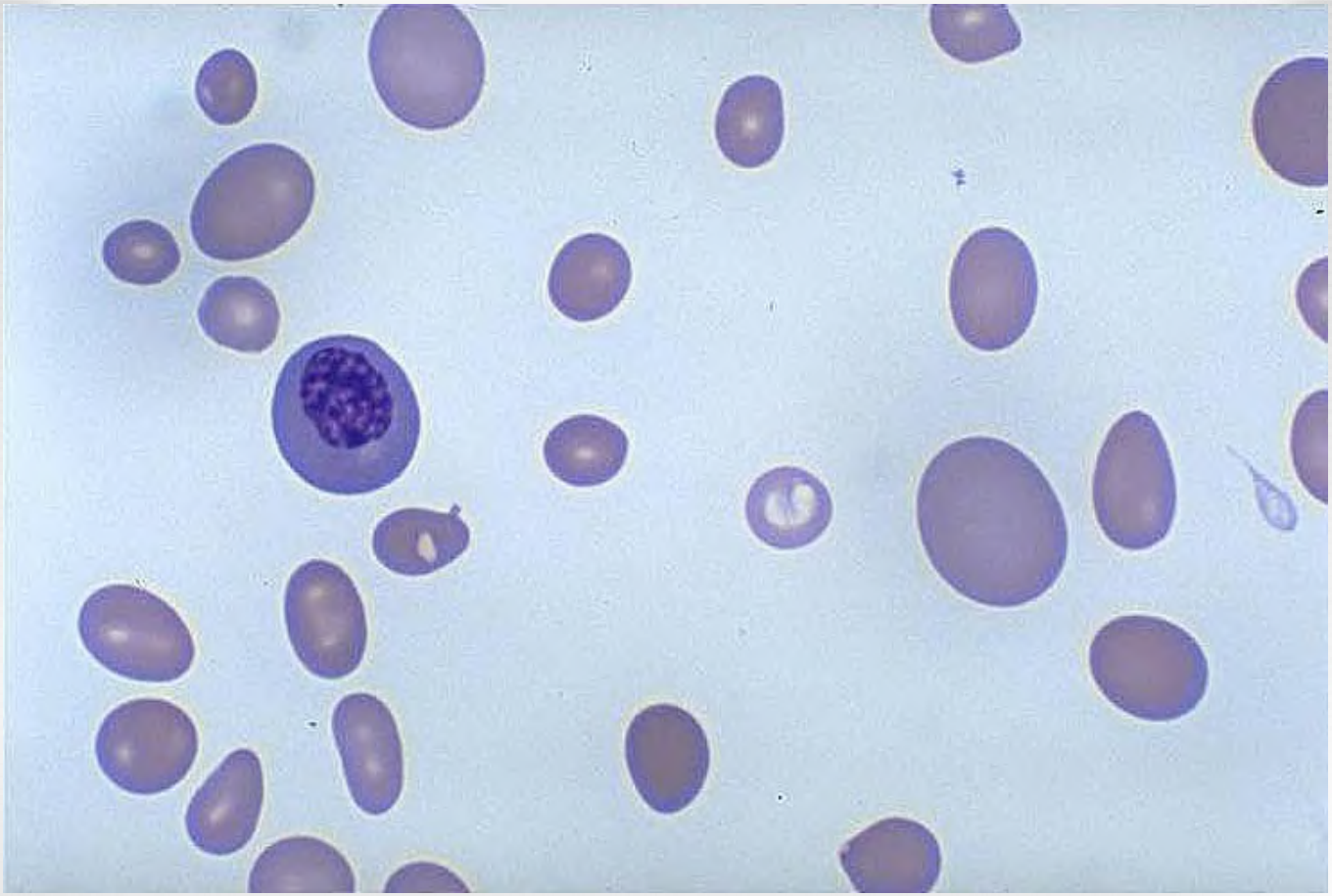
3. Neurologic syndrome:

Usually begins with paresthesia in feet and fingers, associated with disturbances of vibratory sense and proprioception. The lateral columns (pyramidal tracts) become involved in the later and more severe stages of the illness. Weakness and spastic or “scissors” gait may develop. If untreated, the neurologic disorder progresses to spastic ataxia resulting from degenerative changes of the dorsal and lateral columns. The most striking neuropathologic feature is demyelination. Besides the peripheral nerves and the spinal cord, the brain is affected by cobalamin deficiency. Somnolence together with perversion of taste, smell, vision, and a chronic, progressive dementing illness can develop. Franc psychosis in cobalamin deficiency has been termed megaloblastic madness. Fever of several degrees is common when the anemia is severe and may occur in the absence of infection.

GLOSSITIS IN PATIENT WITH VITAMIN B_{12} DEFICIENCY ANEMIA

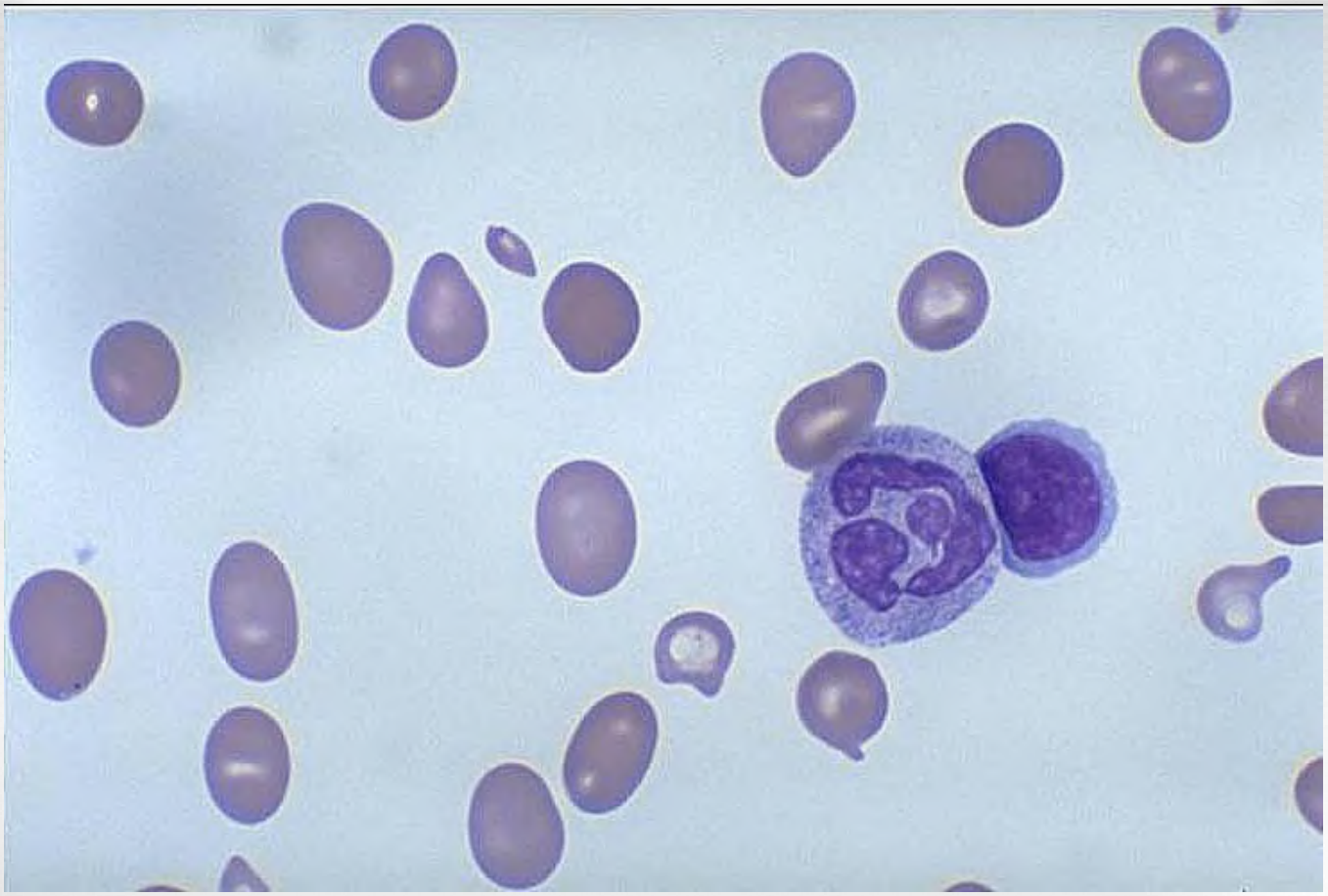


BLOOD SMEAR IN VITAMIN B_{12} DEFICIENCY ANEMIA



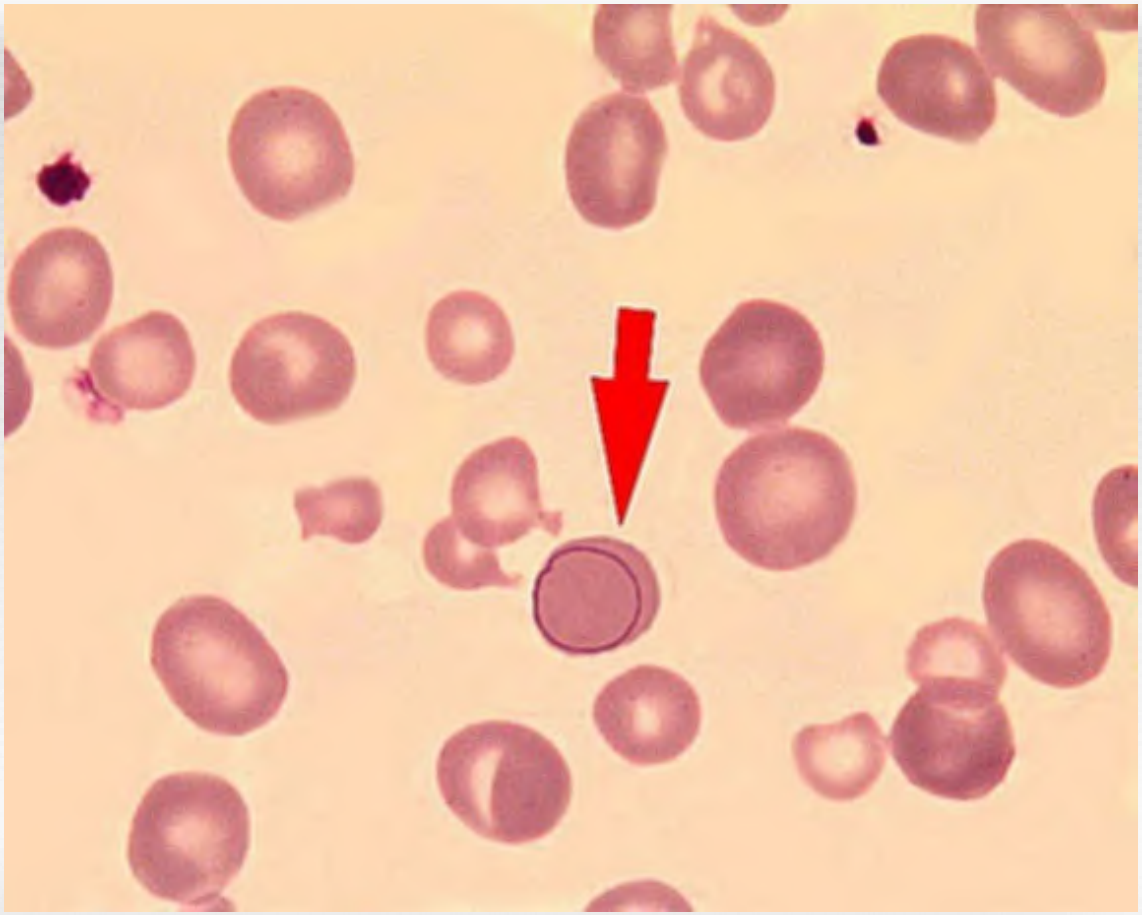
May-Giemsa stain, x1000

BLOOD SMEAR IN VITAMIN B_{12} DEFICIENCY ANEMIA



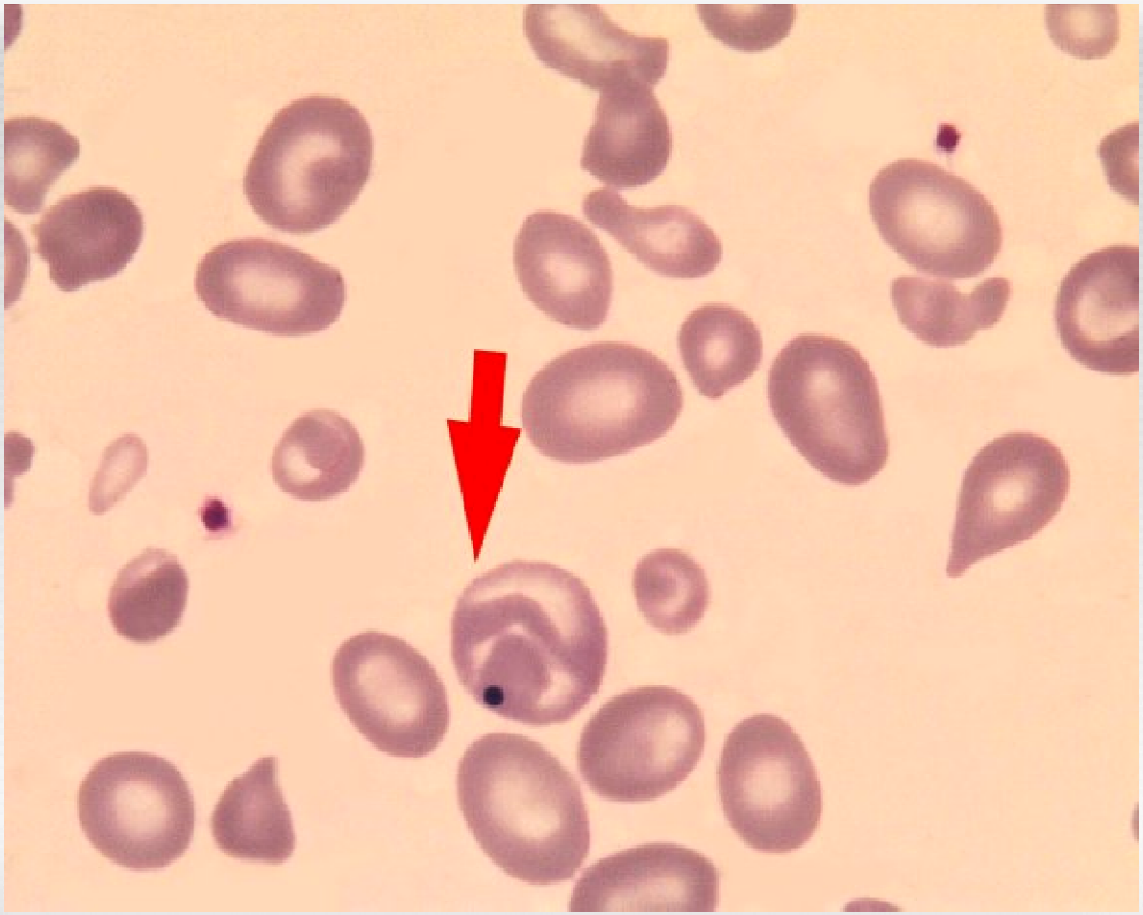
May-Giemsa stain, x1000

BLOOD SMEAR IN VITAMIN B_{12} DEFICIENCY ANEMIA



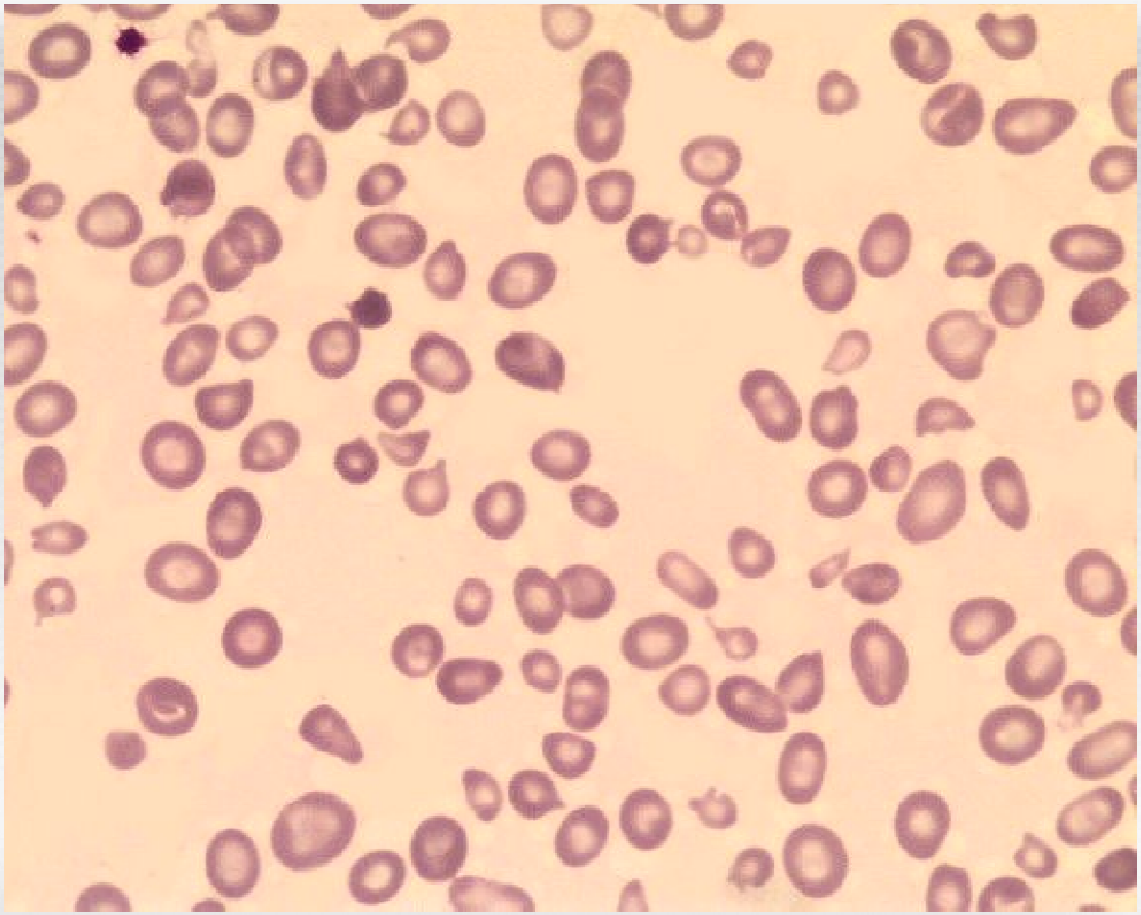
Cabot rings
Staining: MGG
Magnification: x 1000

BLOOD SMEAR IN VITAMIN B_{12} DEFICIENCY ANEMIA



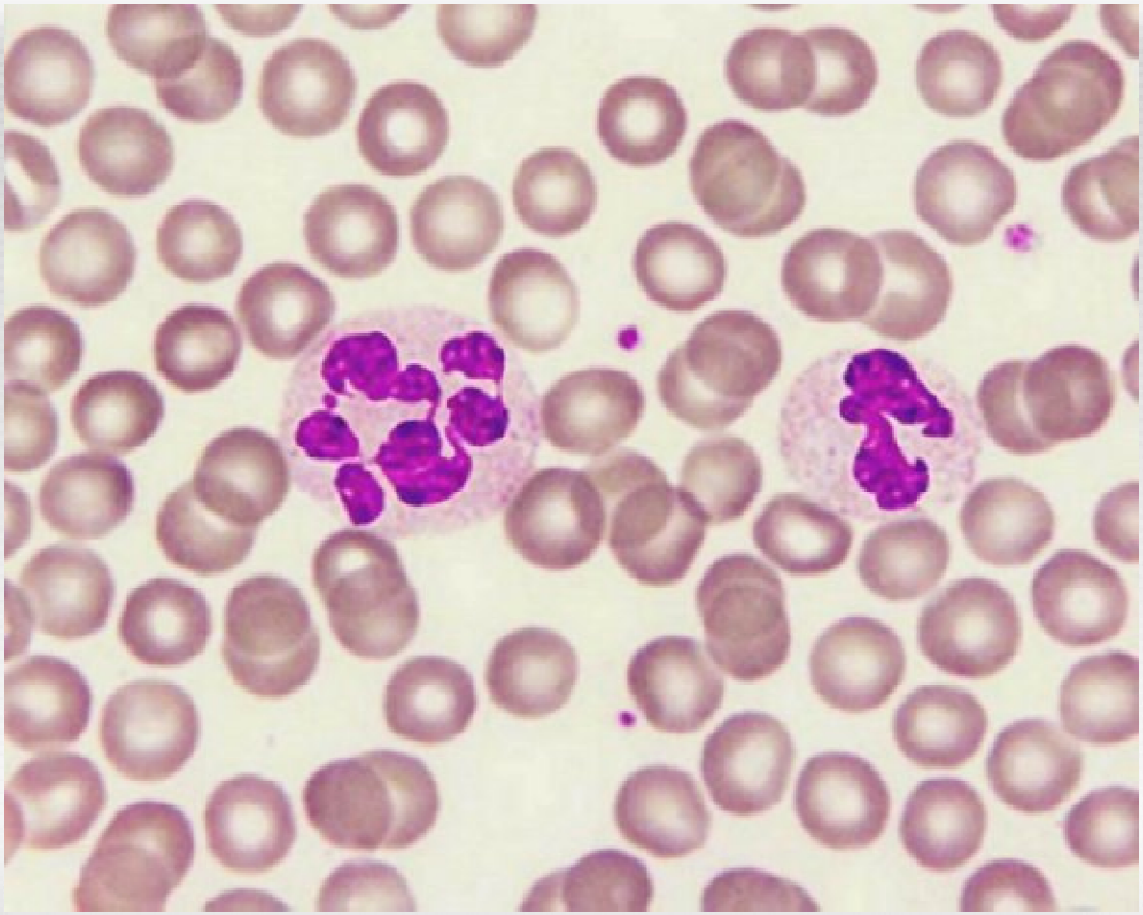
Howell-Jolly bodies
Staining: MGG
Magnification: x 1000

BLOOD SMEAR IN VITAMIN B_{12} DEFICIENCY ANEMIA



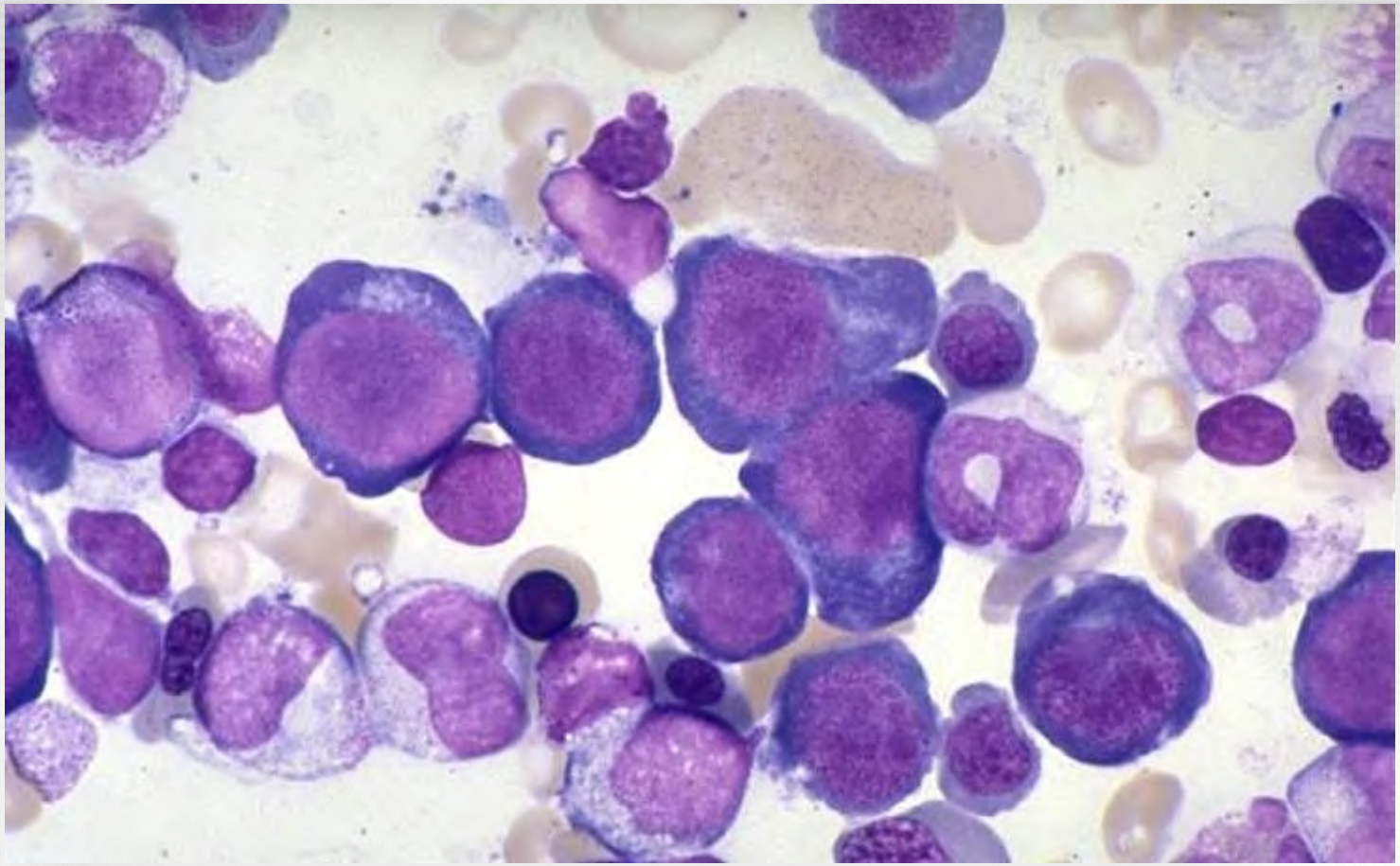
Marked anisocytosis and poikilocytosis with presence of ovalocytes and schistocytes
{MGG stain, magnification × 500}

BLOOD SMEAR IN VITAMIN B_{12} DEFICIENCY ANEMIA



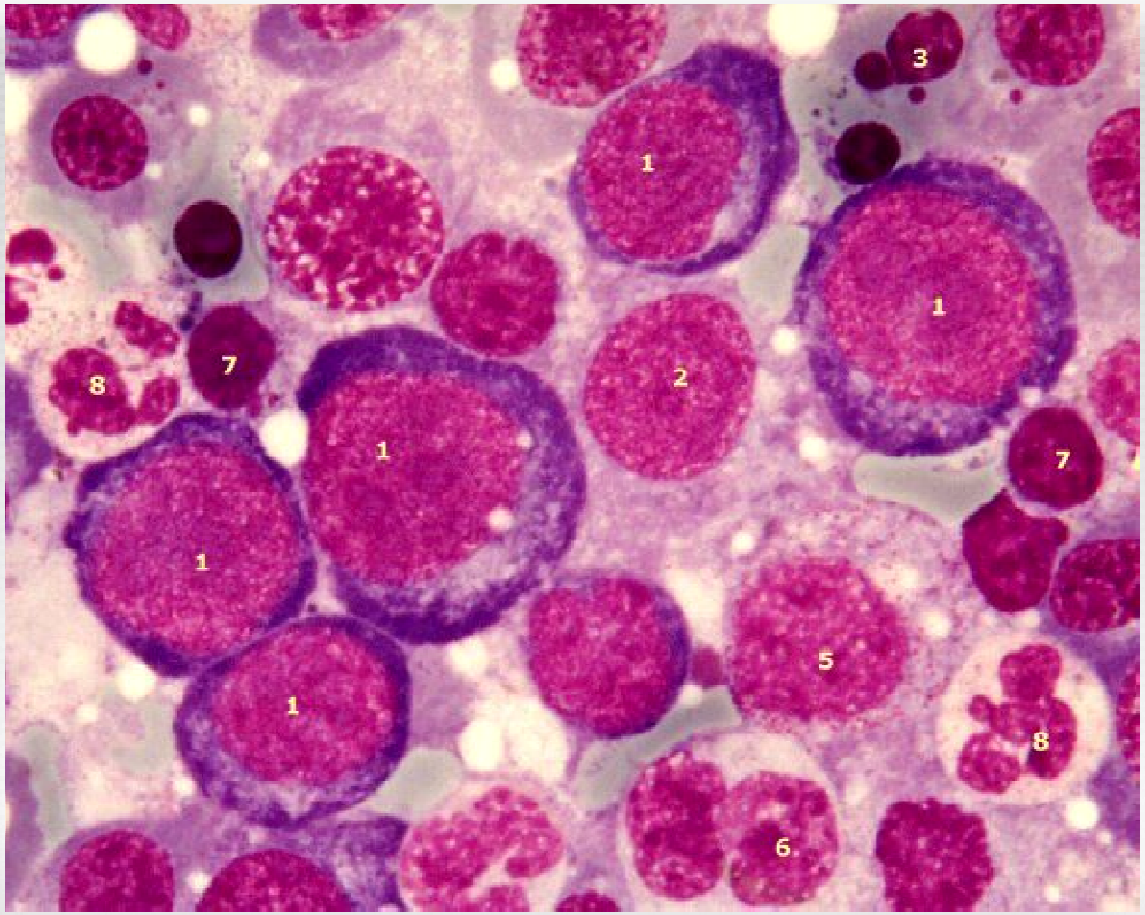
Two mature neutrophils
One (on the left) is hypersegmented and has megaloid appearance
Staining: Pappenheim

BONE MARROW SMEAR IN VITAMIN B_{12} DEFICIENCY ANEMIA



May-Giemsa stain, x1000

BONE MARROW SMEAR IN VITAMIN B_{12} DEFICIENCY ANEMIA



Promegaloblasts and megaloblastic form of erythroblasts, paraerythroblasts, neutrophils and lymphocytes can be seen.
{MGG stain, magnification × 1000}

1. promegaloblast 2. polychromatic (intermediate) normoblast 3. paraerythroblast 4. pycnotic (late) normoblast 5. promyelocyte 6. giant band neutrophil 7. lymphocyte 8. segmented neutrophil

TREATMENT OF VITAMIN B_{12} DEFICIENCY ANEMIA

At present vitamin B_{12} deficiency anemia is curable in all cases due to the therapy with vitamin B_{12}. To administer the rich in vitaminB_{12} raw liver is not only wasteful but also potentially dangerous regarding the possibility of infestation. Blood transfusions are rarely needed in pernicious anemia and may be indicated only in anemic precoma and coma.

Treatment consists of parenteral cobalamin (cyanocobalamin or hydroxocobalamin) in amount sufficient to normalize hemoglobin level and to refill storage pools. A typical treatment schedule is as follows: (1) 1000 μg /day intramuscularly for 10 days (if neurologic syndome is present); (2) 200-400 μg /day until the hemoglobin and erythrocyte count are normal; and the same dose weekly for the lifetime of the patient. Oral cobalamin should be reserved for patients who refuse parenteral injections or those in whom parenteral therapy may be hazardous (a coexisting disorder of hemostasis, hypersensitivity reactions to the vitamin B_{12}). To these patients the vitamin B_{12} must be given in huge doses (1000 μg /day) subligually or by mouth to force a small amount across the intestinal epithelium by mass action.

Hydroxocobalamin is more effective pharmaceutical form due to better inclusion in the cell metabolism and firm fixation to the tissue proteins. It may be administered with large intervals that is convenient for maintenance therapy (as an example, 500 μg every 6 – 8 weeks). Hemoglobin levels rise, reaching normality within 4 – 6 weeks. Retuculocytosis begins abruptly on days 4 to 5, sometimes later (on days 7 to 8). The intensity of the reticulocytosis roughly corresponds to the severity of anemia. Neurologic syndrome regresses slower.

The patients with vitamin B_{12} deficiency anemia must be under the supervision of a doctor. They are examined every 6 months. Fibrogastroscopy is compulsory because vitamin B_{12} deficiency anemia is considered a precancerous condition.

ETIOLOGIC FACTORS IN FOLIC ACID DEFICIENCY ANEMIA

I. ***Decreased dietary intake;***

II. ***Increased folic acid requirements*** **(especially in pregnants);**

III. ***Impaired absorption of folic acid*** **(chronic enteritis, sprue, extensive resections of jejunum, inherited folate malabsorption, malabsorption syndrome, alcohol consumption);**

IV. ***Increased folate consumption*** **(hyperactive erythropoiesis in cases of hemolytic crisis, hemorrhages, in patients with myeloproliferative disorders);**

V. ***Utilization of antifolic drugs*** **(methotrexate);**

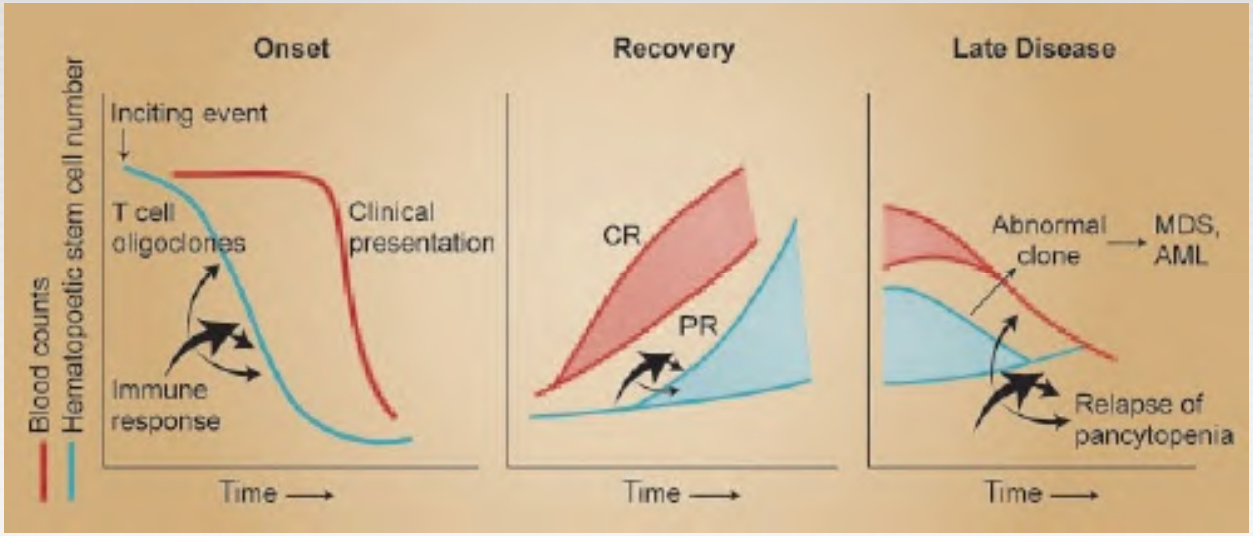
VI. ***Folate destruction*** **(in patients treated with anticonvulsive or tuberculostatic drugs for a long period of time).**

ETIOLOGIC FACTORS IN APLASTIC ANEMIA

1. ***Cytotoxic antitumorigenic drugs;***
2. ***Ionizing radiation*** **(roentgen rays, radioactive isotopes, atomic bombs, etc.);**
3. ***Some other drugs*** **(antimicrobal agents: chloramphenicol, sulfonamides; analgesics: acetyl salicylic acid, indomethacin; sedatives: meprobamate, chlordiazepoxide, chlorpromazine, etc.);**
4. ***Chemical agents:*** **benzene, its derivatives, insecticides;**
5. ***Viral infections*** **(usually hepatitis C virus, Epstein-Barr virus, etc.). Severe aplastic anemia may develop within several weeks to 8 months after onset of the acute viral hepatitis;**
6. ***Pregnancy*** **(aplastic anemia may be the form of gestosis and is cured after the interruption of pregnancy);**
7. ***Aplastic crisis in hemolytic anemias*** **(paroxysmal nocturnal hemoglobinuria);**
8. ***Immunologic*** **(humoral, cellular).**

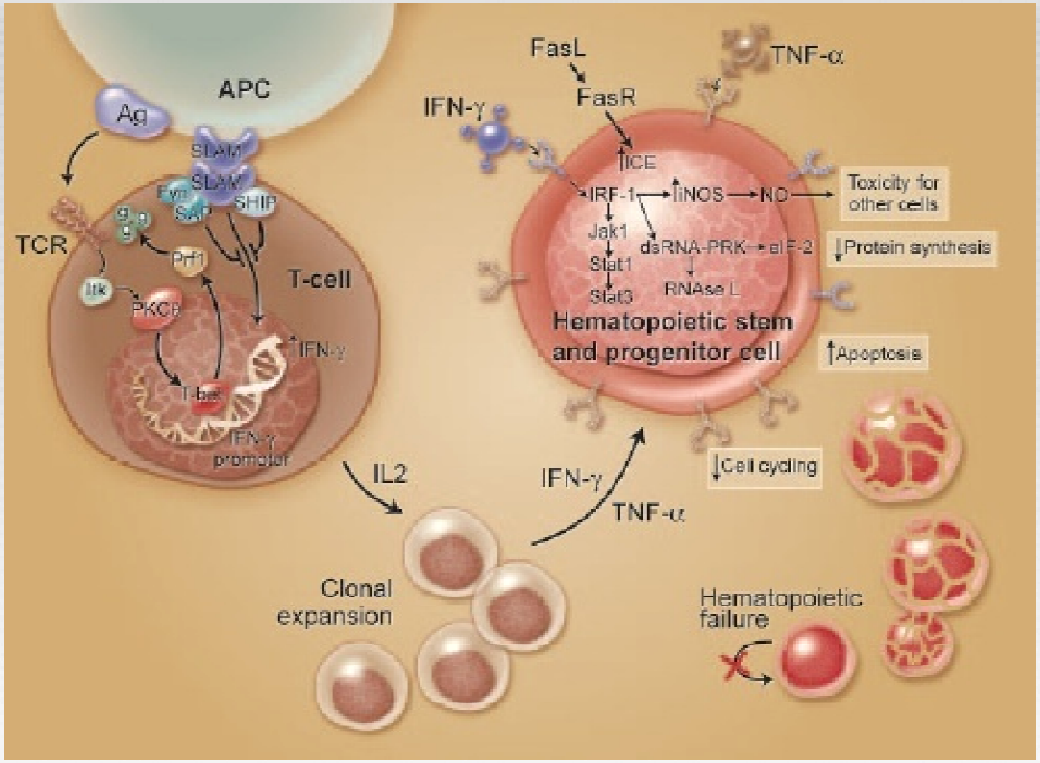
PATHOPHYSIOLOGY OF ACQUIRED APLASTIC ANEMIA

(American Society of Hematology, Blood, 2006,108)



IMMUNE DESTRUCTION OF HEMATOPOIESIS IN ACQUIRED APLASTIC ANEMIA

(American Society of Hematology, Blood, 2006,108)



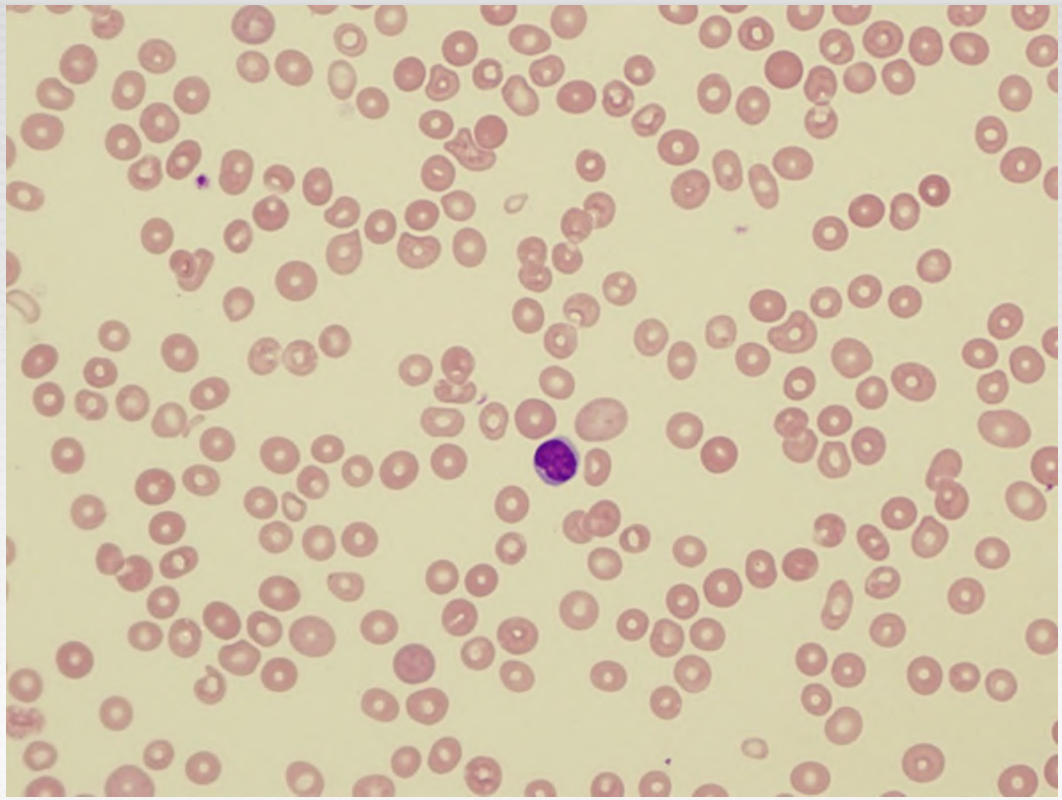
Antigens are presented to T lymphocytes by antigen-presenting cells (APCs), which trigger T cells to activate and proliferate. T-bet, a transcription factor, binds to the interferon- (INF-) promoter region and induces gene expression. IFN- and TNF-α up-regulate other T cells' cellular receptors and also the Fas receptor. Increased production of interleukin-2 leads to polyclonal expansion of T cells.

CRITERIA FOR SEVERE APLASTIC ANEMIA

(by the International Group for Study of aplastic anemia)

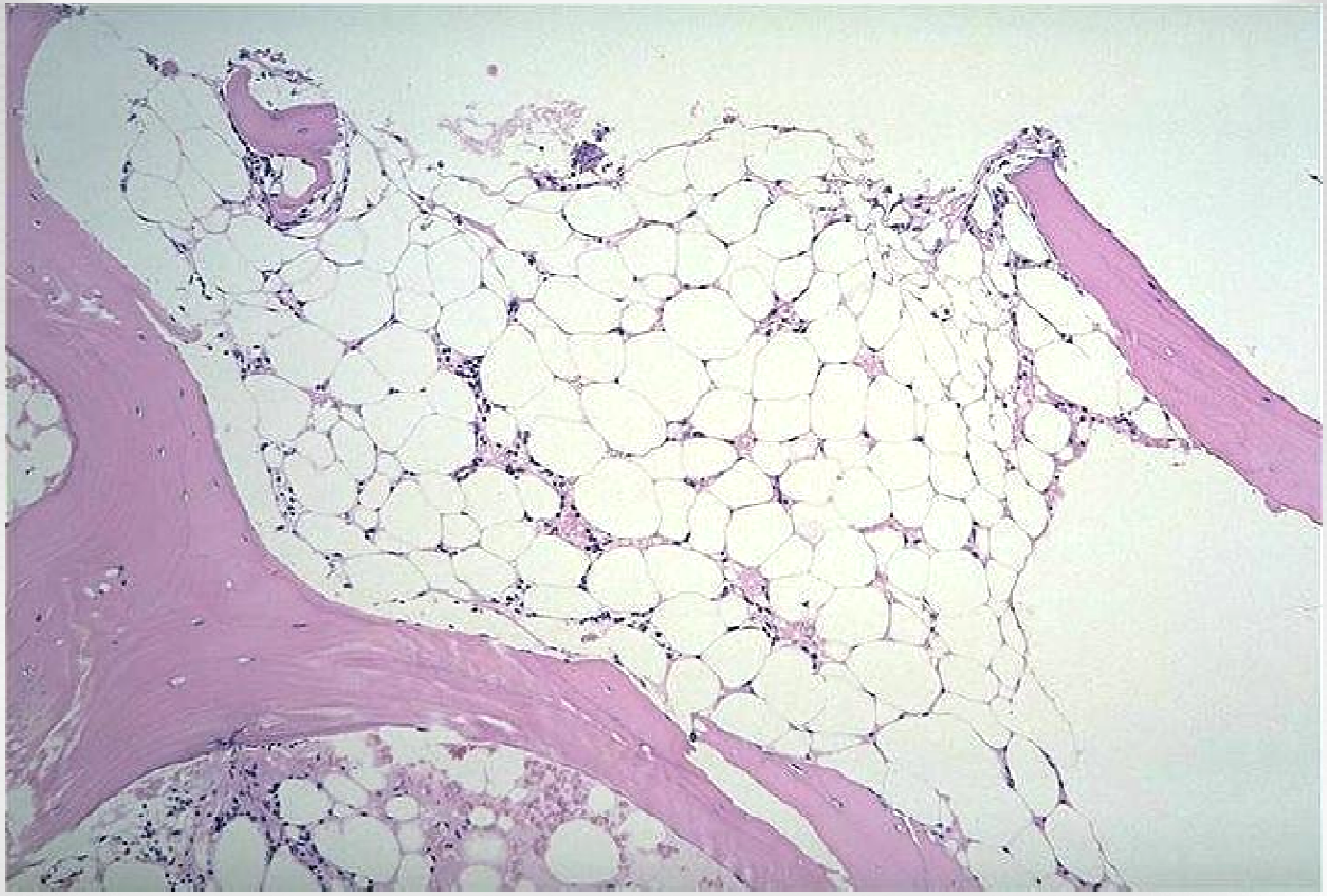
Criteria	Severe aplastic anemia (Camitta et al., 1976)	Very severe aplastic anemia (Bacigalupo et al., 1988)	Non-severe aplastic anemia
Bone marrow cellularity, %	< 25, or 25–50% with < 30% residual hemopoietic cells	< 25	25 – 50
Neutrophil count, x 10^9/l	< 0,5	< 0,2	> 0,5
Platelet count, x 10^9/l	< 20	< 20	> 20
Reticulocyte count, %	< 1	< 1	> 1
Complications	infections, bleeding	severe infections, bleeding	– – –

BLOOD SMEAR IN APLASTIC ANEMIA



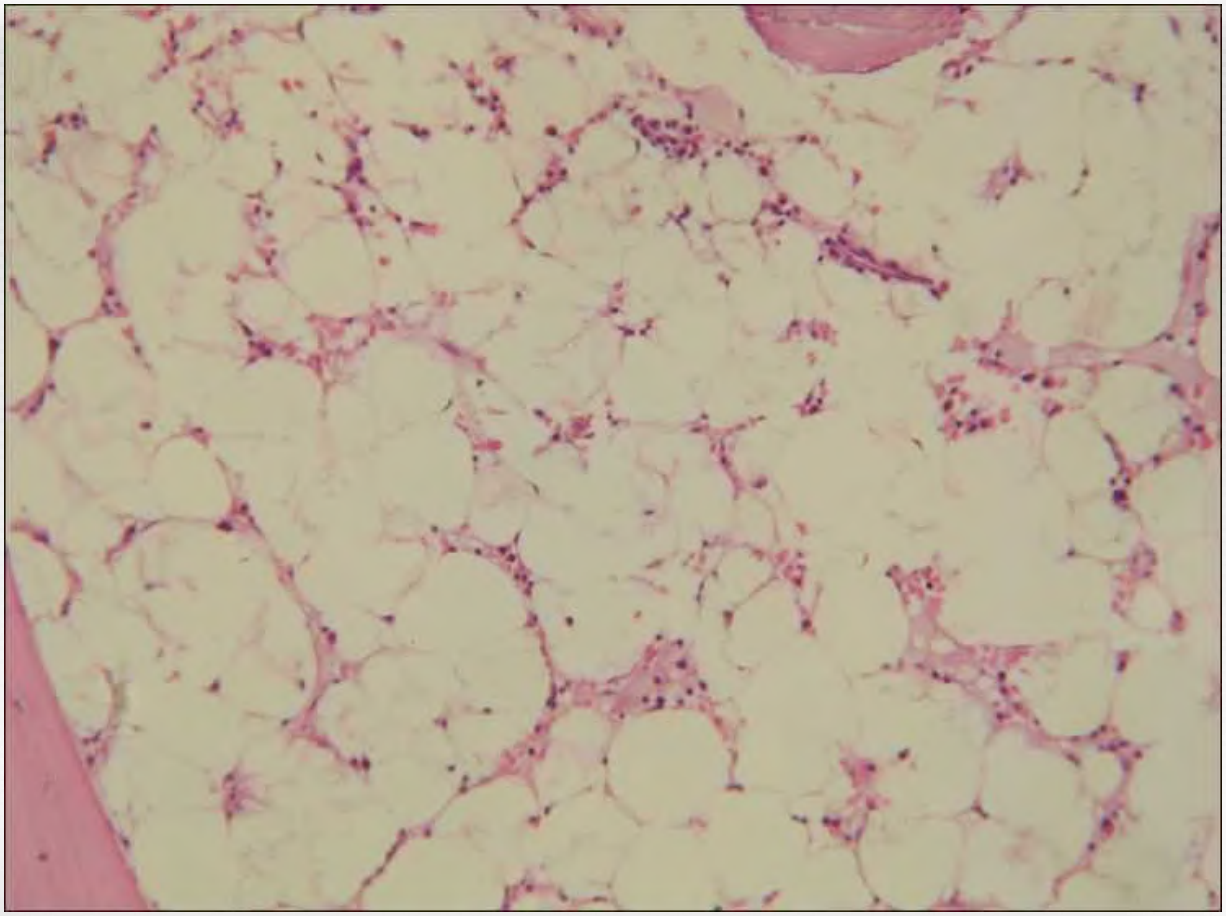
Hematoxylin and eosin stain, x 500

BONE MARROW BIOPSY IN APLASTIC ANEMIA



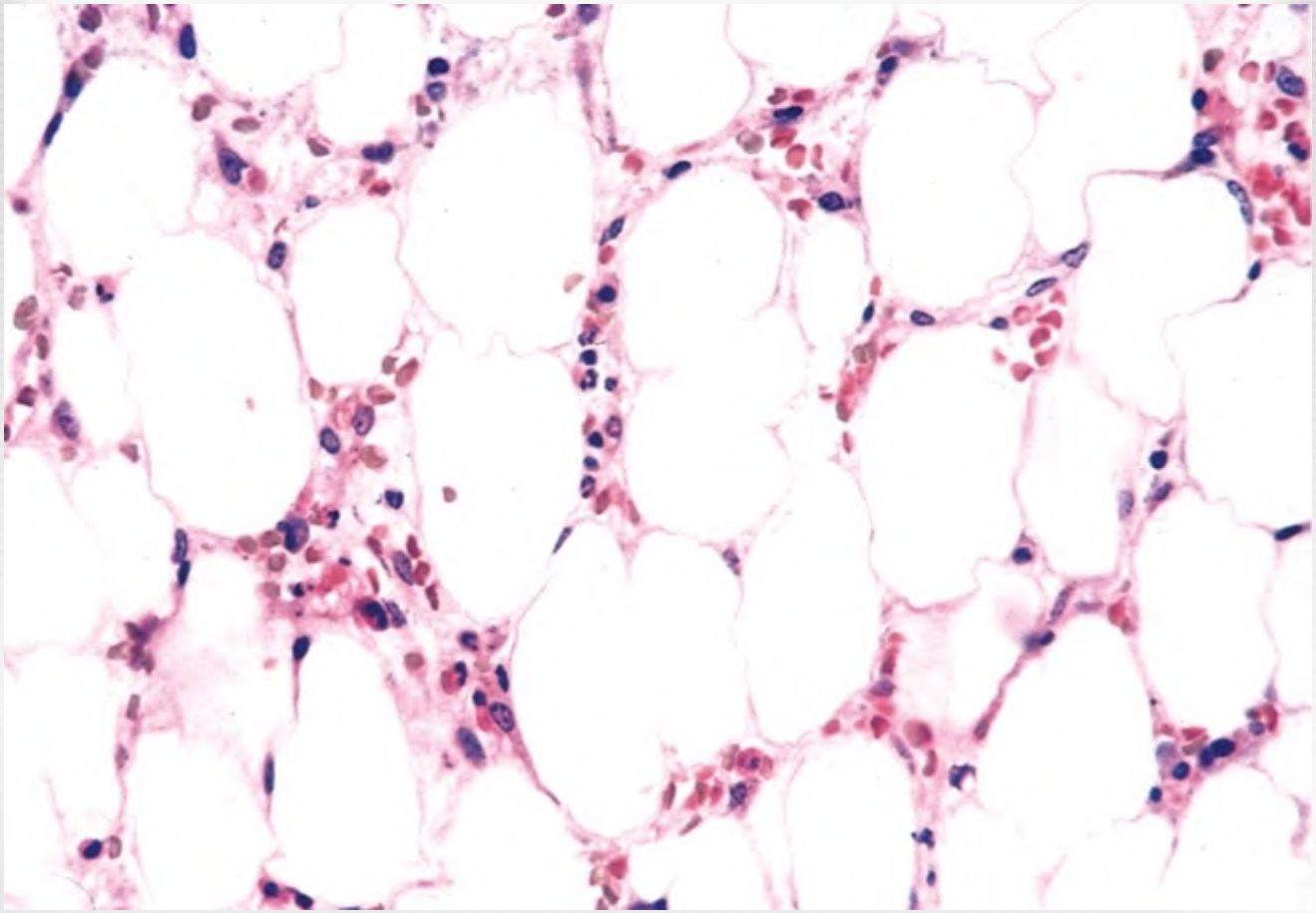
Hematoxylin and eosin stain, x100

BONE MARROW BIOPSY IN APLASTIC ANEMIA



Hematoxylin and eosin stain, x 400

BONE MARROW BIOPSY IN APLASTIC ANEMIA



Hematoxylin and eosin stain, x 500

TREATMENT OF ACQUIRED APLASTIC ANEMIA

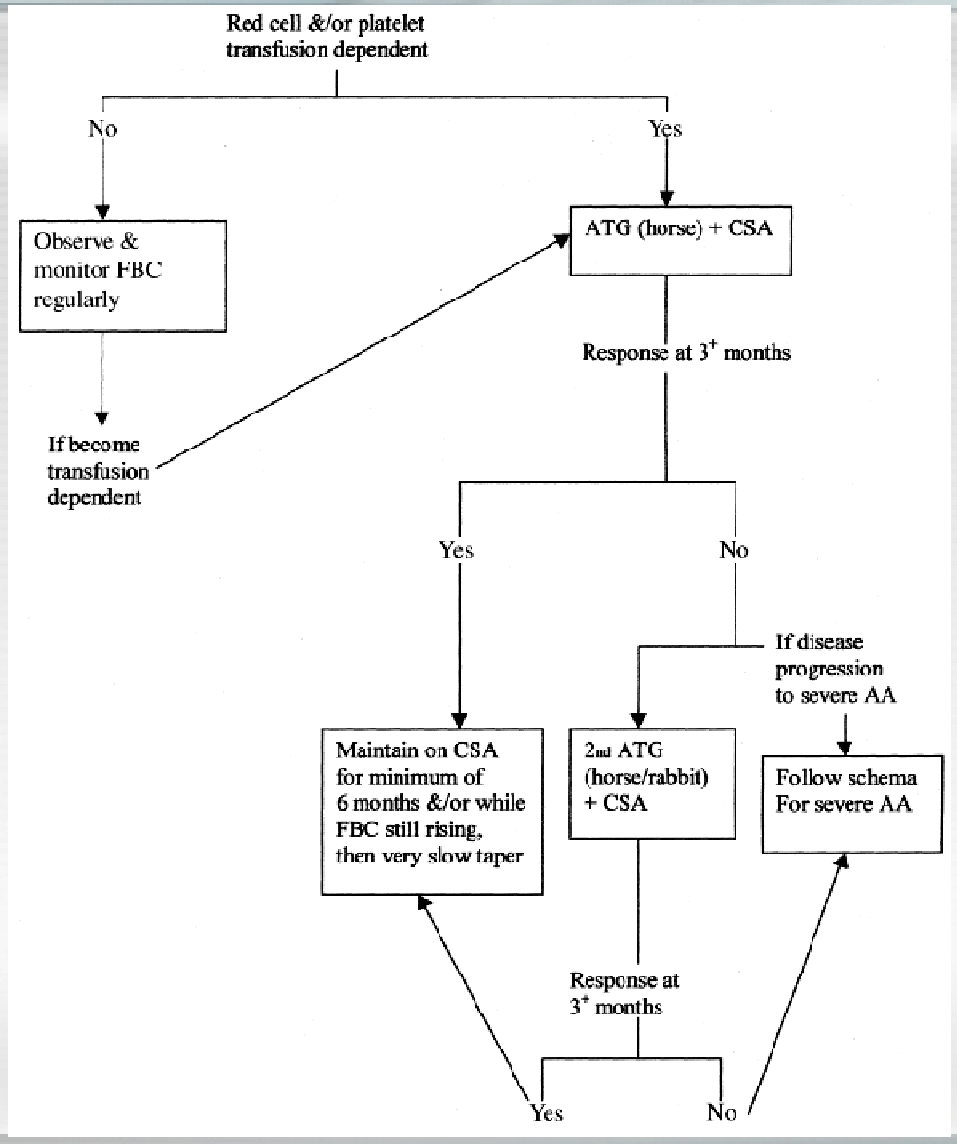
Patients with aplastic anemia must be treated in the specialized hematology departments. Once the history has been obtained and the diagnosis has been established, management includes:

- **Transfusion therapy with blood components (red cell transfusions, platelet transfusions) to support the patient during the period of no marrow function.**
- **Prevention and management of infection (restriction of visitors, isolation, preventive supportive care, antibiotics).**
- **Stimulation of hematopoiesis and marrow regeneration (androgen therapy: nandrolone)**
- **Conventional and high – dose glucocorticoids for stimulation of hemopoiesis and management of hemorrhagic complications.**
- **Immunosuppressive therapy (antilymphocyte or antithymocyte globulin, cyclosporine A).**
- **Splenectomy is recommended to improve blood counts due to withdrawal of an inhibitory immunologic effect on hematopoiesis and removal of a site, where red cells and platelets may be sequestered or destroyed.**
- **Bone marrow transplantation.**

The overall mortality of adults with aplastic anemia has been reported to be about 50 – 90 %. In patients with acute toxic forms of aplasia, the mortality constitutes 75% , being lower in those with chronic forms (30 – 50%). When the marrow aplasia follows an attack of viral hepatitis, the mortality is extremely high (90%). In patients receiving marrow transplants the prognosis is much better, with the survival rate of 50 – 80% (Cammita B.M. et al., 1982).

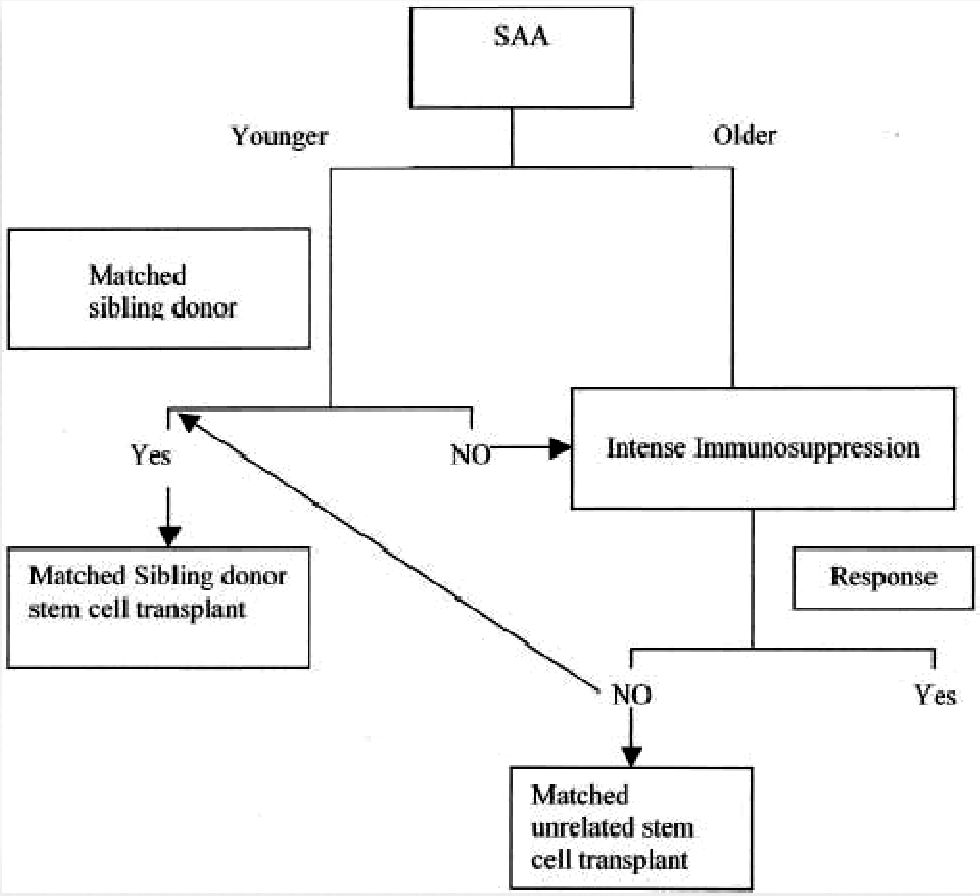
TREATMENT ALGORITHM FOR NON-SEVERE ACQUIRED APLASTIC ANEMIA

(British Committee for Standards in Hematology, British Society for Hematology; British Journal of Haematology, 2003, 123)



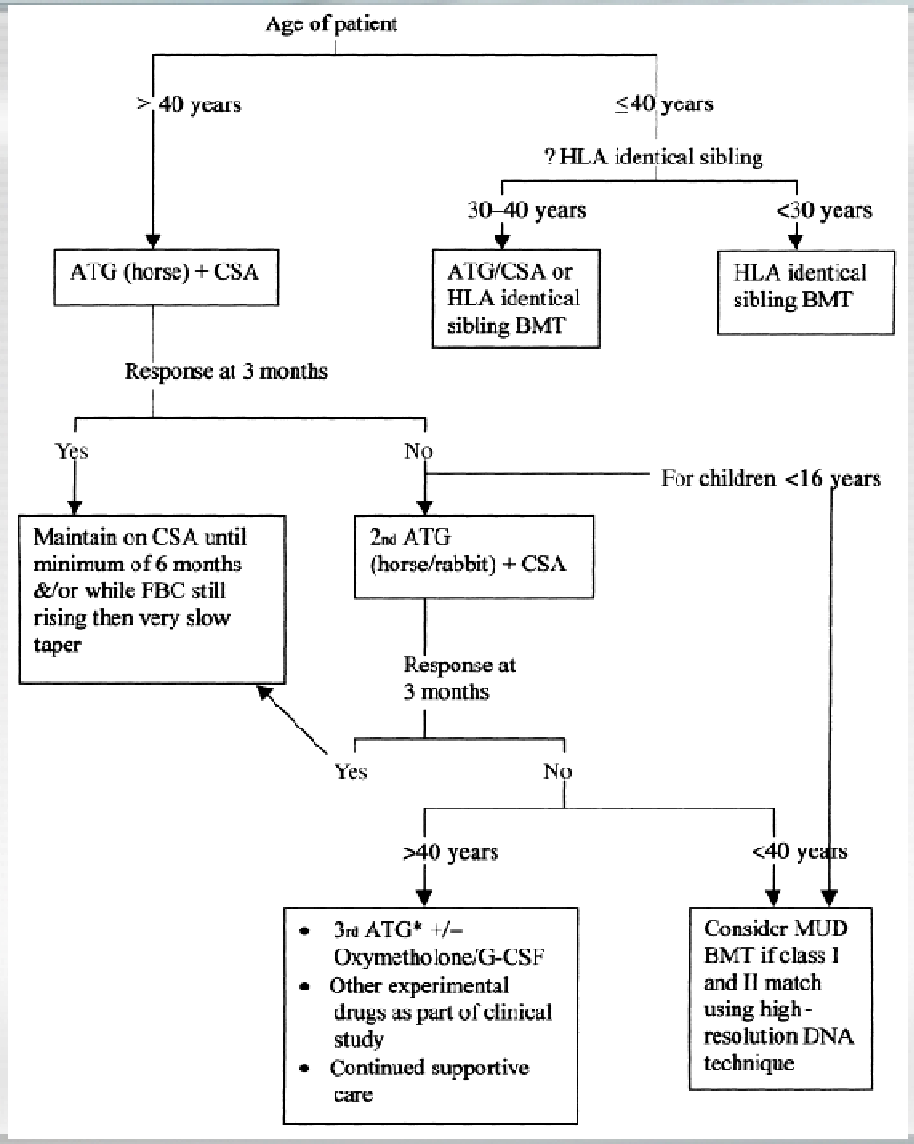
THERAPEUTIC ALGORITHM FOR SEVERE APLASTIC ANEMIA

(American Society of Hematology; Hematology, 2005)



TREATMENT ALGORITHM FOR SEVERE ACQUIRED APLASTIC ANEMIA

(British Committee for Standards in Hematology, British Society for Hematology; British Journal of Haematology, 2003, 123)



APLASTIC ANEMIA

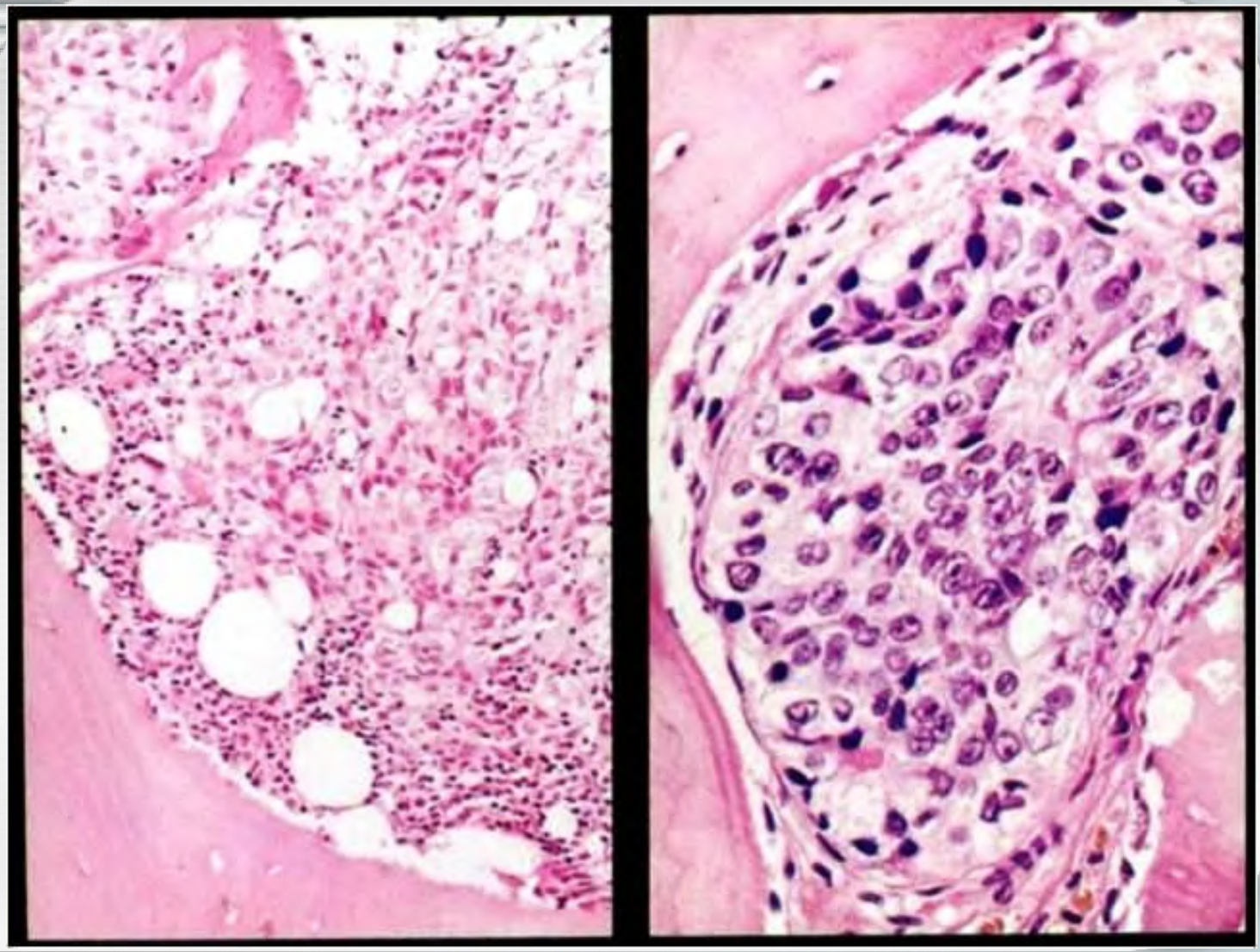
Aplastic Anemia.mp4

LABORATORY DIFFERENTIATION OF IRON DEFICIENCY ANEMIA (IDA) VERSUS ANEMIA OF CHRONIC DISEASE (ACD)

(Iron Deficiency - Investigation and Management. Guidelines and Protocols Advisory Committee; British Columbia, Canada, 2010)

Investigation	Results In		
	IDA	**ACD**	**ACD + IDA**
Serum Ferritin	↓	↑	↓ or normal
Serum Iron	↓	↓	↓
Iron Binding Capacity	↑	↓	↓ or low normal
Transferrin Saturation / Fraction Saturation	↓	↓ or normal	↓

BONE MARROW BIOPSY IN METAPLASTIC ANEMIA: NEOPLASTIC INFILTRATION OF THE BONE MARROW



Hematoxylin and eosin stain, x 500

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