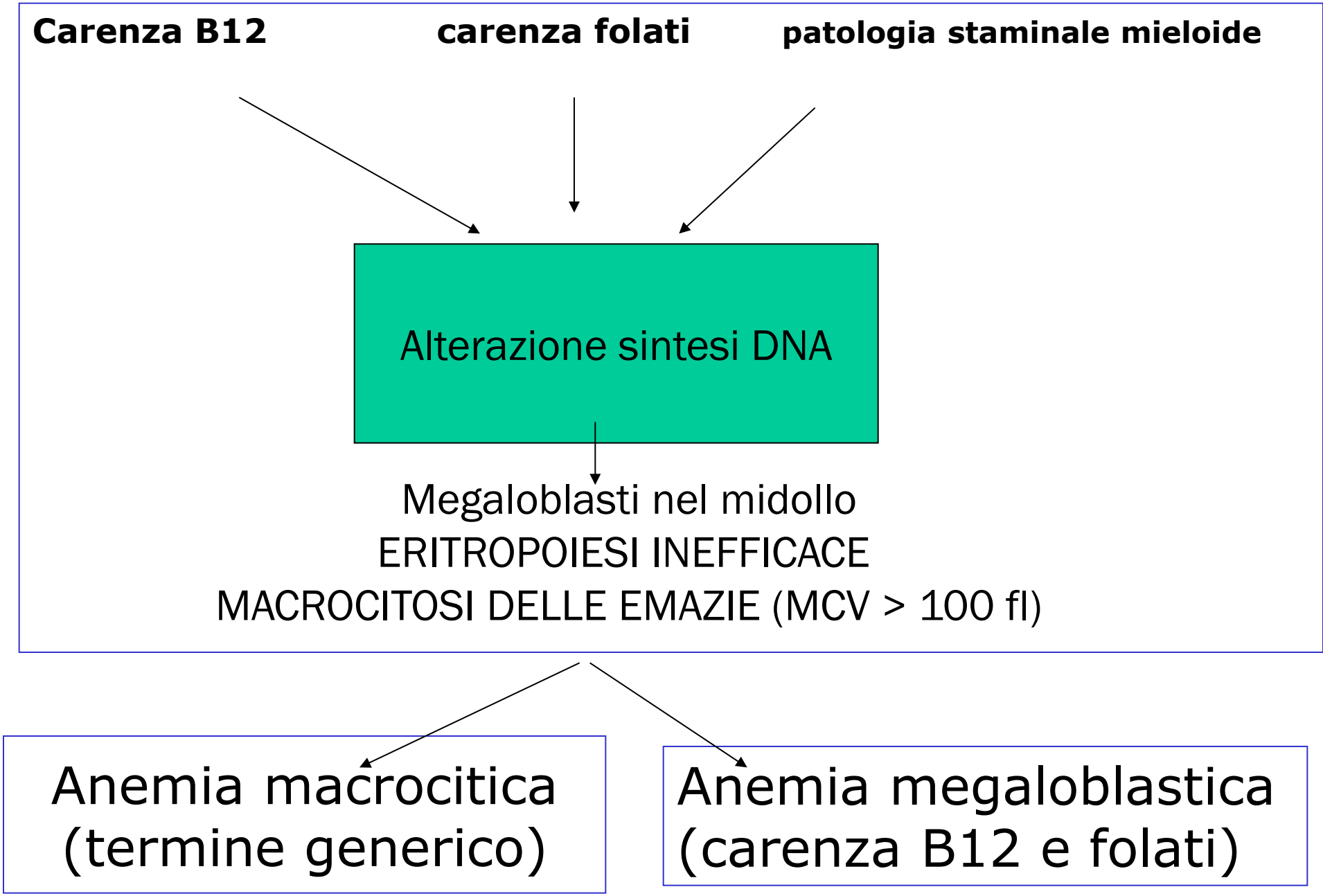
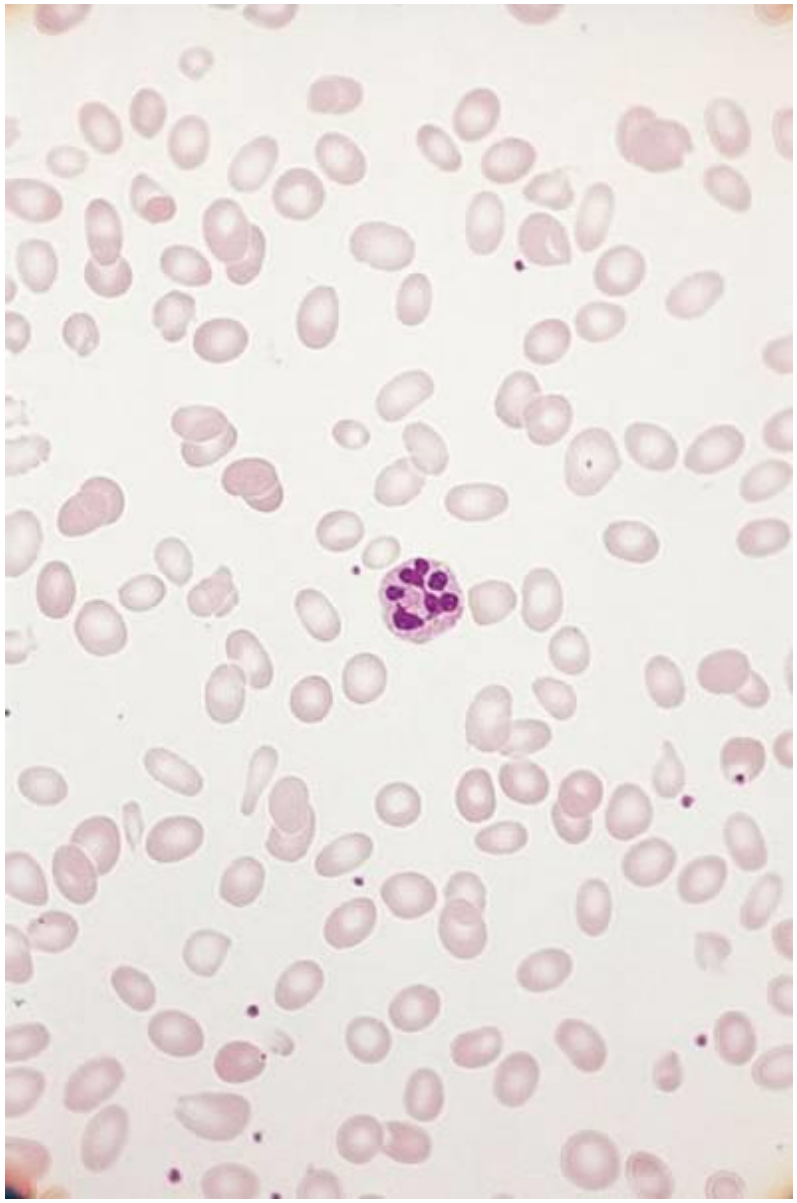
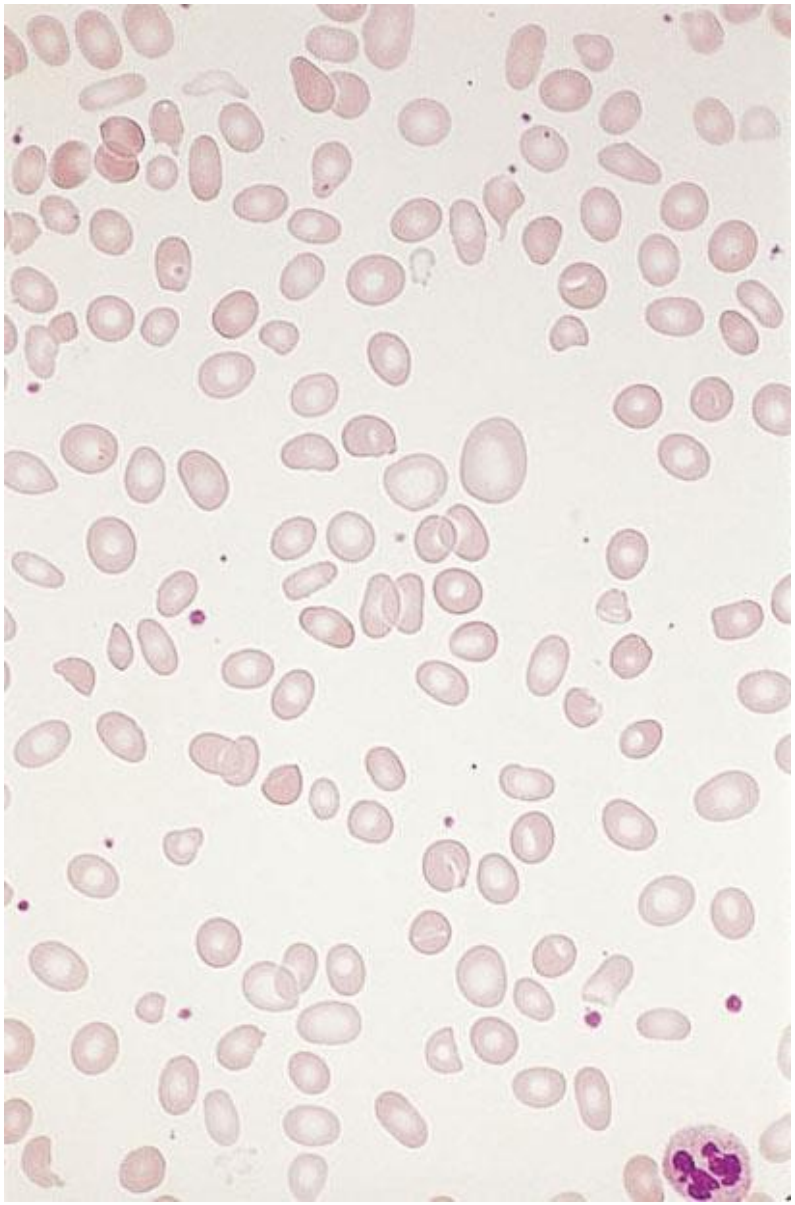
Valori ematici in un caso di anemia macrocitica da carenza di B12

WBC	3.300
Hb	7,3
GR	1,900.000
MCV	123
MCH	26
Pst	98.000

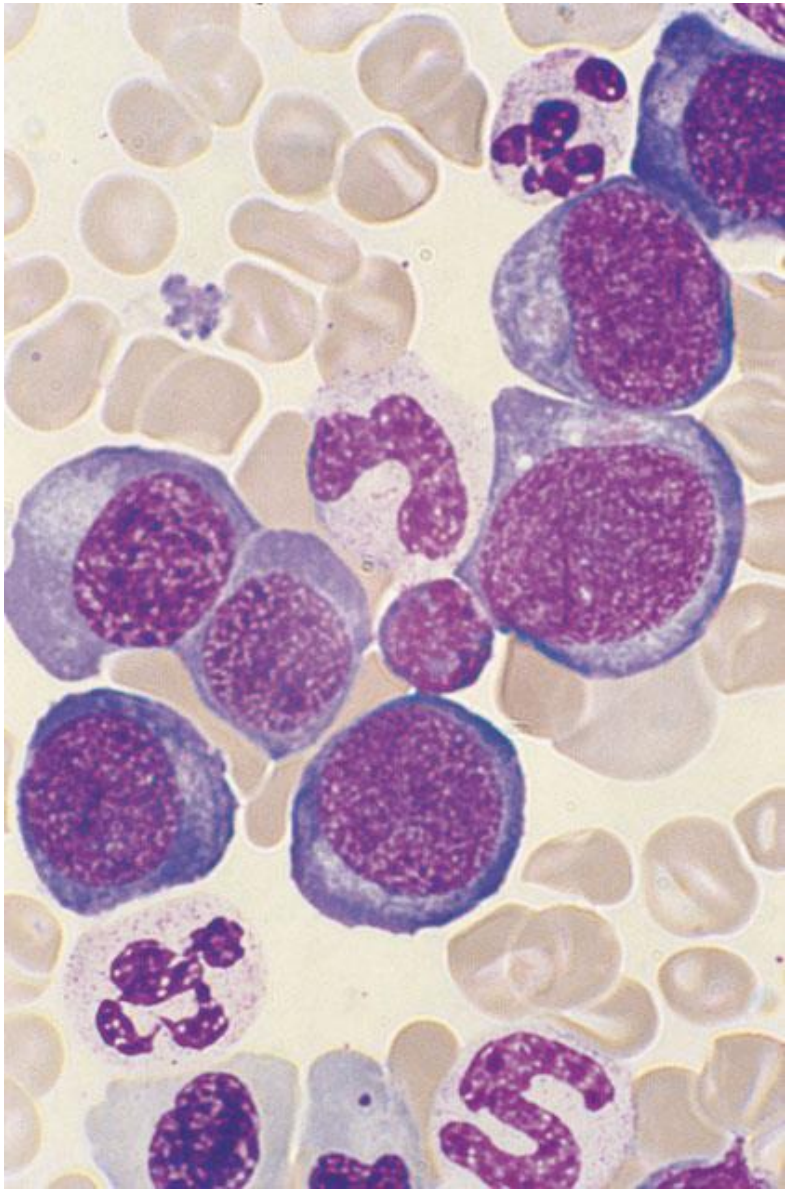

Carenza B12
carenza folati
patologia staminale mieloide
Alterazione sintesi DNA
Megaloblasti nel midollo
ERITROPOIESI INEFFICACE
MACROCITOSI DELLE EMAZIE (MCV > 100 fl)
Anemia macrocitica (termine generico)
Anemia megaloblastica (carenza B12 e folati)

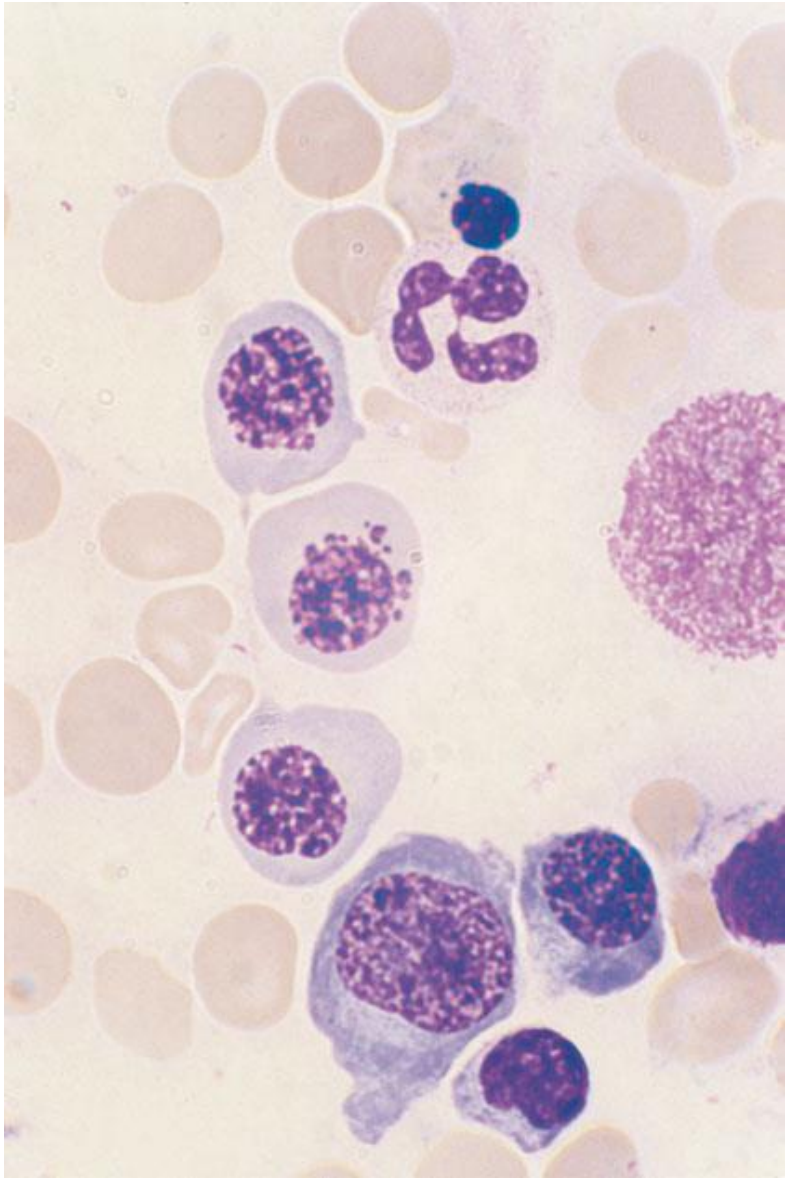
ANEMIA MEGALOBLASTICA: neutrofili iperlobulati

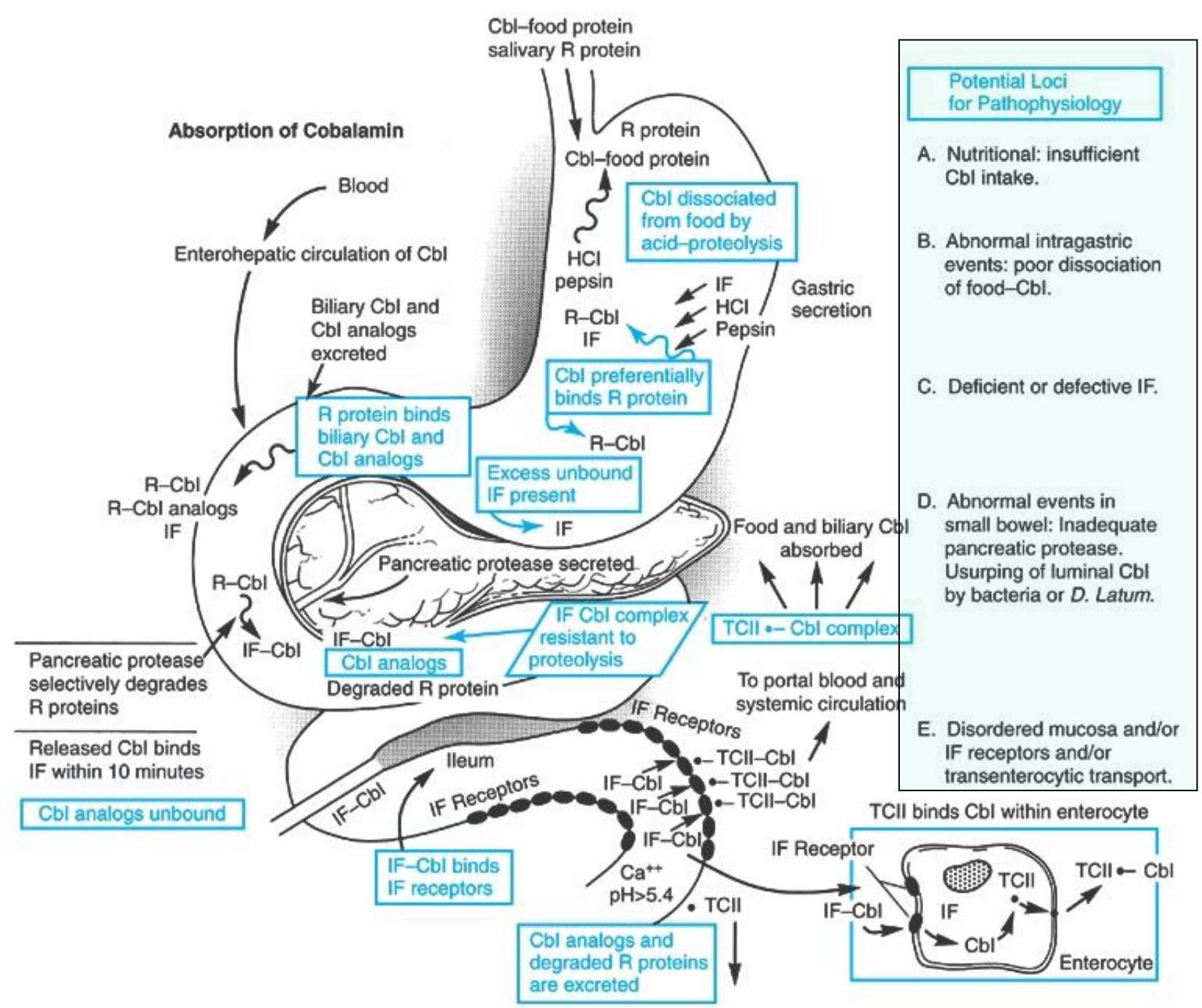




QUADRO MIDOLLARE NELL'ANEMIA MEGALOBLASTICA DA CARENZA DI B12
Numerosi megaloblasti (midollo blu) e frammentazioni nucleari (eritropoiesi inefficace)







Cause di anemia megaloblastica

Carenza B12

Deficit alimentari (rari)
- dieta vegetariana

Deficiente secrezione FI:
- gastrite atrofica (atc anti mucosa gastrica)
- Atc anti FI
- gastrectomia totale
- irradiazione gastrica

Alterazioni intestinali
- Sprue tropicale
- estese resezioni ileali
- Crohn
- Ansa cieca
- Botriocefalo
- S Imerslund

Carenza folati

Deficit alimentari (frequenti)
- alcolismo
- malnutrizione

Malassorbimento
- Alcolismo,
- celiachia
- Zollinger Ellison
- sprue
- estese resezioni ileali
- Crohn
- Sclerodermia

Aumentato fabbisogno
- Gravidanza
- emolisi cronica
- dermatiti esfoliative

Riduzione scorte epatiche
- cirrosi
- alcolismo

Farmaci e altre condizioni

Inibizione diidrofolato-redutasi
- metotrexate
- pirimetamina,
- trimetoprim

Interferenza metabolismo folati
- anticonvulsivanti
- sulfamidici

Inattivazione B12
- protossido d'azoto
- metformina

Interferenze sintesi basi DNA
- 5-FU
- idrossiurea
- citarabina
- azatioprina

Anemia refrattaria (SMD)

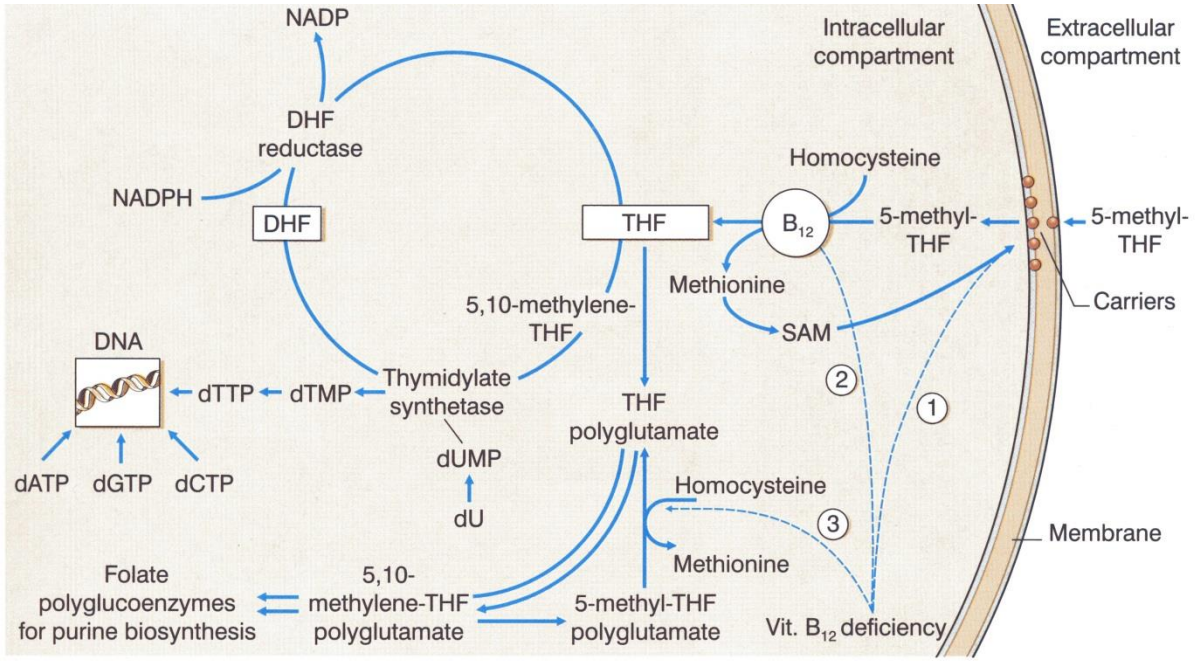


Figure 36 It is still uncertain how the principal features of megaloblastic proliferation i.e., abnormal size of the cells and asynchronous maturation of the nuclear and cytoplasmic components are related to the metabolic disturbances of these cells. While the nucleo-cytoplasmic dissociation has been attributed to delayed condensation of the chromatin in the maturing erythroblasts [131], the enlarged diameter of the cells indicates a normal rate of RNA and protein synthesis [140] in the presence of blocked DNA replication and cell division. Impaired DNA synthesis is due to defective conversion of deoxyuridylate by thymidylate synthetase. However thymidylate synthesis may be affected only indirectly by vitamin B_{12} and folate deficiency, since these factors do not appear actively involved in any step of DNA synthesis. Possibly, vitamin B_{12} deficiency causes a failure of homocysteine methylation to methionine leading to reduced conversion of 5-methylene-tetrahydrofolate to tetrahydrofolate (THF). Thus, since most of the folate is trapped as methyl-THF, in the cells there is a decrease of the 5,10-methylene-THF, a folate coenzyme required for methylation of deoxyuridine in the synthesis of thymidilate. The scheme summarizes some further data relevant to the methyl folate trap hypothesis. Since vitamin B_{12} deficiency results in a decreased rate of demethylation of both 5-methyl-THF ② and 5-methylpolyglutamate-THF ③, the intracellular pool of 5-methyl-THF appears to increase initially by delaying the release of membrane carriers from the internal surface of the cell membrane; then, an equilibrium is reached by exchange with the extracellular fluid or degradation to pteridines. Reduction of methionine synthesis and SAM (S-adenosyl-methionine) results in a further decrease of THF methyltransferase activity and a loss of feedback inhibition of methylene THF reductase. Impairment of SAM synthesis possibly influences directly the cellular transport systems. This effect is shared in turn by vitamin B_{12} deficiency ① [141]. **dUMP**, deoxyuridine monophosphate; **dTMP**, deoxythymidine monophopsphate; **dTTP**, deoxythymidine triphosphate; **dCTP**, deoxycytidine triphosphate; **dGTP**, deoxyguanosine triphosphate; **dATP**, deoxyadenosine triphosphate.

SINTOMI

- legati all'anemia (a lenta insorgenza)
- specifici

Table 34-4 Similarities of Clinical Manifestations and Megaloblastic Sequelae of Folate and Cobalamin Deficiency*

System	Manifestations
Hematologic	Pancytopenia with megaloblastic marrow
Cardiopulmonary	Congestive heart failure
Gastrointestinal	Beefy-red tongue and added stigmata of broad spectrum malabsorption in folate deficiency†
Dermatologic	Melanin pigmentation and premature graying
Genital	Cervical or uterine dysplasia
Reproductive	Infertility or sterility
Psychiatric	Depressed affect and cognitive dysfunction
Neuropsychiatric‡	Unique to cobalamin deficiency with cerebral, myelopathic, or peripheral neuropathic disturbances, including optic and autonomic nerve dysfunction

*However, the neurologic spectrum of dysfunction in cobalamin deficiency is distinct. Inadequate hemoglobinization (from inadequate iron stores or globin synthesis) can mask the expected erythroid megaloblastic morphology in the bone marrow and peripheral smear, and only specific therapy (i.e., iron) can unmask classic megaloblastic manifestations (i.e., masked megaloblastosis). Megaloblastic leukopoiesis is unchanged.
†If folate deficiency is uncorrected for 2 to 3 years, cobalamin deficiency will supervene.
‡Dorsal tract involvement is earliest manifestation in more than 70% of patients with cobalamin deficiency. Neuropsychiatric manifestations are not associated with megaloblastosis in up to 30% of patients.

Diagnosi

Emocromo (anemia, possibile leucopiastrinopenia)
- a megaloblastica
- Neutrofili ipersegmentati

Dosaggio B12 e folati (ridotto)

Bilirubinemia (aumento bil indiretta – eritropoiesi inefficace)

Sideremia (elevata - emolisi intramidollare, mancato utilizzo)

LDH (aumento che riflette espansione eritroide intramidollare)

Aspirato midollare (midollo Blu)

Escludere altre cause di megaloblastosi

Ex-adjuvantibus (crisi reticolocitaria dopo 5-7 gg di terapia)

Table 34-5 Clinical Conditions Not To Be Confused with Megaloblastosis

Macrocytosis* without Megaloblastosis†
Reticulocytosis ←
Liver disease ←
Aplastic anemia ←
Myelodysplastic syndromes (especially $5q^-$) ←
Multiple myeloma
Hypoxemia
Smokers
Spurious Increases in MCV without Macro-ovalocytosis‡
Cold agglutinin disease ←
Marked hyperglycemia
Leukocytosis
Older individuals

*The central pallor that normally occupies about one third of the normal red blood cell is decreased in macro-ovalocytes. This contrasts with the finding of thin macrocytes, in which the central pallor is increased.
†Although megaloblastosis implies that a bone marrow test has been performed, with the addition of highly sensitive tests for the specific diagnosis of cobalamin and folate deficiency, the need for a bone marrow test is often dictated by the urgency to make the diagnosis.
‡When the Coulter counter readings of a high MCV are not confirmed by looking at the peripheral smear.
MCV, mean corpuscular volume.

Differential diagnosis

MDS: check for neutropenia, cytogenetics, ex adjuvantibus

Aplastic Anemia: BM aspiration

Liver disease: think about it!

Pancytopenia due to BM infiltration

Treatment

Administer B12 vitamin (IM) and folate

Never folate alone (neurologic damage may worsen)

Check for reticulocytosis after 5-7 days

Check for Hb increase (at least 1-2 gr/dL after 20 days)

Check for correction of anemia after 1-2 months

Table 34-6 Causes of Megaloblastosis Not Responding to Therapy with Cobalamin or Folate

Wrong diagnosis
Combined folate and cobalamin deficiencies being treated with only one vitamin
Associated iron deficiency
Associated hemoglobinopathy (e.g., sickle cell disease, thalassemia)
Associated anemia of chronic disease
Associated hypothyroidism

Table 34-7 Indications for Prophylaxis with Cobalamin or Folate

Prophylaxis with Cobalamin
Infants of mothers with pernicious anemia*
Infants on specialized diets*
Vegetarians and poverty-imposed near-vegetarians*
Total gastrectomy†
Prophylaxis with Folic Acid‡
All women contemplating pregnancy (at least 400 μg/day)§
Pregnancy and lactation, premature infants
Mothers at risk for delivery of infants with neural tube defects¶,¶
Hemolytic anemias/hyperproliferative hematologic states
Patients with rheumatoid arthritis or psoriasis on therapy with methotrexate**

*For vegetarians, prophylaxis with cobalamin (5- to 10-μg tablet/day) orally should suffice. In food-cobalamin malabsorption from an inability to cleave food cobalamin by acid and pepsin, replacement therapy should be with daily tablets of more than 100 μg taken orally. In all other conditions involving any abnormality of cobalamin absorption, cobalamin tablets of 1000 μg/day should be administered orally to ensure that cobalamin transport by passive diffusion across the intestine is sufficient to meet daily needs.

†Consider late development of cobalamin deficiency and iron malabsorption (prophylaxis with oral cobalamin and iron).

‡Ensure that the patient does not have a cobalamin deficiency before initiating long-term folate prophylaxis.

§For prevention of first occurrence of neural tube defects.

¶Previous delivery of a child with neural tube defects (e.g., anencephaly, spina bifida, meningocele) imparts a 10-fold greater risk for subsequent delivery of infant with neural tube defects.

¶Folic acid (4 mg/day) administered periconceptionally and throughout the first trimester.

**To reduce toxicity of the antifolate.