Diyala University – collage of medicine
Hematology -5th stage
Lec 5:

MEGALOBLASTIC ANEMIA

By:
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DEFINITION AND PATHOPHYSIOLOGY

- Anemia characterized by impaired DNA synthesis of many causes principally to B12 and Folate deficiency, resulting in distinctive cytological and functional abnormalities in blood and bone marrow
- The cellular gigantism occur secondary to impaired DNA synthesis and subsequent delay in nuclear maturation and cell division

CAUSES OF MACROCYTOSIS:

1. **Megaloblastic**
   - Vit.B12(cobalamin)deficiency or dysfunction.(Most important)
   - Folic acid deficiency or dysfunction.(Most important(
   - In dependent on B12 / FA causes
2. **non megaloblastic Macrocytosis**
   - Alcohol
   - Liver disease (especially alcoholic)
   - Reticulocytosis (haemolysis or haemorrhage)
   - Aplastic anaemia or red cell aplasia
   - Hypothyroidism
   - Myelodysplasia
   - Myeloma and macroglobulinaemia
   - Leucoerythroblastic anaemia
   - Myeloproliferative disease

FOLIC ACID METABOLISM:

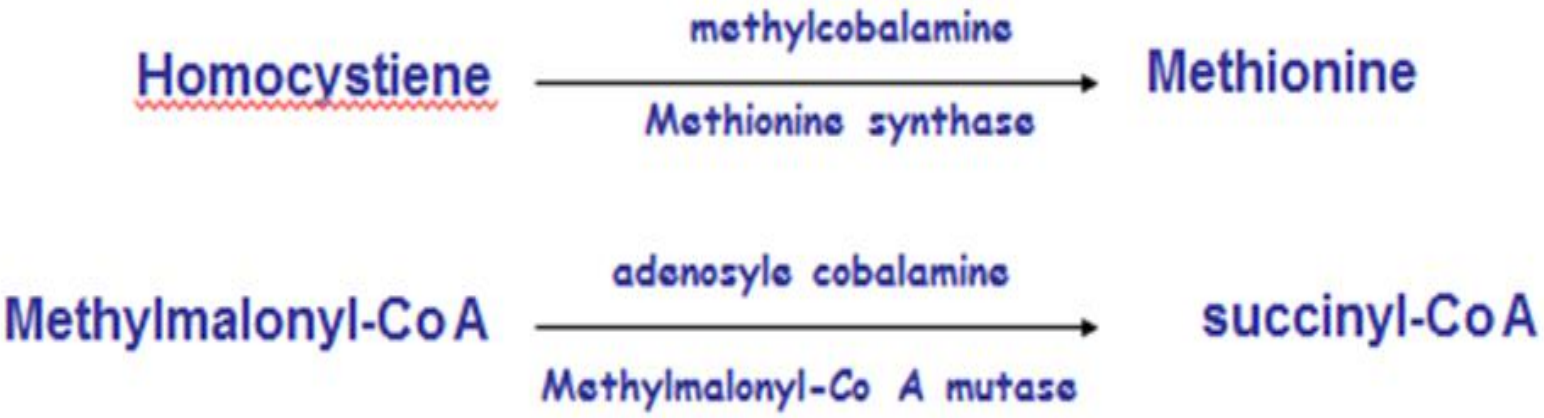
- 2 Forms: Polyglutamates and Monoglutamates.
- Main source are vegetable and fruits.
- Folates are present in Liver, kidney.
- Daily requirement 100-150 µg.
- Body stores are ~ 5-20 mg , enough for 4 months.
- Absorption: take place in upper 1/2 of small intestine.
- Functions: As a co-enzyme in purine and pyrimidine synthesis.
- Transport: weakly bound to albumin.
- Excretion: by bile and urine

B12 (COBALAMIN) METABOLISM

- 4 Forms of vit.B12:-
  - Methylcobalamin
  - Adenosylcobalamin
  - Cyanocobalamin
  - Hydroxycobalamin
- Present only in food of animal origin and less in dairy products.
- Daily requirement 1-3 µg.
- Body store 2-5 mg, enough for 3-4 years.
- Excretion: by bile only
- Transport in plasma by: Trascobalamin I, II and III

BIOCHEMICAL FUNCTIONS OF VITAMIN B12

1. Conversion of Homocystiene to Methionine (methyle cobalamine).
2. Maintaining the active form of folate inside the cells and available for DNA synthesis (methyle cobalamine).
3. Conversion of Methylmalonyl-Co A into succinyl-Co A (adenosyle cobalamine).



BIOCHEMICAL BASIS OF MBA

- DNA synthesis required polymerization of 4 deoxyribonucleoside triphosphates
- FA deficiency impaired thymidylate of dUMP to dTMP.
- B12 required to achieve the active form of folate inside the cell
- Other congenital or acquired causes of MBA inhibit purine or pyrimidine synthesis at one other step
- Neurological manifestations only with B12 def

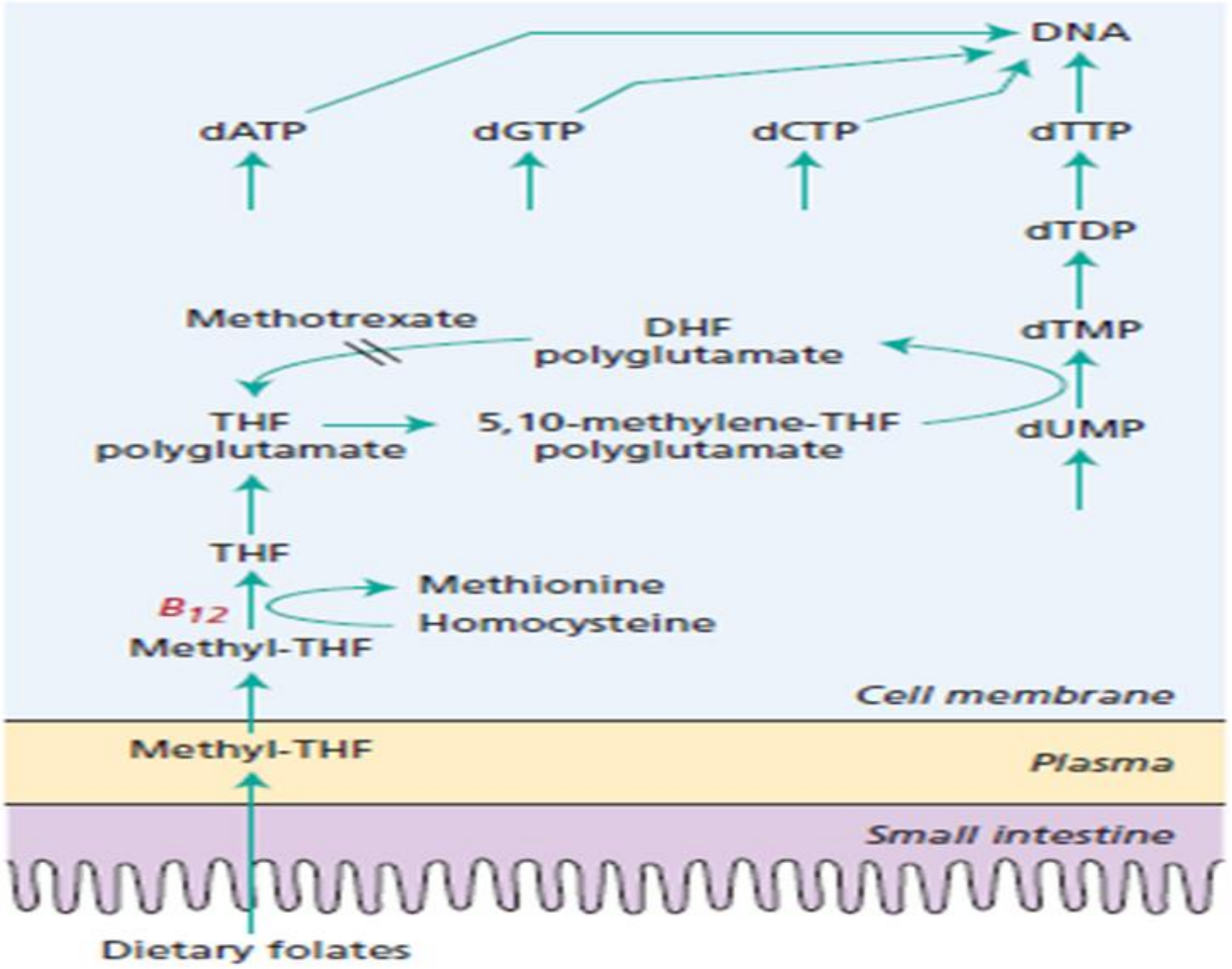
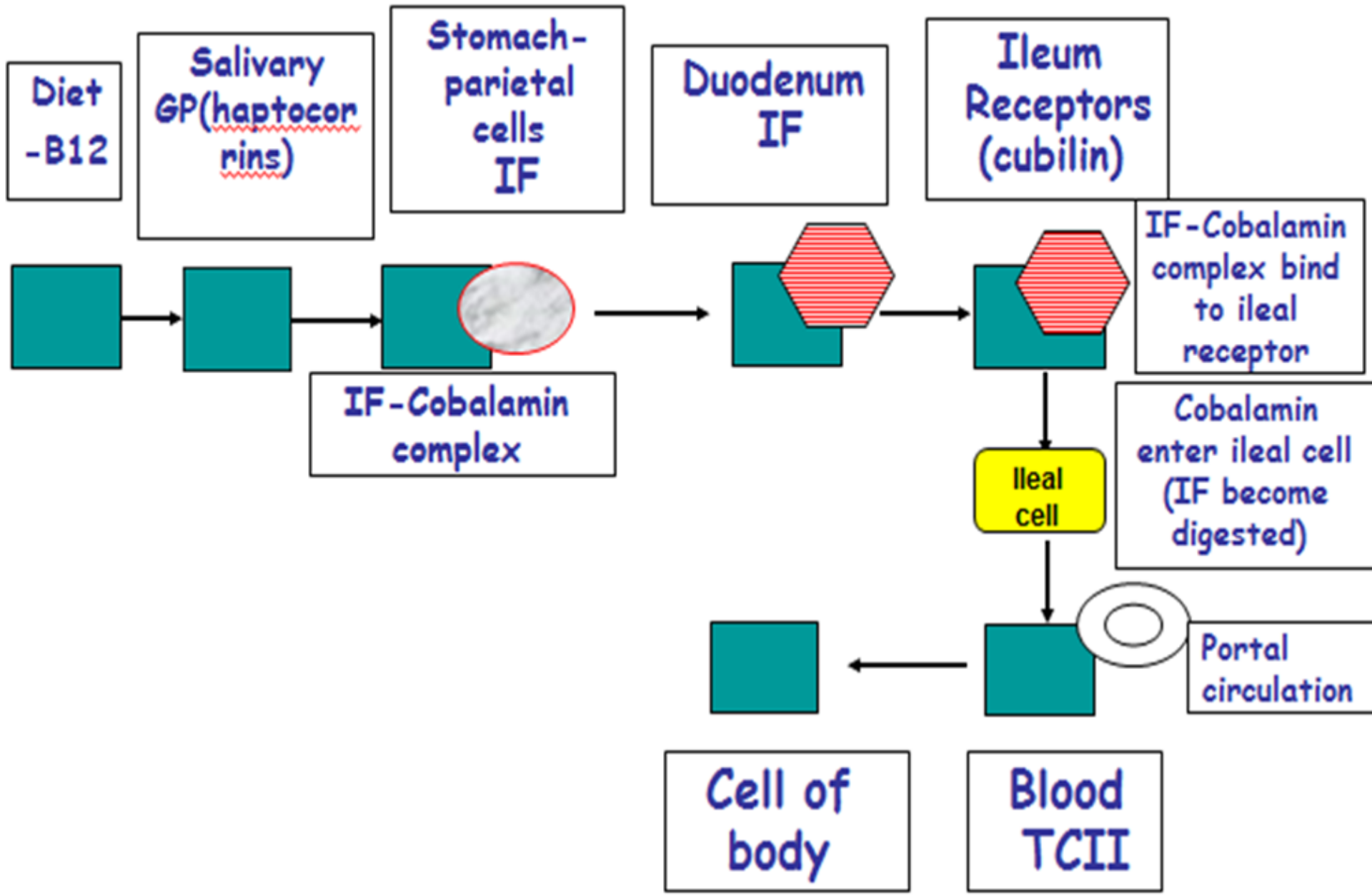
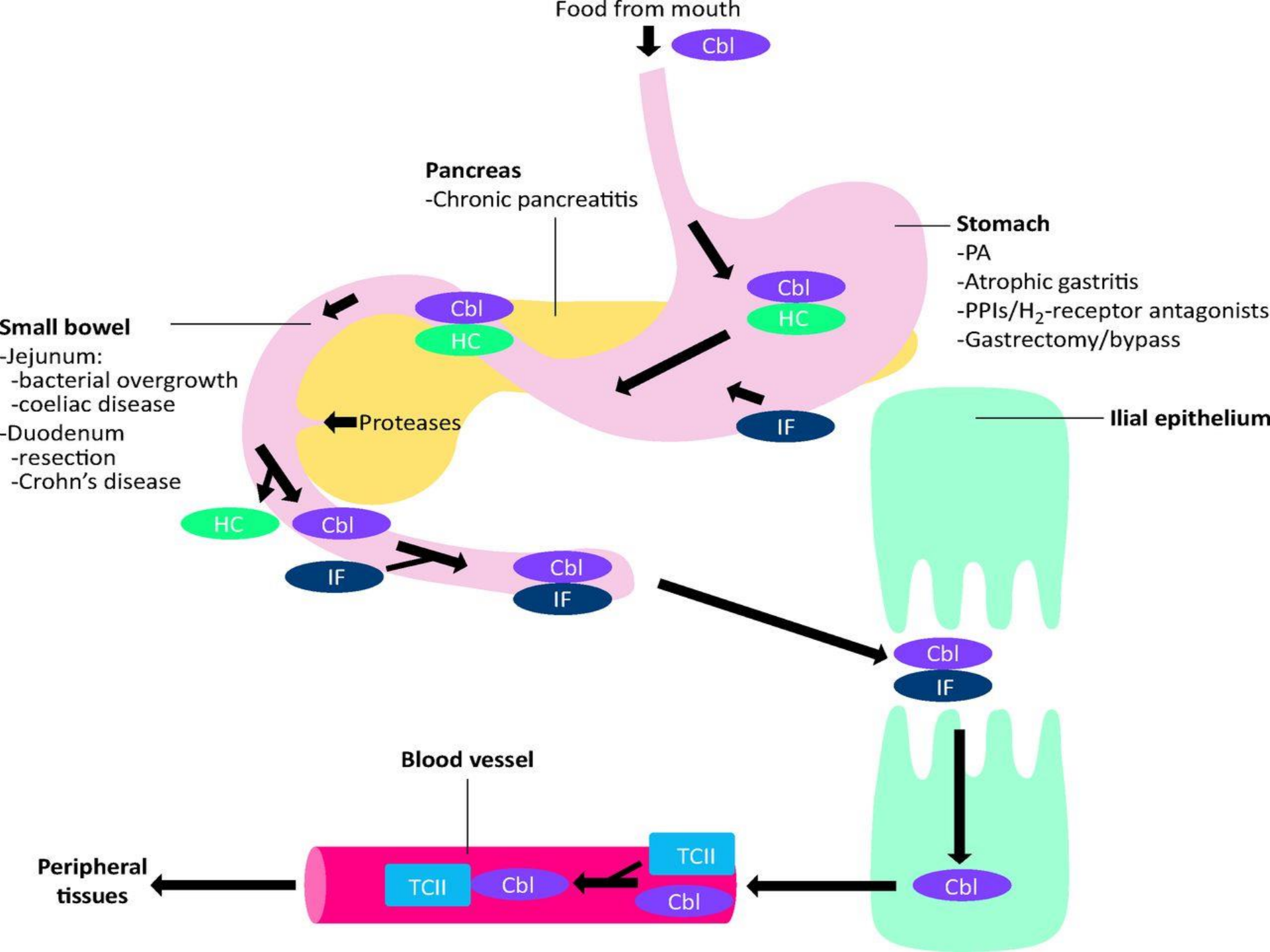


Figure 5.1 Role of folate (as 5,10-methylene-THF polyglutamate) and methylcobalamin in DNA synthesis. THF, tetrahydrofolate; MP, monophosphate; TP, triphosphate; d, deoxyribose; A, adenine; T, thymine; C, cytosine; G, guanine; B12, vitamin B12, cobalamin.

Summary of Absorption of B12




Food from mouth
Cbl
Pancreas
-Chronic pancreatitis
Stomach
-PA
-Atrophic gastritis
-PPIs/H2-receptor antagonists
-Gastrectomy/bypass
Cbl
HC
Cbl
HC
Small bowel
-Jejunum:
-bacterial overgrowth
-coeliac disease
-Duodenum
-resection
-Crohn's disease
Proteases
IF
Ilial epithelium
HC
Cbl
IF
Cbl
IF
Cbl
IF
Blood vessel
Peripheral tissues
TCII
Cbl
TCII
Cbl
Cbl

CAUSE OF VIT. B12 DEFICIENCY:

1. **Malabsorption (Main cause)**
   - Gastric cause, as pernicious anemia.
   - Intestinal cause, as ileal resection, (fish tapeworm), stagnant loop syndrome,
2. **Dietary deficiency**:
3. **Inborn error**: as IF def., TC II def.
4. **Others** as acquired abnormal B12 metabolism (Nitrous oxide inhalation), sever chronic pancreatitis, HIV, radiotherapy.

CAUSES OF FA DEFICIENCY:

1. **Inadequate dietary intake** (common cause): old age, poverty, alcoholism, psychiatric disturbance, goat milk anemia, etc.
2. **Malabsorption**: coeliac, tropical sprue, crohn's .
3. **Increase requirement or loss:**
   - Physiological
   - Pathological
4. **Ant folate drugs** as anticonvulsants, alcohol.
5. **Inborn error** of FA metabolism: cong.malasorption, DHFR def

CLINICAL FEATURES OF MBA (BOTH B12 & FA DEF.)

- **May be asymptomatic**. Usually insidious onset of sign and symptom of anemia.
- **Mild Jaundice** (due to intramurals destruction)
- **Epithelial tissue changes** as glossitis, angular stomatitis.
- **May occurs melanin pigmentation** (unclear mechanism(SM in severe anemia)
- **Bleeding manifestation.**

- **Sterility** may occur in both sexes.
- **NTD** (neural tube defect) in FA def. And B12 deficiency of unclear mechanisms.
- Many **neurological manifestations** .
- **Psychiatric** abnormality (MB madness)
- Increase risk of **MI, CVD, and thrombosis**

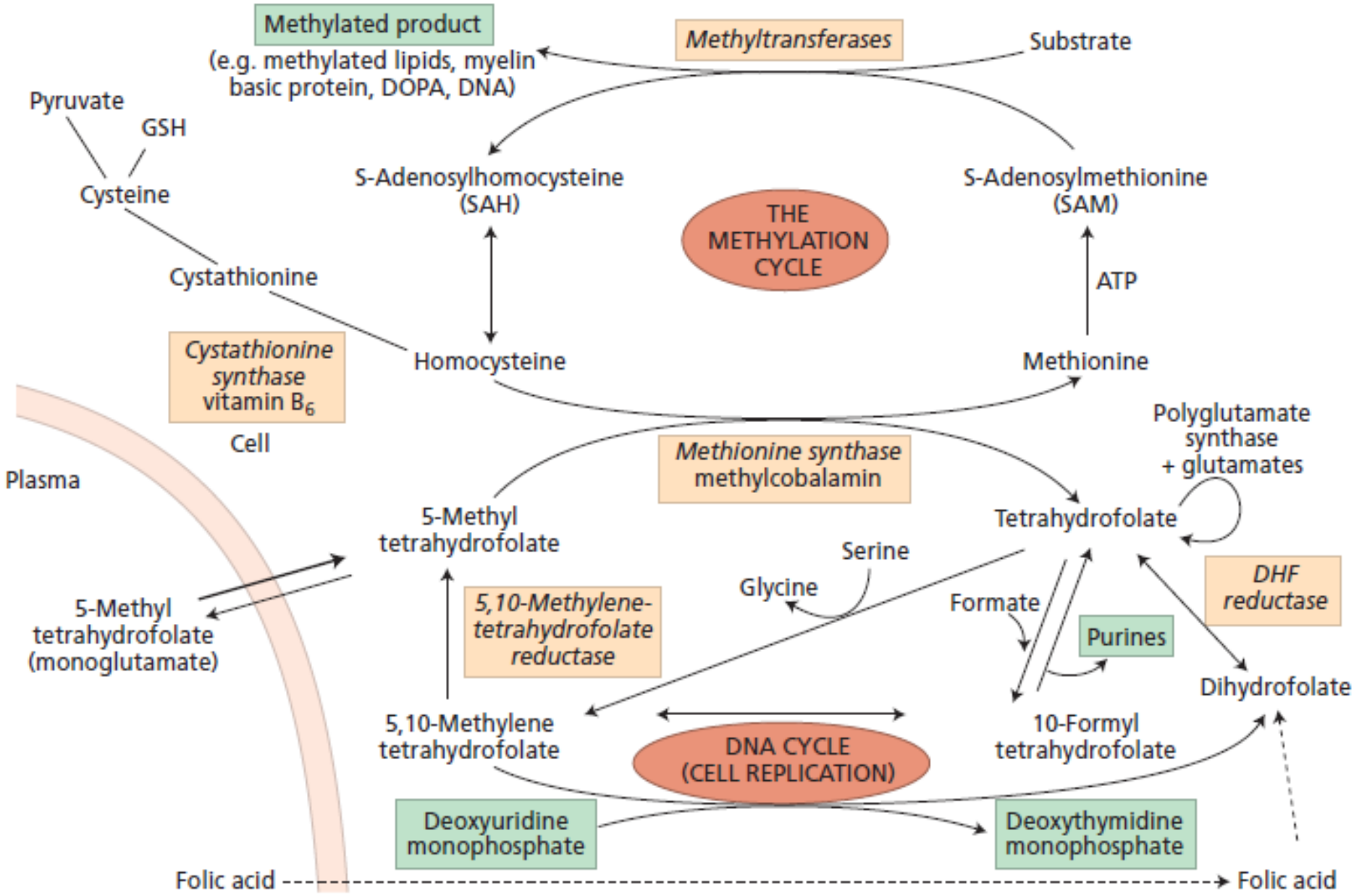


Figure 5.3 The role of folates in DNA synthesis and in formation of *S*-adenosylmethionine (SAM), which is involved in numerous methylation reactions. Enzymes are shown in pink boxes. (Figure prepared in conjunction with Professor John Scott.)

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Fatigue

Memory Loss

Depression

B12 DEFICIENCY SYMPTOMS

Shortness of Breath

Numbness

Muscle Weakness

Digestive Problems

VITAMIN B12 DEFICIENCY

signs and symptoms

DIZZINESS

HIGH TEMPERATURE

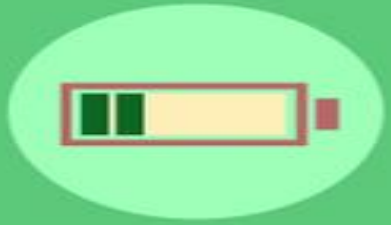
MOOD CHANGES

CHANGES TO MOBILITY

PALE/JAUNDICED SKIN

GLOSSITIS/ MOUTH ULCERS

DISTURBED VISION



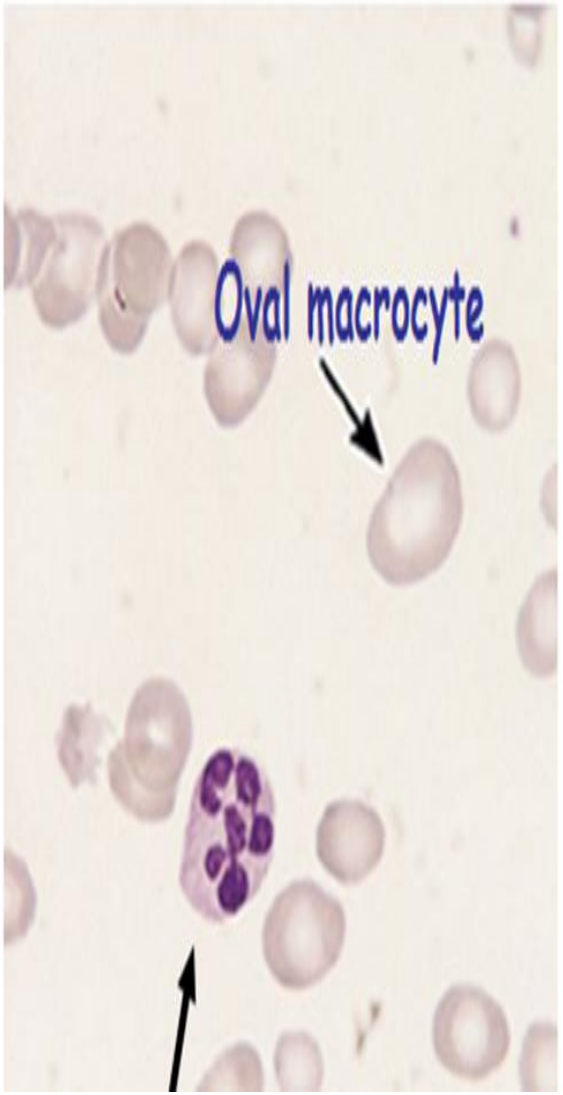
FATIGUE

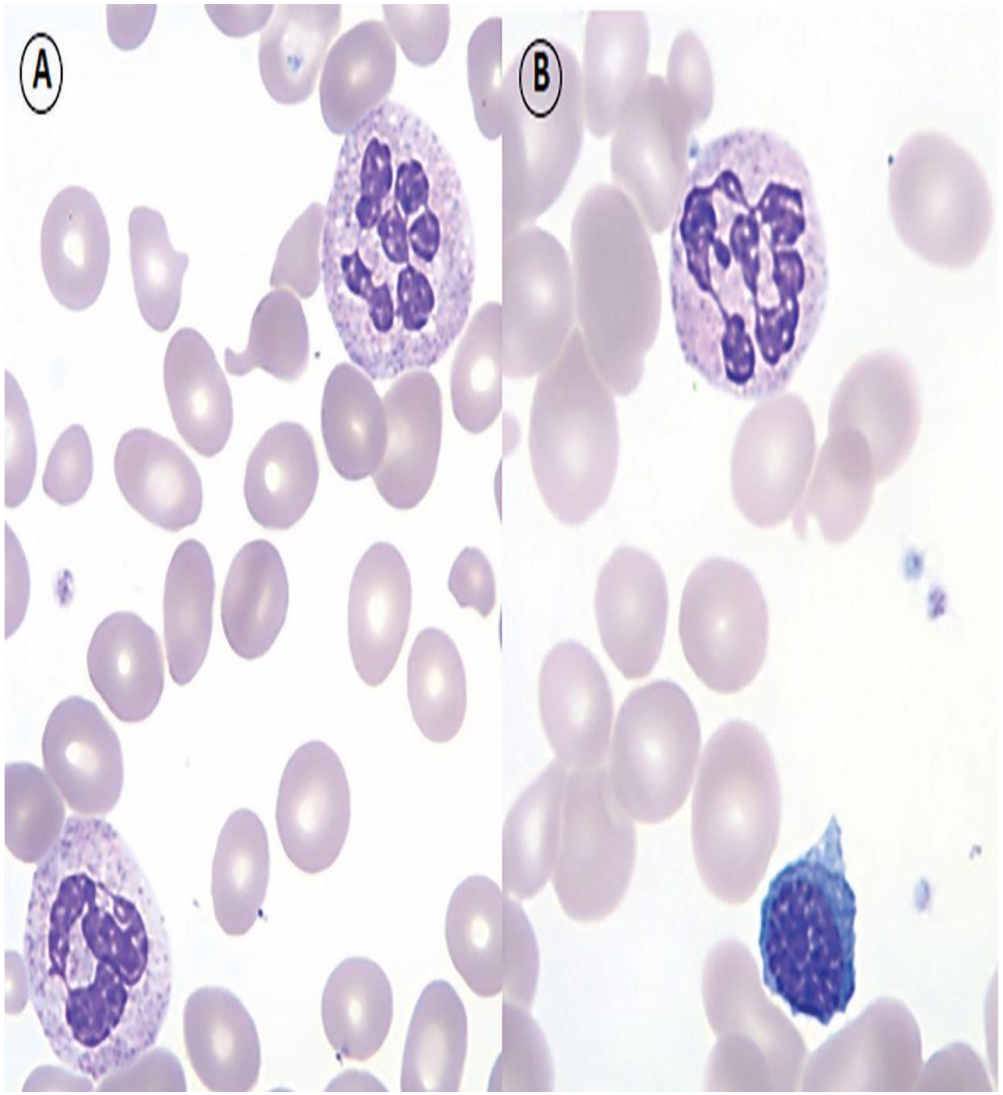
SENSATIONS OF PINS AND NEEDLES

LABORATORY FINDINGS OF MBA

1. **Hematological findings**
   - Variable degree of anemia, may reach a low of 2-3g/dl.
   - MCV increased >100 fl, may be up to 135.
   - Low retics.
   - Leucocytes may be reduced, Platelets may be reduced.
   - **Blood film:** Oval macrocytes, proportion of neutophils showing hyper segmentation, leucoerythroblastic picture may found .

Blood film in megaloblastic anaemia

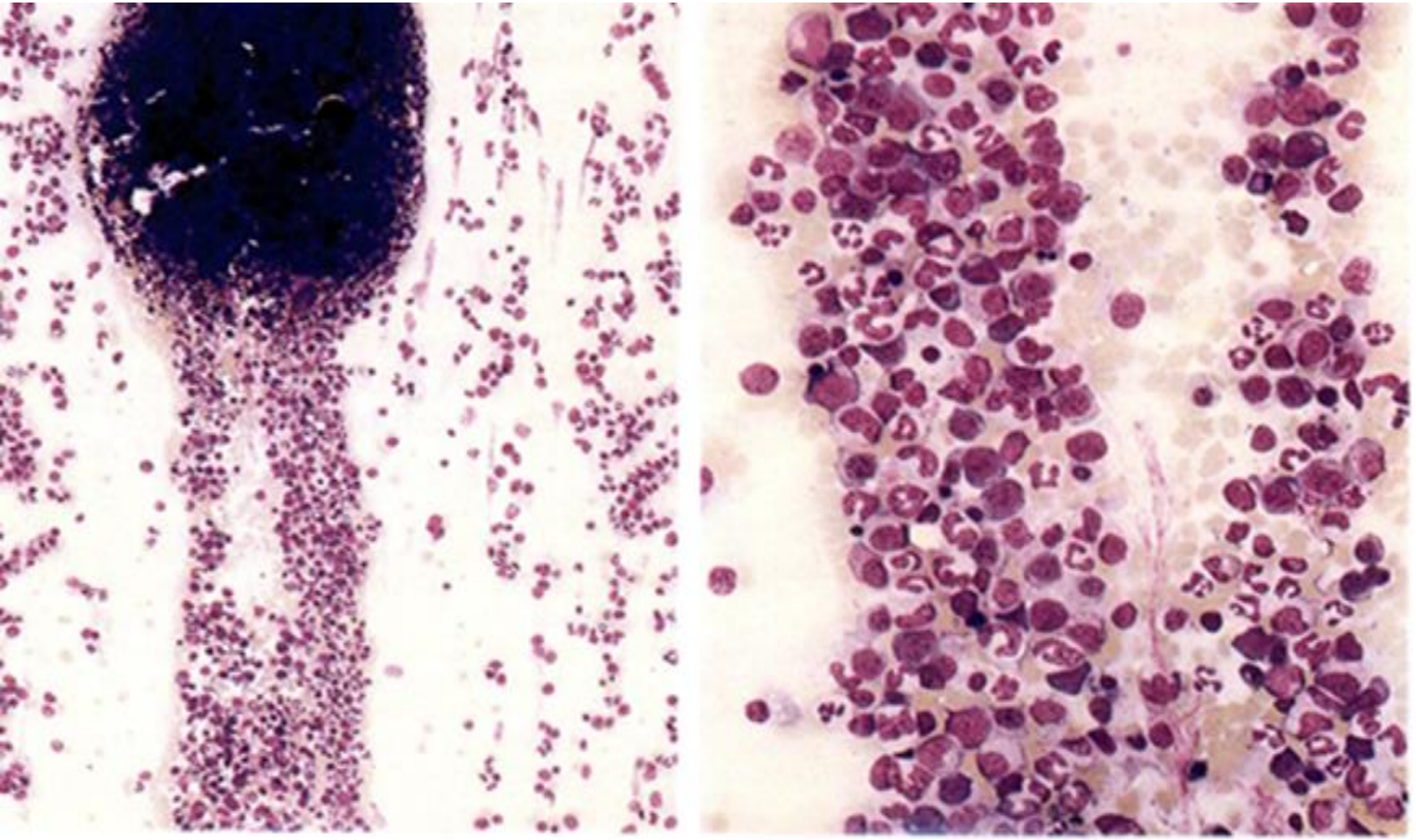




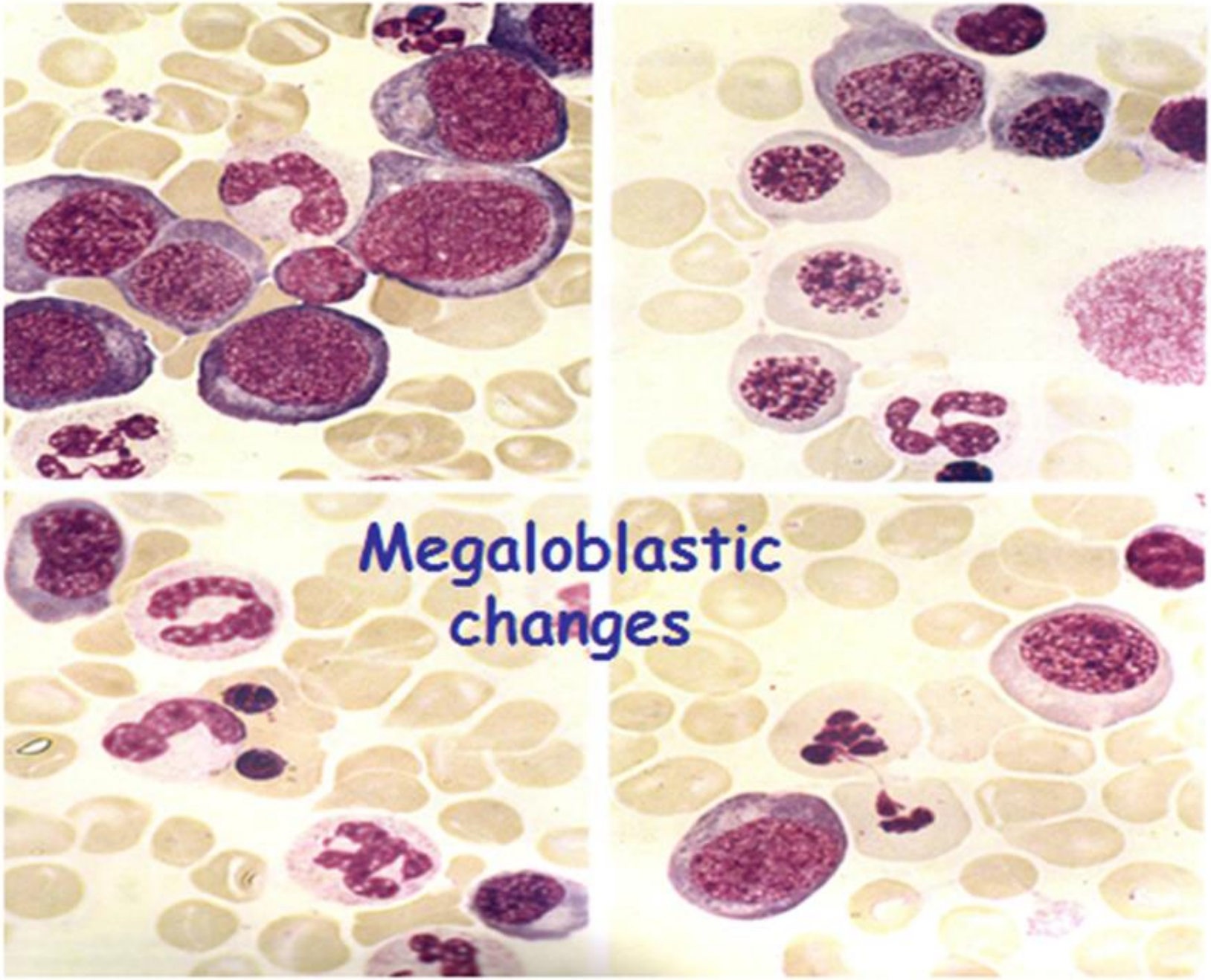
BM findings:

- **Hypercellular** marrow (blue marrow), with **megaloblastic** changes including; giant (megaloblastic) early precursors, unbalance N/C maturation specially in late erythroblasts, with normal Hbnization
- Giant and abnormal shape metamyelocyte or myelocytes cells with enlarge and hyperpolypliod megakaryocytes
- **Increase iron** storage in uncomplicated cases

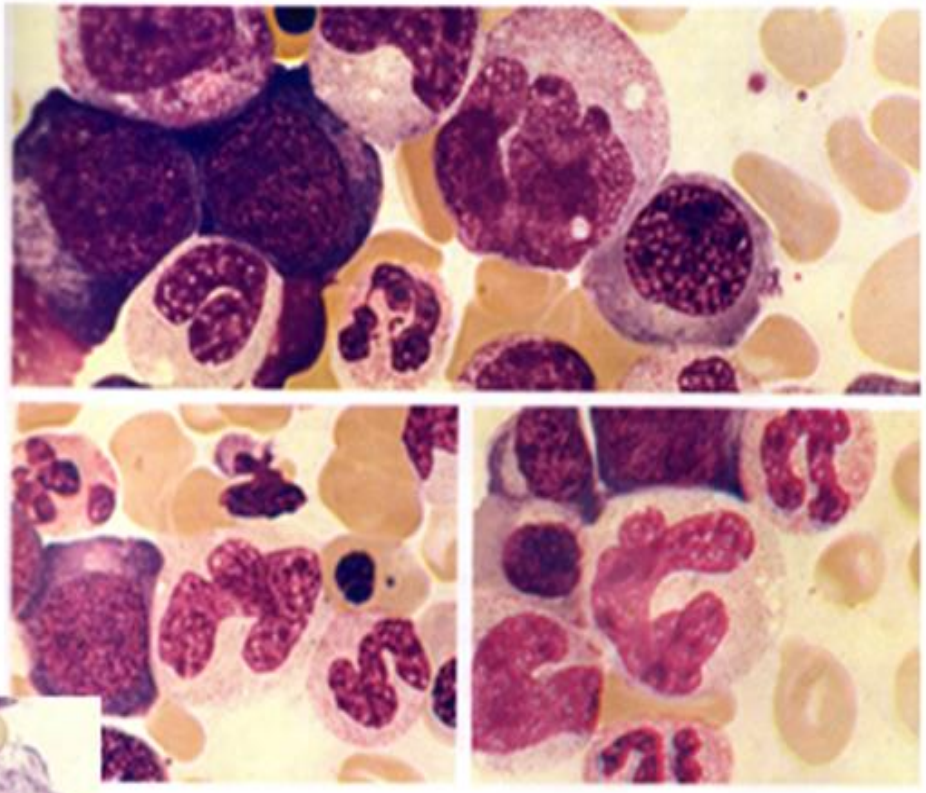
BM FINDINGS:

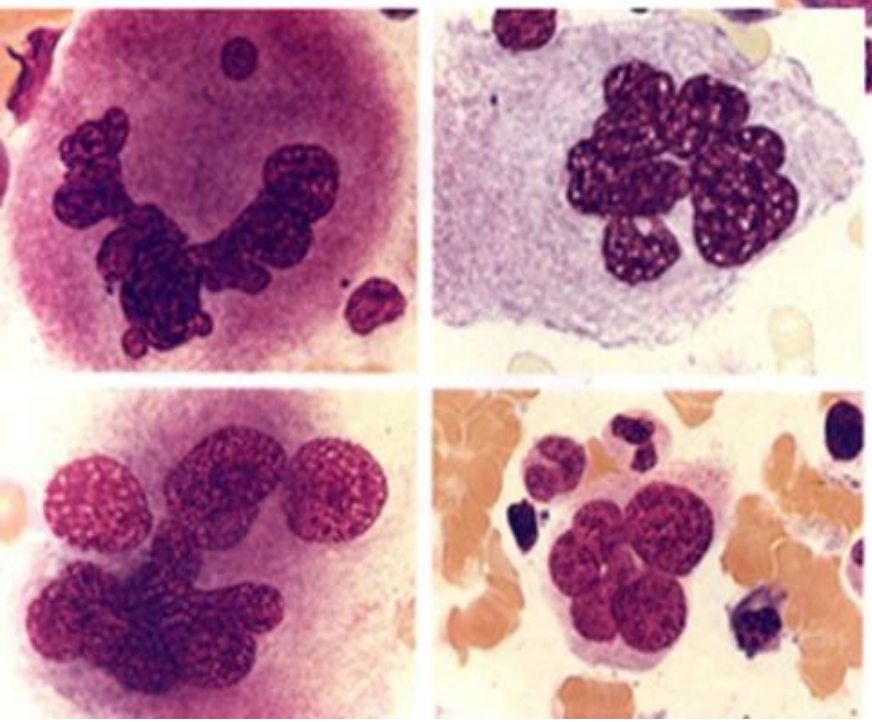


Hypercellular marrow fragment and trails


Megaloblastic
changes

Giant and abnormal granulocytic cells





Enlarge and hyperpolypliod megakaryocytes.

Laboratory Diagnosis of Megaloblastic Anemias

Test	Cobalamin Deficiency	Folate Deficiency
Serum cobalamin	Decreased	Usually normal
Serum folate	Normal to increased	Decreased
Erythrocyte folate	Decreased	Decreased
Serum methylmalonic acid	Increased	Normal
Serum homocysteine	Increased	Increased (moderately)

MANAGEMENT:

- Blood sample and BM done before any treatment.
- General measures may require as platelets, K supplement, RBC concentrate.
- Treatment with specific vitamin if known, otherwise both should be given.
- B12: lifelong B12 therapy using Hydroxocobalamin by injection.
  - 6 injections of 1mg (1000 µg) IM for body restore.
  - then monthly injection for life
  - Should never give folate on its own in cobalamin deficiency.
  - B12 prophylaxis in total gastrectomy, ileal resection.

- FA: Folic acid given orally 5-15 mg / day.
  - Duration usually 4 months, but depend on the underlying pathology.
  - FA prophylaxis in Pregnancy, pre-maturity (1mg/day), sever HA and dialysis.

Response to treatment

- ✓ Correct pt. behavior and appetite within 1-2 day
- ✓ Retic count peak at 7 days may reach 40-50%
- ✓ Hb increase 2-3 gm/dl each fortnight, and corrected in 5-6 wks.
- ✓ BM response (start in 8-12 hrs) within 2-3 days with normoblasts but giant metamyelocytes persists 12 days.
- ✓ Peripheral neuropathy may partially improve but spinal cord damage is irreversible.
- ✓ Follow up the patient with Hb and retic not by BM.


Thank You