

MEGALOBLASTIC ANAEMIA

BY:

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LEARNING OBJECTIVES

- To understand the mechanisms by which macrocytic anaemia may arise
- To appreciate the signs and symptoms of macrocytic anaemia
- To understand how macrocytic anaemia can be classified
- To be able to know the causes of macrocytic anaemia
- To understand the normal metabolism of vitamin B12 and folic acid, and to appreciate how megaloblastic anaemia may arise
- To suggest some normoblastic causes of macrocytosis

Normal adult red cell values

	Male	Female
Haemoglobin* (g/L)	135 – 175	115 – 155
Haematocrit (PCV) (%)	40 – 52	36 – 48
Red cell count (x10¹²/L)	4.5 – 6.5	3.9 – 5.6
Mean cell haemoglobin (pg)	27 – 34	
Mean cell volume (fL)	80 – 95	
Mean cell haemoglobin concentration g/L)	300 – 350	
Reticulocyte count (x10⁹/L)	25 – 125 (1.0 – 2%)	

* In children normal haemoglobin values are: newborn, 150 – 210g/L; 3 months, 95 – 125g/L; 1 year to puberty, 110 – 135g/L.

* PCV, packed cell volume.

NORMAL WHITE CELLS (WBC) COUNT IN ADULTS

TOTAL	4.0 - 11.0 X 10 ⁹ /L
Neutrophils	2.5 - 7.5 x 10 ⁹ /L
Lymphocytes	1.5 - 3.5 x 10 ⁹ /L
Monocytes	0.2 - 0.8 x 10 ⁹ /L
Eosinophils	0.04 - 0.44 x 10 ⁹ /L
Basophil	0.01 - 0.1 x 10 ⁹ /L
Platelets	150-450 x 10 ⁹ /L

* Children have higher lymphocytes count

Microcytic, Hypochromic Anaemia

MCV < 80 fL

MCH < 27pg

Iron deficiency

Thalassaemia

Anaemia of chronic disease (some cases)

Lead poisoning

Sideroblastic anaemia (some cases)

Normocytic, Normochromic Anaemia

MCV 80 – 95 fL

MCH > 26 pg

Many haemolytic anaemias

Anaemia of chronic disease (some cases)

After acute blood loss

Renal disease

Mixed deficiencies

Bone marrow failure, e.g. post-chemotherapy, infiltration by carcinoma, etc.

MACROCYTIC ANAEMIA

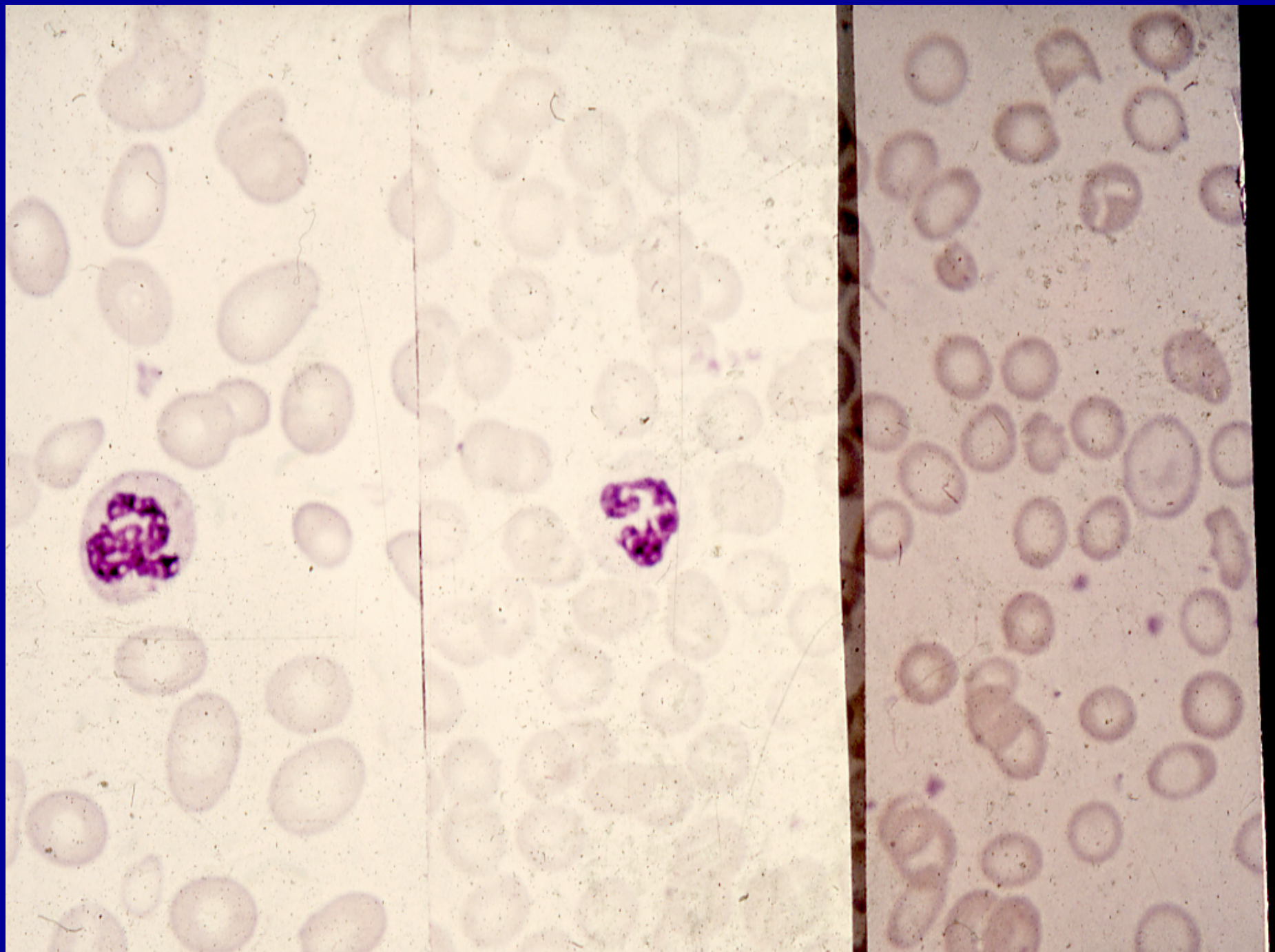
Macrocytic anaemias can be divided into those showing:

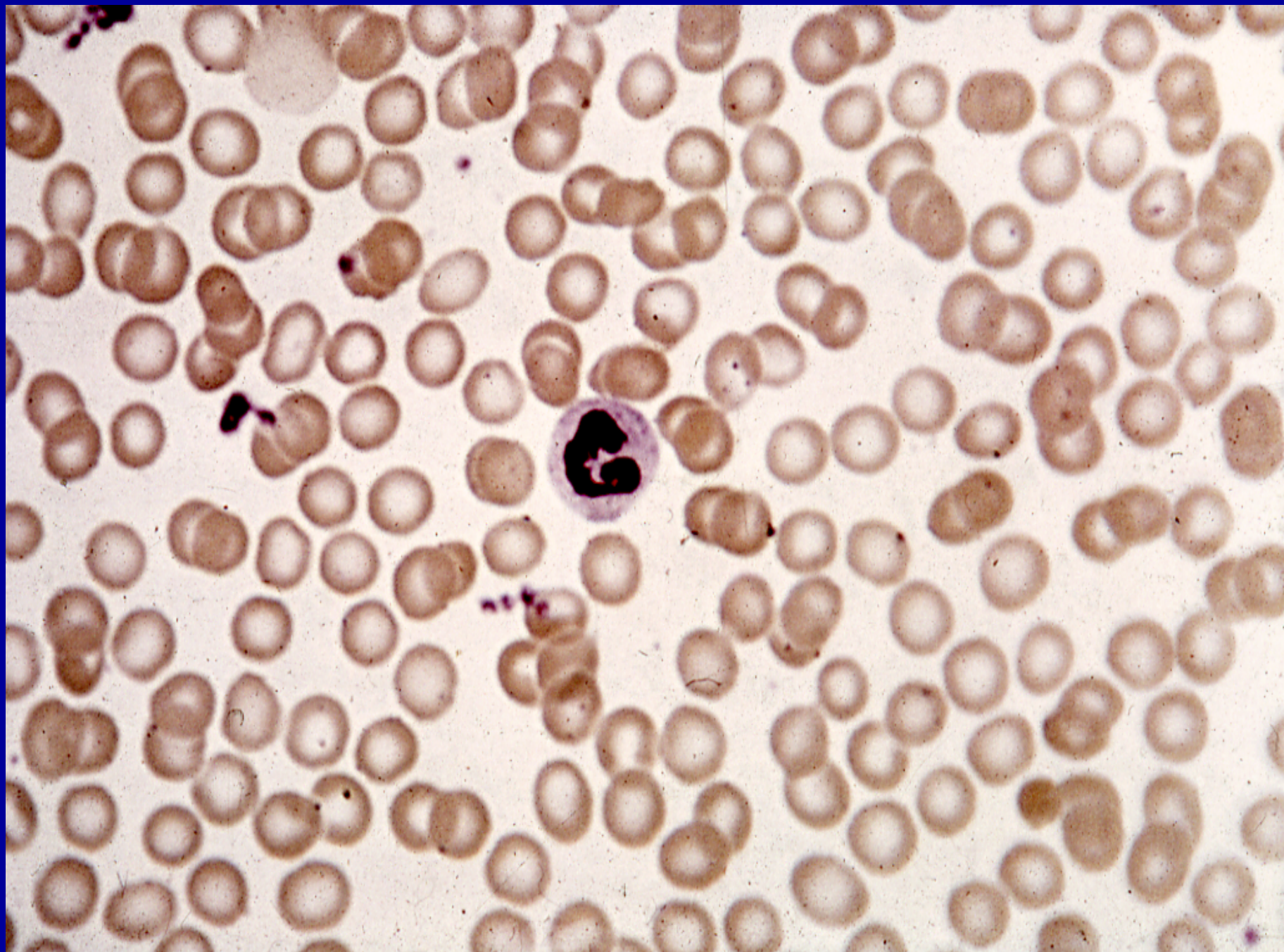
1. Megaloblastic erythropoiesis

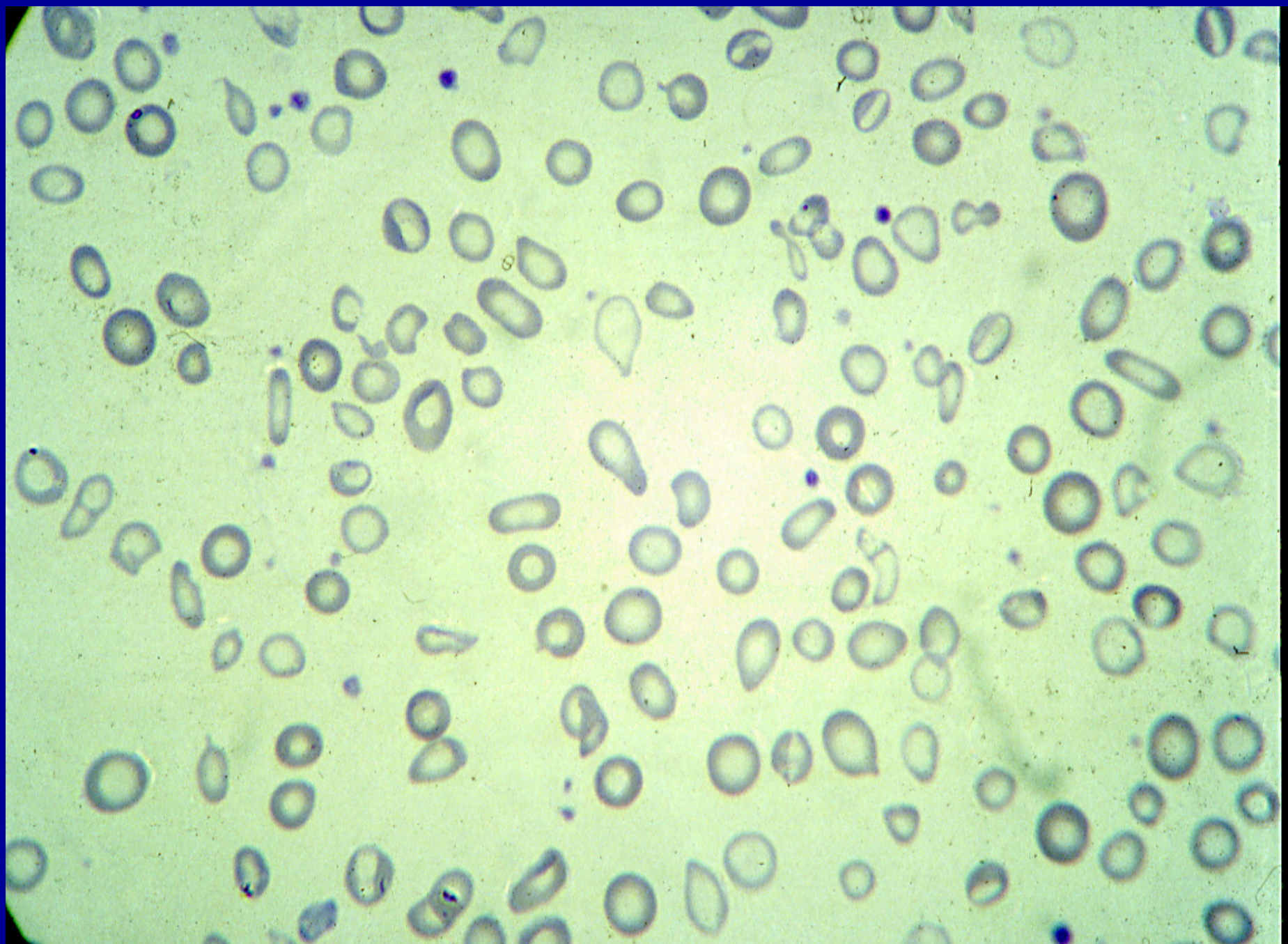
2. Normoblastic erythropoiesis

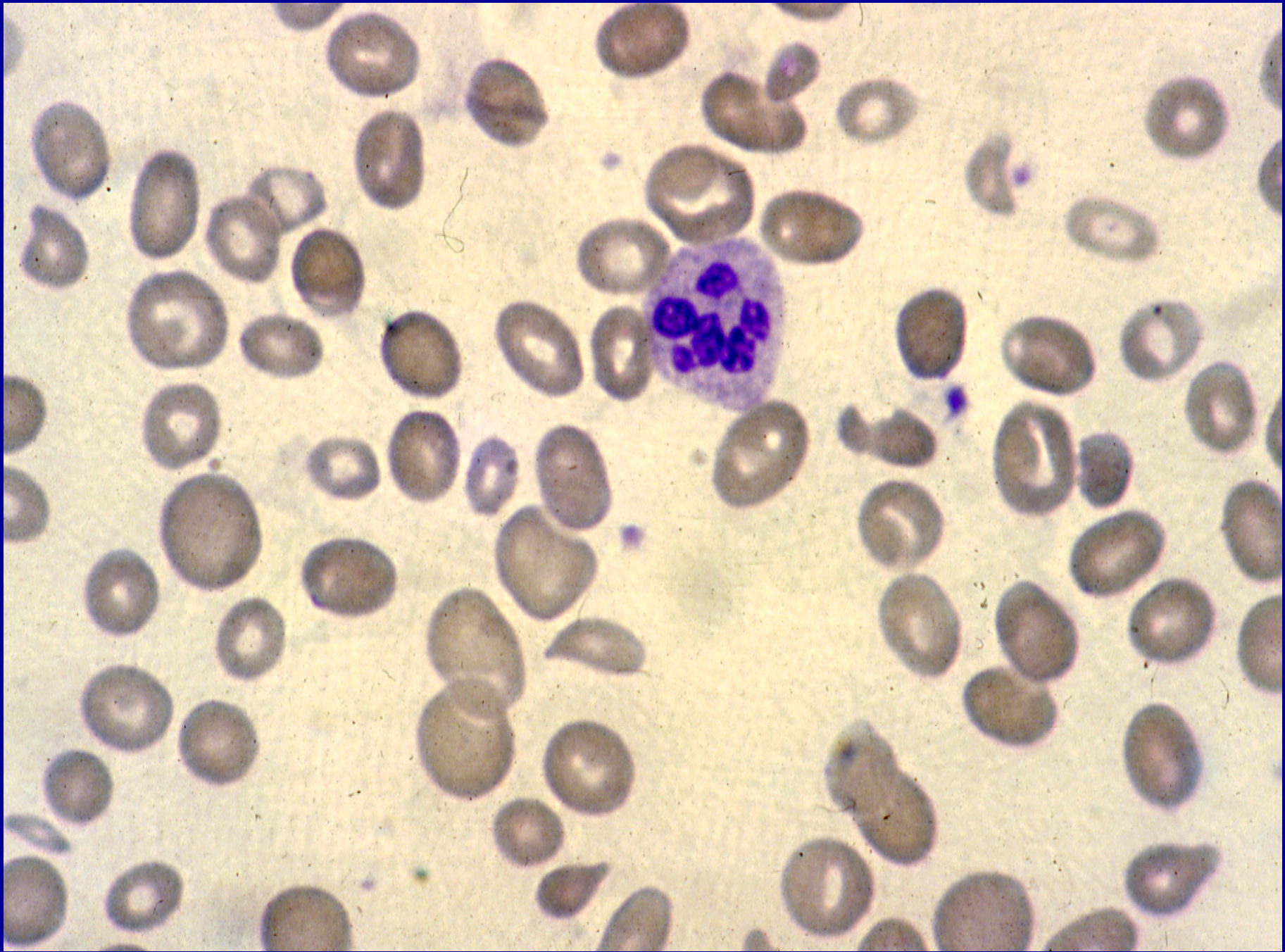
Megaloblastic erythropoiesis - describes abnormal red cell development characterized by a lack of synchrony between the maturation of the red cell nucleus and its cytoplasm. It arises as a consequence of disordered DNA synthesis and results in a macrocytic anaemia.

Normoblastic erythropoiesis - describes the normal appearance of red cell maturation - but may still be associated with a macrocytosis in the peripheral blood.









Conditions in which Macrocytosis or hypersegmented neutrophils may occur in the absence of megaloblastic anaemia

Macrocytosis

Alcohol

Liver disease (especially alcoholic)

Reticulocytosis (haemolysis or haemorrhage)

Aplastic anaemia or red cell aplasia

Hypothyroidism

Myelodysplasia including acquired Sideroblastic anaemia

myeloma and macroglobulinaemia

Leucoerythroblastic anaemia

Myeloproliferative disease

Pregnancy

Newborn

? Chronic respiratory failure

Hypersegmented

Renal failure

Neutrophils

Congenital (familial) abnormality

? Iron deficiency

Note:- High MCV recorded when cold agglutinins or paraproteins are present.

Macrocytosis with Normoblasts

- * **Normal neonates (Physiological)**
- * **Chronic alcoholism***
- * **Myelodysplastic syndromes***
- * **Chronic liver disease***
- * **Hypothyroidism**
- * **Normal pregnancy**
- * **Therapy with anticonvulsant drugs***
- * **Haemolytic anaemia**
- * **Chronic lung disease (with hypoxia)**
- * **Hypoplastic and aplastic anaemia**
- * **Myeloma**

Causes of megaloblastic anaemia :

1. **Cobalamin deficiency or abnormalities of cobalamin metabolism**
 2. **Folate deficiency or abnormalities of folate metabolism**
 3. **Therapy with antifolate drugs (e.g. methotrexate)**
 4. **Independent of either cobalamin or folate deficiency and refractory to cobalamin and folate therapy.**
 - a. **Some cases of acute myeloid leukaemia, myelodysplasia.**
 - b. **Orotic aciduria (responds to uridine)**
 - c. **Therapy with drugs interfering with synthesis of DNA (e.g. cytosine arabinoside, hydroxyurea, 6-mercaptopurine, azidothymidine (AZT))**
 - d. **Thiamine responsive**
 5. **Suggested but poorly documented causes of megaloblastic anaemia not due to cobalamin or folate deficiency or metabolic abnormality:**
 - a. **Vitamin E deficiency**
 - b. **Lesch-Nyhan syndrome (?responds to adenine)**
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Other causes of megaloblasts :

Abnormalities of nucleic acid synthesis

Drug therapy

Antipurines (mercaptopurine, azathioprine)

Antiprimidines (fluorouracil, zydovudine (AZT))

Others (hydroxyurea)

Orotic aciduria

Uncertain aetiology

Myelodysplastic syndromes, * erythroleukaemia

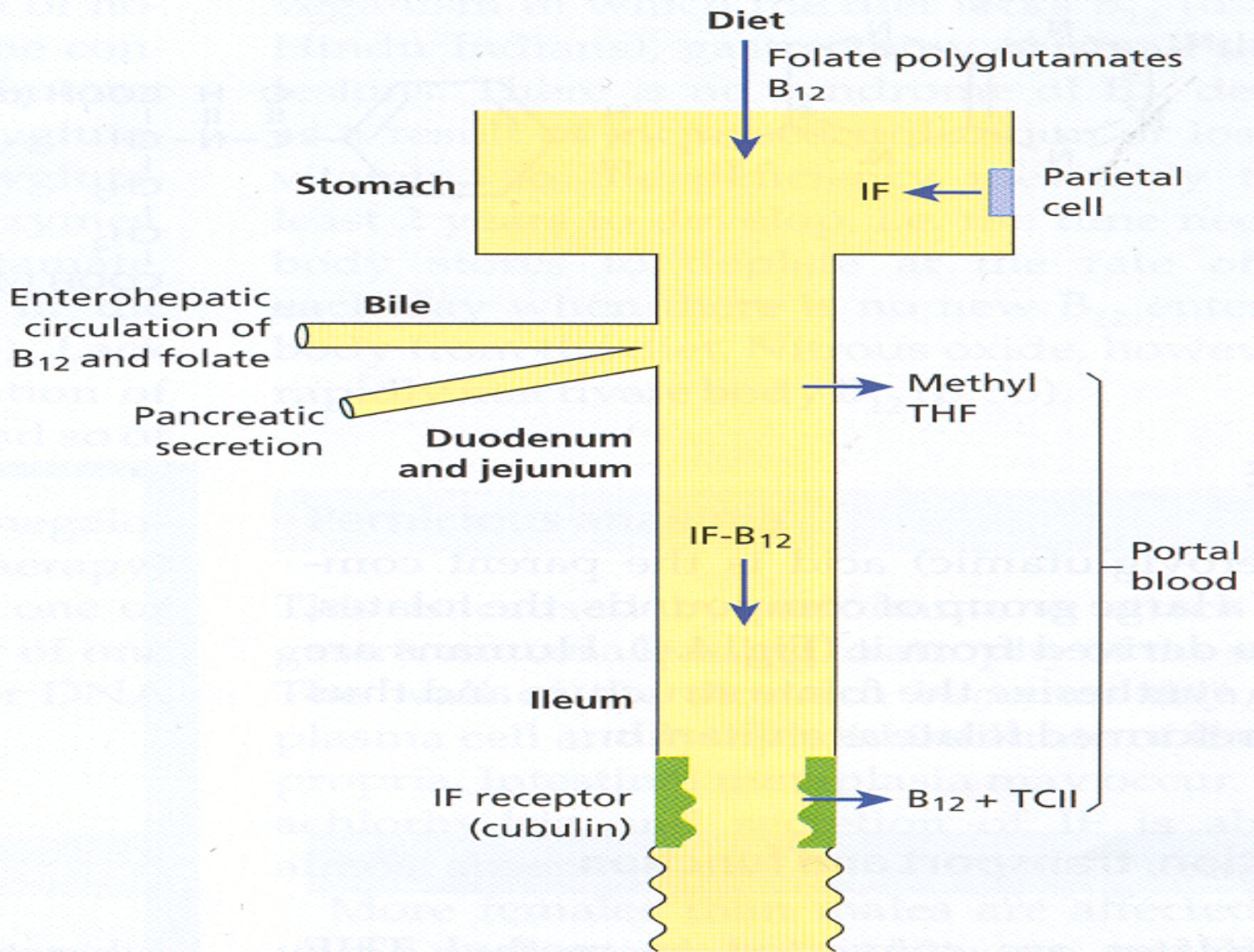
Some congenital dyserythropoietic anaemias

Vitamin B₁₂ and folate nutrition and absorption

	Vitamin B12	Folate
Dietary source	Only food of animal origin, especially liver	Most foods, especially liver, green vegetable and yeast; destroyed by cooking
Average daily intake*	7 - 30 µg	200-250 µg
Minimum daily requirement*	1-3 µg	100-200 µg†
Body stores*	3-5 mg, mainly in the liver	8-20 mg, mainly in the liver
Time to develop deficiency in the absence of intake or absorption*	Anaemia in 2-10 years	Macrocytosis in 5 months.
Requirements for absorption	Intrinsic factor secreted by gastric parietal cells	Conversion of polyglutamates to monoglutamates by intestinal folate conjugase
Site of absorption	Terminal ileum	Duodenum and jejunum

* In adults.

† Higher during pregnancy and lactation.



Vitamin B₁₂ Deficiency

- **Inadequate intake**
- **Veganism**
- **Inadequate secretion of intrinsic factor**
- **Pernicious anaemia**
- **Total or partial gastrectomy**
- **Congenital intrinsic factor deficiency (rare)**
- **Partial gastrectomy, vagotomy, gastritis, acid-suppressing drugs, alcohol abuse**
- **Abnormal intestinal bacterial flora, multiple jejunal diverticula, small intestinal strictures**
- **Diphyllobothrium latum**
- **Malabsorption**
- **Crohn's disease, ileal resection, chronic tropical sprue**

Causes of folate deficiency

Inadequate dietary intake

Malabsorption

Coeliac disease, jejunal resection, tropical sprue

Increased requirement

Pregnancy, premature infants, chronic haemolytic anaemias, myelofibrosis, various malignant diseases

Increased loss

Long-term dialysis, congestive heart failure, acute liver disease

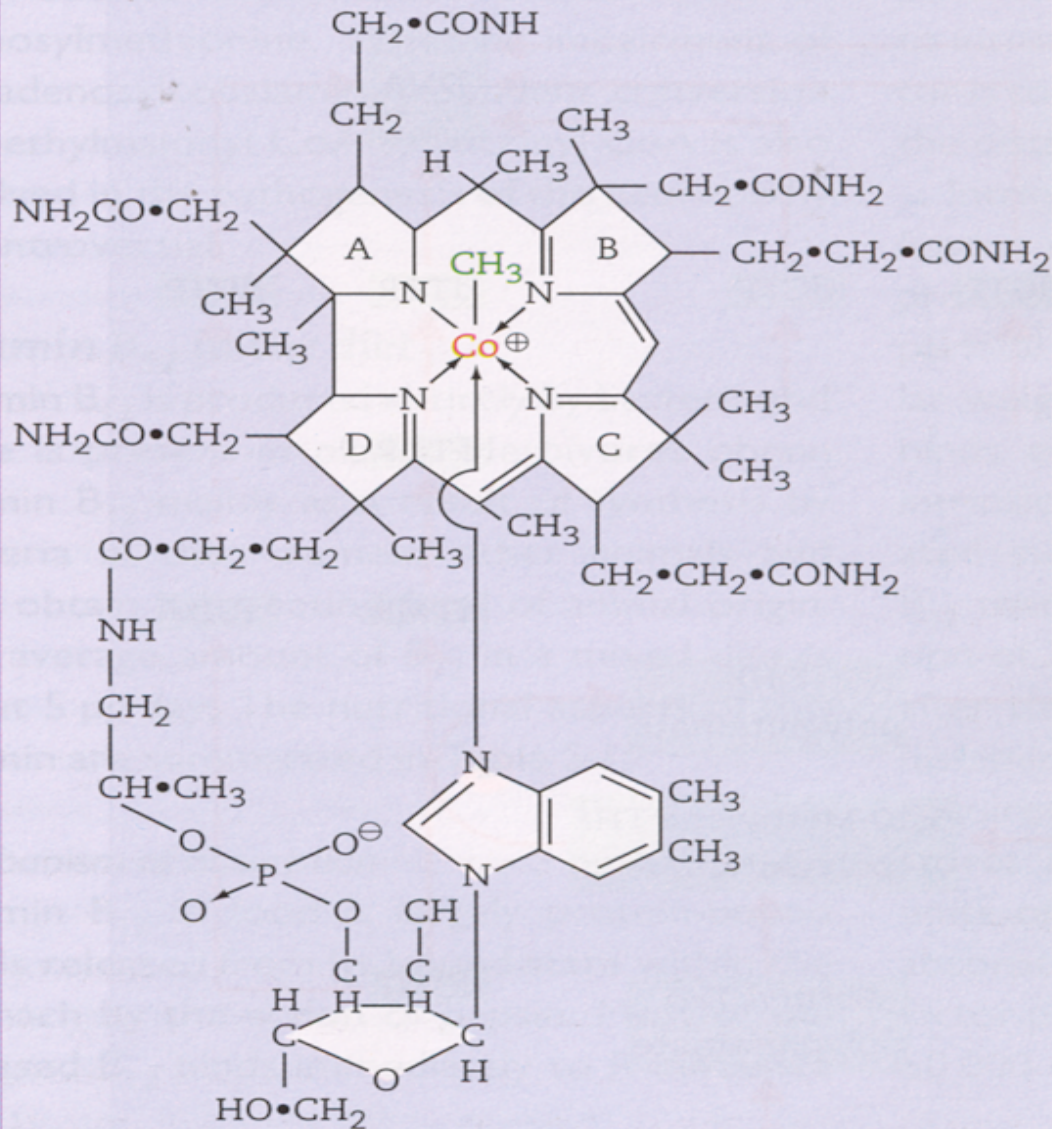
Complex mechanism

Anticonvulsant therapy, * ethanol abuse*

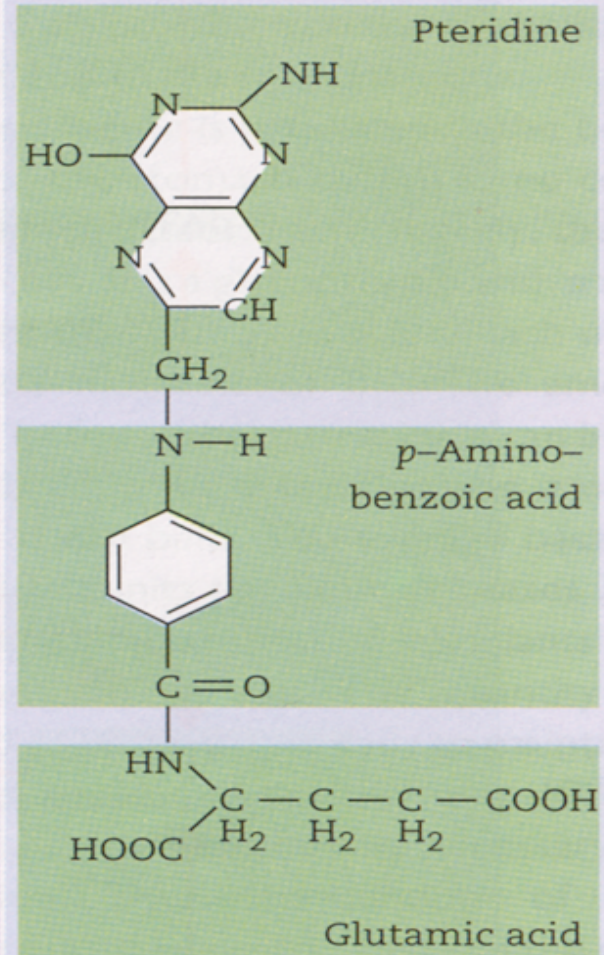
*** Only some cases with macrocytosis are folate deficient.**

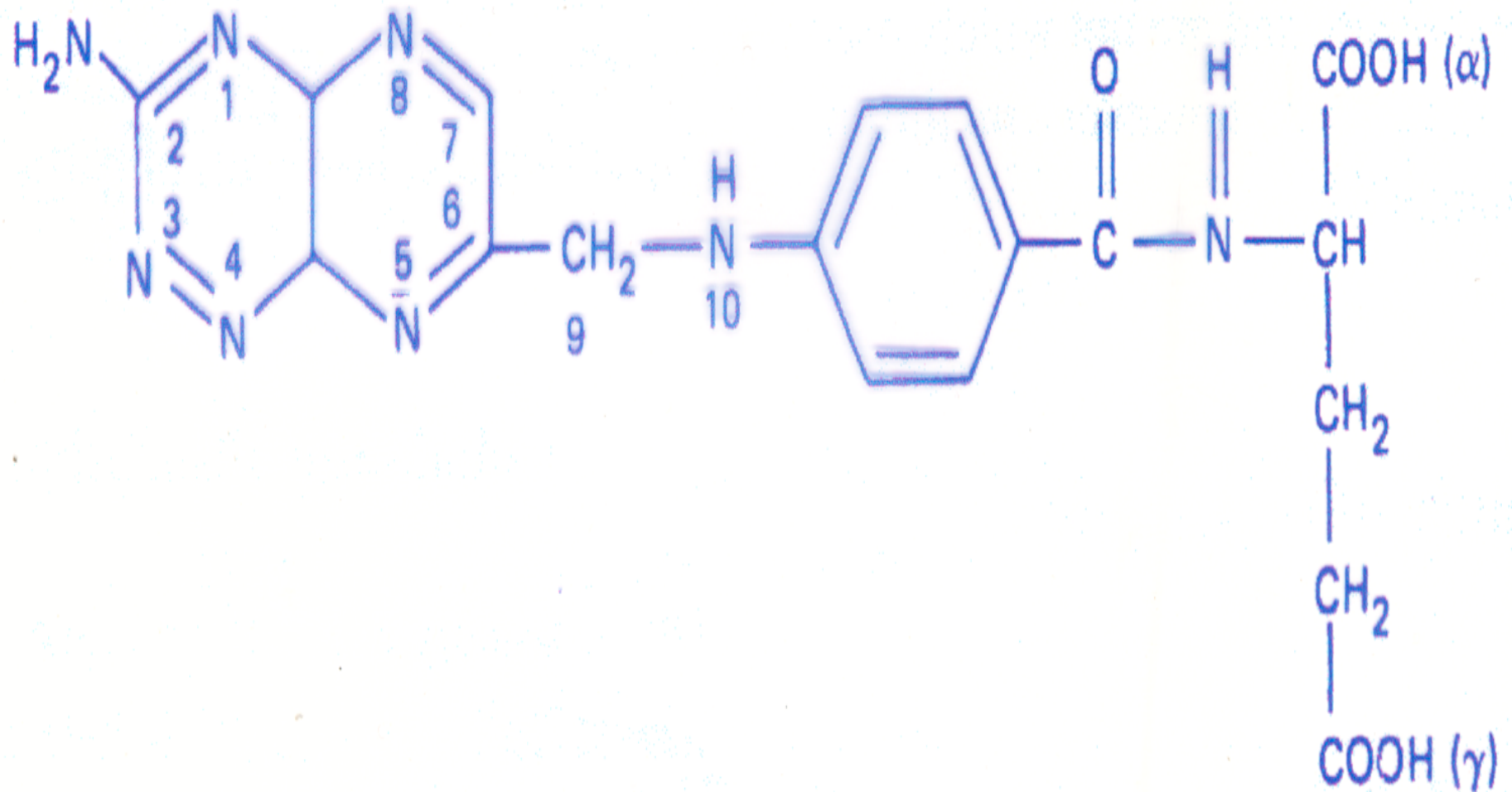
STRUCTURES OF VITAMIN B₁₂ AND FOLIC ACID

Methylcobalamin

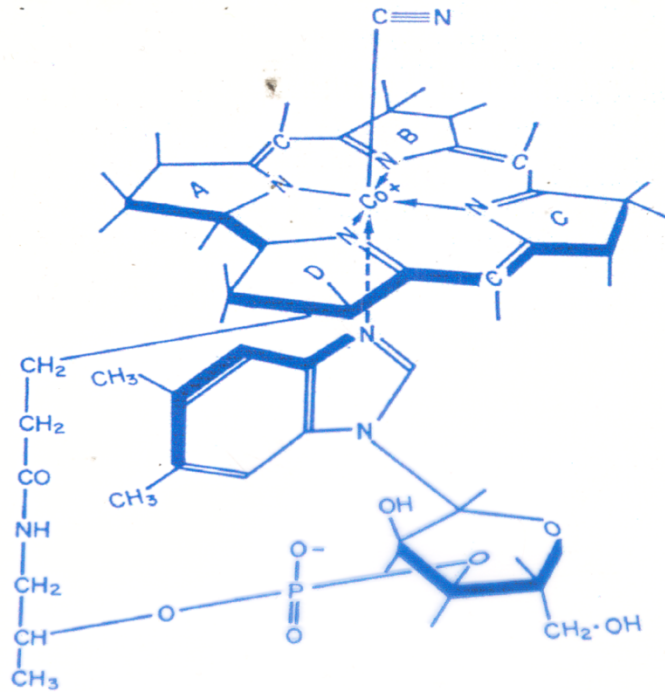


Folic acid

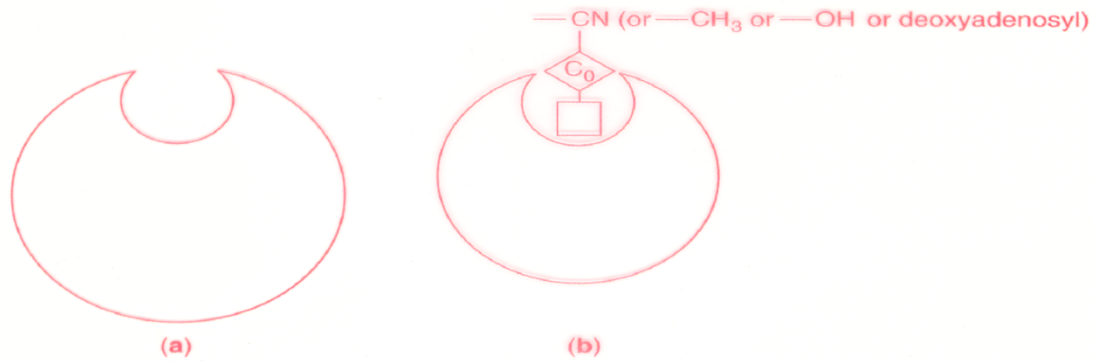




The structure of folic acid (pteroylglumatic acid).



The structure of vitamin B₁₂ (cyanocobalamin).



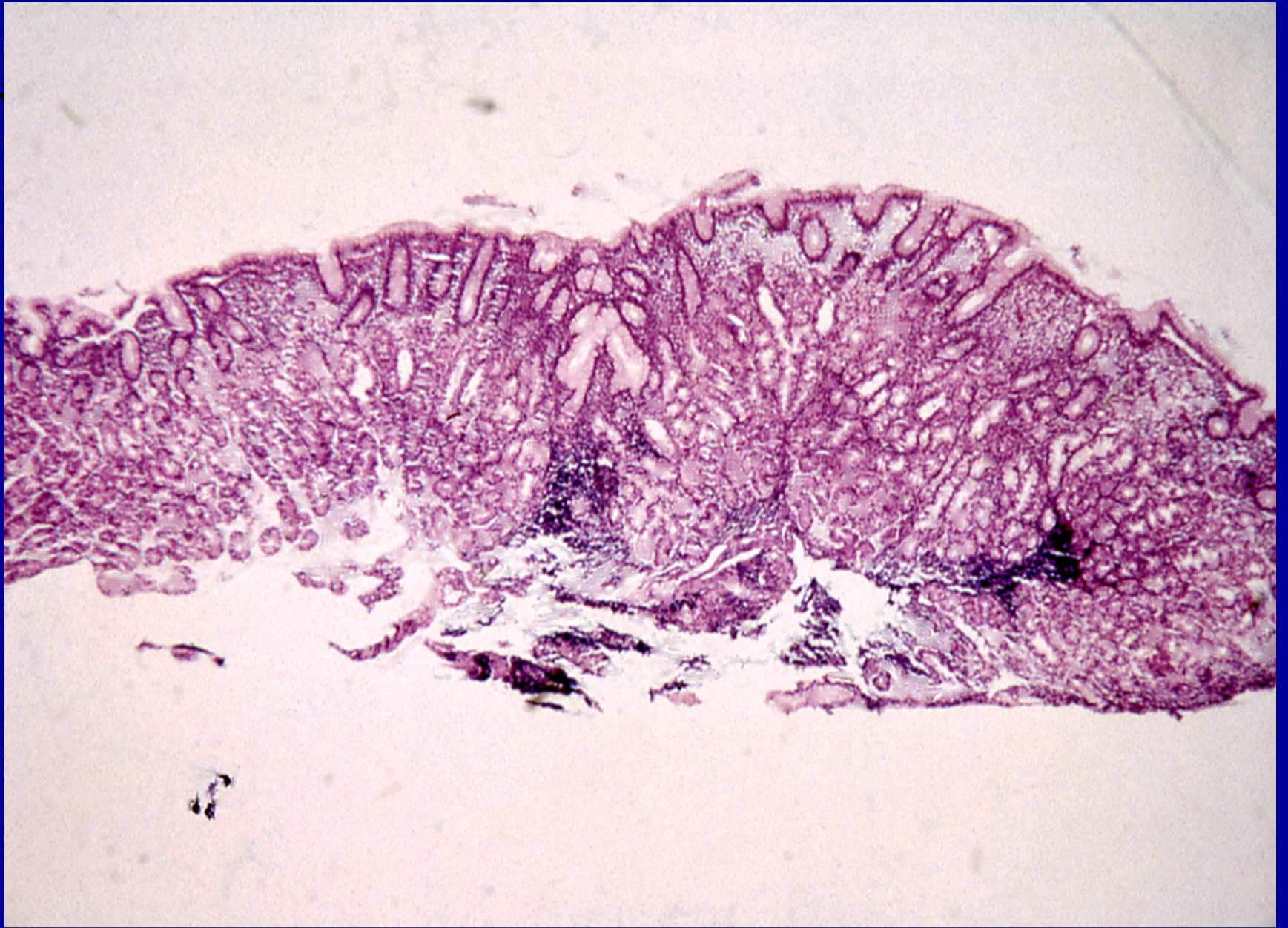
(a) Intrinsic factor and **(b)** intrinsic factor-cobalamin complex. Intrinsic factor has been estimated to have a molecular radius of 3.6 nm, vitamin B₁₂ 0.8 nm, and the complex 3.2 nm.

PERNICIOUS ANAEMIA

- Severe megaloblastic anaemia due to autoimmune attack on the gastric mucosa leading to atrophy.
- More common in elderly female patients than males (1.6:1) at the age of 60 and above
- More common in Northern European and tends to be in families
- The mucosa become thin with plasma cells and lymphoid infiltration of the lamina propria.
- Intestinal metaplasia may occur.
- It maybe associated with autoimmune diseases including the autoimmune poly-endocrine syndrome

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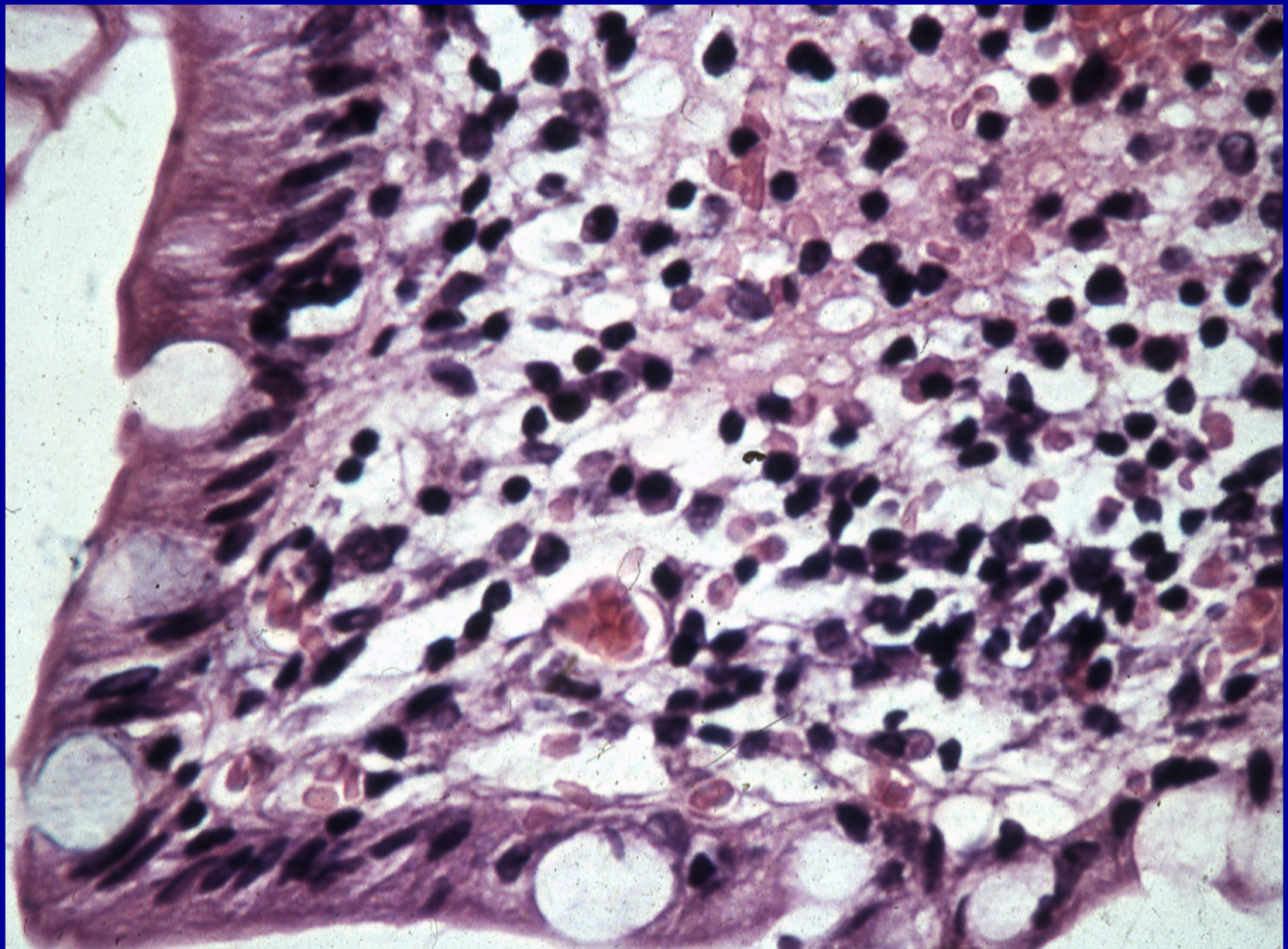
- Achlorhydria and absent secretion of intrinsic factor (IF).
- Progressive neuropathy is a common feature
- Absent serum vitamin B12 level or almost absent level
- Raised serum gastrin levels
- *Helicobacter pylori* infection may be the cause which present in younger age as iron deficiency anaemia and in the elderly as pernicious anaemia
- Increased incidence of gastric carcinoma in (2-3% of pernicious anaemia patients).



Normal gastric mucosa



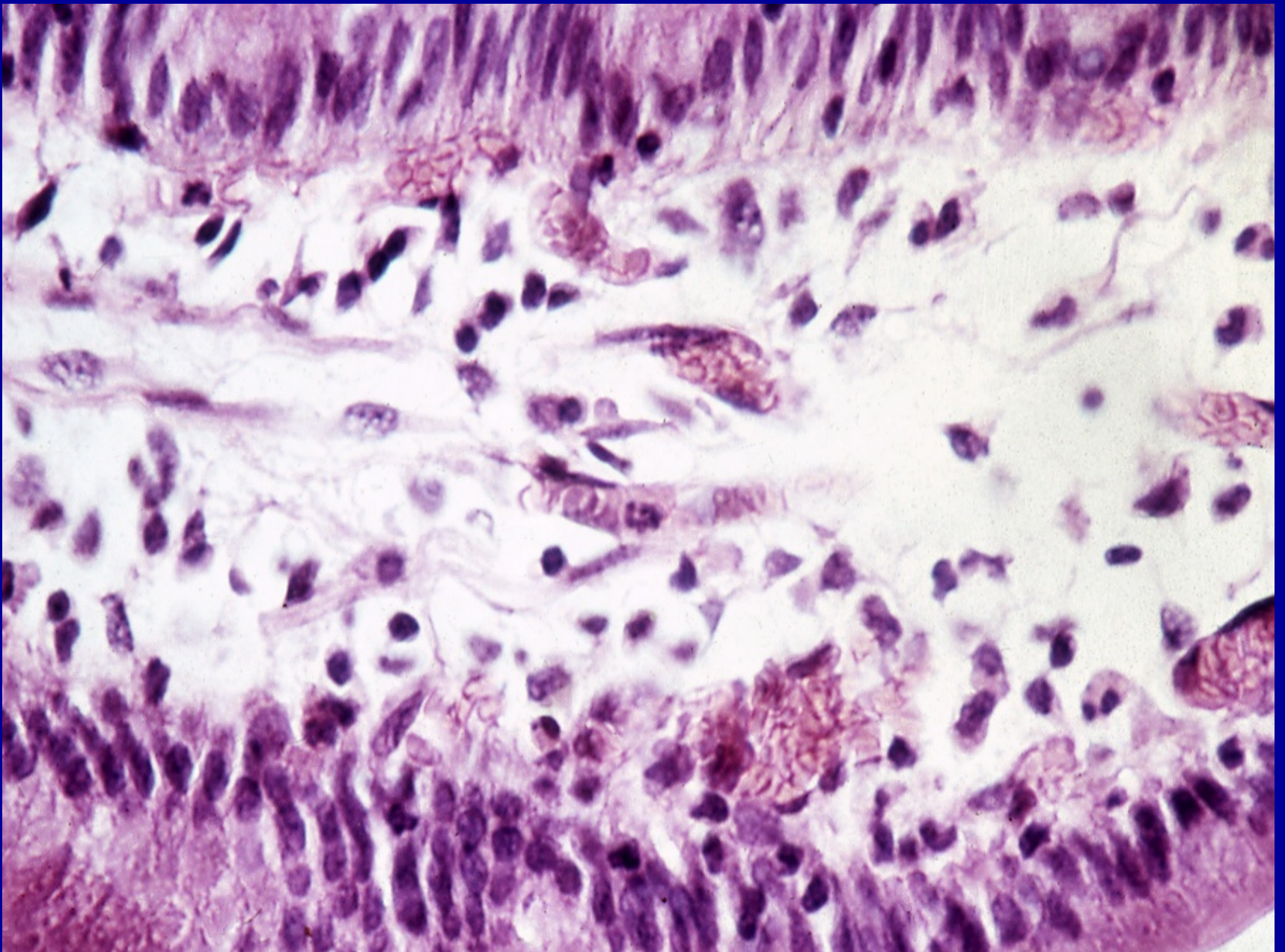
Gastric atrophy in patients with pernicious anaemia



Heavy infiltration of lamina propria with plasma cells and lymphocytes in patients with pernicious anaemia



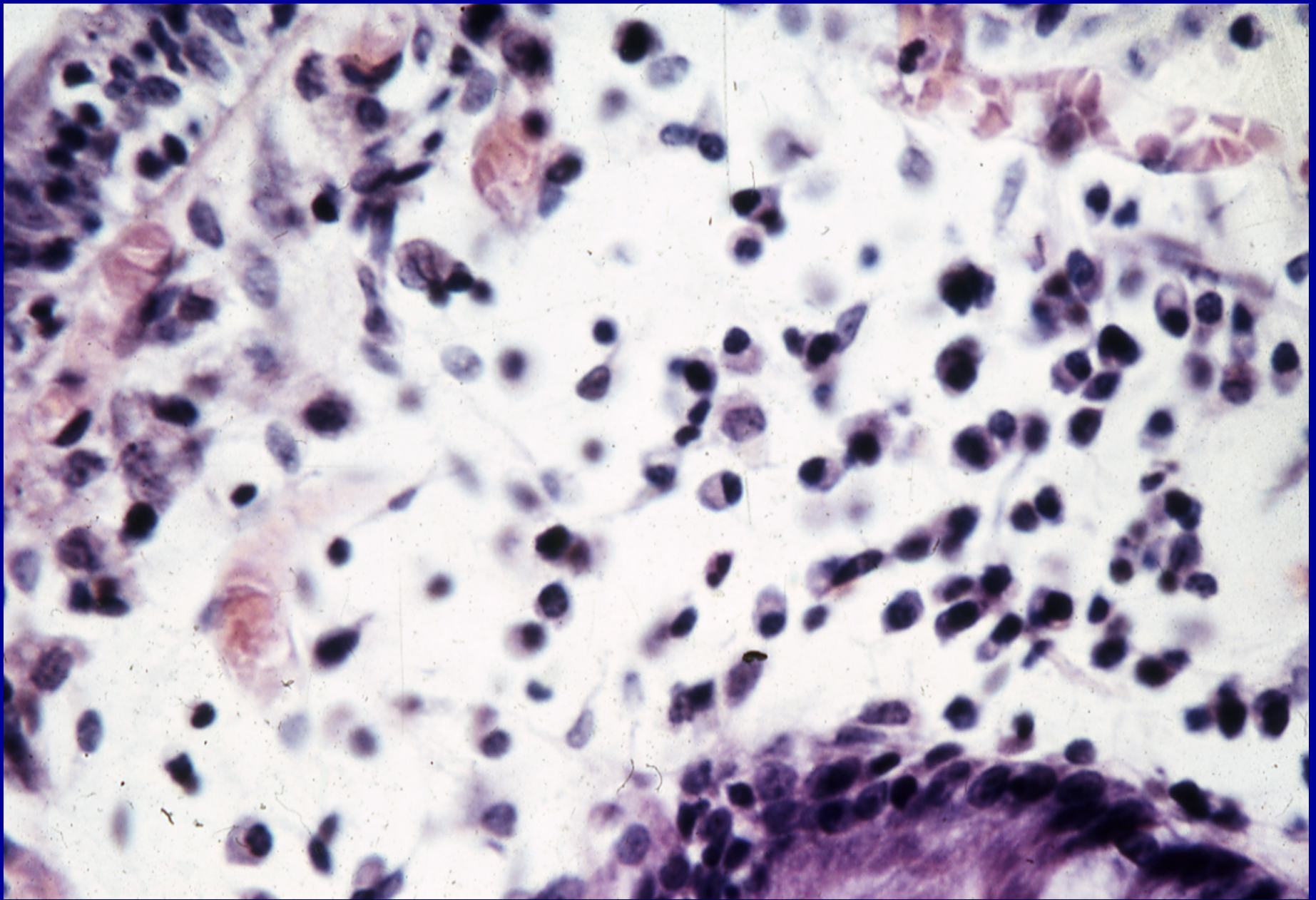
Normal small intestinal mucosa



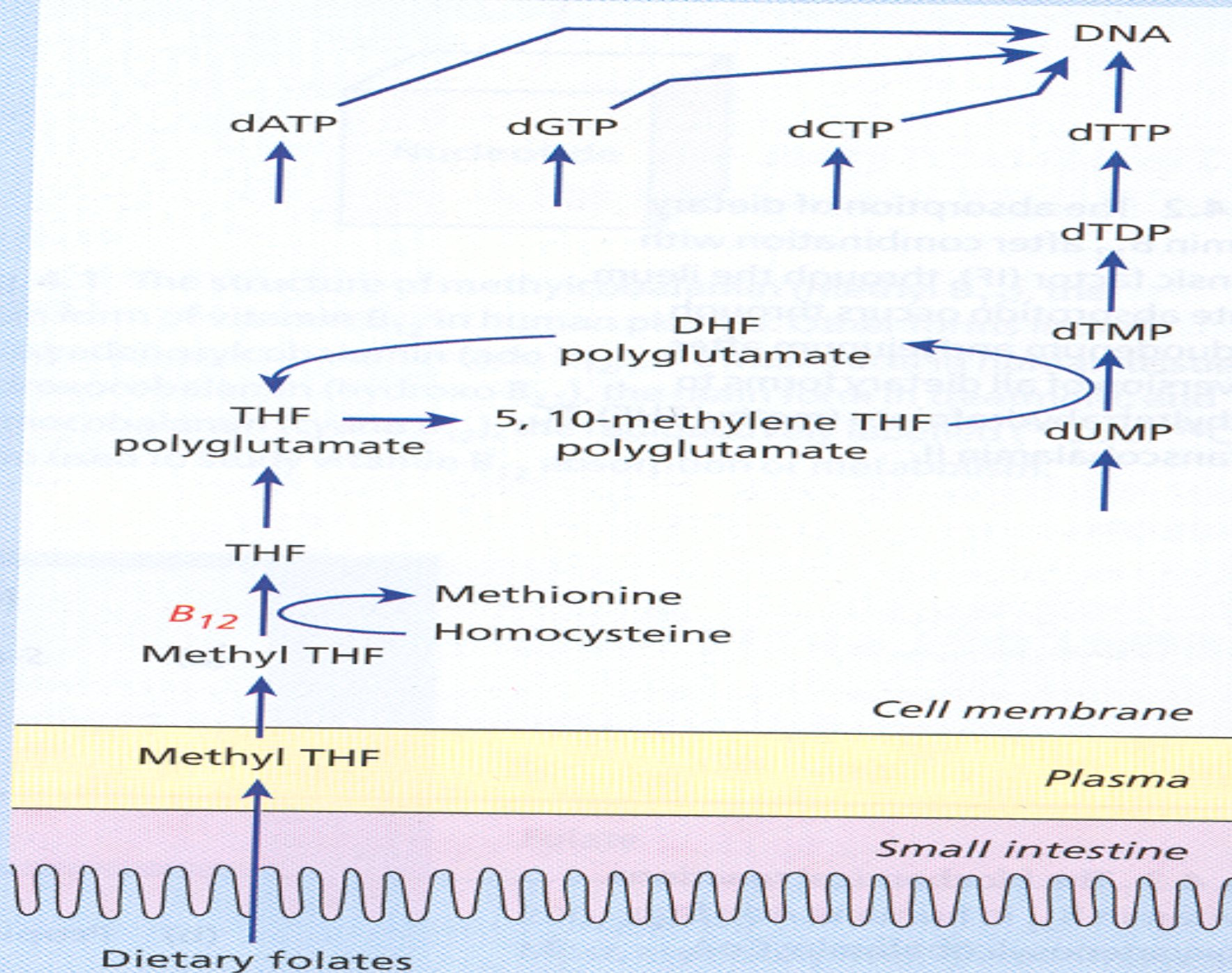
Normal histology of small intestinal mucosa

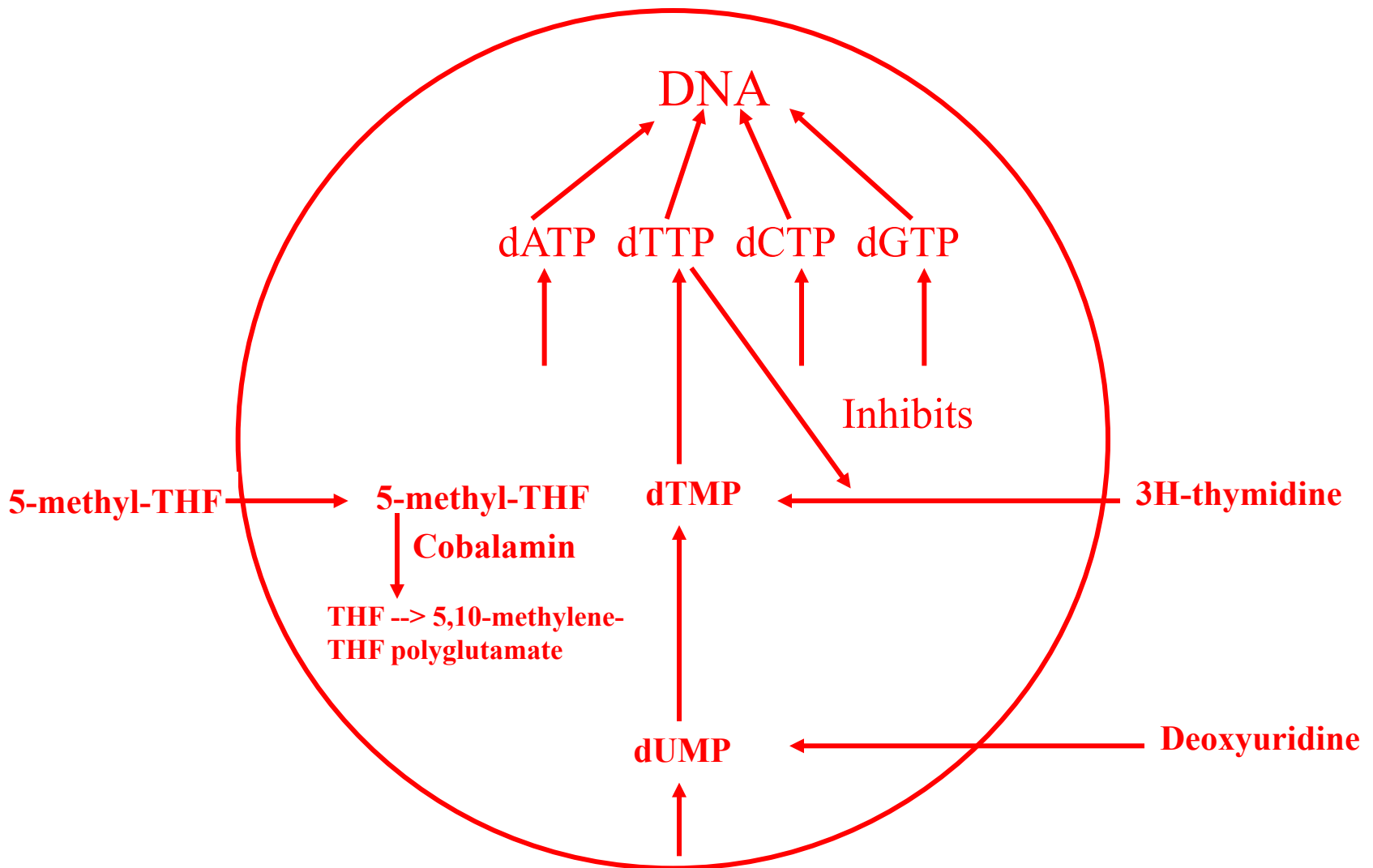


Flattening of small intestinal mucosa in malabsorption syndrome



Histopathology of small intestinal mucosa in malabsorption syndrome





Deoxyuridine suppression test. The circle represents a bone marrow or other haemopoietic cell. THF = tetrahydrofolate; MP = monophosphate; TP = triphosphate; d= deoxyribose; A – adenine; T= thymine ; C = cytosine; G= guanine.

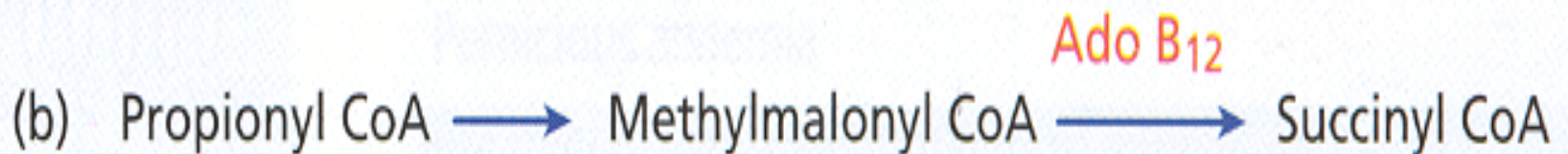
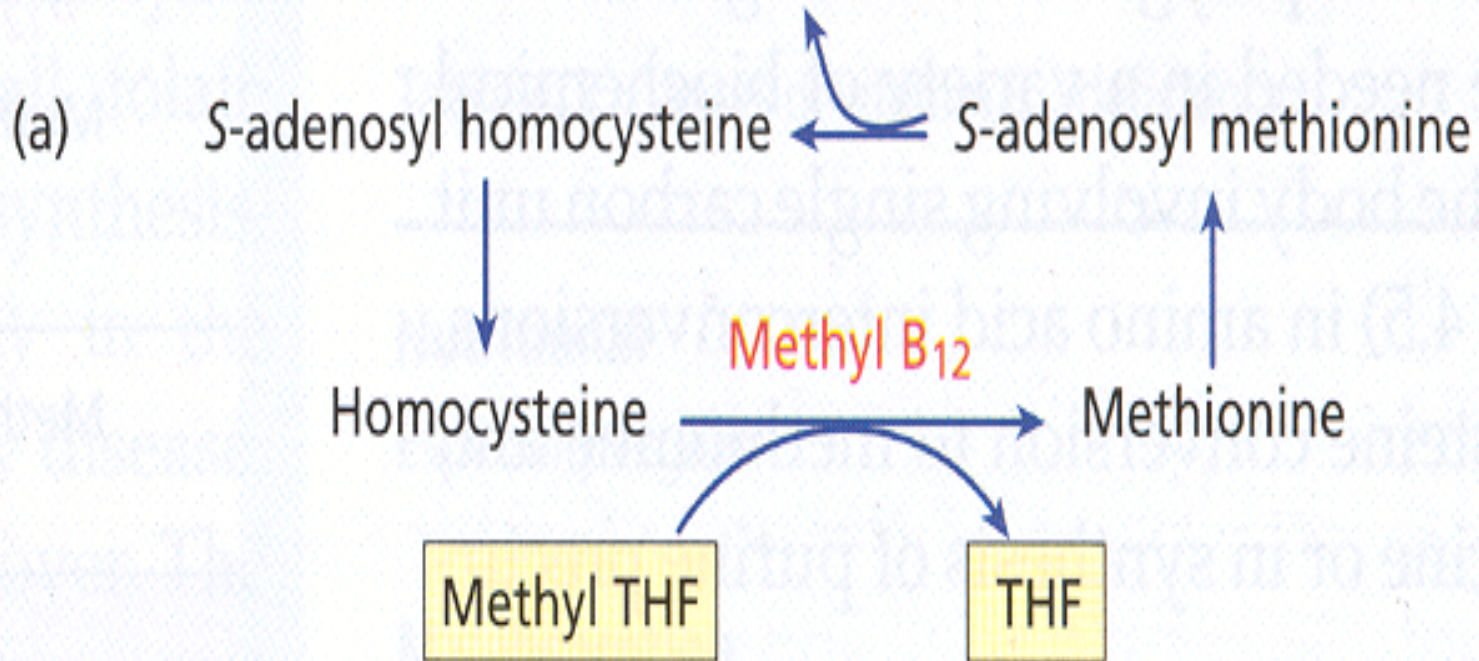
Homocysteine
Methyltransferase
Methylcobalamin

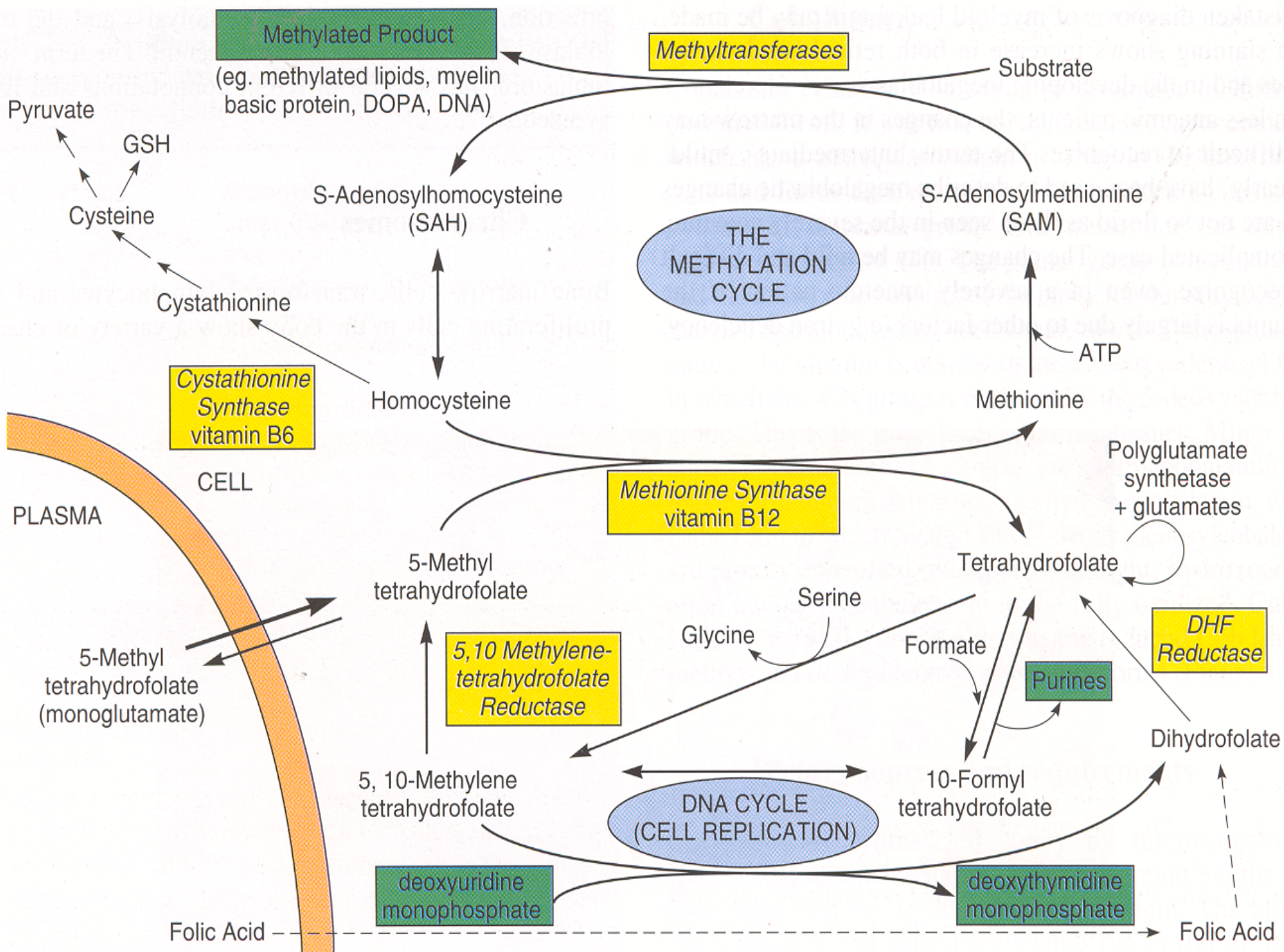


5-Methyltetrahydrofolate

Tetrahydrofolate

Methylation of DNA, myelin, amines, proteins, etc.





Clinical Features of Megaloblastic Anaemia – Progressive symptoms and signs of anaemia

- ❖ Weakness, anorexia, weight loss, diarrhoea or constipation, tiredness, shortness of breath, angina of effort, heart failure
 - ❖ Mild jaundice, glossitis, stomatitis, angular cheilosis.
 - ❖ Purpura, melanin pigmentations.
 - ❖ Infections
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TO IDENTIFY DEFECT (A-F) (ANTICIPATE) STUDY

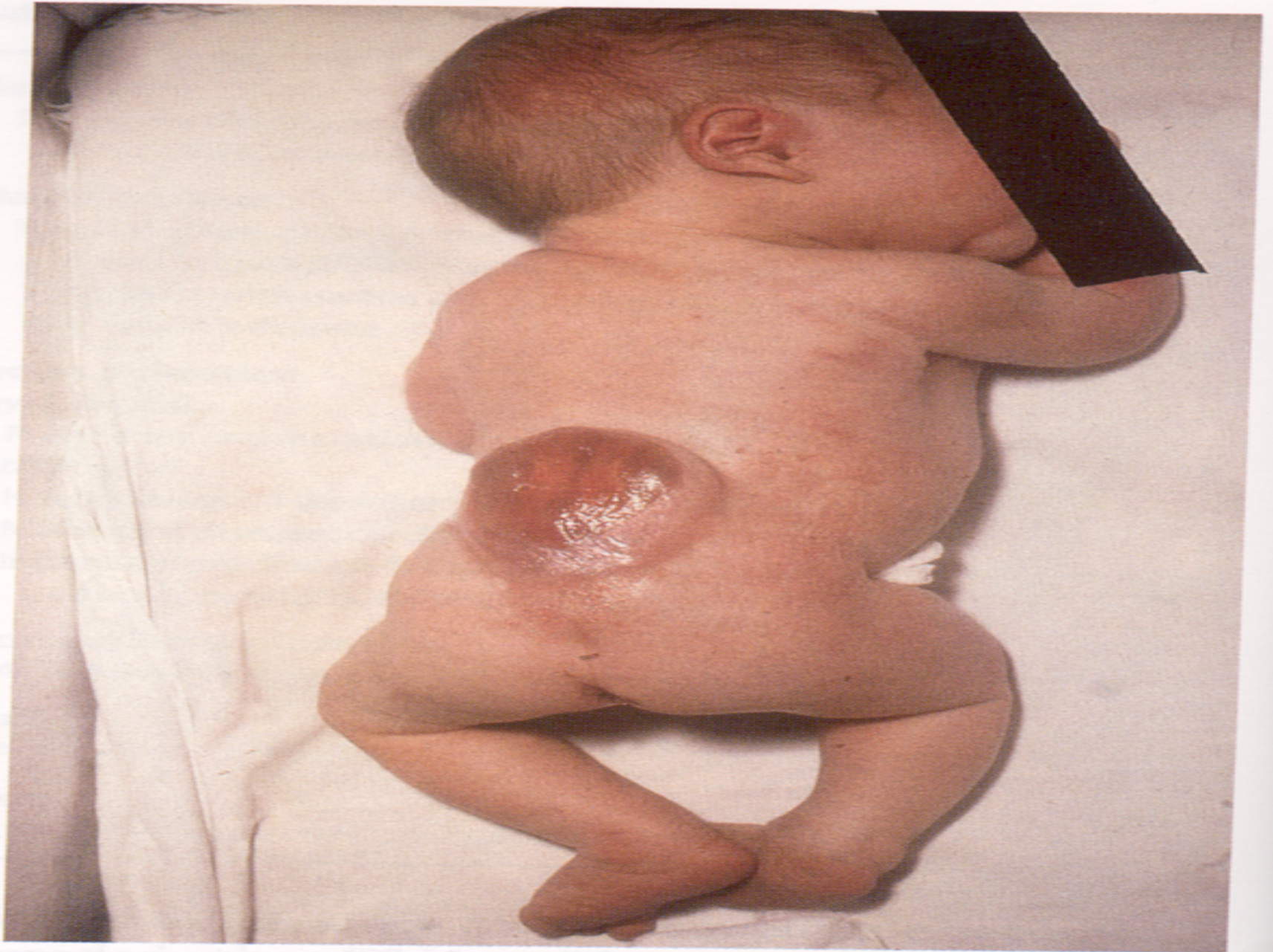
Neuropathy due to Vit B₁₂ and folate deficiency

Progressive neuropathy affecting

- **The peripheral sensory nerves**
 - **Posterior and lateral columns of the spinal cord (subacute combined degeneration of the cord)**
 - **Optic atrophy**
 - **Psychiatric symptoms**
 - **The neuropathy is likely due to accumulation of S-adenosyl homocysteine and reduced level of S-adenosyl methionine in nervous tissue resulting in defective methylation of myelin and other substrates.**
 - **Neuropathy is mostly due to vitamin B₁₂ deficiency.**
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Neural tube defect (NTD)

- (Anencephaly, spina bifida or encephalocoele) in the fetus due to folate or Vit B₁₂ deficiency in the mother. This results in build-up of homocysteine and S-adenosyl homocysteine in the fetus which impairs methylation of various proteins and lipids.
 - Polymorphism in the enzyme 5,10 methylene tetrahydrofolate reductase (5,10-MTHFR). This mutation (677 C→T) in the MTHFR gene results in low serum and red cell folate and high serum homocysteine in the parents and fetus with NTD.
 - Cleft palate and hair lip.
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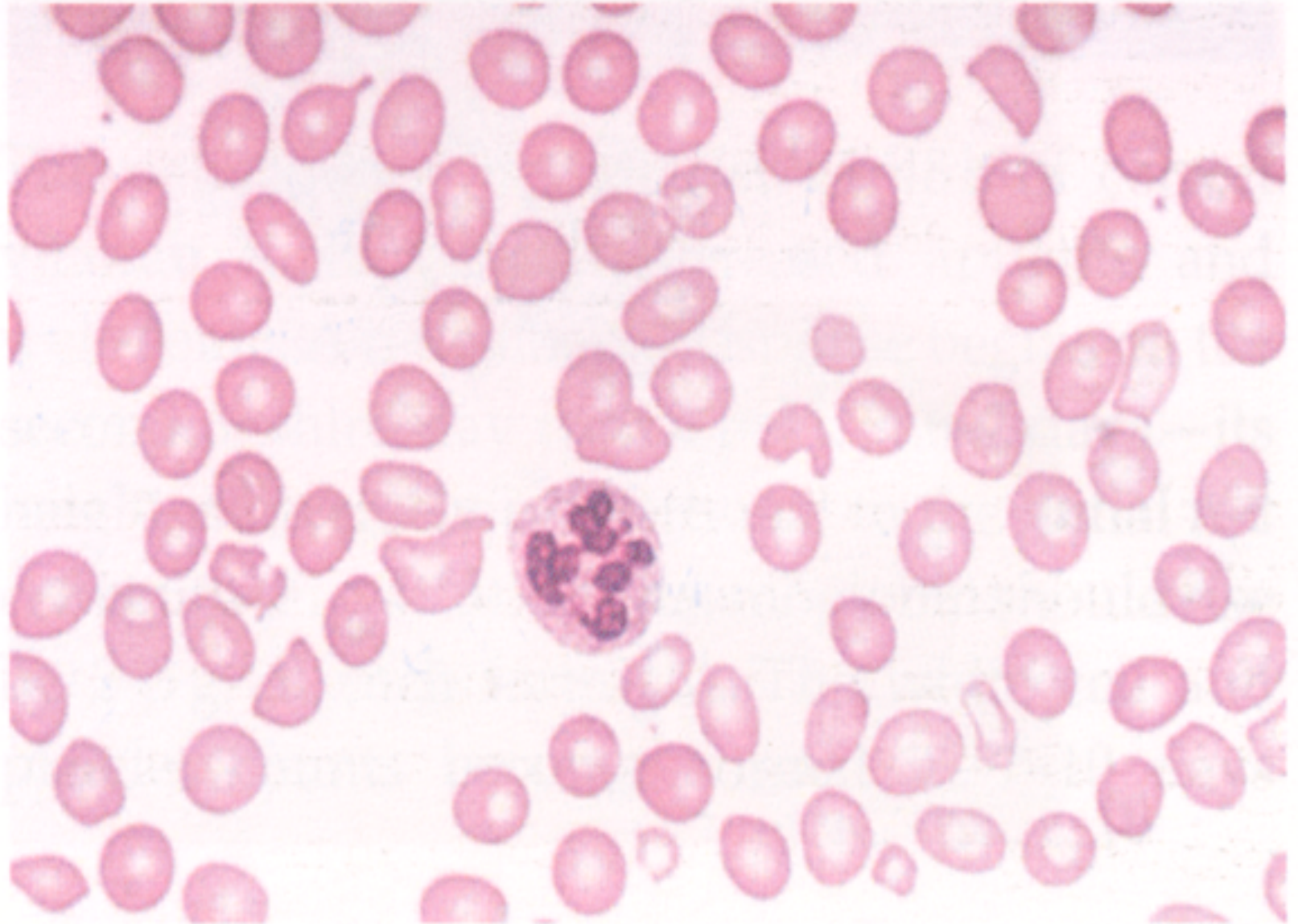


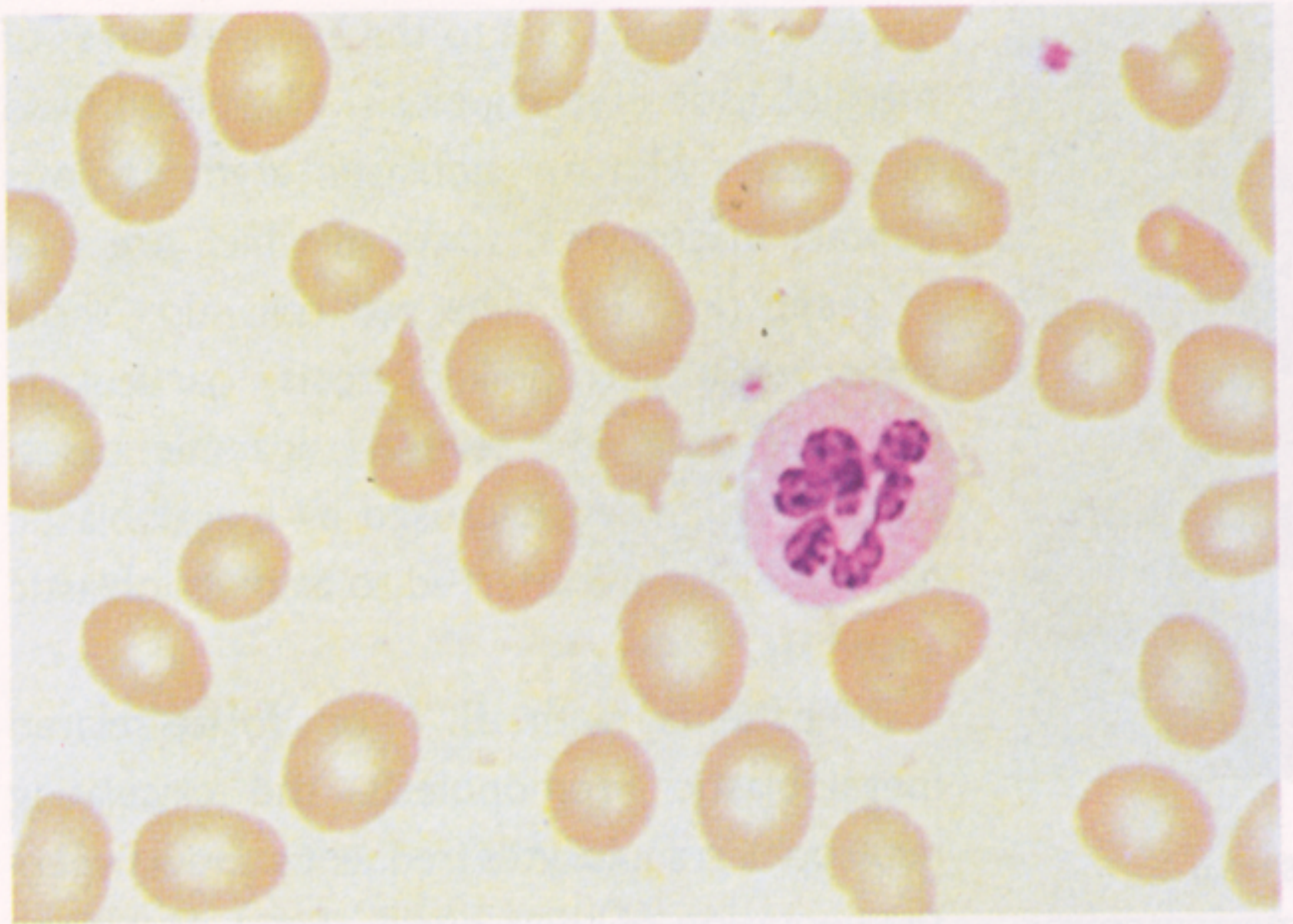


Haematological findings in Megaloblastic Anaemia

Peripheral Blood:

- ❖ **Macrocytic anaemia, oval macrocytes, anisocytosis, poikilocytosis high MCV.**
 - ❖ **Dimorphic anaemia when it is associated with iron deficiency or with thalassaemia trait.**
 - ❖ **Hypersegmented neutrophils.**
 - ❖ **Leucopenia and thrombocytopenia**
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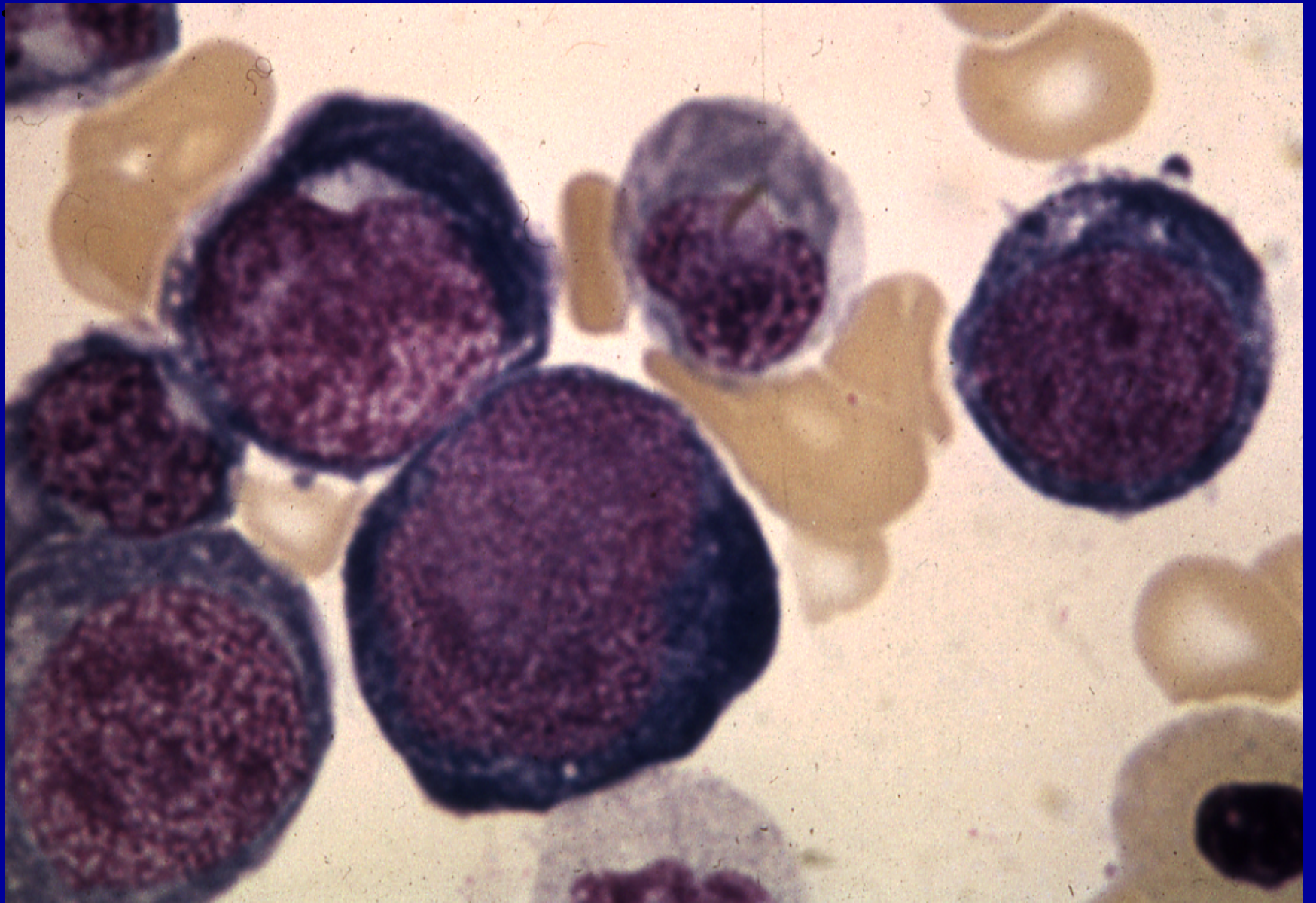


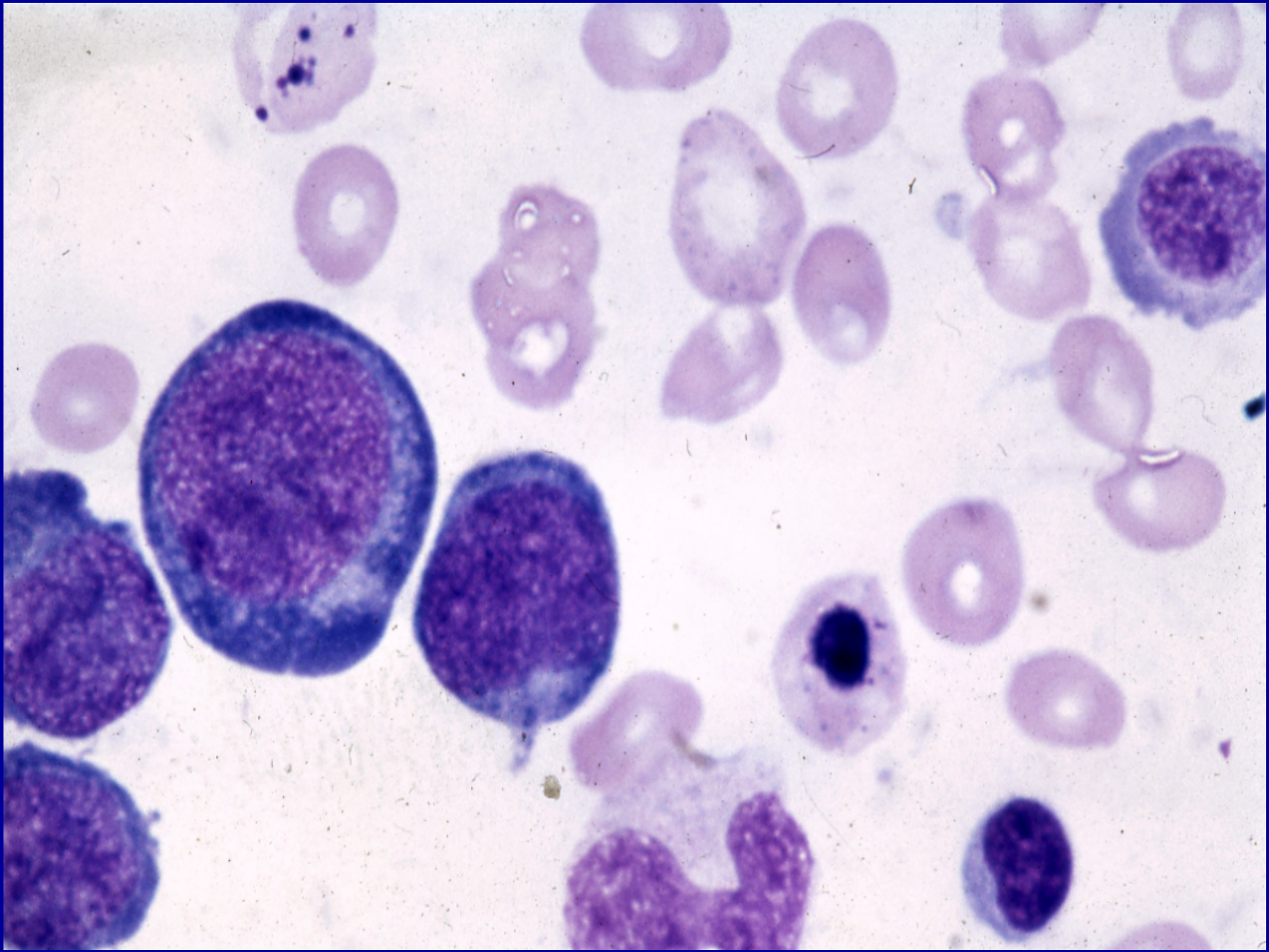


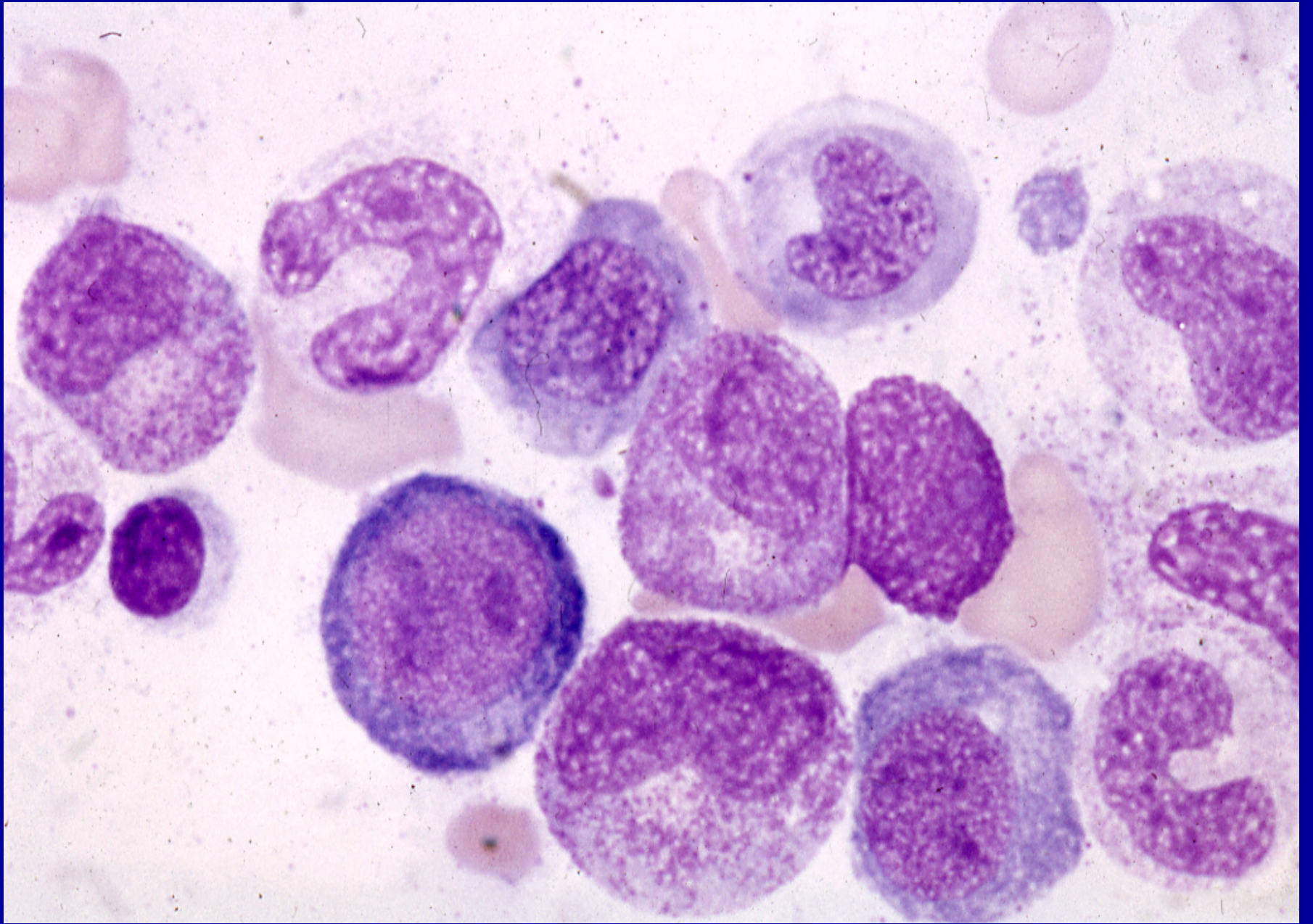
Haematological Findings in Megaloblastic Anaemia

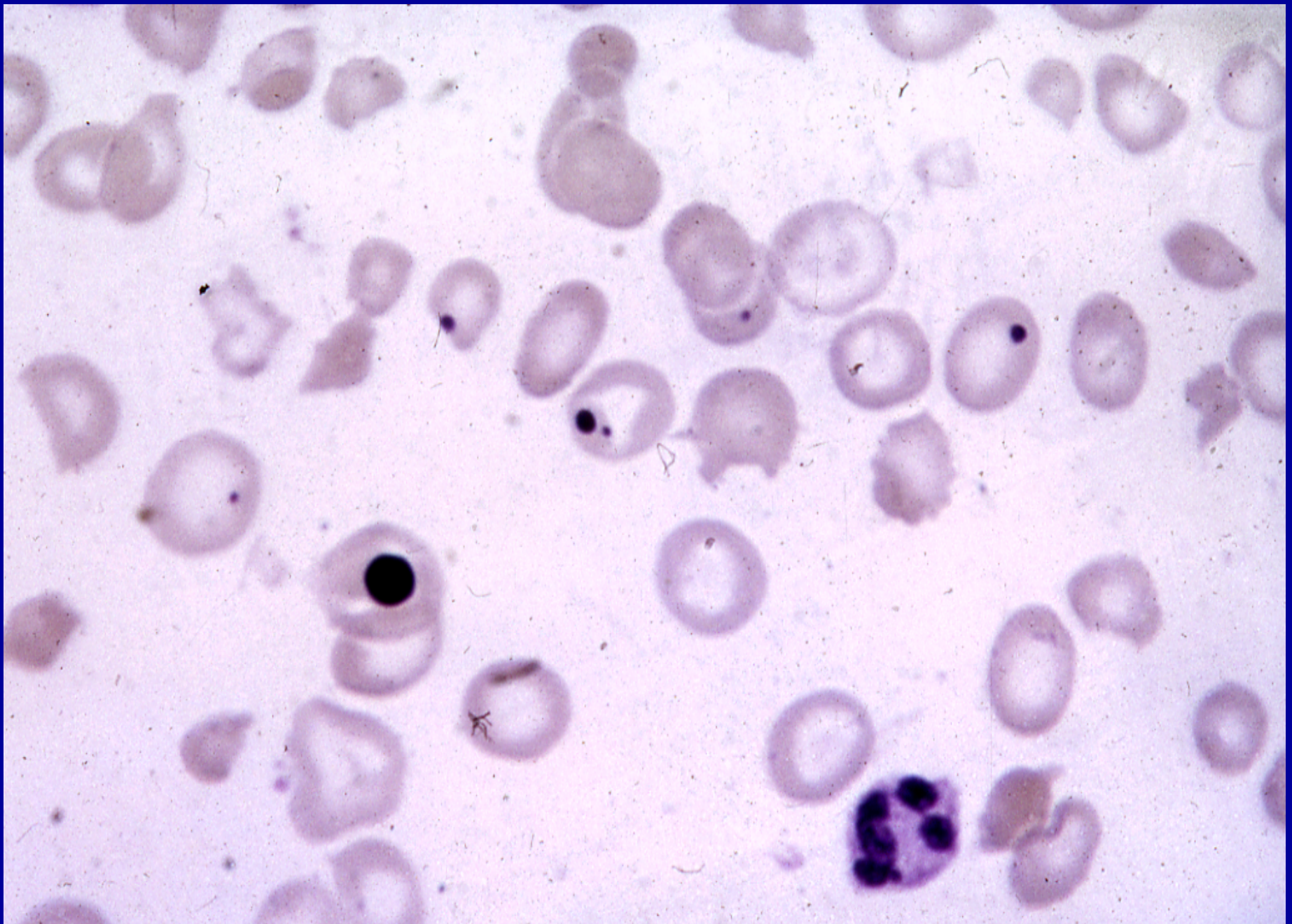
Bone Marrow:

- ❖ **Hypercellular marrow with M:E ratio in normal or reduced.**
- ❖ **Accumulation of primitive cells due to selective death of more mature cells.**
- ❖ **Megaloblast (large erythroblast which has a nucleus of open, fine, lacy chromatin).**
- ❖ **Dissociation between the nuclear and cytoplasmic development in the erythroblasts.**
- ❖ **Mitosis and dying cells are more frequent than normal.**
- ❖ **Giant and abnormally shaped, metamyelocytes, polypoid megakaryocytes.**
- ❖ **Increased stainable iron in the macrophage and in the erythroblasts.**



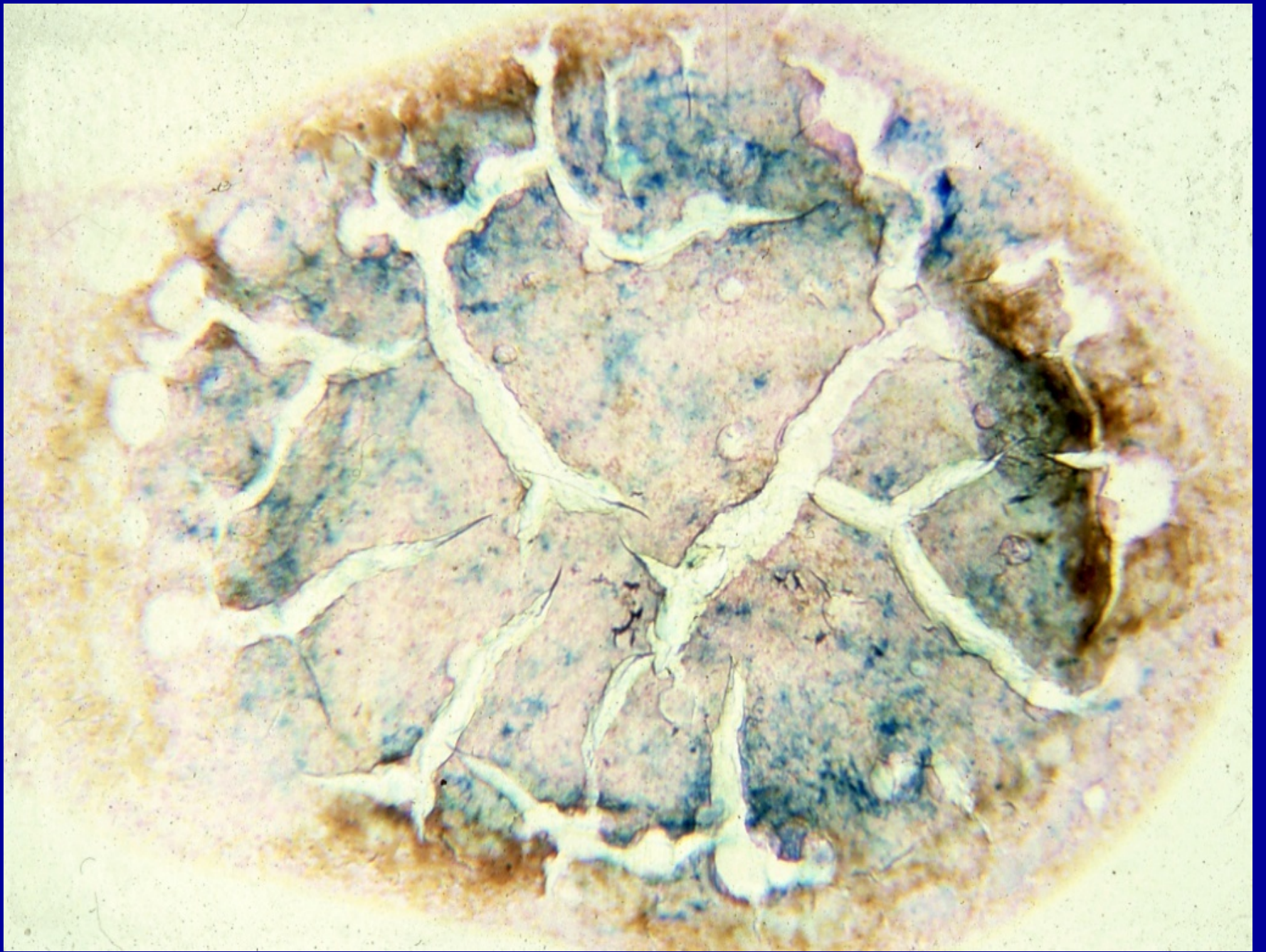






Other laboratory abnormalities

- ❖ **Chromosomal abnormalities**
 - ❖ **Ineffective haemopoiesis. (Intramedullary cell death by apoptosis) associated with increased serum indirect bilirubin.**
 - ❖ **↑ urobilinogen and faecal stercobillinogen.**
 - ❖ **↑ LDH ↑ serum iron ↑ blood carbon monoxide.**
 - ❖ **↑ serum lysozyme**
 - ❖ **↓ reduced haptoglobins**
 - ❖ **Positive schumm's test**
 - ❖ **Positive urine haemosiderin.**
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Treatment of megaloblastic anaemia

	Vitamin B ₁₂ deficiency	Folate deficiency
Compound	Hydroxocobalamin	Folic acid
Route	Intramuscular	Oral
Dose	1000 µg	5mg
Initial dose	6X1000 µg over 2-3 weeks	Daily for 4 months
Maintenance	1000 µg every 3 months	Depends on underlying disease; life-long therapy may be needed in chronic inherited haemolytic anaemia, myelofibrosis, renal dialysis
Prophylactic	Total gastrectomy Ileal resection	Pregnancy, severe haemolytic anaemias, dialysis, prematurity

A tropical beach scene at sunset. The sky is a mix of deep blue, purple, and orange, with large, dark clouds. Several palm trees are silhouetted against the sky. The ocean is visible in the background, and a small island or reef is visible in the distance. The text "Thank you !!!" is written in a bold, yellow, serif font at the bottom of the image.

Thank you !!!