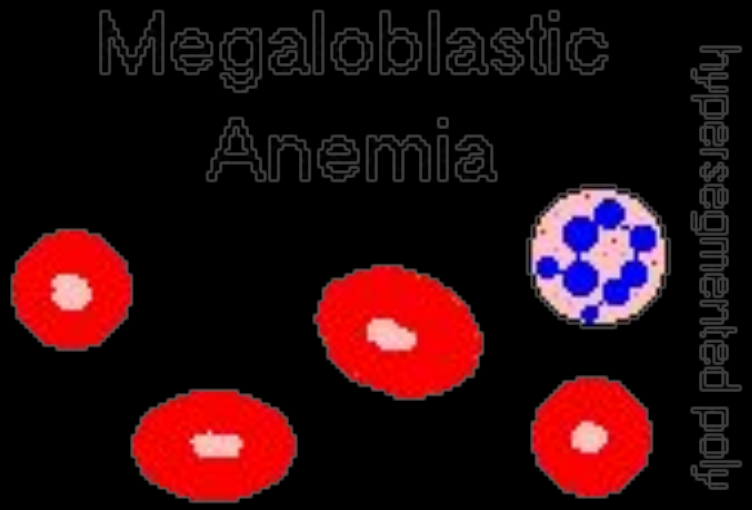
Megaloblastic Anemia



Objectives

- Body stores and daily requirements of vitamin B12 and folate
- Absorption of vitamin B12 and folate from the gut
- Causes of vitamin B12 and folate deficiency
- Hematological consequences of vitamin B12 and folate deficiency
- Neurological sequelae of vitamin B12 deficiency
- Diagnosis and management of megaloblastic anemia
- Diagnosis and management of Pernicious Anemia

Requirements for Red Blood Cell Production

- Proteins, required for globin synthesis
- Iron
- Erythropoeitin
- Vitamin B12 and folic acid
- Vitamin B6
- Vitamin C
- Thyroid hormones, estrogens and androgens

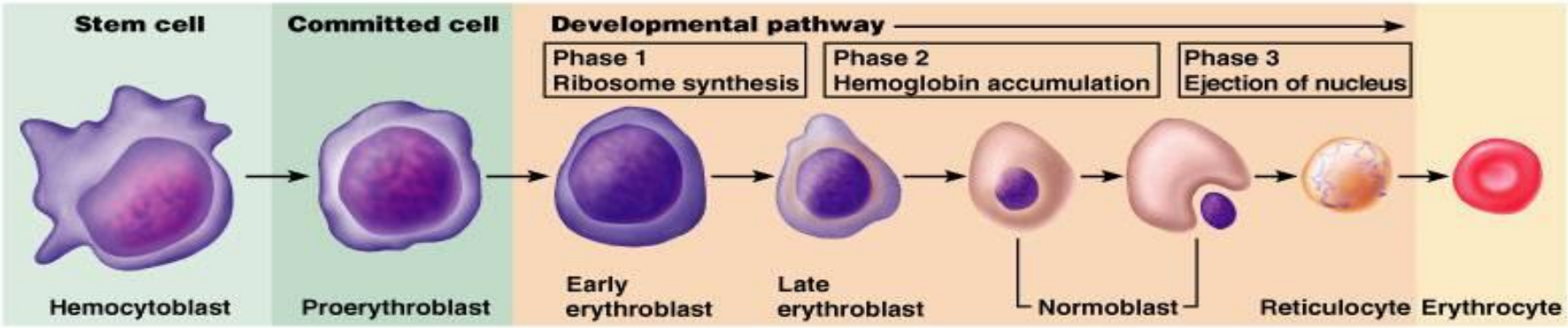
Vitamin B 12 and Folate

Effects of deficiency

- Megaloblastic anemia, sore tongue, abnormal gut mucosa (both)
- Demyelination in the CNS (B12 only)
- Hyperhomocysteinemia

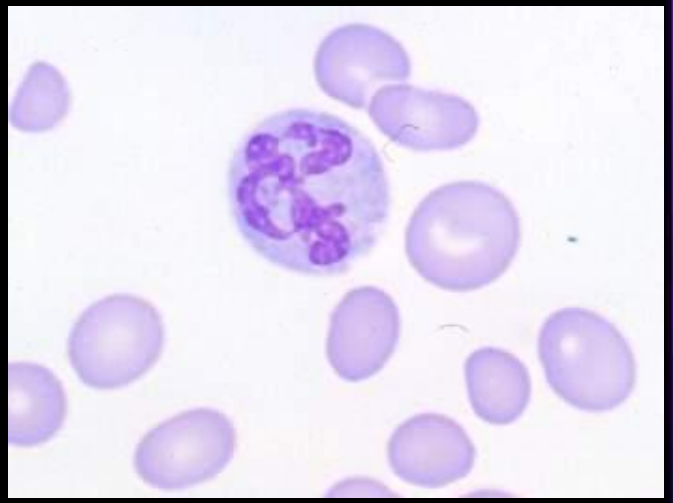
MEGALOBLASTIC ANEMIA

- Hemoglobin production probably normal
- Defect in nuclear replication & division
- Affects all marrow elements



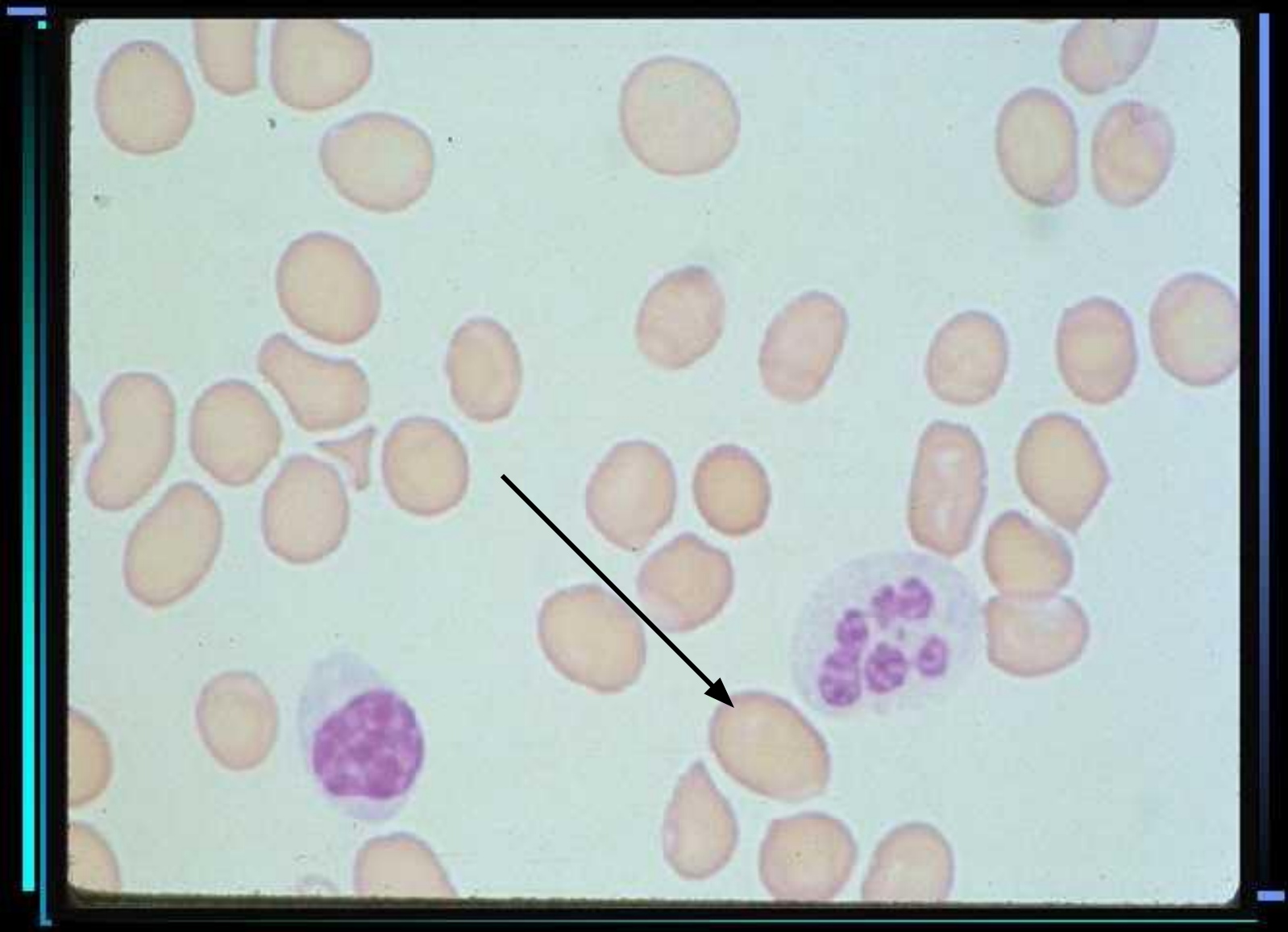
MEGALOBLASTIC ANEMIA

- Trademark cell: Oval macrocyte, (MCV > 100 fl)
- Hypersegmented neutrophils - 98%
- Pancytopenia, esp if anemia severe
- Reticulocytopenia
- LDH elevated (90%)
- Serum Fe normal or elevated
- Serum B_{12} or folate low
- Marrow ⊠ classic megaloblastic changes

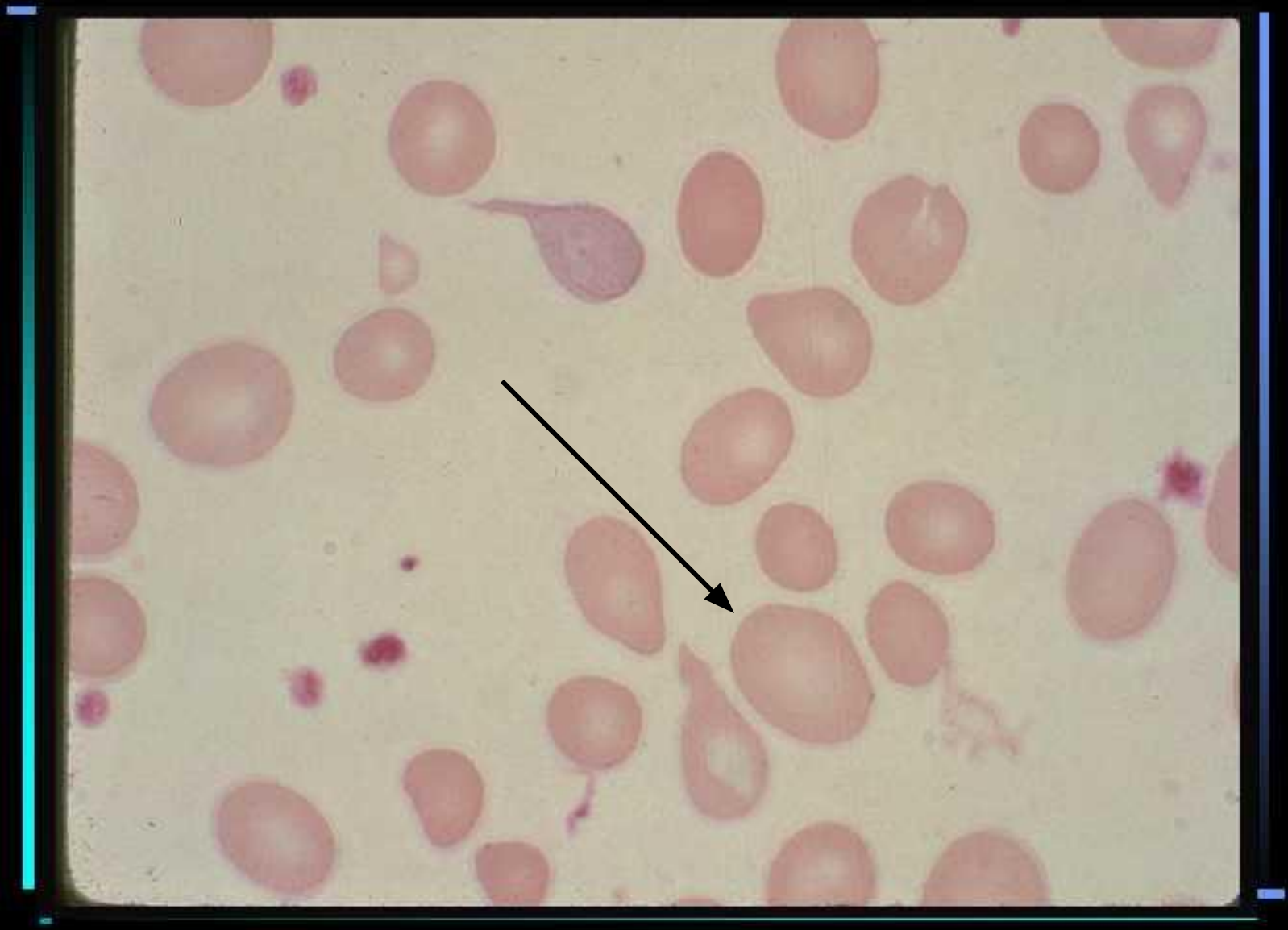


Macrocytic anemia with hypersegmented neutrophil

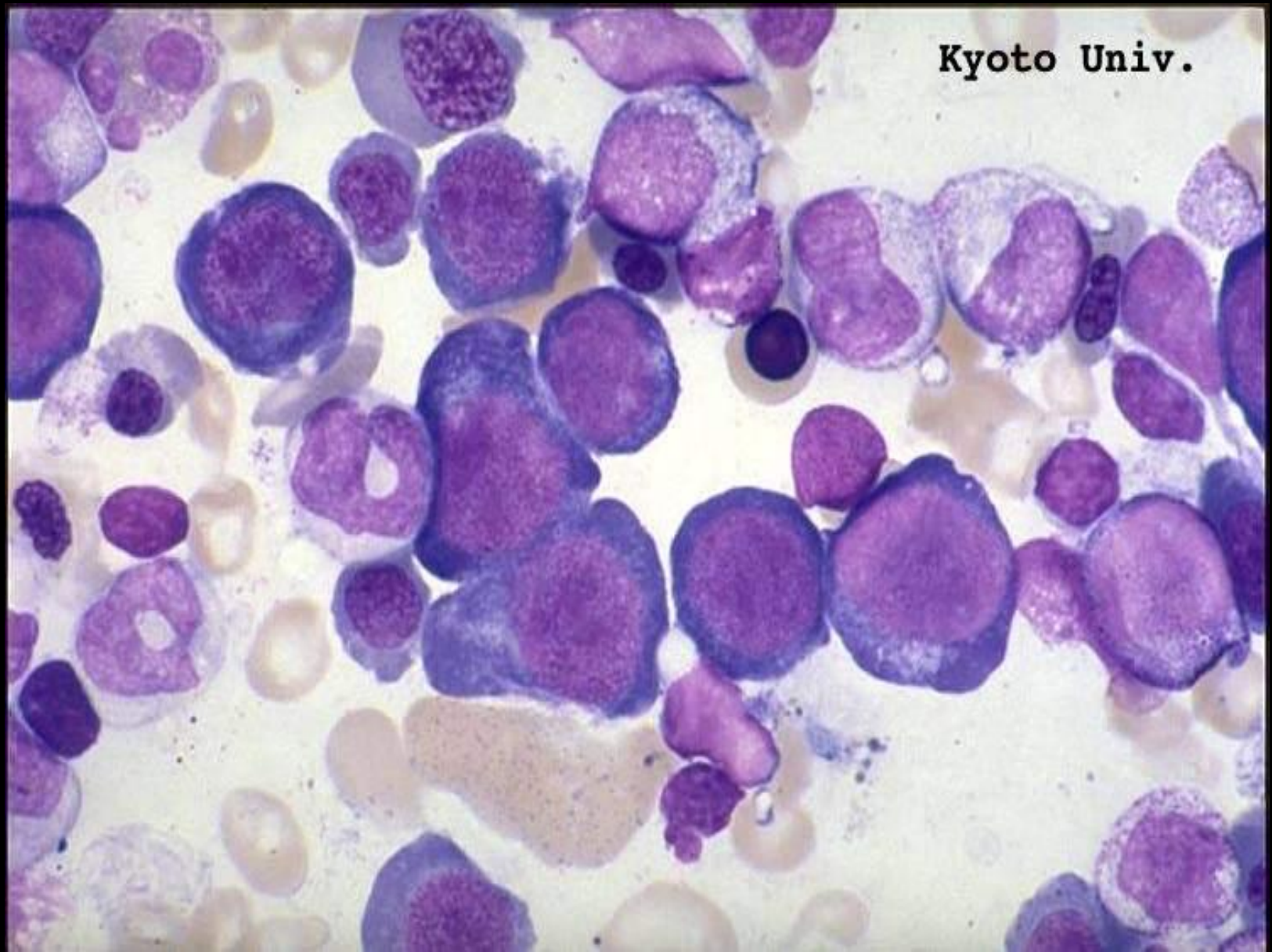
Macro-ovalocyte in megaloblastic anemia



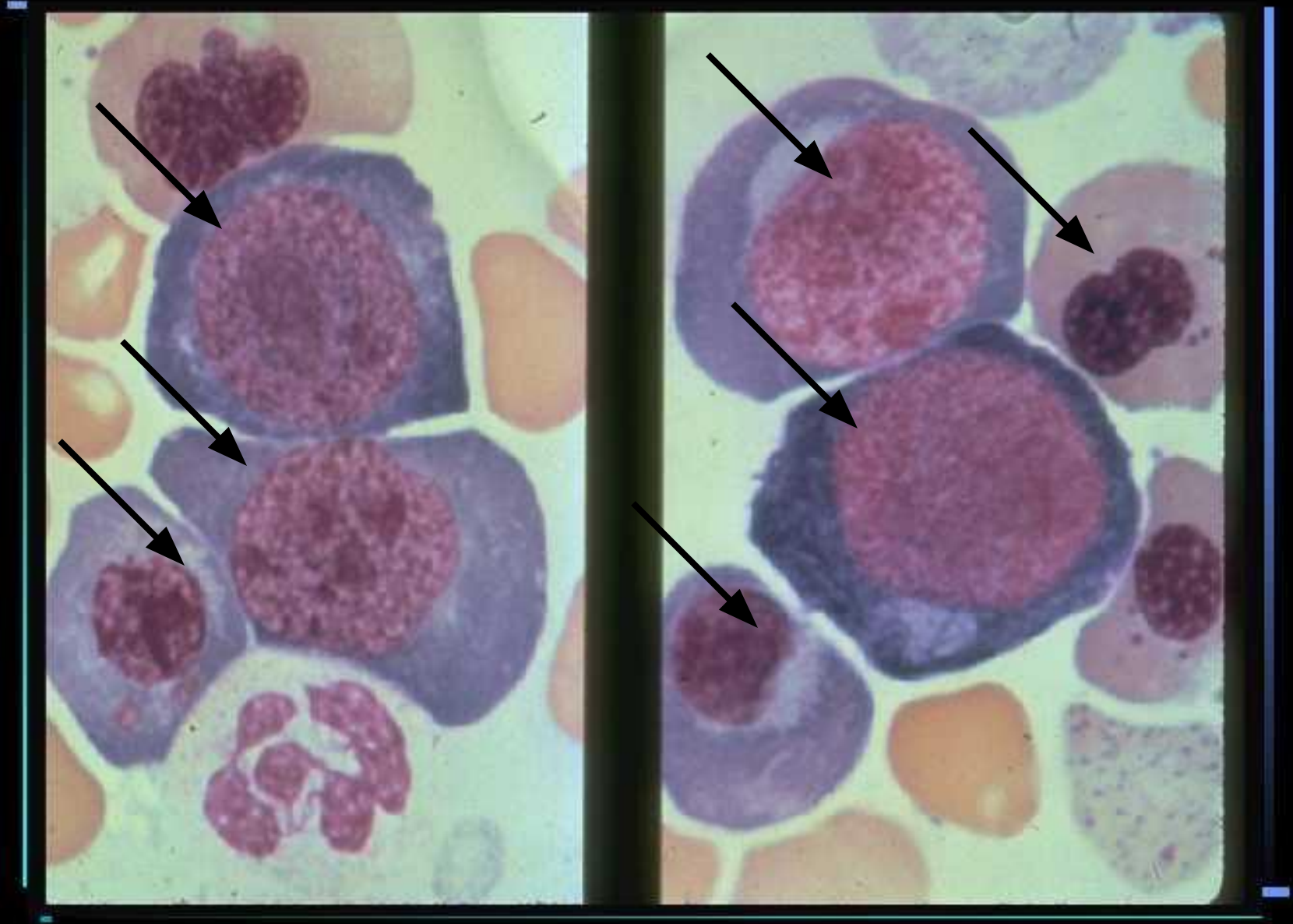
Macro-ovalocyte in megaloblastic anemia

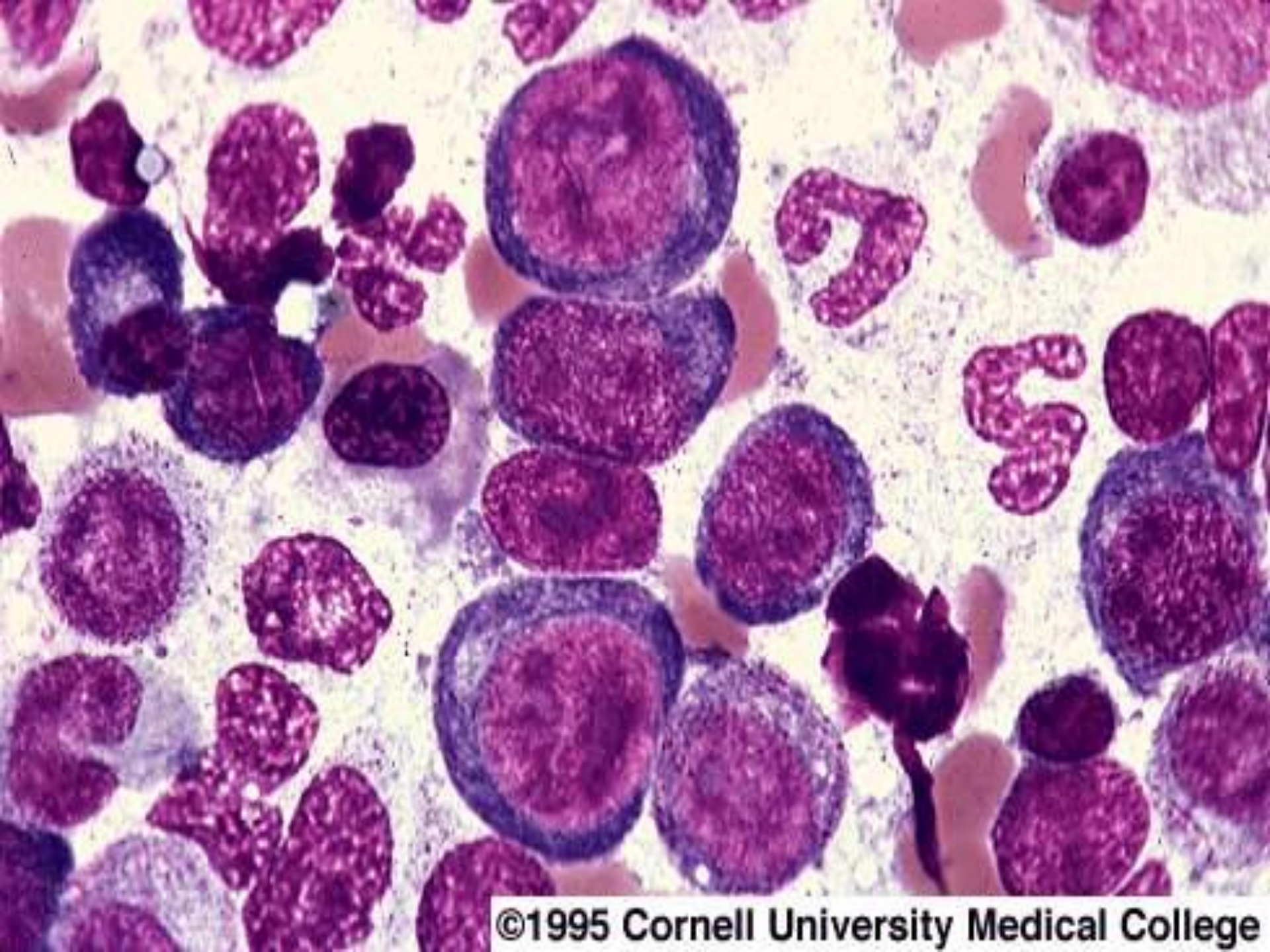


Megaloblastic Anemia – Bone Marrow



Bone marrow - megaloblasts

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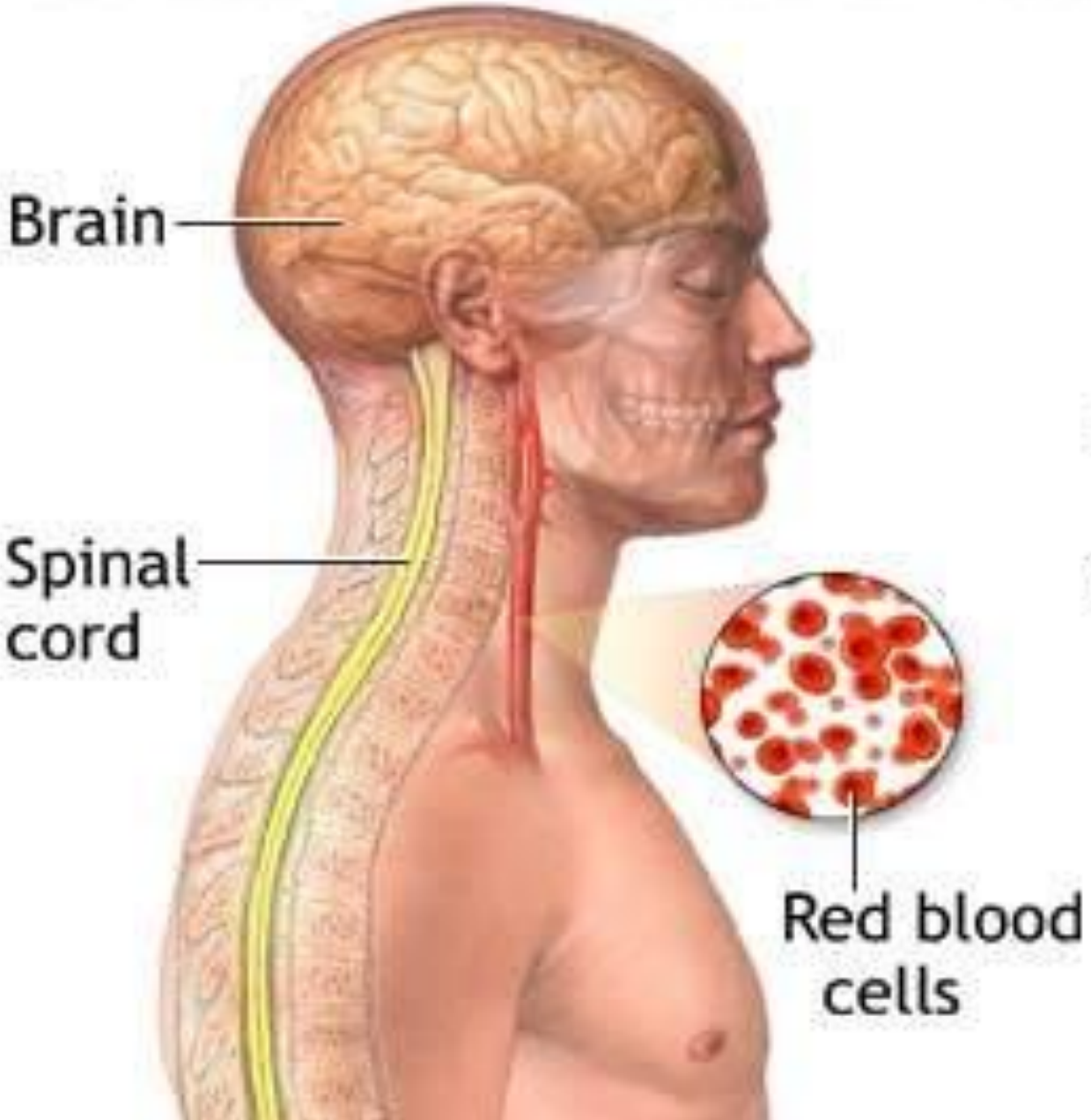
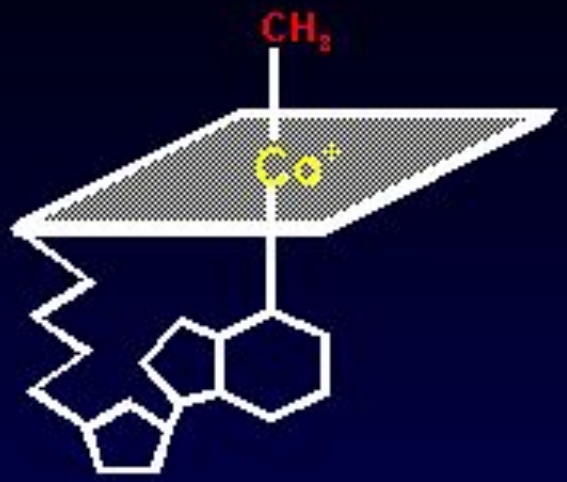
Vitamin B12



Vitamin B12 is important for metabolism, the formation of red blood cells, and the maintenance of the central nervous system, which includes the brain and spinal cord

Methylcobalamin



Corrin ring

Dimethylbenzimidazole ligand

Linker chain and side chain (f)

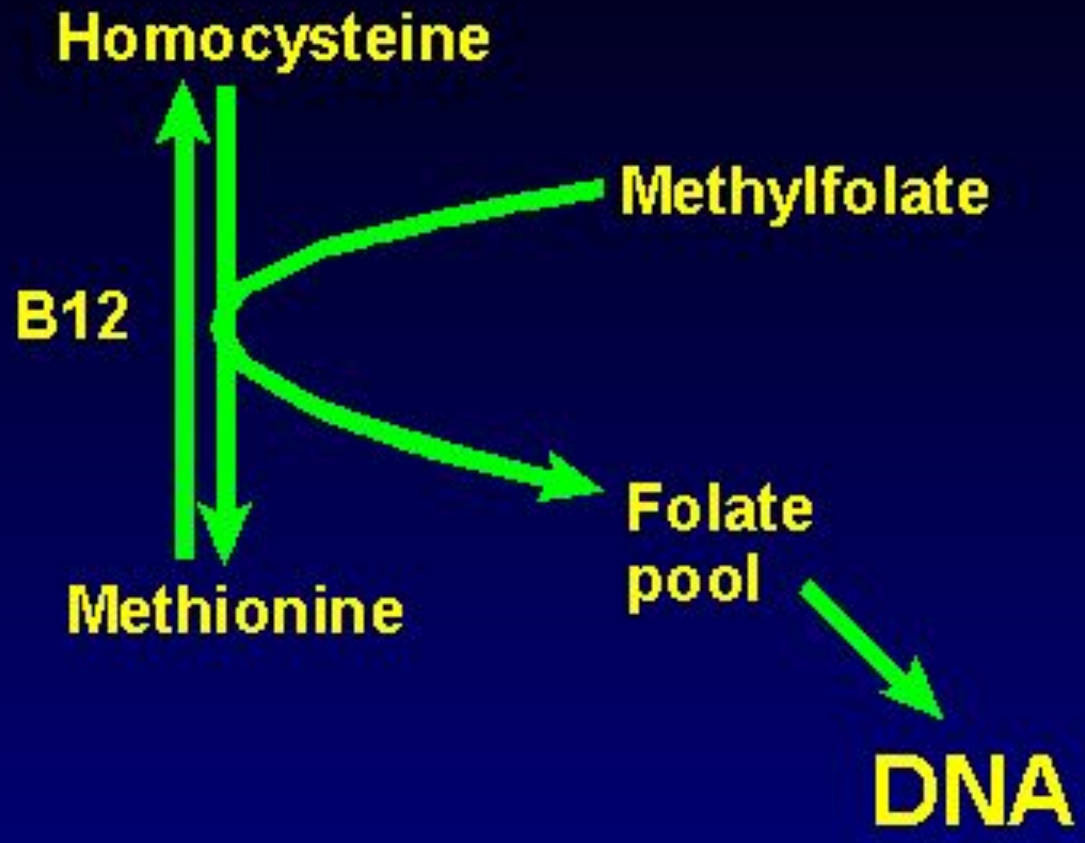
Biochemistry of B12

Important for DNA synthesis, nervous tissue and fat metabolism in the liver

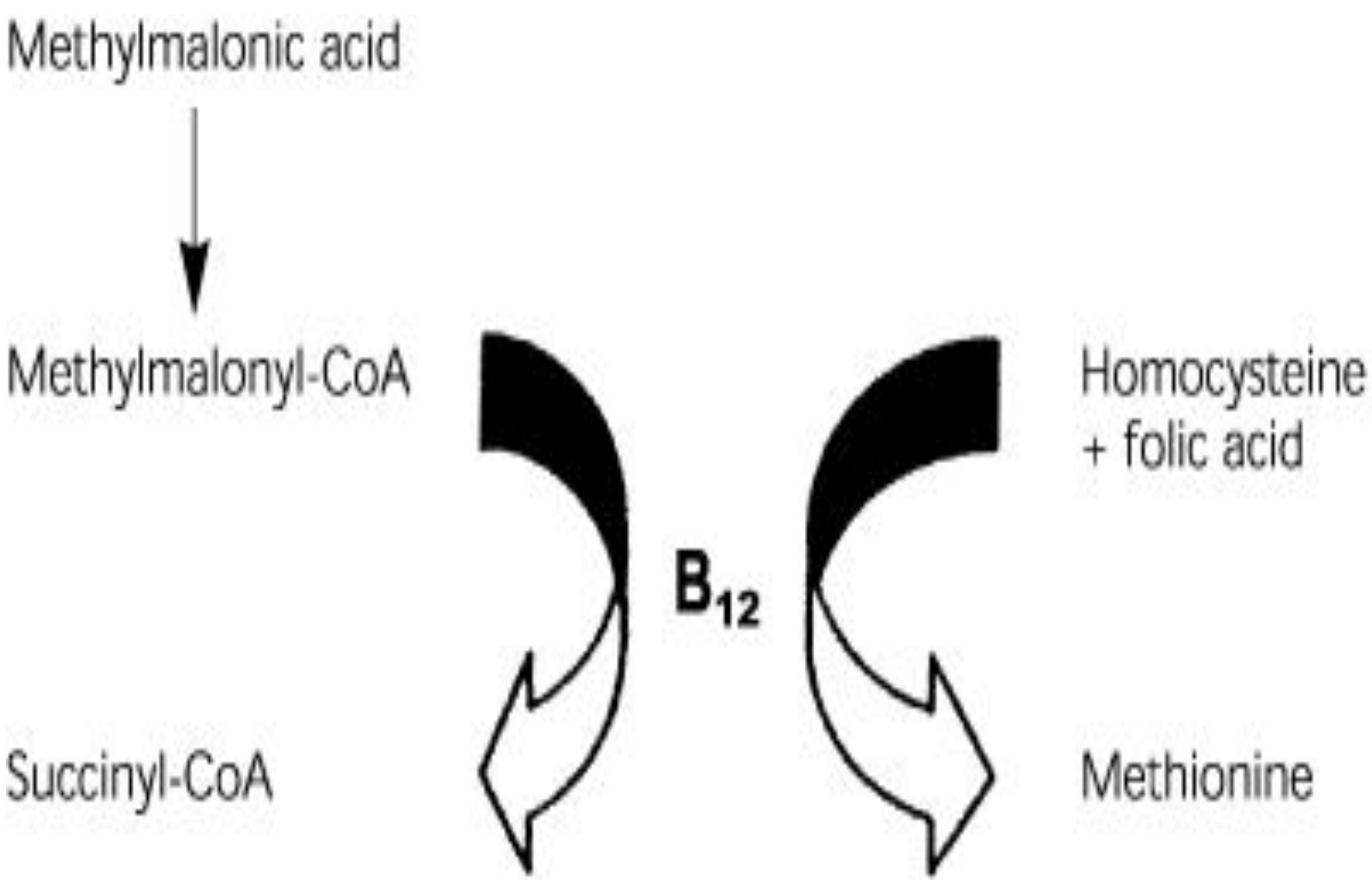
an intermediate of the citric acid cycle, porphyrin synthesis

(Heme synthesis)

DNA synthesis & vitamin B_{12} and folate - the methylfolate 'trap'



The methionine synthase reaction


Methylmalonic acid
Methylmalonyl-CoA
Succinyl-CoA
B12
Homocysteine
+ folic acid
Methionine

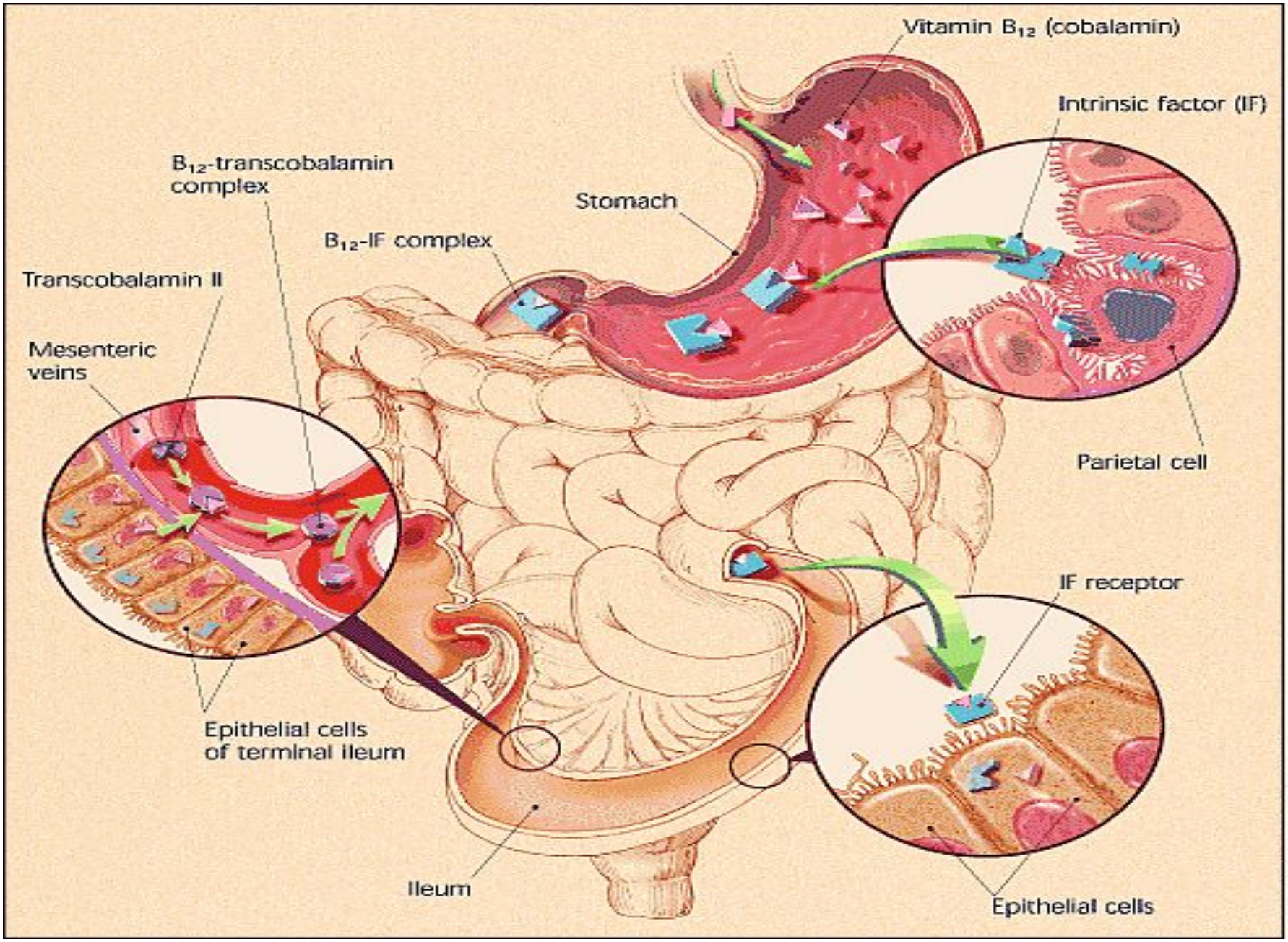
Dietary vitamin B_{12} and its absorption

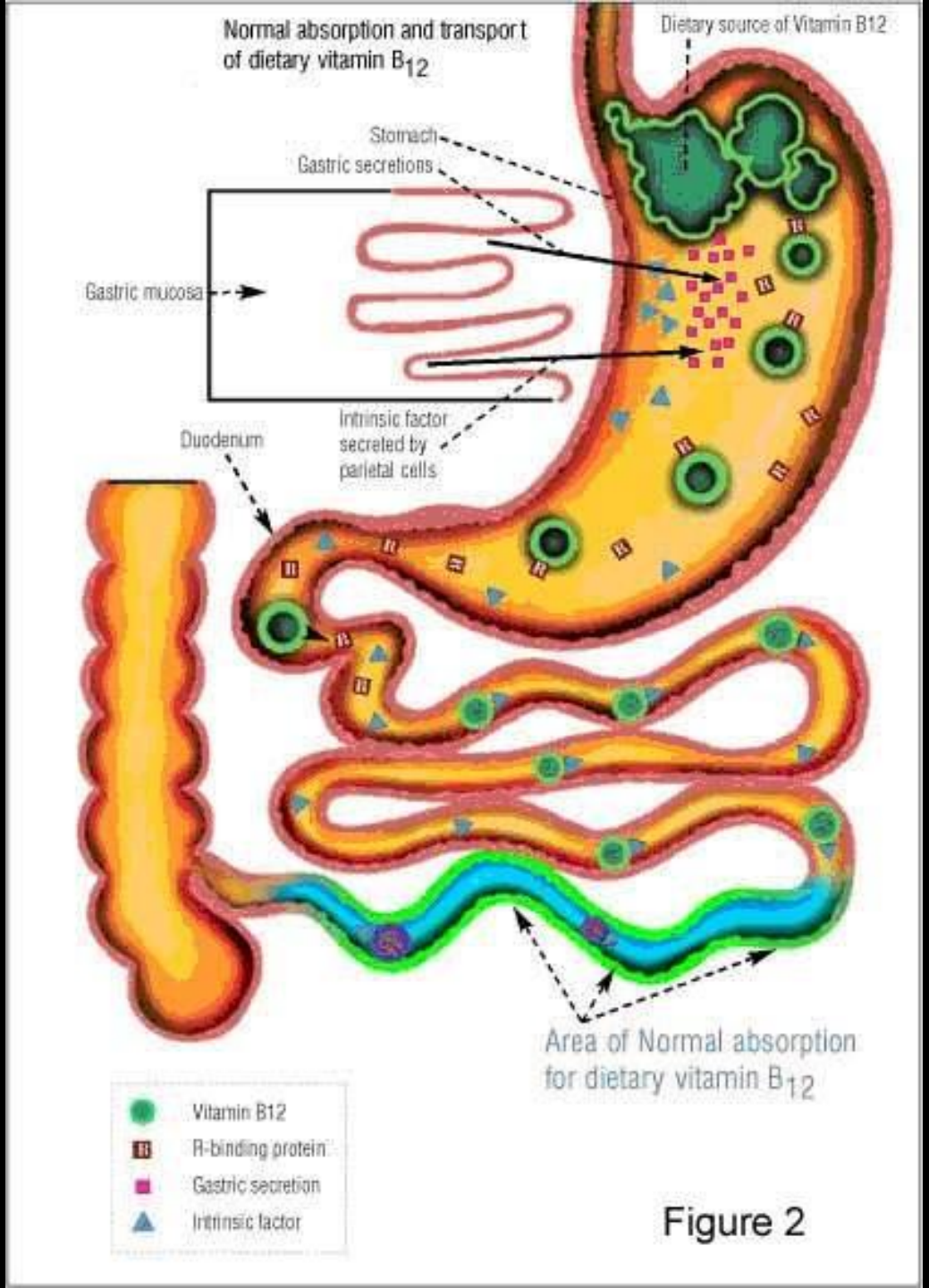
- "Everything that walks swims or flies contains vitamin B_{12}. Nothing that grows out of the ground contains vitamin B_{12}"
- Intrinsic Factor-dependent absorption from terminal ileum
- Requirements 1-3 mcg per day
- Vitamin B_{12}-free diet causes deficiency after **years**

Vitamin B12

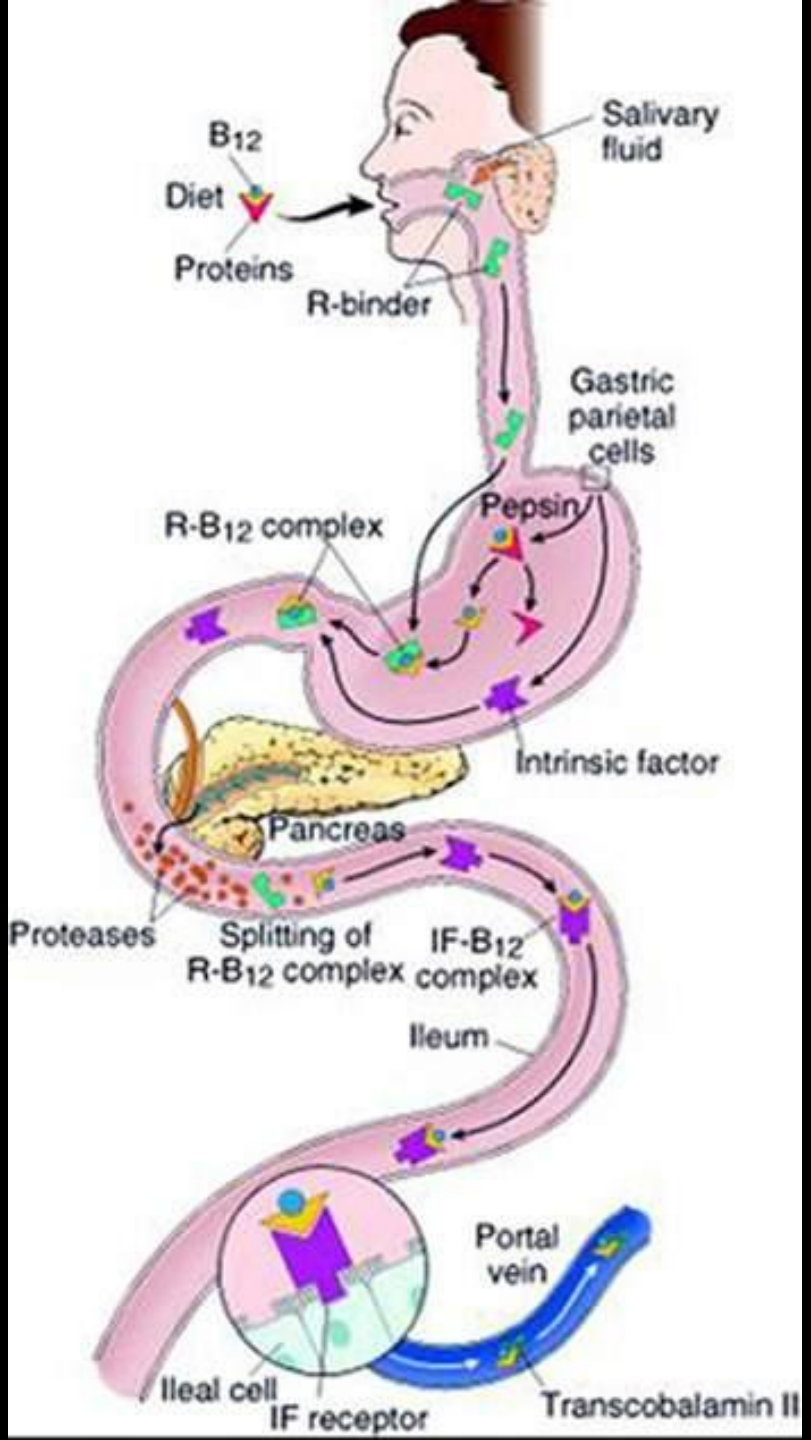
Food sources of vitamin B12:

Eggs, meat, poultry, shellfish, milk and milk products



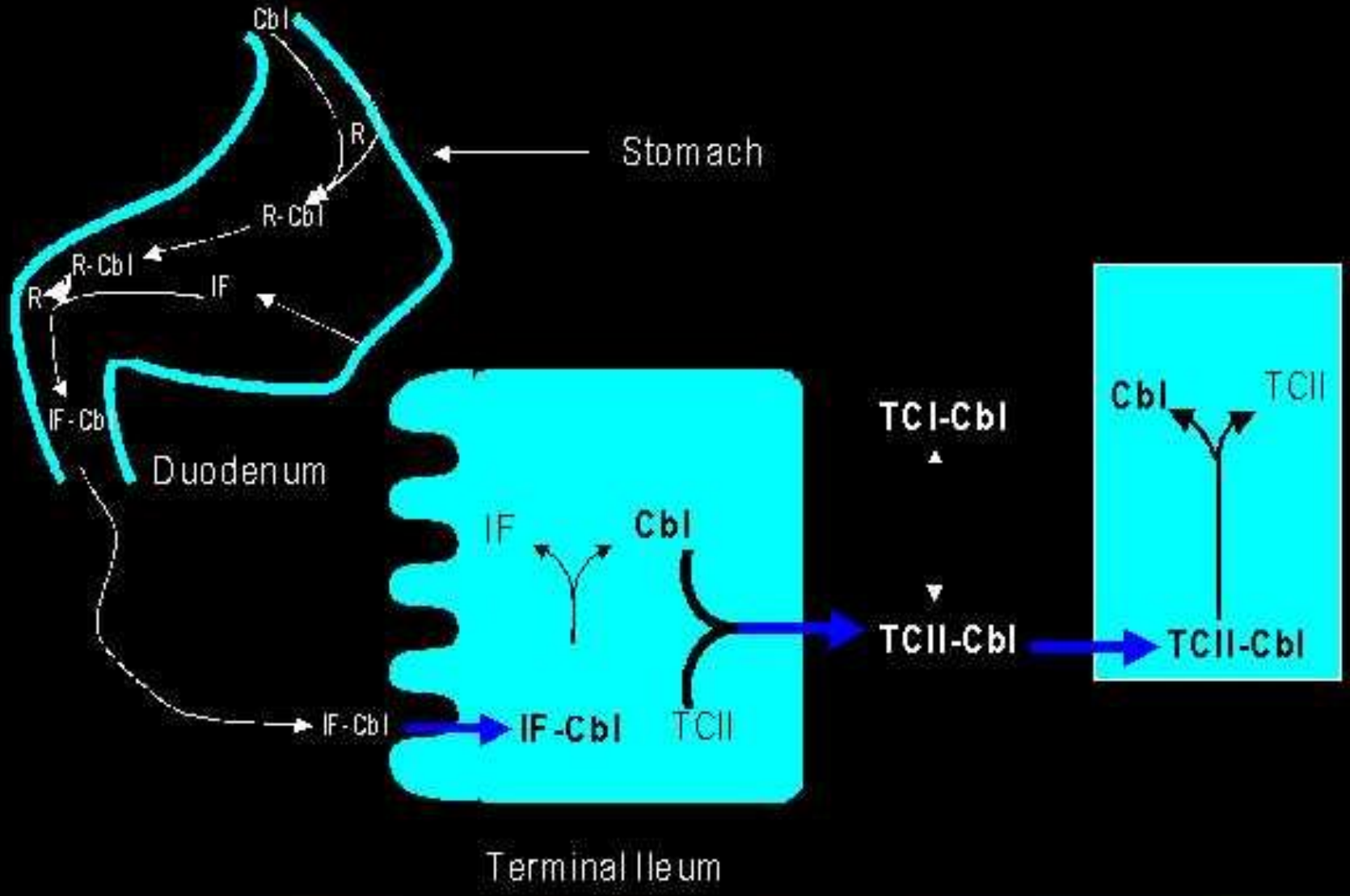


Absorption and transport of vitamin B12



Absorption and transport of vitamin B12

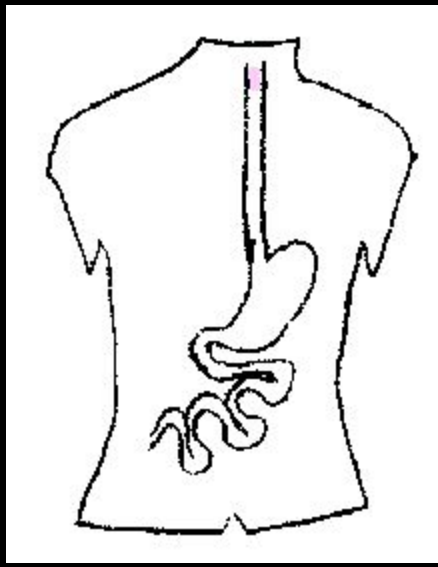
GI ABSORPTION OF COBALAMIN

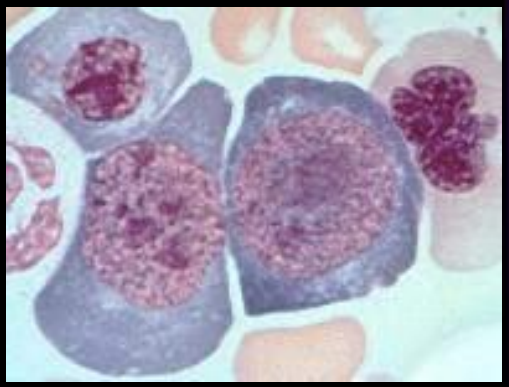


B_{12} / COBALAMIN DEFICIENCY

Causes

- Gastric Failure
  - Pernicious Anemia
  - Total gastrectomy
- Ileal Failure
  - Regional enteritis (Crohn's disease)
  - Ileal resection
  - Tropical sprue
- Competing organisms
  - Bacterial overgrowth (Blind loop)
  - Diphyllobothrium latum





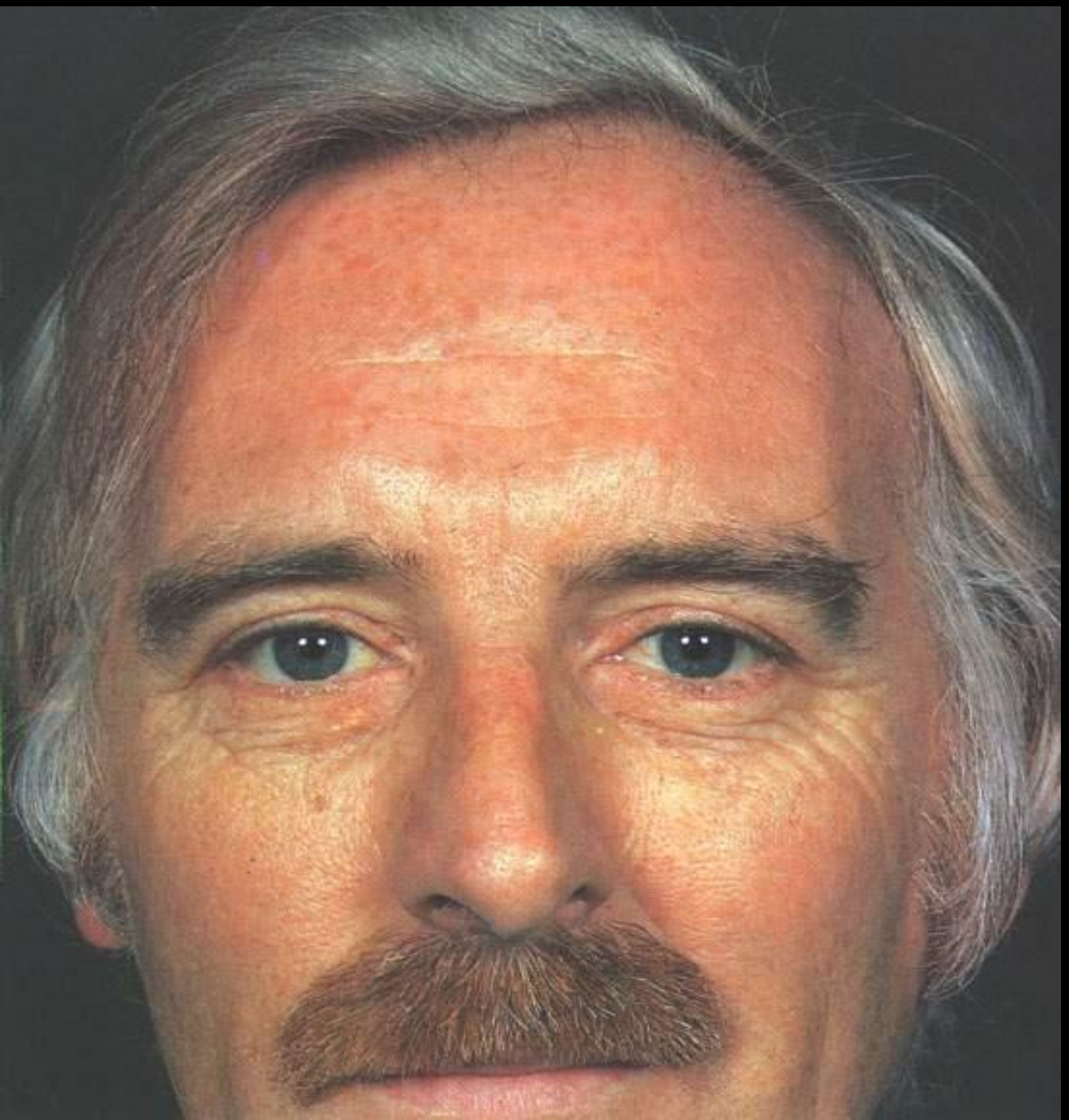
Causes of vitamin B12 deficiency

- Inadequate intake
  - vegans
- Absorption defects
  - blind loop syndrome, tropical sprue
- Intrinsic Factor Deficiency
  - Pernicious Anemia
  - Gastrectomy
  - Other

PERNICIOUS ANEMIA

- Autoimmune destruction of parietal cells
- Antibodies vs. parietal cells, intrinsic factor
- Achlorhydria is universal
- Increased incidence of gastric cancer
- Increased incidence American blacks, northern Europeans
- Often associated with other immune diseases (eg Hashimoto's thyroiditis)

Pernicious Anemia (PA)



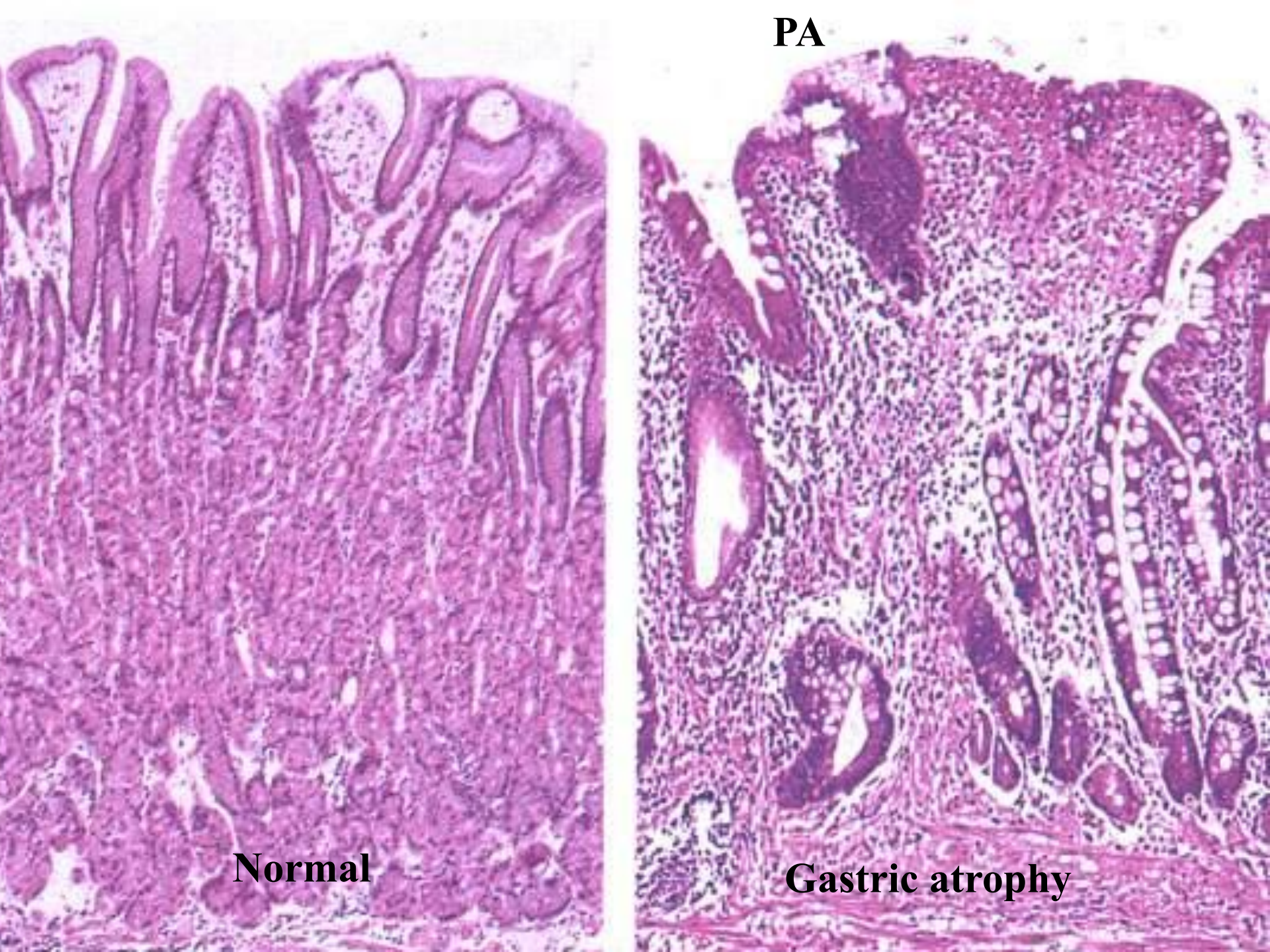
- Early graying of hair
- Blue eyes

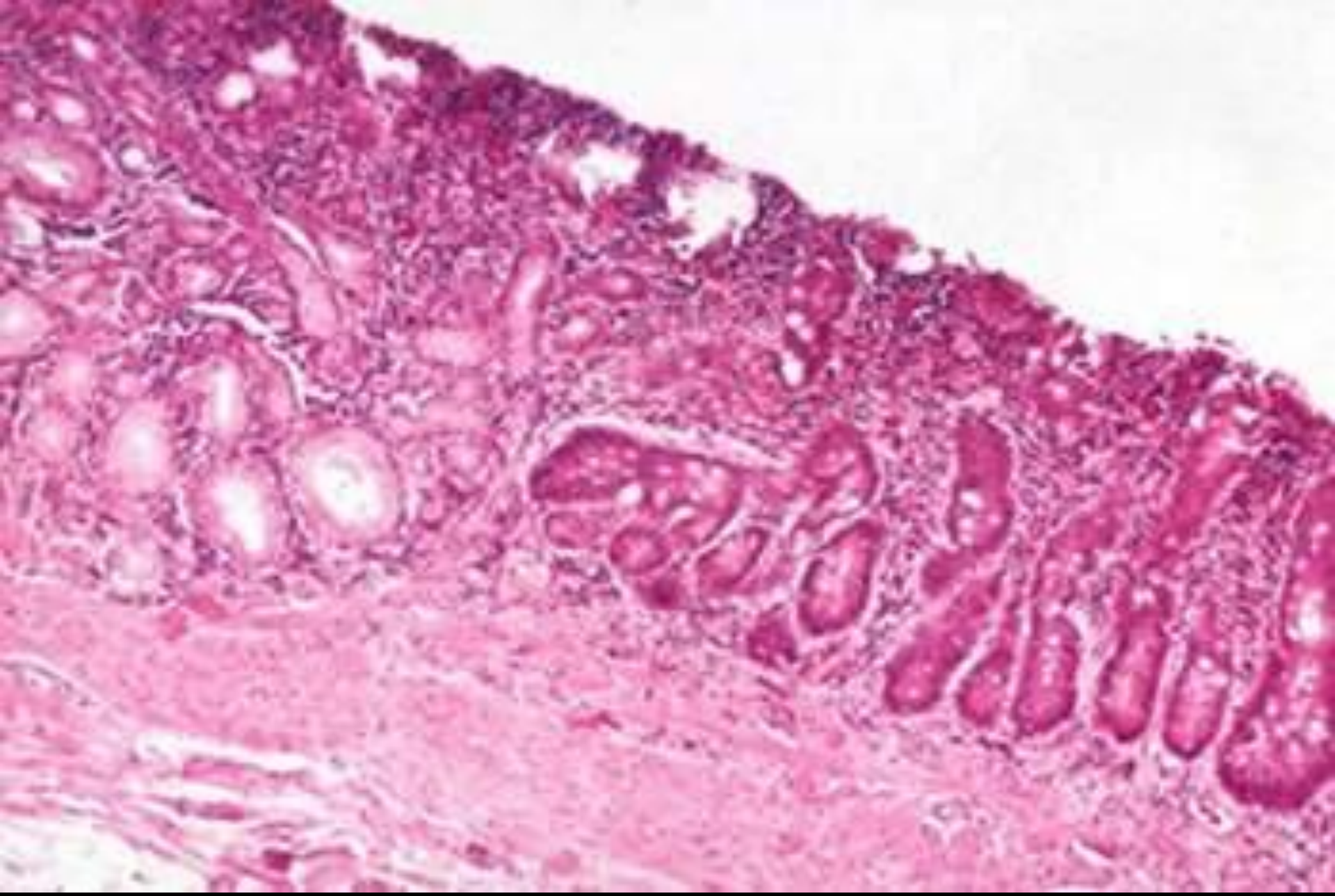
Pernicious Anemia

- Red beefy tongue

Pernicious Anemia

- **Vitiligo**


PA
Normal
Gastric atrophy



Atrophic Gastritis

Pernicious Anemia

Normal

Pernicious Anemia

Stomach

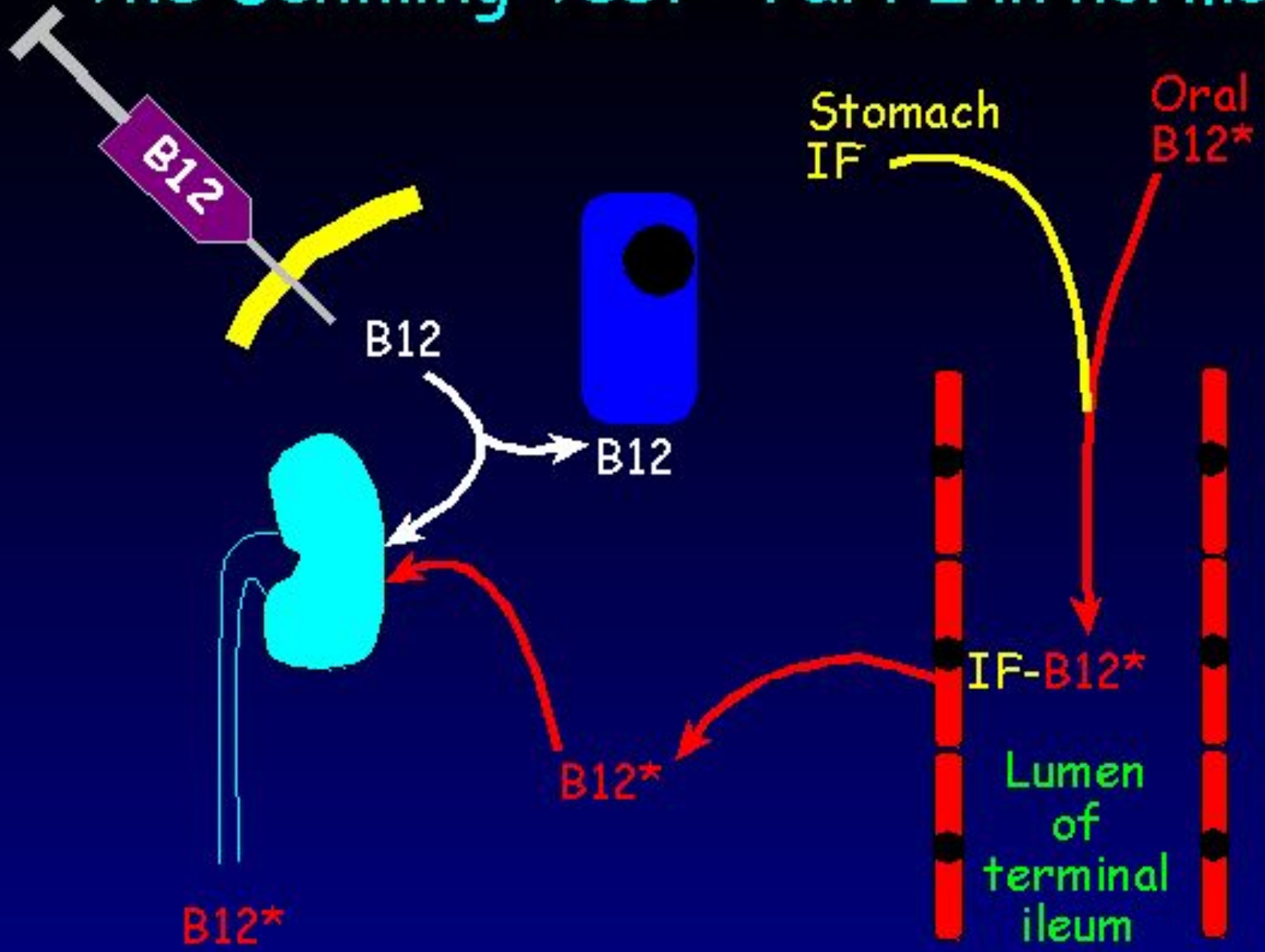
Acid +
IF

Normal
gastric parietal
cells

Stomach

Atrophic gastritis
Achlorhydria
No IF

The Schilling Test - Part I in normal



SCHILLING TEST

Cause of Cobalamin Deficiency	Part I Without IF	Part II With IF	Part III After Ab
Pernicious Anemia	Low	Normal	Not needed
Bacterial Overgrowth	Low	Low	Normal
Ileal dysfunction	Low	Low	Low

Clinical Manifestations of Vitamin B12 Deficiency

Hematologic
Megaloblastic anemia
Pancytopenia (leukopenia, thrombocytopenia)
Neurologic
Paresthesias
Peripheral neuropathy
Combined systems disease (demyelination of dorsal columns and corticospinal tract)
Psychiatric
Irritability, personality change
Mild memory impairment, dementia
Depression
Psychosis
Cardiovascular
Possible increased risk of myocardial infarction and stroke

COBALAMIN DEFICIENCY

Peripheral Manifestations

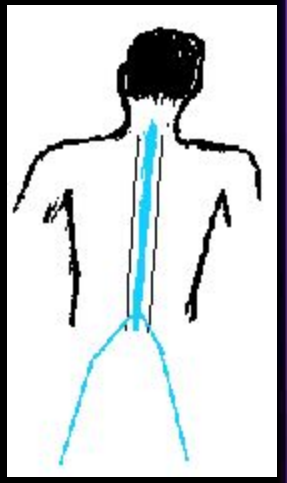
- Megaloblastic anemia - Indistinguishable from folate deficiency & due to intracellular folate deficiency
- Stomatitis/glossitis
- GI Mucosa alterations
- Can correct all of the above with high dose folate;

DON'T DO THIS!!!!!

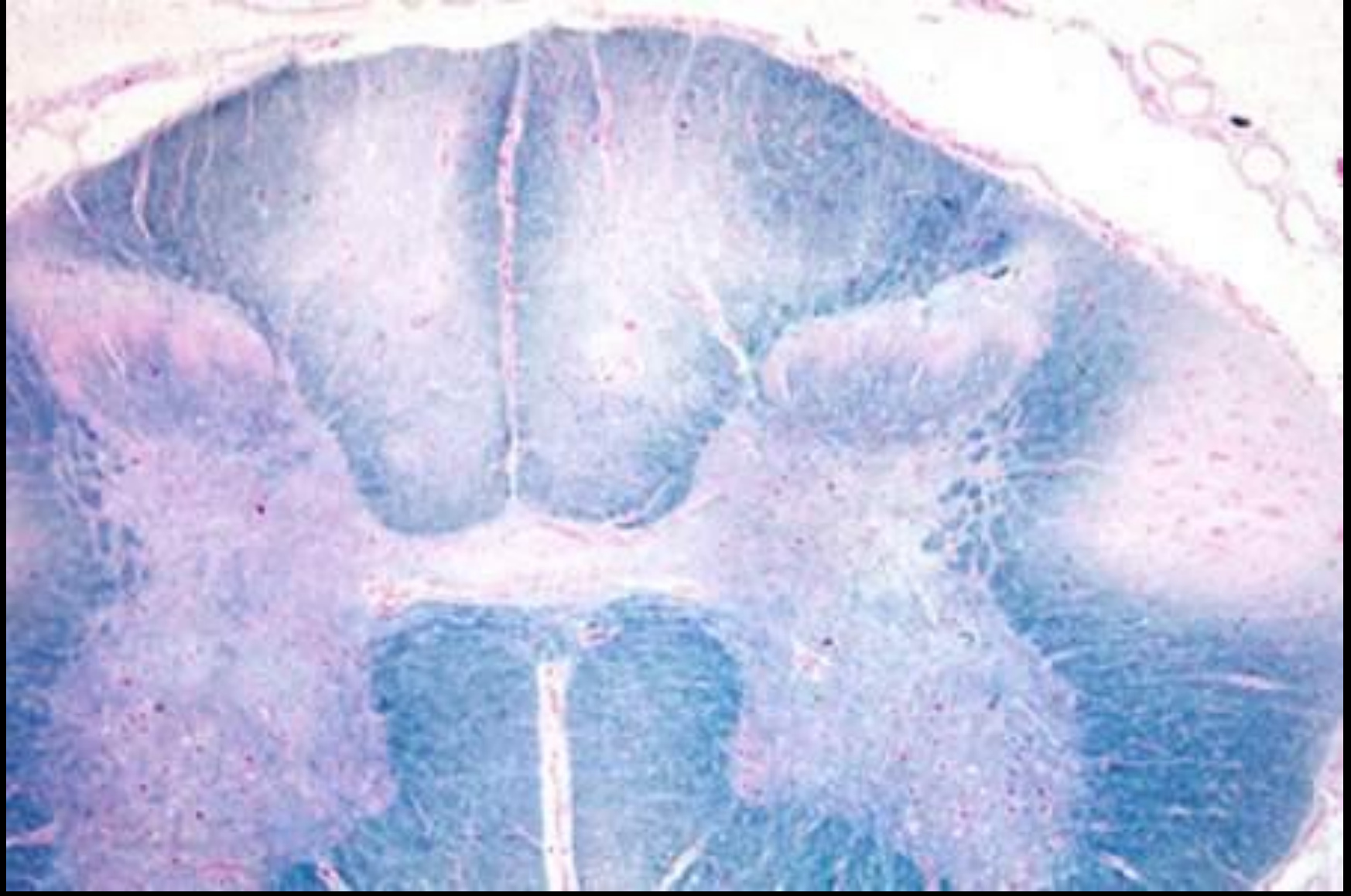
COBALAMIN DEFICIENCY

Manifestations-Central

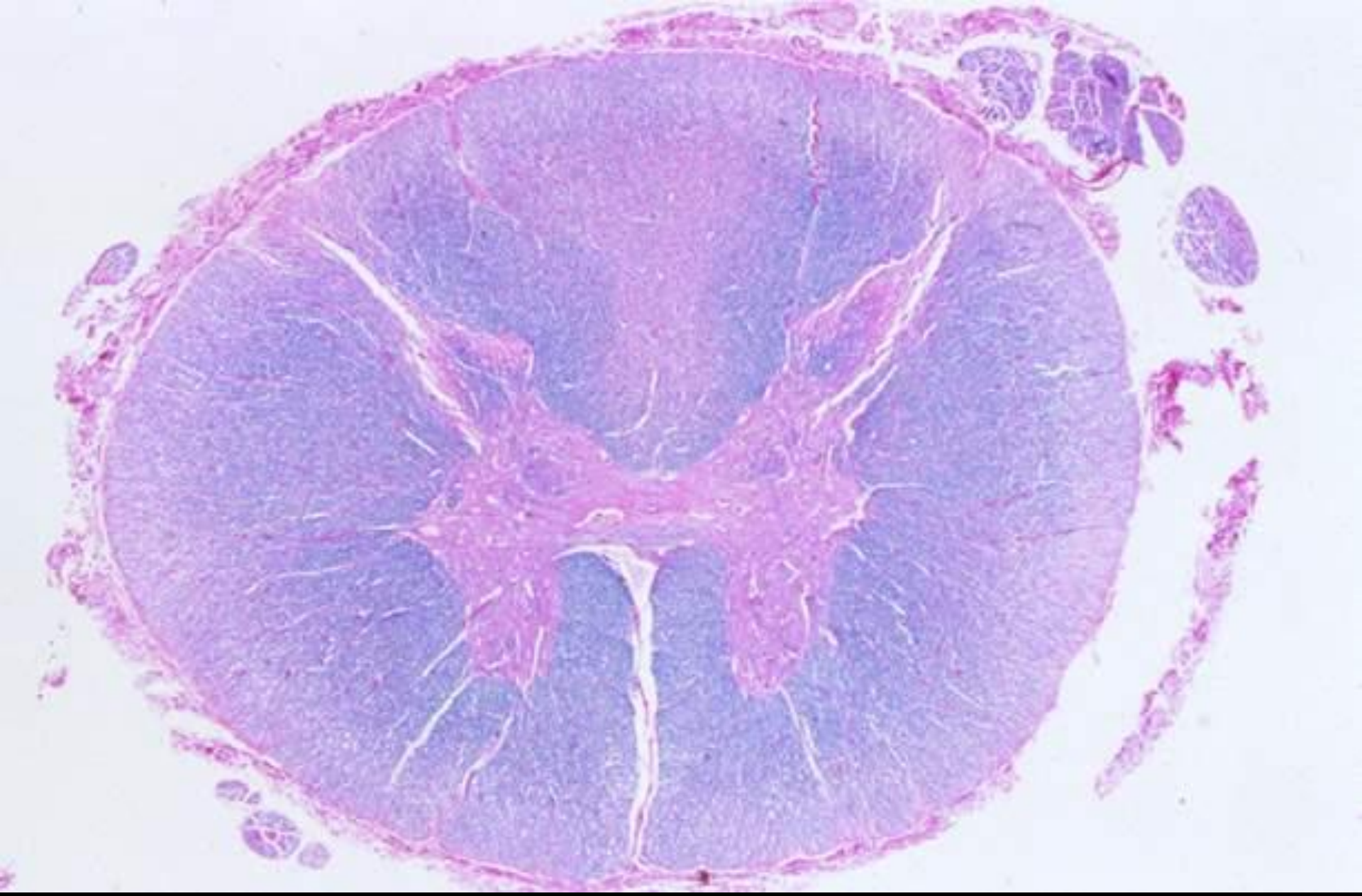
- Both brain and spinal cord
- Brain:
  - Dementia
  - Psychological disturbances
- Spinal cord:
  - Demyelinating disease
  - Loss of posterior & lateral columns- hence name "Combined system disease"



- Neurologic disease stabilized with treatment, but usually not reversed
- Treatment with folate does nothing for neurologic disease



The patient was a 45 year old woman. She had a swollen tender tongue, parasthesias of both feet and hands, decreased proprioception and vibratory sensation, ataxia and leg weakness.

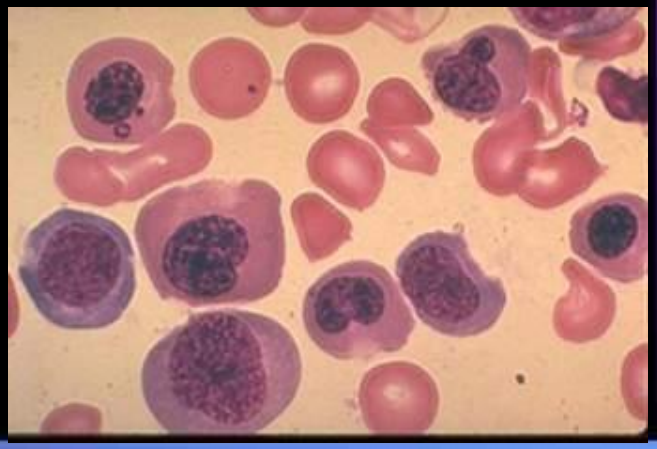


Subacute Combined Degeneration of Spinal Cord

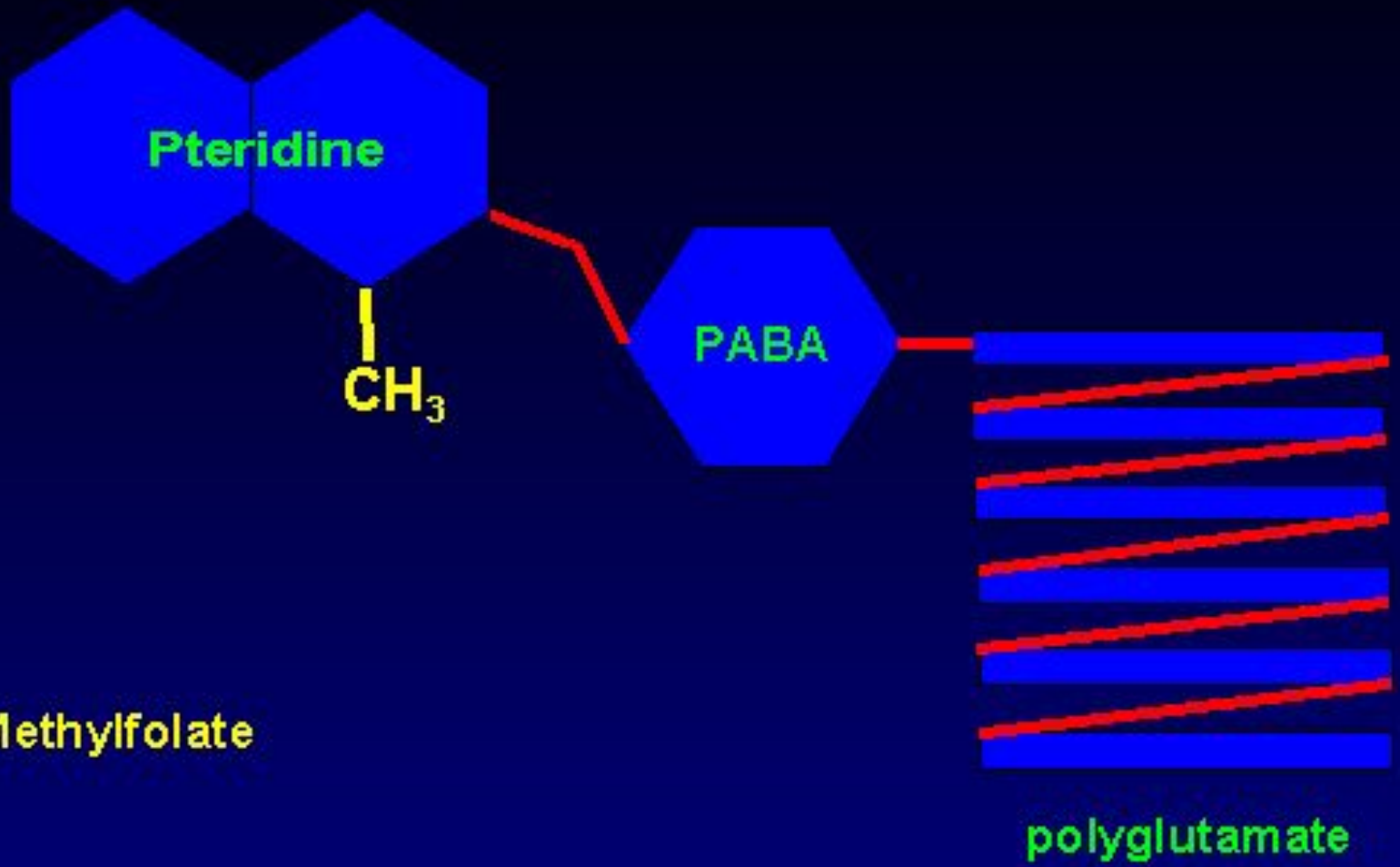
COBALAMIN DEFICIENCY

Usual Sequence of Events

- Serum homocysteine & methylmalonic acid rise
- Serum cobalamin falls
- MCV rises; neutrophil hypersegmentation
- MCV rises above normal
- Anemia
- Symptoms

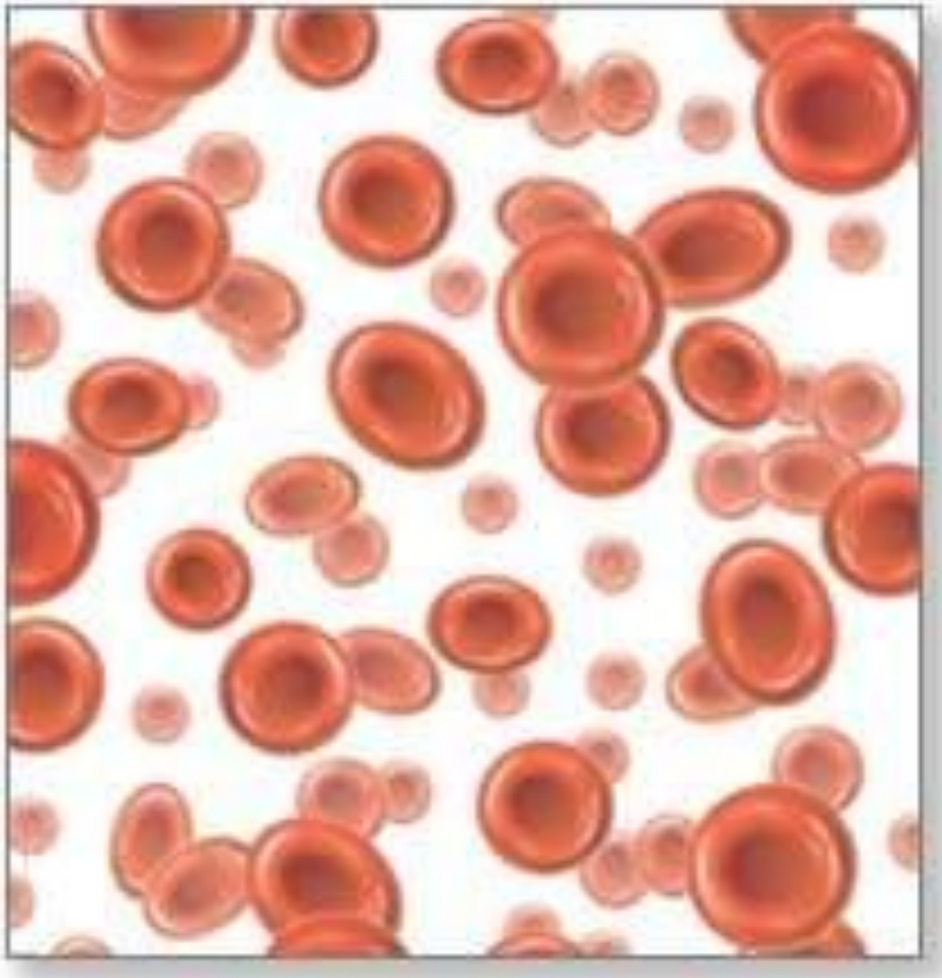


Folates - 1-carbon carrier molecules



Biochemistry of folate

Folic acid is necessary for red blood cell production and neural tube formation



Sources of Folic Acid

- Liver
- Yeast
- Nuts
- Dried beans
- Whole grains
- Spinach and other leafy greens
- Oranges
- Avacados

Source: The Nutrition Bible

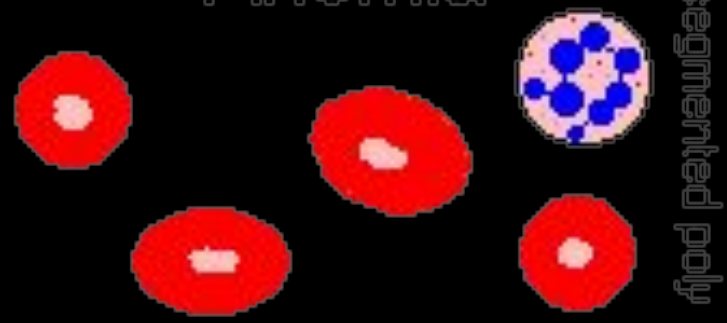
Dietary Folate and its absorption

- vegetables, liver and meat
- degraded by prolonged boiling
- daily requirement roughly 100 mcg
- folate-free diet causes deficiency in a few weeks
- absorption is largely through the jejunum.

FOLATE DEFICIENCY

Causes

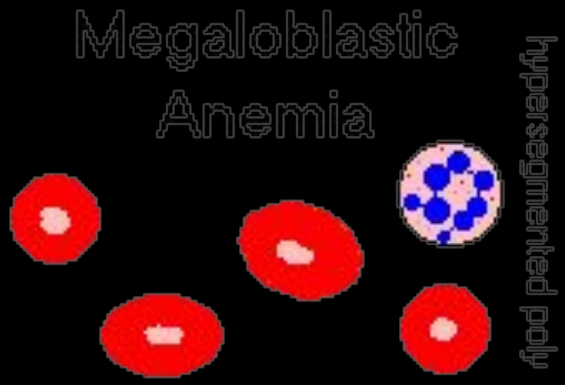
- Folate-poor diet
  - Alcoholism
  - Severe poverty
- Increased folate requirement
  - Pregnancy
  - Severe hemolytic anemia
  - Severe Psoriasis
- Drug therapy
- Malabsorption
  - Tropical sprue



FOLATE DEFICIENCY

Manifestations

- Megaloblastic anemia
- Glossitis/stomatitis



FOLATE/COBALAMIN

Properties

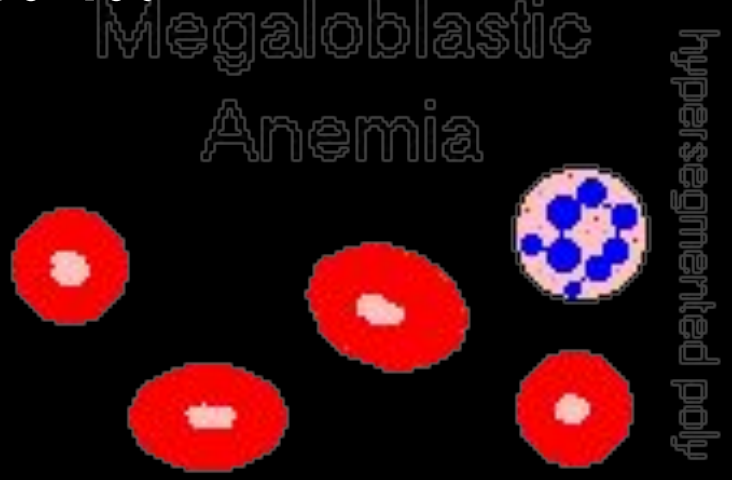
Property	Folic Acid	Cobalamin
Food Source	Almost all foods	Animal protein only
Water soluble	Yes	Yes
Site of absorption	Duodenum/Jejunum	Ileum
Mech of absorption	Deconjugation of poly-Glu	Uptake of IF-Cbl complex
Metabolic Function	One Carbon transfers	Unknown
Body stores	4-5 months	2-12 years
Dietary deficiency	Common	Rare
Deficiency states		
Megaloblastic anemia	Yes	Yes
Neurologic disease	No	Yes

Clinical features of the megaloblastic state

- Common to both B12 and folate
  - megaloblastic anemia
  - fatigue, weight loss, diarrhea, loss of appetite, fever, sore tongue, jaundice, fundal haemorrhages in severe cases
- Vitamin B_{12} deficiency
  - paraesthesiae, dementia, neuropathy, demyelination of spinal cord
- Specific for Pernicious Anemia
  - family and personal history of vitiligo, autoimmune thyroid disease, and PA itself

CBC:

Hb	**106 g/l**	**(120-160)**
Hct	**32%**	**(35-46)**
MCV	**125 f**	**(80-100)**
MCH	**35.8 pg**	**(27-33)**
RDW	**14.9%**	**(9-15)**
WBC	**3.2**	**(4.8-10.8)**
Plt	**100**	**(150-400**



Macrocytosis

- Megaloblastic
  - deficiency of B 12/folate
- Non-megaloblastic
  - alcohol
  - liver
  - myelodysplasia
  - reticulocytosis
  - other


Hematologic, neurologic, or psychiatric abnormalities
Gastric or ileal surgery
Prolonged use of histamine H_2-receptor blockers or proton pump inhibitors
Chronic gastrointestinal symptoms
Age >65 years
Measure serum vitamin B_{12} and folic acid levels.
Recheck vitamin B_{12} and folic acid levels.
Folic acid normal
Folic acid low
Treat with folic acid.
Serum vitamin B_{12} level
<100 pg per mL (74 pmol per L)
100 to 400 pg per mL (74 to 295 pmol per L)
>400 pg per mL
Vitamin B_{12} deficiency
Check serum methylmalonic acid and homocysteine levels.
No vitamin B_{12} deficiency
Either level is elevated.
Both levels are normal.
Vitamin B_{12} deficiency*
No vitamin B_{12} deficiency

Laboratory diagnosis

- In all cases
  - Blood count, serum vitamin B_{12}, erythrocyte folate
- In selected cases
  - Bone Marrow, homocysteine and methylmalonic acid, serum folate, LDH, bilirubin
- Where pernicious anemia suspected
  - Schilling Test (vitamin B12 absorption)

MEGALOBLASTIC ANEMIA

Diagnosis /Therapy

- Draw levels at first suspicion of problem,BEFORE ANY THERAPY
- Once levels drawn, begin treatment with both B_{12} and folate
- Once levels are back, can stop the normal vitamin
- Transfusions to be avoided unless hemodynamic compromise is present, or patient having angina

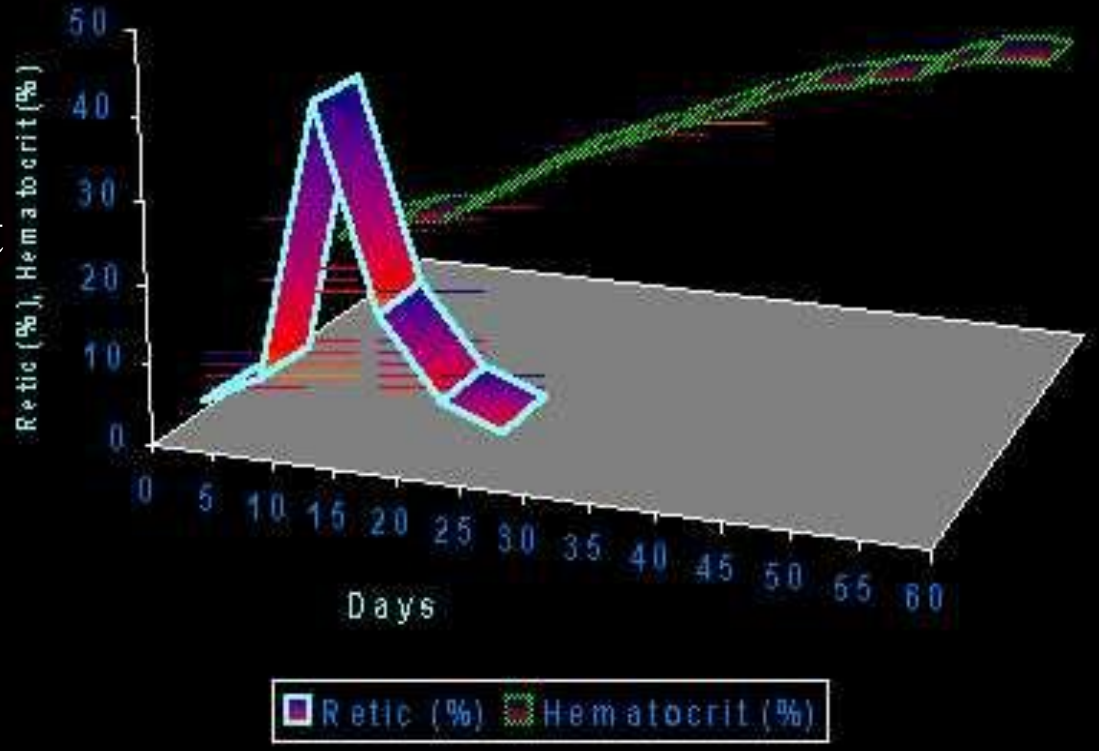
Treatment of megaloblastic anemia

- If necessary, transfuse with **care**
- Vitamin B_{12} oral or parenteral
- Folic acid tablets
- Beware hypokalemia in severe cases

MEGALOBLASTIC ANEMIA

Response to Therapy

Retic count



MEGALOBLASTIC ANEMIAS

Summary

- Deficiency in folate or B_{12}
- Macrocytic anemia; ± other cytopenias
- Slowly developing anemia, usually well compensated
- Response to therapy rapid and dramatic
- Treatment essential to avoid other complications
- Anemia is secondary to an underlying disease process

Thank You