Diagnosis and management of vitamin B12 disorders

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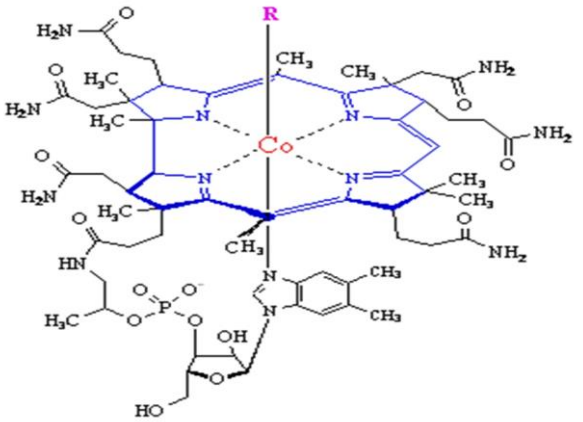
Learning objectives (1)

- Review the epidemiology of vitamin B12 deficiency
- Review the causes of vitamin B12 deficiency
- Describe the clinical features of vitamin B12 deficiency
- Review the diagnostic pathway of vitamin B12 deficiency
- Review the management of patients with vitamin B12 deficiency

Learning objectives (2)

- Review the epidemiology of high vitamin B12
- Review the pathophysiology of high serum vitamin B12 in clinical practice
- Review the management of patients with high vitamin B12

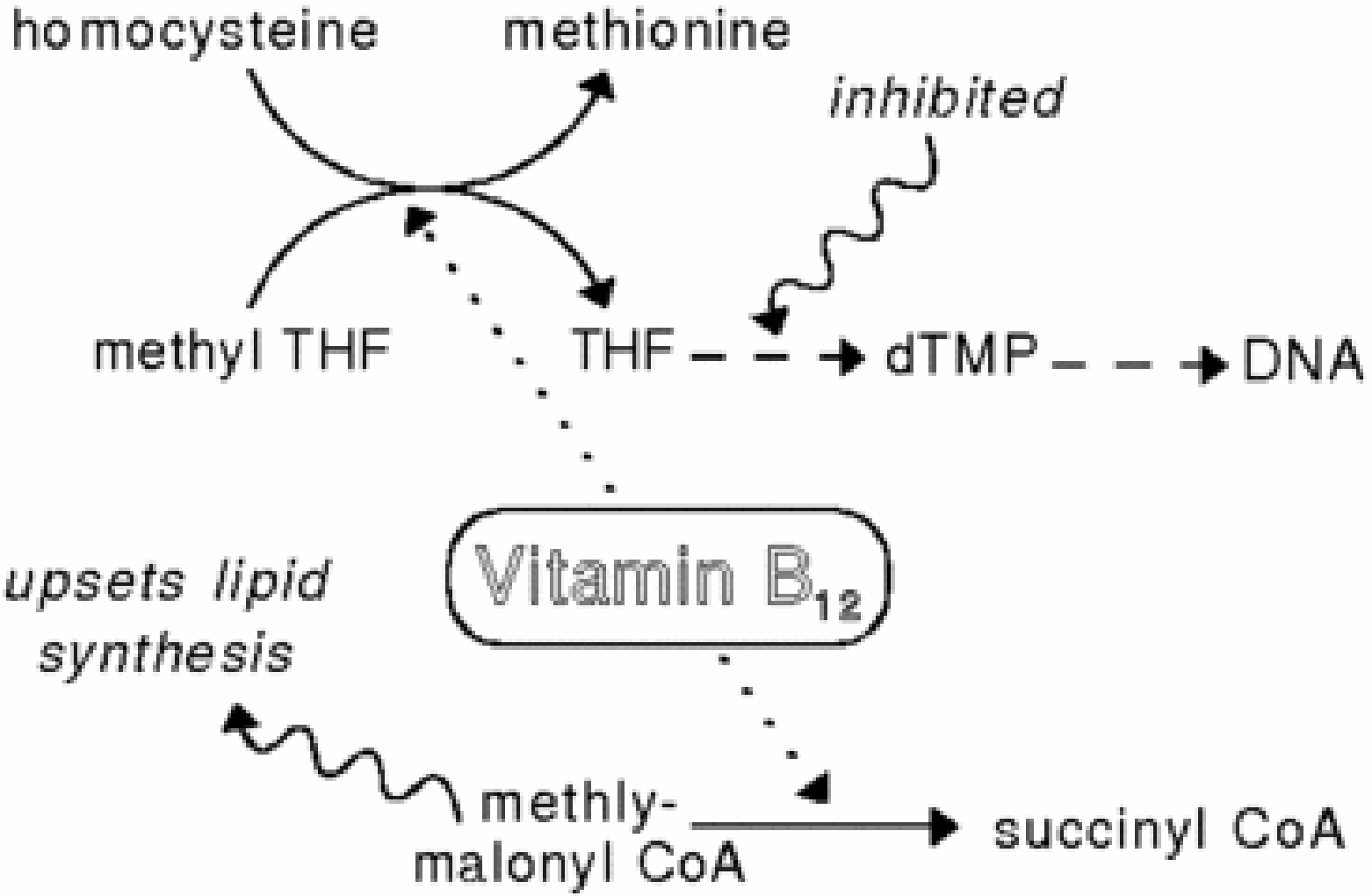
Vitamin B12



- Also called **cobalamin**, is a water-soluble vitamin with a key role in the normal functioning of the brain and nervous system and for the formation of blood cells.

- It is involved in the metabolism of every cell of the human body, affecting DNA synthesis and regulation but also fatty acid synthesis and energy production.

Vitamin B12 functions



Daily vitamin B12 requirement

- Only source available to man is dietary (liver, kidney, red meat, eggs, shellfish and dairy products).
- Normal mixed diet contains 5-30 µg /day.
- Typical daily losses 1-4 µg (lost mainly in urine and faeces).
- Since normally there is no consumption of vitamin B12 within the body, the daily requirement matches daily losses.

Vitamin B12 stores

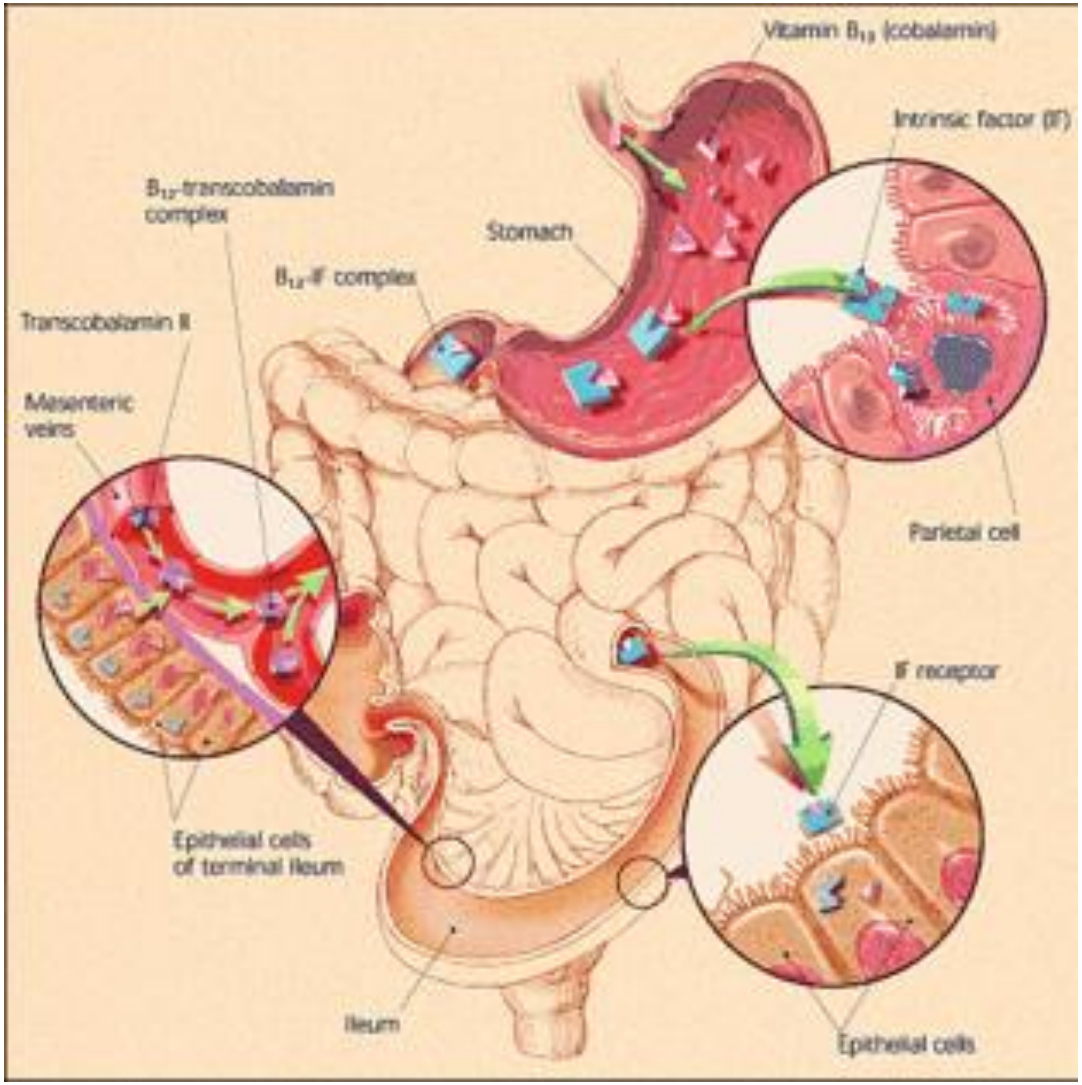
- Normal body stores of vitamin B12 about 3-4 mg, primarily in liver.

- This would be sufficient for 3 years if dietary intake ceased or if the ability to absorb the vitamin was lost.

Vitamin B12 absorption

- Vitamin B12 forms a complex with intrinsic factor (IF) in the stomach.
- IF is a glycoprotein synthesized and secreted by gastric parietal cells.
- IF: B12 complex then progresses to the ileum where it attaches to specific receptors on the ileal mucosal cells.
- The vitamin is internalized from the complex and released into the portal circulation after 6 hours.

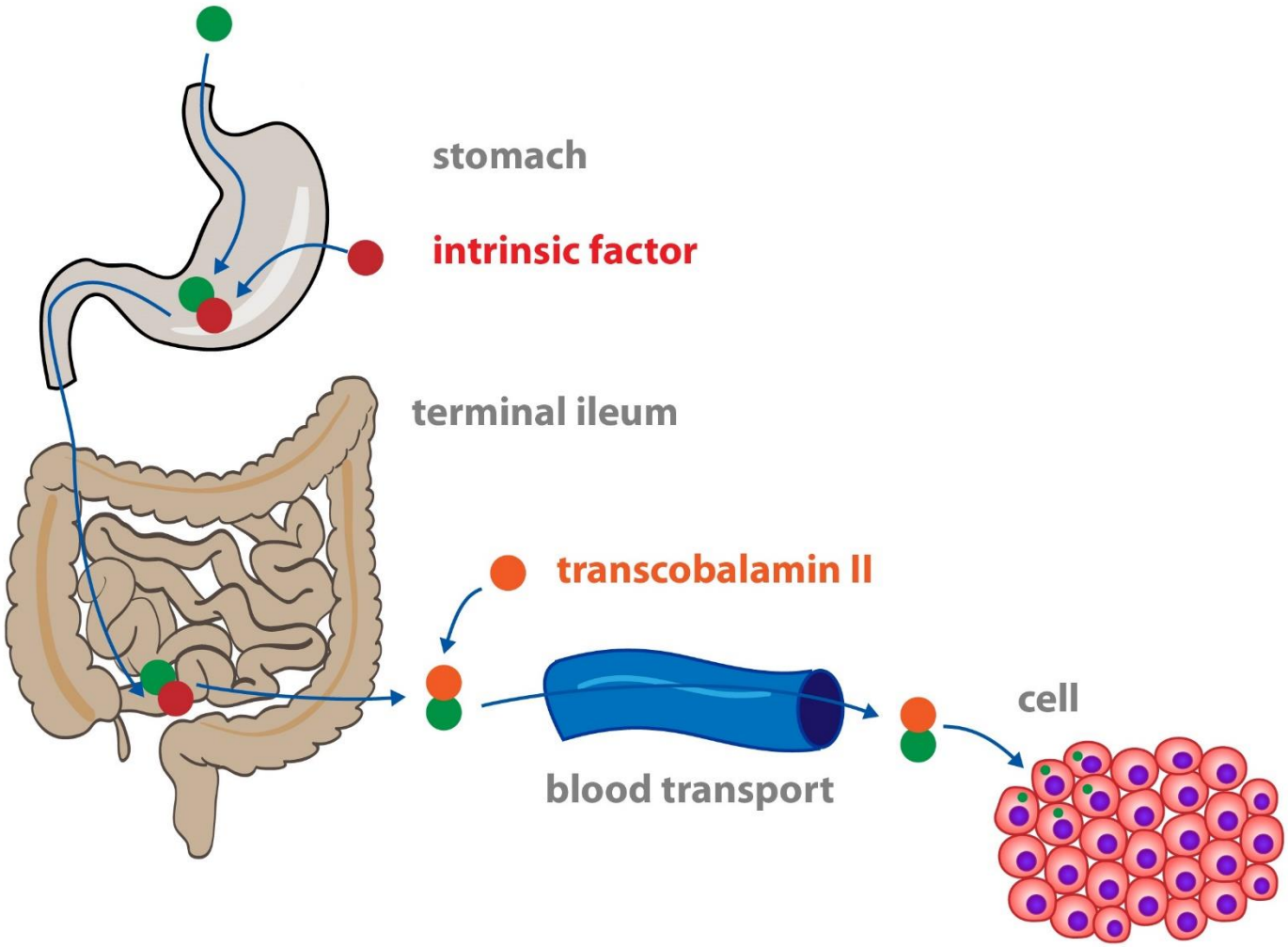
Vitamin B12 absorption



Vitamin B12 transport

- The transport of vitamin B12 in the blood as well as its hepatic and tissue uptake require the presence of TRANSCOBALAMINS (TCBs)
- TCB I and III ensure the binding of 80% of circulating B12
- TCB II plays the predominant role in tissue and hepatic uptake of vitamin B12
- Congenital absence of TCB II causes severe anaemia within weeks of birth

Vitamin B12 transport



Tests to assess vitamin B12 status

- Serum cobalamin (<148 pmol/l)
  (low cost, widely available)
- Plasma Methylmalonic acid
  (high cost test, falsely elevated in pts with renal disease)
- Serum Holotranscobalamin
  (very sensitive but not available in most labs)
- Plasma homocysteine (>15 µmol/l)
  (elevated in pts with renal failure)

Vitamin B12 deficiency Epidemiology

Prevalence varies by age groups and increases with age

- <1% in infants and children
- 3-5% in young adults
- Up to 20% in elderly patients

Causes of vitamin B12 deficiency

Intestinal malabsorption

- Inadequate dietary intake
- Increased requirements, which cannot be met from the diet
- Failure of utilization of absorbed vitamin

Causes of vitamin B12 deficiency divided by age groups

All ages	Infections Malabsorption Medical conditions (Crohn's disease, gastric resection) Inadequate dietary intake
Infants and children	Genetic disorders (Transcobalamin deficiency) Inadequate maternal dietary intake
Women of child-bearing age	Pregnancy and lactation
Older persons	Malabsorption (Achloridia due to atrophic gastritis and proton pump inhibitors

Who is at risk?

- Strict vegetarians who eat NO animal food and their infants
- Elderly people as B12 uptake ability decreases with age

Inadequate dietary intake

This is uncommon for three main reasons:

- Vitamin B12 is present in a wide range of readily available foodstuffs.
- Vitamin B12 is relatively heat-stable.
- Body stores of vitamin B12 are sufficient to meet the requirements for at least three years following complete cessation of dietary intake or intestinal absorption.

Malabsorption of vitamin B12

The most common cause of the deficiency, which could be due to:

- Lack of intrinsic factor
- Gastrointestinal disease
- Drug-induced Malabsorption

Megaloblastic anaemia

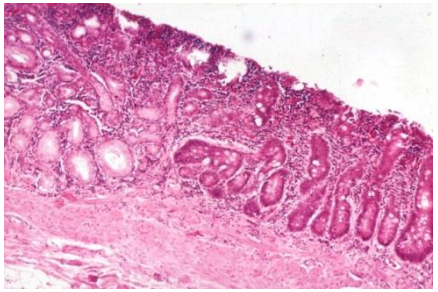
- Megaloblastic anemia is referred to a group of panhypoplastic disorders, characterized by retardation of DNA synthesis while RNA synthesis proceeds at a normal rate.

- The resulting asynchrony between nuclear and cytoplasm maturation in developing cells is responsible for the distinctive morphological and biochemical features of megaloblastic anaemias.

Pernicious anaemia

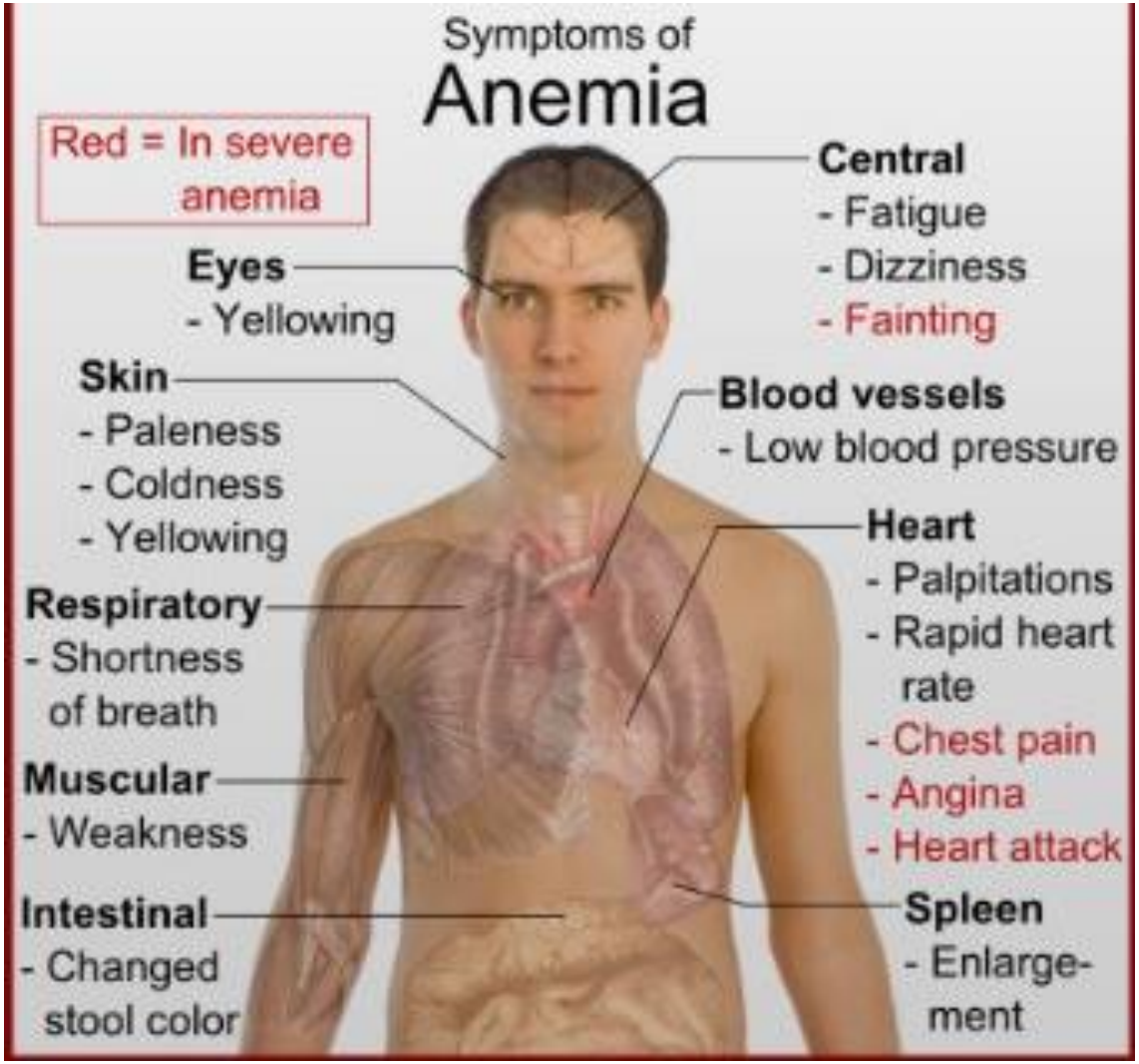
- It is by far the most common cause of B12 deficiency.
- It is especially common among the elderly.
- It is more common in women than in men and is associated with blood group A.

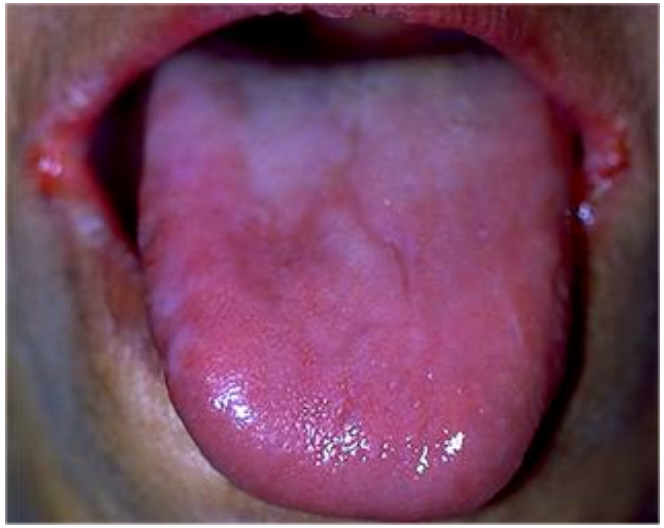
Pernicious anaemia



- Autoimmune atrophic gastritis
- 0.1% prevalence in the general population
- 1.9% in subjects over the age of 60 years
- Biologically characterised by the presence of anti-IF antibodies

Clinical findings





Classic triad

- Sore tongue
- Weakness
- Paresthesias

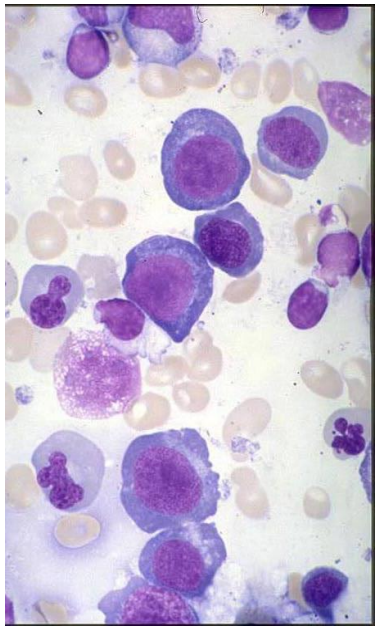
Megaloblastic hematopoiesis

Raised MCV >100 fl

Anaemia +/- leukopenia +/- Thrombocytopenia

Causes of cytopenias:

- Deranged DNA synthesis
- Ineffective hematopoiesis
- Shortened RBC survival



Other causes of macrocytosis

- Drugs affecting DNA synthesis
  (Hydroxyurea, methotrexate, zidovudine)

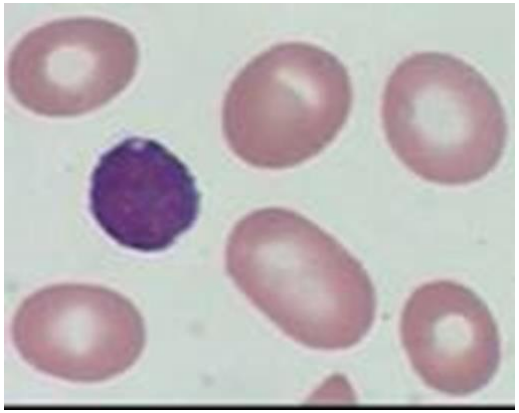
- Hepatic disease
  (Increased deposition of cholesterol and phospholipids on the membrane of circulating RBCs)

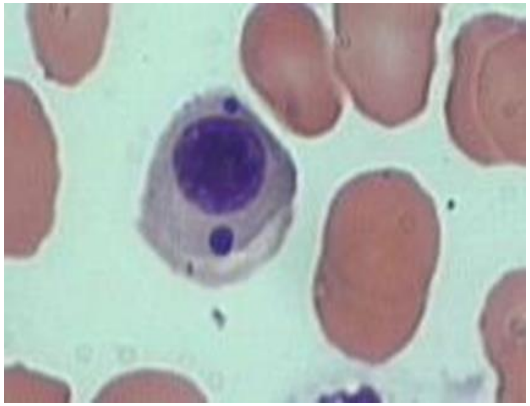
- Hemolytic anaemia (reticulocytosis)

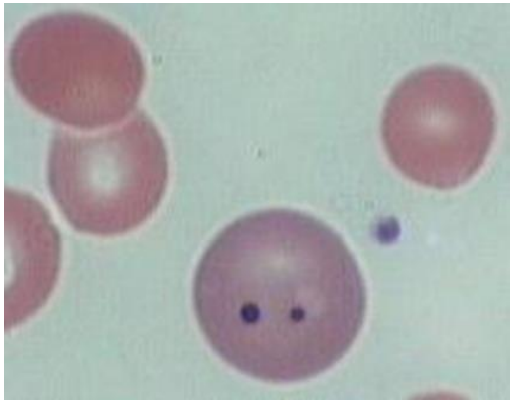
- Alcoholism
  (direct effect on bone marrow)

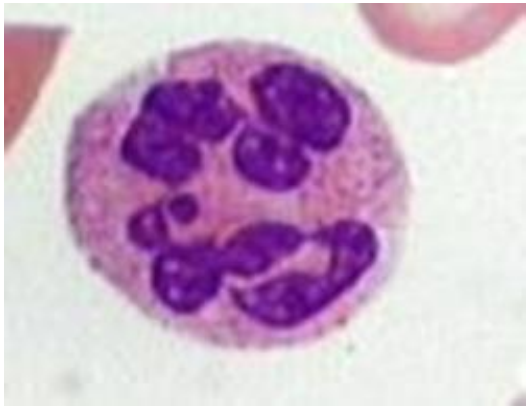
- COPD
  (excess cell water secondary to carbon dioxide retention)

Blood film examination

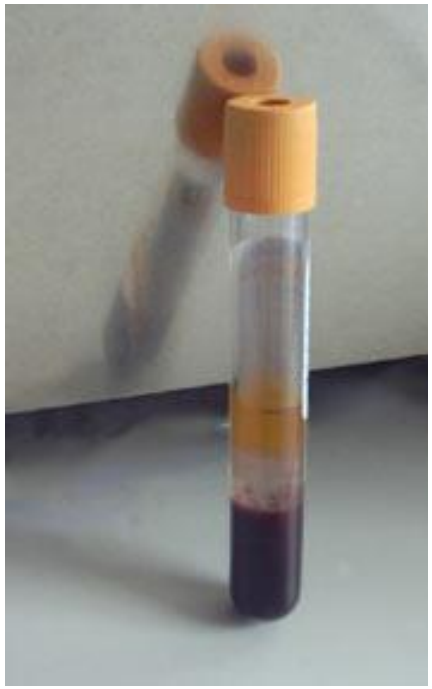








Biochemical findings



- Raised LDH
- Raised indirect bilirubin
- Reduced haptoglobin
- Increased ferritin and serum iron

Effects of cobalamin replacement

- Neurological response is unpredictable
- BM megaloblastic changes are lost in 1-3 days
- Reticulocytosis resolved in 5-8 days
- Neutrophil hypersegmentation lost in 1-2 weeks
- Hb normalises in 5-6 weeks
- MCV normalises in 10 weeks

Assessment of patients with suspected vitamin B12 deficiency (1)

Evaluation of diet

- Is patient vegan or vegetarian?
- Is patient anorexic or has poor diet?

Personal or family history of autoimmune disease

- Does patient, parent or sibling have hypothyroidism or pernicious anaemia?

History of parasthesiae, unsteadiness, peripheral neuropathy

Assessment of patients with suspected vitamin B12 deficiency (2)

Features of malabsorption

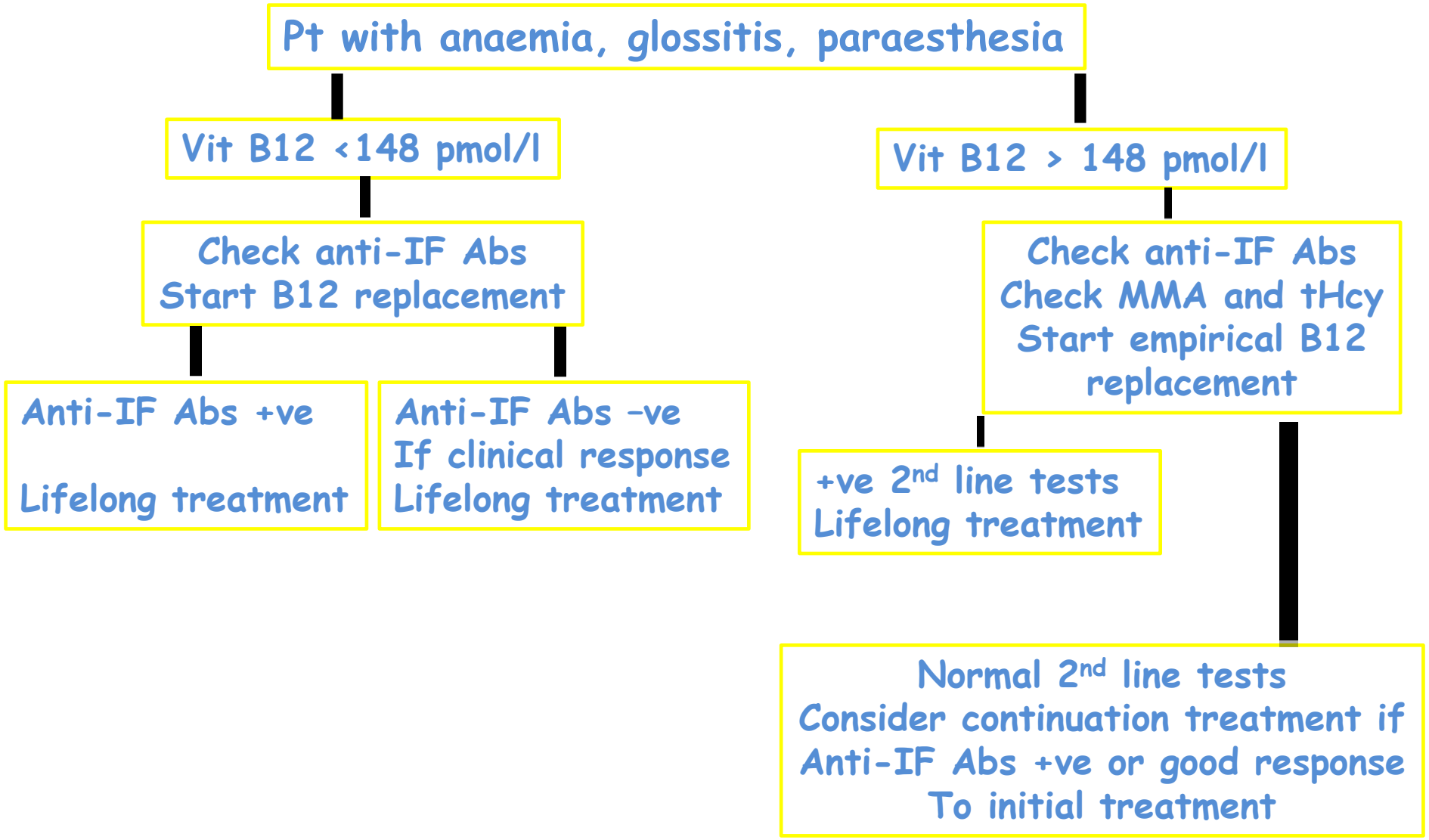
- Previous gastric surgery or small bowel resection?

Drug history

- Prolonged protein pump inhibitors, metformin, contraceptive pill

Pregnancy

Strong suspicion of vitamin B12 deficiency: what should I do?



Conclusions (1)

- There is no gold standard to define deficiency
- Serum cobalamin remains the 1st line test
- MMA and homocysteine can be used in case of uncertainties of underlying deficiency
- In the presence of discordance between test results and strong clinical picture of deficiency, treatment should not be delayed to avoid neurological impairment

Conclusions (2)

- All patients with anaemia, neuropathy or glossitis should be tested for anti IF abs regardless of serum cobalamin levels
- Patients found to have positive anti IF abs should have lifelong therapy with cobalamin
- Patients negative for IF abs with no other causes of deficiency should be treated as anti IF abs negative pernicious anaemia. Lifelong therapy should be continued in the presence of an objective clinical response

Case report 1

36 year old male

Found unconscious on the floor of his flat

No signs of violence

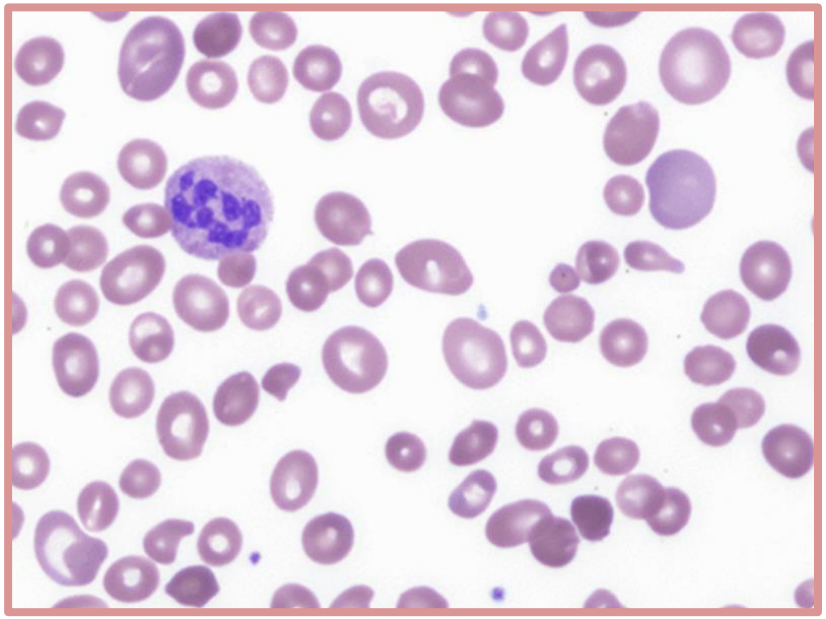
No medical hx available

No drug hx available

Laboratoristic findings

- FBC: Hb 20 g/l; WCC 12.3; Neutr. 9.2; Plt 14; MCV 100 fl; Retic. 1.5%
- Clotting screen: PT 36.6 s; APTT 34.5 s; Fbg 2.5 g/l
- LDH 5600; Bil 108; ALT 1300;
- Creatinine 65 umol/l Urea 8.1 mmol/l
- B12 283 ng/l (160-800); serum folate 9.4 ug/l (>2.7)
- Ferritin 4000 ug/l; Transferrin sat. 27%
- CRP 34

Blood film examination



- Macrocytosis
- Red cell fragments
- Hypersegmented neutrophils
- Tear drop cells

Differential diagnosis

Red cell fragments
Thrombocytopenia
Neurologic manifestations

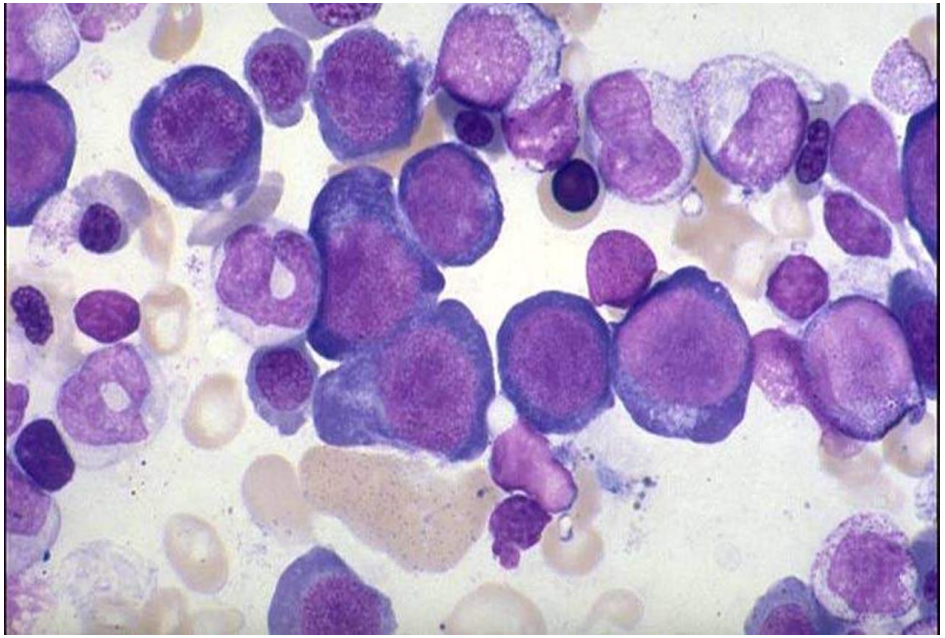
?

TTP

Additional tests

- Toxicologic tests → neg
- Viral screen → neg
- Anti-IF antibodies → neg
- ADAMS 13 → 7%
- Troponin → raised
- Autoimmune screen → neg

Bone marrow findings



- Erythroid hyperplasia
- Megaloblastic erythroid precursors

Management

- Plasma exchange
- B12 and folate replacement

Outcome

- Complete resolution of neurological manifestations
- Normalisation of FBC within a month
- Patient discharged after two weeks with no clinical sequelae
- Patient was a strict vegan !!!

Elevated Vitamin B12 levels: clinical significance and epidemiology

- Frequent and underestimated anomaly
- Clinically can be paradoxically accompanied by signs of deficiency
- The aetiological profile encompasses severe disease entities for which early diagnosis is critical for prognosis
- Prevalence of 12% in a retrospective study by Deneuville et al. including 3702 hospitalised patients.

High vitamin B12 and cancer

- Association between elevated B12 and cancer first described in 1975 by Carmel et al.

- Carcinomas most frequently involved are HCC and metastatic colon, breast and pancreatic cancer.

- Chiche et al. showed that 23% of patients with high B12 had a previously unknown solid cancer in 73% of cases, which was still at a non-metastatic stage in 80% of cases.

Transcobalamins

- TCB I and III are produced by granulocytes (Increased in myeloproliferative disorders)
  Apart from antibacterial role, their exact function is not known.

- TCB II is primarily produced by hepatocytes but also by endothelial, monocytic and intestinal cells.
  It is essential in the delivery of vitamin B12 to cells and tissues.

Pathophysiology of high vitamin B12

- Excess B12 intake
- Excess production of TCBs
  (liver disease, MPD, neoplasms, inflammation)
- Defect in clearance of TCBs
  (Renal failure, anti TCB antibodies)
- Congenital deficiency in TCBs
- Defect in TCB-B12 affinity
- Hepatic release of B12 and TCBs
  (Liver disease)

Excess vitamin B12 intake

- Ingestion of multivitamin complex tablets (often not spontaneously reported!!!)
- Parenteral administration of vitamin B12 (more frequent in the past when Schilling test was available)

High vitamin B12 and solid neoplasms

- Carcinomas most frequently involved are: hepatocellular carcinoma and secondary liver tumours

- Correlation between size of tumors and degree of elevation of vitamin B12

- Primary mechanisms implicated:
  1) increased levels of TCBs due to excess degradation of hepatocytes
  2) decreased hepatic clearance of HC-cobalamin complex

High vitamin B12 and blood disorders

- High vitamin B12 is frequently observed in myeloproliferative disorders (CML, PV, MF)
- A statistically significant association was found between vitamin B12 levels >1275 pg/ml and haematological malignancies.
- The elevated B12 levels in myeloid neoplasms are primarily linked to the increased production and release of TCBs by tumour granulocytes.

High vitamin B12 and liver diseases

- Acute liver disease (hepatitis)
  (excess release of B12 by the liver)

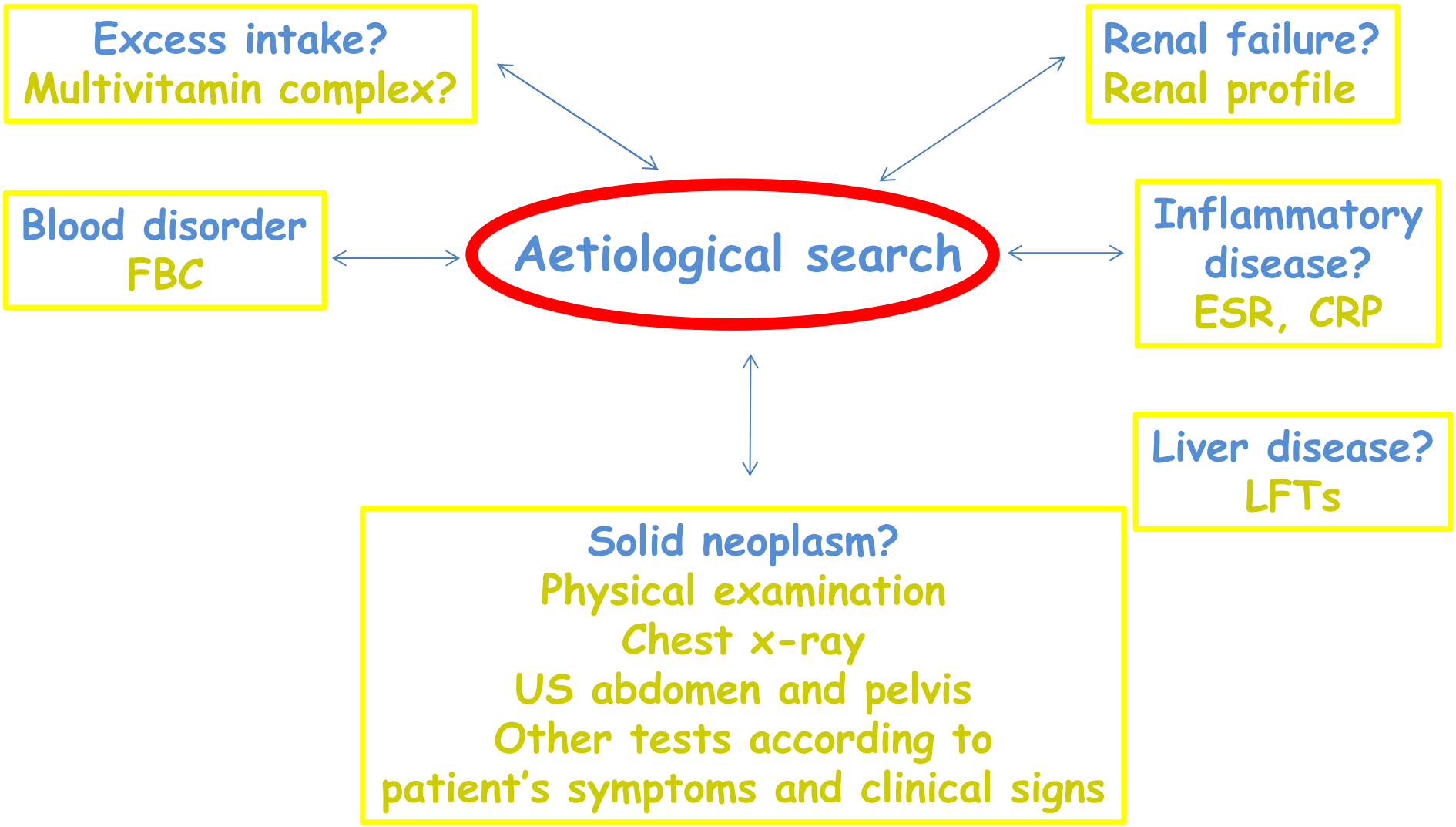
- Chronic liver disease (cirrhosis)
  (the degree of elevated vitamin B12 is correlated with the severity of cirrhosis)

- Alcoholic liver disease
  (increase in plasma levels of TCB I and III and decrease in TCB II)

Other causes of high vitamin B12

- Renal failure (serum accumulation of TCBs)
- Autoimmune conditions (SLE, RA)
- Inflammatory diseases
  (increased release of TCB II)

High vitamin B12: clinical approach



Conclusions

- High serum cobalamin could represent an early marker of a variety of diseases, including cancer.

- A codified approach is needed to determine the potential indications of the search for excess vitamin B12 and the approach to adopt upon discovery of high serum cobalamin.

Case report 2

- 45 year old lady
- Serum B12 > 1000 pg/ml on routine bloods
- No constitutional symptoms
- No significant PMH
- Heavy smoker (25-30 sigarettes daily)
- Drinks 20 Units of alcohol weekly
- Not on any regular medications

Investigations

- FBC unremarkable
- Biochemistry profile unremarkable
- Inflammatory markers negative
- Chest x-ray NAD
- US abdomen + pelvis NAD

Follow up at six months

- Patient still asymptomatic
- Physical examination unremarkable

Investigations

- FBC unchanged
- Biochemistry profile unremarkable
- Inflammatory markers negative
- Serum B12 normal

Discussion

- Should we perform a CT total body in every young patient with unexplained elevated vitamin B12?
- How long do we need to follow them up for?
- What information should we deliver to the patient?
- When should we check vitamin B12 levels?

Take home message

The clinical picture is the most important factor to consider in assessing the significance of vitamin B12 status.

We treat patients not numbers!!!

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Thank you