Problems with the diagnosis of Vitamin B_{12} deficiency

Vitamin B_{12} deficiency is a major problem. There is no consensus on how to diagnose the deficiency; the various tests are not perfect. The problem is increasingly common, particularly mild sub-clinical deficiency in the elderly.

The classical Pernicious Anaemia presentation of macrocytic anaemia, paraesthesia, abnormal gait and glossitis, is rare. Most patients have subtle clinical features or only laboratory abnormalities, making the diagnosis of true tissue deficiency difficult.

It is important to keep Vitamin B_{12} deficiency high on the differential list as irreversible neuro-psychiatric defects can occur without appropriate replacement therapy. A significant minority of patients will have no anaemia or macrocytosis but only present with neurological or psychiatric features.

SUSPECT B_{12} DEFICIENCY IN:

- Unexplained anaemia (usually macrocytic, but not always)
- Unexplained neurological or psychiatric features (eg reduced proprioception and paraesthesia) [even in absence of anaemia or macrocytosis]
- GI manifestations (sore tongue, anorexia, diarrhoea); gut surgery, IBD
- The elderly [quite common, subtle deficiency]
- Prolonged PPI, H2 blocker or metformin therapy

B_{12} Absorption:

- Average diet = 7 - 30 mcg/day
- Daily requirements = 1-5 mcg/day
- Body Stores = 2-3mg (4 years supply)

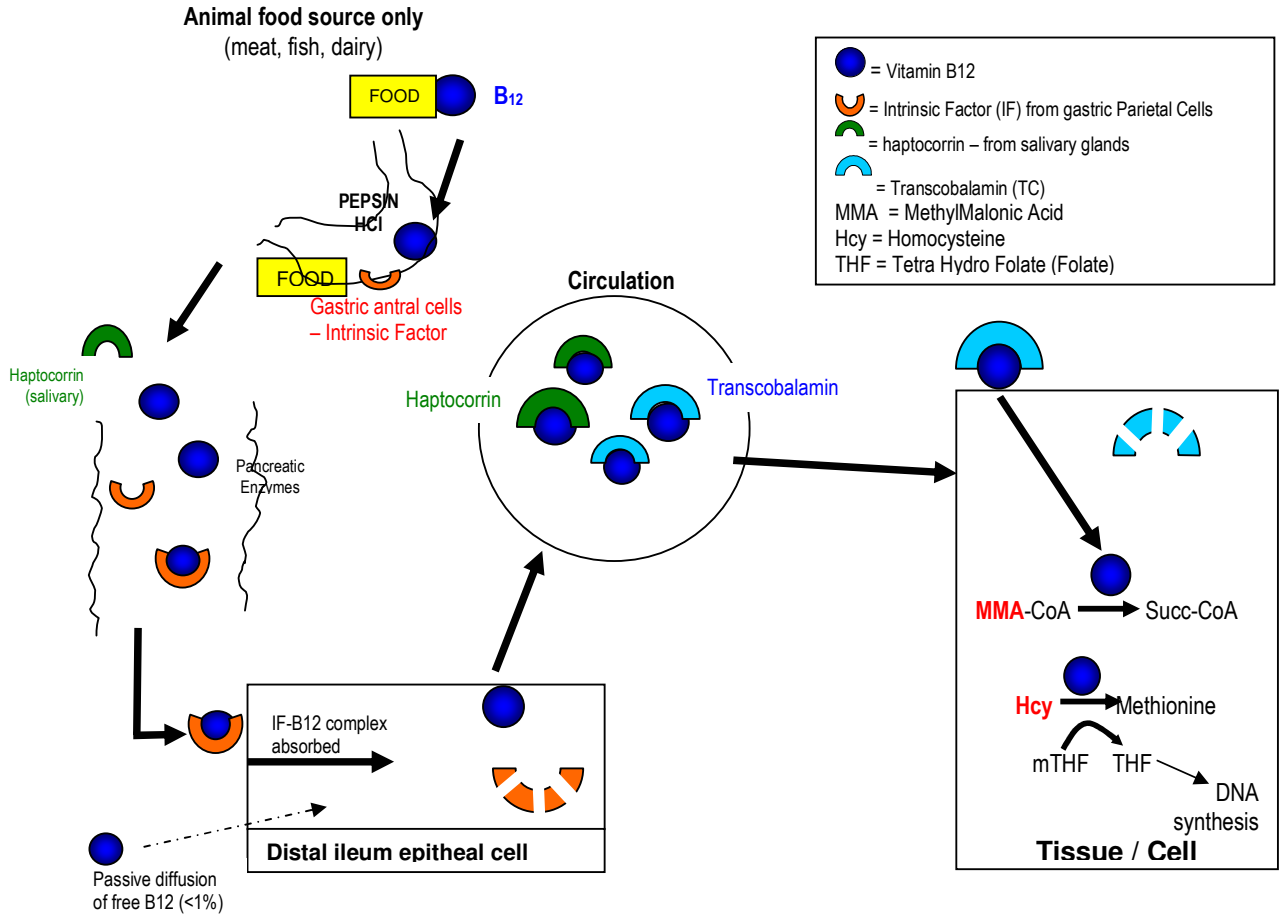
Causes of B_{12} Deficiency

1. Reduced intake:	Diet - vegan
2. Malabsorption	Intrinsic Factor (IF) deficiency = Pernicious Anaemia Ileal disease; gastric disease; parasites; pancreatic disease Food-B_{12} malabsorption (? reduced salivary haptocorrin) Achlorhydria – impairs extraction of B_{12} from food Drugs: PPI, H_2 antagonists or biguanides may impair B_{12} absorption
3. Increased Requirements	Pregnancy
4. Decreased Utilisation	Enzyme deficiency, N_2O

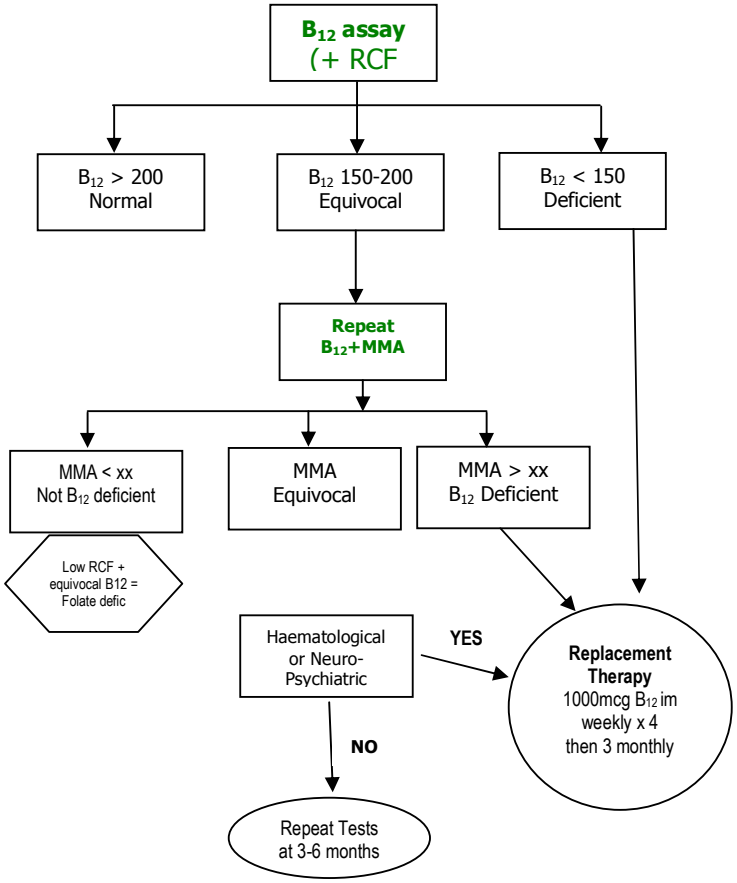
Lab Tests used to diagnose vitamin B_{12} deficiency

The challenge is to find a reliable test for true vitamin B_{12} deficiency. To date no single test is without flaws.

Test	Benefits	Problems
Vitamin B_{12} blood level	↓ in B_{12} deficiency cheap; easy test; widely available	Poor sensitivity & specificity False +ve if low HC False –ve if HC high (CML) Borderline levels in Folate deficiency
Methylmalonic Acid (MMA)	↑in B_{12} deficiency highly sensitive	Not easily accessible ? specificity False +ve in CRF
Homocysteine (Hcy)	↑in B_{12} deficiency highly sensitive	Low specificity (smoking, alcohol,…) False +ve in Folate & B_6 Defic, CRF
Holotranscobalamin (holoTC) TC with B12	↓in B_{12} deficiency ? high sensitivity	?? specificity not routinely available



Schema for diagnosing Vitamin B_{12} Deficiency



Determining the cause of vitamin B_{12} Deficiency

- **Clinical History** – any features of autoimmune disorders (thyroid, vitiligo, etc) associated with PA; gastric or ileal surgery; malabsorption
- **Drugs:** PPI, H_2 blockers, metformin
- **Intrinsic Factor Abs**: present in around 50% of PA and very specific [parietal cell Ab common in around 90% of PA but not specific]
- Schillings Test: Obsolete; not available [beef source of IF therefore potential for vJCD]
- The serum folate level will be high but red cell folate equivocal in B_{12} deficiency

Haematological Features

- Macrocytosis (high MCV often >120); oval macrocytes; red cell stippling;
- Low retics; ±nRBC
- Hypersegmented neutrophils (early); pancytopenia
- High LDH; High bili [ineffective erythropoiesis and degree of haemolysis]
- Hypercellular marrow; megaloblastic; giant metamyelocytes

Neurological Features

- **S**ub-**A**cute **C**ombined **D**egeneration (SACD) of the spinal cord. Leads to posterior and lateral column defect and peripheral sensory neuropathy. Paraesthesia in hands & feet; early loss of vibration and joint position sense; progressive spastic & ataxic weakness ± superimposed peripheral neuropathy leads to loss of reflexes.

Differential Diagnosis

Megalobastic Anaemia: B12 and/or folate deficiency
Abnormal B12/folate metabolism: congential enzyme deficiency, TCII defic, N_2O, DHF reductase inhibitors (Methotrexate, sulphas), chemotherapy (Thioguianine, Mercaptopurine, azathioprine, 5-flurouracil)
DNA synthesis defects: orotic aciduria, drugs (cytarabine, hydroxyurea), sideroblastic anaemia, erythroleukaemia, Leish-Nyhan
Macrocytic: alcohol, liver disease, myxoedema, reticulocytosis, cytotoxics, aplastic anaemia, pregnancy, MDS, myeloma

Therapy

- Vitamin B_{12} replacement
  - Vitamin B_{12} 1000mcg im weekly for 4 weeks; then 3 monthly for life
  - Oral therapy is adequate for vegans with no pathology
- Replacing B_{12} will lead to a huge increase in haemopoiesis and can lead to rapid depletion of folate and iron stores; this can then limit the expected recovery of Hb. Both iron and folate may be needed.

Note
Giving Folate to a B_{12} deficient person without B_{12} can lead to an irreversible exacerbation in neurological features.