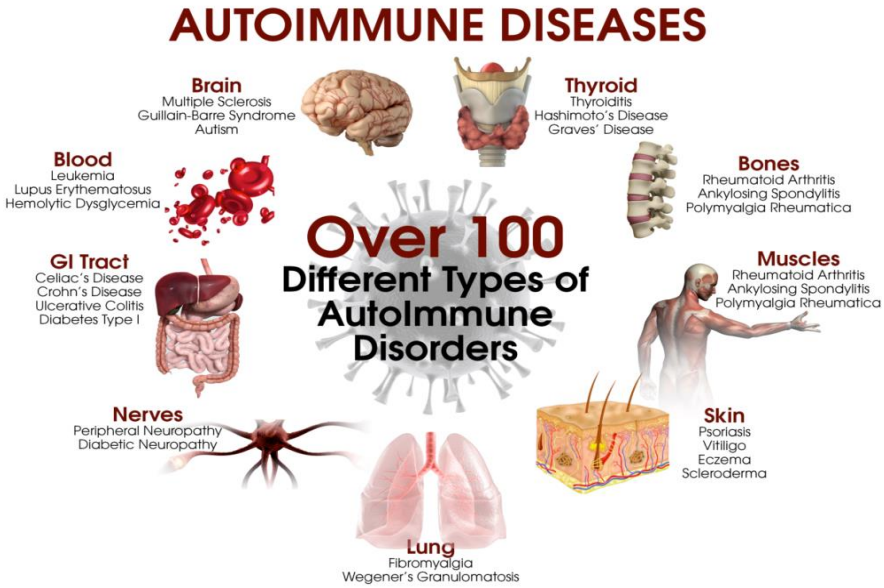
Part 3 : Autoimmune and other Conditions & B12



Autoimmune Conditions

- A disease in which **the body produces antibodies that attack its own tissues**, causing deterioration and in some cases the destruction of the tissue (Janeway, Travers, Walport & Shlomchik 2001).
- Individuals who have one autoimmune disease tend to develop other autoimmune diseases, when left undiagnosed or unchecked (Cojocaru, Cojocaru & Silosi 2010).

3

What's The Connection Between B12 & Autoimmunity?

B12 = DNA synthesis, RBC formation and neurological function

- An underlying B12 abnormality or long term deficiency may have an autoimmune atrophic effect at a tissue cellular level (Cavalcoli, Zilli, Conte & Massironi 2017).
- A co-factor approx 100 proteins, hormones and lipids.
- People with thyroid and adrenal issues may have low stomach acid (hydrochloric acid or HCl) necessary to break down protein.
- Achlorhydria (Achlorhydria 2018)
- Liver function tests may be disturbed in up to 50% of people with hypothyroidism, leading to reduced output of bile, which helps us digest lipids (Daher, Yazbeck, Jaoude & Abboud 2009).
- Notably, bile stones and gallstones are also more common in Hashimoto.

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TNF

- TNF - shorthand for tumor necrosis factor, a macrophage protein in your body that causes inflammation and/or febrile response and helps coordinate the process.
- Similar to IL-1 there is evidence that TNF will induce IL-1
  - Inflammation happens when your immune system - is fighting a possible threat.
  - Eg: Your sinuses swell when you catch a cold or get a cut, your finger turns warm and red
- However sometimes, inflammation IS NOT good for the body.
  - If you have a disease like Rheumatoid Arthritis your immune system may get confused and attack healthy tissue you have too much tumor necrosis factor - a type called TNF alpha.

"Tumor Necrosis Factor - an Overview | ScienceDirect Topics." Accessed May 4, 2018. https://www-sciencedirect-com.ezproxy.une.edu.au/topics/medicine-and-dentistry/tumor-necrosis-factor.

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Vitamin B12 Deficiency & TNF-A

- Vitamin B12 deficiency has been shown to be associated with elevated levels of tumor necrosis factor-alpha and decreased levels of epidermal growth factor in both rats and humans.
- This suggest a pathogenetic mechanism underlying the neuropathology of vitamin B12 deficiency.
- They may also explain the supposed relationships between vitamin B12 deficiency and certain disorders, including Alzheimer's disease, rheumatoid arthritis, and AIDS (Miller 2002).

6

Theoretical MOA's Linking B12 Deficiency With Autoimmunity... Food For Thought

Environmental factors (tobacco use), EBV, and CMV may trigger clinical autoimmune phenotypes in genetically susceptible patients (Lee 2017).

*We know that B12 deficiency has been associated with many autoimmune conditions, **SO...** could B12 deficiency influence the 'switching on' of genetic mutations associated with increased incidence of Multiple Autoimmune Syndrome (MAS) (3 or more concurrent autoiummune conditions in the one individual)????????*

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Theoretical MOA's Linking B12 Deficiency With Autoimmunity... Food For Thought

- Many autoimmune conditions share pathogenic features, inc. T-helper cell-mediated inflammatory reactions and the production of inflammatory cytokines, as well as relevant genetic susceptibilities (Lee 2017).
- *Given that decreased serum B12 concentrations have been associated with increased levels of pro-inflammatory cytokines in adults (Al-Daghri 2016).... B12 deficiency possibly influences the development of autoimmune contitions and MAS via the increased production/release of inflammatory cytokines (TNF-α, IL-23, IL-17, etc)*

FURTHER RESEARCH WARRANTED AND REQUIRED

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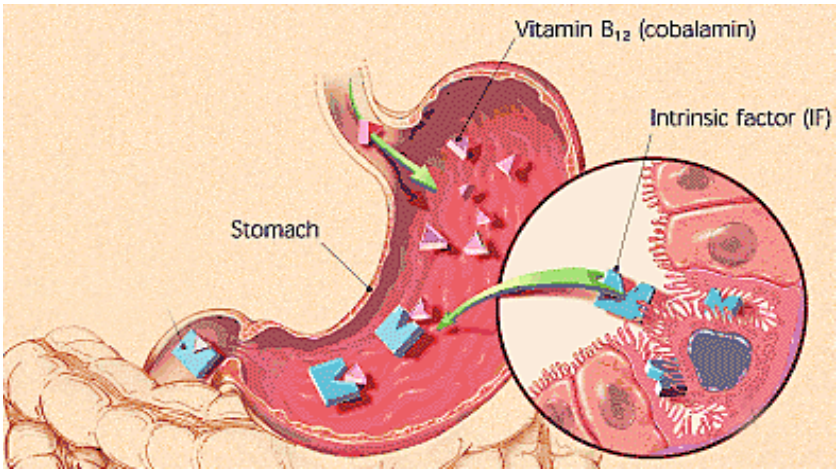
Autoimmune Diseases Impacted By B12

- Pernicious anaemia
- Autoimmune gastritis
- Coeliac disease
- Inflammatory bowel disease
  - Crohns; Ulcerative colitis
- Diabetes mellitus
- Diabetic neuropathy
- Hashimoto's thyroiditis
- Grave's disease
- Psoriatic arthritis
- Multiple Sclerosis
- Autism/Schizophrenia
- Lupus Erythematosus
- Peripheral Neuropathy
- RA
- Psoriasis
- Vitiligo
- Scleroderma
- Alopecia

B12 Autoimmune Deficiency



- ***This is the Autoimmune component of B12 deficiency***

Pernicious Anaemia

- Parietal Cells in the lining of the stomach secrete:
  - ***Intrinsic Factor (IF)*** a protein produced by parietal cells in the stomach essential for B12 absorption.
  - ***Hydrochloric Acid (HCL)*** allows B12 to be released from food.
- Parietal Cells may be negatively impacted by infection (*Helicobacter pylori*) or from ***Parietal Cell Antibodies*** that kill off the Parietal Cells.

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Pernicious Anaemia

- If a patient produces parietal cell antibodies these attack the parietal cells meaning they won't produce IF.
- The onset of the disease is slow and may span decades.
- Typically doesn't present before age 30.
- Estimated to be present in approximately 2% of individuals over 60.
- Vitamin B12 deficiency that results from impaired uptake of vitamin B12 due to the lack of a substance known as intrinsic factor (IF) produced by the stomach lining.

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Pernicious Anaemia (PA)

- May lead to neurological complications as nerve cells and blood cells require B12 for healthy function.
- If bodily B12 stores are adequate prior to the onset of PA, it may take years for deficiency symptoms to develop.
- Treatment generally requires B12 injections, bypassing the intestinal absorption route. Repeated injections are necessary because of the inability to metabolise B12
  - Most common co-existing autoimmune disease with PA is Hashimoto's Thyroiditis - Gastrin function?(Boelart2010)

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Autoimmune Gastritis

- A chronic inflammatory disease with destruction of the parietal cells of the stomach.
- Causes vitamin B12 deficiency (+ iron and folate) and if untreated progresses to pernicious anaemia.
- Management in the early stages aims to prevent B12, folate and iron deficiencies
- Management in later stages when pernicious anaemia is present aims to replenish B12 reserves via initial B12 injections, followed by life-long maintenance with oral B12 supplements (and oral iron supplementation) (Neumann 2013)

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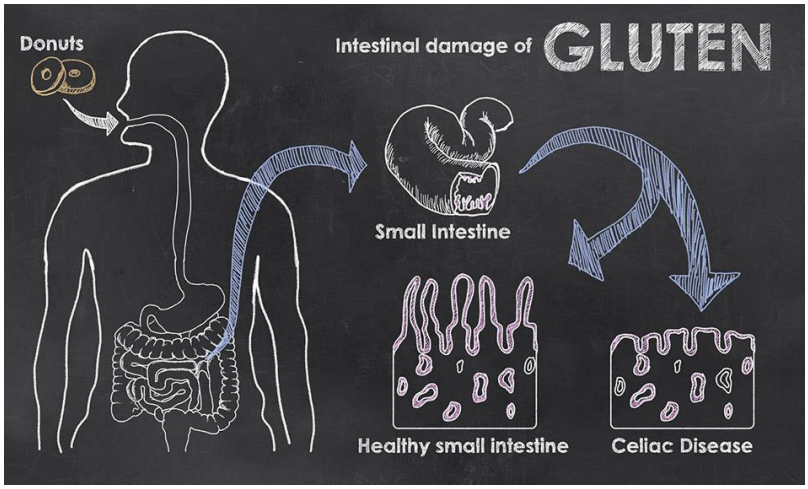
Coeliac Disease (CD)



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Coeliac disease is the 'great imitator'

Sherwan (2009) refers to Coeliac disease as an endocrine cousin:

- It causes as much fatigue as hypothyroidism
- It causes menstrual irregularities likely via nutritional deficiencies
- It causes miscarriages
- Psychiatric problems such as anxiety and depression
- Poor memory and concentration via vitamin B12 deficiency or insufficiency. (Jones 2009, fernandez 2001)

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Coeliac Disease (CD)

- In a 2001 prospective study of 39 biopsy-proven coeliac disease patients, 41% were B12 deficient as defined in the study as <162pmol/L (Dahele 2001)
- Nutrient deficiencies including B12 in CD and non-coeliac gluten sensitivity has a significant impact on fertility and pre-conception care.
- CD should be considered in the pre-conception screening of patients with reproductive disorders

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Inflammatory Bowel Disease

- Crohn's Disease (CD) may affect any segment of the gastrointestinal tract
- Patients with CD often present with isolated ileal disease or ileocolonic disease.
- Ileal disease or resection may cause Cbl malabsorption, so patients with CD are assumed to be at greater risk for deficiency (Battat 2014, 2017)

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Inflammatory Bowel Disease

- Other mechanisms for Cbl deficiency in CD include
  - Fistulas
  - SIBO
  - Reduced intake
  - Increased physiologic requirements
  - Protein losing enteropathy and hepatic dysfunction
  - One case study identified gastric CD causing Cbl deficiency, mimicking autoimmune gastritis and subsequent pernicious anemia (Battat 2014)

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Diabetes

Biochemical and clinical B12 deficiency has been demonstrated as highly prevalent among patients with type T1DM & T2DM.

Clinical manifestations range from:

- Impaired memory
- Dementia
- DeliriumPeripheral neuropathy
- Sub-acute combined degeneration of the spinal cord, megaloblastic anemia and pancytopenia

(Gupta 2018, Ahmed 2016, Wang 2017)

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Diabetes

- Metformin used to treat T2DM inhibits the calcium dependent absorption of Vitamin B12-IF complex (Kibirige 2013)
- Primary Autoimmune Hypothyroidism and Coeliac disease are frequent co-morbidities in T1DM and directly effect B12 metabolism.(Krzewska 2016)
- B12 deficiency, Hyperhomocysteinemia and/or elevated MMA cause distinct sensory polyneuropathy which mimics diabetic neuropathy (Kibirige 2013)

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Diabetic Neuropathy

- Diabetic neuropathy is nerve damage that is caused by diabetes. Over time, high blood glucose levels, also called blood sugar, and high levels of fats, such as triglycerides, in the blood from diabetes can damage your nerves. Symptoms depend on which type of diabetic neuropathy you have.
- Peripheral neuropathy is a type of nerve damage that typically affects the feet and legs and sometimes affects the hands and arms. This type of neuropathy is very common. About one-third to one-half of people with diabetes have peripheral neuropathy.

https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/nerve-damage-diabetic-neuropathies

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AITD/Hashimoto's Thyroiditis

- Believed to be the most common cause of primary hypothyroidism.
- Painless thyroid enlargement and symptoms of hypothyroidism.
  - Diagnosis includes high thyroperoxidase antibodies (TPOAb) and less commonly antithyroglobulin antibodies
- Hashimoto's thyroiditis is autoimmune inflammation of the thyroid.
  - T4 and TSH levels initially are normal, but later T4 declines and TSH rises, and patients become clinically hypothyroid.
  - Lifelong thyroid hormone replacement is typically needed

(MSD Manual 2018)

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Primary Hypothyroidism – Hashimoto's Thyroiditis

- Patients with Autoimmune Thyroid disease (AITD) have a **higher prevalence of pernicious anemia and B12 deficiency** compared with the general population.
- *Clinical signs of B12 deficiency may be subtle and missed, particularly in patients with known autoimmune disease.*
- The evaluation of B12 deficiency can be simplified by measuring fasting serum gastrin and, if elevated, referring the patient for gastroscopy
- (Ness-Abramof 2006).

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Primary Hypothyroidism – Hashimoto's Thyroiditis

- Serum B12 levels measured in 115 AITD patients
- In patients with serum B12 ≤133 pmol/L
  - Fasting serum gastrin and parietal cell antibodies (PCA) were measured.
- 32 patients (28%) had low B12 (≤133 pmol/L)
  - Fasting serum gastrin was measured in 26 and was higher than normal in 8 patients.
  - PCA were measured in 27 - 8 were positive (Ness-Abramof et al 2006)

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Graves Disease

- A complex patient with a hx of Graves' disease presented with pancytopenia (decreased levels of RBC, WBC & platelets), initially suspected of being due to aplastic anaemia.
- After presenting with progressive neurological symptoms, he was reassessed and evaluated for B12 deficiency
- He was diagnosed with B12 deficiency as a result of pernicious anaemia (PA).
- Failure to recognise PA as a cause of pancytopenia resulted in delayed treatment causing neurological complications.
- Treatment with B12 resolved the issue (Loh 2013, Burns 1996)

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Alopecia areata

- *Alopecia areata* frequently occurs in association with other autoimmune disorders such as:
  - Vitiligo, Lichen planus, Atopic dermatitis, Hashimoto's thyroiditis, Hypothyroidism. Addison's disease. ***Pernicious anemia***, Lupus erythematosus, Diabetes mellitus
- One of the main systemic associations of autoimmune disease is with thyroid abnormalities

(Lewinski, Broniarczyk-Dyla, Sewerynek, Zerek-Melen, & Szkudlinski, 1990, Ramsay & Rushton, 1990)

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Alopecia areata

- There is evidence of a correlation between pernicious anaemia, and *alopecia areata universalis*
- A 27-year-old male, who had developed diabetes mellitus type 1 (DMT1) since the age of eighteen and *alopecia areata universalis* nine months
- Presented with general fatigue and shortness of breath
- A Schilling test was indicative of pernicious anemia
- Antigastric parietal cell (AGPA) and anti-intrinsic factor antibodies were positive, confirming diagnosis of pernicious anemia. (Tzellos 2009)

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Psoriasis

- Homocysteine (Hcy), a sulfur-containing amino acid, is associated with autoimmunity, inflammation, CVD, methylation issues and so on.
- Patients with psoriasis had plasma homocysteine levels higher than controls
- Folic acid levels were lower in patients with psoriasis compared with controls (Malerba 2006)
- Plasma homocysteine levels in patients with psoriasis correlated directly with disease severity (PASI) and inversely with folic acid levels.
- Serum folate levels were inversely correlated with the PASI. No abnormalities of serum vitamin B6 and B12 were found.
- Patients with psoriasis may have a tendency to hyper-homocysteinaemia, which may predispose to higher cardiovascular risk (Malerba 2006).

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Multiple Sclerosis

- Vitamin B12, plays important structural and functional roles in nervous system function and deficiency leads to demyelination, followed by axonal degeneration and eventually irreversible damage due to axonal death.
- B12 deficiency causes some clinical and pathological characteristics similar to that of MS patients, potentiating misdiagnosis.
- The relation between MS and B12 deficiency is unclear at present in the clinical literature, yet could be the result of overlapping autoimmune disorders or maybe reflects increased B12 demand for myelin repair?

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Multiple Sclerosis

- However, if MS patients have decreased B12 levels, irrespective of the cause, treatment is easy and important to prevent permanent disability.
- There are anecdotal reports of MS improving with B12 supplementation, however this form of evidence has limited reliability.

(Al-Khamis, 2016, Miller, Korem, Almog, & Galboiz, 2005)

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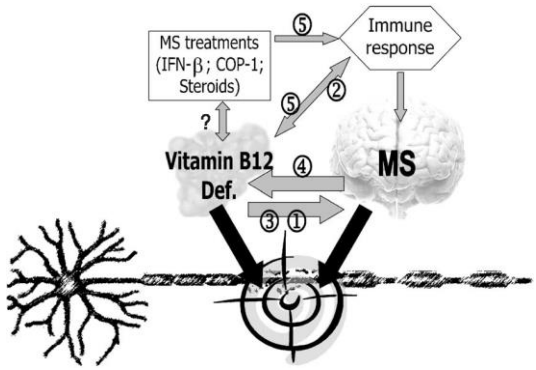
Blood Chemistry in MS

↓ Serum vitamin B12 (and/or Folate)
↑ Hcy
↓ Hb
↓ Hct levels
↓ MCV (concurrent iron deficiency?)
Oligoclonal band presence
Immunoglobulin G (IgG)
↓ Vitamin D
↓ B6?



(Miller, Korem, Almog, & Galboiz, 2005)

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Case Study 38 year old woman

- Progressive weakness of lower limbs, burning and tingling and numbness of feet and hand that started approx. 1 year ago.
- For 2-3 weeks pre-admission she had a feeling of "heavy legs" and gait disturbances.
- Hx thyroid goitre.
- No memory disturbances, depression or other neuropsychiatric problems.
- Macrocytic anaemia (↓ RCC; ↑ MCV 103fL (normal 80-100). TSH and thyroid hormones within normal limits, ANA not present)

(Kurkowska et al 2006)

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Case Study 38 year old woman

- Oligoclonal bands were positive – MS diagnosed put on methylprednisolone after not responding.
  - Level of B12 then assessed **extremely low at 7.38pmol/L** (normal 148–664 pmol/L).
- After administration of B12 daily for 14 days followed by weekly and then monthly, patient gradually improved and besides slight gait disturbances, became asymptomatic within 6 months.
- Neurologic status remained stable during further observation (12 years).

(Kurkowska et al 2006)

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Case Study 32 year old woman

- Presented with dizziness, gait disturbances and depression, of increasing severity over approx. 6 months.
- Hx spontaneous abortion and uterine myomas surgery.
- Treated for anaemia several times without further evaluation.
- Eventually admitted to a neurological department with dizziness, weakness of legs, urinary urgency and Lhermitte's sign (electric shock-like sensation on flexion of the neck) which lasted several days.
- Found to have Anaemia (↓ RCC), negative boreliosis serology, and MRI showed lesions. (Kurkowska 2006)

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Case Study 32 year old woman

- B12 levels were never tested.
- Diagnosed with MS put on methylprednisolone & B12 intramuscularly with iron supplementation
- Subsequent improvement for two years, patient then ceased B12 supplementation – two week later neurological symptoms appeared
- Vitamin B12 was measured at 62.7pmol/Lml
- One month after B12 administration symptoms started to improve >six months no impairment
- No further deterioration seen >5 years. (Kurkowska 2006)

Kurkowska-Jastrzębska, Iwona, W Wicha, and A Członkowska. "Vitamin B12 Deficiency Can Mimic Multiple Sclerosis - Report of Two Cases." *Case Reports and Clinical Practice Review* 7 (March 31, 2006): 64–68.

46

Autism/Schizophrenia

- A study of more than 2,700 mothers of children with autism shows that about one in 10 mothers have antibodies in their bloodstream that react with proteins in the brain of their babies.
- This indicates that while the blood-brain barrier in the adult women prevents them from being harmed by the antibodies, that same filter in the fetuses is not well-developed enough
- Allowing the "anti-brain" antibodies to pass through to the babies' brains, possibly causing autism by Auto-Immune mediation

(Brimberg 2013, Diamond 2013)

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Autism/Schizophrenia

- Researchers found children under age 10 with autism had brain B12 levels 3 times lower than other children of the same age have – about the same levels considered normal in healthy adults in their 50s. The findings indicate a premature decline in the vitamin.
- There is no definitive research proving a link between autism, schizophrenia, and B12 deficiency, however studies suggest links between vitamin and nutrient deficiencies, depression, and memory loss.
- Both neurological conditions are associated with oxidative stress, which plays a significant role in aging.
- Researchers believe oxidative stress may be the underlying cause of decreased B12 levels in the brain (Zhang et al, 2016)

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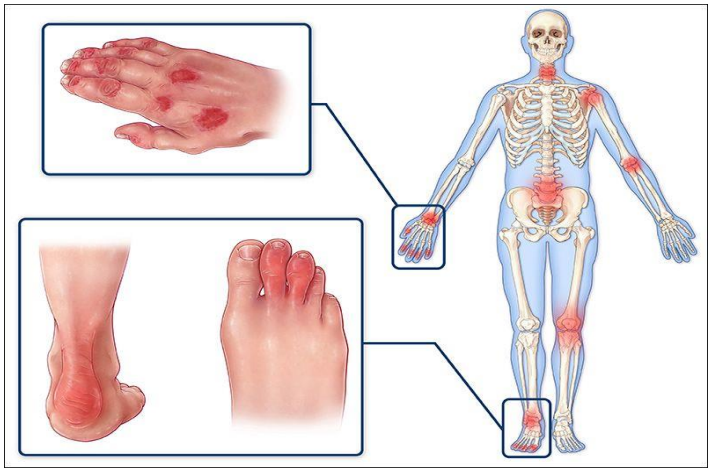
Psoriatic Arthritis



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Lupus Erythematosus

- Lupus is an autoimmune disease, and the antibodies produced by the immune system in lupus cause inflammation, tissue damage and pain.
- **Estimated to affect more than 20,000 people in Australia and New Zealand**
- characterised by flare ups and periods of improvement (remissions), and can can affect almost any organ or system of the body.
- In most people only the skin and joints are affected. However, in some people SLE can also affect the kidneys, lungs, heart, blood vessels and/or brain.(www.allergy.org.au)

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Rheumatoid Arthritis

- Rheumatoid arthritis (RA) is an autoimmune disease that causes pain and swelling in the joints. This happens because the immune system attacks the lining of the joints causing inflammation and joint damage.
- RA usually affects the smaller joints, such as those in the hands, feet and wrists, although larger joints such as the hips and knees can also be affected.

https://www.healthdirect.gov.au/rheumatoid-arthritis

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Psoriatic arthritis/RA/SLE

- **A**nemia is frequent in inflammatory rheumatic diseases.
- A 2004 study analyzed the incidence and nature of B12 and folic acid (FA) in 276 rheumatic patients presenting with
  - rheumatoid arthritis (RA)
  - psoriatic arthritis (PsA)
  - systemic lupus erythematosus (SLE).
- Levels of B12, FA, and parameters of anemia were recovered or examined in 276 outpatients.
- In those with recent findings of low serum B12 levels further investigations were undertaken(Segal 2004)

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- Further studies of serum homocysteine (Hcy) and urine methylmalonic acid (MMA) levels were performed (Segal 2004).
- Anemia was high: 49%, 46%, and 35%, in RA, SLE, and PsA
- Low serum B12 were also frequent (24%), with almost similar occurrence in the three disease groups
- In the 15 patients with recently detected low B12 levels, Hcy and MMA were evaluated before and following B12 therapy
- 10 had high baseline Hcy levels, while MMA was increased in one patient only.

- **CONCLUSIONS:** The incidences of anemia and decreased serum B12 levels were high in these three groups of rheumatic patients (Segal 2004)

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OTHER CONDITIONS ASSOCIATED WITH B12 DEFICIENCY

- Cognitive decline, Dementia & Alzheimer's disease
- Infertility
- Altered/delayed brain development in children
- Depression
- Cardiovascular disease
- Osteoporosis
- Medicinal & Recreational Nitrous oxide exposure

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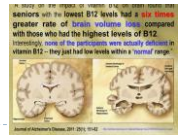
Cognitive Decline, Dementia & Alzheimer's Disease



Objectives: To investigate the relationship between markers of vitamin B12 status and brain volume loss per year over a 5-year period in an elderly population.

Methods: A prospective study of 107 community-dwelling volunteers aged 61 to 87 years without cognitive impairment at enrollment. Volunteers were assessed yearly by clinical examination, MRI scans, and cognitive tests. Blood was collected at baseline for measurement of plasma vitamin B12, transcobalamin (TC), holotranscobalamin (holoTC), methylmalonic acid (MMA), total homocysteine (tHcy), and serum folate.

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Cognitive Decline, Dementia & Alzheimer's Disease

Results: The decrease in brain volume was greater among those with lower vitamin B12 and holoTC levels and higher plasma tHcy and MMA levels at baseline. (Vogiatzoglou et al 2008)

- B12 deficiency is particularly common in the elderly and has been associated with Alzheimer's disease.
- One study found lower B12 levels in the cerebrospinal fluid of patients with Alzheimer's disease than in patients with other types of dementia
- Though blood levels of vitamin B12 did not differ (Nourhashemi 2000)

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Cognitive Decline, Dementia & Alzheimer's Disease

- The mechanism for the association of low vitamin B12 status and Alzheimer's disease is unclear.
- B12 deficiency, like folate deficiency, may lead to decreased synthesis of methionine and S-adenosylmethionine (SAMe), adversely affecting methylation reactions essential for the metabolism of myelin sheath components, as well as for synthesis of neurotransmitters

(Scalabrino 2009)

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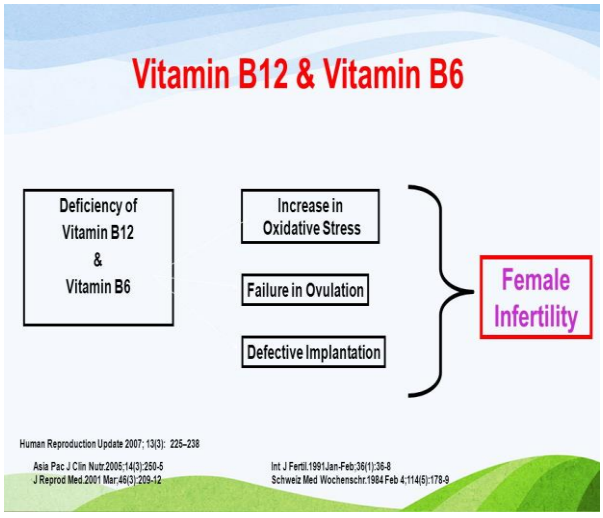
Infertility



Bennett, M. "Vitamin B12 Deficiency, Infertility and Recurrent Fetal Loss." *The Journal of Reproductive Medicine* 46, no. 3 (March 2001): 209–12.

58

Infertility

- A 2001 study examined the relationship of infertility & recurrent foetal loss in B12 deficient patients.
- The obstetric histories of 14 patients with Hx of vitamin B12 deficiency were analysed. Infertility (two to eight years) had been present in four episodes, and recurrent foetal loss was a feature in eleven.
- Hypercoagulability due to raised Hcy levels may lead to foetal loss when vitamin B12 deficiency first develops
- A more prolonged deficiency results in infertility by causing changes in ovulation or development of the ovum or changes leading to defective implantation (Chavarro 2008, Bennett 2001)

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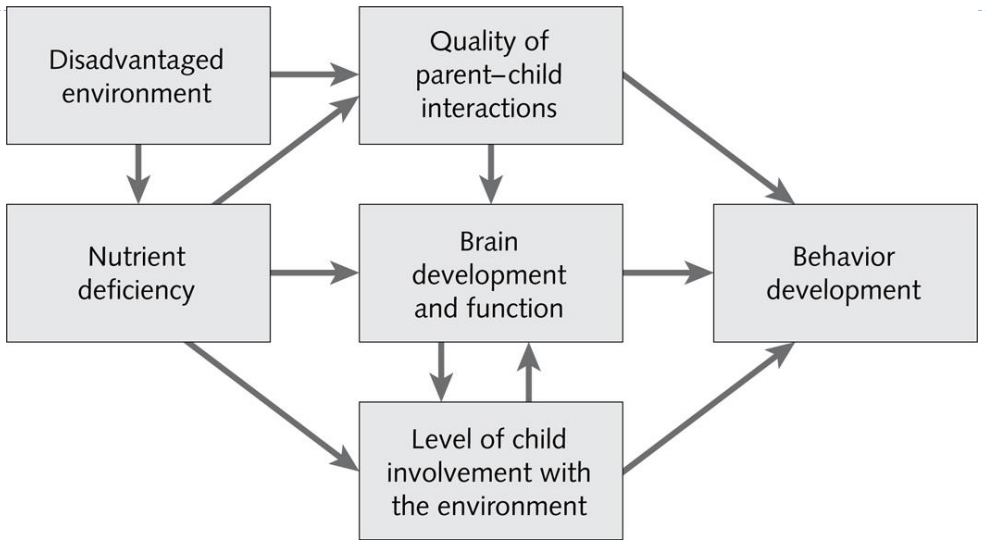
B_{12} and folate deficiency on brain development in children



60

Black, Maureen M. "Effects of Vitamin B12 and Folate Deficiency on Brain Development in Children." *Food and Nutrition Bulletin* 29, no. 2 Suppl (June 2008): S126–31

Brain Development in Children

- Brain growth is very rapid during the first 2 years of life, particularly in the cortex, which is associated with higher-order thinking.
- In addition, myelination of the brain, which is concentrated from mid-gestation through the second year of life, but continues through puberty, may be vulnerable to vitamin B_{12}deficiency.
- In infants, vitamin B_{12} deficiency has been associated with demyelination and brain atrophy (Black 2008)

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Black, Maureen M. "Effects of Vitamin B12 and Folate Deficiency on Brain Development in Children." *Food and Nutrition Bulletin* 29, no. 2 Suppl (June 2008): S126–31

Learning & B12

- The signs and symptoms of pediatric B_{12} deficiency frequently mimic those of autism spectrum disorders.
- Both autistic and brain-injured B_{12}- deficient children have obsessive-compulsive behaviors and difficulty with speech, language, writing, and comprehension. B_{12} deficiency can also cause aloofness and withdrawal.
- Few children presenting with autistic symptoms receive adequate testing for B_{12} deficiency.
- Infants and young children are often misdiagnosed.
- Irritability or gastric symptoms of B_{12} deficiency can be easily mistaken for colic or gastroenteritis.

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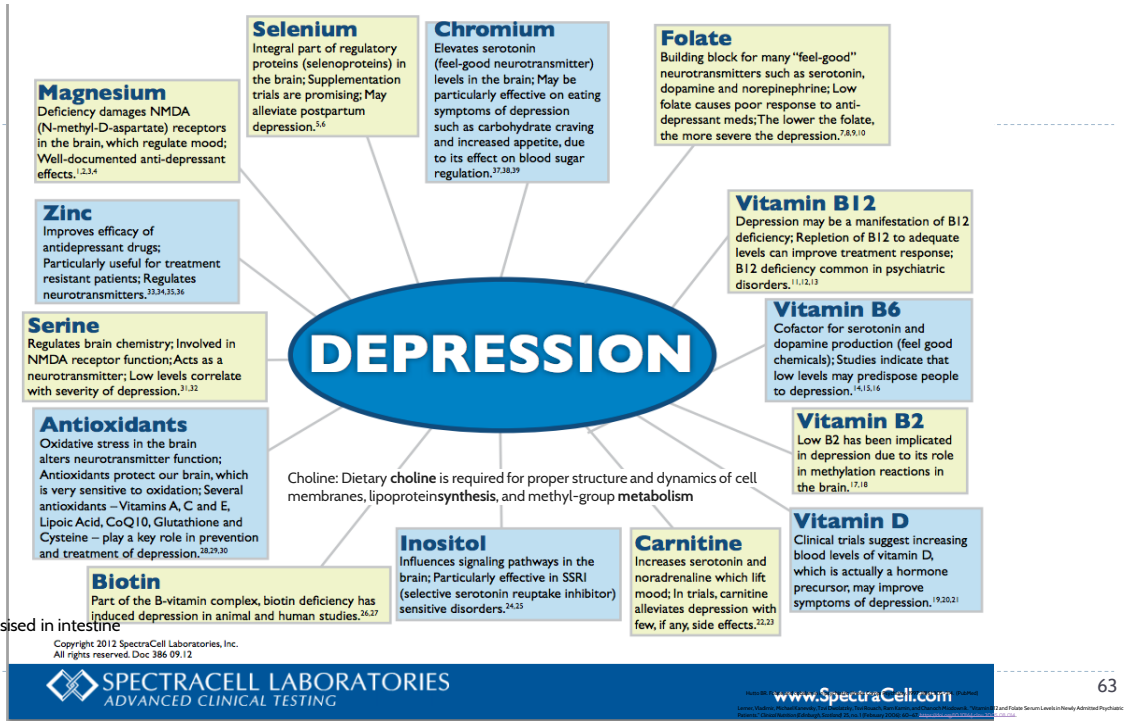

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Depression & B12

- Observational studies have found as many as 30% of patients hospitalized for depression are deficient in vitamin B_{12} (Hutto 1997)
- A cross-sectional study of 700 community-living, physically disabled women over the age of 65 found that vitamin B_{12}-deficient women were twice as likely to be severely depressed as non-deficient women (Penninx 2000) (62).
- A population-based study in 3,884 elderly men and women with depressive disorders found that those with vitamin B_{12} deficiency were almost 70% more likely to experience depression than those with normal vitamin B_{12} (Tiemeier 2002)

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Depression and B12

- The association of vitamin B(12) and folate with depressive disorders may have different underlying mechanisms.
- Proposed mechanicsms involve
  - Methyl Group Donor metabolism ie. <SAM - neurotransmitters (Mischoulon 2002)
  - DNA methylation in the brain (Fernandez-Rog 2012)
- SAM supplementation may improve symptoms in some individuals (Bressa 1994)
- Increased homocysteine level is another nonspecific biomarker of vitamin B_{12} deficiency that has been linked to depressive symptoms in the elderly, Supplementation may be helpful in the long term management in special populations (Almeida 2008, 2015)

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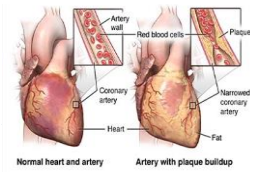
Cardiovascular Disease (CVD)



- Even moderately elevated levels of homocysteine in the blood raise the risk of CVD (Gerhard 1999, BMJ 1998) The mechanism is still not understood
- Homocysteine in the blood is regulated by at least three vitamins: folate, vitamin B6 and vitamin /b12 Folic acid supplementation (0.5-5 mg/day) had the greatest lowering effect on blood homocysteine levels (25% decrease) (BMJ 1998)
- Co-supplementation with folic acid and vitamin B12 (500 µg/day) provided an additional 7% reduction (32% decrease) in blood homocysteine concentrations (Quinlivan 2002, Stabler 1997)

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Cardiovasular Disease (CVD)

- The results of a sequential supplementation trial in 53 men and women indicated that after folic acid supplementation, vitamin B_{12} became the major determinant of plasma homocysteine levels
- Elevation of homocysteine levels may be partly due to vitamin B12 deficiency in individuals over 60 years of age (Quinlivan 2002)
- Two studies found blood methylmalonic acid (MMA) levels to be elevated in more than 60% of elderly individuals with elevated homocysteine levels. (Stabler 1997)

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Osteoporosis

- B12 is a determinant of homocysteine metabolism
- Risk of osteoporotic fractures in elderly might be enhanced by B12 deficiency.
- High homocysteine levels may affect bone re-modelling by increasing bone resorption (breakdown), decreasing bone formation, and reducing bone blood flow.
- Another proposed mechanism involves the binding of homocysteine to the collagenous matrix of bone, which may modify collagen properties and reduce bone strength. (Vacek 2013)

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Osteoporosis

- Since vitamin B12 is a determinant of homocysteine metabolism, it was suggested that the risk of osteoporotic fractures in older subjects might be enhanced by vitamin B12 deficiency.
- A meta-analysis of four observational studies n7,475 older individuals p=3 to 16 years, found a weak association between an elevation in vitamin B12 of 50pmo/L in blood and a reduction in fracture risk (Wijngaarden 2013)
- RCS placebo-controlled two-year study n559 with low serum folate and B12 at increased risk of fracture received 5mg daily of folic and 1.5mg daily
- B12 - supplementation improved B-vitamin status, decreased homocysteine concentrations, and reduced risk of total fractures compared to placebo (Sata 2005)

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Recreational Drug Use - Nitrous Oxide

- Nitrous oxide is often used as a recreational drug.
- Prolonged use of nitrous oxide can have disabling neurological sequelae due to functional inactivation of vitamin B12.
- Two individuals received nitrous oxide as a consequence of repeated hospital attendance and the third via 'Whippit' canisters used in cream dispensers
- Two developed sensorimotor peripheral neuropathy with demyelinating features with no clinical or imaging evidence of myelopathy, emphasising that not all patients develop subacute combined degeneration of the spinal cord (the typical presentation of functional vitamin B12 deficiency) (Cabo et al., 2015)

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Elevated B12

- The underlying pathogenesis leading to high Cbl levels is poorly elucidated
- It is not thought to involve increased Cbl intake because intestinal absorption capacity is saturable and high physiological consumption does not increase plasma Cbl levels substantially.
- Only Cbl therapy in the form of injections or extremely high oral doses can produce high circulating levels, and in a large cohort study >23,000 patients treated with Cbl were excluded (Arendt 2013)

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Elevated B12

- Cancer patients with elevated Cbl levels had higher mortality than those with normal Cbl levels. These findings may have clinical significance for assessing the prognosis of cancer patients.
- Mechanisms resulting in high Cbl levels may be related to malignant pathogenesis.
- Studies showed that levels of the circulating Cbl binding protein haptocorrin were high in patients with high plasma Cbl levels

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Elevated B12

- Cancer was associated with high Cbl and high haptocorrin levels. Haptocorrin is a protein is elevated in patients with some cancer types it has been suggested as a marker for disease progression
- Haptocorrin may be a candidate factor to include in future studies of the possible pathogenic mechanisms leading to high Cbl levels in cancer patients
- Elevated B12 may be associated with serious causations including solid neoplasms, haematological malignancies & liver disease. These need to be ruled out.

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Elevated B12?

- **High B12 may reflect a functional deficit via these proposed mechanisms:**
  - **Decreased ability to attach to TCB11**, decreasing B12 delivery to the cells, meaning that B12 levels remain higher in the blood.
  - **Inefficient hepatic up-take of B12 from the serum**, meaning that B12 levels remain higher in the blood.
  - **Excessive hepatic release of B12** (*think post viral/liver damage?), meaning that B12 levels are elevated in the blood.
  - **Decreased hepatic synthesis of TCB11** which is essential for the binding of B12 for delivery to the tissues.
    - *TCB11 delivers B12 to the tissues*
    - *TCB1 Binds to 80% of B12 rendering it unavailable for binding to TCB11*

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Polycythemia

- Polycythemia is a condition that results in an increased level of circulating RBC in the bloodstream. People with polycythemia have an increase in Hct, Hb or RCC above the normal limits.
- Polycythemia is normally reported in terms of increased Hct or Hb concentration
- Hematocrit (Hct): Polycythemia is considered when the hematocrit is greater than 48% in women and 52% in men.

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Polycythaemia

- Hemoglobin (Hb): Polycythemia is considered when a hemoglobin level of greater than 16.5g/dL in women or hemoglobin level greater than 18.5 g/dL in men.
- Polycythaemia can be divided into two categories:
  - primary and secondary.
- Primary polycythaemia:
  - the increase in red blood cells is due to inherent problems in the process of red blood cell production.
- Secondary polycythaemia:
  - generally occurs as a response to other factors or underlying conditions that promote red blood cell production.

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Idiopathic Thrombocytopenic purpura

- Studies have found the simultaneous presence of chronic idiopathic thrombocytopenic purpura (ITP) and pernicious anaemia (PA)
- Serum pepsinogen I was low in 20.3% of the 133 patients studied.
- Gastrin was elevated in 15. 2% of patients, but the coexistence of both abnormalities was rather low (7.6% of patients).
- Progressive decrease in serum cobalamin as biochemical abnormalities related with atrophic gastritis appeared was noticeable.
- The time to progression to frank PA from type A atrophic gastritis may span some years.

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Complement

- **Complement** is a **system** of plasma proteins that can be activated directly by pathogens or indirectly by pathogen-bound antibody, leading to a cascade of reactions that occurs on the surface of pathogens and generates active components with various effector functions.
- It enhances (**complements**) the ability of antibodies and phagocytic cells to clear microbes and damaged cells from an organism, promotes inflammation, and attacks the pathogen's cell membrane. The cascade ends with the formation of the membrane attack complex (MAC).
  - Formed by the complement proteins C1 through C10.
  - Adaptive immune system

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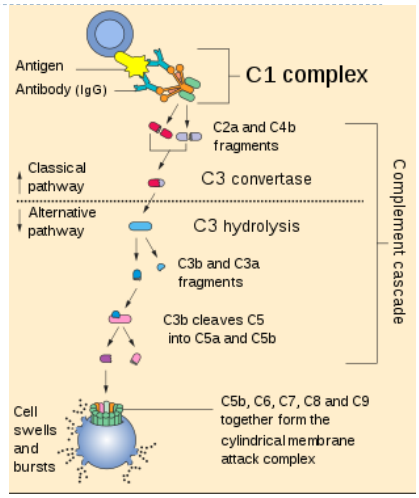
Complement C3 and C4

- C3 is the most abundant of the 11 complement proteins. It is also among the best studied
- C4 is the most second-most abundant of the 11 complement proteins (after C3). It is also among the best studied.
- Levels of C3/C4 are known to increase during inflammation and tissue destruction, and decrease during autoimmune disorders



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C3/C4 levels

A high value (greater than 45 mg/dL) for the test may indicate:

- Acute rheumatic fever
- Infection
- Cancer

A low value (less than 15 mg/dL) for the test may indicate:

- Systemic lupus erythematosus (SLE)
- Acute post-streptococcal glomerulonephritis
- Cirrhosis
- Multiple sclerosis
- Anemia
- Bacterial endocarditis
- Glomerulonephritis
- Septicemia

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Reversible C3 hypocomplementaemia

- Serum C3 and C4 levels have been determined in patients with Addisonian pernicious anaemia (PA) and megaloblastic anaemia due to vitamin B12 deficiency from other causes
  - C3 levels are significantly reduced in vitamin B12 deficiency and return to normal on treatment
  - These observations suggest that the observed C3 hypocomplementaemia is not a consequence of immune mechanisms, but may be due to altered synthesis of C3 complement component.

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Case Studies

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Alopecia

Severe Alopecia >3 years
Thyroid Autoantibodies
- Thyroid peroxidase Ab H 137.6 (<5.6
- Thyroglobulin Ab normal
  - (comment hashimotos likely)
  - Biochemistry normal
- Albumin H48 (36-47)
- Globulin L21 (23-39)
- No abnormalities in Haemoglobin bloods
- Neutrophils L 1.98 (2.0-7.5)
- B12 373
- Red Blood Cell Folate 2309 (776-1784)
- (But normal Serum Folate

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Psoriasis

> Five years
Diagnosised Beta Thalassemia (Minor)
- ❑ B12 levels normal
- ❑ Folate high
- ❑ Treat with Methyl Folate internally
- ❑ Topically B12 lotion
- ❑ Severe psoriasis on feet & hands
- ❑ Chef
- ❑ Feet resolved with 6 months with 1 Folate supplement daily
- ❑ Energy improved, less fatigue

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Auto-Immune Urtica (Hives)

- **Autoimmune** Urticaria (Hives) Mast cells are the cells in the skin and mucous membranes that contain **histamine**
- **Release** of **histamine** causes the allergic symptoms of hives and angioedema (swelling of large areas of the body)
- Antibodies that react with body tissues are felt to contribute to joint swelling and pain