Anaemias

Anaemia is a decrease in number of red blood cells or less than the normal quantity of hemoglobin in the blood. Anaemia may also be diagnosed where there is decreased oxygen-binding ability of each hemoglobin molecule due to deformity or lack in numerical development as in some other types of hemoglobin deficiency.

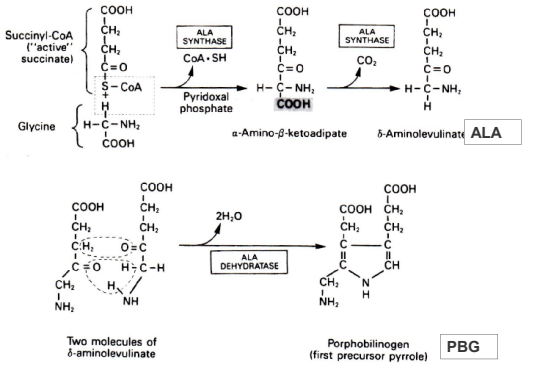
1. Red cell aplasia
2. Aplastic anaemia
3. Microcytic anaemia – Iron deficiency
4. Macrocytic anaemia's –
Vitamin B12
Folic acid
5. Hemolytic anaemia
6. Blood loss
7. Fluid overload

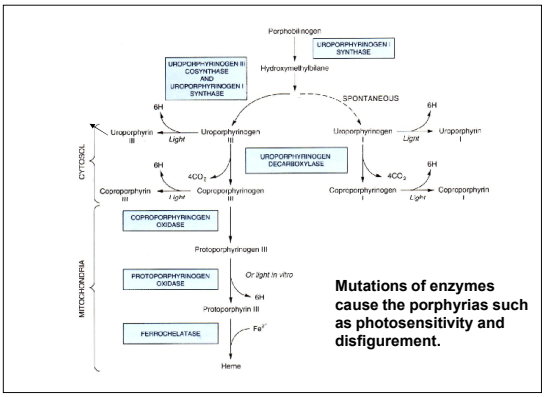
Iron deficiency maybe due to
1. **Diet**
2. **Malabsorption**
3. **Parasites**
4. **Haemorrhage**

Supplement with
Ferrous phosphate RED body types
Ferrous Chloride GREEN body types
Ferrous sulphate BLUE body types

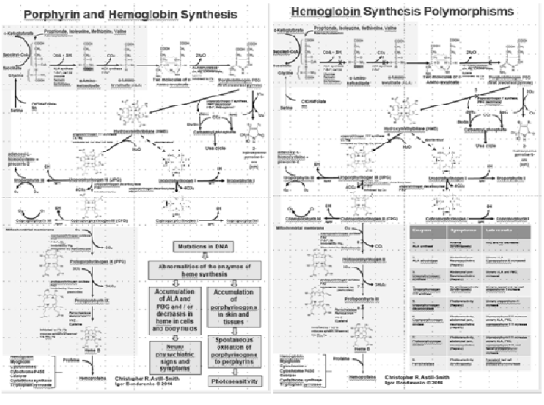
Hemoglobin and Myoglobin contain heme, a cyclic tetrapyrrole constisting of 4 molecules of pyrrole. One atom of ferrous iron resides at the centre.

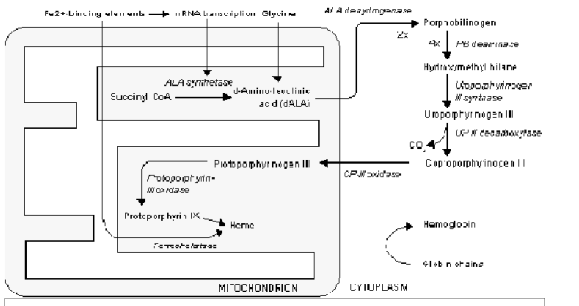
Heme-dependent enzymes, which play key roles in anti-oxidant defense, include catalase, peroxidase, NO-synthase, cystathionine synthase, heme-hemopexin (synthesis of metallothionein), cytochrome p450, and cytochromes for energy production.





Mutations of enzymes cause the porphyrias such as photosensitivity and disfigurement.

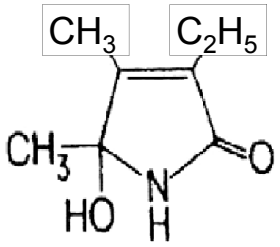




Heme synthesis—note that some reactions occur in the cytoplasm and some in the mitochondrion (yellow).

Pyroluria is known by many different names including Pyrrole Disorder, Kryptopyrrole, Kryptopyrroluria, Pyrroluria, Pyrolle Disorder, Mauve Factor and Hemepyrrole. Pyroluria can best be described as the abnormal synthesis and metabolism of the oxygen carrying molecule haemoglobin. As with all cells there are waste or by-products produced and the by-product of haemoglobin is a metabolite called hydroxyhemopyrrolin-2-one (HPL) also known as Pyrrole. The metabolite was originally thought to be a Kryptopyrrole but further studies have proven this not to be the case.

The Mauve Factor

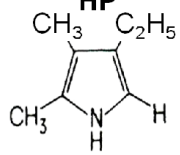


OHHPL (hydroxyhemopyrrolin-2-one)

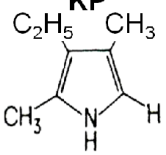
OHHPL (Mauve Factor)

- In human urine, blood and CSF
- Mistakenly identified as kryptopyrrole, a persistent erroneous term
- Chemically similar to kryptopyrrole, which can be used for OHHPL assay

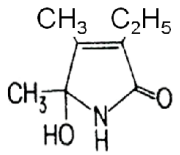
hemopyrrolle
HP



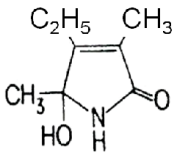
kryptopyrrole
KP



hydroxyhemopyrrolin-2-one
OHHPL



hydroxykryptopyrrole lactame
OHKPL



Mauve history

- Discovered in urine in 1957
- Named for lilac-coloured appearance on paper chromatograms developed with Erhlich's reagent
- Labile and elusive
- Abram Hoffer is the father of Mauve

Hoffer *J Neuropscyh* 1961

- Qualitative Mauve assay
- All normals mauve-negative
- 27/39 early schizophrenics positive
- All 7 who recovered on niacinamide converted to negative

Hoffer 1961

- Relapses associated with reappearance of Mauve
- Apparent role in other behaviours: Alcoholism, depression.
- A "mentally retarded" mauve-positive child responded dramatically to niacinamide

Hoffer and Mauve

- Heat and light sensitive
- Relatives should be tested
- Preventive potential
- 10/14 criminal / deviant positives
- Report on 740 patients in 1966
- All recovered schizophrenics negative, unrecovered 50% positive

O'Reilly 1965

- **Report on 850 behavioural patients**
- **25% of "disturbed children" mauve-positive, vs 12% of well children**
- **First documented observation of Mauve association with <u>stress</u>**

High-Mauve and behaviour

- **Down syndrome 70%**
- **Schizophrenia 40-70%**
- **Autism 50%**
- **ADHD 30%**
- **Alcoholism 20-80%**

Mauve levels

- **Clinicians: behavioural symptoms in individuals correlate with level**
- **Irvine 1972: likelihood of depressive reactions correlate with level**
- **Cutler 1974: B6 dose needed to normalize Mauve proportional to level**
- **McCabe 1983: Mauve can be normalized with high-dose B6 only**

Pfeiffer 1983

- Symptoms may improve in 24 hours, usually within 1 week
- May need months for full recovery
- Relapse within days or weeks if no nutrients
- Changing needs

Pfeiffer correlates

- Nail spots
- Stretch marks
- Pale skin
- Poor tanning
- Knees and joints
- Constipation
- Dream recall
- Morning nausea
- Light and sound
- Odour intolerance
- Migraines
- Stitch-in-side

Walsh

- Low stress tolerance
- Anxious, overly pessimistic
- Explosive anger
- Hyperactivity

Kruesi

- Social withdrawal
- Emotionally labile
- Loss of appetite
- Easily fatigued

- Abnormal fat distribution
- Irritable bowel
- Delayed puberty
- Irregular periods
- Overcrowded teeth
- Joint pains
- Reading difficulties
- Motion sickness
- Auditory processing disorder
- Memory loss
- Insomnia

- Sugar craving
- Poor morning appetite
- Frequent infections
- Allergies
- Impotence
- Sweet breath and body odour
- Paranoia
- Seizure
- Intolerance to bright light

Mauve and stress

- Mauve is associated with stress, including, emotional stress.

  Audhya 1992. Cold-immersion increased Mauve <1 hour

- The correlation is well-documented over decades

Non-behavioural Mauve

- **Acute Intermittent Porphyria**
- **Cutler 1974: High-mauve obesity and abnormal glucose tolerance**
- **Hoffer 1966: 33/99 Cancer patients, 7/8 lung cancer patients**
- **Riordan and Jackson: 43% of general medical patients: arthritis, chronic fatigue, heart disease, hypertension, irritable bowel, migraine. Range 20-40 mcg%.**

Thinking points

- **B3, Zn and B6 are anti-oxidant**
- **Strong stress / Mauve association**
- **Emotional stress clearly causes oxidative stress**
- **The behavioural and somatic high-Mauve disorders feature high oxidative stress**

Zinc is anti-oxidant

- **Shields -SH groups**
- **Blocks lipid peroxidation and PLA_2**
- **Induces metallothionein**
- **Constituent of SOD**
- **Maintains vitamin A**
- **Deficiency increases intestinal $NO^{\cdot}$**

Zinc deficiency increases oxidative stress

- **Lower glutathione, vitamin E, GST, GSHPx and SOD**
- **Increased reactive species and lipid peroxides in tissue, membranes and mitochondria**

Oxidants mobilize zinc

- **Oxidants release complexed zinc from zinc-binding proteins, including metallothionein and albumin**
- **It is likely--but unproven--that zinc retention is reduced in direct relationship to oxidative stress**

B6 is anti-oxidant

- **P5P for Glutathione, Metallothionein, CoQ10 and Heme synthesis**
- **With Zn, cofactor for GAD**
- **P5P protects vulnerable lysinyl groups, as in GSHPx**

Marginal B6 deficiency:

Lowers GSHPx

Lowers glutathione reductase

Promotes mitochondrial decay

Raises lipid peroxide levels

B6 and oxidative stress

- **Binding of P5P-dependent enzymes is subject to carbonyl inhibition**
- **Binding of key P5P-dependent enzymes such as GAD *(glutamate decarboxylase)* impaired by oxidants generally**
- **$OH^{\cdot}$ and $^1O_2$ attack B6 vitamins**

B3 is anti-oxidant

- **NADPH for reduction of glutathione**
- **Potent free-radical quencher: protects both lipids and proteins from oxidation**
- **Blocks $NO^{\cdot}$ neurotoxicity**
- **High tissue levels: better lipoxidation prevention than ascorbate**

B3 is anti-oxidant

- Niacin antagonists increase lipoxidation
- Low B3 decreases MT and increases apoptosis in brain cells
- Neuroprotective in experimental mitochondrial toxicity

Require heme

- Cystathionine synthase
- Catalase
- Heme-hemopexin for MT translation
- Pyrrolase
- Guanylate cyclase
- Cytochromes
- Sulfite reductase
- NOS

Regulatory heme

- Sustains zinc, vitamin A and melatonin levels
- Differentiation, response to growth factors and resistance to viruses
- Levels lowered by toxins: gasoline, benzene, arsenic, lead. mercury and cadmium

Low Heme is pro-oxidant

- **Ames 2002. Experimental heme depression in cultured brain cells:**

Decreased Complex IV
50% reduction in intracellular Zn
Increased intracellular Fe

People who suffer from Pyroluria produce excessive amounts of these Pyrroles which bind to or inhibit the nutrients; Zinc, Biotin, vitamin B6, and Omega 6 Fat GLA from reaching their targets within the body. This effectively renders these nutrients unavailable.

Igor Bondarenko PhD
"It may well be a P450 enzyme that oxidises hemopyrrole and kryptopyrrole.
2-hydroxyhemopyrrolene-2-one is either an intense chelator of vit. B6 and zinc, or it facilitates their urinary excretion, or both".

Igor Bondarenko PhD
"Interestingly, PBG is broken down by a deaminase, and the release of ammonia from it may presume more P-5-P for utilising the formed ammonia in, for example, glutamine synthetase-catalysed reaction".

HPL inhibits heme synthesis (Graham). Experimentally, heme inhibition results in lower cellular zinc, and higher iron and oxidative-stress levels (Ames).

Mauve Factor is strongly associated with depletion of arachidonic acid (Bibus), which is attacked by free radicals to form levuglandins and isolevuglandins, which in turn produce pyrrolic tissue adducts. These pyrrolic adducts consistently auto-oxidize to form a hydroxy-lactam (Salomon), and the pyrrolic moiety of these adducts corresponds precisely to the structure of HPL. Urinary pyrroles are known to result from the formation of pyrrolic tissue adducts (Batoreu).

Pyroluria and Gluten Sensitivity
It is not uncommon for those with this condition to have gluten and casein sensitivity. This condition is more prevalent in many of the same populations that we see increased prevalence of gluten sensitivity. It can cause wide ranging symptoms

Access Pyroluria patients with
Pyridoxal-5-phosphate
Zinc picolinate / chloride / sulfate
Niacinamide
Manganese picolinate / chloride / sulfate
Magnesium phosphate / chloride / sulphate
Borage / EPO / Blackcurrant seed oil
Vitamin E
Vitamin C
Inositol

Patients with positive HPL tests may need anywhere from 100-250mg of zinc. The B6 dosage may range from 100mg up to 400mg.

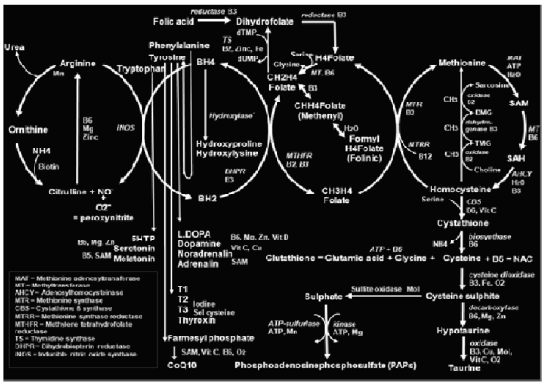
Vitamin B12
1. Hydroxycobalamin
2. Adenosylcobalamin
3. Methylcobalamin
Vitamin B_{12} is a water soluble vitamin with a key role in the normal functioning of the brain and nervous system, and for the formation and maturation of red blood cells.

It is normally involved in the metabolism of every cell of the human body, especially affecting DNA synthesis and regulation, but also fatty acid synthesis (especially odd chain fatty acids) and energy production.

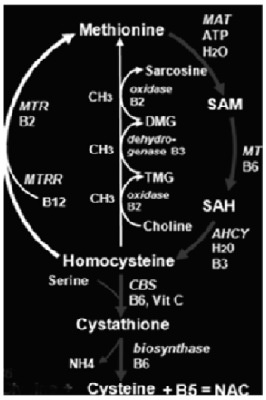
Only bacteria have the enzymes required for its synthesis, although many foods are a natural source of B_{12} because of bacterial symbiosis and usually produce hydroxocobalamin), but conversion between different forms of the vitamin can be accomplished in the human body.

Vitamin B_{12} was discovered from its relationship to the disease pernicious anemia, which is an autoimmune disease in which parietal cells of the stomach responsible for secreting intrinsic factor are destroyed, the same cells responsible for secreting acid in the stomach.

Intrinsic factor is crucial for the normal absorption of B_{12}, so a lack of intrinsic factor, as seen in pernicious anemia, causes a vitamin B_{12} deficiency. Many other subtler kinds of vitamin B_{12} deficiency and their biochemical effects have since been elucidated.



Methionine synthase, **is a methyltransferase enzyme, which uses the MeB_{12} to catalyze the conversion of the homocysteine back into methionine. This functionality is lost in vitamin B_{12} deficiency, and can be measured clinically as an increased Homocysteine level.**



Myelin damage resulting from B_{12} deficiency, even in the presence of adequate folate and methionine, is more specifically and clearly a vitamin deficiency problem. It has been connected to B_{12} most directly by reactions related to *MUT*, which is required to convert methylmalonyl coenzyme A into succinyl CoA.

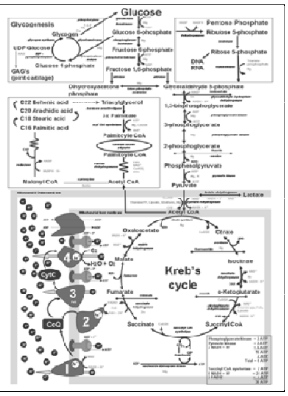
Failure of this second reaction to occur results in elevated levels of MMA, a myelin destabilizer. Excessive MMA will prevent normal fatty acid synthesis, or it will be incorporated into fatty acid itself rather than normal malonic acid.

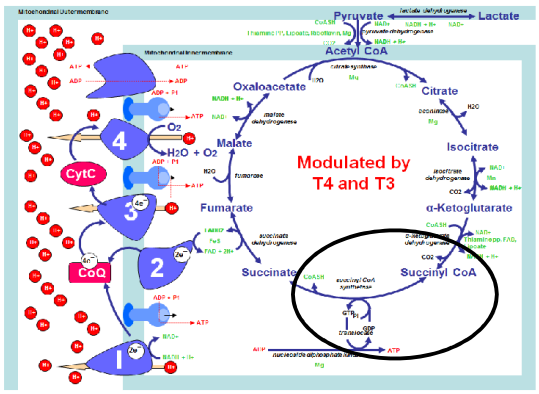
If this abnormal fatty acid subsequently is incorporated into myelin, the resulting myelin will be too fragile, and demyelination will occur.

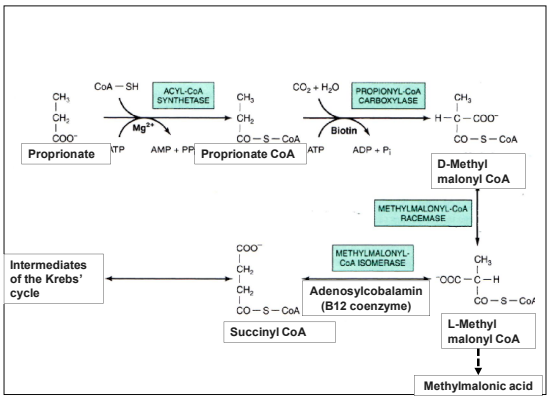
Methylmalonyl CoA is formed as an intermediate in the catabolism of valine and by the carboxylation of proprionyl CoA arising in the catabolism of isoleucine, cholesterol and odd numbered fatty acids or directly from proprionate a major product of microbial fermentation in the rumen.

Energy production

1.Glycolysis
2.Krebs' Cycle
3.Electron transport





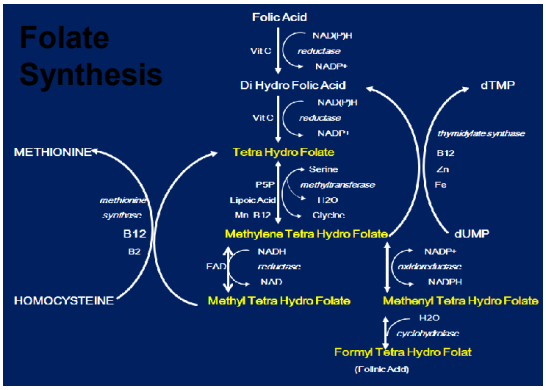


Folate deficiency limits cell division, erythropoiesis, production of red blood cells, is hindered and leads to megaloblastic anemia, which is characterized by large immature red blood cells.

This pathology results from persistently thwarted attempts at normal DNA replication, DNA repair, and cell division, and produces abnormally large red cells called megaloblasts (and hypersegmented neutrophils) with abundant cytoplasm capable of RNA and protein synthesis, but with clumping and fragmentation of nuclear chromatin.

Folic acid is itself not biologically active, but its biological importance is due to tetrahydrofolate and other derivatives after its conversion to dihydrofolic acid in the liver.

H4Folate Tetrahydrofolate
CHH4Folate Methenyl tetrahydro folate
CH2H4Folate Methylene tetrahydro folate
CH3H4Folate Methyl tetrahydro folate



Heart Muscle Function

Cardiac muscle like skeletal is striated but exhibits intrinsic rhythmicity. In cardiac muscle the sarcoplasmic reticulum is less extensive and thus the intracellular supply of Ca^{++} for contraction is less, thus relying upon extracellular Ca^{++} for contraction. If deprived of extracellular Ca^{++} the heart ceases to beat within 1 minute.

Ca^{++} enters muscle cells through voltage gated Ca^{++} specific channels opening during depolarisation induced by spread of the cardiac action potential and closing when the action potential declines.
Activation of protein kinase enzymes (Mg^{++} dependant) modulate intracellular Ca^{++} entry.

Ca^{++} entry requires optimal cell membrane integrity and the presence of trans fatty acids or oxidised fatty acids will inhibit this. Thus the necessity for good organic cold pressed unsaturated oils such as flax seed etc. Pyridoxal-5-phosphate (Vitamin B6) is important in the stabilization of cell membranes.

Low magnesium levels have been found to be the best predictor of heart disease, contrary to the traditional belief that cholesterol or saturated fat play the biggest roles.

Research scientist Andrea Rosanoff, PhD., and her colleagues conducted a detailed review of cardiovascular disease research, using studies dating back to 1937.

Research has revealed low magnesium to be linked with all known cardiovascular risk factors like: Hypertension, Arterial plaque build-up Calcification of soft tissues, Cholesterol Hardening of the arteries

"By 1957 low magnesium was shown to be, strongly, convincingly, a cause of atherogenesis and the calcification of soft tissues. But this research was widely and immediately ignored as cholesterol and the high saturated-fat diet became the culprits to fight. Ever since this early 'wrong turn', more and more peer-reviewed research has shown that low magnesium is associated with all known cardiovascular risk factors, such as cholesterol and high blood pressure."

Optimizing Cardiac Function
Magnesium –phosphate, chloride, sulphate, citrate
Calcium – lactate,chloride, sulphate, citrate
Pyridoxal-5-phosphate
Heart tissue extract
Vitamin E – wheat germ oil
Vitamin C – SMART C
Essential fatty acids / Lecithin