Iron Function
Iron plays an essential role in life by accepting and donating electrons. Iron proteins are involved in oxygen transport, mitochondrial oxidative energy, muscle function, inactivation of toxins and DNA synthesis.

Iron Metabolism (Figure 1)
Iron is mostly ingested in the poorly soluble oxidised ferric state. To be absorbed, gastric acid is needed to reduce iron to the ferrous state where it can be taken up by the duodenal enterocyte. Iron is taken up by a divalent metal transporter in the duodenal brush border and this protein requires a low pH for activity. Iron export from the duodenal lining to the blood is by the iron transport protein ferriportin 1, again in the reduced ferrous form. In the circulation, iron is bound to transferrin. Transferrin bound iron has to be oxidised again which is carried out by ceruloplasmin.

A major control of iron absorption is by the protein hepcidin which is synthesised by the liver. Although it is not fully understood, hepcidin is controlled by serum iron levels. Increasing serum iron results in increased synthesis of hepcidin which binds to ferriportin inactivating it and thus preventing absorption of iron. Similarly, ingestion of iron tablets by mouth rapidly increases hepcidin concentration, causing a secondary downturn in iron absorption.

Hepcidin is an inflammatory marker and cytokines or other causes of inflammatory reactions result in increased hepcidin and impaired iron absorption and low serum iron.

Hepcidin is also important for the uptake of iron into macrophages and is controlled by similar cytokines. Increased hepcidin associated with inflammatory stimuli leads to impaired release of iron from macrophages. This leads to functional iron deficiency; in part contributing to the anaemia of chronic disease. Hepcidin production is suppressed by iron deficiency, hypoxia and increased erythropoietic activity leading to increased iron absorption. All forms of genetic haemochromatosis in man are characterised by diminished hepcidin production or activity which results in unbridled continuing iron absorption and iron overload.

Iron Deficiency
Iron deficiency in adults is associated with impaired work capacity, mental symptoms such as irritability and tiredness in addition to that associated with anaemia. Children with iron deficiency have impaired mental development and ability to learn which is restored by correcting the iron deficiency.

Iron deficiency is most likely the result of blood loss either menstrual or gastrointestinal. Adult males and post-menopausal females need to have gastroenterological examination including an immunochromical faecal occult blood test, endoscopy and colonoscopy. Sometimes capsule endoscopy will be necessary when bleeding has been demonstrated and the cause has not been found in the upper or lower gastrointestinal tract. These investigations are frequently negative in young women and even in a proportion of post-menopausal women, and men where the reason for the iron deficiency is more obscure.

Malabsorption as a Cause of Iron Deficiency
Coeliac Disease
Coeliac disease can present as iron deficiency without the typical symptoms of gluten intolerance. In recent years, blood tests have been used for identifying coeliac disease, most recently anti-tissue transglutaminase. These antibody tests may be falsely negative if the patient has taken themselves off gluten in the diet and the antibody levels consequently fall. Similarly endoscopy and biopsy may have returned to normal if gluten is still not being ingested. Iron absorption will return to normal when the duodenal mucosa returns to normal after gluten withdrawal.
Iron Deficiency: Not Just Anaemia

by the bacteria. The major effect is likely to be the adverse effect of H. pylori on gastric acid production.

**Suggested Investigations for Obscure Iron Deficiency**

The following tests should be done:

1. Rapid screening test for coeliac disease
2. Anti-parietal cell antibodies and fasting gastrin for autoimmune gastritis
3. IgG antibodies to H. pylori together with urease breath test for Helicobacter infection
4. Unfortunately serum hepcidin measurement is still a research tool not available for routine use

**Iron and the Athlete**

As expected, haemoglobin iron, when lacking, will alter ability to exercise by a decrease in the oxygen transported to exercising muscle.

Although non-haem iron associated with enzyme systems forms only 1% of the total body iron, marked deficits of these cellular enzymes will have a detrimental effect on athletic performance. Studies indicate that maximal oxygen uptake is determined primarily by the oxygen carrying capacity of the blood and is thus correlated with the degree of anaemia. There is a strong association between the ability to maintain prolonged maximal exercise and the activity of iron dependent oxidative enzymes.

A study in normal healthy young mountain climbers showed that when these individuals were exposed to hypoxia at a level of 5,000 metres, the muscle iron content diminished by 30% over a period of a week to ten days. To make up the shortfall in red cell oxygen carrying capacity, their haemoglobin rose by an average of 30g/L, rising from a mean of 140g/L to 170g/L over a week. Studies however have not shown an increased performance in athletes who train at high altitude and then perform at low altitude, (a physiologic form of ‘blood doping’.) Runners appear to be most at risk from iron deficiency and, on average, their iron stores are lower than their sedentary counterparts from the non-athletic population. There is a high iron turnover particularly in young female athletes with significant iron loss compared to the non-athletes.

**Blood Donation in Menstruating Females**

Menstruating females have lower iron stores than their male equivalents. A blood donation of approximately 500mL contains haemoglobin and haemoglobin bound iron. Since regulation by the TGA, the Australian Red Cross Blood Service does not perform iron studies on blood donors and the situation of iron deficiency in the presence of an acceptable haemoglobin can occur. This will result in non-anaemic symptomatology of iron deficiency; although the average female will restore her haemoglobin after donation in approximately eight weeks. (It will be faster if there is iron supplementation.) On average 200mg of iron is lost with each blood donation, if the net iron absorption is 1mg this will take two hundred days to repair, although iron deficiency itself will lead to faster iron absorption.

There needs to be increased awareness of iron deficiency in this group of altruistic women. If a woman is iron deficient and wants to donate then plasmapheresis donation for plasma or platelets for example would not lead to significant blood loss.

**Some Notes on Iron Therapy**

There are a significant number of iron preparations available over the counter. The ‘full strength’ iron brands such as Fefol, Ferrograd C, Ferro-F-tab and Ferrogradumet contain around 100mg of elemental iron per tablet. Preparations of multi-vitamins usually contain significantly less and as a consequence there is less iron absorbed. However, these preparations also have fewer side effects such as bloating and constipation which affects a significant proportion of the population taking iron therapy. Iron is absorbed best when the stomach is empty and there is hydrochloric acid to keep the iron in the ferrous form. Foods which interfere with

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**Autoimmune Atrophic Gastritis**

Achlorhydric gastric atrophy was described early in the twentieth century and was recognised as a major cause for iron deficiency anaemia. It is an autoimmune disease with antibodies against gastric mucosal epitopes. It is a relatively common cause of iron deficiency in young women. Investigations include an elevated fasting serum gastrin and the presence of anti-parietal cell antibodies. These patients often have a coexistent Helicobacter pylori infection. It is thought that, as the pathologic process progresses, anti-intrinsic factor antibodies develop and lead to failure of production of intrinsic factor. This results in consequent malabsorption of vitamin B12 later in life, producing classical pernicious anaemia. Impaired iron absorption in pernicious anaemia is corrected by normal acid gastric juice but not by pH neutral gastric juice, confirming that the lack of gastric acidity is an important cause of iron deficiency. The use of protein pump inhibitors also leads to diminished gastric acid production and consequent diminished iron absorption.

**Helicobacter Pylori Gastritis**

Population studies have shown that the presence of Helicobacter infection is associated with a lower ferritin than is seen in subjects not infected.

In a subset of patients a cause and effect relationship between H. pylori and gastric body atrophy leading to iron malabsorption has been established. Successful eradication of H. pylori leads to improved iron absorption in the majority of these people. However, there is a point beyond which their stomach cannot recover. The role of H. pylori gastritis in iron deficiency may be multi-factorial including blood loss from erosions and competition for dietary iron...
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continued

Iron absorption include black and green tea, coffee, wheat germ, nuts, oats, beans, eggs, soy protein and calcium.

Iron can interfere with the absorption of other drugs and other drugs can interfere with the absorption of iron. Reduction of absorption can be produced by antacids, protein pump inhibitors, tetracyclines, fluoroquinolones, ace inhibitors, etidronate, zinc supplementation and bile acids sequestrants.

Iron will be absorbed poorly where there is malabsorption as in atrophic gastritis or untreated coeliac disease and intravenous iron infusions should be considered for this group.

Diagnosing Iron Deficiency in the presence of Anaemia of Chronic Disease

Anaemia of chronic disease can sometimes make iron deficiency and the blood film change. The serum ferritin can sometimes be misleading; the inflammatory state induces a rise in the ferritin level rather than a fall. The serum iron is low in both iron deficiency and the anaemia of chronic disease and cannot be used to discriminate the two. However, a soluble transferrin receptor assay can be performed which will be normal in the anaemia of chronic disease but raised in iron deficiency, even when associated with the anaemia of chronic disease (Table 1).

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| Table 1. Diagnosing Iron Deficiency in the Presence of Anaemia of Chronic Disease |
|---------------------------------|-------------------------------|-------------------------------|
| Fe Deficiency                  | Anaemia Of Chronic Disease (ACD) | Combined Fe deficiency and ACD |
| Mean Cell Volume (MCV)         | ↓                              | N or ↓                       |
| Mean Cell Haemoglobin (MCH)    | ↓                              | N or ↓                       |
| Serum Ferritin                 | ↓                              | N or ↑                       |
| Serum Iron                     | ↓                              | ↓                            |
| Transferrin saturation         | ↓                              | ↓                            |
| Soluble Transferrin Receptor (STf. R.) | ↑                              | N                            |
| C Reactive Protein (CRP)       | N                              | N or ↑                       |

Combined Fe deficiency and ACD: N or ↑