Vitamin B12 Deficiency

B12 deficiency is common. It is generally considered that 6% of thegeneral population and 10% to 20% of those over 60 years are deficient. However, this is likely to be an underestimate. Dr Chandy, an international authority on Vitamin B12, found that 18% of patients in his practice had B12 deficiency. Katherine Tucker found an incidence of 39% in the USA. (Am J Clin Nutr, 2000 Feb;71(2):514-22. doi: 10.1093/ajcn/71.2.514.)

The cost of this failure to diagnose patients with B12 deficiency has been estimated at £894 million per year.

You might wonder why B12 deficiency is underdiagnosed. There are two reasons:

1) **The test for detecting B12 deficiency is thoroughly flawed**
2) **Most doctors don't know it is flawed (though experts in the field do know this)**

B12 Deficiency

Vitamin B12 deficiency is often confused with **pernicious anaemia (PA).** In fact, according to Dr Chandy, less than 10% of patients with B12 deficiency have pernicious anaemia. It is thought that B12 deficiency, if untreated, progresses to an auto-immune condition. This develops in the later stages of the disease (and can then be associated with other auto-immune disorders). This can occur with or without anaemia but typically auto-antibodies are found at this stage. When the picture includes anaemia, it is called pernicious anaemia.

Although there are different causes, typically there is atrophy (wasting) of the parietal cells in the stomach or an antibody blocks the production of intrinsic factor. Normally parietal cells produce intrinsic factor which combines with B12 broken down from food in the stomach. Later this complex of intrinsic factor and B12 is absorbed in the terminal ileum (last part of small intestine). Atrophy of parietal cells or antibodies to intrinsic factor will block this absorption.

Benefits of Vitamin B12

B12 reduces homocysteine. Raised homocysteine increases the risk of cancer and heart disease. Raised homocysteine accelerates aging.

B12 binds toxins and heavy metals.

B12 is essential for myelin formation and because of this B12 deficiency causes a variety of neurological disorders.

B12 increases CD8+ T cells which prevent autoimmunity. This might explain why as autoimmunity develops as B12 deficiency progresses. There is a high incidence of hormonal disorder (hypothyroid, hypoadrenalism) and of autoimmune disease associated with advanced B12 deficiency. Early treatment with B12 may prevent these.

Dr Chandy noted that of over a thousand patients in his practice treated for B12 deficiency **not a single one developed cancer.** (When I read this, I wondered if there could be anything more beneficial than B12 in medicine).

Folate is given routinely in pregnancy to prevent spina bifida and other abnormalities. **B12 does exactly the same but receives almost no attention**. Levels of B12 go down in pregnancy (presumably as the foetus uses up mother's B12). A recognised problem in vegans and vegetarians is very low B12 in breast milk causing developmental and other problems in the baby as well as postpartum depression in the mother (formula feeds contain B12).

The offspring of animals deprived of B12 in the womb develop immune problems, hypertension and insulin resistance.

Drugs

Some drugs block the production of acid or intrinsic factor in the stomach and therefore produce B12 deficiency. Top of the list are proton pump inhibitors (PPIs) such as lansoprazole and omeprazole (and in my experience B12 is never checked in these patients). The diabetic drug metformin can also block B12 absorption. Other acid-blockers such as ranitidine, plus anti-inflammatory drugs (such as ibuprofen), the pill and some epilepsy drugs can cause problems.

Diet

Vegetarians and vegans can develop B12 deficiency. There is usually enough B12 in the diet, especially from meat, fish and diary. For vegetarians, fortification of foodstuffs, like cereals, with B vitamins gives some protection. Oddly enough, All-bran is high in B12. Mushrooms, especially shiitake mushrooms are a good vegetarian source of B12. One of the main sources of B12 is from friendly bacteria in our gut but these

can be damaged and reduced in number, notably after taking antibiotics but also by eating ultra-processed foods.

Toxicity

The world's most widely used herbicide is **glyphosphate.** Residues can be found in many foods, including 80 to 90% of wheat products. It is also high in oats, corn and soy but can be found in most fruit and vegetables. It does not wash off. Once it enters the body it can diffuse across membranes, especially in an acidic environment such as the stomach. Here it damages parietal cells, which are essential for B12 absorption. Exposure to glyphosphate can accelerate B12 deficiency.

Surgery

Stomach surgery (gastric by-pass) or surgery to the terminal ileum can cause B12 deficiency. Nitrous oxide anaesthesia can cause rapid B12 deficiency as can street use of this substance.

Pathogens

Rare causes are the fish tapeworm (diphyllobothrium latum) and the parasite, giardia lamblia. A clue to either of these is high eosinophils in the blood.

SYMPTOMS

B12 deficiency can cause a wide variety of symptoms but **fatigue** is the most common and neurological symptoms such as nerve damage are the most serious (this can happen if the disease is left untreated). In addition, brain fog, breathlessness, swollen cracked tongue, dry skin, premature greying, imbalance and weakness. A paper from 1956 noted that **confusion and memory defects** were key symptoms. Other symptoms and signs include brittle nails with ridges 49%, waking tired 36%, memory loss 68%, confusion 62%, burning feet and legs 35%, diarrhoea 70%, abdominal cramps 45%, indigestion 42%, irritable 80%, impotence 65%, mood swings 60%, Depression is common, and psychosis can also occur.

B12 deficiency inhibits myelin production in nerves and subacute combined degeneration (SACD) can result. This can very closely mimic multiple sclerosis, even on MRI scans, and can also closely mimic other neurological conditions.

DIFFICULTIES WITH DIAGNOSIS

Unfortunately, this is not straightforward as **there is no gold standard test**. The standard B12 test can be wildly misleading and nearly half of patients get misdiagnosed initially. A B12 level under 200 suggests deficiency and a level below 330 is suboptimal and could represent B12 deficiency. The BMJ Best Practice suggest that anything below 350 should be regarded as possible deficiency. **It is worrying that the B12 test can be normal in 22 to 35% of people with B12 deficiency.** Perhaps because of this 14% of patients with B12 deficiency wait 10 years before diagnosis.

The test is unreliable because the test measures two forms of B12: the inactive form, holohaptocorrin and the active form holotranscobalamin. As little as 10% of B12 can be in the active form. This means it is possible to have a deficiency of active B12 and for the test to be completely normal (if there is plenty of inactive B12 present). To complicate things further, high levels of intrinsic factor antibodies can falsely raise the level of B12.

Taking B vitamins can also give a false normal reading in B12 deficiency.

It is possible to check the active part of B12 by means of the **holotranscobalamin** test but this is not available in most labs (although widely used in Europe and the USA). Another test, **methylmalonic acid (MMA),** is raised in B12 deficiency and gives a further guide. Again, it is not available in many labs. **Homocysteine** is another useful test in suspected B12 deficiency and is typically raised.

A further two tests are used. These are **intrinsic factor antibodies** and **parietal cell antibodies**. If intrinsic factor antibodies are present this is **virtually diagnostic of auto-immune B12 deficiency** (in other words late-stage disease) but unfortunately only 40 to 60% of patients with B12 deficiency react positively to this test. The parietal cell antibodies are present in 80% of cases of PA sufferers but 10% of the normal population also have these antibodies so it is not diagnostic.

The bottom line is that it is entirely possible to have B12 deficiency with normal B12 levels and negative antibody tests. Sometimes the only way to confirm the diagnosis is with a trial of B12.

TREATMENT

Treatment is normally by injections of B12 with hydroxocobalamin. However, it is possible to use B12 tablets (cyanocobalamin). A small

fraction (1%) of B12 is absorbed at the terminal ileum without intrinsic factor. If a large enough quantity of B12 is present then enough can be absorbed. However, absorption is unpredictable. B12 deficiency from other causes can manage with tablets better so in these cases tablets may be best. The dose of tablets normally given (50 to 150 mcg daily) is not enough. Dr Chandy recommends 1mg (1000 mcg) daily.

The preferred treatment is with injections. *Even with injections there can be a problem. Hydroxocobalamin (from the injection) is converted to the active form, methylcobalamin. Unfortunately, some people cannot convert hydroxocobalamin to methylcobalamin and need methylcobalamin injections. These are no longer available on the NHS.*

Normally, after diagnosis, 3 injections weekly are given for two weeks and then treatment is given 3 times monthly. If there is nerve damage, treatment is given 3 times a week until improvement occurs.

There is a major problem with these guidelines. The amount of B12 that is needed varies markedly, probably for genetic reasons, and many B12 deficiency patients need injections every month (monthly treatments are standard in the USA and many European countries and were the norm in the UK until 1974). **Dr Chandy found 80% needed monthly injections to stay well and some needed injections more frequently.**

A particular area of confusion is blood tests done after treatment. The only purpose of these is to show if the levels are low. Sometimes doctors mistakenly stop B12 because they are worried by the patient's B12 being above the upper level (usually 900). This is a serious error. The US Institute of Medicine has stated that "**no adverse effects have been associated with excess B12 from food or supplements in healthy individuals".** Stopping B12 for this reason is likely to result in the illness relapsing and sometimes triggering psychosis.

To give an idea of how safe B12 is consider the late Dr Patrick Kingsley who treated over 9000 patients with multiple sclerosis with a high degree of success. He often used 20,000 micrograms daily (the standard injection is 1000 mcg every 3 months).

Patients with B12 deficiency will need treatment for the rest of their lives.