

The Enterohepatic Circulation of Vitamin B₁₂



THE ENTEROHEPATIC CIRCULATION OF VITAMIN B12

Introduction

In 1964 Dorothy Crowfoot Hodgkin was awarded the Nobel Prize for Chemistry. She had headed a team which – via X-Ray Crystallography – had determined the molecular structure of Vitamin B12.

Despite the brilliance of the achievement, though, Professor Hodgkin's team left us with a legacy we could well do without. This is taken from

<http://www.chm.bris.ac.uk/motm/vitb12/b12.htm>

“The first type of Vitamin B12 to be isolated had a cyanide group attached to the cobalt; this was picked up during the purification of the vitamin, and is the form which is still referred to as “Vitamin B12”.

Now that is a peculiar thing to say. Either the molecule **is** B12, or it isn't. In this case, it clearly isn't. It's adulterated. It is honest to call the compound cyanocobalamin; it is completely fraudulent to say that it is “a form of B12”. The article goes on to say this:

The principal coenzymatic form of Vitamin B₁₂ is 5'-deoxyadenosylcobalamin. The notable feature of the molecule is the cobalt-carbon bond between the 5' carbon of the 5'-deoxyadenosyl moiety (the sugar part) and the cobalt of cobalamin. In Vitamin B₁₂ as it is extracted, a cyanide replaces this sugar link, this occurs during the final purification with active charcoal. Aquacobalamin and hydroxycobalamin, with water and hydroxide are also known, as is the methylated form, methylcobalamin

What that is saying is that the most common, **naturally occurring** molecule which we choose to call Vitamin B12 is 5'-deoxyadenosylcobalamin (adenosylcobalamin, cobamamide, ad-B12, dibenzocoid – take your pick). The paragraph also nods to the existence of methylcobalamin and aquacobalamin (methylcobalamin occurs naturally) and to hydroxocobalamin (which may be natural, or may just be a breakdown product of other, natural cobalamins).

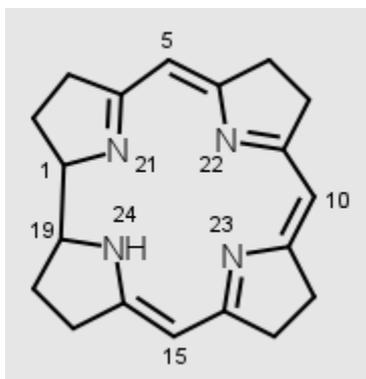
The sentence highlighted in red in effect says “in synthesising what many please themselves to market as vitamin B12, a naturally-occurring chunk of the molecule is removed, and replaced with a [CN]- (cyanide) radical.”

“Naturally occurring” water is H-OH (hydrogen hydroxide, if you will). Perhaps we could replace the [OH]- (hydroxyl) radical with a [CN]-, and still call the molecule “water” and not “hydrogen cyanide”!

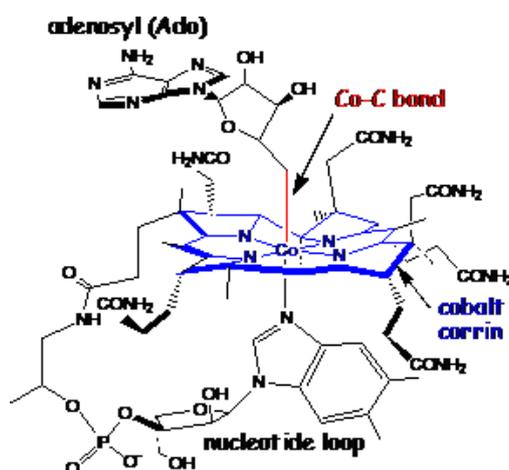
The main legacy we now have to live with is confusion about what B12 is (and isn't); and extremely sloppy terminology from people who should know a lot better. So, to try to avoid it myself, I'll begin at the beginning:-

Cobalamins

There are compounds called corrinoids <http://goldbook.iupac.org/C01350.html> . Their defining, central structures (called corrins) typically look like this:



Cobalamins are a specific sub-group of corrinoids, centred on a single atom of cobalt. Below is a view of adenosylcobalamin, and you can see the single cobalt atom sitting like a spider at the centre of the corrinoid web:



This, once again, is from <http://www.chm.bris.ac.uk/motm/vitb12/b12.htm>

“A number of other cobalt-carbon bonded compounds have been prepared synthetically, but are not known to occur in vivo.”

Cyanocobalamin is a cobalt-carbon bonded compound “not known to occur in vivo”! The last time I went looking, I found mention of up to 38 naturally-occurring and man-made substances which could all be termed “cobalamins”.

The bit labelled “adenosyl (Ado)” is the chunk that is pulled off and replaced with a cyanide radical. As you’ll see, it’s quite a modification!

There are other naturally-occurring cobalamins; glutathionylcobalamin (for example) is biologically stable, and is a most important controller of energy production within animal cells. Sulphitocobalamin is also known to occur in animal cells.

In summary, there are lots of things that can be legitimately termed “cobalamins”. However, only a handful of those have animal relevance; and, really, we shouldn’t be lumping them together as “Vitamin B12.” They have individual names and applications, and we would be wise to learn them. In this essay, I’ll use “B12” **only** to mean “animal-relevant cobalamins.”

Animal-Relevant Cobalamins

I read the discussions on the PA forum about this item:

<http://www.cobento.dk/gfx/content/pdf/Cobalamin%20Uptake%20and%20Utilization.pdf> The author of the text is Lotte Neergard Jacobsen; the paper is pretty authoritative, but it has lost something in the translation from – I think – Danish. The terminology can be misleading as well, and it tends to use the word “cobalamin” when it means “cobalamins”. Eg:

“Cobalamin in food is bound to peptides and other compounds.”

Most people are aware that there is a class of material called “steel”; they will also be aware that there are many different types of “steels” within that class. In the same way “cobalamin” is a class of compound, and “cobalamins” are individuals within that class.

The cobalamins which form part of us are tied up within the structures of our cells. Most of the cobalamin in what you eat is adenosylcobalamin or methylcobalamin. The following quotations all come from the Jacobsen paper:

“The human well-being depends upon the coenzymes adenosylcobalamin and methylcobalamin, which are indispensable from human metabolism. In all eukaryotic cells intracellular cobalamin exists in two forms:

- ***Methylcobalamin found primarily in the cytoplasm***
- ***Adenosylcobalamin found mainly in mitochondria.”***

All animal well-being depends on them, which is why they are in the meat you eat. However, the paragraph is not strictly correct, since glutathionylcobalamin and aquacobalamin (and possibly other cobalamins besides) also exist in mammal cells - but it’s not really relevant to this discussion.

“Bile, which is made in the liver and needed to digest fat, daily secretes small amounts of cobalamin into the small intestine. It is then almost completely reabsorbed at the end of the small intestine and taken back into the liver, where it is used again.”

We know that that is what happens. What we want to know, though, is “why” and “how”. This next sentence is, however, something of a non-sequitur:

“The reabsorption of bile cobalamin explains why it takes approximately 20 years to get cobalamin deficiency after ending consuming dietary cobalamin but only 1-3

years if one stops absorbing cobalamin due to diseases in the stomach, pancreas or ileum.

It **does** explain it – but only if you understand the explanation already!

PA patients – along with other sufferers of conditions inhibiting digestive secretions - tend to “crash” far more quickly than people such as I, who – through vegetarian ignorance – simply starve ourselves of B12. Digestive secretions are the clue.

To show clearly where I am going, I have to go back a bit and to look at a couple of other things that Ms Jacobsen says, starting with haptocorrin:

“The function of Haptocorrin is almost unknown, although in plasma it binds about 60% of the circulating cobalamin.”

“The enterohepatic circulation may help the clearance of cobalamin analogues that might be formed by bacteria, especially since HC is known to bind tightly a wide variety of cobalamin analogues.”

{“Cobalamin analogues” is sloppy terminology again; what is meant is “B12 Analogues” – ie “animal-irrelevant” cobalamins.}

Intrinsic Factor (IF) is secreted within the stomach; it is a glycoprotein whose task is to transport B12 through part of the absorption process. In addition to IF, there are 3 more substances which also transport cobalamins within the body; each has a different role. Collectively, they are known as Transcobalamins and they have been labelled TCI, TCII, and TCIII. “Haptocorrin” – which is produced as a component of saliva - is another name for TCI: <http://www.clinchem.org/cgi/content/full/53/2/367> ; and we know enough about what haptocorrin does to make intelligent guesses about (at least some of) its biochemical roles. The roles of the other two TCs are discussed later in this essay.

Ingestion of Cobalamins

Haptocorrin is produced in saliva, and – whilst travelling from the mouth, and through the stomach – binds to any cobalamins we ingest as part of our diet; the molecule is then referred to as “holohaptocorrin”. Within the strongly acidic environment of the stomach, haptocorrin has great affinity for cobalamins, whilst IF has very little. (<http://www.ajcn.org/cgi/reprint/59/5/1213S>)

One source of cobalamins is oral bacteria. Over the past twenty years or so, new Serum Tests have continually been developed, each with better ability to discriminate between cobalamins which are animal-relevant, and those which are not. However, some papers are based on data from older, less discriminatory tests, and they draw very questionable conclusions. There is a tale, for instance, that your oral bacteria produce enough B12 to sustain life; they don't; they produce “B12 Analogues” – cobalamins which closely resemble B12, but which your body cannot use: <http://www.roylretreat.com/articles/b12.html>

Some plants contain cobalamins, and marketing claims are made that these too are

“B12”; the Vegan Society cautions strongly against believing them:

<http://www.veganhealth.org/b12/plant>

Some B12 Analogues can block, or compete for, reaction sites within our cells, interfering with our assimilation and use of B12 itself. In encapsulating all of the cobalamins it encounters, haptocorrin appears to take the first step in a process which – eventually – ensures that working cells are presented only with B12.

In the duodenum, the ingested food bolus encounters pancreatic juices which are alkaline, and which contain the proteases trypsin and chymotrypsin; these partially dismantle a proportion of the holohaptocorrin molecules as they travel through the ileum, exposing any B12 they may contain. In this more alkaline environment, IF has great affinity for B12, and each available IF molecule binds to an exposed B12 molecule.

Some of the remaining holohaptocorrin finds its way into the bloodstream; the rest travels onwards (and out) through the digestive system

Some of what we digest is ourselves

<http://www.vivo.colostate.edu/hbooks/pathphys/digestion/smallgut/lifecycle.html>

“Villi are projections into the lumen covered predominantly with mature, absorptive enterocytes, along with occasional mucus-secreting goblet cells. These cells live only for a few days, die and are shed into the lumen to become part of the ingesta to be digested and absorbed.”

All of those “bits of us” contain B12. Within the alkaline environment of the ileum, uncommitted IF molecules are able to pick up any free B12 molecules they may encounter; the pancreatic proteases are also able to expose – for IF pick-up - B12 contained in cellular organelles (eg mitochondria) by dissolving the organelles’ protein structures.

The IF/B12 molecules eventually arrive at specialised cells at the terminal area of the ileum; there – by a process of transiting through individual cells – the B12 is shuttled from IF molecules to molecules of transcobalaminII. The combined molecule - referred to as “holotranscobalaminII” - moves into the bloodstream. HolotranscobalaminII molecules travel with the blood, identifying and servicing cells in need of B12.

Holohaptocorrin within the bloodstream finds its way specifically into cells of the liver, and thence into the bile; the bile duct returns it from the gallbladder to the duodenum where the digestive process has further opportunity to extract any B12 the holohaptocorrin may contain. This is the same digestive process applied to holohaptocorrin exiting the stomach, and it requires the same digestive enzymes.

This constant re-processing of holohaptocorrin through the duodenum, ileum, bloodstream, and liver is “The Enterohepatic Circulation of Vitamin B12”. It may have evolved in response to the unreliability of supplies of dietary B12; as a way of maximising the extraction of B12 from the diet using only a relatively short length of intestine; or as a combination of both.

A consequence of its existence is that – if the supply of dietary B12 is simply cut off by, for instance, a deliberate change in eating habits – it can be over 20 years before B12 Deficiency problems start to appear. However, where one, or more, of the substances involved in the B12 transfer “chain” is absent (for example, IF in the case of a PA sufferer) neither dietary B12, nor enterohepatic B12, nor the B12 shed along with the luminal lining of the ileum can be accessed and moved on to the next stage of the process. Thus, whilst PA is in the process of establishing itself - with consequent diminution in the availability of IF - the sufferer will be able to access less and less B12 – either from dietary intake, or via the enterohepatic circulation.

B12 is not “consumed”, but it does get lost – in apoptosis, accident, immune response, etc. Another transport molecule – transcobalaminIII – appears to have evolved to retrieve as much of the “lost” B12 as possible.

For PA sufferers – the eventual absence of IF means that there is no mechanism to replace the B12 lost during routine cellular activities. From the moment B12 processing stops, a PA victim is running only on the B12 already at work in the tissues, or still available within circulating holotranscobalaminII. As this declines, s/he experiences increasingly severe signs and symptoms of B12 Deficiency. An elapsed period of just 2-3 years is typically quoted.

Some phagocyte cells of the reticuloendothelial system are also able to intercept holohaptocorrin molecules; since the task of such cells is to identify and to destroy invading antigens, it is feasible that they may be the graveyards of any circulating holohaptocorrin which does not contain B12.

Liver “Storage” of B12

There is no quibbling with the numbers researchers quote; the liver undoubtedly contains a lot of B12 – pound for pound. The problem comes when physicians consider that – simply because there is a lot of B12 there – then that somehow makes the liver a “store”. Taking such a view wouldn’t normally matter; the body hoards stuff all over the place, “mining” it when the need arises, and replacing it on an opportunity basis: eg <http://www.thewolfeclinic.com/calciumworks.html> . The problem arises when you start to believe that the damage accruing from a long term deteriorative process can be fixed with a handful of injections, and when you take serum levels as a direct measure of the functioning of a distant, complex organic process.

Osteoporosis is a common enough problem, confirmed by a bone density scan; it is also commonly associated with low serum calcium levels:

http://www.healingwithnutrition.com/odisease/osteoporosis/calcium_estrogen.html

Administering calcium in a suitable supplemental form will have the effect of raising low serum concentrations to more normal levels. Nevertheless, it is not customary to tell patients that their osteoporosis has been satisfactorily treated because their serum calcium levels have become “adequate.” Yet this is analogous to what is done in the case of B12 Deficiency.

To view the liver simply as a “B12 store” is to be profoundly misled. The liver is the core of an elegant B12 re-cycling machine, and the process is fundamentally different from

the extraction and replacement of, for instance, skeletal calcium. Many of the B12 molecules within the cycle are the same ones over and over, whereas dietary calcium is used steadily to replace the atoms taken from bone for other purposes.

B12 is water soluble, difficult to obtain, and difficult to retain. Travelling in the circulation as free molecules, it would simply be dumped overboard in our urine (interestingly colouring it, as many B12 supplementers will attest). To counter this, animals have evolved an elegant system for conserving it, and the “store” is – in truth - an expression of the limitations of the capacity of the conservation system. (Oh, would that the same applied to fats! “Limitless” adipose tissue is a **real** storage system.)

If the liver “stored” B12 in the way that we store surplus energy as adipose tissue, then – logically – there would be a mechanism for “drawing” on it in lean times. However, the only mechanism anyone seems to have found - configured to move B12 from the liver into the rest of the body – is the enterohepatic circulation. Its operation is akin to the circulation of lubricating oil within an engine, with B12 an integral component of the system. The system “pumps” B12 throughout the body to support hundreds of processes, then scavenges it for re-use.

An idea seems to have taken hold that the majority of the body’s daily B12 support is derived from dietary input, and that the enterohepatic circulation is just a kind of sideshow to this main event. Three pieces of evidence strongly suggest that the opposite is true:

- a. Daily dietary input is minuscule, compared with the quantity of B12 within the body’s tissues – including the liver. Dietary input seems to be no more than a “top up” to replace the tiny amount lost daily by a healthy body.
- b. If all dietary B12 input ceases completely, then the enterohepatic circulation will **still** support a healthy body for up to about a quarter of a century before the cracks begin to show.
- c. Far from distributing the B12 “store” in the event of failure of dietary assimilation – the system becomes even more miserly in conserving it.

In good times, we have enough B12 for our needs via dietary uptake, and the scavenge pump of the enterohepatic circulation; the system runs at “normal” efficiency, and some B12 even goes overboard in the faeces. In lean times, we have only the mechanism of the scavenge pump, which – simply because of its elegant configuration – becomes increasingly efficient. Consider this:

(http://whqlibdoc.who.int/publications/2004/9241546123_chap14.pdf)

“The absorption of vitamin B12 mediated by the glycoprotein, intrinsic factor, is limited to 1.5–2.0mg per meal because of the limited capacity of the receptors.”

and this:

“for daily intakes of less than 1.5–2.0mg of free vitamin B12, the intrinsic factor-mediated system absorbs that entire amount”

Ie- with adequate dietary intake, and with a healthy enterohepatic system running at full capacity - we actually consume more B12 in our food than our systems need – or can cope with. The limiting factor is the availability of IF, with any excess B12 going overboard in faeces; furthermore, as dietary intake falls, then so too does the amount jettisoned.

Any process has inefficiencies; under normal circumstances, the enterohepatic circulation will inevitably fail to trap and to re-cycle all of the B12 within the system; dietary top-up balances the loss.

There appears to be no feedback mechanism to link the synthesis of IF to the availability of dietary B12. In the event of a restriction to dietary B12 intake, there is therefore an excess of IF over B12 available within the ileum.

Thus, the poorer the dietary supply of B12, the more “surplus” IF there is available to take part in the scavenging process, the more B12 is scavenged, and the more the perceived efficiency of the system improves.

The time at which B12 Deficiency signs/symptoms begin seriously to make their presence felt is a reflection of the point at which any given individual’s enterohepatic cycle ceases to cope – ie, the point at which re-cycling/re-supply ceases adequately to support the body’s demands.

Supplementation

Supplemental B12 is processed in a profoundly different way from that acquired naturally through diet.

Returning to the Jacobsen paper

<http://www.cobento.dk/gfx/content/pdf/Cobalamin%20Uptake%20and%20Utilization.pdf> this sentence is to be found in the introduction:

“Because of the highly polar nature of cobalamin(s), only 1% of an oral intake can traverse plasma membranes by passive diffusion.”

This figure is often quoted, and it refers specifically to the absorption of “free” B12 from the intestinal lumen, through the ileal cells, and into the bloodstream. The importance of it here is to show that – despite its being a moderate-sized molecule – B12 is

nevertheless small enough actually to gain access to cells independently of the active transport mechanism of IF and transcobalaminII, and to leave them again. That B12 can freely move – in bulk – through cell membranes, when conditions are artificially right, is indicated here: <http://www.ncbi.nlm.nih.gov/pubmed/4048655>

The movement is effected by the fundamental physics of diffusion. The wall of a cell is a semi-permeable membrane; create a steep enough concentration gradient - of any water-soluble substance – between the outside and the inside of the cell, and the solute has the potential to migrate into the cell. The sheer size of some molecules (proteins and starches, for instance) can bar this from happening; but the B12 molecule appears to be able to slip through – provided a gradient exists.

Oral supplementation will – during the transit of the digestive bolus containing the supplement – raise the B12 concentration within the ileum to a level higher than that within some of the ileal cells, and diffusion will take place. This – in its turn – will create a “free B12” diffusion gradient first between the ileal cells and the bloodstream, and then between the bloodstream and the tissues. This simple physical process will cause B12 to diffuse into the cytoplasm of any cells it can access – provided the B12 concentration in the bloodstream is higher than that of the tissue cell in question.

Because the molecule is small enough to diffuse into our cells, it’s also – unfortunately - small enough to be processed out of the bloodstream by the kidneys. The trick is therefore to persuade diffusion to continue strongly enough, and for long enough to do some good. Creating a steep diffusion gradient, whilst – at the same time – temporarily overwhelming the kidneys’ ability to deal with the circulating material, would be a good way to do the job. Theory strongly suggests that large, frequent doses will do the trick. The practical experience and Net research of a lot of B12-Deficient individuals appears to confirm it.

The efficiency of oral administration is implicitly poor because it involves three separate diffusion pathways – from the bolus into the ileal cells, from the ileal cells into the bloodstream, and from the bloodstream into the tissues. Sublingual administration – a more “designer” version - still involves multiple pathways; however, its efficiency can be improved by careful selection of the excipients to be used in the tablets, and by the patient’s own technique. Through design and intent, efficiencies as high as 15-25% can be achieved.

Subcutaneous injection delivers 100% of the active content directly into the bloodstream.

The maintenance of progress is dependent on the maintenance of a diffusion gradient “sloping” into the cells; the steeper the slope, the better the results appear to be. To reverse the slope after some arbitrary period – as preached by current medical practice – is to invite B12 already in the cells to diffuse out again. It is the experience of many people discussing the subject on the Net that cutting back on doses causes an almost immediate deterioration in health; it’s a way of life to PA sufferers treated “conventionally”!

B12 is deeply implicated in cellular replication, and in the replication and day-to-day functioning of the mitochondria. One hypothesis has it that many B12-Deficiency problems have their roots in falling mitochondrial populations, and the poor functioning of those that remain. "Breeding" adequate and active mitochondrial populations depends on there being abundant B12 in the cytoplasm - sufficient to assist in replication, and to be taken up within the cristae of the new organelles. There seems little sense in routinely denying patients a dietary necessity throughout this process - particularly when it is likely to lead to the leaching out (by reversed diffusion) of "ready for use" B12 already available within the cytoplasm.

What physicians are taught, believe, and practise is absurd; or it would be, if it didn't condemn millions of people to the living death of inadequate and incomprehensible treatment with no discernible justification in research, theory, or therapeutic results.

I am the simplest of B12-Deficient creatures - the starved vegetarian; my demise - from start to finish - took 21 years. However, my collapse - when it eventually came - was rapid, and spectacular; and my signs/symptoms were serious and legion. I have made a remarkable recovery, and continue to improve - using large, and frequent, injected doses.

I am in everyday contact with many other B12 Deficiency sufferers; the reasons underlying their individual conditions are as varied as their backgrounds. In many cases, the cause has been genetic - coding errors inhibiting adequate synthesis of transcobalamins, for instance, and - of course - PA; others have been damaged by prescribed medications such as Metformin, Omeprazole, Fluoroquinolone, and some oral contraceptives; other sufferers attribute their problems to nitrous oxide exposure, to coeliac disease, to stomach surgery, or to helicobacter. There are many more causes, but one that is particularly relevant to this discussion is direct interference with enterohepatic circulation via cholecystectomy,

We all have a number of findings in common:

- a. Throwing a lot of B12 at the problem causes steady reversal of damage.
- b. The repair of damage attributable to B12 Deficiency - and subsequent reconstruction - both benefit from additional supplements which vary from person to person.
- c. Cutting back on B12 supplementation causes an immediate worsening of signs/symptoms.

The research described in this paper <http://www.ajcn.org/cgi/reprint/8/3/285.pdf> makes it clear that supplemental B12 finds its way to the liver. However - although the paper talks in terms both of diseased and healthy livers - it only describes livers which are still taking some part in the active circulation of the vitamin. I can find nothing to suggest that supplementing a fully-depleted liver will cause the enterohepatic circulation immediately to re-start functioning.

The idea that there is a direct relationship between liver and serum B12 content has little in the way of factual data to support it either; in fact, this paper: <http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1413443&blobtype=pdf> says exactly the opposite:

P233: “There was little relation between liver B12 content and serum biochemical values”

P234: “No correlation was apparent between serum B12 levels and liver B12 contents”

That paper was written in 1963, and draws support from far earlier work. It stands in direct contradiction to the notion that measuring serum levels somehow indicates how “full” a previously-depleted liver has become.

Common medical practice regarding B12 supplementation therefore seems to rest on two very shaky assumptions:

- a. That there is a direct relationship between serum levels and liver content of B12.
- b. That supplementation will – in a very short time – re-start a failed enterohepatic circulation.

The first assumption is contradicted by research; the second appears to have none to support it.

In this paper: <http://www.hbot4u.com/autismdoc2.pdf> – devoted specifically to the effects of “large” doses of methylcobalamin on autism – the author puts forward the suggestion that – in effect – some people become “B12 Dependent” rather than “B12 Deficient”; it forms part of his reasoning to explain the success that his methods appear to have. I don’t know whether he is right or wrong; I don’t know whether – if I was dying of thirst – that would be because I was “Water Dependent” or “Water Deficient”. Whatever the full justification for what happens, though, the paper reflects the experience of many, many people that large frequent doses of methylcobalamin steadily improve the patient’s condition, whereas small, infrequent doses (even of methylcobalamin) merely postpone her/his death.

It may well be that – with over two years of effective supplementation, and steady improvement, behind me - my enterohepatic circulation is now firing on all cylinders; it is possible that I could function – as before – at far less than my current rate of supplementation. However, I doubt whether I shall ever know, because – for the foreseeable future - I have no intention of cutting back.