INTERNATIONAL HEALTH NEWS

Your Gateway to Better Health!

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Welcome back to this the first issue of a brand new year. I am very pleased to introduce you to a long-time reader, Georges Mouton MD, as our newest guest author. Over the years, I have received numerous enquiries from readers who have been discovered to have abnormally high vitamin B12 levels, even though they have not been supplementing with the vitamin. I have consulted various experts in the field, but have been unable to receive a satisfactory explanation for this phenomenon – until now.

Georges Mouton, in his fascinating research report "Elevated Blood Levels of Vitamin B12", provides substantial evidence that the problem of otherwise unexplainable vitamin B12 excess is due to bacterial overgrowth in the intestines. Dr. Mouton also relates a case history in which the patient normalized her vitamin B12 levels through dietary changes and supplementation. This is a MUST read!

Also in this issue researchers confirm the benefits of fish and fish oils in cardiovascular disease, vitamin D supplementation may reduce the risk of cancer, and magnesium is essential for bone health.

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All the best,
Hans

Highlights

Review supports benefits of omega-3 fatty acids for prevention of heart disease

ATLANTA, GEORGIA. Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have been linked to lower mortality from coronary heart disease (CHD) in several, but not all, observational studies on the topic. Prevention trials of n-3 PUFAs have also supported a role in CHD prevention, but several different varieties of n-3 PUFAs were used.

Now, researchers from Emory University School of Medicine have reviewed the data from randomized controlled clinical trials on n-3 PUFAs and CHD. The studies were divided into those using plant-based n-3 PUFAs (alpha-linolenic acid, ALA), fish-based n-3 PUFAs (eicosapentaenoic acid, EPA, and docosahexaenoic acid, DHA), and fish consumption in the diet. Fourteen randomized clinical trials were included in the review, six of which were of fish oil, including one large trial of 10,000 participants. The researchers report a clear trend suggesting that there are important differences in CHD outcomes when using fish-based EPA or DHA compared with plant-based

ALA. Most of the fish oil trials suggest a significant reduction in total mortality and CHD deaths and a possible strong antiarrhythmic effect. The dietary fish trials also suggest a reduction in mortality and reduced arrhythmia, supporting the theory that fish-based n-3 PUFAs may impart their cardioprotective effect by acting as an antiarrhythmic agent. They may do so by stabilizing the electrical activity of heart muscle cells or by decreasing the heart rate. The trials of ALA supplements and ALA-enriched diets, including walnut, soybean, or flaxseed oil, were less reliable, but showed possible benefits in reducing mortality.

The review concludes that the evidence suggests a role for fish oil (EPA, DHA) or fish in secondary prevention, as clinical trial data demonstrate a significant reduction in total mortality, coronary heart disease death, and sudden death. However the data on ALA is limited by studies of limited quality. Several previous studies have suggested that n-3 PUFAs reduce heart attack risk through benefiting endothelial function (cells of blood vessel walls), reducing inflammation, and the risk of thrombosis (blood clotting). The American Heart Association has published guidelines for patients with CHD recommending a consumption of fish and fish oil, totaling 1g/day of EPA and DHA.

Harper, C.R. and Jacobson, T.A. Usefulness of Omega-3 Fatty Acids and the Prevention of Coronary Heart Disease. American Journal of Cardiology, Vol. 96, December 2005, pp. 1521-29

Vitamin D in pregnancy protects children's bones

SOUTHAMPTON, UNITED KINGDOM. Giving pregnant women vitamin D could mean their babies grow stronger bones in later life and will therefore be at lower risk of sustaining bone fractures, a new study suggests. The study found that the mothers of children with weaker bones were lacking in vitamin D while they were pregnant. Vitamin D is needed for bone development during childhood, yet women of childbearing age are often deficient.

A team at the MRC Epidemiology Resource Center, Southampton General Hospital gathered data on 198 children born in 1991 and 1992 and compared it against the vitamin D status of their mothers, assessed by a blood test in late pregnancy. Nearly half the women (49 per cent) had insufficient vitamin D at this point. When the children reached nine years of age, the researchers measured their body size and bone mass and found that children whose mothers were lacking in vitamin D had weaker bones and a higher fracture risk. The authors explain that these findings provide evidence that maternal vitamin D status during pregnancy influences the bone growth of the offspring, and their risk of osteoporosis in later life. Maternal vitamin D levels have not previously been measured in relation to children's bone mass.

The results add to a large body of evidence suggesting that development within the womb and during the time shortly after birth contributes to bone mineral accrual and thereby osteoporosis risk. The findings also point to preventive strategies which now require evaluation in randomized controlled trials, say the authors. Vitamin D supplementation of pregnant women, especially during winter months, could lead to long-lasting reductions in the risk of bone fracture in their children. Vitamin D is crucial for the absorption of calcium which is central to the formation of healthy bones. Levels can be improved though diet (oily fish and eggs), supplementation, and sunlight, which enables the body to make vitamin D in the skin.

Javaid, M.K. et al. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. Lancet, Vol. 367, January 2006, pp.36-43

Only a small minority of Americans follows a healthy lifestyle

EAST LANSING, MICHIGAN. So-called 'diseases of comfort' have emerged as the price of living in today's society. As human progress and civilization continue toward better (or more comfortable) living, it is inevitable that diseases caused by obesity and physical inactivity will become more common and more disabling. The importance of following a healthy lifestyle is emphasized in public health guidelines and shown in studies to have substantial health benefits. Researchers from Michigan State University set out to assess the proportion of Americans who follow the four main 'rules' of good health: don't smoke, maintain a normal weight (BMI of 18.5-25), eat five servings of fruits and

vegetables a day, and take 30 minutes of exercise five times a week.

To discover the prevalence of these healthy lifestyle characteristics, they took data from more than 153,000 adults from the year 2000 behavioral risk factor surveillance system sponsored by the Centers for Disease Control and Prevention - the world's largest telephone survey, tracking health risks in the United States. Over three-quarters (76 per cent) of adults followed the advice on smoking, 40 per cent on weight, 23 per cent on fruits and vegetables, and 22 per cent on exercise. But only three per cent followed all four 'rules'. The researchers conclude that a healthy lifestyle is undertaken by very few adults in the United States. They add that, although women, older people, white people, better educated people, people in good health, and wealthier people did a little bit better, no subgroup followed this combination to a level remotely consistent with clinical or public health recommendations.

The effect of following these lifestyles is greater than anything else medicine has to offer, they write, adding that we could eliminate the vast majority of chronic disease by following a healthy lifestyle. They suggest that doctors guide patients in simple ways to incorporate 10 more minutes of exercise three times a day into their schedule or to include a few more fruits and vegetables in their meals. Public health needs to be more passionate about health issues associated with human progress and adopt a health promotion stance, they conclude.

Reeves, M.J. and Rafferty, A.P. Healthy Lifestyle Characteristics Among Adults in the United States, 2000. Archives of Internal Medicine, Vol. 165, April 2005, pp. 854-57

Magnesium benefits bone health

MEMPHIS, TENNESSEE. Magnesium could be as important to bone health as calcium, new research suggests. A team from the University of Tennessee investigated the links between magnesium intake and bone mineral density (BMD) by studying data on 2,038 black and white men and women aged between 70 and 79 years. The participants were enrolled in the Health, Aging and Body Composition Study (Health ABC) initiated in 1996 by the Geriatric Epidemiology Section of the National Institute on Aging.

Participants were given tests to measure their BMD, and the results were compared with data from questionnaires covering food and supplement intake of magnesium. Analysis showed that magnesium intake was significantly linked to higher BMD throughout the whole body, but only in the white men and women. The effect was stronger in women than men - BMD was higher by 0.04g per square centimeter in women and 0.02g/cm2 higher in men in the top fifth for magnesium intake compared with the bottom fifth. This effect was independent of several other factors including age, osteoporosis or bone fractures, calorie intake, calcium and vitamin D intake, BMI, smoking, alcohol and exercise.

The researchers believe that magnesium's role is similar to that of calcium. They calculate that for every 100 milligram per day increase in magnesium intake, there is a one per cent increase in BMD. They report that although this one per cent increase seems small, across a population it may have large impact, and explain that most older adults get far less than the recommended daily allowance of magnesium (320 mg/day for women and 420/mg day for men). They add that black people might process vitamin D and other calcium regulating hormones slightly differently to whites, but magnesium may still have an association with BMD. Previous observational and clinical studies have suggested an association between low magnesium status and increased risk of cardiovascular diseases, hypertension, osteoporosis, diabetes, and other chronic diseases.

Ryder, K.M. et al. Magnesium Intake from Food and Supplements Is Associated with Bone Mineral Density in Healthy Older White Subjects. The Journal of the American Geriatrics Society, Vol. 53, November 2005, pp. 1875-80

Editor's comment: Magnesium deficiency is widespread in the western world. Daily intake should be at least 400 mg. While some of this may be obtained from food (blackstrap molasses, buckwheat flour, oat bran, and pumpkin seeds are good sources), the majority of people would no doubt need to supplement to achieve an adequate daily intake. The absorbability of magnesium, unfortunately, varies widely. Only 4 per cent of the magnesium oxide found in most multivitamins is actually absorbed, making this particular form of the mineral next to useless. The most bioavailable form of magnesium is chelated magnesium, also known as magnesium glycinate.

Evidence points to vitamin D for cancer prevention

SAN DIEGO, CALIFORNIA. Many lives could be saved each year through higher vitamin D consumption, suggests a review of the scientific evidence. The review of 63 observational studies on vitamin D and cancer risk concluded that 1,000 international units (IU), or 25 micrograms, of vitamin D3 every day lowers the risk of developing colon cancer by half, and the risk of breast and ovarian cancer by 30 per cent. Vitamin D3 is found in eggs, organ meats, animal fat, cod liver oil and fish. It is equivalent to the form of vitamin D formed in skin from sunlight.

The review team, from the University of California in San Diego, is now demanding public health campaigns to increase vitamin D intake. They believe it is a cheap and easy way to prevent countless deaths. The authors report that early detection of breast cancer using mammography reduces mortality rates by approximately 20 per cent. But use of vitamin D might prevent this cancer in the first place. The review concludes that the high prevalence of vitamin D deficiency, combined with the discovery of increased risks of certain types of cancer in those who are deficient, suggest that vitamin D deficiency may account for several thousand premature deaths from colon, breast, ovarian and other cancers annually. It also found that people living in the northeastern United States are at an increased risk of vitamin D deficiency, as are individuals with higher skin pigmentation because this reduces the skin's ability to synthesize vitamin D.

Researcher Cedric F. Garland pointed out that a preponderance of evidence, from the best observational studies the medical world has to offer, gathered over 25 years, has led to the conclusion that public health action is needed. We now have proof that the incidence of colon, breast, and ovarian cancer can be reduced dramatically by increasing the public's intake of vitamin D, he believes.

Garland, C.F. et al. The Role of Vitamin D in Cancer Prevention. The American Journal of Public Health. Published online December 2005, in print February 2006

Editor's comment: Foods, including fortified milk, are generally very poor sources of vitamin D. Therefore, if you reside in northern climes, are housebound, use sunscreens, or generally do not get at least a ½ hour of unprotected sunlight exposure every day, it is necessary to supplement with at least 1000 IU/day of vitamin D3 (cholecalciferol). Vitamin D2 (ergocalciferol) should not be used since it is synthetic and can be toxic.

Bone loss risk from alcohol underestimated

OMAHA, NEBRASKA. The risk posed to bone health by alcohol is underappreciated, a new report has found. A researcher from the Omaha Veterans Affairs Medical Center examined the current evidence and concluded that there is a common basis for the adverse effects of alcohol on bone health. Chronic consumption of excessive alcohol is linked to skeletal abnormalities such as bone loss, fracture and deficient bone healing, he found. In each of these cases, alcohol adversely affects osteoblast (new bone cell) activity, thus suppressing new bone formation needed in both normal bone growth and fracture healing. At any given time during adult life, and in various parts of the skeleton, small portions of old bone are removed by cells called 'osteoclasts,' and new bone is formed by cells called 'osteoblasts.' In a healthy person, the two activities are in balance so that there is no net loss of bone. But in heavy drinkers, the empty space created by normal bone-removing activity is inadequately filled by newly formed bone. The cumulative effect of this process is manifested as measurable bone loss over a period of just a few years. Eventually, chronic consumption of excessive alcohol results in an 'osteopenic' skeleton - a decrease in bone density that paves the way for osteoporosis.

The review covered human, animal and cell-culture studies of alcohol and bone health, and confirmed that alcohol-induced osteoporosis is distinct from postmenopausal osteoporosis, resulting mainly from decreased bone formation rather than increased bone breakdown. It also found strong evidence that alcohol has a dose-dependent toxic effect on osteoblast activity.

It concludes that many people know about alcohol's effects on the liver and the damage it can cause to this organ after years of heavy drinking, but considerably fewer people know about alcohol-induced bone disease. The researcher recommends future studies to resolve current ambiguities over alcohol-induced bone disease, especially as he feels that current knowledge is insufficient to develop interventional strategies for the prevention and treatment of alcohol-induced bone disease.

Chakkalakal, D.A. Alcohol-Induced Bone Loss and Deficient Bone Repair. Alcoholism: Clinical & Experimental Research, Vol. 29, December 2005, pp. 2077-90

NEWSBRIEFS

Paracetamol (Tylenol) causing liver failure

Sales of a widely-used painkiller should be restricted to prevent its high risk of liver failure, experts believe. Acetaminophen, also called Paracetamol or Tylenol, is currently the top cause of acute liver failure in the US, report researchers from the University of Texas Southwestern Medical Center. Although the over-the-counter drug is considered safe, it can lead to liver failure at surprisingly low doses and overdose is accidental in more than half of cases. Data from 275 patients in a coma following acetaminophen-induced liver failure showed a clear threshold for overdose - as little as 10g a day for three days - regardless of the length of time since the drug was taken. The authors recommend that limits be placed on the package size to limit high-risk use, as is done in the UK, and warn that the prescription of narcotic-acetaminophen combinations should be restricted. They also support identification of susceptible groups and educational programs for physicians, pharmacists, and consumers.

Larson, A.M. et al. Acetaminophen-induced acute liver failure: Results of a United States multicenter, prospective study. Hepatology, Vol. 42, December 2005, pp. 1364-72

Magnet therapy condemned by experts

Magnet therapy has been attacked by health and physics experts who criticize its supposed benefits for pain relief. In a journal editorial, Leonard Finegold of Drexel University and Bruce Flamm of the Kaiser Permanente Medical Center pointed out the lack of reliable evidence. Extraordinary claims demand extraordinary evidence, they believe. But sifting through the research studies they fail to be convinced, and state that any healing effect of magnets must be small since published research is weighted heavily against any therapeutic benefit. Patients should be advised that magnet therapy has no proved benefits, they recommend, adding that the funding would be better spent on evidence-based medicine. Magnetic products include bracelets, insoles, wrist and knee bands, back and neck braces, and pillows and mattresses. They currently make around a billion US dollars each year for their manufacturers. Given the way they are marketed, it is not surprising that some patients believe the claims made for the therapeutic value of magnets, but the experts say that even theoretically, magnet therapy seems unrealistic.

Finegold, L. and Flamm, B.L. Magnet therapy - Extraordinary claims, but no proved benefits. British Medical Journal, Vol. 332, 7 January 2005, p. 4

Editor's comment: I seem to recall seeing similar attacks being made on acupuncture 20 years or so ago.

Vitamin deficiency can follow obesity surgery

Gastric bypass surgery for obesity can lead to a dangerous vitamin deficiency, neurologists from the University of Rochester have warned. The operation involves stapling the stomach to form a small pouch so that food bypasses the remainder of the stomach and some of the intestine. It can lead to a dramatic reduction in nutrient intake. One essential nutrient is vitamin B1 - a deficiency can lead to Wernicke's encephalopathy, a severe brain disorder causing nausea, anorexia, fatigue, hearing loss, forgetfulness, and ataxia, or an inability to coordinate muscle movements. One 35-year-old woman developed problems following the operation. After 12 weeks she had lost 40 pounds and had difficulty walking and concentrating. Vitamin B1 deficiency was diagnosed using an MRI scan which highlighted abnormalities in the patient's brain. She recovered following intravenous doses of the vitamin. The neurological complications following gastric bypass surgery are diverse. Vitamin B1 deficiency and Wernicke's encephalopathy should be carefully considered in surgically treated obese patients, the authors recommend.

Foster, D. et al. Wernicke encephalopathy after bariatric surgery: Losing more than just weight. Neurology, Vol. 65, December 2005, p. 1987

Heart failure patients may benefit from exercising

Should patients with heart failure undertake any sort of physical exercise? New findings will help doctors answer this question. A team from the University of Colorado and Ohio State University set out to discover whether exercise would improve the prognosis of patents with congestive heart failure (CHF), or put excessive stress on their hearts. Using rats which were certain to develop CHF, they studied the effects of low-intensity exercise, equivalent to a "brisk, but not taxing, walk". The rats that exercised had significantly lower mortality, and their CHF was delayed or suppressed. The researchers state that low intensity exercise training markedly delayed the onset of overt CHF. They also found that some of the cellular changes normally associated with the development of CHF were suppressed by exercise. They believe that using exercise early in CHF might delay the need for drugs and stem the downward spiral in heart failure.

Emter, C.A. et al. Low-intensity exercise training delays the onset of decompensated heart failure in the spontaneously hypertensive heart failure (SHHF) rat. American Journal of Physiology-Heart and Circulatory Physiology, Vol. 289, November 2005, pp. 2030-38

Stress increases cancer risk

Further evidence has come to light on the relationship between stress and illness. It is already well known that chronic (long-term) stress suppresses the immune system, but now researchers show that it also increases the risk of cancer following exposure to a potentially cancer-causing agent. A team at Ohio State University exposed rats to ultraviolet (UV) radiation, an established risk factor for the form of skin cancer called squamous cell carcinoma. Half of the rats were also exposed to chronic stress by being restrained in a very small cage in an attempt to mimic a sense of confinement. Both groups of mice showed a suppressed immune system, but the mice under stress formed skin cancer tumours faster than those exposed to UV radiation alone. After analysing blood and skin samples, the team found that chronic stress suppressed certain components of the immune system including protective T cells and chemical messengers called type 1 cytokines. They report that UV radiation and chronic stress act together to increase susceptibility. This is important as many people are exposed to both stress and sunlight on a regular basis.

Saul, A.N. et al. Chronic Stress and Susceptibility to Skin Cancer. The Journal of the National Cancer Institute, Vol. 97, December 2005, pp. 1760-67

Doubts over fiber benefit for colon cancer

Eating fiber has long been thought to protect against colon cancer, but new research is casting doubt on this advice. Researchers from the Harvard School of Public Health discovered that the supporting evidence is inconsistent. While some studies have found a correlation, those, which have followed people over time, have found no link. The team took data from 13 long-term studies covering 725,628 men and women, each followed for up to 20 years. Overall, those eating the most fiber had a 16 per cent lower chance of colorectal cancer than those eating the least. But when the researchers analysed the data taking into account other dietary factors, the link was no longer significant. However the team concludes that a diet high in fiber from whole plant foods can be advised because this has been related to lower risks of other chronic conditions such as heart disease and diabetes. A commentary adds that that the findings provide at least some indications that dietary fiber is related in some way to colon and rectal cancer risk.

Park, Y. et al. Dietary Fiber Intake and Risk of Colorectal Cancer: A Pooled Analysis of Prospective Cohort Studies. The Journal of the American Medical Association, Vol. 294, December 2005, pp. 2849-57

RESEARCH REPORT

Elevated Blood Levels of Vitamin B12

by Georges Mouton, MD

Physicians sometimes encounter cases where a patient's blood level of vitamin B12 (cobalamin) is substantially higher than the normal upper limit. These cases are often assumed to be due to excessive supplementation, consumption of cobalamin-fortified energy drinks or from intramuscular injections or oral supplements prescribed by a health care professional. In most cases, no action is taken upon discovering the anomaly.

However, careful enquiry very frequently demonstrates that no external human intervention explains the finding of high vitamin B12 levels. Thus the answer to the puzzle must be found within the body's internal metabolic processes. It is clear that the amount of vitamin B12 excreted in human faeces does not only correspond to what was not absorbed in the ileum (the last of the three sections of the small intestine), but also reflects the production of significant amounts of cobalamin by the colonic microflora [1].

Intestinal Vitamin B synthesis

The fact that intestinal micro-organisms produce significant amounts of B vitamins is fully accepted and has been published in peer-reviewed international medical journals [2,3]. Intestinal bacterial B vitamin biosynthesis involves at least vitamin B1 (thiamine) [4], vitamin B2 (riboflavin) [5], vitamin B5 (pantothenic acid) [6], vitamin B8 (biotin) [6, 7], vitamin B9 (folic acid) [8,9],and vitamin B12 (cobalamin) [1]. As a matter of fact, bacteria obtained from dairy and belonging to the genus *Propionibacterium* (also abundant in the human intestinal microflora) are extensively used for the biological production of cobalamin [10].

Concerning vitamin B8, also called biotin, "it has long been recognized that the normal microflora of the large intestine synthesize considerable amounts of biotin" [6]. In fact, several studies have shown that the colon is capable of absorbing free biotin and *HM Said* has shown, for the first time in 1998, the functional existence of a specialized carrier-mediated system for biotin uptake in colonic epithelial cells [7]. "In addition, the uptake process is shared by another water-soluble vitamin, pantothenic acid, (…) which is also synthesized by the normal microflora of the large intestine", as biotin inhibited the uptake of vitamin B5 and vice versa [6].

The specialized vitamin B transporter has been cloned in the rabbit intestine by another team in 1999 [11] and named the **sodium-dependent multivitamin transporter (SMVT)**. This transporter is also highly expressed in human enterocytes (cells found in the internal lining of the intestines) [11,12], where it serves to take up not only pantothenate and biotin, but also lipoate (the ion from lipoic acid) [11].

Half a century ago, vitamin B2 (also called riboflavin) was known to be synthesized by intestinal bacteria and the amount provided by this source appears to become significantly higher when adhering to a vegetarian diet [13]. Interestingly, as he did for other water-soluble vitamins B, *HM Said* demonstrated in 2000 "for the first time, the existence of a specialized carrier-mediated mechanism for riboflavin uptake in an in vitro cellular model of human colonocytes" (cells found in the lining of the colon) [5]. Once again in 2001, *HM Said* showed that a model of human-derived colonic epithelial cells possesses a specific carrier-mediated system for thiamine (vitamin B1) uptake [4]. "It is suggested that bacterially synthesized thiamine in the large intestine may contribute to thiamine nutrition of the host, especially towards (…) the local colonocytes" [4].

Certain bacterial species present in the rat colon are also capable of *de novo* synthesis of vitamin B9, better known as folic acid [8]. As clearly evidenced by the use of tritiated (marked with radioactive hydrogen) para-aminobenzoic acid (3H PABA), the experimental "data provide direct evidence that some of the folate synthesized by the microflora in the rat large intestine is incorporated into the tissue folate of the host" [8].

More recently, the same methodology has been utilized with humans in order to determine whether folate synthesized by bacteria in the small intestine rather than in the colon is assimilated by the human host [9].

Indeed, the perfusion of tritiated PABA, a classic precursor substrate for the bacterial folate synthesis, led to the identification of bacterially synthesized (as marked) folates aspirated from in the small intestine. Subsequently, tritiated 5-methyltetrahydrofolate, a major metabolite of folate, was isolated from the human host urine, demonstrating that the human host did absorb and consequently metabolized these bacterially synthesized folates [9].

Intestinal Vitamin B12 Synthesis

Coming back to cobalamin, it has been shown, already in 1980, that "at least two groups of organisms in the small bowel, *Pseudomonas* and *Klebsiella sp.*, may synthesize significant amounts of the vitamin [B12]" [1]. Obviously, the two accepted dogma of vitamin B metabolism in the digestive tract don't seem to correspond to reality: several compounds (vitamins B1, B2, B5, B8 and B9) supposedly absorbed by the small intestine may be assimilated by the colonocytes, while several compounds (vitamins B9 and B12) supposedly synthesized by colonic bacteria may actually be generated in the small intestine! Unfortunately, if we wanted to explain the high vitamin B12 blood levels by some colonic absorption, we must underline that absolutely nothing has been published about this and what seems true for other vitamins B would not be so for cobalamin.

Consequently, we should rather focus on the possibility that bacterially-produced vitamin B12 is absorbed in the small intestine, where most of the assimilation process of other B vitamins takes place. Two different specific proteins ensure the uptake of thiamine (vitamin B1) in the enterocytes of the proximal small intestine and are structurally close to a specific folic acid carrier [14]. Indeed, the intestinal folate (vitamin B9) absorption process occurs via a specialized mechanism that involves the reduced folate carrier (RFC) in the jejunum (the middle part of the small intestine) [15, 16]. We have already mentioned earlier the existence, in the proximal small intestinal enterocytes, of a sodium-dependent multivitamin transporter (SMVT) taking care of biotin (vitamin B8) and of pantothenic acid (vitamin B5). The involvement of a specialized carrier-mediated mechanism for pyridoxine (vitamin B6) by the intestinal epithelial cells has been demonstrated for the first time in 2003 [17]. Finally, a specialized carrier for niacin (vitamin B3) has been uncovered very recently, the article only being published in July 2005 [18].

In contrast to all the other B vitamins, cobalamin is not absorbed in the jejunum or in the proximal (first part of) ileum as they are, but only in the terminal ileum from a quite complex absorption process. This makes absorption very sensitive to diseases affecting specifically, or more frequently, this portion of the digestive tract such as Crohn's disease.

Vitamin B12 Absorption

The term vitamin B12 or cobalamin actually refers to four different forms found in the diet and mostly bound to proteins: **methylcobalamin, hydroxocobalamin, cyanocobalamin,** and **deoxyadenosylcobalamin.**

The absorption process involves five steps:

1. The cobalamins are released from their protein complexes through the action of acid or pepsin in the stomach.

2. They bind to R proteins – cobalamin-binding glycoproteins secreted in saliva and in gastric juice.

3. The cobalamin-protein complexes must then be degraded by pancreatic proteases. This important step may be jeopardized in case of pancreatic insufficiency [19].

4. The free cobalamin combines in the duodenum with another glycoprotein called *intrinsic factor* which is secreted by the stomach parietal (oxyntic) cells; this glycoprotein dimerises and each part of the dimer binds one molecule of cobalamin, making the complex resistant to digestion [20]. The formation of the cobalamin-intrinsic factor complex appears indispensable for the vitamin to be absorbed in the terminal ileum via an active transport system [19].

5. The brush border membrane of the terminal ileum enterocytes contains a specific receptor for the dimeric complex and its importance in the process is shown by a congenital vitamin B12 malabsorption syndrome due to a defect in this receptor. The absorption is hampered by an abnormally low ileum pH, which may occur in some diseases such as the Zollinger-Ellison syndrome.

The problem with vitamin B12 absorption lies in the small safety margin between the dietary requirements for the vitamin and the maximal absorptive capacity of the five-step process outlined above. Cobalamins can also be absorbed passively, but the passive pathway only accounts for 1 or 2 % of the ingested vitamin, explaining the development of anemia when one of the five steps is not functioning properly [20]. The most frequent cause for vitamin B12 malabsorption is represented by the lack of intrinsic factor [19], which may be explained by a genetic defect, an auto-immune condition (auto-antibodies targeting either the parietal cells or the intrinsic factor itself), or a surgical gastrectomy (removal of part or all of the stomach). But further problems can occur at the level of the blood carriers, transcobalamin I and transcobalamin II, which may be impaired [21].

Now, supposing that all these steps leading to an effective absorption of vitamin B12 function adequately, then the presence in significant amounts of bacteria producing cobalamin in the terminal ileum would explain - at least theoretically - a sharp increase in absorption and lead to higher blood levels of this vitamin. If we consider some specific circumstances in the above mentioned study about folate absorption [9], we might discover the mechanism which could lead to an excessive absorption of cobalamin and to an elevation of blood levels.

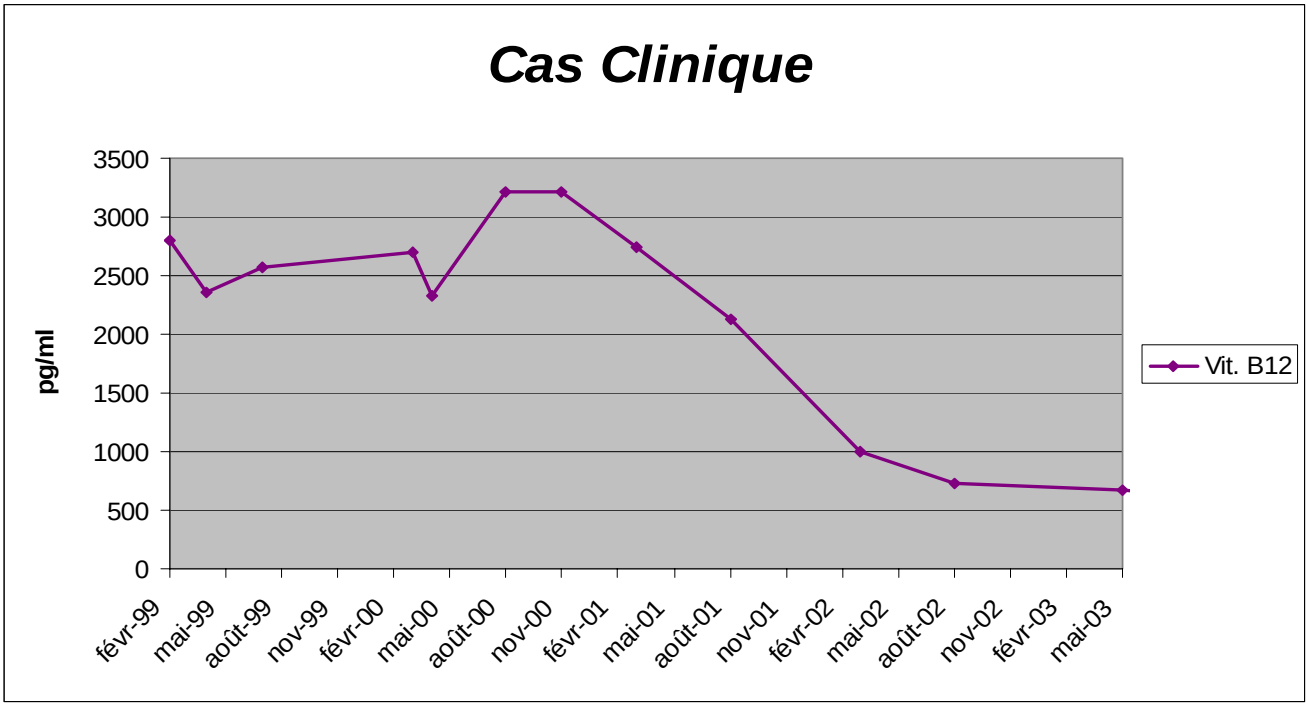
The Role of Small Intestinal Bacterial Overgrowth

In an exemplary functional medicine study, two groups of patients were involved - healthy volunteers and subjects suffering from gastric arthritis (inflammation of the stomach lining). The participants were evaluated before and after the administration of omeprazole (a proton pump inhibitor that turns off gastric acid production) [9]. As expected, both patients with atrophic gastritis (chronic inflammation of the stomach lining) and those receiving omeprazole showed an increased duodenal pH (which stands for less acidity), but also an overgrowth of the small intestinal microflora [9]. Under normal physiological conditions, bacterial growth in the small intestine is inhibited by the acidic environment caused by the presence of hydrochloric acid. However, with an increase in pH the small intestinal environment, normally hostile to the local microflora, becomes friendlier and enables what is called a "**small intestinal bacterial overgrowth" (SIBO)** either in case of atrophic gastritis [22] or in case of drug-induced hyperchlorhydria [23], especially among "subjects taking a hydrogen pump blocking agent [such as] omeprazole" [24]. Interestingly, SIBO seems to provide "a unifying framework for understanding irritable bowel syndrome (IBS) and other functional disorders" [25], such as fibromyalgia [25, 26].

We come back once again to the experimentation with labelled folate to review its conclusions as presented in the corresponding abstract: "(1) Mild bacterial overgrowth caused by atrophic gastritis and administration of omeprazole are associated with *de novo* folate synthesis in the lumen of the small intestine; (2) the human host absorbs and uses some of these folates" [9]. Indeed, the unexplained increase of blood levels that we are describing about vitamin B12 may also occur with folic acid. We present a first case study concerning a four-year old boy who suffered from diarrhoea and abdominal bloating. Celiac disease had been ruled out, but he showed an increase of specific urinary organic metabolites corresponding to a bacterial overgrowth, typically from *Clostridium*. This child had never been treated with vitamins at the time of his first blood check, though his erythrocytic folate level (folic acid in red blood cells) was measured at 913µg/l whereas 257µg/l - 582µg/l represents the lab's normal range for the parameter. Besides, the plasma level of cobalamins was raised to 1324ng/l, contrasting with the laboratory's normal range of 450ng/l to 1200ng/l. He was treated for intestinal dysbiosis and put on a casein-free diet, improved dramatically… and was not blood tested again!

Case Study involving Elevated Vitamin B 12 Levels

We present a second case study concerning a thirty-year old woman (in 1999) whose blood parameters were monitored for unrelated matters but strikingly presented repetitive high vitamin B12 levels without any related supplementation neither from the vitamin itself, nor through vitamin B complexes / multivitamin formulas.



The original data from our records are presented above. All the results for vitamin B12 are expressed in pg/ml and the normal range provided by the Belgian laboratory is 200pg/ml to 900pg/ml, even if the lower limit could be considered as too low to be compatible with optimal health. We see that the five first measurements, from February 1999 to April 2000, were quite consistently fluctuating around 2500pg/ml (respectively 2796pg/ml on 6/2/99, 2355pg/ml on 19/4/99, 2572pg/ml on 30/7/99, 2697pg/ml on 7/3/2000 and 2325pg/ml on 17/4/00), which is much too high! At the time, the patient's blood had to be monitored in relation to a drug-based anti-epileptic treatment. However, the young woman was not complaining about her digestive system, even if she occasionally mentioned some severe but transitory abdominal cramps.

Her digestive problems started during the summer season in 2000, with IBS like symptoms, bloating, diarrhoea and excruciating pain in the belly. She was examined thoroughly and the gastroenterologist initially suspected Crohn's disease due to the presence of mucosal ulcerations in the proximal small intestine. During that period of major clinical deterioration, blood vitamin B12 level increased even further as seen from two measurements performed on 25/08/00 (3220pg/ml) and on 28/11/00 (3221pg/ml). Then, she refused to take the corticoids prescribed by the specialist and went on a natural treatment based on diet modifications (exclusion of high IgG foods, in her case: dairy products, beef, bananas and black pepper), supplements (according to her biological results in blood and in 24-hour urine), antimicrobial herbs (such as grapefruit seed extracts) and probiotics.

She didn't improve dramatically, but slowly started to complain less within a few weeks, then was feeling slightly better in March 2001 and significantly better when she came back five months later, in August 2001. Very interestingly, vitamin B12 blood levels started to decrease to 2740pg/ml on 24/3/01 and then down to 2132pg/ml on 22/08/01. In fact, the last result provided her lowest blood value since the beginning of the study. In September 2001, we then asked the gastroenterologist to perform a new endoscopy, in order to dismiss the diagnosis of Crohn's disease and make sure that we were not harming her by not giving the prescribed drugs. The digestive exploration was then considered as normal, besides some "non specific mucosal inflammation".

So the case was much less worrying and it took about seven months before she consulted again, in March 2003. She was symptom-free, finally expressing a much better digestive capacity since she was on this diet, even though she hadn't renewed her supplements for a while. The cramps had disappeared and her blood reading

for the vitamin B12 was 1001pg/ml on 26/3/02, almost back to the normal range. She definitely reached and stayed within the normal range on further checks with 726pg/ml on 31/08/02, 677npg/ml on 21/5/03 and finally 516pg/ml on 15/5/04. The last time, she was still symptom-free, but also dairy-free. She might have to consider taking vitamin B12 supplements one day in the future, but that's another story…

About the author: Georges Mouton MD is a medical doctor specializing in functional medicine with practices in Brussels, London and Madrid. His website can be found at http://www.gmouton.com

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