

# Addiction and Mood Food (2)



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Cutting Edge Biotechnology

ISSUE 12 in a series written by SureScreen

In Issue 11 we saw how genetic or chemically induced hypodopaminism (low activity of the 'pleasure' neurotransmitter dopamine) is associated with various substance addictions and addictive behaviours. Here we will confine ourselves to discussing how shortages of **vital nutrients like vitamins, minerals and fatty acids** can trigger some chemical addictions and can be the result of others, especially in stimulant users and in alcoholics.

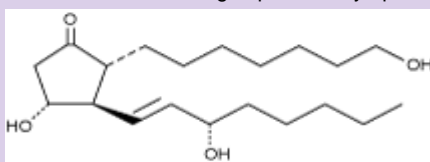
## ALCOHOLIC DEFICIENCIES

Alcoholics are usually malnourished because poor diet and the interference of ethanol with gastrointestinal absorption and utilisation of these nutrients within the body causes deficiency of vitamins, minerals and other nutrients. Alcohol irritates the gut lining, producing gastritis, anorexia, retching and vomiting. This leads to loss of valuable electrolytes (mineral salts) and problems with absorption of specific nutrients like vitamin B1, B6, B12, folate, glucose and amino acids. Ethanol-induced damage also impairs pancreatic enzyme secretion which leads to malabsorption of vitamin B12, essential fatty acids, fat soluble vitamins (A, D, E and K) and calcium and steatorrhea (undigested fat in the stool).

Alcoholic liver damage also leads to reduced storage of Vitamin A and zinc, a failure to store vitamins B6, B12 and an interruption of protein synthesis and amino acid imbalances. These deficiencies can then lead to **night blindness, diminished taste and olfactory sensitivity, cirrhosis and impaired immune function.**

The omega 6 essential fatty acids like gamma-linolenic acid (GLA) and Dihomo-gamma linolenic acid (DGLA) are often found to be deficient in alcoholics before they even start drinking. The common starting material linoleic acid is supplied by the diet from foods like vegetable oils, poultry, eggs, nuts and cereals. Providing there is enough zinc, magnesium, vitamins B3, B6 and C around, most of us can convert linoleic acid firstly into GLA and then into DGLA which is then shunted into the manufacture of a series of important immune biochemicals and neurotransmitters called prostaglandins. Prostaglandin E1 (PGE1) is one such anti-depressive neurotransmitter which is found to be genetically deficient in some alcoholics. This causes lifelong depressive symptoms.

**'Ethanol is no lasting substitute for these vital nutritional substances.'**



Prostaglandin E1

Alcohol use and its breakdown product acetaldehyde blocks the activity of the enzyme delta-6-desaturase (D6D) responsible for the conversion of linoleic acid to GLA but, unlike trans-fatty acids, it stimulates the enzyme delta-5 desaturase (D5D) and thereby enhances the conversion of DGLA into PGE1. This has the twofold effect of temporarily lifting depressive symptoms by raising PGE1 levels, and quickly using up DGLA stores without being able to replenish them, leading to rebound depression.

Not only that but with D6D and GLA production increasingly blocked, linoleic acid tends to get converted into arachidonic acid (AA) and the prostaglandin E2 (PGE2) series of immune biochemicals (e.g. TXA2, PGF2A etc) involved in inflammation and chronic disease. Alcohol not only blocks the enzymatic formation of GLA but, as we shall discuss in greater detail below, also eventually depletes the body of the zinc, magnesium, B3, B6 and C cofactors required for these enzymes to function.

This keeps these drinkers **locked into an addictive cycle** of highs and lows for a want of GLA and the vitamin and mineral cofactors required for PGE1 production. The more severe the deficiency of these substances the more severe is the alcohol withdrawal syndrome and the more debilitating the cognitive impairments experienced. Experimental animals made deficient in B-vitamins and certain minerals

are also more likely to choose alcohol than water when given the choice in an attempt to overcome the 'brain-drain' that these missing nutrients prevent. Unfortunately ethanol depletes these vital substances, worsening the situation even more for individuals with existing deficiencies.

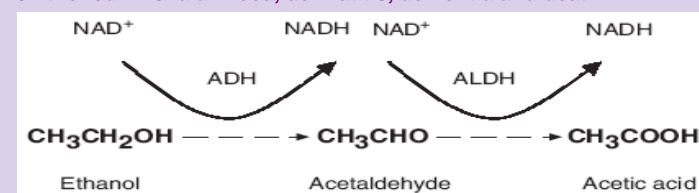
One of these missing vitamins, B1 (thiamine), is so essential to brain function that it is often called the 'nerve vitamin'. Perhaps its calming effect on the nervous system is the reason why rats on a low thiamine diet given free choice of either water or alcohol will consume more of their calories in the form of alcohol than those on optimum thiamine-rich diets. But ethanol is no lasting substitute for thiamine as it interferes with the absorption of thiamine from the gut and its utilisation by the body and its storage in the liver.

Ethanol disturbs the active transport of thiamine into the enterocytes of the intestine. By interfering with the enzyme thiamine diphosphokinase it also prevents the transformation of absorbed thiamine into the phosphate-containing forms thiamine pyrophosphate (thiamine diphosphate).

**In chronic alcoholics** ethanol can cause excessive urinary and gastrointestinal losses of magnesium required for the binding of these vitamin-phosphates to the thiamine-using enzymes within the cell. The alcohol breakdown product acetaldehyde (AH) is detoxified by thiamine but this can greatly reduce body stores of the vitamin. Low thiamine phosphates can lead to impaired carbohydrate metabolism, slowed production of the 'energy molecule' Adenosine triphosphate (ATP) and reduced formation of the 'memory transmitter' acetylcholine (Ach). In extreme cases deficiency can lead to Wernicke's encephalopathy and Korsakoff's psychosis (**Wernicke-Korsakoff's syndrome**) consisting in the first instance of symptoms of acute confusion, delirium, nystagmus (irregular eye movements), ophthalmoplegia (partial paralysis of the eye muscles), anisocoria (unequal pupil sizes) and ataxia (muscle incoordination), coma and in the second instance progress to amnesias and confabulation (false memories, imagination), all of which may become irreversible and even fatal without immediate intravenous vitamin B-1 supplementation. Poor B-1 utilisation on the other hand resulting from magnesium deficiency can lead to **alcoholic polyneuropathy**. In these cases blood thiamine levels may be normal but its utilization is subnormal as demonstrated by measurements of red blood cell transketolase activity.

Alcohol and its metabolite acetaldehyde (AH) also deplete vitamin B3 (niacin) from the body because it is used up during the liver's detoxification of ethanol. Alcohol is metabolised in a two step process firstly by oxidation from ethanol to AH which depends on the enzyme alcohol dehydrogenase (ADH) and then by oxidation from AH to acetic acid by a second enzyme aldehyde dehydrogenase (ALDH).

Both of these steps require niacin in its active coenzyme form Nicotine Adenine dinucleotide (NAD+) to function. This enzyme-mediated oxidation of ethanol results in the transfer of one hydrogen atom from the alcohol molecule to the co-factor NAD+, converting the coenzyme to its reduced inactive form NADH. Unfortunately only the NAD+ form can be used by cells so the overall rate of ethanol oxidation is largely determined by the capacity of the liver to re-oxidise or recycle NADH back to NAD+. When alcohol and AH levels exceed the liver's ability to regenerate NAD+, the inactive form of the coenzyme NADH accumulates leading to a functional deficiency of the vitamin despite normal blood levels of niacin. Extreme niacin deficiency produces the classic nutritional disease pellagra which can easily be identified in those affected by looking for **'the four D's' diarrhoea, dermatitis, dementia and death.**

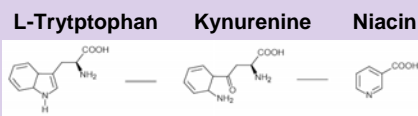


In order for the active NAD<sup>+</sup> to be recycled, NADH then donates its surplus hydrogen atom to pyruvate which is the end product of glucose

breakdown (glycolysis). Pyruvate then becomes the end-product lactate which is what makes our muscles ache after exercise. Unfortunately lactate is a panic-producing substance and so for many alcoholics who drink a lot and produce excess lactate, there often follows anxiety neuroses symptoms keeping them returning to a drink to tranquillise their nerves.

The only way to keep lactate levels down is to ensure that pyruvate is converted into the 'energy molecule' Acetyl CoA instead. Acetyl CoA powers the Krebs cycle which produces 90 percent of all energy used by every cell in the body, including brain cells). Unfortunately the enzyme responsible for this process – **pyruvate dehydrogenase (PD)** – is inhibited by acetaldehyde (AH); it also has a high requirement of vitamins B1, B2, B3, B5 and the antioxidant lipoic acid which are depleted by alcohol. To make matters worse AH not only opposes the formation of CoA from vitamin B5 and Acetyl CoA from acetic acid but it tends to combine with Acetyl CoA suppressing its activity. This effectively blocks the lactate-lowering pathway which is bad news for the anxious alcoholic. It also reduces the availability of Acetyl CoA for the synthesis of the 'memory transmitter' Ach making these anxious alcoholics confused, disorientated and forgetful.

Another problem is that when alcohol has depleted niacin reserves, the body is then forced to manufacture it from the amino acid **L-tryptophan**. This must occur through the formation of the metabolic intermediate and excitotoxin kynurenine (associated with behavioural tics, anxiety and possibly alcoholic stroke/seizures). This 'emergency supply' route for niacin robs the brain of L-tryptophan which is the precursor to the 'mood' neurotransmitter serotonin (5-HT). The result is that the damaged pleasure-reward circuit of the addict is left without adequate 5-HT to reinforce the regular natural dependencies of life like eating, sleeping, sex, working etc. This, along with his rising anxiety levels, increasingly turns him on to chemical substances to fill the gap.



As many as 57 percent of alcoholics have a functional deficiency of **vitamin B6** in the presence of normal

blood levels and between 80-100 percent of those with alcoholic liver disease have pyridoxine deficiency. This finding can partly be explained because the ethanol by-product AH inhibits the pyridoxine kinase enzyme responsible for converting the dietary vitamin into its intermediate pyridoxine phosphate (PP) form. To make matters worse if any PP gets converted into the final active pyridoxal-5-phosphate form of the vitamin, AH stimulates the activity of P5P phosphatase enzyme which degrades it releasing the free pyridoxal into the intracellular fluid where it is subjected to an increased rate of destruction. This leaves behind a functional deficiency of the active form of the vitamin in the presence of apparently normal blood levels of pyridoxine. If that wasn't enough alcoholic liver disease also reduces the manufacture of the binding protein serum albumin which is required to deliver P5P to peripheral tissues for use.

Alcohol also prevents the absorption of **vitamin B-2 (riboflavin)**, and increases urinary losses of magnesium and zinc required for the conversion of pyridoxine to its active form making P5P deficiency all the more likely. P5P acts as a coenzyme or 'assembly line worker' for a wide variety of metabolic transformations of amino acids as well as for enzymatic steps in the metabolism of brain nutrients like **tryptophan, tyrosine, sulphur-containing amino acids and other hydroxyaminoacids**. The decarboxylase enzymes which require it as an essential coenzyme are vital for the biosynthesis of brain neurotransmitters (NTs) like dopamine (DA), serotonin (5-HT), gamma-aminobutyric acid (GABA) involved in the proper functioning of the brain's pleasure-reward (PR) pathway often found to be genetically damaged in alcoholics. Alcohol-induced deficiency of P5P then could easily lead to a shortage of all these vital NTs thus worsening the clinical outlook for the addictive personality. The essential fatty acid manufacturing enzyme D6D also depends on adequate P5P for the brain's production of the brain antidepressant PGE1 which makes alcohol so enjoyable for some melancholic types. P5P is also necessary to convert Vitamin B3 into the active coenzyme form NAD+ for the very alcohol detoxification process we described previously. Finally the enzyme delta-amino levulinic acid synthetase requires P5P for proper haemoglobin synthesis; without it heme biosynthesis can become defective and the body gets overloaded with iron as is often seen in alcoholics.

Chronic alcoholism may lead to Vitamin B12 (cobalamin) deficiency especially in those with alcoholic gastritis and alcoholic hepatitis. Ethanol irritates and damages the parietal cells of the stomach, which ordinarily produces a special glycoprotein known as Intrinsic Factor (IF) essential for the absorption of dietary Vitamin B12 in the small intestine leading to deficiency. Alcoholic damage to the pancreas can also impair enzyme secretion required for the normal dissociation of Vitamin B12 from binding proteins in the stomach. This can also induce deficiency states by preventing B12's uptake by IF in the small intestine. Such is the case for most alcoholics. However blood levels of Vitamin B12 are too high in

chronic alcoholics with liver disease. This paradoxical situation reflects the failure of a damaged liver to take up from the serum cobalamin and its analogues coupled with the leakage of these compounds and their binding proteins into the serum. The alcohol by-product AH is also an enemy of cobalamin.

Both alcohol toxicity and poor folate intake are the most common cause of megaloblastic anaemia owing to **folate deficiency** accounting for some 89.6 percent of cases in some western cities. Alcoholism heavily depletes blood and liver folic acid levels whilst increasing its excretion. Monkeys fed alcohol to make up around a third of their daily calorific intake for a few months experience not only lowered plasma, red blood cell but also lower folate levels. These animals quickly develop a tendency towards **megaloblastic anaemia** (given by the presence of lots of large immature red blood cells in the bone marrow) with lowered haemoglobin levels and red blood cell counts. Ethanol also increases urinary excretion of folic acid, which over time may lead to folate deficiency and depression. Folic acid is essential for the biological process of methylation, the formation of tetrahydrobiopterin (BH4) – a cofactor involved in the manufacture of monoamine NTs required for the functioning of the addict's ailing PR circuit – and also for the disposal of the excitotoxin homocysteine (HC). Unfortunately the ethanol metabolite AH depletes the metabolically active form of folic acid tetrahydrofolate (THF) slowing down many of these vital functions, worsening hypodopaminism and often causing depression.

Because ethanol lowers levels of vitamin B6, B12 and folate and these nutrients are required for the disposal of the excitotoxin HC, alcoholics often present with higher than normal levels of this excitotoxin. It is a by-product of sulphur metabolism generated from the inter-conversion of the amino acids methionine and cysteine. Excess HC is an independent risk factor for cardiovascular and neurological disorders. Its derivative homocysteic acid also binds to the excitatory N-methyl D-aspartate (NMDA) glutamate receptor which, along with magnesium and zinc deficiency, may be responsible for lowering the threshold for alcoholic seizures and strokes. Interestingly mutations in the NMDA-Glutamate transporter such as the EAAT G603A silent mutant produces overactive glutamate neurotransmission and this has been found to be associated with ethanol craving and alcoholism.

Chronic alcohol ingestion also lowers liver levels Vitamin E (alpha-tocopherol) by increasing the vitamin's conversion to tocopheryl quinone. Rats given alcohol as one third of their calories result in 25 percent less liver Vitamin E content and as much as 55 percent less vitamin in the mitochondria. Conversely alcoholic liver damage or cirrhosis also depresses blood levels of Vitamin E.

**'Alcoholics get anxious, confused, disorientated and forgetful'**

Hypomagnesaemia (low magnesium status) occurs in 30 percent of hospitalised alcoholics and, apart from inadequate intake, is directly caused by ethanol-induced effects of malabsorption, excessive renal (kidney) losses and reduced uptake at the cellular level (which can cause cardiomyopathy in some drinkers). Although it is not thought to trigger withdrawal symptoms, lowered serum magnesium in fact coincides with the early stages of the alcoholic withdrawal syndrome **delerium tremens (DT)** commonly known as the 'DTs' and its blood levels predict the syndrome's duration. The reason for this is interesting. Over time chronic alcohol consumption makes the brain's 'tranquillizing' GABA<sub>A</sub> receptors underactive and its excitatory N-methyl D-aspartate (NMDA) receptors overactive which not only increases craving for alcohol but lowers the threshold for seizure and stroke and places the alcoholic suffering from DT at risk of serious injury.

Magnesium has an important regulatory effect on the alcoholic brain acting as a sort of ballast to counteract these changes by sustaining GABA transmission (as a GABA agonist) and suppressing the over-active NMDA-glutamate receptor calcium ion channel (as a non-competitive NMDA receptor antagonist). For this reason blood magnesium levels are a good predictor of the severity of withdrawal syndrome, which, if untreated, can be fatal in as many as 35 percent of cases. Like pyridoxine and folate, magnesium is also another important cofactor to those brain decarboxylases responsible for the manufacture of reward-reinforcement NTs like DA, 5-HT and GABA in the addict's sluggish PR circuit. It is also required for the formation of the antidepressant PGE1 and other chemical messengers involved in human behaviour like tryptamine, phenethylamine (PEA) histamine. Ethanol-induced hypomagnesaemia can also contribute to the development of alcoholic encephalopathy which responds dramatically to intravenous magnesium therapy.

Hypophosphatemia (low phosphorous status) common to hospitalised alcoholics, like hypomagnesaemia, results from the same deleterious effects of ethanol on absorption, kidney excretion and cellular utilisation of phosphorous. It may develop two to four days after admission and, when

severe, its neurological features are similar to DT being associated with hallucinations. Unlike magnesium deficiency, some researchers say that DT may actually be fostered by hypophosphatemia.

Zinc, like thiamine is another nutrient, which, when made deficient in laboratory rats, increases voluntary alcohol consumption as compared with normals. Unfortunately, as with thiamine, chronic alcohol consumption also depresses the body's **zinc level**. Forced intoxication of rats with ethanol solution for nine months, for instance, causes a reduction in zinc brain content. This like pyridoxine, folate and magnesium deficiency, deprives brain carboxylases enzymes of essential cofactors and slows manufacture of NTs in the under-functioning PR circuit of the addict as well as impacting PGE1, PEA and histamine biosynthesis. This can worsen the grip of addiction that a genetically addictive personality can find himself in. Zinc deficiency in turn impairs the liver's ability to detoxify ethanol. As we saw earlier alcohol is metabolised in a two step process by the liver enzymes ADH and ALDH which also happen to be **zinc metalloenzymes**. Zinc deficiency makes these enzymes sluggish which can elevate and prolong blood alcohol levels, increasing the risk of liver damage. Because zinc, like magnesium, is an NMDA-glutamate receptor antagonist, deficiency of this mineral can increase brain excitotoxicity, severity of withdrawal symptoms and the withdrawal seizure susceptibility of alcoholics.

Levels of the trace mineral **molybdenum** can suffer as a result of chronic ethanol consumption because the detoxification of consistently elevated AH levels may require the additional oxidative capacity of the molybdenum-dependent enzyme aldehyde oxidase which over time will tire molybdenum stores. Interestingly once molybdenum levels are depleted a drinker may start to experience allergies to certain chemicals like sulphites – found in wines (and other foods like processed, fried and fermented foods and cooked meats) and salicylates found in wines, beers, dark spirits (as well as in berries, vegetables, spices and food additives). This intolerance to alcoholic beverages materialises once molybdenum levels have dropped sufficiently low to impair the function of other molybdenum-dependent enzymes sulphite oxidase, cysteine dioxygenase, and phenol sulphur transferase (PST). The caffeine (and salicylates) in tea and coffee may also start to become a problem for drinkers over time as the enzyme responsible for its breakdown — **xanthine oxidase** – is also molybdenum dependent.

Apart from depleting the body's vitamin and mineral stores the ethanol oxidation byproduct AH also robs the addicts dysfunctional brain of vital NTs like 5-HT, DA involved in mediating proper reward-reinforcement responses to ordinary activities like eating, drinking, sleeping, and sex. AH destroys the 'mood transmitter' 5-HT by condensing with it, and its downstream product tryptamine, to form anxiety-provoking substances called tetrahydro-beta-carbolines (THBCs) like norharman (2-beta-carboline), tetrahydroharman (1-methyl-tetrahydro-beta-carboline) and harman (1-methyl-beta-carboline) which paradoxically increase the anxious alcoholic's need for another drink. It also destroys the 'pleasure-transmitter' DA by forming from it addictive tetrahydroisoquinolines (THIQs) like tetrahydropapaveroline (a morphine precursor also found in the opium poppy) and reticuline (a precursor to the brain's own supply of morphine), which reinforces this vicious circle of drinking to alleviate anxiety. Unfortunately the tetrahydropapaveroline byproduct acts as a 'false transmitter' which is taken up, stored and released like a regular NT, but, in the process, displaces and destroys what is left of not only DA and the brain's own natural opioids (e.g. enkephalins, endorphins and dynorphins) but also, to a lesser extent, 5-HT from their neuronal storage sites. As we have seen in previous bulletins 5-HT is intimately involved in firing up the reward-reinforcement process in the hypothalamus, with endogenous opioids responsible for amplifying this signal in the ventral tegmentum area (VTA) until this triggers the final release and interaction of DA with receptors in the pleasure centre of the nucleus accumbens. Ethanol then has the effect of draining the mesolimbic PR circuit of these vital NTs until stores are eventually exhausted making the alcoholic dependent on THP's short-lived high to feel normal.

We have already noted how ethanol depletes brain levels of the Omega-6 fatty acids GLA and PGE1. Several studies have demonstrated that chronic alcohol intoxication also depletes long-chain omega-3 essential fatty acids (such as those found in marine oils like eicosapentaenoic acid – EPA and docosahexanoic acid – DHA) from neuronal membranes which may in turn facilitate depressive symptoms and the learning deficits commonly seen in alcoholics.

### **OPiate INDUCED DEFICIENCIES**

The situation with opiate-induced nutrient deficiencies is fortunately far less complex than that of alcohol on the body's nutritional biochemistry although no less serious. The adverse effects of these agents seem to be confined to a general lowering of the anti-oxidant nutrients like vitamins, A, C, E and the carotenes. These nutrients are essential in preventing the generation of reactive metabolic by-products called free radicals. These trouble-makers are produced whenever a chemical in the body is oxidised or loses electrons to a stronger agent. The resulting free radicals exist in an unbalanced state and can wreak havoc by starting chain reactions throughout the body

that damage the proteins, lipids and DNA in cells. Antioxidant vitamins terminate these 'live wires' by giving them back lost electrons to balance their reactivity. Oxidation reactions that grab electrons like this are actually essential, particularly in producing the 'energy molecule' ATP, but when unbalanced they can be damaging. So the body must keep antioxidants in good supply and that not only means vitamins A, C, E and carotenes but also minerals like zinc and selenium (not strictly speaking antioxidants in themselves), sulphur bearing antioxidants like lipic acid and glutathione, brain antioxidants like melatonin and antioxidant enzymes like catalase, superoxide dismutase and peroxidases.

It is still unclear whether these antioxidant deficiencies are as a direct result of heroin and methadone consumption or whether they result from the poor lifestyle and diets of these subjects. The opiate withdrawal syndrome for instance, like exercise, burns up much more oxygen than when the body is at rest resulting in the generation of massive levels of free radicals and resultant oxidative stress. This places raised demands on the anti-oxidant system for the whole duration of the syndrome, which in its acute stages can last between five and eight days. If this is repeated on a regular basis it can put a major drain on body stores of these vital nutrients.

It has been suggested that some of the adverse effects of heroin withdrawal may in fact be attributed to this increase in the **free-radical to antioxidant ratio**. This has been observed in chronic heroin users who have increased plasma values of lipoperoxidation, nitric oxide and red blood cell lipoperoxidation accompanied by gradually decreasing concentrations of the antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GSHPx). Lowered GSHPx has the effect of inhibiting the function of glutathione (GSH) the body's major antioxidant. Morphine-addicted mice routinely present with depleted levels of GSH in the cerebrospinal fluid owing to the conjugation of morphine (a morphine metabolite) with GSH.

**'Supplementation with minerals is cost effective but often Ignored'**

Unfortunately for opiate users antioxidants like GSH are required to re-balance free-radicals generated by oxidative stress (e.g. exercise, illness or drug withdrawals) and may be a risk factor in the severity and mortality of the opiate withdrawal syndrome. When a heroin addict goes 'cold turkey' his adrenal gland automatically increases its secretion of glucocorticoids like cortisol which has the effect of further draining nutrients like vitamins A, C, and E and the heavy-weight antioxidant glutathione (GSH) as well as flushing out vital B-vitamins, minerals like zinc, chromium, magnesium and robbing the bones of calcium. GSH in particular is essential for phase II liver detoxification of drugs and may be implicated in impaired liver conjugation and detoxification seen in opiate users. Interestingly Paracetamol overdoses deplete intracellular liver stores of GSH resulting in liver failure and this is also the case for some prescription opiates like buprenorphine (a heroin replacement therapy) which has been shown to cause hepatotoxicity if not outright hepatitis in some cases.

As we saw in the last bulletin, there are major changes in food selection and intake during the drug withdrawal period resulting in either weight gain or loss depending on the drug of abuse and the individual. In general opiates suppress appetite over time (leading to malnutrition and emaciation) and increase cravings for the wrong foods (like the simple sugars in sweets, the psychoactive amines in chocolate and the narcotic exorphins in milk) in an effort to raise deficient brain levels of 5-HT, opioids and DA. This keeps users locked in a cycle of addictive eating which excludes proper intake of antioxidant-rich fruit and vegetables depriving them of vitamins A, C, E, carotenes and lycopenes. Paradoxically other 'staples' that form part of the opiate user's unhealthy diet like tea, coffee, chocolate and red wine may actually help offset these deficiencies by providing their own powerful polyphenolic antioxidants like resveratrol and certain flavinoids.

Antioxidants are essential for proper immune function and researchers have now discovered that both medicinal and recreational administration of opiates like heroin and methadone cause immunodepression. Although evidence of a causal relationship between antioxidant deficiency and immunosuppression in opiate users is lacking, these drugs (by some mechanism) routinely decrease white blood cell function and differentiation particularly macrophages (responsible for engulfing and digesting infectious pathogens) and lymphocytes (responsible for defending the host against infection). This is of particular importance to intravenous drug abusers who have a higher risk of contracting HIV infections especially when it is understood that the same trouble-making free-radicals are involved in the pathogenesis of these viral infections. Deficiency of vitamin A, for instance, results in lowered resistance to infections but when restored to proper levels it protects against the free-radical damage of macrophages and stimulates both arms of the im-

immune system – T lymphocyte cell-mediated immunity and B lymphocyte humoral (antibody) related immunity. A good supply of vitamin C stimulates Natural Killer (NK) cell function and soaks up the free radicals given off by phagocyte function preventing tissue damage. It also inhibits the replication of HIV-1 virus and enhances the activity of white blood cells like neutrophils. Optimum vitamin E levels do a similar job stimulating NK activity and lymphocyte cell counts, their proliferation and response. In one study, adequate vitamin E intake reduced the progression of HIV to AIDs by 34 per cent. Even a marginal deficiency of this nutrient impairs immune response. The so-called ‘anti-oxidant minerals’ are important here too. Zinc deficiency can impair both T and B-lymphocyte function. Selenium intake, on the other hand, enhances it and protects against free-radical tissue damage and reverses immunosuppression in immunocompromised patients. Selenium status has even been shown to determine survival times in some AIDS patients, and is recommended as a supplement in viral and cancer cases.

Quite apart from immunosuppression and increased risk of viral infections like HIV, deficiency of vital antioxidants among heroin users may increase the incidence of other chronic diseases. Long term free radical exposure predisposes opiate addicts to cardiovascular diseases, diabetes, rheumatoid arthritis, neurodegenerative conditions like Alzheimers and Parkinson’s disease and stroke. Antioxidant deficiency also causes lipid peroxidation, a process whereby free radicals rob electrons from the unsaturated fats that make up cell membranes resulting in cell damage and cancers.

### STIMULANT INDUCED DEFICIENCIES

All stimulant drugs like amphetamines, cocaine, Ritalin™, MDMA, ephedrine, caffeine and nicotine to some extent have an anorectic (appetite suppressant) action from their ability to raise DA and norepinephrine (NE) levels in the brain. Over time this can result in significant caloric restriction and possibly nutrient deficiencies in stimulant users.

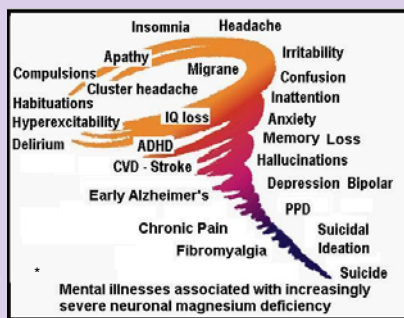
Raised brain levels of NE in particular can also kick start the whole stress response machinery which heavily consumes vital substances like vitamins, minerals, fats and NTs. This happens via two pathways: Directly NE works through its excitation of the sympathetic (stimulating) branch of the body’s autonomic nervous system to stimulate target organs into action and get the adrenal glands to release their stored up adrenaline. Indirectly elevated brain NE activates what has become known as the hypothalamic-pituitary-adrenal axis (HPA axis) which via a chemical cascade effect starting with the release of corticotrophin-releasing hormone (CRH) from the hypothalamus, secretion of adrenocorticotrophic hormone (ACTH) from the pituitary gland and ending with adrenaline manufacture and secretion of the glucocorticoid ‘stress hormone’ cortisol from the adrenal gland.

Unfortunately cortisol has a dark side. When it is artificially raised by drugs like this it can deplete antioxidants, flush B-vitamins out of the body, rob calcium from the bones and inhibit the ‘mood transmitter’ 5-HT in its reward reinforcement role. Cortisol also causes the kidney to retain sodium and excrete valuable reserves of the tranquillising minerals magnesium and potassium. Eventually with chronic stimulant abuse the situation of adrenal burnout will arise where adrenal cortisol output starts to fall short. Lowered glucocorticoids reduce the liver’s synthesis of the copper-binding protein ceruloplasmin and this allows free (bio-unavailable) copper levels to rise. Elevated free copper interferes with brain function by increasing the breakdown of NTs involved in the reward-reinforcement system such as 5-HT, GABA and DA and raising levels of the stress transmitter NE which keeps the vicious cycle of stress-induced drug use turning. It also disables the metallothionein (MT) protein which lowers body zinc levels and further impairing brain function.

It is probably precisely through this hypercortisolemia (raised cortisol) that amphetamines have been found to lower magnesium levels. Amphetamine addicts routinely demonstrate the same chewing and grinding movements (bruxism) that magnesium deficiency brings about. They also quickly start to feel the myalgia (muscle aches and pains) associated with hypomagnesaemia. Contrary to its sedative reputation magnesium is in fact critical for the body’s production of the ‘energy molecule’ ATP and is involved in over 300 enzyme-regulated reactions. Unfortunately inadequate intake of this nutrient affects an estimated 75-95 per cent of all westerners. This places the 16.8 per cent of young British adults (15-34 years) who have tried amphetamines particularly at risk of developing hypomagnesaemia-related illnesses like hypertension (high blood pressure), cardiovascular disease, depression, insomnia, migraine, diabetes, ADHD (attention deficit hyperactivity disorder),

asthma, allergies and chronic fatigue.

Controversially the main drug of choice to treat ADHD, Ritalin™ (methylphenidate) – is a magnesium-depleting stimulant. According to some



authorities it also depletes another vital brain nutrient vitamin B6. This is big news when it is understood that 95 per cent of ADHD sufferers are deficient in magnesium and some have combined deficiencies of magnesium and vitamin B6. A Ritalin™-induced shortage of these nutrients then would further impair the activity of brain carboxylases that depend on them and slow the manufacture of transmitters like 5-HT and DA involved in the

reward-reinforcement cascade paradoxically creating an even greater need for the drug. Stimulant-induced magnesium deficiency may worsen the addictive potential of these drugs. We saw earlier how magnesium blocks the ion channel of the neuroadaptive NMDA-glutamate receptor. Ordinarily these receptors are involved in the neurobiological process of learning to be less sensitive to a drug (tolerance) which downregulates DA activity in the mesolimbic and mesocortical pathways of the brain and leads to withdrawal effects when the drug is removed. Neuroscientists have shown that intrathecal (injections into the spinal canal) administration of magnesium can attenuate the development of tolerance to certain drugs of abuse and reset DA activity back towards normal. Amphetamine-induced deficiency of magnesium over time then might be expected to decrease the sensitivity of the DA system in the brain and hence increase dosage requirement of the drug to dangerous levels. This may be more of a problem with potent analogues like methamphetamine.

Stimulant-induced magnesium depletion also unfavourably alters the calcium-magnesium balance in the body leading to calcium deposition in tissues. Since blood is 90 per cent water and calcium is not very soluble in water without sufficient magnesium, a deficiency of magnesium can lead to precipitation of excess calcium in tissues. This can create muscle spasms, fibromyalgia, hardening of the arteries (arteriosclerosis), dental cavities, calcification of breast tissue and kidney stones. In the case of cocaine abuse it can even cause life-threatening strokes.

Unlike the general hypomagnesaemia induced by amphetamines, cocaine abuse results in a rapid loss of whole brain quantities of intracellular magnesium. Because this mineral is essential for regulating the contraction of smooth muscle around blood vessels and hence blood flow to the brain, recent research indicates that cocaine-induced magnesium deficiency may explain why abuse of this stimulant is associated with an ever-growing number of brain incidents like aneurysmal subarachnoid hemorrhages, intracerebral hemorrhages, brain edema, cerebrovasospasm and stroke. Recent animal studies confirm that a cocaine-induced loss of cerebral vascular smooth muscle levels of magnesium which ordinarily regulates metal traffic across cell membranes allows sudden toxic influxes of extra-cellular calcium ions into smooth muscle cells. This then triggers the contractile machinery of the tissue resulting in cerebrovasospasm followed by hypoxia, ischaemia and stroke. As we have already seen elsewhere in this bulletin, magnesium is also involved in antagonising glutamate release and blocking NMDA receptors — both of which are involved in mediating the effects of stroke.

### CONCLUSIONS

Understanding how substances of abuse can rob the body of vital nutrients can help clinicians create better recovery programmes aimed at alleviating physical health problems and also resolving the complex neuropsychiatric symptoms that increasingly seem to depend on adequate nutrition (see issue 11). Supplementation with **zinc, magnesium, selenium**, and other minerals that should be in the diet is very cost effective but is usually ignored.

\*Magnesium graph courtesy of Dr George Eby. <http://george-ebey-research.com/html/depression-anxiety.html>

## Next issue – Cocaine

### Back Issues:

- Issue 1 - How drugs are handled by the body
- Issue 2 - Drug retention times and cut-off levels
- Issue 3 - Alcohol
- Issue 4 - Oral Fluid, Urine and Hair testing
- Issue 5 - Definitive Guide to Urine
- Issue 6 - Definitive Guide to Oral Fluid
- Issue 7 - Definitive Guide to Hair Testing
- Issue 8 - Electronic Curfew Monitoring
- Issue 9 - Addiction
- Issue 10 - Testing solid drugs
- Issue 11 - Mood Food and Addiction (1)
- Issue 12 - Mood Food and Addiction (2)

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