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PYRIDOXINE - VITAMIN B-6

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INTRODUCTION

In 1966 Goldberger described a disease in rats, called acrodynia which was a form of dermatitis. Gyorgy in 1934, identified a vitamin B agent that healed this dermatitis and he subsequently named the substance pyridoxine. In 1938 several groups isolated vitamin B6 in crystalline form and the substance was identified as 2-methyl-3-hydroxy-5-hydroxymethylpyridine.

The B6 group is composed of three naturally occurring compounds - pyridoxine (PN), pyridoxamine (PM) and pyridoxal (PL). All three vitamins exist primarily as the 5-phosphates in tissues. Pyridoxine is available as the hydrochloride salt for use as a supplement.

ABSORPTION AND TRANSPORT

The three forms of vitamin B6 are absorbed in the jejunum by a process that is non-saturable. PN is found in foods in the free form and as the glycoside which is absorbed directly or after hydrolysis by lumenal enzymes and/or microflora. PL and PM require hydrolysis before absorption. All three forms are subsequently trapped by phosphorylation. Experiments in the rat suggest that PLP (pyridoxal phosphate) utilisation might be affected by agents that raise gastric pH. Disorders of the small intestine, such as coeliac disease reduce vitamin B6 status but there is little good evidence that alcohol reduces B6 absorption.

Experimental animals are able to easily absorb doses of B6 several hundred times the RDA. In humans a 100 mg dose will produce a plasma peak in 2 hours with a subsequent half life of 8 hours. Doses of over 25 mg produce little change in plasma PLP[1].

In the blood PL and PLP are tightly bound to albumin, PN and PL are rapidly accumulated by erythrocytes.

METABOLISM AND EXCRETION

Figure 1 gives a very simplified representation of the course of B6 through the body. A crucial stage in its metabolism is the conversion of the three vitamins to the active form pyridoxal 5-phosphate (PLP). PN, PM and PL are converted to PNP, PMP and PLP by a single kinase enzyme which in the brain and liver is most active with zinc; the erythrocyte kinase prefers cobalt or manganese. PNP and PMP are then converted to PLP by a flavin dependent oxidase which is the reason that vitamin B2 deficiency causes a fall in available PLP.

The liver is the major source of plasma PLP, although muscle may be an additional source during conditions of muscle turnover (moderately severe exercise increases circulating PLP). PLP does not cross cell membranes and the vitamin must be dephospholated at the external surface and then undergo rephosphorylation intracellularly. The major factor that determines plasma PLP level appears to be the balance that is struck between liver formation and its breakdown by alkaline phosphatase. Thus circulating PLP is increased in patients with hypophosphatasia, an inborn error of metabolism characterised by deficient alkaline phosphatase activity. Similarly the lower PLP levels that have been recorded in middle aged women may be related to the trend for higher alkaline phosphatase levels in this age group[2]. The lower plasma PLP levels in cirrhosis of the liver are also probably related to increased liver phosphatase activity.

Plasma PLP is abnormally low in many patients with chronic renal failure and those on dialysis or with a kidney transplant. Spannuth et al.[3] concluded that this was due to increased metabolic clearance of PLP rather than a loss in dialysis fluid. Kopple et al.[4] found that in undialysed patients with renal failure or patients undergoing peritoneal dialysis 2.5-5.0 mg per day of B6 normalised B6 status as measured by the EGPT index.

PL released in the circulation is used as needed by tissues and the excess is then taken up by the liver which is the main site of degradation to pyridoxic acid. If tritiated B6 is injected into rats the radioactivity reaches a maximum in the liver after about 1 hour. However the brain takes 7 days to reach a peak reading.

Alcohol reduces the hepatic reserves of PLP in rats and again this is probably the result of accelerated hydrolysis by alkaline phosphatases.

BIOCHEMISTRY

PLP is involved in over 60 enzymatic reactions. Some of the major functions as reviewed by Merrill and Burnham[5] are as follows:

Aminotransferase reactions

These involve the interconversion of amino acids and their corresponding -ketoacids. In some instances these reactions provide a link between an amino acid and glycolysis (e.g. alanine and pyruvate) or the tricarboxylic acid cycle (e.g. glutamate and -ketoglutarate).

Decarboxylation reactions

The many substances that are synthesised through this class of reaction include: serotonin, catecholamines and polyamines such as spermine, tyramine, histamine and GABA. B6 is also involved in the synthesis of phosphatidylethanolamine which is an intermediate in the synthesis of choline and phosphatidylcholine. Two important additional reactions combine decarboxylation with carbon-carbon bond formation. These are the initial and regulatory steps of heme and sphingolipid synthesis. Sphingolipids are major constituents of plasma membranes.

Site-chain cleavage reactions

These include:

(a) The transfer of a hydroxymethyl group from serine to tetrahydrofolate to form glycine and 5,10-methylene-tetra-hydrofolate.

(b) PLP is involved in a number of ways with sulphur amino acid metabolism. For example it is involved in taurine synthesis and in the degradation of cystathionine as shown in Figure 2. This is a clinically relevant reaction as B6 deficiency may lead to the

accumulation of homocysteine which would predispose to arterial damage.

(c) B6 is involved in tryptophan metabolism and nicotinamide formation as shown in Figure 3. The profile of metabolic products from this pathway in response to a tryptophan load has been used as the basis of a test for B6 status. This will be discussed below.

Dehydratase reactions

An example of this class of reaction is the de-amination and dehydration of serine to pyruvate, ammonia and water by L-serine dehydratase.

Other functions

Glycogen phosphorylase requires PLP. There is accumulating evidence that vitamin B6 affects the action of steroid hormones. In a review of B6 and glucocorticoid action Compton and Cilowski[6] state that in vivo studies and cell culture experiments have demonstrated that exogenous vitamin B6 or its precursors can antagonise the action of glucocorticoids. They are unable to state however whether endogenous levels of vitamin B6 actually modulate glucocorticoid actions. Bender[7] has extensively reviewed the topic of oestrogen and vitamin B6 and concludes that moderate vitamin B6 deficiency enhances the hyperplastic response of target tissues to steroid hormones. In noting that this could be important in the induction and subsequent development of hormone dependent cancer of the breast or prostate, he suggests that vitamin B6 supplementation might act as a useful adjunct to other therapy in these cancers.

Pyridoxine, together with zinc and magnesium is required for the action of delta-6 desaturase, the first step in the conversion of essential fatty acids to regulatory compounds[8]. Recent evidence also suggests that it plays a part in regulating smooth muscle calcium channels[9].

DRUG and NUTRIENT INTERACTIONS

As stated above vitamin B2, zinc, manganese and cobalt are all involved in the activation of pyridoxine. The combination of zinc and B6 is a popular one amongst vitamin manufacturers. The rationale for such formulations seems to be based on Karl Pfeiffer's[10] many publications on zinc and other micro-nutrients. Pfeiffer frequently links zinc and B6 on the basis that these two nutrients in particular are depleted by the presence of kryptopyrole in the urine. Many readers will be familiar with the theory that this substance is found in excess in various forms of mental illness, but especially schizophrenia, but also in an appreciable percentage of the population (10.5-15%). There seems to be scant evidence for these theories in the scientific literature and no compelling rationale for inevitably combining B6 and zinc. A study by Evans[11] suggests that in rats, B6 enhances the absorption of zinc but Moser-Veillon and Reynolds[12] were able to find no effect from vitamin B6 intake on plasma, erythrocyte or milk zinc concentration in lactating mothers. Since however zinc is bound in tissues by a zinc-metallothioneine complex and metallothioneine levels are affected by stress and inflammatory reactions we can easily trace a link between these conditions and B6 status because of zinc's role in B6 activation[13].

Vitamin B6 promotes iron excretion and this has been used as a rationale for treatment in iron storage diseases. Vitamin B6 also increases magnesium transport across cell membranes[14]. In experimental animals vitamin B5 deficiency increases pyridoxine excretion[15]. The important relationships to riboflavin and folic acid have been described above.

Drugs that have the potential for causing B6 deficiency include: isoniazid, penicillamine, cyclosporine and the antiturbulous drug pyrazinamide. In some instances these drugs form a complex with B6 that is inhibitory for pyridoxal kinase and in other instances they may positively displace PLP from binding sites[16]. Modest doses of B6 will completely inactivate L-Dopa which has been taken for Parkinson's disease. This problem has, of course, now been obviated by the use of carbidopa which inhibits systemic decarboxylation. Cigarette smoking is associated with lower plasma levels of PLP[17] although this may be linked with the trend towards a deficient diet among smokers. Interestingly, alcohol consumption in experimental animals does not seem to affect B6 metabolism or tissue stores[18], but progression to cirrhosis of the liver is associated with decreased plasma and hepatic PLP levels which seem to be associated with increased B6 degradation. Acute ingestion of glucose also decreases plasma PLP[19]. The relationship between sex hormones and vitamin B6 will be dealt with under the section on assessment.

REQUIREMENTS and AVAILABILITY

In the United States the National Research Council's (1989) RDA for B6 is 2.0 mg for adult males and 1.6 mg for adult females. Pregnancy and lactation add 0.6 mg and 0.5 mg respectively to the RDA for women. Requirements for infants begin at 0.3 mg/day and increases to 0.6 mg for older infants. Because of its close relationship to amino acid metabolism, daily requirement may be more accurately expressed in terms of protein intake. In Australia the National Health and Medical Research Council has set the requirement as 0.02 mg of B6 per gram of protein per day. Interestingly, an elevated fat intake also increases the requirement for vitamin B6, but this probably arises from the increased metabolic demand on vitamin B2.

The assessment of nutrient status in populations is fraught with difficulties. Even if accurate records of food intake have been obtained there are always uncertainties regarding the actual vitamin content of foods. Biochemical estimates of nutriture may or may not be done and varying tests may be used. The relationships between intake and biochemical parameters may also be hard to interpret. A study by Driskell et al.[20] illustrates some of these points. This research group looked at 22 healthy males aged 20-37 years and found that they had normal plasma PLP levels. Values of B6 intake over four weeks as calculated from food tables yielded a range of 1.22 mg to 1.67 mg per day. Actual analysis of the foods eaten over this period however gave intakes of 0.75 mg to 0.98 mg per day.

Bearing in mind the above reservations, there is a strong impression from dietary studies that B6 intake is often inadequate. In a study of preschool children Driskell et al.[21] found that 17% of the children consumed less than the RDA for vitamin B6 and this was reflected in lower plasma levels of PLP. Plasma PLP levels also correlated well with parents' estimate of their childrens' overall eating habits. Barbara Brown et al.[22] looked at young women between 17 and 25 years and found that 25% did not meet the RDA intake for vitamin B6. Similarly in the well known Busselton study in Western Australia23 Davis examined blood samples for serum and red cell folate, B1, B6 and B12. In the female population 10.7% had levels below the reference range for B6, making it by far the commonest B group deficiency. In a study of 435 elderly Danish men and women Osler and Schroll[24] found that 40% had low serum levels of B6.

Pregnant women are particularly at risk for low blood levels of PLP and Temesvari et al.[25] found that 100 mg of B6 given to pregnant women at term decreased maternal and new born cord blood oxygen affinity.

Vitamin B6 occurs widely in foods with meats, whole grains, legumes, leafy vegetables, potatoes and bananas being particularly good sources. Bran can reduce the biological availability of B6, but this will only be significant if large quantities are taken in the diet. Storage and processing lead to B6 losses, particularly the application of dry heat as in baking or toasting.

The availability of B6 in the diet is quite high. Tarr et al.[26] studied the

different plasma PLP and urinary B6 responses to B6 in a typical American diet and B6 in supplementary form. They found that the availability of B6 in the diet ranged from 61% - 81% when compared to plasma PLP responses to the pure vitamin.

DEFICIENCY SYNDROMES

Experimental induction of B6 deficiency in a variety of animal species tends to produce the following problems:

> delayed growth, reduced appetite and poor utilisation of feed, abnormalities in skin, fur or plumage, general weakness, seizures, demyelination of peripheral nerves and anaemia.

Considerable experimental evidence has accumulated on rats who show: growth impairment, weakness, anaemia, a dermatitis with crusts around eyes, paws and tail (acrodynia), infertility, oedema, demyelination of peripheral nerves and seizures[27].

Evidence for a deficiency syndrome in humans has arisen by observation of pyridoxine's effect on a variety of symptoms in malnourished individuals. Its most pronounced effects have been on weakness, sleeplessness and depression. In addition investigations have been done with a combination of B6 deficient diets and B6 antagonists. Adult subjects in these circumstances tend to develop the symptoms and signs listed below:

General - weakness, reduced resistance to infections and weight loss.

CNS - apathy, depression, irritability, sleeplessness and peripheral neuropathy.

Skin - scaling, seborrhoea-like dermatosis in the eye/nose/mouth region, a pellagra-like dermatitis and an acneiform papular rash of the forehead.

Mouth - glossitis/stomatitis indistinguishable from that caused by other B group vitamins.

Immune - tendency to develop infections particularly of the genito-urinary tract.

In the 1950s there were several reports of convulsive seizures and nervous irritability in infants fed on autoclaved commercial milk formula low in B6. The symptoms responded to B6 supplementation and clinical improvement corresponded with a return to normal of EEG patterns. Only a few years later Dr. John Ellis published some further pioneering observations on B6 and human health[28]. He noted in particular that B6 deficiency seemed to be associated with the following problems:

1. Swelling of hands or feet, premenstrual oedema, oedema associated with pregnancy or oral contraceptives and post myocardial infarction.
2. Stiffness and joint pain, particularly in hands, arms and shoulders.
3. Cramps in hands, legs or feet.
4. Arthritic problems associated with the menopause.
5. Peripheral neuritis affecting the upper limbs.
6. Carpal Tunnel syndrome.

In most cases Ellis found that these conditions responded to modest supplementation in the 50-100 mg range.

ASSESSMENT

There is no completely satisfactory way of biochemically assessing vitamin B6 status. A number of different approaches have been developed, but each is associated with advantages and disadvantages that will be outlined below.

Plasma B6 Levels

Because of the existence of multiple B6 vitamins there is no simple chemical technique that will estimate the total B6 content of plasma or other biological samples. Thus estimation of total B6 still depends on microbiological assay. As might be expected the total plasma B6 relates more to recent B6 intake than to underlying nutritional status. Plasma pyridoxal phosphate however does correlate well with whole-body B6 stores[29]. In view of the 8 hour half life described above it is preferable to have fasting samples, especially in those individuals taking B6 supplements. It has already been noted that circulating PLP levels can be affected by alkaline phosphatase activity and exercise. In addition extracellular PLP may be redistributed intracellularly after a myocardial infarction. These factors have led Vermaak et al.[30] to propose that RBC PLP and/or PL may be better indicators of B6 status than plasma PLP.

Pyridoxic Acid Excretion

About half of the normal dietary intake of B6 is excreted as 4-pyridoxic acid. Urinary excretion largely reflects recent intake of the vitamin rather than overall nutritional status.

Enzyme Assays

These tests measure the saturation of B6 dependent transaminases by comparing basal activity with stimulated activity after the addition of PLP. An activation coefficient is then derived from the following ratio:

$$\text{activation coefficient} = \frac{\text{stimulated activity}}{\text{basal activity}}$$

Both alanine and aspartate transaminases in erythrocytes and plasma have been used. Measurement of plasma transaminase is of limited value since the level of these enzymes fluctuates in the blood as a result of tissue damage and turnover. There is also the problem that the saturation of plasma transaminases will depend partly on the affinity of the albumin to which PLP is bound. Erythrocyte transaminase activation does not change in response to acute B6 depletion as rapidly as other indices and this reflects the duration of RBC life in the circulation (approx. 100 days). Thus a normal activation coefficient may be seen despite deficiency. An abnormally elevated coefficient however tends to indicate a relatively long term deficiency. There are other disadvantages to enzymic methods; abnormalities in RBC transaminase arise in liver disease[31] or in B1, B2 and B5 deficiencies[32]. In addition alanine amino transaminase activity differs among three phenotypes and thus the assays is only accurate if the phenotype is known[33].

Metabolic Loading Tests

This type of assessment has the advantage that it tests an individual subject's capacity to deal with metabolic stress. The tryptophan loading test is based on the biochemical pathway illustrated in Figure 3. Under normal conditions the enzymes tryptophan oxygenase is the rate limiting step. In conditions of vitamin B6 deficiency the activity of the pyridoxine dependent enzyme kynureninase falls below that of tryptophan oxygenase and this leads to the accumulation of intermediates and an increased excretion of kynurenic and xanthurenic acids. These metabolic products are easy to measure in urine and thus this loading test has been widely adopted as an index of B6 status. Unfortunately there are a number of problems with this test and these have been reviewed by Bender[7]. Tryptophan oxygenase activity varies with a number of factors which include substrate availability, hormonal induction (e.g. glucocorticoids), feedback by NAD and NADP and availability of the haem cofactors. In addition a wide variety of unrelated diseases seem to affect the test independently of

B6 status. These abnormalities have been observed in Hodgkin's lymphoma, rheumatoid arthritis, schizophrenia, porphyria, renal tuberculosis and aplastic anaemia. Alterations in kynurenine excretion may also reflect altered renal clearance rather than hepatic metabolism.

In the past it was thought that abnormalities in the tryptophan loading test indicated B6 depletion in women taking oestrogens. It is now apparent that oestrogens directly inhibit kynureninase and this makes the test inappropriate for women taking oestrogens and perhaps for women in general[7]. Methionine loading can also be used to test B6 status (see Figure 2): Cystathionase is particularly sensitive to B6 depletion and under such circumstances a methionine load will lead to accumulation of cystathionine. However the determination of cystathionine is less convenient and sensitive than that for kynurenine and so the test has been used much less frequently in B6 research. However there does appear to be good agreement between impairment of methionine catabolism and indices of B6 nutritional status.

To summarise we can say that for routine purposes a fasting plasma PLP is the investigation of choice. In the future erythrocyte PLP or the methionine loading test may become more accepted and more widely available.

CLINICAL ASPECTS

Cardiovascular disease

As long ago as 1949 it was demonstrated that monkeys fed a B6 deficient diet developed atherosclerosis[34]. The situation in humans, however, is far less clear. PLP levels are lower in patients who have suffered a myocardial infarction but it is not clear whether this is a primary or a secondary phenomenon[35]. There are a number of theoretical reasons however, to believe that vitamin B6 deficiency may be a risk factor for cardiovascular disease. Some of these are as follows:

(a) Hyperhomocyst(e)inemia

The theory that abnormally high levels of homocysteine may predispose to atherosclerosis has been reviewed by Soo-Sang Kang et al.[36]. Homocysteine is metabolised through the pathways shown in figure 2. In some cases high levels seem to reflect a dietary deficiency of folate or B6, but in others there appears to be a genetically based defect in the production of 5-methyl tetrahydrofolate which may affect up to 5% of the population. This inherited vitamin dependency is correctable by modest folate supplementation. Mason & Miller[37] have discussed the effects of folate, B6 and B12 on blood homocysteine levels. It is not clear, as yet, what synergies might exist by adding B6 or B12 to a regime of folate for this condition. Monreal et al.[38] have described the apparently successful treatment with B6 of a young woman with occlusive arterial disease secondary to B6 responsive homocystinuria.

(b) Cholesterol Metabolism

Vitamin B6 deficiency in monkeys causes a decrease in the synthesis of primary bile acids and reduced incorporation of lipoprotein cholesterol into biliary sterols[39]. Humans who have low PLP levels by virtue of an illness such as chronic glomerulonephritis have higher than normal levels of cholesterol[40]. The mechanisms linking B6 and cholesterol are not clear but it is possible that the role of B6 in prostanoid metabolism (see above) is involved. Decreased bile acid synthesis might be secondary to altered amino acid and/or taurine metabolism.

(c) Platelet Aggregation

Although B6 seems to inhibit platelet aggregation in vitro, this has been difficult to demonstrate in healthy adults given 100 mg of B6 orally per day[41].

(d) Connective Tissue Synthesis

Elastin and collagen cross linking occur through the activity of the B6 dependent enzyme lysyl oxidase.

(e) Vascular Tone

Oral B6 (200 mg/day) has been shown to significantly improve RBC and plasma magnesium levels[42]. These results appear to indicate that B6 plays a role in the transport of magnesium across cell membranes. The relationship between magnesium status and vascular tone has not been clearly established however[43].

Psychiatric Illness

There seems to be a clear relationship between vitamin B6 deficiency and depression. More specifically, Carney et al.[44] found that a raised red cell aspartate transaminase correlated with endogenous depression as opposed to other psychiatric diagnoses. In addition Carney[45] found that a combination of B6 and B2 deficiency was associated with the diagnosis of affective disorder in a large sample of psychiatric hospital admissions. In a more recent article on the relationship between vitamins and mental health the same author states that avitaminosis is commonly associated with the use of most psychotropic preparations[46]. Treatment with pyridoxine is commonly used for women who have become depressed while taking oral contraceptives and the efficacy of modest does of B6 (40 mg) has been demonstrated by Adams et al. in a double-blind crossover study[47]. Bender[7] has commented on the possible biochemical mechanisms. In the synthesis of serotonin and the catecholamines, the rate limiting step is hydroxylation of the parent amino acid and not the decarboxylation step for which B6 is co-factor. Severe B6 deficiency in rats has little effect on the activity of the appropriate CNS decarboxylase and in patients dying from dialysis encephalopathy who have a greatly reduced brain content of PLP there is no reduction in the levels of serotonin or catecholamine metabolites. It is possible, therefore, that B6 deficiency has its effect through the built up of circulating kynurenine and hydroxykynurenine. These metabolites compete with tryptophan for uptake into the brain and will therefore affect the rate limiting factor in serotonin synthesis. An alternative or complementary mechanism may lie in the fact that in experimental animals large doses of B6 lead to a significant inhibition of hepatic tryptophan oxygenase and a large increase in the circulating level of tryptophan.

In acute coeliac disease ingested B6 appears more slowly as PLP in the blood and the site of absorption appears to shift from the jejunum to more distal pockets of the intestine. Depression is sometimes found in adult coeliac disease and Hallert et al. found that 80 mg/day of B6 led to a fall in MMPI "D" scores. Unfortunately there seem to be few other therapeutic studies relating B6 treatment to depression. A recent exception is to be found in a study by Bell et al.[49] in which an elderly population with depression were treated with a tricyclic antidepressant with either 10 mg each B1, B2 and B6 or a placebo. In a randomised double-blind format the active vitamin group demonstrated trends towards greater improvement in scores rating depression and cognitive function. Interestingly, the vitamin group also showed improved nortriptyline levels.

Use of vitamin B6 in autism was pioneered by Bernard Rimland in the 1970s[50]. Since then thousands of children have been treated with doses ranging from 75-1,000 mg/day and without apparent serious side effects. The efficacy of B6 in combination with magnesium has been demonstrated in properly controlled double-blind studies by Marteau et al.[51] and Lelord et al.[52]. These studies have also demonstrated significant decreases in urinary homovanillic acid - one of the main dopamine metabolites. The difficulty of giving large doses of B[redacted]n has been overcome by the use of a spec[redacted]hera, Kirkland Laboratories) which cont[redacted]500 mg, magnesium 250 mg and a spec[redacted]inerals[53].

Although earlier studies suggested a positive role for B6 in hyperkinetic children[54] later double-blind studies which had used B6 in conjunction with other nutrients (e.g.. B3, B5 and C) have not confirmed a role for mega-vitamin therapy in attention-deficit hyperactivity disorder[55,56].

The situation with regard to learning and learning disabilities is far less clear. Broad spectrum vitamin and mineral supplementation (100% RDA) seems to have a definite effect on non-verbal intelligence, especially in poorly nourished children[57] and broad spectrum supplementation of vitamins and minerals together with improved whole food diets seems to be beneficial for children with learning problems[58]. The role that vitamin B6 might play in these nutritional strategies is, however, far from clear and no studies have examined its role in isolation.

There have been occasional reports of pyridoxine's efficacy in schizophrenia[59,60] but no convincing evidence from large scale controlled trials. The case of a 15 year old woman presenting with psychotic symptoms secondary to homocystinuria has been described in which she responded to a combination of folic acid and pyridoxine[61]. Carl Pfeiffer[62] has published a good deal over the years on the sub-typing of schizophrenia including the concept of pyroluria - a condition which is supposedly responsive to vitamin B6 and zinc. Cruz & Vogel[63] were unable to confirm pyroluria as a marker in chronic schizophrenia.

Several papers published and summarised by Hoes, imply that a combination of tryptophan and B6 may be effective in anxiety states. Unfortunately this author's use of idiosyncratic terminology to describe anxiety states and their relationship to stress makes it difficult to arrive at definite conclusions. Buist[65] in discussing the lactate hypothesis of panic disorder points out that B6 supplementation may diminish the conversion of pyruvate to lactate by facilitating transamination reactions which would feed substrate into Krebs Cycle.

Pyridoxine may be deficient in Alzheimer patients compared to healthy elderly controls[66] but there is no evidence relating B6 treatment to clinical improvement. Similarly women with anorexia tend to have depressed vitamin B6 activity[67] but no information suggesting that B6 is specifically therapeutic. A combination of B6 and tryptophan did, however, produce improvement in mood and eating behaviour in a group of women with bulimia[68].

Alcoholics are often deficient in vitamin B6[69] although this will not show up in an enzyme assay because acetaldehyde blockades the PLP binding centres on the apoenzyme[70]. Despite the ubiquity of vitamin B deficiency in alcohol dependent patients, there seem to be no properly controlled studies on the short or long term affects of B complex or individual B vitamins in the rehabilitation of this group.

Immunity

Vitamin B6 deficiency is associated with impairment in both humoral and cell mediated immunity. This is in part due to impairment in the enzyme serine hydroxymethyltransferase which catalyses the reaction shown in Figure 2. The impairment in folate metabolism can seriously compromise nucleotide metabolism. The addition of the B6 antagonist deoxypyridoxine to lymphocyte cultures markedly inhibits the activity of T helper cells (but interestingly not T suppressor cells) and the production of interleukin receptors is also affected[71]. In healthy elderly subjects depletion-repletion studies indicate that a B6 deficiency interferes with lymphocyte proliferation and interleukin-2 production[72]. Supplementation with B6 in elderly patients has been shown to promote lymphocyte proliferation and increase percentages of T3 and T4 (but not T8) cells[73]. A study by Baum et al.[74] suggests that vitamin B6 deficiency is prevalent in stage III HIV-I-infected subjects and that this contributes to immune dysregulation. When given to enhance immunity B6 is usually given with other immune stimulating nutrients such as folate, riboflavin, ascorbic acid, iron and zinc amongst others. Recent evidence suggests that coenzyme Q10 acts synergistically with B6 to stimulate IgG and T4 lymphocyte levels[75].

The relationship between B6 metabolism and cancer has been reviewed by Merrill & Henderson[76]. In mice vitamin B6 deficiency may increase susceptibility to virus induced tumour growth, but in other studies B6 deficiency has been found to slow the growth of some types of tumour. Pyridoxine has a toxic effect on hepatoma cells and will inhibit the growth of B16 melanoma cells in culture and after their establishment in mice. The situation in humans is not clear. Abnormal B6 metabolism has been reported in patients with breast cancer and Hodgkin's disease. Ladner & Salkeld[77] reported that the 5 year survival rate in patients with stage-II endometrial carcinoma was increased by administration of B6 and that the correction of vitamin B6 deficiency increases the survival of patients with cervical carcinoma. Bell[78] reported that women with a less than average pyridoxic acid excretion had a higher probability of recurrence of breast cancer and Byar & Blackard[79] found a positive effect of pyridoxine compared with placebo on the long term outcome of stage-II bladder cancer. A previously unknown metabolite of vitamin B6 has been found to account for up to 30% of the total intracellular vitamin B6 observed in tumour cells. This diethylthioether compound may prove to be a circulating marker of cancer[80].

Neurology

Vitamin B6 dependent seizures in infants were first described 40 years ago. Crowell & Roach[81] point out that there are two types of situation in which pyridoxine dependent seizures or irritability may occur. The first situation describes an insufficient intake of B6 due either to breast feeding by malnourished mothers, inadequately fortified formulas or the use of B6 inhibiting drugs. In these cases deficiency usually becomes obvious 3-6 months after birth and is simply corrected by supplementation and proper nutrition. The second type of seizure however, results from a true B6 dependency in which there is an increased requirement resulting from a genetically determined enzyme defect. This enzyme deficiency presumably resides with glutamate decarboxylase which is responsible for the synthesis of GABA from glutamic acid. Typically these children begin to have symptoms soon after birth and will require indefinite supplementation with 25 mg - 50 mg of B6 for the rest of their lives.

Although the literature on the beneficial effects of B6 in many cases of infantile seizures/spasms is generally positive, the situation in adults is far less clear. Although there are isolated reports of pyridoxine's efficacy in grand and petit mal seizures[82] there are no acceptable studies as yet. Bernstein[83] however, in his review of vitamin B6 in clinical neurology suggests that B6 may prove to be a useful addition to currently used medications. The experimental evidence certainly suggests that this might be so. Ebadi et al.[84] for example, showed significant differences in cortical and cerebellar B6 concentrations between normal and epilepsy prone rats. As noted above, anticonvulsive medication may compromise B6 status. Krause et al.[85] looked at 146 epileptic patients receiving various anticonvulsive drugs. Vitamin status was measured by blood levels and enzyme activation tests. Compared to normal controls the epileptic patients were at risk for folic acid, biotin and vitamin B deficiencies. In addition there was a higher risk of developing vitamin B2 deficiency in females and vitamin B6 deficiency in males.

There have been isolated reports of pyridoxine's usefulness in movement disorders. Thus an early study by Baker[86] found that 10-100 mg pyridoxine daily produced improvement in bladder control, gait, trembling and rigidity in Parkinson's disease. Barker et al.[87] failed to confirm these results, however. More recently a Soviet study looked at 60 patients with Parkinson's disease and found that intramuscular B6 in doses of 3-4 mg/day either alone or with medication (other than L-Dopa) produced significant improvements in tremor[88]. There is similarly tentative evidence for the usefulness of pyridoxine

in tardive dyskinesia[89]. Individuals with Down's Syndrome seem to show abnormal vitamin B6 metabolism and significantly lower platelet PLP levels[90]. Supplementation with pharmacological doses of B6, however failed to produce significant differences in mental age, cranial circumference or tongue protrusion in a double-blind study[91].

Bernstein[83] comments that headache and chronic pain are two very common symptoms in neurological patients and that B6 offers some promise of therapeutic help, especially as in the limited number of studies to date B6 seems to be as effective as amitryptline in the treatment of headache.

Women's Health

Pyridoxine has now become widely accepted in the treatment of premenstrual syndrome (PMS) and a majority of clinical trials confirm its efficacy[92]. Until recently the syndrome has been poorly defined and this has led to difficulties in researching its aetiology and treatment. Dennerstein[93] has pointed out that although hormonal factors during the premenstruum are likely to account for the physical and psychological symptoms, no oestrogen/progesterone imbalance has been confirmed. In reviewing biochemical theories of PMS, Brush[94], suggests that the most likely explanation for pyridoxine's efficacy is to be found either in its effect on serotonin and dopamine synthesis in the hypothalamus and/or as a co-factor in the production of essential fatty acids. In the same article Brush suggests that a dose of 150-200 mg/day tends to be most beneficial and incurs only a small incidences of side-effects. It also seems likely that vitamin B6 may modulate the effects of circulating hormones as described above. Allgood & Cidlowski[95] for example, showed that oestrogen induced gene expression was reduced by 30% under conditions of elevated intracellular vitamin B6 and was enhanced by 85% in conditions of vitamin deficiency. They suggest that B6 may modulate the expression of a diverse array of hormonally responsive genes.

In an isolated report Abraham[96] found that a combination of B6 and magnesium was beneficial for dysmenorrhoea which gradually improved over 4-6 months.

Blood levels of vitamin B6 are often lower in pregnancy[97] and maternal deficiency may be exacerbated by toxaemia[98] or hyperemesis gravidarum[99]. An early study by Wachstein et al.[100] suggested that a multivitamin with 10 mg of B6 was effective in reducing the incidence of toxaemia. A more recent study by Sahakian et al.[101] examined a group of 59 women with nausea and vomiting of pregnancy in a double-blind randomised placebo controlled study. Patients on active treatment were given 25 mg tablets orally every 8 hours for 72 hours. The results were highly significant in favouring B6 as an effective treatment.

High doses of B6 are antilactogenic, an effect which is probably mediated through dopamine's suppression of prolactin[102]. According to Andon et al.[103] a typical multivitamin supplement elevates plasma and milk PLP without reducing prolactin or lactation. Burkhart[104] has reported the use of 400 mg per day of B6 in the treatment of herpes gestationis in the third trimester of pregnancy.

B6 in moderate doses seems to be completely safe in pregnancy and no foetal abnormalities have been reported in animals or man[105]. Elmazar et al.[106] have shown that a combination of B6, B12 and folinic acid exerts a partially preventive effect in valproic acid induced teratogenesis in pregnant mice.

Haematology

Pyridoxine deficiency or dependency can cause a sideroblastic anaemia. In those cases with dependency the defect appears to lie with delta-amino levulinate (ALA) synthetase-an enzyme on the synthetic pathway for porphobilinogen. There also appears to be a vitamin B6 deficiency associated with sickle cell anaemia but B6 has not yet shown a convincing therapeutic effect[107]. Abnormal red cell metabolism of pyridoxine has also been associated with beta-thalassemia[108].

Inborn Errors of Vitamin B6 Dependent Metabolism

Homocystinuria is the second most common disorder of amino acid metabolism after phenylketonuria. Symptoms include dislocation of the eye lens, thromboses, abnormal skeletal formation and mental retardation. These effects are largely due to the accumulation of toxic homocysteine and its metabolites. The biochemical mechanisms have been described above in connection with the adult, milder form of homocysteinaemia. Approximately 50% of individuals respond to vitamin B6 in doses of up to 1500 mg/day. Betaine, which promotes the methylation of homocysteine to methionine may be helpful for some patients with unresponsive homocysteinaemia. Homocysteinuria may also result from slow B12 dependent synthesis of methionine. Other defects in B6 dependent metabolism include cystathioninuria, xanthurenic aciduria, hyperglycinaemia and histidineamia.

Pyridoxine has been used to treat type I and type II primary hyperoxaluria. In the infantile form B6 is used in combination with B1 and magnesium, but treatment is necessary before oxalosis develops. De Zegher et al.[109] described the treatment of an 8-week old infant with primary hyperoxaluria with 1000 mg B6/daily. The hyperoxaluria was reversed but the infant became hypotonic and developed neuropathy and encephalopathy. These symptoms abated when the dose was reduced to 400 mg/daily. Yendt & Cohanim[110] have described the successful treatment of a case of type-I primary hyperoxaluria with a low dose range 2-25 mg/day. They suggest that in some individuals a B6 rich diet or B6 containing multivitamins may be masking primary hyperoxaluria in individuals with calcium oxalate stones whose urinary oxalate excretion does not warrant a diagnosis of primary hyperoxaluria.

Pyridoxine dependent infantile seizures have been described above.

Other Conditions

Pyridoxine is frequently recommended for acne vulgaris but there is little experimental information to support this treatment. Snider & Dieteman[111] found that B6 50 mg daily for 1 week prior to and during menstruation improved premenstrual acne flare up. Since seborrhoea is a possible symptom of B6 deficiency it is not surprising that this condition sometimes responds to supplementation. Pyridoxine responsive arthritis as described by John Ellis has been mentioned above. There are however no confirmatory studies on B6 in arthritis. The situation with regard to carpal tunnel syndrome (CTS) is also unclear, with both positive and negative studies. Byers et al.[112] have suggested that patients with CTS responsive to pyridoxine may in fact have an unrecognised peripheral neuropathy.

Reynolds et al.[113] found a significantly high incidences of low plasma PLP in a group of hip fracture patients. They hypothesised that deficiency of B6 may be an aetiological factor in fractures, especially as B6 deficiency in rats may result in defective bone formation which is possibly the result of decreased activity of ornithine decarboxylase.

There are a small number of studies on B6 and asthma using dose ranges from 50-300 mg/day. Results are conflicting with both positive[114] and negative[115] outcomes. The latter study by Sur et al. noted that patients on regular theophylline had lower plasma B6 levels.

Supplementation with B6 may help diabetic neuropathy[116] and improve glucose tolerance in gestational diabetes[117]. As a result of long term follow up of patients with diabetes and carpal tunnel syndrome who have been on B6, Ellis[118] has observed a striking absence of diabetic retinopathy. Pyridoxine has been recommended for the so-called "Chinese restaurant syndrome" on the basis that it facilitates the conversion of glutamates (e.g.. MSG) to glutamine. A recent very thorough study by Tarasoff & Kelly[119] at the University of Western Sydney casts doubt on the existence of this syndrome. Participants

were given MSG or a placebo before or after a light breakfast. Some reaction to MSG was experienced by 15% of volunteers, but there was also a 14% reaction rate to placebo. Tarasoff suggests that reactions to Chinese meals may actually be provoked by histamines present in such ingredients as soya sauce and black bean and shrimp paste.

There is some evidence that B6 may reduce muscle fatigue in experimental animals[120].

TOXICITY

Schaumberg et al.'s[121] report of a sensory neuropathy in a group of adults consuming large doses of B6 is now well known. Daily intakes were in the 2000-6000 mg/day range over periods from 2 to 14 months. All seven patients displayed a "stocking-glove" sensory loss with numbness in hands, feet and perioral areas and an unstable gait. Impairment of position and vibratory sense were most noticeable. Symptoms reversed over a period of several months. Rudman & Williams[122] have suggested mechanisms which may have caused this toxicity. In the first instance the dorsal root ganglia lie outside the blood brain barrier and are therefore not protected in the same way as the motor outflow from the spinal cord. Secondly, inactive circulating pyridoxine may occupy various enzyme sites and prevent access by the active pyridoxal-5-phosphate. It is interesting that Snell[123] had hypothesised many years previously that adverse reactions might result from accumulated pyridoxine for just this same reason. Katherine Dalton[124] subsequently published a report describing a relationship between high serum B6 levels and toxicity symptoms resulting from doses of B6 in the 50-300 mg/day range. Brush & Perry[125] questioned both the diagnosis of neurotoxicity and the B6 assay methods used in this study quoting an analysis of their own patients, 630 of whom had taken 80-200 mg B6/day for PMS. They noted no cases of neuropathy and a 70%-80% improvement in PMS symptomatology.

There is an isolated report on a group of medical students taking 100-500 mg B6/day who appeared to show some memory impairment while carrying out a digit coding test over a 15 day period[126]. A group of obese patients on a low energy diet taking 1000 mg B6/day showed poor performance in word recognition and visual retention tests[126]. There are apparently no other reports of cognitive impairment with high doses of pyridoxine.

It may well be that some of the reported toxicity of pyridoxine relates to its consumption in high doses without balance from other members of the B group. In this connection it is interesting that Buist[127] in reviewing the safety of vitamin B6, reports anecdotal information that some patients taking vitamin B6 while on a dairy free or low vitamin B2 diet have complained of gritty eyes, sore tongue and angular stomatitis. These symptoms were presumably due to a vitamin B2 deficiency since the symptoms vanished with riboflavin supplementation.

Bernard Rimland who has probably treated thousands of autistic children with high doses of vitamins, states in an information brochure for parents[53], that he has not seen any neurotoxic effects from B6 and believes that such effects may result from deficiencies in magnesium and/or other nutrients which he prescribes in a balanced formula to complement the high levels of ingested vitamin B6.

[illustrations on pages 9 - 11]

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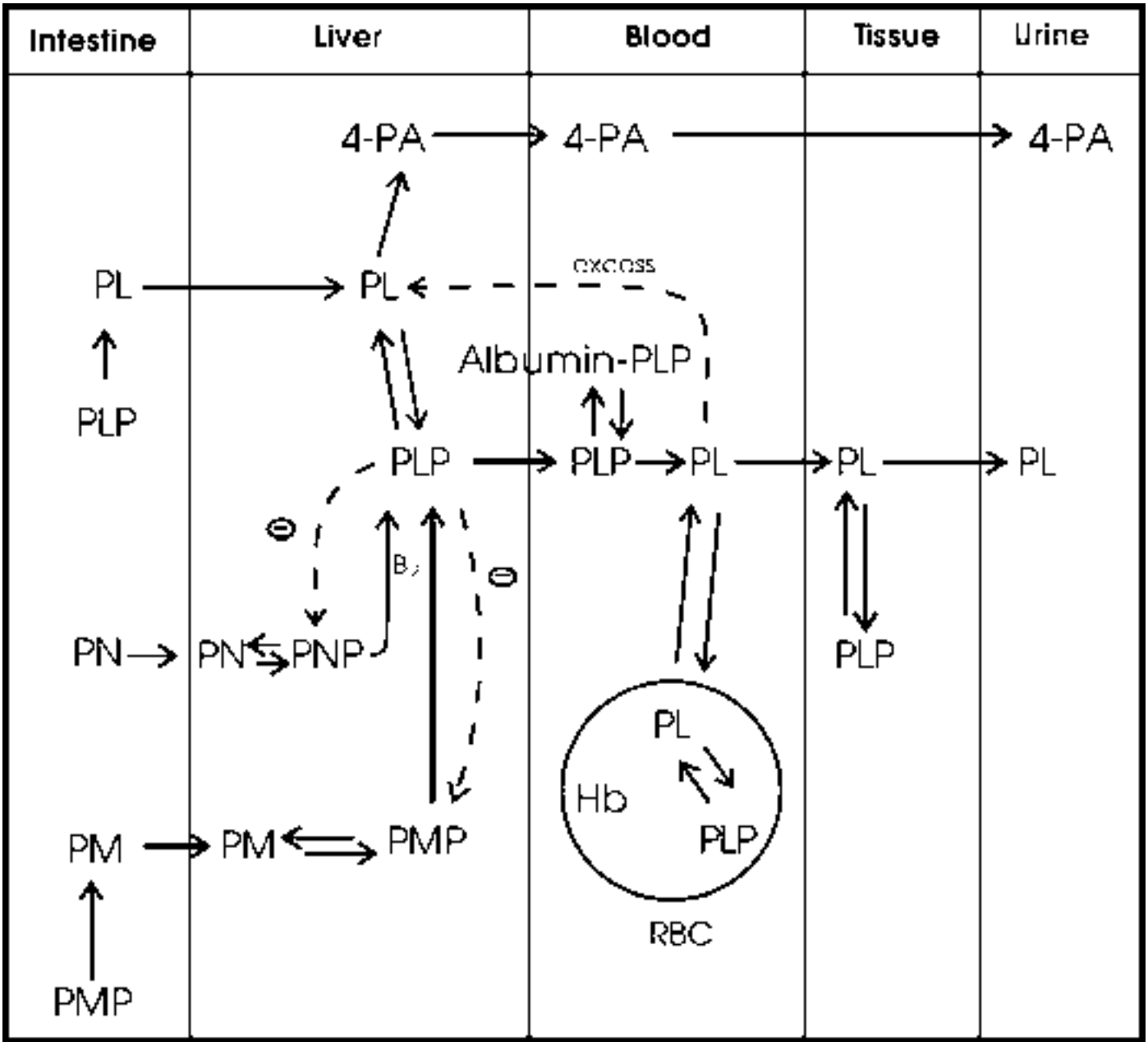
[illustrations on pages 9 - 11]

Figure 1 - Simplified view of B6 metabolism and transport



PL - pyridoxal PN - pyridoxine PM - pyridoxamine 4-PA - pyridoxic acid
PLP - pyridoxal 5-phosphate PNP - pyridoxine 5-phosphate PMP - pyridoxamine 5-phosphate
RBC - red blood cell ⊖ - feedback inhibition B2 - riboflavin

Figure 2 - Homocysteine Metabolism

(Pyridoxine - Vitamin B6)

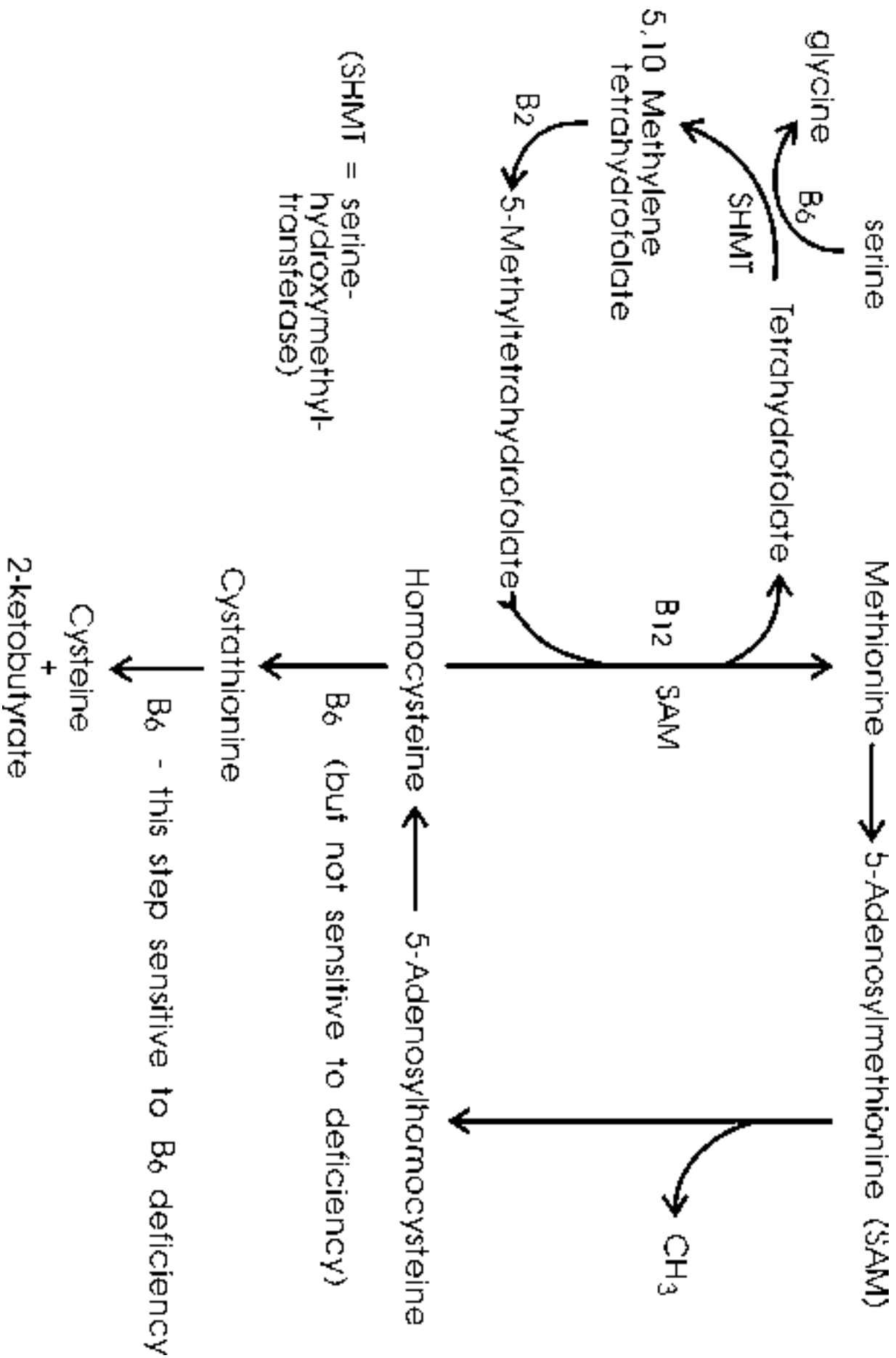


Figure 3 - Tryptophan Metabolism