Functional Nutrient Deficiency in Chronically Multi-symptomatic People — A Pilot Study

Laraine C. Abbey, R.N., M.S.[1]

This pilot study was done in partial fulfillment of the M.S. degree requirements at the University of Bridgeport.

Abstract

Functional vitamin testing utilizing in vitro enzyme stimulation assays was performed on 22 office clients, many of whom had no evidence of organic disease, but who had sought nutritional assessment for help with various multiple chronic symptoms unresolved by traditional medical treatment. These 22 clients with identified underactivity of various vitamin dependent enzymes (functional vitamin deficiency), despite use of multivitamins, were supplemented with pharmacological dosages of the functionally deficient nutrients). The supplementation was associated with significant symptom reduction or elimination and enhanced feelings of well being.

The client improvement was concomitant with changes in enzyme activity demonstrated through follow-up enzyme stimulation assays. These assays demonstrated normalization after a period of pharmacological vitamin supplementation.

The data indicates an apparent relationship between chronic, non-specific symptoms (including the so-called psychoneurotic symptoms like fatigue, anxiety, depression, and muscle tension) and nutritional-biochemical imbalance. Many such imbalances are now measurable and appear to be responsive to dietary and nutrient manipulation often requiring pharmaco-logical doses of specific B-vitamins to normalize the functionally vitamin deficient assay and reduce or eliminate the symptoms.

Introduction

We are quite literally the product of our own nutrition ... built and maintained by the progressive breakdown of food into various metabolites which are in turn ultimately transported in and out of cells.

This process of intermediary metabolism, regulated by enzymes, is subject to manipulation by various factors including vitamins. Such manipulation is possible, even in the absence of classical vitamin deficiency, since vitamins form coenzymes and many enzymes are not fully saturated with coenzymes under physiological conditions (Holtzman, 1980; Dakshinamurti, 1977; Martin, 1981).

The author has observed that multi-symptomatic people who institute dietary changes often experience symptom reduction, including behavioral change, along with an enhanced sense of well-being. Many individuals who fail to experience significant symptom reduction with dietary changes and routine vitamin therapy do experience marked improvement from pharmacological levels of various specific nutrients following functional vitamin testing (Abbey, 1982).

Various chronic symptoms in people with or without diagnosable disease were associated with underactivity of various vitamin dependent enzymes which were responsive to pharmacological vitamin supplementation. This can be the result of the vitamin's effect upon a particular enzyme system's activity rather than because the total body vitamin pool was low as in a deficiency.

An understanding of enzyme kinetics helps to clarify the role of vitamins in increasing an enzyme's reaction product through increasing the percentage of functioning apoenzymes and holoenzymes and further by increasing the rate or velocity of its reaction (Partridge, 1977).

It is well documented that depriving individuals of certain vitamins may result in a variety of symptoms and personality

1. RNA LifesStyle, Warren Plaza West, Route 130, East Windsor. N.J. 08520.

changes (Lonsdale & Shamberger, 1980; Lonsdale, 1975; Abbey, 1982; Axelrod, 1964, 1971a, 1971b; Lipton, 1979; Roe, 1978; Horwitt, 1980; Sauberlich, 1980; Brewster, 1980; Krehl, 1970).

In this paper the author submits evidence to indicate that pharmacological doses of specific nutrients can be utilized to alleviate a variety of common symptoms and personality manifestations that have been documented as associated (though not necessarily causal) with various nutritional deficiencies.

Nutritional deficiency symptoms can occur in the absence of (or before the onset of) classical deficiency diseases. These symptoms have been associated with, and appear to result from, altered vitamin dependent enzyme activity (Lonsdale & Shamberger, 1980; Krehl, 1970; Abbey, 1982).

Symptoms provoked by depriving individuals of various nutrients are numerous and include depression as cited by Adams (1973; Carney (1979); Lonsdale (1975); Sauberlich (1980); Krehl (1970), et al.

Aggressive behavior was reported by Lonsdale and Shamberger (1980) in a population of patients generally considered to be neurotic in who thiamine deficiency was identified. Lonsdale alone (1975) and with Schamberger (1980) also listed the following as some of the symptoms of early thiamine deficiency: fatigue, stomach distress, chest pains, edema, irritability, memory impairment, failure to concentrate, muscle weakness, neuritis, insomnia, dizziness, muscle aches, palpitations, numbness and tingling, and headaches. Many such symptoms were also noted and published by this author associated with the disorder agoraphobia which this author found to be highly responsive to nutritional therapy as 83% of the study group exhibited dramatic improvement (Abbey, 1982).

Nutritional symptoms and neurotic anxiety syndrome were also reported by Axelrod, Dakshinamurti, and Lonsdale (1971a).

Gastrointestinal symptoms, plus neurological and mood disturbances associated with vitamin B_6 deficiency and niacin deficiency have frequently been reported by researchers including Roe (1976, 1979), Horwitt (1980), and Sauberlich (1980).

Skin symptoms from vitamin deficiency including seborrheic dermatitis and ocular lesions have been noted in Lipton's review (1979), as well as Horwitt (1980), Roe (1978), and Krehl (1970).

Behavioural changes are evidenced in even marginal vitamin deficiency as noted by Brin (1979).

The importance of various nutrients in the regulation of the immune system has been noted by Beisel, et al (1981) and Duchateau, et al (1981). Thus, frequent infections may be an indication of poor nutritional status. The role of B_6 in particular in the immune system was emphasized by Axelrod (as early as 1964), Sergeev (1978), and Willis-Carr (1978).

Vitamin B_6 is necessary for the production and cytotoxicity of T-lymphocytes, vital to normal immune function, and for the formation of the hormone-like prostaglandins, (Horrobin, 1981) from essential fatty acids. In addition, vitamin B_6 plays a major role in the enzyme activity of most of the neurotransmitters through its coenzyme function as pyridoxal-5-phosphate which interacts with tyrosine, dopamine, epinephrine, norepinephrine, tryptophan, serotonin, and gamma-amino-butyric acid.

A profound role for vitamin B_6 in hormonal activity was discussed by Rose (1978) in his review paper on B_6 and hormone interaction.

It is worth noting as did Wiss (1964) that the ultimate causation of symptoms from a vitamin deficiency has to be attributed to an impairment of enzymes. This is so, since a major known function of vitamins is the formation of co-enzymes to bind with and activate enzymes.

Vitamin deficiencies cause alterations in enzyme systems. Since co-enzymes have varying affinities for enzymes and since inducible enzymes fail to increase when there is a deficiency of the vitamin needed for holoenzyme formation (Wiss, 1964), varying biochemical effects could manifest. Altered enzyme activity can thus be dietar-ily induced. But dietary factors are not the only ones influencing enzyme activity. Enzyme activity is also genetically determined since genes synthesize enzymes and, further, enzyme activity is environmentally mediated through such factors as environmental

chemicals (Yagi, et al, 1979, 1979a and Yagi & Itokawa, 1979, 1979b), drug therapy (Roe, 1978, and Yui, 1980) and alcohol ingestion (Roe, 1979).

The vitamin dependent genetic diseases as noted by Rosenberg (1973), Coursin (1964), Scriver (1960, 1965), Hunt (1954), Cotzias (1972), Heeley (1978), Mudd(1971), Nyhan (1981), Dakshinamurti (1977), and Dancis (1970) are dramatic examples of biochemical individuality as discussed by Williams (1956). Roger Williams reports that a respect for biochemical individuality dates back to Sir A. E. Garrod in *Inborn Errors of Metabolism* when in 1902 Garrod wrote, "The thought naturally presents itself that these [alkaptonuria, etc.] are merely extreme examples of variations of chemical behavior which are probably present everywhere in minor degrees and that just as no two individuals of a species are absolutely identical in bodily structure, neither are their clinical processes carried out on the same lines." (Williams, p. 97).

Roger Williams expands on this concept in his book, *Biochemical Individuality*. Dancis (1970) and Coursin (1964) also expound on this theme. Williams (1956) makes the point, as does Dancis (1970), that enzyme disturbances may be associated with common disorders. Dancis states on page 1446 of his article, "Furthermore, our increased awareness of the variations in enzyme activities manifest among populations suggests that partial reductions in enzyme activities may be considerably more frequent than the metabolic defects recognized so far, and that the subjects may also benefit from the application of the nutritional information derived from the study of the rare inborn errors of metabolism."

Further, Coursin (1964) also supports the hypothesis of genetic gradients as put forth by Williams (1954) when he states on p. 779: "that the possibilities of differences in individuals also is important in that the degree of affinity of an enzyme system in any given person may be of a different order of magnitude than that normally seen in the general population therefore requiring more of a vitamin than might ordinarily be expected." He further notes that the complexities and interrelationships of substrates, enzymes, and allied biochemical factors may produce an inhibitory or stimulant effect that is independent of the availability of the vitamin co-factor.

It's important to note that vitamin dependency states do not necessarily manifest with abnormal routine biochemical tests and that systemic metabolism of a vitamin may otherwise be quite normal except for specific defective enzymes it activates (Heeley, 1978). Enzyme defects should not necessarily be expected to produce signs readily observable on routine physical and biochemical examination. Thus, it shouldn't be presumed that various health complaints as expressed by patients are necessarily psychogenic when, in fact, they may arise from altered enzyme activity.

Methodology

Over a period of time in this author's office practice functional vitamin tests were performed on many clients reporting a wide variety of subjective and objective symptoms such as those previously cited (example: fatigue, seborrhea, etc.). Many such clients had unsaturated vitamin dependent enzymes (functional vitamin deficiency) identified despite vitamin supplementation.

The tests and test methods performed are itemized as follows and are reviewed in the very well-referenced text by CRC Press; *Laboratory Assessment of Nutritional Status* (Sauberlich, Dowdy, Skala,T977). Thiamin (B_1) (Sauberlich, 22-29) Thiamine pyrophosphate percentage uptake by the erythrocyte transketolase enzyme referred to as TPP% uptake or TPP effect)

Transketolase is a thiamin-pyrophosphate requiring enzyme which catalyzes the following two reactions in the pentose phosphate pathway:

1) xylulose-5-phosphate+ribose-5-phosphate ---------» sedoheptulose-7-phosphate+glyceraldehyde-3-phosphate
2) xylulose-5-phosphate+erythrose-4-phosphate ---------- fructose-6-phosphate +glyceraldehyde-3-phosphate

The erythrocyte transketolase activity assay involves the incubation of hemolyzed whole blood samples in a buffered medium with an excess of ribose-t-phosphate in both the presence and absence of excess

thiamin pyrophosphate. After a period of time the ribose-5-phosphate or the sedo-heptulose-7-phosphate are measured. The disappearance of the former or increase in the latter are indicative of the activity of the erythrocyte transketolase enzyme which is responsible for the conversion of the former to the latter. The response obtained without additional thiamin pyrophosphate establishes the absolute enzyme activity. This is determined by the amount of coenzyme already available within the erythrocytes. When additional thiamin pyrophosphate is added to the blood sample exogenously, any decrease in ribose-5-phosphate or increase in sedoheptulose-7-phosphate indicates the amount of transketolase apoenzyme as yet uncomplexed. The enhanced enzyme activity which results from such added thiamin pyrophosphate is referred to as the TPP% effect. Such measurements provide a convenient, specific and sensitive functional test of thiamin nutriture.

Riboflavin (B-2) Erythrocyte glutathione reductase (EGR) activity coefficient. The enzyme catalyzes the reduction of oxidized glutathione (GSSG) as follows:

$$\text{NADPH (NADH)} + \text{H} + \text{GSSG} \xrightleftharpoons{\text{EGR}} \text{NADP(NAD)} + 2\,\text{GSH}$$

The assay results, expressed as activity coefficients (AC) is the degree of enzyme stimulation which results from the exogenous addition of the active coenzyme form of riboflavin known as flavin adenine dinucleotide (FAD). The activity coefficients are expressed as follows:

$$\text{AC} = \frac{\text{Reduction of absorbance with added FAD/10 min.}}{\text{Reduction of absorbance without added FAD/10 min.}}$$

In normal subjects, an AC of approximately 1.00 ± 0.10 is obtained indicating little or no stimulation. During riboflavin deficiency a marked stimulation occurs. Thus an AC of 1.2 and above indicates a functional deficiency of riboflavin.

Pyridoxine (B_6) The measurement of the activity of the erythrocyte glutamate-oxaloacetate transminase (EGOT) and erythrocyte glutamate-pyruvate transaminase (EGPT) before and after exposure to the active coenzyme form of vitamin B_{fi} as pyridoxal-5-phosphate provides for a functional test of B_6 status. Even normals can have a significant stimulant effect upon the enzyme by pyridoxal-phosphate. EGOT activity is rarely stimulated more than 50% and EGPT is rarely stimulated by more than 25%.

In order to minimize differences among normals the use of an erythrocyte transaminase index has been proposed. Further studies will be needed to clarify the validity and usefulness of such indexes.

The index is as follows:

$$\text{EGPT index} = \frac{\text{EGPt+B-6 phosphate}}{\text{EGPT (-B-6 phosphate)}}$$

$$\text{EGOT index} = \frac{\text{EGOT+B-6 phosphate}}{\text{EGPT (-B-6 phosphate)}}$$

Vitamin B_{12} There is no functional enzyme stimulation assay test. Serum B_{12} has been the most common procedure used in the assessment of deficiency. Urinary excretion of methylmalonic acid (MMA) occurs in the presence of B_{12} deficiency since the conversion of methylma-lonyl CoA to succinyl CoA is activated by the vitamin B_{12} dependent enzyme: methyl-malonyl coenzyme A mutase.

In Babior's text, Cobalamin (1976, p. 410) MMA is noted as a reliable and sensitive indicator of vitamin B_{12} deficiency, "except in the rare cases in which it is due to an inborn error of metabolism." It is well documented in Sauberlich's review that urinary excretion of MMA is increased in the majority of patients deficient in vitamin B_{12}. Thus, MMA could be a valuable functional test of B_{12} status.

From the large group of my office clients found with various functional abnormalities small groups were distilled down in which the functional deficiencies and treatment approach were essentially the same and noted as follows.

Office clients are routinely given extensive dietary counseling and asked to modify their diets accordingly. This includes the elimination of caffeine, refined carbohydrates, alcohol, chemical additives, plus reduction in fats with emphasis on increased consumption of fish, beans, vegetables, fruits, and whole grains.

They are then placed on a nutrient

supplementation program with a specific multivitamin and multimineral formulation* and then monitored for six weeks at which time their improvement is evaluated by means of a systems review symptom checklist completed on the initial visit and then reviewed at six-week intervals. Those clients in whom the primary symptoms persist, are then treated for functional vitamin deficiency. One or more functional vitamin deficiencies were found among these symptomatic clients.

Data was then organized according to the following criteria:

1) By functional vitamin deficiencies: See Table 1.

Group	Functional Deficiency
1.	B,
2.	B_1, B_6
3.	B_1, B_6, B_{12}
4.	B_6

2) Whether or not the abnormal test(s) were repeated: Many clients with functionally abnormal tests exhibited a dramatic improvement following a pharmaceutical dosage of their specific functionally abnormal vitamin(s), but once recovered did not wish to submit to the inconvenience and expense of repeat testing.

It is worth noting that almost all of my office clients in hundreds thusly tested who had repeated such tests had normalization of the test on high dose vitamin therapy. Therefore it would be reasonable to predict the likelihood that the overwhelming majority of those abnormal tests not repeated would have normalized as well.

3) By dosage of vitamin(s) given.

Each client had also been asked initially to identify his or her major health problems, symptoms and goals for nutrient therapy. See table two. On follow-up visits they were asked to report on their progress.

* The multi-vitamin contains: vitamin A - 10,000 IU; vitamin D - 400 IU; vitamin E -150 IU; vitamin C - 250 mg; B-vitamins -75 mg or mcg, plus folic acid - 400 mg; zinc - 15 mg; iron - 10 mg; manganese - 5 mg; plus extra calcium - 1,000 mg and magnesium - 500 mg; and extra vitamin C - 2,000 mg.

This is expressed as client reported problems and client reported response.

Client symptoms and response were reviewed at six and then again at twelve weeks on the pharmacological vitamin dose(s) and placed in one of four categories at twelve weeks as follows: P = persist; S = slight improvement; M = marked improvement; G = gone.

For statistical purposes the symptom groups G (gone) and M (marked improvement) were then combined to form the category D which constitutes dramatic improvement. The percentage of dramatic improvement was then calculated for each client and for the group as a whole.

Results (See Tables pages 80-85)

Discussion

This author's decision to implement functional nutrient testing with the use of enzyme stimulation assays and urinary metabolites was based on a belief that the source of various common and chronic symptoms suffered by individuals might rest with defective enzyme activity. As previously noted, many factors including stress, lack of exercise, drugs, toxins in air, food, or water, allergens and genetics impact upon enzyme activity. This, in turn, may result in various symptoms, signs, and even ultimately, diseases.

This author stated in a recent publication (Abbey, 1982), "The real concern which must be extracted from all this is that a population with increasing numbers of persistent symptoms and signs would appear to be suffering from genetic damage" ... "as evidenced by a requirement for pharmacological levels of vitamins to correct functional vitamin status [or defective enzyme activity] as measured by the enzyme stimulation assays;" and "that such damage can result largely from dietary abuse, particularly in depletion of many vitamins, minerals, and trace elements as a consequence of overconsumption of refined, processed foods with disturbed macro/ micro nutrient ratios." It would not seem odd that long term in vivo disturbances in macro/micro nutrient ratios ultimately might result in enzymopathies and genetic mutations at the level of transcription and translation since they are under enzymatic

Table 1

Group 1 — Vitamin B_1, functionally deficient. Normal value: 0-17.3% TPP Dosage given unless otherwise noted: 500 mg. OD

Patient	Starting Percentage	Follow-up Percentage	Dosage
1. H.H.	36.84	0.0	
2. B.K.	39.6	0.0	
3. J.R.	66.0	0.0	
4. G.Mc.	66.8	16.6*	200 mg* OD
5. L.A.	64.0	0.0	
6. S.L.	320.0	no repeat	
7. R.C.	90.0	no repeat	

* Note: although within normal range, this enzyme is not totally saturated on this lower dose of vitamin Bi

Group 2 — Vitamin B1 & Vitamin B6 functionally deficient.
Normal value Bj: 0-17.3% TPP / Normal value B_6: below 1.25% EGPT index
Dosage given unless otherwise noted: 500 mg. of each (OD)

Patient	Starting Percentage or Index	Follow-up Percentage or Index	Dosage Bi or Bg
8. N.W. (B0	29.2	0.0	
(B_6) 9.	**1.51**	**.86**	
S.M. (B0	96.5	0.0	
(B_6)	2.13	1.12	200 **mg OD**
10. **P.G. (B0**	34.0	0.0	
(B6)	1.49	1.0	
11. **M.C. (B0**	20.0	0.0	200 **mg OD**
(B6)	1.37	1.13	

Group 3 — Vitamin B1, B_6, & B_{12} functionally deficient
Normal value B1: 0-17.3% TPP / Normal value B_6: below 1.25% EGPT index
Normal value Bi_2: 0-3 mg per 24-hr. urine of MMA
Dosage given unless otherwise noted: B1: 500 mg OD / B_6: 500 mg OD
B12: 1,000 micrograms (megs) OD

Patient		Starting Percentage Index or Mgs.	Follow-up Percentage Index or Mgs.	Dosage
12 L.T.	(B.)	26.9	0.0	
.				
	(B_6)	1.29	1.08	
	($B_{,2}$)	55.51	0.0	
13 W.R,	• (B.)	125.0	12.0	
.				
	(B_6)	1.89	1.01	
	($B_{,2}$)	22.9	0.0	
14 C.H.	(B,)	74.0	0.0	
.				
	(Be)	2.07	.74	
	(Biz)	23.0	3.3	

Table 1 (cont'd.)

Group 4 — Vitamin B_6 functionally deficient
Normal value: below 1.25 EGPT index
Dosage given unless otherwise noted: 500 mg OD

Patient	Starting Index	Follow-up Index	Dosage
15. M.H.	1.93	.92	
16. J.A.	1.30	1.02	
17. J.S.	1.74	1.09	
18. V.B.	2.40	no repeat	
19. R.K.	1.31	.81	
20. L.T.	1.64	no repeat	200 mg OD
21. L.F.	1.33	no repeat	200 mg OD
22. E.M.	1.66	no repeat	

Table 2

The following data is the Symptom Response by the total of 22 clients comprising the previous four groups. The total number of possible symptoms on Systems Review is 281 (see chart 1). Response to therapy is noted as each symptom is placed in one of four categories as follows: G = Gone; M = Marked Improvement; S = Slight Improvement; P = Persist; D = Dramatic Improvement (is equal to the sume of Gone plus Marked Improvement).

Client	# Symptoms Before Treatment	Client Reported Problems	#Symptoms After Treatment	Client Reported Response	% Symptoms Dramatically Improved
1. H.H.	73	Irritable bowel syndrome, peptic ulcer, hypertension, diverticulosis, nervousness, depression, irritability, chest pain, dermatitis, allergies. These symptoms have plagued him over a period of ten year's duration.	G-44 M-18 S-14 P-7 D=62	Virtually all of these symptoms *Se* problems were eliminated.	85
2. B.K.	36	Panic attacks, extreme nervousness, migrating body pains.	G-21 M-9 S-2 P-4	Dramatic improvement, panic attacks stopped, reports	83
3. J.R.	36	Very low energy, constipated, extreme lethargy after eating carbohydrates especially sugary foods.	G-12 M-5 S-3 P-16 D=17	Energy greatly improved, feels better generally *Se* no longer apathetic	47

Table 2 **(cont'd.)**

Client	# Symptoms Before Treatment	Client Reported Problems	#Symptoms After Treatment	Client Reported Response	% Symptoms Dramatically Improved
4. G.Mc.			S-2 P-0 D^S	within 24 hours with tremendous improvement.	
5. L.A.	44	Agoraphobia, panic attacks, severe obsessional headaches, nausea, dizziness & fatigue.	G-32 M-10 S-l P-l D=42	Totally recovered from agorapho-bia, all obses-sions & panic attacks gone. This dramatic improvement occurred in spite of stress of husband divorcing her.	53
6. S.L.					
	15 80 31	Depression, fatigue, gastric distress.	G-7 M-l S-l P-6 D=8	G.I. distress gone, energy normal, depres-sion markedly improved.	44 84
7. R.C.		Frequent panic attacks, agoraphobia, chronic severe anxiety.	G-16 M-19 S-10 P-35 D=35	Marked reduc-tion in severity *Ec* frequency of panic attacks & chronic anxiety.	61
8. N.W.	23 Loss of appetite, fatigue, gastroin testinal distress & gas after meals, asthma.	Agoraphobia, chronic panic attacks, daily headaches, numbness in left arm, chest pain.	G-18 M-8 S-2 P-3 D=26	Major symptoms virtually gone, no headaches, numbness, panic attacks or chest pain.	
9. S.M.		Agoraphobia, panic attacks & severe chronic anxiety, seborrhea, eczema.	G-10 M-6 S-3 P-l D=14	Feel wonderful, all agoraphobia symptoms gone (no panic, no anxiety), eczema clear, seborrhea improved.	
10. P.G. 16 10	Letharg ic, short-term memor y loss, palpitat ions.	G-7 & M-6 asthma S-3 appe-P-0 D=13 G-7 M-l gone	G.I. distress gas gone, improved, tite & energy better Palpitations completely	81 80 95	

Table 2 (cont'd.)

Client	# Symptoms Before Treatment	Client Reported Problems	#Symptoms After Treatment	Client Reported Response	% Symptoms Dramatically Improved
11. M.C.	14	Failing school, behaviour problems, visual disperceptions.	G-10 M-l S-2 P-l D=ll	Dramatic improvement in behavior; school performance greatly improved	79
12. L.T.	37	Anxiety, irritability, edema, muscle spasm, dizziness, migraines,	G-14 M-14 S-l P-8	Greatly improved. Feel much better, most symptoms	76
13. W.R.	32	rhinosinusitis,	D=28	gone or occasional	50
14. C.H.	39 13	abdominal pain.	G-ll	now.	69
15. M.H.	49	Medical diagnosis:	M-5	Significant	85
16. J.A.		autonomic nervous system imbalance & endometriosis.	S-6 P-10 D=16	improvement in energy, indigestion, blood sugar levels	32
		Diabetes, Parkinsons, hypertension, indigestion, constipation, respiratory allergies, fatigue.	G-9 M-18 S-9 P-3 D=27	more normal, pulse rate down from 100 to 78, no change in Parkinson tremor.	
		Chronic fatigue, headaches, spastic colon.	G-9 M-18 S-l P-3 D=ll	Great improvement in most symptoms including fatigue and headaches,	
		Chronic vaginal *Se* rectal candidiasis, dysmenorrhea, premenstrual syndrome (PMS), breast tenderness, bloating, dizziness.	G-12 M-4 S-21 P-12 D=16	headaches persist at menses. Dramatic improvement, no vaginal-rectal candidiasis, near elimination of all PMS, concentration now normal.	
		Agoraphobia, chronic panic attacks, suicidal.		Dramatic improvement in her nervous symptoms (anxiety, depression, panic).	

Table 2 (cont'd.)

Client	# Symptoms Before Treatmeni	Client Reported t Problems	#Symptoms After Treatment	Client Reported Response	% Symptoms Dramatically Improved
17. J.S.	**35**	Rheumatoid arthritis for 10 years, 5 years on gold shots.	G-9 M-20 S-4 P-0 D=29	Overall arthritis pain much improved, shoulder pain gone, ankles markedly improved, hand *8c* foot pain slightly improved.	83
18.	**72**	Shortness of breath, gastritis, irritability, anxiety, fatigue, dizziness, tremors, irregular pulse.	**G-40** M-15 S-10 P-7 **D=55**	Dramatic improvement, all major symptoms eliminated or dramatically improved.	76
19. R.K.	**50**	Arthritis with deformity, extreme fatigue, muscle spasm pains in thighs & calves.	**G-40** M-5 S-4 P-l **D=45**	All pain *Se* fatigue gone. "Feel wonderful."	90
20. L.T.	**47**	Constant fatigue, depression, mood swings, migraines, heavy menstrual bleeding, food binging.	**G-30** M-5 S-8 P-4 **D=35**	Great improvement, moods stable, energy normal, periods shorter with normal flow.	75
21. L.F.	**25**	Severe premenstrual syndrome.	G-17 M-5 S-1 P-2 **D=22**	No PMS, completely recovered.	88
22. E.M.	**11**	Rheumatoid arthritis, constant pain persisting with progressively increasing stiffness despite use of drug therapy.	G-0 M-9 S-0 P-2 D=9	Marked improvement stiffness & pain, off all cortisone, managing with occasional aspirin.	82

Table 3

Client No.	*A	*B	*C
1.	73	62	85
2.	36	30	83
3.	36	17	47
4.	16	13	81
5.	10	8	80
6.	44	42	95
7.	15	8	53
8.	80	35	44
9.	31	26	84
10.	23	14	61
11.	14	11	79
12.	37	28	76
13.	32	16	50
14.	39	27	69
15.	13	11	85
16.	49	16	32
17.	35	29	83
18.	72	55	76
19.	50	45	90
20.	47	35	75
21.	25	22	88
22.	11	9	82
Mean:	35	25	71%
Standard Deviation:	20	13	17%

*A = Number symptoms before treatment *B = Number of symptoms that dramatically improved *C = Percentage of improvement

(continued from p. 79)

control by zinc activated enzymes (RNA-DNA polymerase).

Refined food diets lacking in micro nutrients, deplete nutritional reserves. Enzymes (derived from amino acids) are both composed of and activated by various macro and micro nutrients.

We need to appreciate that enzyme activity and nutritional balance are ultimately related, each having a profound effect upon the other.

It is important to recognize that there is a major difference between dietary nutritional adequacy and cellular nutritional adequacy. There are important distinctions between blood levels of vitamins, levels of the coenzymes formed from these vitamins, and levels of enzymes formed by the binding of coenzymes to apoenzymes all of which may vary as a result of acquired or genetic enzyme disturbances.

Acquired and/or genetic disturbances in enzyme activity can inhibit the ability of vitamins to form coenzymes and can affect the binding of coenzymes with their respective apoenzymes in the formation of operational holoenzymes (Hammes, 1971).

Altered enzymes which may result from nutritional deficiency or genetic factors can play a major role in the development of further cellular or functional nutrients deprivation also referred to as secondary nutrient deficiencies (Krehl, 1970).

The role of vitamins in metabolic disease of the inherited or genetic type is now gaining recognition as the list of vitamin responsive inborn errors of metabolism expands rapidly (Scriver, Cotzias, Dancis, Heeley, Hunt, Mudd, Nyhan, Rosenberg, etc.)

Given the fact that certain inborn errors of metabolism with gross symptomatology respond to pharmacological levels of specific vitamins, it should not seem strange that subtler, less dramatic symptoms might likewise respond to pharmacological vitamin therapy by impacting on subtler disturbances in enzyme activity.

The genetic basis of biochemical individuality and the biochemical basis of genetic disease are being elucidated by many researchers as previously noted. Apoenzymes as expressions of genes have varying affinities for their co-enzymes for genetic and acquired reasons and exhibit various degrees of saturation under physiological conditions. As noted earlier, many enzymes are not saturated under physiological conditions and can therefore often be stimulated with the addition of more coenzyme which, in turn, may occur in the presence of more of the respective vitamin. Increasing the concentration of a vitamin's coenzyme or of amino acids can result in increased synthesis of inducible enzymes. Enzyme induction by substrates and hormones allows for economy in the use of various amino acids, vitamins, minerals, trace elements, and metabolic energy. This

is so because inducible enzymes are made only when needed. Such enzymes, often present in trace amounts, increase markedly when their substrates are present (Lehninger, 1975). Tryptophan pyrrolase and tyrosine transaminase are examples of inducible enzymes. They are involved in neurotransmitter synthesis and therefore in mood and behaviour, as well as autonomic nervous system function.

Stress, by virtue of stimulating these and other inducible enzymes, creates increased demands for nutrients which irva system lacking nutritional reserves could readily create metabolic disturbances. This could in turn result in pansymptomology since specific enzymes are present in many different organs and tissues within the body. Stress potentially involves both overproduction of behaviour altering metabolites, and the depletion of various nutrients from other cells which could thus create biochemical lesions.

For example, stress stimulates the release of glucocorticoids which in turn results in increased concentrations of the inducible B_6 dependent enzyme tyrosine transaminase (Martin, 1981). "Nearly every tissue in the mammal has been shown to contain specific glucocorticoid receptors, and it now appears that glucocorticoids may be developmental hormones, capable of eliciting certain patterns of gene expression," (Lehninger, 1975 p. 994).

It must be remembered that the behaviour of enzymes is determined by the nutrient derived metabolites in the immediate vicinity of the enzyme in question rather than the overall level of specific nutrients in the body (Martin, Mayes, Rodwell, 1981). The simple presence of a particular vitamin, trace element, or amino acid in the body in no way establishes local saturation of all the various enzymes, cells, and tissues which depend upon such nutrients for their function.

While many enzyme reactions are not subject to nutritional manipulation many others are directly subject to such control. This knowledge has not filtered down to most health practitioners who still do not realize there is any other function for a vitamin other than the prevention of vitamin deficiency diseases. This belief prevails despite the rapidly amassing biochemical data on nutrients, enzyme kinetics, and molecular biology.

The use of vitamins and other food factors to alter intermediary metabolism through manipulation of enzyme activity may provide new strategies for preventing, modifying, or eliminating certain metabolic disturbances and diseases.

New names like dietary precursor therapy are now being used but the concept, labeled and defined by Linus Pauling as Orthomolecular medicine is essentially the same: altering body chemistry by manipulating levels of naturally occurring substances present in the body (Pauling, 1973).

Conclusion

The clients in this study had previously been involved long term with traditional and symptomatic treatments. The chronic symptoms, signs, and disorders for which they sought nutritional assessment had failed to respond to the previously pursued traditional treatment approaches.

In this study most clients' responses to pharmacological vitamin supplementation resulted in either complete elimination or marked improvement in chronic symptoms and signs, a positive outcome associated with pharmacological vitamin therapy. Vitamin therapy was administered at arbitrary levels. Clients cited here had already failed to improve from a super-nutrition diet and a trial of higher than RDA levels of multivitamins and testing showed functional vitamin deficiency (unsaturated vitamin dependent enzymes) concomitant with persistence of symptoms. When the higher dosages of the functionally deficient vitamins were administered there was dramatic improvement in symptoms in most clients. This improvement was associated with normalization of follow-up functional tests. There were no other known changes in the clients' lifestyles.

The clients served as their own controls. They were chronically symptomatic in most cases for many years. A mean improvement of 71% in six to twelve weeks following treatment could not reasonably be expected to occur as a placebo response. Even the best placebo would not generate a 71% mean dramatic improvement or mode of 80-85% dramatic improvement in

clients who had failed to respond to previous non-nutritional traditional treatments.

Nutrients, as in food and in supplement form, as therapeutic agents may be among the most powerful tools available to us in manipulating biochemistry to prevent, modify, or eliminate various symptoms, signs, and chronic diseases.

The implications for the preventive and therapeutic use of nutrients are profound. Studies demonstrating relationships and associations between nutrient metabolism and chronic disease are voluminous and are increasing exponentially. Such studies are needed to continue to define and clarify the role of nutrition in the prevention and treatment of disease as well as in the promotion and maintenance of optimal health.

References

1. Abbey L: Agoraphobia, *Jour. Orthomolecular Psych'.;* 11,4 1982, pp 243-259.
2. Adams PW, et al: Effect of Pyridoxine HCL Upon Depression Associated with Oral Contraception. *Lancet* 2; pp 897-904: 1973.
3. Axelrod AE & Trakateelis AC: Relationship of Pyridoxine to Immunological Phenomena. Vitamins 8c Hormones 22; Ed. Harris, R. et al: pp 559-607: Academic Press, N.Y., 1964.
4. Axelrod J: The Neurotic Anxiety Syndrome. *Scientific America?!:* June 1971a.
5. Axelrod J: Immune Processes in Vitamin Deficiency States. *Amer. Jour. Clin. Nutri.* 24;pp265: 1971b.
6. Babior BM ed., *Cobalimme Biochemistry ir Pathophysiology:* John Wiley & Sons, N.Y., 1976.
7. Beisel WR, Edelman R, Nauss K, Suskind R: Single Nutrient Effects on Immunologic Functions. *Jour. Amer. Med. Assoc.* 245; pp 54-58; 1981.
8. Brewster MA, Naito HK: *Nutritional Elements ir Clinical Biochemistry,* Plenum Press, N.Y., 1980.
9. Brin M: Erythrocyte as a Biopsy Tissue in the Functional Evaluation of Thiamin Status. *Jour. Amer. Med. Assoc.* 187; p 762; 1964.
10. Brin M: Examples of Behavioural Changes in Marginal Vitamin Deficiency. *VSDHEW publication:* pp 79-1906, 1979.'
11. Carney MWP, Williams DG, Sheffield BF: Thiamine and Pyridoxine Lack in Newly-Admitted Psychiatric Patients. *Brit. Jour. Psych.* 135;p 249-254, 1979.
12. Cotzias G, Tang L, Mitler S: A Mutation Influencing the Transportation of Manganese, L-Dopa and Tryptophan. *Science* 176; pp 410-412, 1972.
13. Coursin DB: Vitamins B_{fi} Metabolism in Infants and Children, *Vitamins and Hormones,* ec. Harris, R., et al; Academic Press, N.Y. 22; pp 775-785, 1964.
14. Dakshinamurti K: B Vitamins and the Nervous System, *Nutrition and the Brain,* 1; pp 249-318; eds. Wurtman, R.J., Wurtman, J.J.; Raven Press, N.Y., 1977.
15. Dancis J: Nutritional Management of Hereditary Disorders. *Medical Clinics of North America* 57, 6; pp 1431-1448; 1970.
16. Duchateau J, Delepesse G, Vrijens R, Collet H: Beneficial Effects of Oral Zinc Supplementation on the Immune Response of Old People. *The Amer. Jour, of Med.* 70; pp 1001-1004; 1981.
17. Growdon JH: Neurotransmitter Precursors in the Diet; Their Use in the Treatment of Brain Diseases, *Nutrition ir the Brain* 3; pp 117-181, eds. Wurtman, R.T., Wurtman, J.J.; Raven Press, N.Y.; 1979.
18. Hammes GG, Wu CW: Regulation of Enzyme Activity. *Science* 176; pp 205-1211; 1971.
19. Heeley A, et al: Pyridoxal Metabolism in Vit. B_6 Responsive Convulsions or Early Infancy. *Arch. Dis. Chil.* 53; pp 794-802; 1978.
20. Holtzman NA, Batshaw M, ValleO: *Genetic Aspects of Human Nutrition in Health ir Disease,* eds. Goodhart, R. Shils, M., Lea *Se* Febiger, PA; 1980.
21. Horrobin D: Essential Fatty Acids: A Review; *Cli?iical Uses of Essential Fatty Acids; ed.* Horrobin, D.; Eden Press, London, 1981.
22. Horwitt MK: Foundations of Nutrition: The Vitamins. *Modern Nutrition in Health ir Disease,* eds. Goodhart, R., Shells, M., Lea & Febiger, pp 197-204; PA, 1980.
23. Hunt AD, Jr. et al: Pyridoxine Dependence — A Report of a Case of Intractable Convulsions in an Infant Controlled by Pyridoxine. *Pediatrics* 13: pp 140-145, 1954.
24. Krehl WA: The Evaluation of Nutritional Status. *Med. No. Amer.* 54; ed. Helpern; pp 1129-1140, 1970.
25. Lehninger AL: The Molecular Basis of Cell Structure and Function. *Biochemistry;* pp 978-994; Worth Publishers, N.Y., 1975.
26. Lipton MA, Mailman RB, Nemeroff CB: Vitamins, Megavitamin Therapy, and the Nervous System. *Nutrition and the Brain* 3; pp 183-264, eds, Wurtman, R.J., Wurtman, J.J.; Raven Press, N.Y. 1979.
27. Lonsdale D: Thiamine Metabolism in Health and Disease. *CRC Critical Reviews;* pp 289-313, 1975.

28. Lonsdale D, Shamberger R: Red Cell Transketolase as an Indicator of Nutritional Deficiency. *Amer. Jour. Clin. Nutri.* 33; pp 205-211. 1980.
29. Martin D, Mayes P, Rodwell V: *Harper's Biochemistry,* pp 71-96; Lange Publishers, CA, 1981.
30. Mudd H: Pyridoxine-Responsive Genetic Disease, *Federation Proceedings* 30, 3; pp 970-976, 1971.
31. Nyan W: Nutritional Treatment of Children with Inborn Errors of Metabolism. *Textbook of Pediatric Nutrition;* ed. Suskind, R.; Raven Press, N.Y., 1981.
32. Partridge W: Regulation of Amino Acid Availability to the Brain. *Nutrition and the Brain* 1; pp 141-204, eds. Wurtman, R.J., Wurtman, J.J.; Ryan Press, N.Y., 1977.
33. Pauling L: *Orthomolecular Psychiatry;* W.H. Freeman & Co. SF, 1973.
34. Roe D: *Drug Induced Nutritional Deficiencies.* AVI Publ. Co., Ct, 1979.
35. Roe D: *Alcohol and the Diet.* AVI Publ. Co., Ct, 1979.
36. Rose DP: The Interaction Between Vitamin B_6 and Hormones 36. *Vitamins & Hormones;* Academic Press, N.Y. 1978.
37. Rosenberg LE: Vitamin Dependent Genetic Disease, *Medical Genetics;* pp 73-79; ed. McKusick & Claiborne, HP Press, N.Y., 1973.
38. Rosenberg LE: Vitamin-Responsive Inherited Diseases Affecting the Nervous System. *Brain Dysfunction in Metabolic Disorders.* ed. F. Plum, Res. Publ. Assoc. Nerv. Ment. Dis., pp 53; Raven Press, N.Y., 1974.
39. Sauberlich H, Dowdy K, & Skala J: Laboratory Tests for the Assessment of Nutritional Status; *CRC Press,* OH, 1977.
40. Sauberlich HE: Foundations of Nutrition: The Vitamins. *Modern Nutrition in Health & Disease,* eds. Goodhart, R., Shils, M., Lea & Febiger, PA, 1980.
41. Scriver C: Urinary Vitamin B_6 and 4-Pyri-doxic Acid in Health and Vitamin B_6 Dependency. *Pediatrics* 36, 1, pp 14-20; 1965.
42. Scriver C: Vitamin B_6 Dependency and Infantile Convulsions. *Pediatrics* 26, pp 62-74, 1960.
43. Scriver C, Rosenberg L: Vitamin Responsive Amino Acidopathies. *Amino Acid Metabolism and its Disorders,* Saunders, pp 453-478; PA, 1973.
44. Sergeev AV, Bykovskoja SN, Luchanskaja LM, Rauschenbach MS: Pyridoxine Deficiency and Cytotoxicity of T-Lymphocytes in Vitro. *Cellular Immunology* 38, pp 187-192, 1978.
45. Williams RJ: *Biochemical Individuality,* Univ. of TX Press, TX, 1956.
46. Willis-Carr JI, St. Pierre RL: Effects of Vitamin B^ Deficiency on Thymic Epithelial Cells and T-Lymphocyte Differentiation. *The Journal of Immunology* 120, pp 1153-1159,1978.
47. Wiss O, Weber F: Biochemical Pathology of Vitamin B_{fi} Deficiency. *Vitamins ir Hormones* 22; Ed. Harris, R. et al, Academic Press, N.Y., pp 495-501, 1964.
48. Yagi N, Itokawa Y: Cleavage of Thiamine by Chlorine in Tap Water. *Jour. Nutri. Sci. Vitaminol.* 25; pp 281-287, 1979.
49. YHagi N, Kamohara K, Itokawa Y: Thiamine Deficiency Induced by Polychlorinated Biphenyls (PCB) and Dichlorodiphenyl-trichloroethane (DDT) Administration to Rats. *Jour. Envir. Path, ir Toxic.* 2; pp 1119-1125, 1979.
50. Yui Y, Itokawa Y, Kawai C: Furosemide Induced Thiamine Deficiency. *Cardiovascular Research* 14; pp 537-540, 1980.