

# Nutrition and Candidiasis

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Illness caused by *Candida* species may take several forms.

1. Invasion of skin and mucous membranes by *C. albicans* has been known for centuries. Therapeutic use of broad-spectrum antibiotics and immunosuppressant drugs has made *Candida* invasion of vital organs a major cause of death following cancer chemotherapy, organ transplantation and open heart surgery.<sup>1</sup> Invasive candidiasis appears to require morphological change of the organism from a yeast to a hyphal growth pattern.<sup>2</sup> The hyphae secrete a phospholipase which disrupts cell membranes and allows intra-cellular penetration by the fungus.<sup>3</sup>

2. Allergy to *Candida* has been frequently described over the past three decades, especially by European clinicians.<sup>4,8</sup> Manifestations of *Candida* allergy have included asthma, migraine headaches, mucous colitis and various skin rashes, among them eczema, perioral dermatitis and psoriasis. Reported treatments have been immunotherapy and anti-fungal drugs.

3. Systemic toxicity from alimentary tract colonization by yeasts was first described by Orian Truss.<sup>9,11</sup> Since then, Truss's observations have been confirmed by many other observers, although published reports are rare.<sup>12,13</sup> Truss proposed that gastrointestinal

*Candida* ferments dietary carbohydrate to produce acetaldehyde, which is absorbed with adverse effects on the metabolism of the host.<sup>14</sup> Iwata has described several *Candida* endo- and exotoxins.<sup>15</sup> These initiate the classical and alternative complement cascades, causing inflammation and cell necrosis in experimental animals. Zymosan is a yeast membrane polysaccharide which directly activates the alternative complement pathway. Rosenberg and his colleagues suggest that zymosan plays an important pathogenetic role in psoriasis and possibly in Crohn's disease.<sup>16,17</sup> The variety of toxic substances produced by *Candida* explains the protean expression of *Candida* toxicity; inflammation, auto-immunity and neuropsychiatric manifestations predominate. *Candida* toxicity does not require tissue invasion. Fermentation and production of Iwata's candidatoxin

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are greatest under conditions of rapid growth and yeast rather than hyphal morphology.

While treating several hundred patients with Candida related illness over the past three years, I have seen that invasive, allergic and toxic effects may exist separately or together in an individual patient. Candida toxicity often appears after evidence of invasive candidiasis (e.g., vaginitis) has subsided. I have also been impressed with the high frequency with which a specific constellation of nutritional deficiencies accompanies all forms of chronic candidiasis. A triad of magnesium, essential fatty acid and vitamin B6 deficiencies appears to be the rule, especially when toxic or allergic manifestations are present. In this paper, I report the results of metabolic studies performed on 104 patients with Candida allergy or toxicity. They were seen during a one-year period and selected to meet the following criteria:

- a. Chronic illness with onset or exacerbation following pregnancy or exposure to antibiotics, oral contraceptives or adrenal steroids.
- b. 1. history of chronic or recurrent monilia infection and/or;  
2. hypersensitivity to yeast antigen. This hypersensitivity may be demonstrated by dietary elimination and challenge, immediate cutaneous hypersensitivity to intradermal challenge or a Herxheimer-type reaction in response to oral nystatin therapy.
- c. Remission or cure of illness associated with oral nystatin therapy.

The patients reported met all three criteria. The nutritional parameters studied are presented in Table 1.

#### **Abnormal Metabolism of Essential Fatty Acids (EFAs)**

EFAs are long chain polyunsaturated fatty acids of 18 to 20 carbons in length, containing 2-6 double bonds. They play important roles in determining the viscosity of cellular membranes and as precursors of prostaglandins and leukotrienes. There are two general classes of EFAs: the n-6 fatty acids have the first double bond on the 6th carbon from the -CH<sub>3</sub> end of the molecule, and the n-3 fatty acids have the first double bond on the 3rd carbon from the -CH<sub>3</sub> end of the molecule. The normal metabolism of EFAs

is shown in Figure 1. The major dietary EFA is linoleic acid (LA; 18:2 n-6; 18 carbons, 2 double bonds, n-6 configuration). LA is metabolized by an alternating series of desaturations and elongations to produce a final product which has 22 carbons, 5 double bonds and which maintains the n-6 structure.<sup>18</sup> Stops along the way include dihomo-gamma linolenic acid (DGLA, 20:3 n-6), the precursor of prostaglandin E1, and arachidonic acid (AA, 20:4 n-6), the precursor of most prostaglandins and leukotrienes. The major n-3 fatty acid in most diets is linolenic acid (LNA, 18:3 n-3). LNA is metabolized by the same enzymes that desaturate and elongate LA; the final product of its metabolism is docosahexaenoic acid (DHA, 22:6 n-3), a major brain fatty acid. Timnodonic acid (TDA, 20:5 n-3), one of the metabolic derivatives of LNA, is the precursor of the uncommon prostaglandins which are trienoic and described by the number 3. (e.g. -thromboxane A3).

Physical findings of EFA deficiency are not highly specific. They include dry skin, flaky paint dermatitis, follicular keratoses, brittle nails, and dry straw-like hair.<sup>19-20</sup> Two or more of these physical findings were present in 65% of the candidiasis patients. Levels of circulating EFAs were determined in 37 patients. In 20 patients the determinations were conducted on serum phospholipid fatty acids at Monroe Medical Research Laboratory, Southfield, N.Y.; in 17 cases the determination was performed using plasma and erythrocyte phospholipid fatty acids at Efamol Research Laboratory, Kentville, Nova Scotia. The results are presented in Table 2. Compared to the reference population of both laboratories, there were numerous abnormalities in the levels of various EFAs. The commonest was a general depression in all components of the n-3 family. The clinical importance of n-3 EFA deficiency has been well documented by Donald Rudin.<sup>21,23</sup> Abnormalities in the metabolism of n-6 fatty acids were present in two-thirds of the patients studied, the commonest abnormality being an elevated AA concentration. Since the conversion of dietary LA to AA is performed by the same enzymes which metabolize LNA, a deficiency of n-3 fatty acids would be expected to allow increased formation of AA and

possibly increased formation of prostaglandins and leukotrienes derived from AA.

Red cell fatty acid studies, however, suggest that the abnormal EFA metabolism involves more than just a deficiency of n-3 fatty acids. As is evident from the results presented in Table 3, the levels of 22:4 n-6 and 22:5 n-6 were significantly depressed in candidiasis, suggesting a block in the elongation and further desaturation of AA. The reason for this block in AA metabolism is unclear. Fatty acid elongation requires acetyl-CoA as a donor of the 2-carbon moiety and vitamin B6 as a co-factor. Chronic exposure to acetaldehyde may interfere with the formation of acetyl-CoA and with the availability of vitamin B6 as a co-factor.

### Vitamin B6 Deficiency and Dependency

Vitamin B6 exists in 6 different forms. Their relationship is described in Figure 2. The major dietary form is Pyridoxine. Biological activity of B6 depends upon its phosphorylation and oxidation to pyridoxal-5-phosphate (P5P).<sup>24,25</sup> The phosphorylation of Pyridoxine is zinc and magnesium dependent; the oxidation is riboflavin dependent. The total level of vitamin B6 was determined in 59 patients by the Vitamin Assay Center of the New Jersey College of Medicine and Dentistry. Their bioassay measures all 6 vitamers of B6. Levels were low in only 5 patients (8%). Plasma P5P was measured fluorometrically in 39 patients by Monroe Medical Research Laboratory. P5P was low in 26 (67%). Eighteen patients had both the total B6 and P5P determinations done. Fourteen of these had low plasma P5P. In only one was plasma total B6 also low. Total B6 was normal in 9 and elevated in 4. P5P and total B6 values were highly correlated ( $r=0.773$ ). This suggests a vitamin B6 dependency state with impaired formation of P5P from B6.

Since zinc and riboflavin are essential for P5P synthesis, I compared indices of zinc and riboflavin status with B6 status. Plasma zinc was determined in 83 patients. A plasma zinc of less than 80 mg/dl was found in 14 (16.9%). Circulating levels of less than 100 mg/dl were present in 30 (36.1%). If standards for normal plasma zinc are taken from the literature of experimental zinc deficiency in humans,<sup>26</sup> then 17.3% of these patients

show significant risk of zinc deficiency. Nonetheless, the prevalence of zinc deficiency was considerably lower than the prevalence of vitamin B6 dependency and there was no correlation between P5P levels and plasma zinc. Riboflavin status was determined by two methods. Circulating riboflavin was measured in 59 patients by BioAssay at the Vitamin Assay Center of the New Jersey College of Medicine and Dentistry. No patients showed low riboflavin levels by this method. The erythrocyte glutathione reductase activity coefficient was used as a measure of riboflavin status in 17 patients. This test was performed at Monroe Medical Research laboratory and is the standard functional test of riboflavin nutriture. Using this method, riboflavin deficiency was found in 29%. The relationship between riboflavin status (as determined by EGR activity coefficient) and P5P was determined in 28 patients. This included 17 patients who were part of the study group being reported upon in this paper and 11 additional patients who presented for treatment too late to be included in the remainder of this study. The association between P5P deficiency and riboflavin deficiency was high ( $X^2 = 7.97$ ,  $p < 0.01$ ). It is, therefore, possible that in some patients a functional riboflavin deficiency contributes to the vitamin B6 dependency state. The importance of riboflavin for normal Pyridoxine activity has been established clinically. Riboflavin's role in P5P synthesis requires prior phosphorylation of riboflavin itself by a magnesium requiring enzyme.

### Magnesium Deficiency, Latent Tetany and the Yeast Problem

Magnesium (Mg) is the second major intracellular cation and is an obligate cofactor for all chemical reactions in which ATP is involved. Definition of Mg status by laboratory testing is difficult and controversial. Because Mg is primarily an intracellular cation, serum levels are a poor reflection of body stores.<sup>27</sup> Since P5P increases cellular uptake of Mg,<sup>28</sup> serum Mg is a particularly poor index of Mg status in P5P deficient individuals. Erythrocyte Mg may be a better indicator of tissue stores, but the correlation between erythrocyte Mg and levels in other tissues (e.g., cardiac or skeletal muscle) is

poor.<sup>27</sup> Determination of erythrocyte Mg levels is furthermore subject to a number of technical difficulties. The Mg load test has been advanced as the most sensitive index of Mg nutriture in patients with normal renal function.<sup>27</sup> The performance and interpretation of this test are described in Appendix I. Six patients in this study underwent Mg load tests and in all cases the results were consistent with Mg deficiency. I have since had the opportunity to perform Mg load tests in 35 additional patients with candidiasis. None of these patients have shown a normal result. In many cases the baseline Mg excretion is inappropriately elevated, suggesting impaired renal Mg conservation in the face of deficiency.

Because Mg deficiency produces neuromuscular hyperexcitability, functional measures of neuromuscular hyperexcitability are useful as indices of Mg status. Using electromyography, electroencephalography and electronystagmometry, Durlach and his colleagues have described a functional condition of latent tetany (e.g., measurable neuromuscular hyperexcitability) and have documented its association with Mg deficiency.<sup>29-31</sup> Latent tetany affects 15% of the general population in France and is highly associated with allergy, premenstrual syndrome and prolapse of the mitral valve, all conditions which have been anecdotally associated with chronic candidiasis. Eighty percent of patients with latent tetany show Chvostek's sign. The proper elicitation of Chvostek's sign is described in Appendix II. Ten of the patients in this study were examined for the presence of Chvostek's sign and it was present in all 10. We currently find that Chvostek's sign is present in about 80% of Candida patients seen at the Gesell Institute.

### Mitral Valve Prolapse

Mitral valve prolapse (MVP) is the commonest form of valvular heart disease in the United States, with a prevalence of 7-15%.<sup>32</sup> It is inherited as an autosomal dominant trait with delayed and variable expression.<sup>33</sup> Durlach believes that Mg deficiency is the major factor which governs expression of the MVP gene. I have found a high prevalence of MVP among patients with candidiasis, an association noted by other clinicians

as well (Truss, personal communication). Among the 104 patients in the present study, physical examination revealed auscultatory findings of MVP in 46. The presence of MVP was significantly associated with dermatologic signs of EFA deficiency ( $X^2 = 4.74$ ,  $p < 0.05$ ).

The high frequency of prolapse among patients with candidiasis suggests that there are individuals whose genetic endowment predisposes them to chronic Candida infection, possibly because of disturbances in Mg or EFA metabolism. MVP is associated with minor skeletal anomalies, the commonest being a loss of normal thoracic kyphosis (the "straight back").<sup>34</sup> About two-thirds of the Candida patients I examine show this anomaly, whether or not they have MVP, again suggesting a congenital susceptibility to this illness. A number of symptoms have been attributed to MVP, both by patients and clinicians. These include chest pain, palpitation, fatigue, dizziness, poor exercise tolerance, anxiety and hyperventilation. My experience with treatment suggests that these symptoms are usually due to Candida allergy or toxicity and occasionally to Mg or EFA deficiency; they rarely have any direct relationship to the valvular lesion.

### Other Nutrient Deficiencies

Some of these are listed in Table 4. The commonest deficits were low stores of iron, as measured by serum ferritin levels; depressed serum folate, as measured by the Vitamin Assay Center of the New Jersey College of Medicine and Dentistry; and low levels of vitamin A. Since iron deficiency is known to predispose to Candida infection,<sup>35</sup> low ferritin levels in a patient with candidiasis should be taken seriously. As folate deficiency can impair immune function, low serum folate may contribute to infection in some patients. The low vitamin A levels are particularly interesting. None of the vitamin A deficient patients had low serum carotene. In four patients the carotene level was actually high. Montes and his colleagues,<sup>36</sup> in 1972, described vitamin A deficiency and normal carotene in 13 patients with chronic mucocutaneous candidiasis. Since dietary carotene is the major source of vitamin A, it seems that vitamin A deficiency in Candida patients is not secondary to poor diet or

malabsorption but to impaired oxidation of carotene to retinol. Beta-carotene oxygenase is primarily found in intestinal mucosa and its activity may be impaired in diseases which involve the intestinal mucosa. Vitamin A deficiency in patients with candidiasis is most likely a manifestation of intestinal candidiasis. Because vitamin A is necessary for the function of cytotoxic T cells and for the integrity of mucous membranes, vitamin A deficiency will aggravate yeast infection. In correcting this deficiency the possible deficit in carotene oxygenase activity should be kept in mind. Carotene may be of little biological value as a retinol precursor in these patients. Zinc deficiency can depress serum retinol despite normal stores of vitamin A in liver. While there is no relationship between zinc and vitamin A deficiency in the patients in this study, we have found it useful to pay close attention to zinc nutrition in patients with refractory vitamin A deficiency.

#### **Monilia's Metabolic Maelstrom**

The triad of Mg-related latent tetany, EFA deficiencies, and vitamin B6 dependency occurs with great consistency in our work with Candida patients at the Gesell Institute. Possibly the association is fortuitous. Seelig has presented evidence to suggest that dietary Mg deficiency is widespread in the United States,<sup>27</sup> Rudin has described an epidemic of dietary n-3 EFA deficiency<sup>23</sup> and Gaby has hypothesized an epidemic of vitamin B6 dependency due to exposure to environmental B6 antagonists.<sup>37</sup> Furthermore, a deficiency of one of these may engender deficits of the other two. Vitamin B6 is needed for the cellular uptake of Mg. Mg is a cofactor for virtually all B6 mediated reactions, and is both directly and indirectly involved in the conversion of Pyridoxine to P5P. Mg and B6 deficiency both increase EFA requirements by impairing EFA metabolism.<sup>38-39</sup> Prostaglandins may have important effects on Mg transport. Deficiencies of each of the three nutrients has been demonstrated to suppress immune function. A key line of defense against Candida infection is the alternative pathway of complement.<sup>40</sup> Mg is essential for the activity of this pathway so that Mg deficiency, in addition to its general immunodepressant effect will

especially impair anti-fungal defenses.

My clinical sense in evaluating several hundred patients, reviewing their family histories and their personal life chronologies, suggests a much more intimate relationship among all these abnormalities. Many Candida patients seem to develop their nutritional problems after exposure to antibiotics. Some behave like Mg sieves, requiring 1000-2000 mg of Mg a day to avoid deficiency. Nutritional therapy alone is merely palliative in most patients and specific anti-fungal therapy is required for an optimum therapeutic response. The success of *C. albicans* as a modern parasite may lie in its ability to further undermine our weakest metabolic links. This concept is presented in Figure 3. How Candida does this can be explained in part by Truss's acetaldehyde hypothesis: acetaldehyde leads to selective destruction of P5P and, as described earlier, interferes with fatty acid elongation. Complement-activating yeast toxins, in addition, increases phospholipase activity in remote tissues producing damage to cell membranes, stimulating prostaglandin and leukotriene synthesis and promoting formation of peroxides. This oxidative damage increases destruction of EFAs and allows loss of Mg from cells. Binding of zinc to damaged cell membranes would increase zinc requirements (all of the Candida patients I've studied with low plasma zinc have elevated red cell zinc, paradoxically). A nutritional deficiency which was latent or sub-clinical, or to which an individual was genetically prone, then becomes overt. Environmental factors such as diet, stress and exposure to petrochemicals or radiation amplify the damage. Nutritional support for patients with chronic candidiasis requires that particular attention be paid to the EFAs (especially the n-3 EFAs), Mg and vitamin B6. Careful examination of the skin and its appendages, testing for neuromuscular hyperexcitability, and functional studies of vitamin B6 activity have been of particular value in my experience. Mg salts, linseed oil and vitamin B6 (sometimes administered as P5P itself) are important adjuncts in the treatment of these patients.

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**Appendix I: Mg Load Test, Parenteral**

1. Obtain a 24-hour urine for magnesium.
2. Administer 2cc of 50% MgSO4 in each buttock. This will be the equivalent of 200 milligrams of elemental Mg.
3. Immediately obtain another 24-hour urine for Mg.

Interpretation: the normal excretion of magnesium on day 1 (baseline) should be between 30 and 100 Mg (2.2-8 mEq). Values under 30 mg suggest Mg deficiency with renal compensation or a very low Mg intake. Values greater than 150 mg suggest a very high Mg intake or renal Mg wasting. A value greater than 50 milligrams in a Mg deficient patient who is not taking any Mg supplementation suggests impaired renal conservation of Mg in response to the deficiency. At least 90% of the administered load of Mg should be excreted on the second day. In other words, the Mg excretion on day 2 should be 180 to 200 mg more than the excretion on day 1. Less than 80% excretion of the administered load suggests an increased avidity of cells for Mg and consequently Mg deficiency. Severely deficient patients may paradoxically excrete less Mg after the parenteral load than before it. Renal Mg wasters may show a false negative result.

**Appendix II: Chvostek's Sign**

Chvostek's sign is elicited by tapping the facial nerve as its fibers cross the edge of the masseter muscle in the hollow of the cheek. The nerve should be tapped very lightly with

a pediatric reflex hammer. A positive response is twitching of the upper lip in the mid line. Chvostek's sign is a normal finding in newborns and usually disappears early in infancy. Its presence may be masked by drugs which decrease neuromuscular excitability, such as calcium channel blockers and tranquilizers. Its absence does not preclude severe Mg deficiency. It may also appear during calcium deficiency and hyper-ventilation.

**Table 1  
Nutritional Parameters**

- Diet and drug history
- Physical examination
- Serum Albumin, transferrin, ferritin
- Plasma vitamins (B1, B2, B3, B6 (total and P-5-P), B12, folate, biotin, C, E, A, carotene)
- Serum minerals (Na, K, Cl, Ca (total and ionized), Mg, Zn, Cu, Fe)
- Erythrocyte and lymphocyte magnesium
- Magnesium load test
- Plasma and erythrocyte phospholipid fatty acid profile
- Urinary amino acid fractionation

**Table 2  
EFA Lesions in 37 Candida Patients**

	N	% Deficient
n3 vs n6	27	72.9
A6 Desaturase Block	24	64.9
Abnormal n6 metabolism	25	67.6
Elevated Arachidonic	25	67.6
Decreased DGLA	15	40.5
Low DGLA/AA ratio	21	56.8

**Table 3 n6 EFAs in RBC Phospholipids of 17 Candida Patients**

Patients	Controls		P/C	Value
18:2	13.50 ±2.40	9.78 ±1.64	1.3	<0.001
20:3	1.53 ±0.63	1.37 ±0.37	1.1	NS
20:4	17.91 ± 1.45	15.13 ± 1.98	1.2	< 0.001
22:4	3.22 ±1.48	5.54 ±1.37	0.6	< 0.001
22:5	0.76 ±0.28	3.99 ±1.85	0.2	< 0.001

Table 4

Less Common Nutrient Deficiencies in Candida Patients (n = 101)

Ionized Calcium	Low	12%
	High	4%
Folate, serum	Low	15%
Ferritin	Low	10%
Vitamin C, Leukocytes	Low	5%
Vitamin B3, Whole Blood	Low	2%
Vitamin B1, Whole Blood	Low	1%
Vitamin B12, Plasma	Low	1%
Biotin, Whole Blood	Low	1%
Vitamin A < 25mg/dl		13%
Low Carotene		0/13
Normal Carotene		9/13
High Carotene		4/13

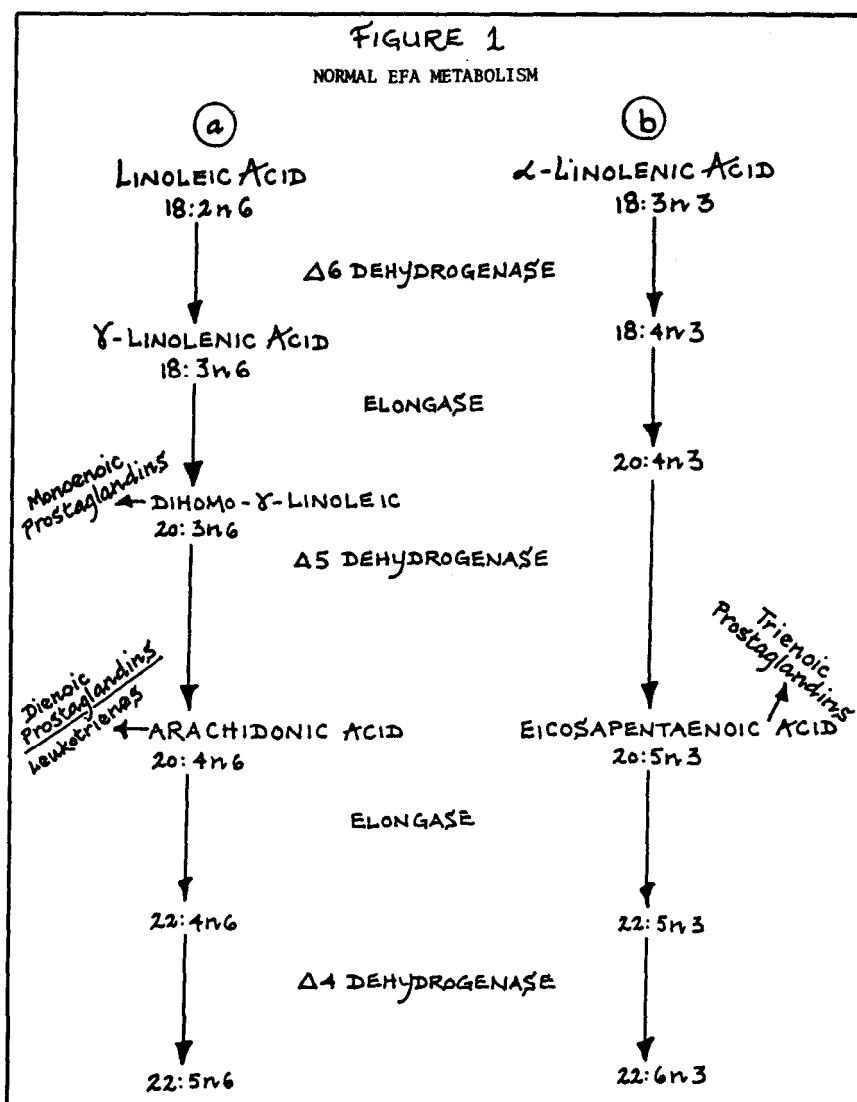


FIGURE 2  
Vitamin B<sub>6</sub> Metabolism

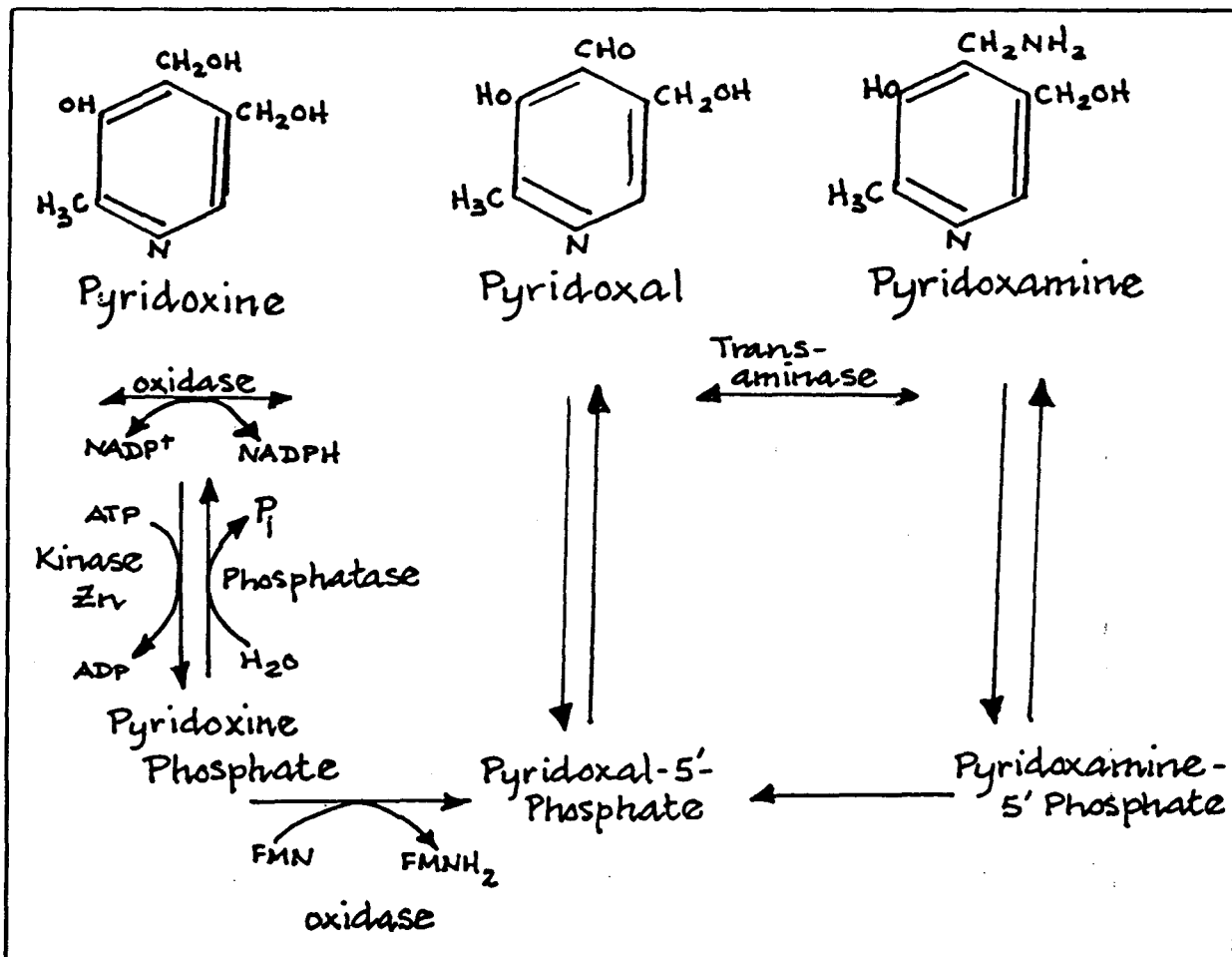




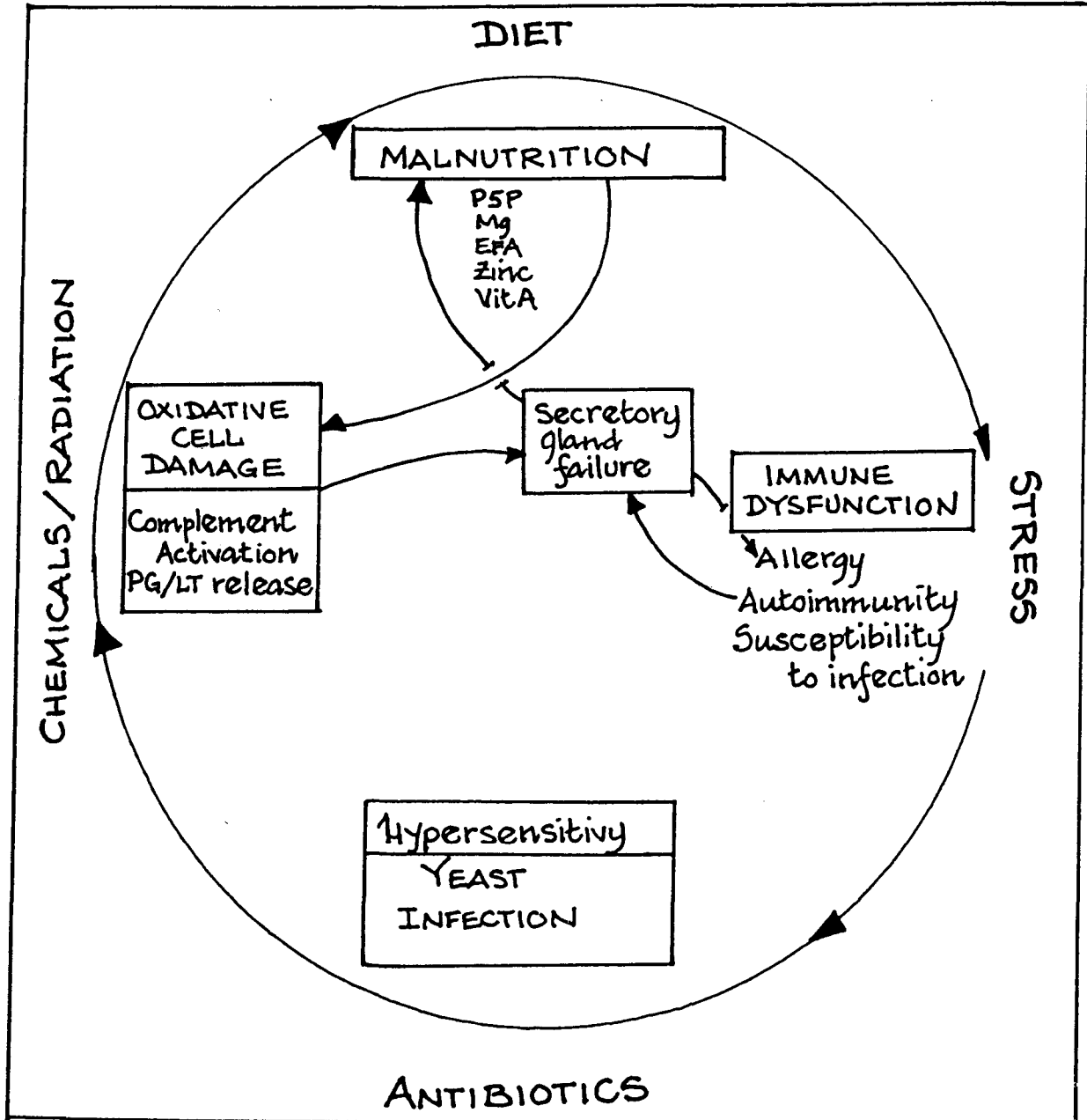
FIGURE 3

# Monilia's Metabolic Maelstrom

## Genetics

Latent tetany proneness  
HLA-BW35?

atopy  
CMC  
familial endocrine adenopathy



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