Marginal Vitamin Deficiency: The "Gray Area" of Nutrition[1]

- *Is there a state of* optimal *nutrition beyond what is commonly accepted as* adequate *nutrition?*
- *Does marginal vitamin deficiency have any clinical significance?*
- *Can nutritional status affect behavior and personality?*
- *Can vague symptoms such as irritability, insomnia, and lethargy be caused by vitamin depletion?*
- *Are marginal deficiencies a widespread problem? At what point does such a problem merit consideration as a public health problem?*

Introduction

Marginal vitamin deficiency is a middle ground between adequate nutritional status and the point at which frank deficiency disease symptoms develop. Because there are no specific symptoms, this intermediate stage of depletion is not apparent. In lay terms, it may be just the difference between feeling "at one's best" and feeling "under the weather." Many scientists now believe that such vague symptoms such as lethargy, irritability, insomnia and difficulty in concentrating may in some cases reflect an underlying physiological condition that is related to nutritional status. Marginal deficiency, they believe, may affect the body's ability to resist disease and infection, its ability to recover from surgery, stress or disease, the ability of the brain to function at a high level and, in general, the optimal development and efficient functioning of the total person.

Considerable differences of opinion exist among health and nutrition professionals regarding this concept. Traditionally, nutritionists and doctors have presumed that if a person shows no clinical signs of classical deficiency disease — that is, scurvy, pellagra, beriberi, rickets, etc. — then he or she is adequately nourished.

Those who argue that greater attention should be focused on the area of marginal deficiencies base their reasoning both on new biochemical evidence accumulated in recent years and on the medical field's collective experience with other diseases. Experience has shown that detecting and treating disease at the early stage of cellular biochemical abnormality, rather than waiting for the clinical signs, is highly beneficial. For example, it is now widely accepted that diabetes mellitus should be treated once hyperglycemia is discovered, as this reduces the danger of diabetic arteriosclerosis and retinopathy. One physician commented recently, "Clinicians have absolutely no difficulty in dealing with the concept of latent diabetes mellitus ... Why is it then that we have such difficulty

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envisioning the concept that people might have a latent nutritional deficiency?"[1]

The concept of marginal deficiency has evolved slowly in conjunction with vitamin research over the past several decades. As scientists learned more and more about how vitamins function at the cellular level, they realized that deficiency diseases were only the end product of a long and complex series of nutrient depletion reactions. Nutritional status is influenced not only by dietary intake, but also by the ability of the body to utilize vitamins normally. This ability may be affected by drugs, hormones, disease, surgery, stress, and emotional and behavioral factors.[2] One nutrition scientist summarized recently:

"Nutrition is not just a science of good eating. Nutrition is really biochemistry, metabolism and endocrinology — the ability of the body to utilize the nutrients in the proper fashion."[3]

Some 20 years ago, a team of researchers matched earlier data with their own observations and concluded:

"Studies with the experimental animal have shown, beyond question, that vitamin undernutrition sufficient to affect adversely the biological efficiency of the animal is compatible with a normal growth rate and the appearance of good health. In other words, 'subclinical' vitamin deficiency states do exist, at least in the laboratory. That man may resemble the laboratory animal in the respect that for him, also, minimal nutrition ... may not be adequate nutrition is at present the subject of much debate and is likely to remain so for many years to come"[4]

Since that time, much work has been done towards the development of a clearer definition and understanding of "marginal deficiency" in precise biochemical terms.

What is Marginal Deficiency?

"Marginal deficiency" is now defined as a state of gradual vitamin depletion in which there is evidence of personal lack of well-being associated with impairment of certain biochemical reactions.[5] The reactions impaired are those that depend on the presence of sufficient amounts of vitamin.

Vitamin deficiency is not something that occurs abruptly or acutely. Body stores of a micronutrient are gradually depleted during a *preliminary stage.*[6] The depletion of these stores marks the beginning of a second stage called the biochemical stage. Various enzymes need vitamins in order for essential biochemical reactions to take place. When there is not enough vitamin to saturate the enzymes that need it, the body's biochemistry is impaired. To this point in the depletion process, there is no indication of this condition in terms of the organism's growth or appearance.

The third stage of depletion is called the physiological stage. When enzyme activity has been sufficiently impaired, behavioral and personality changes begin to appear. The changes are "nonspecific symptoms" which one might not associate with nutrient deficiencies — common human traits and frailties such as loss of appetite, depression, irritability, anxiety, insomnia or somnolence. The person is not sufficiently ill to seek medical care or go to a hospital, yet his or her general health is less than optimal. These three stages comprise a continuum of gradual vitamin depletion which is called marginal deficiency.

If the deficiency continues, signs and symptoms of classical deficiency disease will appear. This is called the *clinical stage.* Left untreated, it is followed by the *anatomical stage* in which death will ensue without nutritional intervention.[6]

Classical deficiency diseases have all but disappeared in the United States because of improved nutritional knowledge and the enrichment of certain foods. Marginal deficiencies, however, are much more subtle and are difficult to identify. Only in recent years has sufficient evidence accumulated to call attention to this "gray area" of nutrition.

How Do We Know They Exist?

Since there are not overt signs or symptoms of marginal deficiencies, how are they detected? How do we assess the nutritional status of apparently healthy individuals?

1. Biochemical Analysis

Some laboratory methods have been developed to measure the vitamin levels in blood, plasma or urine. These are called "static" methods, because they measure the amount of vitamin present at a single point in time.[5]

Because of the complex roles vitamins play in metabolism, sometimes it is

substances or processes other than the vitamin itself, but dependent on the presence of the vitamin that are indicators of vitamin sufficiency/deficiency. These are called "functional" methods, because they measure a physiological or biochemical function which is directly related to the adequacy of a specific nutrient.[5]

Examples of static and functional methods used to evaluate nutritional status in the laboratory are:[5]

Nutrient	Static	Functional
Vitamin A	Plasma level	Night blindness
Vitamin E	Plasma Level	RBC hemolysis
Vitamin K	—	Prothrombin time
Thiamin transketolase	Urine excretion	RBC activity
Riboflavin glutathione	Urine excretion	RBC reductase activity
Niacin	Metabolite excretion	—
Pyridoxin tesl	Plasma B6P	Tryptophan load
Folacin	Plasma level	Histidine load test
Vitamin B12	Plasma level	MMA excretion

During recent years, the U.S. government has sponsored a number of broad studies to monitor the nutritional status of the population using biochemical analysis of blood samples along with physical examination. The HANES (Health and Nutrition Examination Survey) of 1971-1972 and the Ten State Nutrition Survey of 1968-69 were two such studies which revealed marginal deficiencies, of not only vitamins but also minerals, among substantial portions of the population.

According to the Food and Nutrition Board of the National Research Council, the Ten State Nutrition Survey showed that:

"On the basis of biochemical evidence from this survey, nutritional iron deficiency of varying degrees of severity existed in all population groups studied. Some vitamin A values ... were regarded as inadequate, with marginal blood levels occurring in most population groups surveyed. Riboflavin appeared to be inadequate, or at best marginal, among black and Spanish-American ethnic groups, particularly at the lower income levels. Deficient thiamin and vitamin C values were found in a small number of groups studied."[7]

Similar patterns were revealed by HANES data. The study showed that up to 50% of the population was below RDA levels for some vitamins and minerals. Calcium, iron, vitamin A and vitamin C were the nutrients found most frequently lacking.[8] Whereas the Ten State Survey had concentrated on lower socio-economic populations, the HANES studied all population groups and revealed that inadequate vitamin and mineral intakes extended across all socio-economic classifications.

In addition to these broad governmental studies, a number of independent studies have been conducted among specific U.S. populations. A study of New York City school children in 1968 revealed low serum levels of thiamin, riboflavin, folic acid and iron, as well as some evidence of zinc deficiency.[9]

Preliminary results from a current study of teenagers in Miami reveal that "15% had deficient levels of folic acid and 30% had low levels. When red cell blood folic acid levels were determined, 13% had low levels and 40% had deficient levels. Deficient or low levels of iron were found in 14% of the girls... low hemoglobin levels were found in 18% of the boys and 34% of the girls."[9]Yet there were no clinical signs of folacin deficiency.

The Texas Nutrition Survey measured seven different biochemical nutrients and found two or more to be deficient among some 30% of the individuals surveyed.[10] A high percentage of people studied in the Galveston, Texas area was found to be deficient in folacin, vitamin B12, vitamin E and riboflavin.[10]

These and other studies [11-15] confirm the pattern revealed by the government surveys, namely, that biochemically measurable sub-clinical deficiencies of micronutrients are prevalent among significant segments of the population, although there are no clinical signs.

2. Dietary Assessment

Another method for evaluating nutritional status is dietary assessment, used concurrently with the biochemical analyses in the **HANES** and Ten State Surveys, and as a single methodology in such studies as the USDA Nationwide Food Consumption Surveys. Many public health clinics and medical centers also use dietary history as a rough index of nutritional status. The drawback of this method is that not all the food reported

may in fact have been consumed, neither is there any provision for determining whether nutrients consumed have been utilized normally by the body. However, dietary assessment provides useful support data for biochemical assays of nutritional status, and it has the additional advantage of being easy to conduct among large groups of people in a non-traumatic fashion.

The USDA's Market Basket Survey of 1965 concluded that some 30-35% of U.S. diets were inadequate for at least one nutrient.[16]

The Nationwide Food Intake of Individuals (USDA, 1972) revealed that the diets of both adolescent girls and women were below recommended amounts of calcium, iron and thiamin, and for some age groups, vitamin A and riboflavin were also insufficient. Older men also have diets low in vitamin A value, riboflavin, vitamin C and calcium.[7]

The 1977-78 Nationwide Food Consumption Survey by the USDA showed that vitamin B6 intakes were 35-40% below RDA levels among females 15 and older.[17]

Dietary information obtained in the Ten State Nutrition Survey of 1968 indicated that "significant numbers of people in the population studied had intakes below the RDA for calcium, iron and vitamin A and that pregnant and lactating females tended to have low intakes of protein,"[18]

These surveys did not assay for all vitamins, therefore, the findings could be even more extensive.

3. Special Risk Situations

Even when nutrient intake may be sufficient, there are a number of life situations that influence vitamin needs or influence blood levels of vitamins. Studies have shown that blood plasma levels of vitamin C in heavy smokers may be up to 40% lower than in non-smokers.[19,20] Women who use oral contraceptive steroids may have reduced blood levels of vitamins B1, B2, B6, folacin and vitamin B12.[21,37]

Heavy alcoholic consumption may interfere with the utilization of vitamins B1, B6 and folacin.[38-44] People who regularly take certain types of prescribed medication may experience the need for higher amounts of particular nutrients.[45]

Also, people on weight-reducing diets may not realize that by reducing their food intake, they are also reducing their vitamin intake. Vitamin requirements continue regardless of caloric intake, even during total fasting.[46,47] So by virtue of reducing food intake, one may be at risk for vitamin insufficiency.

The combined weight of biochemical evidence, nutritional assessment data and the existence of common risk situations indicates that marginal deficiency may be a widespread problem.

Behavioral Effects

If an individual is slightly lacking in one nutrient or another, what are the consequences? Does marginal deficiency have any clinical significance?

As early as 1946, one scientist observed that "a liberal thiamin intake improved a number of mental and physical skills of orphanage children."[48] In another study, the same man found that "supplementation of the pregnant and lactating mothers' diet by vitamins increased the intelligence quotients of their offspring at three and four years of age."[49]

One of the collaborators in the classical studies on human starvation observed human thiamin deficiency in close detail and found that a lack of "feeling of well-being," anxiety, hysteria, nausea, depression and loss of appetite preceded any aspect of the clinical state of beriberi. These personality changes were all typical of pure thiamin deficiency and were normalized within a short period following thiamin repletion. [50] The physiological changes occurred during the period of marginal depletion, before the severity produced any clear or overt signs or tissue damage.[5]

Studies of marginal thiamin deficiency in Germany report similar observations: "Symptoms... include fatigue, mental weakness, lack of endurance, reduction in blood pressure, etc."[46]

Using a behavior test called the Minnesota Multiphasic Personality Index (MMPI), other studies have demonstrated that adverse behavioral changes precede specific clinical findings in deficiencies of vitamin C, thiamin and riboflavin. The deficiencies were induced in human subjects under carefully controlled laboratory conditions, and then the subjects were given the MMPI test. Adverse scores

including hypochondria, depression, hysteria, and in some cases hypomania and psychopathic deviation were described by the investigators as occurring before any specific signs of vitamin deficiency were observed.[50,51,52]

Extensive studies on the effects of thiamin depletion on erythrocyte transketolase activity in man have correlated biochemical changes with behavioral effects. [6,53,54,55] Depleted subjects most commonly complained of lethargy, anorexia and fatigue. "Since no physical clinical signs of thiamin deficiency were noted, these behavior consequences may be regarded as the consequence of marginal thiamin deficiency. Behavior reverted to normal within two or three days of repletion."[53]

Physiological Effects

In addition, marginal vitamin depletion has been shown to influence the metabolism of drugs and environmental chemicals in both man and animals[56,57,58], as well as influencing their immunity to disease.[59-66] Vitamins E, C, B6 and A specifically were studied under controlled conditions; adverse effects were corrected by repletion with the missing vitamin.

VNIS Position

The fact that health, appearance and physical stamina can be enhanced by eating a varied and well-balanced diet has been known for centuries. Nonetheless, specific data linking behavioral and physiological findings with low biochemical levels of nutrients are only now forthcoming. Likewise, data assessing the nutritional status of large numbers of Americans have become available only during the past decade. Even though knowledge about marginal deficiencies for all nutrients is incomplete, the growing body of evidence is highly suggestive and raises provocative questions for the future of nutrition research.

The U.S. RDA's have been established at levels sufficient to fulfill the nutritional function of vitamins for most people — that is, levels sufficient to prevent the development of classical deficiency disease symptoms. However, this may be just *one* of the important functions of vitamins. Their complete role in human health is far more complex, involving a multitude of biochemical reactions at the cellular level. As we learn more about these reactions, we also learn more about human vitamin requirements.

RDA's are periodically reviewed and adjusted to take advantage of new scientific knowledge about essential nutrients. For example, vitamins E, B6, B12 are relatively recent additions to the list of nutrients for which RDA's have been established. "Estimated safe and adequate daily intakes" are given instead of RDA's for biotin and pantothenic acid, because they are "nutrients known to be needed by humans but for which less quantitative evidence exists,"[67] Human requirements do not change, but our knowledge of these requirements is constantly changing. One eminent scientist has written:

"While the concept of optimal dietary intakes is now well established for animals, the present available data do not allow us to establish similar optimal levels for the human ... Our lack of knowledge of the best intake per day is shown conclusively by the wide range recommended in different countries."[68]

In light of the new insights which are continually revealed by vitamin research, the VNIS believes that recommended levels should remain flexible and be open to discussion according to new developments. Increased knowledge about the determinants of optimal nutrition may help to solve many of today's most perplexing public health problems. We support the efforts of nutrition researchers who are probing for answers to such questions as:

- What are the long-term effects of marginal vitamin deficiencies, in terms of survival, performance, wound healing, resistance to disease, etc.?
- Are suboptimal intakes contributing to subtle behavioral effects that are escaping detection by the usual parameters of physical and laboratory examinations?
- What functional impairments at the cellular level might result from suboptimal intakes?
- How do marginal deficiencies affect the immune competency of the body?
- What is the relationship, if any, of the body's nutritional status to the development

and progression of chronic diseases such as arteriosclerosis?

• Have all the signs of malnutrition been discovered, or are we still missing some?

In future years, the VNIS hopes to see improved nutrition become a significant contributor to the overall health of the population. We urge all members of the nutrition community to foster a climate of awareness and discovery — open to new knowledge, but judicious in its application.

Bibliography

1. Krehl, Willard A., at Vitamin Nutrition Issues, Boca Raton, FL. 1979.
2. McCann, Mary, "The Role of Vitamins in Human Nutrition," at Vitamin Nutrition Issues, Boca Raton, FL, 1979.
3. Rivlin, Richard, "Fundamentals and Levels of Depletion," at Vitamin Nutrition Issues, Boca Raton, FL, 1979.
4. Goodhart, Robert S., Chow, Bacon Y., and Yeh, Samuel D., "Marginal Deficiencies of Vitamins: (1) In Animals, (2) Observations on Man," *Journal of New Drugs*, Vol. 1, No. 1, Jan.-Feb., 1961.
5. Brin M., "Dilemma of Marginal Vitamin Deficiency," Proc. 9th Int. Congr. Nutrition, Mexico, 1972, Vol. 4, pp. 102-115 (Karger, Basel 1975).
6. Brin, M., "Erythrocyte as a biopsy tissue in the functional evaluation of thiamin status," *J. Amer. Med. Assoc.* 187:762,1964.
7. Proposed Fortification Policy for Cereal-Grain Products, Food and Nutrition Board, Divsn. of Biol. Sci., Ass. of Life Sci., Natl. Research Council, Nat'l. Acad, of Sci., Washington, D.C., 1974.
8. HANES: *Health and Nutrition Examination Survey*, U.S. Department of HEW Publication No. (HRA) 74-1219-1, Rickville, MD, 1974.
9. Christakis, George, "Socio-Economic and Long Term Effects of Teenage Nutrition" at Teenage Nutrition: Threat or Threshold to a Healthy Adult Life, New York, NY, 1980.
10. McGanity, William, "Why It Is Important," at Teenage Nutrition: Threat or Threshold to a Healthy Adult Life, New York, NY, 1980.
11. Brin, M., Dibble, M.V., Peel, A., McMullen, E., Bourquin, A., and Chen, N. Some preliminary findings on the nutritional status of the aged in Onondaga County, NY. *Am J. Clin. Nutr.*, 17:240-258,1965.
12. Brin, M., Schwarteberg, S.H., and Arthur-Davies, D. A vitamin evaluation program as applied to 10 elderly residents in a community home for the aged. *J. Am. Geriat. Soc.*, 12: 493-499,1964.
13. Davis, T.R.A., Gershoff, S.N., and Gamble, D.F. Review of studies of vitamin and mineral nutrition in the United States (1950-1968) J. *Nutr. Edn.*, Supplement 1, pp. 41057,1969.
14. Dibble, M.V., Brin, M., McMullen, E., Peel, A., and Chen, N. Some preliminary findings on the nutritional status of Syracuse and Onondage County, New York junior high school children. *Am. J. Clin. Nutr.*, 17: 218-239,1965.
15. Thiele, V.F., Brin, M., and Dibble, M.V. Preliminary biochemical findings in Negro migrant workers at King Ferry, New York, *Am. J. Clin. Nutr.* 21: 1229-1238,1968.
16. "Vitamins and Health," Man *and Molecules*, American Chemical Society, Script #852, Washington, D.C., April, 1977.
17. USDA Household Food Consumption Survey, Family Economics Research Group, Science and Education Administration, U.S. Dept. of Agriculture, Hyattsville, MD 20782,1980.
18. Ten State Nutrition Survey, Publ. No. 72 - 8130 to 8134. Washington D.C.: United States Dept. of Health, Education and Welfare, 1970.
19. Pelletier, Omer, "Vitamin C and Cigarette Smokers," Second Conference on Vitamin C, Annals of New York Academy of Sciences, Vol. 258: 156-166, 1975.
20. U.S. Department of Health, Education and Welfare, "The Health Consequences of Smoking," January 1973.
21. Commentary, Oral Contraceptives and Nutrition, *J.A.D.A.* 68: 419420, May 1976.
22. Adams, P.W., D.P. Rose, J. Folkard, V. Wynn, M. Seed and R. Strong, Effects of Pyridoxine Hydrochloride (Vitamin Be) Upon Depression Associated With Oral Contraception. *Lancet I:* 897-904, April 28,1973.
23. Adams, P.W., V. Wynn, M. Seed and J. Folkard, Vitamin B6, Depression and Oral Contraception, *Lancet 2:* 516, August 31,1974.
24. Ahmed, F., M.S. Bamji and L. Iyengar, Effect of Oral Contraceptive Agents on Vitamin Nutrition Status, *Am. J. Clin. Nutr.* 28: 606-615,1975.
25. Anon. Oral Contraceptive Agents and Vitamins, *Nutrition Rev.* 30(10): 229-231,1972.
26. Briggs, M. and M. Briggs, Oral Contraceptives and Vitamin Requirements, *Med. J. Austral. I:* 407, March 22,1975.
27. Harris, A.B., M. Pillay and S. Hussein, Vitamins and Oral Contraceptives, *Lancet 2:*82-83, July 12, 1975.
28. Hodges, R.E. Nutrition and "The Pill", *J.A.D.A.* 59: 212-217,1971.
29. Larsson-Cohn, U., Oral Contraceptives and Vitamins: A Review, *Am. J. Obstet. Gynecol. 121:* 84-90, January 1,1975.
30. Luke, B., Think Nutrition If She's On The Pill, *RN 38:* 33-35, March, 1976.
31. Rivers, J.M. and M.M. Devine, Relationships of Ascorbic Acid to Pregnancy, And Oral Contraceptive Steroids, *Ann. N.Y. Acad. Sci. 258:*465-479, 1975.
32. Rose, D.P., J.E. Leklem, R.R. Brown and H.M. Linkswiler, Effect of Oral Contraceptives and Vitamin B« Deficiency on Carbohydrate Metabolism, *Am. J. Clin. Nutr. 28:* 872-878,1975.
33. Shojania, A.M., Vitamins and Oral Contraceptive Use, Lancer, /: 1198, May 24,1975.
34. Streiff, R.R., Folate Deficiency and Oral Contraceptives, JAMA *214:*105-108, October 5,1970.
35. Wild, J., C.J. Schorah and R.W. Smithells, Vitamin A, Pregnancy and Oral Contraceptives, *Brit. Med. J. I:* 57-58, January 12,1974.

36. Winston, F., Oral Contraceptives, Pyridoxine, and Depression, *Am. J. Psych. 130:* 1217,1973.
37. Wynn, V., Vitamins and Oral Contraceptive Use, Lancef /: 561-564, March 8,1975.
38. Leevy, Caroll M. and Baker, Herman, "Vitamins and Alcoholism" *Am. J. Clin. Nutr.* Vol. 21, No. 11, November 1968.
39. Lieber, Charles S., "Alcohol and Malnutrition in the Pathogenesis of Liver Disease and Nutrition, Veterans Administration Hospital and Department of Medicine, Mt. Sinai School of Medicine of the City University of New York, Bronx, NY, September, 1975.
40. Baker, Herman; Frank, Oscar; Zetterman, Rowen K.; Rajan, K.S.; ten Hove, William and Leevy, Carroll, M., "Inability of chronic alcoholics with liver disease to use food as a source of folates, thiamin and vitamin B6" Amer. *J. Clin. Nutri.,* 28: 1377-1380,1975.
41. Payne, Irene R., Lu, Gina H.Y. and Meyer, Kathleen, "Relationship of dietary tryptophan and niacin to tryptophan metabolism in alcoholics and nonalcoholics," *Amer. J. Clin. Nutr.,* 27:572-579, June 1974.
42. Lumeng, Lawrence and Li, Tink-Kai, "Vitamin B6 Metabolism in Chronic Alcohol Abuse," *J. of Clin, lnvestgtn.,* Vol. 53, March 1974.
43. Hines, John D. and Cowan, Dale H., "Studies on the pathogenesis of alcohol-induced sideroblastic bone-marrow abnormalities," *N.E.J, of Med.* Vol. 238, No. 9, August 27,1970.
44. Leevy, Carroll M.; Baker, Herman; ten Hove, William; Frank, Oscar; and Cherrick, Gilbert R., "B-Complex Vitamins in Liver Diseases of the Alcoholic," *Amer. J. Clin. Nutri,* Vol. 16, No. 4, April 1965.
45. Ovesen, Lars, "Drugs and Vitamin Deficiency, *Drugs:* 18(4): 278-298,1979.
46. Kasper, H., "Vitamins in Prevention and Therapy: Recent Findings in Vitamin Research," *Fortschrite derMedizin,* Vol. 82, No. 22, Nov., 1964. Institute for Nutritional Science, Justus — Liebig University, Giessen, Germany.
47. Horo, E.H., Brin, M. and Faloon, W.W., "Fasting in obesity: thiamine depletion as measured by erythrocyte activity changes," *The Archives of Internal Medicine, 117:*175-81, 1966.
48. Harrell, R.J., "Mental response to added thiamine," *J. Nutrition* 31:283,1946.
49. Harrell, R.J., Woodyard, E. and Gates, Arthur I., "The Effect of Mothers' Diets on the Intelligence of Offspring," New York, Teachers College, Columbia University, 1955.
50. Brozek, J., "Physiological effects of thiamine restriction and deprivation in young men," *Amer. J. Clin. Nutr.* 26:150,1973.
51. Hodges, R.E., E.M. Baker, J. Hood, H.E. Sauber-lich and S.C. March, "Experimental scurvy in man," *Amer. J. Clin. Nutri.* 22:535,1969.
52. Sterner, R.T. & W.R. Price, "Restricted riboflavin: within subject behavioral effects in humans," *Amer. J. Clin. Nutr.* 26:150,1973.
53. Brin, M., "Examples of Behavioral Changes in Marginal Vitamin Deficiency in the Rat and Man," as presented at the International Nutritional Conference, "Behavioral Effects of Energy and Protein Deficits," Nov. 30 - Dec. 2, 1977, Washington, D.C.; NIH Publication No. 79 -1906.
54. Brin, M., "Erythrocyte transketolase in early thiamin deficiency, *Ann. N.Y. Acad. Sci.* 98:528, 1962.
55. Brin, M., Shohet, S.S., and Davidson, C.S., "The effect of thiamine deficiency on the glucose orida-tive pathway of rat erythrocytes," *J. Biol. Chem. 230:*319-26,1958.
56. Brin. M., "Drugs and environmental chemicals in relation to vitamin needs. In: *Nutrition and Drug Interrelationships,* edited by J.N. Hathcock and J. Coon, New York; Academic Press, 1978.
57. Brin, M. and D. Soe, "Drug-diet interactions," J. *Fla. Med. Assoc.* 66: 422.1979.
58. Horn, L.R., I.J. Machlin, M.O. Baker and M. Brin, "Drug metabolism and hepatic hemeproteins in the vitamin E deficient rat," *Arch. Biochem. Biophs.* 172:270,1978.
59. Axelrod, A.E., "Immune processes in vitamin deficiency status," *Amer. J. Clin. Nutr.* 24:265, 1971.
60. Heinzerling, R.H., C.F. Nockels, C.I. Quarles and R.E. Tengerdy, Protection of chicks against E. coli infection by dietary supplementation with vitamin E. *Proc. Soc. Exptl. Bio. Med.* 146:279,1974.
61. Campbell, P.A., H.R. Cooper, R.H. Heinzerling and R. Tengerdy. Vitamin E enhances in vitro immune response by normal and non-adherent spleen cells. Proc. *Soc. Exptl. Biol. Med.* 146:465, 1974.
62. Thurman, G.B., and A.L. Goldstein, Suppression of immunological responsivity in guinea pigs by ascorbic acid. *Federation Proc.* 38:1173,1979.
63. Prinz, W.R. Bortz, B. Bregin and M. Hersch. Effect of ascorbic acid supplementation on some parameters of the human immunological defense system. *Internat. J. Vitamin Nutr. Res.* 47:248, 1977.
64. Cohen, B.E., andl.K. Cohen. Vitamin A: Adjuvant and steroid antagonist in the immune response. *J. Immunol.* 3:1376,1973.
65. Cohen, B.E., and R.J. Elin. Vitamin A induced nonspecific resistance to infection. *J. Infect. Diseases* 129-597,1974.
66. Palmer, S. Influence of vitamin A nutriture on the immune response: findings in children with Down's syndrome. *Internat. J. Vitamin Nutr. Res.* 48:188,1978.
67. *Recommended Dietary Allowances,* Ninth Edition 1980, National Research Council, National Academy of Sciences, Washington, D.C.
68. Marks, John, *A Guide to Vitamins.* Medical and Technical Publishing Company, Ltd. St. Leonard's House, Lancaster, England.
69. Lonsdale, Derrick and Shamberger, Raymond J., "Red cell transketolase as an indicator of nutritional deficiency," *Amer. J. Clin. Nutr.* 33:, February, 1980.
70. Brin, M., "Red cell transketolase as an indicator of nutritional deficiency," Editorial, *Amer. J. Clin. Nutr.* 33: February, 1980.
71. Leevy, Carroll M., "Red cell transketolase as an indicator of nutritional deficiency," Editorial, *Amer. J. Clin. Nutr.* 33: February, 1980.