UNIT 1

Micronutrients, Human Health and Well Being

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I. OVERVIEW

Historically, nutrition science came into being because of the discoveries of the roles of certain nutrients in disease development. Examination of the early medical literature is especially revealing in this respect. The Egyptian papyri, the early Greek writings, the monastic scripts, and even passages of the bible describe the role of food in the prevention or treatment of diseases. For example, ox liver was frequently prescribed for anemia. Those early physicians did not know what ox liver actually did, but they knew that the pale and listless people who came to them for help would improve if they consumed this food item. Later, as humans became more adventurous and left the shores of their homelands to explore the world in ships, other diseases became apparent. Through astute observations, a number of physicians/scientists found that simple diet modifications could prevent or cure these disorders. The British physician, Lind, made the connection between citrus fruit and scurvy. Bonitus and Takaki likewise made the connection between brown rice and beriberi. Through the years these diseases have become uncommon in today's world. They have not disappeared, however, because whenever a population faces a food crisis, be it due to war or crop failure or financial collapse, nutrient deficiencies will appear and have adverse effects on health. They also appear in people who, through ignorance of the importance of consuming a wide variety of foods, select foods that do not provide sufficient amounts of the micronutrients. These people may be of normal weight or even overweight yet they may be inadequately nourished with respect to one or more of the essential vitamins and minerals. As scientists became aware of this problem within an ostensibly well-nourished group of people, they developed techniques that would sensitively detect marginal or inadequate intakes of specific nutrients. This work is ongoing and is the basis for nutrition assessment. Through work with animals that develop analogous deficiency symptoms, these techniques or tests of intake adequacy were related to particular biochemical functions of the individual micronutrients. These then, became the tools for assessment of the nutritional status of humans. The results of these tests also became the basis for the continuing evaluation of nutrient intake and the recommendations for daily intake, presently known as the Recommended Dietary Allowance (RDA), for each of the needed nutrients. Not all of the micronutrients described in this text have an RDA because sometimes there are insufficient data to support

such a recommendation. However, for several nutrients there are recommendations of an intake that should be safe and adequate. The RDA table not only is used as a guide for determining diet adequacy, it is also a device for planning food aid, i.e., food stamps, school lunch programs, etc. The table is used as a basis for educating people about food choice and is used by the food industry (in a modified form) for its food packaging labels.

II. ASSESSMENT

Assessment of the nutritional status of populations as well as individuals occurs at several levels. Overall assessment examines birth and death statistics, life span, family size, economic factors, food distribution, food handling and preservation, and food disappearance from the marketplace. These measures or databases are all useful in assessing the likelihood of intake adequacy for large populations and can serve as barometers of diet adequacy and inadequacy. They do not apply to the individual.

More detailed methods are needed for an individual nutritional assessment vis à vis intake adequacy. An individual assessment requires a careful analysis of the foods consumed concomitant with whole-body assessment and then a functional, physiological, and biochemical assessment of organs and tissues. This type of nutritional assessment can be quite detailed and very expensive. Except under research conditions where very specific questions are being addressed, this detailed assessment is usually not needed.

As detailed in Unit 1 of *Advanced Nutrition: Macronutrients*, food surveys, epidemiological studies, and population statistics provide a wealth of information about large groups of people and, as detailed in Unit 2 of that text, assessment of body size and composition can provide, from an anthropometric point of view, information on an individual's health status. Measurements of height, weight, bone density, fat mass, and muscle mass indicate whether the energy and protein needs are being met. Normal growth and development do not occur when macronutrient intake is inadequate. On the other hand, there can be specific tissue or cell failures when one or more of the micronutrient requirements are not met. Rickets, a breakdown in the growth and development of bone, is one such failure. Anemia, a failure to produce functionally adequate red blood cells, is another. Signs and symptoms of each of these as well as other failures are sought when the nutritional status of the individual is determined. One of the most accessible tissues for use in assessing micronutrient status is the blood. Both red cells (erythrocytes) and white cells (leukocytes) can be examined, as can the sera. Red cells are easier to isolate and assess than are white cells because of their larger size and greater number. However, because malnutrition is frequently characterized by anemia, there may be fewer red cells to work with for these analyses. Anemia can be due to inadequate hemoglobin synthesis, inadequate red cell synthesis and maturation, or both. Vitamin A, B_6, folacin, B_{12}, ascorbic acid, iron, copper, and zinc deficiencies can have anemia as a characteristic. Red cells are constantly being replaced; hence, a deficiency in any one of the many components needed for the replacement of the red cell and its chief component, hemoglobin, will result in anemia. Furthermore, in the hierarchy of essential needs for these nutrients, red cell replacement may be relatively low; therefore, anemia can be a fairly sensitive indicator of nutrient status. The body has many red cells and can function, if necessary, with fewer. A 10 or 20% reduction in functional capacity is not incompatible with life. However, optimal function of that body might not be realized.

Erythrocytes at maturity are circular, biconcave disc-like cells having no nucleus. They are about 7.7 μm in diameter. Their principal function is to carry oxygen from the lungs to all the cells of the body and exchange this oxygen for carbon dioxide which is then transported back to the lungs for expiration. The average adult male has 5.5 to 7×10^5 red cells per milliliter of blood whereas the average adult female has 4.5 to 6×10^5 red cells per milliliter whole blood. These red cells contain hemoglobin, a globular protein having the iron-containing heme as an essential component. It is this iron-containing hemoglobin that carries the oxygen or carbon dioxide.

Table 1 Normal Blood Values for Measurements Made to Assess the Presence of Anemia

Measurement	Normal Values	Iron Deficiency Anemia	Chronic Disease	B_{12} or Folic Acid Deficiency
Red blood cells (10^6/ml^3)	Males: 4.6–6.2 Females: 4.2–5.4	Low	Low	Low
Hemoglobin (g/dl)	Males: 14–18 Females: 12–16	Low	Low	Low
Hematocrit (vol %)	Males: 40–54 Females: 37–47	Low	Low	Low
Serum iron	60–280 µg/dl	Low	Low	Normal
TIBC[a]	250–425 µg/dl	High	Low	Normal
Ferritin	60	Less than 12	Normal	Normal
Percent saturation	90-100%	Low	Normal to high	Normal
Hypochromia	No	Yes	Slight	None
Microcytes	Few	Many	Slight	Few
Macrocytes	Few	Few	None	Many
RDW (RBC size)		High	Normal to low	Very high
Red cell folate	>360 nmol/l	Normal	315–358	<315
Serum folate	>13.5 mg/ml	Normal	Normal	Low (<6.7 mg/ml)
Serum B_{12}	200–900 pg/ml	Normal	Normal	Low
MCV[b]	82–92 µl^3	Less than 80	Normal	Greater than 80 to 100

[a] Indirect measure of serum transferrin; iron binding capacity.
[b] Mean cell volume. When volume increases, the size of the red cell has increased (↑ % of megaloblasts).

The life span of the red cell is about 120 days; thus, the half life is 60 days. That is, it would take 4 months to replace every red cell in the body or 2 months to replace 50% of them. Anemia results when there is a failure to replace these cells. Table 1 summarizes the features of the various forms of anemia. Normal values for these measurements are also shown.

Red cells are synthesized in the red marrow (Figure 1) of bone. The reticular cells give rise to daughter cells called hemocytoblasts. These in turn divide into basophilic erythroblasts. These erythroblasts are large, nucleated cells with a red cytoplasm and traces of hemoglobin. As development proceeds, the hemoglobin concentration increases. The cell proceeds from the basophilic erythroblast to the megaloblast and from there to the mature normoblast. The mature normoblast resembles the mature erythrocyte in size and hemoglobin content but still has a nucleus. This is lost in the final stage of red cell development when the normoblast divides and becomes the mature erythrocyte. Almost all of the latter stages of red cell development can be found in normal blood. Megaloblasts, normoblasts, and mature red cells are found in varying amounts. In persons with pernicious anemia there will be far more immature cells than normal cells because erythropoiesis is not occurring normally. Only vitamin B_{12} deficiency (due to inadequate uptake) results in pernicious anemia.

However, both B_{12} and folacin are needed for red cell replication and development. Hence, both vitamin deficiencies are characterized by megalobastic anemia. B_6 deficiency will result in microcytic anemia. This is characterized by a reduction in hemoglobin synthesis as well as red cell production. Hence the red cells are fewer in number and smaller in size. Serum iron may be increased under these conditions and as soon as B_6 is provided this excess iron is incorporated into the hemoglobin structure and erythropoiesis is restored to normal.

Microcytic anemia may also be observed when either copper or iron intake is inadequate. In this situation the serum iron level (<75 µg/dl) is below normal rather than elevated, as is the case with B_6 deficiency. Zinc deficiency likewise can affect both red cell production and hemoglobin synthesis. The effect of zinc is an indirect one due to its role in protein synthesis and gene expression. Zinc deficiency in part mimics iron deficiency.

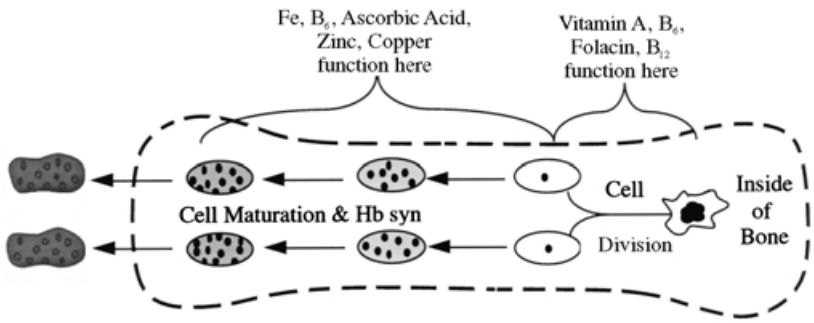

Figure 1 Red cell formation and maturation.

The laboratory tests for anemia as well as for other nutrition related disorders assume that the deficiency condition is a simple one. That is, that the deficiency is due to the inadequate intake of one nutrient or nutrient class. Rarely does that occur. Because intake adequacy is an attribute of the food supply, a single deficiency is unlikely. Rather, the deficient state may develop as a response to a nutrient-nutrient interaction whether it be a macronutrient-micronutrient, mineral-mineral, mineral-vitamin, or vitamin-vitamin interaction effect. Shown in Table 2 is a compilation of interacting nutrients with notations as to where these interactions take place. With many of the mineral-mineral interactions it is the effect of one on the other with respect to absorption by the enterocyte.

Assessment of micronutrient status also includes the determination of the concentration of nutrients in the serum or plasma. These indicate how much of that nutrient is being transported. These levels do not give an indication of the stores, but if the diet intake has been assessed the investigator can make some assumptions about the nutrient with regard to whether it is moving towards a tissue reservoir or away from it. With most of the water-soluble vitamins, tissue reservoirs are negligible. That is, very small amounts of these vitamins are stored for future use. With the other micronutrients such is not the case. The fat-soluble vitamins can be stored as detailed in Unit 4 and the minerals likewise as detailed in Units 6 and 7. Table 3 gives the normal blood levels of micronutrients in addition to those values presented in Table 1.

Urine analysis can also provide information about micronutrient status. The excretion of some minerals and vitamin metabolites can provide an indication of intake and use. Described in Units 3 and 4 are the various metabolites one could expect to find in well-nourished healthy individuals. Not all of the minerals (see Units 6 and 7) will be found in urine because of differences in absorption efficiency. Those that are well absorbed, i.e., sodium, potassium, and chloride, can be found in the urine while most of the others will be found in the feces as unabsorbed ions or salts. Fecal analysis is rarely used in nutritional status assessments. Normal values for nutrients in the urine are presented in Table 4. In some instances, the assessment of status is performed by providing a load of either the nutrient or another nutrient that requires a certain vitamin for its metabolism. For example, a load dose of ascorbic acid might be given followed by a 24-hr urine collection, which in turn is used to determine the amount of ascorbic acid excreted. Knowing the urinary ascorbic acid level before and after the load allows for the calculation of percent recovery and this in turn reflects tissue saturation or status. With folacin, a load of histidine is administered as a challenge and FIGLU (formiminoglutamic acid) is measured in the urine excreted over 8 hours, following the load. Histidine is metabolized to formininoglutamate which reacts with tetrahydrofolate to generate N^5formiminotetrahydrofolate that can then serve in 1-carbon transfers. One-carbon transfer is essential to purine synthesis (see Units 2 and 5). Inadequate folacin status will result in more FIGLU excretion because there is an inadequate supply of the vitamin to transfer the forminino group. The same principle is applied to the evaluation of B_{12} status. However, in this instance the substance used is valine, not histidine, and the metabolite (methylmalonic acid) will rise in concentration when B_{12} intake is low. This is because B_{12} participates as a coenzyme in the synthesis of succinyl

Table 2 Micronutrient Interactions

	Calcium	Phosphorus	Potassium	Sodium	Magnesium	Zinc	Iron	Copper	Iodine	Fluorine	Vitamin A	Vitamin D	Vitamin E	B_{12}	Vitamin K	Riboflavin	Niacin	Thiamin	Ascorbic acid	B_6	Folacin
Calcium	X	↑a	↓a	↓a↑m	↑m↓a						↑a	↑a, m							↑m		
Phosphorus	↑a	X	↑m	↑m	↓a							↑a				↑m	↑m	↑m			
Potassium	↑↓m	↑a	X	↑a	↓a, ↑m							↑a								↑↓m	
Sodium	↑↓m	↑a		X	↓a, ↑m							↑m								↑↓m	
Magnesium	↓a	↑m		↓a, ↑m	X				↑m			↑a						↑m	↑m	↑m	
Zinc						X		↓a, ↑m			↑m	↑a	↑m				↑m			↑m	
Iron	↑m	↓a				↓a	X	↓a, ↑m						↑m		↑m	↑m		↑a	↓a	↑m
Copper						↓a	↓a, ↑m	X			↑m					↑m				↑m	
Iodine									X			↓a		↑a			↑m		↑m		
Fluorine	↓a									X											
Cobalt							↓a														
Chromium						↓a															
Manganese					↓a		↓a														
Molybdenum							↑m	↓a													
Selenium								↑m													

Note: ↑ increase; ↓ decrease; a, absorption; m, metabolism.

Table 3 Normal Values for Micronutrients in Blood

Ascorbic acid, plasma	0.6–1.6 mg/dl	Phosphorus	3.4–4.5 mg/dl
Calcium, serum	4.5–5.3 meq/l	Potassium	3.5–5.0 meq/l
β-Carotene, serum	40–200 µg/dl	Riboflavin, red cell	>14.9 µg/dl cells
Chloride, serum	95–103 meq/l	Folate, plasma	>6 ng/ml
Lead, whole blood	0–50 µg/dl	Pantothenic acid, plasma	≥6 µg/dl
Magnesium, serum	1.5–2.5 meq/l	Pantothenic acid, whole blood	≥80 µg/dl
Sodium, plasma	136–142 meq/l	Biotin, whole blood	>25 ng/ml
Sulfate, serum	0.2–1.3 meq/l	B_{12}, plasma	>150 pg/ml
Vitamin A, serum	15–60 µg/dl	Vitamin D 25(OH)–D_3, plasma	>10 ng/ml
Retinol, plasma	>20 µg/dl	α-Tocopherol, plasma	>0.80 mg/dl

Note: For more information on blood analysis see: NHANES Manual for Nutrition Assessment, CDC, Atlanta, GA (contact Elaine Gunter); ICNND Manual for Nutrition Surveys, 2nd ed., 1963, U.S. Government Printing Office, Washington, D.C.; Sauberlich et al., 1974, *Laboratory Tests for the Assessment of Nutritional Status,* CRC Press, Boca Raton, FL.

Table 4 Normal Values for Micronutrients in Urine

Calcium, mg/24 hr	100–250
Chloride, meq/24 hr	110–250
Copper, µg/24 hr	0–100
Lead, µg/24 hr	<100
Phosphorus, g/24 hr	0.9–1.3
Potassium, meq/24 hr	25–100
Sodium, meq/24 hr	130–260
Zinc, mg/24 hr	0.15–1.2
Creatinine, mg/kg body weight	15–25
Riboflavin, µg/g creatinine	>80
Niacin metabolite,[a] µg/g creatinine	>1.6
Pyridoxine, µg/g creatinine	≥20
Biotin, µg/24 hr	>25
Pantothenic acid, mg/24 hr	≥1
Folate, FIGLU[b] after histidine load	<5 mg/8 hr
B_{12}, methylmalonic acid after a valine load	≤2 mg/24 hr

Note: For more information on urine analyses see: ICNNO, 1963, *Manual for Nutrition Surveys,* 2nd ed., U.S. Government Printing Office, Washington, D.C.; Sauberlich et al., 1974, *Laboratory Tests for the Assessment of Nutritional Status,* CRC Press, Boca Raton, FL; NHANES Manual for Nutrition Assessment, CDC, Atlanta, GA; Gibson, R.S., 1990, *Principles of Nutrition Assessment,* Oxford University Press, New York.

[a] N^1-methylnicotinamide.
[b] Formiminoglutamic acid.

CoA from methylmalonyl CoA. This reaction is part of the degradation of propionate. Thus, in the deficient state one would be able to find methylmalonic acid in the urine after a valine load since a catabolite of valine is propionate.

Evaluation of status should include a physical examination of the subject. As mentioned, this includes body weight, height, and composition. It also includes a careful clinical evaluation of the hair, joints, nails, skin, muscle, nervous system, and endocrine system. Questions about appetite, physical activity, and emotional state can also be included. Shown in Table 5 are features that are usually included in a clinical evaluation. Decreased appetite, for example, can suggest thiamin or zinc deficiency as well as protein-energy malnutrition. This probably would result in weight loss — particularly of the fat mass and muscle mass. Subjects that are pale likely are anemic and could

Table 5 Clinical Evaluation of Nutritional Status

Feature
Body weight for height, age, gender
Appetite
Skin: color, texture, general appearance
Hair: appearance, texture, strength
Mouth, teeth, and tongue: carries, gum health, color
Neck: shape, strength
Abdomen: liver size, absence of tenderness
Extremities: absence of edema, bone and joint strength and flexibility, muscle strength
Neurologic signs: tetany, tingling, poor or exaggerated reflex activity, decreased mental clarity, disorientation, impaired balance

be malnourished with respect to folacin, B_{12}, or iron. This finding would be confirmed with blood analysis, as described. Vitamin A deficiency could be observed through the skin lesion, follicular hyperkeratosis. This is a rough texture found on the legs and arms, particularly on the backs of the upper arm. A generalized dermatitis would suggest inadequate essential fatty acid, zinc, or B-vitamin intake, whereas numerous bruises would suggest inadequate vitamin C or K status. Hair texture is a clue to inadequate protein synthesis, which in turn is related not only to protein intake but also to energy intake and secondarily to those vitamins and minerals essential to protein synthesis.

A shiny, smooth tongue, bleeding gums, and cracks in the corners of the mouth typify riboflavin deficiency, but can also suggest ascorbic acid deficiency. An enlarged thyroid gland suggests an iodine deficiency. An enlarged liver could be due to general malnutrition but could also be due to exposure to toxins that in turn result in an inability to use the energy and protein and micronutrients consumed. Bone malformation typifies vitamin D inadequacy, but can also be due to inadequate intake of vitamin C or the minerals needed for bone. Neurologic symptoms of tetany could be due to calcium and/or magnesium inadequacy or to B_6 deficiency. Thiamin and niacin deficiency can result in loss of foot or hand reflexive responses and can also be characterized by disorientation and/or dementia. All of these clinical impressions must be confirmed with biochemical/physiological assessments before a diagnosis of malnutrition can be accepted. Of course, reversal of symptoms with appropriate supplementation supports the diagnosis of inadequate nutrient intake.

III. FACTORS AFFECTING MICRONUTRIENT NEEDS

The scientists providing the recommendation for micronutrient requirements and their associated recommended dietary allowances assume that the consumer is healthy with no inherent metabolic or physiologic problems. This is not always true. People afflicted with one of the many malabsorption diseases, for example, need larger intakes of vitamins and minerals to compensate for their disabilities. The details of these absorption problems are described in each of the micronutrient sections. In addition to these influences on micronutrient intake and use, there are a number of drugs used to treat illnesses that also interfere with nutrient use. Some of these are listed in Table 6.

There are many more drugs that influence nutrient need than can be shown in this table. However, a large database describing and quantifying these interactions is not available. In many instances, the influence of the chronic use of a given drug on the need for one or more nutrients has not been studied. In other instances, data are available only from acute studies. This is an area of research that has not been widely addressed.

Lastly, micronutrients, especially the vitamins, can themselves be drugs when taken to excess. Detailed in Units 3 and 4 are the consequences of vitamin toxicity. Not all vitamins will be toxic when consumed in excess, but with some this can be a problem that needs recognition.

Table 6 Drugs That Influence Vitamin Use

Drug Class	Nutrient Affected
Diuretics	
Spironolactone	Vitamin A
Thiazide	Potassium
Bile acid sequestrant	
Cholestyramine	Vitamin A, Vitamin B_{12}, folacin
Colestipol	Vitamin A, Vitamin K, Vitamin D
Laxative	
Phenolphthalein	Vitamin A, Vitamin D, Vitamin K, potassium
Anticonvulsant	
Phenytoin	Vitamin D, Vitamin K, folacin
Anticoagulant	
Coumarin, decoumarol	Vitamin K
Warfarin	
Immunosuppressant	
Cyclosporin	Vitamin K
Antibacterial	
Isoniazid	Niacin, B_6
Sulfasalazine	Folacin
p-Aminosalicylic acid	Vitamin B_{12}
Neomycin	Vitamin B_{12}
Tetracycline	Calcium, magnesium, iron, zinc
Anti-inflammatant	
Phenylbutazone	Niacin
Chelating agents	
EDTA	Calcium, magnesium, lead
Penicillamine	Copper, Vitamin B_6
Thiosemicarbazide	Vitamin B_6
Anticholinergic	
L-DOPA	Vitamin B_6
Antihypertensive	
Hydralazine	Vitamin B_6
Antimalarial	
Pyrimethamine	Folacin
Antineoplastic	
Methotrexate	Folacin
Antihistamine	
Ametidine	Vitamin B_{12}
Theophylline	Protein
Antacids	
Aluminum hydroxide	Folate, phosphate
Magnesium hydroxide	Phosphate
Sodium bicarbonate	Folacin
Other	
Ethanol	Niacin, folacin, thiamin
Mineral oil	Vitamin A, β-carotene