**General Principles: Multisystem processes – Nutrition (from 2004 Content Description and Sample Test Materials)**

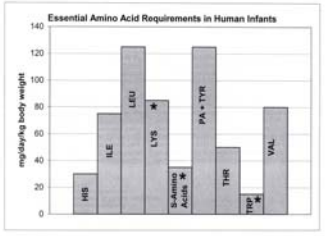
- generation, expenditure and storage of energy at the whole-body level
- assessment of nutritional status across the lifespan, including calories, proteins, essential nutrients, hypoalimentation
- functions of nutrients, including essential, trans-fatty acids, cholesterol
- protein-calorie malnutrition
- vitamin deficiencies and/or toxicities
- mineral deficiencies and toxicities
- eating disorders (e.g., obesity, anorexia, bulimia)

## Protein quality measures - essential amino acids (EAAs)

a. NPU or PDCAAS is determined by EAA quantities/ratios and digestibility

b. Applies to individual proteins or to total dietary protein consumed daily

c. Combining lower value proteins can provide a good quality meal (principle of complementarity in vegetarian diets




d. Rule of thumb: Regardless of protein sources, if tryptophan, lysine and sulfur (S)-amino acid (*) intake is sufficient ("limiting amino acids"), the remaining EAAs are likely to be adequate in the overall daily diet

## Macronutrients. Dietary protein (~4 kcal/g)

1. **Protein usefulness/quality measures and essential amino acids**

a. BV, Biological Value is roughly the proportion of dietary protein absorbed that is used by the body. Limited because it does not account for protein digestibility

b. NPU, Net Protein Utilization takes into account BV and digestibility

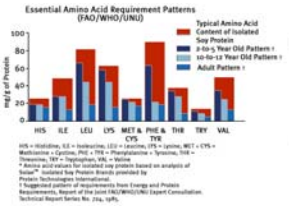
c. PDCAAS, Protein Digestibility-Corrected Amino Acid Score is a recent improvement over NPU that corrects for "true" digestibility

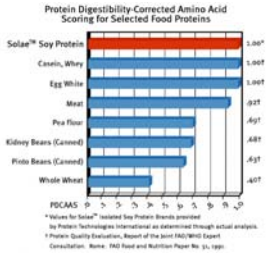
THE COMPOSITION OF ESSENTIAL AMINO ACIDS ULTIMATELY DETERMINES THE PROTEIN'S (AND THE MEAL'S) QUALITY

| Food | PDCAAS (%) |
|---|---|
| egg white | 100 |
| milk protein | 100 |
| tuna | 100 |
| ground beef | 97 |
| chicken dogs | 97 |
| soy protein | 94 |
| whole wheat-pea flour* | 82 |
| garbanzos | 69 |
| kidney beans | 68 |
| peas | 67 |
| pork | 63 |
| lentils | 52 |
| peanuts | 52 |
| whole wheat | 40 |
| | |

*example of protein complementarity

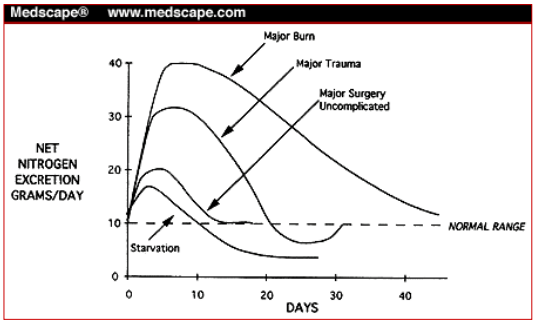
## A further look at soy protein



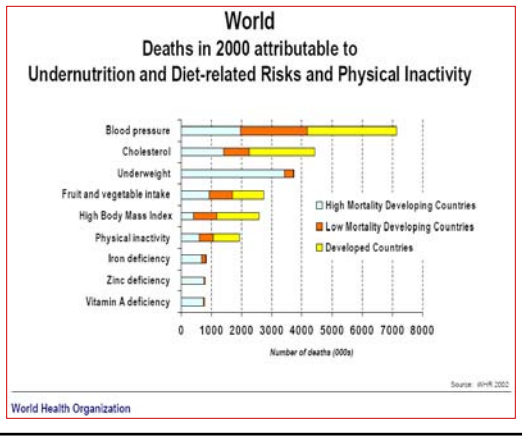

**Causes of Inadequate Nutrient Intake (Quantity or Quality)**

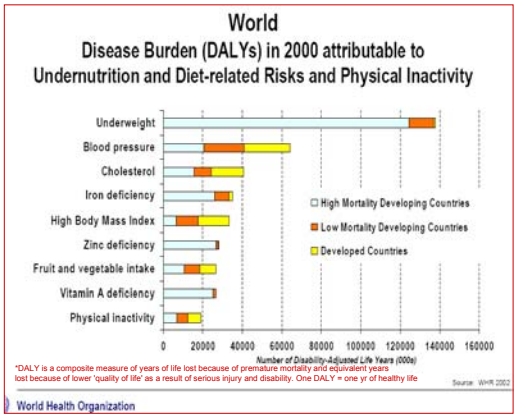
Aging
Mental illness
Alcoholism
Drug addiction
Avoidance of specified food groups
(meat, eggs, milk, fruits and vegetables, grains)
Poor dentition
Food idiosyncrasies
Poverty, isolation
Anorexia (from disease process, drugs, emotional problems)
Recent weight loss or gain
Inappropriate food choices from lack of information



## Marasmus and Kwashiorkor compared

| Disease | Clinical setting | Time course | Clinical features | Laboratory findings | Clinical course | Mortality |
|---|---|---|---|---|---|---|
| MARASMUS (Childhood starvation) | ↓ Calorie Intake | · Months to years | · Starved appearance<br>· Weight < 80% standard for height | · Creatinine-height index <60% standard | · Reasonably preserved responsiveness to short term stress | · Relatively low, unless underlying disease |
| KWASHIORKOR | ↓ Protein intake during stres state | · Weeks | · Well- nourished appearance<br>· Edema<br>· Easy hair pluckability | · Serum albumin <2.8 g/dl<br>· Total iron-binding capacity <200 µg/dl<br>· Lymphocytes <1500/mm³<br>· Anergy | · Infections<br>· Poor wound healing<br>· Decubitus ulcers<br>· skin breakdown | · High |



# Actual Causes of Death in the United States, 2000

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Donna F. Stroup, PhD, MSc
Julie L. Gerberding, MD, MPH

**Context** Modifiable behavioral risk factors are leading causes of mortality in the United States. Quantifying these will provide insight into the effects of recent trends and the implications of missed prevention opportunities.

**Objectives** To identify and quantify the leading causes of mortality in the United States.

**Design** Comprehensive MEDLINE search of English-language articles that identified epidemiological, clinical, and laboratory studies linking risk behaviors and mortality. The search was initially restricted to articles published during or after 1990, but we later included relevant articles published in 1980 to December 31, 2002. Prevalence and relative risk were identified during the literature search. We used 2000 mortality data reported to the Centers for Disease Control and Prevention to identify the causes and number of deaths. The estimates of cause of death were computed by multiplying estimates of the cause-attributable fraction of preventable deaths with the total mortality data.

**Main Outcome Measures** Actual causes of death.

**Results** The leading causes of death in 2000 were tobacco (435000 deaths; 18.1% of total US deaths), poor diet and physical inactivity (400000 deaths; 16.6%), and alcohol consumption (85000 deaths; 3.5%). Other actual causes of death were microbial agents (75000), toxic agents (55000), motor vehicle crashes (43000), incidents involving firearms (29000), sexual behaviors (20000), and illicit use of drugs (17000).

**Conclusions** These analyses show that smoking remains the leading cause of mortality. However, poor diet and physical inactivity may soon overtake tobacco as the leading cause of death. These findings, along with escalating health care costs and aging population, argue persuasively that the need to establish a more preventive orientation in the US health care and public health systems has become more urgent.

JAMA. 2004;291:1238-1245



**Table 2.** Actual Causes of Death in the United States in 1990 and 2000

| Actual Cause | No. (%) in 1990* | No. (%) in 2000 |
|---|---|---|
| Tobacco | 400 000 (18) | 435 000 (18.1) |
| Poor diet and physical inactivity | 300 000 (14) | 400 000 (16.6) |
| Alcohol consumption | 100 000 (5) | 85 000 (3.5) |
| Microbial agents | 90 000 (4) | 75 000 (3.1) |
| Toxic agents | 60 000 (3) | 55 000 (2.3) |
| Motor vehicles | 25 000 (1) | 43 000 (1.8) |
| Firearms | 35 000 (2) | 29 000 (1.2) |
| Sexual behavior | 30 000 (1) | 20 000 (0.8) |
| Illicit drug use | 20 000 (<1) | 17 000 (0.7) |
| Total | 1 060 000 (52) | 1 159 000 (48.3) |

(or your patients)

**Fats = 9 kcal/g**

## What Kind of Fat Are You Eating?

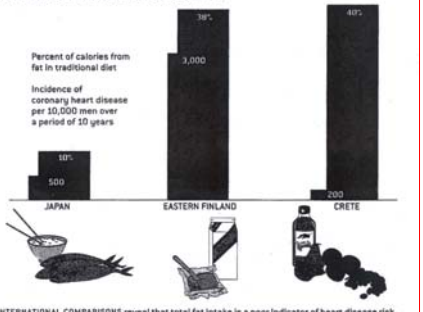
Common food oils ranked by content of saturated fats, from lowest to highest.

| | Cholesterol (milligrams per tbsp.) | Saturated fat | Polyunsaturated fat: Linoleic acid (Omega-6) | Polyunsaturated fat: Omega-3 fatty acid | Monounsaturated fat |
|---|---|---|---|---|---|
| Canola oil | 0 | 6% | 26% | 10% | 58% |
| Safflower oil | 0 | 9 | 78 | trace | 13 |
| Sunflower oil | 0 | 11 | 69 | - | 20 |
| Corn oil | 0 | 13 | 61 | 1 | 25 |
| Olive oil | 0 | 14 | 8 | 1 | 77 |
| Soybean oil | 0 | 15 | 54 | 7 | 24 |
| Peanut oil | 0 | 18 | 34 | - | 48 |
| Cottonseed oil | 0 | 27 | 54 | - | 19 |
| Lard | 12 | 41 | 11 | 1 | 47 |
| Palm oil | 0 | 51 | 10 | - | 39 |
| Beef tallow | 14 | 52 | 3 | 1 | 44 |
| Butter | 33 | 66 | 2 | 2 | 30 |
| Palm kernel oil | 0 | 81 | 2* | - | 11 |
| Coconut oil | 0 | 92 | 2 | - | 6 |

* Believed to be linoleic acid

Source: United States Department of Agriculture

## Fat and Heart Disease




INTERNATIONAL COMPARISONS reveal that total fat intake is a poor indicator of heart disease risk. What is important is the type of fat consumed. In regions where saturated fats traditionally made up much of the diet (for example, eastern Finland), rates of heart disease were much higher than in areas where monounsaturated fats were prevalent (such as the Greek island of Crete). Crete's Mediterranean diet, based on olive oil, was even better for the heart than the low-fat traditional diet of Japan.

Willett et al., Scientific American, 2003

## Dietary cholesterol (Ch) and serum Ch

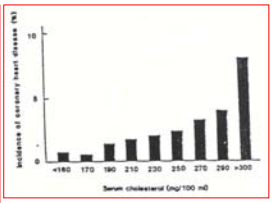
a. Coronary Heart Disease (CHD): No simple relationship to CHD between 190-240 mg/dl serum Ch, but CHD risk is directly related to [LDL-Ch] and inversely related to [HDL-Ch]

b. Reducing Ch intake, in concert with statin inhibitors of HMGCoA reductase, can reduce high serum LDL-Ch levels

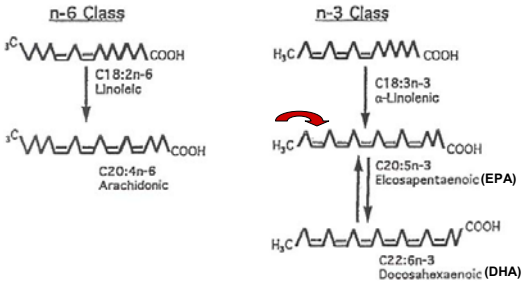
c. Also, increased Ch intake in some studies correlates with increased colon cancer risk

d. Dark side of low plasma Ch levels—increased risk of hemorrhagic (as opposed to ischemic) stroke

e. And Ch levels <150 mg/dl could indicate PEM (check blood protein levels)




## Polyunsaturated Fatty Acids




## Effects of eicosanoids: prostaglandins (PG), thromboxane (TX), and leukotrienes (LT)

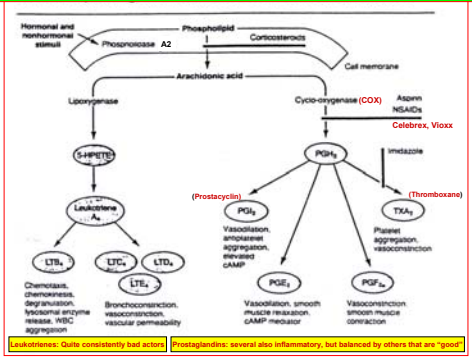


**TABLE 1. Potential Mechanisms by Which Omega-3 Fatty Acids May Reduce Risk for Cardiovascular Disease**

| |
|---|
| Reduce susceptibility of the heart to ventricular arrhythmia |
| Antithrombogenic |
| Hypotriglyceridemic (fasting and postprandial) |
| *Retard growth of atherosclerotic plaque |
| Reduce adhesion molecule expression |
| Reduce platelet-derived growth factor |
| Antiinflammatory |
| Promote nitric oxide–induced endothelial relaxation |
| Mildly hypotensive |

Adapted from Connor.[56]

By suppressing Ca+2 influx in heart cells

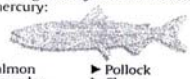
*Stabilize existing plaque and thus thrombotic events (2004)

## What fish should you eat?

Fish that may have high levels of mercury:

- Swordfish
- Shark
- Tilefish
- King mackerel
- Tuna (steak) **bluefin**

Fish that generally have low levels of mercury:



- Salmon
- Flounder
- Cod
- Catfish
- Trout **Sardines**
- Pollock
- Clams
- Shrimp
- Scallops
- Lobster

Source: *Fish Facts for Good Health*, publication of the Washington Department of Health

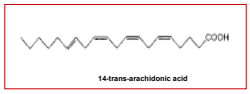
**Possible downsides of increased marine fish consumption:**

**a. mercury contamination, which is potentially damaging to the fetus and its nervous system**

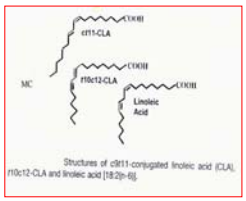
**b. elevated free radical generation (to be discussed) from general increases in easily oxidizable PUFAs; free radicals have been linked to increased cancer risk**

## 9. Concerns about trans-PUFAs

- **a. Trans PUFAs arise mainly during partial hydrogenation of oils, but traces also occur in plants**
- **b. "Mixed" trans-PUFAs are linked to increases in LDL/HDL ratios, and to increased atherosclerosis**
- **c. Paradoxically, two "conjugated" trans/cis linoleic acids (CLAs) at right are cardioprotective and anticancer in experimental studies**




14-trans-arachidonic acid




Structures of c9t11-conjugated linoleic acid (CLA), t10c12-CLA and linoleic acid [18:2(n-6)].

## C. Dietary Carbohydrate (~4 kcal/g)

1. Carbohydrate ranges from simple and refined sugars (mono- or di-saccharides, often "disguised") to complex digestible amyloses and starches

2. Constitute as much as 250 g daily, supplying >50% of total calories for many people

3. Is a short-term energy source, not "essential" like PUFAs

4. Less than 50 g/day of complex carbohydrate is needed to suppress ketosis from fat metabolism and spare protein

## C. Dietary Carbohydrate, continued:

Glycemic index is the ratio of the area under the blood glucose curve produced by a specific carbohydrate-containing food compared to that produced by equivalent glucose or by plain old white bread

Glycemic load (probably more meaningful value overall) refers to the product of the glycemic index (qualitative measure) multiplied by the actual amount of carbohydrate in the portion of food under concern

Insulinemic index is the insulin response to a given glycemic load, being positively correlated with carbohydrate ingested

**GLYCEMIC LOAD OF A SAMPLING OF FOODS**

| Food (one serving) | Carbohydrate content (in grams) | Glycemic Index* (percent expressed as decimal) | Glycemic Load (rounded to nearest tenth) |
|---|---|---|---|
| Potato (1 baked) | 37 | 1.21 | 45 |
| Carrots (½ cup cooked) | 8 | 1.31 | 10 |
| Lentils (½ cup cooked) | 20 | 0.41 | 8 |
| Dry beans (½ cup cooked) | 27 | 0.60 | 16 |
| White rice (⅔ cup cooked) | 35 | 0.81 | 28 |
| Wild rice (⅔ cup cooked) | 18 | 0.78 | 14 |
| White bread (2 slices) | 24 | 1.00 | 22 |
| Whole grain bread (2 slices) | 24 | 0.64 | 15 |
| Pasta (1 cup cooked) | 40 | 0.71 | 28 |
| Cheerios (1 cup) | 22 | 1.06 | 23 |
| All-Bran (1 cup) | 24 | 0.60 | 14 |
| Grape-Nuts (¼ cup) | 47 | 0.96 | 45 |
| Corn flakes (1 cup) | 26 | 1.19 | 31 |
| Corn chips (1 oz) | 15 | 1.05 | 16 |
| Popcorn (air-popped, 1 cup) | 5 | 0.79 | 4 |

* Standard reference for this table is white bread.

(Carbohydrate content and GI values derived from various sources, including the Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School; "International Tables of Glycemic Index," *American Journal of Clinical Nutrition* (1995): Vol. 62, 871S-93S; and *The Complete Book of Food Counts*, 5th Edition (Dell, 2000), by Corinne T. Netzer.)

## 9. Diseases associated with carbohydrate metabolism

a. Diabetes mellitus - glucose intolerance (elevations) due to lack of insulin production (type I) or insulin resistance (type II) leading eventually to organ failures and peripheral nerve degeneration; approaching epidemic proportions in USA and most developed countries

b. Obesity (also a major risk factor for Type II diabetes)

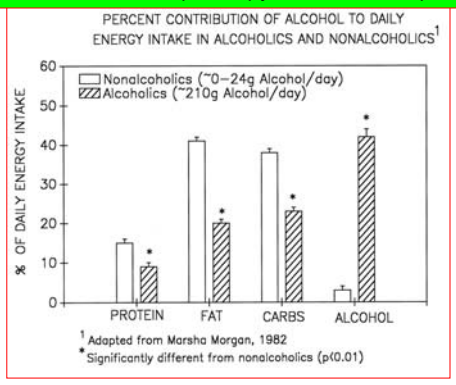
c. Lactose intolerance due to lactase deficiency

d. Studies suggest a link between:

- 1) excess dietary carbohydrate and CHD, with possible mechanisms involving excessive circulating insulin
- 2) high glycemic index diets and risk of CHD in women
- 3) low glycemic index diets and reductions in LDL cholesterol, especially in women subjects studied


## D. Alcohol (ethanol, ~7 kcal/g), often a major source of dietary calories:

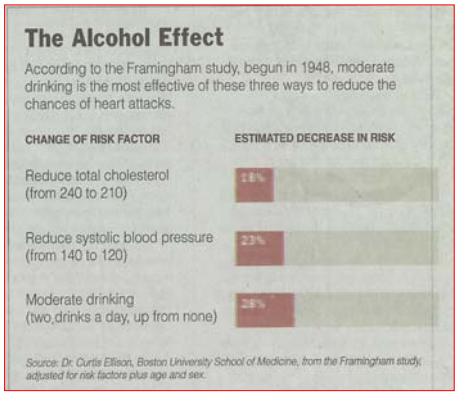
**1. Excessive alcohol consumption = empty calories and nutrient depletor**



MINIMAL TIME OF HEAVY ALCOHOL USE FOR DEPLETION OF NUTRIENTS TO OCCUR

| 2-4 Weeks | 4-12 Weeks | 12-26 Weeks | 6 Months or Longer |
|---|---|---|---|
| folate | niacin | ascorbic acid | calcium |
| magnesium | nicotinamide | long-life proteins | copper |
| potassium | pantothenate | | retinol |
| zinc | phosphate | | selenium |
| short-life proteins | pyridoxine | | 25-hydroxy D |
| | riboflavin | | vitamin $B_{12}$ |
| | thiamine | | vitamin E |
| | medium-life proteins | | vitamin K |

**In addition to low dietary intake, depletion could also arise from impaired absorption and deficient metabolic activation of nutrient vitamins caused by chronic alcohol abuse**




**The softer side of ethanol: moderate* intake:**

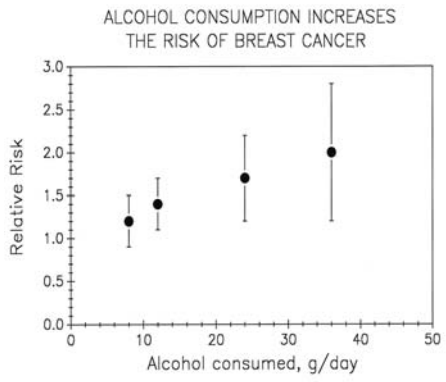
a. correlates with a reduced risk of heart disease ("the French Paradox")

b. is linked in some (but not all) studies to lower risks of stroke

c. has been shown in several recent epidemiological studies to be associated with a reduced risk of dementia, including Alzheimer's

d. BUT still may increase risks of cancers of the breast, intestine, liver and larynx (interpretation complicated by smoking, poor diets)

***definitions vary, but usually a maximum of 2 drinks/day for men and 1 for women (~15 g ethanol/drink), or 7-14 drinks a week (sorry, not all on a weekend night)**



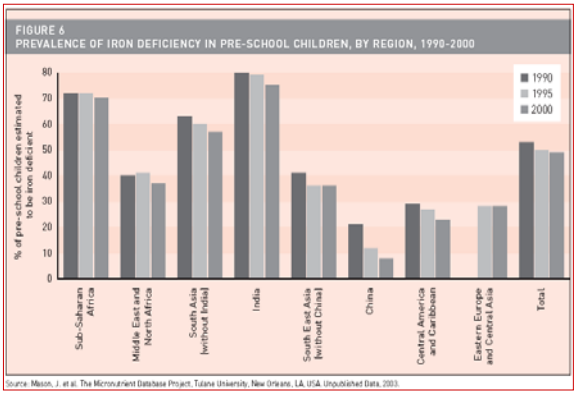

## Minerals

| MINERAL | DOSAGE | BENEFIT |
|---|---|---|
| **Boron** | *500 mcg to 4 mg* | Aids in bone health. |
| **Calcium** | *500 to 1,500 mg* | Crucial for women. Doctors routinely recommend 800 to 1,200 mg from daily supplement. |
| **Chromium** | *50 to 300 mcg* | Marketed aggressively as weight-loss agent. Helps body maintain normal glucose levels. Consult your physician before using higher doses (some practitioners recommend up to 600 mcg daily), especially if you are diabetic. |
| **Copper** | *1 to 3 mg* | Underrated mineral is reputed to improve heart health, promote fertility and maintain healthy skin. Be careful about higher doses; taking, say, 10 mg at one time can cause nausea and muscle pain. |
| **Iron** | *4 to 18 mg* | Men and post-menopausal women should avoid iron supplement to avoid building potentially harmful surplus. Women with poor diet or expectant mothers should be in higher range. |
| **Magnesium** | *100 to 400 mg* | Protects against heart disease, heartbeat irregularity, diabetes, fatigue and muscle cramps. Best to take a combined calcium-magnesium because the two minerals work in balance to regulate body cells. |
| **Potassium** | *20 to 100 mg* | Can lower blood pressure but avoid if you have kidney troubles or take hypertension medication. Most of us get enough in food, including bananas, oranges and potatoes. |
| **Selenium** | *20 to 400 mcg* | An increasingly studied companion of vitamin E to prevent heart disease and cancer. Also helps protect eyes against cataracts and macular degeneration. Dose of 100 to 400 mcg considered best for prevention. Taking too much—900 mcg daily or more—can cause serious side effects, including fatigue, hair loss and depression. |
| **Zinc** | *15 to 30 mg* | Some natural health practitioners tout mineral as a common-cold stopper, not a consensus view among scientists. In any case, zinc is important for men targeting good prostate health. |

## Vitamins

*KEY TO DOSAGE AMOUNTS:* **IU:** International units **mg:** Milligrams **mcg:** Micrograms

| VITAMIN | DOSAGE | BENEFIT |
|---|---|---|
| **Vitamin A** | *No more than 2,500 IU* | Fat-soluble, vision-building vitamin A can build up surplus in the system, causing unwanted side effects. |
| **Beta carotene** | *2,500 to 25,000 mg* | Converts to vitamin A in the body as needed. |
| **B-1/thiamin** | *1.5 to 90 mg* | Federal guideline is 1.5 mg but some nutrition practitioners consider B vitamins a weakness in most Americans' diets. For instance, thiamin is most available in pork, legumes, nuts and fortified cereals. Promotes healthy nervous system. |
| **B-2/riboflavin** | *1.7 to 90 mg* | If you lead a stressful life—raise your hands, everybody—consider taking at least 35 mg per day. |
| **B-3/niacin** | *20 to 100 mg* | A recognized cholesterol fighter, but be cautious about taking too much. It can cause skin flushing; consult your doctor if you have diabetes, low blood pressure, gout or ulcers. |
| **B-5/pantothenic acid** | *10 to 100 mg* | Good for reducing stress. Look to take at least 50 mg daily. |
| **B-6** | *2 to 50 mg* | Helps prevent heart disease, big-time stressbuster (take 50 mg daily), recommended by some practitioners (100 mg therapeutic dose) for carpal-tunnel symptoms. |
| **Folate, folic acid** | *200 to 1,000 mcg* | B vitamin fights cardiovascular problems; 800 daily mcg is now considered a must before pregnancy for women to prevent birth defects. |
| **B-12** | *6 to 800 mcg* | Has reputation as energy booster, especially as we age. |
| **Biotin** | *200 to 600 mcg* | Lesser-known B vitamin helps the body use glucose more effectively (particularly important for diabetics) and promotes healthy nails and hair. |
| **Vitamin C** | *60 to 1,000 mg* | The debate rages on whether regular C doses can prevent colds. If you are a believer, 1,000 to 2,000 mg per day in split doses (500 mg at a time) is a good strategy. Taking more than 2,000 mg can lead to digestive upset. |
| **Vitamin D** | *400 to 800 IU* | Sunlight helps the body produce vitamin D. Milk is another good source. If you lack these two items in daily life, supplement is wise. |
| **Vitamin E** | *200 to 800 IU* | The private Council for Responsible Nutrition estimates about 50 percent of cardiologists themselves take an E supplement for heart health. Scientists are finding it can help prevent Alzheimer's and certain cancers. Preliminary research suggests your vitamin E product might need to be "full spectrum," including gamma-tocopherols and tocotrienols (check the label) along with the more standard alpha-tocopherols. |
| **Vitamin K** | *25 to 300 mcg* | Adding leafy greens to your diet is enough vitamin K for most adults. Bone-building formulations contain 300 mcg. |




## Dietary "Micro" minerals:
## a. Iron - indispensable, yet double-edged

(1) Two forms of iron in diets:
- a) 20-25% readily absorbed heme iron (1/2 comes from fish, meats)
- b) 75-80% non-heme iron in vegetables, legumes, etc., with absorption ranging from 2-20% depending on diet, body needs

(2) Iron, a key component as a heme and non-heme constituent in many proteins, cytochromes, and lysosomal enzymes

(3) Iron has a complex physiology, operating in a relatively closed system: relatively limited absorption and negligible loss (figure)

(4) Non-heme iron absorption is promoted significantly by vitamin C, which reduces ferric to ferrous ion, freeing it for mucosal uptake

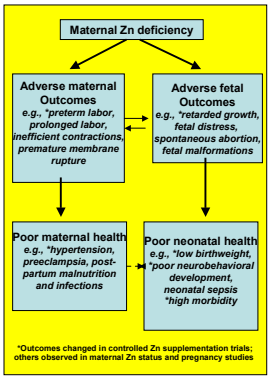
## Aspects of Zinc deficiency in underdeveloped world

One in five people are very deficient, esp. women and children, because of food poor in Zn (Zn-rich foods: whole grains, green veggies, legumes, seafood, meat)

Along with iodide, iron and Vit. A, Zn deficiency is now considered a global health problem that needs to be overcome (UN WHO and UNESCO studies, 2001-04)

Zn deficiency is connected with maternal and child health problems: diarrheal diseases, poor immune function, impaired wound healing, increased morbidity and mortality

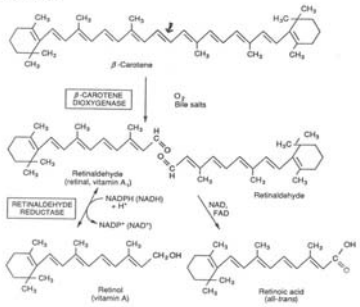
Caveat: High Zn supplementation is potentially damaging to developing and adult brain: like iron, a double-edged mineral

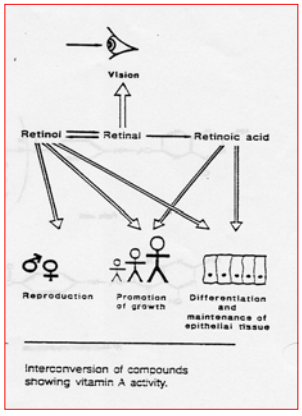


## Four lipid-soluble vitamins

1. VITAMIN A (Retinoids) from Carotenoids (especially β-carotene)

Structures:



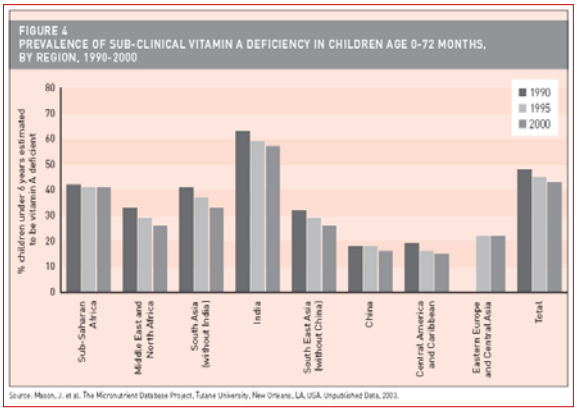




Interconversion of compounds showing vitamin A activity.

(Keratomalacia)

*In extreme cases, vitamin A deficiency attacks the eye, leading to permanent blindness. Much more widespread is the kind of vitamin A deficiency which has no outward sign but which opens the doors to disease and leads over a million children a year to their deaths.*
Photograph: Jørgen Schytte

Unicef Vitamin and Mineral Global Progress Report 2003





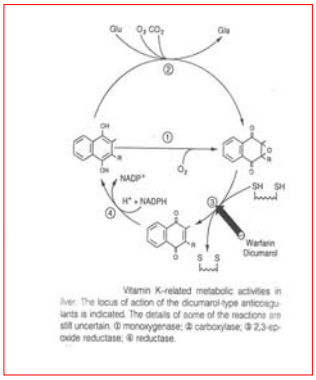
And add Zinc Deficiency to this trio

## d. Best understood biochemical role for Vitamin K isomers

(1) Cofactor for carboxylation of glutamyl sidechains in prothrombin and other proteins in the blood coagulation cascade; this favors prothrombin binding to $Ca^{+2}$ and membrane, and its conversion to thrombin

(2) Vitamin K also has similar glutamyl carboxylation roles in bone, kidney and muscle processes

**(3) Clinically important oral anti-coagulants (cumarols), discovered when sheep began dying after eating spoiled hay, and structurally similar warfarin (rat poison), block the reductase cycling Vit K**




Vitamin K-related metabolic activities in liver. The locus of action of the dicumarol-type anticoagulants is indicated. The details of some of the reactions are still uncertain. ① monoxygenase; ② carboxylase; ③ 2,3-epoxide reductase; ④ reductase.

## e. Manifestations of Vitamin K deficiency or excess

(1) Basically, Vit. K deficiency results in hemorrhage

(2) Although Vit. K is widespread in diets, deficiencies occur during antibiotic therapy (kills intestinal bacterial source) and fat malabsorption syndromes

(3) Vit. K status is (usually) determined before surgeries to avoid excessive bleeding

(4) Newborns (esp. premees), prone to hemorrhage because they lack Vit. K stores and breast milk is a limited source, are routinely treated with
1 mg Vit. K until their bacteria rev up

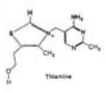
**(5) Because it is readily excreted, Vit. K is relatively nontoxic**

A newborn suffering from brain hemorrhaging due to Vitamin K deficiency (Vietnam). (Photo courtesy of Project Vietnam)

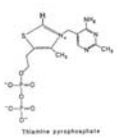
## D. WATER-SOLUBLE "ENERGY-RELEASING" VITAMINS

### 1. VITAMIN $B_1$ (Thiamine), a key decarboxylation co-factor in energy metabolism

Structure:



Thiamine

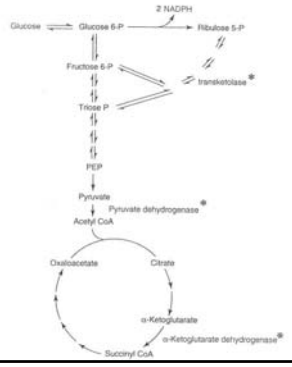



Thiamine pyrophosphate

**a.** Thiamine, generally as its pyrophosphate (TPP), is needed for key decarboxylation reactions in glycolysis and TCA cycle, pyruvate dehydrogenase and α-keto-glutarate dehydrogenase; and in pentose phosphate shunt, transketolase. (RBC transketolase activity is one clinical measure of thiamine status).

**b. Fortified in many commercial breads and cereals; also in grains, seeds (sunflower), green vegetables, nuts, organ meats, pork and milk products, etc.**

## Summary of biochemical reactions* involving thiamine pyrophosphate




## Hyperhomocysteinemia: Importance of vitamin $B_{12}$ in convergence with folate and vitamin $B_6$

1) Elevated plasma homocysteine is an independent risk factor for cardiovascular disease & stroke--So how do the vitamins converge?

2) Homocysteine promotes arteriosclerosis by as yet unclarified mechanisms. Recent evidences also link hyperhomocysteinemia to Alzheimers' dementia, pregnancy complications, inflammatory bowel disease, and increased risk of osteoporotic fractures.

3) A common polymorphism sometimes involved: greatly increased homocysteine and increased risk of stroke in some individuals deficient in activity of 5-MeTHF-forming enzyme (5,10-MTHF reductase)

4) Animal and human studies confirm that supplementation with vitamin $B_{12}$, folate and vitamin $B_6$ can reduce elevated homocysteine by promoting its metabolism

5) Lowering an elevation in plasma homocysteine by 1 umole/L results in a 10% reduction in the risk of cardiovascular disease (JAMA 1995)

## Niacin ($B_3$): Deficiencies or problems of excess

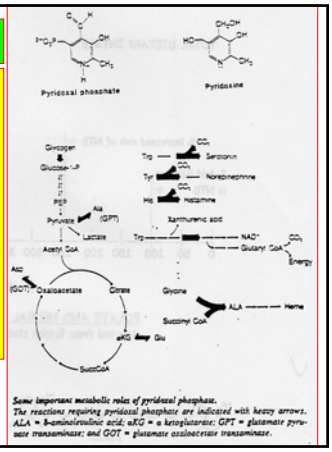
- Severe niacin deficiency leading to **Pellagra**, characterized by the 3 D's (dermatitis, diarrhea, and dementia, and often the 4th big one), is now rare in US because of public health measures (food fortification), but still a common test question
- Moderate niacin deficiency, leading to anorexia, muscle weakness, mucus membrane lesions and burning sensations, occurs frequently in elderly populations and alcoholics
- Large nicotinic acid doses can lower plasma lipids, but side effects can include flushing, hyperglycemia, and reversible liver dysfunction

**Co-factor functions of Vit. $B_6$**

(1)Essential in amino acid decarboxylations, transaminations, deaminations, and aminolevulinic acid (ALA) formation

(2) Stabilizes glycogen phosphorylase

(3) Important in regulating homocysteine levels (detailed later)

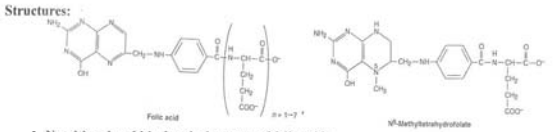



*Some important metabolic roles of pyridoxal phosphate. The reactions requiring pyridoxal phosphate are indicated with heavy arrows. ALA = δ-aminolevulinic acid; aKG = α-ketoglutarate; GPT = glutamate pyruvate transaminase; and GOT = glutamate oxaloacetate transaminase.*

## The Lack of which vitamin is involved with these?

## FOLIC ACID (Folacin), one of two hemopoietic vitamins

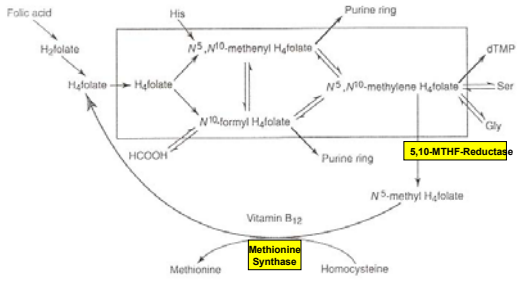
Structures:



a. Nutritional and biochemical aspects of folic acid:

(2) Folic acid utilized in the cellular one-carbon pool as tetrahydrofolate (THF), formed by THF reductase and then metabolically interconverted to important derivatives as shown in the following diagram. N5-Methyl-THF is main circulating form and is very important in limiting homocysteine accumulation (more later).

## Folate: enters one carbon pool as tetrahydrofolate ($H_4$folate or THF)




## Folic acid (folate) deficiency:

(1) provokes hemolytic megaloblastic anemia

a) due to decreased synthesis of purines and deoxy-thymidylic acid (dTMP), which then blocks erythrocyte maturation and results in large ("macrocytic"), easily hemolyzed RBCs

b) underlies anemia in >40% of hospitalized alcoholics, but not only due to low dietary folate, but also to alcohol's inhibition of folate absorption, and (aggravated by liver disease) impaired folate activation, storage

(2) is a major reason for neural tube defects—e.g., spina bifida and anencephaly---so folate supplementation throughout pregnancy, with its already decreased folate absorption, is *muy importante* (fetal development, with rapid cell division, needs folate)

(3) is associated with increased risk of cancer of the colon, possibly through chromosome breaks, and with childhood neuroblastoma

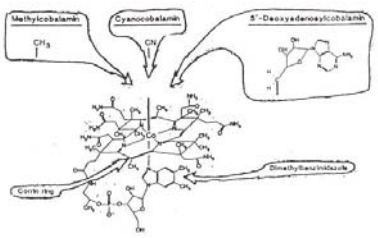
(4) may increase the risk of ischemic stroke, since new studies show that folate intake (and also vit. $B_{12}$ intake) is associated with a reduction in this risk

(5) is linked along with vit. $B_6$ and vit. $B_{12}$ to hyperhomocysteinemia

## Vitamin $B_{12}$ (Cobalamin, the mini-micronutrient)

**Structure:**

Unique "corrin" ring and cobalt (its only biological role), co-ordinated with anionic groups

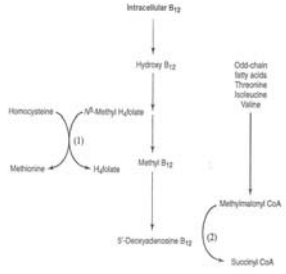


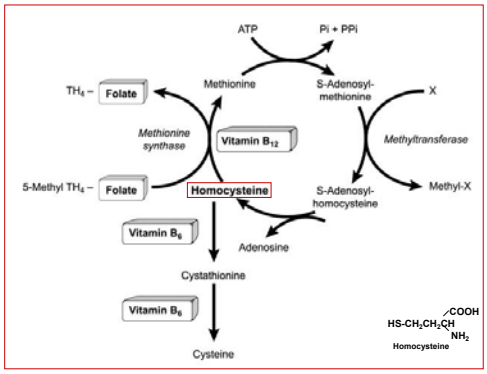

## $B_{12}$ in methionine synthesis, THF regeneration, and methyl-malonyl CoA metabolism

- $B_{12}$ participates in two main biochemical reactions (below right), but are they important:
  (1) the synthesis of methionine, which removes homocysteine and regenerates THF ($H_4$folate)
  (2) the metabolism of methyl-malonyl CoA

**Vitamin $B_{12}$ deficiency results in two problems that are consistent with these reactions:**

- Prolonged intracellular $B_{12}$ deficiency causes **Pernicious Anemia (PA)** that has hematopoietic and neurological components.
- Hematopoietic component, anemia, is actually folic acid deficiency, due to $B_{12}$ requirement in THF regeneration. Can be rescued (treated) with folic acid, but:
- More serious neurological deficits arise from progressive brain demyelination, perhaps because ↑methyl-malonyl CoA blocks myelin fatty acid turnover. Not rescued by folate.




Biological Methylation Reactions and Homocysteine Metabolism

## Diseases with underlying micronutrient deficiencies

**BERI-BERI** and **WERNICKE'S** (Wernicke-Korsakoff: alcoholics)
**Thiamine (B1) deficiency**, affecting pyruvate dehydrogenase

**PELLAGRA** (also alcoholics)
**Niacin (B3) deficiency**, affecting many NAD- and NADH-dependent enzymes

**SCURVY** (sometimes alcoholics)
**Vitamin C (ascorbic acid) deficiency**, affecting proline and lysyl hydroxylases, among others

**NYCTALOPIA** (nightblindness), **XEROPHTHALMIA** (keratinosis and "dry eye"), and **KERATOMALACIA** (permanent blindness)
Progressive retinal damage due to **Vitamin A deficiency** in underdeveloped world

**RICKETS** (childhood osteomalacia)
Deficiency in biosynthesis (lack of sunlight) and/or intake of Vit.D

## TWO VITAMIN CO-FACTORS FOR DECARBOXYLATIONS

**Thiamine (B1) in pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, and branched chain ketoacid dehydrogenase (all α-keto acid decarboxylations)**

**Pyridoxal Phosphate (B6) in DOPA-, histidine-, glutamate-, cysteine ulfinate- and phosphatidyl serine-decarboxylases**

## TWO VITAMIN CO-FACTORS FOR CARBOXYLATIONS

**Vitamin K in vit. K-dependent carboxylases in blood-clotting cascade and bone**

**Biotin in four different ATP-dependent carboxylases (pyruvate carboxylase is a recognizable one from gluconeogenesis)**

## NUTRIENT DEFICIENCIES THAT CAN LEAD TO ANEMIAS

Iron – microcytic hypochromic anemia

Zinc and Copper - basically iron-deficient anemia: zinc is needed in protein metallothionin, which is involved in copper absorption, and copper is a component in ferroxidase [ceruloplasmin], a protein required for iron absorption

Vitamin A - also an iron-deficient anemia: Vit. A is needed for the synthesis of transferrin

Riboflavin (B2) – rare deficiencies can promote anemia: possibly due to impairment of iron metabolism and hemoglobin synthesis

Folate - hemolytic megaloblastic anemia

Vitamin B12 - same as folate: B12 is required to regenerate active tetra-hydrofolate for one-carbon pool metabolism and DNA synthesis

Vitamin E - severe deficiency (very rare) can precipitate hemolysis and a resultant normocytic anemia

**F. Summary of health problems related to nutrition**

| DEFICIENT NUTRIENT | SOME HEALTH PROBLEMS WHEN SEVERE OR CHRONIC |
|---|---|
| "Micronutrient" minerals: | |
| Calcium | Osteoporosis; muscle & bone pain |
| Magnesium | Heart arrhythmia; nerve excitability |
| Iron (1st of world's 3 top deficiencies) | Anemia; susceptibility to infections |
| Iodide (2nd of " " " " ) | Increased infant mortality; cretinism; goiter |
| Zinc | Impaired wound healing; reduced immunocompetence |
| Copper | Aortic rupture (collagen lack); brain lesions; anemia |
| Selenium | Muscle wasting; heart disease |
| "Micronutrient" vitamins, lipid-soluble: | |
| Vitamin A retinoids (3rd of world's top 3) | Increased infant mortality; nightblindness |
| Vitamin E (tocopherols) | Vascular leakage; impaired immune & nerve function |
| Vitamin D (calciferols) | Hypocalcemia; rickets; osteomalacia |
| Vitamin K (phylloquinone) | Hemorrhage! |
| "Micronutrient" vitamins, water-soluble: | |
| Thiamine (B-1) | Beri-beri; Wernicke's syndrome |
| Riboflavin (B-2) | Skin lesions; ocular problems |
| Niacin (B-3) | Pellegra |
| Pyridoxine (B-6) | Seizures (kids); dermatitis |
| Folic acid | Neural tube defects (infants); anemia |
| Cobalamin (B-12) | "Pernicious" anemia (anemia as above, along with irreversible brain myelin loss- |
| Ascorbic acid (vitamin C) | Scurvy; connective tissue problems |
| "Macronutrients" | |
| Protein (major problem in 3rd World) | Protein-energy malnutrition; impaired immune function; kwashiorkor! |
| Lipids (specifically, essential fatty acids) | Impaired brain development; skin rashes |
| Fiber | Increased risk of hypertension, cancer, heart prob. |

| EXCESS NUTRIENT | SOME HEALTH PROBLEMS WHEN SEVERE OR CHRONIC |
|---|---|
| Sodium | Increased hypertension risk |
| Iron | Hemochromatosis; increased free radical damage? |
| Fluoride | Fluorosis (mottled, weakened teeth) |
| Zinc | Can cause iron and copper deficiencies |
| Copper | Brain degeneration (as in Wilson's disease) |
| Cobalt | Congestive heart failure (cobalt-spiked beer story) |
| Manganese | Brain degeneration (especially parkinsonism) |
| Selenium | Cirrhosis; muscle weakness; increased cancer risk (?) |
| Vitamin A | Teratogenic (fetal malform.), and liver toxicity |
| Vitamin D | Hypercalcemia; weakness; diarrhea; confusion |
| Saturated lipids | Hypertriglyceridemia; obesity; atherosclerosis |
| Essential fatty acids (unsaturated fats) | Increased risk of some cancers |
| Protein | Kidney problems; calcium losses |
| Simple carbs (sucrose, glucose) | Some risk of insulin resistance; diabetes; obesity |

**Summary of dietary antioxidant defenses: nutrients making significant contributions**

- Vitamin E in membranes and lipid phases
- Vitamin C in aqueous phases of compartments
- Vitamin A and carotenoids, particularly β-carotene
- Vitamin $B_2$ (riboflavin) as cofactor in glutathione reductase
- Selenium, cofactor required for activity of glutathione peroxidase
- Manganese and copper, cofactors required for superoxide dismutases
- Many plant phenolic derivatives and phytochemicals, particularly flavonoids
- Iron, as a heme constituent in catalase and peroxidases

☹ Note of caution from the National Academy Institute of Medicine: Although many lab experiments indicate the importance of dietary antioxidants, evidence from human studies that supplements actually decrease mortality rates from chronic diseases is still very limited.

**Another Summary**

Review of Epidemiological Studies on Association Between Fruit and Vegetable Consumption and Cancer Risk at Various Sites

| Cancer site | Proportion of Studies with Statistically Significant Protective Effect of Fruits and/or Vegetables[a] | Percent of Studies with Protective Effect |
|---|---|---|
| Larynx | 6/6 | 100 |
| Stomach | 28/30 | 93 |
| Mouth, oral cavity, and pharynx | 13/15 | 87 |
| Bladder | 6/7 | 86 |
| Lung | 11/13 | 85 |
| Esophagus | 15/18 | 83 |
| Pancreas | 9/11 | 82 |
| Cervix | 4/5 | 80 |
| Endometrium | 4/5 | 80 |
| Rectum | 8/10 | 80 |
| Colon | 15/19 | 79 |
| Colon/rectum | 3/5 | 60 |
| Breast | 8/12 | 67 |
| Thyroid | 3/5 | 60 |
| Kidney | 3/5 | 60 |
| Prostate | 1/6 | 17 |
| Nasal and nasopharynx | 2/4 | —[b] |
| Ovary | 3/4 | — |
| Skin | 2/2 | — |
| Vulva | 1/1 | — |
| Mesothelium | 0/1 | — |
| TOTAL | 144/183 | 79 |

Notes: a. Based on standard statistical tests; see the source publication for further information.
b. — = fewer than 5 studies; no percent was calculated.
Source: World Cancer Research Fund (1997). *Food, Nutrition and the Prevention of Cancer: A Global Perspective* (Washington, D.C.: American Institute for Cancer Research, 1997).

## Nutrition in biological and physiological function– I

***Reading assignment*: Devlin 5th Ed., pp. 1053-63; pp. 1117-35; Boron & Boulpaep, pp. 1224-25**

**Lecture 83: Monday April 11th, 8:30-9:30 am**

**Learning Objectives:**

- **Understand the relation of essential amino acid content to the biological value of protein, and how combining "deficient" proteins is nutritionally acceptable.**
- **Explain positive and negative nitrogen balance and conditions under which they occur.**
- **Define marasmus and kwashiorkor as components of PEM, and the effects of coexisting micronutrient and infections in susceptible infants and children.**
- **Understand the structural differences between saturated, mono-unsaturated and poly-unsaturated (PUFA) dietary fatty acids and food oils from which they are derived.**
- **Be familiar with the role of arachidonic acid in forming cell-specific eicosanoid messengers---particularly prostaglandins, thromboxane and leukotrienes.**
- **Explain the structural difference between n-6 and n-3 PUFA and in general why they are essential in human nutrition,**
- **Clarify the importance of increased n-3 PUFA intake and the predominant dietary sources.**
- **Define glycemic index and glycemic load, and relate them to the question of low carbohydrate diets and insulin in weight loss and preventive health.**

## Nutrition in biological and physiological function– II

***Reading assignment*: Devlin 5th Ed., pp. 1053-63; pp. 1117-35; Boron & Boulpaep, pp. 1224-25**

**Lecture 84: Monday April 11th, 9:30-10:30 am**

**Learning Objectives:**

- **Know the effects of chronic alcohol abuse on nutrient absorption and utilization.**
- **Detail major health risks of chronic alcohol abuse that you will almost certainly see in your respective practices.**
- **Describe the nature of dietary fibers, and the nutritional benefits of their increased consumption in balanced diets.**
- **Understand how environmental causes such as poor diets can overlap in some instances with genetics, as exemplified by leptin, to increase obesity risk.**
- **Explain the dietary significance of the food pyramids for healthy nutrition, pointing out the differences between them.**
- **Identify key reactive oxygen and nitrogen species involved in oxidative stress, and the cellular proteins/peptides that sustain antioxidative cytoprotection.**
- **Be familiar with how micronutrients (retinoids, vit. E and C; copper, manganese and selenium) are important for functioning of the above antioxidant proteins.**
- **Understand the functions of ferritin and transferrin in cellular iron regulation, and the role of iron in cellular energy metabolism.**
- **Describe potential deleterious effects of excess iron absorption.**

# Nutrition in biological and physiological function– III

***Reading assignment*: Devlin 5th Ed., pp. 1047-49; pp. 1137-68; Boron & Boulpaep, pp. 1226-27**

**Lecture 85: Tuesday April 12th, 8:30-9:30 am**

**Learning Objectives:**

- **Explain the relationship of dietary carotenoids to retinoids, and the roles of retinoids in normal physiology.**
- **Describe the two forms of vitamin K, and the specific role of vit. K in blood clotting.**
- **Identify the specific functions of thiamine in energy metabolism.**
- **Describe and define the progressive outcome of thiamine deficiency in chronic alcoholism.**
- **Identify pellagra's clinical signs and the nutritional deficiency that underlies it.**
- **Explain the relationship between folic acid and neural tube defects, describing the vitamin's role in the one carbon pool and DNA synthesis.**
- **Clarify the pernicious part of pernicious anemia, and the essentiality of vitamin B12 in the prevention of the disease.**
- **Describe the significance of hyperhomocysteinemia, and the biochemical roles of vitamins B6 and B12 and folic acid in countering the condition.**
- **Explain how a biochemical function of Vitamin C is critical for preventing scurvy.**
- **Describe the cellular antioxidant relationship between Vitamin C and Vitamin E.**
- **Summarize the nutritional components of a diet high in vegetables, fruits, marine fish and whole grains (and some green tea) that are important in reducing risks of heart disease, stroke and cancers.**