

Nutrition for the Gastroenterologist

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Disclosures

- UpToDate – Nutrition Section Editor: royalties
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Nutritional Deficiency Syndromes

Nutritional deficiencies in gastrointestinal disease relate directly to sites and mechanisms of nutrient absorption in the GI tract; hence, it is important to know the anatomy and physiology of protein, carbohydrate, fat, water soluble vitamin, fat soluble vitamin, mineral, and trace mineral absorption. With specific site dysfunction of the small intestine, pancreas, and/or hepato-biliary tree, nutritional abnormalities can be understood and rationally treated.

Major nutritional deficiencies associated with a variety of GI disorders include:

- Protein-calorie malnutrition (manifested by weight loss and/or marasmus)
- Growth retardation
- Nutritional anemias (iron, folate, B-12)
- Bone disease (decreased bone mineral density and osteomalacia)
- Vitamin deficiencies (A, thiamine, riboflavin, niacin, pyridoxine, D, K)
- Mineral deficiencies (iron, calcium, magnesium, phosphorus)
- Trace element deficiencies (copper, selenium, zinc)
- Trace element toxicity (manganese)

The pathogenesis of nutritional deficiencies in GI disease includes:

- Decreased and inadequate oral intake, secondary to:
 - anorexia, nausea and/or vomiting, severe diarrhea, dysphagia or odynophagia, abdominal pain, obstruction
 - iatrogenic:
 - ✓ diagnostic testing
 - ✓ “bowel rest” as part of therapy
 - ✓ restrictive, non-nutritious diets with dietary manipulation
- Maldigestion and malabsorption
 - mucosal disease
 - decreased absorptive surface area
 - pancreatic insufficiency
 - bile salt insufficiency and malabsorption
 - bacterial overgrowth
 - drug induced
 - ✓ corticosteroids (calcium)
 - ✓ sulfasalazine/methotrexate (folate)
 - ✓ cholestyramine (fat and fat soluble vitamins)
- Gastrointestinal loss
 - diarrhea and bleeding
 - fistulae
 - protein-losing enteropathy
- Increased nutritional requirements—active catabolism
 - active inflammation
 - fever
 - corticosteroid Rx

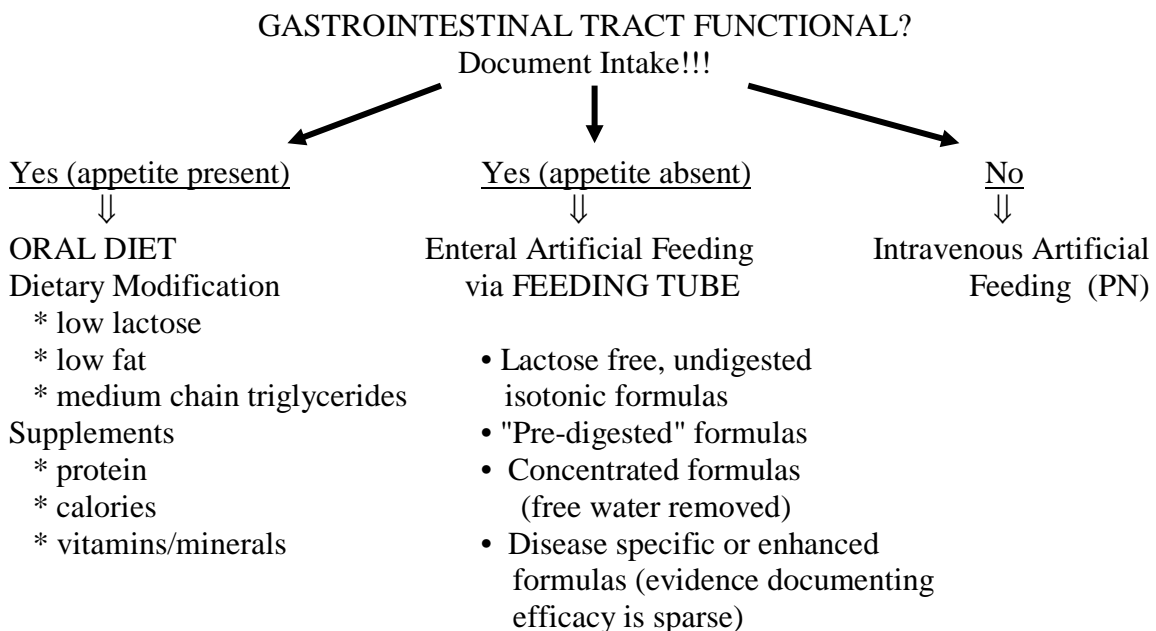
A partial list of GI diagnoses, which may have long term nutritional consequences:

- Inadequate bowel - short gut syndrome
- Crohn's disease
- Celiac disease
- Gastrectomy with Bilroth-II anastamosis, Bariatric surgery
- Chronic pancreatitis
- Chronic liver disease and cholestatic liver disease

Nutrition Support (Artificial Feeding) In GI Disease

Nutritional intervention in GI disease may be via an oral diet, often with modifications or supplements, enteral nutrition (Gastrointestinal Artificial Feeding) via nasogastric, gastrostomy, or jejunial tube, or parenteral nutrition (PN or Intravenous Artificial Feeding). Aggressive artificial feeding can be used to either prevent or treat starvation induced malnutrition; artificial feeding will not cure any underlying disease nor reverse catabolism masquerading as “malnutrition.”

The approach to nutritional therapy depends upon the known or expected defects, the length of time during which starvation has occurred or is expected to occur, the presence or absence of global functioning of the GI tract, and the presence or absence of an appetite. A decision tree for artificial feeding can be formulated as below.



Some Basic Issues in Artificial Feeding (Nutrition Support)

- Nutrition Assessment: there is no single marker for malnutrition. A number of methods have been used to try to establish a diagnosis of malnutrition and assess

prognosis. Unfortunately, these have not differentiated between catabolic effects of disease and results of pure starvation – both may produce the same endpoints. Treatment of starvation will not affect, prevent, or cure catabolism.

- Nutrition Assessment Methods
 - Nutrition History
 - Weight & weight loss
 - Physical exam/body composition
 - Serum proteins: albumin; retinal binding protein/pre-albumin
 - ✓ Albumin is a good negative catabolic marker and a poor nutritional marker
 - Delayed hypersensitivity skin tests
 - Muscle function
 - Prognostic indices: e.g., PNI (Prognostic Nutritional Index: albumin, transferrin, triceps skin fold, delayed hypersensitivity)
 - Subjective Global Assessment: mild, moderate, or severe
 - ✓ History and physical findings: weight loss!!!, subcutaneous fat loss, edema, muscle wasting
 - ✓ Gastrointestinal symptoms: anorexia, nausea, vomiting, diarrhea
 - ✓ Estimate of oral intake
 - ✓ Estimate of strength and stamina
 - ✓ Estimate of metabolic demand: fever, infection, inflammation, trauma
- Predictors of poor outcome
 - Weight loss > 10% in recent past
 - Low serum albumin
 - Anergy
 - Abnormal muscle function
 - High Prognostic Nutrition Index
 - “Severe malnutrition” by Subjective Global Assessment
- Predictor of poor outcome ≠ improved outcome with artificial feeding!!!
- Monitoring for artificial feeding
 - ✓ Nutrient adequacy
 - ✓ Fluid, glucose, renal, electrolyte, and mineral status
 - ✓ Avoidance of complications: from products and delivery
- Overfeeding Complications
 - Hyperglycemia
 - Hyperlipidemia
 - Fluid overload
 - Increased metabolic rate
 - Increased work of breathing
 - Fatty liver

Enteral Artificial Feeding

- Enteral artificial feeding involves direct access to the gastrointestinal tract via a tube, i.e., bodily invasion
- Products: Requiring intact digestive and absorptive mechanisms

- “Standard” lactose free, isotonic, nutritionally complete @ 1500-2000 Kcal
- Nutrient dense: increased macronutrient concentration, usually either protein or fat, providing energy
- Concentrated, free water removed: 1½ - 2 Kcal/cc; can cause dehydration
- Added substrates
 - ✓ “Immunonutrition”: ω-3 fatty acids, ribonucleic acid, arginine, with or without glutamine
 - ✓ soluble fiber
- Disease specific: diabetes, pulmonary, hepatic, renal formulations, critical care. There is little documentation of efficacy for these formulas.
- Products: “pre-digested” but require intact absorption
 - Peptides &/or amino acids
 - Simple carbohydrates
 - Low fat, often with medium-chain triglycerides
 - Hypertonic

Efficacy of enteral artificial feeding: it is assumed that enteral artificial feeding is the same as eating, but this is not true. Enteral artificial feeding is a medical technology with complications associated with the feeding formulations as well as tube insertions. Risks vs benefits should be factored into any decision to initiate artificial feeding.

- Evidence for benefit [i.e., improved clinical outcome] from enteral artificial feeding based upon randomized controlled trials is limited
 - Therapy can be considered for perioperative use to prevent post-operative infections (positive effect seen only in low-quality, high risk-of-bias trials; high quality, low-bias risk trials failed to demonstrate any benefit or harm; 10 to 20 patients would need to be treated to prevent one infection)
 - Therapy can be considered for use in chronic liver disease (improvement in survival was seen in three low-quality, high risk-of-bias trials without improvement in any disease-associated morbidity)
 - Therapy can be considered in critically ill patients to prevent infections (recommendation rests on analysis of three low quality, high risk-of-bias trials; six patients need to be treated to benefit one)
 - Available evidence does not justify use in patients receiving chemotherapy or radiation therapy for solid cell cancers, for inflammatory bowel disease, and in hip fracture
 - Therapy definitely should not be used in the first week of dysphagic stroke
 - Clinical guidelines recommend early enteral artificial feeding in critically ill patients; however, evidence for efficacy comes from clinical trials with high risk of bias, i.e., likely to overestimate treatment benefit
 - There is no data available to assist decision making regarding use in any other clinical scenario
 - Acute pancreatitis: enteral artificial feeding delivered beyond the ligament of Treitz results in decreased infections and shortened length of stay as compared to intravenous artificial feeding (PN); however, there is almost no data comparing enteral artificial feeding to “standard” NPO plus fluid and electrolytes in acute

pancreatitis, and since intravenous artificial feeding (PN) may be harmful, the absolute value of enteral artificial feeding is not established. Nasogastric feeding may be equivalent to jejunal feeding, but evidence is based upon one underpowered clinical trial

- If given a choice, enteral artificial feeding is associated with lower morbidity than intravenous artificial feeding (PN)
- That's it!! Almost all other therapy is based upon "expert" opinion, and belief that intervention is beneficial

Although it is stated that enteral artificial feeding is safer than intravenous artificial feeding (PN), enteral artificial feeding is associated with mechanical, metabolic, infectious, and lethal complications.

- Complications from naso-enteric tube insertion: naso-pulmonary intubation ⇒ pneumonia, pneumothorax, hydropneumothorax; esophageal perforation; laryngeal injuries, cranial insertion
- Complications from indwelling naso-enteric feeding tube: aspiration pneumonia, nasal alar pressure necrosis, sinusitis and otitis, esophageal stricture, carotid artery erosion
- Complications from percutaneous gastrostomy insertion: death, bleeding, esophageal laceration/perforation, colonic perforation, liver injury, cellulitis, necrotizing fasciitis, exit site leakage, buried bumper and transgastric/intraperitoneal migration, migration of balloon gastrostomy tubes into pylorus ⇒ gastric outlet obstruction.
- Delivery and feeding related complications
- Aspiration: gastrostomy and any form of jejunostomy do not decrease pulmonary aspiration
- Intravenous administration of enteral product
- Tube occlusion
- Metabolic
 - ✓ Glucose, electrolytes
 - ✓ Dehydration from "concentrated, free-water removed" formulas
- Drug-nutrient interactions
 - ✓ Dilantin inactivated by enteral artificial feeding
 - ✓ Coumadin: vitamin K in products will alter prothombin time
 - ✓ Inappropriate preparation of pill medications, especially long acting medications crushed
 - ✓ Sucralfate and fiber containing formulas can result in intestinal bezoars and obstruction
- Diarrhea: generally NOT a result of tube feeding product *per se*
 - Antibiotic related diarrhea
 - Clostridium difficile*
 - Medications, esp laxatives
 - Liquid medications with sorbitol
 - Intestinal "failure" in the ICU as part of multi-organ failure
 - Bacterial contamination of feeding product
 - NOT related to tonicity of product

NOT a reason to stop enteral artificial feeding

Intravenous Artificial Feeding (Total Parenteral Nutrition [TPN]/Parenteral Nutrition [PN])

- The decision process for initiation of intravenous artificial feeding should include:
 - The presence of a dysfunctional gut
 - The underlying disease state and current nutrition status
 - Length of time of starvation, actual or anticipated: >10-14 days
 - Philosophy: likelihood of benefit; long-term prognosis; willingness to tolerate starvation
 - Evidence-based medicine based upon prospective randomized controlled trials:
 - ✓ Inflammatory bowel disease: equivalent to oral feeding or enteral artificial feeding in both ulcerative and Crohn's colitis
 - ✓ Acute pancreatitis (harmful compared to standard NPO/IVs or enteral artificial feeding)
 - ✓ Perioperative: small benefit in surgical patients with 6% reduction in post-operative complications; benefit seen only in surgery for upper gastrointestinal tract malignancies and well-nourished patients
 - ✓ Oncology: increased risk of infection and decreased tumor response rate
 - ✓ Enteric fistulas: benefit established from case series
 - ✓ Short gut: no randomized controlled trials, but obviously life saving in appropriate individuals

Composition of intravenous artificial feeding solutions includes, and when writing orders, attention should be paid to:

- Protein source—usually 1-1.2 g amino acids per Kg body weight
 - ✓ Need to consider type of amino acid—general vs. “disease specific”: evidence is at best controversial for branched chain enriched formulas for hepatic encephalopathy and catabolic stress
 - ✓ 1 g Nitrogen = 6.25 g protein; 1 g protein = 4 cal
- Energy source
 - ✓ carbohydrate ± fat: energy needs are modest
~25cal/Kg body weight
 - ✓ Carbohydrate is given as glucose; usually total 400 - 500 g per day; 1 cal glucose in intravenous artificial feeding = 3.4 cal (not 4 cal, because dextrose exists as a monohydrate)
 - ✓ Intravenous fat is predominately linoleic acid based; 500 cc of a 10% solution, 1-2 times per week, will prevent fatty acid deficiency but will not provide sufficient fat soluble vitamins; 1 g fat = 9 cal; 500 cc of 10% solution is often given daily for calories
- Micronutrients
 - ✓ Vitamins (“MVI” is a brand name of a commercial product, containing both water soluble and fat soluble vitamins)
 - ✓ Need to know vitamin K status of commercial multivitamin preparation being used, as some now contain vitamin K and others do not

- ✓ Electrolytes: sodium and potassium need to be added. Bicarbonate should never be added to intravenous artificial feeding solutions because it will precipitate with calcium
- ✓ Minerals: Ca, PO₄ (more than 9 meq Ca and 15 mmol PO₄ per liter may precipitate and cause lethal emboli).
- ✓ Trace minerals: correct additions are not well established. Zinc, copper, chromium and iodine are probably bare minimums. Many add iron. Selenium, manganese, and molybdenum are often added for long term use. Single trace minerals for intravenous use are not available in the U.S.; additives are restricted to commercially available multi-mineral formulations.
- Early weight gain with any form of nutritional therapy is usually from water. Subsequent weight gain is from fat. Protein accrual in the form of increased muscle mass is almost never a function of artificial feeding. Increase in muscle mass results from use/exercise.
- Major complications of central intravenous artificial feeding (PN) include:
 - ✓ Mechanical: from insertion of catheter — pneumothorax, hydropneumothorax, arterial insertion, brachial plexus injury, insertion into internal jugular vein. Precipitation of improper combinations of additives may occur in “3-in-1” solutions, resulting in non-visualized “concretions” which may embolize.
 - ✓ Infectious: usually from improper care of catheter; may have bacterial contamination of amino acid/glucose solution or fungal contamination of intravenous fat.
 - ✓ Metabolic
 - Glucose homeostasis
 - Electrolyte, acid-base, and mineral aberrations: esp, K⁺, PO₄⁻, Ca⁺⁺
 - ✓ Essential fatty acid deficiency
 - prevented by intravenous fat given twice a week
 - biochemical manifestations occur in 2-4 weeks
 - clinical manifestations occur in 2-4 months
 - ✓ Zinc deficiency
 - Prolonged prothrombin time: until recently, vitamin K was not in multivitamin preparations; antibiotics may destroy intestinal or colonic bacteria synthesizing vitamin K; NPO status precluded oral intake of vitamin K; the combination of no oral intake plus antibiotics could result in vitamin K deficiency and necessitated monitoring prothrombin time. Now, some intravenous multivitamin preparations include vitamin K; it behooves the practitioner to know which preparation is being used in his/her patient
 - ✓ Refeeding syndrome: clinical decompensation &/or death shortly after aggressive over-feeding in starved, malnourished individual
 - Cardiac and respiratory failure
 - Neurologic dysfunction/muscle weakness
 - RBC & WBC dysfunction
 - Phosphorus, potassium, glucose, thiamine, magnesium, fluids important in etiology and treatment

- ✓ Hepato-biliary tree dysfunction
 - In adults, high % of patients with low grade aminotransferase &/or alkaline phosphatase elevations; etiology of early liver enzyme elevation not clear
 - Choline absence from intravenous artificial feeding solutions and subsequent deficiency has been postulated to be causal in liver abnormalities
 - Virtually all adult patients will develop biliary sludge and high % of these develop stones when on intravenous artificial feeding for longer than 6 – 8 weeks; appears to be consequent to NPO & lack of CCK stimulation to gall bladder emptying rather than toxicity *per se* of intravenous artificial feeding
 - Over 25% of patients on home intravenous artificial feeding may develop cholestasis, fibrosis, cirrhosis, progressive liver failure & death, as reported in some series; other centers have far lower rates of liver failure; etiology unknown; ursodeoxycholic acid and metronidazole have been used to treat
 - Manganese accumulation in long-term intravenous artificial feeding may be associated with cholestasis and extrapyramidal neurological symptoms
 - Copper may accumulate in patients who develop cholestasis, since copper is excreted in the bile
- ✓ “Metabolic” bone disease - complication of home intravenous artificial feeding (PN)
 - Asymptomatic to disabling bone pain ± fractures
 - Normo- or hypercalcemic; hypercalcuric with negative calcium balance; reduced skeletal calcium
 - Normophosphatemic/ low serum 1,25 (OH)₂ D
 - Osteomalacia on bone biopsy

Micronutrients

Vitamin A (fat soluble) - specifically retinol; retinal (retinol aldehyde) often included; β-carotene and similar carotenoids are precursors.

- Dietary Sources: pigmented veggies & fruits, liver, enriched dairy products.
- Absorption: primarily in jejunum; intact fat absorptive mechanisms required, including pancreatic &/or brush border hydrolysis of conjugates, incorporation into chylomicrons, and chylomicron transport.
- Storage: attached to retinol binding protein (RBP) and stored in liver stellate cells.
 - Stellate cells are fat storage cells located in space of Disse; active in hepatic fibrosis
 - 3-5 stellate cells/60-100 hepatocytes
 - defects in enterohepatic circulation can result in vitamin A deficiency
- Function: epithelial maintenance & integrity; normal visual & reproductive function
- Deficiency: poor dark adaptation; xerophthalmia, dry skin, increased infections
- Toxicity: (with “mega”-doses)
 - liver disease - hepatomegaly, cirrhosis, portal hypertension, ascites, microscopic: fibrosis, increased # & size of stellate cells

- bone pain; osteoporotic bone fractures associated with HIGH NORMAL intake
- irritability, dry skin & desquamation, myalgia, arthralgia, fatigue, headache
- signs and symptoms of increased intracranial pressure

Carotenoids: about 600 hundred identified; only a few are vitamin A precursors; β -carotene best characterized; humans ingest 40 different carotenoids, and 20 different carotenoids isolated from plasma and tissues

Sources: green, yellow, and red vegetables

Lycopene, the predominant carotenoid in tomatoes, associated with decreased risk of gastric, colon, and prostate cancers

Toxicity: yellow-orange skin

Vitamin D: (fat soluble): a group of lipid soluble compounds with a four-ringed cholesterol backbone

- Sources: contained in very few foods (fatty fish and eggs). Main dietary source is fortification of dairy products. Primary source is dermal photoisomerization from sun and ultraviolet light exposure. This system is efficient and provides an estimated equivalent of 200 IU with just brief daily sun exposure of skin and face
 - Daily requirements unclear, but may increase with aging, secondary to decreased hepatic bioconversion and/or decreased intestinal absorption
 - Supplements may be necessary with fat malabsorptive disorders or chronic corticosteroid use
- Absorption: requires intact fat absorptive mechanisms
- Metabolism: hydroxylated in the liver to 25-(OH) vitamin D and further hydroxylated in the kidneys to 1,25-(OH)₂ vitamin D
- Function: closely linked to calcium absorption and homeostasis, modulated by parathyroid hormone, calcium itself, and phosphorus. Many extraskeletal functions demonstrated *in vitro* and experimentally. Clinical significance of these functions is unclear. Induces apoptosis, prevents angiogenesis, and regulates cell proliferation
- Deficiency (for the gastroenterologist):
 - Dietary inadequacy (vegans, poor intake of milk and fish)
 - Limited sun exposure
 - Fat malabsorption (Crohn's disease, celiac sprue, short gut, etc)
 - Chronic liver disease, impairing conversion to 25-(OH)-vitamin D
 - Osteopenia and osteoporosis in adults with deficiency
- Toxicity: hypercalcemia, hypercalciuria, confusion, polyuria, polydipsia, anorexia, vomiting, muscle weakness, and bone demineralization with pain. May occur with excess supplementation

Vitamin E: (fat soluble): ~8 tocol and tocotrienol derivatives, predominately α -, β -, γ -, and δ -tocopherols

- Sources: vegetable oils
- Function:

- antioxidant effects at physiologic intake; found in lipid membranes; prevents oxidation of LDL
- epidemiologic evidence: observational studies have suggested that pharmacologic doses protective against cardio and cerebral vascular disease; not confirmed by prospective randomized controlled clinical trials
- Toxicity: uncommon, but increased bleeding, decreased level of vitamin K dependent clotting factors, impaired immune function, promotion of tumor growth, exacerbation of pre-existing autoimmune disease, antagonism of other fat soluble vitamins have been reported. Pharmacologic doses may have pro-oxidant effects. Has been shown to interfere with beneficial effects of “statins” on lipid profile and atherogenic progression
Recent systemic reviews have suggested that there may be increased risk for gastrointestinal malignancy and increased all cause mortality with intake of pharmacologic doses of vitamin E (i.e., from supplements)

Vitamin K (fat soluble)

- Sources: green leafy veggies & colonic bacteria
- Function: carboxylation of selected amino acid residues on proteins, conferring calcium binding properties to the proteins; important co-factor in bone mineralization
- Absorption: proximal jejunum for oral vit K & colon for bacterial origins; micellar formation and lymphatic transport in small bowel; little liver long-term storage
- Deficiency: Occurs with fat malabsorption or combination of lack of oral intake plus antibiotic Rx eliminating colonic bacterial production.
 - Changes in diet, or initiation of enteral artificial feeding, may alter vitamin K intake and thus affect therapeutic anti-coagulation status. Vitamin K is present in some, but not all, parenteral “multivitamin” preparations given with intravenous artificial feeding (PN). Prothrombin time should be monitored in patients receiving intravenous artificial feeding (PN) plus antibiotics.
 - May contribute to osteopenia/osteoporosis in gastrointestinal diseases associated with fat malabsorption

Thiamine: Vitamin B1 (water soluble): a precursor of thiamine pyrophosphate, a co-enzyme in oxidative decarboxylation of α -ketoacids to aldehydes.

- Sources: found in a wide variety of animal and vegetable products, but abundant in only a few — yeast, pork, legumes
- Function: critical in glucose and energy metabolism; requirement depends upon energy intake; required for pyruvate entry into Kreb’s cycle; without thiamine, pyruvate accumulates & is converted into lactate.
- Absorption: efficiently by active and passive transport. Alcohol impairs absorption
- Deficiency:
 - Wet beriberi: unresponsive severe lactic acidosis; high output cardiac failure; hypotension;
 - Wernicke’s - Korsakoff’s encephalopathy: mental status changes, nystagmus, ophthalmoplegia, ataxia, coma, death
 - May have gastrointestinal symptoms/signs with thiamine deficiency

- National shortage of parenteral multivitamin preparations in late 1990s resulted in intravenous artificial feeding (PN) patients developing complications from acute thiamine deficiency, manifested by symptoms of wet beriberi and Wernicke's Korsakoff's encephalopathy; current shortages may result in similar problems
- Wernicke's syndrome **reported after bariatric surgery** and chronic alcoholism with poor thiamine intake
- Toxicity: excess amounts rapidly excreted. No evidence for toxicity

Riboflavin: Vitamin B2 (water soluble; natural precursor for flavoenzymes *flavin mononucleotide* [FMN] and *flavin-adenine dinucleotide* [FAD]) as well as other flavins

- Sources: widely distributed in food — eggs, lean meat, milk, broccoli, enriched flour
- Function: participates in oxidation-reduction reactions in a variety of metabolic pathways as well as in energy production via the respiratory chain. Flavoproteins catalyze a number of reactions
- Absorption: proximal small intestine via an active saturable transport system with bile salts appearing to facilitate uptake; a modest enterohepatic circulation exists
- Deficiency: isolated deficiency uncommon; usually in combination with other vitamin deficiencies; experimentally: sore throat, glossitis, cheilosis, angular stomatitis, seborrheic dermatitis, normochromic/normocytic anemia
- Toxicity: almost non-existent

Niacin Vitamin B3 (water soluble; nicotinic acid and nicotinamide); tryptophan a precursor

- Sources: meats, fish, legumes, some grains
- Function: greater than 200 enzymatic reactions are dependent upon nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP)
- Absorption: intestinal facilitated diffusion at low concentrations and passive diffusion at higher concentrations
- Deficiency: pellagra -- 4 "D"s: dermatitis, dementia, diarrhea, and death; also, angular stomatitis and painful tongue
 - Pellagra reported after bariatric surgery
- Toxicity: hepatic injury, flushing, gastrointestinal disturbances, burning of hands & feet

Pyridoxine Vitamin B6 (water soluble, pyridoxal 5'-phosphate)

- Sources: variety of foods
- Function: a variety of enzymatic reactions involving gluconeogenesis, niacin formation, lipid metabolism, erythrocyte metabolism and function, synthesis of neurotransmitters, and hormone modulation
- Absorption: passive process in jejunum
- Deficiency: isolated deficiency uncommon; usually occurs with other B vitamin deficiency; isoniazid and penicillamine bind and may induce iatrogenic deficiency
- Toxicity: peripheral neuropathy with megadoses

Folate (water soluble; pteroylpolyglutamate; folic acid is the synthetic form)

- Sources: ubiquitous in food, but may be destroyed by protracted cooking or processing
- Function: required for a variety of methylation reactions and nucleotide biosynthesis
- Absorption: primarily from proximal small intestine; intraluminal hydrolysis of “excess” glutamates from pteroylpolyglutamate form to monoglutamate form necessary prior to absorption; alcohol, anticonvulsants, cholestyramine, sulfasalazine may impair absorption; synthetic form is folic acid (monoglutamate form), which is more bioavailable by 50%; metabolism may differ from food folate
- Deficiency: neural tube defects in fetus, megaloblastic anemia, megaloblastic intestinal epithelium, hyper-homocysteinemia possibly inducing/aggravating occlusive vascular disease, colon cancer, and dementia; elevated plasma homocysteine occurs with deficiency. Although observational data has suggested that high folic acid/folate intake prevents cardiovascular disease, randomized controlled trials have failed to find a protective benefit. Most, but not all, observational studies have suggested protective effect for prevention of colon cancer. Folate/folic acid may reduce the risk of initiation of colon cancer, but may promote growth once existent.
- Drug - Nutrient interactions: important with several drugs potentially used in GI disease; drug may impair absorption and/or metabolism of folate — esp: sulfasalazine; methotrexate
- Toxicity: extremely rare, if at all, but concern exists of masking B12 deficiency if provided in pharmacologic doses

Vitamin B12 (water soluble, cobalamin) - complex absorptive pathway rendering it susceptible to gastrointestinal tract dysfunction.

- Function: active co-enzyme in two pathways – conversion of homocysteine to methionine and catalysis of the final step in propionic acid metabolism
- Source: animal sources only; produced by bacteria which are ingested by animals; absent from strict vegetarian (vegan) diet; produced by human colonic bacteria, but not absorbed
- Absorption & transport: food-cobalamin complex hydrolyzed by gastric acid and pepsins; then bound to haptocorrin (R proteins) found in saliva, food, & gastric juice. R protein-B12 complex hydrolyzed by pancreatic proteases in small intestine and bound to intrinsic factor, secreted by gastric parietal cells. Cobalamin-intrinsic factor complex transported across ileum by specific receptor. After absorption, transported via transcobalamin II; stored in liver bound again to haptocorrin; secreted in bile and enters enterohepatic circulation with same digestive-absorptive mechanisms.
- Deficiency may occur with any disturbance in digestive/absorptive pathway
 - Hypochlorhydria: failure to split B12 bound to food; found in 5-15% of population >age 65
 - Proton pump inhibitors and other acid reduction agents
 - Recent literature suggests association with *H pylori* related chronic gastritis
 - Intrinsic factor deficiency - pernicious anemia; partial or total gastric resection
 - Pancreatic insufficiency
 - Bacterial overgrowth (competition for available cobalamin)

- Ileal disease or loss or genetic receptor deficiency
- Celiac disease – mechanism is unclear, but not related to autoimmune phenomenon. B12 deficiency has been reported to be “common” in celiac disease, warranting checking B12 status in everyone with this diagnosis
- Diagnosis of deficiency may be made by low serum B-12 levels or elevated homocysteine and/or methylmalonic acid levels
- Toxicity: ~ none

Vitamin C (water soluble, ascorbic acid)

- Sources: fruits & veggies
- Functions:
 - antioxidant action: direct reduction of free radicals
 - collagen formation
 - carnitine biosynthesis
 - neurotransmitter synthesis
 - mixed-function oxidase metabolism
 - iron absorption
- Deficiency: scurvy — petechiae, perifollicular hemorrhages, inflamed and bleeding gums, joint effusions, edema, impaired wound healing, lethargy; gastrointestinal petechiae and hemorrhages may occur.
- Toxicity: osmotic diarrhea, renal calculi, iron overload, infertility, xerostomia

Magnesium

- The Food and Drug Administration (FDA) has warned (March 2011) that prescription proton pump inhibitors (PPI) may cause hypomagnesemia if taken for prolonged periods of time (e.g., more than one year). This information will be added to the WARNINGS AND PRECAUTIONS sections for all prescription PPIs
 - Warning based upon 38 reports from the Adverse Event Reporting System (AERS) and 23 cases from the medical literature (8 cases overlapped); available data are insufficient to quantify an incidence rate for hypomagnesemia with PPI therapy
 - Most reports are after \geq one year of use
 - Serious adverse events included tetany, seizures, tremors, carpo-pedal spasm, atrial fibrillation, supraventricular tachycardia, and/or abnormal QT intervals
 - Median time for the magnesium to normalize was one week after PPI discontinuation
 - Median time to develop hypomagnesemia again after rechallenge with PPI was two weeks
 - The mechanism for hypomagnesemia with long term PPI use remains unclear, but could be related to altered intestinal absorption of magnesium
 - Appears to be associated with diuretic use in age \geq 66
- Magnesium is absorbed by two mechanisms
 - 90% by passive paracellular transport
 - 10% by an active transcellular transport mechanism

Zinc

- Zinc content in humans approaches that of iron (1.5 – 2.5 g)
- Source: meats/fish
- Function: co-factor in >120 enzymes, including alkaline phosphatase, carbonic anhydrase, alcohol dehydrogenase, RNA & DNA polymerases
- Absorption: inefficient (20%) in upper small intestine
 - absorption impaired by dietary binders (phytates) and pancreatic insufficiency
 - metallothionein, a zinc binding protein, appears to regulate absorption and metabolism
- Deficiency: normal excretion from lumen and pancreas; excess losses occur with diarrhea; deficiency may occur with mucosal disease and chronic pancreatitis; manifestations of deficiency include:
 - Dermatologic: symmetrical involvement of face, scalp, perianal area, hands/feet (pustular, vesicular, bullous, seborrheic or acneform), alopecia
 - Neurologic deterioration: personality changes, lethargy, irritability
 - Other manifestations: growth retardation, dysgeusia, anorexia, male infertility, impaired T cell function
- May be a useful adjunct in the treatment of acute and persistent watery diarrhea; evidence that zinc added to Oral Rehydration Solutions reduces duration and severity of diarrhea
- Factors altering Plasma Zinc levels: hypoalbuminemia, infection, organ failure, tissue injury and surgery, strenuous physical exercise, pregnancy, intestinal disease decreasing zinc absorption
- Acrodermatitis enteropathica is an inherited defect of intestinal zinc absorption
 - Secondary to mutations in SLC39A4 gene on chromosome 8q24.3, which appears to encode a protein involved in zinc transport
 - Clinical manifestations similar to zinc deficiency outlined above
 - Rx with oral zinc supplements
- Toxicity: from excessive supplementation; nausea and vomiting; abnormal lipoproteins; can cause copper malabsorption and deficiency
- Conclusions: zinc is critical for immunity, insulin action, and anabolism; requirements are increased by diarrhea and critical illness

Copper

- Functions: essential co-factor in a variety of enzymes; iron utilization; formation of collagen and elastin; synthesis of neurotransmitters; melanin synthesis; T cell function
- Metabolism: absorption primarily in proximal intestines; regulated negatively by metallothionein; transported to liver bound mostly by albumin and transcuprin; incorporated in liver into ceruloplasmin; bile excretion
- Deficiency: dietary deficiency rare; deficiencies reported many years after gastric surgery, presumably secondary to bypassing sites of absorption and with intravenous artificial feeding (PN), secondary to failure to add copper as a trace element:
 - neutropenia & hypochromic, ± microcytic anemia (appears similar to iron deficiency anemia)

- skeletal abnormalities: osteoporosis, fibrosis of epiphyses; subperiosteal new bone formation
- neurologic disorders with myeloneuropathy, similar to clinical syndromes seen with vitamin B12 deficiency; recent case reports of patients developing neurologic complications after gastrectomy or gastric bypass; may be growing problem after bariatric malabsorptive procedures
- Toxicity: acute: nausea & vomiting, hepatic necrosis, renal failure, death; chronic: liver failure, cholestasis, neurologic abnormalities, renal damage, hemolysis

Selenium

- Function: required cofactor for protein and DNA synthesis; part of a host of enzymes, many responsible for homeostasis of the redox systems – i.e., antioxidant functions
- Human deficiency:
 - Keshan disease: low soil selenium areas of China → cardiomyopathy
 - Kashin-Beck disease: arthritis
 - Increased cancer risk
 - Intravenous and enteral artificial feeding (case reports): cardiomyopathy; skeletal muscle myopathy; RBC macrocytosis; pseudoalbinism
- Toxicity: narrow therapeutic range; pro-oxidant damage; hair loss & brittle nails

Chromium

- Exists in food as chromium-nicotinic acid complex called *glucose tolerance factor*
- Function: appears to be necessary for normal glucose and lipid homeostasis;
- Deficiency: hyperglycemia, glucose intolerance, insulin resistance, peripheral neuropathy, ataxia; evidence for beneficial effects of chromium supplementation is weak to modest, at best

Manganese

- Function: component of key mitochondrial metalloenzymes, involving antioxidant protection and energy metabolism
- Deficiency: extremely rare
- Toxicity: amount given with intravenous artificial feeding (PN) may be toxic with chronic administration ⇒ extrapyramidal sx; accumulates in brain with dx by MRI; associated with cholestasis, but not clear whether hypermanganesemia induces cholestasis or cholestasis induces hypermanganesemia

Molybdenum

- Necessary part of apoenzymes for several oxidases
 - Metabolism of sulfur amino acids and uric acid
 - Transformation of sulfite to sulfate
 - Hypoxanthine to xanthine to uric acid
- Deficiency only by case report
 - Hypermethionemia, hypouricemia, hypouricosuria, low urinary excretion of sulfate

Trace Mineral Nutrition in the Individual is Dependent Upon:

- Pre-existent levels of trace minerals; stool &/or urine losses
- Nutrient bioavailability: nutrient - nutrient interactions; presence of intestinal ligands; intestinal pH
 - Oral zinc or molybdenum inhibits copper absorption
 - Phytates/fiber decrease zinc absorption
 - Brewer's yeast chromium absorbed 10x more efficiently than inorganic chromium
- Trace mineral analysis
 - Serum measurements often do not reflect tissue stores; e.g. zinc & copper levels decrease in sepsis because of compartmental shifts
 - Changes in binding proteins:
 - ✓ low zinc with low serum albumin
 - ✓ estrogens elevate ceruloplasmin which increase serum copper levels
- Simultaneous serum/urine levels probably truer measure of tissue stores
- Hair analysis commercially popular; ? clinically valid
- Trace mineral dependent enzymes may be more appropriate marker of trace mineral nutrition; e.g. - selenium dependent platelet glutathione peroxidase

Nutritional Pot Pouri

Obesity – major public health problem because of: high prevalence, associative and perhaps causal relationships with serious medical problems, and economic impact

- Importance to the gastroenterologist
 - Common problem which will be seen by gastroenterologists in clinical practice
 - Associated with a number of GI-Hepato-Biliary diseases
 - Gastrointestinal tract is a target for anti-obesity therapy
 - GI hormones are involved with regulation of food intake and are targets for future therapeutic developments
 - Many GI hormones affect satiety, mostly depressing appetite, including: CCK, amylin, GLP-1, Peptide YY (3-36), APO-AIV, Enterostatin, Bombesin/GRP, Oxxytomodulin, gastric leptin
 - Ghrelin (rhymes with “fell-in”): appetite stimulating (orexigenic) hormone secreted by gastric and intestinal cells; implicated in short-term control of pre-meal hunger; evidence suggests that ghrelin may participate in meal initiation and that nutrients suppress ghrelin levels; may also be important for long-term weight regulation; involved in gastric motility
- Endoscopist needs to recognize surgical alterations, and patients may be referred to the gastroenterologist for post-operative complications
- GI complications associated with obesity
 - Esophageal reflux; perhaps Barrett's & adenocarcinoma
 - Gallstones
 - Pancreatitis
 - Fatty liver
 - Diverticulosis complications – diverticulitis and diverticular bleeding

- Increased risk of many GI cancers, including: colon & rectum, pancreas, stomach, esophagus, liver, gallbladder
- Potential mechanisms for obesity-associated gastrointestinal malignancy
 - ✓ Insulin signaling
 - ✓ IGF-1 signaling
 - ✓ Adipokines
 - ✓ Sex hormones
 - ✓ Genetic factors
 - ✓ Inflammation
 - ✓ Endotoxemia
 - ✓ Intestinal microbiota
- Therapies involving GI tract
 - *Olestra*[™] – sucrose polyester. Fat substitute for snack foods and may produce gastrointestinal symptoms of pain, bloating, flatulence, and/or diarrhea.
 - Orlistat – inhibition of gastric and pancreatic lipases, inducing fat malabsorption. Malabsorptive symptoms may occur, and fat soluble vitamins may need to be replaced.
- Surgery – Types of Bariatric Operations
 - ✓ Gastric restrictive procedures
 - Adjustable gastric band
 - Sleeve gastrectomy
 - Vertical banded gastroplasty
 - ✓ Malabsorptive procedure
 - Jejun-ileal bypass: no longer done
 - ✓ Malabsorptive and gastric restrictive
 - Roux-en-Y gastric bypass
 - Biliary-Pancreatic diversion
 - Duodenal switch
- Bariatric surgery complications relevant to the gastroenterologist:
 - ✓ Marginal ulcers, staple line dehiscence, anastomotic leaks, stomal stenosis and obstruction, bleeding, gastric remnant distension
 - ✓ Cholelithiasis
 - ✓ Intestinal ischemia -> infarction -> short gut
 - ✓ Dumping syndrome
 - ✓ Change in bowel habit: loose stool, diarrhea
 - ✓ Bypassing duodenum: malabsorption of iron, calcium, copper
 - ✓ Malabsorption of fat soluble vitamins: A, D, E, & K
 - ✓ Water soluble vitamin deficiency (B12, thiamine [Wernicke's encephalopathy], niacin [Pelagra])
 - ✓ Protein-calorie malnutrition
 - ✓ Decreased bone mineral density (osteopenia, osteoporosis)

Osteoporosis, Osteopenia, and Osteomalacia – decreased bone mineral density or abnormal mineralization, resulting in vertebral crush fractures, hip fractures, other fractures, and considerable disability

- Gastrointestinal-hepatobiliary diseases associated with bone mineral inadequacy

- Inflammatory bowel disease, especially Crohn's disease
- Celiac disease
- Short gut
- Chronic cholestatic syndromes (esp PBC & PSC)
- Postgastrectomy
- Duodenal bypass (e.g., gastro-enterostomy, bariatric gastric bypass)
- Long-term intravenous artificial feeding (PN)
- Proton Pump Inhibitor (PPI): potential association(s) with increased fracture risk &/or decreased bone mineral density is controversial; available literature is not consistent
- Nutrient and disease specific etiologies of bone disease
 - Inadequate calcium and vitamin D intake
 - “Lactose intolerance” – real or perceived
 - Life-style changes: soft drinks for milk, lack of home cooking
 - Fat soluble vitamin malabsorption (vitamin D) – e.g., mucosal disease, bile salt deficiency
 - Bone wasting effects of corticosteroids
 - Inflammatory cytokines (Crohn's disease): TNF- α , interferon- γ , and interleukin-6 disproportionately stimulate osteoclast activity, resulting in bone remodeling imbalance
 - Sarcopenia
 - Genetic predisposition
 - Vitamin K deficiency: several recent reports suggest that vitamin K sufficiency is important for bone health
 - Elevated serum homocysteine is associated with osteoporosis. Causality is not established, but suggests the importance of maintaining adequate folate, cobalamine (B12), and pyridoxine (B6) nutrition for bone health
- Potential diagnostic and therapeutic approaches
 - DEXA (dual energy x-ray absorptiometry scanning) for diagnosis
 - Understand “Z-scores”: comparison to age-matched population
 - Understand “T-scores”: comparison of the individual with a norm at peak bone mass
 - Normal: T- score > -1.0
 - Osteopenia: T-score between -2.49 and -1.0 (Standard Deviations)
 - Osteoporosis: T-score ≤ -2.5 (Standard Deviations)
 - No consensus on diagnosis of osteoporosis in men or on an appropriate reference population for generating a T-score.
 - Be Aware:
 - Osteopenia and osteoporosis diagnosis on DEXA scans are SURROGATE markers and may not translate into fracture risk (some studies indicate no increased fracture risk in GI disease, although surrogate markers are abnormal).
 - Much outcome data is extrapolated from menopausal outcomes, assuming fracture risks are similar
 - Increased recent data available re IBD

- Assure adequate intake of calcium and vitamin D; diet preferred over supplements, but diet is usually inadequate and supplements may be needed; recent secondary analysis of large scale intervention trials suggests that calcium supplements may increase risk of cardiovascular disease (MI, stroke)
- Assure adequate intake of vitamin K, folate, pyridoxine, and B12
- Address other risk factors: advanced age, prior fracture history, family history of osteoporosis, smoking, alcohol, exercise, other medical conditions (renal failure, endocrine disorders), medications, hypogonadal states, sarcopenia
- Medical Rx: calcitonin, bisphosphonates
 - one systematic review and meta-analysis found no evidence to support the use of bisphosphonates for osteopenia or osteoporosis in Crohn's disease
 - another recent systematic review and meta-analysis suggests bisphosphonates as a class, but not individual bisphosphonates, Ca/vitamin D, or fluoride increase bone mineral density and may reduce hip fractures

Homocysteine:

- Amino acid converted to methionine
- Serum levels elevated with deficiency of pyridoxine, folate, and/or cobalamin
- Elevated levels associated with cardiovascular disease, cognitive dysfunction, colon cancer, and osteoporotic fractures. Not clear that vitamin replacement reverses chronic disease

Essential Fatty Acids - linoleic and probably linolenic acid

- Eighteen chain fatty acids which cannot be synthesized by the human organism and are thus essential nutrients
- Important components of cell membranes and prostaglandin precursors; thus required for structure and function in every cell of the body
- Deficiency manifested first by biochemical abnormality in the triene to tetraene ratio
- Clinical deficiency manifested by dermatitis: dry scaly skin progressing to an exfoliative dermatitis

Short Chain Fatty Acids

- Acetic, propionic, and butyric acids
- Products of dietary fiber fermentation
- Stimulate colonic blood flow
- Enhance colonic fluid & electrolyte absorption
- Trophic effects on colonic mucosa
- Butyrate may be preferred fuel for colonocyte

Antioxidants

- Free radical = reactive oxygen radical: chemical species with unpaired electron
 - Unstable, reactive
 - Tends to react with other molecules to pair electron & generate more stable species
- Sources: products of normal metabolism, sunlight, ozone, radiation, tobacco smoke, environmental pollutants

- Free radical examples: superoxide radical — O_2^- ; hydroxyl radical — OH^-
- Free radical damage
 - React with first molecule available: ~ lipids or cell membranes
 - Generation of fatty acid peroxy radicals \Rightarrow reaction with other lipids, proteins, and nucleic acids
- Associated diseases: cardiovascular disease (atherogenesis & atherosclerosis); cancer; neurologic injury; cataracts; reperfusion injury
- Beneficial effects of free radicals
 - Metabolic processes essential for life
 - Neutrophilic activity
 - Arachadonic acid \Rightarrow prostaglandins
- Free radical defenses
 - Antioxidant enzymes: prevent generation of toxic substances superoxide dismutase (SOD); glutathione peroxidase; catalase activity dependent upon “antioxidant minerals”: zinc, copper, manganese, selenium
- Antioxidant small molecules: food derived substances which interact with & neutralize reactive species — “scavenger” function
- Specific antioxidants: Vitamin E, Vitamin C, carotenoids, zinc, selenium
- “Non-essential” antioxidants: flavenoids/polyphenols (found in fruits, veggies, tea, red wine); lycopene (tomatoes); conjugated linoleic acid; carnosine; pyrroloquinoline quinone
- Endogenous antioxidants: glutathione \Rightarrow glutathione peroxidase;
- Taurine: ? retina protection
- Increased all-cause mortality found with beta-carotene, vitamin A, & Vitamin E supplements taken in pharmacologic (as opposed to physiologic) amounts

Conditionally Essential Nutrients

- Normally with diet “non-essential” nutrients are provided or can be synthesized from precursors
- Under certain conditions or with certain diseases, normal synthetic mechanisms may not work
- These nutrients are not contained in standard intravenous artificial feeding (PN) solutions
- **Carnitine** - functions as a vehicle for the transfer of fatty acids from cytoplasm to mitochondria, followed by β -oxidation of the fatty acid.
 - Hypocarnitemia occurs both in infants and adults receiving intravenous artificial feeding (PN); clinical significance is unknown
- **Choline** - essential for synthesis of acetylcholine, phosphatidyl choline, and other phospholipids
 - Hepatic synthesis from methionine; ?absent first pass effect with intravenous artificial feeding (PN)
 - Levels may be decreased with intravenous artificial feeding (PN); significance is unclear; decreased levels postulated to cause liver abnormalities and cognitive dysfunction

- **Cysteine** - occurs in most proteins as the free sulfhydryl compound and as the disulfide (cystine)
 - Synthesized from methionine in liver via transsulfuration pathway
 - Premature infants may lack converting enzyme cystathionase
 - Subnormal plasma cystine in adults maintained on intravenous artificial feeding (PN), suggesting conversion of methionine to cysteine is facilitated by first pass ingestion of methionine through the liver
 - Cirrhotics on intravenous artificial feeding (PN) developed hypocystinemia; corrected with oral cystine.
- **Glutamine**
 - Most abundant amino acid; considered non-essential
 Nutritional requirements during catabolic illness may differ from those during health
 - ✓ Decreased skeletal muscle pools
 - ✓ Ammonia donor for renal excretion of H⁺
 - ✓ Primary oxidizable fuel for enterocytes in rats
Role in humans is unclear
 - ✓ Supports fibroblastic proliferation
 - ✓ Energy substrate for lymphocytes
 - ✓ Clinical use is unproven
 - ✓ Generally safe; however, concerns re increased liver enzymes, enhancement of dementia, promotion of tumor growth
- **Taurine** - end product of transsulfuration pathway
 - Concentrated in heart, skeletal muscle, retina, brain, & bile
 - Important for retina function; may be problematic in infants on intravenous artificial feeding (PN)
 - Decreased serum taurine in adults on intravenous artificial feeding (PN); may affect bile physiology
- **Tyrosine** - occurs in all proteins
Synthesized from phenylalanine in the liver
Essential amino acid in phenylketonuria secondary to phenylalanine hydroxylase deficiency
 - Decreased plasma tyrosine levels and negative nitrogen balance in selected cirrhotics given intravenous artificial feeding (PN); corrected with oral tyrosine

Dietary Fiber

- Heterogeneous non-starch polysaccharides plus lignen, including both insoluble and soluble components
- Insoluble fiber - “wheat bran” model
 - Increased stool mass by water holding capacity
 - Decreased intestinal transit time
- Soluble fiber – “oat bran” model
 - Pectins, guar gum, alginates, beta-glucan
 - Bacterial fermentation produces colonic short chain fatty acids
 - Increase in fecal mass by increase in fecal bacterial count
 - Hypocholesterolemic; enhances fecal bile acid excretion

- Role in gastrointestinal disease unclear; may require high dietary intake for disease reduction, especially colon cancer

Quick Takes – Clinical Pearls

- Nutrition related skin lesions
 - Pellagra – niacin
 - Essential fatty acid deficiency
 - Zinc
 - Vitamin C
- Intravenous artificial feeding (PN) complications
 - Mechanical – catheter misadventures and misplacement
 - Metabolic
 - Short term: glucose homeostasis, electrolytes, minerals
 - Long term: liver, bone
 - Infectious
 - Catheter
 - Solution contamination
- Intravenous artificial feeding (PN) associated liver disease (adults)
 - Short term – mild hepatocellular
 - 3-4 weeks – mild cholestasis
 - 6-8 weeks – gallbladder sludge/stones
 - > 6 months – fibrosis, chronic liver disease, death
- Obesity
 - GI complications – GERD, gallstones +/- pancreatitis, NAFL, most GI cancers, diverticular disease complications
 - Bariatric surgery – gastric restriction, gastric bypass
 - GI hormones – ghrelin, peptide YY
 - GI Rx: malabsorption – sucrose polyester, lipase inhibition
- Antioxidants – Selenium, zinc, vitamins A, C, and E
- Iron
 - Proximal small bowel absorption
 - Deficiency – think anatomically
- Copper – hypo-chromic anemia associated with deficiency in intravenous artificial feeding (PN) solutions; neuromuscular abnormalities after gastric resection or gastric bypass surgery
- Zinc – nitrogen balance, skin, smell, alkaline phosphatase, growth retardation, male infertility
- Manganese – intravenous artificial feeding (PN) toxicity: extra-pyramidal sx (basal ganglia), cholestasis
- Chromium – diabetes
- Selenium – cardiac and skeletal muscle dysfunction
- Vitamin A – liver and bone pathology (toxicity)
- Thiamine – intravenous artificial feeding (PN) deficiency, bariatric surgery complication: wet beriberi, Wernicke’s encephalopathy, lactic acidosis
- B-12 – read the text, homocysteine and MMA (methylmalonic acid) both elevated

- PPI-nutrient interactions – all possible, but clinical importance unclear
 - Inorganic iron absorption -> iron deficiency ??
 - Increased fracture risk; ?? decreased calcium absorption
 - Clinical hypoMagnesemia
 - B12 insufficiency/malabsorption
- Folate
 - Homocysteine elevated
 - Deficiency associated with colon CA
 - Drug-nutrient interactions – sulfasalazine, methotrexate

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BOARD REVIEW TYPE QUESTIONS

1. A 39 year old woman with a 15 year history of ileo-colonic Crohn's disease comes into your office stating that she is worried about osteoporosis, since she heard that she might be at increased risk after listening to a talk-radio show. She has an asthenic body habitus, but has not had any weight change in the past fifteen years. Her two older siblings do not have Crohn's disease, but have been diagnosed with osteopenia. She is still having menstrual periods. An appropriate first step would be to:

- A. Reassure her that since she has not reached menopause, she is not at risk for osteoporosis.
- B. Suggest that she start vitamin K.
- C. Obtain a dietary and sun exposure history, a serum 25-(OH) vitamin D level, and a baseline DEXA scan.
- D. Check a serum homocysteine level and give B vitamins if it is elevated.

2. Congestive heart failure and respiratory depression develop two days after your surgical colleagues have started intravenous artificial feeding (Parenteral Nutrition) in a 73 year old, 46 kg man, giving him 2700 Kcal/day to "beef him up" for surgery in a week. You are asked to make recommendations as to management. The next appropriate step would be to:

- A. Give three "IV runs" of KCl, 20meq each.
- B. Check a fingerstick glucose and administer an amp of D50W.
- C. Stop the TPN and check serum glucose and phosphate.
- D. Give a "banana" bag (multivitamin infusion) with added thiamine and folic acid.

3. A 55 year old man is referred to you for evaluation of iron deficiency anemia. He has had a colonoscopy twice by a surgeon in another city. He underwent gastric resection thirty years ago for peptic ulcer disease. He has had a five pound unintentional weight loss over the past year and occasionally complains of dyspeptic symptoms. He claims to be a reformed alcoholic. Before rushing to endoscopic or capsule procedures, you think about possible malabsorptive causes for his iron deficiency, rather than blood loss. Which of the following might be a cause of his iron deficiency?

- A. Gastric resection (from his old ulcer surgery)
- B. Non-ulcer dyspepsia

- C. Alcoholic hepatitis
- D. Chronic pancreatitis

4. A 50 year old obese woman (Body Mass Index {BMI} = 38) is referred to you for a screening colonoscopy. You have just aced your GI Boards, in part due to your excellent knowledge of nutrition. You decide that you should try to counsel this patient about potential cancer risk related to obesity. You consider informing her that she is at significant risk for which of the following cancers and might reduce her cancer risk with effective weight loss:

- A. Colon and rectum only
- B. Pancreas only
- C. Colon and rectum, pancreas, stomach, and liver
- D. There is no increased risk of GI cancers associated with obesity, only non-GI cancers

5. A surgical colleague refers you a 73 year old man who has been on home intravenous artificial feeding (Parenteral Nutrition) for the past eight weeks because of a post-operative entero-cutaneous fistula. The man's wife thought that he looked yellow. Laboratory data reveals an Hct of 30%, a normal chemistry and mineral panel, a total Bilirubin of 6.5mg/dl with a Conjugated Bilirubin of 4.2mg/dl, alkaline phosphatase 345 mU/ml, AST 85 mU/ml, ALT 43 mU/ml, and LDH 240 mU/ml. The appropriate next step and its reasoning would be:

- A. Check for surreptitious anabolic steroids, which he might be using for potency.
- B. Ignore because these are routine liver enzyme abnormalities associated with intravenous artificial feeding (Parenteral Nutrition)
- C. Perform a liver biopsy to rule out progressive chronic fibrosis seen with long-term intravenous artificial feeding (Parenteral Nutrition)
- D. Order an abdominal ultrasound to rule out choleducolithiasis

6. You are caring for a 41 year old woman with short gut syndrome on home intravenous artificial feeding. After doing well for the past two years, she rapidly develops nausea, vomiting, bilateral sixth nerve palsies, nystagmus, ataxia, and slow mentation. You remember learning about this complication at the Willaim Steinberg Board Review Course. Your immediate next action is to:

- A. Eliminate copper from the trace element formulation because of acute copper toxicity causing an iatrogenic Wilson's disease.
- B. Query the Home IV company about whether they have been adding vitamins to the solutions. Immediately request high doses of thiamine to correct thiamine deficiency, which has caused multiple neurological complications.
- C. Eliminate vitamin A from the solution because this represents acute vitamin A toxicity.

D. Query the Home IV company about whether they have been adding vitamins to the solutions. Immediately request high doses of niacin to correct niacin deficiency causing pellagra.

7. You are asked to evaluate a 73 year woman with anemia. Iron studies show an iron of 45 mcg/dl, a total iron binding capacity of 243 mcg/dl, a ferritin of 275 ng/dl, and a serum B12 of 210 pg/ml (a borderline low level). In order to further evaluate her anemia, you order serum methyl malonic acid and homocysteine. These are found to be elevated. Which of the following might cause the elevated serum homocysteine and methylmalonic acid levels?

- A. GERD on chronic PPI
- B. Cholecystitis
- C. Colon cancer
- D. Osteoporosis

8. You are called by the Emergency Room to inform you that a 72 year old male patient of yours has just been seen for tetany, seizures, and supraventricular tachycardia.

Which of the following laboratory tests was found to be critically low:

- A. Serum manganese
- B. Serum calcium
- C. Serum phosphate
- D. Serum magnesium

Which medication is the probable likely cause of this abnormality?

- A. Chronic PPI intake
- B. Acute PPI intake
- C. Chronic histamine 2 receptor antagonist intake
- D. Acute histamine 2 receptor antagonist intake

Answers:

1. Answer: C

Because of the ileal Crohn's disease, and perhaps family history, she is at increased risk for decreased bone mineral density, even though she is not menopausal. This occurs as a result of fat soluble vitamin D deficiency secondary to fat malabsorption, which is itself consequent to bile salt malabsorption. Additionally, in the US dietary intake of both calcium and vitamin D are often inadequate and sun exposure may be suboptimal as well for vitamin D. A reasonable first step, which would help in both diagnosis and potential

treatment, would be to obtain a history to assess adequacy of calcium and vitamin D intake as well as sun exposure, check her serum vitamin D level, and obtain the DEXA scan to determine her bone density. Although decreased bone mineral density has been associated with vitamin K deficiency and elevated homocysteine levels, starting vitamin K or checking serum homocysteine levels would not be an appropriate first step.

2. Answer: C

This is a classic example of the “refeeding syndrome” in which an individual with chronic starvation is fed too quickly. Clinical manifestations include cardiac, pulmonary, and neuromuscular failure. A single etiology has not been defined, but fluid overload, insufficient thiamine for carbohydrate metabolism, as well as phosphate depletion resulting in an inability to form high energy bonds -- all have been implicated. The best treatment is prevention, but once incurred, the most reasonable step would be to stop the aggressive fluid intake and glucose load as well as check glucose, electrolyte, and mineral levels. Although hypokalemia may occur, this is not usually a primary cause and blindly administering potassium would not be appropriate. Usually, the problem is hyperglycemia, not hypoglycemia, so D50W is not appropriate. Giving more fluids and vitamins is not addressing the fundamental issue of fluid overload and excess glucose without sufficient thiamine for effective metabolism.

3. Answer: A

Iron, like other divalent cations, is absorbed proximally in the duodenum and upper jejunum. Patients with a Bilroth II gastrojejunostomy bypass the main intestinal absorptive surface for iron uptake. Other potential causes might include celiac disease in which patients may malabsorb iron. There is also recent evidence that patients with celiac disease may lose iron. Finally, the rare Crohn’s disease patient with proximal intestinal disease may malabsorb iron; more often these patients have colonic blood loss from inflammation. Non-ulcer dyspepsia (assuming no PPI use), alcoholic hepatitis, and chronic pancreatitis are not associated with iron malabsorption.

4. Answer: C

Obesity appears to be associated with an increased risk for many GI and non-GI cancers. The risk is increased for all of the GI cancers mentioned. The attributable risk for cancer death due to obesity is 14-20%. In other words, it has been calculated that cancer mortality could be reduced in the U.S. by 14-20% if the entire population were to achieve weight reduction to a “normal” body weight.

5. Answer: D

After 6 weeks of intravenous artificial feeding (Parenteral Nutrition), virtually 100% of patients will develop gall bladder sludge, and a few patients will have developed stones. Almost all patients (adults) will develop mild amino transferase elevations (2-4 times upper limit of normal) after one to two weeks of intravenous artificial feeding (Parenteral Nutrition) and mild alkaline phosphatase elevations (2-3 times upper limits of normal) after two to three weeks of intravenous artificial feeding (Parenteral Nutrition). Elevated bilirubin is extremely rare after short term intravenous artificial feeding (Parenteral

Nutrition). The progressive liver failure seen in some patients with “home” intravenous artificial feeding (Parenteral Nutrition) rarely occurs before 6 months and usually not until several years out. Anabolic steroid use is a red herring, although always a possibility; however, it has nothing to do with intravenous artificial feeding (Parenteral Nutrition) associated liver disease.

6. Answer: B

This picture is classic for the acute neurological manifestations of thiamine deficiency: ophthalmoplegia, peripheral neuropathy, and Wernicke-Korsakoff syndrome. Many cases occurred a number of years ago because of a national shortage of parenteral multivitamins and the failure to arrange for appropriate vitamin therapy in patients on long term intravenous artificial feeding. To my knowledge acute copper toxicity has not been reported as a complication of intravenous artificial feeding (Parenteral Nutrition). Acute pellagra could occur consequent to vitamin insufficiency, but this has not been reported, and the manifestations would include diarrhea and dermatitis. The described symptom complex is not that of vitamin A toxicity.

7. Answer: A

Elevated homocysteine and/or methyl malonic acid levels are found with tissue B12 insufficiency or deficiency, even in the presence of low normal serum B12 levels. Chronic PPI intake suppressing acid production may interfere with cleavage of B12 bound to food and result in B12 insufficiency or deficiency. Other causes of B12 deficiency include normal aging, atrophic gastritis, and history of gastric resection. 5% to 15% of the population >65 years old may be unable to cleave B12 from its binding with food, presumably secondary to decreased acid production. These individuals can absorb crystalline, or non food-bound, B12. 2% of the population >65 years old with atrophic gastritis will lack intrinsic factor – Pernicious Anemia. Hemigastrectomy causing achlorhydria and perhaps intrinsic factor loss, can also result in B12 deficiency. B12 insufficiency has been found in up a third of patients with a history of gastric surgery. Cholecystitis and colon cancer do not cause B12 deficiency. Osteoporosis has been suggested to be result of elevated homocysteine, but it is not a cause of the elevation.

8. Answers: D for questions for first question and A for second question

Chronic PPI use (>1 year) has been associated with severe and often symptomatic hypomagnesemia. The absolute risk is unknown, but appears to be real and potentially life threatening when it occurs. Treatment is discontinuation of the PPI. One case control observational cohort study has found that this complication may only occur with concomitant intake of diuretics.