National Liver Conference 2015 Nutrition in Health and Liver Disease

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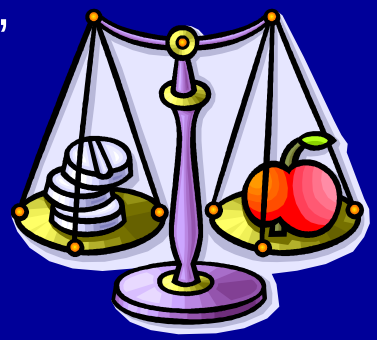
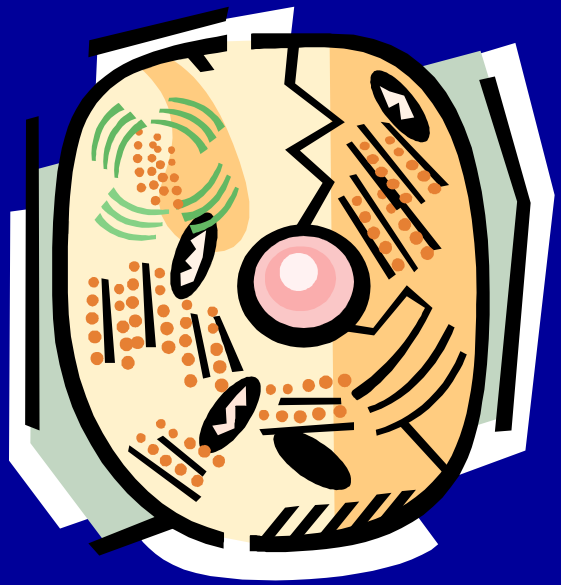
Essential Nutrients

Carbohydrate	glucose; dietary fiber
Lipid	linoleic acid (ω-6); linolenic acid (ω-3)
Protein	tryptophan, threonine, histidine, leucine, lysine, isoleucine, methionine, valine, phenylalanine
Vitamins	thiamin, riboflavin, niacin, pyridoxine (B_6) folic acid, cobalamin (B_{12}), pantothenic acid, biotin, ascorbic acid (C); retinol (A), cholecalciferol (D), tocopherol (E), phylloquinone (K)
Minerals	calcium, phosphorus, magnesium, sulfur;sodium, potassium, chlorine; iron, zinc, copper, iodine, chromium, selenium, manganese, fluorine, molybdenum
Energy	kilocalories or kilojoules
Fluid	water

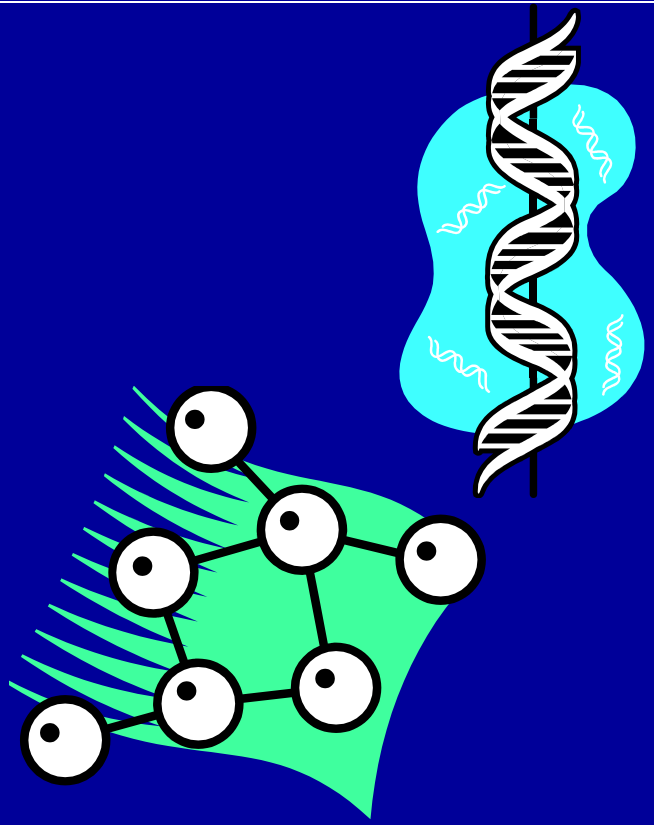


Cellular Roles of Nutrients

- Provide energy
- Incorporated into cellular compounds
- Provide structural elements
- Support mechanical, chemical, electrical processes



Molecular Roles of Nutrients

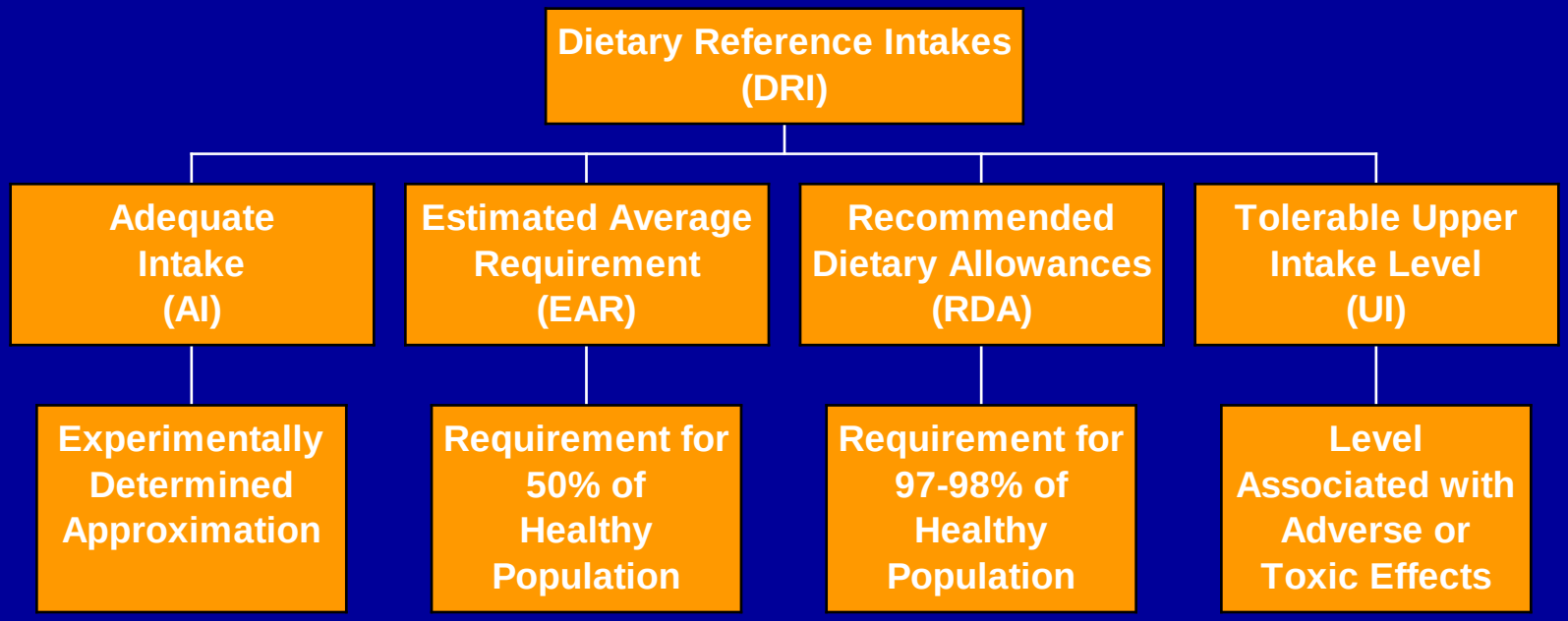


- regulate gene expression
- protect, function, and support catalytic activities of enzymes
- demonstrate hormone-like activity
- facilitate hormone receptor binding and activity
- support and regulate immune system activities

Examples of Structural and Functional Roles of Nutrients

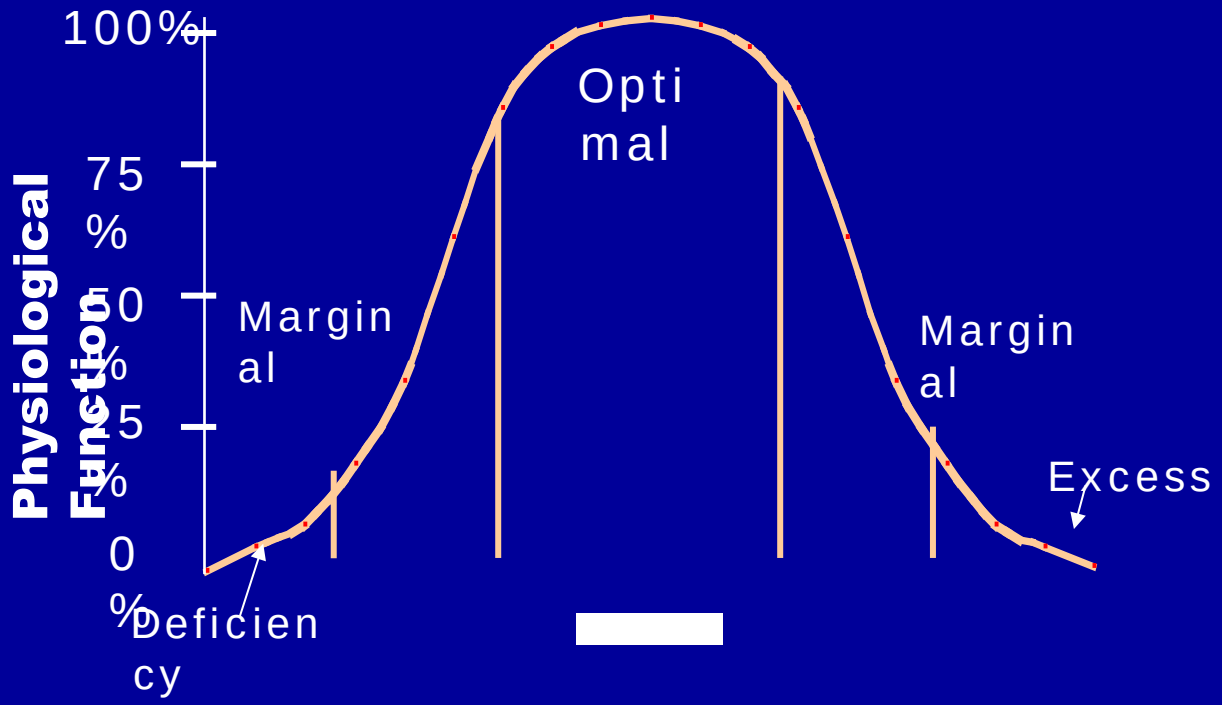
Role	Structure	Function
Enzymes/ Coenzymes	Zn, Fe, pyridoxal phosphate, NAD, FAD	vitamin C
Regulation of cell processes	polyunsaturated fatty acids, amino acids	Ca, Na, K,
Tissue synthesis/ repair	amino acids, Ca, P	Zn, vitamin C, Cu, Fe, vitamin D, Mg
Protection	vitamin E, amino acids	vitamin C, Se, Fe, polyunsaturated fatty acids
Energy	Fe, Cu, P, Mg	niacin, riboflavin, thiamin, glucose, fatty acids

Nutrient Requirements*



*as defined by the Food and Nutrition Board, National Academy of Sciences and the Institute of Medicine (1998)

Effects of Nutrient Intakes on Physiological Function

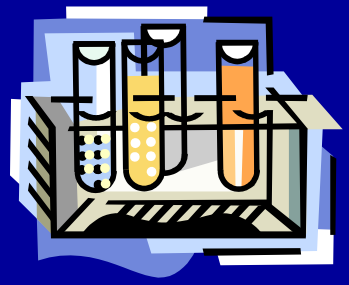


Adapted from: The Surgeon General's Report on Nutrition and Health, 1984.

Identification of Nutrient Deficiencies

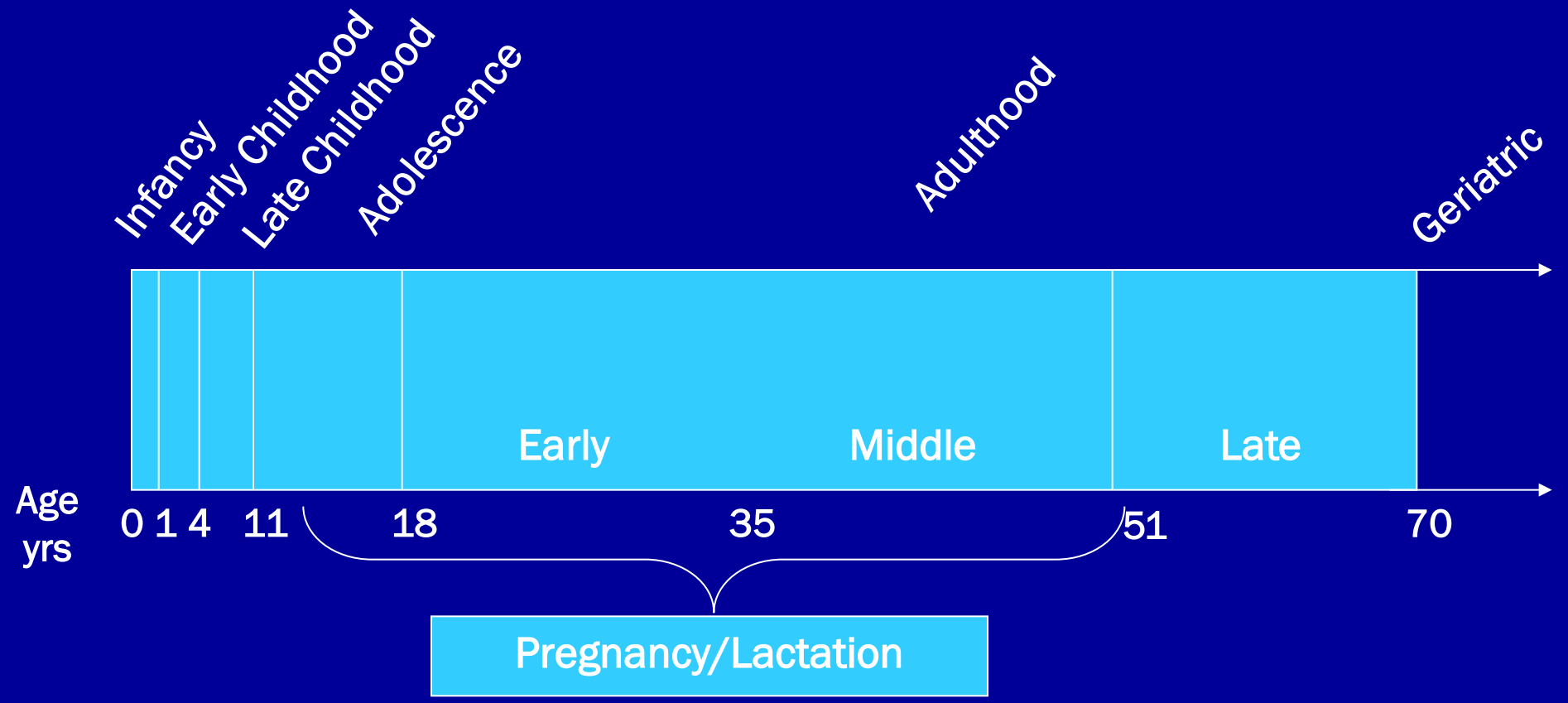
- ✓ Classic Symptoms
  - energy
  - protein
  - fluid
  - vitamin C
  - folate
  - B-complex
  - iron
  - vitamin A
  - vitamin D

- ✓ Biochemical Signs
  - copper
  - vitamin B_{12}
  - vitamin E
  - vitamin K
  - zinc



- ✓ No well-defined signs
  - selenium
  - magnesium
  - calcium

Age and Developmental Stages that Define Nutrient Requirements



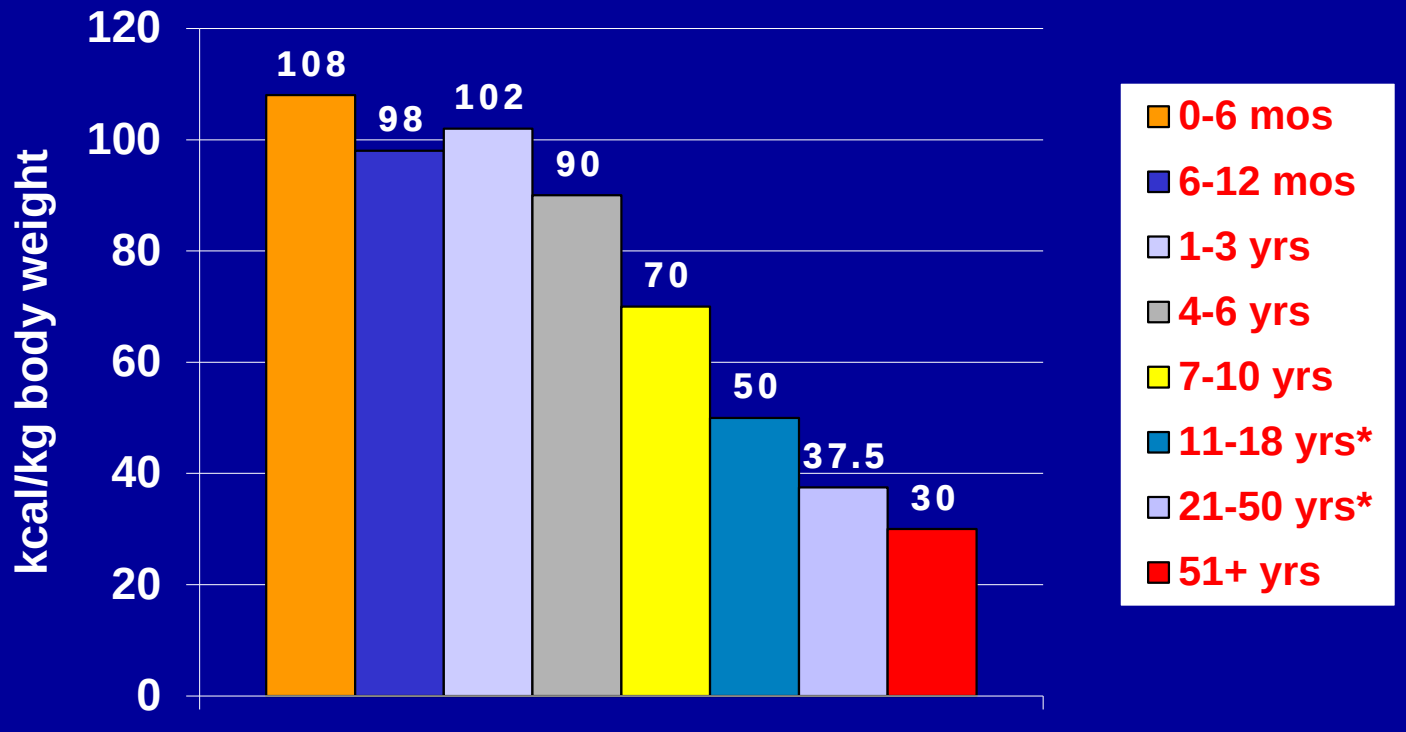
Nutrient Needs By Life Stage

Life Stage	Age (yrs)	Nutritional Considerations
Infancy	0-0.5 0.5-1	Term/Preterm Birth Age/Weight Growth
Early Childhood	1-3	Growth and Immunity
Late Childhood	4-10	Growth, Immunity, Activity
Adolescence	11-18	Gender Differences, Growth Spurt, Hormonal Changes
Adulthood	19-25; 26-51 51-70; 70+	Inactivity, Disease Risk Factors, Menopausal Status

Nutrient Needs By Life Stage

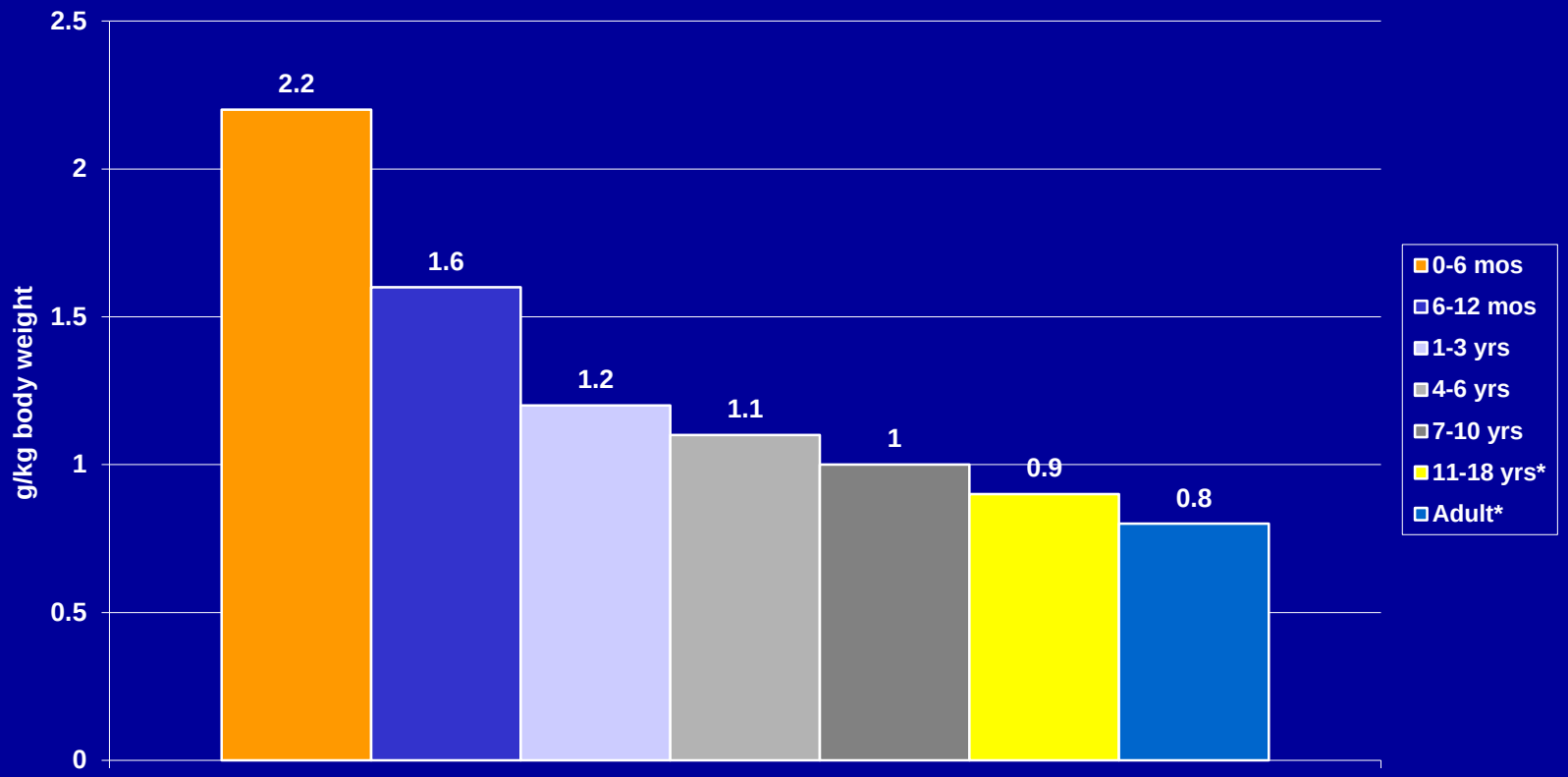
Life Stage	Time Frame	Nutritional Considerations
Pregnancy	2nd and 3rd trimester	Pre-pregnancy body weight and nutritional status; age; presence of disease
Lactation	1-6 months 6-12 months	Milk volume and nutrient composition

Energy Requirements By Age
Light to Moderate Activity



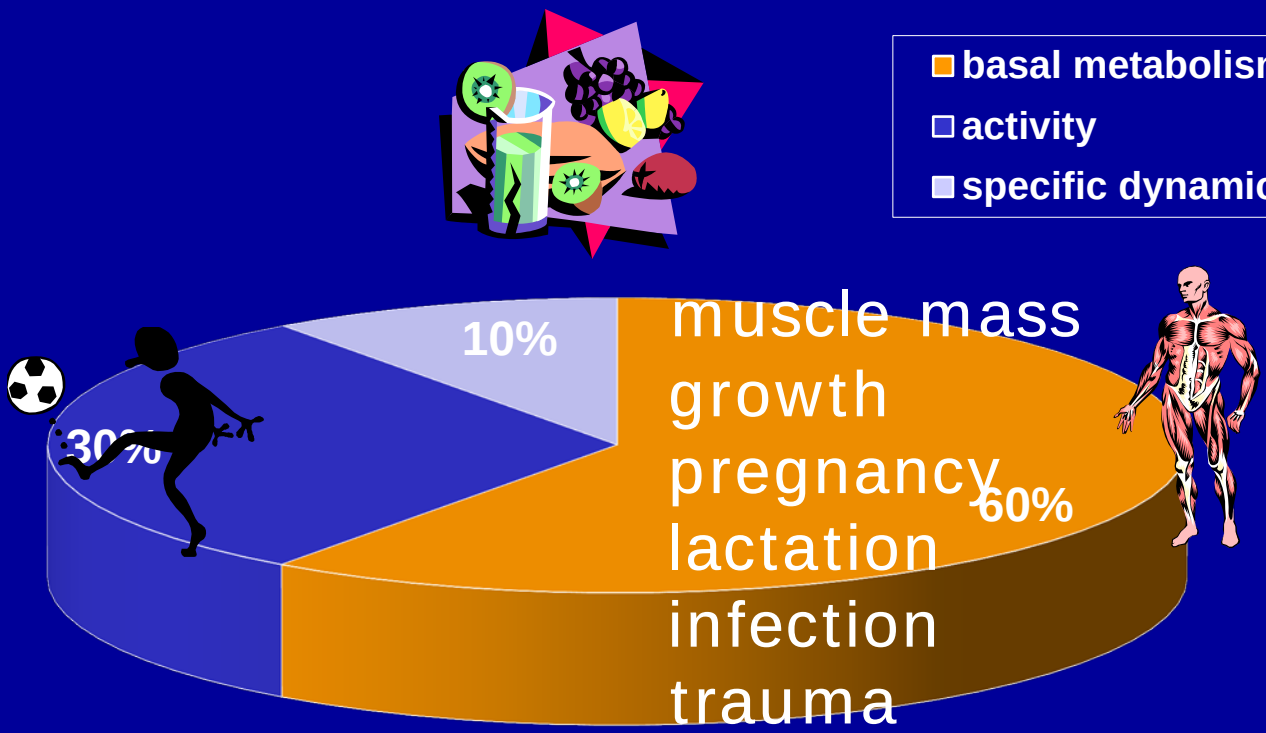
* Average for males and females

Protein Requirements by Age

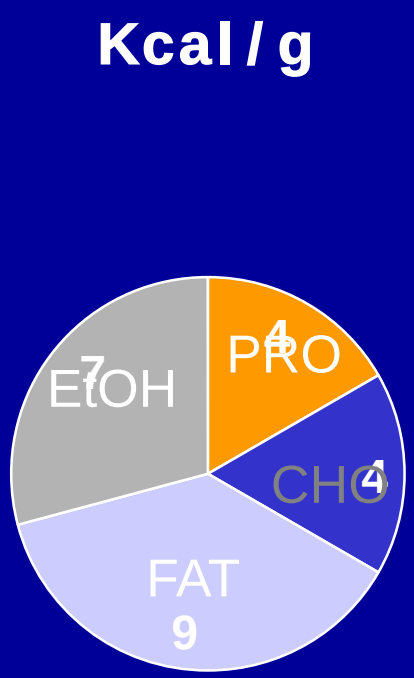


* Average for males and females

Contribution of Basal Metabolism to Total Energy Requirements

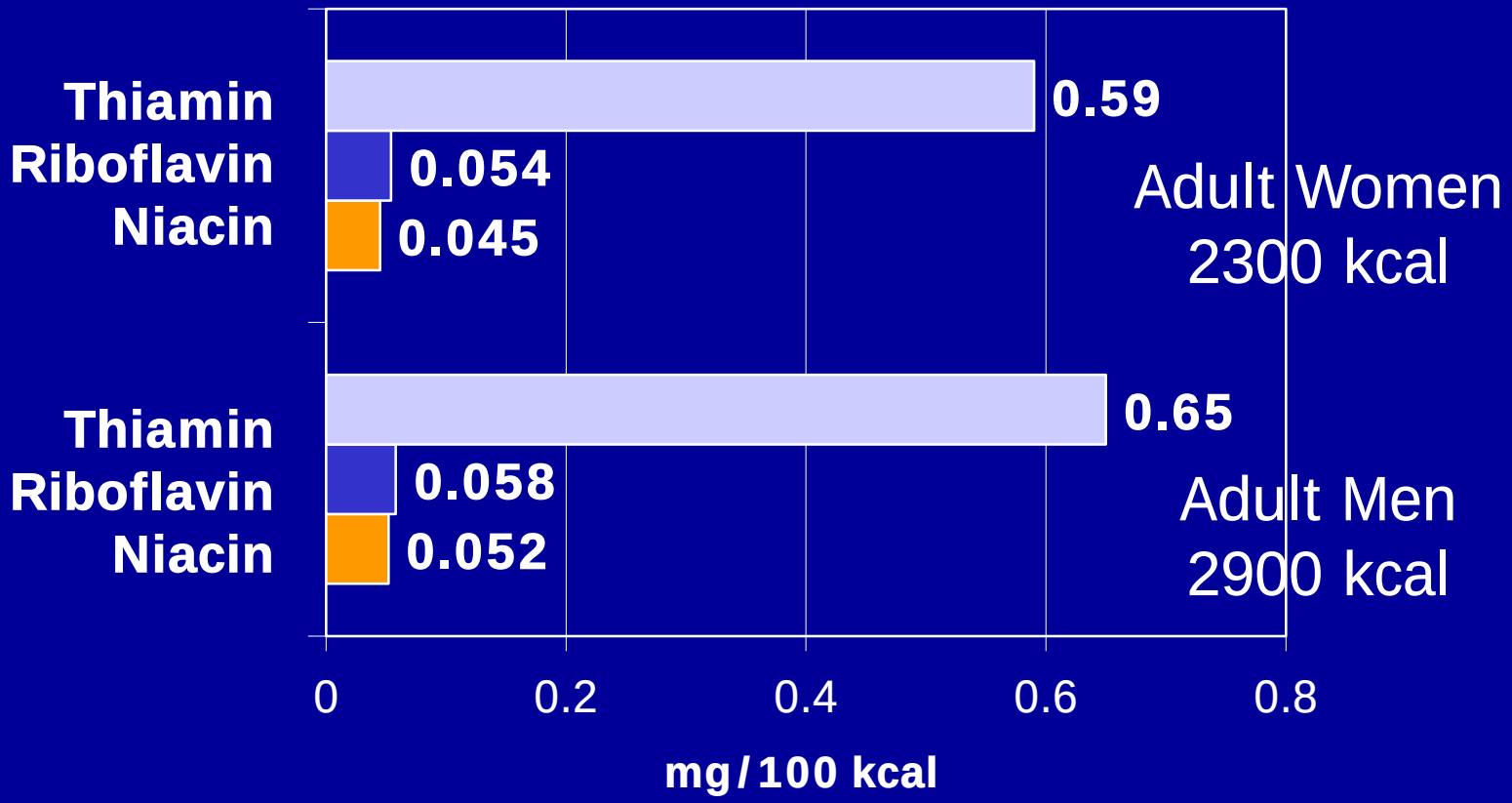


Sources of Metabolic Fuel

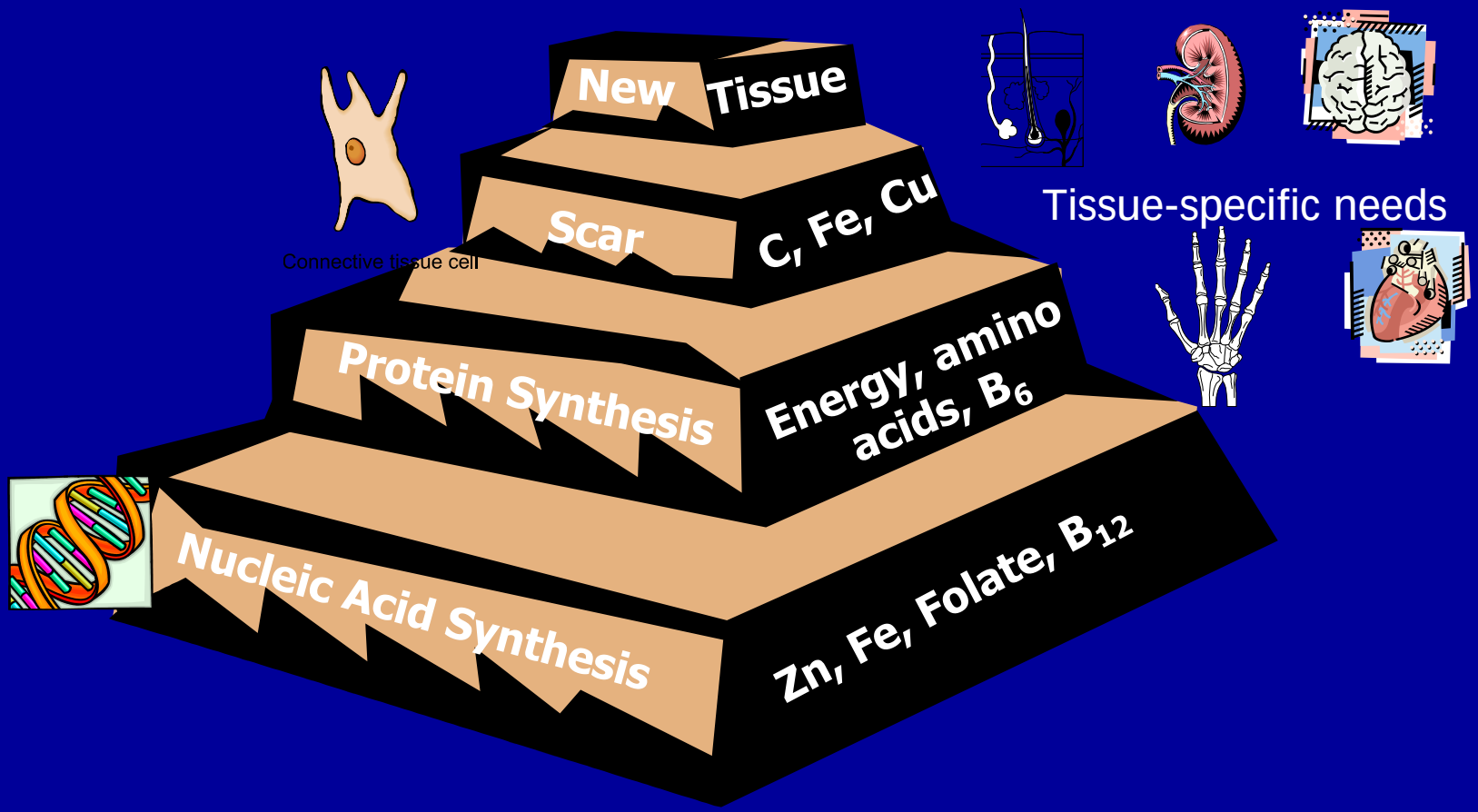


- Carbohydrate (Glucose)
  - Preferred fuel
  - Highest energy yield/mole
  - Supports fat oxidation
- Fatty acids (Fat)
  - High energy density
  - Storage fuel
- Alcohol (Acetate)
  - Metabolic fate same as fat
- Protein (Amino Acids)
  - Not efficiently utilized
  - Conserved for other roles

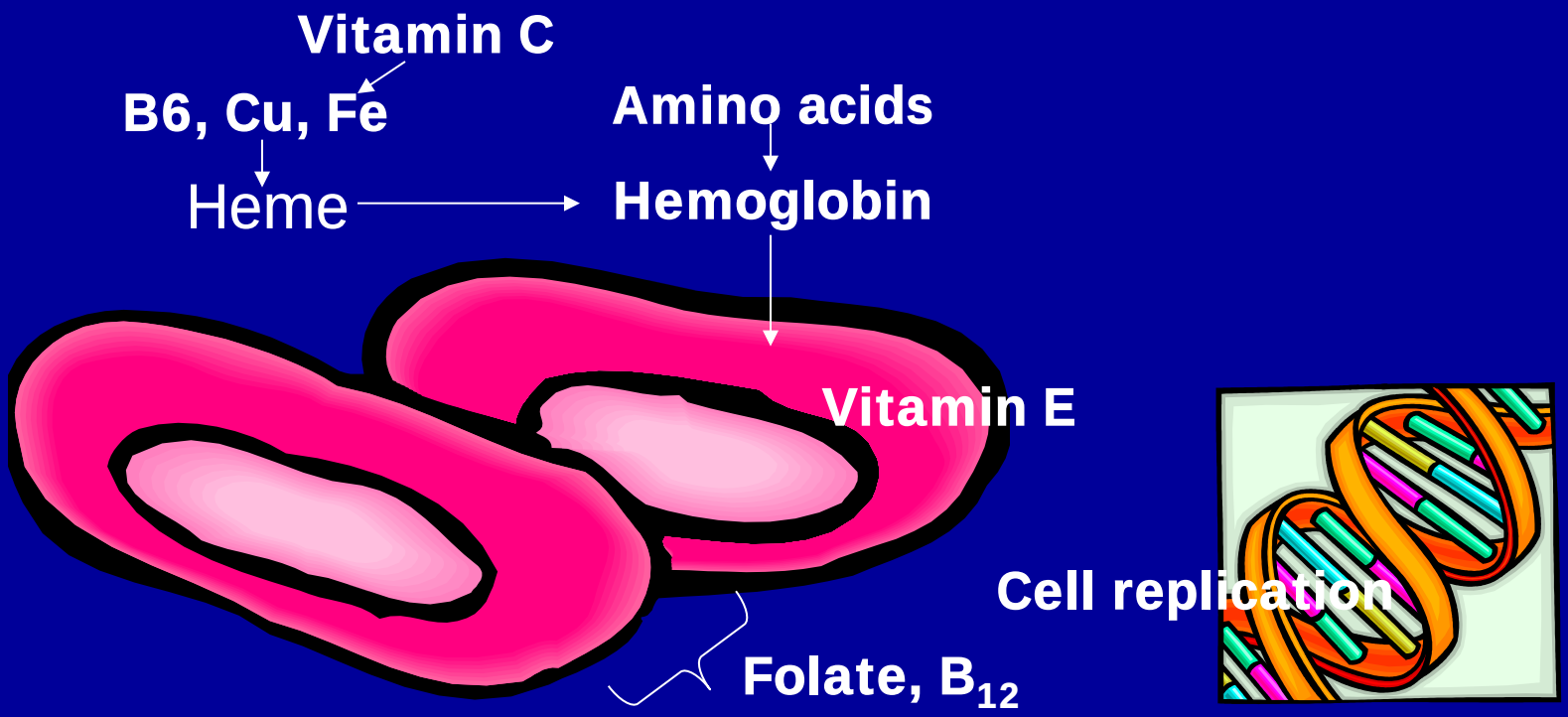
Vitamin Requirements as a Function of Energy Intake



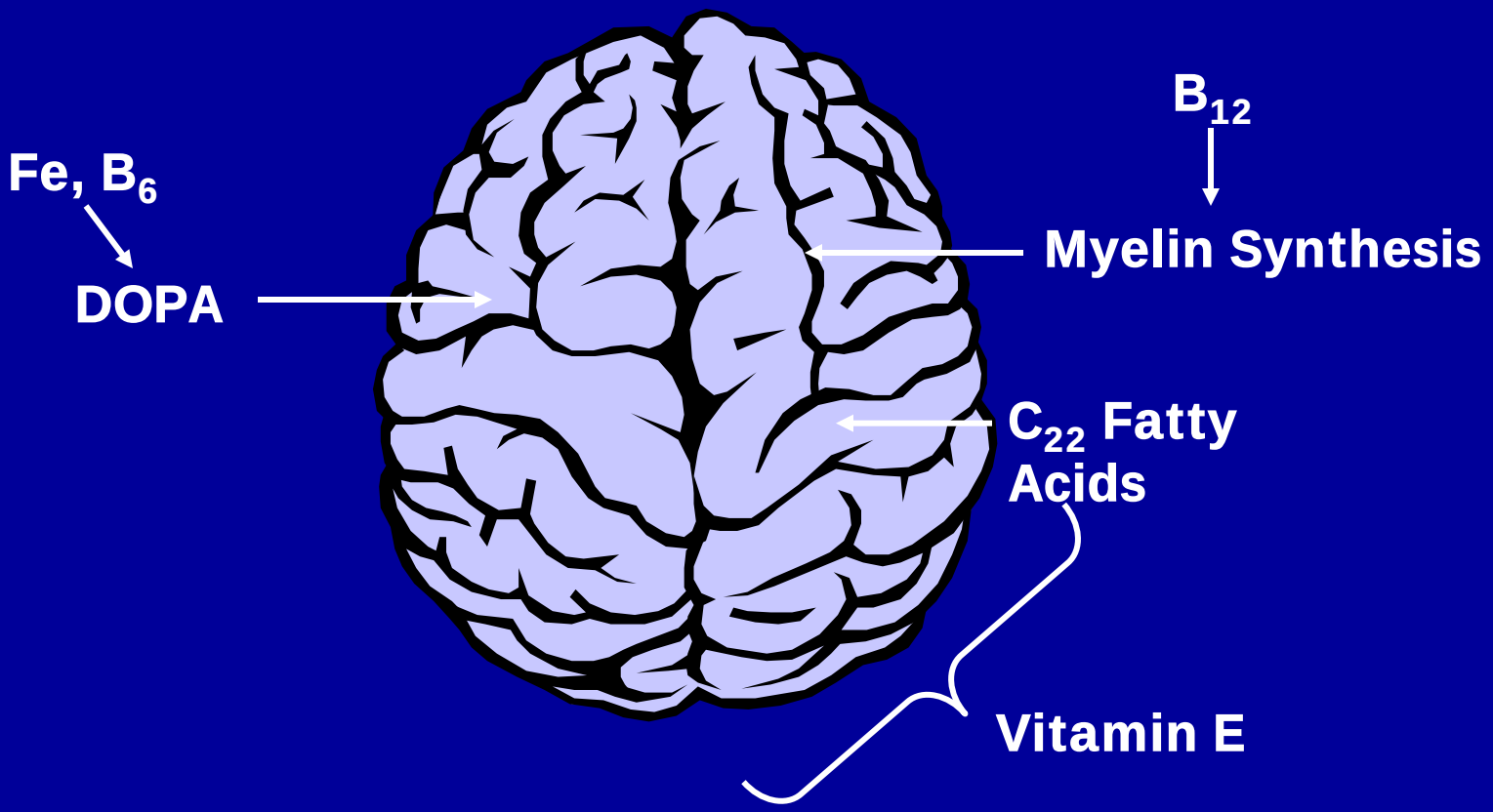
Tissue Synthesis: Growth, Replacement, Repair



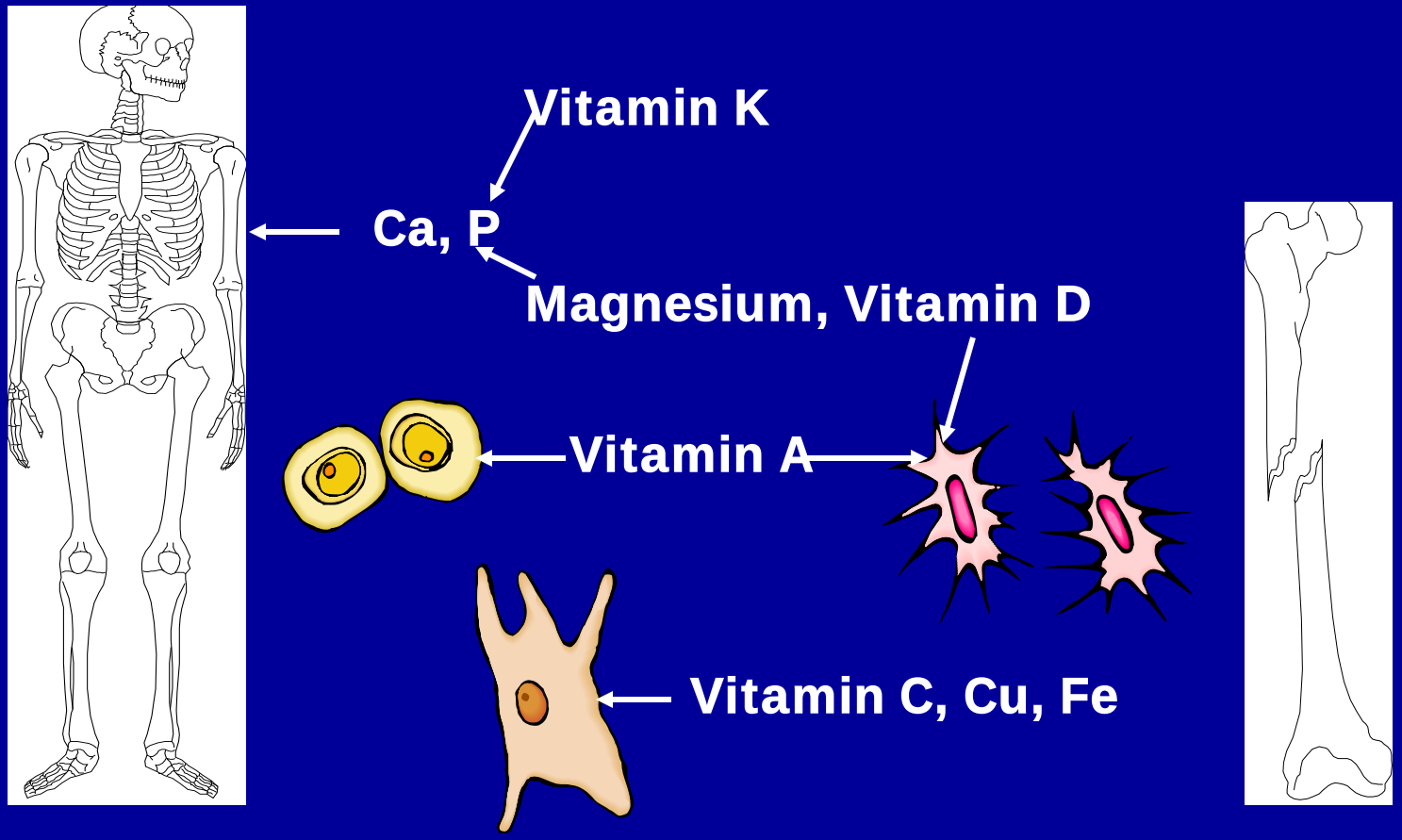
Erythropoiesis



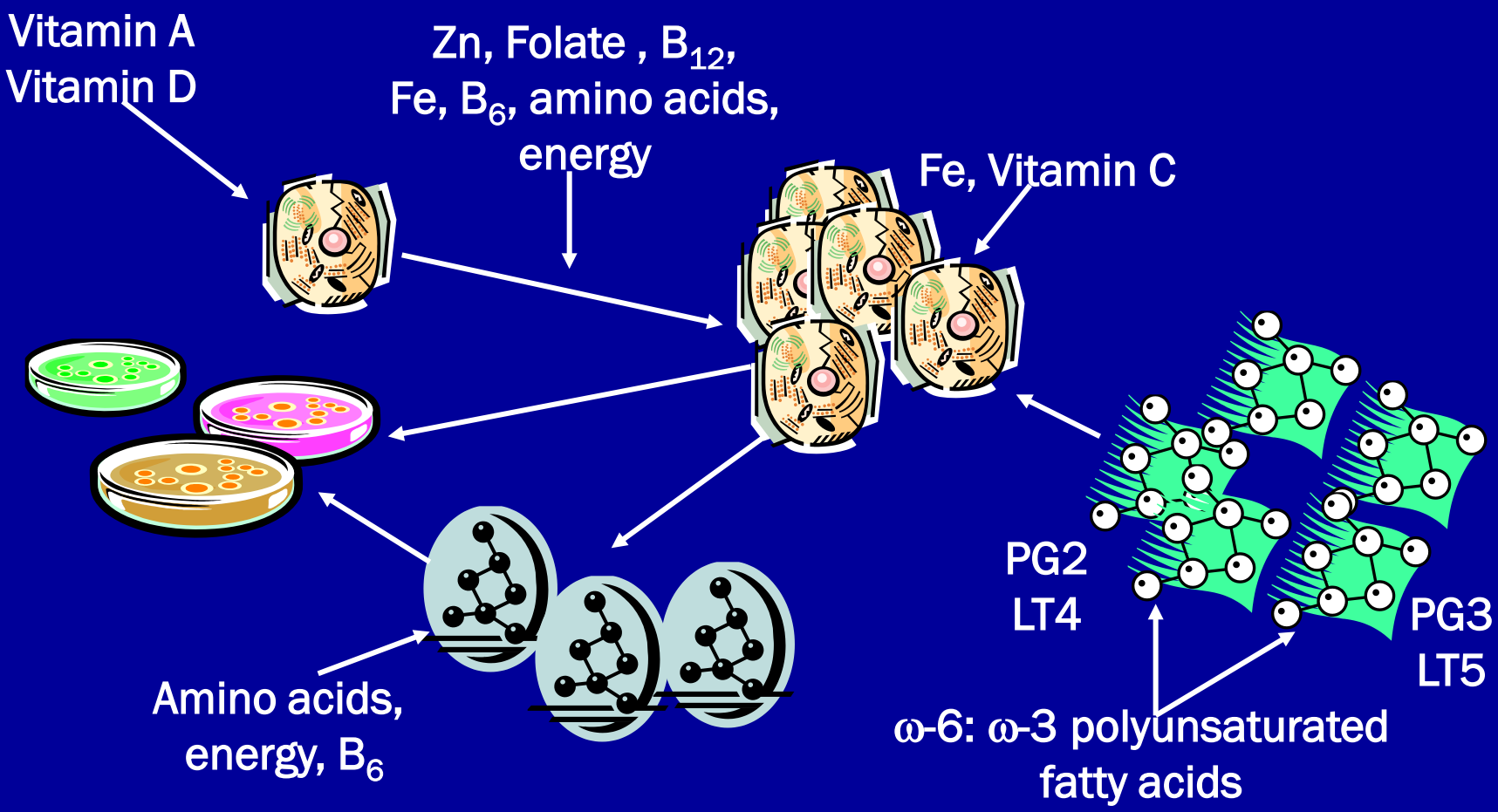
Cognitive Development and Neurological Function



Skeletal Development & Remodeling

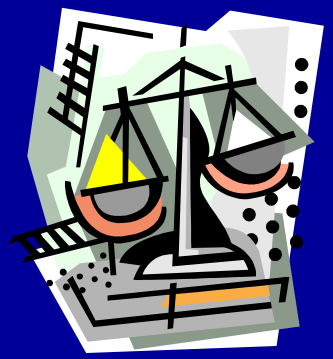


Immune Response



Importance of Balance in Nutrient Intakes

- Immunocompetence
  - protein
  - energy
  - vitamin B_6
  - vitamin A (D?)
  - folate
  - vitamin B_{12}
  - vitamin C
  - iron
  - zinc



- Immunosuppression
  - high fat (ω-6 or ω-3)
  - high iron
  - high zinc
  - high vitamin A
  - high vitamin E
  - obesity
  - weight loss >20% ideal body weight

Water Soluble Vitamins

- Excessive alcohol intake can lead to deficiencies in thiamin, niacin, vitamin B-6, vitamin B-12, folate, and vitamin C
- Thiamin → polyneuropathy
- Niacin → pellagra
- B-6 → sideroblastic anemia
- B-12 → Won't be absorbed
- Folate → megaloblastic anemia
- Vitamin C → scurvy

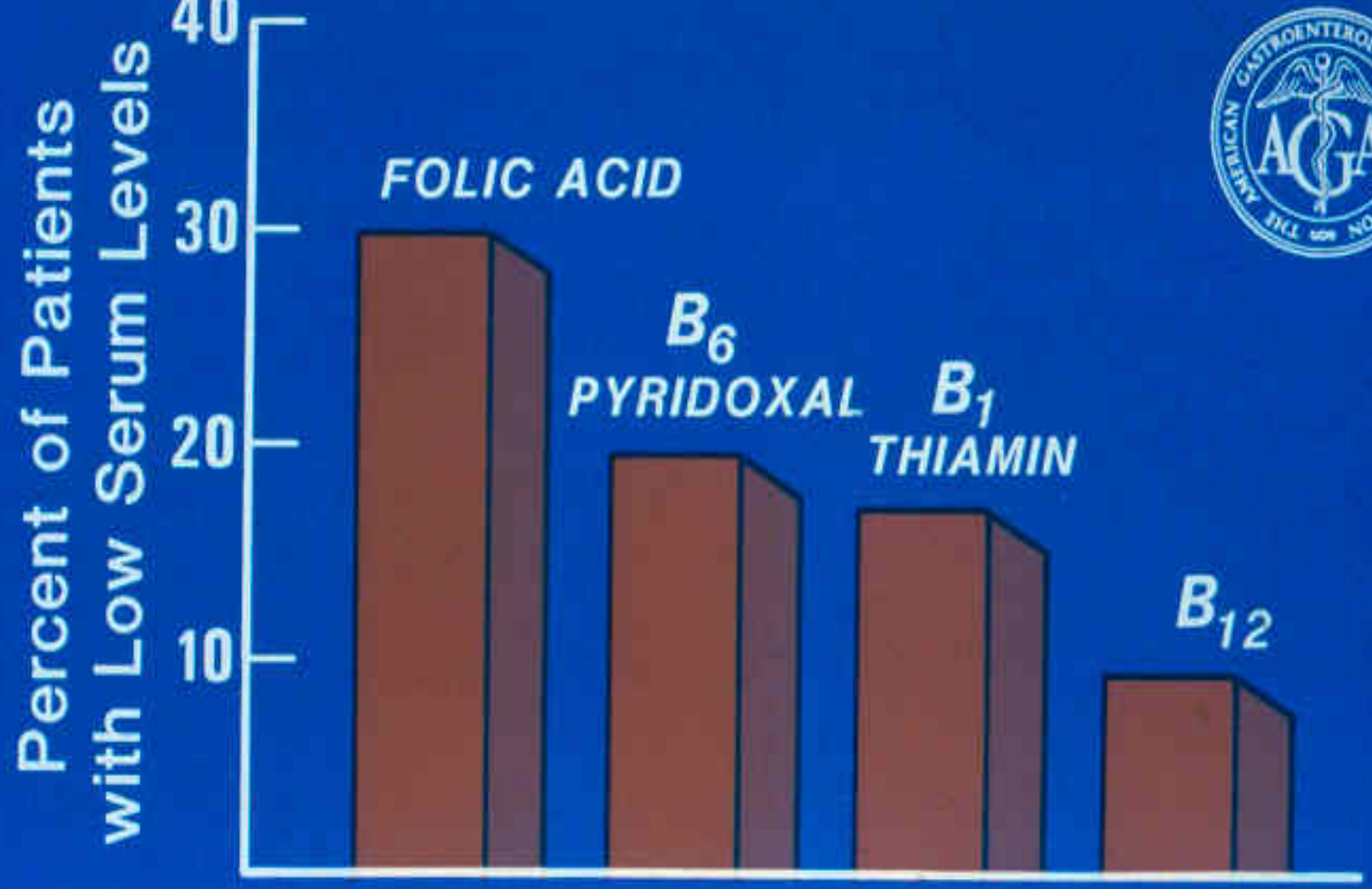
Fat Soluble Vitamins

- Excessive alcohol intake can result in deficiencies in vitamins A, D, E, and K.
- Vitamin A → trouble seeing in the dark
- Vitamin D → Osteoporosis
- Vitamin E → Peripheral neuropathy, tunnel vision
- Vitamin K → Less able to synthesize clotting factors

Minerals

- Individuals who abuse alcohol can also develop problems with magnesium, zinc, and iron metabolism
- Magnesium → Tetany
- Zinc → Changes in taste, smell, impaired wound healing
- Iron → deficiency or increased uptake that hastens development of cirrhosis

VITAMIN LEVEL CAN BE LOW IN ALCOHOL ABUSERS WITHOUT CLINICAL LIVER DISEASE



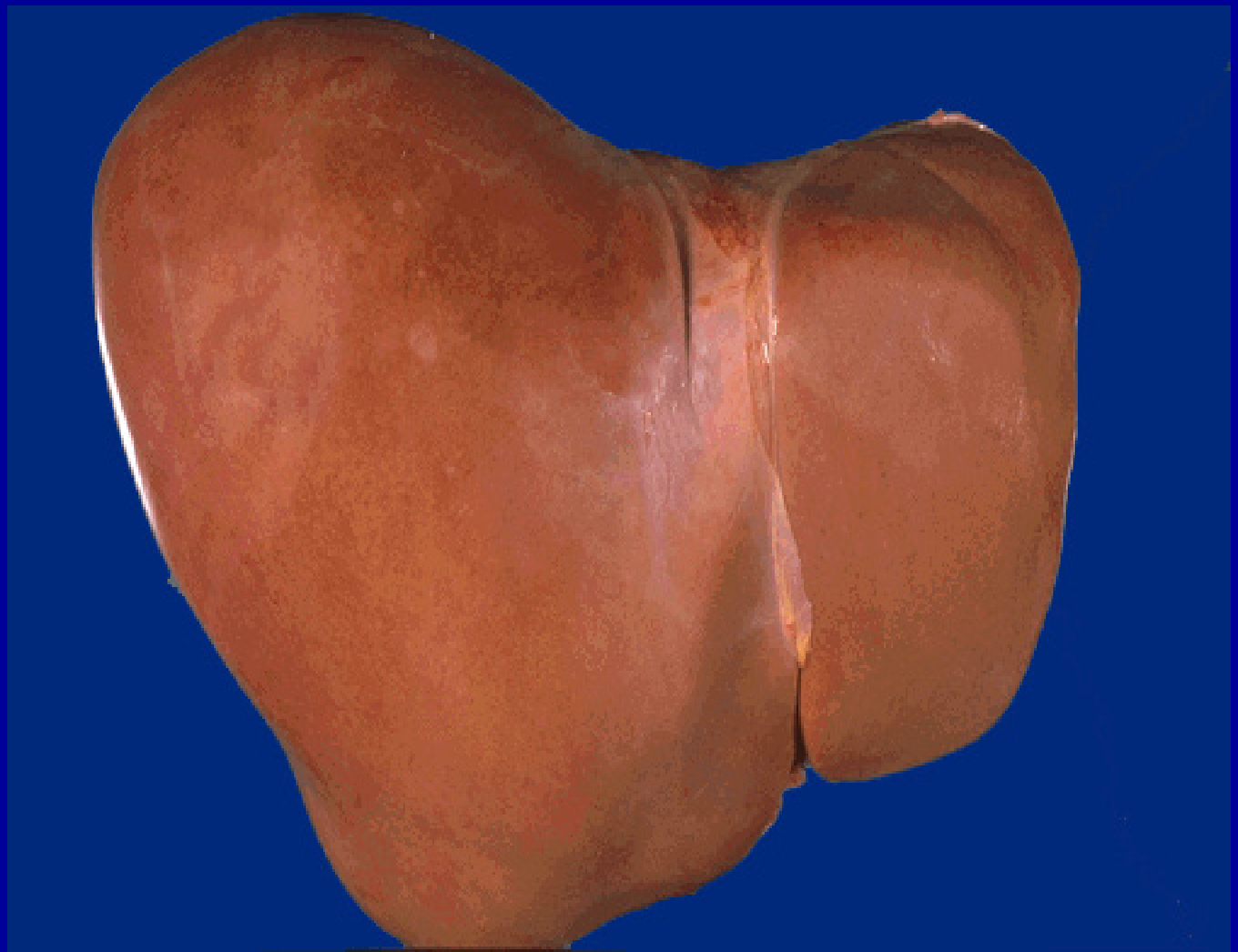
ALCOHOL ABUSE CAUSES CONDITIONED DEFICIENCIES

Zinc
Magnesium
Phosphate

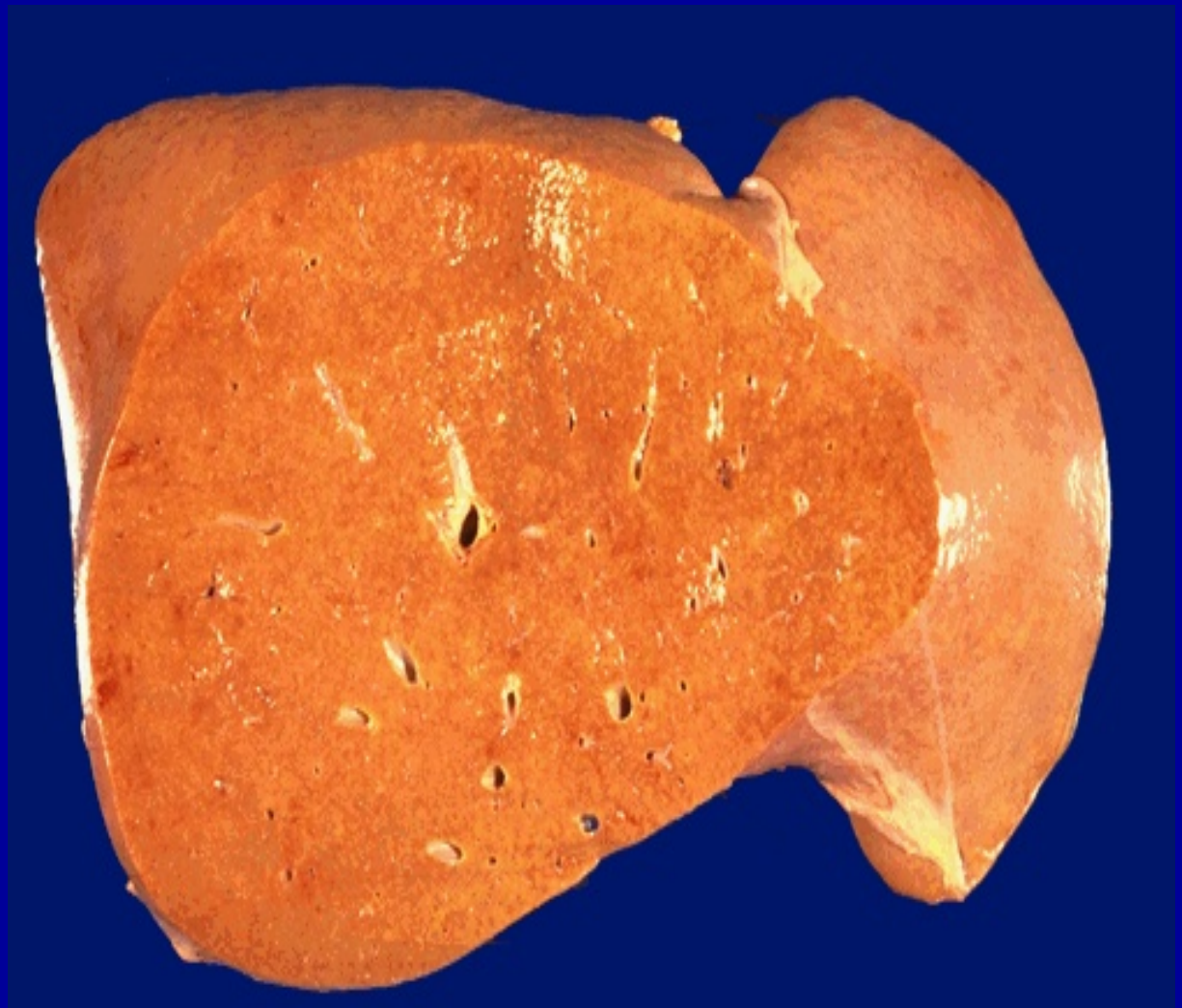
Vitamin A
Vitamin D
Riboflavin

Nicotinic acid

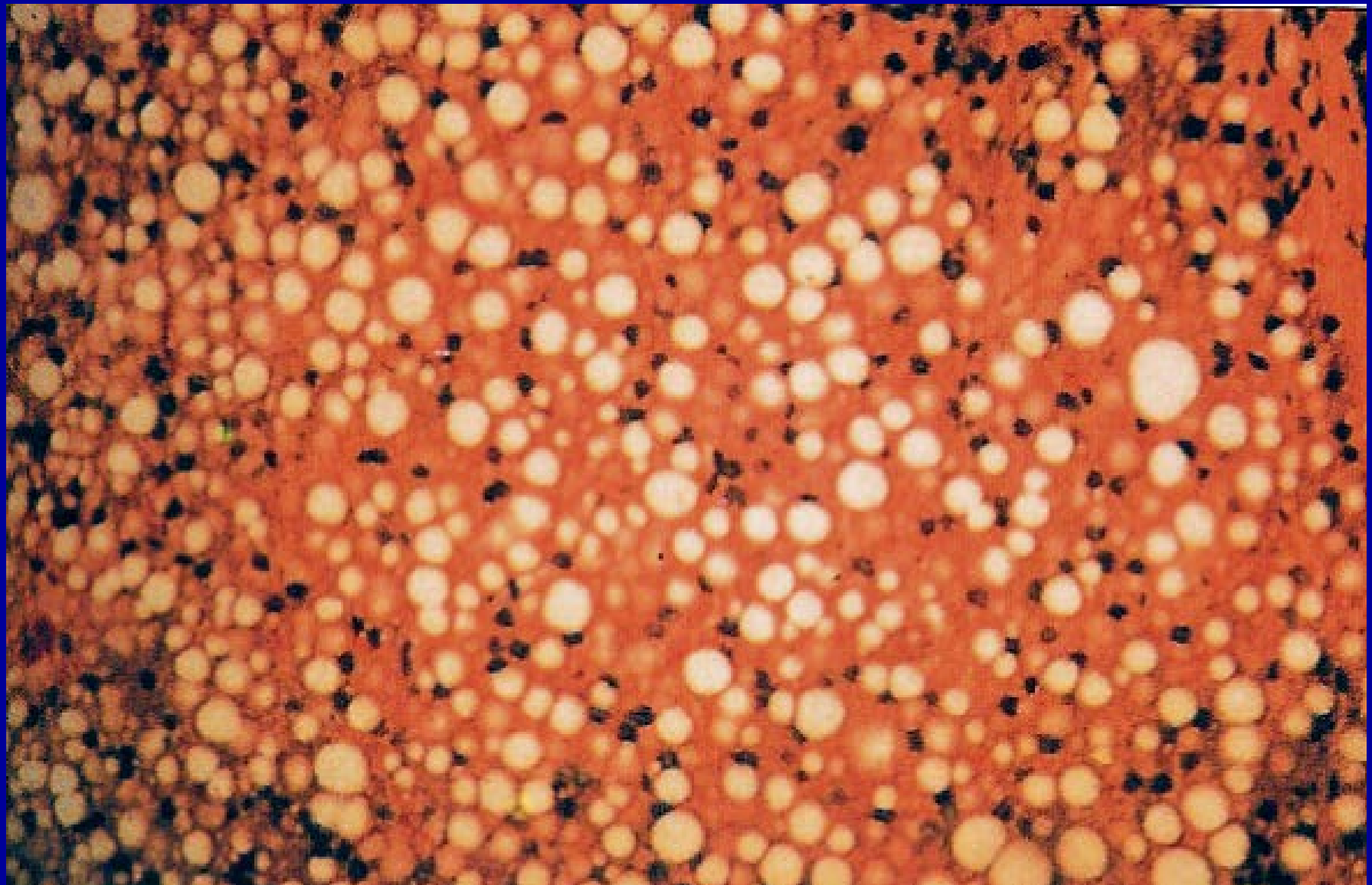
Normal Liver



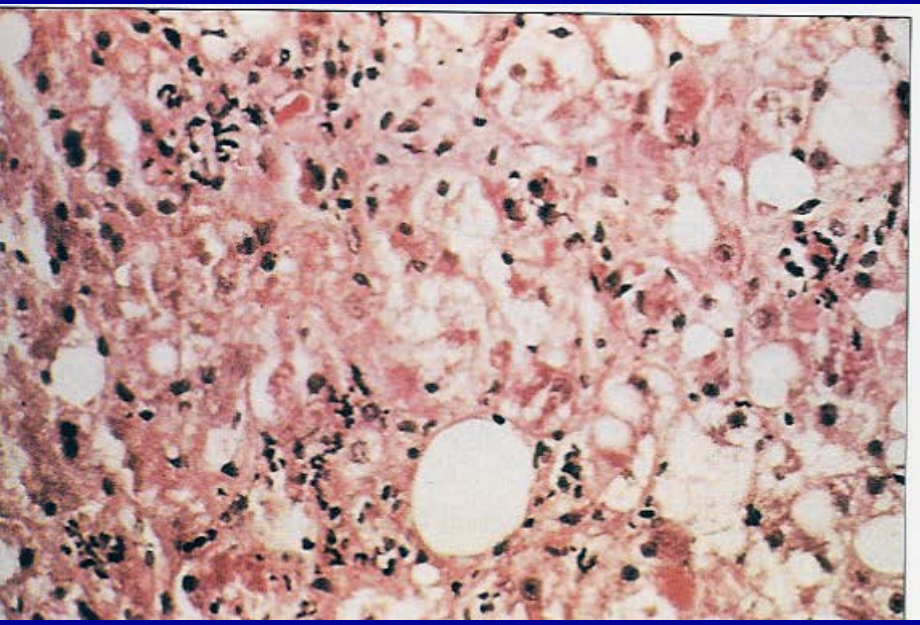
Fatty Liver

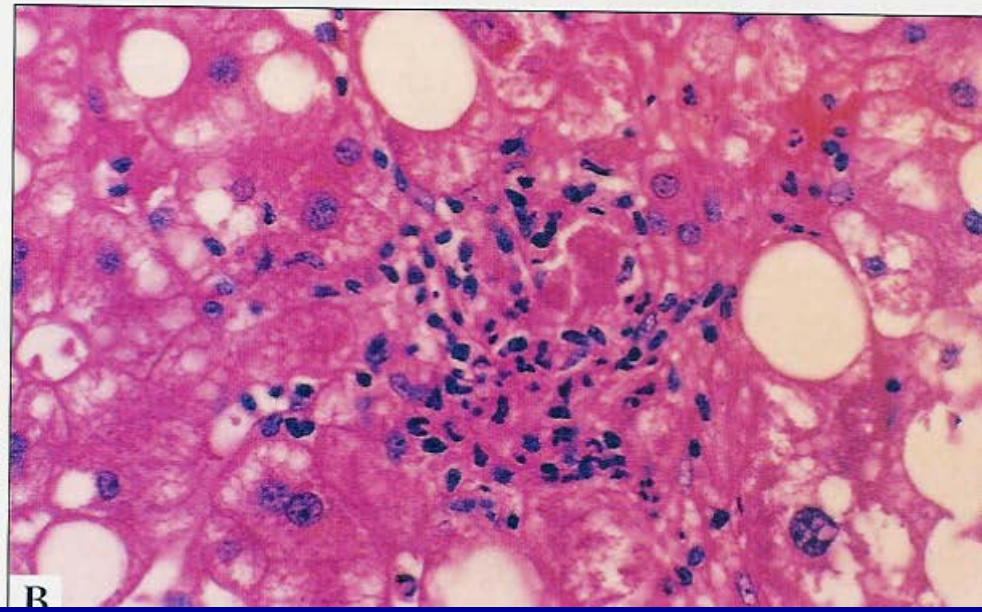


Alcoholic steatosis



Alcoholic Hepatitis with Mallory Hyaline





Cirrhosis of the liver

ALCOHOL: NUTRITION

- Ethanol contains 7.1 cal/g
- Vitamin deficiencies: folate, thiamine, pyridoxine
- Malabsorption and impaired hepatic metabolism
- Poor energy yield from fat oxidation

Harris-Benedict formula (BMR based on total body weight)

Men: BMR = 66 + (13.7 X wt in kg) + (5 X ht in cm) - (6.8 X age in years)

Women: BMR = 655 + (9.6 X wt in kg) + (1.8 X ht in cm) - (4.7 X age in years)

Activity Multiplier Sedentary = BMR X 1.2 (little or no exercise, desk job)

Lightly active = BMR X 1.375 (light exercise/sports 1-3 days/wk)

Mod. active = BMR X 1.55 (moderate exercise/sports 3-5 days/wk)

Very active = BMR X 1.725 (hard exercise/sports 6-7 days/wk)

Extr. active = BMR X 1.9 (hard daily exercise/sports & physical job or 2X day training, i.e marathon, contest etc.)

Diet

- Regular Diet supplemented with 1600 kcal/day and 60 g protein for 30 days
- Then 1200 kcal /day and 45 g/day for 60 days
- May be given per oral and or as enteral feed via feeding tube if ill
- Branched chain amino acids are no more helpful than standard amino acid preparations

Nutritional Status in Liver Disease

- Predictor of morbidity and mortality
- Worsens as Child-Pugh status advances
- 50-90% prevalence of malnutrition among cirrhotics
- Greater incidence of complications such as ascites, hepatorenal syndrome, hepatic encephalopathy, infections, compromised respiratory function
- Associated with longer hospital stays

Etiology of Malnutrition

- Anorexia, poor oral intake
- Hypercatabolic state
- Malabsorption
- Altered macronutrient metabolism

Anorexia

- Nausea, bloating, fatigue, vomiting
- Dysgeusia associated with zinc deficiency
- Mechanical compression from ascites
- Increased TNF-alpha
- Increased leptin
- Dietary restrictions- sodium, preoperative fasting, protein restriction in hepatic encephalopathy
- Poor and irregular feeding among alcoholics

Hypercatabolic State

- From concurrent infection, sympathetic overactivity, inflammatory phenotype of liver disease, neural dysregulation
- Harris Benedict Equation/ Resting Energy Expenditure (REE)

Male = 66.5 + (13.75 x weight in kg) + (5.003 x height in cm) - (6.775 x age)

Female = 655.1 + (9.563 x weight in kg) + (1.85 x height in cm) - (4.676 x age)

Stress Factor 1.1-2.0

- Hypermetabolism is a REE > 120% of predicted
- 15-30% of cirrhotics are hypermetabolic

Malabsorption

- Portosystemic shunting causes nutrients to bypass liver
- Chronic pancreatitis in alcoholics
- Intraluminal bile acid deficiency, impairing micelle formation
- Alternate route for fat absorption via portal vein bypasses lymphatics, resulting in excess hepatic fat storage

Altered Macronutrient Metabolism

- Reduced ability to synthesize, store and break down glycogen
- Increased gluconeogenesis from fats and protein
- Insulin resistance with higher fasting plasma insulin, further depleting hepatic glycogen reserves
- Increased plasma glucagon, increasing gluconeogenesis
- Increased protein catabolism

Altered Macronutrient Metabolism

- Increased cytokines activate proteolysis causing muscle cell breakdown
- Cytokines also increase oxidation of branched chain aromatic acids
- Using oxidative fuels increases lipid oxidation

Micronutrient Deficiencies

- Zinc
- Magnesium
- Vitamin A
- Vitamin D
- Vitamin B6 and folate in HCV
- Vitamins B1 and B2 in patients undergoing therapy with pegylated interferon and ribavirin

Nutrition Assessment

- Subjective Global Assessment
- Anthropometric measurements
- Bioelectric impedance analysis
- Handgrip strength test

Subjective Global Assessment

- Simple, cost-effective bedside tool
- Information on intake, weight change, GI symptoms
- Examination for subcutaneous fat loss, muscle wasting, edema, ascites
- May underestimate frequency and severity of malnutrition Not

Subjective Global Assessment

Name:
Date:

Medical History	A	B	C
WEIGHT Usual weight……. Current weight…… Not change past 6 months Amount weight loss…. % weight loss…… 0 <5% loss 5-10% loss >10% loss	•	▪	▪
Weight change past 2 weeks Amount…… No change; normal weight Increase to within 5% Increase (but still above) No change, but below usual wt Increase to within 5-10% Decrease		•	▪
DIETARY INTAKE No change: adequate	•	•	▪

Physical examination	A	B	C
SUBCUTANEOUS FAT…… Under the eyes Triceps Biceps	…… Slightly bulging area Large space between fingers Large space between fingers	…… ……	…… Hollowed look, depression, dark circles… Very little space between fingers, or fingers touch… Very little space between fingers, or fingers touch
MUSCLE WASTING… Temple Cave Shoulder Scapula/ribs Quadriceps Calf Ankle Interosseus muscle between thumb and forefinger OEDEMA (related to malnutrition)	…… Well-defined muscle/flat not done in males; may be visible but not prominent in females Rounded Bones not prominent; no significant depressions Well rounded; no depressions Well developed Bones not prominent …… Muscle protrudes, collapse) in females No sign	…… Slight depression Some depression; may not be all the way along No square look; acromion process may protrude Mild depressions or bone may show slightly; not all areas. Mild depression …… Mild to moderate	Following depression. Protruding/prominent bone Square look; bones prominent Bones prominent; significant depressions Depression; thin Thin; no muscle definition Bones prominent …… Flat or depressed area Severe
ASCITES (related to malnutrition)	No sign	Mild to moderate	Severe
OVERALL ASSESSMENT RATING	A	B	C

Adapted from: Detsky et al., 1994[8]; Baxter Healthcare Corporation, 1993; Mccann, 1995; Ferguson, Baker, Banks, Capra, 1996 ©

Posted: May 2009
Due for Review: November 2014

Tools for Assessing Oral Intake

- 24-hour recall- inaccurate with encephalopathy
- Food frequency questionnaire- no data on portion sizes
- Calorie count- subjective
- Food diary- time-consuming, assumes high level of literacy

Anthropometric Measures

Men lose 20% of total body protein, women lose 11%

- Women lose a greater proportion of fat
- Muscle wasting more evident in temporal, clavicular, scapular areas
- Weight- affected by ascites
- Body mass index- need dry weight
- Mid-arm circumference- not a strong predictor of malnutrition
- Waist circumference
- Triceps skin-fold thickness

Bioelectric Impedance Analysis

- Estimates total body water, body fat, fat-free mass
- Phase angle alpha- relative contribution of fluid (resistance) and cellular membranes (capacitance)
- Lower phase angles indicate cell death
- Inaccurate with ascites

Handgrip Strength Test

- Malnourished if grip strength < 2 SD from mean of age and sex
- Predictor of uncontrolled ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome
- Needs dynamometer

Other Measures of Nutritional Status

- Albumin and prealbumin/transthyretin reflect severity of underlying illness and inflammation rather than nutrition status
- 24-hour creatinine excretion

Other Measures of Nutritional Status

- Total body potassium count
- Dual-energy x-ray absorptiometry- expensive
- In-vivo neutron activation analysis
- Isotope dilution
- Air plethysmography
- Body cell mass- validation tool

Cochrane Review of Nutritional Support in Liver Disease 2012

- 37 trials from studies collected over 3 decades
- Trials had a high risk of bias and potentially overestimated benefits
- Most analyses showed no significant differences
- Medical patients had improvements in ascites, infection and encephalopathy on oral nutrition
- Medical patients had improved nitrogen balance on enteral nutrition
- Medical patients had reduced bilirubin on parenteral nutrition
- Surgical patients had reduced ascites

Caloric Requirements

- ASPEN: 25-35 kcal/kg/day without encephalopathy, 35 kcal/kg/day with acute encephalopathy
- ESPEN: 35-40 kcal/kg/day for all patients with stable cirrhosis
- ESPEN: oral supplements or overnight enteral feeds as needed
- Caloric requirements based on dry weight or on ideal body weight if with ascites
- Large amount of calories lost from large-volume paracentesis

Cheung et al. Clin Gastro Hepatol 2012; 10:120.

Protein Intake

High-protein diets well-tolerated by cirrhotics

- High-protein diets improve prognosis and mental status
- Protein restriction 0.5g/kg/day leads to increased protein catabolism
- Recommended protein intake 1-1.5g/kg/day
- Use dry weight or estimated dry weight
- Whole protein formulas generally recommended

Protein Intake and Hepatic Encephalopathy

- High protein diets well-tolerated by patients with moderate hepatic encephalopathy
- Temporary protein restriction in acute encephalopathy 0.6-0.8 g/kg/day until cause is eliminated
- ESPEN does not recommend even transient protein restriction

Carbohydrate Intake

- Carbohydrate restriction not recommended
- Carbohydrates should make up 45-65% of caloric intake
- Frequent meals and snacks reduce hypoglycemic episodes

Fat Intake

- 25-35% of calories from fat
- Medium-chain triglyceride supplementation only if abnormal 72-hour 100g fecal fat test

Fluid Balance

- Fluid intake 30-40mL/kg/day maintains fluid balance
- Dilutional hyponatremia develops due to decreased renal blood flow and greater free water accumulation
- Fluid restriction of 1.5L/day only if with ascites and hyponatremia <120mEq/L

Nutritional Supplementation

- In early cirrhosis normal food intake with nutritional counseling is adequate
- Vitamin A deficiency associated with increased risk of progression to hepatocellular carcinoma
- Association between vitamin D deficiency and Child-Pugh score
- Improved zinc levels associated with improvement in liver function

Nutritional Supplementation

- Vitamins A, D, E, and K, zinc and selenium supplementation for all cirrhotics
- If with chronic cholestasis, check serum levels of vitamin A and 25(OH)-D annually
- B12 levels falsely elevated due to inactive cobalamin analogues
- Alcoholics need folate and thiamine supplements
- Glutamine supplements metabolized to ammonia, avoid for now

Sodium Restriction

- Limit sodium to <2g/day if with edema and ascites
- More severe restriction will lead to poor compliance

Probiotics

- 25% of cirrhotics have small intestinal bacterial overgrowth
- Probiotics decrease intestinal pH, inhibiting growth of pathogenic bacteria
- Probiotics with fructo-oligosaccharides equal to lactulose for hepatic encephalopathy
- Generally safe and well-tolerated
- Strain and dose unknown

Branched-Chain Amino Acids

- Cirrhotics have lower concentrations of leucine, isoleucine, valine
- Cirrhotics have a low ratio of branched-chain amino acids (BCAAs) to aromatic amino acids (AAAs)
- AAAs increased due to impaired deamination
- BCAAs decreased due to use by skeletal muscle as an energy substrate
- Brain uptake of AAA tryptophan increased, causing neurotransmitter synthesis

BCAA Supplementation

- Reduces ammonia levels
- Inhibits muscle proteolysis
- Improves manifestations of recurrent hepatic encephalopathy
- Heterogeneity in clinical trials in mode of administration and methods of assessing hepatic encephalopathy
- Recommended by ESPEN because of increased albumin, and lower combined rates of decompensation and death
- Dose 0.25g/kg
- Long-term effects unlikely after stopping treatment

Nocturnal Supplements

- To decrease length of overnight fast
- To reduce gluconeogenesis and protein catabolism
- BCAA-rich snacks improve albumin

Feeding Methods

- 4-6 small meals per day
- If >10 hour fast, start IVF with 2-3g/kg/day glucose
- Nasoenteral tube if enable to meet energy goals orally
- If with gastroparesis advance tube beyond pylorus

Feeding Methods

- If hyponatremic use concentrated calorie dense feedings 1.5cal/mL
- Renal/low electrolyte formulas may be useful in hepatorenal syndrome
- Enteral nutrition may improve liver function, reduces complications and prolongs survival

Feeding Methods

- Parenteral feeding only if oral and enteral feedings are contraindicated or caloric intake is inadequate despite best efforts
- Proteins 1.2g/kg/day for compensated cirrhosis, 1.5g/kg/day for decompensated cirrhosis
- CHO 50-60%, lipids 40-50% of nonprotein energy requirements
- Lipid emulsions should provide 1g/kg/day or less of fat

Parenteral Nutrition

- Risk of catheter-related infections
- Parenteral feeding requires strict glucose monitoring
- Cyclic parenteral infusion if liver enzymes worsen with continuous infusion
- Do not overfeed

Obesity

- Obese cirrhotic patients are often protein depleted
- If BMI>25, gradual weight loss of 5-10% improves insulin sensitivity
- Weight loss achieved by creating deficit of 500-1000 calories/day
- Rapid weight loss with bariatric surgery or weight loss medications may cause decompensation
- Maintain intake during illness or hospitalization

Summary

- Malnutrition is common among cirrhotics
- Malnutrition is multifactorial
- Malnutrition has prognostic implications
- Bedside assessment tools can be useful
- Cirrhotics require more protein and calories
- Vitamin supplementation is a reasonable option
- Probiotics and BCAAs may be useful adjuncts
- More research is needed using hard endpoints in adequately powered studies

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Conclusion

- While nutritional deficiencies contribute to overall morbidity and mortality, nutritional support has conclusively shown to improve survival in Alc Hep with tube feeding
- Several promising therapies in combination with nutrition appears to be most promising

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