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NUTRITIONAL DISORDERS

Required Reading: ***Robbins Basic Pathology, 7th edition pp290-306***

An adequate diet should provide: (1) carbohydrate, fat and protein energy; (2) essential and non-essential amino acids and fatty acids; and, (3) vitamins and minerals. **Nutrients** are substances not synthesized by the body (must be supplied by the diet), which provide energy or building materials needed for the survival and growth of the organism. **Malnutrition** is the state in which the available nutrient supply is inadequate to meet the needs of the organism. **Primary malnutrition** results from a diet deficient in essential nutrients or calories, whereas, **secondary malnutrition** refers to malabsorption, impaired utilization or storage, excess losses, or increased needs of these nutrients.

Predisposing conditions for malnutrition include:

1. Poverty and ignorance (most common in the world)
2. Acute and chronic illnesses
3. Genetic diseases
4. Chronic alcoholism
5. Gastrointestinal disorders
6. Restricted diets (may be self-imposed)
7. Drug-induced malnutrition
8. Total parenteral nutrition (TPN)
9. Depression (particularly elders), dementia

Identifying predisposing conditions help us in the initial diagnosis or evaluation of a person with a nutritional disorder. We can also suspect a nutritional disorder if there is an unintentional weight loss of > 10% of the body weight, in the presence of gastrointestinal symptoms such as dysphagia, abdominal pain, vomiting or diarrhea, or through a physical examination that shows decreased subcutaneous tissue or muscle wasting.

A series of steps occur before the insufficient supply of a nutrient produces clinical manifestations: 1) Decrease in supply or increase in the needs of the organism. 2) Decreased tissue concentration of the nutrient or metabolites. 3) Deficiency in the biochemical process or processes that require the nutrient. 4) Establishment of a “biochemical lesion” accompanied by functional changes. 5) Development of anatomical changes. The clinical and pathologic features associated with these disorders are usually a late manifestation of the disease. As a general rule, the morbidity and mortality of a nutritional disorder is greater in children because of their increased nutritional demands.

I. PROTEIN-ENERGY MALNUTRITION (PEM)

PEM includes marasmus, kwashiorkor, cachexia, and less severe forms and overlapping combinations. Up to 25% of children in third world countries may be affected with PEM, where it is a major factor of high mortality of those younger than 5 years. The **somatic** (i.e. skeletal muscle) and the **visceral** (i.e. liver) proteins are two functional components regulated and affected differently in marasmus and kwashiorkor. The diagnosis of severe PEM is obvious, in less severe cases you can determine body weight in relation to height, measure skin folds or midarm circumference, and measure serum protein levels. Vitamin deficiencies and secondary infections are frequently associated with PEM, these infections add to the insult by increasing catabolism.

A. Kwashiorkor: Term first used by Williams (JAMA 1953; 153: 1280-1285) referring to the name given to the disease by the Accra people. The word may mean red Kwashi. Kwashi is the name for a boy born on a Sunday. It is not clear if the redness refers to raw areas where the skin has peeled, or to the color of the hair. This is a more severe form of PEM than marasmus, with severe loss involving visceral protein compartment.

1. Etiology: results from a diet deficient in protein even though total calorie intake is adequate.

2. Children are usually affected.
   a. Hospital acquired (Kwashiorkor-like syndrome)

3. Findings:
   a. Growth failure (may be masked by edema)
   b. Peripheral edema
   c. Apathy
   d. Moon-face
   e. Enlarged fatty liver (hepatomegaly due to reduced synthesis of carrier proteins)
   f. Low serum albumin
   g. Skin changes "flaky paint"-areas of skin depigmentation or hyperpigmentation
   h. Hair loss and depigmented zones “flag sign"
   i. Muscle atrophy
   j. Subcutaneous fat present
   k. Anemia (iron and protein deficiency)
   l. Small bowel mucosa atrophy (disaccharidase deficiency)
   m. Predisposition to infection (T-cell immunity particularly affected)

B. Marasmus: Children are usually affected. A child with expected weight < 80% of normal is considered malnourished, if this falls to < 60% the child has marasmus.

1. Etiology: A form of protein-energy malnutrition with body wasting, resulting from prolonged and severe caloric deficit.

2. Findings:
   a. Stunted growth
   b. Loss of subcutaneous fat and muscle atrophy (adaptation response to provide energy)-emaciated arms and legs
   c. Pinched, wizened facies
   d. Mentally alert and hungry
   e. No hepatomegaly and no edema (normal levels or only marginal depletion of visceral proteins)
   f. Predisposition to infections (T-cell immunity particularly affected)

Marasmus and kwashiorkor refer to extremes of a disease spectrum. Many intermediate forms exist. A number of factors (i.e. trauma, infection, injury) can increase protein demand causing a marasmic state to evolve into kwashiorkor, or can worsen an existing kwashiorkor state. Timely treatment with adequate diet, control of infection, and a reasonable lifestyle usually permit "catch-up" growth and restoration of physical and intellectual health.

Secondary PEM (marasmus-like or kwashiorkor-like) is not uncommon in chronically ill or hospitalised patients. The marasmus-like form evolves over a span of months in the setting of chronic illness with weight loss, muscle wasting and loss of subcutaneous fat. The kwashiorkor-like syndrome occurs over weeks, in a more acute setting of catabolic illness such as severe trauma, burns or sepsis; on physical examination there is edema, but we do not observe muscle wasting or loss of subcutaneous fat. These two syndromes underscore the differences between the metabolic responses to PEM due to starvation (energy derived from body stores), or acute stress (loss of visceral proteins such as albumin to provide amino acids for gluconeogenesis). When unchecked, the accelerated protein catabolism of severe acute illness can deplete 50% of body proteins within 3 weeks.

C. Anorexia Nervosa and Bulimia

1. Etiology: Anorexia nervosa is a self-induced starvation resulting in marked weight loss; bulimia is characterized by food-binging, followed by induced vomiting

2. Usually seen in previously healthy women who become obsessed with thinness.

3. Findings:

anorexia nervosa

a. severe PEM	b. bradycardia
c. cold intolerance (decreased thyroid hormone release)	d. dry, scaly yellow skin
e. constipation	f. decreased bone density (osteopenia)
g. fine lanugo hair	h. arrythmia/sudden death (hypokalemia)
i. Anemia, lymphopenia	j. Amenorrhea (due to decreased secretion of GnRH)

bulimia

a. hypokalemia	b. pulmonary aspiration
	c. esophageal and cardiac rupture

D. Cachexia: A state of weight loss and decreased appetite, seen frequently in patients with advanced cancer. Tumor-derived and host-derived factors alter metabolism and establish a vicious circle in which protein catabolism, glucose intolerance and lypolisis cannot be reversed by the provision of calories.

1. A form of secondary PEM with loss of fat and muscle mass
2. Unlike anorexia, calorie expenditure is high and basal metabolic rate is increased
3. May be potentiated by tumor-produced cytokines such as TNF- , IL-1 and IL-6

II. PATHOLOGY DUE TO VITAMIN FLUXES

Vitamins are a group of chemically unrelated compounds required for normal metabolic functioning. They are required nutrients that are inadequately synthesized or not synthesized by the human diet and need to be provided as part of a normal diet. Diseases may follow vitamin deficiencies or excesses. Vitamins are either fat-soluble (A, D, E, K) or water-soluble (C and B complex). Fat-soluble vitamins may be poorly absorbed in gastrointestinal disorders characterized by fat malabsorption.

Similar to PEM, vitamin deficiencies may be primary or secondary. Deficiencies of a single vitamin are uncommon. Overt dietary vitamin deficiencies are uncommon in the more economically advantaged western countries unless the person is ill or alcoholic; subclinical deficiencies diagnosed by laboratory testing are common in the normal population, particularly in the geriatric group.

Vitamin body stores vary greatly. Vitamin B 12 and vitamin A stores may not be depleted for 1 or more years following a deficient diet; folate and thiamine stores may become depleted within weeks following a deficient diet. Deficiencies are not only dietary in origin; hemodialysis is a therapeutic modality that removes water-soluble vitamins.

TABLE 10-21. VITAMINS: MAJOR FUNCTIONS AND DEFICIENCY SYNDROMES

Nutrient	Function	Deficiency Syndromes
Fat-Soluble Vitamins		
Vitamin A	Visual protein; hormonal regulation of cell growth	Night blindness, xerophthalmia, keratomalacia, metaplasia of columnar epithelium, immune deficiency
Vitamin D	Facilitates Ca and PO_4 absorption from intestine; helps maintain plasma Ca and PO_4 levels	Rickets in children, osteomalacia in adults, hypocalcemic tetany
Vitamin E	Antioxidant; maintenance of nervous system	Spinocerebellar syndrome
Vitamin K	Cofactor for hepatic carboxylation of prothrombin; factors VII, IX, and X; protein C and S	Bleeding diathesis
Water Soluble Vitamins		
Thiamine (B1)	As thiamine pyrophosphate functions as a coenzyme essential for maintaining nervous system	Wet and dry beriberi; Wernicke-Korsakoff syndrome
Riboflavin (B2)	Cofactor in several enzymes, including FMN and FAD	Ariboflavinosis: cheilosis, glossitis, dermatitis, keratitis
Niacin	Component of coenzymes NAD and NADP	Pellagra: dementia, diarrhea, dermatitis (3 D's)
Pyridoxine (B6)	Forms pyridoxal-5-phosphate, a coenzyme in many reactions	Cheilosis, glossitis, dermatitis, peripheral neuropathy
Pantothenic acid	Component of coenzyme A and acyl carrier protein	Recognized only under experimental conditions: constitutional and gastrointestinal symptoms, paresthesias, cramps, impaired coordination
Biotin	Cofactor in several carboxylation reactions	Deficiencies extremely rare: lassitude, anorexia, dermatitis, atrophic glossitis, myalgia, ECG changes, hypothermia, mild anemia
Folate	Coenzyme in transfer and utilization of 1-carbon units; essential step in nucleic acid synthesis	Megaloblastic anemia
Cyanocobalamin (B12)	Role in utilization of folate in nucleic acid synthesis, also essential for maintenance of nervous system	Megaloblastic anemia, subacute combined degeneration
Vitamin C	Cofactor in hydroxylation and amidation reactions	Scurvy

From Kumar, V., Cotran, R., and Robbins, S. Basic Pathology (W.B. Saunders) 6th edition, pg 440, 1999

A. Vitamin A (Retinol)

1. Occurrence of deficiency states:
    a. A global problem, in the Third World due to general undernutrition.
    b. In developed countries among economically deprived and as a conditioned deficiency, e.g. secondary to malabsorption of fat.
2. Biological functions:
    a. Maintaining normal vision in reduced light, 11-cis-retinal and opsin forms rhodopsin, the photosensitive pigment of rod cells.
    b. Potentiates the differentiation of specialized epithelial cells, mainly mucus-secreting cells.
3. Dietary sources: Available in animal-derived foods e.g. eggs, butter, whole milk, and fish livers as retinyl esters or as the provitamin carotenoids in plants.
4. Pathology of well-established deficiency states:
    a. Nyctalopia - night blindness
    b. Epithelial metaplasia

1) Xerophthalmia - Bitot's spots (conjunctival keratinization)
2) Keratomalacia (corneal softening and ulceration)
3) Corneal scarring and blindness
4) Squamous metaplasia of respiratory and GI/GU tracts

c. Impaired immune response with increased mortality from infections (in children.

5. Toxicity: Brain pseudotumor and increased incidence of congenital malformations.

B. Vitamin D

1. Etiology of deficiency states (rickets and osteomalacia):
   a. In developing countries due to a combination of dark skin, inadequate exposure to sunlight and primary malnutrition.
   b. In industrialized countries in infancy and childhood from nonuse of fortified foods (Vitamin D-milk), lack of sunlight, poverty and in elderly due to restricted or bizarre diets.
   c. Malabsorption of fats, e.g. cholestatic liver disease.
   d. Deranged metabolism of vitamin D, diffuse liver disease, chronic renal failure, drugs, e.g. phenobarbital, vitamin D dependent rickets type 1 (a genetic disease).
2. Biological functions:
   a. Maintenance of normal plasma levels of calcium and phosphorous-involves action on the intestine, bones, and kidneys.
   b. Vitamin D is activated through hydroxylation in the liver first then in the kidney by a process controlled by parathyroid hormone (PTH). The activated vitamin D ($1,25(OH)_2D$) increases the serum calcium levels by facilitating the absorption of calcium in the small intestines and kidneys and by mobilizing calcium from the bones.
3. Sources:
   a. Vitamin D is synthesized in the skin by the UV irradiation (from sunlight) of 7-dehydrocholesterol, may provide 80% of the body's needs.
   b. Deep-sea fish, ergosterol in plants and grains, fortified foods e.g. milk.

Table 10-22, CAUSES OF RICKETS OR OSTEOMALACIA

Decreased Endogenous Synthesis of Vitamin D
Inadequate exposure to sunlight
Heavy melanin pigmentation of skin (blacks)
Decreased Absorption of Fat-Soluble Vitamin D in the Intestine
Dietary lack
Biliary tract, pancreatic, or intestinal dysfunction
Enhanced Degradation of Vitamin D and 25(OH)-D
Phenytoin, phenobarbital, rifampin induction of cytochrome P-450 enzymes
Impaired Synthesis of 25(OH)-D
Diffuse liver diseases
Decreased Synthesis of $1,25(OH)_2$-D
Advanced renal disease with failure
Vitamin D-dependent rickets type I (inherited deficiency of renal $alpha_1$-hydroxylase)
Target Organ Resistance to $1,25(OH)_2$-D
Vitamin D dependant rickets type II (congenital lack of or defective receptors for active metabolite)
Phosphate Depletion
Poor absorption-long-term use of antacids, which bind phosphates and render them insoluble
Renal tubular disorders, acquired or genetic, causing increased excretion

From Kumar, V., Cotran, R., and Robbins, S. Basic Pathology (W.B. Saunders) 6th edition, pg444, 1999

4. Pathology of deficiency states:
    a. Rickets in children, osteomalacia in adults and hypocalcemic tetany.
    b. Basic derangement in rickets and osteomalacia is delayed and/or inadequate mineralization and an excess of unmineralized matrix (osteoid).
    c. Rickets
        1) Clinical appearances
            a) Craniotabes
            b) Frontal bossing
            c) Rachitic rosary
            d) Pigeon-breast deformity
            e) Bowing of weight-bearing bones
        2) Pathologic findings
            a) Failure of bony osteoid to mineralize
            b) Excessive proliferation of osteoid
            c) Failure of cartilage calcification
            d) Failure of cartilage maturation
            e) Disorderly osteochondral junction
    d. Osteomalacia
        1) Clinically, fractures of vertebrae, hips, wrists and ribs and deformity of vertebral column.
        2) Pathology, osteopenia "too little bone", inadequate mineralization, excess osteoid.
5. Toxicity: Soft tissue calcifications.

C. Vitamin E (alpha-tocopherol)

1. Occurrence of deficiency states:
    a. Uncommon in the Western world.
    b. Associated with disorders affecting its absorption and transport.
    c. Some premature and low birth weight infants.

2. Biological functions: one of a group of antioxidants, scavenges free-radicals (like selenium).

3. Sources: Abundant in many foods, vegetables, grains, nuts, dairy, fish and meat - a diet which sustains life is unlikely to be insufficient in vitamin E.

4. Pathology of deficiency states:
    a. Deficiency may cause edema and hemolytic anemia in premature infants.
    b. Secondary deficiency states in children result in a spinocerebellar degeneration and regressive changes "dying back" in sensory neurons; clinically appears as ataxia of gait, depressed or absent deep tendon reflexes, loss of position and vibratory sense and pain sensation.
5. Toxicity: Depresses vitamin K procoagulant levels.

D. Vitamin K (see also lectures on Hemostasis and Thrombosis)

1. Occurrence of deficiency state:
    a. Newborn-lack of intestinal colonization.
    b. Malabsorption syndrome, principally biliary tract disease.
    c. Patients on coumarin anticoagulant.
    d. Diffuse liver disease.

2. Biological functions: Vitamin K is a required cofactor for a hepatic carboxylase which modifies blood clotting factors II, VII, IX, and X. (necessary for normal functioning of the vitamin K-dependent clotting factors).

3. Sources:
    a. Vitamin K is synthesized by the intestinal flora (an inadequate source).
    b. A wide variety of plants, vegetables, and vegetable oils.

4. Pathology of deficiency states:
    a. Hemorrhagic disease of the newborn with intracranial bleeding, bleeding from the umbilicus, ecchymoses, hematomas, and hematuria.
    b. In the adult, ecchymoses, gingival bleeding, hematomas, hematuria, and melena.
5. Toxicity: Hemolytic anemia in infants.

E. Vitamin C (L-ascorbic acid)

1. Occurrence of deficiency state:
    a. The elderly, alcoholics, and others with erratic and inadequate eating pattern.
    b. Patients undergoing dialysis.
    c. Infants maintained on formulas of processed milk without supplementation.

2. Biological Function:
    a. Accelerates hydroxylation reactions (post-translational hydroxylation of proline in the formation of collagen, ground substance, osteoid and dentine.
    b. Enhances absorption of iron in the diet.

3. Sources: Variety of fruits and vegetables (most mammals, not including man, can synthesize vitamin C).

4. Pathology of deficiency state: Scurvy (more dramatic in children than in adults) symptoms reflect impaired formation of mature connective tissue.
    a. Hemorrhages - one of the most striking features, due to inadequate support of the walls of capillaries and venules.
        1) Purpura and ecchymoses in the skin along backs of lower legs and in the gingival margin.
        2) Subperiosteal hematomas
        3) Bleeding into the joint spaces
        4) Intracranial bleeding may be fatal
    b. Skeletal changes in infant and child, deficient production of osteoid with normal calcification (opposite of rickets), cartilaginous overgrowth, disorganized epiphyseal plate.
        1) Bowing of long bones of the lower legs
        2) Scorbutic rosary - abnormal depression of sternum with outward projection of ends of ribs
        3) Teeth are loose and may fall out
    c. Gingival swelling, hemorrhages and secondary infection
    d. Petechial hemorrhages
    e. Delayed wound healing
    f. Anemia, bleeding and deranged iron metabolism

F. Thiamine, B1

1. Occurrence of deficiency states:
    a. Underdeveloped countries-individuals on a diet of polished rice (Southeast Asia)
    b. Maltreated POWS
    c. Developed countries-common in chronic alcoholics
    d. Pernicious vomiting during pregnancy
    e. Long-term unsupplemented parenteral nutrition
    f. Debilitating illnesses (with vomiting and diarrhea)

2. Biological function: Thiamine undergoes phosphorylation to thiamine pyrophosphate, the later serves as a coenzyme in:
    a. Oxidative decarboxylation of alpha-ketoacids leading to ATP synthesis.
    b. Transketolase reaction in pentose phosphate pathway.
    c. Maintains neural membranes and normal nerve conduction.

3. Sources: Widely available in the diet, but refined foods e.g. polished rice, white flour, and white sugar contain very little.

4. Pathology of deficiency state: Deficiency of thiamine damages peripheral nerves ("dry" beriberi), the heart ("wet beriberi") and the CNS (Wernicke-Korsakoff syndrome).
    a. Heart - may be markedly enlarged and globular (owing to four-chamber dilatation) with pale, flabby myocardium.
    b. Peripheral nerves - myelin degeneration which may progress to disruption of axons.
    c. CNS - hemorrhagic necrosis in brain

    d. Clinical findings:
        1) Anesthesia
        2) Paresthesia
        3) Muscular weakness (inability to stand up; Beriberi is the Singhalese term for "I cannot")
        4) Myalgia
        5) Muscular atrophy
        6) Edema
        7) Wernicke's syndrome - confusion, ataxia, ophthalmoplegia
        8) Korsakoff's psychosis - confabulation, memory loss
        9) Severely malnourished infants with thiamine deficiency may develop sudden cardiovascular failure, or convulsions and vomiting which may suggest meningitis.

G. Riboflavin (B2)

1. Occurrence of deficiency state:
    a. Economically deprived and developing countries.
    b. In industrialized nations in alcoholics, individuals with chronic infections, advanced cancer, or other debilitating diseases.

2. Biological function: A component of the coenzymes FMN (flavin mononucleotide) and FAD (flavin adenine dinucleotide) involved in many redox reactions.

3. Sources: Meat, dairy products, and vegetables

4. Pathology of deficiency state: Ariboflavinosis -
    a. Cheilosis - cracks and fissures at angles of mouth
    b. Glossitis - red-blue tongue due to atrophy of mucosa
    c. Ocular lesion - interstitial keratitis
    d. Dermatitis - nasolabial folds, scrotal and vulvar lesions
    e. Bone marrow - erythroid hypoplasia and anemia

H. Niacin (vitamin B 3)

1. Occurrence of deficiency state:
    a. Bantus of S. Africa, in Egypt and maize-eating population of India.
    b. In industrialized countries in alcoholics and those with chronic debilitating illnesses.

2. Biological function: a component of NAD and NADP having a central role in cellular intermediary metabolism.

3. Sources:
    a. Grains, legumes, and seed oils.
    b. In corn the niacin is bound and not absorbable.
    c. Niacin can be synthesized endogenously from tryptophan. The drug isoniazid inhibits the conversion of tryptophan to niacin.

4. Pathology of deficiency state: Pellagra-pelle (skin) plus agra (rough). The three D's:
    a. Dermatitis - areas of exposure to chronic irritation or sunlight, (also red, swollen tongue).
    b. Diarrhea
    c. Dementia - degeneration of neurons

I. Pyridoxine (B6)
1. Occurrence of deficiency state:
    a. In infants fed badly controlled dried milk preparations.
    b. Pregnant and lactating women
    c. Hyperthyroidism
    d. Chronic alcoholism

2. Biological function: Active form, pyridoxal 5-phosphate is a cofactor for a large number of enzymes in transaminations, carboxylations, and deaminations in the metabolism of lipids and amino acids, and in the immune response.

3. Sources: Present in all foods but processing may destroy the pyridoxine.

4. Pathology of deficiency state:
    a. Convulsive seizures, anemia and diarrhea in infants
    b. Seborrheic dermatitis, cheilosis, glossitis, peripheral neuropathy and convulsions.
5. Toxicity: Peripheral neuropathies with chronic use at large doses.

J. Folic acid (Folate)(See also Hematology lectures)
1. Occurrence of deficiency state:
    a. alcoholism
    b. anticonvulsants
    c. hemodialysis

2. Biological function: Involved in the transfer of one-carbon units in the synthesis of certain nucleotides and amino acids

3. Sources: Green vegetables, e.g. lettuce, spinach, asparagus and broccoli. Cooking destroys up to 95% of the folate in food.

4. Pathology of deficiency state: megaloblastic anemia: ineffective erythropoiesis, the production of abnormal erythrocytes prone to hemolysis, macrocytic erythrocytes.

K. Vitamin B12 (Cobalamin)(See also Hematology lectures)

1. Occurrence of deficiency state:
   a. Atrophic gastritis (inadequate synthesis of intrinsic factor)
   b. Tapeworms
   c. Malabsorption syndromes
   d. Bowel surgery

2. Biological function:
   a. Conversion of homocysteine to methionine, a reaction involved in folate metabolism
   b. Isomerization of methylmalonyl coenzyme A to succinyl coenzyme A, interruption could lead to deranged neuronal lipid metabolism and myelin breakdown.

3. Sources: Animal products, microorganisms are the ultimate origin of cobalamin (plants and vegetables contain very little).

4. Pathology of deficiency state:
   a. Megaloblastic anemia
   b. Neurologic damage (Pernicious anemia)
   c. Female infertility

III. MINERAL DEFICIENCIES

A. Iron Deficiency (See also hematology lectures)

1. Component of hemoglobin and a number of iron containing metalloenzymes

2. Clinical and pathologic findings include weakness, anemia, pallor and oilonychia in children.

B. Zinc Deficiency

1. Component of enzymes principally oxidases

2. Clinical and pathologic findings include delayed wound healing, growth retardation, poor development of genitalia (infertility), loss of body hair, skin rash (acrodermatitis enteropathica), anorexia and diarrhea.

IV. OBESITY

Obesity is a state of increased body weight, due to adipose tissue accumulation of sufficient magnitude to produce adverse health effects. Medically significant “fatness” varies among individuals and, to some extent, ethnic groups (i.e. obesity confers a greater risk of type 2 diabetes mellitus to Hispanics, African-Americans and Asians than to Caucasians). Body fat has a

permissive effect on reproduction and somatic weight. Weight regulation systems evolved in circumstances of limited or restricted access to calories and high levels of physical activity needed to acquire them. These systems are not designed to protect us against obesity; but to maximize energy storage, invoke food seeking and reduce energy expenditure if energy stores are regarded as insufficient.

A. In U.S. 25% of people over 20 are clinically obese, 50% between 20-75 years are overweight.

B. Measuring fat accumulation

1. Body Mass Index (BMI=weight in kilograms/height in meters^2).
2. Skinfold measurement
3. Body circumference ratios (i.e. waist to hip circumference)

C. Etiology: Complex (genetic, environmental and psychological factors), and incompletely understood. Obesity is ultimately a disorder of energy balance involving intake and expenditure; very small but long-term imbalances can have cumulative effects. The 20 pound weight increase typical of an average American adult between 25 and 55 years of age represent a 0.3% yearly positive imbalance of ingested calories over a 30-year period.

The Ob gene and its product leptin (from the Greek root *leptos*, meaning thin) regulate energy intake and expenditure. Leptin is a cytokine secreted into the blood by adipocytes; regulates energy balance through the signalling pathways of the leptin-regulated central melanocortin circuit. Circulating concentrations of leptin are directly proportional to adipose tissue mass. With abundant adipose tissue, leptin secretion is stimulated and leptin binds to hypothalamic receptors. High leptin levels decrease food intake and increase energy expenditure. Deficiency of leptin action results in extreme obesity and infertility. Leptin binds to and inhibits orexigenic (neuropeptide Y, agouti-related protein) neurons, and also binds to and stimulates anorexigenic (-melanocyte-stimulating hormone, cocaine and amphetamine related transcript) neurons in the hypothalamus; these neuropeptides in turn bind to other receptors like the NPY receptor and the melanocortin 4 receptor. Early-onset obesity due to inactivating mutations in either leptin or leptin receptor genes have been described in several families; at present there is no significant evidence suggesting that these mutations play a significant role in common forms of obesity. Leptin is only one of several regulators of body weight.

D. Clinical manifestations of obesity

Obesity carries an increased risk for diabetes mellitus, hypertension, hypertriglyceridemia, low HDL cholesterol, cholelithiasis, hypoventilation (pickwickian) syndrome, osteoarthritis and possibly coronary artery disease, stroke and certain cancers (breast and endometrium).