

Meds 138 Biochemistry

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**These notes cover biochemistry lectures and small groups
in the GI / Nutrition , Urinary, and
Endocrine / Metabolism Weeks.**

Year 1 GI / Nutrition Weeks

General. Over the two weeks, seven biochemistry lectures will provide a mini nutrition course! The purpose is to describe the function and importance of some nutrients in regard to: a) biochemical role; b) metabolic function; c) clinical involvement. You might test your learning by asking “what? where? how?” in regard to each nutrient met: a) what is it? b) where is it important? c) how does it work? Use this approach to check your broad understanding of nutrition.

“Need to Know”. Learning Objectives for each lecture outline the examinable material. Information placed within **[square brackets]** is for interest only and is **not** examinable.

Nutrition. Nutrition is the science of defining qualitatively and quantitatively the dietary components necessary to maintain good health. Most of the chemicals in our bodies are made from the carbohydrates, proteins and fats in the food that we eat. However, some body constituents cannot be synthesized and are required in the diet. These include minerals, vitamins, certain amino acids and fatty acids. Remember to assess nutritional sufficiency by estimating three essentials: a) the adequacy of diet (quantity and quality); b) intestinal function; and c) the presence of metabolic disease.

Vitamins B₁, B₂, B₃, B₅, C

Learning Objectives

1. To identify thiamin, riboflavin, niacin, pyridoxin, cobalamin, folacin, biotin, cobalamin and pantothenate as members of the vitamin B complex.
2. To define coenzymes and provide examples.
3. To identify the biochemical functions of the B vitamins as key parts of coenzymes for specific enzymes in metabolism.
4. To summarize the biochemical and metabolic involvement of thiamin (B₁), riboflavin (B₂), niacin (B₃), and panthothenate (B₅).
5. To recognize common presentations of thiamine deficiency.
6. To identify niacin deficiency as causing classical pellagra a disease triad of dermatitis, diarrhea and dementia.
7. To associate niacin deficiency as often occurring with dietary protein deficiency.
8. To identify a distinct therapeutic role for nicotinic acid in patients with hyperlipidemia.
9. To summarize the biochemical, metabolic and antioxidant properties of vitamin C
10. To summarize the role of vitamin C in bruising and blood vessel fragility.

Vitamin “B”.

Eight essential vitamins for human nutrition are included in “Vitamin B”: Thiamin (B₁), Riboflavin (B₂), Niacin (B₃), Panthothenate (B₅), Pyridoxin (B₆), Cobalamin (B₁₂), Folate (B₉) and Biotin (“B₇”). All are micronutrients (recommended intake <100mg/day), not stored in appreciable amounts (except B₁₂) and act biochemically in compounds called coenzymes. A coenzyme is a prosthetic group which when bound to its apoenzyme gives a functional enzyme. Coenzymes often are co-substrates in which the vitamin cofactor acts as an acceptor or donor of functional groups that are removed or added to the actual substrate

(Exercise: pick any B vitamin; identify its coenzyme and an enzyme which uses the coenzyme; identify the substrate; what is being added or removed?).

Thiamin.

Biochemical Role: B₁ is phosphorylated in gut to the coenzyme TPP and transported to liver where its biochemical function is in oxidative decarboxylation reactions, e.g.



Another important similar reaction involves conversion of α -ketoglutarate to succinyl CoA (TCA cycle). The transketolase reaction of the phosphogluconate pathway provides a third important involvement of TPP.

Metabolic Role: Without TPP pyruvate cannot enter the TCA. Thiamin: **a)** is intimately connected with carbohydrate metabolism; **b)** is vital for tissue respiration; **c)** is rarely deficient except in alcoholics; and **d)** its deficiency primarily affects nervous and CVS system which is critically dependent on the metabolism of what?

Nutrition: Plentiful in whole grains and cereals, liver, pork. There are variable losses during cooking (conventional or microwave). It is absorbed by an active transport mechanism in the proximal acid portion of duodenum. Absorption is impaired by alcohol consumption.

Deficiency causes *Beriberi* (wet and dry forms). Dry beriberi is characterized by muscle wasting, neurological and cardiovascular problems. The "wet" form refers to edematous complications caused by severe cardiac impairment. In western society, thiamin deficiency is commonly found in chronic alcoholism. *Wernicke Syndrome*, a collection of neurological and behavioral symptoms, occurs in alcoholics and can be treated by large (often intravenous) doses of the vitamin. How does thiamin deficiency cause neurological problems? Alcoholics are appropriately treated with B complex because they are often deficient in other members of the complex.

Riboflavin.

Biochemical Role: B₂ functions as a coenzyme in oxidation-reduction reactions. As flavin mononucleotide (*FMN*) or flavin adenine dinucleotide (*FAD*) it carries two hydrogen atoms in these reactions. Therefore the principal functions of riboflavin are as hydrogen carriers in mitochondrial electron transport system.

Metabolic Role: Important for energy metabolism. Deficiency is uncommon. Experimental deficiency results in cheilosis (lip fissures), glossitis (painful purple tongue) and a scaly dermatitis.

Nutrition: Widely distributed in meat, dairy products, leafy vegetables, whole grains. Flour is fortified with riboflavin. Absorbed by a saturable process in the duodenum. There is little loss in cooking but riboflavin is rapidly destroyed by alkali (soaking peas in baking soda) or uv light. Best dietary source is dairy products.

Niacin.

Biochemical Role: B₃ is as a component of the pyridine nucleotide coenzymes, nicotinamide adenine dinucleotide (*NAD*⁺) and nicotinamide adenine dinucleotide phosphate (*NADP*⁺). These compounds are central in many oxidation-reduction reactions in metabolism.

Metabolic Role: Energy metabolism.

Nutrition: Niacin is a soluble vitamin whose deficiency causes *pellagra*; a triad of Ds; dermatitis (rough dark skin rash in areas exposed to sun), diarrhea (impaired absorption and

GI hemorrhage) and dementia (sleeplessness, irritability, confusion). Classically, *pellagra* is a disease of poor dietary intake (low protein, poor protein, e.g. corn, and low ingestion of other members of the B complex, thiamin and pyridoxin). It is appropriately treated with better diet and B complex. Our requirement is dependent on the intake of the amino acid tryptophan, from which it can be synthesized; 1mg of niacin can be synthesized from 60mg of tryptophan. Therefore the requirement for niacin, unlike other vitamins, is not absolute and diets deficient in niacin are usually deficient in protein as well. Good sources are whole grains and high protein foods. Deficiency of niacin is treated with the amide form of the vitamin, nicotinamide, and not nicotinic acid to avoid the vasodilating effect of nicotinic acid. Nicotinic acid has a therapeutic use outside its vitamin role. It is sometimes given in gram amounts to lower serum cholesterol (inhibits liver VLDL synthesis). 3g/day of nicotinic acid lowers serum cholesterol in some patients. This treatment is usually only considered after diet and bile sequestrants have been tried. As such, it provokes side-effects including flushing, headache, peptic ulcer aggravation and may be hepatotoxic.

[Symptoms of pellagra may also appear in *Hartnup's Disease*, a disorder of neutral amino acid transport in kidney and intestine. Tryptophan "deficiency" occurs because, as a neutral amino acid, it is not reabsorbed by the kidney and appears in urine.]

Pantothenate.

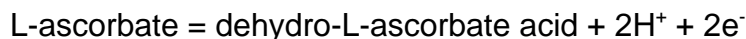
Biochemical Role: B₅ is a constituent of CoA and thus is metabolically-involved in the release of energy from carbohydrate and the degradation and metabolism of fatty acids.

Metabolic Role: B₅ is also important in the synthesis of cholesterol, phospholipids, steroid hormones, porphyrin (for hemoglobin) and choline.

Nutrition: B₅ is essential but there is not enough evidence to determine accurate dietary allowances. Pantothenate is widely distributed in plant and animal tissues. [For additional information see Champe and Harvey (324-325).]

Vitamin C - Ascorbic Acid.

Biochemical Role: Vitamin C is a reducing agent. L-ascorbic acid readily undergoes reversible oxidation and reduction as follows:



Ascorbate is required as a cofactor in hydroxylation reactions using molecular oxygen, and often have Fe or Cu as a cofactor. Here ascorbate is thought to play either of two roles: **a)** as a source of electrons for the reduction of oxygen; or **b)** as a protective agent for maintaining the Fe or Cu in the reduced state. Most notable of these hydroxylations are the formation of hydroxyproline and hydroxylysine during the synthesis of procollagen on the ER of connective tissue cells; synthesis of carnitine from lysine; the hydroxylation of tyrosine in the formation of catecholamines; and probably the hydroxylation of steroid hormones, aromatic drugs or carcinogens through the microsomal monooxygenase systems of the liver ER. Ascorbate may also be involved in the mobilization of stored iron in the spleen. It also enhances the solubility of non-heme iron and thereby aids intestinal iron absorption.

Metabolic Role: Impairment of collagen synthesis is one of the most common results of vitamin C deficiency. This defect is caused by impairment of the hydroxylation of procollagen and by reduced collagen formation and secretion by connective tissue. Nonhydroxylated collagen is unstable and cannot form the triple helix required for normal tissue structure. This results in capillary fragility (hemorrhagic features), poor wound healing,

and bony abnormalities in children perhaps). Severe to moderate anemia is common in both children and adults. It is usually normochromic and normocytic and is due to bleeding into the tissues.

A more general metabolic role is as an antioxidant. A great many studies have sought to demonstrate a role for the vitamin in lowering disease risk. Many such studies are based on epidemiological data and intervention trials and are controversial. Thus ingesting vitamin C-rich foods or taking ascorbic acid supplements has been associated with a reduction in the risk of developing cancers in the GI tract and with improving some indices of immune function in human subjects. Though the results of all studies do not agree, vitamin C supplements may reduce risk factors for cardiovascular disease by increasing high-density lipoproteins and by reducing total cholesterol in hyperlipidemic subjects. Clinical studies have also suggested that vitamin C may reduce the risk of developing cataracts and periodontal disease.

Nutrition: First symptoms of deficiency are petechial (small spotty) hemorrhages and ecchymoses (larger than petechiae). These develop when the body pool size is less than 0.5g; with further depletion (pool size 0.1-0.5g) abnormalities include gum involvement, hyperkeratosis, congested hair follicles, arthralgias, coiled hairs and joint effusions. The optimal body content is 1.3-3g; RDA 60mg, more in pregnancy and lactation; 35-45mg for infants and children; increased requirements may occur in smoking, wound healing, with oral contraceptives and in stress. Manifestations of deficiency correlate better with total body pool size than with plasma or blood levels.

Lipid-Soluble Vitamins: A, K, D, E, β -carotene

Learning Objectives

1. *To identify differences between retinoids and carotenoids.*
2. *To summarize and explain the biochemical and metabolic roles of vitamin A.*
3. *To recognize that vitamin A is widely distributed in plant and animal foods.*
4. *To recognize that vitamin A, or the foods that contain it, can be toxic if taken in excess but that β -carotene is not toxic, even in high doses.*
5. *To summarize the biochemical and metabolic roles of vitamin K.*
6. *To recognize that vitamin K is contained in vegetables, meat (liver) and is synthesized by intestinal bacteria.*
7. *To identify risk of hemorrhage as a consequence result of vitamin K deficiency, especially in the newborn, and to summarize the role of vitamin K antagonists, dicumarol and Warfarin, as anticoagulants.*
8. *To explain the biochemical and metabolic roles of vitamin D and E.*
9. *To identify the functional importance of skin, liver and kidney in vitamin D metabolism*
10. *To recognize that, in excess, vitamin D can be toxic.*

Vitamin A.

Biochemical Role: Vitamin A is the name given to three C_{20} compounds, retinal, retinol and

retinoic acid (see figure). Collectively they are called retinoids. Retinol is the precursor for retinal - a component of vision pigment and retinoic acid - a transcription regulator of certain genes.

Metabolic Role: Vitamin A is essential for vision, the growth and maintenance of epithelial tissues and resistance to infection:

- * Vision: Retinal is a necessary structural component of rhodopsin or visual purple, the light sensitive pigment within rod and cone cells of the retina. If inadequate quantities of vitamin A are present, vision is impaired.

- * Epithelial cell "integrity": Many epithelial cells appear to require vitamin A for proper differentiation and maintenance. Lack of vitamin A leads to dysfunction of many epithelia - the skin becomes keratinized and scaly, and mucus secretion is suppressed. It seems likely that many of these effects are due to impaired transcriptional regulation due to deficits in retinoic acid signalling. Its role in cell differentiation is also likely responsible for the importance of vitamin A in reproduction: both spermatogenic epithelial (Sertoli) cells (males) as well as the female reproductive cycle require adequate availability. Also required for the normal functioning of osteoblasts and osteoclasts in bone remodeling.

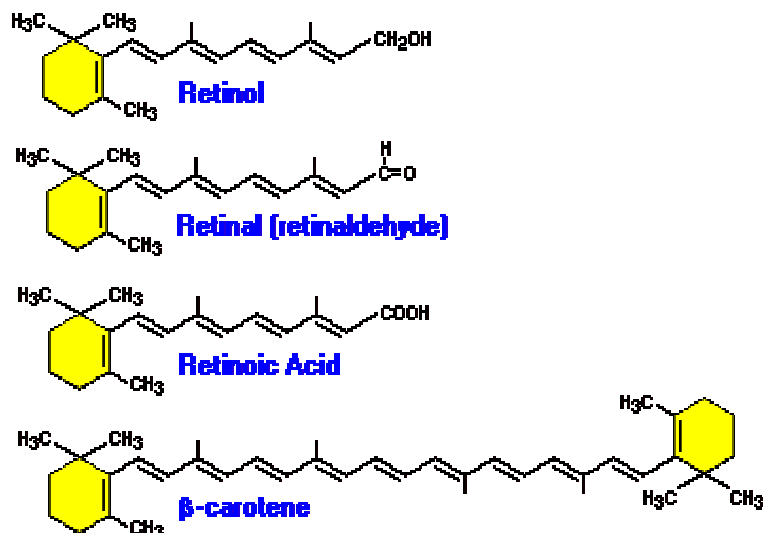
- * Resistance to infectious disease: In almost every infectious disease studied, vitamin A deficiency has been shown to increase the frequency and severity of disease. The "anti-infective" effect of vitamin A is complex, but is due, in part, to the necessity for vitamin A in the differentiation of normal immune cells.

Nutrition:

Vitamin A does not occur in plants, but many plants contain C₄₀ carotenoids such as beta-carotene that can be converted to vitamin A within the intestine and other tissues. Vitamin A is present in many animal tissues, and is readily absorbed from such dietary sources in the terminal small intestine. Liver is clearly the richest dietary source of vitamin A.

Vitamin A deficiency usually results from malnutrition and can cause:

- * Blindness due to inability to synthesize adequate quantities of rhodopsin. Moderate deficiency leads to deficits in vision under conditions of low light ("night blindness"), while severe deficiency can result in severe dryness and opacity of the cornea (xerophthalmia).
- * Increased risk of mortality from infectious disease has been demonstrated in malnourished children. Vitamin A supplementation has been shown to substantially reduce mortality from diseases such as measles and gastrointestinal infections.
- * Abnormal function of many epithelial cells, manifest by such diverse conditions as dry, scaly skin, inadequate secretion from mucosal surfaces, infertility, decreased synthesis of thyroid hormones and elevated cerebrospinal fluid pressure due to inadequate absorption in meninges.

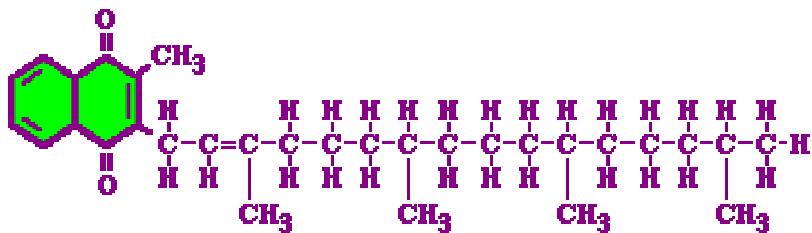


* Abnormal bone growth in vitamin A-deficient animals can result in malformations. Excessive consumption of vitamin A is toxic! Most retinoids (C_{20}) are highly toxic when taken in large amounts and can result in liver failure due to storage toxicity. In contrast, excessive intake of carotenoids (C_{40}) do not cause disease. Eating large amounts of carrots or green vegetables will not cause vitamin A toxicity. Pregnant women are advised not to take excessive vitamin A supplements. It is well-established that Vitamin A is required for the maintenance of epithelial tissues where many cancers are found. However, several studies have failed to show a consistent association between low vitamin A intake and increased risk of developing bladder, prostate or lung cancers. Some pre-cancerous lesions such as oral leukoplakia and esophageal dysplasia respond to vitamin A.

Vitamin K.

Biochemical Role: Naturally-occurring vitamin K include two forms K_1 and K_2 , both of which are quinone derivatives. The structure of vitamin K_1 is depicted here. Vitamin K is a coenzyme for a carboxylase that catalyzes post-translation carboxylation of glutamic acid residues on vitamin

K-dependent proteins with Vitamin K undergoing a cycle of oxidation and reduction that allows its reuse. The target proteins include:



- * Coagulation proteins: factors II (prothrombin), VII, IX and X
- * Anticoagulation proteins: proteins C, S and Z
- * Osteocalcin, an important protein involved in bone remodelling

Specific glutamic acid residues are carboxylated and require this modification to become biologically active. The additional γ -carboxyl groups enable calcium bridges to bind the protein to the negatively-charged phosphate head groups of membrane phospholipids on membrane surfaces. An additional effect is to enable calcium to bind two γ -carboxylated proteins together by forming an intra-chain bridge.

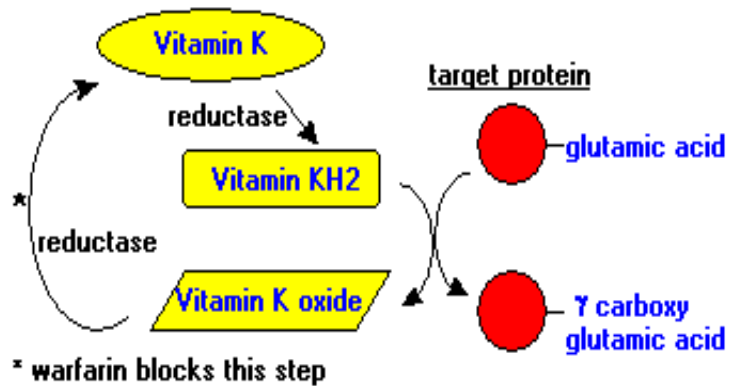
Metabolic Role:

Vitamin K is a necessary for functioning coagulation and anticoagulation. Vitamin K deficiency is manifest as a tendency to bleed excessively. Indeed, many commercially-available rodent poisons (e.g. Warfarin) are compounds that interfere with vitamin K and kill by inducing lethal hemorrhage (see below). Anticoagulants block the reduction of oxidized vitamin K and prevent the γ -carboxylation reaction.

Nutrition: Vitamin K is found in a number of foods, including leafy greens, cauliflower and liver and liver oil. However, much vitamin K is synthesized by intestinal bacteria, and in most cases, absence of dietary vitamin K is not at all deleterious. Vitamin K is a fat-soluble vitamin and both dietary and microbial vitamin K are absorbed into intestinal lymph along with other lipids. The fetus obtains vitamin K from its mother by transplacental transfer. Deficiency in vitamin K and resulting hemorrhagic disease can result in several situations:

- * Poisoning with vitamin K antagonists: Many of the popular rodenticides are used

therapeutically to prevent coagulation and thromboses in patients. If the vitamin K deficiency induced is severe, death may occur by bleeding. Coumarin derivatives such as Warfarin and dicumarol interfere with recycling of vitamin K (see above) and thereby lead to vitamin K deficiency. Some newer types of rodenticides have such long half lives that a single feeding on poison bait can kill not only the rodent, but cause bleeding disease in dogs or cats that subsequently ingest them.



* Liver disease: Vitamin K, as a fat-soluble vitamin, requires proper lipid absorption for its own absorption. Liver disease that results in increased bile salt synthesis leads to impaired vitamin K absorption and deficiency. Additionally, a majority of the clotting factors are synthesized almost exclusively in the liver, so liver disease can cause defects in blood clotting by several mechanisms.

* Intestinal disease: Diseases causing lipid malabsorption in the small intestine can lead to impaired absorption of vitamin K.

* Hemorrhagic disease of the newborn: This results from vitamin K deficiency in human infants, and can lead to death or permanent brain damage. At birth, the liver has essentially no vitamin K reserves and a lack of vitamin K intake or non-production of bacterially-synthesized vitamin K can lead to this situation. Many infants receive vitamin K supplements to preclude this disorder.

[See <http://www.cps.ca/english/statements/FN/fn97-01.htm>]

* Increased risk of fractures or reduced bone density: This can result from inadequate production of bone proteins such as osteocalcin. Several clinical trials have supported the proposition that, in certain situations, vitamin K supplements enhance the integrity of bone. It seems clear that use of vitamin K antagonists like Warfarin for purposes of anticoagulation have toxic effects on rapidly-growing bone.

Vitamin D.

Biochemical Role: A precursor in cholesterol synthesis, 7-dehydrocholesterol, is converted to vitamin D₃ in the skin by the uv rays in sunlight. Vitamins D₂ and D₃ are not active and must be hydroxylated by enzymes present in the liver and the kidney. 25-hydroxyvitamin D is produced in the liver and is the main form of the vitamin present in plasma. This, in turn, is acted up by a 1-hydroxylase in the kidney to produce 1,25-dihydroxyvitamin D which is the most potent form.

Metabolic Role: Vitamin D acts to maintain circulating calcium levels in two ways: a) in a classic steroid-hormone-type-mechanism, it promotes the intestinal gene expression of a calcium-binding protein which increases calcium absorption; and b) along with parathyroid hormone it promotes the solubilization of calcium and phosphate from bone. [Additional details are in Champe and Harvey (pp. 335-338).]

Nutrition: Vitamin D is a lipid-soluble vitamin which exists principally in two forms: ergocalciferol (vitamin D₂), formed from ergosterol in yeasts, and cholecalciferol (vitamin D₃) present in animal tissues. The latter is formed in human skin by exposure to sunlight (ultraviolet radiation) and found chiefly in fish liver oils and egg yolks. Milk is fortified with cholecalciferol in Canada. Synthesis of D₃ in the skin is normally the most important source and individuals spending all of their time indoors must consume dairy products to avoid deficiency.

Vitamin E.

Biochemical and Metabolic Role: Vitamin E is comprised of several kinds of tocopherols. The ring is methylated differentially to give " - \$ (- and * -tocopherols. The structure of tocopherols allow them to act as antioxidants in preventing lipid peroxidation of polyunsaturated fatty acids in cellular membranes. Vitamin E has been studied actively for its antioxidant properties and many studies show some benefit in alleviating or delaying chronic disease, principally cardiovascular disease.

Nutrition: Vegetable oils, nuts, and green leafy vegetables are the main dietary sources of vitamin E. Vitamin E supplements are safe since it is the least toxic of the lipid-soluble vitamins when taken in large amounts.

\$Carotene and Carotenoids.

Biochemical and Metabolic Role: Carotenoids are highly-coloured C₄₀ compounds whereas retinoids (vitamin A) are C₂₀ compounds. \$carotene (essentially two vitamin A molecules joined end-to-end), is not a vitamin in itself although it that can be hydrolysed to vitamin A. This conversion is inefficient in humans. \$carotene is thus not a very effective retinoid but it has important independent effects as an antioxidant.

Nutrition: The antioxidant properties of carotenoids have been clearly demonstrated under laboratory conditions and it has been suggested, therefore, that this is the reason for the ability of foods rich in carotenoids to protect against some degenerative diseases, including some cancers, cardiovascular disease and cataracts. At present it is unclear whether the protective effects are from \$carotene alone, a combination of \$carotene and some carotenoids that do not have vitamin A activity or from other factors in foods rich in carotenoids. Vitamin A can be toxic if taken in excess, but \$carotene is not.

Carotenoids are a group of about 600 nutrients including beta carotene and lycopene. They are found in vegetables such as carrots, pumpkins, sweet potatoes, tomatoes, and other deep green, yellow, orange, and red fruits and vegetables. An increase risk of breast cancer has been associated with low intake of vitamin A and \$carotene.

[Biochemical Testing for Vitamin Deficiency. While a variety of tests are available to measure vitamins or their metabolic functions, they are expensive and not always available. Plasma sodium and potassium are routine determinations in situations of electrolyte or fluid imbalance. Because of the etiology of megaloblastic anemia, plasma (or red cell) folate and vitamin B₁₂ are usually carried out in these cases.

<u>Nutrient</u>	<u>Indicates reduced intake</u>	<u>Indicates impaired function</u>
Protein	Urinary nitrogen	Plasma albumin

Vit. A	Plasma β -carotene	Plasma retinol
Thiamin	Urinary thiamin	TPP effect on red cell transketolase
Riboflavin	Urinary riboflavin	FAD effect on red cell glutathione reductase
Pyridoxin	Urinary 4-pyridoxic acid	Plasma 5' pyridoxal phosphate
Folate	Plasma folate	Red cell folate
B ₁₂	Plasma holo-transcobalamin II	Plasma B ₁₂
Ascorbate	Plasma ascorbate	Leukocyte ascorbate]

Mineral Nutrition: Na, K, Ca, Mg, P, Cu, Zn, Se

Learning Objectives

1. To recognize three biochemical roles of metals as; a) generation of crosslinks in order to coordinate structure; b) accepting or donating electrons in biochemical reactions; and c) binding of oxygen.
2. To broadly summarize the biochemical involvement in metabolism of sodium, potassium, calcium, magnesium, phosphorus, copper, zinc and selenium.
3. To identify the roles of calcium and vitamin supplementation, exercise and hormone replacement therapy in ameliorating osteoporosis.
4. *To explain the essentiality of copper in terms of its biochemical role in several oxidase enzymes.*
5. *To identify metallothionein as a cellular protein induced by several divalent metals.*
6. *To summarize features of Menke's and Wilson Disease.*
7. *To identify zinc as an essential crosslinking or coordinating factor in many proteins and enzymes.*
8. *To identify phytate as an inhibitory factor for zinc (and other divalent metal) absorption and why.*
9. To explain an antioxidant function for selenium in relation to its role in glutathione peroxidase.

Biological Role of Metals. Metals play essential biochemical roles at the reaction centers of metalloproteins and metalloenzymes. They act in one of three ways: **a)** as coordinating, crosslinking or bridging molecules (Mg, Ca, Zn, Mn); **b)** as donors or acceptors in reduction-oxidation (redox) reactions (Fe, Cu, Co); **c)** to bind, transport and release oxygen (Fe, Cu, Mn).

Sodium.

Biochemical and Metabolic Role: Sodium is the major **extracellular** cation. Goes with water and maintains the volume of blood. Intake 5-10g per day, mostly from table salt. Sodium regulation by kidney. Low blood Na stimulates kidney angiotensin. This acts on the adrenal cortex to release aldosterone which increases distal tubular reabsorption of Na in kidney.

Nutrition: Excessive sodium is the issue rather than deficiency and can be harmful for some

individuals at risk for hypertension.

Potassium.

Biochemical and Metabolic Role: Potassium is the principal **intracellular** cation.

Concentration within cells is maintained by the energy-dependent pumping of Na out of the cells (ATPase). K is permeable to membranes and enters to replace the extruded Na. K is involved in neuromuscular irritability and effects on cardiac muscle.

Nutrition: Problems usually only when profound imbalances occur, e.g. major shift in tissue water, diabetic acidosis. Sources: nuts, meat, fruit.

Calcium.

Biochemical Role: In a co-ordinating role, calcium is an important component of bone (hydroxylapatite). Intracellular calcium also plays a crucial role in cellular metabolism, in the transmission of nervous impulses, muscular contraction and as an important intracellular signalling molecule.

Metabolic Role:

The average adult human body contains about 1 kg of calcium with 99.9% of this being in the form of hydroxy apatite in the skeleton. Of the remaining 1g, about 700mg is in the extracellular interstitial space, about 300 mg in blood, and 40 mg is found within cells. Of the 300 mg in blood some 40% is protein bound, 40% is free and in the ionized form, and the remainder is found complexed to other ions. Maintenance of the body calcium stores and plasma calcium concentration ultimately depends on intake, absorption and renal excretion of calcium.

Nutrition: Calcium is found in milk and dairy products, sardines, clams and oysters, kale and collard, turnip greens, mustard greens and broccoli (it is also high in spinach but remains bound tightly to oxalic acid). The Recommended Daily Intake (RDI) varies with age but about an intake of 1000-1200mg per day is now recommended with more for children and adolescents. Intakes up to 2000mg per day are regarded as safe. For some people it will be necessary to take calcium supplements or fortified foods to achieve such intakes. If a calcium supplement is taken, it should be pure and absorbable. Some forms of calcium are contaminated by heavy metals or are not readily absorbable.

Calcium is absorbed by two types of intestinal transport: **a)** one that is carrier-based, i.e. depends on a cellular transport system; and **b)** one that is passive, paracellular and diffusion-based. The former is saturable, dependent on vitamin D (liver and kidney play a role, remember?) whereas the second is only dependent on the concentration of the mineral in the digesta.

If body calcium needs are not met from the diet, metabolism 'borrows' calcium from the skeleton. This is not feasible on an ongoing basis as the skeleton will become porous, weak and predisposed to fractures. As the population ages, osteoporosis becomes more prevalent and there is a tremendous amount of clinical interest in preventing this disease which affects mostly women. At present, advice to prevent (or limit) osteoporosis is to:

- C ensure the growth and development of healthy bones in youth and early adulthood;
- C exercise regularly at all ages. Especially important is to strengthen muscles which are weight-bearing;
- C ensure adequate vitamin D nutrition (sunlight, diet);
- C consume enough dietary calcium to minimize how much the body borrows from bone.

Calcium supplements may be necessary for some individuals who do not consume much dairy products;

[See <http://www.hsph.harvard.edu/nutritionsource/calcium.html>]

Phosphorus.

Biochemical and Metabolic Role: Phosphorus is one of the most abundant elements in the human body and almost all of it is present as phosphate. Phosphate is an integral component of nucleic acids and the phospholipids of cell membranes as well as many important regulatory phosphoproteins. More than 80% (600-700g) is present in bone where it is an important component of hydroxy apatite. In other tissues, phosphate is principally found in the intracellular compartment. As with calcium, phosphate absorption is also under the influence of vitamin D.

Nutrition: Phosphate is found in milk and dairy products, meat, fish and poultry, whole grain cereals, legumes and nuts. Unfortunately there is probably too much of it in some 'foods' such as processed meats and pop (Coke, Pepsi etc). Daily intake should be about 800 mg, equating that of calcium.

Magnesium.

Biochemical and Metabolic Role: Magnesium is a major intracellular divalent cation. It is sometimes convenient to think of Mg as relating to Ca as K does to Na. Magnesium is essential for the production and transfer of energy for protein synthesis by acting as a cofactor for phosphate-requiring enzymes, especially those utilizing ATP. Magnesium affects neuromuscular excitability and cellular permeability.

Nutrition: Magnesium is a macro nutrient found in whole-grain cereals, nuts, meat, milk, dark green vegetables (it is an essential component of chlorophyll) and legumes. Daily intake ought to be about 300 to 400 mg. Body content is about 25g: of this ~50% is in bone, ~50% within cells and <1% in the circulation. 60% of plasma content is free, 30% is protein-bound and 10% is bound to citrate and phosphate. Signs of deficiency are variable but include: personality change, spontaneous muscle spasm, tremor, twitching, tetany and convulsions. Frank hypomagnesemia can appear in patients with intestinal disease (decreased intestinal function) or steatorrhea, wherein Mg is excreted as soaps of fatty acids.

Copper.

Biochemical Role: Copper has a redox role in several oxidase enzymes: *Ceruloplasmin*, a serum protein contains >90% of serum Cu. It is a ferrioxidase that converts Fe(II) to Fe(III). May be involved in the mobilization of Fe from storage sites. *RBC Superoxide Dismutase*, an enzyme that accounts for 60% of RBC Cu and also contains Zn. It destroys superoxide anion radicals. *Cytochrome Oxidase*, the terminal enzyme in the respiratory chain that donates electrons to oxygen. *Dopamine beta-hydroxylase*, in catecholamine synthesis in nervous tissue (norepinephrine) and the adrenal medulla (epinephrine). *Tyrosinase*, is involved in the biosynthesis of melanin. *Lysyl Oxidase*, an enzyme that crosslinks lysines in collagen.

Metabolism and Nutrition: There is about 50-60mg of Cu in the body; daily intake is 0.5-1mg. Both animal tissue (shellfish) and plants (grains) are good sources. Copper is usually absorbed easily and balance is maintained between absorption and excretion in bile. Copper deficiency causes a hypochromic microcytic anemia (ceruloplasmin?). Also a neutropenia (low circulating levels of neutrophils) because of effects on the marrow. Neutrophils are a

major component (50-60%), of leukocytes which are formed in the marrow. Monocytes migrate to tissues and become macrophages. Neutrophils and macrophages destroy invading bacteria, foreign bodies and cell debris (phagocytes).

Diseases of Copper Metabolism: **Menke's Disease** is a rare X-linked disorder of copper transport. Cerebral degeneration, seizures, arterial aneurysms, abnormally textured hair, early death are features of the disease. Although serum, liver and brain copper levels are low, very high copper concentrations are found in other tissues (esp. intestine and kidney).

Wilson Disease is caused by an autosomal recessive defect in the hepatic excretion of copper that results in toxic accumulations of copper in liver, brain and other organs. Low levels of ceruloplasmin are characteristic. About half of the patients present with hepatic involvement. In some patients, neurologic/psychiatric disturbances are the first clinical sign and are always accompanied by Kayser-Fleischer rings. These green or golden deposits of copper in Descemet's membrane of the cornea do not interfere with vision but indicate that hepatic copper has been released and has caused the brain damage. Treatment consists of removing the deposits of copper as rapidly as possible and should be instituted once the diagnosis is secure whether the patient is ill or asymptomatic. Drug of choice is penicillamine given orally in an initial dose of 1g per day in divided doses. Since penicillamine has an antipyridoxin effect in animals, 25mg of vitamin B6 is also given.

Zinc.

Biochemical Role: Zn plays a structural and coordinating role in >250 proteins, particularly enzymes. Because of this widespread involvement in protein function, it is convenient to think of zinc as a growth factor, like protein. If zinc is not present, many proteins would be non-functional.

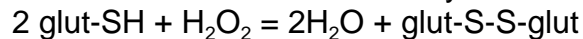
Metabolic Role: Because zinc containing enzymes come from all six classes (oxidoreductases, transferases, hydrolases, lyases, isomerases and ligases) there are very major effects in Zn deficiency. Tissues that turnover rapidly (marrow, intestine, skin, hair) are easily affected. Skin eruptions are common (sometimes superinfected by bacteria and yeasts). Adequate Zn nutrition is essential for growth and development (sexual development in males). Within cells several metals, copper included, are bound to a ubiquitous protein called metallothionein (MT). The protein may be important for metal metabolism in liver, kidney, intestine. It has 61 amino acids of which 20 are cysteine. The protein binds 7-10 metal atoms/molecule (Cu, Zn, Cd, Hg, Ag, Au). Its synthesis is induced by these metals but primarily by Zn and Cd. The enhanced synthesis results from increased transcription of the metallothionein gene.

Nutrition: The body content of zinc is, 2-2.5g; intake is 5-15mg/day. Zn is absorbed easily throughout the small intestine, but, like Fe, is affected by some plant food constituents (principally phytate [inositol phosphate] and fiber). Zn deficiency is rare because the metal is ubiquitous. Zn excretion plays an important role in keeping balance. Major route: pancreas and small intestine (not bile); Minor route: kidney (increased in alcoholics). Zn is poorly available from plant foods. The phytate (inositol hexaphosphate) and fiber contents of foods bind Zn and prevent its absorption. Unleavened bread (no yeast) and soy products contain phytate. Yeast contains an enzyme, phytase, which destroys phytate.

Selenium.

Biochemical Role: Selenium is an essential metal with antioxidant properties. Some effects

are explained by its role in glutathione peroxidase; in that its role overlaps that of vitamin E. Some forms of liver necrosis in rats can be cured by either Se or vitamin E.



Many other effects remain to be explained in terms of Se-proteins. Selenium chemistry is similar to sulfur's and therefore most Se is bound to proteins (Se-proteins).

Metabolic Role: About 5-20 mg is present in the body; wide variation in intake 0.05-0.5 mg/day. Highest concentrations are in RBC, liver, spleen. Absorbed throughout the small intestine. Excreted in pancreatic secretions (enzymes) and also across the gut wall.

Excreted by kidney after metabolism.

Nutrition: Selenium intake has a narrow 'window of effectiveness' above which toxic symptoms can ensue. Toxic effects in cattle and sheep in some countries ("blind staggers"). In humans, toxic effects include damage to liver and muscle but are rare. Need 25-50 x RDI.

Nutrients and Canada's Food Guide

Learning Objectives

1. To summarize nutritional sufficiency as depending on appropriate intake, absorption and metabolism/excretion.
2. To summarize marasmus and kwashiorkor and to identify nutritionally-stressed populations in our society.
3. To define 'nutrients', 'essential nutrients', 'major nutrients', 'macronutrients' and 'micronutrients'.
4. To define the biochemical involvement of micronutrients as essential factors and cofactors in metabolism.
5. To quantitate the energy content of fat, carbohydrate and protein per gram.
6. To identify RDAs RNIs and DRIs as being recommended daily intakes of various nutrients to prevent deficiency disease.
7. To differentiate and summarize the four major Food Groups.
8. To differentiate between 'serving' and 'portion' of various foods.
9. To summarize how Canada's Food Guide can provide for healthy caloric intakes from 1,800 to 3,200 kcal/day.
10. To describe the daily consumption of 2,000kcal and 2,500kcal diets as being average for many moderately-active young women and men, respectively.
11. To summarize Canada's Guide for Healthy Eating.
12. To broadly identify which nutrients come from which foods.

Nutrition.

Nutrition is the science of defining qualitatively and quantitatively the dietary components necessary to maintain good health. Most of the chemicals in our bodies are made from the carbohydrates, proteins and fats in the food that we eat. However, some body constituents cannot be synthesized and are required in the diet. These include minerals, vitamins, certain amino acids and fatty acids. Remember to assess nutritional sufficiency by estimating three essentials: a) the adequacy of diet (quantity and quality); b) intestinal function; and c) the presence of metabolic disease.

Nutrients.

The Nutrients: There are six nutrients, namely, carbohydrate, protein, lipid (quantitatively the most important is fat), minerals, vitamins and water. The first three are sometimes called the major nutrients with the latter three called the minor nutrients.

Essential Nutrients: These include essential fatty acids (linoleic, linolenic and arachidonic acids), essential amino acids (isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, histidine and perhaps arginine), vitamins, minerals and water. We also require a source of energy (usually carbohydrate).

Intakes: Two other terms are based on usual daily intakes: macronutrients are required at >100mg/day; micronutrients have intakes less than this. The "trace" metabolism of micronutrients is related to their biochemical function as metabolic factors and cofactors (e.g. Cu, thiamin). Therefore only very small amounts are needed. A spectrum of effects often exists for micronutrients with a central "window of efficacy". Deficient symptoms occur at low intakes and often toxic effects when high levels are consumed. "Megatherapy" has few demonstrable beneficial effects and is often harmful.

Recommended Intakes of Nutrients.

Recommended intake levels are scientifically based and incorporate a margin of safety. They are set by groups of experts who periodically assess published evidence. The older **Recommended Daily Allowance** [USA] and **Recommended Nutrient Intake** [Canada] are currently being replaced with a new standard **Dietary Reference Intakes (DRIs)**.

See: http://www.hc-sc.gc.ca/hpfb-dgpsa/onpp-bppn/diet_ref_e.html

Nutritional Deficiency Disease.

In areas of the world with chronic nutritional deprivation *marasmus* and *kwashiorkor* occur. *Marasmus* results from a severe lack of calories and can occur in adults and children as a result of famine (no food). Individuals are severely emaciated. *Kwashiorkor*, on the other hand, appears mainly in children about 1-year-old that are eating a diet adequate in calories but deficient in protein. Characteristically the children have edema. *Marasmus* and *kwashiorkor* may be seen as the extremes of protein-calorie malnutrition, but clinically many cases are intermediate.

Problems in the 3rd world occur because of poor quality and inadequate amount of diet, poor general health due to chronic infections and political problems affecting food production and distribution. In our society, better incomes, assistance programs and food supplementation have eliminated major nutritional deficiency in the general population. However, problems still occur in "stressed" populations, e.g. children and infants, pregnant mothers, elderly, vegetarians, faddists, alcoholics, hospital patients (e.g. parenteral feeding), people with malabsorption (e.g. celiac disease), and inflammatory bowel disease (e.g. Crohn's disease).

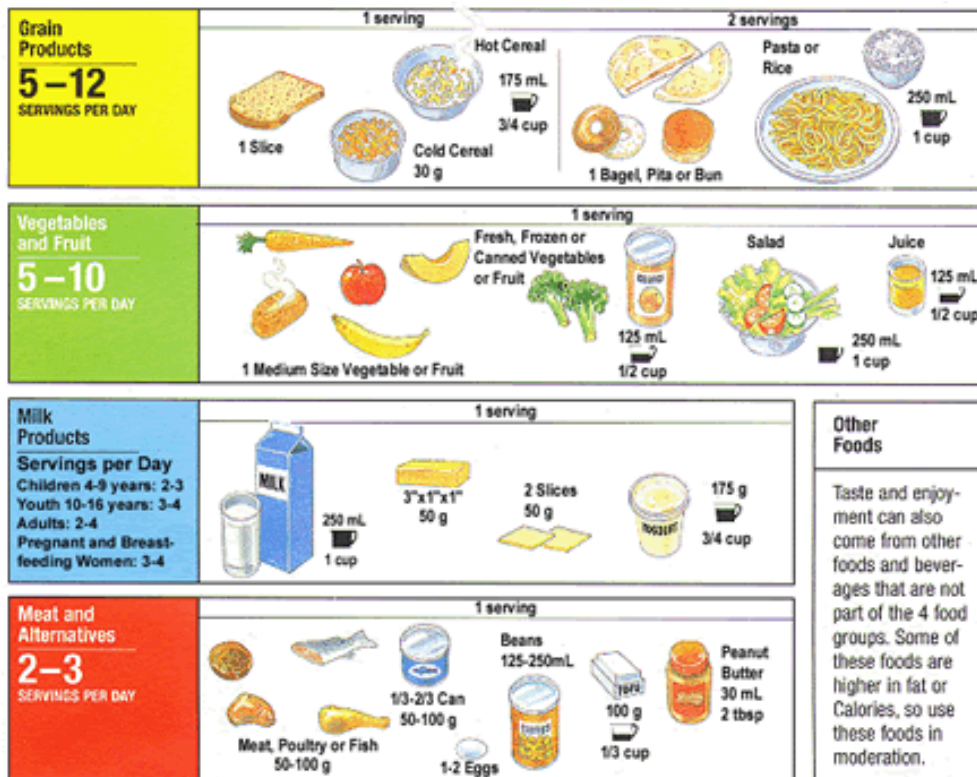
Food and Nutrients.

What is the difference between food and nutrients? Simply that we eat foods whereas cells eat nutrients! Our tissues need all six required nutrients for cellular function. Some "non-nutrients" in our diets still exert important physiological or metabolic effects. Two of these are fibre and alcohol which are "non-nutrients" in different ways. Fiber is a complex carbohydrate which is not absorbed and, therefore, cannot provide energy or nutrients. However, it provides an essential digestive/nutritional function by promoting gastrointestinal transit and

increasing fecal bulk. Alcohol, on the other hand, is absorbed easily and provides calories which can be a used source of energy at intakes less than 25% when it is metabolized by alcohol dehydrogenase. In alcoholics consuming very high amounts of alcohol, alcohol is metabolized by alternate pathways that do not produce ATP (the microsomal ethanol-oxidizing system) and therefore significant energy is not produced.

Energy.

Nutrients provide three important functions to the body: a) structural components for the growth and development of tissues (e.g. protein, Ca, phosphate); b) energy (carbohydrate and fat primarily); and c) metabolism (vitamins and minerals). Energy is provided by the major nutrients. Energy is measured in Calories (kilocalories), i.e. 1 Calorie = 1000 calories = 1 kcal. Conversions are 1 kcal = 4.2 kJoule = 70 watts. The richest source of energy in the diet is fat which provides 9 kcal/gram. Carbohydrate and protein each provide less than half of that by weight, 4 kcal/gram. Alcohol, a component of many daily diets, is obviously not an essential nutrient but does provide energy at a level intermediate between carbohydrate and fat, namely 7 kcal/gram (you should review previous notes - Case 6 and ‘Metabolic Integration’).



Canada's Food Guide.

The Guide is a practical way of translating recommended intakes (RDAs, RNIs and DRIs) into actual foods. It should be the background standard used with patients. No single food contains all the essential nutrients (consider milk, for example). Therefore a good mixture of foods is essential to provide a nutritionally-complete diet. In Canada's Food Guide, food is

divided among four basic food groups: 1) *Milk and Milk Products Group*; 2) *Meat and Alternatives Group*; 3) *Fruit and Vegetables Group*; 4) *Bread and Cereals Group*.
See: http://www.hc-sc.gc.ca/hpfb-dgpsa/onpp-bppn/food_guide_rainbow_e.html

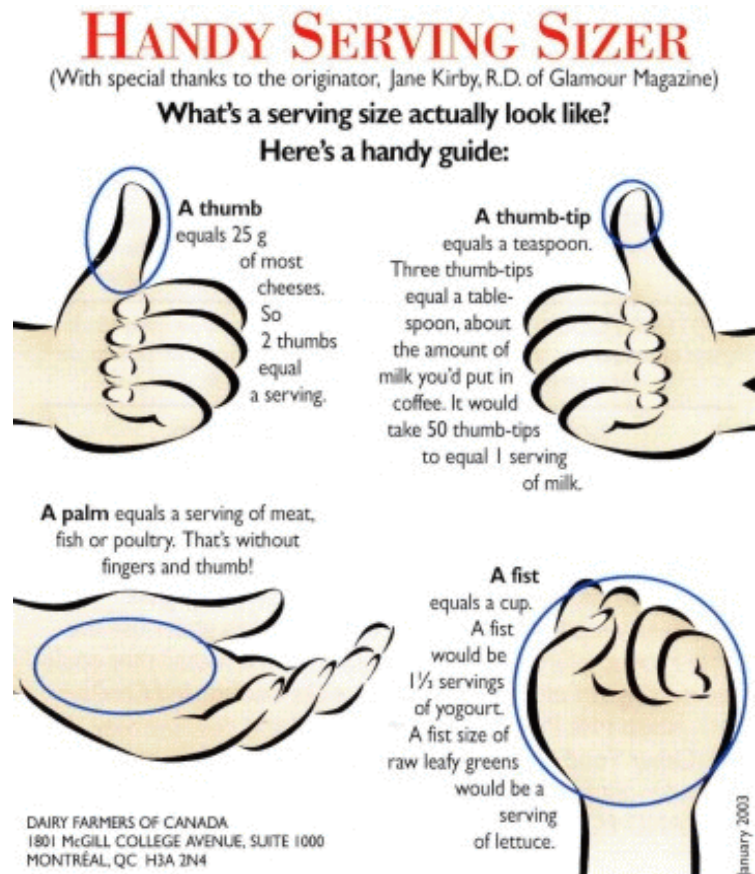
Servings.

Recommended servings address the issue of the quantity of food to be eaten to get recommended nutrient intakes. Canadians are encouraged to eat 2-4 servings of dairy products; 2-3 servings from the Meat & Alternatives Group; 5-10 servings of fruit and vegetables; and 5-12 servings from the grains and cereals group. A serving is defined in terms of an ideal or average portion of a particular food (see diagram). For example, one whole *Small Ham, Pineapple and Cheese Pizza* (20 cm/8 inch) may provide:
3 servings Grain Products (20 cm or 8 inch crust)
1 serving Vegetables & Fruit (50 mL or 1/4 cup of pineapple and 50 mL or 1/4 cup of tomato sauce)
1 serving Milk Products (50 g or 2 oz. of cheese)
1 serving Meat & Alternatives (50 g or 2 oz. of ham)

Most Canadians: a) confuse 'serving' with 'usual portion' and therefore eat too much! For example, a chicken breast (usual portion) may contain 2-4 servings; b) eat too many servings from the dairy and meat & alternatives groups and not enough from the other two food groups. The 'serving' concept, used properly, is very adaptable to variety of individuals and situations, depending on age, sex, pregnancy, breast-feeding and physical activity. For example, young children can choose the lower number of servings, while male teenagers or someone with a very active lifestyle can go to the higher number. By choosing the appropriate number of servings, daily caloric intakes from 1,600 to 3,200 can be achieved using the Food Guide. In terms of average consumption of calories, two numbers are worth remembering. **2,000 kcal** is about the right amount for moderately active women, teenage girls and sedentary men; **2,500 kcal** is a target for many men, teenage boys and active women. Many older adults, children and sedentary women need fewer Calories than 1,800.

Canada's Guidelines for Healthy Eating.

These are broad-based advice to eat healthily and should be used by physicians when assessing and advising patients. The guidelines emphasize two points: a) eat all the food groups every day (variety of nutrients); and b) eat an appropriate number of servings



(quantity of food). Broadly, Canadians are encouraged to: **1)** Eat a variety of foods every day; **2)** Emphasize cereals, breads, other grain products, vegetables, and fruits; **3)** Choose lower-fat dairy products, leaner meats, and foods prepared with little or no fat (limit the fat content of the diet to 30% of total calories with no more than 10% coming from saturated fat and 10% from polyunsaturated fat); **4)** Achieve and maintain a healthy weight by increasing physical activity and eating fewer calories; **5)** Limit salt, alcohol and caffeine. See http://www.hc-sc.gc.ca/hpfb-dgpsa/onpp-bppn/food_guide_e.html

Sources of Nutrients In Typical Foods

<u>Dietary Component</u>	<u>Examples of Typical Foods (NOT complete)</u>
Carbohydrate	starchy vegetables, grains (bread), pasta, rice, fruit
Protein	meat, legumes, eggs, grain products
Fat	meat, eggs, dairy products, fish, margarine, butter, cooking oil
Cholesterol	animal products only
Fiber	fruits and vegetables, whole grain products
Iron	meat , cruciform vegetables (need vitamin C), 'enriched' (fortified) foods
Calcium	dairy products, vegetables, canned fish, seeds, fortified foods
B Vitamins	meat, vegetables, whole grains, fortified foods
Folate	leafy vegetables, fortified foods
Vitamin B12	animal foods only
Vitamin C	fruits, vegetables and their juices
Vitamin A	highly colored vegetables, liver oil
Vitamin K	green leafy vegetables, animal foods
Vitamin D	fortified foods, fatty fish and fish oils
Vitamin E	nuts, seeds and oils from these

[http://www.hc-sc.gc.ca/food-aliment/ns-sc/nr-rn/surveillance/pdf/e_NVSCF_eng.pdf]
 [http://www.hc-sc.gc.ca/hpfb-dgpsa/onpp-bppn/food_guide_background_8_e.html]

[Reading Labels].

Despite the simple nature of the Guidelines for Healthy Eating, it is still difficult to translate

this advice into actual weights of nutrients. Weights are commonly reported on food labels. The following two tables provide a means to convert recommendations into actual amounts.

[Recommended Amounts of Several Important Nutrients]

Nutrient	Calories (kcal)	2,000kcal Diet	2,500kcal Diet
Total fat*	Less than	65g	80g
Saturated fat**	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total carbohydrate		300g	375g
Dietary fibre		25g	30g

* based on 30% of calories

** based on 10% of calories

[Recommended Amounts of Total Fat and Saturated Fat]

Total kcal per day	Total fat (g) (<30% of total kcal)	Saturated fat (g) (<10% of total kcal)
1600	53	18
2000	65	20
2200	73	24
2500	80	25
2800	93	31

Dieting or Weight Management?

Learning Objectives

1. To summarize basal energy expenditure and the influence of physical exercise on daily energy expenditure.
2. To distinguish between “android” and “gynoid” lipidity and to identify android lipidity as identifying excess visceral fat.
3. To identify visceral fatness as a risk factor for several common chronic diseases.
4. To summarize personal / environmental and genetic factors in obesity.
5. To summarize ‘set point’ and lipoprotein lipase theories for maintenance of body weight.
6. To summarize a reasonable goal in a weight-loss program as cutting about 500 kcal

a day from a daily diet, combined with a regular exercise program.

7. *To identify the roles of nutrition education, behavioural modification and psychological support in a clinical weight loss regimen.*
8. *To identify some features of “fad” diets.*
9. *To critique ketogenic and low-carbohydrate diets for weight loss.*
10. *To identify appropriate weight management as a goal for a healthy lifestyle.*

Burning and Storing Energy.

Food calories (energy) can be obtained from only three nutrients: carbohydrate, fat and protein. To remain in weight balance our energy intake must equal our total energy expenditure as work (metabolic + physical activity), heat and energy stored. The human body is similar to a furnace that must be fed with fuel (calories). Calories are burned to meet energy needs for: a) basal metabolism - energy required to sustain living processes - called basal metabolic rate (BMR); b) physical work - an amount of calories that varies according to the intensity of daily activities. In order to get total energy expenditure the BMR can be multiplied by a factor related to average physical activity level of the individual. Some approximate examples follow, based on this simple approach:

If sedentary (little or no exercise, desk job) multiply BMR by 1.2

If lightly active (light exercise/sports 1-3 days/wk) multiply BMR by 1.4

If moderately active (moderate exercise/sports 3-5 days/wk) multiply BMR by 1.6

If doing heavy work or exercise (hard exercise/sports 6-7 days/wk) multiply BMR by 1.8

Obesity - A Biological, Psychological and Sociological Issue.

Health Risk: Obesity is associated with considerable health risks. Primarily, obesity increases atherosclerosis and the risk for coronary heart disease (40% of the incidence is due to obesity) stroke and hypertension. It also increases risk for non-insulin-dependent diabetes (“type 2 diabetes”), osteoarthritis and cancer as well as gall-bladder disease and sleep apnea.

Sociology: Obesity is considered unattractive. It is a fact that both men and women who are obese are less likely to marry. Fatness is also related to economic well-being: one study has demonstrated that working women who are very overweight earn as much as \$10,000 a year less than their slimmer counterparts! Many people want to lose weight (citing health reasons) and perhaps a third of North Americans are consciously trying to lose weight and as many as 50% of all women have been on a diet at one time or another. But dieting appears to quite ineffective in reducing obesity, since obesity is very common in Western (especially North American) society. The prevalence of obesity is at least 30% of the population and in some age/sex groups it is much higher.

[See: <http://www.beyonddieting.com/thesis2.html>]

Definition: Obesity is defined as a “state of lipidosity where the BMI (weight (kg)/height (m)²) is greater than 30. Obesity can be either android or “apple-shaped” with fat around the waist and upper abdomen, or gynoid (“pear-shaped”) which is excessive fat around the thighs and buttocks. It is specifically android, or abdominal obesity, that increases the risk for the diseases (see below). Besides an increased BMI, a WHR of 1.0 (men) or 0.8 (women) is indicative of android obesity and increased risk for obesity-related diseases. So what causes obesity? Is it simply due to overeating? While over-consumption of calories and under-exercise are undoubtedly responsible for much obesity, the factors responsible for obesity are

complex and include:

Genetics.

Obesity is inherited in some families but the specific genes are not well characterized. Presumably these affect energy intake (gut anatomy and biochemistry, appetite, satiety etc - see below) and expenditure (metabolism, BMR, thermogenesis etc). Some examples exist. The relationship between hunger, satiety, fat metabolism and the product of the *ob* gene, leptin, is not completely clear. Leptin, a hormone secreted by adipose cells, is involved in the regulation of body fat by the hypothalamus along with several other proteins and their respective receptors. Some evidence suggests that leptin may become an important target for new therapies for diabetes, especially in overweight persons. Eating behaviour is also affected by melanocortins, the melanocortin receptor and neuropeptide Y.

[See: <http://www.ispub.com/ostia/index.php?xmlFilePath=journals/ijapa/vol1n2/obesity1.xml>]

The metabolism of adipose tissue could be genetically affected. Adipose tissue can increase by increasing the size of cells (*hypertrophy*) or by increasing the number of fat cells (*hyperplasia*). The number of fat cells can increase throughout life, especially when the fat content of existing cells has reached a maximum. The gene(s) and expression of *Lipoprotein lipase* (LPL), the enzyme responsible for releasing triglyceride from VLDL in peripheral tissues, may be altered in obese people. LPL increases when weight is gained and after non-obese persons lose this gain, LPL falls to previous levels. This response does not occur in obese individuals who lose weight which leaves them very susceptible to rapid weight gain when eating resumes. In both non-obese animals and people, deliberate under- or over-feeding with attendant loss or gain of weight is rapidly followed by a return to the initial weight when the altered feeding stops. Such experiments suggest that a "set point" exists in non-obese people which modulates large changes in body weight.

Eating.

Eating behaviour is extremely complicated and multifactorial:

Psychological: appetite and our response to it is a learned behaviour. Similar for satiety. The palatability and preferences we have for food is also learned. Additionally, a person's mood or sense of well-being can significantly affect eating behaviour. Bored or depressed individuals can overeat (they also may be uninterested in food).

Physiological: our learning depends on our subjective response to many neurotransmitters and hormones that affect hunger, taste, gastric emptying etc.;

Lifestyle: Alcohol intake or cessation of smoking are also associated with obesity. Obesity in children, whether due to genetics or inactivity is associated with obesity in adulthood and with consequent health risks;

Economic: obesity is commoner in societies where food is plentiful and cheap and is also associated with lower economic status in those societies;

Sociological: 'eating out' is endemic in 'obese' societies and may, in itself, promote lack of good nutritional practices (meal preparation, education).

Weight Management.

Generally, health professionals should focus efforts on good weight management practices rather than on dieting *per se*. Repeated swings in body weight may not be healthy but convincing evidence of this is lacking. Desirable weight tables and BMI tables are available

for both men and women. Both are useful in counselling patients on appropriate energy intake / expenditure. Most experts agree that the best way to lose weight is to eat fewer calories and burn more energy by increasing physical activity. A reasonable goal is to aim for a loss of about a pound a week. This usually means cutting about 500 kcal a day from a daily diet, combined with a regular exercise program. Assisting patients in a losing weight is a desirable goal because while some dieters succeed in taking off weight, perhaps as few as five percent manage to keep it off in the long run. Besides reducing food intake and increasing daily exercise, successful weight-management programs incorporate good nutritional education, behaviour modification and, possibly, psychological support. While average North American diets usually contain too much fat, the emphasis in dietary restriction should be in total calories (number of servings) rather than only on fat. Some patients, counselled to “eat less fat” will restrict this exclusively thereby depriving themselves of essential fats containing EFAs.

In a detailed position paper, The American Dietetic Association states: “It is the position of the American Dietetic Association that successful weight management to improve overall health for adults requires a lifelong commitment to healthful lifestyle behaviors emphasizing sustainable and enjoyable eating practices and daily physical activity. Americans are increasing in body fat as they become more sedentary. Obesity has reached epidemic proportions and health care costs associated with weight-related illnesses have escalated.” [See: http://www.eatright.org/Public/GovernmentAffairs/92_adar0802.cfm]

Fad Diets.

Diet Claims: Intuitively, physicians and their patients should be skeptical of the claims of diets that are unusually *simplistic* (“Lose weight while you sleep!”); *facile* (“Lose weight and keep it off for good!”); *extraordinary* (“Peter Flanagan lost 84 pounds in six weeks!”); *commercial* (“Lose all the weight you can for just \$99!”); *rapid* (“Lose 30 pounds in just 30 days!”) *unusually innovative* (“Scientific breakthrough... medical miracle!”)

Quasi-Science: Physicians will be called upon to be scientifically literate in answering patient questions since many diets appear to be based on science. Be skeptical! A common statement is: “But it works, doctor!”. Most popular diets will work for a period by: a) restricting calories or b) depressing appetite. The diets call for fewer servings, portion sizes, energy nutrients to be eaten. Alternatively, the patient deliberately or because of body metabolism becomes less inclined to eat regularly, thereby reducing intake. Any diet that restricts a food or a food group runs the risk of unbalancing intake of other nutrients or creating micronutrient deficiency. It is important to convince yourself that metabolism cannot be easily or safely altered as an ongoing way to keep body weight down (see ‘Popular Diets Reviewed’ on the WebCT). All patients should be counselled that the responsible, healthy way towards weight management is by balancing appropriate calorie intake and physical activity.

‘Popular Diets Reviewed’ by the American Dietetic Association

http://www.eatright.org/Public/Files/popdiets_fact_2-04.pdf

‘Campaign Against Fad Diets’ by the American Heart Association

<http://www.americanheart.org/presenter.jhtml?identifier=2172>

‘Popular diets: the good, the fad and the iffy’ by the Mayo Clinic

<http://www.mayoclinic.com/invoke.cfm?objectId=5F0EFE07-2043-411C-A49B407640B28BFE>

Ketogenic Diets for Weight Loss.

The current fad trend is towards low-carbohydrate or ketogenic diets (also sometimes called high-protein or high-protein-high-fat diets). The 'rationale' behind this approach is based on extreme metabolic changes that occur in starvation. When food intake stops, catabolism turns initially towards glycogen stores and then protein and finally fat. While muscle, heart and liver can use fats as fuel, nervous tissue normally requires a supply of glucose. When food is not eaten for several hours extending to a few days and glycogen stores are exhausted, glucose is obtained from protein which is impossible from fat (why?). Ingested carbohydrate is therefore normally 'protein-sparing'. Death would ensue quickly if protein continued to be used for fuel. So the body switches its metabolism to breaking down fat into ketone bodies (acetoacetate, acetone and β -hydroxybutyrate), substances that nervous tissue can use. Without food, survival continues until fat stores are depleted or until lean tissue (protein) is approximately 50% depleted, whichever comes first.

Ketosis is not a 'natural' state for the body and there are several problems with using very low carbohydrate diets to encourage weight loss by ketosis (fat utilization):

- C Such diets tend to include or encourage excessive amounts of foods high in saturated fat and/or cholesterol which are unhealthy;
- C Ketogenic diets tend to depress appetite and cause fluid loss, both of which are unhealthy but give the appearance of effectiveness;
- C Dehydration and electrolyte imbalances can occur since sodium is lost with the diuresis;
- C When carbohydrate is severely restricted, subjects can become constipated (dehydration) and experience weakness and fatigue (lack of carbohydrate for energy) as well as nausea and halitosis (ketosis);
- C Increased uric acid levels can occur leading, in susceptible individuals, to gout and/or the formation of kidney stones;
- C Such diets can restrict micronutrient intake with resultant dependency on supplements;
- C Proponents of these diets typically claim that carbohydrate-containing diets cause an overproduction of insulin and that this causes overeating and obesity and leads to insulin resistance and diabetes. It is not that simple! Obesity and hyperinsulinemia have been linked with diets high in fat and low in fiber and starches. Moreover, it has been shown that increasing dietary fat leads to increases in both caloric intake and body weight. On the other hand, when obese people who are accustomed to a high-fat diet adopt a high-carbohydrate, very-low-fat diet, their caloric intake decreases and they lose weight.

Are Low-Carbohydrate Diets Good for What Ails You?

<http://www.acsh.org/publications/priorities/0804/diets.html>

Some Pediatric and Geriatric Nutrition

Learning Objectives

1. To summarize some nutritional principles in regard to pregnancy.
2. To list common supplements given to pregnant women, and sometimes prior to pregnancy.

3. *To identify human breast milk as a completely adequate source of protein, energy and micronutrients for the initial 4-6 months of life.*
4. *To be aware of several CFPC 10-step programs relating to pediatric care.*
5. *To identify that iron supplementation is required once a baby starts to eat cow's milk.*
6. *To identify linoleic acid as an important essential fatty acid to a baby's initial growth.*
7. *To identify the elderly as a population at risk for malnutrition in our society.*
8. *To identify the importance of simple questioning to identify elderly patients at risk to becoming malnourished.*
9. *To summarize some reasons why the elderly are at risk to nutritional problems.*
10. *To appreciate that most dietary guidelines for the general population are applicable to the elderly.*
11. *To define enteral and parenteral feeding and describe principles in each approach.*

Pregnancy.

By definition a LBW infant is less than 2,500g (5.5 lbs) and is nearly 40 times as likely to die in the first year of life as a normal baby. It is important that women considering pregnancy should be counselled to achieve an IBW (ideal body weight). This is particularly so for underweight women who otherwise will be more likely to bear a low birth weight (LBW) infant. Achieving an IBW before pregnancy is also important for obese women who may be at risk in developing gestational diabetes and hypertension. It used to be the practice to guard against large weight gain during pregnancy. But good weight gain is associated with increased body weight in infants and fewer LBW infants.

Good nutrition before pregnancy is essential because it ensures the adequate growth of the placenta - the organ upon which the fetus depends completely for life and nourishment. Pregnant women's food choices should be towards foods of high nutritional quality and away from calorie-rich foods. Pregnant women and women contemplating pregnancy should be counselled not to smoke or consume recreational drugs including alcohol. All can give rise to LBW infants and poorer outcomes for the baby. The poorer the nutritional status of women entering pregnancy, the more valuable is nutritional supplementation to the course of pregnancy and birth outcome.

Pregnancy Supplementation.

Pregnant women should give special attention to ensuring adequate consumption of energy, protein, iron, calcium, vitamin D, folate and essential fatty acids. Supplementation may be necessary.

[Some specific guidelines are: a) an additional 300 kcal/day of energy; b) an additional 10-15g of protein/day; c) an additional 0.4mg/day of folate. Folate should be increased in all women contemplating pregnancy and during pregnancy. Since the neural tube closes by 28 days of gestation, when few women are aware they are pregnant, it is important that folate nutrition be improved before pregnancy; d) an additional 15mg of iron per day in the 2nd and 3rd trimester; e) emphasize including good dietary sources of calcium and vitamin D.

Occasional supplementation with calcium and vitamin D may be necessary; f) encourage pregnant women to include sources of essential fatty acids such as soybean, canola oils and non-hydrogenated margarines, soy-based products (tofu, vegi burger); g) encourage the proper use of vitamin and mineral supplements. Women taking multivitamin/multimineral

supplements should be cautioned to take no more than one tablet per day to avoid exceeding intake of 10,000 IU (3,330 RE) of vitamin A (retinol) per day.]

Lactation.

Exclusive breastfeeding is encouraged for the first four months of life. The current initiation rate in Canada is about 73%. The “Baby Friendly Hospital Initiative” is an effort by the WHO to encourage breastfeeding worldwide. Women are have been encouraged to ensure that the hospital they choose to have their baby in is “Baby Friendly”. Baby Friendly hospitals:

1. Have a written policy on breastfeeding that all health care staff know.
2. Train all health care staff so they can make the policy work.
3. Teach all expecting mothers what is good about breastfeeding and how to get started.
4. Help mothers start breastfeeding within one-half hour after birth.
5. Show mothers how to breastfeed and how to keep their milk supply if they have to be separated from their baby.
6. Give newborns no food or drink other than breastmilk unless medically necessary.
7. Practice rooming-in - in other words, allow mothers and babies to remain together 24 hours a day.
8. Encourage baby led feedings - no schedules.
9. Give no pacifiers (also called dummies or soothers) to breastfed babies.
10. Encourage the growth of breastfeeding support programs and refer mothers to them.

Since many women do not now spend a lot of time in hospital post-partum now, there is often not adequate time to train mothers. Taking their cue from the WHO, the College of Family Physicians of Canada has developed several “10-Step Programs” to promote various aspects pediatric health, including breastfeeding.

See

<http://www.cfpc.ca/English/cfpc/programs/patient%20care/child%20health/appendices/default.asp?s=1#Appendix%20Ib>

Infants.

Babies initially lose weight but birth weight (BW) should be regained by 7-10 days of life.

Babies usually double their BW by 4-6 months and triple it by one year. The adequacy fo an infant’s nutrition is judged by careful attention to milestones in weight and length.

Babies require more protein than adults (on a weight basis). Human milk is perfectly adequate as a source of energy, protein and fat. After the first 6 months, additional protein may be given as yogurt, strained meat or cereal. Linoleic acid should provide 3% of the baby’s total energy calories (human milk is 5% and formula is usually 10%). Iron absorbability from human milk is 50%, whereas it is only 1% from cow’s milk. Infants fed cow’s milk only are at extreme risk of developing iron deficiency. Iron should be given after 4-6 months as iron-fortified cereal or formula. Fluoride is usually present in prepared foods and not recommended as a supplement.

Some differences regarding energy from human and cow's milk:

	<u>Human</u>	<u>Cow</u>
	<u>% of Calories</u>	
Protein	7%	20%
Lactose	42%	30%
Lipids	51%	50%
(Linoleic Acid	4%	1%)

“Nutrition for a Healthy Pregnancy” is a useful set of guidelines from Health Canada which discuss nutrition and healthy eating not only during pregnancy but throughout the childbearing years as they relate to pregnancy. The guidelines are directed to health practitioners who, through the course of their work, regularly offer nutrition-related advice and guidance to women. A copy of the document is in the LRC. It can also be viewed or downloaded here:

[\[http://www.hc-sc.gc.ca/hppb/nutrition/pube/pregnancy/table.html\]](http://www.hc-sc.gc.ca/hppb/nutrition/pube/pregnancy/table.html)

Nutrition in the Elderly.

Whereas it is children who suffer most from malnutrition in the Third World, it is the elderly who are most at risk in our society. But old people who are disease-free and socially integrated should be at no greater nutritional risk than anyone else. After retirement and removal from the stress of work, elderly people should be encouraged to give more time to enjoyable exercise and to carefully selecting and preparing food. Malnutrition in the elderly is just one of several interacting features including diminished mental function, decreased physical ability, social withdrawal and weight loss.

Nutritional Risk in the Elderly.

Older adults run the risk for malnutrition for many different reasons, poor appetite, lack of money, disease and dental problems are just a few. Recognizing that older adults are at risk is the first step in helping them make changes. Elderly risk can be assessed by the number of positive responses to the following statements:

- C I have an illness that makes me eat different kinds / amounts of food;
- C I eat fewer than two meals a day;
- C I eat few vegetable and fruits and use few dairy products;
- C I have three or more alcoholic drinks per day;
- C I have tooth or mouth problems that make eating difficult;
- C I don't always have money to buy the food I need;
- C I eat alone most of the time;
- C I take 3 or more prescribed or over-the-counter medications per day;
- C Without wanting to, I have lost or gained 10 lbs (4.5kg) in the last 6 months;
- C I am not always physically able to shop, cook, and/or feed myself.

Approach to Patients.

Some of the physical changes affecting nutrition include impairment to: a) the digestive tract which can lose muscular strength and motility - constipation is common; b) hormones. The pancreas secretes less insulin and cells have lowered insulin-sensitivity; c) oral health. Chewing may be more difficult due to tooth loss and sore gums. Salivary output is less; d)

smell and taste can be lowered, causing poor appetite; e) weight loss and decline in healthy lean mass may increase lassitude and lack of energy.

Most dietary guidelines for younger adults hold true for elderly people without disease: a) even though energy intake will be smaller, eat a variety of nutritional foods to ensure a good mix of nutrients; b) guard against obesity which can strain osteoarthritic joints as well as ageing heart and lungs; c) implement regular enjoyable daily physical exercise into the elderly lifestyle; d) reduce saturated fat levels although it is controversial how much survival advantage can be gained in very old people; e) encourage eating plenty of bread and cereals, vegetable and fruit which will add to dietary fibre and decrease risk of constipation; f) Limit alcohol consumption as it is less easily metabolized by smaller livers and the consequences of falls and accidents are more serious; g) cut down on salt to decrease hypertension and risk of stroke.

Care of Seriously Malnourished Patients - Enteral and Parenteral Feeding.

During the care of certain patients in hospital (and increasingly at home) a liquid, homogenized diet or a semi-purified elemental diet will be used to provide adequate nutrition. These expensive and mechanically-challenging treatments are used in specific clinical situations where patients are unable to eat, are seriously ill or post-surgery, or have a problem with some portion of the gastrointestinal tract.

Enteral Feeding: This is the first option to be used in patients whose small intestinal function is maintained. They may have facial/jaw injuries, swallowing disorders, or be immobile from trauma, major burns or in post-operative recovery. Enteral feeding of a liquid diet can be administered via a nasogastric, nasoduodenal or nasojejunal tube depending on the patients GI problem, or feeding tubes can be placed in the stomach or in the intestine surgically or using endoscopy. Since intraluminal nutrients, especially glutamine, promote gastrointestinal function, enteral feeding should be the first option when adequate oral intake is not possible. Enteral feeding is also much less expensive than parenteral nutrition, has fewer complications, and is monitored more easily. A variety of liquid diets are available for enteral feeding including blenderized food, milk-based or lactose-free diets, all of which contain protein, carbohydrate, lipid and micronutrients.

Parenteral Feeding: When patients have a bowel obstruction, intractable vomiting or diarrhea, severe bleeding of the upper GI tract or are at a high risk for respiratory aspiration, then the enteral route must be by-passed for feeding purposes. Total Parenteral Nutrition (TPN) describes the treatment via a peripheral or central vein of a purified diet which meets all of the nutrient requirements of the patient. Long-term TPN is challenging: the entire diet must be prepared and maintained aseptically along with the venous delivery line and site. TPN solutions typically contain all essential amino acids, dextrose, lipids containing essential fatty acids, vitamins, minerals and trace elements.

[See <http://w3.ouhsc.edu/mguild/medicalnutritiontherapy/support.htm>]

Health, Life Extension, Probiotics and Antioxidants

Learning Objectives

1. To summarize that certain oxygen species including singlet oxygen, hydrogen peroxide and free radicals such as superoxide and hydroxyl anions are damaging to cells by oxidizing lipids, proteins and nucleic acids.
2. To recognize that certain vitamins may have functions outside their role in preventing classical deficiency syndromes.
3. To summarize the antioxidant properties of vitamins C and E and β -carotene.
4. To recognize that certain phytochemicals may be responsible for the beneficial effects of fruit and vegetables on the development of cancer.
5. To define probiotics, prebiotics and synbiotics and their role in intestinal microflora.
6. To recognize that 'hard evidence' to support a preventive role for antioxidants in chronic disease is still scarce.
7. To appreciate that routine supplementation with vitamins does not substitute for eating a balanced diet.

Nutrients, Health and Life Extension.

It is important to understand that the 'antioxidant' function of many vitamins stands apart from their role as micronutrients. Micronutrients are required dietary constituents to prevent deficiency disease, whereas antioxidant supplements are often taken in pharmacological amounts to lower the damaging potential of oxidative metabolism. Many patients confuse these and this contributes to the simplistic philosophy "you are what you eat" and that everything can be cured or prevented by diet. This view appears to be particularly prevalent in affluent societies where gross nutritional deficiencies are uncommon!

Oxygen Damage and Antioxidants.

There is much controversy about the possibility that the antioxidant function of vitamins C, β -carotene (and other carotenoids) and E (α -tocopherol) may preserve health and prevent the development of chronic disease. It should be understood that the antioxidant function of these compounds is outside any benefit they have as cofactors in preventing deficiency disease. Our bodies need antioxidants because, while oxygen is essential for life, several reactive forms of oxygen are potentially damaging to cells. These include hydrogen peroxide, singlet oxygen and free radicals such as superoxide ($O_2^{\cdot-}$) and the hydroxyl radical (HO^{\cdot}). These unstable oxygen species have been shown to be very reactive *in vitro* and can damage essential cell components such as lipids, proteins and nucleic acids. As a result they have been implicated in disease processes such as cancer and heart disease, as well as in the mechanism of aging. Peroxidation of polyunsaturated fatty acids in LDL can lead to oxidation of apolipoprotein B. This can predispose the damaged LDL to uptake by scavenger LDL receptors on macrophages. This may transform the macrophages into "foam cells" which participate in the formation of atherosclerotic plaques. Similarly free radical damage may cause mutations to nuclear DNA and, depending on the sequence damaged, may lead to malignant change.

Phytochemicals.

Lots of recent research is taking place on possible health benefits of phytochemicals (*phyton*, Greek for plant), specific chemicals in vegetables which are not vitamins or carotenoids. These include polyphenols and flavonoids, isothiocyanates, monoterpenes, phytoestrogens (isoflavones), saponins, capsaicin and sterols. Several organosulfur compounds being investigated include *sulforaphane*, a compound in cruciferous vegetables (broccoli, bok choy, cabbage, cauliflower, collard) which has been shown to prevent the development of breast tumors in rats by activating several carcinogen detoxifying enzymes within cells. Also garlic and onions contain *allylic sulfides* that may reduce the development of stomach cancer. Such studies of individual phytochemicals are unlikely to demonstrate a single entity that provides a rationale for the beneficial effects of fruits and vegetables on health. It is likely that vegetables and fruits are healthful because of some balance of phytochemicals, carotenoids, vitamins, fibers, and minerals that they contain.

[See <http://www.well-connected.com/report.cgi/fr000039.html>]

Probiotics, Prebiotics, and Symbiotics.

The human gastrointestinal tract is home for over 400 species of bacteria which, for the most part, help keep us healthy. It is well-known that when the balance is disturbed by some by some insult (such as antibiotic use or eating a salmonella infected burger) or condition (Crohn's disease, trauma) illness can result from the elimination of certain protective organisms (such as *Lactobacillus* or *Bifidobacterium* species), by the penetration of the gut wall by pathogens, and/or by the overgrowth of the pathogens. Also the pathogenesis of some GI diseases, e.g. inflammatory bowel disease, and even multiple sclerosis or Reuter's syndrome, is thought to be related to disharmony between intestinal microflora and the patient's intestinal cells and immune response.

In promoting health and disease resistance, there is much interest and research into bacteria that may beneficially affects the human host through their effects in the intestinal tract.

Probiotics are the use of living microbes to confer health benefits to the host. Most probiotics are taken by mouth and designed to impact the intestine. *Prebiotics* are nondigestible food ingredients which microorganisms in the intestine use selectively, the result of which is a health benefit to the host. An example would be fructooligosaccharide. A symbiotic is a food product in which both a probiotic and a prebiotic are combined with a view to providing an additive or synergistically beneficial effect on the host by improving the survival and/or implantation of the probiotic in the intestinal tract.

Some studies have demonstrated that probiotics can improve local and systemic immunity, reduce diarrhea, improve tolerance to milk and reduce milk allergy and may decrease the risk of cancer and heart disease.

[See <http://www.nationaldairycouncil.org/health/digest/dcd70-6.asp>]

So, do Antioxidant Vitamins Prevent Chronic Disease?

Retrospective epidemiological studies have supported the concept that some vitamins are health promoters by showing that intakes of fruits, vegetables and carotenoids may reduce the risk of cancer and/or cardiovascular disease. For example, more than 50 epidemiological studies have found that consumption of foods high in β -carotene is correlated with a reduced rate of certain cancers of epithelial origin. However, the association of reduced cancer risk with specific supplements has been more difficult to demonstrate and the studies are

controversial. Nonetheless antioxidant vitamins are being actively studied as agents to preserve health and the subject is often highlighted in the popular press. Sales of vitamin supplements have soared in recent years. In the U.S. alone in 1993, sales of vitamin B increased by 7%, vitamin C by 10%, β -carotene by 31% and vitamin E by 39% (to \$123 million).

A bottom line on supplements.

While there are several medically-appropriate situations where supplementation is warranted, the current common public practice of taking supplements on a non-prescribed basis is justified by few professionals because the evidence that it reduces mortality or improves morbidity is equivocal. Therefore, before buying any supplement consumers should ask: "Am I likely to be deficient in any vitamin or mineral?", "Are these supplements really necessary for my health?", "Are they good for me?", "Can they be harmful to me?". Here are several reasons why supplements are not a substitute for eating a balanced diet:

1. Food provides all 6 types of nutrients, supplements do not.
2. Many nutrients work together, e.g. iron and vitamin C, calcium and vitamin D.
3. Nutrients in supplements may not be as absorbable as those in food.
4. New functions are continuing to be found for food constituents whose major metabolic function has been long known, e.g. for many years it was thought that β -carotene was only a precursor for vitamin A.
5. Excess of some nutrients can lead to toxicity syndromes.

**[CONTENT OF A VITAMIN AND MINERAL SUPPLEMENT]
(Multivitamin Multimineral Formula Forte)**

The multivitamin-multimineral pills, advertised as “29 Essential Vitamins and Minerals with β -carotene”, were purchased in a drug store. No prescription was required. The table calculates the pill content of various nutrients (mainly micronutrients) in terms of their recommended daily intake amounts. The RDA (Recommended Dietary Allowance) levels were set by the Food and Nutrition Board of the U.S. National Academy of Sciences in 1989. In Canada, the RNI (Recommended Nutrient Intake) values are those from the Report of the Scientific Committee, Health and Welfare Canada, 1990. Tablet contents were converted to units common to RDAs and RNIs. The RDAs and RNIs are given for 25-year-old non-pregnant females (F) and 25-year-old males (M).

<u>Nutrient</u>	<u>1 Tablet Contains</u>	<u>RDA</u>	<u>RNI</u>
[Thiamin (B1)	2.25mg	F1.1 M1.5	F0.8 M1.1
Riboflavin (B2)	2.6mg	F1.3 M1.7	F1.0 M1.4
Niacin	20mg	F15 M19	F14 M19
Pyridoxine (B6)	3mg	F1.6 M2	F1.1 M1.8
Cyanocobalamin (B12) 9: g		FM2	FM1
Folic Acid	400: g	FM200	F185 M230
Biotin	45: g	FM30-100*	-
Panθοthenate	10mg	FM4-7*	-
Vitamin C	90mg	FM60	F30 M40
β -carotene	100RE	-	-
Vitamin A	1,200RE	FM1,000	F800 M1,000
Vitamin D	10: g	FM 5	FM2.5
Vitamin E	20TE	F12 M15	F6 M9
Calcium	175mg	FM800	F700 M800
Phosphorus	125mg	FM800	F850 M1,000
Magnesium	100mg	F280 M350	F200 M250
Potassium	30mg	FM2,000*	-
Choride	27.2mg	FM750*	-
Iron	10mg	F15 M10	F13 M9
Zinc	15mg	F12 M15	F9 M12
Copper	2mg	FM1.5-3*	-
Manganese	5mg	FM2-5*	-
Iodine	150: g	FM150	FM160
Chromium	25: g	FM50-200*	-
Molybdenum	25: g	FM70-250	-
Selenium	25: g	F55 M70	-
Nickel	5: g	-	-
Tin	10: g	-	-
Vanadium	10: g	-	-
Silicon	10: g	-	-

* Indicates where a “safe and effective daily dietary intake” was published rather than a RDA.
- A blank space indicates that insufficient scientific information prevented the setting of an allowance.]

URINANALYSIS LECTURE

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Tel No. 685-8300 ext. 77626

INTRODUCTION

Urinanalysis is among the most common procedures performed both within laboratories and directly at the point-of-care. The reasons for this are that specimens are usually easy to obtain, easy to test and the amount of information obtained is high and can reveal diseases that have gone unnoticed. The most cost-effective device used in urinalysis is the plastic dipstick. The 10-test strip costs about \$0.50 and a sterile container costs \$1.00.

But there are limits to the capabilities of the tests and there are possible errors which must be understood. From this lecture you will learn about the clinical information that can be obtained by examination of a urine sample, the principle features of the common dipstick test and an overview of microscopy of the urine sediment. Additional information will be provided about abnormal proteins in urine and about renal stones.

OBJECTIVES

- Be familiar with techniques of urine specimen collection and handling
- Learn the information that can be obtained from inspection of the urine.
- Understand the chemistries of the dipstick tests for the following:
Leukocytes, Nitrite, Urobilinogen, Protein, pH, Blood, Specific Gravity, Ketones, Billirubin, Glucose.
- Understand the mechanisms for the appearance of increased amounts of protein in urine (proteinuria) and how they are measured and identified.
- Understand the importance of measurement of small increases in urine albumin in certain diseases (microalbuminuria).
- Be familiar with the procedure for performing a microscopic examination of the urine sediment and the identities and main features of the components that can be so examined.
- Be familiar with types of renal stones that can be passed into the urine and the value of knowing their chemical composition.

CLINICAL INDICATIONS FOR UNIANALYSIS

- **Follow-up of renal disease**
- **Abnormal urine:** Dark, bloody, colored
- **Urination symptoms**
 - Pain (dysuria) and retention
 - Frequency (polyuria, nocturia, anuria)
- **Routine prenatal monitoring**
 - protein
 - glucose
- **Investigation of pain**
 - Lumbar
 - Abdominal
 - pelvic
- **Post Trauma** (blood)
- **Investigation of unexplained fever**
- **Investigation of hypertension**

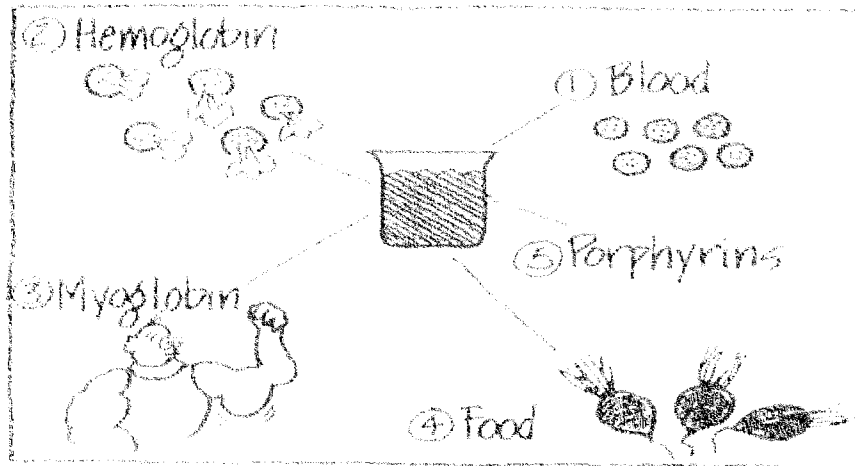
1. COLLECTION AND HANDLING OF URINE

"Random" refers to a single specimen opposed to collection over time (usually 24 h). An early morning sample probably contains most constituents of diagnostic significance. For clean-catch urine collect a mid-stream urine. A midstream urine minimizes urethral and periurethral contamination. In females the periurethral area should be cleaned and the possibility of menstrual contamination should be noted. Catheter specimens may be used and occasionally a clean specimen is best collected by percutaneous needle puncture of the fully distended bladder just above the symphysis pubis. Specimens are placed in prelabelled sterile container and tightly closed. If there is unavoidable delay in analysis, the specimen should be

2. INSPECTION OF THE URINE SPECIMEN

The first part of urinalysis is direct visual observation. Normal fresh urine is clear and pale yellow. If refrigerated it becomes cloudy due to precipitation of urates and phosphates which redissolve upon heating to 50°C for a few minutes. Cloudiness in a fresh sample suggests that white blood cells are present (pyuria) signifying bacterial infection of the urinary tract. Pieces of tissue debris in urine can come from damaged renal papillae or from bladder mucosa. Very dark brown or black urine can be caused by **Ochronosis**, a rare metabolic defect of tyrosine metabolism which causes black urine (Alkaptonuria). Hemoglobin, myoglobin and porphyrine in urine can also turn dark upon standing. **Billirubin** in urine has the appearance of concentrated tea. **Red color** of urine rings the alarm that **blood** may be present but can also be caused by certain foods (commonly beets) and certain drugs and candies. Fresh urine containing intact RBC's has a smokey appearance when swirled against the light. When RBC's disintegrate (1-2 hours) the color is clear red, brown or mahogany, depending on the amount of hemoglobin and the urine acidity. **Myoglobin** in urine cause red color if fresh or dark brown appearance. **Porphyria** is a rare genetic disorder of heme synthesis that can cause purplish red urine and gets dark upon exposure to light. Urine's pungent odor is due to ammonia released by bacterial action on urea. Urine acetone may be smelt in severe ketoacidosis. Some very rare genetic diseases can **Cause atypical odors (e.g. maple syrup urine disease, phenylketonuria)**

RED URINE (Common Causes)



COMMON CAUSES OF RED COLORED URINE

3. URINE DIPSTICK CHEMICAL ANALYSIS

Chemstrip 8 and chemstrip 10 manufactured by Bayer Diagnostics are the most commonly used dipsticks. Chemstrip 8 does not have bilirubin and urobilinogen detection reagents on the strip. In MD offices and small laboratories dipstick tests are performed manually and eyeballed while in high volume laboratories the analysis is automated, the results automatically read out and interfaced into the laboratory computer for reporting. It is most important to be aware of the possible interferences which may mislead the diagnosis by causing **false positive** and **false negative** results.

LEUKOCYTES AND NITRITE

- **Leukocytes**

Dipstick detects Leukocyte Esterase present in white blood cells (either whole or lysed). Pyuria can be detected even if the urine sample contains damaged or lysed WBC's. Infection is not likely in the absence of pyuria.

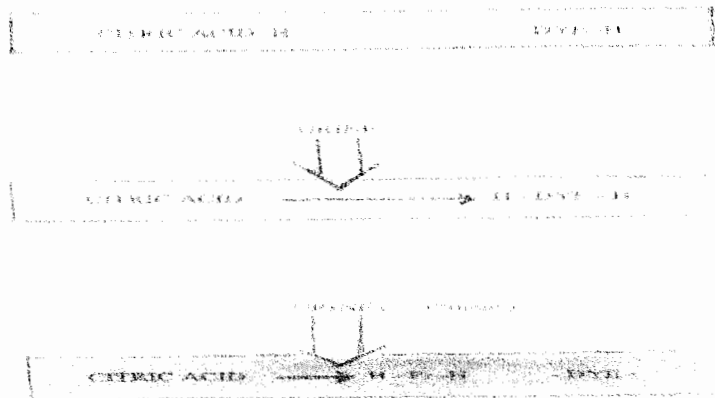
- **Nitrite**

A positive nitrite indicates that bacteria may be Present in significant number. In some routine Labs urine culture is only done when leukocyte/and or Nitrite is positive.

- **Protein**

Healthy glomeruli permit only very small amounts of plasma proteins of MW >65,000 to be filtered because of the small glomerular pore diameters and their prevailing negative charges. Diseased glomeruli permit escape of plasma Proteins, the major one being albumin. The smaller MW plasma proteins MW <35,000 daltons do pass through healthy glomeruli but are normally efficiently reabsorbed the tubules. Normal urine contains less than 150mg of protein per 24 hurs. Which is detected as either "negative" or "trace +" by The dipstick test. Note that the dipstick test is essentially a pH test which uses the buffering effect of protein to cause a +ve result. It is nonselective as to the protein species present in the urine. Albumin is the most common but the urine protein test responds to any protein that is present in sufficient amount to act as a buffer in the test strip. In certain cases it is necessary to identify the urine protein in the laboratory. The dipstick test should not be used as a screen test for free light chains (Bence Jones protein) which may be present in multiple myeloma and in certain other malignancies. These can only be effectively detected by urine protein electrophoresis.

EFFECT OF pH ON DIPSTICK PROTEIN



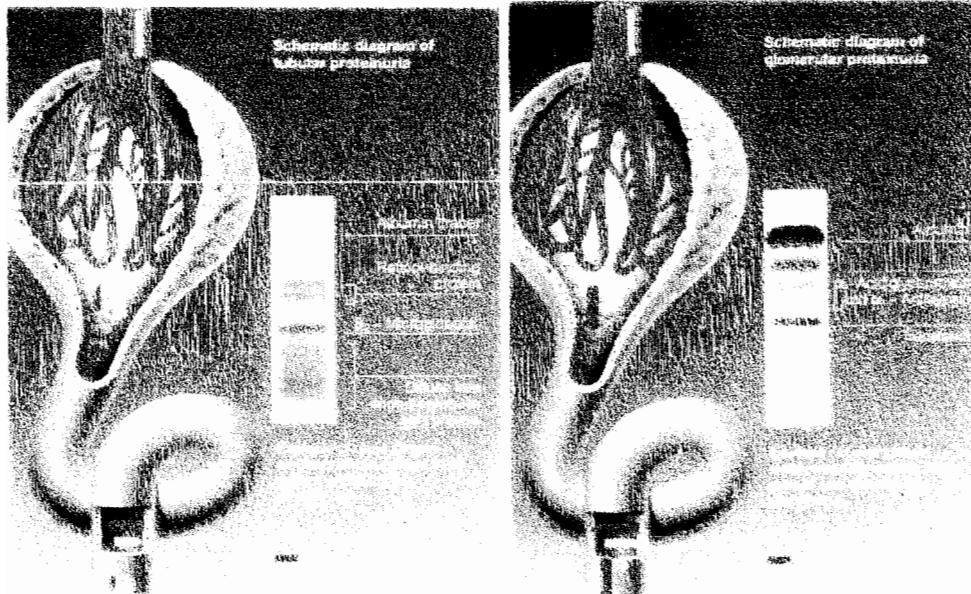
Strip contains an acid buffer and a color indicator which is yellow in acidic pH. Protein picks up Hydrogen ions and makes the Strip alkaline causing a blue color.

PROTEINURIA

Proteinuria (urine protein more than 150mg/day) is classified according to 3 underlying pathophysiological mechanism:

- **Glomerular Proteinuria.** This is the commonest type and usually corresponds to urinary excretion of more than 2 g/day. Major causes are glomerulonephritis and results into plasma albumin and some globulins to pass through glomerulus.
- **Tubular Proteinuria.** This is caused by inadequate reabsorption of small MW plasma proteins by the tubules. The amount of protein is usually below 2.0g/day. Tubular damage can be caused by heavy metal toxicity (Hg, Pb, Cd) , systematic lupus erythematosus, excess free light chain, bacterial infection of the kidney, and others. The predominant urine proteins are alpha and beta globulins (ex. Beta-2-microglobulin).
- 3. **Overflow Proteinuria:** Occurs when there is an **excess plasma level** of a filterable protein. Examples are **hemoglobinuria, myoglobinuria,** and **Bence Jones proteinuria.**

URINE PROTEIN ELECTROPHORESIS TO DIFFERENTIATE BETWEEN GLOMERULAR AND TUBULAR AND MIXED PROTEINURIA



Benign and Isolated Proteinuria

- **Orthostatic Proteinuria**

Occurs in 3-5% of adults less than 30 years old usually males and they excrete less than 2g/day of protein. To diagnose obtain 16 hr. urine with patient performing normal daytime activities then collect an eight hour overnight specimen. The night time would have normal protein, while daytime would be high. Annual urinalysis recommended on these patients.

- **Isolated Proteinuria**

Proteinuria with normal renal function and no evidence of systematic disease which could cause renal dysfunction, normal urine sediment and protein excretion less than 2g/day, monitor by urinalysis and blood pressure and creatinine clearance every 6 months.

- **Fever, Exercise**

- **False Positive**

Very concentrated urine, dehydration, alkaline urine

MICROALBUMINURIA

NOT DETECTED BY DIPSTICK. USED IN MONITORING DIABETIC PATIENTS BY VERY SENSITIVE QUANTITATIVE METHODS (IMMUNOASSAYS). THIS PERMITS EARLY DETECTION OF SMALL INCREASES IN PROTEIN (ALBUMIN) WHICH IS A HAZARD SIGN OF IMPENDING GLOMERULAR DISEASE. MORE AGGRESSIVE TREATMENT OF THESE DIABETICS AT EARLY STAGES OF RENAL DAMAGE WOULD OFTEN DELAY THE ONSET OF RENAL FAILURE. THE TEST CAN BE DONE ON RANDOM URINE AND REPORTED AS ALBUMIN CREATININE RATIO OR ON A 24 HOUR URINE AND REPORTED AS ug/L.

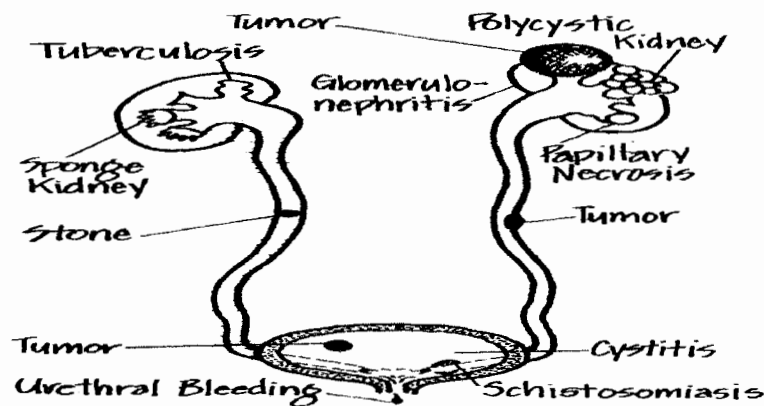
- pH

One of the functions of the kidney is to help maintain a constant pH (Hydrogen Ion Concentration) in the blood (about 7.40). The distal tubule excretes hydrogen and ammonia and reabsorbs bicarb to maintain this constant pH. Urine pH is usually 5.0 – 8.5 . Dipstick reagent contains color indicators which respond to urine pH. Urine can become alkaline on standing due to conversion of urea to ammonia by bacteria.

- Blood

The strip detects the presence of heme which is contained both in hemoglobin and myoglobin. Peroxidase-like activity present in heme oxidizes a reagent causing color Change. Biochemical analysis is required in cases where differentiation of these two abnormal urine constituents is required. The method does not differentiate between Hematuria and hemoglobinuria. See figure on major causes of hematuria.

Causes of Hematuria



CAUSES OF HEMATURIA

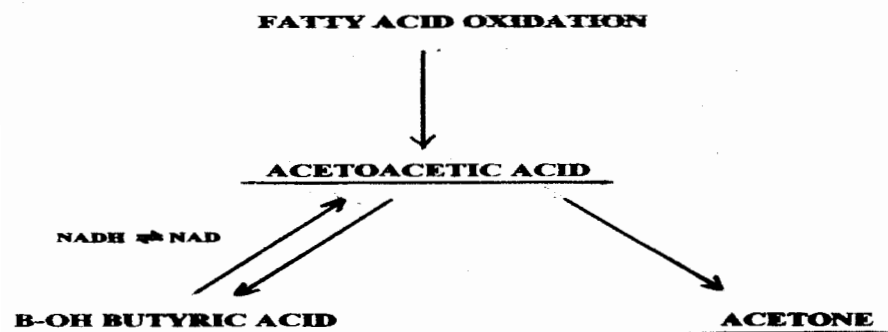
Injury to Kidney (trauma) can also cause hematuria

• Specific Gravity (SG)

The strip responds to total dissolved solids. In random specimens low SG is usually caused by urine dilution from ingested fluids it can also indicate disease eg terminal renal failure or posterior pituitary disease. In some cases persons may purposely dilute their urine to avoid detection of abnormality (eg life insurance or employment application). Refractometer best method for SG.

• Ketones

Normally produced in fasting persons and become detectable in urine. A strong positive test is consistent with ketoacidosis. Dipstick does not detect acetone or B-OH-Butyric acid. Other ketones ex. Phenylketones are not detected by routine dipstick. Phenysticks are specific for phenylketones which are present in phenylketonuria



- **Glucose**

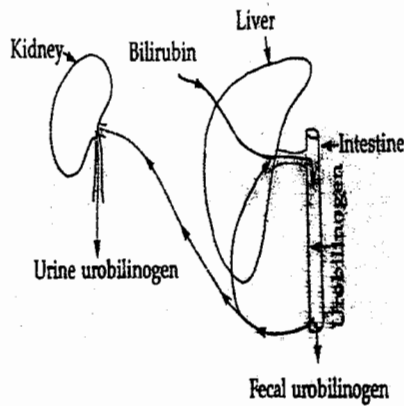
The dipstick detects specifically glucose. It does not detect any other sugars that are sometimes present in urine. An important example is galactose in galactosemia. It and other reducing sugars can be readily detected by the clini-test tablet which uses copper reagent. Increased urine glucose (glucosuria) is hallmark for Diabetes Mellitus but it can also rarely occur in the absence of diabetes eg renal tubular defect for glucose reabsorption.

Reaction used for detection of glucose

GLUCOSE (30 Seconds)



• Billirubin and Urobilinogen



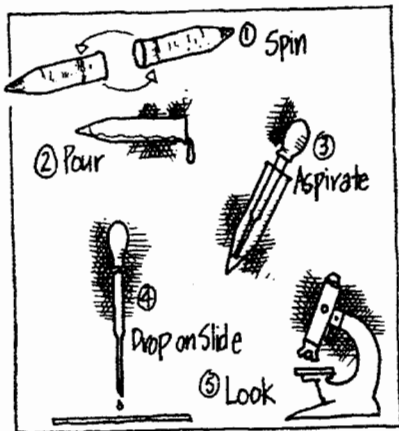
In Hepatic Jaundice there is increase in urine billirubin. Urobilinogen is variable.

In Obstructive Jaundice, billirubin is increased

In Hemolytic Jaundice urobilinogen is increased

Normal pathway of bilirubin and urobilinogen.

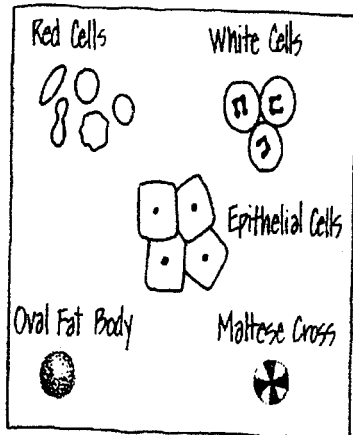
4. MICROSCOPIC URINANALYSIS



STEPS IN PREPARATION OF URINE SEDIMENT

Microscopic examination of the urine sediment for cells and casts is less often performed since the dipstick procedures have become well established. At times it is necessary to examine the urine sediment and a brief overview of the procedure is included here. Microscopic examination requires that urine be centrifuged. The steps in the procedure is shown in the figure. The sediment is examined for crystals cells, casts and bacteria.

Urine Microscopics: CELLS



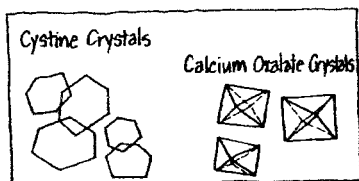
- **Red Blood cells** appear normally shaped, swollen by diluted urine or crenated by concentrated urine. The presence of dysmorphic RBC's in urine suggests a glomerular disease Such as glomerulonephritis. Dysmorphic RBC's have odd shapes as a consequence being distorted via passage through the abnormal glomerular structure.
- **White Blood Cells** (bicumate nucleus)
- **Epithelial cells** are sloughed from lining of urinary tract, if in large number suggestive of nephrotic syndrome and in conditions leading to tubular degeneration
- **Oval fat bodies** are fat laden cells seen in the urine in heavy proteinuria. They have characteristic "Maltese Cross" appearance under polarized light.

FORMED ELEMENTS SEEN IN URINE SEDIMENT

URINE MICROSCOPIC: CRYSTALS

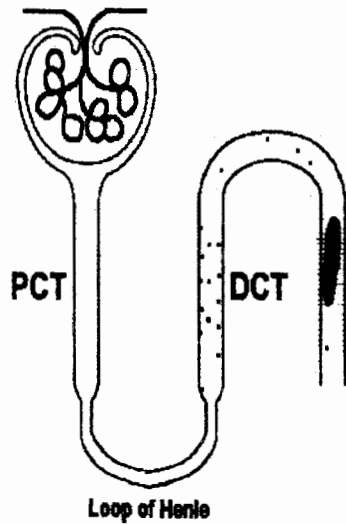


Common crystals can be seen even in Normal patients. Others are suggestive Disease. Crystals include urate , calcium Phosphate, cystine, Thyrosine (on the left) Calcium oxalate, triple phosphate, Leucine, sulfanamide.



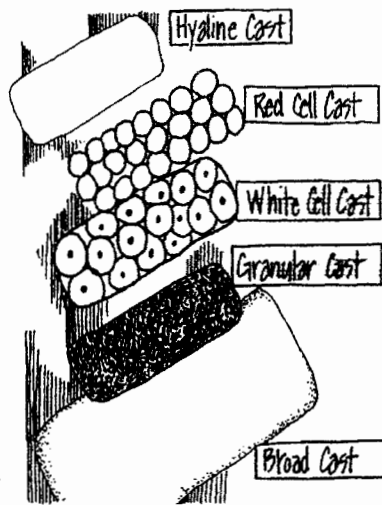
TWO CRYSTALS THAT MAY BE SEEN IN URINE SEDIMENT

URINE MICROSCOPICS: Casts



Urinary Casts are formed only in the distal convoluted tube DCT. and take the shape of the interior of the tubules. Most are about 20 microns in width (about 3 Red-cell diameters)

CASTS ... continuation



TYPES OF CASTS PRESENT IN URINE SEDIMENT

- **Hyaline Casts:** are made of Tamm-Horsfall Protein and normally few seen but more is seen proteinuric states.
- **Red Cell Casts:** can indicate glomerular leakage such as in acute glomerulonephritis, Lupus Nephritis and are diagnostically very important.
- **White Cell Casts:** are made up of pus cells and indicate renal infection or noninfectious inflammation, occasionally can be seen in glomerular disease.
- **Granular Casts:** are indicative of significant renal damage such as pyelonephritis, viral infection and chronic lead poisoning.
- **Epithelial Casts:** formed due to degeneration of renal tubular necrosis. Rare to see.
- **Broad Casts:** are formed in the dilated distal tubules of patients with chronic renal failure. They are up to 70 microns in diameter.
- **Fatty Casts** in nephrotic syndrome and chronic glomerulonephritis.

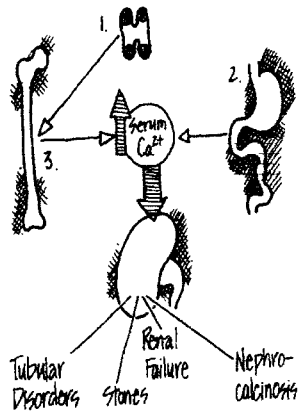
Other microscopic structures

- Bacteria: Unless found in fresh sample may have little significance as contamination or collection is the usual cause
- Yeast: Could indicate a fungal infection of the bladder but more likely is a contaminant from vaginal infection or colonization
- Parasites: Such as Trichomonas Vaginalis are significant but many others can be contaminants from swimming in infected water
- Contaminants such as starch, spermatozoa, threads, fat etc. could be easily identified

5. KIDNEY STONES

Renal colic is the intense pain that is experienced when a stone passes from the renal pelvis into the ureter. The urine passed is frequently collected and examined for the presence of a stone which may be very small. The laboratory recovers these by filtering the urine. They are usually then chemically analysed because the composition of the stone may provide a clue to its cause which may be treatable. Calcium containing stones may be caused by hypercalcemia (eg due to hyperparathyroidism), uric acid stones occur in gout and cystine stones occur in the genetic disorder "cystinuria".

STONES



Most common stones are calcium stones
Such as Calcium Oxalate and calcium
phosphate (90%). Uric acid stones (8%)
Cystine stones (2%).

Struvite are calcific stones which also
Contain Mg, NH₄ and PO₄. These are
infective stones

EFFECTS OF HYPERCALCEMIA ON THE KIDNEY

Objectives for lecture and 2-hr small groups:

The student will be able to describe/discuss:

- the molecular concept of type 1 Diabetes Mellitus
- the fact that insulin amino acid sequence differs amongst animals ... as for many proteins
- the presence of insulin receptors on muscle and fat cells
- the 'absence' of insulin receptors on nerve, glomerular, and eye-lens cells
- ketoacids as a logical result of unsuppressed hormone-sensitive-lipase
- the immediate danger of ketoacidosis due to low insulin, and hypoglycemia due to high insulin, in type 1 patients
- the molecular concept of an injected SC or IM tissue depot of insulin, vs IV
- the fact that care of the diabetic hinges on daily (even hourly) commitment of the patient to self-management, balancing appropriate lifestyle choices with pharmacologic therapy

In Year I Medicine we will consider the relevant molecular underpinning of diabetes, its presentation, and its health impact and management. Further issues of ketoacidosis and treatment will be examined in subsequent years. How might one **define DM?** *a metabolic disorder characterized by hyperglycemia due to defective insulin secretion, insulin action, or both.* The term, *diabetes*, refers to *high urine output*.

We begin with a child diagnosed with type 1 diabetes mellitus. She had presented with symptoms and signs that resulted from having no insulin bound to her insulin receptors on muscle and fat cells, and from a high concentration of glucose in her blood. There was a history of progressive weakness: a previously energetic child becoming less-than-bouncy (always a red flag). The FP had elicited a history of thirst, dry mouth, and painless polyuria. Past medical H_x was negative, and family H_x is usually negative in type 1 DM. Normally a person who has a blood sample drawn before breakfast (a "fasting blood sample") would have a serum glucose concentration of somewhere between 3.3 and 6.0 mmol/l (even a non-fasting sample should be less than about 7.8). For a non-pregnant person a fasting blood glucose level of ≥ 7.0 would provide at least a tentative D_x of diabetes mellitus. We saw that the little girl's was 4 times this range. Nevertheless she seemed alert and oriented. Her temperature was 37.5° C, and auscultation revealed good air entry bilaterally with heart sounds S₁S₂ and regular. HR 75, BP 100/60. The patient seemed to be breathing very deeply. Head and neck examination was remarkable only for dry mucous membranes. The rest of the exam was unremarkable except for warm dry skin.

A urine specimen showed the presence of glucose and ketones (both pathological) when a test strip was dipped into it. Blood was drawn for analysis of CBC, electrolytes, ketones, BUN/creatinine, liver profile, glucose. Creatinine was normal because her renal function was good, but BUN was elevated because she was dehydrated. Serum K⁺ was elevated and she had elevated levels of ketones (acetone, β -hydroxybutyrate, and acetoacetate) in her blood because her insulin receptors were unoccupied.

We will see that after years of poorly-controlled type 1 DM we will be very concerned about damage to the patient's blood vessels, nerves, retinae, and kidneys (and psyche) which are typically considered to result directly or indirectly from high blood glucose levels in particular. Great problems of soft tissue infection and cardiovascular disease will result. But in this young person whose pancreas islet cells are only recently failing, we will not expect such problems. We will be acutely concerned about her state of (de)hydration, the presence of organic acids in her blood, and her dangerously-upset electrolytes (especially

K⁺ which can easily cause her heart to malfunction). Her serum bicarbonate (HCO₃⁻) will be low because of the presence of ketoacids (metabolic acidosis). Glucose will have overflowed into her urine (the kidney proximal tubule can recover all the glucose lost by the glomerulus, *if and only if*, the blood sugar concentration is kept within normal limits). High urine osmolality resulting from high concentrations of glucose and ketone bodies will draw water out with it and dehydrate her tissues. If the vascular volume becomes really low, the tissues will be so poorly perfused (and hence poorly supplied with O₂) that they will rely excessively on anaerobic glycolysis and produce excess lactic acid (which will be only slowly removed and thus will accumulate causing further acidosis).

Type 1 DM is due to failure of the β-cells of the pancreatic islets - presumably due to autoimmune destruction. Hence an exogenous supply of insulin is needed. In an acutely ill patient one will typically deliver this intravenously; but more commonly on a day-to-day basis one will inject small depot doses subcutaneously (since the lifetime of insulin in the bloodstream is minutes, the route of delivery has special significance). Human insulin is available from recombinant DNA technology these days (and has a slightly different amino acid sequence from beef or pork insulin). A major effect of insulin binding to adipocyte surface receptors is to suppress mobilization of adipocyte triglyceride stores (it inhibits the action of *hormone sensitive lipase*), and also to directly push glucose metabolism toward energy production. Thus in the absence of insulin, free fatty acids are high in the bloodstream (and this causes ↓ glycolysis & ↑ gluconeogenesis ... both of which lead to elevated blood glucose).

Insulin increases the amount & activity of key glycolytic enzymes. Insulin also stimulates lipoprotein lipase in the blood vessels to release fatty acids from lipoproteins, and it stimulates adipocyte enzymes that reform these fatty acids into triglycerides for storage. Insulin suppresses the degradation of protein and glycogen, and drives sugar and amino acids from the blood into cells. {by the way, you might guess that in the case of low blood sugar due to an insulin overdose the body would quickly and effectively compensate by secreting glucagon, adrenalin, cortisol, and growth hormone; and by using alternative fuels such as fat ... but it seems that '*pharmacological*' (ie. *unnaturally high*) doses of insulin will over-ride these other signals, and also prevent fatty acid release from adipocytes}

Untreated, a patient with type 1 DM (older names being *juvenile onset diabetes* {JOD} or *insulin dependent diabetes mellitus* {IDDM}) has almost no insulin: this leads to a general inability to utilize glucose. So blood glucose built up in our patient's bloodstream, yet the girl's insulin-receptor-bearing cells were getting none because it was not being transported across their membranes (they need insulin to make insulin transporter proteins). Even glucose that *did* happen to get into such "insulin-responsive tissues" (tissues that normally have insulin receptors) was unused because insulin is needed to stimulate the machinery such as TCA cycle and glycolysis. [Insulin-*unresponsive* cells such as nerves and the lens of the eye still got glucose by insulin-independent transporters.] So in our patient, adrenal cortisol turned on gluconeogenesis and protein degradation, and amino acids began to be looted from proteins to provide carbon skeletons for everyday processes that rely on TCA cycle intermediates (eg. heme manufacture). Lack of suppression by insulin let fat mobilization run wild. Acetyl CoA built up from massive fatty acid release, and channeled more by mass action into acetoacetate → β-

hydroxybutyrate and acetone. These ketoacids, and high serum K^+ (K^+ is normally pumped into cells in response to insulin, as is glucose), led to metabolic acidosis, and compensatory deep breathing to blow off CO_2 . K^+ was steadily lost from cells into the blood, and from the blood into the urine. The high solute load of sugar & ketone bodies in blood and urine dehydrated cells of the body by osmosis. All these things will correct frighteningly rapidly (K^+ and glucose levels could easily over-correct) when you inject insulin, as follows:

An IV would logically be started running normal saline. The protocols for rehydration vary widely, but generally presume that the patient will need lots of fluid and electrolyte replacement over 24 hours. Insulin would be preferably given IV; but likely none would be given immediately if the serum potassium were low. There are also lots of protocols for insulin treatment at this stage, and some argue for an initial *bolus* of insulin (others argue that there is no evidence that this is good and that it is unnecessarily risky). In the older days especially, some insulin might have been given as a bolus IM. In any case, if treated with insulin, the patient's blood picture might be expected to have changed dramatically when checked 15 min later, with a precipitous drop in serum K^+ , glucose 18, pH 7.3, serum osmolality closer to the normal range. The patient might become much more 'peppy'. K^+ concentrations in serum are always carefully watched because the heart's electrical activity needs it to be in a very narrow range and K^+ is strongly affected by insulin. Likely one is going to have to add K^+ and glucose to the IV eventually as their concentrations in the blood drop.

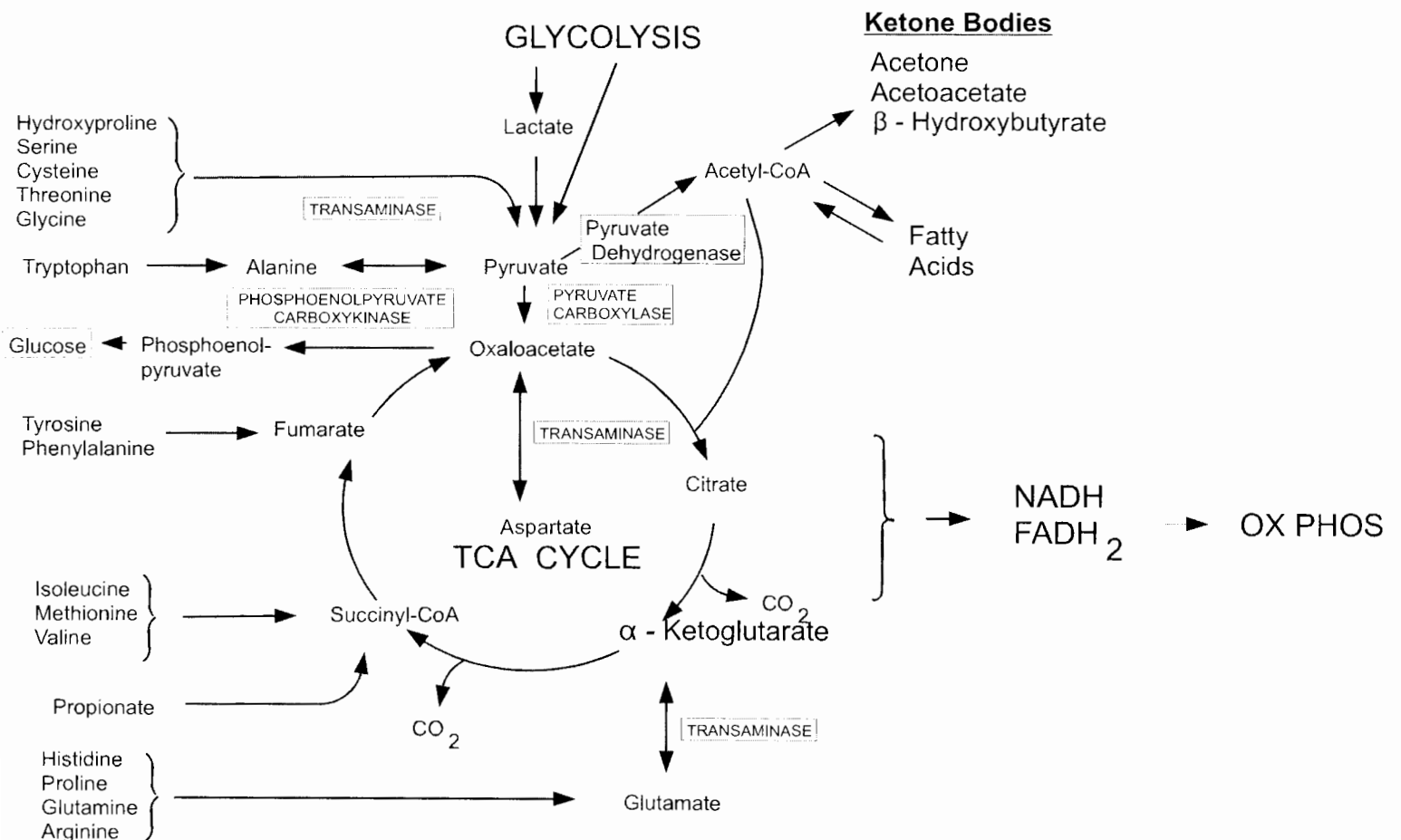
Hormone-sensitive lipase in adipocytes is the most significant control point for fatty acid breakdown. Muscles prefer fatty acids as fuel (most organs do), and can't take up or use glucose from the bloodstream in the absence of insulin. Thus the most important action of insulin in terms of promoting glucose consumption is to stop fatty acid release from adipocytes. But insulin also potentiates glucose use by many large tissues (and K^+ uptake) ... so that injection of insulin to a diabetic can cause rapid reversal of all the above, which is both excellent and dangerous.

The brain consumes a lot of energy constantly in maintaining electrical activity (ion gradients constantly collapsing and being regenerated by membrane pumps). Hence it needs efficient (aerobic) fuel use. Under normal conditions, the brain is almost totally dependent upon glucose as fuel. It has little fuel storage, so low glucose levels are much more deadly than high; and before quick sugar test strips existed, one often gave a glucose bolus before trying to figure out whether an unconscious diabetic was hyper- or hypoglycemic. (In starvation though, over several days the brain up-regulates certain enzymes that permit effective utilization of ketone bodies.)

INSULIN: A 6,000 MW protein. Synthesised (2-4 units/hr) in β -cells of pancreatic islets by cleavage of *C-peptide* from *proinsulin*. Insulin is anabolic: leads to \uparrow transport of glucose and amino acids into muscle, fat cells, and liver; and glucose phosphorylation in the liver. Thus insulin \implies \uparrow synthesis of glycogen, triglyceride, and protein. Monomers of insulin dissolve and diffuse rapidly from tissue injection sites; but big oligomers do not. Insulin self-associates to form oligomers, especially in the presence of Zn^{2+} . The oligomers have to dissociate into monomers before they can dissolve in the tissue fluids and diffuse into the bloodstream from IM or SC injection sites. A number of insulin forms have thus been

developed that alter the rate of dissociation: slow diffusion into the bloodstream from a tissue depot can offer a *convenient* steady supply following a single injection. In contrast, a less convenient, but increasingly popular, alternative is MDI (*multiple daily injections* {often of deliberately-fast-dissociating insulin}) along with frequent self-monitoring.

GLUCAGON: A 3500 MW protein synthesized in pancreas α -cells. It guards against low blood sugar: it leads to \uparrow glycogenolysis and \uparrow gluconeogenesis in liver ... \uparrow lipolysis in fat. If blood sugar gets very low, a surge of catecholamine release will stimulate adipocyte hormone sensitive lipase, and also glycogen breakdown (and sweating, nausea, anxiety). The glucocorticoid, cortisol, has very complex effects. It has important 'permissive' effects on other hormones such as glucagon (helps them do their jobs). When unopposed or excessive though, it is 'catabolic' on proteins: it directs protein degradation, and \uparrow deaminases. It also increases and drives several key gluconeogenic enzymes. Hence excessive cortisol causes predictable effects, including "steroid Diabetes Mellitus".



Objectives of lecture and 2-hr small groups:

The student will be able to discuss:

- intermediary metabolism, from a type 2 DM viewpoint
- high blood glucose leading by mass action to ↑ glycosylated hemoglobin HbA_{1c} & sorbitol
- the fact that the greatest concern in type 2 DM is not acute care, but management of the multi-organ system failure that results from molecular issues such as high blood sugar and hyperinsulinemia
- the fact that type 2 DM patients are much less prone to ketoacidosis
- the fact that there are typically classic differences in the initial presentation of type 2 vs type 1 DM patients
- the fact that type 2 patients are treated differently (from type 1) early in their course
- the importance of lifestyle issues & patient education in DM management
- some basic groups of drugs used in management of type 2 DM

The intern on Emergency at UH is called Friday night to see the victim of a single-car accident brought in by ambulance. He finds a pleasant, obese 31 y.o. ♀ of European/North American Indian descent lying on a stretcher: her right ankle is elevated and the foot appears displaced from a natural position. She is breathing regularly without obvious effort, has no sign of external bleeding, is alert and oriented, and in no apparent distress. On more detailed enquiry, she is complaining of pain in her right ankle only, and he gets the impression that she may be mildly intoxicated. She is moving head, and all limbs but her right leg, freely. The car the patient was driving left a country road and lurched into a ditch after she and her friend left a bar. She had "a few beers"; she claims not to have bumped her head, injured her neck, or lost consciousness. There is no H_x of previous ill health, and no use of medications or drugs other than alcohol.

With regard to family H_x, she volunteers cheerfully that her sister and mother have diabetes, but that *she* is in perfect health.

Examination is unremarkable apart from obvious overweight and a tender, swollen R ankle. Her colour, BP, HR, and chest auscultation are normal. Abdomen is soft and non-tender. Blood is drawn for CBC, electrolytes, BUN/creatinine, glucose, liver enzymes, routine drug screen, and "group and hold". Urine is sent for R & M. The blood tests and urine are normal except for the random glucose which is 13 mmol/L (reference range say < 11.1) and a moderate serum ethanol level. A presumptive D_x of type 2 DM is made. X-rays (including chest) are read as normal except for a bimalleolar fracture of the ankle in question. Orthopedics is consulted and the patient is kept NPO (nothing by mouth) in case surgery is imminent. Periodically the patient states that she wants a donut, and that if the surgeons don't come soon she will insist on being fed. The ortho resident arrives, books the patient for open reduction at 8:00 AM in the morning, and reaffirms NPO status. Other than the diet restriction, no other therapy is undertaken. An IV is started, running normal saline at 100 ml/hr.

Non-Insulin-Dependent and *Adult Onset* Diabetes Mellitus are older names for type 2 DM. This complex pathology accounts for 9 out of 10 diabetics. It is estimated to affect some 10% of North American adults - half of whom are currently unaware that they are diabetic. It is often discovered during routine workup of an 'apparently healthy' person. Simplistically it is associated with a relative insensitivity of cells to insulin, whose level in the blood is often *elevated* (glucose-stimulated insulin release) rather than *reduced* as in

type 1; however it can also be associated (particularly after years of disease) with low pancreatic secretion of insulin; and there have been suggestions that overdriving the insulin-secreting cells leads to toxic byproduct accumulation (killing these cells). Type 2 DM is 80-90% associated with overweight, and often with dyslipidemia (\downarrow HDL, \uparrow VLDL and TG), and quite commonly with hypertension ("syndrome X" = "insulin resistance syndrome" of hyperweight, hypertension, hyperlipids, hypersugar, hyperinsulin). People also talk about a "metabolic syndrome", which has been variously defined, but which seems to basically be someone who has some of the 'hypers' in syndrome X and abdominal obesity. Type 2 DM reflects an uncharacterized genetic predisposition, and tends to be manifest clinically in adulthood - especially age > 40 . Molecular mechanism not clear - but people wonder about less effective insulin receptor pathways and down-regulation of insulin receptors. Usually blood sugars are not grossly elevated, and there is no ketosis (ketosis = high production of ketoacids). Chronically high levels of insulin 'down-regulate' insulin receptors on cell surfaces (existing receptors are internalised and fewer new ones are made) ... but this alone does not seem to explain the reduced intracellular effect of insulin.

Being overweight tends to prevent normal recruitment of glucose transporters from the interior of muscle and adipose cells to their plasma membranes, and to decrease transcription/translation of the genes for this protein and for proteins that metabolize glucose [not examinable]. Hence glucose utilisation is impaired and hyperglycemia arises ... leading to hyperinsulinemia. Insulin promotes triglyceride storage in adipocytes, and inhibits fatty acid release. Insulin promotes VLDL and TG production in the liver. Oddly, high blood lipid concentrations stimulate gluconeogenic enzymes.

Don't forget the concept of the following interesting chemistry. Protein $-NH_2$ groups react non-enzymatically slowly (over a number of weeks) with the aldehyde group ($-CHO$) on sugars such as glucose. Thus hemoglobin in RBC gets partially glycosylated ("glycosylated Hb" or "**HbA_{1c}**"). The upper level of normal for HbA_{1c} in a non-diabetic is about 6.5%: levels 40% above this correlate statistically with a bad outcome in DM (and people like to aim for upper limits of 7% even in DM). A patient's serum levels of HbA_{1c} tell you about their long-term blood sugar control, as opposed to how much they ate in the past few hours.

It is thought that 'Hyperinsulinemia plays a key pathogenic role ... that the R_x for type 2 DM should focus on the improvement or correction of the vicious cycle of obesity-hyperinsulinemia'. In theory, the R_x for type 2 DM could avoid insulin early on (since high serum insulin levels are typical) - trying instead dietary management, exercise, and weight loss. These interventions are often not embraced by patients. Oral hypoglycemic drugs are commonly resorted to as a next level of intervention. Some oral drugs work by pushing the pancreas to produce more insulin (arguably a bad idea in theory), and others improve insulin signalling pathways and/or sugar metabolism, or decrease sugar uptake from the gut. Even with optimal lifestyle modifications, the pancreas β -cells often *eventually* burn out, and there is a requirement for injected insulin: the great benefit to lifestyle improvement is delay in the onset of bad pathology and greatly improved glucose control and much reduced end organ damage (by keeping blood sugars down). In the final analysis, oral drugs are not as potent as injected insulin.

This is probably a gross oversimplification; but it may be useful to consider that the

(sweet-tasting) six-carbon polyalcohol, sorbitol, is formed in cells from glucose *via* a minor pathway. It is only slowly metabolised, and does not cross cell membranes easily. By the same token, it will not leak from cells easily, and accumulates in metabolically-damaging quantities inside cells which are not “insulin-responsive” (the lens of the eye, nerves, renal glomeruli cells) when they are exposed to chronically high levels of blood glucose. Another popular concept is that the glucose aldehyde group can react non-enzymatically with other molecules in cells to form damaging free radicals (hence *more is worse*).

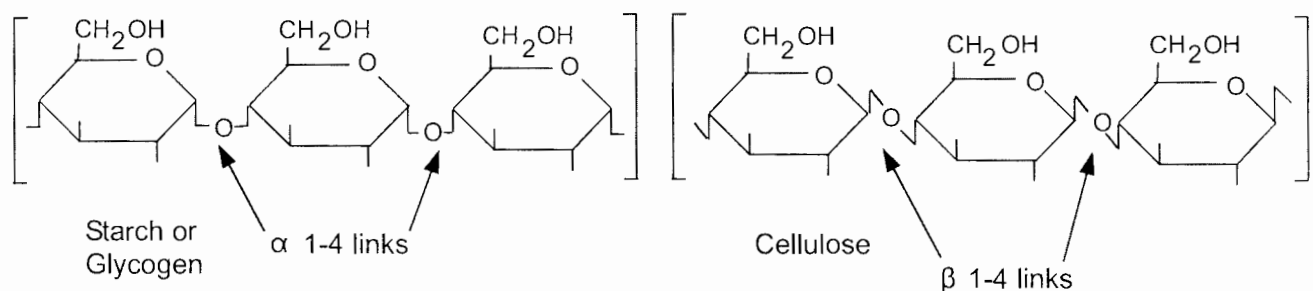
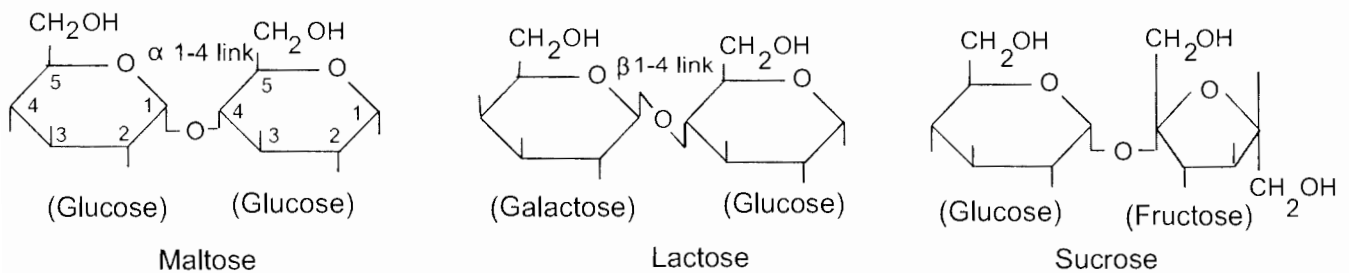
Objectives: The student will be able to discuss concepts (not details) of carbohydrate structure and its relationship to 'indigestion'.

The next patient's chart has a note from the receptionist that over the telephone the patient was evasive about the reason for requesting an appointment. It is an embarrassed-looking 26 year old businesswoman. She doesn't seem to know where to start, but complains vaguely of "indigestion" and wonders about ulcers. The doctor resorts to a proper Review of Systems. It transpires that the patient is constantly with clients during the day and rarely has time to relax over meals. She has put up with a "nervous tummy" for years, but it seems to be worse for the past 6 months to a year. She gets a feeling of vague discomfort, bloating, and (this is why she is so embarrassed) ... flatulence. It has become so consistently upsetting around people that she has contemplated quitting her job. It transpires that the patient had begun over the past year to drink milk in fair quantities because she had heard it was an ulcer remedy and figured it was a soothing food (neither of which are true). The patient looked healthy, and reported no weight loss, nausea/vomiting, fever, fatigue, and no evidence of blood in the stool. Physical exam was normal.

The doctor briefly described the usefulness of fiber in the diet. Food chemists tend to consider *fiber* as oligosaccharide not digestible by man. Then the doctor suggested she cut out milk altogether for a few weeks. The patient was given 6 *stool test packets* to use on her own over the next few days: you smear a bit of stool on a chemically treated strip of paper - colour change from colourless to blue/purple reflects the presence of heme (which happens to have peroxidase activity). 6 negative tests may reasonably encourage one that cancer of the bowel is an unlikely diagnosis. Some physicians might have also done one or more of: CBC, ESR, serum β -carotene, serum or RBC folate, stool for ova and parasites and enteropathogens, serum albumin.

The patient telephoned a week later to say her "problem" was greatly improved (and that all stool samples were negative for occult blood). She swore undying gratitude to the doctor, but did not wish to pursue the provisional diagnosis of lactose intolerance/lactase deficiency with further testing.

Sugars may be linked by α - or β -linkages, as illustrated below.



It is useful to consider the digestive tract as a tube joining mouth and anus. Things in the digestive tract are not actually 'in' the body. Sugars are only significantly absorbed across the gut walls as monosaccharides. These are specifically bound and brought across gut cell membranes by transport proteins.

Amylases are enzymes secreted by salivary glands and pancreas, that catalyse hydrolysis of sugar-sugar linkages in polysaccharides ($C-O-C + H_2O \rightarrow C-OH + HO-C$) to break starches and glycogens into shorter chains. Thus α 1-4 linked polyglucose (starch and glycogen) is broken down to the disaccharide, maltose, which is then hydrolysed by various *maltases* on the intestinal epithelial cells. Amylases fail on β 1-4 polyglucose links as found in cellulose, which therefore serves as inert bulk in diet ("fiber"). The glucose/fructose disaccharide, sucrose, is hydrolysed by *sucrase*, which is adequately present on almost everyone's gut cells. The galactose/glucose disaccharide, lactose, is hydrolysed to monosaccharides if the enzyme, *lactase*, is present on the patient's small intestine mucosal cells. The catch is that (unlike amylase, maltase, and sucrase) lactase is commonly found in very low levels within the normal post-pediatric gut. Any sugar bigger than a monosaccharide passes on to the large intestine, where bacteria use it as an easy food source producing gases (eg. H_2 , CH_4 , CO_2), and organic acids (which irritate mucosal surfaces). Also a high concentration of simple sugars and their breakdown products in the large bowel creates an osmotic drag, pulling water from cells and blood vessels into stools \Rightarrow looser stools (bad news if patient complains of diarrhea; good news if cured of constipation).

Even some *monosaccharides* are not well transported across the small intestine: eg. the fructose transporter in many people is apparently inadequate. Carbohydrates are polyhydroxy aldehydes, polyhydroxy ketones, or compounds that can be hydrolysed to these (not examinable). Sorbitol, which is often used in candy as a "low-calorie" sweetener, is actually a six-carbon polyalcohol: it is called "low-calorie" because it is very poorly transported across cell membranes of the gut (and indeed of human cells in general) - but gut bacteria use it very effectively. Prunes contain lots of sorbitol and fibre.

Certain oligosaccharides of beans are poorly broken down by human enzymes, but are still popular with flora of the large intestine. Insoluble fibers such as cellulose and lignin (eg. in wheat bran) and more soluble fibers such as gums and pectins (eg. in oats, legumes and fruit) are seen as "good" ... they have been said to reduce the incidence of functional bowel disease, diverticulosis, colon cancer, cardiovascular disease, diabetes mellitus. Clinicians often deliberately give lactulose, a 1-3 linked galactose-fructose disaccharide that human gut enzymes can't handle, as a laxative - especially in patients with hepatic encephalopathy (the resultant organic acids in the bowel lumen also remove NH_3 {as NH_4^+ } from the body). Lactulose and sorbitol can be good laxatives in the elderly. There are 'hidden' (ie. unexpected) lactose & sorbitol in many common dietary items and even drugs.

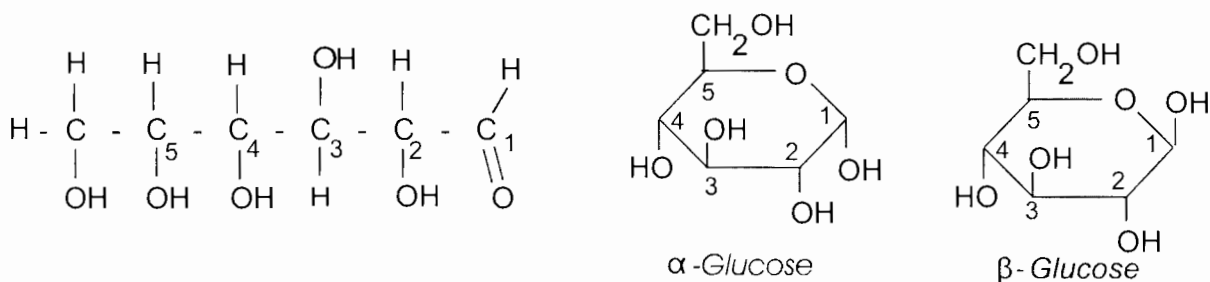
The enzymes that cleave disaccharides to monosaccharides are produced by the brush border mucosal cells of the normal small intestine. Lack of maltases doesn't occur (perhaps because there are at least 4 different ones). Only 100 cases have been reported of sucrase lack. Lactase is pretty well universal in very young children, but even then it is easily lost temporarily (any GI disease that desquamates mucosa {ie. 'secondary' lactose

intolerance}). People of European origin often retain lactase activity as adults ... and there is a continuous range from "intolerant" through 'sometimes deficient' to 'no problem'. You can test a patient by intestinal biopsy, but that seems pretty heroic. In real life a more reasonable test is 50 g of lactose PO (equivalent to ~1 L of milk! so this may be an excessively demanding test): then you can follow by breathalyser for H₂ gas (failed uptake), testing blood samples within 30 min for rapid sugar rise (successful uptake) ... or simply have them drink milk and ask about symptoms next day.

▣▣▣ For people who are lactase-deficient and want to consume dairy products, lactase is available over the counter as Lactaid^R to eat or to add to milk. There is a profitable market for this expensive material. Unfortunately, gut symptoms are so weird and wonderfully variable, that it is often unclear what is attributable to what.

▣▣▣ Acarbose is sort of the opposite: a molecule taken PO that deliberately *inhibits* human α-glucosidases, thus slowing and reducing the digestion of carbohydrate - given to type 2 diabetics trying to avoid surges in blood sugar.

▣▣▣ Olestra^R is a sucrose polyester that has a 'nice' fatty taste and yet is indigestible by human enzymes: the intent is to reduce the fat load in one's diet. It has been claimed by critics to have the potential to drag fat-soluble vitamins along with it, and to cause bloating/cramps and greasy stools (all logical theoretically). Orlistat is a *lipase inhibitor* taken by mouth to reduce fat digestion and hence its intestinal uptake: same side effects.



GLUCOSE IN OPEN AND CLOSED FORMS

THE CARBONS ARE NUMBERED.

NOTE THE OPEN CHAIN THAT A SMALL % OF GLUCOSE MOLECULES WOULD EXHIBIT AT ANY ONE TIME (not on exam): THIS IS THE ALDEHYDE FORM THAT COULD REACT WITH AMINO GROUPS OF PROTEINS (HENCE "GLYCOSYLATED HEMOGLOBIN" AS A MEASURE OF GLYCEMIC CONTROL IN DIABETICS).

Blood sugar reaches its peak value some 30-60 minutes after a meal. 'Normal' transit time for food through the gut is about 4-6 hr in a young healthy person. Diabetics can have altered transit times and digestive problems due to metabolic damage to their sympathetic nervous system. It seems that medical people consider *diarrhea* to be 'more than three stools per day' and *constipation* to be 'fewer than three per week'.

Distinct from failure to get sugars across the gut cell membranes, there are rare inherited defects in enzymes that deal with galactose and fructose. In such cases there is no problem with transport, and the sugars get across the gut walls, but inside cells there is a buildup of galactose or fructose intermediates that can interfere with sugar metabolism. These would most typically show up as failure of an infant to meet developmental milestones, or "failure to thrive" ... so such patients would be triaged to a specialist for diagnosis. [this paragraph not on exam]

Objectives

The student will be able to describe/discuss:

- the concept of a long polypeptide that is split post-translationally to give several peptides.
- the concept of multiple effects of a given peptide *via* different affinities for different receptors on different cells: and if its structure looks a bit like what is ‘supposed’ to bind to a given receptor, it will too ... a bit ... and maybe have a bit of effect.
- introductory aspects of salt/water regulation & Osmolality / Osmolarity.
- a molecular concept of SIADH ... NOT differential diagnosis.

B.D. was a 54 year old Caucasian ♂ well known to the medical team at Victoria Hospital for a long H_x of COPD presumed due to smoking. He was dropped in emerg by his wife Friday evening after the hockey game. She reported that her husband had been showing little energy for the past several days and now seemed confused and antagonistic. The patient was found to be breathing somewhat rapidly (25/min), with costal indrawing; but he had good skin colour. BP was 150/100, HR 80, afebrile, chest was clear with adequate air entry bilaterally. He was not very cooperative. Exam was otherwise unremarkable except for some confusion as to place and date. Medications consisted of a glucocorticoid inhaler, as needed: he used it sporadically, and hadn't used it for the past week. Examination of his two thick hospital charts showed a number of admissions for airway decompensation associated with acute respiratory tract infections. ECG was found to be unchanged from previous ones, and blood gases were better than when he was last discharged. CK and Troponin I were within reference range, and the only blood test that was abnormal was serum Na⁺ of 120 mmol/L (ref range 135 - 146). When tested, serum osmolality was 250 mosm/kg (ref range 278-305) and urine osmolality was 250 (ref range 50-1200). Chest x-ray showed a focal lesion not present previously. *Osmolality* = concentration of total ions + molecules per kg of solvent (*osmolarity* is per liter of solution). SIADH involves *less than maximally dilute urine in the presence of plasma hypoosmolality and hyponatremia*. Logically, one could calculate a predicted serum osmolality as 2[Na⁺] + 2[K⁺] + BUN + Glucose. However it seems that some good clinicians just use, 2[Na⁺] + Glucose apparently because BUN diffuses freely across membranes and because it is too much trouble to add in K⁺ with its small contribution and modest range of values. In any case, sometimes the calculated serum osmolality is say 10-20 units lower than the measured value ... in which case you should presume that your calculation had ignored some molecule such as alcohol.

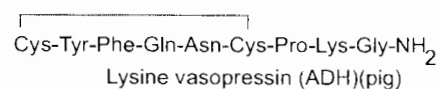
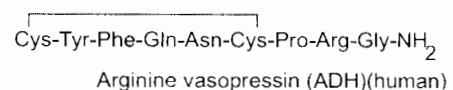
ADH (vasopressin) is a tiny (9 amino acids) peptide synthesized in the endoplasmic reticulum of neurons in the hypothalamus as part of a much longer polypeptide chain. ADH is clipped off while still in the cell, and the whole mass moves down axons into the (posterior) pituitary where it sits awaiting a wide variety of signals (especially from osmoreceptors, then baroreceptors) that induce or suppress its rate of leakage into the bloodstream (by the way, oxytocin has an almost identical biochemical history in neighbouring neurons, but slightly different amino acid sequence - so it and ADH might be expected to bind to each other's receptors to lesser degrees and induce lesser effects).

The receptors for ADH and oxytocin are related proteins that sit in cell plasma membranes in a trans-membrane fashion. Like all trans-membrane proteins, they are enzymatically glycosylated post-translationally, and span the hydrophobic region of the

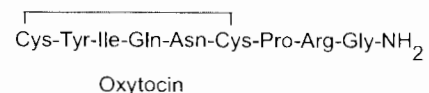
membrane with their glycosylated sites in the extracellular portion. ADH has two types of receptors: the more important one is in the renal collecting tubule cell plasma membranes; and binding to it stimulates adenyl cyclase. This turns ATP to cAMP which binds to kinases in the cytoplasm which phosphorylate other cytoplasmic proteins which eventually lead to insertion of proteins into the plasma membrane which act as water channels. These water channels conduct water (which would have otherwise gone on into the ureter) back into regions of the kidney medulla having high salt concentration and eventually back into the bloodstream [and other receptors similarly stimulated in the same region help generate the salt gradients needed by activating ion transport - but this doesn't help the clinical understanding and will not be emphasized]. The other type of ADH receptor that people think of is the lower affinity receptor in plasma membranes of smooth muscle: their stimulation leads to smooth muscle contraction and vasoconstriction. Clinical use and side effects of oxytocin can be rationalized with the same logic, but presuming that oxytocin binds better to the receptors that cause smooth muscle contraction. The synthetic variant of ADH that one tends to use clinically (dDAVP) binds 'only' to the receptor that affects water channels.

SIADH is to some extent a D_x of exclusion. One would look for: hyponatremia due to water retention, low serum osmolality, probably urine osmolality ~ serum osmolality (maybe even higher), relatively high loss of Na^+ in the urine, and the absence of any other cause (eg. no heart failure, liver failure, kidney failure, or adrenal failure; and no edema and no diuretic use ... not on exam). An important concept is that normal lung cells in the presence of disease (eg. infection) can synthesize proteins containing ADH-like sequences that bind to ADH receptors: this is an interesting example of the importance of regulation of transcription. Alternatively, the neurons of the hypothalamus that manufacture ADH can be overly turned on by a wide range of drugs, and by CNS disease including inflammation, trauma, degeneration. It is not appropriate to cover the differential D_x here since salt imbalance is a complex problem. In this case the likely pathology leading to excessive ADH is a lung cancer. Perhaps the cancer cells themselves are producing a peptide with ADH-like structure and effects: if this is the case, one might argue that this is not *true* SIADH, but rather an "ectopic hormone" phenomenon. Most cases of SIADH are sort of incidental observations and you would just nod and carry on; but when serum Na^+ gets down to 125 and below, you can expect to see some effects of the ion imbalance on neurons - such as the confusion in this patient. One practical 'treatment' of SIADH is *water restriction*; although ideally you would treat the *cause*.

As a totally unrelated aside not on exam: it follows that 'too *little* ADH' also exists as a clinical entity. In such a case the patient would produce large amounts of dilute urine ("Diabetes *Insipidus*" {as distinct from Diabetes *Mellitus*}). Actually clinicians classically break DI into "central" (too little ADH produced) and "peripheral" (rare genetically defective ADH receptors; or more commonly 'damage' to the nephron by some drug effect or vascular or occlusive event).



2



MANAGEMENT OF TYPE 1 DIABETES MELLITUS

1. A 16 year old student was diagnosed with Type 1 diabetes one month ago. He is otherwise healthy and his diabetic control is now stable. He is taking Humalog insulin before each meal and NPH at bedtime. He is very active in sports and plays Junior B hockey. He is anxious to learn if his diabetes will impact on his life-long goal of playing in the NHL.

QUESTIONS

1. Should he set his goal on something else?
 2. Describe the metabolic changes that occur during exercise.
 3. Describe the differences in metabolism that can occur in a diabetes during exercise.
 4. What recommendations would you make to this student re exercise and:
 - a. Insulin?
 - b. Diet?
 - c. Blood glucose monitoring?
-
2. A 9 year old girl with type 1 diabetes for 3 years is on a bid regimen of Regular 10 units and NPH 12 units before breakfast; and Regular 6 units and NPH 8 units before supper. She has consistently had high blood glucose levels in the range of 12-20 mmol/l before breakfast. She has also had some ketones present in the urine before breakfast. The rest of the day her blood sugars are all around 4 - 7 mmol/l and her ketones are negative.

QUESTIONS

1. Describe three physiologic or pathophysiologic reasons for her high morning sugars?
 2. What questions about symptoms would you ask to help you determine which of these events is occurring?
 3. What would you advise her to do if doubts still exist as to the cause?
 4. What changes would you recommend to her insulin regimen?
-
3. A 3 year old with Type 1 diabetes is a picky eater. Currently he is on 1 - 3 units of Regular and 6 units of NPH before breakfast and 0-2 units of Regular and 2 units of NPH before supper. His parents find they just can't predict how much he will eat. Recently he has been having hypoglycemic reactions 2 - 3 times a week due to not completing meals.

QUESTIONS

1. What options are available to the parents to prevent hypoglycemia in this toddler?
 2. List three treatment options for hypoglycemia.
-
4. Mr. Bruce Holt is a 37 year old man with 27 years of Type 1 diabetes. He has recently had coronary artery bypass grafting. His surgeon has placed him on Atenolol and he has been having a lot of problems with low blood sugars. He is testing 3-4 times daily and finds at least once a day he is less than 2 mmol/l. His current insulin program is 5 units Regular, 22 units Ultralente at breakfast, and 7 units Regular, 15 units Ultralente at supper.

QUESTIONS.

What suggestion do you have for Mr. Holt with respect to:

- a. Diet
 - b. Blood glucose monitoring
 - c. Insulin
 - d. Other medications.
-
5. A 14 year old girl presents with polyuria and polydipsia. A random blood glucose is 25.4 mmol/l. Urine is negative for ketones but 3+ glucose.

QUESTIONS.

1. List and discuss 3 demographic factors which may help distinguish Type 1 from Type 2 diabetes.
2. List and discuss 2 clinical features which may help distinguish Type 1 from Type 2 diabetes.

ENDOCRINOLOGY AND METABOLISM SMALL GROUP PROBLEMS
TYPE 2 DIABETES AND INSULIN RESISTANCE
Meds 2007, Thursday May 13, 2004, 1000 to 1150 hours

CASE 1

A 45 year old man presents to your office complaining of dysuria and frequent urination. He has been previously healthy but his last check up with you was more than 5 years ago. On questioning, he admits to drinking large amounts of juices and soda.

On examination, he is overweight with a BMI of 34. His BP is 145/90, pulse 70. He is afebrile. Remainder of examination is normal except for predominant abdominal obesity.

Initial laboratory tests show:

WBC 8×10^9 /L (4-11)
Urinalysis white cells, glucose
Random serum glucose 15mmol/L

Questions

- 1) What is your diagnosis? (2 points)
- 2) What treatment would you start? (4 points)
- 3) What classes of medication are available for treating type 2 diabetes? (4 points)
- 4) How would you assess cardiovascular risk and what would you monitor long term? (10 points)
- 5) For what other complications of diabetes would you monitor? (3 points)

CASE 2

A 27 year old woman presents to your office complaining of irregular menstrual periods. Her last menstrual period was 6 months ago. She is recently married and wants to start a family.

On examination, she is overweight (BMI 35) with increased abdominal obesity. She has increased facial hair with dark terminal hair over her moustache and side burn region. She has acne on her back and face. She is not hypertensive but there is a family history of high blood pressure and diabetes.

Questions

- 1) What skin abnormality may she manifest? (1 point)
- 2) What laboratory investigations would you order? (5 points)
- 3) What is the most likely diagnosis and what is the underlying physiologic mechanism? (2 points)
- 4) What treatment would you recommend? (3 points)

**ENDOCRINOLOGY AND METABOLISM SMALL GROUP PROBLEMS
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CASE 3

A 58-year-old orthopedic surgeon comes to you to discuss his risks for developing type 2 diabetes mellitus. Because of a strong family history of type 2 diabetes, his family physician performed a 75 g oral glucose tolerance test (OGTT) five years ago, which was normal. For the past 2 years, he has had a fasting serum glucose level measured annually; the results were 6.4 mmol/L and 6.2 mmol/L respectively (normal <5.7 mol/L, diabetes >7 mmol/L). He currently has no symptoms of hyperglycemia, such as polydipsia, polyuria, or blurry vision. His weight has been stable. His medications include aspirin 81 mg/day and atorvastatin 10 mg/day for hypercholesterolemia. His family history is also positive for coronary artery disease, stroke and hypertension. He plays tennis for one hour each weekend.

On examination his BMI is 27 kg/m²; his blood pressure is 135/90 mm Hg. Waist circumference is 102 cm. The remainder of the examination is normal.

1. What do you advise him are his risks for developing type 2 diabetes? (2 points)
2. Does he have diabetes at the present time? (1 point)
3. What are the risks of this diagnosis? (2 points)
4. What would you recommend as further investigations and as therapy? (3 points)
- 5.

CASE 4

A 48 year old woman presents to your clinic with a history of obesity, irregular periods and hirsutism. She has a history of hypertension for which she is on medication. Her fasting blood sugar is 7.5 mmol/L. Her fasting cholesterol is elevated at 6.9 mmol/L and her triglycerides are also elevated at 4.2 mmol/L.

1. What would you check for on physical exam? (2 points)
2. What is Syndrome X and what are the associated risks? (4 points)
3. Explain what insulin resistance means. (3 points)