

## Nutrition & Metabolism - Metabolism

1. What are the indispensable (essential) amino acids?
  - PVT TIM HALL
  - Phenylalanine
  - Valine
  - Tryptophan
  
  - Threonine
  - Isoleucine
  - Methionine
  
  - Histidine
  - (Arginine)
  - Leucine
  - Lysine
  
2. Where does protein digestion begin? What initiates digestion?
 

Protein digestion begins in the stomach. There is no protein digestion in the mouth and esophagus. Protein digestion is initiated by the release of HCL, stimulated by gastrin, GRP (glucokinase regulatory protein), acetylcholine, and histamine.
  
3. What are enzymes involved in digestion of protein?
 

Gastrin, GRP, acetylcholine, and histamine, pepsin, pepsinogen, secretin, CCK, bicarbonate, trypsinogen, chymotripssinogen, collage-nase, proelastase, procarboxypeptiases, trypsin, additional peptidases.
  
4. What are the sources of the enzymes that digestion protein?
 

The release of HCL is stimulated by gastrin, GRP, acetylcholine, and histamine, and denatures 4°, 3°, and 2° structure. Pepsin is activated by pepsinogen and yields large polypeptides by breaking long protein chains. Acid chyme in the intestine lowers the pH and stimulates secretin and CCK. The pancreas secretes bicarbonate. Digestive enzymes from the pancreas include trypsinogen, chymotripssinogen, collage-nase, proelastase, procarboxypeptiases. Trypsin is formed and activates others. Additional peptidases in brush border.
  
5. Where are most amino acids absorbed?
 

Most a.a. absorption is in the proximal small intestine (first few feet).
  
6. What is the RDA for protein? Calculate the protein recommendation for someone weighing 154 lbs.
 

The RDA for protein for adults is 0.8 g/kg of body weight.  
 $154 \text{ lbs.} / 2.2 \text{ kg/lb} = 70 \text{ kg.}$   $70 \text{ kg} \times 0.8 \text{ g/kg} = 56 \text{ g. protein required/day.}$

7. When amino acids are degraded, what compound is formed in the largest amounts from the amino group?

Ammonia is formed in the body from chemical reactions such as deamination. The urea cycle, in the liver, is the body's way of removing ammonia.

8. What are four possible fates of the carbon skeleton from amino acids?

Once an amino group has been removed from an amino acid, the remaining molecule is referred to as a carbon skeleton or  $\alpha$ -keto acid. Carbon skeletons of amino acids can be further metabolized with the potential for multiple uses in the cell. An amino acid's carbon skeleton, for example, can be used for the production of

1. Energy                      Energy, CO<sub>2</sub>, NH<sub>4</sub><sup>+</sup> and H<sub>2</sub>O
2. Glucose                      Conversion of a.a. to glucose increased by high glucagon: insulin & cortisol
3. Ketone bodies
4. Cholesterol                Leucine generates HMG CoA; others generate acetyl CoA
5. Fatty acids

9. What is 3-methylhistidine? Why would it be measured?

3-Methylhistidine is an index of protein degradation for tissues in the body. It's an indicator of muscle mass/catabolism.

10. What does a "post-translational" modification mean?

Translation is the process by which genetic information in an mRNA molecule specifies the sequence of amino acids in the protein product. The completed protein dissociates from the mRNA in active form, although some post-translational, chemical modification of the protein is often necessary.

11. Approximately what % of basal energy need is associated with protein turnover?

Protein turnover accounts for 10-25% of resting energy expenditure.

### Amino Acid Metabolism?

~ 20% for protein/N compound synthesis (14% remains in liver for protein synthesis, 6% plasma

proteins - synthesized in liver and secreted into bloodstream)

~ 57% catabolized in liver (assuming adequate a.a. intake).

~ 23% released to systemic circulation -- primarily branched a.a.

12. What are two tissues that have a very high protein turnover rate? What are two tissues that have low turnover rates?

Rapid turnover: plasma protein, visceral protein

Low turnover: muscle protein, bone? nerves?

13. How can a habitually high intake of amino acids affect the mRNA for enzymes that catabolize amino acids?

Protein synthesis is affected by the amount of mRNA, ribosomes, availability of a.a for tRNA and hormonal environment. Amino acid oxidation increases if a.a are in surplus or if an essential a.a is missing. Therefore, a habitually high intake of a.a would induce the production of more enzymes to catabolize a.a.

14. What are some conditions that increase proteolysis of muscle tissue? **Why does each cause these increases?**

- • Counterregulatory hormones, glucagon, catecholamines, and glucocorticoids promote protein degradation and a negative nitrogen balance.
- • Prostaglandins and thyroid hormones can also promote changes in protein turnover.
- • Nitric oxide has been shown to inhibit hepatic protein synthesis.
- • Amino acid oxidation.
- • The molecular form of the consumed nitrogen also appears to affect protein turnover.

15. Is insulin anabolic or catabolic?

Protein digestion by the lysosomal proteases (macroautophagy) is enhanced by glucagon and suppressed by insulin as well as amino acids. i.e., insulin is anabolic. Insulin is anabolic. (So is growth hormone, although it is counterregulatory).

16. If you fast for a day, are you likely to degrade muscle? Why or why not?

No. When gluconeogenesis begins depends on energy needs. Breaking down LBM to use C-skeleton from aa pool may begin in the postabsorptive state (~3 to 12-16 hours), but muscle protein breakdown is the chief gluconeogenesis substrate in the fasting state (after ~48 hrs with no food intake).

17. How does fasting affect circulating insulin and glucagon levels?

Gluconeogenesis occurs in the wake of glycogen depletion to help maintain blood glucose levels. The shift to gluconeogenesis during prolonged fasting is signaled by the secretion of the hormone glucagon and the glucocorticosteroid hormones in response to low levels of blood glucose.

18. How does fasting affect the activity of hormone-sensitive lipase in the adipose tissue?

In the starvation state, the protein-sparing shift is from gluconeogenesis to lipolysis, as the fat stores become the major supplier of energy. The blood level of fatty acids increases sharply, and these replace glucose as the preferred fuel of heart, liver, and skeletal muscle tissue that oxidize them for energy. Therefore, fasting would increase the activity of hormone-sensitive lipase in the adipose tissue.

19. Name a transport protein in serum that is reduced in malnutrition. Would this be the only protein that is reduced?

Albumin which transports a variety of nutrients such as calcium, zinc, and vitamin B<sub>6</sub> is reduced in malnutrition. Transthyretin (formerly called prealbumin), which

complexes with another protein, retinol-binding protein, for the transport of retinol (vitamin A) is also reduced in malnutrition.

20. Give examples of what would cause muscle hypertrophy or muscle atrophy.

There is a threshold for protein intake -- up to this level, secretion of hormones such as growth hormone increase with intake. Above the threshold-- there is little or no effect of increased intake. The threshold is approximately the dietary protein requirement. Insulin promotes protein synthesis. It is affected by the amount of mRNA, ribosomes, availability of amino acids for tRNA and hormonal environment. Insufficient intake causes oxidation of protein for energy needs. During illness, starvation, malnutrition, protein synthesis and degradation are not in balance. In malnutrition, protein synthesis decreases. In starvation, protein catabolism is decreased (begin to use ketones). In sepsis, ketone formation is reduced so the body has to degrade body protein for glucose synthesis.

21. What determines if an amino acid is indispensable or dispensable?

Essential or indispensable a.a's must be provided in the diet. We can't make them at all or in enough quantity. The structure of the carbon chain makes a.a. essential or indispensable, i.e., we can't make a ring structure or branch chains; we have no enzymes to do that. Newer categories added to the essential/indispensable and nonessential/dispensable categories include conditionally or acquired indispensable a.a.'s. A dispensable amino acid may become indispensable should an organ fail to function properly as in the case of infants born prematurely or in the case of disease associated organ malfunction. For example, neonates born prematurely often have immature organ function and are unable to synthesize many nonessential amino acids such as cysteine and proline. Immature liver function or liver malfunction due to cirrhosis, for example, impairs phenylalanine and methionine metabolism, which occurs primarily in the liver. Consequently, the a.a's tyrosine and cysteine normally synthesized from phenylalanine and methionine catabolism, respectively become indispensable until normal organ function is established. In some kidney diseases, serine becomes indispensable because it cannot be synthesized in sufficient quantity by the diseased kidneys. Inborn errors of amino acid metabolism resulting from genetic disorders in which key enzymes in amino acid metabolism lack sufficient enzymatic activity also illustrate a situation in which dispensable amino acids become indispensable. Individuals with classical phenylketonuria (PKU) exhibit little to no phenylalanine hydroxylase activity. This enzyme converts phenylalanine to tyrosine. Without hydroxylase activity, tyrosine is not synthesized in the body and must be provided completely by diet; it is indispensable. In other inborn errors of metabolism, amino acids such as cysteine become indispensable. Thus, a.a's that are normally dispensable may become indispensable under certain physiological conditions.

22. How does the usual amount of dietary protein compare with the amount of protein that is turned over in the body?

RDA for protein is calculated on the basis of 0.8 g protein per kg body weight.

The average American eats 80-100 g protein per day.

Protein turnover is about 4.6 g/kg body weight. (For a 180 lb. person, it's 376 g.) (e.g., for a 70 kg male, protein turnover would be approx. 320 g daily.)

23. Do amino acids compete with each other for transport? Explain.

Competition between a.a for transport by a common carrier has been documented. Multiple energy-dependent transport systems with overlapping specificity for a.a. have been demonstrated in the intestinal brush border. Both sodium dependent and sodium-independent transport systems exist. Amino acids using the same carrier system compete with each other for absorption.

24. What is transamination?

Transamination reactions involve the transfer of an amino group from one amino acid to an amino acid carbon skeleton of  $\alpha$ -keto acid (an amino acid without an amino group). The carbon skeleton/ $\alpha$ -keto acid that gains the amino group becomes an amino acid, and the amino acid that loses its amino group becomes an  $\alpha$ -keto acid.

25. Does catabolism of amino acids increase or decrease after a meal?

Amino acids not used by the intestinal cell are transported across the basolateral membrane of the enterocyte into interstitial fluid, where they enter the capillaries of the villi and eventually the portal vein for transport to the liver. The liver is the primary site for the uptake of most of the amino acids following ingestion of a meal. The liver is thought to monitor the absorbed amino acids and to adjust the rate of their metabolism according to the needs of the body. Approximately 57% of amino acids taken up by the liver are typically catabolized in the liver. "That percentage goes way up if intake is a very big protein meal. Extra a.a are destroyed really rapidly." Therefore, catabolism of amino acids would increase after a meal.

26. If energy is inadequate, are more or less amino acids catabolized than normal?

Amino acids are used for energy in the body when diets are inadequate in energy (measured in kilocalories). Therefore, less amino acids would be catabolized than normal.

27. What is elevated during stress that increases protein breakdown?

With stress, including sepsis, trauma, surgery, and burns, glucocorticoids (primarily cortisol), catecholamines (e.g. epinephrine), insulin, and glucagon release increase. However, the glucagon:insulin ratio favors glucagon. Consequently, tissues become resistant to insulin action, and hyperglycemia (high blood glucose concentrations) persists. In addition, cortisol concentrations may remain elevated in the blood for prolonged periods following severe trauma or stress events. High blood cortisol promotes proteolysis and hyperglycemia.

The principal mechanism of adjustment to starvation is a change in hormone balance. In particular, there is a sharp decrease in insulin production. Decreased insulin activity, coupled with increased synthesis of counterregulatory hormones such as glucagon, promotes fatty acid mobilization from adipose tissue, production of ketones, and the availability of amino acids for gluconeogenesis.

28. What does the half-life of serum or plasma proteins have to do with their effectiveness for measuring nutritional status?

Because of albumin's relatively long half-life (~14-18 days), it is not as good or as sensitive an indicator of visceral protein status as some of the other plasma proteins. The half-life is the time that it takes for 50% of the amount of a protein such as albumin to be degraded. Transthyretin (pre-albumin) and retinol-binding proteins are used as indicators of visceral protein status. However, because these two proteins have relatively shorter half-lives (~2 days and 12 hours, respectively) than albumin, they are more sensitive indicators of changes in visceral protein status than albumin. Pre-albumin is a better indicator for short-term changes than is albumin because of the half-lives of the proteins.

29. Presence of what enzymes in serum is taken as a measure of tissue damage?

Alanine in serum means heart attack (leakage of alanine from damaged tissue to blood).

Aspartate aminotransferase (AST) is highest in heart; serum indicates damage.

30. Are amino acids "stored" in the body like glycogen is?

"You don't store a.a except as in an a.a.-chain (growth hormone, testosterone, synthesize new tissue).

31. What impact does an MAO inhibitor have on metabolism of amino acids or their derivatives?

Monoamine oxidase inhibitors usually inactivate tyramine from food. It is found in red wines, aged cheeses, fermented foods etc. It slows the breakdown of MAO's. An MAO inhibitor may prevent MAO from catabolizing amines in the diet. It may yield vasoconstriction. Increases blood pressure -- precipitously high.

32. What are special roles for glutamine?

- • excitatory
- • synthesis of GABA ( $\gamma$ -amino butyric acid) -- an inhibitory neurotransmitter
- • removal of ammonia as glutamine

33. Elevated levels of what derivative of methionine are considered to be a risk factor for coronary heart disease?

Homocysteine. Elevated levels of homocysteine in the blood have been found as a risk factor for heart disease.

34. Taurine is a derivative of what compound? What is one of the uses of taurine?  
 Taurine, a  $\beta$ -amino sulfonic acid, is concentrated in muscle and the CNS. While taurine is not involved in protein synthesis, it is important
- • in the retina for vision
  - • in membrane stability where it is a scavenger of peroxidative (e.g. oxochloride) products
  - • as a bile salt taurocholate
  - • as an inhibitory neurotransmitter
35. What is phenylketonuria?  
 A genetic absence or deficient activity of phenylalanine hydroxylase results in the genetic disorder phenylketonuria (PKU) and necessitates a phenylalanine restricted diet.
36. What are neurotransmitters/catecholamines produced from metabolism of tyrosine?  
 Tyrosine hydroxylase, an iron-dependent enzyme, catalyzes the first step in tyrosine metabolism to generate 3,4-dihydroxyphenylalanine (L-dopa). Subsequent reactions with L-dopa yield the catecholamines (dopamine, norepinephrine, and epinephrine). In the thyroid gland, tyrosine is taken up and used with iodine to synthesize thyroid hormones.
37. What is melanin? What is its source?  
 Tyrosine hydroxylase, catalysis of tyrosine metabolism also yields in other cells, such as the skin, eye and hair cells, and melanin (a pigment that gives color to skin, eyes, and hair).
38. What neurotransmitter is synthesized from tryptophan? What neurotransmitter?  
 Tryptophan is partially glucogenic as it is metabolized to form pyruvate; it is also partially ketogenic and forms acetyl CoA. It can be metabolized to produce nicotinamide, serotonin, and melatonin.
39. What is melatonin?  
The hormone melatonin is derived in the brain from the a.a. tryptophan. Use of tryptophan supplements to promote sleep has been promoted, as has supplements of melatonin, which is also made from tryptophan in the pineal gland, which lies about in the center of the brain. Melatonin plays a role in the regulation of sleep. Yet, melatonin supplements of 2-500 mg for use as a sleep aid have yielded variable results. The LT use of melatonin and a.a, as well as effective dosing and administration, remain unknown.
40. What is the metabolic role of carnitine?  
 The oxidation of fatty acids is compartmentalized within the mitochondrion. Fatty acids and their CoA derivatives, however, are incapable of crossing the inner mitochondrial membrane, necessitating a membrane transport system. The carrier molecule for this system is carnitine which can be synthesized in humans from lysine and methionine, and which is found in high concentration in muscle.

Carnitine is needed for the transport of long-chain fatty acids across the inner mitochondrial membrane for oxidation. In muscle, carnitine also may serve as a buffer for free coenzyme (Co)A and may be involved in branched-chain amino acid metabolism. Carnitine is also thought to be involved with immune system function.

41. In what tissues are branched chain amino acids metabolized?

Muscle, as well as the heart, kidney, diaphragm, and other organs, possess BCAA transferases, located in both the cytosol and mitochondria. The enzyme complex needed for the next step is found in the mitochondria of many tissues, including liver, muscle, heart, kidney, intestine, and the brain.

42. What are the products of complete catabolism of a simple amino acid?

Energy,  $\text{CO}_2$ ,  $\text{NH}_4^+$  and  $\text{H}_2\text{O}$ .

43. Which tissue has the complete urea cycle? Are these enzymes sensitive to the amount of substrate?

The urea cycle occurs in the liver. Activities of urea cycle enzymes fluctuate with diet and hormone concentrations. For example, with low-protein diets or acidosis, urea synthesis (the amount of mRNA for each of the enzymes) diminishes and urinary urea nitrogen excretion decreases significantly. In the healthy individual with a normal protein intake, blood urea nitrogen (BUN) concentrations range from 8 to 20 mg/dL, and urinary urea nitrogen represents about 80% of total urinary nitrogen. Glucocorticoids and glucagon typically increase mRNA for the urea cycle enzymes.

44. How is urea removed from the body?

Through the urinary system. With normal protein intakes, urea may be 80% of total urinary nitrogen.

45. How is creatinine related to muscle mass?

Urinary excretion of creatinine and 3-methylhistidine are used as indicators of the amount of existing muscle mass and the rate of muscle degradation, respectively. Urinary creatine excretion is considered to be a reflection of muscle mass because it is the degradation product of creatine, which makes up approximately 0.3% to 0.5% of muscle mass by weight. The creatinine excreted in the urine reflects about 1.7% of the total creatine pool per day. However, urinary creatinine excretion is not considered to be a completely accurate indicator of muscle mass because of the variation that occurs in muscle creatine content.

46. What are key metabolic reactions that occur in the mitochondria?

The mitochondria are the primary sites of oxygen use in the cell and are responsible for most of the metabolic energy (adenosine triphosphate, or ATP) produced in cells. The electron transport chain couples the energy released by nutrient oxidation to the formation of ATP. Among the metabolic enzyme systems functioning in the mitochondrial matrix are those catalyzing reactions of



the Krebs cycle and fatty acid oxidation. Other enzymes are involved in the oxidative decarboxylation and carboxylation of pyruvate and in certain reactions of amino acid metabolism. Mitochondrial genes (inherited only from the mother) code for proteins vital to the production of ATP.

47. Can amino acids from muscle be metabolized for energy?

Yes. BCAA + aspartate, asparagine, glutamate are catabolized in skeletal muscle. When insulin increases, BCAA move in.  $\alpha$ -keto acids may be oxidized in muscle (mitochondria) or transported to other tissues. Creatine and CP cyclize to creatinine which is an indicator of the amount of existing muscle mass.

48. When is a person in positive N balance?

During growth, protein synthesis exceeds degradation, and nitrogen intake exceeds excretion, resulting in a positive nitrogen balance. Positive nitrogen balance means there is more coming in than going out. Growth, pregnancy. Excess energy intake fosters nitrogen retention.

49. Describe a situation in which a person would be in negative nitrogen balance.

Protein synthesis and protein degradation are under independent controls. Rates of synthesis can be quite high as with protein accretion during growth. Alternately, protein degradation can be quite high, as during fever. Negative balance means more is going out than coming in. Loss of LBM. Insufficient calories from carbohydrate and/or fat mandate the oxidation of some protein to supply energy needs.

50. Give some examples of transport proteins.

Albumin - transports a variety of nutrients such as calcium, zinc, and vitamin B<sub>6</sub>.  
 Transthyretin (formerly called prealbumin) - complexes with retinol-binding protein, for the transport of retinol (vitamin A).  
 Hemoproteins, iron-containing proteins - bind and/or transport oxygen.  
 Transferrin - an iron transport protein  
 Ceruloplasmin - a copper transport protein

51. What is a protein of the immune system?

Immunoproteins may also be referred to as immunoglobulins (Ig) or antibodies (Ab). Immunoglobulins, of which there are five major classes -- IgG, IgA, IgM, IgE, and IgD -- are Y-shaped proteins made of four polypeptide chains. Immunoglobulins function by binding to antigens and inactivating them. Antigens typically consist of foreign substances such as bacteria or viruses that have entered the body. By complexing with antigens, immunoglobulin-antigen complexes can be recognized and destroyed through reactions with either complement proteins or cytokines. In addition, white blood cells such as macrophages and neutrophils also destroy foreign antigens through the process of phagocytosis.

52. Why is a protein able to serve as a buffer?

Proteins, because of their constituent amino acids, can serve as a buffer in the body. A buffer is a compound that ameliorates a change in pH that would otherwise occur in response to the addition of alkali or acid to a solution. The pH of the blood and other body tissues must be maintained within an appropriate range. Blood pH ranges from about 7.35 to 7.45, whereas cellular pH levels are often more acidic. The H<sup>+</sup> concentration within cells is buffered by both the phosphate system and proteins. For example, the protein hemoglobin functions as a buffer in red blood cells. In the plasma and extracellular fluid, proteins and the bicarbonate system serve as buffers. Amino acids act as acids or bases in aqueous solutions such as in the body by releasing and accepting hydrogen ions, and they thereby contribute to the buffering capacity of proteins in the body. The buffering ability of proteins can be illustrated by the reaction: H<sup>+</sup> + protein <----> Hprotein

53. What are two examples of conjugated proteins?

Conjugated proteins also play important and diverse roles in the body. Conjugated proteins are proteins that are conjugated (joined) to nonprotein components. Examples of some conjugated proteins include glycoproteins, proteoglycans, lipoproteins, flavoproteins, and metalloproteins.

54. Approximately how much protein does the body process per day?

Exogenous sources: Dietary animal and plants products: The average American eats 80-100 g/d.

Endogenous sources: Mucosal cells: ~ 50 g/d from shedding of cells in intestines. Re-used protein.

Digestive enzymes & glycoproteins: ~ 17 g

55. What factors affect protein quality?

Several methodologies are available to determine the protein quality of foods containing protein.

- • Chemical Score (Amino Acid Score) - involves determination of the amino acid composition of a test protein. Only the indispensable amino acid content of the test protein is determined, and then compared with that of egg protein or with an ideal reference pattern of a.a's.
- • Protein Efficiency Ratio - represents body weight gained on a test protein divided by the grams of protein consumed. PER allows determination of which proteins promote weight gain (per gram of protein ingested).
- • Biological Value - a measure of how much nitrogen is retained in the body for maintenance and/or growth versus the amount of nitrogen absorbed. Foods with a high BV are those that provide the amino acids in amounts that are consistent with body amino acid needs. The body will retain much of the absorbed nitrogen, if the protein is of high BV.
- • Net Protein Utilization - measures retention of food nitrogen consumed rather than retention of food nitrogen absorbed. Proteins of higher quality

typically cause a greater retention of nitrogen in the carcass than poor-quality proteins and would have a higher NPU.

56. Explain specifically what the term “limiting amino acid” means.

The term limiting amino acid is used to describe the indispensable amino acid that is present in the lowest quantity in the food.

57. What is the major limiting amino acid in grains? In legumes?

In wheat, rice, corn, other grains and grain products, the limiting a.a.'s are lysine, threonine (sometimes), and tryptophan (sometimes). In legumes, the limiting a.a is methionine.

58. What does a bioassay for protein quality tell you that a chemical score does not?

- • Chemical Score (Amino Acid Score) - involves determination of the amino acid composition of a test protein. Only the indispensable amino acid content of the test protein is determined, and then compared with that of egg protein or with an ideal reference pattern of a.a's.
- • Biological Value - a measure of how much nitrogen is retained in the body for maintenance and/or growth versus the amount of nitrogen absorbed. Foods with a high BV are those that provide the amino acids in amounts that are consistent with body amino acid needs. The body will retain much of the absorbed nitrogen, if the protein is of high BV.

The bioassay (biological value) tells you how much nitrogen was retained versus the amount absorbed, whereas the chemical score only tells you the indispensable amino acid composition of the test protein.

59. What does complementation mean when referring to amino acids?

To ensure that the body receives all the indispensable amino acids, certain proteins can be ingested together or combined so that their amino acid patterns become complementary. For example, legumes, with their high content of lysine but low content of sulfur-containing amino acids, complement the grains, which are more than adequate in methionine and cysteine but limited in lysine.

60. What does a sudden increase in oxidation of an amino acid mean about the adequacy of the diet?

Amino acid oxidation increases if a.a are in surplus. Amino acid oxidation increases if an essential a.a is missing.

61. How does total energy value of the diet affect protein utilization?

If energy intake is too low, protein will be used for energy, not growth. Energy needs must be met first. This is a big factor in developing countries. Insufficient energy intake causes oxidation of protein for energy needs.

62. Is conversion of carbohydrate and protein to triacylglycerols higher in the fed state or in the fasted state? Why?

The fed state favors synthesis of adipose tissue from free fatty acids. In fasting, blood glucose & insulin decrease, allowing lipolytic activity in adipose. FFA oxidized for energy, and some formation of ketone bodies. Excess glucose that cannot be oxidized or stored as glycogen is converted into triacylglycerols for storage. Glucose-rich cells (as in the fed state) do not actively oxidize fatty acids for energy. Instead, a switch to lipogenesis is stimulated, accomplished in part by inhibition of the entry of fatty acids into the mitochondrion. In the fasted state, there is a shift to ketones to support the CNS. Gluconeogenesis is going on in the liver. Muscle protein breakdown is the chief gluconeogenesis substrate. In this circumstance, carbohydrate and protein are not being converted to triacylglycerols. If they were present, they would be used for energy because energy in being used for energy out is more efficient than storing energy and then using it. It requires energy to store it.

63. What are the essential fatty acids?

- • Linoleic (18:2 n-6)
  - ○ Arachidonic (20:4 n-6)
- • Alpha-linolenic (18:3 n-3)

64. In what form is most of the lipid in food?

Fatty acids are of vital importance as an energy nutrient, furnishing most of the calories from dietary fat. Most stored body fat is in the form of triacylglycerols, which represent a highly concentrated form of energy. They account for nearly 95% of dietary fat. Structurally they are composed of trihydroxy alcohol, glycerol, to which are attached three fatty acids by ester bonds.

65. Do plants have cholesterol?

Cholesterol comes from animal tissue. Found in the cell membrane, particularly nerve tissue, it is the precursor for bile acids, estrogens, androgens, cortiosteroids, & vitamin D.

66. How is the absorption of short-chain fatty acids different from the absorption of long-chain fatty acids. Explain in detail.

The process of absorption of free fatty acids is a function of the chain length of the fatty acids involved. Fatty acids having more than 10 to 12 carbon atoms are first activated by being coupled to coenzyme A by the enzyme acyl CoA synthetase. They are then reesterified into triacylglycerols, phosphatidylcholine, and cholesteryl esters. Short-chain fatty acids, those containing fewer than 10 to 12 carbon atoms, in contrast, pass from the cell directly into the portal blood. In the blood, short-chain fatty acids attach to albumin for transport to other tissues for processing. The different fate of the long- and short-chain fatty acids is due to the specificity of the acyl CoA synthetase enzyme for long-chain fatty acids only.

67. Where is bile synthesized?

Bile is synthesized in the liver, in the hepatocytes. Bile is composed of mainly bile acids (and/or salts) but also cholesterol, phospholipids, and bile pigments (bilirubin and biliverdin) dissolved in an alkaline solution. Hepatic synthesis of the bile salts, indispensable for the digesting and absorbing dietary lipids, is one of its functions.

68. What are chylomicrons?

Chylomicrons are the primary form of lipoprotein formed from exogenous (dietary) lipids. Chylomicrons belong to a family of compounds called lipoproteins. Lipids resynthesized in the enterocytes, together with fat-soluble vitamins, are collected in the cell's endoplasmic reticulum as large fat particles. While still in the endoplasmic reticulum, the particles receive a layer of protein on their surface, which tends to stabilize the particles in the aqueous environment of the circulation, which they eventually enter. The particles are pinched off as lipid vesicles that then fuse with the Golgi apparatus. There, carbohydrate is attached to the protein coat, and the completed particles, called chylomicrons, are transported to the cell membrane and exocytosed into the lymphatic circulation.

69. What role do lipids have in membrane structure?

Meats, egg yolk, and dairy products contain fairly large amounts of cholesterol, and the sterol is an essential component of cell membranes, particularly those comprising nerve tissue. Cholesterol enhances the mechanical stability of the membrane and regulates its fluidity. Cholesterol helps to form the lipid bilayer. By regulating fluidity of the membrane, cholesterol regulates membrane permeability, thereby exercising some control over what may pass into and out of the cell. Fluidity of the membrane also appears to affect the structure and function of the proteins embedded in the lipid membrane.

70. Where are long-chain fatty acids oxidized?

Many tissues are capable of oxidizing fatty acids by way of a mechanism called  $\beta$ -oxidation. The oxidation of fatty acids is compartmentalized within the mitochondrion. The activated fatty acid is joined covalently to carnitine at the cytoplasmic side of the mitochondrial membrane by a transferase enzyme. The oxidation of the activated fatty acid in the mitochondrion occurs via a cyclic degradative pathway, by which two-carbon units in the form of acetyl CoA are cleaved one by one from the carboxyl end.

71. Fatty acids are elongated or oxidized from which end of the chain?

The carboxyl end.

72. What is the role of lipoprotein lipase?

Lipid undergoes hydrolysis by LPL. Chylomicrons and VLDL, which is formed endogenously in the liver, are transported by the blood throughout all tissues in the body while undergoing intravascular hydrolysis at certain tissue sites. This hydrolysis occurs through the action of the enzyme lipoprotein lipase, associated with the endothelial cell surface of the small blood vessels and capillaries within

adipose and muscle tissue. Its extracellular action on the circulating particles releases free fatty acids and diacylglycerols, which are quickly absorbed by the tissue cells. In this manner, chylomicrons and VLDL are cleared rapidly from the plasma in a matter of minutes and a few hours, respectively, from the time they enter the bloodstream. It is the large, triacylglycerol-laden chylomicrons that account for the turbidity of postprandial plasma. Because lipoprotein lipase is the enzyme that solubilizes these particles by its lipolytic action, it is sometimes referred to as "clearing factor." That which is left of the chylomicron following this lipolytic action is called a chylomicron remnant -- a smaller particle relatively less rich in triacylglycerol but richer in cholesterol. These are removed from the bloodstream by liver cell endocytosis. Nascent VLDL of liver origin also undergoes triacylglycerol stripping by lipoprotein lipase at extracellular sites, resulting in the formation of a transient IDL particle, and finally, a cholesterol-rich LDL. ApoC-II is an activator of lipoprotein lipase and a component of both chylomicrons and VLDL.

73. What is the role of hormone-sensitive lipase?

The key enzyme for the mobilization of fat is hormone-sensitive triacylglycerol lipase, found in adipose tissue cells. Lipolysis is stimulated by such hormones as epinephrine and norepinephrine, adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), glucagon, growth hormone, and thyroxine. Insulin antagonizes the effects of these hormones by inhibiting the enzymatic activity.

74. What typically happens to free fatty acids if they are taken up by muscle? By adipose tissue?

In muscle, FFA is used for energy. In adipose tissue, FFA is used for synthesis. LPL removes FFA leaving more cholesterol -- remnants removed in liver.

75. Triacylglycerol from liver is secreted into the blood as part of which lipoprotein?

Chylomicrons.

76. Why is there increased delivery of fatty acids to the muscle during exercise?

Plasma free fatty acids are mobilized from adipose tissue -- their importance increases with duration of exercise. In the fasted state, at 25-30%  $VO_2$  max, most energy is from plasma fatty acids. As intensity increases to 65-85%, f.a. are not replaced in plasma fast enough and more glycogen is used. At  $VO_2$  max, carbohydrate becomes ~sole energy source.

77. What are ketone bodies?

In addition to its direct oxidation via the Krebs cycle, acetyl CoA may follow other catabolic routes in the liver, one of which is the pathway by which the ketone bodies (acetoacetate,  $\beta$ -hydroxybutyrate, and acetone) are formed.

78. What is the substrate for the synthesis of ketone bodies? Are ketone bodies produced during normal metabolism?

Ketone body formation is actually an "overflow" pathway for acetyl CoA use (i.e., the substrate), providing another way for the liver to distribute fuel to peripheral cells. Normally, the concentration of the ketone bodies is very low in the blood, but it may reach very high levels in situations of accelerated fatty acid oxidation combined with low carbohydrate intake or impaired carbohydrate use. Such a situation would occur in diabetes mellitus, starvation, or simply a very low-carbohydrate diet.

79. What is ketosis? In what type of patient is ketosis particularly a problem?

The shift to fat catabolism, coupled with reduced oxaloacetate availability, results in an accumulation of acetyl CoA. A sharp increase in ketone body formation follows as would be expected, resulting in the condition known as ketosis.

Ketosis can be dangerous in that it can disturb the body's acid-base balance (two of the ketone bodies are organic acids). However, the liver's ability to deliver ketone bodies to peripheral tissues such as the brain and muscle is an important mechanism for providing fuel in periods of starvation. It is the lesser of two evils. Ketone bodies can fuel muscle & brain during fasting & starvation. Ketosis is particularly a problem in diabetes mellitus. Ketosis changes the binding capacity of hemoglobin for O<sub>2</sub> (ability to bind O<sub>2</sub> decreases). Therefore, hemoglobin carries less O<sub>2</sub>.

80. What is an average daily dietary cholesterol intake? How much cholesterol is synthesized in the body per day?

The average intake is about 600 mg/day -- but only half is absorbed. Endogenous cholesterol production is ~ 1 gram/day. Therefore, there is not much response from dietary change. Endogenous cholesterol accounts for greater than two-thirds of the total cholesterol store.

81. Cholesterol synthesis begins with what compound?

Nearly all the tissues in the body are capable of synthesizing cholesterol from acetyl CoA.

82. Why is HMG CoA reductase important in cholesterol synthesis?

The conversion of HMG-CoA to squalene includes the important rate-limiting step of cholesterol synthesis in which HMG-CoA is reduced to mevalonic acid by HMG-CoA reductase. This rate-limiting step is targeted by statin drugs which attempt to lower serum cholesterol levels.

83. Explain the pattern of double bonds in an omega-3 and an omega-6 fatty acid.

In an omega-3 fatty acid, the first double bond will be between the third and fourth carbon from the omega (methyl) end. In an omega-6 fatty acid, the first double bond will be between the sixth and seventh carbon from the omega (methyl) end.

84. What are some health advantages of omega-3 fatty acids?

- • hypolipidemic

- • antithrombotic (reduce blood clotting)

Good sources are soy, canola, linseed, fish & shellfish (EPA), human milk, fish (DHA)

85. What is a good source of EPA? Of DHA?

Eicosapentaenoic acid (EPA) - good source is cold water fish. Fish oils are particularly rich in EPA. DHA is a longer chain with 6 double bonds. It is high in breast milk and in fish.

86. Give an example of competing effects of eicosanoids.

- • Prostacyclin ( $\text{PGI}_2$ ) - platelet anti-aggregating - stimulates adenylate cyclase (produces cAMP).
- • Thromboxane  $\text{A}_2$  - inhibits adenylate cyclase & is pro-aggregating
- •  $\text{PGE}_2$  - causes vasodilation of blood vessels
- • vasoconstriction by  $\text{PGF}_2$ .

87. What besides enzymes is required for the digestion of lipid?

Emulsification by bile makes enzyme action possible.

88. Are most naturally occurring double bonds "cis" or "trans"?

Cis is the natural form. Trans is a result of hydrogenation for stability. Trans fits into the membrane differently.

89. What fatty acid is the substrate for prostaglandin synthesis?

The most important fatty acid serving as precursor for eicosanoid synthesis is arachidonate. Its oxygenation follows either of two major pathways:

- • the "cyclic" pathway, which results in the formation of prostaglandins and thromboxanes
- • the "linear" pathway, which produces leukotrienes.

90. Identify a fat or oil that has a large amount (>10%) of omega-3 fatty acids.

Soy.

91. How important a component of cell membranes are the PUFA?

Membranes are sheetlike structures composed primarily of lipids and proteins held together by noncovalent interactions.

92. How/why does fatty acid composition affect membrane fluidity?

Cholesterol enhances the mechanical stability of the membrane and regulates its fluidity. Cholesterol helps to form the lipid bilayer. By regulating fluidity of the membrane, cholesterol regulates membrane permeability, thereby exercising some control over what may pass into and out of the cell. Fluidity of the membrane also appears to affect the structure and function of the proteins embedded in the lipid membrane.



93. Why are PUFA susceptible to lipid peroxidation?

Carbon to carbon double bonds are much more easily attacked by free radicals than are single bonds. The more double bonds in a PUFA, the more vulnerable it is to peroxidation. Normal protection against peroxidation is provided for by anti-oxidant enzymes in the membrane and cytosol and by anti-oxidant vitamins A, E, and C and b-carotene.

94. What are some fatty acids that increase plasma cholesterol concentrations?

Saturated fatty acids (lauric, myristic, palmitic acids).

95. What is the major carrier of cholesterol in the blood?

The LDL fraction is the major carrier of cholesterol, binding about 60% of the total serum cholesterol. Its function is to transport the sterol to tissues, where it may be used for membrane construction or for conversion into other metabolites such as the steroid hormones.

96. What are the results of lack of the LDL receptor?

Mutant cells unable to bind and/or internalize LDL efficiently and thereby deprived of the cholesterol needed for membrane synthesis must obtain the needed sterol via de novo synthesis. In these cells HMG CoA reductase is activated while ACAT is depressed.

97. If cholesterol is taken up by the liver, what is the potential effect on cholesterol synthesis?

The enterohepatic circulation can return absorbed bile salts to the liver. Bile salts returning to the liver from the intestine repress the formation of an enzyme catalyzing the rate-limiting step in the conversion of cholesterol into bile acids. If the bile salts are prevented from returning to the liver, the activity of this enzyme increases, thus stimulating the conversion of cholesterol and therefore its excretion. This effect is exploited therapeutically in the treatment of hypercholesterolemia by the use of unabsorbable, cationic resins that bind bile salts in the intestinal lumen and prevent their return to the liver. As total body cholesterol increases, the rate of synthesis tends to decrease, and this is known to be due to a negative feedback regulation of the HMG-CoA reductase reaction. This suppression of cholesterol synthesis by dietary cholesterol seems to be unique to the liver and is not evident in other tissues to a great extent. The effect of feedback control of biosynthesis depends to a great extent on the amount of cholesterol absorbed. The suppression is not sufficient to prevent an increase in the total body pool of cholesterol when dietary intake is high.

98. Do you want HDL-cholesterol or LDL cholesterol to be higher?

HDL is "helper" cholesterol; LDL is "laying it down" cholesterol. You would want HDL-cholesterol to be higher.

99. What is the usual composition of plaque in the arteries?

Lipid material in the form of foam cells (phagocytic cells that become engorged with lipid) infiltrates the endothelium, and as lipid accumulates, the lumen of the blood vessel involved is progressively occluded. The deposited lipid, known to derive from blood-borne lipids, is called fatty plaque.

100. What are major sources of trans fatty acids in the U.S. diet?

Most natural fats and oils contain only cis double bonds. The much smaller amount of naturally occurring trans fats are found mostly in the fats of ruminants, for example in milk fat, which contains 4% to 8% trans fatty acids. Much larger amounts are found in certain margarines and margarine-based products, shortenings, and frying fats as a product of the partial hydrogenation of PUFA. Trans fatty acids are also high in processed, fried, and frozen foods.

101. Are there health implications for diets high in trans fatty acids?

Still contradictory reports. If at high risk of atherosclerosis, it seems beneficial to avoid a high intake of trans fatty acids. More well-designed research is needed.

102. What is the role of carnitine in lipid metabolism?

The oxidation of fatty acids is compartmentalized within the mitochondrion. Fatty acids and their CoA derivatives, however, are incapable of crossing the inner mitochondrial membrane, necessitating a membrane transport system. The carrier molecule for this system is carnitine, which can be synthesized in humans from lysine and methionine, and which is found in high concentration in muscle. The activated fatty acid is joined covalently to carnitine at the cytoplasmic side of the mitochondrial membrane by the transferase enzyme carnitine acyltransferase I (CAT I). A second transferase, acyltransferase II (CAT II), located on the inner face of the inner membrane, releases the fatty acyl CoA and carnitine into the matrix. The oxidation of the activated fatty acid in the mitochondrion occurs via a cyclic degradative pathway, by which two-carbon units in the form of acetyl CoA are cleaved one by one from the carboxyl end.

103. What is enterohepatic circulation? Explain why it is an important pathway.

The circulation of bile is termed enterohepatic circulation. New bile acids are typically synthesized in amounts about equal to those that are lost in the feces (about 0.5 g daily). New bile mixed with recirculated bile is sent via the cystic duct for storage in the gallbladder. The presence of certain dietary fibers in the gastrointestinal tract, however, may bind to the bile salts and acids and prevent bacterial de-conjugation and conversion to secondary bile acids. The pool of bile is thought to recycle at least twice per meal.

104. Why is olestra “low-calorie”?

Olestra cannot be broken down by pancreatic lipases and thus has no caloric value. It is a non-absorbable lipid in the GI tract.

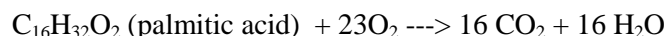
105. What is respiratory quotient?

The respiratory quotient is the ratio of the volume of CO<sub>2</sub> expired to the volume of O<sub>2</sub> consumed. It has served for nearly a century as the basis for determining the relative participation of carbohydrates and fats in exercise.  $RQ = CO_2 / O_2$

For carbohydrate catabolism, the RQ is 1.



For fat catabolism, the RQ is approximately 0.7:



The RQ for protein is about 0.8

106. Would the R.Q. be higher or lower than normal in starvation?

Should the principal fuel source shift from mainly fat to carbohydrate, the RQ correspondingly increases, while a shift from carbohydrate to fat lowers the RQ.

In the starvation state, in an effort to spare body protein, there is a shift from gluconeogenesis to lipolysis -- fat stores become the major supplier of energy. So, in starvation, the RQ would be lower than normal.

107. Why does VO<sub>2Max</sub> have an effect on the ability of an athlete to continue exercise for long periods of time?

VO<sub>2Max</sub> is the workload that places the highest possible demand on the working muscle of that subject, and it is generally used to monitor intensity of exercise. An athlete who can continue exercise for long periods of time will have a high VO<sub>2Max</sub>, because as VO<sub>2Max</sub> increases, your endurance increases. Maximum oxygen uptake (VO<sub>2Max</sub>) refers to the highest rate at which oxygen can be taken up and consumed by the body during intense exercise (Bassett & Howley 2000). Traditionally, the magnitude of an individual's VO<sub>2Max</sub> has been viewed as one of the most important predictors of endurance performance. A classic study, conducted in the 1970's at Ball State University, confirmed the importance of VO<sub>2Max</sub> to endurance performance with findings indicating a strong correlation between VO<sub>2Max</sub> and 10-mile run times (Costill 1970).

Prolonged exercise requires sustained energy provision to maintain muscle contraction and is accomplished through the continual production of ATP. The production of ATP is accomplished through three metabolic pathways (breakdown of a fuel to release energy), which include the phosphagen system (the production of ATP from creatine phosphate), glycolysis (glucose breakdown), and mitochondrial respiration (aerobic metabolism within the mitochondrion of the cell). The first two pathways are only capable of energy production for short durations; consequently, ATP regeneration for extended exercise is accomplished predominantly through mitochondrial respiration.

108. What enzyme removes free fatty acids from circulating triacylglycerols?

The complete hydrolysis of triacylglycerols yields glycerol and three fatty acids. In the body, this occurs largely through the activity of lipoprotein lipase of vascular endothelium and through an intracellular lipase that is active in the liver and particularly active in adipose tissue.

109. What enzyme breaks down triacylglycerols in the tissue to release free fatty acids?

Hormone sensitive lipase hydrolyzes f.a from intramuscular triacylglycerols.

110. What effect does insulin have on hormone-sensitive lipase?

Insulin inhibits the activity of hormone-sensitive triacylglycerol lipase.

111. Is breakdown of triacylglycerols in adipose tissue enhanced or reduced by eating?

Reduced. The fed state favors synthesis. Insulin inhibits adipose tissue lipase.

112. When do you get free fatty acids from adipose tissue?

In fasting, decreased insulin allows lipolytic activity in adipose to become more active. FFA are oxidized for energy. Start releasing FA for energy. Travel to muscle.

113. In what tissue does most of the glycogen accumulate after eating if the body is at rest?

The greatest concentration of glycogen is in the liver, although there is more actual volume of glycogen in the muscle. In the fed state, glucose is sent to muscle for energy and for storage of excess as glycogen.

114. Why is utilization of fatty acids (as percentage of fuel) decreased at very high work intensity?

At very high work intensity, utilization of FFA is reduced because you can't get enough oxygen to utilize it.  $VO_{2Max}$  becomes the limiting factor.

115. What duration of energy expenditure does the ATP/creatine phosphate system support?

Creatine phosphate lasts about 10 seconds.

116. What duration of energy expenditure does the lactic acid system support?

High intensity events of 20 seconds to a few minutes.

117. Why is aerobic energy metabolism classed as "more efficient"?

It is efficient in terms of ATP generation. This system involves the Krebs cycle, through which carbohydrates, fats, and proteins are completely oxidized to  $CO_2$  and  $H_2O$ . The system, which requires oxygen, is highly efficient from the standpoint of the quantity of ATP produced. Since oxygen is necessary for the system to function, an individual's  $VO_{2Max}$  becomes an important factor in his or her performance capacity.

118. What is a mineral that can be limiting for full efficiency of aerobic energy metabolism?

Iron is a vital component of hemoglobin and affects the oxygen-carrying capacity of blood. Also, the transfer of electrons along the electron transport chain is made possible by the change in the oxidation state of iron.

119. What are ways that training enhances aerobic energy metabolism?

Some effect on cardiovascular function such as increased exchange in lungs and increased cardiac output. The main adaptation may be an increase in the number of

mitochondria in skeletal muscle. This is very important and very fast (1-2 weeks). Elite runners can run much farther on the same amount of glycogen (not "hitting the wall").

120. What is the primary fuel for low intensity exercise (25-30%  $VO_{2max}$ )

In the fasted state, at 25-30%  $VO_{2Max}$ , most energy is from plasma fatty acids. As intensity increases to 65-85%, f.a. are not replaced in plasma fast enough and more glycogen is used. At  $VO_{2Max}$ , carbohydrate becomes ~sole energy source. Marathon runner uses f.a.'s.

121. What is the purpose of carbohydrate loading?

Because muscle glycogen was identified as the limiting factor for the capacity to exercise at intensities requiring 70% to 85%  $VO_{2Max}$ , dietary manipulation to maximize glycogen stores is called carbohydrate loading.

122. Why does carbohydrate loading frequently produce muscle stiffness?

Your body has to store 4g water per 1g glycogen. This results in stiffness.

123. What nutrient is MOST important for athletes?

Water is the most important nutrient for athletes because of the need for hydration and lowering temperature.

124. Why are glycogen stores very important as exercise intensity approaches  $VO_{2max}$

High muscle glycogen levels allow exercise to continue longer at a submaximal workload. Even in the absence of carbohydrate loading, a strong positive correlation exists between initial glycogen level and time to exhaustion and/or performance during exercise periods lasting at least 1 hour. Glycogen depletion is a limiting factor under these conditions.

125. What are products of aerobic metabolism? How are they removed?

In the Krebs cycle, carbohydrates, fats, and proteins are completely oxidized to  $CO_2$  and  $H_2O$ .

126. What are products of anaerobic metabolism? How are they removed?

Glycolysis is the initial way of utilizing glucose in all cells, and is used exclusively by certain cells to provide ATP when insufficient oxygen is available for aerobic metabolism. Glycolysis doesn't produce much ATP in comparison to aerobic metabolism, but it has the advantage that it doesn't require oxygen. In addition, glycolysis occurs in the cytoplasm, not the mitochondria. So it is used by cells which are responsible for quick bursts of **speed** or **strength**. Like most chemical reactions, glycolysis slows down as its product, pyruvic acid, builds up. In order to extend glycolysis the pyruvic acid is converted to lactic acid in a process known as fermentation. Lactic acid itself eventually builds up, slowing metabolism and contributing to muscle fatigue.

Ultimately the lactic acid must be reconverted to pyruvic acid and metabolized aerobically, either in the muscle cell itself, or in the liver. The oxygen which is "borrowed" by anaerobic glycolysis is called **oxygen debt** and must be paid back. Oxygen debt is partly oxygen reserves in the lungs, tissues, and myoglobin in the lungs (**alactacid oxygen debt**). But mostly it is the amount of oxygen which will be required to metabolize the lactic acid produced.

Strength training increases the myofilaments in muscle cells and therefore the number of crossbridge attachments which can form. Training **does not increase the number of muscle cells** in any real way. (Sometimes a cell will tear and split resulting in two cells when healed). Lactic acid removal by the cardiovascular system improves with training which increases the anaerobic capacity. Even so, the **glycolysis-lactic acid system** can produce ATP for active muscle cells for only about a minute and a half.

127. What is a tissue that predominately uses fatty acids for fuel? What is a tissue that cannot use fatty acids for fuel?

Fatty acids are the preferred fuel for most tissues. Red blood cells cannot use fatty acids for fuel because they have no mitochondria. The brain and neurons cannot use fatty acids because they cannot pass the blood-brain barrier.

128. Can the body synthesize glucose from fatty acids?

No. Fatty acids can never form glucose.

129. What is the primary source of blood glucose after 24 hrs of fasting?

The post-absorptive state or "early fasting state" is ~3 to 12-16 hrs. Gluconeogenesis begins. Breakdown of LBM to use C-skeleton from a.a. pool.

130. Which yields more energy----complete oxidation of 1 gram of glucose or complete oxidation of 1 gram of fatty acids? How much? Why?

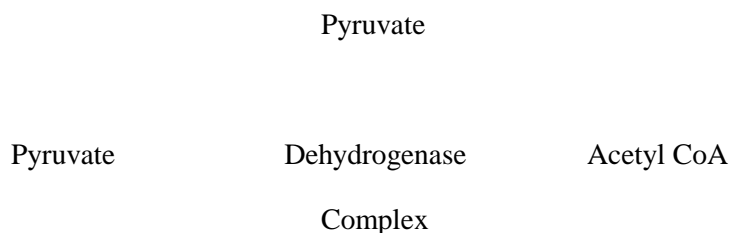
CHO yields 4 kcal/g and fat yields 9 kcal/g.

Fatty acids are a very rich source of energy, and on an equal-weight basis they surpass carbohydrates in this property. This is because fatty acids exist in a more reduced state than that of carbohydrate and therefore undergo a greater extent of oxidation en route to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ .

131. Why is pyruvate dehydrogenase such an important enzyme in metabolism of energy nutrients? Is it reversible?

The pyruvate dehydrogenase reaction is a complex one requiring a multienzyme system and various cofactors. The cofactors include coenzyme A (CoA), thiamine pyrophosphate (TPP),  $\text{Mg}^{+2}$ ,  $\text{NAD}^+$ , FAD, and lipoic acid. Four vitamins are therefore necessary for the activity of the complex: pantothenic acid (a component of CoA), thiamine, niacin, and riboflavin. The net effect of the complex results in decarboxylation and dehydrogenation of pyruvate, with  $\text{NAD}^+$  serving as the terminal hydrogen acceptor. This reaction therefore yields energy, because the reoxidation by electron transport of the NADH produces 3 mol of ATP by oxidative phosphorylation. The reaction is regulated negatively by acetyl CoA and by NADH, and positively by ADP and  $\text{CA}^{+2}$ .

The pyruvate dehydrogenase reaction is shown below. It is not reversible.



132. Can cholesterol be formed from acetyl CoA? Does this mean that cholesterol can



ultimately be derived from carbohydrate or protein?

Nearly all the tissues in the body are capable of synthesizing cholesterol from acetyl CoA. Yes. Acetyl CoA is the starting point. At least 26 steps are known to be involved in the formation of cholesterol from acetyl CoA.

133. What are ketone bodies?

In addition to its direct oxidation via the Krebs cycle, acetyl CoA may follow other catabolic routes in the liver, one of which is the pathway by which the so-called ketone bodies (acetoacetate,  $\beta$ -hydroxybutyrate, and acetone) are formed. Ketone body formation is actually an "overflow" pathway for acetyl CoA use, providing another way for the liver to distribute fuel to peripheral cells. Normally, the concentration of the ketone bodies is very low in the blood, but it may reach very high levels in situations of accelerated fatty acid oxidation combined with low carbohydrate intake or impaired carbohydrate use. Such a situation would occur in diabetes mellitus, starvation, or simply a very low-carbohydrate diet.

134. Where is urea formed?

The urea cycle, which is found in the liver, is important for the removal of ammonia from the body.

135. What organ is responsible for synthesis of most of the plasma proteins?

Albumin, the most abundant of the plasma proteins, is synthesized by the liver. Other proteins synthesized by the liver and released into the plasma include transthyretin (formerly called pre-albumin), retinol-binding protein (complexed together and involved with retinol and thyroid hormone transport), blood-clotting proteins, and globulins.

136. What enzyme (specific) releases free fatty acids from chylomicrons?

Chylomicrons and VLDL, which is formed endogenously in the liver, are transported by the blood throughout all tissues in the body while undergoing intravascular hydrolysis at certain tissue sites. This hydrolysis occurs through the action of the enzyme lipoprotein lipase, associated with the endothelial cell surface of the small blood vessels and capillaries within adipose and muscle tissue. Its extracellular action on the circulating particles releases free fatty acids and diacylglycerols, which are quickly absorbed by the tissue cells.

137. Why is glucose metabolized to lactate in the red blood cell?

The erythrocyte, in the process of maturing, disposes of its mitochondria and must depend solely on the energy produced through anaerobic mechanisms, primarily glycolysis. Glycolysis is the pathway by which glucose is degraded into two units of pyruvate, a triose. Under anaerobic conditions-- that is, in a situation of oxygen debt -- pyruvate is converted to lactate. In cells that lack mitochondria, such as the erythrocyte, the pathway of glycolysis is the sole provider of ATP by the mechanism of substrate-level phosphorylation of ADP.

138. What compound is depleted first to maintain blood glucose levels?

In the course of an overnight fast, nearly all reserves of liver glycogen and most of the muscle glycogen have been depleted.

139. What are three very different compounds that can be synthesized from acetyl CoA?

Acetyl CoA produced from whatever source must be used for energy, lipogenesis, cholesterologenesis, or ketogenesis, i.e., lipid, cholesterol, ketones. A most significant reaction linking glucose metabolism to fatty acid synthesis is the reaction of the pyruvate dehydrogenase complex, which converts pyruvate to acetyl CoA by dehydrogenation and decarboxylation. Acetyl CoA is the starting material for the synthesis of long-chain fatty acids as well as a variety of other lipids.

140. If you fast for a day and a half, are you likely to degrade muscle? Why or why not?

Yes. Gluconeogenesis begins in the postabsorptive state of early fasting -- ~3 to 12-16 hours. After 48 hours with no food intake, the fasting state is in progress with gluconeogenesis in the liver using muscle protein breakdown as the chief gluconeogenesis substrate. When gluconeogenesis begins depends on energy needs; it involves breaking down lean body mass to use the C-skeleton from a.a pool. A day and a half (36 hours) is well within the time in which this process would begin occurring, and by 48 hours, it would be well underway with a shift to ketones to support the CNS..

141. How does fasting affect circulating insulin and glucagon levels?

During fasting, low blood glucose causes glucagon and glucocortico-steroid hormones to rise. Insulin is low because of the low blood glucose.

142. Name a transport protein in serum that is reduced in malnutrition. Would this be the only protein that is reduced?

Albumin is reduced in malnutrition; it is used quite extensively as an indicator of visceral protein status. Albumin functions in the plasma to maintain oncotic pressure as well as to transport nutrients such as vitamin B6, minerals including zinc, calcium, and small amounts of copper, nutrients such as fatty acids; and the amino acid tryptophan. Some drugs and hormones such as the thyroid hormones are also transported by albumin. Transthyretin (pre-albumin) is also reduced in malnutrition, as is retinol-binding protein.