Medical Biochemistry Examination II
November 12, 1999
Kresge Auditorium

Please follow these directions:

1. Do not begin the exam until all students have received a copy of the exam. You will be instructed as to when to break the seal.

2. The exam consists of 81 questions on 19 pages, with this title page considered page 1. There are 150 points on this exam. The point value for each question is indicated by the question. For multiple answer questions without a defined number of answers 0.25 points will be deducted for each incorrect answer, although the lowest point value assigned for a question is 0. **No multiple answer question will have more than 4 correct answers. If a question has a defined number of answers, there is no penalty for guessing.**

3. Place your ID number on every page of the exam booklet and on the answer sheet you will hand in. Also, print your name on the line provided on the answer sheet.

4. There is one answer sheet for this exam. **Four questions (78 - 81 on pages 15-19) should be answered within the exam booklet itself. Use a No. 2 pencil only.** Fill in the circle for the correct answer(s) completely. If you believe that a question has more than one correct answer fill in all answers for that question completely. If you wish to change an answer, be sure to erase cleanly. **Make sure that you use your biochemistry ID number to fill in the ID box. You should use the three leftmost boxes to insert your number.**

5. When you are finished with the exam, return both the test booklet and the answer sheets. The test booklet will be returned to you when the grading is complete. **Be sure to pick up the next section of the course syllabus as you leave.**

6. Questions will not be allowed during the exam. If you believe there is a typographical error do the best you can with the information available. Do not spend extra time on the question. If it is determined that the information presented is ambiguous, or in error, then the question will not be counted in the final scoring.

7. Following the last page of the exam are two blank pages for your use, and a third page which can be used by you to list your answers. You can take this sheet with you from the exam, and use it to check your answers against the posted answers (outside of room 3109 MSB). **You will not be given extra time to fill out this answer sheet.** Answers will be posted on November 17th, at 2:00 pm, assuming that all students attend the exam at its scheduled time.

8. You will have **3.5 hours (until 5:00 pm)** to complete this exam. Good luck.
1. (1 point) Glycogen synthesis results in a branched chain polymer of glucose residues. In order to create this polymer, which of the following component are required? This question may have more than one correct answer. Indicate all correct answers on the answer sheet.

A. UDP-glucose
B. UDP-fucose
C. Glycogen synthase
D. Thiamine pyrophosphate
E. Pyridoxal phosphate
F. Branching enzyme
G. Debranching enzyme
H. Glycogen primer
I. Alternating glucose-galactose primer

2. (1 point) Which of the following activities are a component of the branching enzyme? This question may have more than one correct answer. Indicate all correct answers on the answer sheet.

A. An alpha 1,6 glucosidase activity
B. An alpha 1,4 glucosidase activity
C. An alpha 1,6 synthetic activity
D. An alpha 1,4 synthetic activity
E. A beta 1, 4 glucosidase activity
F. A beta 1, 6 synthetic activity

3. (1 point) Which of the following activities are a component of the debranching enzyme? This question may have more than one correct answer. Indicate all correct answers on the answer sheet.

A. An alpha 1,6 glucosidase activity
B. An alpha 1,4 glucosidase activity
C. An alpha 1,6 synthetic activity
D. An alpha 1,4 synthetic activity
E. A beta 1, 4 glucosidase activity
F. A beta 1, 6 synthetic activity

4. (1 point) Which ONE of the following glycogen storage diseases is fatal at a young age unless a liver transplant is performed?

A. Von Gierke’s disease
B. McArdle’s disease
C. Anderson’s disease
D. Cori’s disease
E. Kreb’s disease
F. Lesch-Nyhan disease
5. (1 point) Glycogen degradation requires the involvement of which of the following factors? This question may have more than one correct answer. Indicate all correct answers on the answer sheet.

A. Phosphorylase
B. Glycogen synthase
C. Thiamine pyrophosphate
D. Pyridoxal phosphate
E. UDP-glucose
F. ATP
G. Phosphate ion
H. Phosphoenolpyruvate

6. (1 point) Release of epinephrine will tend to promote which of the following events? This question may have more than one correct answer. Indicate all correct answers on the answer sheet.

A. Fatty acid synthesis in the adipocyte
B. VLDL release by the liver
C. Chylomicron release by the intestine
D. Glycogen degradation in the muscle
E. Insulin release from the pancreas
F. Glucose export by the muscle

7. (1 point) The non-oxidative conversion of six molecules of ribose-5-phosphate to five molecules of glucose-6-phosphate requires all of the enzymes listed below except for which THREE?

A. Transketolase
B. Aldolase
C. Fructose 1,6 bisphosphatase
D. Triose-phosphate isomerase
E. Glucose-6-phosphatase
F. Glyceraldehyde-3-phosphate dehydrogenase
G. Glucose-6-phosphate dehydrogenase

8. (1 point) Superoxide dismutase catalyzes which ONE of the following reactions?

A. $O_2^- + e^- + 2H^+ \text{ yields } H_2O_2$
B. $2 O_2^- + 2H^+ \text{ yields } H_2O_2 + O_2$
C. $O_2^- + HOC+ H+ \text{ yields } CO_2 + H_2O$
D. $H_2O_2 + O_2 \text{ yields } 4 H_2O$
E. $O_2^- + H_2O_2 + H^+ \text{ yields } 2 H_2O + O_2$
The regulation of glycogen metabolism is quite complex. Questions 9 - 15 (2 points each) list enzymes involved in glycogen metabolism. Pick from choices A through I the one answer which best represents the allosteric modifier of the enzyme listed in the question, and then pick a second answer from choices J or K which describe whether the modifier activates or inhibits the enzyme activity. Thus, each question should have two correct answers, unless your answer to part 1 is I, none of the above. In that situation, you should not answer J or K since you did not believe that the proper allosteric modifier was included in the list.

9. Muscle phosphorylase-a  A. AMP  J. Activates
10. Liver phosphorylase-a  B. ATP  K. Inhibits
11. Muscle glycogen synthase-D  C. Calcium ions
12. Liver phosphorylase kinase-b  D. Creatine-phosphate
13. Muscle phosphorylase-b  E. cyclic AMP
14. Protein kinase A  F. Glucose
15. Protein phosphatase-1  G. Glucose-6-phosphate  
   H. Phosphate ions
   I. None of the above

16. (1 point) A deficiency in vitamin B1 would lead to an inability to carry out which TWO of the following reactions?
   A. Glucose-6-phosphate to fructose-6-phosphate
   B. Glucose-6-phosphate to ribulose-5-phosphate
   C. Fructose 1,6 bisphosphate to dihydroxyacetone-phosphate + glyceraldehyde-3-phosphate
   D. Isocitrate to alpha ketoglutarate + carbon dioxide
   E. Sedoheptulose-7-phosphate + glyceraldehyde-3-phosphate to erythrose-4-phosphate + fructose-6-phosphate
   F. Pyruvate to acetyl-CoA + carbon dioxide
   G. Xylose-5-phosphate + ribose-5-phosphate to sedoheptulose-7-phosphate + glyceraldehyde-3-phosphate

17. (1 point) Which ONE of the following statements best describes carbon flow through the HMP shunt pathway when fatty acid synthesis is occurring, but not DNA or RNA synthesis?
   A. Only the oxidative steps of the pathway are used.
   B. Only the non-oxidative steps of the pathway are used.
   C. A combination of both oxidative and non-oxidative steps of the HMP shunt are used, along with some steps from gluconeogenesis.
   D. The HMP shunt is inactive under these conditions; only glycolytic reactions are required.
Questions 18-29 (2 points each) are based on the following scenario. You are taking a walk in the woods, contemplating your soon to be eaten lunch. You spot two alligators, which are eyeing you for their lunch. You run away to safety, and the length of time of your run is ten minutes. Indicate the phosphorylation and activity state of the enzymes listed in the questions at the very end of the run. There is only ONE answer per question, to be chosen from the letters A through F.

<table>
<thead>
<tr>
<th>Question</th>
<th>Enzyme</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>Muscle phosphorylase</td>
<td>A. The enzyme is phosphorylated by the cAMP dependent protein kinase and is active.</td>
</tr>
<tr>
<td>19</td>
<td>Muscle phosphorylase kinase</td>
<td>B. The enzyme is phosphorylated by the cAMP dependent protein kinase and is inactive.</td>
</tr>
<tr>
<td>20</td>
<td>Muscle protein kinase A</td>
<td>C. The enzyme is phosphorylated, but not by the cAMP dependent protein kinase, and is active.</td>
</tr>
<tr>
<td>21</td>
<td>Liver glycogen synthase</td>
<td>D. The enzyme is phosphorylated, but not by the cAMP dependent protein kinase, and is inactive.</td>
</tr>
<tr>
<td>22</td>
<td>Liver phosphofructokinase-1</td>
<td>E. The enzyme is not phosphorylated under these conditions, and is active.</td>
</tr>
<tr>
<td>23</td>
<td>Liver pyruvate kinase</td>
<td>F. The enzyme is not phosphorylated under these conditions, and is inactive.</td>
</tr>
<tr>
<td>24</td>
<td>Adipocyte acetyl-CoA carboxylase</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Adipocyte hormone sensitive lipase</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Muscle carnitine acyl-transferase I</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Liver glucose-6-phosphate dehydrogenase</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Muscle protein inhibitor I</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>Muscle protein phosphatase I</td>
<td></td>
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30. (1 point) Indicate which ONE of the following compounds would provide the largest amount of ATP when oxidized completely to carbon dioxide and water.

<table>
<thead>
<tr>
<th></th>
<th>Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Propionyl-CoA</td>
</tr>
<tr>
<td>B</td>
<td>Sucrose</td>
</tr>
<tr>
<td>C</td>
<td>(C_{16:0})</td>
</tr>
<tr>
<td>D</td>
<td>Cis (\Delta^9), C_{18:1}</td>
</tr>
<tr>
<td>E</td>
<td>Cis (\Delta^6,9), C_{18:2}</td>
</tr>
</tbody>
</table>

31. (1 point) Coenzyme A and the acyl carrier protein have which of the following features in common? This question may have more than one correct answer. Indicate all correct answers on the answer sheet.

<table>
<thead>
<tr>
<th></th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A free terminal sulphydral group</td>
</tr>
<tr>
<td>B</td>
<td>A phosphopantetheine residue</td>
</tr>
<tr>
<td>C</td>
<td>Adenine</td>
</tr>
<tr>
<td>D</td>
<td>The amino acid glycine</td>
</tr>
<tr>
<td>E</td>
<td>Pyridoxal phosphate</td>
</tr>
<tr>
<td>F</td>
<td>Biotin</td>
</tr>
</tbody>
</table>
32. (1 point) The cyclical process of fatty acid synthesis can best be described by which ONE of the following? Following the condensation step there is:

A. Oxidation, followed by hydration, followed by oxidation.
B. Reduction, followed by dehydration, followed by reduction
C. Oxidation, followed by hydration, followed by reduction
D. Reduction, followed by hydration, followed by oxidation
E. Hydration, followed by oxidation, followed by oxidation
F. Hydration, followed by reduction, followed by reduction

33. (1 point) Major differences between fatty acid synthesis and degradation include which of the following? This question may have more than one correct answer. Indicate all correct answers on the answer sheet.

A. The compartment of the cell in which the pathway is located
B. One pathway utilizes NADPH; the other generates NADPH
C. The required number of enzyme molecules is different for each pathway
D. The synthetic pathway can be regulated by citrate whereas the degradative pathway can be regulated by malonyl-CoA
E. FADH2 is used to create double bonds in fatty acid synthesis, whereas it is used to reduce carbonyl groups in fatty acid oxidation
F. Fatty acid synthesis is promoted by insulin release, whereas fatty acid degradation is inhibited by insulin release

34. (1 point) In a cell free extract containing all of the enzymes needed for the synthesis of fatty acids, $^{14}\text{CO}_2$ is present. In which position of palmitic acid will this label be found? Choose the ONE best answer.

A. None
B. Every
C. All odd carbons
D. All even carbons
E. All even carbons except for the omega carbon

35. (1 point) Which of the following omega series of fatty acids are derived from the essential fatty acids? This question may have more than one correct answer. Indicate all correct answers on the answer sheet.

A. Omega-3
B. Omega-6
C. Omega-7
D. Omega-9
E. Omega-11
36. (1 point) Which ONE of the following fatty acids cannot be synthesized by mammals?

A. Cis Δ 13 C_{20:1}
B. Cis Δ 9, 13 C_{20:2}
C. Cis Δ 8, 11 C_{18:2}
D. Cis Δ 5, 8, 14 C_{20:3}
E. Cis Δ 6 C_{18:1}

37. (1 point) Regulation by long-term adaptation occurs for all of the following enzymes except for which ONE?

A. Transketolase
B. Glucose-6-phosphate dehydrogenase
C. Fatty acid synthase
D. Aceytl-CoA carboxylase
E. Malic enzyme
F. Citrate lyase

38. (1 point) Hypoglycemia is a result of all of the following conditions except for which ONE?

A. MCAD deficiency
B. Von Gierke’s disease
C. Type 0 glycogen storage disease
D. VLCAD deficiency
E. Excessive insulin in the bloodstream

39. (1 point) Potential treatments for obesity include all of the following except for which ONE?

A. Increasing circulating levels of leptin.
B. Permanently activating the leptin receptor.
C. Partially activating natural uncoupling proteins found in the mitochondrial inner membrane.
D. Sensible diets and increased exercise.
E. Introducing malate synthase and isocitrate lyase into human liver cells.
Thus far in the course a large number of vitamins have been discussed. Questions 40-46 (1 point each) are reactions. For each reaction indicate the vitamin(s) which are required for those reactions to proceed. There may be more than one answer per question; indicate all correct answers on the answer sheet. An answer may be used once, more than once, or not at all.

40. Glycogen
    yields G-1-P + glycogen
    A. Vitamin B1
    n
    n-1

41. Propionyl-CoA yields methylmalonyl-CoA
    B. Vitamin B2

42. Sedoheptulose-7-phosphate + glyceraldehyde-3-
    phosphate yields ribose-5-phosphate and Xyulose-5-
    phosphate
    C. Vitamin C
    D. Vitamin B6
    E. Vitamin B12

43. Sedoheptulose-7-phosphate + glyceraldehyde-3-
    phosphate yields erythrose-4-phosphate + fructose-6-
    phosphate
    F. Biotin
    G. Lipoic acid
    H. Niacin

44. Methylmalonyl-CoA yields succinyl-CoA
    I. Phosphopantetheinic
    J. None of the above

45. Steric acid yields oleic acid

46. Glucose-1-phosphate + UTP yields UDP-glucose + PP
    I.

47. (1 point) Citrate plays a number of important roles in intermediary metabolism. These roles include which TWO of the following?

A. An inhibitor of a key enzyme of gluconeogenesis.
B. An activator of a key enzyme of glycolysis.
C. A carrier of acetyl-CoA equivalents across the inner mitochondrial membrane.
D. An activator of fatty acid synthase.
E. An inhibitor of thermogenin, so maximal activity can be obtained from oxidative phosphorylation.
F. A key intermediate of the Krebs tricarboxylic acid cycle.

48. (1 point) Forms of diabetes can result from all of the following conditions except for which ONE?

A. Inability to produce or secrete insulin from the pancreas.
B. Mutations in pancreatic glucokinase.
C. Inactivating mutations of the insulin receptor.
D. Auto-immune antibodies directed against either insulin, or the insulin receptor.
E. Inability to produce leptin.
49. (1 point) The complete oxidation of citrate to carbon dioxide and water will require all of the following enzymes except for which ones? This question may have more than one correct answer. Indicate all correct answers on the answer sheet.

A. Citrate synthase  
B. PEP carboxykinase  
C. Pyruvate dehydrogenase  
D. Pyruvate kinase  
E. Succinate thiokinase  
F. Malate synthase  
G. Enolase

50. (1 point) The generation of ATP in muscle, in terms of moles formed per minute, is most rapid from which ONE of the following energy sources?

A. Liver glycogen  
B. Adipocyte glycerol  
C. Muscle glycogen  
D. Adipocyte NEFA  
E. Liver ketone bodies

Questions 51-54 (1 point each) relate to the hormones listed by the question. Match the ONE best answer with the hormone in the question. An answer may be used ONLY ONCE!

51. Insulin  
52. Epinephrine  
53. Glucagon  
54. Leptin  

A. Produced by the liver  
B. Produced by the muscle  
C. Produced by the adipocyte  
D. Stimulate glycogen degradation in the muscle and adipocyte  
E. Stimulates glycogen synthesis in the liver and muscle  
F. Inhibits glycolysis in the muscle  
G. Stimulates insulin release from the pancreas  
H. Binds to a serpentine receptor and inhibits fatty acid synthesis in the liver
Questions 55-56 should be answered from the lettered list A through F. An answer may be used once, more than once, or not at all.

55. (2 points). An infant with elevated urinary salt secretion is found to have an absence of mineralocorticoids, glucocorticoids, androgens, and estrogens. Family history indicates an inherited, SINGLE gene recessive disorder. What is the most likely defect?

A. 7-α-hydroxylase
B. 3-β-hydroxysteroid dehydrogenase
C. 21-α-hydroxylase
D. 17-α-hydroxylase
E. 11-β-hydroxylase
F. 12-α-hydroxylase

56. (2 points). Another young patient presents with similar symptoms but careful analysis of the family history indicates a more complex mode of inheritance suggesting the involvement of TWO separate genes. Furthermore, although mineralocorticoids, glucocorticoids, androgens and estrogens are all absent, the levels of progesterone are elevated. Which TWO enzymes are affected?

A. 7-α-hydroxylase
B. 3-β-hydroxysteroid dehydrogenase
C. 21-α-hydroxylase
D. 17-α-hydroxylase
E. 11-β-hydroxylase
F. 12-α-hydroxylase

57-60. (1 point each) The linkage between obesity and the development of non-insulin dependent diabetes mellitus (NIDDM) is thought to involve exhaustion of the ability of the pancreas to synthesize insulin. The four conditions (A-D) listed below are thought to constitute some of the crucial steps in this linkage. Place these steps in their proper sequential order starting with obesity. Each answer is to be used only once.

Obesity → 57. ___ → 58. ___ → 59. ___ → 60. ___ → Decreased insulin synthesis

A. increased serum glucose levels
B. increased serum FFA
C. chronic stimulation of insulin secretion
D. increased hepatic gluconeogenesis & decreased muscle glucose utilization
Questions 61-70 should be answered from the lettered list A through R below. The number of answers is indicated in each question. A term may be used once, more than once, or not at all.

61. (4 points) Defects in each of these **FOUR** items may give rise to symptoms such as night blindness, peripheral neuropathies, defective blood clotting or reduced bone calcification.

62. (2 points). These **TWO** lipoproteins are most likely to be elevated in non-insulin dependent diabetes mellitus (NIDDM).

63. (2 points). Increased serum levels of this **ONE** compound are due to a receptor defect that results in reduced rates of clearance of cholesterol by the liver and peripheral tissues.

64. (2 points). An inherited deficiency of this **ONE** protein gives rise to cholesterol enriched remnants of chylomicrons and VLDL which migrate with the β band on lipoprotein electrophoresis. In knockout mice the absence of this protein causes development of atherosclerosis.

65. (4 points). Elevations in the levels of these **FOUR** items would be likely to enhance the rate of removal of cholesterol from the body.

66. (2 points) Inability to synthesize this **ONE** compound would cause a buildup of lipids in enterocytes and an absence of chylomicrons.

67. (2 points). The absence of this **ONE** compound would be expected to result in premature clearance of chylomicrons and VLDL.

68. (1 points). This **ONE** item acts as a chemoattractant for monocytes.

69. (1 points). This **ONE** item is taken up in an unregulated manner by macrophages.

70. (1 points) This **ONE** item facilitates the movement of cholesterol between the cytoplasm and the extracellular fluid.

A. Pancreatic lipase
B. Lipoprotein lipase
C. Co-lipase
D. Chylomicrons
E. VLDL
F. LDL
G. Oxidized LDL
H. HDL
I. LCAT
J. ApoA-I
K. ApoB48
L. ApoB100
M. ApoC-II
N. ApoC-III
O. ApoE
P. ACAT
Q. 7-α-Hydroxylase
R. ABC-1
71. (4 points) Chronic exposure to insulin can lead to decreased insulin receptor sensitivity in the brain as well as the rest of the body. However, loss of insulin receptor sensitivity in the arcuate nucleus of the brain would be expected to have which of the following effects? This question may have more than one correct answer. Indicate all correct answers on the answer sheet.

A. Increase appetite
B. Decrease appetite
C. Increase whole body energy consumption
D. Decrease whole body energy consumption
E. Increase neuropeptide Y release
F. Decrease neuropeptide release
G. Increase norepinephrin release
H. Decrease norepinephrin release
I. Increase HDL levels
J. Decrease HDL levels
K. Increase chylomicron levels
L. Decrease chylomicron levels

72. (2 points) Which **ONE** of the following is not used by the body as part of the normal mechanisms for regulating cholesterol metabolism?

A. LDL receptor synthesis
B. Insulin release
C. Glucagon release
D. Activity of HMGCoA synthase
E. Degradation rate of HMGCoA reductase
F. ACAT

73. (2 points) Bile acids are

1. secreted from either the gall bladder or the liver into the duodenum
2. synthesized at higher rates when hepatic cholesterol levels are high
3. involved in both the emulsification of lipids and in the formation of mixed micelles.
4. converted into bile salts by intestinal bacteria.

A. Answers 1, 2, and 3 are correct
B. Answers 1 and 3 are correct
C. Answers 2 and 4 are correct
D. Answer 4 only is correct
E. All four answers are correct
74. (2 points) A mutation which renders protein inhibitor-1 incapable of being phosphorylated would be expected, directly or indirectly, to

1. Increase the activity of HMGCoA reductase
2. Decrease glycogen synthesis
3. Increase the activity of ACAT
4. Decrease serum concentrations of LDL

A. Answers 1, 2, and 3 are correct
B. Answers 1 and 3 are correct
C. Answers 2 and 4 are correct
D. Answer 4 only is correct
E. All four answers are correct

75. (2 points) Uptake of cholesterol by cultured fibroblast cells results in:

1. activation of cholesterol esterification catalyzed by lecithin:cholesterol acyltransferase.
2. suppression of synthesis of the membrane receptors for low density lipoprotein.
3. stimulation of the synthesis of cholesterol-containing lipoproteins.
4. reduction of cholesterol synthesis by suppressing 3-hydroxy-3-methylglutaryl-CoA reductase activity.

A. Answers 1, 2, and 3 are correct
B. Answers 1 and 3 are correct
C. Answers 2 and 4 are correct
D. Answer 4 only is correct
E. All four answers are correct

76. (2 points) Bile salts:

1. facilitate the digestion of ingested lipids.
2. are amphipathic molecules.
3. are components of the major pathway for cholesterol elimination.
4. are comprised of bile acids conjugated with glycine or taurine

A. Answers 1, 2, and 3 are correct
B. Answers 1 and 3 are correct
C. Answers 2 and 4 are correct
D. Answer 4 only is correct
E. All four answers are correct
77. (2 points) Which of the following conditions is associated with a decreased incidence of atherosclerotic disease?

1. Low LCAT levels
2. Hypobeta-lipoproteinemia
3. Hyperbeta-lipoproteinemia
4. Hyperalpha-lipoproteinemia

A. Answers 1, 2, and 3 are correct
B. Answers 1 and 3 are correct
C. Answers 2 and 4 are correct
D. Answer 4 only is correct
E. All four answers are correct
78. (15 points) As part of an epidemiological project in Family Practice Medicine, you have been screening populations for abnormalities in lipid metabolism. Among the genetically linked abnormalities you have identified are two families with what appear to be inherited deficiencies in enzyme activities. Affected individuals in both families suffer from multiple, severe symptoms. In the first cohort (group A) there is a marked reduction in the ability of Farnesyl pyrophosphate synthase to condense geranyl pyrophosphate and isopentenyl pyrophosphate to form farnsyl pyrophosphate. In the second cohort (group B) there is a marked deficiency of squalene oxidocyclase which is required for conversion of squalene to lanosterol.

Both cohorts have a number of biochemical abnormalities in common and these abnormalities are associated with severe clinical symptoms. Group A has an additional constellation of biochemical abnormalities and clinical symptoms not present in group B. (Hint: The consequences of these abnormalities can be quite far reaching. Don't limit your answers to the most immediate biochemical and clinical consequences. You may use the other side of this page if necessary.) This question has four parts, distributed over this and the next page.

(Please note that the answers to questions 78 and 79 as written here are more detailed than required)

A. (6 points) What biochemical abnormalities would you expect both groups to exhibit?

Both enzyme deficiencies are on the pathway to cholesterol biosynthesis. Since there are no alternate entry points into this pathway, these defects will result in a reduced ability to synthesize cholesterol. In addition, cholesterol is a required precursor for the synthesis of bile salts, steroid hormones (including androgens, estrogens, mineralocorticoids, and glucocorticoids) and vitamin D, so deficiencies in the levels of these metabolites would also be expected to be present.

Cholesterol itself is required for the formation of new membranes and, in the absence of adequate endogenous synthesis, it can therefore become a limiting factor in the rate at which cells can grow and divide. Reduced availability of cholesterol will also lead to a reduction in levels of serum LDL cholesterol and this will in turn give rise to an up regulation of LDL receptors. Lower than usual amounts of cholesterol will be transported from the cells to HDL for delivery to the liver via the reverse cholesterol transport pathway, so serum HDL cholesterol will be low.

As a consequence of reduced bile salt production, the efficiency with which all classes of lipids can be digested in the intestine will be impaired and some will pass through the GI tract, without being absorbed. When this occurs chronically, it can lead to caloric malnutrition and to deficiencies in essential fatty acids. Fat soluble vitamins are also commonly lost along with the undigested lipids.

As a consequence of the reduced availability of cholesterol for steroid hormone production, there may be inadequate levels of progesterone leading to reduced amounts of mineralocorticoids, glucocorticoids, androgens and estrogens.
B. (3 points) Based on these biochemical changes, what clinical symptoms would you predict?

Reduced rates of cellular growth could give rise to slowed rates of organ growth during development and smaller body size as well as impaired rates of wound healing. On the other hand, reduced levels of serum LDL might have some protective effects in atherosclerosis, although this might be offset by reduced HDL levels.

Bile salt deficiencies commonly lead to steatorrhea and the associated losses of vitamins A, D, E, and K may be expressed as problems with night vision, bone formation, peripheral nerve sensation, and blood clotting.

Inadequate levels of steroid hormones will lead to symptoms of water loss (mineralocorticoids), impaired stress responses (glucocorticoids), and the development of secondary sexual characteristics.

C. (3 points) What additional biochemical defects would you predict for group B and what would be the most likely clinical consequences?

The defective enzyme in Group A will block formation of farnesyl pyrophosphate, a precursor for the synthesis of ubiquinone (Coenzyme Q) and dolichol phosphate. The former is required for proper functioning of the electron transport chain and a deficiency would therefore be expected to result in an impaired capacity for generating ATP. This might be particularly evident during exercise. The latter is required for the addition of sugars to proteins so that a deficiency might lead to problems with intracellular protein sorting as well as to problems related to cell-cell recognition. And finally, some proteins are posttranslationally modified by the addition of farnesyl so that in its absence there may be a loss of the proper trafficking of specific proteins to cell membr

D. (3 points) Can you think of any way to help treat these patients? Why would this work?

The most straightforward way to treat these patients would be to increase the amount of cholesterol in their diets. Initially this may need to be done with some supplementation of free cholesterol to avoid problems with lack of deesterification in the intestine. This dietary regimen should alleviate all of the symptoms of the Group B patients and many of the symptoms of Group A patients.

Unfortunately, enzyme replacement remains largely a hope rather than a reality and phosphorylated compounds such as farnesyl pyrophosphate are usually membrane impermeable. It may, however, be possible to successfully treat the energy problems of Group A patients with dietary supplements of CoQ
(5 points) Because of your reputed knowledge of lipid metabolism, you have been called in on a gastroenterological consult for a young woman with unusually severe symptoms of dietary lipid intolerance. Most of the triglycerides, cholesterol esters, and phospholipids which she ingests appear unmodified in her stools. Extensive family history and careful biochemical analyses have revealed that this unfortunate patient has inherited two abnormalities: one results in the synthesis of defective secretin and the other blocks the conjugation of bile acids to form bile salts.

Why would you expect the presence of these two defects to produce symptoms that are synergistically more severe than those found in either defect alone?

**Answer:**

One of the functions of secretin is to raise the pH of the contents of the stomach as they are emptied into the duodenum. It does this by stimulating the secretion into the intestine of a watery, bicarbonate buffered fluid.

Bile acids and bile salts must be in their ionized forms in order to act as emulsifiers and to form micelles. At pH levels found in gastric juice, bile acids become protonated, thereby losing their negative charge. Because the glycine and taurine moieties of the bile salts are more acidic than the bile acids, they can remain charged at these pHs.

Thus, if the only defect is an absence of secretin function, considerable emulsifying capacity remains in the form of ionized bile salts, despite the low pH of the intestinal milieu. On the other hand, in the absence of bile salts, considerable emulsifying capacity remains in the form of bile acids provided that the pH is not too low. Together, however, these two problems act synergistically.
80. (6 points) Explain the biochemical basis (including regulatory points) as to why untreated type I diabetics develop ketoacidosis.

The high glucagon:insulin ratio helps hormone-sensitive lipase with its phos, active state (PKA is active). This leads to NEFA release from adipocyte into circulation, where liver takes up the fatty acids. PKA is active in the liver, so PFK-II and PK are phosphorylated and inactive; thus glycolysis is inactive, and gluconeogenesis is favored. AcCoA carboxylase is phos and inactive thus carnitine acyltransferase I is active, and activated cytoplasmic fatty acids are transferred to the mitochondrial matrix for oxidation. Fatty acid oxidation in the mitochondria is rapid, leading to Acetyl CoA accumulation due to low OAA levels, since OAA is being used for gluconeogenesis. Insulin represses PEPCK transcription, and in the absence of insulin, PEPCK levels are high. The high AcCoA levels in the mitochondria lead to acetoacetyl-CoA, then HMG-CoA synthesis, which leads to acetoacetate formation. The acetoacetate (and β-hydroxybutyrate, if NADH levels are high) leaves the mite, and the liver, to travel to other tissues. In the absence of insulin, ketone body synthesis continues unchecked until dangerously high levels are present in the blood and tissues.
81. (6 points) Indicate the pathway required for the net synthesis of alpha-ketoglutarate from propionyl-CoA as the sole carbon source. Assume that unlimited supplies of carbon dioxide are also present. Indicate all relevant cofactors for each reaction you propose in your pathway. Structures and enzyme names are not required for this answer!!
Answers to Exam II

82. A, C, F, and H
83. B and C
84. A, B and D
85. C
86. A, D and G
87. D
88. E, F and G
89. B
90. D and K
91. F and K
92. G and J
93. C and J
94. A and J
95. E and J
96. I
97. F and G
98. C
99. C
100. A
101. E
102. B
103. F
104. B
105. B
106. A
107. E
108. F
109. A
110. F
111. D
112. A and B
113. B
114. A, C, D and F
115. A
116. A and B
117. D
118. A
119. D
120. E
121. D
122. F
123. A
124. J
125. E
126. H and I
127. J
128. C and F
129. Delete
130. F and G
131. C
132. E
133. Delete
134. H
135. C
136. Delete
137. Delete
138. B
139. D
140. A
141. C
142. A, C, K and Q
143. D and E
144. F
145. O
146. H, I, J and R
147. K
148. N
149. G
150. G
151. R
152. A, D, E and H
153. D
154. A
155. B
156. C
157. E
158. C