NAME_________________

BIO 451              14 December 2000

FINAL EXAM

KEY

This exam will be taken apart for grading. Please PRINT your name on each page.
If you do not have sufficient room for your answer in the space provided, please continue on the
back of the page on which the question appears.

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TOTAL   133

Exam I Exam II Exam III Final Total*/3.3 = Course Avg.

Normalized Score on :
Total* = Sum of two best scores + points earned on the Final

[COURSE GRADE ON REVERSE SIDE] FINAL
I. [10 points]
For each description (below) select the ONE most appropriate vitamin.

1. Required for oxidative decarboxylation of β-keto acids ___D__ or ___K__

2. Contains a residue of glutamic acid ___F___

3. Participates in the conversions involving free radicals ___B___

4. Participates in 1C transfers at the level of a formyl group ___F___

5. Participates in 1C transfers at the level of a carboxyl group ___A___

6. Participates in hydride ion transfers ___K___

7. Participates in the transfer of two hydrogen atom transfers, each with one electron ___E___ or ___C___

8. Participates in postranslational hydroxylation ___C___

9. A derivative of cholesterol ___H___

10. The precursor for FMN ___E___

A. Biotin
B. Vitamin B₁₂
C. Ascorbic acid
D. Thiamine
E. Riboflavin
F. Folic acid
G. Vitamin A
H. Vitamin D
I. Vitamin K
J. Vitamin E
K. Niacin

I. [16 points] [1 point for each correct response; some items are used more than once]
NAME_________________

Match the metabolic pathways below with the cellular compartments in which they occur:
A. Cytosol  B. Inner mitochondrial membrane
C. Mitochondrial matrix  D. Mitochondrial intermembrane space
E. Endoplasmic reticulum

__A__ Glycolysis  __C__ Palmitoyl-CoA oxidation
__A__ Lactic fermentation  __A__ Palmitate synthesis
__C__ Citric acid cycle  __C__ Pyruvate dehydrogenation
__B__ Proton-driven phosphorylation of ADP  __A,C__ Amino acid degradation
__A__ Pentose phosphate pathway  __A,C__ Gluconeogenesis
__E__ Fatty acid elongation and desaturation  __A__ Cholesterol synthesis
__A,C__ Urea cycle

[See Companion]

III. [ 10 points ] (2 points for each correct response)

For each description associated with enzyme kinetics or inhibition, select the corresponding constant, type of inhibition, or appropriate term/abbreviation.

a) $E_t$  
$C$ measure of catalytic efficiency
b) $k_{CAT}$  
$E$ [S] at 2 $V_M$

__J__ a mechanism of inhibition in which an inhibitor binds preferentially to the ES complex
c) $k_{CAT}/K_M$
d) $K_d$  
_____ a form of inhibition that gives an increased $V_M$ but an identical $K_M$

__G__ inhibition that is overcome at saturating [S]
e) $K_M$  
_____ $A$ initial velocity at saturating [S] is first order in this variable.
f) $V_M$
g) Competitive inhibition
h) Noncompetitive inhibition
i) Suicide inhibition
j) Uncompetitive inhibition

IV. [15 points]
For each of the following, choose the ONE best answer (TWO for item M). One point for each
correct response.

A. Which ONE of the following is NOT a cause of gout? __D___
   a. Leukemia and related malignancies
   b. Genetic diseases that limit the amount of phosphate available for purine salvage reactions
   c. Decreased sensitivity of the regulated step in purine biosynthesis to its inhibitors
   d. Genetic defects that cause overproduction of pyrimidines
   e. Chronic renal insufficiency

B. All of the following statements concerning the conversion of ribonucleotides to deoxyribonucleotides are correct EXCEPT: __D____
   a. The ultimate source of reducing equivalents for the reaction is NADPH.
   b. Ribonucleotide reductase has specificity sites that bind different nucleoside diphosphates that determine which ribonucleotides are going to be reduced.
   c. Ribonucleotide reductase has activity sites that bind ATP, GTP, CTP and UTP, which selectively turn the enzyme on or off depending on the nucleotide bound.
   d. Ribonucleotide reductase converts ribonucleoside triphosphates into deoxynucleotide triphosphates.
   e. Thioredoxin is an essential intermediate in the regeneration of ribonucleotide reductase to its active (reduced) form.

C. Hormonal stimulation of the second messenger inositol 1,4,5-triphosphate [IP3] quickly leads to the release of which intracellular second messenger? __D___
   a. cAMP
   b. GDP
   c. prostaglandin
   d. calcium
   e. leukotriene

D. A strong cup of coffee would be expected to ___C__
   a. interfere with the synthesis of prostaglandins
   b. decrease the effects of glucagon
   c. enhance the effects of epinephrine
   d. provide the vitamin niacin
   e. none of the above

E. The lock-and-key model of substrate recognition by an enzyme states that __C__
a. substrates bind to and activate an enzyme so that it can catalyze conversion of other substrate molecules.

b. the enzyme binds the substrate that alters it in such a way as to increase its inherent free energy.

c. the conformation of the enzyme forms an active site that is complementary to the structure of the substrates.

d. the enzyme locks the product in a conformation that prevents it from being converted back to substrate.

F. Which of the following enzymes catalyzes the hydrolysis of proteins on the carboxyl side of W, F and Y? ___B___

   a. Carboxypeptidase B
   b. Chymotrypsin
   c. Elastase
   d. Pepsin
   e. Trypsin

G. After an injection of insulin in a diabetic patient with hyperglycemia, there is a prompt normalization of plasma glucose, due to the recruitment of which of the following transport proteins to the plasma membrane? ___D____

   a. GLUT 1
   b. GLUT 2
   c. GLUT 3
   d. GLUT 4
   e. GLUT 5

H. The activity of which of the following enzymes is decreased in scurvy? ___C___

   a. branched-chain amino acid decarboxylase
   b. malate dehydrogenase
   c. prolyl hydroxylase
   d. pyruvate dehydrogenase
   e. cytochrome P450

I. Glycolysis is the only ATP-producing pathway in ___A___

   a. erythrocytes
   b. lymphocytes
   c. reticulocytes
   d. hepatocytes
   e. neurons
   f. adipocytes
J. In the normal resting state of humans, most of the blood glucose burned as fuel is consumed by __B__
   a. the liver
   b. the brain
   c. the kidneys
   d. adipose tissue
   e. muscle

K. The problem of regenerating NAD+ from NADH for cytoplasmic processes by using mitochondria is solved in the most energy-efficient manner by which one of the following intracellular shuttle mechanisms? __C__
   a. Citrate pyruvate shuttle
   b. DHAP glycerophosphate shuttle
   c. Malate aspartate shuttle
   d. Citrate citrate shuttle
   e. Lactate pyruvate shuttle

L. Elevation of cytosolic calcium from intracellular stores can be caused by __D__
   a. cAMP
   b. cGMP
   c. cCDP
   d. inositol 1,4,5-triphosphate [IP3]
   e. diacylglycerol

M. Match each description of an enzyme deficiency with the appropriate enzyme from the list below
   a. adenosine deaminase
   b. G-6-Pase
   c. hexosaminidase A
   d. hypoxanthine-guanine phosphoribosyltransferase
   e. phenylalanine hydroxylase
   __A__ deficiency associated with combined immunodeficiency disease
   __D__ deficiency associated with Lesch-Nyhan disease

V. [6 points]
Answer A OR B OR C, but NOT ALL THREE. ONLY YOUR FIRST ANSWER WILL BE
A. A significant number of criminal investigations focus on the possibility that the victim may have been injected with a lethal dose of insulin. What is the biochemical basis of insulin toxicity?

*Excess insulin will lower the [Glucose] concentration to a level where there would be insufficient energy to maintain brain function.*

B. Virtually all biochemistry texts state that epinephrine is lipolytic while insulin is lipogenic. What are the biochemical bases of both statements?

**Adipose tissue:**

*Epinephrine*

\[
\text{Triacylglycerols [TG's]} \quad \diamondsuit \quad \diamondsuit \quad \text{Glycerol} \quad + \quad \text{FA's}
\]

*Initiated by activation of Hormone-sensitive lipase*

*Insulin-sensitive insulin transporter [GLUT 4] is brought to the cell surface under the influence of insulin.*

The glucose is the required carbon source for the synthesis of the glycerol that is required for TG synthesis in the fed state.

C. Folic acid deficiency, believed to be the most common vitamin deficiency, causes a type of anemia in which hemoglobin synthesis is impaired and erythrocytes do not mature properly. What is the metabolic relationship between hemoglobin synthesis and folic acid deficiency? Your rationale must be clear.

*Glycine is one of the two required precursors for heme synthesis.*

*THF is a required substrate for serine/glycine hydroxymethyltransferase.*

*Folic acid is required for THF synthesis.*
VI. [8 points]
Mutant cells defective in thymidylate synthase survive and grow in a nutrient medium containing thymidine and methotrexate. However, when normal cells are cultured in nutrient medium containing thymidine and methotrexate they die. Explain BOTH observations. For full credit you must be specific.

See text problem 22-7

VII. [8 points]
Answer A OR B, but NOT BOTH. ONLY YOUR FIRST ANSWER WILL BE GRADED.

A. RE: Signal Transduction
1. What does the term "signal transduction" mean? [2 points]

See page 673, paragraph #2.

2. Describe one such signaling system in as much detail as you are able. [Please use the reverse side of this page] [4 points]

See Fig 21-12 OR 21-19, and associated text. Full credit was given for those answers that provided the relevant details in the clearest manner.

3. In the context of signal transduction, what is meant by desensitization and why is it important? (2 points)

See the last paragraph on page 676 and the seven lines that follow on page 677.

Alternative answers to some of the questions on this page are acceptable if you can demonstrate to me that they clearly address the question and are consistent with the text. I will not accept answers to part 2 that are not consistent with the detail indicated above.

B. Fluorouracil is a chemotherapeutic agent.

1. Identify the derivative that is the active agent. (1 point)

FlurodeoxyUMP
2. Describe the mode of action of this derivative you do not need to provide a lot of chemical detail but you must be specific. (2 points)

_There is a reactive thiol in ribonucleotide reductase that is involved in the formation of an abortive ternary complex that is comprised of the reductase, THF and the flurodeoxyUMP._

3. Outline the pathway by which flurouracil is converted to the active compound? (3 points)

\[
FU + \text{PRPP} \rightarrow FUMP \rightarrow FUDP \rightarrow FdUDP \rightarrow FdUMP
\]

4. Why not administer the active compound instead? (1 point)

_Such charged species do not readily cross the plasma membrane._

VIII. [10 points]
Each of the following items represents a tissue or a substance that is essential for heme metabolism [biosynthesis + catabolism] and/or intertissue cooperation. Illustrate your familiarity with heme metabolism by providing a brief but informative statement that clearly describes the role of these items. Choose FIVE (2 points each). Only the first five answers will be graded.

Bone marrow
PBG deaminase
Spleen
Ferritin
Reticulocyte
Liver

Transferrin
Bilirubin
Verdoglobin
Porphobilinogen
Serum albumin
Enzymes of intestinal bacteria

_Please see the related question in the fall final for 1999, or your text, or your notes/handouts._
IX. [10 points]
A. Excluding gross changes in protein conformation that may occur at extremes of pH, why are enzymatic reactions typically pH dependent?

*Certain functional groups (ionizable side chains) that are involved in catalysis and/or substrate binding may be more 'active' in a particular state of ionization.*

B. On the graph below sketch the pH profile of an enzyme for which an unprotonated H side chain is the most active enzyme species. For full credit your answer must reflect clear awareness of the pH range that is likely to be most important as well as relevant features of the shape of the curve over this range. Your rationale must be clear. You may ignore the pH range above pH 8 and below pH 5

*For full credit you must draw a curve that approximates a titration curve that has an inflection near the $pK_a$ for the imidazole side chain of H.*

X. [10 points]
An individual experiencing painful joints and excreting abnormally high levels of uric acid, was found to exhibit normal levels of all relevant enzymatic activities, including PRPP synthetase [PRS]. The $K_m$ for ribose-5-phosphate, however was several fold lower than in normal individuals. Does this biochemical modification provide an adequate explanation for excess uric acid production? Explain in detail.

\[
\text{R-5-P} + \text{ATP} \longrightarrow \text{PRPP} \longrightarrow \text{PRA} \rightarrow \text{IMP}
\]

\[
\text{ASA} \rightarrow \text{AMP}
\]

\[
\text{IMP} \rightarrow \text{XMP} \rightarrow \text{GMP}
\]

*Ultimately, all these purine nucleotides are degraded to Uric acid.*

*Flux through this pathway is highly dependent on [PRPP].

A lower $K_m$ for R-5-P means that the PRPP synthetase will be saturated at a lower [S]. This will enhance the concentration of PRPP and increase the flux through the de
novo purine biosynthesis pathway.

\[ \text{more purine biosynthesis, more urate production.} \]

XI. [10 points]
Both adenosine deaminase [ADO] and AMP-deaminase [AMPD] catalyze the hydrolysis of the exocyclic amino group at position 6 of the purine ring of their respective substrates. A genetic defect in muscle adenylate deaminase is associated with muscle weakness during exercise. A competitor in the Special Olympics who was AMPD-deficient remarked that he was grateful that he was not ADO-deficient. **For full credit you must provide sufficient biochemical detail to illustrate your familiarity with the subject matter.**

A. Why do AMPD-deficient individuals experience muscle weakness during exercise?

*The purine nucleotide cycle involves the sequential action of AMPD \( \rightarrow \) ASA synthetase \( \rightarrow \) Adenylosuccinase. It is postulated that the fumarate produced from the action of adenylosuccinase, provides energy [citric acid cycle] for muscle during exercise.*

B. Why did the athlete mentioned above feel that he was fortunate not to be ADO deficient?

ADO deficiency is associated with severe immunodeficiency.

XII. [10 points]
A. (6 points) Describe the regulatory roles of Egl-1 and Ced-9 in the apoptotic pathway. Your answer must demonstrate an understanding of the apoptotic pathway in regards to the C. elegans model.

Ced-9 is a pro-survival molecule that under normal circumstances functions to inhibit apoptosis. Egl-1 binds to the Ced-9 / Ced-4 complex causing Ced-4 to dissociate. Ced-4 is then able to activate Ced-3 and lead to apoptosis.

B. (4 points) In class, two types of cell death were described. Name them and provide a simple definition for each.

Apoptosis is a programmed cell death whereas necrosis is brought about by external stimuli or damage to the cell.

XIII. [10 points]
A. Should the natural form of the Hammerhead sequence be considered a true enzyme? Why or why not? [4 points]
No. The hammerhead sequence is consumed over the course of the reaction it catalyzes. Therefore, it is not capable of multiple turnover and is not an enzyme.
B. The large ribosomal subunit contains both protein and RNA. Does the peptidyl transferase activity belong to the protein component, or the RNA? Briefly describe two lines of evidence which support your answer. [6 points]

Peptidyl transferase is an RNA enzyme. This is supported by several lines of evidence discussed in class including:

1) the protein can be >95% removed from the ribosome without a loss of activity, but point mutations in the RNA destroy activity.

2) most of the conserved sequences are found in the RNA. The most highly conserved RNA sequences all localize to the peptidyl transferase site.

3) most antibiotics with known binding sites bind to the RNA, not the protein.

4) the nearest protein atom to the nascent peptide bond is over 18 angstroms away in the co-crystal with CCADP-puromycin.