WEEK NO.3

METABOLISM

DOCTOR 2019 | MEDICINE | JU

DONE BY :

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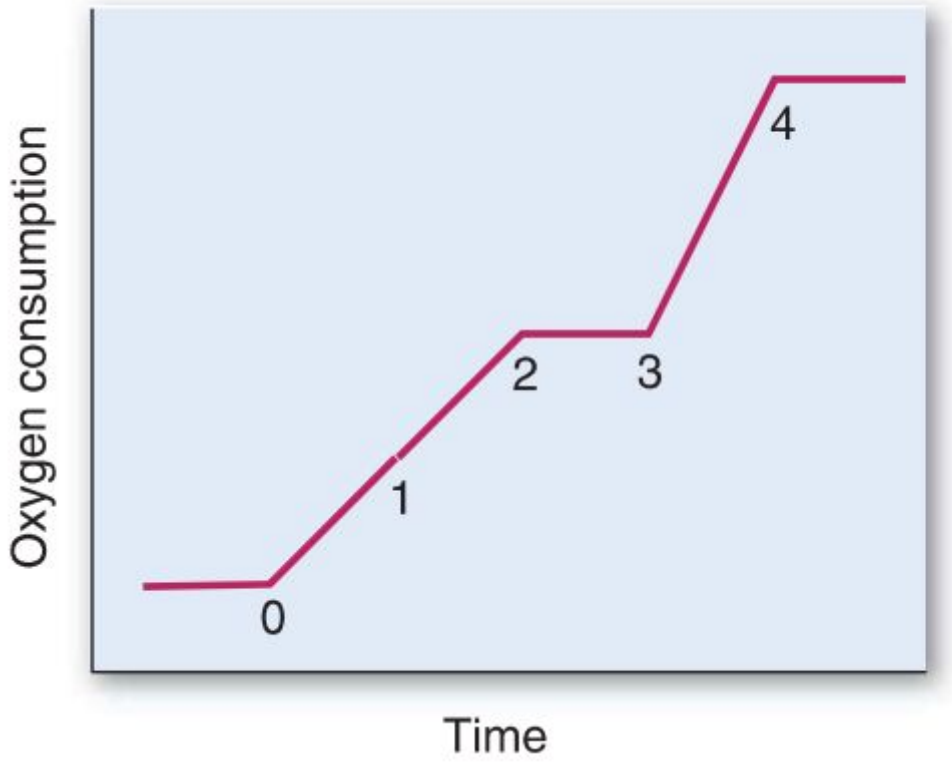
-TCA CYCLE + ELECTRON TRANSPORT CHAIN:

1-A scientist is conducting an experiment on isolated mitochondria in a buffered solution, in the presence of ADP. At time = O, oxygen and succinate were added to the mitochondrial suspension, and oxygen consumption measured as a function or time. At various times after starting the experiment (labeled as 1, 2, 3, and 4 in the figure shown), different chemicals were added to the solution.



Which one of the following correctly describes which chemicals were added at times 1, 2, 3, and 4?

	Time 1	Time 2	Time 3	Time 4
(A)	Antimycin	Oligomycin	Cyanide	Carbon monoxide
(B)	Antimycin	Cyanide	Dinitrophenol	Oligomycin
(C)	Rotenone	Oligomycin	Dinitrophenol	Cyanide
(D)	Rotenone	Dinitrophenol	Oligomycin	Carbon monoxide
(E)	Dinitrophenol	Rotenone	Oligomycin	Cyanide
(F)	Dinitrophenol	Cyanide	Oligomycin	Dinitrophenol

2-A patient suffering a heart attack was brought to the ER. An atherosclerotic plaque had blocked a major coronary artery, preventing blood from reaching a region of her heart. As a result, in cells or the affected heart muscle, there was an increase in which one of the following:

(A) The rate of C02 production
(B) The rate of electron transport by the electron transport chain
(C) The concentration of ADP
(D) The proton gradient across the inner mitochondrial membrane
(E) The rate of 02 consumption

3-A firefighter is brought to the emergency room (ER) from the scene of a fire complaining of headaches, weakness, confusion, and difficulty in breathing. His skin and mucous membranes appear very pink/red. The causative agent of these symptoms inhibits electron transport and oxidative phosphorylation by which one of the following mechanisms?

(A) Uncoupling of electron transport and phosphorylation
(B) Combining with NADH dehydrogenase
(C) Combining with cytochrome oxidase
(D) Inhibiting an adequate supply of ADP
(E) Combining with CoQ

4-Which one of the following components of the electron transport chain only accepts electrons and does not donate them?

(A) Cytochrome b
(B) Oxygen
(C) CoQ
D) FMN
E) Cytochrome cl

5-Which one of the following is a property of pyruvate dehydrogenase?

(A) The enzyme contains only one polypeptide chain.
(B) The enzyme requires thiamin pyrophosphate as a cofactor.
(C) The enzyme produces oxaloacetate from pyruvate.

(D) The enzyme is converted to an active form by phosphorylation.
IE) The enzyme is activated when NADH levels increase.

6-In the TCA cycle, a role for thiamin pyrophosphate is which one of the following?

(A) To accept electrons from the oxidation of pyruvate and a-ketoglutarate
(B) To accept electrons from the oxidation of isocitrate
(C) To form a covalent intermediate with the a-carbon of a-ketoglutarate
(D) To form a thioester with the sulfhydryl group of CoASH
IE) To form a thioester with the sulfhydryl group of lipoic acid

Question 7 and 8 require reference to the following reactions and associated values when answering them.

Reaction	Approximate $\Delta G^{\circ\prime}$ (kcal/mol)
$Acetate + 2\ O_2 \rightarrow 2\ CO_2 + 2\ H_2O$	−243
$NADH + H^+ + ½\ O_2 \rightarrow NAD^+ + H_2O$	−53
$FADH_2 + ½\ O_2 \rightarrow FAD + H_2O$	−41
$GTP \rightarrow GDP + P_i$	−8
$ATP \rightarrow ADP + P_i$	−8

7-Of the total energy available from the oxidation of acetate, what percentage 11 transferred via the TCA cycle to NADH, FADh2 and GTP1

(A) 38%
(B) 42%
(C) 81%
(D) 86%
(E) 100%

8-What percentage of the energy available from the oxidation of acetate is converted to ATP?

(A) 3%
(B) 30%
(C) 40%
(D) 85%
(E) 100%

9-A patient is undergoing an appendectomy under general anesthesia (succinylcholine and an inhaled anesthetic) when she begins to develop muscle rigidity, tachycardia, and hyperthermia. Which of the following best describes the mechanism of this process?

(A) Uncoupling of electron transport and phosphorylation
(B) Inhibition of NADH dehydrogenase
(C) Inhibition of cytochrome oxidase
(D) Inhibiting an adequate supply of ADP
(E) Combining with CoQ

10-A man presents to the ER after ingesting an insecticide. His respiration rate is very low. Information from the Poison Control Center indicates that this particular insecticide binds to and completely inhibits cytochrome c. Therefore, which one of the following would occur in this man's mitochondria?

(A) CoQ would be in the oxidized state
(B) Cytochromes a and as would be in the reduced state
(C) The rate of ATP synthesis would be approximately zero
(D) The rate ofC02 production would be increased
(E) The rate of oxygen consumption would be increased

11-As one molecule of NADH is oxidized via the electron transport chain:(NOT MENTIONED BY THE DOCTOR)

A. 1.5 molecules of ATP are produced in total.
B. 1 molecule of ATP is produced as electrons pass through complex IV.

C. 1 molecule of ATP is produced as electrons pass through complex II.
D. 1 molecule of ATP is produced as electrons pass through complex III.
E. 0.5 of a molecule of ATP is produced as electrons pass through complex I.

12. The number of ATP molecules produced for each molecule of FADH2 oxidized via the electron transport chain is:
A. 1
B.2.5
C. 1.5
D. 2
E. 0.5

13. A number of compounds inhibit oxidative phosphorylation—the synthesis of ATP from ADP and inorganic phosphate linked to oxidation of substrates in mitochondria. Which of the following describes the action of oligomycin?
A. It discharges the proton gradient across the mitochondrial inner membrane.
B. It discharges the proton gradient across the mitochondrial outer membrane.
C. It inhibits the electron transport chain directly by binding to one of the electron carriers in the mitochondrial inner membrane.
D. It inhibits the transport of ADP into, and ATP out of, the mitochondrial matrix.
E. It inhibits the transport of protons back into the mitochondrial matrix through ATP synthase.

14. A number of compounds inhibit oxidative phosphorylation—the synthesis of ATP from ADP and inorganic phosphate linked to oxidation of substrates in mitochondria. Which of the following describes the action of an uncoupler?
A. It discharges the proton gradient across the mitochondrial inner membrane.

B. It discharges the proton gradient across the mitochondrial outer membrane.
C. It inhibits the electron transport chain directly by binding to one of the electron carriers in the mitochondrial inner membrane.
D. It inhibits the transport of ADP into, and ATP out of, the mitochondrial matrix.
E. It inhibits the transport of protons back into the mitochondrial matrix through the stalk of the primary particle.

15. A student takes some tablets she is offered at a disco, and without asking what they are she swallows them. A short time later she starts to hyperventilate, and becomes very hot. What is the most likely action of the tablets she has taken?
A. An inhibitor of mitochondrial ATP synthesis
B. An inhibitor of mitochondrial electron transport
C. An inhibitor of the transport of ADP into mitochondria to be phosphorylated
D. An inhibitor of the transport of ATP out of mitochondria into the cytosol
E. An uncoupler of mitochondrial electron transport and oxidative phosphorylation

16. The flow of electrons through the electron transport chain and the production of ATP are normally tightly coupled. The processes are uncoupled by which of the following?
A. Cyanide
B. Oligomycin
C. Thermogenin
D. Carbon monoxide
E. Hydrogen sulphide

17. Which of the following statements about ATP synthase is INCORRECT?
A. It is located in the inner mitochondrial membrane.
B. It requires a proton motive force to form ATP in the presence of ADP and Pi.
C. ATP is produced when part of the molecule rotates.

D. One ATP molecule is formed for each full revolution of the molecule.
E. The F1 subcomplex is fixed to the membrane and does not rotate.

18-Which of the following substrates is used in heme synthesis?
a)Citrate
b)Fumarate
c)Succinate
d)Succinyl-CoA

19. An individual displays lactic acidemia as well as a reduced activity of α- ketoglutarate dehydrogenase activity. The most likely single enzymatic mutation that leads to these changes would be in which one of the following proteins?
A. The E3 subunit of pyruvate dehydrogenase
B. The E1 subunit of pyruvate dehydrogenase C. The E2 subunit of pyruvate dehydrogenase
C. Lactate dehydrogenase
D. Pyruvate carboxylase

20. A patient diagnosed with thiamin deficiency exhibited fatigue and muscle cramps. The muscle cramps have been related to an accumulation of metabolic acids. Which one of the following metabolic acids is most likely to accumulate in a thiamin deficiency?
A. Isocitric acid
B. Pyruvic acid
C. Succinic acid
D. Malic acid
E. Oxaloacetic acid

21. Succinate dehydrogenase differs from all other enzymes in the TCA cycle in that it is the only enzyme that displays which one of the following characteristics?
a. It is embedded in the inner mitochondrial membrane.
b. It is inhibited by NADH.

c. It contains bound FAD.
d. It contains Fe–S centers.
e. It is regulated by a kinase.

22. During exercise, stimulation of the TCA cycle results principally from which one of the following?
A. Allosteric activation of isocitrate dehydrogenase by increased NADH
B. Allosteric activation of fumarase by increased ADP
C. A rapid decrease in the concentration of four-carbon intermediates
D. Product inhibition of citrate synthase
E. Stimulation of the flux through several enzymes by a decreased NADH/NAD+ ratio

23. A deficiency of which one of the following compounds would lead to an inability to produce coenzyme A?
A. Niacin
B. Riboflavin
C. Vitamin A
D. Pantothenate
E. Vitamin C

24. One of the major roles of the TCA cycle is to generate reduced cofactors for ATP production from oxidative phosphorylation. The compound donating the net eight electrons to the cofactors is which one of the following?
A. Pyruvate
B. Acetyl-CoA
C. Lactate
D. Oxaloacetate
E. Phosphoenolpyruvate

25. Atherosclerosis can narrow the coronary arteries, leading to decreased blood flow and hypoxia of cardiac cells (cardiomyocytes). This causes the patient to experience angina.

Which one of the following is likely to occur in the cardiomyocytes during the hypoxic event?

A. The TCA cycle in the cytosol is greatly impaired.

B. Pyruvate oxidation is increased.

C. Lactate cannot be used as a fuel.

D. Citrate accumulates.

E. Succinyl-CoAaccumulates.

26. At birth, a full-term male neonate was found to be severely acidotic. His condition was found to result from an X-linked dominant mutation of the α- subunit of E1 in the PDC. Compared with a healthy neonate in the same dietary state, what would be the consequences of this mutation?

a. An increase in plasma concentrations of lactate and pyruvate

b. A higher ATP/ADP ratio in cells of the brain

C. A decrease in the rate of glycolysis in brain cells

d. An increase in the activity of the electron-transfer chain in brain cells

e. An increase in plasma acetyl-CoA levels .

27. A pyruvate carboxylase deficiency will lead to lactic acidemia because of which one of the following?

A. An accumulation of acetyl-CoA in the mitochondria

B. Allosteric activation of lactate dehydrogenase

C. An accumulation of NADH in the mitochondrial matrix D. Allosteric activation of the PDC

E. An accumulation of ATP in the matrix

28. 1. Consider the following experiment. Carefully isolated liver mitochondria are incubated in the presence of a limiting amount of malate. Three minutes after adding the substrate, cyanide is added, and the reaction is allowed to proceed for another 7 minutes. At this point, which of the following components of the electron-transfer chain will be in an oxidized state?

A. Complex I

B. Complex II

C. Complex III

D. CoQ
E. Cytochrome c

29. Consider the following experiment. Carefully isolated liver mitochondria are placed in a weakly buffered solution. Malate is added as an energy source, and an increase in oxygen consumption confirms that the ETC is functioning properly within these organelles. Valinomycin and potassium are then added to the mitochondrial suspension. Valinomycin is a drug that allows potassium ions to freely cross the inner mitochondrial membrane. What is the effect of valinomycin on the proton motive force that had been generated by the oxidation of malate?
A. The proton motive force will be reduced to a value of zero.
B. There will be no change in the proton motive force.
C. The proton motive force will be increased.
D. The proton motive force will be decreased but to a value greater than zero.
E. The proton motive force will be decreased to a value less than zero.

30. Dinitrophenol, which was once tested as a weight-loss agent, acts as an uncoupler of oxidative phosphorylation by which one of the following mechanisms?
A. Activating the H+-ATPase
B. Activating CoQ
C. Blocking proton transport across the inner mitochondrial membrane
D. Allowing for proton exchange across the inner mitochondrial membrane
E. Enhancing oxygen transport across the inner mitochondrial membrane

31. A 25-year-old woman presents with chronic fatigue. A series of blood tests is ordered, and the results suggest that her red blood cell count is low because of iron-deficiency anemia. Such a deficiency would lead to fatigue because of which one of the following?

A. Her decrease in Fe–S centers is impairing the transfer of electrons in the ETC.
B. She is not producing enough H_2O in the electron-transport chain, leading to dehydration, which has resulted in fatigue.
C. Iron forms a chelate with NADH and FAD(2H) that is necessary for them to donate their electrons to the ETC.
D. . Iron acts as a cofactor for α-ketoglutarate dehydrogenase in the TCA cycle, a reaction required for the flow of electrons through the ETC.
E. Iron accompanies the protons that are pumped from the mitochondrial matrix to the cytosolic side of the inner mitochondrial membrane. Without iron, the proton gradient cannot be maintained to produce adequate ATP.

32. Which one of the following would be expected for a patient with an OXPHOS disease?
A. A high ATP:ADP ratio in the mitochondria
B. A high NADH:NAD+ ratio in the mitochondria
C. A deletion on the X chromosome
D. A high activity of complex II of the ETC
E. A defect in the integrity of the inner mitochondrial membrane

33. A 5-year-old boy was eating paint chips from the windowsill in his 125- year-old home, and he developed an anemia. Bloodwork indicated high levels of lead, which interfere with heme synthesis. Reduced heme synthesis would have little effect on the function of which one of the following proteins or complexes?
A. Myoglobin
B. Hemoglobin
C. Complex I
D. Complex III
E. Complex IV

34. Rotenone, an inhibitor of NADH dehydrogenase, was originally used for fishing. When it was sprinkled on a lake, fish would absorb it through their gills and die. Until recently, it was used in the United States as an organic pesticide and was recommended for tomato plants. It was considered nontoxic to mammals and birds,

neither of which can readily absorb it. What effect would rotenone have on ATP production by heart mitochondria, if it could be absorbed?

A. There would be no reduction in ATP production.
B. There would be a 95% reduction in ATP production.
C. There would be a 10% reduction in ATP production.
D. There would be a 50% reduction in ATP production.
E. There would be a 50% increase in ATP production.

35.In order for cells to function properly, energy is required; for most cells, the energy is primarily derived from the high-energy phosphate bonds of ATP, which is produced through oxidative phosphorylation. Which one of the following is a key component of oxidative phosphorylation?

A. Using NADH and FAD(H2) to accept electrons as substrates are oxidized.
B. Creating a permeable inner mitochondrial membrane to allow mitochondrial ATP to enter the cytoplasm as it is made.
C. An ATP synthase to synthesize ATP
D. An ATP synthetase to synthesize ATP
E. A source of electrons, which is usually oxygen in most tissues

36. Carefully isolated intact mitochondria were incubated with a high-salt solution, which is capable of disrupting noncovalent interactions between molecules at the membrane surface. After washing the mitochondria, pyruvate and oxygen were added to initiate electron flow. Oxygen consumption was minimal under these conditions because of the loss of which one of the following components from the electron-transfer chain?

A. Complex I
B. CoQ
C. Complex III
D. Cytochrome C
E. Complex IV

37. UCPs allow oxidation to be uncoupled from phosphorylation. Assume that a drug company has developed a reagent that can

activate several UCPs with the goal being the development of a weight-loss drug. A potential side effect of this drug could be which one of the following?

A. Decreased oxidation of acetyl coenzyme A

B. Decreased glycolytic rate

C. Increase in body temperature

D. Increased ATP production by the ATP synthase

-The Answers and Explanations:

1-C.

At time = 0, succinate is donating electrons to the electron transfer chain through complex II. Succinate is converted to fumarate, and the FADH2 generated donates the electrons to CoQ via complex II. The addition of a chemical at time = I does not affect oxygen consumption, and the rate of oxygen consumption is the same as before adding the chemical. Rotenone inhibits at complex I and would not affect electrons being donated through complex II. Antimycin blocks the transfer of electrons from complex III to complex IV and would be expected to block electron transfer, and oxygen consumption, from electrons donated from complex II. Dinitrophenol is an uncoupler and would be expected to increase the rate of oxygen consumption when added, because the uncoupler dissipates the proton gradient and makes it easier for the electron transfer chain to pump protons out of the mitochondria. At time = 2, electron flow stops, but it restarts at time = 3, and at a faster rate. Thus, at time = 3, an uncoupler (dinitrophenol) is added. The fact that electron flow can start again, after stopping, suggests that the chemical added at time = 2 inhibited phosphorylation because phosphorylation and oxygen consumption are coupled. Inhibiting phosphorylation, via oligomycin, will block oxygen consumption without inhibiting any steps in the electron transfer chain. This is why oxygen consumption can resume again once the uncoupler is added. At time = 4, all electron flow stops and that can be due to either the addition of cyanide or carbon monoxide, both of which inhibit at complex Iv.

2- C

A lack of blood flow decreased the flow of 0 2 to the heart, which slowed down the electron transport chain. The reduction in the rate of the electron transfer chain will lead to an increase in intramitochondrial NADH levels, which slows down the TCA cycle. A slowdown of the TCA cycle leads to a reduction in carbon dioxide production. ATP levels within the mitochondria would also drop

because the ATP was transported into the cytoplasm in exchange for ADP. Because oxidative phosphorylation was blocked, the ADP that enters the mitochondria cannot be converted back into ATP, leading to an accumulation of ADP under these conditions.

3- C.

The symptoms experienced by the firefighter could be caused by either cyanide or carbon monoxide, both of which inhibit cytochrome c oxidase. Both carbon monoxide and cyanide are byproducts of fuel oxidation and would be generated during a fire. The firefighter most likely inhaled smoke that contained one or both of these compounds. Both agents will block the reduction of oxygen to water, thereby halting the electron transfer chain and oxidative phosphorylation. Neither agent is an uncoupler, nor do they block the ANT (so ADP levels will not be decreased). Rotenone, a fish poison, complexes with NADH dehydrogenase (complex I) to inhibit electron flow from complex I to CoQ. Neither cyanide nor carbon monoxide will bind to CoQ and block its ability to either accept or donate electrons.

4- B.

Under physiologic conditions, oxygen is the terminal electron acceptor in the electron transport chain, and water will not donate electrons to other substrates to regenerate oxygen. The cytochromes, FMN, and CoQ both accept and donate electrons during the course of electron flow through the electron transport chain.

5- B.

Pyruvate dehydrogenase converts pyruvate to acetyl-CoA. It contains multiple subunits: a debydrogenase component that oxidatively decarboxylates pyruvate, a dihydrolipoyl transacetylase that transfers the acetyl group to CoA, and a dihydrolipoyl dehydrogenase that reoxidizes lipoic acid. Thiamin pyrophosphate, lipoic acid, CoA, NAD+, and FAD serve as cofactors for these reactions. In addition, a kinase is present that phosphorylates and inactivates the decarboxylase component. Acetyl-CoA and NADH

activate this kinase, thus inactivating pyruvate dehydrogenase. A phosphatase dephosphorylates the decarboxylase subunit, thereby reactivating pyruvate dehydrogenase.

6- C.

Thiamin pyrophosphate is involved in the making and breaking of carbon-carbon bonds. It is a necessary cofactor for oxedative phosphorylation reactions, in which a carbon carbon bond is broken and carbon dioxide is released. Mechanistically, thiamin pyrophosphate forms a covalent intermediate with the a-carbon of an a-keto acid substrate, which. in the TCA cycle, is a.-ketoglutarate. Thiamin pyrophosphate is not involved in redox reactions or in thioester formation.

7- D.

In the TCA cycle, each turn of the cycle produces 3 NADH, 1 FADH21 and 1 GTP. Each NADH releases 53 kcal/mol; the 3 NADH thus yield 159 kcal/mol of energy. FADh2 releases 41 kcal/mol, and GTP 8 kcal/mol. The energy captured is 159 + 41+8, or 208 kcal/mol. The total energy available is 243 kcal/mol, so the fraction of energy captured Is 208/243, or 86%.

8- B.

About 10 ATP (7.5 from NADH, 1.5 from FADH21 and 1 from GTP) are produced by the TCA cycle (l0 x 8 kcal = 80 kcal). The percentage of the total energy available from oxidation of acetate that is converted to ATP is 80/243, or 33%.

9- A.

The patient is experiencing malignant hyperthermia, which is similar in symptoms to the uncoupling of the electron transfer chain from ATP synthesis. Succinylcholine and several inhaled anesthetics can act as uncouplers of electron transport in susceptible individuals. An inhibition of complex I (NADH dehydrogenase), or cytochrome oxidase, would block both electron flow and ATP synthesis, and muscle rigidity and

hyperthermia would not result. The same is true if CoQ were prevented from accepting and donating electrons. An uncoupler will not lead to a decrease in ADP levels because ATP cannot be synthesized under these conditions, and ADP levels would be expected to increase.

10- C.

If cytochrome c cannot function, all the components of the electron transport chain between it and o2 remain in the oxidized state, and the components of the chain before cytochrome care reduced. The electron transport chain will not function o2 will not be consumed; a proton gradient will not be generated; and ATP will not be produced. NADH will not be oxidized, there by increasing the NADH/NAD+ ratio. Owing to this increased ratio, the TCA cycle will slow down, and therefore, C02 production will decrease

11. D.

Oxidation of one molecule of NADH via the electron transport chain generates 2.5 molecules of ATP in total. One is formed via complex I, 1 via complex III and 0.5 via complex IV because the complex I and III pumps 4 protons and each 4 protons give 1 ATP but the complex IV pumps 2 protons which give 0.5 ATP.

12. C

1.5 molecules of ATP are formed in total as FADH2 is oxidized (1 via complex II and 0.5 via complex IV) EXTRA INFO.

13. E.

Oligomycin blocks oxidation and ATP synthesis as it prevents the flow of electrons back into the mitochondrial matrix through ATP synthase

14. A.

Uncouplers allow electrons to reenter the mitochondrial matrix without passing through ATP synthase.

15. E.

In the presence of an uncoupler, the energy release as electron flow into the mitochondrial matrix is not captured as ATP and is dissipated as heat.

16. C.

Thermogenin is a physiological uncoupler found in brown adipose tissue. Its function is to generate body heat.

17. D.

Three ATP molecules are generated for each revolution of the ATP synthase molecule.

18-D

19. A.

The E3 subunit of pyruvate dehydrogenase, the dihydrolipoyl dehydrogenase activity (with bound FAD), is shared among all the α-keto acid dehydrogenases. Thus, with this mutation, both pyruvate dehydrogenase activity and α-ketoglutarate dehydrogenase activity would be defective. This defect would then lead to an accumulation of pyruvate (because pyruvate dehydrogenase activity is reduced), and the accumulated pyruvate is converted to lactate (to regenerate NAD+ to allow glycolysis to continue), leading to an elevation of lactate in the bloodstream and a lowering of blood pH (lactic acidemia). A defect in pyruvate carboxylase will also result in an elevation of pyruvate levels, and lactic acidemia, but there would be no defect in α-ketoglutarate dehydrogenase activity with a pyruvate carboxylase deficiency. The E1 and E2 subunits of pyruvate dehydrogenase are unique to pyruvate dehydrogenase, and are not shared with any other enzymes, so defects in these subunits will lead to lactic acidemia but would not affect α-ketoglutarate dehydrogenase. A defect in lactate dehydrogenase would result in an inability to produce

lactate, and lactic acidemia would not result from a defect in that enzyme.

20. B.

TTP is a required coenzyme for the α-ketoglutarate dehydrogenase and pyruvate dehydrogenase complexes. With these complexes inactive, pyruvic acid and α-ketoglutaric acid accumulate and+ dissociate to generate the anion and H . Because α-ketoglutarate is not listed as an answer, the only possible answer is pyruvate.

21. A.

Succinate dehydrogenase is the only TCA cycle enzyme located in the inner mitochondrial membrane. The other enzymes are in the mitochondrial matrix. Answer B is incorrect because succinate dehydrogenase is not regulated by NADH. Answer C is incorrect because α-ketoglutarate dehydrogenase also contains a bound FAD (the difference is that the FAD[2H] in α-ketoglutarate dehydrogenase donates its electrons to NAD+, whereas the FAD[2H] in succinate dehydrogenase donates its electrons directly to the electron-transfer chain). Answer D is incorrect because both succinate dehydrogenase and aconitase have Fe–S centers. Answer E is incorrect because succinate dehydrogenase is not regulated by a kinase. Kinases regulate enzymes by phosphorylation (e.g., the regulation of pyruvate dehydrogenase occurs through reversible phosphorylation).

22. E.

NADH decreases during exercise in order to generate energy for the exercise (if it were increased, it would inhibit the cycle and slow it down); thus, the NADH/NAD+ ratio is decreased, and the lack of NADH activates flux through isocitrate dehydrogenase, α-ketoglutarate dehydrogenase, and malate dehydrogenase. Isocitrate dehydrogenase is inhibited by NADH, so answer A is not correct. Fumarase is not regulated; thus, answer B is incorrect. The four-carbon intermediates of the cycle are regenerated during each turn of the cycle, so their concentrations do not decrease (thus, C

is incorrect). Product inhibition of citrate synthase would slow the cycle and not generate more energy (hence, D is incorrect).

23. D.

Pantothenate is the vitamin precursor of coenzyme A. Niacin is the vitamin precursor of NAD, and riboflavin is the vitamin precursor of FAD and FMN. Vitamins A and C are used with only minor modifications, if any, and are not involved in any TCA cycle reactions.

24. B.

The net equation of the TCA cycle, in terms of carbon atoms, is that acetyl-CoA is converted to two molecules of CO2. The eight electrons associated with the two carbon atoms of acetyl-CoA are removed and placed in three molecules of NADH and one molecule of FAD(2H). The TCA cycle does not generate reduced cofactors from pyruvate, lactate, oxaloacetate, or phosphoenolpyruvate. Those compounds would need to be converted to acetyl-CoA in order for the cycle to generate the reduced cofactors.

25.C.

With hypoxia, the TCA cycle would slow down because of the accumulation of NADH (which cannot donate electrons to oxygen) caused by the lack of oxygen. The high NADH inhibits pyruvate dehydrogenase, so pyruvate will accumulate, and the high levels of pyruvate will block lactate from being converted to pyruvate (the lactate dehydrogenase reaction), leading to lactate accumulation. Because the operation of the TCA cycle is greatly reduced, citrate and succinyl-CoA will not be produced, so they will not accumulate. The enzymes of the TCA cycle are located in the mitochondria, not in the cytoplasm.

26.A.

A deficiency of the E1 subunit of pyruvate dehydrogenase would decrease conversion of pyruvate to acetyl-CoA, leading to an accumulation of pyruvate. Pyruvate is converted to lactate to allow glycolysis to continue to generate ATP from substrate-level phosphorylation. The pyruvate to lactate conversion regenerates the NAD+, which is required for glycolysis to proceed. Cells of the brain have a high ATP requirement and are highly dependent on glycolysis and pyruvate oxidation in the TCA cycle to meet this demand for ATP.Without pyruvate oxidation in the TCA cycle, glycolysis will try to produce ATP as fast as possible (because of an increase of AMP levels, which activates PFK-1); however, the amount of ATP produced by glycolysis alone is not sufficient to meet the brain's needs. Thus, the ATP/ADP ratio actually decreases. Even though the brain cells are low in ATP levels, the decreased production of acetyl-CoA from pyruvate will not provide sufficient substrate to substantially increase the activity of the electron-transfer chain in brain cells. Fatty acids do not cross the blood–brain barrier, so ketone body oxidation would be required to increase acetyl-CoA levels within the mitochondria to allow rapid functioning of the TCA cycle. Acetyl-CoA is not produced from glucose when pyruvate dehydrogenase is defective, and acetyl-CoA cannot be exported to the circulation.

27.A.

When pyruvate carboxylase is deficient, pyruvate cannot be converted to oxaloacetate, thereby reducing the ability to replenish TCA cycle intermediates as they are being used for other pathways. As oxaloacetate levels decrease, acetyl-CoA cannot be converted to citrate, and acetyl-CoA will accumulate within the mitochondria. The elevated acetyl-CoA inhibits pyruvate dehydrogenase, which, coupled with the reduced activity of pyruvate carboxylase, leads to pyruvate accumulation in the cytoplasm. The increased pyruvate is then converted to lactic acid, leading to lactic acidemia. Pyruvate is not an allosteric activator of lactate dehydrogenase. Because the TCA cycle is slowed owing to lack of oxaloacetate, NADH is not accumulating in the mitochondrial matrix, nor is ATP. Pyruvate is

not an activator of the pyruvate dehydrogenase complex (NAD+ and free coenzyme A are the primary activators, along with ADP).

28.B.

For a component to be in the oxidized state, it must have donated, or never received, electrons. Complex II will metabolize succinate to produce fumarate (generating FAD[2H]), but no succinate is available in this experiment. Thus, complex II never sees any electrons and is always in an oxidized state. The substrate malate is oxidized to oxaloacetate, generating NADH, which donates electrons to complex I of the ETC. These electrons are transferred to CoQ, which donates electrons to complex III, to cytochrome c, and then to complex IV. Cyanide will block the transfer of electrons from complex IV to oxygen, so all previous complexes containing electrons will be backed up and the electrons will be "stuck" in the complexes, making these components reduced. Thus, answers A and C through E must be incorrect.

29.D.

The proton motive force consists of two components, a ΔpH, and a Δψ (electrical component). The addition of valinomycin and potassium will destroy the electrical component but not the pH component. Thus, the proton motive force will decrease but will still be greater than zero. Thus, the other answers are all incorrect.

30.D.

Dinitrophenol equilibrates the proton concentration across the inner mitochondrial membrane, thereby destroying the proton motive force. Thus, none of the other answers is correct.

31.A.

A deficiency of Fe–S centers in the ETC would impair the transfer of electrons down the chain and reduce ATP production by oxidative phosphorylation. Answer B is incorrect because the decreased production of water from the ETC is not of sufficient

magnitude to cause her to become dehydrated. Answer C is incorrect because iron does not form a chelate with NADH and FAD(2H). Answer D is incorrect because iron is not a cofactor for α-ketoglutarate dehydrogenase. Answer E is incorrect because iron does not accompany the protons that make up the proton gradient.

32.B.

NADH would not be reoxidized as efficiently by the ETC, and the NADH/NAD+ ratio would increase. Answer A is incorrect because ATP would not be produced at a high rate. Therefore, ADP would build up and the ATP:ADP ratio would be low. Answer C is incorrect because OXPHOS diseases can be caused by mutations in nuclear or mtDNA, and not all OXPHOS proteins are encoded by the X chromosome. Answer D is incorrect because, depending on the nature of the mutation, the activity of complex II of the ETC might be normal or decreased, but there is no reason to expect increased activity. Answer E is incorrect because the integrity of the inner mitochondrial membrane would not necessarily be affected. It could be, but it would not be expected for all patients with OXPHOS disorders.

33.C

Heme is required for the synthesis of cytochromes. Complex I, although containing iron, does so in iron–sulfur centers and contains no cytochromes. Complexes III and IV contain cytochromes, whereas myoglobin and hemoglobin contain heme as the oxygen binding component of those proteins. Defects in heme synthesis, then, would have a negative impact on the function of complexes III and IV, as well as hemoglobin and myoglobin, without greatly affecting the functioning of complex I.

34.B.

Because rotenone inhibits the oxidation of NADH, it would completely block the generation of the electrochemical potential gradient in vivo and, therefore, it would block ATP generation. In the presence of rotenone, NADH would accumulate and NAD+ concentrations would decrease. Although the mitochondria might

still be able to oxidize compounds like succinate, which transfer electrons to FAD, no succinate would be produced in vivo if the NAD+-dependent dehydrogenases of the TCA cycle were inhibited. Thus, very shortly after rotenone administration, there would not be any substrates available for the electron transfer chain, and NADH dehydrogenase would be blocked, so oxidative phosphorylation would be completely inhibited. If glucose supplies were high, anaerobic glycolysis could provide some ATP, but not nearly enough to keep the heart pumping. Anaerobic glycolysis produces 2 ATP per glucose molecule, compared with 32 ATP molecules generated by oxidative phosphorylation, which is a reduction of approximately 95%.

35.C.

NAD+ and FAD are electron acceptors and NADH and FAD(2H) are electron donors. Oxygen is the terminal electron acceptor and is not an electron donor. The inner mitochondrial membrane must be impermeable to most compounds, including protons; otherwise, the proton gradient that drives ATP synthesis could not be created or maintained. The enzyme ATP synthase contains a proton pore that spans the inner mitochondrial membrane and a catalytic headpiece that protrudes into the matrix. Protons are driven through the pore and change the conformation of the subunits in the headpiece, thereby producing ATP. If protons enter the mitochondria other ways then through the pore, no ATP is generated by the ATP synthase (partial uncoupling). A synthetase is an enzyme that uses high-energy phosphate bonds (usually from ATP) to catalyze its reaction, and the ATP synthase creates high-energy phosphate bonds and does not use them.

36.D.

Complexes I, III, and IV are protein complexes that span the inner mitochondrial membrane, and their location within the membrane would not be disrupted by a high-salt solution. Cytochrome c is a small protein in the intermembrane space that binds to the inner mitochondrial membrane through noncovalent interactions. High salt can dislodge cytochrome c from the inner membrane, and the

mitochondria would become cytochrome c–deficient. Electron flow would stop in the absence of cytochrome c owing to an inability to transfer electrons from complexes III to complex IV. CoQ is a lipid-soluble quinone that diffuses in the lipid membrane, and it would not be removed from the membrane by a high-salt solution.

37.C.

Uncouplers uncouple oxidation from phosphorylation such that oxygen consumption is increased, there is an increased flow of electrons through the electron-transfer chain, but ATP synthesis via oxidative phosphorylation is diminished. ATP production is reduced owing to the reduction in the size of the proton gradient across the inner mitochondrial membrane because the UCPs allow protons to enter the matrix of the mitochondria without going through the ATP synthase. Because the energy of electron transfer is no longer being used to generate a proton gradient, it is released as heat, and an individual taking such a drug would be expected to exhibit an increased body temperature. Owing to the uncoupling, the oxidation of acetyl coenzyme A (acetyl- CoA) would increase, as would the glycolytic rate, in attempts to generate ATP for the cell. The ATP synthase would be producing less ATP, and glycolysis would be producing more ATP. The weight loss would come about because of the inefficiency in ATP generation via acetyl-CoA oxidation, as more fatty acids would have to be metabolized in order to generate a certain amount of ATP from the acetyl-CoA derived from the fatty acids.

*The Sources:

1- MARK'S BASIC MEDICAL BIOCHEMISTRY
2- BRS BIOCHEMISTRY, MOLECULAR BIOLOGY, GENETICS 7TH EDITION
3- HARPERS ILLUSTRATED BIOCHEMISTRY 30TH EDITION

-LIPPINCOTT'S QUESTIONS:

1-The conversion of pyruvate to acetyl coenzyme A and CO2:

A. involves the participation of lipoic acid.

B. is activated when pyruvate decarboxylase of the pyruvate dehydrogenase (PDH)
complex is phosphorylated by PDH kinase in the presence of ATP.

C. is reversible.

D. occurs in the cytosol.

E. requires the coenzyme biotin.

2- Which one of the following conditions decreases the oxidation of acetyl coenzyme A
by the citric acid cycle?

A. A high availability of calcium

B. A high acetyl CoA/CoA ratio

C. A low ATP/ADP ratio

D. A low NAD+/NADH ratio

3- The following is the sum of three steps in the citric acid cycle.
A + B + FAD + H2O → C + FADH2 + NADH
Choose the lettered answer that corresponds to the missing "A," "B," and "C" in thequation.

Reactant A	Reactant B	Reactant C
A. Succinyl CoA	GDP	Succinate
B. Succinate	NAD^+	Oxaloacetate
C. Fumarate	NAD^+	Oxaloacetate
D. Succinate	NAD^+	Malate
E. Fumarate	GTP	Malate

4- A 1-month-old male shows neurologic problems and lactic acidosis. Enzyme assay for pyruvate dehydrogenase (PDH) complex activity on extracts of cultured skin fibroblasts showed 5% of normal activity with a low concentration of thiamine pyrophosphate (TPP), but 80% of normal activity when the assay contained a thousand-fold higher concentration of TPP. Which one of the following statements concerning this patient is correct?

A. Administration of thiamine is expected to reduce his serum lactate level and improve his clinical symptoms.

B. A high carbohydrate diet would be expected to be beneficial for this patient.

C. Citrate production from aerobic glycolysis is expected to be increased.

D. PDH kinase, a regulatory enzyme of the PDH complex, is expected to be active.

5- Which coenzyme-cosubstrate is used by the dehydrogenases of both glycolysis and the tricarboxylic acid cycle?

6- 2,4-Dinitrophenol, an uncoupler of oxidative phosphorylation, was used as a weight-

loss agent in the 1930s. Reports of fatal overdoses led to its discontinuation in 1939.
Which of the following would most likely be true concerning individuals taking 2,4-
dinitrophenol?
A. Adenosine triphosphate levels in the mitochondria are greater than normal.
B. Body temperature is elevated as a result of hypermetabolism.
C. Cyanide has no effect on electron flow.
D. The proton gradient across the inner mitochondrial membrane is greater than
normal.
E. The rate of electron transport is abnormally low.

7- Which of the following has the strongest tendency to gain electrons?
A. Coenzyme Q
B. Cytochrome c
C. Flavin adenine dinucleotide
D. Nicotinamide adenine dinucleotide
E. Oxygen

8- Explain why and how the malate-aspartate shuttle moves nicotinamide adenine
dinucleotide reducing equivalents from the cytosol to the mitochondrial matrix.

9- Carbon monoxide binds to and inhibits Complex IV of the electron transport chain.
What effect, if any, should this respiratory inhibitor have on phosphorylation of
adenosine diphosphate to adenosine triphosphate?

-The Answers and Explanations:

1- A.

Lipoic acid is an intermediate acceptor of the acetyl group formed in the reaction. Pyruvate dehydrogenase complex catalyzes an irreversible reaction that is inhibited when the decarboxylase component is phosphorylated. The enzyme complex is located in the mitochondrial matrix. Biotin is utilized by carboxylases, not decarboxylases.

2- D.

A low NAD+/NADH ratio limits the rates of the NAD+-requiring dehydrogenases. High availability of calcium and substrate (acetyl CoA), and a low ATP/ADP ratio stimulates the cycle.

3- B.

Succinate + NAD+ + FAD + H2O → oxaloacetate + NADH + FADH2

4- A.

The patient appears to have a thiamine-responsive pyruvate dehydrogenase (PDH) complex deficiency. The pyruvate decarboxylase (E1) component of the PDH complex fails to bind thiamine pyrophosphate at low concentration, but shows significant activity at a high concentration of the coenzyme. This mutation, which affects the Km of the enzyme for the coenzyme, is present in some, but not all, cases of PDH complex deficiency. Because the PDH complex is an integral part of carbohydrate metabolism, a diet low in carbohydrates would be expected to blunt the effects of the enzyme deficiency. Aerobic glycolysis generates pyruvate, the substrate of the PDH complex. Decreased activity of the complex decreases production of acetyl coenzyme A, a substrate for citrate synthase. PDH kinase is allosterically inhibited by pyruvate and, therefore, is inactive.

5-

Oxidized nicotinamide adenine dinucleotide (NAD+) is used by glyceraldehyde 3-phosphate dehydrogenase of glycolysis and by isocitrate dehydrogenase, α-ketoglutarate dehydrogenase, and malate dehydrogenase of the tricarboxylic acid cycle.

6- B.

When phosphorylation is uncoupled from electron flow, a decrease in the proton gradient across the inner mitochondrial membrane and, therefore, impaired ATP synthesis is expected. In an attempt to compensate for this defect in energy capture, metabolism and electron flow to oxygen is increased. This hypermetabolism will be accompanied by elevated body temperature because the energy in fuels is largely wasted, appearing as heat. The electron transport chain will still be inhibited by cyanide.

7- E.

Oxygen is the terminal acceptor of electrons in the electron transport chain (ETC). Electrons flow down the ETC to oxygen because it has the highest (most positive) reduction potential (E0). The other choices precede oxygen in the ETC and have lower E0 values.

8-

There is no transporter for nicotinamide adenine dinucleotide (NADH) in the inner mitochondrial membrane. However, NADH can be oxidized to NAD+ by the cytoplasmic isozyme of malate dehydrogenase as oxaloacetate is reduced to malate. The malate is transported across the inner membrane, and the mitochondrial isozyme of malate dehydrogenase oxidizes it to oxaloacetate as mitochondrial NAD+ is reduced to NADH. This NADH can be oxidized by Complex I of the electron transport chain, generating three ATP through the coupled processes of oxidative phosphorylation.

9-

Inhibition of the electron transport chain by respiratory inhibitors such as carbon monoxide results in an inability to maintain the proton gradient. Phosphorylation of ADP to ATP is, therefore, inhibited, as are ancillary reactions such as calcium uptake by mitochondria, because they also require the proton gradient.

Corrected by :
Hayat suwi
Yamama alabbadi

أحلى مشهد فى the good doctor كلير داخلة تعمل أول عملية ليها و بتتصور مع اسمها اللى مكتوب على أوضة العمليات و بعتت رسالة لأمها قالتلها " it's happening " 😍 😍
نفس الإحساس ده بالمللى بنحسه لما نعرف نشخص حد أو نفهم هو عنده ايه من أعراضه اللى هو ايه ده الماكينة طلعت قمااااااااااش يا ناس طلعت قماش و بقينا دكاترة😂❤️
نفس احساسنا لما كنا فرحانين بالبالطو و العضم لحد ما كنا بنصور كارنيه سنة خامسة فى أول السنة وصورتنا قدام مستشفى الباطنة كأننا بنقول للناس نحن هنا و الفيديوهات اللى بنحدف فيها البلاطى أخر يوم امتحانات اللى كان أكتر أغنية ماشية عليها و الله و عملوها الرجالة ✌️

الحقيقة إننا مميزين بعلمنا و عملنا و السخط اللى جوانا ده على نظام الكلية مش على الطب نفسه ..... اعتزوا بنفسكم يا جماعة احنا نستحق بعد كل التعب و المرمطة نبقي حاجة ❤️✌️