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Item 1 of 40
Question Id: 1067

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A 23-year-old apparently healthy man who recently immigrated to the United States comes to an outpatient clinic to establish care. When asked about his past medical history, he says that he has no significant medical problems. However, his mother told him that he was born with "a problem metabolizing sugar." The patient maintains no dietary restrictions and regularly eats vegetables, fruits, meats, and processed foods. Urine samples show a repeatedly positive copper reduction test, but glucose oxidase dipstick testing is negative. Which of the following enzymes is most likely to be deficient in this patient?

A. Acid α-glucosidase
B. Aldolase B
C. Fructokinase
D. Galactose-1-phosphate uridyl transferase
E. Lactase

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Item 1 of 40
Question Id: 1067

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A 23-year-old apparently healthy man who recently immigrated to the United States comes to an outpatient clinic to establish care. When asked about his past medical history, he says that he has no significant medical problems. However, his mother told him that he was born with "a problem metabolizing sugar." The patient maintains no dietary restrictions and regularly eats vegetables, fruits, meats, and processed foods. Urine samples show a repeatedly positive copper reduction test, but glucose oxidase dipstick testing is negative. Which of the following enzymes is most likely to be deficient in this patient?

- A. Acid α-glucosidase [8%]
- B. Aldolase B [12%]
- ✔ C. Fructokinase [62%]
- D. Galactose-1-phosphate uridyl transferase [10%]
- E. Lactase [6%]

Omitted
Correct answer
C

62%
Answered correctly

12 Seconds
Time Spent

10/31/2018
Last Updated

Explanation

Disorders of fructose metabolism

Glucose

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Item 1 of 40
Question Id: 1067

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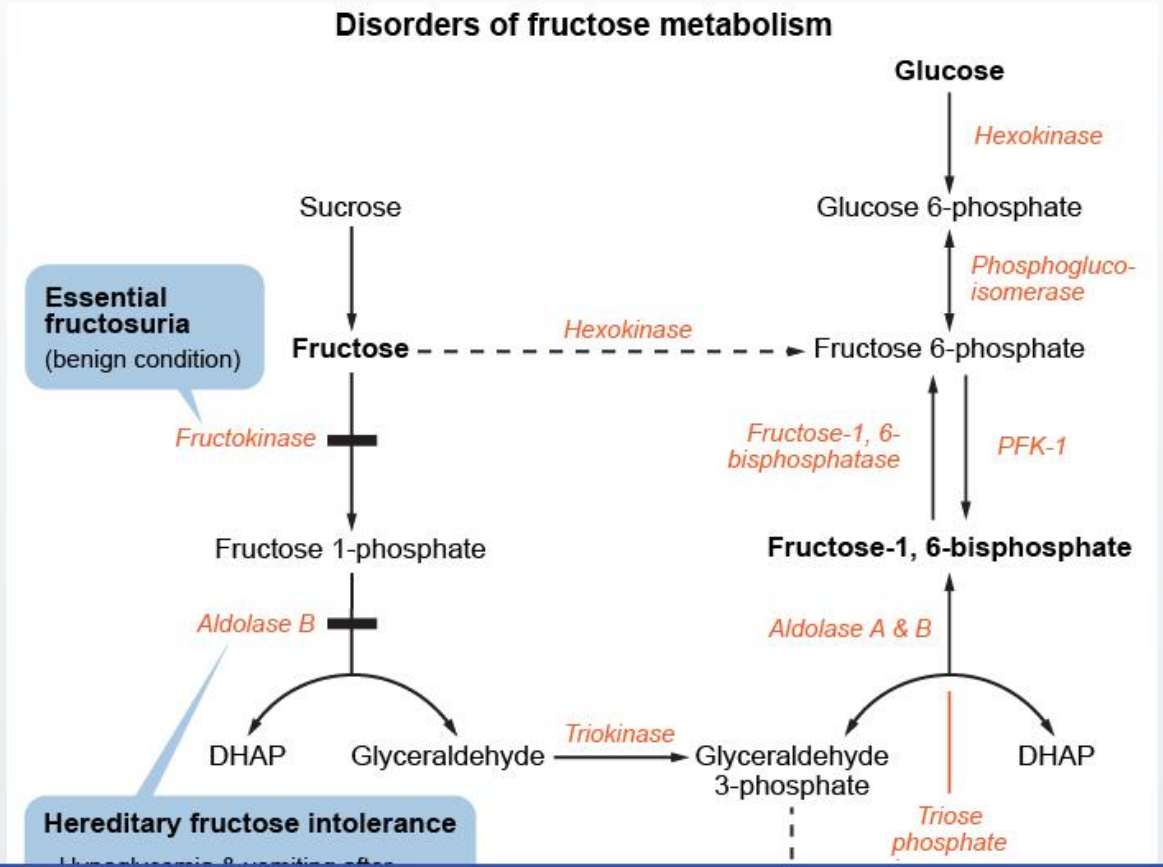
Explanation



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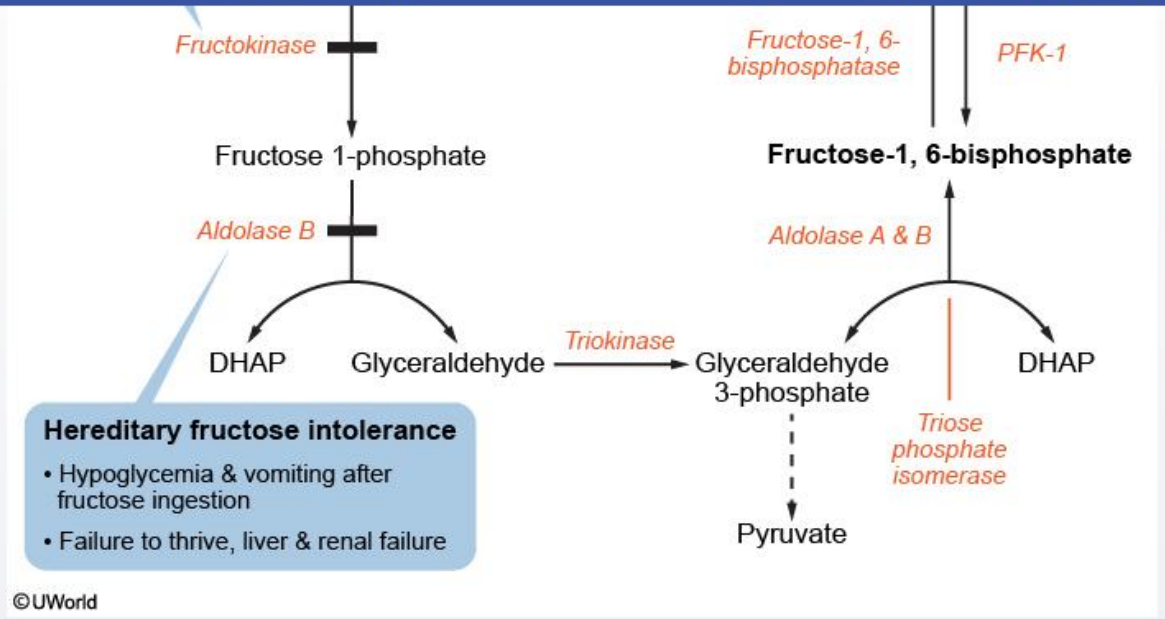

This asymptomatic patient with history of an inborn error of sugar metabolism most likely has **essential fructosuria**. This benign, autosomal recessive disorder causes some of the dietary fructose load to be secreted in the urine unchanged due to defective metabolism by **fructokinase**. Fructose, similar to glucose and galactose, is a **reducing sugar** and can be detected by a **copper reduction test**, which nonspecifically detects the presence of reducing sugar. A urine dipstick, however, uses glucose oxidase to ascertain the presence of urinary glucose and will not test positive in the presence of fructose or galactose.

(Choice A) Acid α-glucosidase (or acid maltase) deficiency causes glycogen storage disease type II (Pompe disease). Affected infants have cardiomyopathy, muscle weakness, and hypotonia.

(Choice B) Aldolase B deficiency is a life-threatening disorder caused by the inability to metabolize fructose-1-phosphate (a toxic intermediate

This asymptomatic patient with history of an inborn error of sugar metabolism most likely has **essential fructosuria**. This benign, autosomal recessive disorder causes some of the dietary fructose load to be secreted in the urine unchanged due to defective metabolism by **fructokinase**. Fructose, similar to glucose and galactose, is a **reducing sugar** and can be detected by a **copper reduction test**, which nonspecifically detects the presence of reducing sugar. A urine dipstick, however, uses glucose oxidase to ascertain the presence of urinary glucose and will not test positive in the presence of fructose or galactose.

(Choice A) Acid α-glucosidase (or acid maltase) deficiency causes glycogen storage disease type II (Pompe disease). Affected infants have cardiomyopathy, muscle weakness, and hypotonia.

(Choice B) Aldolase B deficiency is a life-threatening disorder caused by the inability to metabolize fructose-1-phosphate (a toxic intermediate that accumulates in cells and depletes intracellular phosphate). Patients become acutely symptomatic after ingesting fructose-containing foods and eventually develop liver failure. Treatment includes elimination of dietary fructose.

(Choice D) Galactosemia is an autosomal recessive disorder caused by galactose-1-phosphate uridyl transferase deficiency. It is characterized by neonatal jaundice, vomiting, cataract formation, hepatomegaly, and failure to thrive. Treatment includes elimination of all milk products from the diet and feeding with soy-based infant formula.

(Choice E) Lactase is a mucosal enzyme responsible for the digestion of lactose. Acquired lactase deficiency is the most common cause of selective carbohydrate malabsorption. Patients with lactase deficiency experience gastrointestinal symptoms (eg, bloating, diarrhea) following the ingestion of dairy products.

Educational objective:
Unlike hereditary fructose intolerance (aldolase B deficiency) and classic galactosemia (galactose-1-phosphate uridyl transferase deficiency), essential fructosuria (fructokinase deficiency) is a benign disorder. Although affected patients are asymptomatic, their urine will test positive for a reducing sugar due to the presence of unmetabolized fructose.

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Item 2 of 40
Question Id: 995

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A research scientist develops an agent that specifically blocks the interaction of inositol triphosphate with its intracellular receptor. A study is then performed in which vascular smooth muscle cells are divided into 2 groups: an experimental group treated with the receptor blocker and an untreated control group. Both groups are exposed to phenylephrine. Compared to the control cells, decreased activity of which of the following enzymes is most likely to be observed in the experimental cells?

A. Adenylate cyclase
B. Lipoxygenase
C. Phosphodiesterase
D. Phospholipase C
E. Protein kinase C

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Item 2 of 40
Question Id: 995

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A research scientist develops an agent that specifically blocks the interaction of inositol triphosphate with its intracellular receptor. A study is then performed in which vascular smooth muscle cells are divided into 2 groups: an experimental group treated with the receptor blocker and an untreated control group. Both groups are exposed to phenylephrine. Compared to the control cells, decreased activity of which of the following enzymes is most likely to be observed in the experimental cells?

- A. Adenylate cyclase [9%]
- B. Lipoxygenase [0%]
- C. Phosphodiesterase [4%]
- D. Phospholipase C [36%]
- ✔ E. Protein kinase C [49%]

Omitted
Correct answer
E

49%
Answered correctly

5 Seconds
Time Spent

01/15/2019
Last Updated

Explanation

G protein-coupled receptors have a characteristic structure with 7 transmembrane regions, an extracellular domain, and an intracellular domain coupled with a G protein. In their inactivated state, G proteins exist as heterotrimers consisting of alpha, beta, and gamma subunits with GDP tightly bound to the alpha subunit. G proteins are activated after **ligand binding to the extracellular domain** of the receptor. The first step in

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2/6/2019

Explanation

G protein-coupled receptors have a characteristic structure with 7 transmembrane regions, an extracellular domain, and an intracellular domain coupled with a G protein. In their inactivated state, G proteins exist as heterotrimers consisting of alpha, beta, and gamma subunits with GDP tightly bound to the alpha subunit. G proteins are activated after **ligand binding to the extracellular domain** of the receptor. The first step in activation occurs when GDP is exchanged for GTP on the alpha subunit. Once bound to GTP, the alpha subunit dissociates from the beta and gamma subunits and activates either adenylate cyclase or phospholipase C, depending on the ligand.

When phenylephrine binds to an alpha-1 receptor on vascular smooth muscle cells, the alpha subunit of the G protein (G_q) **activates phospholipase C**, which breaks down phosphatidylinositol bisphosphate into inositol triphosphate (IP_3) and diacylglycerol (DAG). DAG stimulates protein kinase C, which phosphorylates downstream intracellular proteins to produce its physiologic effects (eg, smooth muscle contraction). **IP_3** produces most of its effects by **increasing intracellular calcium**, which also **activates protein kinase C**. In the study described above, protein kinase C activity would be reduced in the experimental group compared to the control group as calcium release from the endoplasmic reticulum is interrupted.

(Choice A) Activation of adenylate cyclase leads to the formation of cAMP and subsequent activation of protein kinase A. Protein kinase A phosphorylates intracellular proteins to produce its effects.

(Choice B) Lipoxygenase is an enzyme responsible for the formation of leukotrienes from arachidonic acid. It is not directly involved in the phosphatidylinositol second messenger system.

(Choice C) Phosphodiesterase is an enzyme that terminates the effects of ligands that act via cAMP or cGMP second messenger systems. It has no direct effect on the phosphatidylinositol second messenger system.

(Choice D) The activity of phospholipase C would be unchanged if IP_3 were blocked because phospholipase C exerts its effect before IP_3 in the phosphatidylinositol second messenger system.

Educational objective:

After a ligand binds to a G protein-coupled receptor that activates phospholipase C, membrane phospholipids are broken down into diacylglycerol

protein kinase C, which phosphorylates downstream intracellular proteins to produce its physiologic effects (eg, smooth muscle contraction). **IP_3** produces most of its effects by **increasing intracellular calcium**, which also **activates protein kinase C**. In the study described above, protein kinase C activity would be reduced in the experimental group compared to the control group as calcium release from the endoplasmic reticulum is interrupted.

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(Choice D) The activity of phospholipase C would be unchanged if IP_3 were blocked because phospholipase C exerts its effect before IP_3 in the phosphatidylinositol second messenger system.

Educational objective:
After a ligand binds to a G protein-coupled receptor that activates phospholipase C, membrane phospholipids are broken down into diacylglycerol (DAG) and inositol triphosphate (IP_3). Protein kinase C is subsequently activated by DAG and calcium; the latter is released from the endoplasmic reticulum under the influence of IP_3.

References

- G protein-dependent regulation of phospholipase C by cell surface receptors.
- Role of inositol lipid breakdown in the generation of intracellular signals. State of the art lecture.

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Item 3 of 40
Question Id: 1889

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An 18-year-old girl with a history of type 1 diabetes mellitus comes to the emergency department after several hours of nausea, vomiting, and abdominal pain. The patient reports that she is on vacation visiting friends and has not taken insulin in the last 2 days. Physical examination shows breath with fruity odor and dry mucosal membranes. Laboratory studies show a blood glucose level of 452 mg/dL and high anion gap metabolic acidosis. Urinalysis is positive for ketones. It is determined that the patient's insulin deficiency is causing increased production of gluconeogenic precursors that are subsequently converted to glucose in the liver. Which of the following enzymes is most likely to provide these precursor substrates?

A. Acetyl CoA carboxylase
B. Acyl CoA synthetase
C. ATP citrate lyase
D. Glucose-6-phosphate dehydrogenase
E. Glycerol kinase

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Item 3 of 40
Question Id: 1889

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An 18-year-old girl with a history of type 1 diabetes mellitus comes to the emergency department after several hours of nausea, vomiting, and abdominal pain. The patient reports that she is on vacation visiting friends and has not taken insulin in the last 2 days. Physical examination shows breath with fruity odor and dry mucosal membranes. Laboratory studies show a blood glucose level of 452 mg/dL and high anion gap metabolic acidosis. Urinalysis is positive for ketones. It is determined that the patient's insulin deficiency is causing increased production of gluconeogenic precursors that are subsequently converted to glucose in the liver. Which of the following enzymes is most likely to provide these precursor substrates?

A. Acetyl CoA carboxylase [41%]
B. Acyl CoA synthetase [25%]
C. ATP citrate lyase [4%]
D. Glucose-6-phosphate dehydrogenase [8%]
✔ E. Glycerol kinase [19%]

Omitted
Correct answer
E

19%
Answered correctly

5 Seconds
Time Spent

11/09/2018
Last Updated

Explanation

This patient in **diabetic ketoacidosis** is experiencing increased triglyceride breakdown in adipose tissue due to her insulin deficiency.

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2/6/2019

Explanation

This patient in **diabetic ketoacidosis** is experiencing increased triglyceride breakdown in adipose tissue due to her insulin deficiency. Triglycerides stored in adipose tissue are metabolized to free fatty acids and **glycerol** by hormone-sensitive lipase in response to low insulin and high catecholamine levels. Adipocytes are unable to metabolize glycerol, so it is secreted into the circulation and transported to the liver, where it is phosphorylated to glycerol-3-phosphate by **glycerol kinase**. Glycerol-3-phosphate is subsequently converted by glycerol-3-phosphate dehydrogenase to dihydroxyacetone phosphate (DHAP), which can be used to produce **glucose** through **gluconeogenesis**.

(Choice A) Acetyl CoA carboxylase is a biotin-dependent enzyme present in both liver and adipose tissues. It catalyzes the first committed step in fatty acid synthesis, the conversion of acetyl CoA to malonyl CoA.

(Choice B) Fatty acids must first be activated by acyl CoA synthetase in the cytoplasm in order to undergo beta-oxidation in mitochondria. Although beta-oxidation of fatty acids is increased in diabetic ketoacidosis, the resulting acetyl-CoA is used for energy and ketone body formation (not glucose production).

(Choice C) In contrast to fatty acid oxidation, which occurs in mitochondria, fatty acid synthesis occurs in the cytosol. Acetyl CoA generated in mitochondria during glycolysis is transferred to the cytosol as citrate. In the cytoplasm, ATP citrate lyase converts citrate back into acetyl CoA that can be used for fatty acid chain elongation.

(Choice D) Glucose-6-phosphate dehydrogenase is the first enzyme of the hexose monophosphate (HMP) shunt. The HMP shunt produces pentose sugars for nucleotide synthesis and NADPH, which is necessary for cholesterol and fatty acid biosynthesis.

Educational objective:
Glycerol produced by the degradation of triglycerides in adipose tissue can be used by glycerol kinase in the liver and kidney to synthesize glucose during gluconeogenesis.

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Item 4 of 40
Question Id: 1247

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A 78-year-old woman comes to the office due to tenderness and easy bleeding of the gums when she brushes her teeth. The patient has brushed her teeth twice a day for as long as she can remember and has not experienced these symptoms before. Physical examination shows swollen gingiva that bleed on probing. Her skin findings are shown in the image below.

Further questioning reveals that the patient lives alone and that her diet consists primarily of tea and toast. Her symptoms are most likely caused by hypoactivity of an enzyme found in which of the following compartments?

A. Extracellular space
B. Golgi apparatus
C. Lysosomes
D. Mitochondria
E. Nucleus
F. Rough endoplasmic reticulum

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Item 4 of 40
Question Id: 1247

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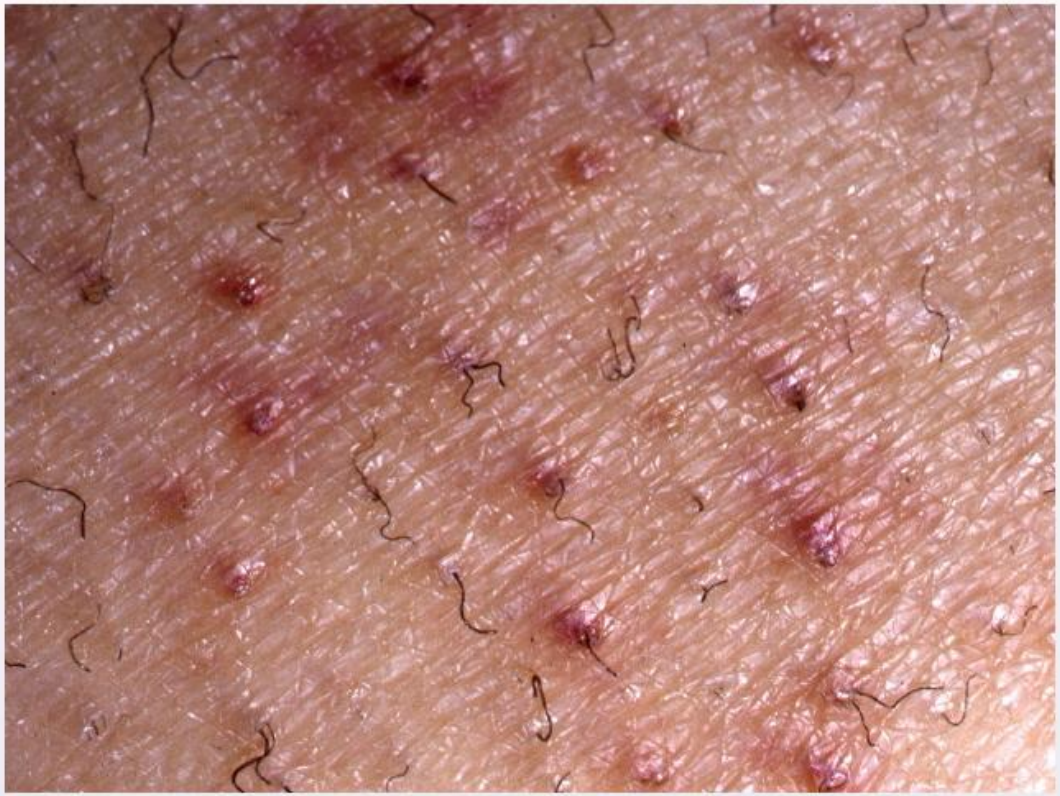

Further questioning reveals that the patient lives alone and that her diet consists primarily of tea and toast. Her symptoms are most likely caused

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Item 4 of 40
Question Id: 1247

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A. Extracellular space
B. Golgi apparatus
C. Lysosomes
D. Mitochondria
E. Nucleus
F. Rough endoplasmic reticulum

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Item 4 of 40
Question Id: 1247

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Further questioning reveals that the patient lives alone and that her diet consists primarily of tea and toast. Her symptoms are most likely caused by hypoactivity of an enzyme found in which of the following compartments?

A. Extracellular space [15%]
B. Golgi apparatus [14%]
C. Lysosomes [4%]
D. Mitochondria [10%]
E. Nucleus [3%]
✔ F. Rough endoplasmic reticulum [50%]

Omitted
Correct answer
F

50%
Answered correctly

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Explanation

This patient likely has vitamin C deficiency (scurvy). In the United States, vitamin C deficiency is seen primarily among malnourished

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Explanation

This patient likely has **vitamin C deficiency (scurvy)**. In the United States, vitamin C deficiency is seen primarily among malnourished populations, including alcoholics, the poor, and the elderly. The symptoms of scurvy reflect impaired formation of collagen and include **gingival swelling/bleeding**, petechiae, ecchymoses, and poor wound healing. **Perifollicular hemorrhages and coiled (corkscrew) hairs** are also commonly seen.

Collagen synthesis is a complex process that begins with the transcription of collagen genes in the nucleus **(Choice E)**. Collagen α-chains are then synthesized by rough endoplasmic reticulum (RER)-bound ribosomes and directed into the cisternae of the RER. Within the RER, specific **proline and lysine** residues are post-translationally **hydroxylated** to hydroxyproline and hydroxylysine by prolyl hydroxylase and lysyl hydroxylase, respectively. **Vitamin C** is a **required cofactor** for this post-translational modification. Defective hydroxylation of these residues severely diminishes the amount of collagen secreted by fibroblasts and impairs triple helix stability and covalent crosslink formation.

(Choices A and B) After formation of the triple helix, procollagen molecules are secreted from the cell via the Golgi apparatus. Propeptides at the N- and C-terminals are cleaved by extracellular procollagen peptidase to form insoluble tropocollagen molecules. These monomers then self-assemble into collagen fibrils that are subsequently crosslinked via lysyl oxidase.

(Choices C and D) Lysosomes and mitochondria are not directly involved in the synthesis of collagen.

Educational objective:
The hydroxylation of proline and lysine residues in collagen helps it attain its maximum tensile strength. This process occurs in the rough endoplasmic reticulum and requires vitamin C as a cofactor. Impaired collagen synthesis resulting from vitamin C deficiency (scurvy) can lead to fragile vessels, predisposing to gingival bleeding, ecchymosis, and petechia.

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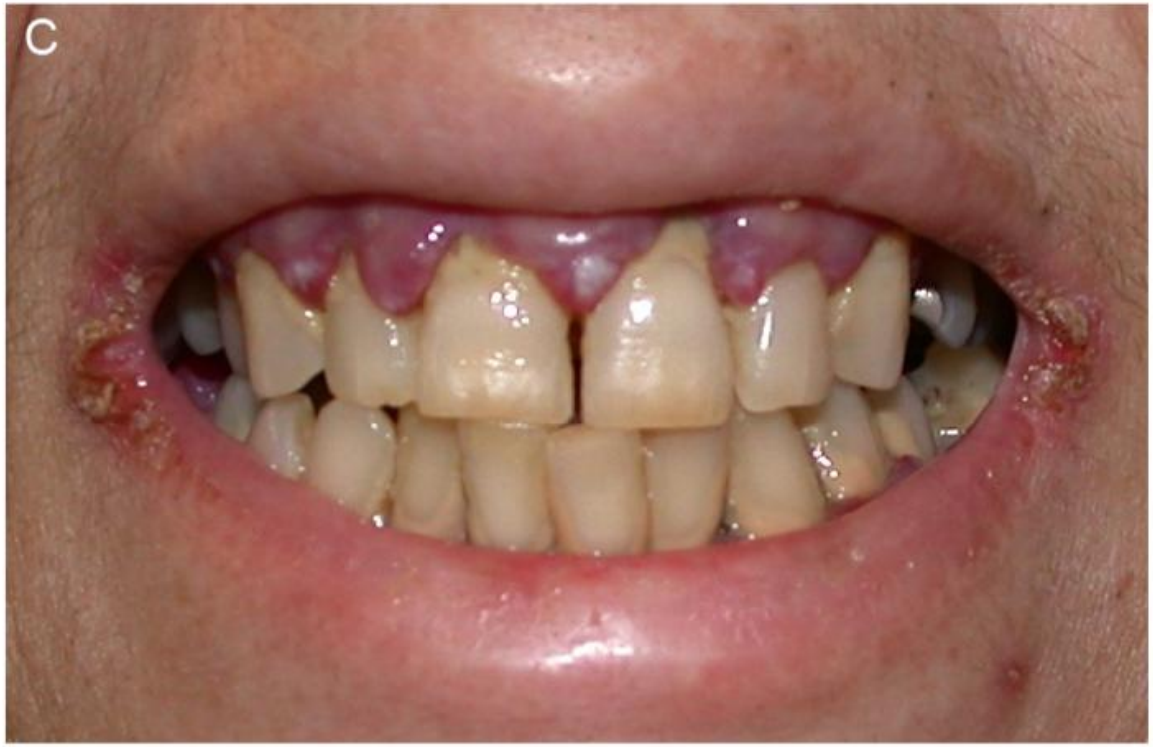

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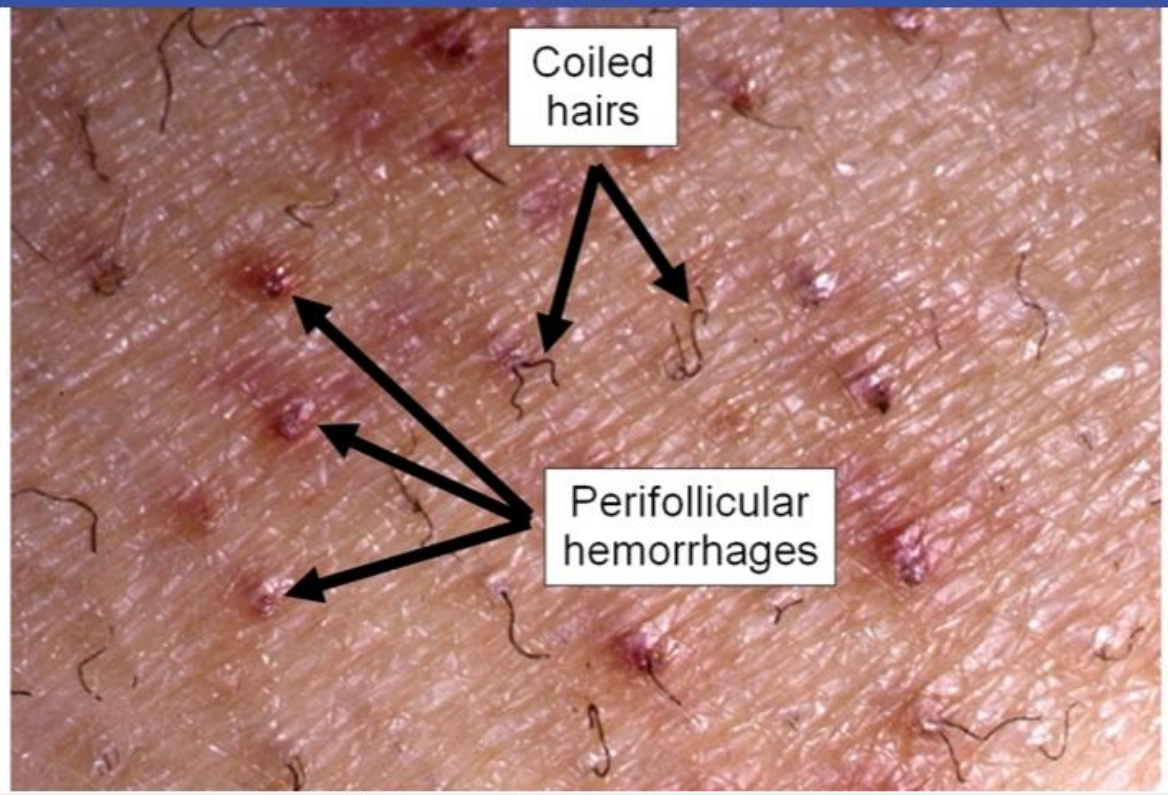

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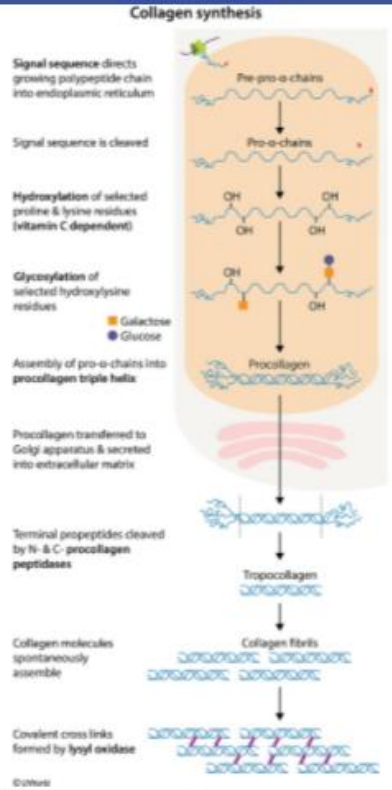

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Item 5 of 40
Question Id: 1066

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A 35-year-old man comes to the office with progressively worsening fatigue associated with dark urine and back pain. Two days ago, the patient ate some large, flat beans brought home by his wife after a business trip to Egypt. Physical examination shows jaundice and pallor. Laboratory results reveal a hemoglobin level of 8 g/dL. Further evaluation reveals deficiency of an enzyme involved in the conversion of glucose-6-phosphate to ribulose-5-phosphate. The substance generated during this conversion is necessary for which of the following biochemical processes?

A. ADP phosphorylation
B. Fatty acid synthesis
C. Glycogen storage
D. Ketone body synthesis
E. Protein degradation

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Item 5 of 40
Question Id: 1066

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A 35-year-old man comes to the office with progressively worsening fatigue associated with dark urine and back pain. Two days ago, the patient ate some large, flat beans brought home by his wife after a business trip to Egypt. Physical examination shows jaundice and pallor. Laboratory results reveal a hemoglobin level of 8 g/dL. Further evaluation reveals deficiency of an enzyme involved in the conversion of glucose-6-phosphate to ribulose-5-phosphate. The substance generated during this conversion is necessary for which of the following biochemical processes?

- A. ADP phosphorylation [29%]
- ✔ B. Fatty acid synthesis [44%]
- C. Glycogen storage [9%]
- D. Ketone body synthesis [8%]
- E. Protein degradation [8%]

Omitted
Correct answer
B

44%
Answered correctly

3 Seconds
Time Spent

11/15/2018
Last Updated

Explanation

Pentose phosphate pathway

OXIDATIVE
(IRREVERSIBLE)

Glucose-6-phosphate

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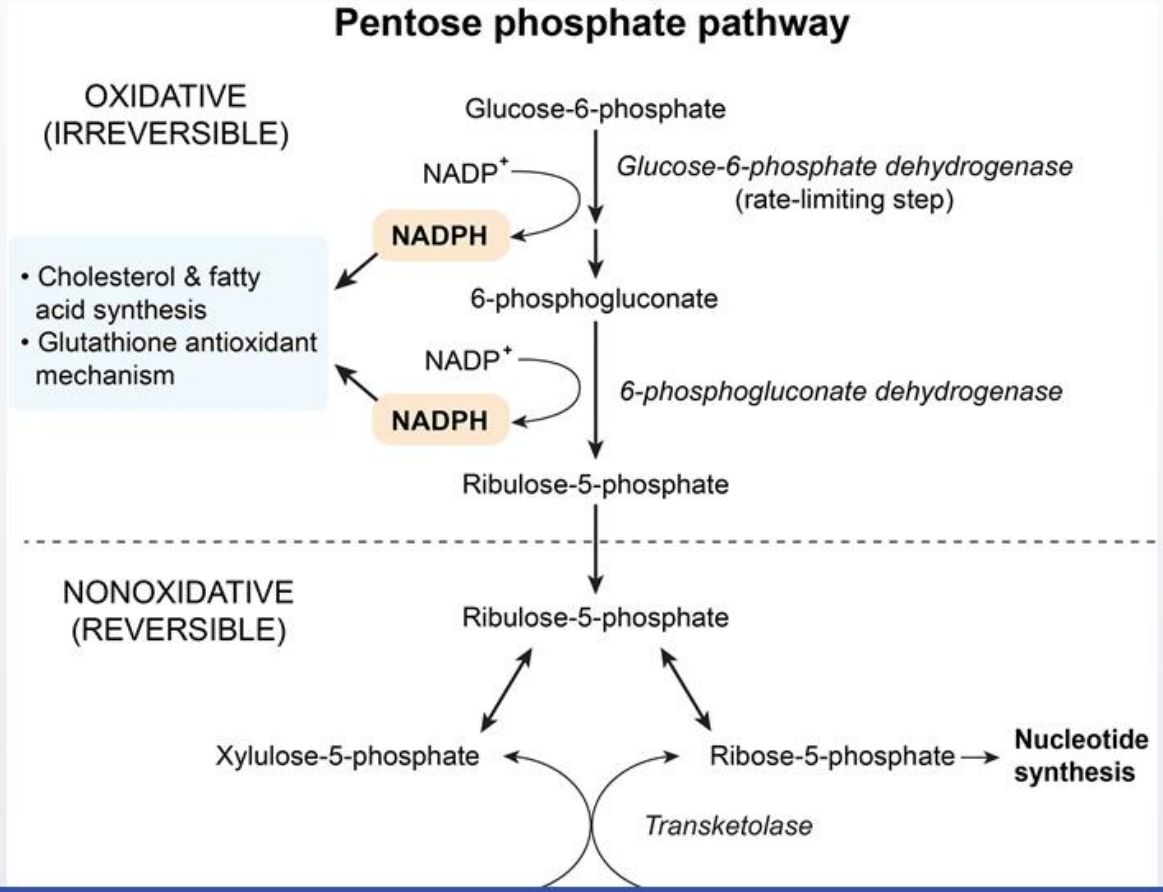
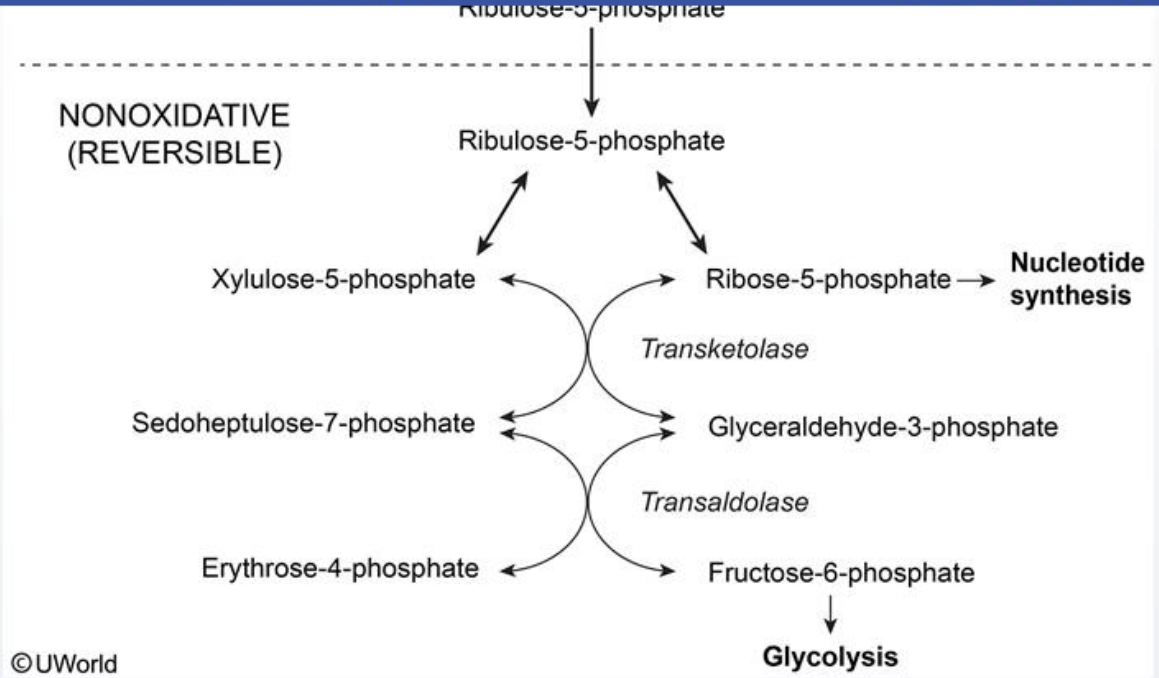
2/6/2019

Explanation





This patient most likely has **glucose-6-phosphate dehydrogenase (G6PD) deficiency**. G6PD catalyzes the first step in the pentose phosphate pathway (PPP), the oxidative portion of which generates 2 molecules of NADPH while converting glucose-6-phosphate to ribulose-5-phosphate. The nonoxidative reactions of the PPP reversibly convert ribulose-5-phosphate into ribose-5-phosphate (substrate for nucleotide synthesis) or glycolytic intermediates that can be used for energy production.

Because the PPP is the **main source of NADPH**, the pathway is particularly active in:

- Cells experiencing **high oxidative stress** (eg, erythrocytes) in which NADPH is used to regenerate reduced glutathione, an antioxidant that

Because the PPP is the **main source of NADPH**, the pathway is particularly active in:

- Cells experiencing **high oxidative stress** (eg, erythrocytes) in which NADPH is used to regenerate reduced glutathione, an antioxidant that helps maintain cell integrity
- Organs such as the liver and adrenal cortex that are involved in **reductive biosynthesis** (eg, synthesis of fatty acids, cholesterol, steroids) and cytochrome P450 metabolism
- Phagocytic cells generating a respiratory burst via NADPH oxidase

In patients with G6PD deficiency, erythrocytes are unable to maintain a sufficient supply of reduced glutathione during periods of increased oxidative stress, which can occur with certain infections (eg, pneumonia, viral hepatitis), consumption of fava beans, or specific medications (eg, primaquine, sulfa drugs). The resulting oxidative damage causes **acute hemolytic anemia** and jaundice.

(Choice A) NADH can be used as a reducing agent to convert ADP to ATP during oxidative phosphorylation. In contrast to NADH, NADPH cannot be used to convert ADP into ATP.

(Choice C) Glycogenesis is the process by which glucose is stored for later use through the addition of glucose molecules to glycogen chains. It does not require NADPH.

(Choice D) Ketone bodies are formed mainly in the liver during times of fasting when there is increased fat degradation. Cytosolic HMG-CoA synthase is the starting point of cholesterol synthesis whereas the mitochondrial version of the enzyme is the rate-limiting step in ketone body synthesis. Unlike cholesterol synthesis, ketone body production does not require NADPH.

(Choice E) Protein catabolism begins with the hydrolysis of polypeptides into amino acids. These subsequently undergo transamination reactions that funnel the amine nitrogen predominately into glutamate, which is oxidatively deaminated to produce ammonia. The urea cycle then converts ammonia into urea for elimination in the urine.

Educational objective:

Glucose-6-phosphate dehydrogenase is the rate-limiting enzyme in the pentose phosphate pathway, the major source of cellular NADPH. This

- Organs such as the liver and adrenal cortex that are involved in **reductive biosynthesis** (eg, synthesis of fatty acids, cholesterol, steroids) and cytochrome P450 metabolism
- Phagocytic cells generating a respiratory burst via NADPH oxidase

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(Choice E) Protein catabolism begins with the hydrolysis of polypeptides into amino acids. These subsequently undergo transamination reactions that funnel the amine nitrogen predominately into glutamate, which is oxidatively deaminated to produce ammonia. The urea cycle then converts ammonia into urea for elimination in the urine.

Educational objective:
Glucose-6-phosphate dehydrogenase is the rate-limiting enzyme in the pentose phosphate pathway, the major source of cellular NADPH. This molecule is necessary for reducing glutathione (protects red blood cells from oxidative damage) and for the biosynthesis of cholesterol, fatty acids, and steroids.

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Item 6 of 40
Question Id: 1334

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A 12-year-old boy is brought to the office due to gait instability and pruritic skin rash for the past several weeks. His mother reports that he has also been irritable and had loose stools during this time. The patient's childhood development has been unremarkable except for several episodes of similar skin rash that resolved spontaneously. Examination shows scaly, erythematous skin lesions in sun-exposed areas and cerebellar ataxia. Laboratory evaluation shows increased levels of neutral amino acids in the urine. This patient's symptoms would most likely respond to which of the following supplements?

A. Ascorbate
B. Folic acid
C. Niacin
D. Pyridoxine
E. Riboflavin
F. Thiamine
G. Tocopherol

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Item 6 of 40
Question Id: 1334

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

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- A. Ascorbate [2%]
- B. Folic acid [2%]
- ✔ C. Niacin [55%]
- D. Pyridoxine [16%]
- E. Riboflavin [4%]
- F. Thiamine [11%]
- G. Tocopherol [6%]

Omitted
Correct answer
C

55%
Answered correctly

3 Seconds
Time Spent

10/29/2018
Last Updated

Explanation

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Explanation

This patient likely has **Hartnup disease**, an autosomal recessive metabolic disorder caused by inactivating mutations affecting the **neutral amino acid transporter**. This results in impaired transport of neutral amino acids, particularly tryptophan, in the small intestine and proximal tubule of the kidney.

Tryptophan is an essential amino acid and a precursor for niacin, serotonin, and melatonin. Conversion of **tryptophan to niacin** is responsible for the generation of up to half of the nicotinamide adenine dinucleotide (NAD+) required for redox reactions; the clinical manifestations of Hartnup disease are primarily due to niacin deficiency. Patients present with intermittent attacks of **pellagra-like skin eruptions** (development of a red, rough rash following sun exposure) and **cerebellar ataxia** in early childhood that become less severe with increasing age.

The diagnosis is confirmed by detecting excessive amounts of neutral amino acids (alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, and tryptophan) in the urine (**neutral aminoaciduria**). A high-protein diet along with daily niacin or nicotinamide supplementation generally results in significant symptom improvement.

(Choice A) Ascorbate (vitamin C) is a water-soluble vitamin required for hydroxylation of proline and lysine residues during collagen synthesis. Deficiency results in scurvy, a disease characterized by bone pain, easy bruising, and poor wound healing.

(Choice B) Both folic acid and vitamin B_{12} deficiencies result in a megaloblastic anemia. However, neurologic manifestations of subacute combined degeneration of the posterior and lateral columns are specific to vitamin B_{12} deficiency.

(Choice D) Pyridoxine (vitamin B_6) acts as a coenzyme in the decarboxylation and transamination of amino acids, including the metabolism of tryptophan to niacin. Deficiency of pyridoxine leads to anemia, peripheral neuropathy, and dermatitis. Supplementation in Hartnup disease is not effective due to underlying tryptophan malabsorption.

(Choice E) The coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) form the prosthetic groups of several enzymes important in electron transport; both are synthesized from riboflavin (vitamin B_2). Clinical features of deficiency include sore throat, stomatitis, glossitis, normocytic anemia, and seborrheic dermatitis.

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(Choice F) Thiamine use by the body is maximal in states of accelerated carbohydrate metabolism because thiamine acts as a cofactor for the enzymes transketolase (pentose phosphate pathway), α-ketoglutarate dehydrogenase (TCA cycle), and pyruvate dehydrogenase (forms acetyl-CoA).

(Choice G) Tocopherol (vitamin E) is a fat-soluble vitamin that functions as a scavenger of free radicals (antioxidant). Deficiency of vitamin E is rare but can result in neurologic dysfunction (ataxia, hyporeflexia, loss of sensation) as well as hemolytic anemia.

Educational objective:
Hartnup disease is caused by impaired transport of neutral amino acids in the small intestine and proximal tubule of the kidney. Symptoms include pellagra-like skin eruptions and cerebellar ataxia, which occur as a result of niacin deficiency. The diagnosis can be confirmed through detection of excessive amounts of neutral amino acids in the urine.

References

- Hartnup disease.
- Hartnup disorder: unraveling the mystery.

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Item 6 of 40
Question Id: 1334

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the kidney.

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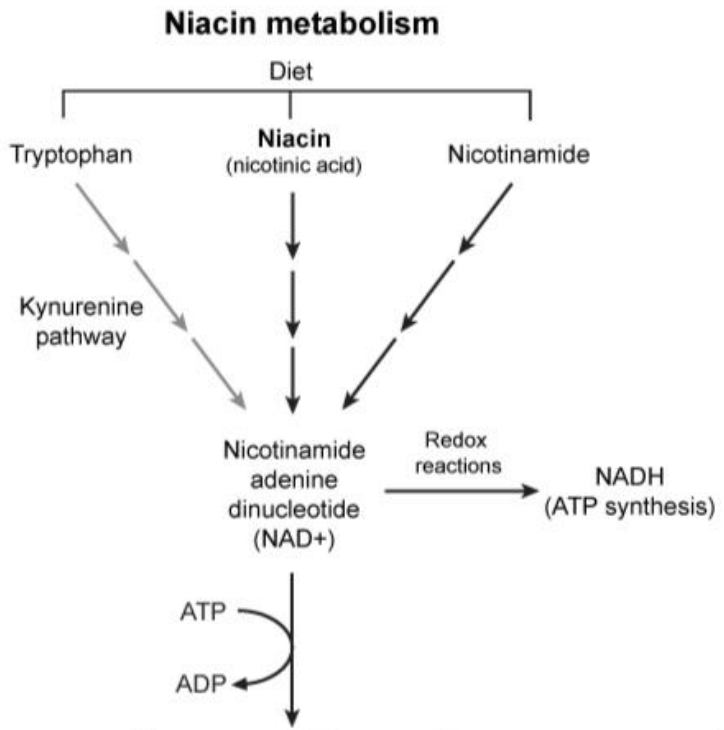

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(Choice G) Tocopherol (vitamin E) is a fat-soluble vitamin that functions as a scavenger of free radicals (antioxidant). Deficiency of vitamin E is

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Item 6 of 40
Question Id: 1334

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the kidney.

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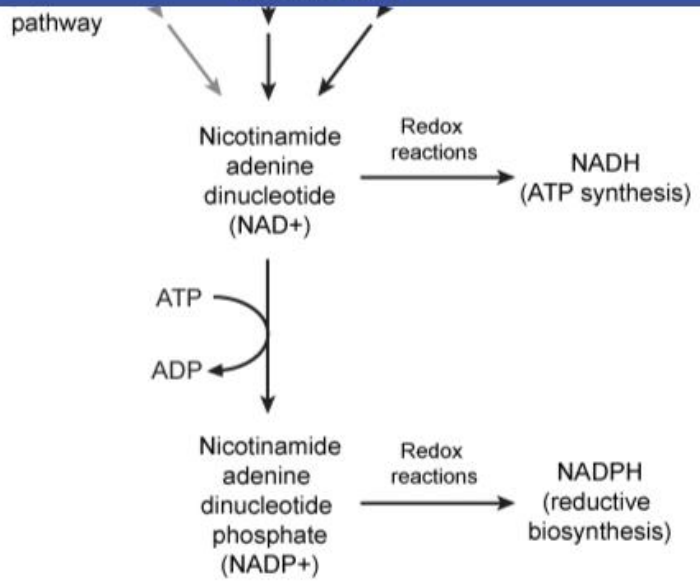

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Item 7 of 40
Question Id: 1243

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An infant born to a Greek immigrant appears healthy at birth but develops transfusion-dependent hemolytic anemia by the age of 6 months. His erythrocytes contain insoluble aggregates of hemoglobin subunits. The child developed normally in utero because at that time he produced high quantities of:

A. α-globin
B. β-globin
C. γ-globin
D. δ-globin
E. ζ-globin

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Item 7 of 40
Question Id: 1243

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

An infant born to a Greek immigrant appears healthy at birth but develops transfusion-dependent hemolytic anemia by the age of 6 months. His erythrocytes contain insoluble aggregates of hemoglobin subunits. The child developed normally in utero because at that time he produced high quantities of:

A. α-globin [3%]
B. β-globin [3%]
✔ C. γ-globin [84%]
D. δ-globin [5%]
E. ζ-globin [3%]

Omitted
Correct answer
C

84%
Answered correctly

3 Seconds
Time Spent

02/06/2019
Last Updated

Explanation

In adults, hemoglobin A is the predominant form of hemoglobin. It is a tetramer consisting of two alpha and two beta chains. Normally the synthesis of alpha and beta chains is tightly regulated such that one α-chain is synthesized for every β-chain. Hemoglobin formation begins within a few weeks of conception. The initial hemoglobin formed by a fetus in utero is called embryonic hemoglobin (Gower). This hemoglobin is composed of two zeta (ζ) and two epsilon (ε) chains (ζ2ε2) and is produced in the embryonic yolk sac. Within a few weeks the fetal liver starts

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Thalassemias are hereditary hemolytic anemias resulting from defective synthesis of globin chains. As described above, the synthesis of alpha and beta globin chains is very coordinated. In patients with thalassemia, the synthesis of either alpha or beta chains is defective. Beta thalassemia is caused by defective synthesis of beta chains. There are two copies of the beta globin gene (one from each parent). If only one gene is defective the patient will have beta thalassemia trait (beta thalassemia minor) and lack significant anemia. A defect in both beta globin genes results in severe hemolytic anemia known as beta thalassemia major. In this disease, alpha chains are produced normally but they cannot form stable tetramers due to the lack of beta globin chains. This failure to form stable hemoglobin leads to precipitation of alpha globin chains and premature lysis of red blood cells. Beta thalassemia cannot become symptomatic as long as there are significant amounts of gamma chains present because gamma chains make up for the absence of HbA beta chains in forming tetramers. Thus, in late gestation and early postnatal life, the expression of hemoglobin A is offset by gamma chain production **(Choice C)**. As gamma chain production wanes, patients will become symptomatic.

(Choice A) α-globin is a normal component of both HbA and HbF. α-globin synthesis is defective in α-thalassemia but it is normal in β-thalassemia. α-globin is able to combine with γ-globin to form HbF. This allows patients with β-thalassemia major to be asymptomatic in utero and in the first few months following birth.

(Choice B) β-globin synthesis is defective in patients with b-thalassemia.

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(Choice B) β-globin synthesis is defective in patients with b-thalassemia.

(Choice D) δ-globin is a minor globin gene that is expressed at very low levels in normal adults. Two α-globins and two δ-globins combine to form hemoglobin A2.

(Choice E) ζ-globin is a component of hemoglobin Gower, the initial hemoglobin formed by the embryo very early in embryogenesis.

Educational Objective:
HbF contains γ-globin instead of β-globin. Patients with homozygotic β-thalassemia (β-thalassemia major) are asymptomatic at birth due to the presence of γ-globins and HbF. Switching to HbA production and the cessation of γ-globin synthesis precipitates the symptoms of β-thalassemia.

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Item 8 of 40
Question Id: 1241

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A 7-year-old African American boy is brought to the office by his parents. The parents state that the boy has been hospitalized several times for severe pains in his back and extremities. The patient is very active when he is not in pain but gets quite tired by the end of the day. He has no other medical problems and takes no medications except acetaminophen for pain control. On examination, the conjunctivae are pale. Blood count reveals a hemoglobin level of 7.8 mg/dL and a reticulocyte count of 15%. A valine for glutamic acid substitution at position 6 of the β globin chain of the hemoglobin molecule is suspected. This patient's hemoglobin would most likely aggregate upon which of the following?

A. 2,3-bisphosphoglycerate depletion
B. β globin chain folding
C. Capillary pH values >7.4
D. Interaction with fetal hemoglobin
E. Oxygen unloading

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Item 8 of 40
Question Id: 1241

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- A. 2,3-bisphosphoglycerate depletion [11%]
- B. β globin chain folding [9%]
- C. Capillary pH values >7.4 [5%]
- D. Interaction with fetal hemoglobin [4%]
- ✔ E. Oxygen unloading [68%]

Omitted
Correct answer
E

68%
Answered correctly

3 Seconds
Time Spent

12/25/2018
Last Updated

Explanation

In **sickle cell (hemoglobin S [HbS]) anemia**, the nonpolar amino acid valine replaces the charged amino acid glutamate at position 6 of the β globin chain. This results in the alteration of a hydrophobic portion of the β globin chain that fits into a complementary site on the α globin chain of another hemoglobin molecule. As a result, hemoglobin molecules aggregate under anoxic conditions. After polymerization, HbS initially forms a

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Explanation

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Sickling is promoted by conditions associated with **low oxygen** levels, increased acidity, or low blood volume (dehydration). Sickled cells are not flexible enough to pass through microvasculature. As a result, they impede blood flow and cause microinfarcts in tissues and painful vasoocclusive crises. Organs in which blood moves slowly (eg, spleen, liver) are predisposed to lower oxygen levels or acidity. Organs with particularly high metabolic demands (eg, brain, muscles, placenta) promote sickling by extracting more oxygen from the blood (**oxygen unloading**). The sickling process is complex and incompletely understood.

(Choices A and C) The molecule 2,3-bisphosphoglycerate (2,3-BPG) binds the 2 β globin chains ionically and stabilizes the taut (T) deoxyhemoglobin. This binding decreases hemoglobin's oxygen affinity, facilitating oxygen release at the tissue level. With 2,3-BPG depletion, hemoglobin affinity for oxygen increases (left shift on **oxygen-hemoglobin dissociation curve**), and this results in oxygen uptake by hemoglobin; therefore, erythrocyte sickling will decrease. Similarly, increased acidity or low pH is associated with sickling, so decreased acidity with elevated capillary pH values >7.4 would not promote sickling.

(Choice B) The globin chains in the hemoglobin tetramer are folded compactly, with nonpolar hydrophobic residues in the interior and charged polar residues on the surface. A valine for glutamic acid substitution does not result in a significant change in β globin folding. It is the mature hemoglobin tetramer that undergoes polymerization, not individual globin chains during folding.

(Choice D) HbS does not polymerize when fetal hemoglobin (HbF) is present, so patients with sickle cell anemia often do not have symptoms until the HbF fraction decreases a few months after delivery. Some patients with HbS may have fewer clinical manifestations because they produce larger amounts of HbF as adults.

Educational objective:

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Educational objective:
Hemoglobin S (HbS) aggregates in the deoxygenated state. HbS polymers form fibrous strands that reduce red blood cell membrane flexibility and promote sickling. Sickling occurs under conditions associated with anoxia including low pH and high levels of 2,3-bisphosphoglycerate. These inflexible erythrocytes predispose to microvascular occlusion and microinfarcts.

References

- Newer aspects of the pathophysiology of sickle cell disease vaso-occlusion.
- Sickle cell anemia, the first molecular disease: overview of molecular etiology, pathophysiology, and therapeutic approaches.

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Item 9 of 40
Question Id: 788

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A 34-year-old previously healthy man comes to the emergency department due to a 3-hour history of chest pain, diaphoresis, and dyspnea. He does not smoke, exercises regularly, and eats a balanced diet. His father died at age 56 from a myocardial infarction. His blood pressure is 110/70 mm Hg and pulse is 110/min and regular. Physical examination is unremarkable. ECG shows ST elevation in the anterolateral leads. Coronary angiogram reveals proximal left anterior descending artery stenosis and thrombosis, which is treated with angioplasty and stent placement. Laboratory results are as follows:

Total cholesterol	160 mg/dL	
Low-density lipoprotein	90 mg/dL	
Glucose, serum	98 mg/dL	
Homocysteine, plasma	21.5 µmol/L	(normal: 4-14 µmol/L)

Further testing reveals a homozygous mutation in the methylene tetrahydrofolate reductase gene that leads to decreased enzymatic activity. Due to this defect, the patient most likely has impairment converting homocysteine to which of the following?

A. Cystathionine
B. Cysteine
C. Methionine
D. Methylmalonyl-CoA
E. Succinyl-CoA

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Total cholesterol	160 mg/dL	
Low-density lipoprotein	90 mg/dL	
Glucose, serum	98 mg/dL	
Homocysteine, plasma	21.5 µmol/L	(normal: 4-14 µmol/L)

Further testing reveals a homozygous mutation in the methylene tetrahydrofolate reductase gene that leads to decreased enzymatic activity. Due to this defect, the patient most likely has impairment converting homocysteine to which of the following?

- A. Cystathionine [9%]
- B. Cysteine [10%]
- ✔ C. Methionine [68%]
- D. Methylmalonyl-CoA [9%]
- E. Succinyl-CoA [2%]

Omitted
Correct answer

68%
Answered correctly

5 Seconds
Time Spent

10/19/2018
Last Updated

Elevated levels of plasma homocysteine are an independent risk factor for **thrombotic events**, including venous thromboses, coronary artery disease, and ischemic stroke. The mechanism is thought to be due to direct and indirect induction of **endothelial damage**.

Homocysteine can be metabolized to **methionine** via remethylation or to **cystathionine** via transsulfuration. Remethylation to methionine occurs with the donation of a methyl group from methyl-tetrahydrofolate via **methionine synthase**, with vitamin B_{12} (cobalamin) as an important cofactor. Methyl-tetrahydrofolate is regenerated by the enzyme **methylene tetrahydrofolate reductase (MTHFR)**, using FAD as a cofactor. Homocysteine can also undergo transsulfuration via cystathionine-β-synthase to cystathionine **(Choice A)** and subsequently to cysteine **(Choice B)** via the enzyme cystathionase, using vitamin B_6 as a cofactor.

Elevations in plasma homocysteine can occur due to genetic mutations in critical enzymes and vitamin (cofactor) deficiencies. MTHFR deficiency is the most common genetic cause of hyperhomocysteinemia. Low levels of the B vitamins cobalamin, pyridoxine, and folate are associated with hyperhomocysteinemia. However, supplementation of B vitamins for patients with mildly to moderately elevated homocysteine levels has not demonstrated a decrease in cardiovascular risk or mortality.

(Choices D and E) Vitamin B_{12} is a cofactor for the enzyme methylmalonyl-CoA mutase in the conversion of **methylmalonyl-CoA to succinyl-CoA**, a reaction that occurs in the breakdown of odd-chain fatty acids and some amino acids. As a result, patients with vitamin B_{12} deficiency have elevated methylmalonyl-CoA levels that subsequently result in buildup of neurotoxic methylmalonic acid. Symptomatic consequences include lethargy, seizures, paresthesias, and hypotonia. Homocysteine is elevated in both folate and vitamin B_{12} deficiencies, but methylmalonyl-CoA is elevated in vitamin B_{12} deficiency only.

Educational objective:
Elevated levels of plasma homocysteine are an independent risk factor for thrombotic events. Homocysteine can be metabolized to methionine via remethylation or to cystathionine via transsulfuration. Hyperhomocysteinemia is most commonly due to genetic mutations in critical enzymes or deficiencies of vitamin B_{12}, vitamin B_6, and folate.

References

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Item 10 of 40
Question Id: 1479

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Microbiologists are investigating sugar metabolism in wild-type and mutant strains of *Escherichia coli*. Both strains are found to grow viable colonies on lactose-containing media. Each strain is then cultured on a new growth medium containing only glucose. Representative colonies of each strain from the new media undergo Western blot processing using a fluorescently labeled probe specific for β-galactosidase. Wild-type bacterial colonies are found to contain only trace quantities of β-galactosidase. However, the mutant colonies express significant amounts of β-galactosidase. Further analysis reveals that the variant strain contains a mutation that inhibits the binding of a certain protein to its regulatory sequence. In which of the following locations did this mutation most likely occur?

A. Activator protein (CAP) binding site
B. Operator locus
C. Promoter region
D. Activator protein (CAP) gene
E. RNA polymerase cistron

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Item 10 of 40
Question Id: 1479

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Microbiologists are investigating sugar metabolism in wild-type and mutant strains of *Escherichia coli*. Both strains are found to grow viable colonies on lactose-containing media. Each strain is then cultured on a new growth medium containing only glucose. Representative colonies of each strain from the new media undergo Western blot processing using a fluorescently labeled probe specific for β-galactosidase. Wild-type bacterial colonies are found to contain only trace quantities of β-galactosidase. However, the mutant colonies express significant amounts of β-galactosidase. Further analysis reveals that the variant strain contains a mutation that inhibits the binding of a certain protein to its regulatory sequence. In which of the following locations did this mutation most likely occur?

- A. Activator protein (CAP) binding site [19%]
- ✔ B. Operator locus [43%]
- C. Promoter region [27%]
- D. Activator protein (CAP) gene [8%]
- E. RNA polymerase cistron [1%]

Omitted
Correct answer
B

43%
Answered correctly

3 Seconds
Time Spent

08/11/2018
Last Updated

Explanation

The *lac* operon consists of a regulatory gene (*lac I*), a promoter region (*lac p*), an operator region (*lac o*), and three structural genes (*lac Z, lac Y,*

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Explanation

The *lac* operon consists of a regulatory gene (*lac I*), a promoter region (*lac p*), an operator region (*lac o*), and three structural genes (*lac Z, lac Y,* and *lac A*). The *lac Z* gene codes for β-galactosidase, which is responsible for the hydrolysis of lactose to glucose and galactose. The *lac Y* gene codes for permease, which allows lactose to enter the bacterium. The *lac p* region is the binding site for RNA polymerase during the initiation of transcription. The Lac I repressor protein is the product of the *lac I* gene and is constitutively expressed. Repressor proteins, when bound to the operator region, prevent binding of RNA polymerase to the promoter region, thus decreasing transcription of the *lac Z, lac Y,* and *lac A* genes. Culture of *E coli* in lactose-containing media causes a conformational change in the repressor protein, preventing its attachment to the operator region and increasing transcription of the *lac* operon structural genes.

Culturing *E coli* in media containing glucose results in reduced expression of the *lac* operon, even when the media contains lactose as well. This occurs because the *lac* operon is positively regulated by the binding of catabolite activator protein (CAP) to a site slightly upstream from the promoter region. This only occurs when cAMP concentrations are high. Since glucose decreases the activity of adenylyl cyclase (reducing intracellular cAMP), the *lac* operon is repressed in high-glucose conditions. In summary, the *lac* operon is regulated by 2 distinct mechanisms:

1. Negatively by binding of the repressor protein to the operator locus
2. Positively by cAMP-CAP binding upstream from the promoter region

Mutations impairing the binding of the repressor protein to its binding site at the operator region will prevent repression of the genes of the *lac* operon in the absence of lactose. This results in increased transcription of the genes of the *lac* operon in lactose-deficient media, although the presence of glucose will prevent maximal transcriptional activity.

(Choices A and D) Mutations that impair the binding of cAMP-CAP to its regulatory site upstream from the promoter will decrease transcription of the *lac* operon, as cAMP-CAP is a positive regulator.

(Choices C and E) Mutations impairing the binding of RNA polymerase to the promotor region will also reduce transcription of the *lac* operon.

Educational objective:

transcription. The Lac I repressor protein is the product of the *lac I* gene and is constitutively expressed. Repressor proteins, when bound to the operator region, prevent binding of RNA polymerase to the promoter region, thus decreasing transcription of the *lac Z, lac Y,* and *lac A* genes. Culture of *E coli* in lactose-containing media causes a conformational change in the repressor protein, preventing its attachment to the operator region and increasing transcription of the *lac* operon structural genes.

Culturing *E coli* in media containing glucose results in reduced expression of the *lac* operon, even when the media contains lactose as well. This occurs because the *lac* operon is positively regulated by the binding of catabolite activator protein (CAP) to a site slightly upstream from the promoter region. This only occurs when cAMP concentrations are high. Since glucose decreases the activity of adenylyl cyclase (reducing intracellular cAMP), the *lac* operon is repressed in high-glucose conditions. In summary, the *lac* operon is regulated by 2 distinct mechanisms:

1. Negatively by binding of the repressor protein to the operator locus
2. Positively by cAMP-CAP binding upstream from the promoter region

Mutations impairing the binding of the repressor protein to its binding site at the operator region will prevent repression of the genes of the *lac* operon in the absence of lactose. This results in increased transcription of the genes of the *lac* operon in lactose-deficient media, although the presence of glucose will prevent maximal transcriptional activity.

(Choices A and D) Mutations that impair the binding of cAMP-CAP to its regulatory site upstream from the promoter will decrease transcription of the *lac* operon, as cAMP-CAP is a positive regulator.

(Choices C and E) Mutations impairing the binding of RNA polymerase to the promotor region will also reduce transcription of the *lac* operon.

Educational objective:
The *lac* operon is regulated by two distinct mechanisms: negatively by binding of the repressor protein to the operator locus and positively by cAMP-CAP binding upstream from the promoter region. Constitutive expression of the structural genes of the *lac* operon occurs with mutations that impair the binding of the repressor protein (Lac I) to its regulatory sequence in the operator region.

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Item 11 of 40
Question Id: 997

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A healthy 34-year-old coal mine worker is trapped underground following partial collapse of an access shaft. Rescue efforts are directed toward clearing the obstructed tunnel, but it takes 2 days to reach him. While being taken to the surface, the miner tells rescuers that he feels dizzy and weak. He had an emergency supply of water but has not eaten anything for over 30 hours. Fingerstick blood glucose concentration is 78 mg/dL. Which of the following biochemical reactions is most likely responsible for maintaining this patient's current blood glucose levels?

A. Acetoacetyl CoA → 3-hydroxy-3-methylglutaryl-CoA
B. Acetyl CoA → palmitic acid
C. Fructose 6-phosphate → fructose 1,6-bisphosphate
D. Glycogen → glucose-1-phosphate
E. Oxaloacetate → phosphoenolpyruvate

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Item 11 of 40
Question Id: 997

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A. Acetoacetyl CoA → 3-hydroxy-3-methylglutaryl-CoA [13%]
B. Acetyl CoA → palmitic acid [7%]
C. Fructose 6-phosphate → fructose 1,6-bisphosphate [3%]
D. Glycogen → glucose-1-phosphate [25%]
✔ E. Oxaloacetate → phosphoenolpyruvate [50%]

Omitted
Correct answer
E

50%
Answered correctly

3 Seconds
Time Spent

11/08/2018
Last Updated

Explanation

The 2 major processes that maintain plasma glucose between meals are glycogenolysis and gluconeogenesis. Glycogenolysis is the primary source of glucose for the first 12-18 hours of fasting. Once hepatic glycogen stores become depleted, **gluconeogenesis** becomes the major process used by the body to keep blood glucose levels within the normal range. During gluconeogenesis, glucose is formed from lactate, glycerol,

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The 2 major processes that maintain plasma glucose between meals are glycogenolysis and gluconeogenesis. Glycogenolysis is the primary source of glucose for the first 12-18 hours of fasting. Once hepatic glycogen stores become depleted, **gluconeogenesis** becomes the major process used by the body to keep blood glucose levels within the normal range. During gluconeogenesis, glucose is formed from lactate, glycerol, and glucogenic amino acids. This process uses many of the enzymes involved in glycolysis. However, hexokinase, phosphofructokinase, and pyruvate kinase are unidirectional and must be **bypassed** by distinct gluconeogenic enzymes.

The first committed step of gluconeogenesis is the biotin-dependent carboxylation of pyruvate to oxaloacetate by mitochondrial **pyruvate carboxylase**. Oxaloacetate is subsequently converted to malate by malate dehydrogenase to facilitate exit from the mitochondria, and then is converted back to oxaloacetate by cytosolic malate dehydrogenase (malate shuttle). In the cytosol, **phosphoenolpyruvate carboxykinase** (PEPCK) converts oxaloacetate to phosphoenolpyruvate. Therefore, pyruvate carboxylase and PEPCK work together to bypass pyruvate kinase. The 2 other unique gluconeogenic enzymes are **fructose 1,6-bisphosphatase** (bypasses phosphofructokinase) and **glucose-6-phosphatase** (bypasses hexokinase).

(Choice A) Conversion of acetoacetyl-CoA to 3-hydroxy-3-methylglutaryl-CoA occurs during the synthesis of cholesterol and ketone bodies. Ketone body synthesis is increased in starvation situations, however, ketone bodies cannot be used to synthesize glucose.

(Choice B) Palmitic acid is the first fatty acid produced from acetyl CoA during lipogenesis in the fed state. However, during prolonged fasting, lipolysis predominates and leads to generation of glycerol and fatty acids.

(Choice C) Conversion of fructose 6-phosphate to fructose 1,6-bisphosphate occurs during glycolysis and is catalyzed by phosphofructokinase. During starvation, glycolysis is minimized and gluconeogenesis predominates.

(Choice D) The first step of glycogenolysis is breakage of 1-4 glycosidic linkage to form glucose-1-phosphate. After 24 hours of fasting, maintenance of blood glucose levels is achieved mostly through gluconeogenesis, not by glycogenolysis.

Educational objective:
After 12-18 hours of fasting, gluconeogenesis becomes the principal source of blood glucose. Gluconeogenesis uses many glycolytic enzymes, but hexokinase, phosphofructokinase, and pyruvate kinase need to be bypassed as they are unidirectional. The initial steps of gluconeogenesis

pyruvate kinase are unidirectional and must be **bypassed** by distinct gluconeogenic enzymes.

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(Choice A) Conversion of acetoacetyl-CoA to 3-hydroxy-3-methylglutaryl-CoA occurs during the synthesis of cholesterol and ketone bodies. Ketone body synthesis is increased in starvation situations, however, ketone bodies cannot be used to synthesize glucose.

(Choice B) Palmitic acid is the first fatty acid produced from acetyl CoA during lipogenesis in the fed state. However, during prolonged fasting, lipolysis predominates and leads to generation of glycerol and fatty acids.

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(Choice D) The first step of glycogenolysis is breakage of 1-4 glycosidic linkage to form glucose-1-phosphate. After 24 hours of fasting, maintenance of blood glucose levels is achieved mostly through gluconeogenesis, not by glycogenolysis.

Educational objective:
After 12-18 hours of fasting, gluconeogenesis becomes the principal source of blood glucose. Gluconeogenesis uses many glycolytic enzymes, but hexokinase, phosphofructokinase, and pyruvate kinase need to be bypassed as they are unidirectional. The initial steps of gluconeogenesis involve the conversion of pyruvate to oxaloacetate and oxaloacetate to phosphoenolpyruvate by pyruvate carboxylase and phosphoenolpyruvate carboxykinase, respectively.

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Item 12 of 40
Question Id: 1338

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A 22-year-old woman comes to the hospital due to a 5-day history of nausea, constipation, and severe, poorly localized abdominal pain. She also reports anxiety, difficulty concentrating, poor sleep quality, and tingling of the limbs. The patient has had several similar episodes in the past. She does not take any medications or use tobacco, alcohol, or illicit drugs. The patient has been restricting her diet to lose weight. On examination, the abdomen is soft, nontender, and nondistended. Bowel sounds are decreased. The patient receives an intravenous infusion of a heme preparation that leads to rapid resolution of her symptoms. The improvement in symptoms is most likely due to treatment-induced downregulation of which of the following enzymes?

A. Aminolevulinate dehydratase
B. Aminolevulinate synthase
C. Bilirubin glucuronyl transferase
D. Ferrochelatase
E. Porphobilinogen deaminase

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Item 12 of 40
Question Id: 1338

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- A. Aminolevulinate dehydratase [9%]
- ✔ B. Aminolevulinate synthase [52%]
- C. Bilirubin glucuronyl transferase [4%]
- D. Ferrochelatase [12%]
- E. Porphobilinogen deaminase [19%]

Omitted
Correct answer
B

52%
Answered correctly

3 Seconds
Time Spent

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Explanation

This patient with neurologic symptoms (eg, tingling, difficulty concentrating) and recurrent episodes of nonspecific abdominal pain likely has **acute**

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Explanation

This patient with neurologic symptoms (eg, tingling, difficulty concentrating) and recurrent episodes of nonspecific abdominal pain likely has **acute intermittent porphyria** (AIP), an autosomal dominant disease characterized by **porphobilinogen (PBG) deaminase** deficiency. Management of AIP attacks includes infusion of hemin, which downregulates hepatic **aminolevulinate (ALA) synthase** (rate-limiting enzyme in hepatic pathway of heme synthesis).

Heme, a porphyrin, is synthesized in the liver for use in the cytochrome p450 enzyme system and in the bone marrow for hemoglobin use (these 2 synthesis pathways are regulated differently). A deficiency in any of the enzymes responsible for porphyrin synthesis can result in porphyria. Clinical manifestations result from the accumulation of porphyrin precursors in blood, tissues, and urine. AIP attacks, which are characterized by acute abdominal pain and neurologic symptoms, are due to accumulation of **ALA** and **PBG**, generally resulting from a combination of 2 factors:

- PBG deaminase deficiency (inherited)
- ALA synthase induction, typically precipitated by certain medications (eg, phenobarbital, griseofulvin, phenytoin), alcohol use, smoking, progesterone (eg, puberty), or a low-calorie diet (as seen with this patient)

Glucose or **hemin** inhibit ALA synthase and are used in AIP management. PBG deaminase deficiency by itself is generally not sufficient for development of AIP attacks (many patients with PBG deaminase deficiency are asymptomatic), and PBG deaminase enzyme activity is not directly affected by hemin infusion **(Choice E)**.

(Choices A and D) Deficiencies of ALA dehydratase and ferrochelatase (inhibited by lead) are seen with lead poisoning. Ferrochelatase deficiency is also seen with erythropoietic protoporphyria, characterized by cutaneous photosensitivity beginning in early childhood.

(Choice C) Bilirubin glucuronyl transferase is a hepatic enzyme that is responsible for the conjugation of bilirubin (byproduct of heme catabolism) with glucuronide, a polar molecule that improves bilirubin solubility for subsequent biliary excretion. A decrease in glucuronyl transferase activity results in unconjugated hyperbilirubinemia.

of heme synthesis).

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- PBG deaminase deficiency (inherited)
- ALA synthase induction, typically precipitated by certain medications (eg, phenobarbital, griseofulvin, phenytoin), alcohol use, smoking, progesterone (eg, puberty), or a low-calorie diet (as seen with this patient)

Glucose or **hemin** inhibit ALA synthase and are used in AIP management. PBG deaminase deficiency by itself is generally not sufficient for development of AIP attacks (many patients with PBG deaminase deficiency are asymptomatic), and PBG deaminase enzyme activity is not directly affected by hemin infusion **(Choice E)**.

(Choices A and D) Deficiencies of ALA dehydratase and ferrochelatase (inhibited by lead) are seen with lead poisoning. Ferrochelatase deficiency is also seen with erythropoietic protoporphyria, characterized by cutaneous photosensitivity beginning in early childhood.

(Choice C) Bilirubin glucuronyl transferase is a hepatic enzyme that is responsible for the conjugation of bilirubin (byproduct of heme catabolism) with glucuronide, a polar molecule that improves bilirubin solubility for subsequent biliary excretion. A decrease in glucuronyl transferase activity results in unconjugated hyperbilirubinemia.

Educational objective:
Acute intermittent porphyria attacks are due to the accumulation of aminolevulinate (ALA) and porphobilinogen (PBG), resulting from inherited PBG deaminase deficiency combined with ALA synthase induction (typically due to certain medications, alcohol use, or a low-calorie diet). Management with glucose or hemin inhibits ALA synthase activity.

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Item 13 of 40
Question Id: 1335

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A 3-day-old boy is brought to the office due to poor feeding, vomiting, and progressive lethargy. The parents also report that his diapers have a "burnt sugar smell" differing from their previous children's diapers. The mother and infant were discharged from the hospital yesterday after a normal pregnancy and spontaneous vaginal delivery. The mother is exclusively breastfeeding. Her other 2 children are healthy and have no medical problems. Physical examination shows a lethargic infant with dry mucous membranes and generalized hypertonia. Which of the following should be restricted from this infant's diet?

A. Galactose
B. Leucine
C. Methionine
D. Phenylalanine
E. Tyrosine

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Item 13 of 40
Question Id: 1335

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A 3-day-old boy is brought to the office due to poor feeding, vomiting, and progressive lethargy. The parents also report that his diapers have a "burnt sugar smell" differing from their previous children's diapers. The mother and infant were discharged from the hospital yesterday after a normal pregnancy and spontaneous vaginal delivery. The mother is exclusively breastfeeding. Her other 2 children are healthy and have no medical problems. Physical examination shows a lethargic infant with dry mucous membranes and generalized hypertonia. Which of the following should be restricted from this infant's diet?

- A. Galactose [8%]
- ✔ B. Leucine [71%]
- C. Methionine [2%]
- D. Phenylalanine [14%]
- E. Tyrosine [2%]

Omitted
Correct answer
B

71%
Answered correctly

2 Seconds
Time Spent

11/07/2018
Last Updated

Explanation

This infant has symptoms typical of **maple syrup urine disease** (MSUD), an autosomal recessive inborn error of metabolism due to branched-chain α-ketoacid dehydrogenase complex (BCKDC) deficiency. This enzyme normally allows for the breakdown of **leucine**, **isoleucine**, and

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Explanation

This infant has symptoms typical of **maple syrup urine disease** (MSUD), an autosomal recessive inborn error of metabolism due to branched-chain α-ketoacid dehydrogenase complex (BCKDC) deficiency. This enzyme normally allows for the breakdown of **leucine**, **isoleucine**, and **valine** into substrates for entry into the TCA cycle.

BCKDC deficiency is **neurotoxic** primarily due to elevated levels of leucine. Infants present in the first few days of life with progressive irritability, poor feeding, lethargy, and increased muscle tone. The urine characteristically has a sweet, **"maple syrup" odor**. Diagnosis can be confirmed by the presence of **elevated branched-chain amino acid levels**. Therapy consists of **dietary restriction** of branched-chain amino acids, but patients remain at lifelong risk for neurotoxicity in the setting of intercurrent illnesses and fasting.

(Choice A) Galactosemia is an autosomal recessive disorder due to galactose-1-phosphate uridyltransferase deficiency. The buildup of galactose (normally found in breast milk and regular infant formula) leads to neonatal jaundice, cataracts, hepatomegaly, and frequently *Escherichia coli* sepsis. Dietary restriction of galactose is the mainstay of treatment.

(Choice C) Homocystinuria is an autosomal recessive disorder marked by a defect in cystathionine β-synthase, resulting in elevated levels of homocysteine and methionine. Restriction of methionine for these patients is one aspect of therapy.

(Choice D) Phenylketonuria is an autosomal recessive disorder characterized by phenylalanine hydroxylase deficiency, leading to hyperphenylalaninemia. Untreated patients develop intellectual disability, seizures, decreased hair/skin pigmentation, and a "musty" odor.

(Choice E) Dietary tyrosine restriction may be beneficial for patients with hypertyrosinemia (progressive liver and renal disease) or alkaptonuria (pigmented osteoarthritis).

Educational objective:
Maple syrup urine disease classically presents with irritability, dystonia, poor feeding, and a "maple syrup" scent to the patient's urine within the first few days of life. Dietary restriction of branched-chain amino acids (eg, leucine, isoleucine, valine) is the hallmark of treatment.

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Item 14 of 40
Question Id: 1023

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A 5-month-old boy is brought to the office due to poor feeding. His mother says that he has difficulty holding his head up while breastfeeding and his suckling seems weaker than it used to be. His current weight is between the 5th-10th percentile, and length and head circumference are tracking along the 25th percentile. Physical examination shows hepatomegaly and hypotonia in all 4 limbs. Cardiac auscultation reveals a gallop rhythm, and chest x-ray shows severe cardiomegaly. Muscle biopsy shows enlarged lysosomes containing periodic acid-Schiff (PAS)-positive material. Which of the following enzymes is most likely deficient in this patient?

A. Acid α-glucosidase
B. Debrancher enzyme
C. Galactokinase
D. Glucose-6-phosphatase
E. Glycogen phosphorylase
F. Pyruvate kinase

Submit

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Item 14 of 40
Question Id: 1023

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A 5-month-old boy is brought to the office due to poor feeding. His mother says that he has difficulty holding his head up while breastfeeding and his suckling seems weaker than it used to be. His current weight is between the 5th-10th percentile, and length and head circumference are tracking along the 25th percentile. Physical examination shows hepatomegaly and hypotonia in all 4 limbs. Cardiac auscultation reveals a gallop rhythm, and chest x-ray shows severe cardiomegaly. Muscle biopsy shows enlarged lysosomes containing periodic acid-Schiff (PAS)-positive material. Which of the following enzymes is most likely deficient in this patient?

- ✔ A. Acid α-glucosidase [56%]
- B. Debrancher enzyme [14%]
- C. Galactokinase [4%]
- D. Glucose-6-phosphatase [8%]
- E. Glycogen phosphorylase [12%]
- F. Pyruvate kinase [2%]

Omitted
Correct answer
A

56%
Answered correctly

3 Seconds
Time Spent

11/14/2018
Last Updated

Explanation

This patient most likely has glycogen storage disease type II (**Pompe disease**). This condition is caused by deficiency of **acid α-glucosidase**

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2/6/2019

Explanation

This patient most likely has glycogen storage disease type II (**Pompe disease**). This condition is caused by deficiency of **acid α-glucosidase** (acid maltase), an enzyme responsible for breaking down glycogen within the acidic environment of lysosomes. Although most glycogen is degraded in the cytoplasm, a small amount is inadvertently engulfed by lysosomes, especially in cells containing high amounts of glycogen such as hepatocytes and myocytes. As such, deficiency of acid maltase results in pathologic accumulation of glycogen within liver and muscle lysosomes. Cardiac and skeletal muscle are particularly susceptible, as the ballooning lysosomes interfere with contractile function.

The classic form of the disease presents in early infancy with marked **cardiomegaly**, severe generalized **hypotonia**, macroglossia, and hepatomegaly. Blood glucose levels are normal, unlike with glycogen storage diseases that primarily affect the liver (eg, von Gierke). A key distinguishing feature is that muscle biopsy will show accumulation of **glycogen in lysosomes**.

(Choices B, D, and E) Other glycogen storage diseases are caused by deficiencies of glucose-6-phosphatase, glycogen phosphorylase, and debrancher enzyme. However, glycogen accumulation within lysosomal vacuoles is specific for acid α-glucosidase deficiency.

(Choice C) Galactokinase catalyzes the phosphorylation of galactose to galactose-1-phosphate in the first committed step of **galactose catabolism**. Galactokinase deficiency causes neonatal cataract formation due to accumulation of galactitol in the lens.

(Choice F) Pyruvate kinase deficiency causes chronic hemolytic anemia, splenomegaly, and iron overload as a result of impaired erythrocyte survival.

Educational objective:
Acid maltase (α-glucosidase) deficiency presents in early infancy with cardiomegaly, macroglossia, and profound muscular hypotonia. Abnormal glycogen accumulation within lysosomal vesicles is seen on muscle biopsy.

References

- Lysosomal dysfunction in muscle with special reference to glycogen storage disease type II.

A group of investigators is studying the mechanisms involved in cancer pathogenesis. Their research focuses on the intracellular signaling cascades that begin after receptor tyrosine kinases are activated by their respective ligands. They find that interaction of a certain growth factor with its receptor leads to the following sequence of events:

Binding of growth factor

↓

Autophosphorylation of tyrosine residues

↓

Activation of phosphoinositide 3-kinase

↓

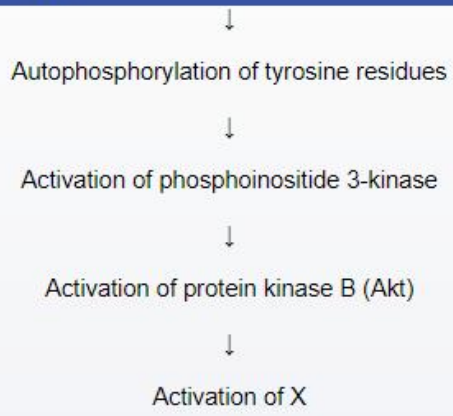
Activation of protein kinase B (Akt)

↓

Activation of X

Which of the following is the most likely direct effect of X upon activation?

A. Ca^{2+} efflux from endoplasmic reticulum
B. cAMP accumulation
C. Dimerization of STAT proteins
D. Rapid decrease in cGMP levels



Which of the following is the most likely direct effect of X upon activation?

A. Ca^{2+} efflux from endoplasmic reticulum
B. cAMP accumulation
C. Dimerization of STAT proteins
D. Rapid decrease in cGMP levels
E. Translocation to the nucleus and gene transcription

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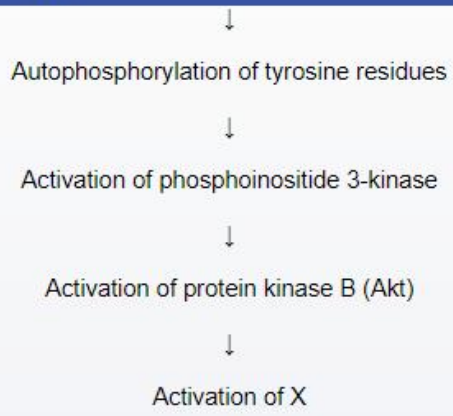

Which of the following is the most likely direct effect of X upon activation?

- A. Ca^{2+} efflux from endoplasmic reticulum [16%]
- B. cAMP accumulation [8%]
- C. Dimerization of STAT proteins [16%]
- D. Rapid decrease in cGMP levels [3%]
- ✔ E. Translocation to the nucleus and gene transcription [55%]

Omitted
Correct answer

55%
Answered correctly

8 Seconds
Time Spent

08/24/2018
Last Updated

Explanation

Growth factors can stimulate cell proliferation by altering the expression of certain genes in the nucleus. After a growth factor binds to its cell membrane receptor, signal transduction systems transfer the signal to the nucleus. Examples of signal transduction systems include:

1. MAP-kinase pathway
2. PI3K/Akt/mTOR pathway
3. Inositol phospholipid pathway
4. cAMP pathway
5. JAK/STAT pathway

The PI3K/Akt/mTOR pathway is an intracellular signaling pathway that is important for cellular proliferation. This pathway is typically activated when a growth factor binds to its receptor tyrosine kinase, causing auto-phosphorylation of specific tyrosine residues within the receptor. These phosphotyrosine residues activate phosphoinositide 3-kinase (PI3K), which then phosphorylates PIP_2 found in the plasma membrane to PIP_3. This leads to activation of a protein called Akt (or protein kinase B), a serine/threonine-specific protein kinase. Subsequently, Akt activates mTOR (mammalian target of rapamycin), which translocates to the nucleus to induce genes involved in cell survival, anti-apoptosis, and angiogenesis. mTOR activation is inhibited by PTEN (phosphatase and tensin homolog), a tumor suppressor protein that removes the phosphate group from PIP_3.

The PI3K/Akt/mTOR pathway is highly active in many cancer cells as a result of mutations causing increased activity of PI3K or Akt or loss of function of PTEN. Mutations involving certain growth factor receptors (eg, epidermal growth factor) can also enhance activity. Several drugs targeting this pathway (eg, mTOR inhibitors including rapamycin [sirolimus]) have shown benefit in treating certain cancers.

(Choice A) The inositol phospholipid pathway utilizes G_q proteins that stimulate hydrolysis of membrane-bound phospholipids via phospholipase C. This pathway increases cytoplasmic Ca^{2+} levels through IP_3- mediated Ca^{2+} efflux from the endoplasmic reticulum.

(Choice B) Some G protein-coupled receptors utilize cAMP as a second messenger. For example, β-adrenergic receptors activate G_s, which in turn activates adenylate cyclase and increases intracellular cAMP levels.

This leads to activation of a protein called Akt (or protein kinase B), a serine/threonine-specific protein kinase. Subsequently, Akt activates mTOR (mammalian target of rapamycin), which translocates to the nucleus to induce genes involved in cell survival, anti-apoptosis, and angiogenesis. mTOR activation is inhibited by PTEN (phosphatase and tensin homolog), a tumor suppressor protein that removes the phosphate group from PIP_3.

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(Choice A) The inositol phospholipid pathway utilizes G_q proteins that stimulate hydrolysis of membrane-bound phospholipids via phospholipase C. This pathway increases cytoplasmic Ca^{2+} levels through IP_3- mediated Ca^{2+} efflux from the endoplasmic reticulum.

(Choice B) Some G protein-coupled receptors utilize cAMP as a second messenger. For example, β-adrenergic receptors activate G_s, which in turn activates adenylate cyclase and increases intracellular cAMP levels.

(Choice C) Most cytokine receptors lack intrinsic kinase activity and instead transduce their signals through associated intracellular tyrosine kinases known as Janus kinases (JAK). These in turn activate cytoplasmic STAT (signal transducer and activator of transcription) proteins, which dimerize and translocate to the nucleus.

(Choice D) Phosphodiesterases (PDE) degrade cGMP by hydrolyzing it into GMP. PDE inhibitors prevent the degradation of cGMP, thereby enhancing and prolonging its effects. For example, sildenafil enhances the vasodilatory effects of cGMP within the corpus cavernosum by inhibiting PDE 5.

Educational objective:
The PI3K/Akt/mTOR pathway is an intracellular signaling pathway important for anti-apoptosis, cellular proliferation, and angiogenesis. Mutations in growth factor receptors, Akt, mTOR, or PTEN that enhance the activity of this pathway contribute to cancer pathogenesis.

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Item 16 of 40
Question Id: 1047

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A 78-year-old man comes to the office due to a one-month history of progressive dyspnea, generalized weakness, fatigue, and palpitations. He also reports tingling and numbness in both lower limbs. His daughter, who is visiting from another state, adds that since his wife's death a year ago, the patient has not been taking care of himself. Blood pressure is 105/50 mm Hg and pulse is 104/min. Cardiovascular examination shows a displaced apical impulse at the sixth intercostal space, a third heart sound, and high-volume, collapsing carotid pulses. Bilateral basal crackles, 2+ bilateral pedal edema, and mild hepatomegaly are also present. Neurologic examination shows decreased light touch and vibration sense in the feet, with decreased knee and ankle reflexes bilaterally. Laboratory evaluation shows normal blood counts. Deficiency of which of the following nutrients is most likely responsible for this patient's symptoms?

- A. Ascorbic acid
- B. Cobalamin
- C. Niacin
- D. Pyridoxine
- E. Retinol
- F. Riboflavin
- G. Thiamine

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Item 16 of 40
Question Id: 1047

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- A. Ascorbic acid [1%]
- B. Cobalamin [35%]
- C. Niacin [3%]
- D. Pyridoxine [11%]
- E. Retinol [0%]
- F. Riboflavin [1%]
- ✔ G. Thiamine [45%]

Omitted
Correct answer
G

45%
Answered correctly

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Explanation

Thiamine deficiency causes infantile and adult beriberi as well as **Wernicke-Korsakoff syndrome** (confusion, ataxia, oculomotor abnormalities, and permanent memory deficits). Manifestations of infantile beriberi appear at age 2-3 months and include a fulminant cardiac syndrome with cardiomegaly, tachycardia, cyanosis, dyspnea, and vomiting. Adult **beriberi** is categorized as dry or wet depending on cardiac involvement. Dry beriberi is characterized by symmetrical **peripheral neuropathy** of the distal extremities, with resulting sensory and motor impairments. Wet beriberi includes the addition of **cardiac involvement** (cardiomyopathy, high-output congestive heart failure, peripheral edema, and tachycardia). Central nervous system involvement (ie, Wernicke-Korsakoff syndrome) occurs primarily in alcoholics.

(Choice A) Ascorbic acid (vitamin C) deficiency causes scurvy (petechial hemorrhages, gingival swelling, impaired wound healing, and weakened immune response).

(Choice B) Vitamin B_{12} (cobalamin) deficiency typically presents as macrocytic anemia. Neurologic involvement can cause upper and lower motor neuron dysfunction and sensory peripheral neuropathy.

(Choice C) Niacin deficiency causes pellagra (dementia, dermatitis, and diarrhea).

(Choice D) Pyridoxine (vitamin B_6) deficiency is characterized by cheilosis, glossitis, dermatitis, and affective symptoms.

(Choice E) Vitamin A (retinol) deficiency is characterized by night blindness, xerophthalmia, and vulnerability to infection (especially measles).

(Choice F) Common manifestations of vitamin B_2 (riboflavin) deficiency include cheilosis, stomatitis, glossitis, anemia, and seborrheic dermatitis.

Educational objective:
Thiamine deficiency causes beriberi and Wernicke-Korsakoff syndrome. Dry beriberi is characterized by symmetrical peripheral neuropathy; wet beriberi includes the addition of high-output congestive heart failure.

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Item 17 of 40
Question Id: 12278

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A 54-year-old man comes to the emergency department with a 3-month history of fatigue and exertional dyspnea. He has early satiety and frequent upper abdominal discomfort. On physical examination, the patient has palpable splenomegaly but no lymphadenopathy. Laboratory tests are as follows:

Complete blood count	
Hemoglobin	9.2 mg/dL
Platelets	80,000/mm^3
Leukocytes	56,000/mm^3

Reverse transcription polymerase chain reaction is used to diagnose chronic myelogenous leukemia in this patient. Which of the following is most likely to be detected by this test?

A. Chromosomal position of the *BCR* and *ABL* genes
B. DNA rearrangement in the *BCR* promoter region
C. Fusion protein containing BCR and ABL domains
D. Messenger RNA transcript containing *BCR* and *ABL* exons
E. Point mutation in the *ABL* enhancer region

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Item 17 of 40
Question Id: 12278

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

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Complete blood count	
Hemoglobin	9.2 mg/dL
Platelets	80,000/mm^3
Leukocytes	56,000/mm^3

Reverse transcription polymerase chain reaction is used to diagnose chronic myelogenous leukemia in this patient. Which of the following is most likely to be detected by this test?

A. Chromosomal position of the *BCR* and *ABL* genes [26%]
B. DNA rearrangement in the *BCR* promoter region [10%]
C. Fusion protein containing BCR and ABL domains [30%]
✔ D. Messenger RNA transcript containing *BCR* and *ABL* exons [28%]
E. Point mutation in the *ABL* enhancer region [3%]

Omitted
Correct answer

28%
Answered correctly

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09/04/2018
Last Updated

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Explanation

Reverse transcription polymerase chain reaction (RT-PCR) is used to detect and quantify levels of **messenger RNA** (mRNA) in a sample. It is similar to regular PCR in that it uses sequence-specific primers, thermostable DNA polymerase, and a pool of deoxyribonucleoside triphosphates to amplify a DNA template. In RT-PCR, this template is generated by the action of **reverse transcriptase** on the mRNA sample, producing a complementary DNA (cDNA) strand that can then be amplified by PCR. Because cDNA is complementary to the mRNA sequence, it contains the **exons** of a gene along with the 5′ and 3′ untranslated regions.

Chronic myelogenous leukemia (CML) is characterized by uncontrolled proliferation of the myeloid stem cell line due to a chromosomal translocation. This translocation causes the *BCR* gene on chromosome 22 to fuse with the *ABL* gene on chromosome 9, forming the *BCR-ABL* fusion gene. The BCR-ABL fusion protein product is a constitutively active tyrosine kinase that accelerates cell division and increases genetic instability. RT-PCR can be used to identify mRNA transcribed from the *BCR-ABL* fusion gene and therefore diagnose CML.

(Choice A) Fluorescence in situ hybridization (FISH) techniques allow direct localization of genes to their respective chromosomes by using a labeled DNA probe complementary to the sequence of interest.

(Choices B and E) RT-PCR amplification uses an mRNA template, so it cannot detect changes in the parts of the gene that are not transcribed (eg, promoter and enhancer regions). Other PCR techniques that use chromosomal DNA can detect changes in these nontranscribed regions.

(Choice C) RT-PCR is used to detect levels of mRNA expression; it does not identify proteins. A Western blot study can detect the BCR-ABL protein by using monoclonal antibodies directed against BCR or ABL.

Educational objective:
Reverse transcription polymerase chain reaction (RT-PCR) is used to detect and quantify levels of mRNA in a sample. It uses reverse transcription to create a complementary DNA template that is then amplified using the standard PCR procedure. RT-PCR can be used to diagnose chronic myelogenous leukemia by identifying an mRNA transcript containing both *BCR* and *ABL* exons in affected cells.

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Item 18 of 40
Question Id: 1503

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A 38-year-old man comes to the office due to pain in multiple joints. He has a 5-year history of lumbar pain and a 2-year history of bilateral knee pain. The patient works in construction and his pain is worst after a long day on his feet. He has taken ibuprofen intermittently, but the pain is no longer tolerable. The patient has a paternal aunt with osteoarthritis. Physical examination shows blue-black spots on his sclerae and diffuse darkening of the auricular helices. Which of the following is the most likely cause of this patient's arthritis?

A. Homogentisic acid dioxygenase deficiency
B. Hyperuricemia
C. Multifactorial articular cartilage failure
D. Recent infection with *Salmonella*
E. Tyrosinase deficiency

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Item 18 of 40
Question Id: 1503

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

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- ✔ A. Homogentisic acid dioxygenase deficiency [69%]
- B. Hyperuricemia [3%]
- C. Multifactorial articular cartilage failure [18%]
- D. Recent infection with *Salmonella* [0%]
- E. Tyrosinase deficiency [6%]

Omitted
Correct answer
A

69%
Answered correctly

3 Seconds
Time Spent

11/06/2018
Last Updated

Explanation

Alkaptonuria is a relatively benign childhood disorder that is marked by severe **arthritis** in adult life. This **autosomal-recessive** disorder is caused by **deficiency of homogentisic acid dioxygenase**, which normally metabolizes homogentisic acid into maleylacetoacetate. Accumulated homogentisic acid causes pigment deposits in **connective tissue** throughout the body. During adulthood, these **blue-black**

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Alkaptonuria is a relatively benign childhood disorder that is marked by severe **arthritis** in adult life. This **autosomal-recessive** disorder is caused by **deficiency of homogentisic acid dioxygenase**, which normally metabolizes homogentisic acid into maleylacetoacetate. Accumulated homogentisic acid causes pigment deposits in **connective tissue** throughout the body. During adulthood, these **blue-black deposits** become apparent in the sclerae and ear cartilage. Deposits also occur in the large joints and spine, causing ankylosis, motion restriction, and significant pain. A distinctive characteristic of alkaptonuria is that the urine of these patients turns black when exposed to air due to oxidization of homogentisic acid.

(Choice B) Hyperuricemia can cause acute monoarticular gouty arthritis due to urate crystal deposition in joints (usually the great toe or knee). These acute attacks resolve in days to weeks and are not associated with connective tissue hyperpigmentation.

(Choice C) Osteoarthritis is due to combined genetic, metabolic, and mechanical factors that result in defects in articular cartilage. Polyarticular joint involvement of the fingers (including **Heberden** and Bouchard nodes), knees, hips, and spine classically occur. Joint pain typically peaks in the afternoon or evening after activity, but osteoarthritis is not associated with the blue-black deposits.

(Choice D) Reactive arthritis can occur following enteric or genitourinary infections with organisms such as *Salmonella*, *Shigella*, *Campylobacter*, and *Chlamydia*. The typical pattern is asymmetric involvement of lower extremity joints accompanied by enthesitis (inflammation at insertion of tendons), conjunctivitis, and urethritis. Reactive arthritis has no associated skin findings in contrast to alkaptonuria.

(Choice E) Albinism is caused by defects in biosynthesis and distribution of melanin. Melanocytes synthesize melanin from tyrosine via the enzyme tyrosinase.

Educational objective:
Alkaptonuria is an autosomal-recessive disorder caused by a deficiency of homogentisic acid dioxygenase, an enzyme involved in tyrosine metabolism. Excess homogentisic acid causes diffuse blue-black deposits in connective tissues. Adults have sclerae and ear cartilage hyperpigmentation along with osteoarthropathy of the spine and large joints.

References

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Item 19 of 40
Question Id: 1470

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A 6-year-old African American boy is brought to the physician because of easy fatigability. Physical examination reveals splenomegaly, and his complete blood count shows mild anemia. Hemoglobin electrophoresis is performed at alkaline pH on a cellulose acetate strip. Findings for the patient are shown below compared to individuals with normal hemoglobin and known sickle cell disease.

Which of the following is the most likely cause of this patient's condition?

- A. Alpha globin gene deletion
- B. Missense mutation
- C. Nonsense mutation
- D. Silent mutation
- E. Trinucleotide expansion

Submit

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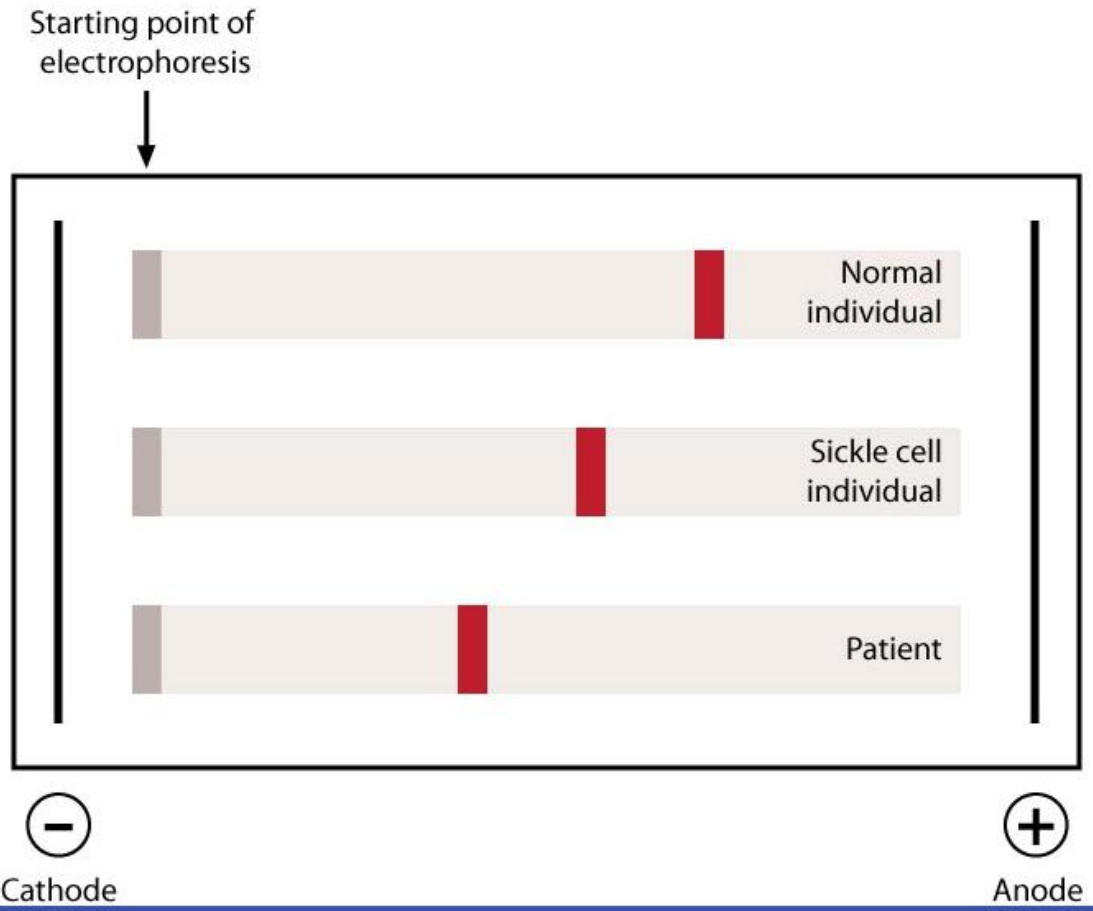
patient are shown below compared to individuals with normal hemoglobin and known sickle cell disease.



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Item 19 of 40
Question Id: 1470

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

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- C. Nonsense mutation
- D. Silent mutation
- E. Trinucleotide expansion

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Item 19 of 40
Question Id: 1470

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Which of the following is the most likely cause of this patient's condition?

A. Alpha globin gene deletion [23%]
✔ B. Missense mutation [55%]
C. Nonsense mutation [14%]
D. Silent mutation [0%]
E. Trinucleotide expansion [6%]

Omitted
Correct answer
B

55%
Answered correctly

2 Seconds
Time Spent

09/08/2018
Last Updated

Explanation

Hemoglobin electrophoresis is used to assess for different forms of hemoglobin in patients with suspected hemoglobinopathy. Normal hemoglobin consists primarily of **hemoglobin A** (HbA), which **migrates rapidly** toward the positive electrode (anode) because of its negative charge. Hemoglobin S (HbS) is an abnormal type of hemoglobin in which a nonpolar amino acid (valine) replaces a negatively charged amino

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Hemoglobin electrophoresis is used to assess for different forms of hemoglobin in patients with suspected hemoglobinopathy. Normal hemoglobin consists primarily of **hemoglobin A** (HbA), which **migrates rapidly** toward the positive electrode (anode) because of its negative charge. Hemoglobin S (HbS) is an abnormal type of hemoglobin in which a nonpolar amino acid (valine) replaces a negatively charged amino acid (glutamate) in the beta globin chain. This amino acid replacement decreases the negative charge on the HbS molecule, which causes **HbS** to move more **slowly** toward the anode. Similarly, hemoglobin C (HbC) has a glutamate residue replaced by lysine in the beta globin chain. Because lysine is a positively charged amino acid, **HbC** has even less total negative charge than HbS and moves **even more slowly** toward the anode. Both HbC and HbS result from **missense mutations**, a type of mutation in which a single base substitution results in a codon that codes for a different amino acid.

Patients with sickle cell disease have HbS mutations in both beta chains; those with HbC disease have HbC mutations involving both beta chains. Patients with hemoglobin SC disease have 1 HbS allele and 1 HbC allele and will have 2 hemoglobin bands on electrophoresis. This patient's electrophoresis results show a **single band** that **migrates less than the HbA and HbS** bands, meaning that he has **HbC disease**. Patients with HbC disease are typically asymptomatic and often have mild hemolytic anemia and splenomegaly.

(Choice A) Deletions involving the alpha globin genes cause alpha thalassemia, which results in imbalanced beta chain production and formation of beta tetramers (hemoglobin H) that migrate further than HbA during electrophoresis.

(Choice C) Nonsense mutations introduce a stop codon within gene sequences, resulting in the formation of truncated proteins. As a result of their decreased size, these proteins tend to move further during electrophoresis.

(Choice D) Silent mutations are point mutations that have no effect on the protein formed. A mutation from UCA to UCC does not result in any change in protein structure as both codons result in the placement of serine into the growing polypeptide chain.

(Choice E) Trinucleotide expansions increase the number of trinucleotide repeats within a gene, resulting in large, unstable proteins or alterations in the epigenetic effects. These proteins would tend to move less during electrophoresis due to their increased size. However, the hemoglobinopathies are not caused by trinucleotide expansions, as the hemoglobin genes do not contain trinucleotide repeat regions.

Because lysine is a positively charged amino acid, **HbC** has even less total negative charge than HbS and moves **even more slowly** toward the anode. Both HbC and HbS result from **missense mutations**, a type of mutation in which a single base substitution results in a codon that codes for a different amino acid.

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Educational objective:
Hemoglobin C is caused by a missense mutation that results in a glutamate residue being substituted by lysine in the beta globin chain. This results in an overall decrease in negative charge for the hemoglobin molecule. The speed of hemoglobin movement during gel electrophoresis is hemoglobin A > hemoglobin S > hemoglobin C.

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Question Id: 1470

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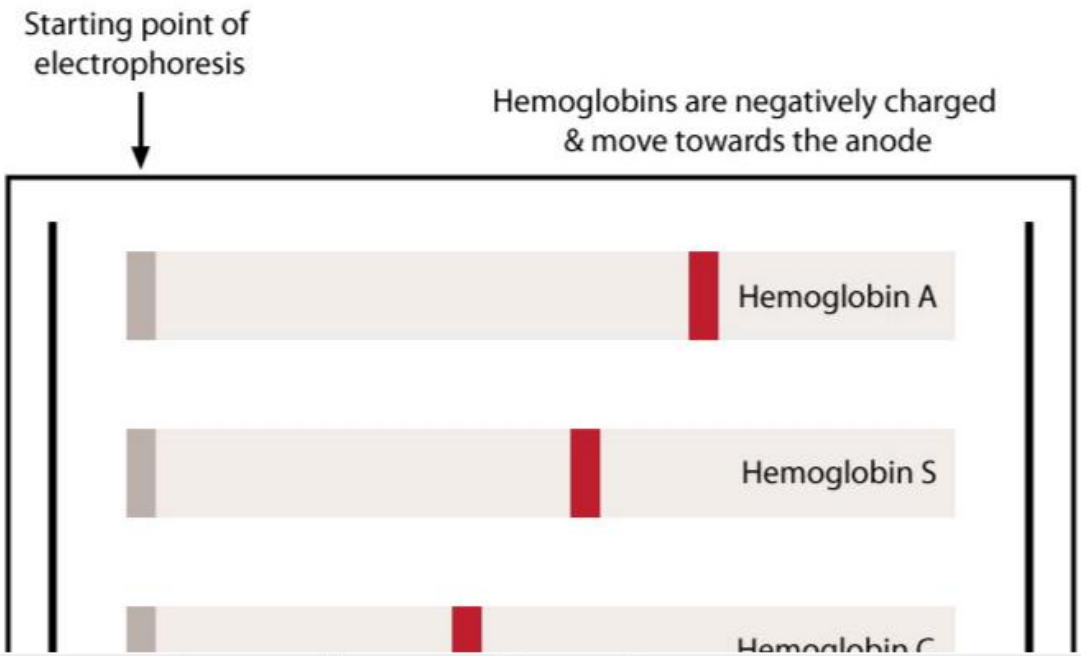
Exhibit Display

Hemoglobin electrophoresis



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their decreased size, these proteins tend to move further during electrophoresis.

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Item 19 of 40
Question Id: 1470

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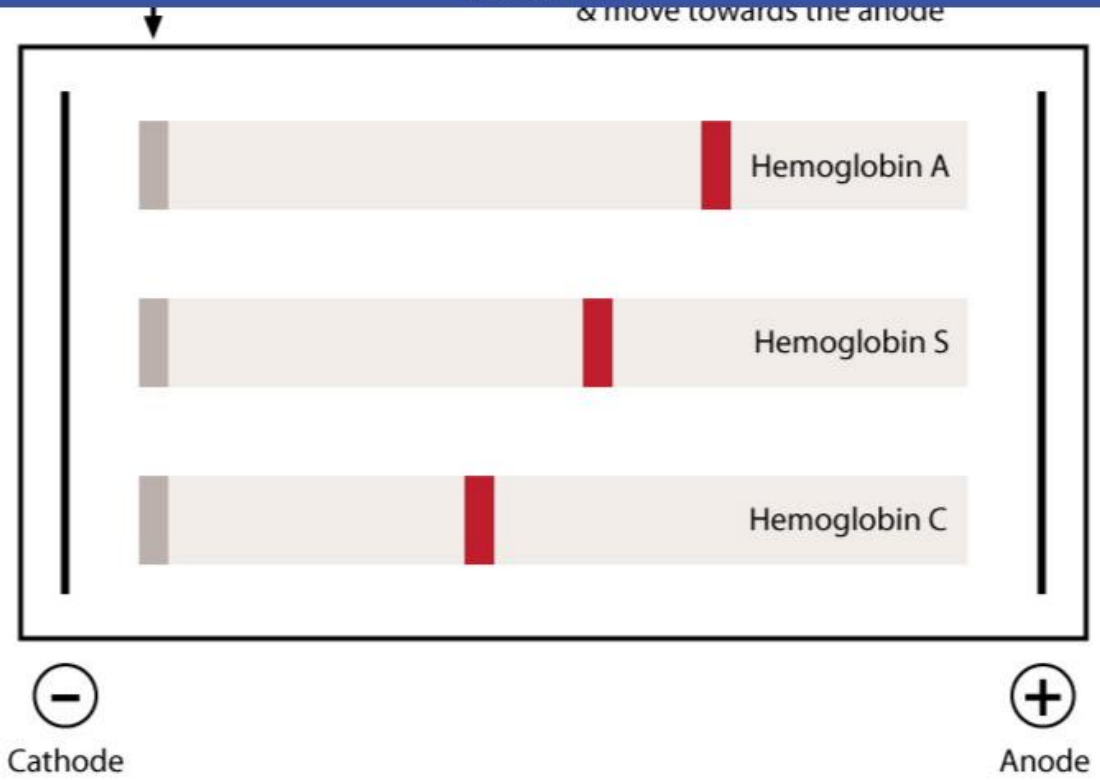
Exhibit Display



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Item 20 of 40
Question Id: 2044

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Molecular biologists undertake a series of experiments designed to classify proteins involved in various intracellular signaling pathways. During one of the experiments, a protein mixture obtained from a cell culture is separated by gel electrophoresis and subsequently transferred to a filter membrane. Labeled double-stranded DNA probes are then used to detect a specific protein of interest in the sample. Which of the following proteins is most likely to be detected by this method?

A. Ras
B. c-Jun
C. β1-adrenoreceptor
D. S-100
E. Adenylate cyclase

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Item 20 of 40
Question Id: 2044

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Molecular biologists undertake a series of experiments designed to classify proteins involved in various intracellular signaling pathways. During one of the experiments, a protein mixture obtained from a cell culture is separated by gel electrophoresis and subsequently transferred to a filter membrane. Labeled double-stranded DNA probes are then used to detect a specific protein of interest in the sample. Which of the following proteins is most likely to be detected by this method?

A. Ras [35%]
B. c-Jun [27%]
C. β1-adrenoreceptor [3%]
D. S-100 [13%]
E. Adenylate cyclase [19%]

Omitted
Correct answer
B

27%
Answered correctly

2 Seconds
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Explanation

Blotting technique	Substance detected	Type of probe
Northern	RNA	

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Explanation

Blotting technique	Substance detected	Type of probe
Northern	RNA	Single-stranded DNA or RNA (hybridization probe)
Southern	DNA	
Western	Protein	Antibody
Southwestern	DNA-binding protein	Double-stranded DNA

The Southern, Western, Northern, and Southwestern blot procedures are powerful techniques used to analyze and identify DNA fragments, proteins, mRNA, and DNA-bound proteins, respectively. The same basic technique underlies all of the blot procedures. First, the unknown sample is separated by gel electrophoresis. Separation occurs based on a molecule's size and charge. The separated molecules form bands on the gel that are then blotted onto a nitrocellulose membrane and incubated with a labeled probe to identify the specific DNA fragment, RNA molecule, or protein of interest.

Southwestern blots are used to identify and isolate proteins that bind DNA. In this technique, the target protein binds to a labeled, double-stranded DNA probe that is homologous to the protein's regulatory sequence. Of the molecules listed, c-Jun is the only DNA-binding protein. c-Jun and c-Fos are nuclear transcription factors that directly bind DNA via a leucine zipper motif. The genes that code for c-Jun and c-Fos are proto-oncogenes, genes that can become oncogenes following a mutation or with constitutive expression.

(Choice A) Ras is a proto-oncogene that codes for a membrane-bound G-protein. This G-protein acts as a secondary mediator for several hormones and cytokines that act on cell membrane receptors. Ras activation activates the MAP kinase pathway and ultimately affects

sample is separated by gel electrophoresis. Separation occurs based on a molecule's size and charge. The separated molecules form bands on the gel that are then blotted onto a nitrocellulose membrane and incubated with a labeled probe to identify the specific DNA fragment, RNA molecule, or protein of interest.

Southwestern blots are used to identify and isolate proteins that bind DNA. In this technique, the target protein binds to a labeled, double-stranded DNA probe that is homologous to the protein's regulatory sequence. Of the molecules listed, c-Jun is the only DNA-binding protein. c-Jun and c-Fos are nuclear transcription factors that directly bind DNA via a leucine zipper motif. The genes that code for c-Jun and c-Fos are proto-oncogenes, genes that can become oncogenes following a mutation or with constitutive expression.

(Choice A) Ras is a proto-oncogene that codes for a membrane-bound G-protein. This G-protein acts as a secondary mediator for several hormones and cytokines that act on cell membrane receptors. Ras activation activates the MAP kinase pathway and ultimately affects transcription. However, Ras itself does not bind directly to DNA.

(Choices C and E) The β1-adrenergic receptor is a classic Gs-protein-coupled receptor located in the cell membrane. It does not interact directly with DNA. Adenylyl cyclase is the enzyme that cleaves ATP to form cAMP, the second messenger associated with G_s-protein-coupled receptors. cAMP activates protein kinase A for further downstream signaling.

(Choice D) S-100 proteins are homodimeric calcium-binding proteins, similar in structure to calmodulin and important in intracellular functions such as protein phosphorylation and cell growth and differentiation. S-100 is a marker for cells of neural crest derivation (melanocytes and Schwann cells), as well as Langerhans cells and other dendritic cells.

Educational objective:
Southwestern blotting is used to detect DNA-binding proteins such as transcription factors, nucleases, and histones.

References

- Southwestern blotting in investigating transcriptional regulation.

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Item 21 of 40
Question Id: 1244

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A 24-year-old woman comes to the office for a preemployment medical evaluation. The patient has no known medical problems but reports that her skin bruises and scars easily. She says that most of her family members have a very "flexible" body, and her brother works in a circus as a contortionist. The patient takes no medications and has no allergies. She does not use tobacco, alcohol, or drugs. Physical examination findings are shown in the **exhibit**. This patient most likely has an inherited defect in which of the following proteins?

A. Collagen
B. Elastin
C. Fibrillin-1
D. Hyaluronic acid
E. Laminin
F. Proteoglycan

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Item 21 of 40
Question Id: 1244

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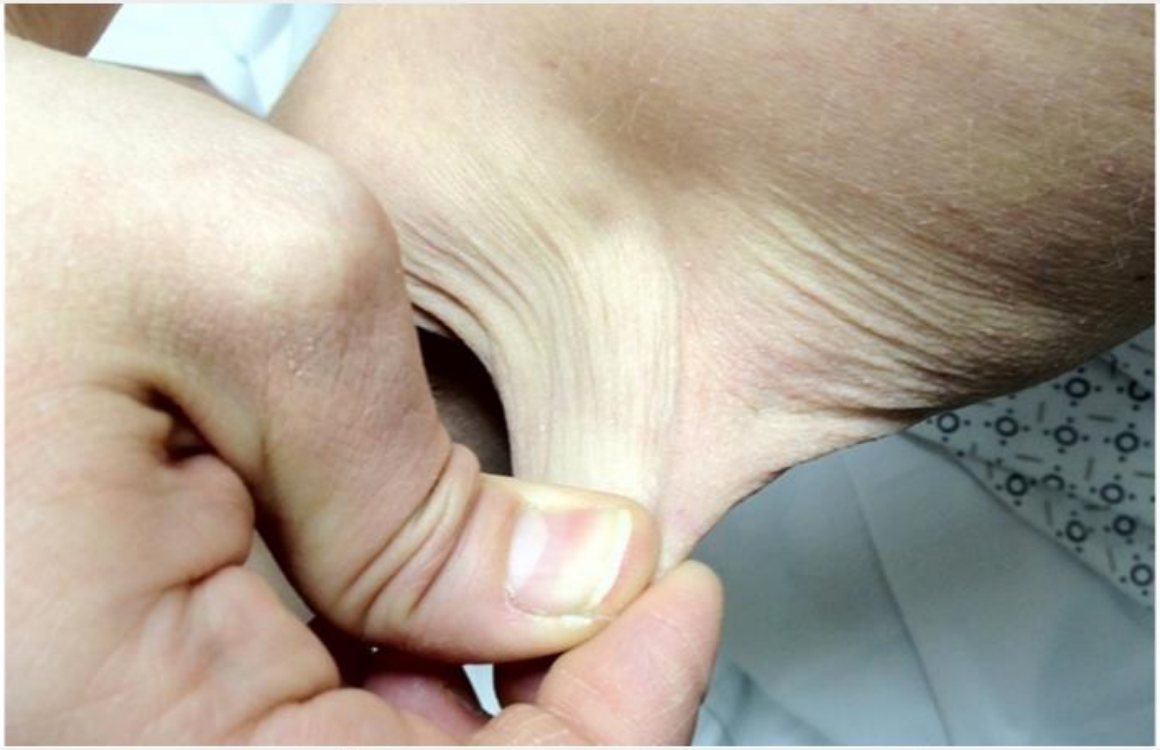
Exhibit Display

Exhibit 1 Exhibit 2



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Item 21 of 40
Question Id: 1244

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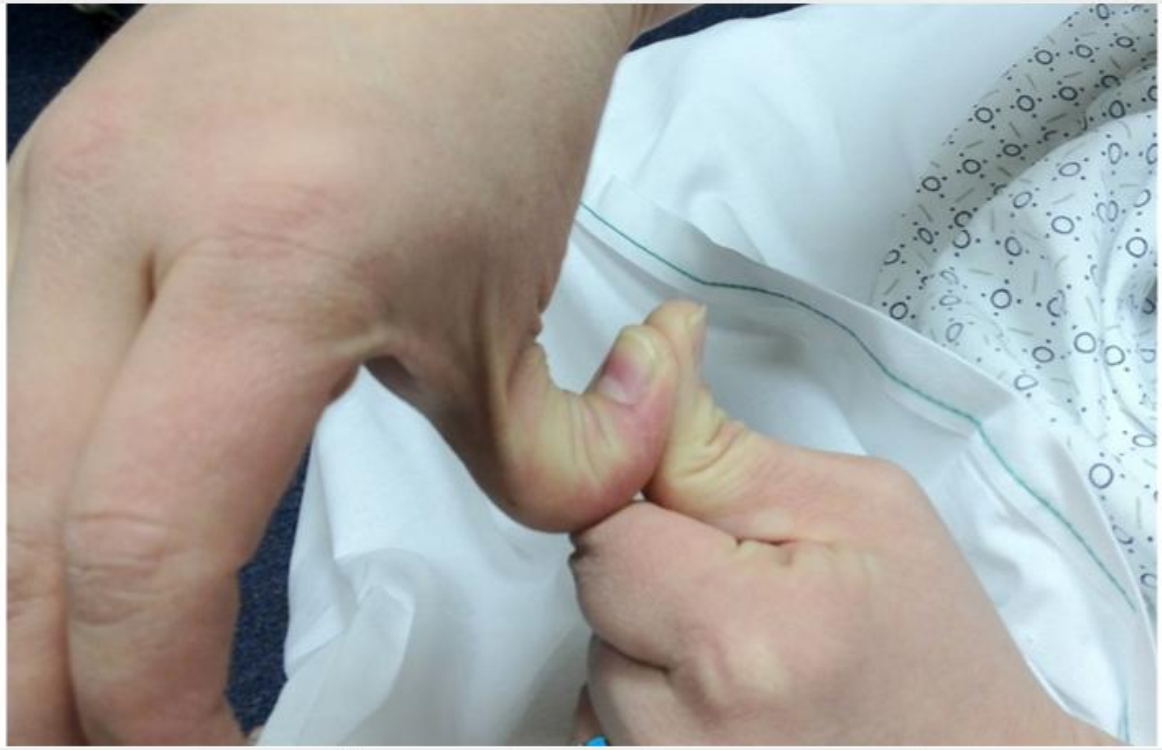
Exhibit Display

Exhibit 1 Exhibit 2



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Item 21 of 40
Question Id: 1244

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- A. Collagen [76%]
- B. Elastin [14%]
- C. Fibrillin-1 [8%]
- D. Hyaluronic acid [0%]
- E. Laminin [0%]
- F. Proteoglycan [0%]

Omitted
Correct answer
A

76%
Answered correctly

53 Seconds
Time Spent

02/06/2019
Last Updated

Explanation

Collagen synthesis

Block Time Remaining: 00:02:13
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Item 21 of 40
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Correct answer
A

76%
Answered correctly

53 Seconds
Time Spent

02/06/2019
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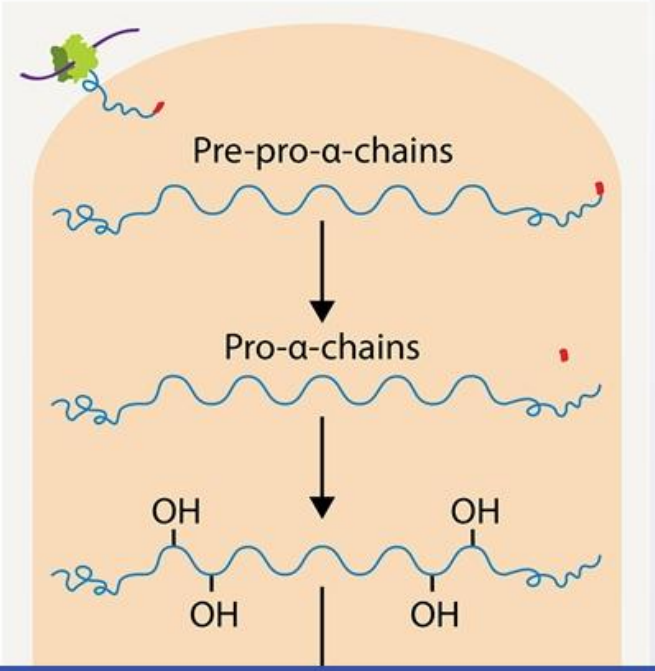
Explanation

Collagen synthesis

Signal sequence directs growing polypeptide chain into endoplasmic reticulum

Signal sequence is cleaved

Hydroxylation of selected proline & lysine residues **(vitamin C dependent)**



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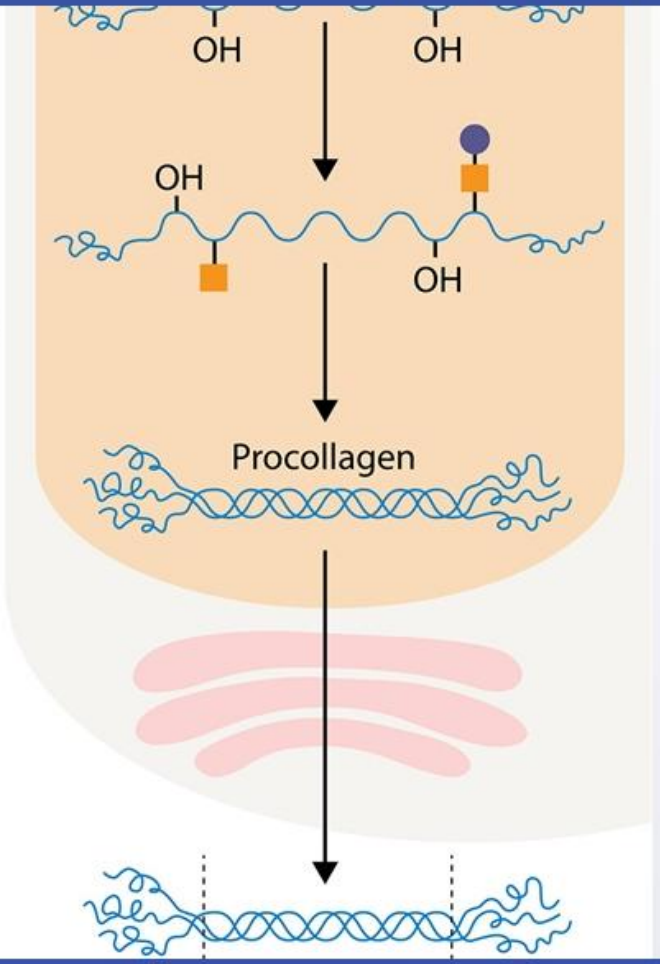
(vitamin C dependent)

Glycosylation of selected hydroxylysine residues

Galactose
Glucose

Assembly of pro-α-chains into **procollagen triple helix**

Procollagen transferred to Golgi apparatus & secreted into extracellular matrix



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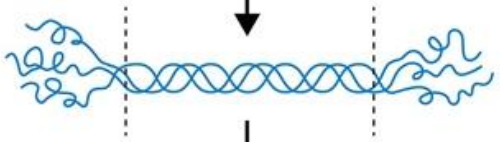
Procollagen transferred to Golgi apparatus & secreted into extracellular matrix



Terminal propeptides cleaved by N- & C- **procollagen peptidases**

Tropocollagen

Collagen molecules spontaneously assemble

Collagen fibrils

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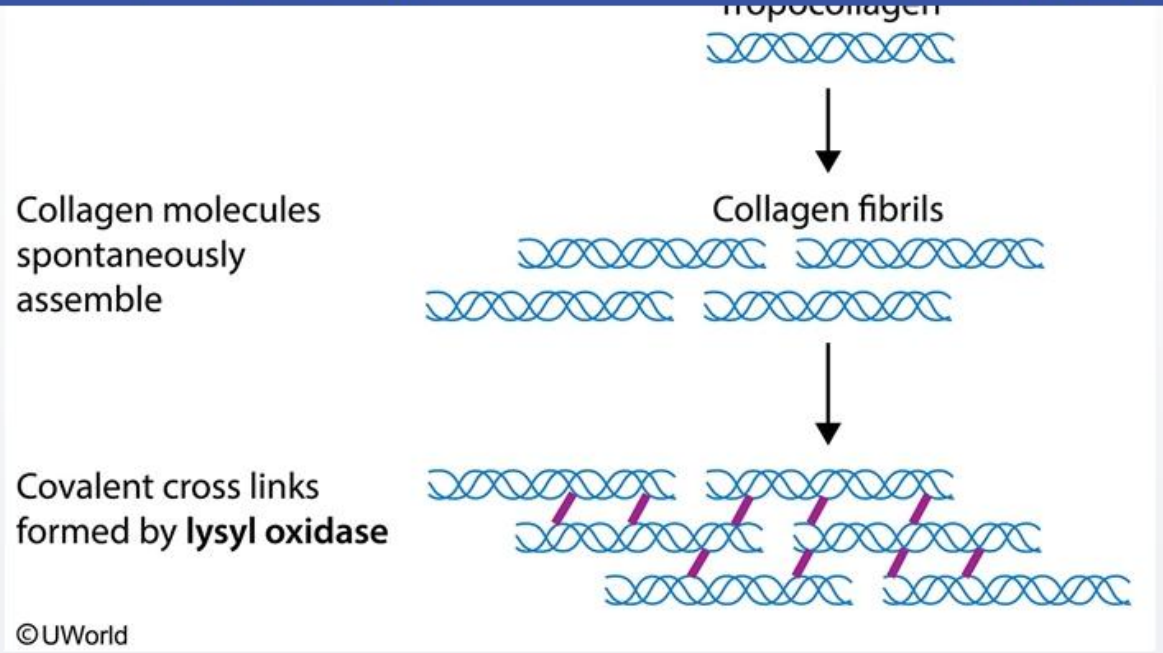
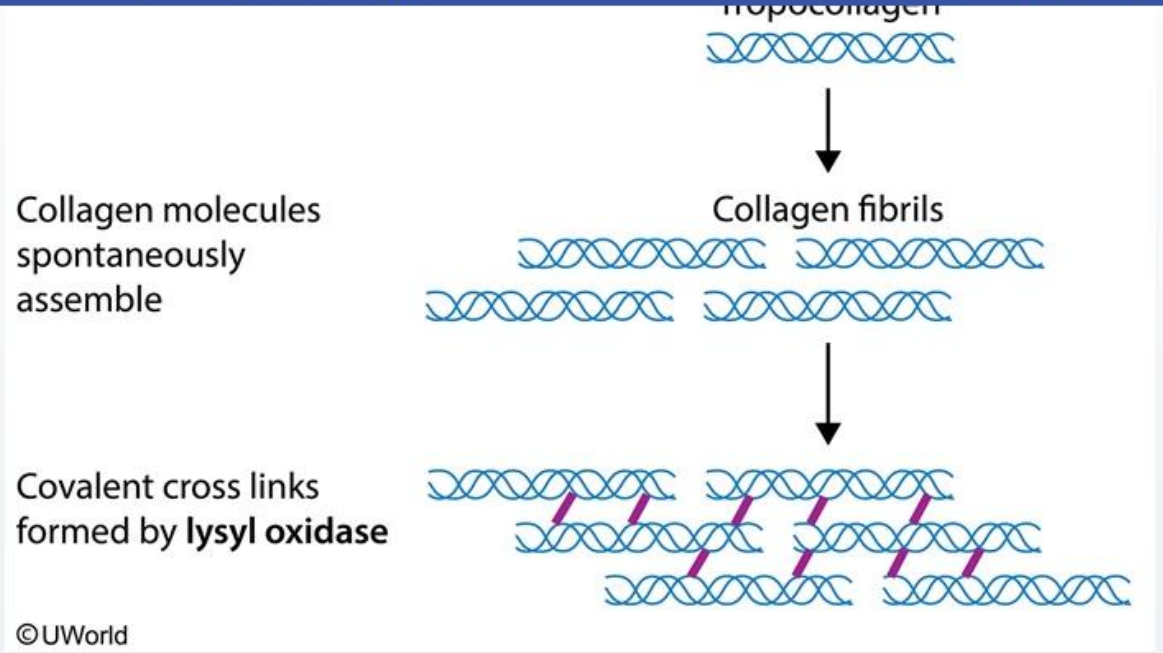


The extracellular matrix is a network of interstitial proteins that maintain normal tissue architecture. **Collagen** is a major component of **connective tissue** and consists of 3 polypeptide α chains held together by **hydrogen bonds** to form a ropelike triple helix structure (tropocollagen). **Lysyl oxidase** then forms covalent bonds between individual tropocollagen molecules, generating mature collagen fibers. The variation in amino acid sequences in the collagen α chains gives rise to collagen diversity in different tissues. Collagen types I, II, III, and V provide **tensile strength** in skin, bones, cartilage, tendons, and blood vessels.

Ehlers-Danlos syndrome (EDS) is a group of hereditary disorders involving a defect in collagen synthesis. EDS usually manifests clinically as **hypermobile joints**, **overelastic skin**, and fragile tissue susceptible to bruising, wounds, and hemarthrosis. Common mutations leading to EDS



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skin, bones, cartilage, tendons, and blood vessels.

Ehlers-Danlos syndrome (EDS) is a group of hereditary disorders involving a defect in collagen synthesis. EDS usually manifests clinically as **hypermobile joints**, **overelastic skin**, and fragile tissue susceptible to bruising, wounds, and hemarthrosis. Common mutations leading to EDS phenotypes include deficiencies of the lysyl hydroxylase and procollagen peptidase enzymes responsible for collagen synthesis.

(Choice B) Elastin, a fibrous protein in the connective tissue, is named for the elastic properties it imparts to skin, blood vessels, and lung alveoli. Elastin fibers can be stretched to several times their original length but will recoil when the stretching forces are withdrawn. Elastin is synthesized from the polypeptide precursor tropoelastin.

(Choice C) Fibrillin-1 is a major component of the microfibrils that form a sheath around elastin. Microfibrils are abundantly present in blood vessels and in the suspensory ligaments of the lens. Defects in the *fibrillin-1* gene cause classic autosomal dominant Marfan syndrome.

(Choice D) Hyaluronic acid is another major component of the soft tissue's extracellular matrix, including synovial fluid and skin. Exogenous injection can be used to restore viscoelasticity to the synovial fluid in osteoarthritis; soft-tissue fillers can also be used in patients concerned about age-related volume loss (eg, nasolabial folds).

(Choice E) Laminins are heterotrimeric glycoproteins that bind to type IV collagen underlying epithelial cells. They contribute to the organization and function of the basal lamina (basement membrane).

(Choice F) Proteoglycans are composed of glycosaminoglycans (GAGs), which provide compressibility to tissues. Patients with deficiencies in lysosomal enzymes cannot break down GAGs, resulting in mucopolysaccharidoses (eg, Hurler syndrome, Hunter syndrome) characterized by soft tissue and skeletal disease.

Educational objective:
Ehlers-Danlos syndrome (EDS) is a heritable connective tissue disease associated with abnormal collagen formation. EDS usually manifests clinically as overflexible (hypermobile) joints, overelastic (hyperelastic) skin, and fragile tissue susceptible to bruising, wounding, and hemarthrosis.

References

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Item 22 of 40
Question Id: 1068

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Biochemistry researchers are investigating the speed at which various carbohydrates are metabolized within the liver. They hypothesize that different monosaccharides delivered to the liver have different rates of intracellular metabolism. Which of the following substances is most likely to have the fastest rate of metabolism in the glycolytic pathway?

A. Fructose-1-phosphate
B. Galactose-1-phosphate
C. Glucose-1-phosphate
D. Glucose-6-phosphate
E. Mannose-6-phosphate

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Item 22 of 40
Question Id: 1068

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Item 22 of 40
Question Id: 1068

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- A. Fructose-1-phosphate [39%]
- B. Galactose-1-phosphate [1%]
- C. Glucose-1-phosphate [11%]
- D. Glucose-6-phosphate [45%]
- E. Mannose-6-phosphate [1%]

Omitted
Correct answer
A

39%
Answered correctly

3 Seconds
Time Spent

12/18/2018
Last Updated

Explanation

Non-glucose monosaccharides (eg, galactose, mannose, fructose) enter the glycolytic pathway at different points as **intermediates of glycolysis**. Of these, **fructose** is the only one whose metabolites **bypass phosphofructokinase**, one of the key enzymes involved in regulating the rate of glycolysis. As a result, fructose is metabolized by the liver faster than the other monosaccharides and is rapidly cleared from the bloodstream following dietary absorption.

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Item 22 of 40
Question Id: 1068

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Omitted
Correct answer
A

39%
Answered correctly

3 Seconds
Time Spent

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Last Updated

Explanation

Non-glucose monosaccharides (eg, galactose, mannose, fructose) enter the glycolytic pathway at different points as **intermediates of glycolysis**. Of these, **fructose** is the only one whose metabolites **bypass phosphofructokinase**, one of the key enzymes involved in regulating the rate of glycolysis. As a result, fructose is metabolized by the liver faster than the other monosaccharides and is rapidly cleared from the bloodstream following dietary absorption.

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Omitted
Correct answer
A

39%
Answered correctly

3 Seconds
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Explanation

Non-glucose monosaccharides (eg, galactose, mannose, fructose) enter the glycolytic pathway at different points as **intermediates of glycolysis**. Of these, **fructose** is the only one whose metabolites **bypass phosphofructokinase**, one of the key enzymes involved in regulating the rate of glycolysis. As a result, fructose is metabolized by the liver faster than the other monosaccharides and is rapidly cleared from the bloodstream following dietary absorption.

Metabolism of fructose in the liver begins with phosphorylation by fructokinase to **fructose-1-phosphate (F1P)**. Aldolase B can use both fructose-1,6-bisphosphate and F1P as substrates; it converts F1P into **dihydroxy acetone phosphate (DHAP)** and **glyceraldehyde**. Glyceraldehyde can be either phosphorylated to glyceraldehyde-3-phosphate by triokinase or converted to DHAP. DHAP is converted by triose phosphate isomerase to glyceraldehyde-3-phosphate, which continues down the glycolytic pathway.

(Choices B, C, D, and E) Galactose-1-phosphate, glucose-1-phosphate, glucose-6-phosphate, and mannose-6-phosphate enter glycolysis upstream of phosphofructokinase, a major rate-limiting enzyme of glycolysis. This slows down the rate of their metabolism relative to fructose and its metabolites (eg, F1P).

Educational objective:
Dietary fructose is phosphorylated in the liver to F1P and is rapidly metabolized because it bypasses PFK-1, the major rate-limiting enzyme of glycolysis. Other sugars (eg, glucose, galactose, mannose) enter glycolysis prior to PFK-1 and as a result are metabolized more slowly.

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Item 23 of 40
Question Id: 1428

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A geneticist is performing an experiment to alter protein structures by incorporating modified amino acids into their polypeptide sequences. During the process, she incubates dermal fibroblasts in a medium containing fluorescently labeled lysine residues. After several hours, she finds that aminoacyl tRNA synthetase in the fibroblasts "loads" lysine residues onto tRNA molecules containing the anticodon UUU. This residue most likely attaches to tRNA at which of the following sites in the image shown below?

A. A
B. B
C. C
D. D
E. E
F. F

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Item 23 of 40
Question Id: 1428

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A. A
B. B
C. C
D. D
E. E
F. F

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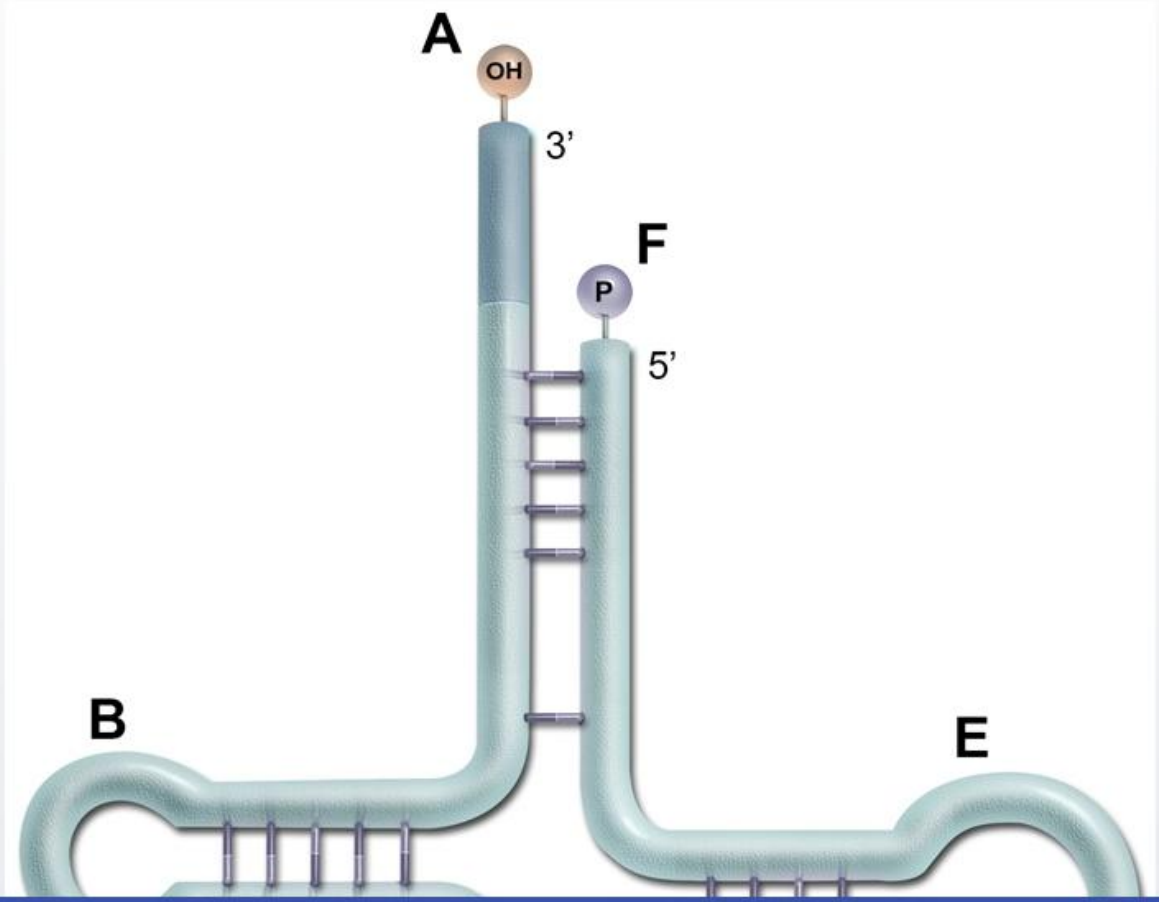
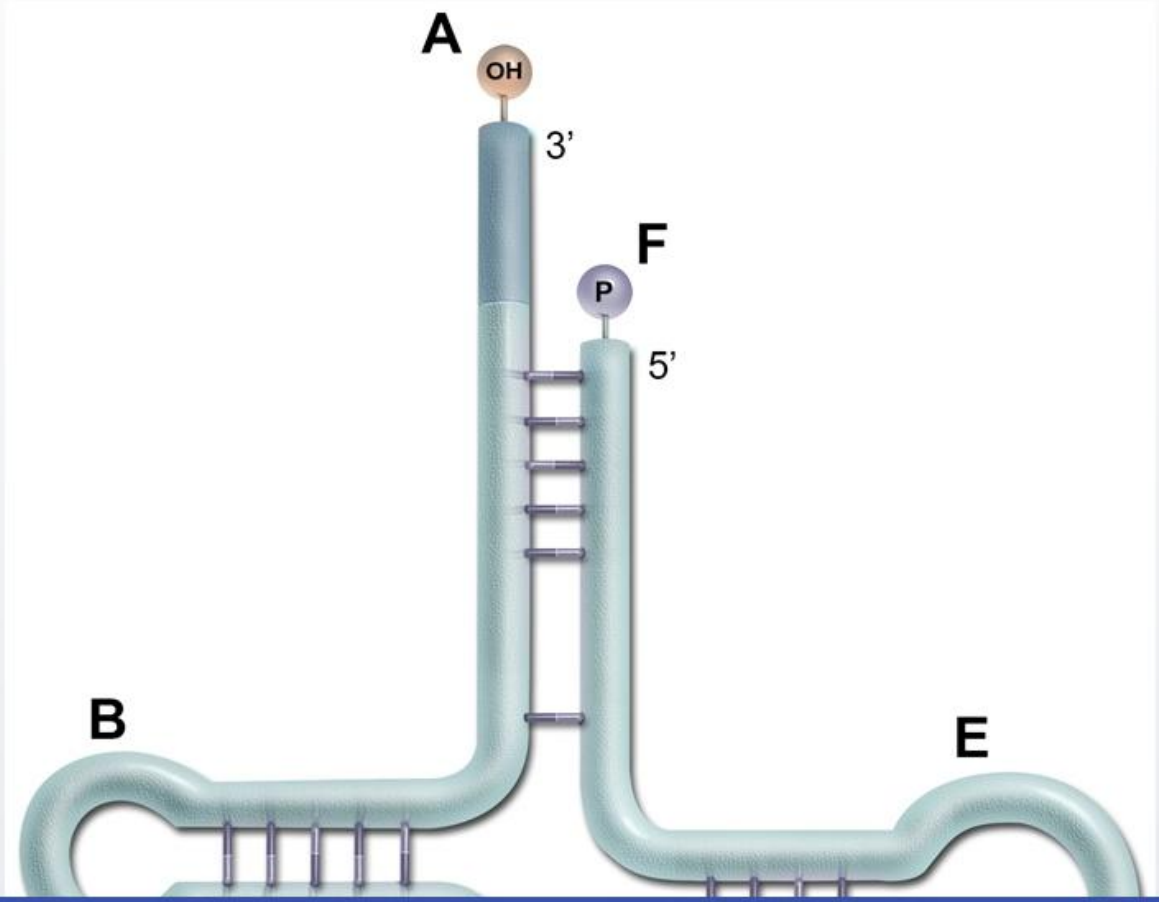
attaches to tRNA at which of the following sites in the image shown below?



attaches to tRNA at which of the following sites in the image shown below?



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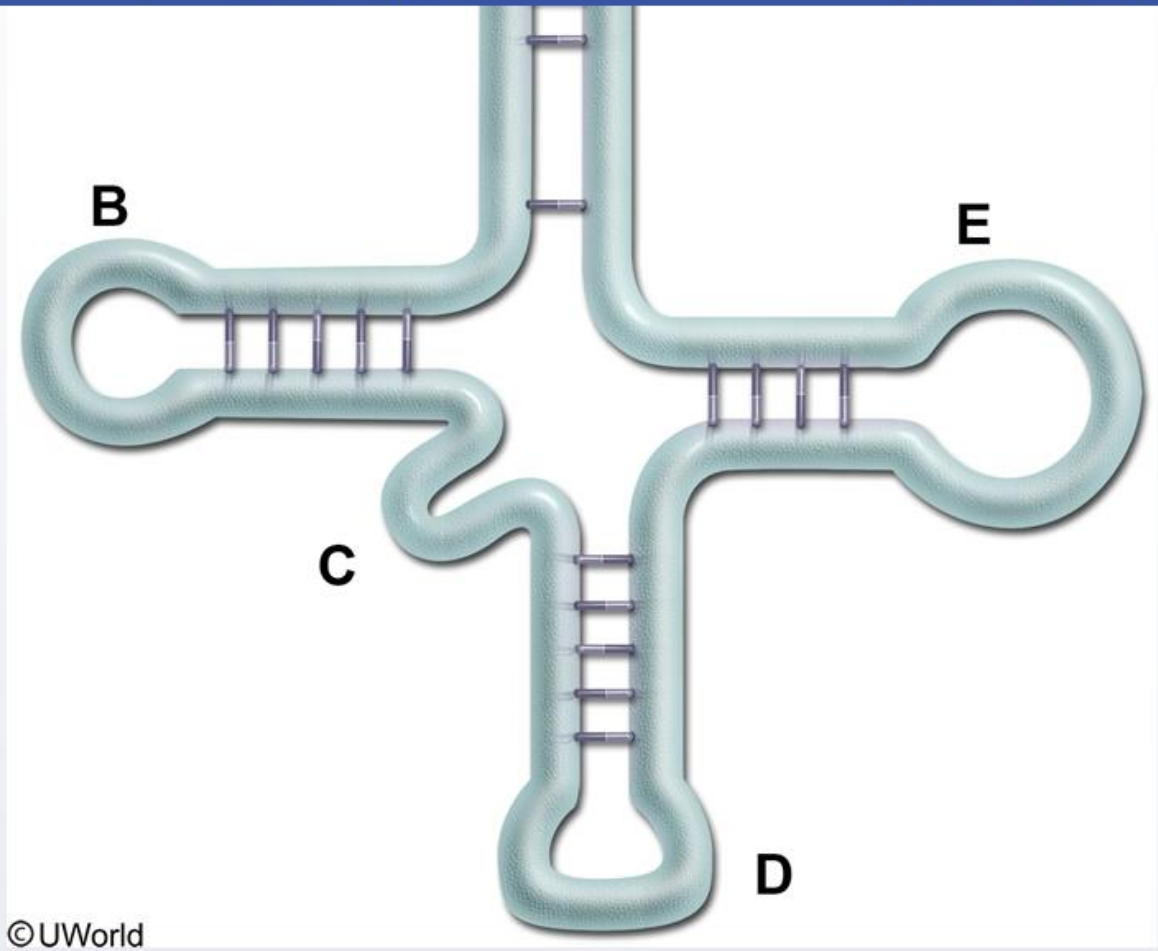

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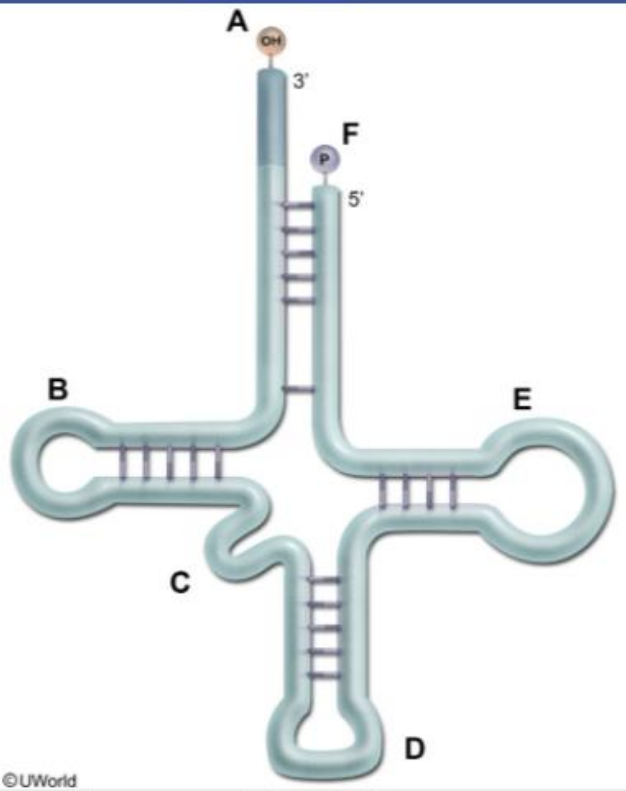

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Item 23 of 40
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A geneticist is performing an experiment to alter protein structures by incorporating modified amino acids into their polypeptide sequences. During the process, she incubates dermal fibroblasts in a medium containing fluorescently labeled lysine residues. After several hours, she finds that aminoacyl tRNA synthetase in the fibroblasts "loads" lysine residues onto tRNA molecules containing the anticodon UUU. This residue most likely attaches to tRNA at which of the following sites in the image shown below?

A. A
B. B
C. C
D. D
E. E
F. F

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Item 23 of 40
Question Id: 1428

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A geneticist is performing an experiment to alter protein structures by incorporating modified amino acids into their polypeptide sequences. During the process, she incubates dermal fibroblasts in a medium containing fluorescently labeled lysine residues. After several hours, she finds that aminoacyl tRNA synthetase in the fibroblasts "loads" lysine residues onto tRNA molecules containing the anticodon UUU. This residue most likely attaches to tRNA at which of the following sites in the image shown below?

- A. A [67%] ✔
- B. B [2%]
- C. C [2%]
- D. D [17%]
- E. E [2%]
- F. F [9%]

Omitted
Correct answer
A

67%
Answered correctly

2 Seconds
Time Spent

08/22/2018
Last Updated

Explanation

The image above shows the "cloverleaf" secondary structure of **transfer RNA (tRNA)**, a small, noncoding subtype of RNA that is responsible for transporting amino acids to the site of protein synthesis and introducing them into the growing polypeptide chain at the correct locations.

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The image above shows the "cloverleaf" secondary structure of **transfer RNA (tRNA)**, a small, noncoding subtype of RNA that is responsible for transporting amino acids to the site of protein synthesis and introducing them into the growing polypeptide chain at the correct locations.

The acceptor stem of tRNA is created through the base pairing of the 5'-terminal nucleotides with the 3'-terminal nucleotides. It contains the **CCA tail**, which is added to the **3'** end of tRNA as a post-transcriptional modification and serves as the **amino acid binding site**. Aminoacyl tRNA synthetase is the enzyme responsible for "loading" the appropriate amino acid to the 3' terminal hydroxyl group of the CCA tail. The acceptor stem helps mediate correct tRNA recognition by the proper aminoacyl tRNA synthetase.

(Choice B) The T loop contains the TΨC sequence, which is necessary for the binding of tRNA to ribosomes. The TΨC sequence refers to the presence of the chemically modified bases ribothymidine and pseudouridine, and cytidine.

(Choice C) The variable loop contains a variable number of bases that lie between the T and anticodon loops. The variable loop is not present in all tRNAs.

(Choice D) The anticodon loop contains sequences that are complementary to the mRNA codon. During translation, the tRNA anticodon binds to the mRNA codon and assures placement of the proper amino acid in the growing polypeptide chain.

(Choice E) The D loop contains numerous dihydrouridine residues, which are modified bases often present in tRNA. The D loop (along with the acceptor stem and anticodon loop) facilitates correct tRNA recognition by the proper aminoacyl tRNA synthetase.

(Choice F) The 5' end of tRNA contains a terminal phosphate group that does not participate in amino acid or mRNA binding.

Educational objective:
The 3' CCA tail of tRNA serves as the amino acid binding site. Aminoacyl tRNA synthetase is the enzyme responsible for "loading" the appropriate amino acid to the 3' terminal hydroxyl group of the CCA tail.

References

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Item 24 of 40
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A researcher is studying the structure of different hormone receptors. Receptor proteins are isolated and purified from a homogenized tissue sample. Detailed structural analysis shows that one of the proteins contains a 30-amino acid motif coordinating a zinc molecule, as shown in the image below.

A receptor for which of the following hormones was most likely isolated in this experiment?

- A. Adrenocorticotropic hormone
- B. Antidiuretic hormone
- C. Epinephrine
- D. Glucagon
- E. Growth hormone
- F. Insulin
- G. Thyroid hormone

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Item 24 of 40
Question Id: 11950

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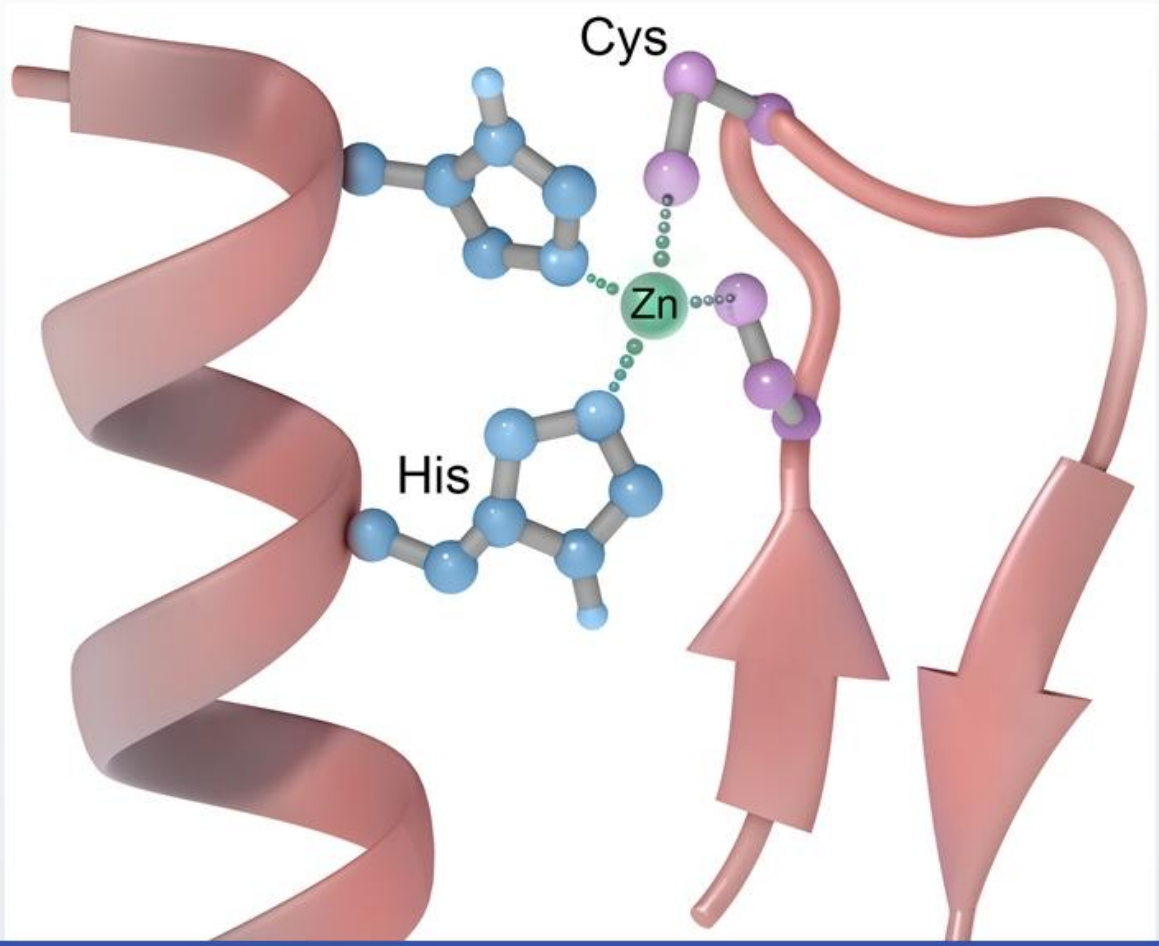

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Question Id: 11950

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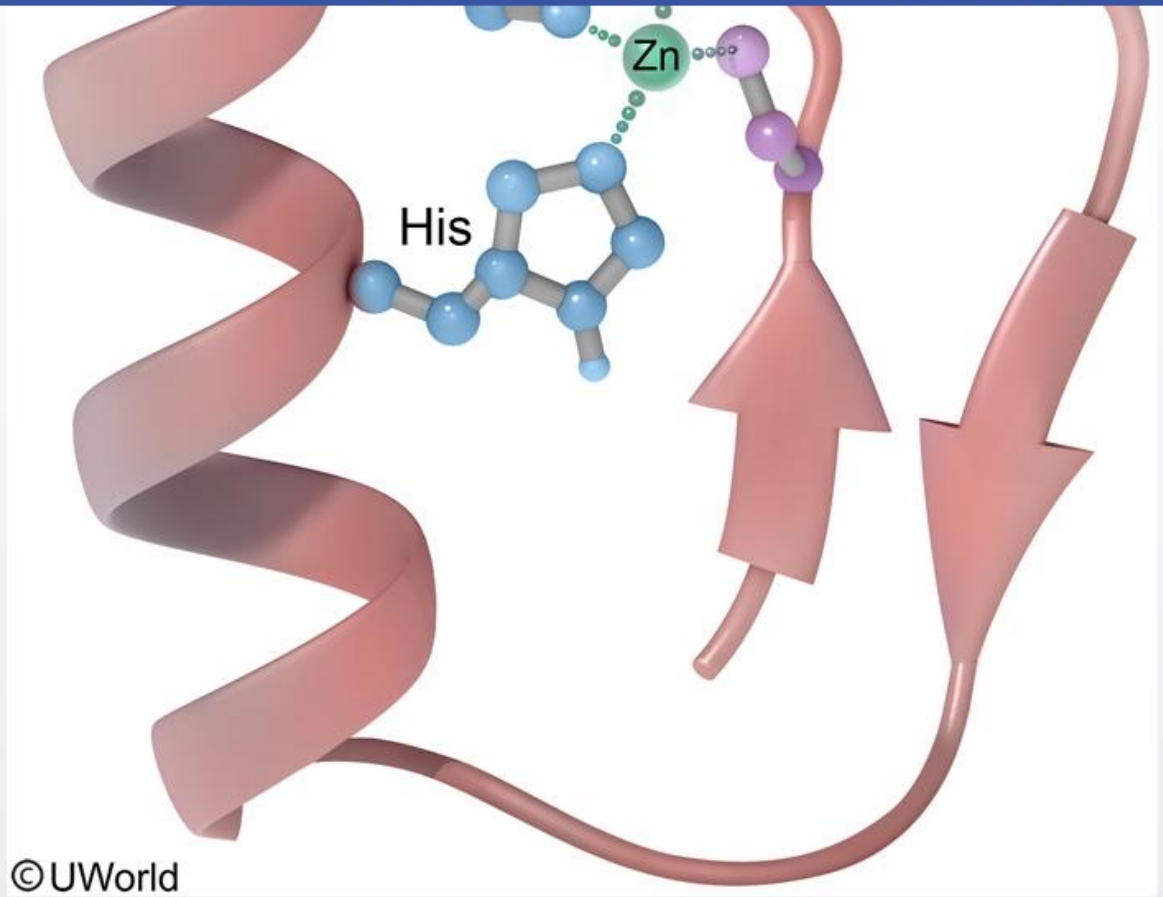

A receptor for which of the following hormones was most likely isolated in this experiment?

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Question Id: 11950

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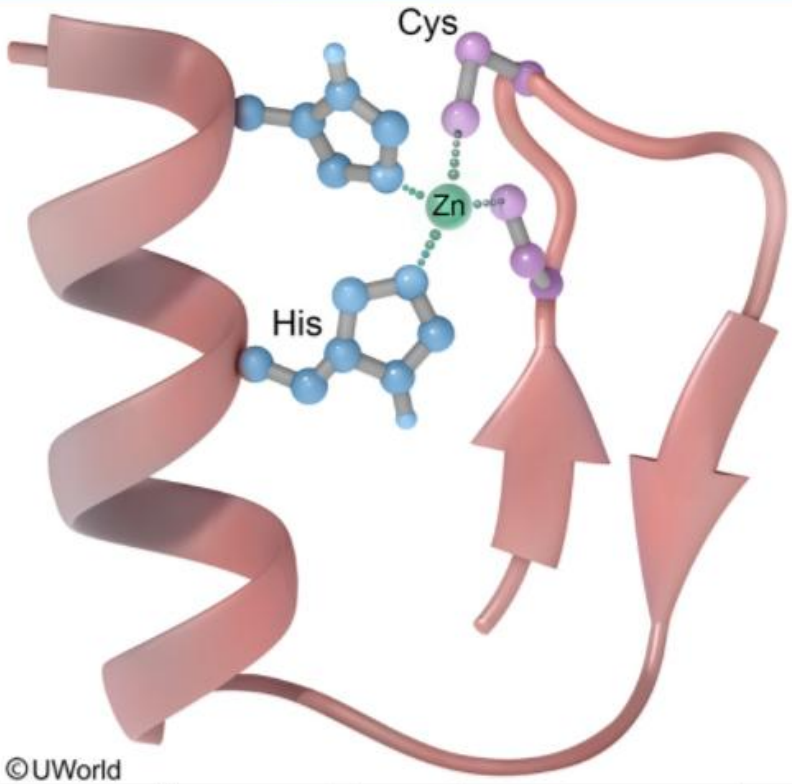

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Item 24 of 40
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A researcher is studying the structure of different hormone receptors. Receptor proteins are isolated and purified from a homogenized tissue sample. Detailed structural analysis shows that one of the proteins contains a 30-amino acid motif coordinating a zinc molecule, as shown in the image below.

A receptor for which of the following hormones was most likely isolated in this experiment?

- A. Adrenocorticotropic hormone
- B. Antidiuretic hormone
- C. Epinephrine
- D. Glucagon
- E. Growth hormone
- F. Insulin
- G. Thyroid hormone

Submit

Block Time Remaining: 00:02:19
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Item 24 of 40
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A researcher is studying the structure of different hormone receptors. Receptor proteins are isolated and purified from a homogenized tissue sample. Detailed structural analysis shows that one of the proteins contains a 30-amino acid motif coordinating a zinc molecule, as shown in the image below.

A receptor for which of the following hormones was most likely isolated in this experiment?

A. Adrenocorticotropic hormone [11%]
B. Antidiuretic hormone [5%]
C. Epinephrine [5%]
D. Glucagon [6%]
E. Growth hormone [20%]
F. Insulin [16%]
✔ G. Thyroid hormone [34%]

Omitted
Correct answer
G

34%
Answered correctly

3 Seconds
Time Spent

10/05/2018
Last Updated

Explanation

Block Time Remaining: 00:02:21
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Explanation

The **zinc-finger** structure represents the most commonly identified **DNA-binding domain** in humans. Zinc-finger motifs are composed of chains of amino acids bound together around a zinc atom via linkages with cysteine (and sometimes histidine) residues. This forms a stable, finger-shaped structure containing 2 antiparallel β- strands and an α-helix. Unique combinations of amino acids as well as the specific histidine and cysteine linkages determine DNA-binding specificity. Many transcription factors use multiple zinc-finger motifs to recognize specific genes and alter their activity.

Although most hormones alter transcription regulation to some degree in target cells, only **intracellular receptors** located in the cytoplasm or nucleus can **act directly as transcription factors**. These intracellular receptors typically bind **lipid-soluble hormones** because the ligand has to diffuse across the cell membrane to reach the receptor. Once bound to their ligand, these receptors bind directly to target DNA sequences via zinc fingers to regulate gene expression. Examples include steroid (eg, estrogen, aldosterone, cortisol), **thyroid hormone**, and fat-soluble vitamin receptors.

In contrast, non-lipid-soluble hormones interact with transmembrane receptors found on the cell membrane. These receptors use a signal transduction cascade involving second messengers with subsequent activation of non-receptor-associated transcription factors; they do not contain DNA-binding domains. Examples include the G-protein-coupled receptors that bind ACTH, ADH, epinephrine, and glucagon **(Choices A, B, C, and D)** as well as receptors with intrinsic and associated tyrosine kinase activity (eg, insulin and growth hormone receptors, respectively) **(Choices E and F)**.

Educational objective:
Zinc-finger motifs are composed of chains of amino acids bound together around a zinc atom via linkages with cysteine and histidine residues. They recognize specific DNA sequences and are used by many transcription factors to bind DNA and alter activity of target genes. Intracellular receptors that bind steroids, thyroid hormone, and fat-soluble vitamins act directly as transcription factors and contain zinc-finger binding domains.

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Explanation

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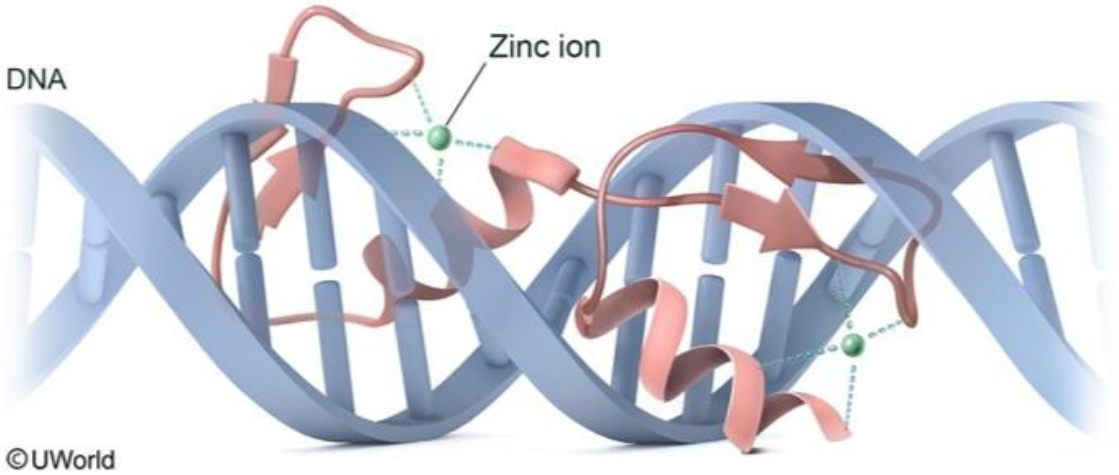
Exhibit Display

Zinc finger



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Item 25 of 40
Question Id: 1250

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A 34-year-old man develops severe chest and abdominal pain while shopping in a mall. Paramedics arrive and find him in severe distress. Several minutes later, he suffers a cardiac arrest with pulseless electrical activity and cannot be resuscitated. Postmortem examination reveals an internal hemorrhage as the cause of death. Histochemical evaluation of the patient's tissues reveals a defect affecting a large extracellular glycoprotein. This protein is normally found abundantly in large blood vessels, periosteum, and zonular fibers of the lens and functions to form microfibrils by surrounding elastin. This patient most likely suffered from which of the following conditions?

- A. Ehlers-Danlos syndrome
- B. Homocystinuria
- C. Marfan syndrome
- D. Osteogenesis imperfecta
- E. Polycystic kidney disease
- F. Vitamin C deficiency

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Item 25 of 40
Question Id: 1250

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A 34-year-old man develops severe chest and abdominal pain while shopping in a mall. Paramedics arrive and find him in severe distress. Several minutes later, he suffers a cardiac arrest with pulseless electrical activity and cannot be resuscitated. Postmortem examination reveals an internal hemorrhage as the cause of death. Histochemical evaluation of the patient's tissues reveals a defect affecting a large extracellular glycoprotein. This protein is normally found abundantly in large blood vessels, periosteum, and zonular fibers of the lens and functions to form microfibrils by surrounding elastin. This patient most likely suffered from which of the following conditions?

- A. Ehlers-Danlos syndrome [15%]
- B. Homocystinuria [1%]
- ✔ C. Marfan syndrome [80%]
- D. Osteogenesis imperfecta [1%]
- E. Polycystic kidney disease [0%]
- F. Vitamin C deficiency [0%]

Omitted
Correct answer
C

80%
Answered correctly

3 Seconds
Time Spent

01/26/2019
Last Updated

Explanation

Clinical features of Marfan syndrome

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Clinical features of Marfan syndrome	
Skeletal	• Arachnodactyly • ↓ Upper-to-lower body segment ratio, ↑ arm-to-height ratio • Pectus deformity, scoliosis, or kyphosis • Joint hypermobility
Ocular	• Ectopia lentis
Cardiovascular	• Aortic dilation, regurgitation, or dissection • Mitral valve prolapse
Pulmonary	• Spontaneous pneumothorax from apical blebs
Skin	• Recurrent or incisional hernia • Skin striae

Fibrillin-1 is a major component of microfibrils that form a sheath around elastin fibers. Microfibrils are abundant in blood vessels (eg, aortic media), periosteum, and the suspensory ligaments of the lens. Fibrillin in the extracellular space acts as a scaffold for deposition of elastin extruded from connective tissue cells. Defects in fibrillin-1 cause mechanical weakening in the connective tissues and abnormal activation of transforming growth factor beta.

Marfan syndrome is caused by an inherited defect in the fibrillin-1 gene. Patients with Marfan syndrome can often be identified due to a characteristic **body habitus**, with long thin extremities, loose joints, and long fingers (arachnodactyly). The cause of death in Marfan syndrome is most often due to cardiovascular complications (eg, **aortic root dilation, dissection, and rupture**).

(Choice A) Ehlers-Danlos syndrome is a collection of heritable disorders of connective tissue characterized by skin and joint hypermobility. Like

transforming growth factor beta.

Marfan syndrome is caused by an inherited defect in the fibrillin-1 gene. Patients with Marfan syndrome can often be identified due to a characteristic **body habitus**, with long thin extremities, loose joints, and long fingers (arachnodactyly). The cause of death in Marfan syndrome is most often due to cardiovascular complications (eg, **aortic root dilation, dissection, and rupture**).

(Choice A) Ehlers-Danlos syndrome is a collection of heritable disorders of connective tissue characterized by skin and joint hypermobility. Like those with Marfan syndrome, these patients are at risk for aortic rupture. However, Ehlers-Danlos syndrome affects the formation and extracellular structuring of collagen rather than microfibrils.

(Choice B) Homocystinuria is a rare inherited metabolic disorder due to cystathionine synthase deficiency. It is characterized by very high circulating homocysteine levels, marfanoid habitus, and increased risk for premature atherosclerotic cardiovascular disease.

(Choice D) Osteogenesis imperfecta results from defects in the genes encoding type I collagen, a major component of bones. Defects in type I collagen in osteogenesis imperfecta result in reduced bone mass and fragility fractures. Other manifestations of the disease include blue sclera, dental abnormalities, and hearing loss.

(Choice E) Autosomal dominant polycystic kidney disease is a disorder of tubular epithelial cells. It causes enlargement of the kidneys with numerous parenchymal cysts. Patients are also at risk for cardiac valvular disorders and ruptured cerebral aneurysms.

(Choice F) Deficiency of vitamin C (scurvy) causes impaired hydroxylation of proline and lysine residues in collagen. Clinical features include skin fragility, easy bleeding, and poor dentition.

Educational objective:
Marfan syndrome is due to a defect in fibrillin-1, an extracellular glycoprotein that acts as a scaffold for elastin. It is abundant in the zonular fibers of the lens, periosteum, and aortic media. Aortic root dilation with dissection and rupture is a common cause of death.

References

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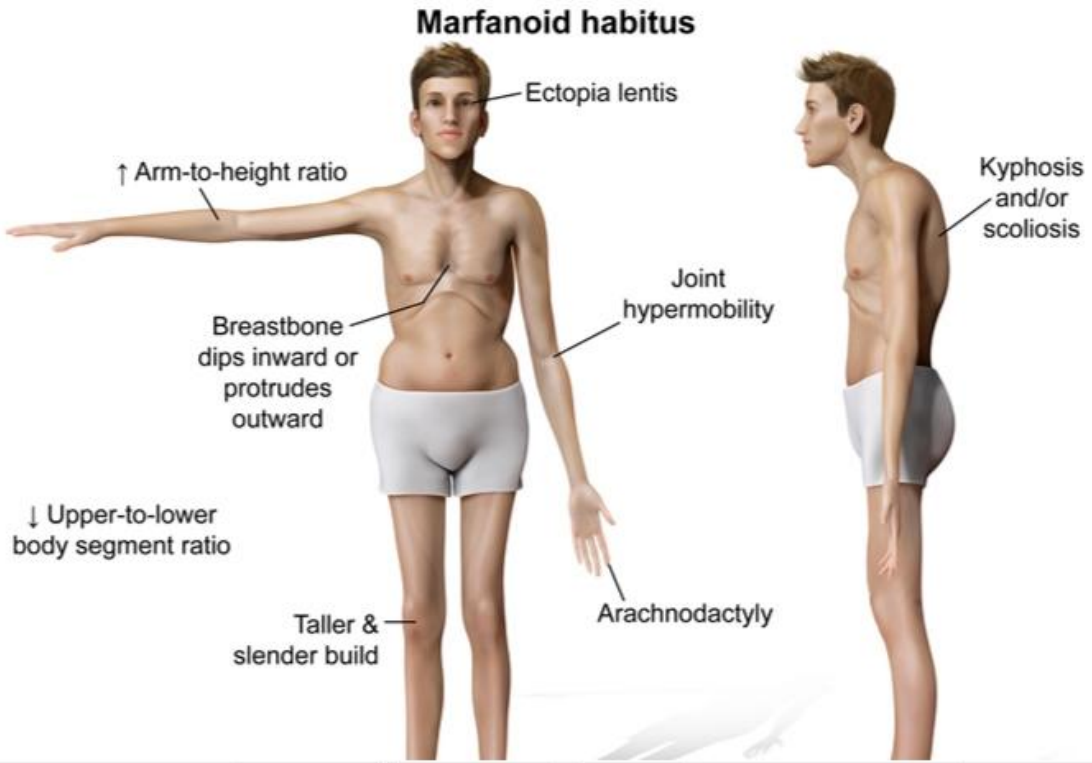

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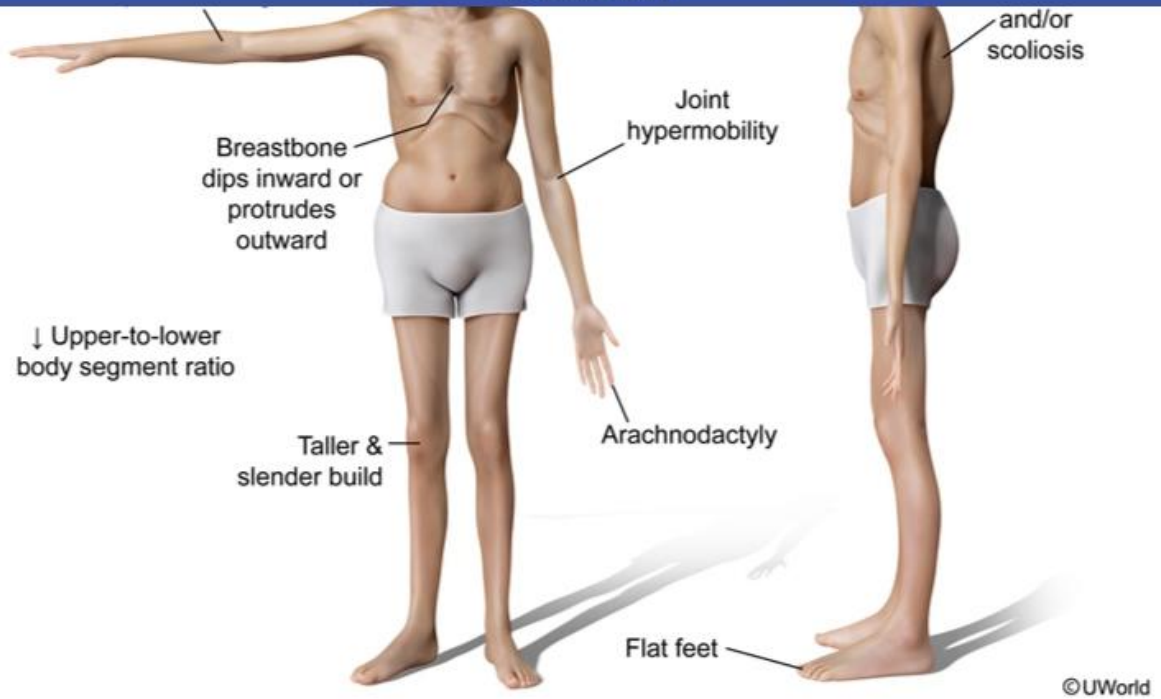

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Item 26 of 40
Question Id: 1504

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A 5-year-old boy with developmental delay is brought to the office due to difficulty "seeing the board" at school. Examination shows a boy with a tall, thin habitus with elongated limbs. Funduscopy shows bilateral lens subluxation. Four years later, the patient dies suddenly of a massive cerebrovascular accident. Autopsy shows middle cerebral artery thrombosis and old renal infarcts. His parents wish to know if anything could have been done to have prevented his death. Which of the following would have been the most appropriate supplementation for this patient?

A. Ascorbic acid
B. Carnitine
C. Pyridoxine
D. Thiamine
E. Tyrosine
F. Vitamin K

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Item 26 of 40
Question Id: 1504

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A 5-year-old boy with developmental delay is brought to the office due to difficulty "seeing the board" at school. Examination shows a boy with a tall, thin habitus with elongated limbs. Funduscopy shows bilateral lens subluxation. Four years later, the patient dies suddenly of a massive cerebrovascular accident. Autopsy shows middle cerebral artery thrombosis and old renal infarcts. His parents wish to know if anything could have been done to have prevented his death. Which of the following would have been the most appropriate supplementation for this patient?

A. Ascorbic acid [31%]
B. Carnitine [7%]
✔ C. Pyridoxine [39%]
D. Thiamine [5%]
E. Tyrosine [6%]
F. Vitamin K [9%]

Omitted
Correct answer
C

39%
Answered correctly

29 Seconds
Time Spent

09/15/2018
Last Updated

Explanation

This patient's presentation is most consistent with homocystinuria, the most common inborn error of methionine metabolism. Most patients present at age 3-10 with **ectopia lentis (dislocated lens)**. About half of patients have **intellectual disability**. Other clinical manifestations

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2/6/2019

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Explanation

This patient's presentation is most consistent with homocystinuria, the most common inborn error of methionine metabolism. Most patients present at age 3-10 with **ectopia lentis (dislocated lens)**. About half of patients have **intellectual disability**. Other clinical manifestations include a **Marfanoid habitus** (eg, elongated limbs, arachnodactyly, scoliosis). Patients are at high risk for **thromboembolic occlusion** of both large and small vessels, especially those of the brain, heart, and kidneys. Thromboembolic complications are the major cause of morbidity and mortality in these patients.

Homocystinuria is most frequently caused by an **autosomal recessive** deficiency of cystathionine beta-synthase, an enzyme that requires **pyridoxine (vitamin B6)** as a cofactor. Approximately 50% of affected patients respond to high doses of pyridoxine, which improves residual enzymatic activity and reduces plasma homocysteine levels. Additional treatment includes dietary **restriction of methionine**.

(Choice A) Vitamin C is a necessary cofactor for the hydroxylation of proline and lysine residues in collagen. Vitamin C deficiency results in decreased strength of collagen fibers and causes **scurvy**.

(Choice B) Carnitine assists with long-chain fatty acid transport into mitochondria. Deficiencies in carnitine (eg, primary systemic carnitine deficiency) lead to fatty acid oxidation defects in cardiac and skeletal muscle.

(Choice D) Thiamine (vitamin B1) deficiency can cause dry and wet beriberi and Wernicke-Korsakoff syndrome.

(Choice E) Tyrosine is a nonessential amino acid and the precursor for catecholamines such as dopamine, epinephrine, and norepinephrine.

(Choice F) Vitamin K is involved in the post-translational conversion of glutamate to gamma-carboxyglutamic acid. This modification is necessary for the function of many clotting factors and regulatory proteins involved in the coagulation cascade.

Educational objective:
Homocystinuria is most commonly caused by cystathionine synthase deficiency. Affected individuals have marfanoid habitus, ectopia lentis, and

mortality in these patients.

Homocystinuria is most frequently caused by an **autosomal recessive** deficiency of cystathionine beta-synthase, an enzyme that requires **pyridoxine (vitamin B6)** as a cofactor. Approximately 50% of affected patients respond to high doses of pyridoxine, which improves residual enzymatic activity and reduces plasma homocysteine levels. Additional treatment includes dietary **restriction of methionine**.

(Choice A) Vitamin C is a necessary cofactor for the hydroxylation of proline and lysine residues in collagen. Vitamin C deficiency results in decreased strength of collagen fibers and causes **scurvy**.

(Choice B) Carnitine assists with long-chain fatty acid transport into mitochondria. Deficiencies in carnitine (eg, primary systemic carnitine deficiency) lead to fatty acid oxidation defects in cardiac and skeletal muscle.

(Choice D) Thiamine (vitamin B1) deficiency can cause dry and wet beriberi and Wernicke-Korsakoff syndrome.

(Choice E) Tyrosine is a nonessential amino acid and the precursor for catecholamines such as dopamine, epinephrine, and norepinephrine.

(Choice F) Vitamin K is involved in the post-translational conversion of glutamate to gamma-carboxyglutamic acid. This modification is necessary for the function of many clotting factors and regulatory proteins involved in the coagulation cascade.

Educational objective:
Homocystinuria is most commonly caused by cystathionine synthase deficiency. Affected individuals have marfanoid habitus, ectopia lentis, and developmental delay. Significant morbidity and mortality are due primarily to thromboembolism. Many patients with homocystinuria respond dramatically to pyridoxine (vitamin B6) supplementation.

References

- Hypermethioninemias of genetic and non-genetic origin: A review.
- Overview of homocysteine and folate metabolism. With special references to cardiovascular disease and neural tube defects.

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Item 27 of 40
Question Id: 2017

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A 34-year-old woman with a history of recurrent urinary tract infections comes to the physician with dysuria and increased urinary frequency. Her urine culture grows colonies of Gram-negative bacteria. The bacteria are isolated and placed in a growth-enhancing nutrient solution, where they undergo rapid cellular division. As they are actively dividing, the bacterial cells are lysed and their DNA is extracted and purified. Analysis of the partially replicated DNA fragments shows the presence of uracil. This finding is most likely mediated by which of the following enzymes?

A. DNA ligase
B. DNA polymerase I
C. DNA polymerase III
D. Gyrase
E. Helicase
F. Primase

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2/6/2019

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Item 27 of 40
Question Id: 2017

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A 34-year-old woman with a history of recurrent urinary tract infections comes to the physician with dysuria and increased urinary frequency. Her urine culture grows colonies of Gram-negative bacteria. The bacteria are isolated and placed in a growth-enhancing nutrient solution, where they undergo rapid cellular division. As they are actively dividing, the bacterial cells are lysed and their DNA is extracted and purified. Analysis of the partially replicated DNA fragments shows the presence of uracil. This finding is most likely mediated by which of the following enzymes?

- A. DNA ligase [2%]
- B. DNA polymerase I [15%]
- C. DNA polymerase III [18%]
- D. Gyrase [2%]
- E. Helicase [1%]
- ✔ F. Primase [59%]

Omitted
Correct answer
F

59%
Answered correctly

11 Seconds
Time Spent

12/09/2018
Last Updated

Explanation

Prokaryotic DNA replication fork

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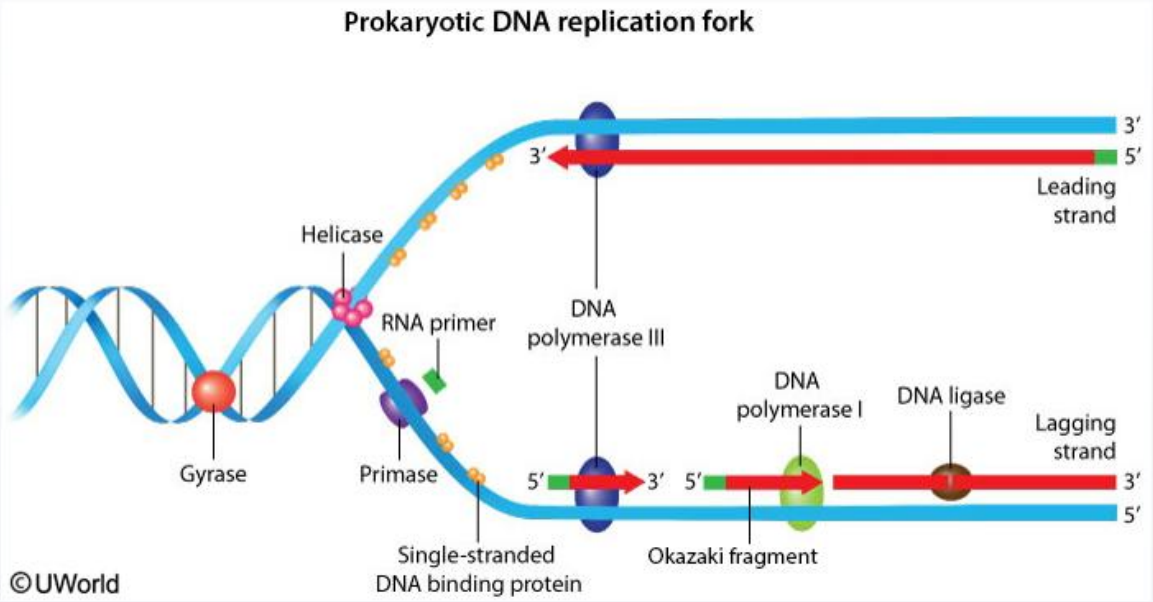
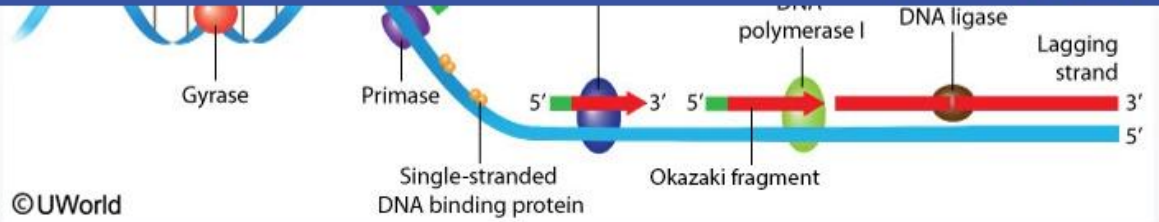
Explanation



This question describes a scenario in which uracil is found in association with bacterial DNA during prokaryotic DNA replication. In general, uracil is found only in RNA, so the question essentially asks which enzyme involved in DNA synthesis catalyzes the formation of RNA strands. In prokaryotic DNA replication, primase (an RNA polymerase) is responsible for synthesizing a short RNA primer using the separated strands of DNA at the replication fork as templates. DNA replication then proceeds, with DNA polymerase using the 3' hydroxyl group of the RNA primer as a starting point for synthesis. Primase is a crucial enzyme for bacterial replication as DNA polymerase cannot initiate DNA synthesis without this



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(Choice A) DNA ligase is the enzyme that repairs single-strand breaks in duplex DNA during DNA replication and repair.

(Choices B and C) During replication, DNA polymerase III is the primary enzyme responsible for synthesis of daughter DNA strands; DNA polymerase I functions chiefly to replace the RNA primers with DNA segments. Unlike DNA polymerase III, DNA polymerase I has 5'→ 3' exonuclease activity that can remove RNA primers and damaged DNA segments. The 3'→ 5' exonuclease activity of DNA polymerase I and III provides a proofreading function that fixes mismatched nucleotides in the newly formed daughter strands.

(Choices D and E) Helicase unwinds DNA at the replication fork. However, this process results in supercoiling of the DNA. DNA gyrase is a type II topoisomerase that helps to relieve the resultant strain.

Educational objective:
Primase is a DNA-dependent RNA polymerase that incorporates short RNA primers into replicating DNA.

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Item 28 of 40
Question Id: 1245

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A 2-year-old boy is evaluated for easy bruising. His parents report that he develops marked bruising and open wounds following minor trauma. The skin is difficult to suture due to its extreme fragility. Physical examination reveals hyperextensible skin, multiple ecchymoses over the forearms and pretibial regions, and an umbilical hernia. A skin biopsy is performed, and histochemical evaluation of the biopsy reveals a defect in extracellular processing of collagen. Which of the following steps of collagen synthesis is most likely impaired in this patient?

A. Glycosylation of hydroxylysine residues
B. Interchain C-terminal disulfide bond formation
C. N-terminal propeptide removal
D. Proline residue hydroxylation
E. Triple helix formation

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Item 28 of 40
Question Id: 1245

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

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- A. Glycosylation of hydroxylysine residues [10%]
- B. Interchain C-terminal disulfide bond formation [18%]
- ✔ C. N-terminal propeptide removal [23%]
- D. Proline residue hydroxylation [17%]
- E. Triple helix formation [29%]

Omitted
Correct answer
C

23%
Answered correctly

3 Seconds
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12/20/2018
Last Updated

Explanation

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Item 28 of 40
Question Id: 1245

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Correct answer
C

23%
Answered correctly

3 Seconds
Time Spent

12/20/2018
Last Updated

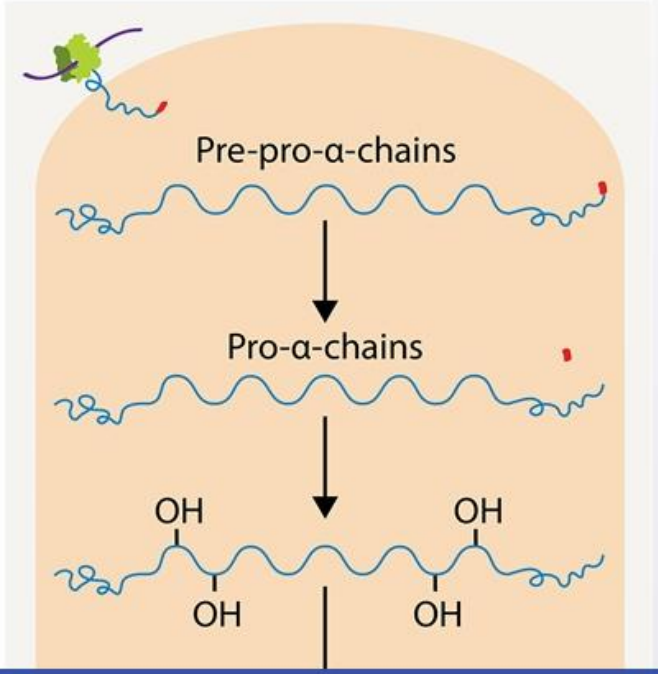
Explanation

Collagen synthesis

Signal sequence directs growing polypeptide chain into endoplasmic reticulum

Signal sequence is cleaved

Hydroxylation of selected proline & lysine residues **(vitamin C dependent)**



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Item 28 of 40
Question Id: 1245

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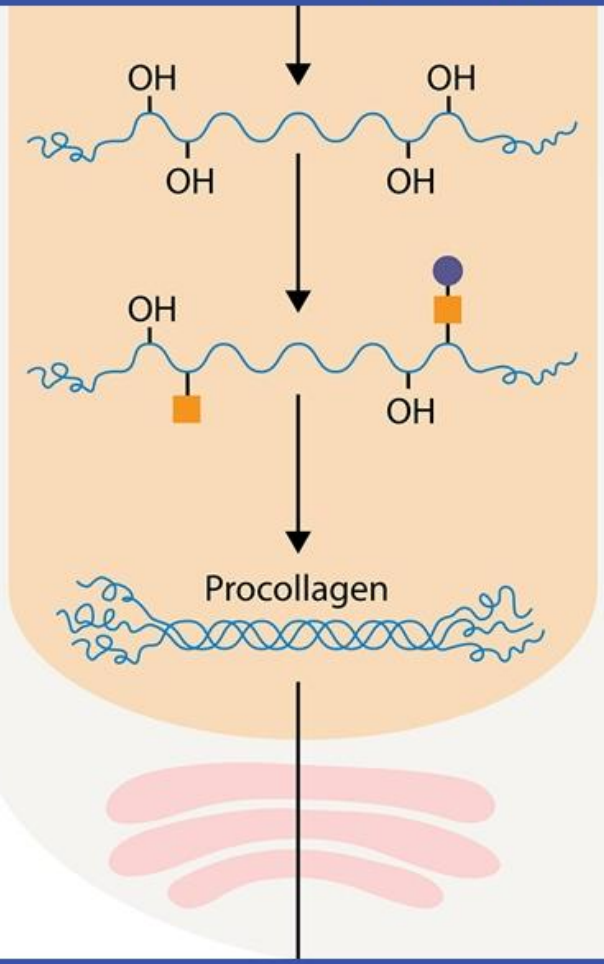
Hydroxylation of selected proline & lysine residues **(vitamin C dependent)**

Glycosylation of selected hydroxylysine residues

- Galactose
- Glucose

Assembly of pro-α-chains into **procollagen triple helix**

Procollagen transferred to Golgi apparatus & secreted into extracellular matrix



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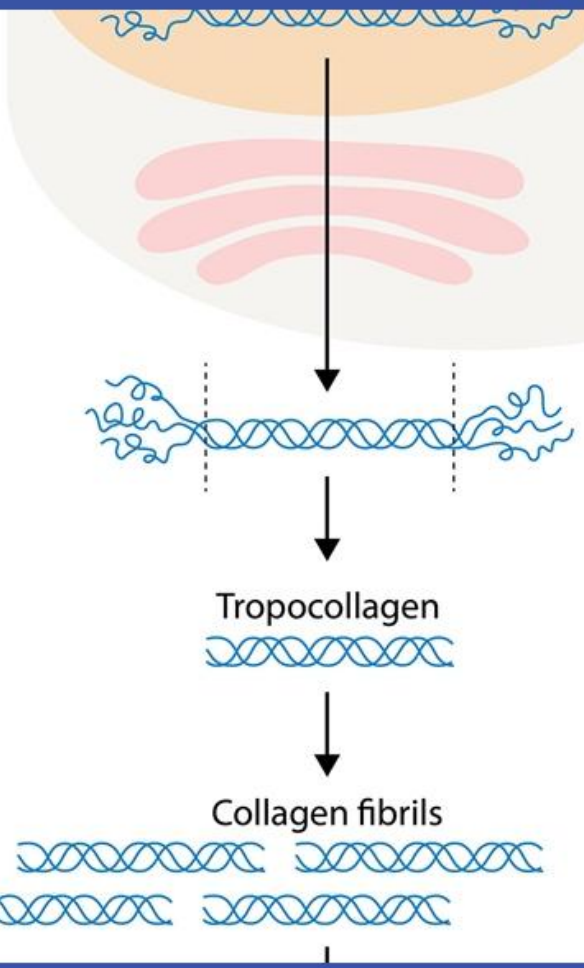
procollagen triple helix

Procollagen transferred to Golgi apparatus & secreted into extracellular matrix



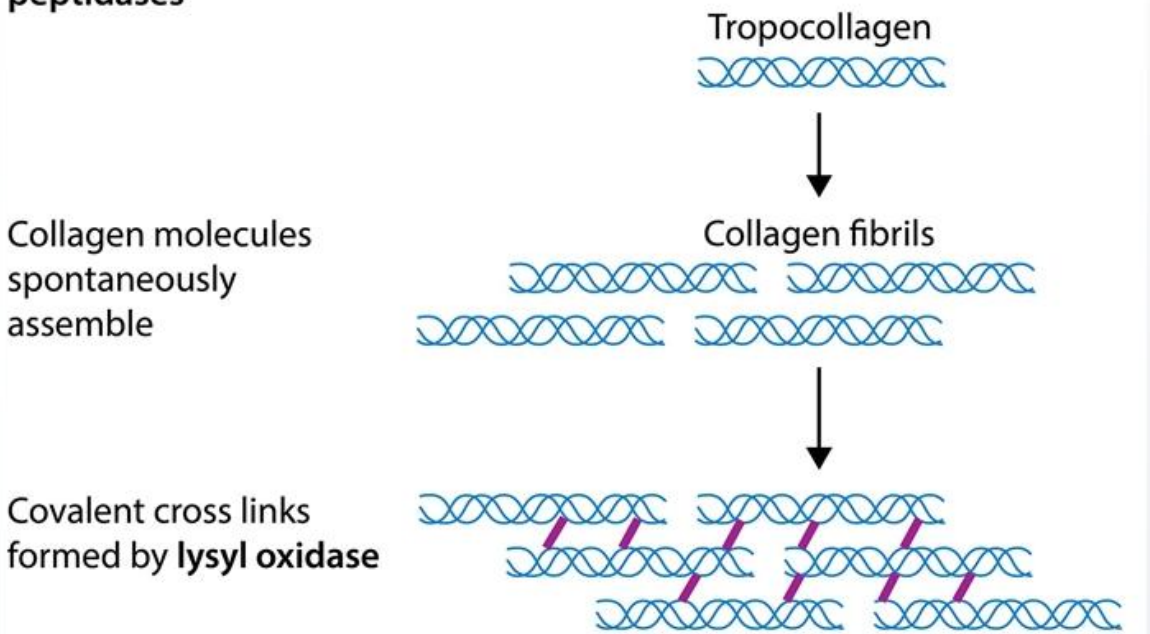
Terminal propeptides cleaved by N- & C- **procollagen peptidases**

Tropocollagen

Collagen molecules spontaneously assemble

Collagen fibrils

peptidases



This child likely has **Ehlers-Danlos syndrome**, a group of rare hereditary disorders characterized by **defective collagen synthesis**. The condition can be caused by a **deficiency** in **procollagen peptidase**, the enzyme that cleaves terminal propeptides from procollagen in the extracellular space. Impaired propeptide removal results in the formation of soluble collagen that does not properly crosslink. Consequently, patients often have joint laxity, **hyperextensible skin, fragile tissue** with easy bruising, and poor wound healing.

Each collagen molecule consists of 3 polypeptide α-chains held together by hydrogen bonds, forming a triple helix. Collagen assumes this conformation because each of the α-chains has a simple, repetitive amino acid sequence represented as $(Gly\text{-}X\text{-}Y)_n$. The smallest amino acid,

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Each collagen molecule consists of 3 polypeptide α-chains held together by hydrogen bonds, forming a triple helix. Collagen assumes this conformation because each of the α-chains has a simple, repetitive amino acid sequence represented as $(Gly\text{-}X\text{-}Y)_n$. The smallest amino acid, glycine (Gly), is necessary at every third position to ensure compact coiling of the helix. Many of the amino acids represented by X and Y are proline residues, which kink the polypeptide chain and enhance the rigidity of the helical structure due to their ring configuration.

Mature collagen is synthesized by fibroblasts, osteoblasts, and chondroblasts through the following steps:

1. As translation begins in the cytoplasm, an amino acid signal sequence at the N-terminus of the α-chain facilitates ribosomal binding to the rough endoplasmic reticulum (RER) and passage of the growing polypeptide chain (pre-pro-α-chain) into the RER.
2. Inside the RER, the hydrophobic signal sequence is cleaved to yield the pro-α-chain. Proline and lysine at the Y positions of the pro-α-chain are hydroxylated to hydroxyproline and hydroxylysine, respectively **(Choice D)**. Glycosylation of select hydroxylysine residues also occurs within the RER **(Choice A)**.
3. The central helical region of the pro-α-chain is flanked by N- and C-terminal propeptides. Disulfide bond formation between the C-terminal propeptide region of 3 α-chains brings the chains into an alignment favorable for assembly into a triple helix (procollagen molecule) **(Choices B and E)**.
4. Procollagen molecules are then transported through the Golgi apparatus into the extracellular space. The N- and C-terminal propeptides are cleaved by procollagen peptidases, converting procollagen into less soluble tropocollagen.
5. Tropocollagen monomers self-assemble into collagen fibrils. Finally, lysyl oxidase helps create covalent crosslinks between collagen fibrils to form strong collagen fibers.

Educational objective:

Mature collagen is synthesized by fibroblasts, osteoblasts, and chondroblasts through the following steps:

1. As translation begins in the cytoplasm, an amino acid signal sequence at the N-terminus of the α-chain facilitates ribosomal binding to the rough endoplasmic reticulum (RER) and passage of the growing polypeptide chain (pre-pro-α-chain) into the RER.
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5. Tropocollagen monomers self-assemble into collagen fibrils. Finally, lysyl oxidase helps create covalent crosslinks between collagen fibrils to form strong collagen fibers.

Educational objective:
Ehlers-Danlos syndrome is a group of rare hereditary disorders characterized by defective collagen synthesis. It can be caused by procollagen peptidase deficiency, which results in impaired cleavage of terminal propeptides in the extracellular space. Patients often have joint laxity, hyperextensible skin, and tissue fragility due to the formation of soluble collagen that does not properly crosslink.

References

- Defect in conversion of procollagen to collagen in a form of Ehlers-Danlos syndrome.
- Defects in the biochemistry of collagen in diseases of connective tissue.

A 2-year-old boy is brought to the office by his parents. He is currently toilet-training during the day and at nighttime. After he urinated in the toilet last night, his parents forgot to flush the toilet and noticed that the boy's urine turned black overnight. The child has no significant past medical history and takes no medications. He can say 2-word sentences, follow 2-step directions, and jump with 2 feet off the ground. Examination shows a well-nourished child with no swelling or tenderness of any joints. Urinalysis results are as follows:

Color	black
Specific gravity	1.022
Protein	none
Blood	negative
Glucose	negative
Ketones	negative
Leukocyte esterase	negative

Which of the following conversion pathways is most likely deficient in this patient?

A. Leucine to acetoacetate
B. Phenylalanine to tyrosine
C. Serine to cysteine
D. Tyrosine to fumarate
E. Valine to glutamic acid

a well-nourished child with no swelling or tenderness of any joints. Urinalysis results are as follows:

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Submit

a well-nourished child with no swelling or tenderness of any joints. Urinalysis results are as follows:

Color	black
Specific gravity	1.022
Protein	none
Blood	negative
Glucose	negative
Ketones	negative
Leukocyte esterase	negative

Which of the following conversion pathways is most likely deficient in this patient?

- A. Leucine to acetoacetate [6%]
- B. Phenylalanine to tyrosine [19%]
- C. Serine to cysteine [15%]
- ✔ D. Tyrosine to fumarate [54%]
- E. Valine to glutamic acid [3%]

Omitted
Correct answer

54%
Answered correctly

7 Seconds
Time Spent

10/19/2018
Last Updated

Explanation

Alkaptonuria is an **autosomal recessive** disorder of **tyrosine metabolism**. Deficiency of homogentisic acid dioxygenase blocks homogentisic acid metabolism, preventing the conversion of tyrosine to fumarate. Homogentisic acid accumulates in the body and is excreted in the urine, imparting a **black color** to the **urine** if allowed to sit and undergo oxidation. In patients with alkaptonuria, the retained homogentisic acid selectively binds to collagen in connective tissues, tendons, and cartilage. This leads to "**ochronosis**," a blue-black pigmentation most evident in the ears, nose, and cheeks, and **ochronotic arthropathy**, which typically manifests during adulthood.

(Choice A) Leucine is a branched-chain amino acid that is elevated in maple syrup urine disease. Isoleucine and valine are also increased. Impaired metabolism of these amino acids leads to cerebral edema, seizures, and a sweet smell of the urine.

(Choice B) Conversion of phenylalanine to tyrosine is defective in phenylketonuria and usually occurs due to a defect in phenylalanine hydroxylase. Undiagnosed and untreated phenylketonuria results in significant intellectual disability not seen in this patient.

(Choice C) Impaired renal cystine (a homodimer of cysteine) transport leads to cystinuria, a disease characterized by flank pain, hematuria, and renal stones in childhood or adolescence.

(Choice E) Sickle cell anemia results from the substitution of valine for glutamic acid due to a single-nucleotide polymorphism. This mutation leads to loss of red cell elasticity, polymerization of sickle hemoglobin, and sickling of red blood cells, which results in vasoocclusive crises.

Educational objective:
Alkaptonuria is an autosomal recessive disorder in which the lack of homogentisic acid dioxygenase blocks the metabolism of tyrosine, leading to an accumulation of homogentisic acid. Clinical features include a black urine color when exposed to air, a blue-black pigmentation on the face, and ochronotic arthropathy.

References

- Alkaptonuria.

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Item 30 of 40
Question Id: 1386

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Molecular biologists studying the properties of hemoglobin are investigating the structural changes associated with oxygen loading and unloading. During the transition from point 1 to point 2 on the graph shown below, hemoglobin molecules are most likely to release which of the following?

A. Chloride
B. Heme
C. Oxygen
D. Phosphate
E. Protons

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Item 30 of 40
Question Id: 1386

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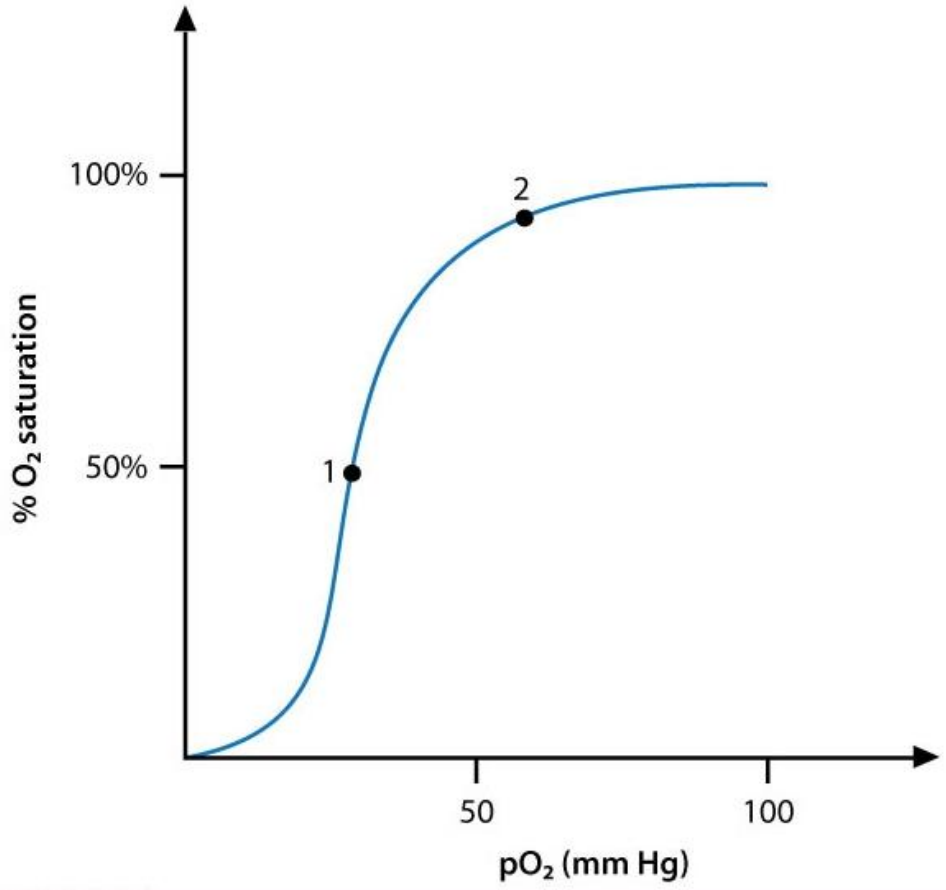

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Item 30 of 40
Question Id: 1386

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

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Block Time Remaining: 00:03:15
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Molecular biologists studying the properties of hemoglobin are investigating the structural changes associated with oxygen loading and unloading. During the transition from point 1 to point 2 on the graph shown below, hemoglobin molecules are most likely to release which of the following?

- A. Chloride [13%]
- B. Heme [1%]
- C. Oxygen [19%]
- D. Phosphate [6%]
- ✔ E. Protons [58%]

Omitted
Correct answer
E

58%
Answered correctly

3 Seconds
Time Spent

01/08/2019
Last Updated

Explanation

The transition from point 1 to 2 on the graph represents the loading of O_2 onto partially deoxygenated hemoglobin as occurs in the **lungs**. At very low partial pressure of O_2 (pO_2), hemoglobin is mostly deoxygenated, and binding of O_2 molecules is relatively difficult (as indicated by the early flatness of the curve). As the partial pressure of O_2 increases, O_2 binds to 1 of the 4 binding sites on hemoglobin and **increases the O_2-binding affinity** of the other available binding sites (steepening of the curve), a phenomenon known as **cooperative binding**. Subsequently, additional O_2 molecules bind more easily as the pO_2 increases until hemoglobin becomes nearly fully saturated.

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The binding of O_2 molecules to hemoglobin in the lungs has two consequences, known as the **Haldane effect**:

- The affinity of hemoglobin for CO_2 is decreased, resulting in unloading of CO_2 from hemoglobin (this accounts for a small percentage of overall CO_2 in the blood and is not pictured above).
- The acidity of the hemoglobin molecule is increased; in response, **protons (H^+ ions) are released** from the hemoglobin binding sites.

The H^+ ions combine with bicarbonate ions (the primary form of CO_2 in the blood) in the lungs to facilitate the production of water (H_2O) and CO_2. The CO_2 is then transferred to the alveoli and expired while oxygen is taken up by hemoglobin.

In the peripheral tissues, high levels of CO_2 create an increase in ambient acidity that shifts the **hemoglobin dissociation curve** to the right and facilitates the unloading of O_2 (**Bohr effect**). The CO_2 (and water) are converted into H^+ and HCO_3^-. The H^+ ions are carried by hemoglobin while the HCO_3^- is transferred to the plasma for transport back to the lungs.

(Choice A) In the lungs, chloride ions shift out of red blood cells and into the plasma in exchange for HCO_3^-. These chloride ions are not bound to or released by hemoglobin.

(Choice B) Heme is not released from hemoglobin during O_2 loading or unloading. However, it is released during the normal destruction of aged red blood cells in the spleen.

(Choice C) O_2 molecules bind to hemoglobin to increase hemoglobin saturation.

(Choice D) 2,3-diphosphoglycerate contains 2 phosphate groups and binds to hemoglobin to facilitate unloading of O_2 in the tissues. However, phosphate molecules are not directly bound or released by hemoglobin.

Educational objective:

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Educational objective:
The binding of O_2 to hemoglobin increases the affinity for binding of subsequent O_2 molecules (cooperative binding). In the lungs, the binding of O_2 to hemoglobin drives the release of H^+ and CO_2 from hemoglobin (Haldane effect). In the peripheral tissues, high concentrations of CO_2 and H^+ facilitate O_2 unloading from hemoglobin (Bohr effect).

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Question Id: 1386

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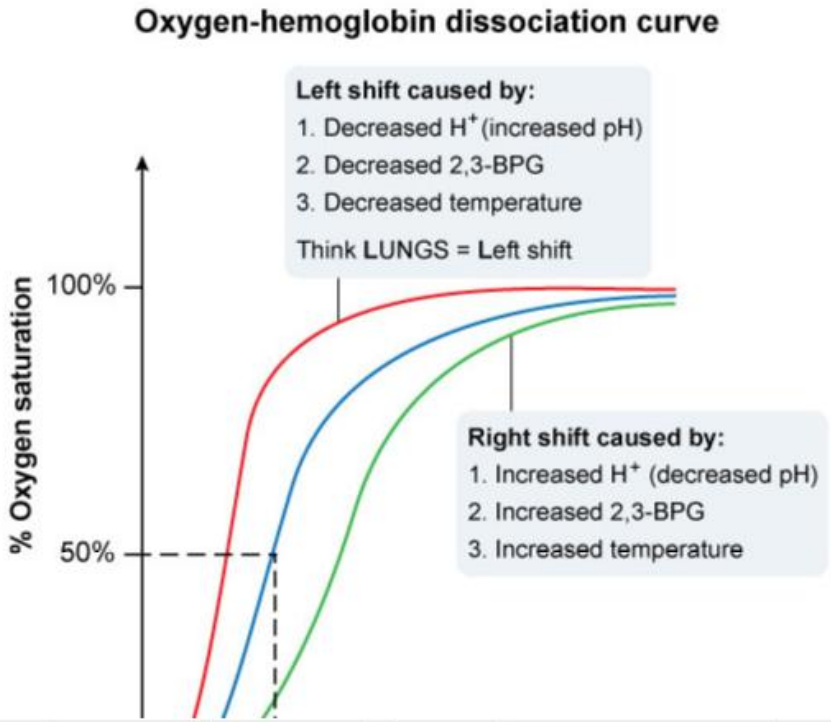

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Item 30 of 40
Question Id: 1386

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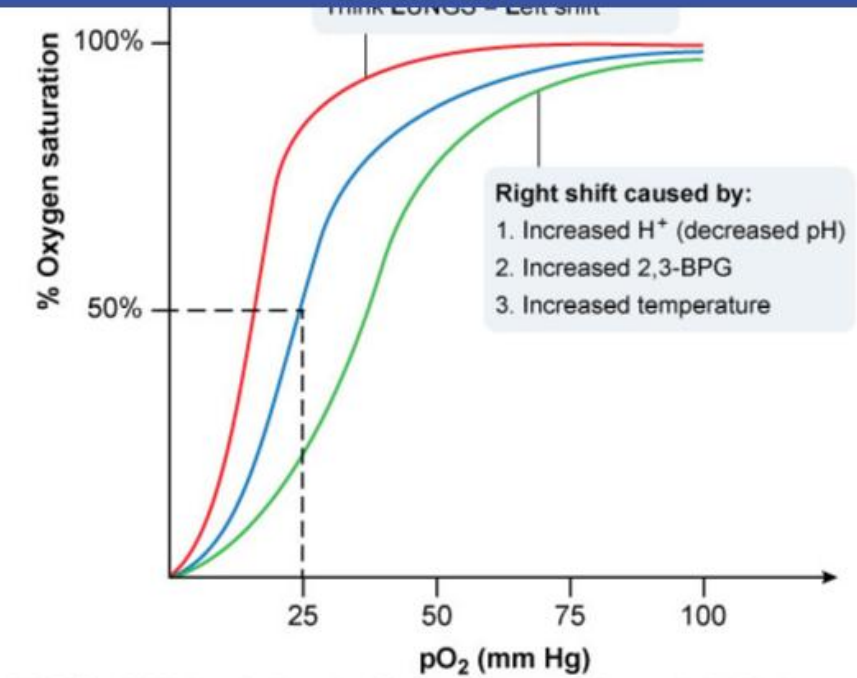
Exhibit Display



2,3-BPG = 2,3-bisphosphoglycerate; pO_2 = partial pressure of oxygen in the blood.

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Item 31 of 40
Question Id: 1471

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A microbiologist performs a genetic experiment in which cultures of *Escherichia coli* are treated with a chemical that induces a high frequency of mutations. Individual bacterial colonies are isolated to identify a mutant strain that lacks a specific enzyme involved in DNA replication. This specific enzyme is responsible for removing short fragments of RNA that are base paired to the DNA template. Which of the following enzymes is most likely deficient in this strain of *E coli*?

- A. DNA polymerase I
- B. DNA polymerase III
- C. Gyrase
- D. Helicase
- E. Ligase
- F. Primase

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Item 31 of 40
Question Id: 1471

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A microbiologist performs a genetic experiment in which cultures of *Escherichia coli* are treated with a chemical that induces a high frequency of mutations. Individual bacterial colonies are isolated to identify a mutant strain that lacks a specific enzyme involved in DNA replication. This specific enzyme is responsible for removing short fragments of RNA that are base paired to the DNA template. Which of the following enzymes is most likely deficient in this strain of *E coli*?

- A. DNA polymerase I [55%] ✔
- B. DNA polymerase III [17%]
- C. Gyrase [3%]
- D. Helicase [1%]
- E. Ligase [8%]
- F. Primase [13%]

Omitted
Correct answer
A

55%
Answered correctly

3 Seconds
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Last Updated

Explanation

Prokaryotic DNA replication fork

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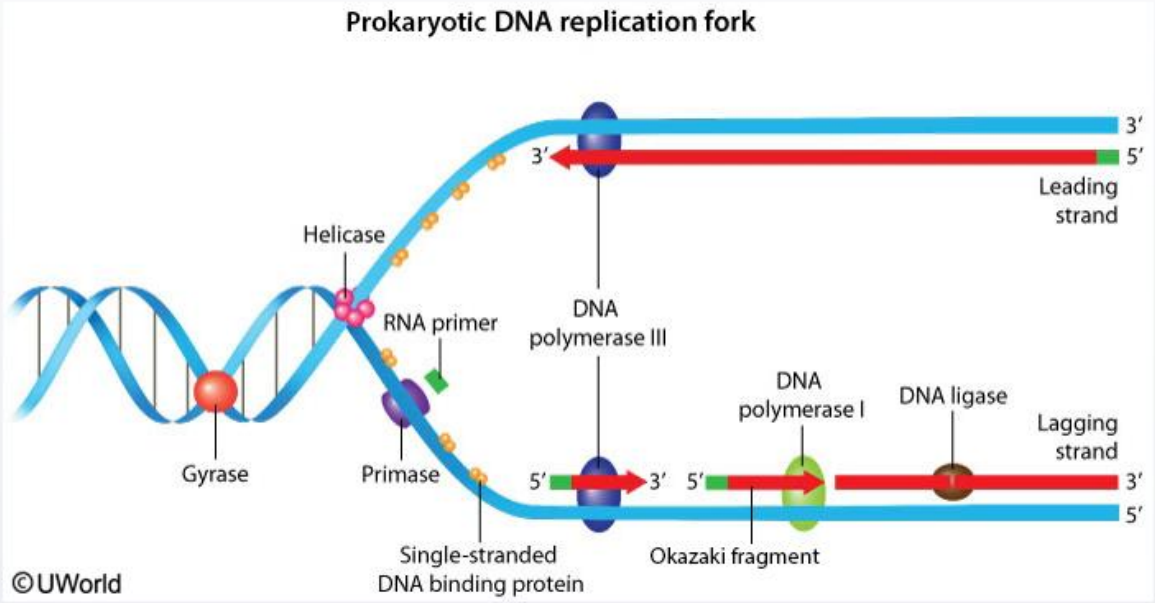
A

Answered correctly | Time Spent | Last Updated

Explanation



Bacterial DNA replication is coordinated by the actions of multiple enzymes and **proteins**. Before DNA synthesis begins, helicase binds double-stranded DNA at the origin of replication with the assistance of DnaA protein and acts at the replication fork to unwind and separate the DNA **(Choice D)**. Single-stranded DNA-binding protein then attaches to the separated strands to prevent their reannealing. Unwinding and separation of DNA produces positive supercoils that can lead to DNA fracture if not relieved. Topoisomerase II (DNA gyrase) relieves the tension created

Bacterial DNA replication is coordinated by the actions of multiple enzymes and proteins. Before DNA synthesis begins, helicase binds double-stranded DNA at the origin of replication with the assistance of DnaA protein and acts at the replication fork to unwind and separate the DNA **(Choice D)**. Single-stranded DNA-binding protein then attaches to the separated strands to prevent their reannealing. Unwinding and separation of DNA produces positive supercoils that can lead to DNA fracture if not relieved. Topoisomerase II (DNA gyrase) relieves the tension created during unwinding by introducing negative supercoils into the DNA **(Choice C)**.

Before DNA polymerase III can begin elongating a new DNA strand, it requires an RNA primer made up of short RNA sequences base-paired to the parent DNA. This primer is synthesized by the enzyme primase (DNA-dependent RNA polymerase) **(Choice F)**. DNA synthesis then proceeds in the 5' to 3' direction with the leading strand being formed continuously toward the replication fork and the lagging strand being formed discontinuously away from the replication fork. Replication of the lagging strand results in the formation of numerous short DNA segments called Okazaki fragments. These fragments are ultimately bound together by the enzyme ligase after their RNA primers have been removed and replaced with DNA **(Choice E)**.

The **removal of RNA primers** and their replacement with DNA is accomplished by **DNA polymerase I**, the only bacterial DNA polymerase with **5' to 3' exonuclease activity**. DNA polymerase III has 5' to 3' polymerase and 3' to 5' exonuclease ("proofreading") activity; however, it cannot remove RNA primers as it lacks 5' to 3' exonuclease activity **(Choice B)**.

Educational objective:
During bacterial DNA replication, DNA polymerase I functions to remove RNA primers (via 5' to 3' exonuclease activity) and replace them with DNA (via 5' to 3' polymerase activity). DNA polymerase I is the only bacterial DNA polymerase that possesses 5' to 3' exonuclease activity.

References

- DNA replication fidelity in Escherichia coli: a multi-DNA polymerase affair.

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Exhibit Display

Proteins & their function in prokaryotic DNA replication	
Helicase	Unwinding of double helix
Topoisomerase II (DNA gyrase)	Removal of supercoils
Single-stranded DNA-binding protein	Stabilization of unwound template strands
Primase (RNA polymerase)	Synthesis of RNA primer
DNA polymerase III	5' to 3' DNA synthesis & 3' to 5' exonuclease ("proofreading") activity
DNA polymerase I	Same as DNA polymerase III Also removes RNA primer (5' to 3' exonuclease

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Exhibit Display

DNA-binding protein	
Primase (RNA polymerase)	Synthesis of RNA primer
DNA polymerase III	5' to 3' DNA synthesis & 3' to 5' exonuclease ("proofreading") activity
DNA polymerase I	Same as DNA polymerase III Also removes RNA primer (5' to 3' exonuclease activity) & replaces it with DNA
DNA ligase	Joining of Okazaki fragments (lagging strand)

Zoom In | Zoom Out | Reset | Add To Flash Card

Settings

Item 32 of 40
Question Id: 1029

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A researcher is studying the role of glucose metabolites in normal cellular function. A specific human cell type is incubated in glucose-rich media. Intracellular levels of glucose metabolizing enzymes, intermediate products, and generated ATP are measured. In these cells, glycolysis of a single glucose molecule always yields pyruvate but sometimes generates no net ATP. Which of the following cells is most likely being studied in this experiment?

- A. Adipocytes
- B. Erythrocytes
- C. Hepatocytes
- D. Neurons
- E. Skeletal muscle cells

Submit

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A researcher is studying the role of glucose metabolites in normal cellular function. A specific human cell type is incubated in glucose-rich media. Intracellular levels of glucose metabolizing enzymes, intermediate products, and generated ATP are measured. In these cells, glycolysis of a single glucose molecule always yields pyruvate but sometimes generates no net ATP. Which of the following cells is most likely being studied in this experiment?

- A. Adipocytes [8%]
- ✔ B. Erythrocytes [70%]
- C. Hepatocytes [8%]
- D. Neurons [2%]
- E. Skeletal muscle cells [9%]

Omitted
Correct answer
B

70%
Answered correctly

3 Seconds
Time Spent

09/20/2018
Last Updated

Explanation

Erythrocytes use glycolysis as the major pathway to generate energy as they do not have mitochondria and therefore cannot use the citric acid cycle. During normal glycolysis, ATP is generated when 1,3-BPG is converted to 3-phosphoglycerate by the enzyme phosphoglycerate kinase. However, erythrocytes can bypass this part of the pathway using **bisphosphoglycerate mutase**, an enzyme that converts 1,3-BPG to **2,3-BPG** in

Explanation

Erythrocytes use glycolysis as the major pathway to generate energy as they do not have mitochondria and therefore cannot use the citric acid cycle. During normal glycolysis, ATP is generated when 1,3-BPG is converted to 3-phosphoglycerate by the enzyme phosphoglycerate kinase. However, erythrocytes can bypass this part of the pathway using **bisphosphoglycerate mutase**, an enzyme that converts 1,3-BPG to **2,3-BPG** in a step that produces **no ATP**. 2,3-BPG is subsequently catabolized to 3-phosphoglycerate by bisphosphoglycerate phosphatase in a step that also yields no ATP. By generating 2,3-BPG rather than proceeding with regular glycolysis, erythrocytes sacrifice the net ATP gain achieved in normal glycolysis.

The major function of erythrocytes is to carry hemoglobin-bound oxygen from the lungs to the peripheral tissues, and 2,3-BPG is a very important regulator of oxygen-hemoglobin binding. The conversion of 1,3-BPG to 2,3-BPG is increased in **hypoxia** and chronic anemia. 2,3-BPG allosterically decreases hemoglobin's affinity for oxygen. As a result, in the presence of lower blood oxygen concentrations, higher 2,3-BPG levels within erythrocytes enable **increased oxygen delivery** in the peripheral tissues.

(Choices A, C, D, and E) The enzyme bisphosphoglycerate mutase is present in large amounts in erythrocytes. However, it is present in insignificant quantities in adipocytes, hepatocytes, neurons, and myocytes; this causes virtually negligible 2,3-BPG production in these cell types.

Educational objective:
2,3-BPG decreases hemoglobin's affinity for oxygen. Therefore, in the presence of lower blood oxygen concentrations, higher 2,3-BPG levels within erythrocytes enable increased oxygen delivery in the peripheral tissues. 2,3-BPG is produced from 1,3-BPG by the enzyme bisphosphoglycerate mutase. This reaction bypasses an ATP-generating step of glycolysis, causing no net gain in ATP.

References

- Dephosphorylation of 2,3-bisphosphoglycerate by MIPP expands the regulatory capacity of the Rapoport-Luebering glycolytic shunt.
- The energy-less red blood cell is lost: erythrocyte enzyme abnormalities of glycolysis.

A 23-year-old man is brought to the emergency department by paramedics following a motor vehicle accident. He was an unrestrained passenger in the front seat. Several days after hospitalization, his fluid volume and plasma osmolarity are measured and illustrated in the image below (solid line, normal; dotted line, patient).

Which of the following conditions is most likely to cause the findings shown in the image?

- A. Acute gastrointestinal hemorrhage
- B. Adrenal insufficiency
- C. Diabetes insipidus
- D. Hypertonic saline infusion
- E. Primary polydipsia

Submit

Settings

Item 33 of 40
Question Id: 1379

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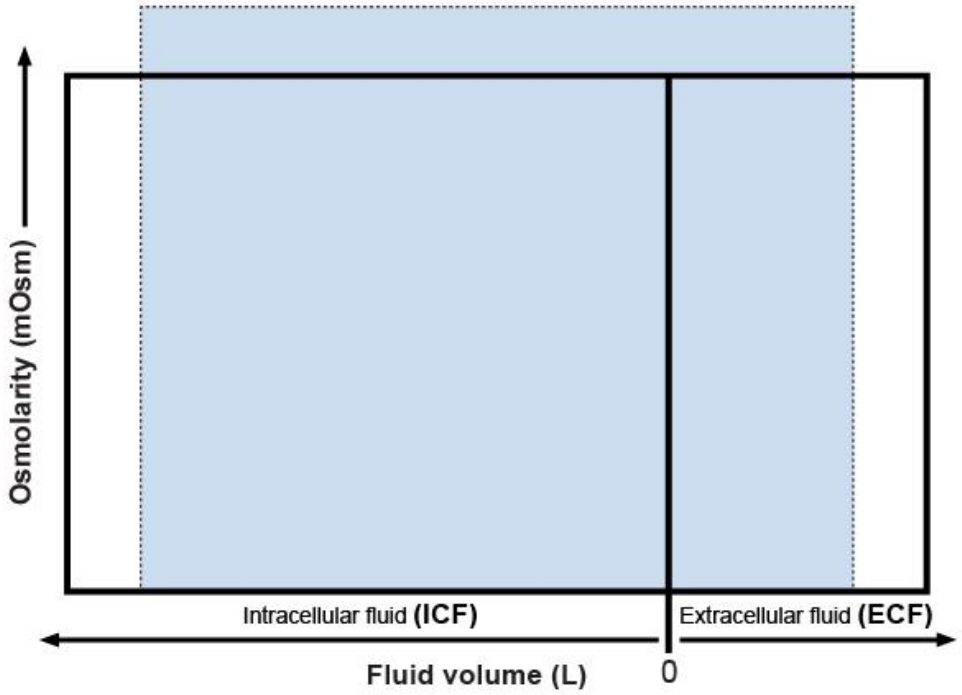

Which of the following conditions is most likely to cause the findings shown in the image?

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A 23-year-old man is brought to the emergency department by paramedics following a motor vehicle accident. He was an unrestrained passenger in the front seat. Several days after hospitalization, his fluid volume and plasma osmolarity are measured and illustrated in the image below (solid line, normal; dotted line, patient).

Which of the following conditions is most likely to cause the findings shown in the image?

- A. Acute gastrointestinal hemorrhage
- B. Adrenal insufficiency
- C. Diabetes insipidus
- D. Hypertonic saline infusion
- E. Primary polydipsia

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Item 33 of 40
Question Id: 1379

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A 23-year-old man is brought to the emergency department by paramedics following a motor vehicle accident. He was an unrestrained passenger in the front seat. Several days after hospitalization, his fluid volume and plasma osmolarity are measured and illustrated in the image below (solid line, normal; dotted line, patient).

Which of the following conditions is most likely to cause the findings shown in the image?

- A. Acute gastrointestinal hemorrhage [17%]
- B. Adrenal insufficiency [7%]
- ✔ C. Diabetes insipidus [55%]
- D. Hypertonic saline infusion [14%]
- E. Primary polydipsia [3%]

Omitted
Correct answer
C

55%
Answered correctly

3 Seconds
Time Spent

09/07/2018
Last Updated

Explanation

The figure shows the volume of the intracellular (ICF) and extracellular (ECF) fluid compartments (x-axis) and the osmolarity of the fluid in those compartments (y-axis).

This patient's recent head trauma is consistent with central diabetes insipidus due to hypothalamic/pituitary damage. The resulting decrease in

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Explanation

The figure shows the volume of the intracellular (ICF) and extracellular (ECF) fluid compartments (x-axis) and the osmolarity of the fluid in those compartments (y-axis).

This patient's recent head trauma is consistent with central diabetes insipidus due to hypothalamic/pituitary damage. The resulting decrease in vasopressin secretion leads to excessive free water excretion by the kidneys, causing **hyperosmotic volume contraction**. This condition occurs when the loss of free water exceeds the loss of electrolytes, resulting in increased osmolarity and contracted volumes in both the ICF and ECF compartments. Hyperosmotic volume contraction can occur in the setting of **diabetes insipidus**, decreased fluid intake (**dehydration**), and with **profuse sweating** (due to the hypotonic nature of sweat).

(Choice A) **Acute gastrointestinal hemorrhage** (or diarrhea) would cause an isotonic loss of ECF volume, with no effects on osmolarity or ICF volume. This is referred to as isosmotic volume contraction.

(Choice B) The lack of aldosterone in **adrenal insufficiency** causes loss of NaCl with ECF volume depletion (hyposmotic volume contraction). The low osmolarity of the ECF results in shifting of free water into the ICF compartment, causing ICF expansion.

(Choice D) Infusion of large amounts of **hypertonic saline** leads to hypertonic volume expansion. Both the volume and osmolarity of the ECF are increased. The high osmolarity of the ECF leads to shifting of water from the ICF, further increasing the ECF volume.

(Choice E) **Primary polydipsia** (excessive water consumption) and SIADH (inappropriately high vasopressin levels) both cause retention of free water in the body. This leads to expansion of the ICF compartment and a decrease in the osmolarity of both compartments (hyposmotic volume expansion). Expansion of the ECF compartment is limited in these conditions due to compensatory secretion of aldosterone and natriuretic peptides, which help to normalize the extracellular fluid volume. Thus, affected patients are clinically euvolemic.

Educational objective:
Volume contraction and expansion can be divided into isosmotic, hyposmotic, and hyperosmotic states. Hyperosmotic volume contraction is caused by a loss of free water (with retention of electrolytes). It can occur in patients with diabetes insipidus or as a result of decreased fluid

compartments (y-axis).

This patient's recent head trauma is consistent with central diabetes insipidus due to hypothalamic/pituitary damage. The resulting decrease in vasopressin secretion leads to excessive free water excretion by the kidneys, causing **hyperosmotic volume contraction**. This condition occurs when the loss of free water exceeds the loss of electrolytes, resulting in increased osmolarity and contracted volumes in both the ICF and ECF compartments. Hyperosmotic volume contraction can occur in the setting of **diabetes insipidus**, decreased fluid intake (**dehydration**), and with **profuse sweating** (due to the hypotonic nature of sweat).

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(Choice D) Infusion of large amounts of **hypertonic saline** leads to hypertonic volume expansion. Both the volume and osmolarity of the ECF are increased. The high osmolarity of the ECF leads to shifting of water from the ICF, further increasing the ECF volume.

(Choice E) **Primary polydipsia** (excessive water consumption) and SIADH (inappropriately high vasopressin levels) both cause retention of free water in the body. This leads to expansion of the ICF compartment and a decrease in the osmolarity of both compartments (hyposmotic volume expansion). Expansion of the ECF compartment is limited in these conditions due to compensatory secretion of aldosterone and natriuretic peptides, which help to normalize the extracellular fluid volume. Thus, affected patients are clinically euvolemic.

Educational objective:
Volume contraction and expansion can be divided into isosmotic, hyposmotic, and hyperosmotic states. Hyperosmotic volume contraction is caused by a loss of free water (with retention of electrolytes). It can occur in patients with diabetes insipidus or as a result of decreased fluid intake/excessive sweating.

Settings

Item 34 of 40
Question Id: 1456

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A 34-year-old man comes to the emergency department due to a facial injury. He reports getting hit on the face during a fistfight at a bar. Examination shows dark blue periorbital ecchymosis on the right side. Ophthalmic and neurologic examinations are otherwise normal. After appropriate evaluation, the patient is discharged home. Several days later, the bruise becomes greenish in color. This change in color is best explained by the activity of which of the following enzymes?

A. Bilirubin glucuronyl transferase
B. Ferrochelatase
C. Heme oxygenase
D. Porphobilinogen deaminase
E. Uroporphyrinogen decarboxylase

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Item 34 of 40
Question Id: 1456

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 34-year-old man comes to the emergency department due to a facial injury. He reports getting hit on the face during a fistfight at a bar. Examination shows dark blue periorbital ecchymosis on the right side. Ophthalmic and neurologic examinations are otherwise normal. After appropriate evaluation, the patient is discharged home. Several days later, the bruise becomes greenish in color. This change in color is best explained by the activity of which of the following enzymes?

- A. Bilirubin glucuronyl transferase [17%]
- B. Ferrochelatase [8%]
- ✔ C. Heme oxygenase [54%]
- D. Porphobilinogen deaminase [12%]
- E. Uroporphyrinogen decarboxylase [6%]

Omitted
Correct answer
C

54%
Answered correctly

6 Seconds
Time Spent

08/22/2018
Last Updated

Explanation

This patient has a resolving **hematoma** after a traumatic injury. Following the injury, hemoglobin-containing erythrocytes escape into the periorbital tissues, giving the bruise its initial purple or bluish color. Erythrocyte destruction causes the release of iron-containing heme molecules. **Heme oxygenase** (contained in macrophages, among other cells) degrades heme into **biliverdin**, carbon monoxide, and ferrous iron while

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Omitted
Correct answer
C

54%
Answered correctly

6 Seconds
Time Spent

08/22/2018
Last Updated

Explanation

This patient has a resolving **hematoma** after a traumatic injury. Following the injury, hemoglobin-containing erythrocytes escape into the periorbital tissues, giving the bruise its initial purple or bluish color. Erythrocyte destruction causes the release of iron-containing heme molecules. **Heme oxygenase** (contained in macrophages, among other cells) degrades heme into **biliverdin**, carbon monoxide, and ferrous iron while consuming oxygen and electrons provided by NADH and NADPH-cytochrome P450 reductase. Biliverdin is **green** in color and is further reduced (by the enzyme biliverdin reductase) to the yellow pigment bilirubin, which is then transported to the liver bound to albumin.

(Choice A) Bilirubin glucuronyl transferase, or uridine 5'-diphospho-glucuronyl transferase (UGT), is the enzyme necessary for bilirubin conjugation to glucuronic acid. Lack of UGT or the use of medications that interfere with its activity impairs the liver's ability to conjugate bilirubin.

(Choices B, D, and E) Ferrochelatase (inhibited by lead) is the final enzyme in the heme synthetic pathway. Porphobilinogen deaminase (PBG deaminase) and uroporphyrinogen decarboxylase (UROD) are also involved in heme production, not degradation; UROD deficiency can be seen in porphyria cutanea tarda, the most common porphyria, and PBG deaminase deficiency can be seen in **acute intermittent porphyria**.

Educational objective:
Heme oxygenase converts heme to biliverdin, a pigment that causes the greenish color to develop in bruises several days after an injury.

Settings

Item 35 of 40
Question Id: 1384

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 13-year-old girl is undergoing hematologic evaluation. She is found to have a hemoglobin mutation that changes the partial pressure of oxygen at which hemoglobin is 50% saturated to 20 mm Hg. In comparison, normal hemoglobin becomes 50% saturated with oxygen at 26 mm Hg. Which of the following sequelae is this patient most likely to develop as a result of her mutation?

A. Erythrocytosis
B. Hypoxia-induced hemolysis
C. Increased erythrocyte osmotic fragility
D. Megaloblastic erythrocyte changes
E. Oxidant-induced hemolysis

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Item 35 of 40
Question Id: 1384

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 13-year-old girl is undergoing hematologic evaluation. She is found to have a hemoglobin mutation that changes the partial pressure of oxygen at which hemoglobin is 50% saturated to 20 mm Hg. In comparison, normal hemoglobin becomes 50% saturated with oxygen at 26 mm Hg. Which of the following sequelae is this patient most likely to develop as a result of her mutation?

- A. Erythrocytosis [53%]
- B. Hypoxia-induced hemolysis [20%]
- C. Increased erythrocyte osmotic fragility [7%]
- D. Megaloblastic erythrocyte changes [2%]
- E. Oxidant-induced hemolysis [16%]

Omitted
Correct answer
A

53%
Answered correctly

3 Seconds
Time Spent

09/07/2018
Last Updated

Explanation

Oxygen-hemoglobin dissociation curve

Left shift caused by:
1. Decreased H^+ (increased pH)

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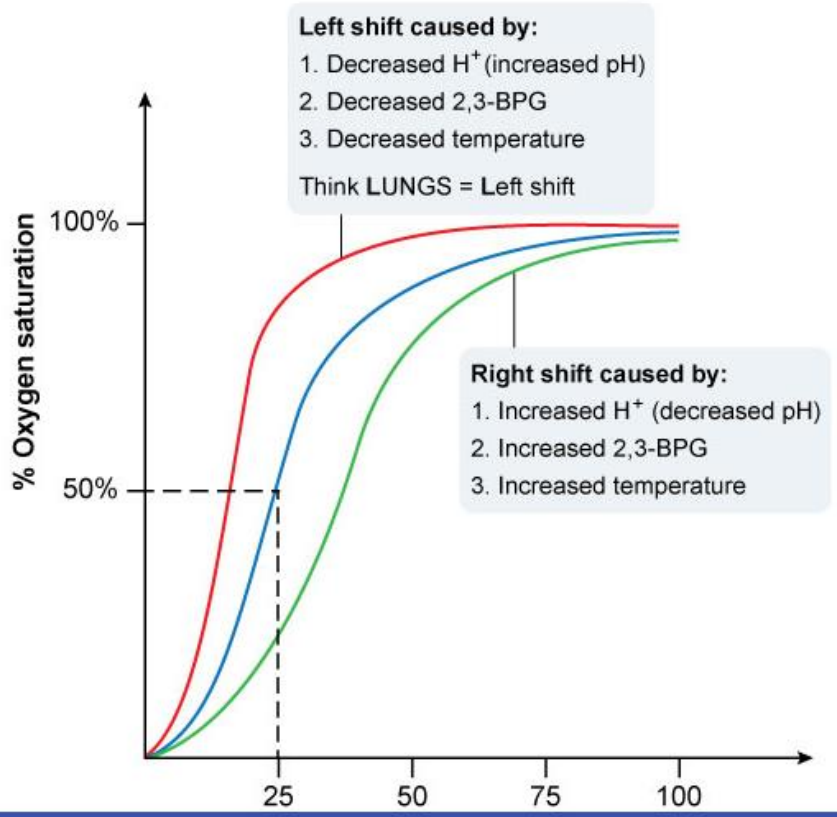
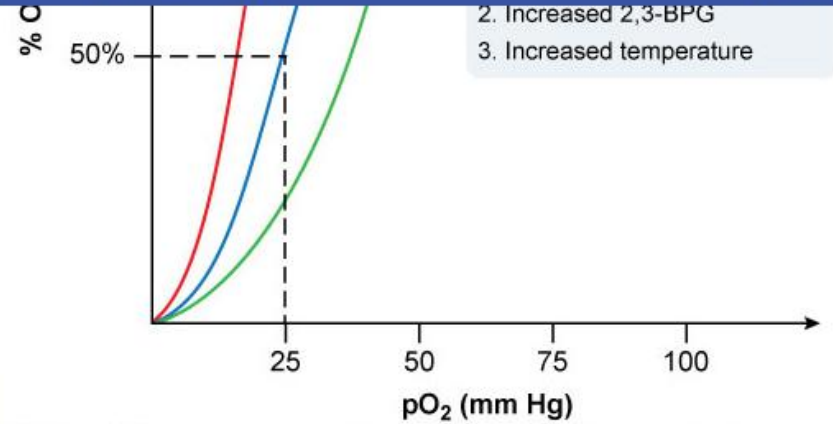
Oxygen-hemoglobin dissociation curve





2,3-BPG = 2,3-bisphosphoglycerate; **pO_2** = partial pressure of oxygen in the blood.

The **oxygen-hemoglobin dissociation curve** describes the relationship between the partial pressure of oxygen in the blood and the oxygen saturation of hemoglobin. The partial pressure of oxygen at which hemoglobin is 50% saturated (**P_{50}**) is a value used as a conventional measure of hemoglobin's affinity for oxygen. The P_{50} is about 26 mm Hg in normal individuals. A P_{50} **shift from 26 to 20 mm Hg** indicates that the affinity of hemoglobin for oxygen is increased (left shift of the oxygen dissociation curve).

Mutations that cause production of hemoglobin with **high oxygen affinity** (eg, hemoglobins Chesapeake and Kempsey) reduce the ability of hemoglobin to release oxygen within the peripheral tissues. Low oxygen levels stimulate the kidneys to increase erythropoietin synthesis, which results in a **compensatory erythrocytosis** that helps maintain normal oxygen delivery. Therefore, patients with high oxygen affinity hemoglobins are typically asymptomatic.

(Choice B) Sickle cell disease can result in hypoxia-induced hemolysis due to the ability of deoxygenated hemoglobin S to polymerize and cause excessive erythrocyte sickling and irreversible cell membrane damage. The oxygen dissociation curve for hemoglobin S is shifted to the right (↓ oxygen affinity) due to the stabilizing effects of polymerization on the deoxygenated form.

of hemoglobin's affinity for oxygen. The P_{50} is about 26 mm Hg in normal individuals. A P_{50} **shift from 26 to 20 mm Hg** indicates that the affinity of hemoglobin for oxygen is increased (left shift of the oxygen dissociation curve).

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(Choice B) Sickle cell disease can result in hypoxia-induced hemolysis due to the ability of deoxygenated hemoglobin S to polymerize and cause excessive erythrocyte sickling and irreversible cell membrane damage. The oxygen dissociation curve for hemoglobin S is shifted to the right (↓ oxygen affinity) due to the stabilizing effects of polymerization on the deoxygenated form.

(Choice C) Hereditary spherocytosis results from a variety of molecular defects involving erythrocyte structural proteins responsible for linking the plasma membrane to the cytoskeleton (eg, spectrin, ankyrin). The resulting membrane instability leads to the formation of spherocytes – small, rounded erythrocytes with increased susceptibility to lyse in hypotonic solutions.

(Choice D) Megaloblastic erythrocyte changes (↑ MCV) are characteristically seen in vitamin B_{12} and folic acid deficiency due to impaired DNA synthesis.

(Choice E) Individuals with glucose-6-phosphate dehydrogenase deficiency develop rapid hemolysis during periods of increased oxidant stress, such as when taking antimalarials or sulfonamides or after ingestion of fava beans.

Educational objective:
P_{50} refers to the partial pressure of oxygen at which hemoglobin is 50% saturated. Hemoglobins with high oxygen affinity have a decreased P_{50} that is represented by a leftward shift of the oxygen dissociation curve. The reduced ability to release oxygen within the peripheral tissues leads to renal hypoxia, increased erythropoietin synthesis, and compensatory erythrocytosis.

References

Settings

Item 36 of 40
Question Id: 1415

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A 34-year-old industry worker experiences rapid-onset shortness of breath, dizziness, palpitations, and flushed skin after accidental exposure to chemical fumes. Examination by an occupational physician shows that the patient is tachypneic and has a reddish discoloration of the skin without cyanosis. The patient is immediately instructed to inhale amyl nitrite from the safety kit. The success of this antidote is dependent upon its ability to convert hemoglobin into a form with increased affinity for which of the following substances?

- A. 2,3-biphosphoglycerate
- B. Carbon dioxide
- C. Carbon monoxide
- D. Cyanide
- E. Iron
- F. Lead

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Item 36 of 40
Question Id: 1415

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 34-year-old industry worker experiences rapid-onset shortness of breath, dizziness, palpitations, and flushed skin after accidental exposure to chemical fumes. Examination by an occupational physician shows that the patient is tachypneic and has a reddish discoloration of the skin without cyanosis. The patient is immediately instructed to inhale amyl nitrite from the safety kit. The success of this antidote is dependent upon its ability to convert hemoglobin into a form with increased affinity for which of the following substances?

- A. 2,3-biphosphoglycerate [23%]
- B. Carbon dioxide [9%]
- C. Carbon monoxide [8%]
- ✔ D. Cyanide [50%]
- E. Iron [6%]
- F. Lead [0%]

Omitted
Correct answer
D

50%
Answered correctly

2 Seconds
Time Spent

11/17/2018
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Explanation

The toxicity of **cyanide** is dependent upon its ability to bind **ferric iron** (Fe^{3+}) with high affinity, inhibiting **cytochrome c oxidase** in the mitochondria. This electron transport chain enzyme is essential for oxidative phosphorylation; inhibition results in severe lactic acidosis and death

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Explanation

The toxicity of **cyanide** is dependent upon its ability to bind **ferric iron** (Fe^{3+}) with high affinity, inhibiting **cytochrome c oxidase** in the mitochondria. This electron transport chain enzyme is essential for oxidative phosphorylation; inhibition results in severe lactic acidosis and death as a result of cells switching to anaerobic metabolism.

Cyanide poisoning presents with **reddish skin discoloration**, tachypnea, headache, and tachycardia, often accompanied by nausea/vomiting, confusion, and weakness. Symptoms develop rapidly and can quickly progress to seizures and cardiovascular collapse. Laboratory studies indicate severe **lactic acidosis** in conjunction with a **narrowing of the venous-arterial PO_2 gradient**, resulting from the inability of tissue to extract arterial oxygen.

Administration of **inhaled amyl nitrite** oxidizes ferrous iron (Fe^{2+}) present in hemoglobin to ferric iron (Fe^{3+}), generating **methemoglobin**. Methemoglobin is incapable of carrying oxygen but has a high affinity for cyanide; it binds and sequesters cyanide in the blood, freeing it from cytochrome oxidase and limiting its toxic effects. Hydroxycobalamin, a vitamin B_{12} precursor, and sodium thiosulfate are also antidotes for cyanide poisoning. Their interactions with cyanide generate relatively nontoxic metabolites that are easily excreted in the urine.

(Choices A and B) The presence of 2,3-biphosphoglycerate causes a right shift in the oxygen-hemoglobin dissociation curve, decreasing hemoglobin's affinity for oxygen and increasing its affinity for carbon dioxide.

(Choice C) Hemoglobin has a much higher affinity for carbon monoxide than it does for oxygen. This is the basis for carbon monoxide poisoning, which is treated with high-flow oxygen.

(Choice E) The affinity of hemoglobin for iron is not affected by nitrite administration, although nitrites do oxidize the heme iron to its Fe^{3+} state.

(Choice F) Lead poisoning causes defective heme synthesis. If lead is acutely ingested, chelation therapy with dimercaprol or edetate disodium calcium ($CaNa_2EDTA$) should be initiated.

Educational objective:

as a result of cells switching to anaerobic metabolism.

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(Choice F) Lead poisoning causes defective heme synthesis. If lead is acutely ingested, chelation therapy with dimercaprol or edetate disodium calcium ($CaNa_2EDTA$) should be initiated.

Educational objective:
Nitrites are oxidizing agents that are effective in treating cyanide poisoning due to their ability to induce methemoglobinemia. Methemoglobin contains ferric (Fe^{3+}) rather than ferrous iron (Fe^{2+}). Cyanide binds to ferric iron more avidly than to mitochondrial cytochrome enzymes, diminishing cyanide's toxic effect.

A researcher is studying the expression pattern of a particular gene. Messenger RNA is isolated from several tissues, subjected to electrophoresis, blotted, and probed with radiolabeled DNA containing sequences from exon 4 from that gene. An x-ray film is then placed over the blotting membrane, with the results of the autoradiogram shown below:

Which of the following best explains the autoradiogram findings in the different tissues?

- A. Alternate RNA splicing
- B. DNA rearrangement
- C. DNA mutation
- D. Enhancer effect
- E. Transcription factor effect

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Item 37 of 40
Question Id: 8276

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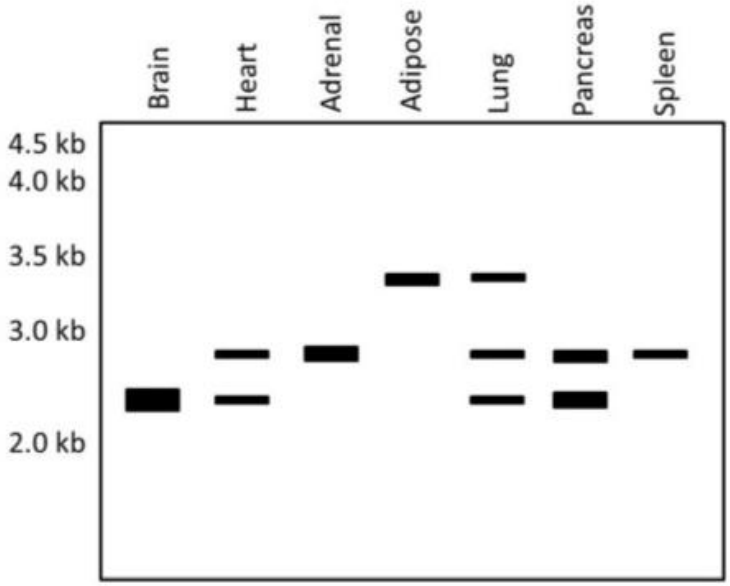

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2/9/2019

A researcher is studying the expression pattern of a particular gene. Messenger RNA is isolated from several tissues, subjected to electrophoresis, blotted, and probed with radiolabeled DNA containing sequences from exon 4 from that gene. An x-ray film is then placed over the blotting membrane, with the results of the autoradiogram shown below:

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- D. Enhancer effect
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Submit

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Which of the following best explains the autoradiogram findings in the different tissues?

- ✔ A. Alternate RNA splicing [78%]
- B. DNA rearrangement [4%]
- C. DNA mutation [2%]
- D. Enhancer effect [4%]
- E. Transcription factor effect [10%]

Omitted
Correct answer
A

78%
Answered correctly

2 Seconds
Time Spent

08/24/2018
Last Updated

Explanation

The experiment described above is known as the Northern Blot technique, a procedure used to detect specific mRNA sequences in a sample to assess for gene expression. In this experiment, the Northern Blot identifies three different mRNA transcripts containing exon 4, with varying patterns of expression in the different tissues. This is consistent with alternative splicing, a process whereby the exons of the pre-mRNA produced

Explanation

The experiment described above is known as the Northern Blot technique, a procedure used to detect specific mRNA sequences in a sample to assess for gene expression. In this experiment, the Northern Blot identifies three different mRNA transcripts containing exon 4, with varying patterns of expression in the different tissues. This is consistent with alternative splicing, a process whereby the exons of the pre-mRNA produced by transcription of a gene are reconnected in multiple ways during post-transcriptional processing. The resulting finalized mRNAs are then translated into different protein isoforms. Thus, a single gene can code for multiple proteins when the same gene is spliced differently in different tissues.

Alternative splicing is a normal phenomenon in eukaryotes that greatly increases the biodiversity of proteins that can be encoded by the genome. It is thought that at least 70% of the 30,000 genes in the human genome undergo alternative splicing, and that on average, a given gene produces 4 alternatively spliced variants. Thus, the human genome is able to encode a total of 80,000 to 100,000 proteins which differ in their sequence and function.

Abnormal variations in splicing are implicated in many diseases (e.g., beta-thalassemia, cancer). Alternative splicing also plays a prominent role in the lifecycle of many retroviruses. For instance, HIV produces a single primary RNA transcript that is alternatively spliced to produce over 40 different mRNAs.

(Choice B) DNA (gene) rearrangement occurs during the development and maturation of B cells and T cells. VDJ (**V**ariable, **D**iverse, and **J**oining) gene recombination is a random process that takes place in the primary lymphoid tissue (the bone marrow for B cells, and Thymus for T cells).

(Choice C) A mutation is a change in the DNA sequence of a gene. While somatic mutations do sporadically occur throughout the body, they do so only in a minority of cells. The vast majority of DNA throughout the body's tissues consists of identical gene coding sequences.

(Choice D & E) Transcription factors influence RNA polymerase's affinity for specific genes by binding to DNA promoter sequences or enhancer regions, which can either stimulate or inhibit gene transcription. Transcription factors and enhancer regions affect the expression of pre-mRNA

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(Choice D & E) Transcription factors influence RNA polymerase's affinity for specific genes by binding to DNA promoter sequences or enhancer regions, which can either stimulate or inhibit gene transcription. Transcription factors and enhancer regions affect the expression of pre-mRNA, but they do not influence post-transcriptional processing.

Educational objective:
Alternative splicing is a process where the exons of a gene are reconnected in multiple ways during post-transcriptional processing. This creates different mRNA sequences and subsequently, different protein isoforms. It is a normal phenomenon in eukaryotes that greatly increases the biodiversity of proteins encoded by the genome.

References

- Expansion of the eukaryotic proteome by alternative splicing.

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Item 38 of 40
Question Id: 1480

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A 3-year-old boy is brought to the office due to abnormal motor development. He was born at 40 weeks gestation and had an unremarkable perinatal course. The boy developed normally during the first year of life. However, for the past 2 years, he has had progressive bilateral leg stiffness and abnormal involuntary movements. His cognitive and motor development is also delayed. There is no significant family history of neurological or muscular disorders. The patient's height, weight, and head circumference are below the 3rd percentile. Examination shows bilateral spastic paresis of his lower extremities and frequent choreoathetoid movements. Comprehensive laboratory testing reveals significantly elevated arginine levels in plasma and cerebrospinal fluid. The deficient enzyme in this patient is normally involved in the production of which of the following?

- A. γ-aminobutyric acid
- B. Glutamine
- C. Homocysteine
- D. Orotic acid
- E. Serotonin
- F. Urea

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Settings

Item 38 of 40
Question Id: 1480

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- A. γ-aminobutyric acid [18%]
- B. Glutamine [9%]
- C. Homocysteine [7%]
- D. Orotic acid [11%]
- E. Serotonin [2%]
- ✔ F. Urea [50%]

Omitted
Correct answer
F

50%
Answered correctly

3 Seconds
Time Spent

08/15/2018
Last Updated

Explanation

Block Time Remaining: 00:03:42
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This patient has features of **arginase deficiency**, including progressive development of **spastic diplegia**, **abnormal movements**, and growth delay in the setting of **elevated arginine levels**. Arginase is a urea cycle enzyme that produces **urea and ornithine** from arginine. Diagnosis is based on elevated arginine levels on plasma amino acid testing. Treatment of arginase deficiency consists of a **low-protein diet** devoid of arginine. Administration of a synthetic protein made of essential amino acids usually results in a dramatic decrease in plasma arginine concentration and an improvement in neurological abnormalities. Unlike other urea cycle disorders, patients with arginase deficiency have **mild or no hyperammonemia**.

(Choice A) The amino acid derivative γ-aminobutyrate (GABA) is a well-known inhibitor of presynaptic transmission in the retina and central nervous system. GABA is formed from glutamate decarboxylation, a reaction catalyzed by glutamate decarboxylase.

(Choice B) Glutamine is the major amino acid in the blood because it transports excess ammonia from peripheral tissues to the kidney. In the nephron, the amide nitrogen is hydrolyzed by glutaminase to regenerate glutamate and a free ammonium ion, which can then be excreted in the urine.

(Choice C) Deficiencies of vitamins B_6, B_{12}, and folate (B_9) are associated with hyperhomocysteinemia, which in turn is associated with atherosclerosis and thrombotic events.

(Choice D) Orotic acid is overproduced when a block in the urea cycle leads to excess carbamoyl phosphate, which is metabolized by dihydroorotate dehydrogenase to orotic acid. Excessive amounts of orotic acid are usually found in citrullinemia and ornithine transcarbamylase deficiency. These urea cycle disorders are also accompanied by hyperammonemia.

(Choice E) Serotonin (5-hydroxytryptamine) is formed by the hydroxylation and decarboxylation of tryptophan by tryptophan hydroxylase. In addition, serotonin is degraded by monoamine oxidase and also undergoes neuronal reuptake.

Educational objective:
Arginase is a urea cycle enzyme that produces urea and ornithine from arginine. Arginase deficiency results in progressive spastic diplegia, growth delay, and abnormal movements. Treatment includes an arginine-free, low-protein diet.

Settings

Item 39 of 40
Question Id: 602

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A group of investigators is studying the regulation of catecholamine synthesis in response to severe stress. In the experiments, subject rats are randomly assigned to either an experimental or a control group. The experimental rats undergo resection of the pituitary gland, and the control rats undergo craniotomy without pituitary resection. The experimental animals are subsequently found to have decreased production of epinephrine by the adrenal medulla and cortisol from the adrenal cortex compared with the control animals. Decreased activity of which of the following enzymes is most likely responsible for the lower epinephrine in the experimental animals?

- A. Catechol-O-methyl transferase
- B. Dopa decarboxylase
- C. Dopamine beta-hydroxylase
- D. Monoamine oxidase
- E. Phenylalanine hydroxylase
- F. Phenylethanolamine-N-methyltransferase
- G. Tyrosine hydroxylase

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Item 39 of 40
Question Id: 602

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- A. Catechol-O-methyl transferase [13%]
- B. Dopa decarboxylase [11%]
- C. Dopamine beta-hydroxylase [16%]
- D. Monoamine oxidase [4%]
- E. Phenylalanine hydroxylase [3%]
- ✔ F. Phenylethanolamine-N-methyltransferase [41%]
- G. Tyrosine hydroxylase [10%]

Omitted
Correct answer
F

41%
Answered correctly

6 Seconds
Time Spent

12/12/2018
Last Updated

Explanation

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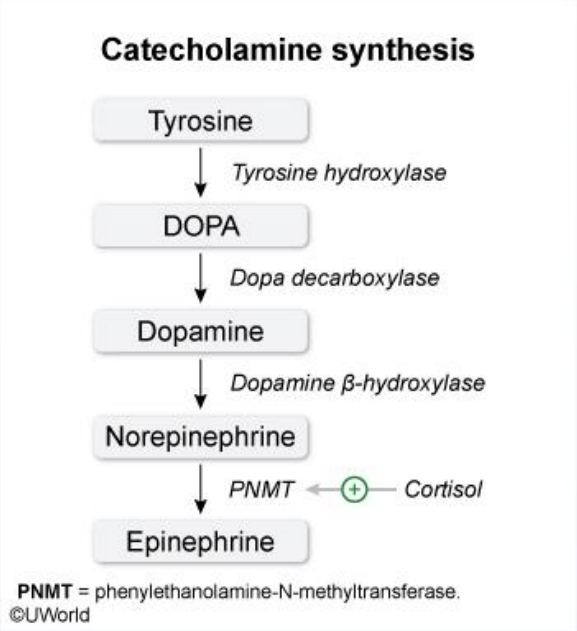
Explanation



PNMT = phenylethanolamine-N-methyltransferase.
©UWorld

The 3 main circulating catecholamines are dopamine, norepinephrine, and epinephrine. Norepinephrine and dopamine are produced in the central as well as the peripheral nervous system, whereas epinephrine is predominantly produced in the **adrenal medulla**. The first step in the synthesis of catecholamines is the conversion of tyrosine to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. This is the rate-limiting step in the synthesis of catecholamines. DOPA is converted to dopamine by dopa decarboxylase **(Choice B)**, which is then converted to norepinephrine by dopamine beta-hydroxylase **(Choice C)**. In the adrenal medulla, norepinephrine is rapidly converted to epinephrine by **phenylethanolamine-N-methyltransferase** (PNMT).

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Expression of PNMT in the adrenal medulla is upregulated by cortisol. Because the venous drainage of the adrenal cortex passes through the adrenal medulla, cortisol concentrations in the medulla can be very high, and PNMT is expressed at a high level. However, following **pituitary resection**, the loss of ACTH leads to decreased synthesis of cortisol in the adrenal cortex. The result is **decreased PNMT activity** and reduced conversion of norepinephrine to epinephrine.

(Choices A and D) Catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) are responsible for inactivation of catecholamines. COMT converts epinephrine to metanephrine and norepinephrine to normetanephrine; MAO converts metanephrine and normetanephrine to vanillylmandelic acid.

(Choices E and G) Tyrosine required for the synthesis of catecholamines is obtained from either dietary intake or by conversion of phenylalanine by phenylalanine hydroxylase in the liver. Deficiency of phenylalanine hydroxylase enzyme causes phenylketonuria. Tyrosine hydroxylase deficiency impairs catecholamine synthesis and causes infantile parkinsonism and progressive encephalopathy.

Educational objective:
Cortisol increases the conversion of norepinephrine to epinephrine in the adrenal medulla by increasing the expression of phenylethanolamine-N-methyltransferase.

References

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Question Id: 1436

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A 13-year-old boy with growth retardation, microcephaly, sun-sensitive skin rash, and recurrent infections is being evaluated for a possible inherited genetic defect. The patient is the second-born child of a first cousin marriage. His parents and siblings are healthy, but 2 of his maternal cousins have similar signs and symptoms. Genetic analysis of the patient reveals a defect in the *BLM* gene that codes for DNA helicase. Which of the following is the most likely site of action of this enzyme in the DNA replication fork shown below?

- A. A
- B. B
- C. C
- D. D
- E. E
- F. F

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Question Id: 1436

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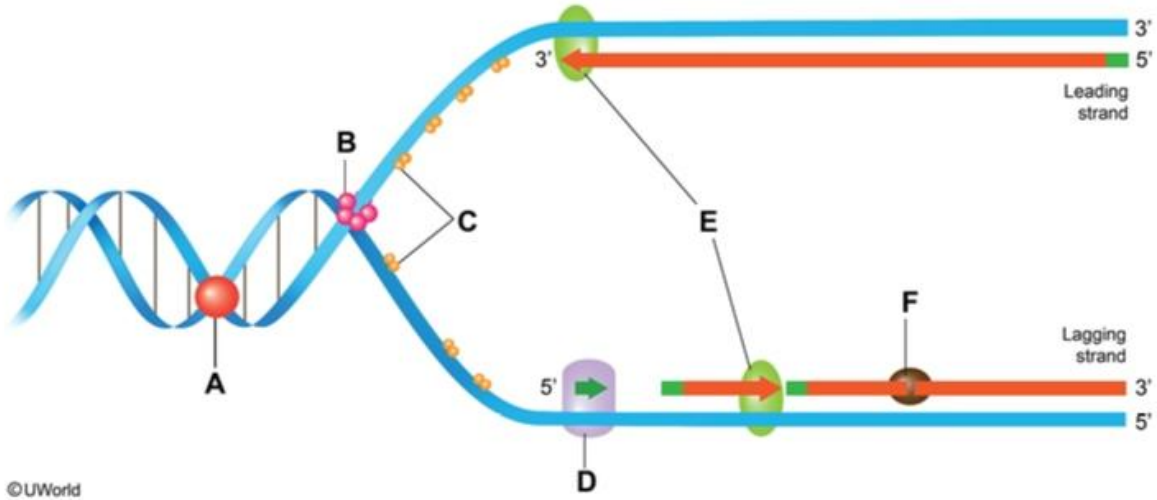

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Item 40 of 40
Question Id: 1436

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- C. C
- D. D
- E. E
- F. F

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Item 40 of 40
Question Id: 1436

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- A. A [6%]
- ✔ B. B [86%]
- C. C [4%]
- D. D [0%]
- E. E [0%]
- F. F [0%]

Omitted
Correct answer
B

86%
Answered correctly

3 Seconds
Time Spent

01/19/2019
Last Updated

Explanation

This patient has **Bloom syndrome**, a rare autosomal recessive disorder caused by mutations in the *BLM* gene. This gene encodes DNA helicase, an enzyme responsible for unwinding of the double helix during DNA replication and repair. **Helicase dysfunction** results in

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Explanation

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DNA replication occurs during the S phase (synthesis phase) of the cell cycle and is coordinated by the effects of multiple proteins. First, the origin of replication is identified and bound by a multi-subunit protein (the origin recognition complex), which locally dissociates double-stranded DNA (dsDNA) into single-stranded DNA (ssDNA). ssDNA-binding proteins then bind to and stabilize the ssDNA, preventing it from reannealing **(Choice C)**.

Helicase subsequently binds to ssDNA at the origin of replication, moves into the replication fork, and proceeds to separate and unwind the dsDNA. As DNA is unwound, superhelical tension is generated as supercoils are being formed. Topoisomerase relieves this tension by introducing transient single- or double-stranded nicks in the DNA. This enzyme is located ahead of helicase on the dsDNA segment of the replication fork **(Choice A)**.

(Choice D) Before DNA polymerase can begin synthesizing DNA, it requires an RNA primer made up of short RNA sequences base-paired to the parent DNA. This primer is synthesized by the enzyme primase (DNA-dependent RNA polymerase).

(Choice E) DNA polymerase synthesizes new daughter strand DNA in the 5' to 3' direction. The leading strand is formed continuously, whereas the lagging strand is formed discontinuously, creating Okazaki fragments.

(Choice F) Okazaki fragments are ultimately bound together by the enzyme ligase.

Educational objective:
Bloom syndrome is a rare autosomal recessive condition caused by mutations in the *BLM* gene encoding helicase, an enzyme that unwinds the

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Educational objective:
Bloom syndrome is a rare autosomal recessive condition caused by mutations in the *BLM* gene encoding helicase, an enzyme that unwinds the double helix during DNA replication. Patients typically present with growth retardation, facial anomalies, photosensitive skin rash, and immunodeficiency due to chromosomal instability and breakage.

References

- Clinical features of Bloom syndrome and function of the causative gene, BLM helicase.
- The replication fork: understanding the eukaryotic replication machinery and the challenges to genome duplication.

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