

※注意：請於試卷內之「選擇題作答區」依序作答。

Part 1. Please read the following abstract and answer the following questions [source: Modified from *Nature* 612, 739-747, 2022].

Exercise exerts a wide range of beneficial effects for healthy physiology. However, the mechanisms regulating an individual's motivation to **engage in** physical activity remain incompletely understood. An important factor stimulating the engagement in both competitive and recreational exercise is the motivating pleasure derived from prolonged physical activity, which is triggered by exercise-induced neurochemical changes in the brain. Here, we report on the discovery of a gut-brain connection in mice that enhances exercise performance by augmenting dopamine signaling during physical activity. We find that microbiome-dependent production of endocannabinoid metabolites in the gut stimulates the activity of TRPV1-expressing sensory neurons and thereby elevates dopamine levels in the ventral striatum during exercise. Stimulation of this pathway improves running performance, whereas microbiome depletion, peripheral endocannabinoid receptor inhibition, **ablation** of spinal afferent neurons or dopamine blockade abrogate exercise capacity. These findings indicate that the rewarding properties of exercise are influenced by gut-derived interoceptive circuits and provide a microbiome-dependent explanation for interindividual variability in exercise performance. Our study also suggests that interoceptomimetic molecules that stimulate the transmission of gut-derived signals to the brain may enhance the motivation for exercise.

1. The phase "engage in" on line 2 is closest in meaning to? (2%)
(A) concentrate on (B) allow to (C) care for (D) participate
2. Based on this abstract, the statement of "The motivation to perform long-term physical activities in mice is driven exclusively by the input of gut bacteria" is (2%)
(A) True (B) False (C) Not mentioned in the article
3. Which one is secreted by gut bacteria? (2%)
(A) dopamine (B) TRPV1 (C) endocannabinoid metabolites (D) ventral striatum
4. Which of the following is NOT mentioned in this abstract"? (2%)
(A) Exercise interferes in a person's movement.
(B) Gut bacteria drive exercise performance in mice.
(C) Depleting gut bacteria decreases exercise performance.
(D) The microbiome uses local neuronal stimulation to access motivational circuits in the brain.
5. The word "ablation" is closest in meaning to? (2%)
(A) removal (B) adaption (C) treatment (D) activation
6. Which is the main communication route between gut bacteria and the brain mentioned in this abstract? (2%)
(A) modulation of immune-system function
(B) direct release of microbiome-produced molecules to the bloodstream
(C) modulation of bacterial colonization
(D) local stimulation of neurons that project to the central nervous system

Part 2. Please read the following abstract and answer the following questions [source: *Cell Metabolism* 34 (11) 1732-1748, 2022].
Monoacylglycerol acyltransferase 2 (MGAT2) is an important enzyme highly expressed in the human small intestine and liver for the regulation of triglyceride absorption and homeostasis. We report that treatment with BMS-963272, a potent and selective MGAT2 inhibitor, decreased inflammation and fibrosis in CDAHFD and STAM, two murine nonalcoholic steatohepatitis (NASH) models. In high-fat-diet-treated cynomolgus monkeys, in contrast to a selective diacylglycerol acyltransferase 1 (DGAT1) inhibitor, BMS-963272 did not cause diarrhea. In a Phase I multiple-dose trial of healthy human adults with obesity (NCT04116632), BMS-963272 was safe and well tolerated with no treatment discontinuations due to adverse events. Consistent with the findings in rodent models, BMS-963272 elevated plasma long-chain dicarboxylic acid, indicating robust pharmacodynamic biomarker

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modulation: increased gut hormones GLP-1 and PYY; and decreased body weight in human subjects. These data suggest MGAT2 inhibition is a promising therapeutic opportunity for NASH, a disease with high unmet medical needs.

7. Which model system was NOT used in this study? (2%)
(A) monkeys (B) humans (C) mice (D) rabbits
8. Based on this abstract, the following statement of “BMS-963272 is an effective therapy for the treatment of diabetes” is (A) True (B) False (C) Not mentioned in this abstract. (2%)
9. Which of the statement is TRUE? (2%)
(A) A single dose of BMS-963272 increased GLP-1 and PYY production in human subjects.
(B) BMS-963272 decreased body weight in cynomolgus monkeys.
(C) Selective DGAT1 inhibitor did not cause unformed feces
(D) Selective MGAT2 inhibitor BMS-963272 did not cause unformed feces
10. Which one is NOT happening or not mentioned in human subjects treated with BMS-963272? (2%)
(A) reduced hepatic inflammation
(B) increased long-chain dicarboxylic acid production
(C) elevated GLP-1 production
(D) increased weight loss
11. Which one of the following lists of “title” fits the abstract best: (2%)
(A) MGAT2 inhibition is a promising approach for the treatment of NASH in human adults
(B) BMS-963272 increased PYY production and increased body weight in human subjects
(C) MGAT2 inhibitor decreases liver fibrosis and inflammation in murine NASH models and reduces body weight in human adults with obesity
(D) Elevation of long-chain dicarboxylic acids is a specific biomarker for DGAT1 inhibitors

Part 3. Please read the following article and answer the following questions [modified from the source: *N Engl J Med* 2020; 383:1492-1494, DOI: 10.1056/NEJMc2026172].

CRISPR (clustered regularly interspaced short palindromic repeats)-based diagnostic tests collectively provide a nascent platform for the detection of viral and bacterial pathogens. Methods such as SHERLOCK (specific high-sensitivity enzymatic reporter unlocking), which typically use a two-step process (target amplification followed by CRISPR-mediated nucleic acid detection), have been used to detect SARS-CoV-2. These approaches, however, are more complex than those used in point-of-care testing because they depend on an RNA extraction step and multiple liquid-handling steps that increase the risk of cross-contamination of samples.

Here, we describe a simple test for detection of SARS-CoV-2. The sensitivity of **this test** is similar to that of reverse-transcription-quantitative polymerase-chain-reaction (RT-qPCR) assays. STOP (SHERLOCK testing in one pot) is a streamlined assay that combines simplified extraction of viral RNA with isothermal amplification and CRISPR-mediated detection. This test can be performed at a single temperature in less than an hour and with minimal equipment.

12. Based on this article, the statement of “SHERLOCK was used in point-of-care testing” is (A) True (B) False (C) Not mentioned in this abstract. (2%)
13. Which of the statement is NOT true? (2%)
(A) SHERLOCK assay uses a two-step process.
(B) An RNA extraction step is not required for RT-qPCR assay.

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- (C) STOP assay can be done within an hour.
(D) Both SHERLOCK and RT-qPCR can be used to detect SARS-CoV-2.

14. What does "this test" in the first line of the second paragraph refer to? (2%)

- (A) SARS-CoV-2 (B) RT-qPCR (C) STOP (D) SHERLOCK

The integration of isothermal amplification with CRISPR-mediated detection required the development of a common reaction buffer that could accommodate both steps. To amplify viral RNA, we chose reverse transcription followed by loop-mediated isothermal amplification (LAMP) because LAMP reagents are widely available and use defined buffers that are amenable to Cas enzymes. LAMP operates at 55 to 70°C and requires a thermostable Cas enzyme such as Cas12b from *Alicyclobacillus acidiphilus* (AapCas12b). We systematically evaluated multiple LAMP primer sets and AapCas12b guide RNAs (a guide RNA helps AapCas12b recognize and cut target DNA) to identify the best combination to target gene N, encoding the SARS-CoV-2 nucleocapsid protein, in a one-pot reaction mixture. We termed this assay STOPCovid, version 1 (STOPCovid.v1). As expected, STOPCovid.v1 detection produced a signal only when the target was present, whereas LAMP alone can produce a nonspecific signal. STOPCovid.v1 is **compatible with** lateral-flow and fluorescence readouts and can detect an internal control with the use of a fluorescence readout.

To simplify RNA extraction and to boost sensitivity, we adapted a magnetic bead purification method. The magnetic beads concentrated SARS-CoV-2 RNA genomes from an entire nasopharyngeal or anterior nasal swab into one STOPCovid reaction mixture. We streamlined the test by combining the lysis and magnetic bead-binding steps and eliminating the ethanol wash and elution steps to reduce the duration of sample extraction to 15 minutes with minimal hands-on time. We **refer to** this streamlined test as STOPCovid, version 2 (STOPCovid.v2).

15. Which of the statement is TRUE? (2%)

- (A) Both STOPCovid.v1 and STOPCovid.v2 assays involve CRISPR-mediated detection.
(B) Magnetic beads are used to purify Cas12b enzymes in STOPCovid.v2 assay.
(C) LAMP is designed for amplification of guide RNAs.
(D) AapCas12b is a thermostable RNA-cleaving enzyme.

16. Based on this article, the statement of "STOPCovid.v2 assay is more sensitive than STOPCovid.v1 assay" is

- (A) True (B) False (C) Not mentioned in this abstract. (2%)

17. The phrase "compatible with" on line 2 is closest in meaning to? (2%)

- (A) compel with (B) coexist with (C) compare with (D) compete with

18. The phrase "refer to" is closest in meaning to

- (A) subjected to (B) in addition to (C) pass over (D) name (2%)

We compared STOPCovid.v2 with the Centers for Disease Control and Prevention (CDC) standard two-step test (i.e., RNA extraction followed by RT-qPCR). The concentration of substrate by magnetic beads in STOPCovid.v2 allowed detection of viral RNA from the entire swab sample, yielding an input (in terms of quantity of viral RNA) that was 600 times that afforded by the CDC test. As a result, STOPCovid.v2 reliably detected a viral load that was one thirtieth that detected by the CDC RT-qPCR test (100 copies per sample, or 33 copies per milliliter, as compared with 1000 copies per milliliter). Analysis of two independent dilution series from nasopharyngeal swab samples **revealed** that STOPCovid.v2 had a limit of detection that was similar to an RT-qPCR cycle-threshold (Ct) value of 40.3.

In blinded testing at an external laboratory at the University of Washington, we tested 202 SARS-CoV-2-positive and 200 SARS-CoV-2-negative nasopharyngeal swab samples obtained from patients. These samples were prepared by adding 50 µL of swab

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specimens obtained from patients with Covid-19 to a clean swab. **in accordance with** the recommendation of the Food and Drug Administration for simulating whole swabs for regulatory applications. This testing showed that STOPCovid.v2 had a sensitivity of 93.1% and a specificity of 98.5%. STOPCovid.v2 false negative samples had RT-qPCR Ct values greater than 37. Positive samples were detected in 15 to 45 minutes. Finally, we used fresh, dry, anterior nasal swabs (collected according to the recommendations of the CDC) to validate STOPCovid.v2, and we correctly identified 5 positive samples (Ct values, 19 to 36) and 10 negative samples. The simplified format of STOPCovid.V2 is suited for use in low-complexity clinical laboratories.

19. The word "reveal" is closest in meaning to (A) repeat (B) display (C) reverse (D) defer. (2%)

20. The phrase "in accordance with" is closest in meaning to
(A) concerned with (B) in contrast with (C) in line with (D) as compared with (2%)

21. Which of the statement is TRUE? (2%)

- (A) STOPCovid.v2 is the CDC standard test for detection of SARS-CoV-2.
- (B) STOPCovid.v2 is a reliable assay to detect SARS-CoV-2 because more swab samples are required.
- (C) STOPCovid.v2 can detect SARS-CoV-2 positive samples in less than an hour.
- (D) Only fresh, dry nasal swab samples are suitable for STOPCovid.v2.

Part 4. Alan is preparing competent cells. Here is the protocol he found from DNA Electrophoresis. Methods in Molecular Biology, vol 1054. Humana Press, Totowa, NJ. https://doi.org/10.1007/978-1-62703-565-1_2. Alan will follow the protocol step by step. Please answer the following questions.

- I. Pick a single colony of a *recA* E. coli strain and start a 10 mL LB broth culture in a 100 mL conical flask. Grow cells overnight on a shaker at 37 °C.
- II. The next morning, dilute the overnight culture 1:100 in 200 mL of fresh LB broth in a 2 L flask. Grow the culture at 37 °C with vigorous aeration.
- III. While the culture is growing, precool a tabletop centrifuge to 4 °C. Also, prechill on ice four 50 mL conical tubes.
- IV. When the bacterial culture OD600 reaches 0.4–0.5, chill the culture rapidly by placing the flask in an ice-water bath for 5 min. Swirl the flask every 10–20 s while it is in the bath to facilitate cooling.
- V. Transfer the culture to the four prechilled 50 mL conical tubes and harvest cells in the prechilled tabletop centrifuge (from step III) at $2,500 \times g$ for 10 min.
- VI. Carefully pour off the supernatants and place the tubes on ice. Use a 1 mL pipetman to remove as much of the remaining media as possible.
- VII. Add 25 mL of ice-cold 0.1 M CaCl_2 to each tube and resuspend the cells by vortexing. No cell clumps should be seen. Incubate cells on ice for 1 h.
- VIII. Combine the four 25 mL aliquots in two tubes and harvest the cells in the prechilled tabletop centrifuge at $2,500 \times g$ for 10 min.
- IX. Carefully pour off the supernatant and place the tubes on ice. Use a 1 mL pipetman to remove as much of the remaining CaCl_2 as possible.
- X. Add 5 mL of ice-cold 20 % glycerol in 0.1 M CaCl_2 to each tube and resuspend the cells by vortexing. No cell clumps should be visible.
- XI. Quickly pipette 100 μL of cells into each tube and close the tubes. Transfer the tubes to a -80 °C freezer.

22. Alan starts with one bottle of 0.1 M CaCl_2 and one bottle of 100% glycerol. What's the minimal volume of 0.1 M CaCl_2 that Alan needs for this experiment? (2%)

- (A) 50 mL (B) 100 mL (C) 108 mL (D) 220 mL

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23. What's the minimal volume of 100% glycerol that Alan needs for this experiment? (2%)
(A) 1 mL (B) 2 mL (C) 5 mL (D) 10 mL

24. Roughly how many competent cell aliquots will Alan end up with? (2%)
(A) 50 (B) 100 (C) 150 (D) 200

25. Which instrument or device is not required for this experiment? (2%)
(A) gel imaging system (B) shaker (C) spectrophotometer (D) centrifuge

Part 5. Reading comprehension. Please read each paragraph and answer the following questions [Source: *Science Translational Medicine* (2022), 10.1126/scitranslmed.add0484].

SARS-CoV-2 causes profound changes in the sense of smell, including total smell loss. Although these alterations are often transient, many patients with COVID-19 exhibit **olfactory** dysfunction that lasts months to years. Although animal and human autopsy studies have suggested mechanisms driving acute anosmia, it remains unclear how SARS-CoV-2 causes persistent smell loss in a subset of patients. To address this question, we analyzed olfactory epithelial samples collected from 24 biopsies, including from nine patients with objectively quantified long-term smell loss after COVID-19. This biopsy-based approach revealed a diffuse infiltrate of T cells expressing interferon- γ and a shift in myeloid cell population composition, including enrichment of CD207+ dendritic cells and depletion of anti-inflammatory M2 macrophages. Despite the absence of detectable SARS-CoV-2 RNA or protein, gene expression in the barrier supporting cells of the olfactory epithelium, termed sustentacular cells, appeared to reflect a response to ongoing inflammatory signaling, which was accompanied by a reduction in the number of olfactory sensory neurons relative to olfactory epithelial sustentacular cells. These findings indicate that T cell-mediated inflammation persists in the olfactory epithelium long after SARS-CoV-2 has been eliminated from the tissue, suggesting a mechanism for long-term post-COVID-19 smell loss.

26. Which term is pertinent to "olfactory"? (3%)
(A) pain (B) heat (C) order (D) sound

27. Which main strategy did the researchers employ to decipher the long COVID syndrome? (3%)
(A) autopsy (B) biopsy (C) amputation (D) appendectomy

28. What was the main cause of the syndrome identified in this study? (3%)
(A) remaining viruses sabotaged the sensory system
(B) diminished T cell immunity caused hypo-inflammation
(C) the reduction of sensory neurons due to the prolonged immunity
(D) all of above

Part 6. Please read the article and answer the following questions [Source: *Cell* (2023), 10.1016/j.cell.2022.12.007].

Metabolism is deeply intertwined with aging. Effects of metabolic interventions on aging have been explained with intracellular metabolism, growth control, and signaling. Studying chronological aging in yeast, we reveal a so far **overlooked** metabolic property that influences aging via the exchange of metabolites. Herein, we uncovered a role of metabolite exchange interactions in cellular aging by studying the metabolism of budding yeast during chronological lifespan (CLS). CLS, monitoring the survival of cells in stationary phase (post-mitotic cells), is a basic aging model that was pivotal in understanding the critical role of conserved regulatory pathways such as the AMPK/sucrose non-fermenting 1 (SNF1, yeast homolog of AMPK) and TOR pathways in cellular aging. We observed that metabolites exported by young, exponentially growing cells are re-imported during the stationary phase when cells age chronologically, indicating the existence of cross-generational metabolic interactions. Increasing metabolic interactions between cells through the use of self-establishing metabolically cooperating communities (SeMeCo), increased

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longevity of the communities. In the search of the underlying mechanisms, we discovered a role for an altered extracellular metabolic environment that is rich in glycerol and that increases the lifespan of the different community members. In SeMeCo, we can explain the formation of this lifespan-extending exometabolome with the metabolic adaptations in methionine consumer cells. These obtain a more glycolytic metabolism and overflow glycerol, extending the lifespan of the methionine producers via a paracrine effect and by inducing lifespan-extending metabolic adaptations, including increased levels of antioxidant metabolites and polyamines.

29. What is the association between “metabolism” and “metabolite” in this paragraph? (3%)
- (A) metabolism is a product of a cellular metabolic process, called metabolite
 - (B) metabolism is the biological metabolic processes that produce metabolites
 - (C) methionine is categorized as a metabolism
 - (D) metabolome represents the status of metabolism
30. Which statement is “NOT” true in the context? (3%)
- (A) yeast cells exchange biochemicals across generations
 - (B) TOR pathways are not associated with cell aging
 - (C) metabolic reconfigurations result in enhanced survival of aged cells
 - (D) glycerol rich extracellular environments can alter cellular life-span
31. What is antonymous to “overlooked”? (3%)
- (A) ignored (B) noticed (C) uneasy (D) omitted
32. What would be the best relevant title to summarize this piece of paragraph? (3%)
- (A) cell-cell metabolite exchange creates a pro-survival metabolic environment that extends lifespan
 - (B) high-throughput metabolomic analysis reveals the aging of eukaryotic cells
 - (C) intercellular dynamics control cellular growth and diseases
 - (D) metabolic engineering restructures cellular metabolism

Part 7. Please read the article and answer the following questions [Source: *Nature Nanotechnology* (2022), <https://doi.org/10.1038/s41565-022-01278-y>].

Cotton textiles are ubiquitous in daily life and are also one of the primary mediums for transmitting viruses and bacteria. Conventional approaches to fabricating antiviral and antibacterial textiles generally load functional additives onto the surface of the fabric and/or their microfibrils. However, such modifications are **susceptible** to deterioration after long-term use due to leaching of the additives. Here we introduce a new strategy of fabricating antimicrobial cotton textiles based on a fundamentally different principle of incorporating copper ions into the cotton structure at the molecular level, utilizing strong coordination bonding between copper ions and the cellulose molecules. This new approach can produce antiviral and antibacterial cotton textiles that are wearable and washable in a scalable and cost-effective manner, enabling practical application in everyday use. The method employs a strategy of disrupting the hydrogen-bonding network interconnecting the cellulose chains, followed by diffusing Cu (II) ions into the swollen cellulosic materials, allowing them to coordinate with the hydroxyl groups on the cellulose chains and form a stable copper ion–cellulose complex. The two processes are accomplished via a one-pot reaction by soaking a cotton textile in a Cu (II)-saturated NaOH solution. The coordination bonding between copper ions and their neighbouring cellulose chains makes this copper ion-textile (Cu-IT) highly stable in air and water, and durable against abrasion. The copper ions can interact with viral genomes and inhibit virus replication, and cause contact killing of bacteria and fungi by rupturing cell membranes and inducing reactive oxygen species (ROS). Cu-IT also shows better mechanical properties, with a ~23% increase in tensile strength compared with unmodified textiles, which is due to the role of the copper ions as ‘crosslinkers’ between the cellulose molecular chains. As a proof-of-concept, we show that Cu-IT exhibits high antiviral and antibacterial activities against tobacco mosaic virus (TMV),

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influenza A virus (IAV), and *Escherichia coli*, *Salmonella typhimurium*, *Pseudomonas aeruginosa* and *Bacillus subtilis* bacteria. Additionally, the fabrication of Cu-IT is simple, scalable and cost-effective, and can be applied to different types of cotton fabrics. This methodology may provide a renewed understanding of the potential of cellulosic materials, adding new dimensions to their application, including improved public health and hygiene.

33. What is the meaning of "susceptible" in this text? (3%)
(A) sturdy (B) vulnerable (C) difficult (D) unaccountable
34. Which of the following is NOT mentioned in the article (3%)
(A) there exist no outstanding cotton-based fabric goods with sustained antibacterial properties
(B) copper ion incorporation slightly would enhance the mechanical performance of the modified cotton fibers
(C) Cu (II)-embed cellulose fibers exhibit strong copper retention capability
(D) Cu (II)-cotton textiles might pose a safety issue to human skin
35. Which of the following is not an activity of Cu (II)-cotton's antimicrobial properties? (3%)
(A) ROS-mediated killing
(B) inhibition of DNA replication
(C) membrane disruption
(D) inhibition of cell wall synthesis

Part 8. Please read the article and answer the following questions [source: <https://www.genengnews.com/>].

Researchers led by a team from George Washington University report they have developed two mRNA vaccine candidates that are effective in reducing both malaria infection and transmission. The team also observed the two experimental vaccines induced a powerful immune response regardless of whether they were given individually or in combination.

The research team focused on the parasite *Plasmodium falciparum*, one of four parasite species that cause malaria and the deadliest to humans. Transmitted through the bite of the Anopheles mosquito, *P. falciparum* together with *P. vivax* are responsible for more than 90% of all malaria cases globally, and 95% of all malaria deaths. Most cases and deaths occur in sub-Saharan Africa but half the world's population is at risk of contracting this deadly disease.

The researchers immunized one group of mice with an mRNA vaccine targeting a protein that helps the parasites move through the body and invade the liver. They immunized another group of mice with a vaccine targeting a protein that helps parasites reproduce in a mosquito's midgut. The team also immunized mice with both vaccines together and found that co-immunization effectively reduced infection and transmission without compromising the immune response. To have a vaccine cocktail that can effectively disrupt multiple parts of the malaria parasite's life cycle is one of the holy grails of malaria vaccine development.

36. What is the main idea described in this article (3%)
(A) new methodologies to study malaria
(B) new drugs to cure malaria
(C) novel strategies to eradicate Anopheles mosquitos
(D) new vaccines to fight against malaria
37. Which of the following statement is NOT true in the context? (3%)
(A) two mRNA vaccine formulations are developed
(B) *P. falciparum* and *P. vivax* are the two major parasites for malaria diseases
(C) the vaccine cocktail is effectively combating malaria
(D) malaria is only posing a major concern in Africa

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Part 9. General comprehension and scientific terms (14 points, 2 points for each question)

38. "From the intricate neuronal networks to the fundamental functions and architecture, the human brain is reluctantly to share its secrets." What does "reluctantly" mean in the sentence? (2%)
(A) slowly (B) in an unwilling way (C) redundantly (D) none of above
39. "This ability is substantially more pronounced in the patient group than in vaccinated healthy individuals." What does "pronounced" mean in the above sentence? (2%)
(A) significant (B) weak (C) unclear (D) irrelevant
40. What _____ is that there's a strong correlation between climate change and extreme weather conditions. (2%)
(A) are we seeing (B) do we see (C) we're seeing (D) none of above
41. Researchers have engineered biomolecules that act like "cellular glue," _____ them to direct in precise fashion how cells bond with each other. (2%)
(A) allowing (B) it allows (C) allows (D) all of above
42. "Quantitative study of macromolecules in solution is made possible by analytical ultracentrifugation (AUC), a strong and adaptable technique." What is the synonym for "quantitative"? (2%)
(A) descriptive (B) immeasurable (C) quantifiable (D) ambiguous
43. "Even if a patient survives a heart attack, over time they might become progressively exhausted, weakened, and ill; in certain cases, heart failure can be fatal." Which statement is NOT true? (2%)
(A) a heart attack is completely curable
(B) a heart attack could result in long-term side effects
(C) the life quality of a patient who had a heart attack might be compromised
(D) heart failure could be lethal
44. Their coincidental discovery emerged while they were conducting a bio-electrosynthesis. What does "coincidental" mean in the sentence? (2%)
(A) extraordinary (B) unexpected (C) envisioned (D) designed

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