There are 6 essays in this test. Each essay contains a text followed by questions. **Please answer these questions BRIEFLY according to the text.**

Essay 1 Doctor says 'spit please' (15%)

It's an often unconsidered gateway to the human body that can reveal whether you're tired, stressed or drunk; how much testosterone, nicotine or caffeine you've ingested; or if you've been infected with HIV, measles or hepatitis. And now, thanks to recent technological advances, scientists are looking to expand the diagnostic range of that most humble of bodily fluids: spit.

To this end, David Wong and colleagues at the University of California at Los Angeles are attempting to catalogue all the proteins present in saliva. Their latest triumph has been to pin down a series of markers linked to an autoimmune disorder called Sjögren's syndrome, which disturbs the function of many of the body's secretory glands, including the pancreas and the tear ducts. It affects more than 4 million people in the United States, mostly women, often leaving them with painfully dry mouths and eyes. While Sjögren's syndrome lends itself naturally to diagnosis via saliva — the salivary glands are a primary target of the disease — Wong is optimistic that spit could be the key to easy diagnosis of other diseases as well. Wong has already published preliminary results on the detection of oral cancer, and is presently exploring the use of saliva to diagnose pancreatic, breast and lung cancers, diabetes and Alzheimer's disease.

The human body produces up to a litre and a half of saliva every day. Although spit is 99% water, the remaining 1% contains salts and proteins, some of which derive from the fluid part of the blood, the serum. Spitting in a cup provides an appealing, needle-free alternative for those who get queasy at the thought of having blood drawn.

In the past, researchers have been daunted by the difficulty of detecting the very low concentrations of protein in saliva. Recent technological advances have lowered that barrier, but another problem remains: contamination. The mouth is a microbial playground, and is highly susceptible to contamination from the outside environment as well. That contamination can complicate the protein landscape, making diagnosis more of a challenge. Still, spit has its advantages. As indicated by a researcher, saliva flows like a river, so you're getting what's happening at that moment in time.

Q1-1: What's spit? (3%)
Q1-2: How can Sjogren's syndrome be diagnosed by spit? (4%)
Q1-3: What are the advantages & limitation for using spit to diagnose diseases? (8%)

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Essay 2 The gene that makes us once bitten, twice shy (16%)

Most people tend to learn from their mistakes and avoid making the same blunder twice. Now research reveals a genetic mutation that helps to determine the extent to which certain people are doomed to repeat history. Drug addicts, alcoholics and compulsive gamblers are known to be more likely than other people to have this genetic mutation, which leaves them with fewer receptors of a certain type in the brain. These receptors — called D2 receptors — are activated when levels of the neurotransmitter dopamine drop.

Dopamine is responsible for signalling fun and pleasure in the brain. But dopamine also helps us learn. When we make a pleasurable decision, dopamine is a chemical treat, urging the brain to repeat the choice. Being deprived of such a treat should theoretically activate D2 receptors and encourage people not to make that same decision again. So it had been theorized that people with fewer D2 receptors might be less capable of learning from negative reinforcement.

To test this, Tilmann Klein and Markus Ullsperger at the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig, Germany, looked at the decision-making of 26 men, while monitoring their brains with a magnetic resonance imaging scanner. Twelve of the volunteers had the gene mutation for low numbers of D2 receptors. The researchers chose men because dopamine levels change during a woman's menstrual cycle, which would have complicated the study.

Volunteers were presented with sets of two symbols on a computer screen, and were asked to select one. After making a choice, either a smiley face or a frown flashed on the screen, providing positive or negative feedback. The results weren't uniform: symbol 'A' was the most positively reinforced, resulting in a smile 80% of the time, while 'B' was the most negatively reinforced, prompting a frown in 80% of trials. Other characters, C through F, spurred responses somewhere in between.

The team next tested whether the volunteers learned to choose symbol 'A' — indicating learning from positive reinforcement — and avoid symbol 'B' — indicating learning by negative reinforcement. Both sets of volunteers learned to choose symbol A. But the men with fewer D2 receptors had trouble learning from the scolding. Brain imaging confirmed the brain regions thought to be involved in learning from mistakes. A brain area called the rostral cingulate zone was more active in the volunteers with normal D2 levels during the learning sessions, compared to those with the D2 mutation. A brain region key to forming memories, the hippocampus, was also more active in the volunteers with normal D2 levels.

It is important to remember that real-life decisions are based on much more than the response of D2 brain receptors, says Ullsperger. But it seems to have some effect on our ability to learn from mistakes. The brains of addicts may be tilted against learning from mistakes. They're wired to sense the good,

such as drug-induced euphoria or a hot streak at the blackjack table, but ignore the losses or consequences.

Q2-1: Why did this study recruit men, but not women, as subjects? (3%)

Q2-2: How did scientists examine correlation between behavior and brain? (5%)

Q2-3: Why do drug addicts have trouble learning from mistakes? (8%)

Essay 3 Cells mend damaged mouse hearts (16%)

Researchers have managed to restore heart function by transplanting muscle stem cells into damaged mouse hearts. Their results suggest that the technique could one day be used to heal heart tissue in humans.

Similar transplants have been tried before in both mice and humans, but have met with little success. Although the grafts sometimes improved the function of the heart, they also raised the risk of abnormally fast heartbeats, in a disorder called ventricular tachycardia. Ventricular tachycardia is the main cause of sudden death in patients who have had a heart attack, killing about 15% of patients within three years of their attack.

Heart attacks in humans are typically caused by a gradual loss of blood flow that slowly starves cardiac cells of nutrients. As the cells die, heart function declines. Researchers have long hunted for a way to either prevent or reverse the effects of heart failure by replacing the damaged heart cells. Early results showed that injecting injured regions of the heart with skeletal-muscle stem cells or even bone-marrow cells could restore some function. Exactly how this works is unclear. Whatever they do, one thing is clear: both cell types sometimes improve the heart's ability to beat, but they also disrupt its beating rhythm.

So Michael Kotlikoff of Cornell University in Ithaca, New York, and Bernd Fleischmann of the University of Bonn in Germany, and their colleagues, tried to transplant a different type of cell, called embryonic cardiac-muscle cells. These cells, they found, coupled physically with the surrounding heart tissue and could exchange electrical signals with their new neighbours — signals that are used to keep a heart beating in time. The result was a well-behaved heart. Relatively few transplanted cells were required to get the effect.

So why were the embryonic cells better at blending in with their surroundings than the adult muscle cells? The researchers thought one explanation might be that both embryonic cells and adult heart cells have higher expression of a protein called connexin 43, which is important for forming connections between cells. Connexin 43 is expressed at lower levels in adult muscle stem cells. To test

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whether connexin 43 was indeed the key factor, the team tried using adult muscle stem cells that had been forced to express the protein. This produced similarly good results. "If you make these cells express connexin 43, they correct or reverse the vulnerability to arrhythmia," says Kotlikoff. This could liberate future researchers from relying on embryonic tissue, which can be more difficult to acquire.

Q3-1: What makes embryonic cardiac-muscle cells a good choice to treat heart? (8%)

Q3-2: What are major problems using skeletal or hemopoietic stem cells? (4%)

Q3-3: Can adult muscle stem cells be used for this purpose? (4%)

Essay 4 Worms live longer on antidepressant (20%)

Cutting back on calories is a sure way to extend the lifespan of any organism, from yeast to mice. Now it seems that an antidepressant can trick worms' brains into thinking they're on a diet, pushing their fleeting lifespan of three weeks to more than four. Such biochemical tinkering could form the basis for drugs that attempt to prevent the onset of age-related diseases, says Linda Buck, a molecular biologist at the Fred Hutchinson Cancer Research Center in Seattle, Washington, who led the work.

The drug that has this effect - mianserin (trade name Tolvon) - is an atypical antidepressant, distinct from the more familiar antidepressants such as Prozac, Paxil and Zoloft. Mianserin works by hampering the brain's response to serotonin, a neurotransmitter that is involved in the regulation of appetite and mood.

The nematode worm, *Caenorhabditis elegans*, has been used as a model of ageing for decades, helping scientists to uncover details about what happens to human bodies as they grow old. Scientists are just starting to find drugs that slow ageing. To speed the search, Buck and colleague Michael Petrascheck tested 88,000 chemicals from a chemical library to see if any of them turned worms into long-lived Methuselahs.

Their five-year hunt turned up more than 100 chemicals that boosted the worms' lifespan. But there was little known about how these chemicals react in biological systems. So Petrascheck scoured catalogues of better studied drugs to see if any had a similar structure to the experimental chemicals. He then checked to see if the drug had the same effect as their chemical had on the worms. It worked. Petrascheck chanced on several drugs that resembled a chemical named 272N18, which had increased lifespan by a fifth in his first round of tests. One of the drugs, mianserin, lengthened the worms' lives by a third.

Mianserin interacts with two brain chemicals involved in hunger: serotonin, which signals the presence of food, and octopamine, which signals starvation. The drug preferentially blocks one kind of serotonin receptor, hindering this receptor from doing its normal job. The drug didn't cause the worms to eat any less, suggesting that it did not slow ageing by actual calorie restriction.

But the researchers do think mianserin works by the same mechanism as calorie restriction. Worms on a strict diet don't get an additional lifespan boost from mianserin, suggesting that whatever benefit is gained by either calorie restriction or the drug gets 'topped out' by that factor. And worms missing some genes known to be involved in the youth-giving effect of calorie restriction get less of a lifespan benefit from mianserin.

Q4-1: An average Taiwanese man lives to 75, assuming mianserin is equally effective in human and *C. elegans*, how long can he expect to live after taking mianserin? (4%)

Q4-2: What evidence shows that mianserin and calorie restriction act via same mechanism? (8%)

Q4-3: How did these researchers find mianserin? (8%)

Essay 5 Older siblings are smarter (13%)

Eldest siblings are, on average, 2.3 IQ points more intelligent than their younger brothers and sisters, says a study of Norweigan kids. And it's not necessarily being born first that makes the difference — it's being raised as the eldest child.

It has been proposed for some time that, on average across a population, first-borns are more intelligent than their younger brethren. There are more first-born sons in prominent positions than might be expected, for example. And some studies have shown a link between birth order and intelligence: the later born, the less smart the child. But the reasons behind this trend, and even whether it's real, have been hotly debated. Families with low-intelligence children tend to be large, so the observation that sixth-born children aren't very smart, for example, could just be a side effect of this, critics have said.

Petter Kristensen, from the University of Oslo, and Tor Bjerkedal from the Norwegian Armed Forces Medical Services in Oslo looked at data gathered from 241,310 Norwegian kids, all aged 18 or 19 years old. The mean IQ of first-born kids was just over 103, second-borns just over 100, and third-borns about 99, they found. But if a child's elder sibling had died, leaving him or her to be raised as first-born, their IQ lept up to match the top scores of 103. Likewise if both of two elder siblings had passed away, these third-born children had IQs matching that of first-borns. In a separate analysis, the researchers show that the trend holds true for distinct pairs of siblings in their study group — even

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within single families, older siblings are on average smarter. "There can be no confounds in this type of study, and so the theory of spurious associations has effectively been refuted in one fell swoop," says Frank Sulloway, an expert on birth order and intelligence from the University of California, Berkeley.

What causes the difference? The fact that it's down to social upbringing rather than biological birth order leads Kristensen to think it's because of factors such as parental attention to older siblings, or time that the elders spend tutoring younger sisters and brothers. Kristensen, a second-born child himself, admits that he did not believe the effect was real at first. "It was intuitively wrong to me that an eldest child should have an advantage." he says, especially since studies have shown that second- and third-born children often have better health than first-born kids.

The work doesn't necessarily show that younger siblings suffer from their lower IQ, Sulloway adds. "There is considerable evidence that first-borns and later-borns are good at different things," he says, citing Charles Darwin as an example. Darwin was the fifth of six children, and didn't fare very well in some of his classes at Cambridge. But Darwin was, famously, described by his uncle Josiah Wedgewood as being a man with "enlarged curiosity".

Q5-1: What are the major factors for the eldest sibling to be the most intelligent? (6%)
Q5-2: Does an eldest sibling make a better scientist? Why? (7%)

Essay 6 Why a person doesn't evolve in one lifetime? (20%)

Evolution is usually thought of as something that happens to whole organisms. But there's no fundamental reason why, for multicelled organisms, it shouldn't happen within a single organism, too. In a colony of single-celled bacteria, researchers can watch evolution in action. As the cells divide, mutants appear; and under stress, there is a selective pressure that favours some mutants over others, spreading advantageous genetic changes through the population. In principle, precisely the same thing could occur throughout our bodies. Our cells are constantly being replaced in vast numbers: the human body typically contains about a hundred trillion cells, and many billions are shed and replaced every day. If this happened simply by replication of the various specialized cells in each tissue, our tissues would evolve: mutations would arise, and some would spread.

Evolutionary biologist John Pepper of the University of Arizona in Tucson and his co-workers came up with a theory for how multicelled organisms avoid this fate. They say it explains why the epithelial tissue cells that line all parts of the body take such an apparently long-winded route to replication, rather than just copying themselves in their mature form. To renew themselves, epithelial tissues retain a population of undifferentiated stem cells that have the ability to grow into different types of

cells. When replacements are needed, some of these stem cells divide to make transient amplifying cells (TACs). The TACs then divide several times, and Pepper and his co-workers think that each division produces cells that are a little more developed into mature tissue cells.

All this costs a lot of metabolic energy, so it is not very efficient. But, the researchers say, it means that the functions of self-replication and proliferation are divided between separate groups of cells. The stem cells replicate, but only a little, and so there's not much chance for mutations to arise or for selective pressure to fix them in place. The proliferating TACS may mutate, but they aren't simply copying themselves, so there isn't any direct competition between the cells to create an evolutionary pressure. As a result, evolution can't get started. Pepper and his colleagues have used computer modelling to show that this proposed mechanism can suppress evolution in a long-lived, multicelled organism.

One case in which this scheme might not operate, they say, is in the immune system. Here evolution is beneficial, as it introduces adaptations that fight previously encountered invaders. One drawback of this, however, is that it would be expected to make the immune system more prone to cancers. And that seems to be so: leukaemia and lymphoma are cancers associated with the immune system, and they seem to be more common in younger people than many other cancers, suggesting that the failure to suppress evolution allows its problems to show up rather quickly.

The researchers think that their hypothesis could provide new insights into cancers more generally. Whereas conventional wisdom has it that cancer is caused by some genetic mutation that leads cells to proliferate uncontrollably, this new picture implies that the problem would lie with TAC mutations that interfere with differentiation — so that a TAC cell ends up just copying itself instead of producing cells on the next rung up on the way to mature tissue cells. If their picture is right, incipient cancer formation might be detected very early by looking for biomolecules in body fluids that signal disruption of cell differentiation, even before there are any physical signs of tumour growth.

Q6-1: How do epithelial tissues avoid evolution with constant replacement? (10%)

Q6-2: According to this hypothesis, why are leukemia and lymphoma, but not other cancers, common in young people? (10%)