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THE ELIXIRS OF LIFE?

Should we drink coffee and beer to stay healthy? A study on the effects of caffeine and alcohol on cellular aging raises some probing questions

A few years ago, I came across an amusing Internet site that presented a list of facts – all of them correct and valid – that led to the inescapable conclusion that eating bread is dangerous. Here are a few of them:

1. More than 98 percent of convicted criminals eat bread.

2. Half of the children who grew up in households where the menu included bread score below average on standardized tests.

3. In the 18th century, a time when all bread was baked at home, the average life expectancy was less than 50 years of age, infant mortality was sky-high, many women died during childbirth, and diseases such as typhoid and influenza were very common.

4. More than 90 percent of violent crimes were committed within 24 hours of consumption of bread.

5. Bread is made from a substance called "dough." It has been proven that a small portion of half a kilogram of dough is enough to suffocate a mouse. The average American eats more than that in one month.

The long list (the original one consists of 12 points) ends with the following fact: Most of the Americans who eat bread cannot distinguish between significant scientific facts and groundless statistical babble. This statement holds true, of course, also for Americans who do not eat bread, as well as citizens of other nations who, for example, eat or do not eat carrots, ride or do not ride a bike and like or dislike the color purple.

The satirical element in all this is clear: One can choose to present certain data and ignore others to prove a certain claim; it is possible to present a correlation between facts in such a manner that there appears to be a cause-and-effect relationship; and there is no difficulty presenting together certain data that have a purely associative connection as if there is a real, significant relationship between them.

People like to think of themselves as intelligent and capable of drawing conclusions. Maybe not like Sherlock Holmes, who plucks bits of clues and ties them together into a solid logical structure that is unassailable, but as people who, upon encountering facts, can examine them logically and articulate the correct connection between them.

"But it is not like that at all," says Prof. Martin Kupiec of the Department of Molecular Microbiology and Biotechnology at Tel Aviv University, who is also president of the Genetic Society of Israel. "As human beings, we are not really good at coping with statistical data or correlations or at drawing conclusions. For example, when parents-to-be are told they have a 25-percent chance of giving birth to a child with a certain disease – what do they understand from that? Or when you hand someone the decoding of his/her DNA, and there's a comment there like 'Your chances of contracting a certain disease are three times higher than those of the general population,' it will usually frighten the person. But if the general population's chances of contracting the disease are only one in a million, then his/her odds of getting sick are three in a million, and that's already a lot less scary.

"We have difficulty understanding probabilities in depth, especially when we are dealing with big numbers, and tend to confuse correlation with a cause-and-effect relationship."

Take, for example, a headline that appeared in a newspaper: "Want a happy marriage? Adopt a dog." The article itself discusses a study that discovered that couples that have a dog are happier than other couples. In other words, a correlation was found between owning a dog and marital bliss. The headline expresses a connection, according to which the dog is the cause of the happiness, and therefore if a couple gets a dog it will improve its marriage. But it is possible, of course, that the connection is different: People who raise a dog are, to begin with, more pleasant and easy-going than average, and these qualities lead them both to adopt a dog and to enjoy a better marital relationship.

"A causal connection is always possible between two factors that are correlated," Kupiec says, "but it is also always possible that a third factor is responsible for both."

Telomeres obsession

We are talking in the wake of a study conducted in Kupiec's lab by Dr. Gal Hagit Romano and Yaniv Harari. The study, which recently appeared in a prestigious scientific journal called PLOS Genetics, shows that caffeine and alcohol affect cellular aging and possibly also the development of cancer. Is it correct to conclude from this that we should drink coffee in the morning and beer in the evening to stay young and healthy? Are we talking about a finding that is valid for esoteric lab animals or that also applies to us, human beings who sometimes rush to adopt hasty conclusions? We met up, therefore, to examine the possible gap between effects and conclusions; the differences between correlation and causality; and the question of how it is even possible to study complex biological systems.

What is cellular aging?

Kupiec: "DNA, which contains our genetic information, is a long molecule that is packed by special proteins into structures called chromosomes. Every time a cell duplicates, the DNA in the chromosomes is copied, so that two identical replicas are formed from each chromosome, and each copy goes to one of the new cells. The ends of the chromosomes, which are made up of DNA and proteins, are called telomeres, and because of a technical problem, every time the copying system gets closer to the end of the DNA molecule, it gets stuck and stops working. This causes the resulting copy not to be entirely true to the original. In each generation of cells, the telomeres are slightly shorter than in the preceding generation. At first this doesn't really bother the cells, but at a certain point telomeres become too short, important information gets lost, and the cells die.

"You might say that telomeres are like the cell's biological clock. The more a cell ages, the shorter the telomeres get, until a critical point at which the cell dies."

A death foretold.

"Not only is it foretold, but its timing is also known in advance: It occurs after a set number of cell divisions, and every cell type has a characteristic critical number of divisions. But there are two types of cells in which telomeres do not grow shorter. These are fetal cells and cancer cells, which are cells that live forever. In these cells there is a unique enzyme – telomerase – that knows how to lengthen the gradually shortening telomeres. It preserves the chromosomes at the same length, and the cells don't die."

In other words, lengthening telomeres turns normal cells with a limited lifespan into cancerous cells that live forever?

"That is the first necessary stage. It is not enough for turning a normal cell into a cancerous one, but it is necessary. Cancerous cells always come up with tricks for lengthening their telomeres, because for a cancerous cell to go on dividing for all eternity, its telomeres must maintain their length."

From left, Yaniv Harari, Martin Kupiec and Gal Hagit Romano. Yeasts constitute model systems for many human diseases.

Photo courtesy of Prof. Martin Kupiec's lab

Kupiec: 'Because aging is such a hot topic, people are eager to find correlations and conclude causality from them. It's easy to find correlations, and countless examples of them have indeed been found.'

Can we say that aging stems from the shortening of telomeres?

"At the cellular level, yes. Telomeres grow shorter the older the cell gets, and after several generations, when they are too short, the cell dies. So it is certainly possible to talk about cellular aging and about its connection to telomere length. On the level of the whole organism, [that connection] is still unclear. But, of course, that's the question that is driving everyone crazy: why do we age and is it possible to influence this process? One of the studies that had a great impact on this field was the one in which they took babies, children, adults and elderly people, drew blood cells from them and measured the telomere length of white blood cells. They found that the higher the age in question, the shorter telomeres were, and from this they concluded that telomeres become shorter with age, and that the shortening is what causes aging. It practically became an obsession."

And this is where we get into the issue of correlation.

"Exactly. If every time you see a fat person with a drink in hand and it turns out to be Diet Coke, that means that Diet Coke is fattening, right? Obviously not, because it isn't right to look at the correlation between body weight and drinking Diet Coke and conclude from it the causality I described. The connection that explains the correlation is the opposite one, of course: Fat people want to lose weight, and so they drink Diet Coke. That is the direction.

"By the same token, you can also examine the correlation between the number of storks and the number of children born in a residential area. It turns out that the more storks there are in an area, the larger the number of children per family, and the conclusion is of course that the storks are the ones delivering the babies. Alternatively, it is possible that we are not dealing with one fact that is a cause and another that is the effect, but rather with the existence of a third factor that affects both these variables independently. You can think, for example, about 'settlement' patterns: The fact that in the country there are more storks than in the city and there are also more children there, but there is no causal relationship between the two."

Stressed vs. non-stressed

Let's get back to telomeres.

"What they found in the study I described earlier was a correlation between the telomere length and age.

"You could say that the shortening of telomeres is what causes aging, and then come out with a headline: 'We found the cause of aging.' But you can also say the opposite: That aging is what causes telomeres to grow shorter, among the ►

◄ other things it brings about. And you can also look for a third, completely different, factor that independently influences both phenomena. Because aging is such a hot topic, people are terribly eager to find correlations and to conclude causality from them. It's very easy to find correlations, and countless examples of them have indeed been found.

"In 2004, Nobel Prize laureate Prof. Elizabeth Blackburn published a study that found that people who live with emotional stress have shorter telomeres than people who do not live with such stress. For the stressed subjects in the research, they took single mothers who have a child with a chronic disease; the non-stressed ones were single mothers with an ordinary child. I'm not sure that control population represented especially relaxed people, but never mind.

"The paper made a lot of noise because it linked a mental state to a molecular measure of aging. Later on, the same authors published that meditation, too, causes telomeres to lengthen since longer telomeres had been found in people who did meditation than in other people.

"Over time, connections were found between the telomere length and lots of other factors: conditions such as the tendency toward heart attacks and cancer, traits such as irritability or introversion, and even social elements like the number of years of schooling. What is the significance of all of this? That is entirely unclear. When is one factor a result of another? When is the second one a result of the first? And when do both stem from a completely different factor?"

So what do we do? How can all this be decided?

"This matter is unresolved and cannot be resolved in humans because to determine a cause-and-effect relationship, you need a system in which it is possible to intervene, to alter one factor and to ascertain whether it affects the second factor."

And you have a system like that.

"We work with yeasts, where the genetics are fully known to us. Their telomeres are well defined, and we can manipulate their environment as we like and check its effect on cellular aging. This is a system from which it is truly possible to draw conclusions of causality and not just of correlation."

It's true that correlations are a shaky basis on which to draw conclusions, but what about drawing conclusions about humans from single-celled organisms that we make rolls with?

"No offense, but we are far less different from those organisms than perhaps we would like to think. Indeed, yeast has 6,000 genes and we have only slightly more than three times that – close to 20,000 – but the similarity in the genes is astounding. Approximately 50 percent of the yeast's genes exist in us as well, and our basic cellular mechanisms are so similar that you can correct a mutant yeast, which has a defective gene, by inserting the human gene into it."

In other words, you are going with a very simple model system on the assumption that the basic and essential processes are similar in all organisms.

"Right. Evolution preserved important structures and processes in all living organisms, and therefore you can often study simple organisms that are easy to work with in order to understand more complex organisms. Simple model systems have led to the most significant breakthroughs in the study of complex processes in biology: memory mechanisms discovered in the flatworm, embryonic development processes in translucent worms and flies, and more.

"Today, yeasts constitute model systems for a great many human diseases, whose molecular basis we want to understand. Many genes that are responsible for hereditary diseases in humans exists in yeasts as well, and so they can be studied in this simple system, which is also an ideal system for seeking cures for those diseases. Yeasts are even used to study diseases that are caused by protein buildup, such as muscular dystrophy, Alzheimer's and Parkinson's. There are a few differences, of course, between yeasts and us, but a certain aspect of those differences is precisely what enables us to work with them. For example, [there's the fact] that they divide faster than our cells, that you can deliberately damage or modify their genes and you can expose them to all kinds of substances to test the effect. You can also put them in the freezer, which is a bit harder to do with humans. But all that makes yeasts a very convenient system for work."

'Precision is critical'

What has this model system enabled you to discover?

"We created, for example, all the mutants of the yeast. Yeast has 6,000 genes and we've got in the freezer 6,000 different strains, each of which is defective in a different gene. It's as if I had in the freezer 20,000 varieties of humans, in each of which there was one inactive gene out of the entire human genome. Such a system can allow us to ascertain the role of each gene separately, and to understand what is the trait for which that gene is responsible.

'A low concentration of **caffeine** (like in a single-shot espresso) caused significant shortening of telomere length, and a low concentration of **alcohol** (as found in beer) caused them to lengthen significantly.'

"To study the role of telomeres in aging, first you have to find all the genes that affect their length. To do that, we scanned all the mutant strains and focused on those that have especially long or short telomeres. That is how we discovered a highly complex system, which controls telomere length and includes more than 400 genes. That is an enormous number and it indicates the significance of telomere length in safeguarding the stability of the genome.

"It turns out that telomere length is something that's very exact, which

Gerbil

Prof. Elizabeth Blackburn. Provocative study.

suggests that precision is critical. The degree of coordination between genes is amazing, and all it takes is for one of these genes to be harmed for the entire mechanism to be disrupted. When my students want to get something to eat at the university, a two-hour discussion ensues about which cafeteria they should go to. Eventually there is one person who decides and everyone follows her lead. Here there is a system of 400 'participants,' who talk to each other and work together, and in the end always make the same decision.

"This is the first time anyone has analyzed a complex system in which all of the genes affecting it are known. In this system, you can play with the genes and engineer them so as to ask questions regarding the interplay between heredity and environment. You can intervene in the environment – for example, by adding substances such as caffeine, and test how it affects telomere length. At long last, we no longer have to settle for correlations: We can actively alter the environment, and ascertain whether we are dealing with a mere correlation or a relationship of cause and effect."

For example?

"For example, it is a unique opportunity to verify in a controlled manner whether stress really does affect cellular aging as claimed in Blackburn's 2004 study."

How? Have you found single-parent yeasts with a sick child?

"Ultimately, psychological pressure, like that tested among single mothers who have a chronically ill chid, translates into chemistry in the body, into molecules such as free radicals. The hypothesis in Blackburn's study was that in view of the emotional pressure single mothers are under, physiological changes take place in their cells such as a buildup of free radicals. These molecules damage the cell and are what causes the shortening of telomeres. In keeping with this hypothesis, we grew our cells in conditions that generate free radicals and tested their effect on telomere length. To our surprise, the length did not change at all. In the wake of this, we decided to grow the cells under a wide range of additional conditions, and we saw that most did not cause a change in telomere length. This stems from the fact that the complex system is able to respond to the environmental cues and preserve the very particular length required."

And the alcohol and caffeine?

"It turned out substances, to which we are exposed in our day-to-day life, had great effect on telomere length, and the most significant were caffeine and alcohol: A low concentration of caffeine (like in a single-shot espresso) caused significant shortening of telomere length, and a low concentration of alcohol (as found in beer) caused them to lengthen significantly."

So is that a recommendation to drink beer?

"These are sexy results, of course, because they can be translated immediately into headlines and dietary recommendations. Because we said that long telomeres may turn cells cancerous and short telomeres characterize aging, we may want to recommend drinking alcohol and coffee evenly and in moderation to maintain balance in the length of the telomeres. But you have to remember that we are talking about yeasts, not humans, and that we are talking about cellular aging and not necessarily the aging of the entire organism."

I guess they'll never take you to advertise coffee or beer.

"Nor will they be taking me to be a consultant for companies that offer to measure the length of your telomeres and, based on that, tell you your life expectancy and the state of your health. There are at least two companies in the world today that do that, and unfortunately there are scientists who cooperate with them."

Nevertheless, what can be concluded from your model system?

"We discovered that despite the fact that telomere length is meticulously controlled, a few specific environmental factors can alter it. We were able to identify the two main players in determining length – two genes that are also the ones directly influenced by the external environment. And now that we have put our finger on the relevant genetic path, we can examine its connection to humans and try to test how certain environmental conditions affect cellular aging, diseases related to aging, and cancer. As I said, because many genetic mechanisms have been preserved in evolution, there is a chance that if we succeed in affecting the length of telomeres and controlling them in yeasts, in the future we will be able to offer prevention and treatment of human diseases by means of medications that influence the length of telomeres."

Some final words on science and its application.

"You could say that science is a great gift to humanity because it finds cures for diseases and invents 'gadgets' that improve the quality of our lives. But, in my opinion, these are merely side effects of the scientific process. The purpose of science is to broaden our knowledge and understanding of the world. Most of the important scientific discoveries, of the kind that altered our understanding of life, have not been aimed at finding a cure for disease or inventing an appliance that will allow us to scratch our backs more efficiently. Telomeres, for example, and the enzyme that lengthens them, were discovered by Elizabeth Blackburn while attempting to understand how cells copy their DNA in full, down to the end of the chromosome, every time a cell duplicates."

So in science, too, the road to Ithaca is what counts.

"Absolutely. Because the road is brimming with amazing discoveries and insights, and some of them will surely also help us to live better." ■