REPAIR
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By James Trefil

How the body defends itself from the risky business of living

Our cells take trillions of 'hits' each day from toxins both natural and man-made, but hardworking enzymes repair the damage

Bruce Ames argues that fruits and vegetables are full of natural poisons—but they're still good for us.

The judges at my table were nervous, casting furtive glances at a small, pleasant-looking man across the room.

"Is Bruce eating his cheesecake?" one asked.

Another glance. "Yes."

Smiles appeared around the table, and we all started in on our desserts.

This follow-the-leader took place at a science workshop for federal judges—the men and women around the table represented some of the best legal minds in the country. The man whose actions were being so closely watched was my fellow lecturer, Bruce Ames, a professor of molecular and cellular biology at the University of California at Berkeley. He has taken the controversial position that the toxins naturally present in our food and elsewhere add up to thousands of times the quantities of man-made toxins we are exposed to, especially the pesticides used on the fruits and vegetables we eat. It is a waste of time to worry about the latter, he says; our bodies can handle most anything nature or we can throw at them. The cells in our body, he tells us, live in a continuous barrage of damaging molecules. Every cell takes a "hit," as he calls it, about every ten seconds. In the time that it takes you to read this article, your body will have been assaulted tens of trillions of times.

Most of the damaging molecules are inescapable byproducts of the chemical processes in our bodies that enable us to live. Others are toxins, natural and man-made, that we take in. ("The world is full of poisons," Ames says, "but it doesn't make any difference.") Still other damage is done by radiation, whether the ultraviolet component of sunlight or the x rays that produce the diagnostic images ordered by physicians.

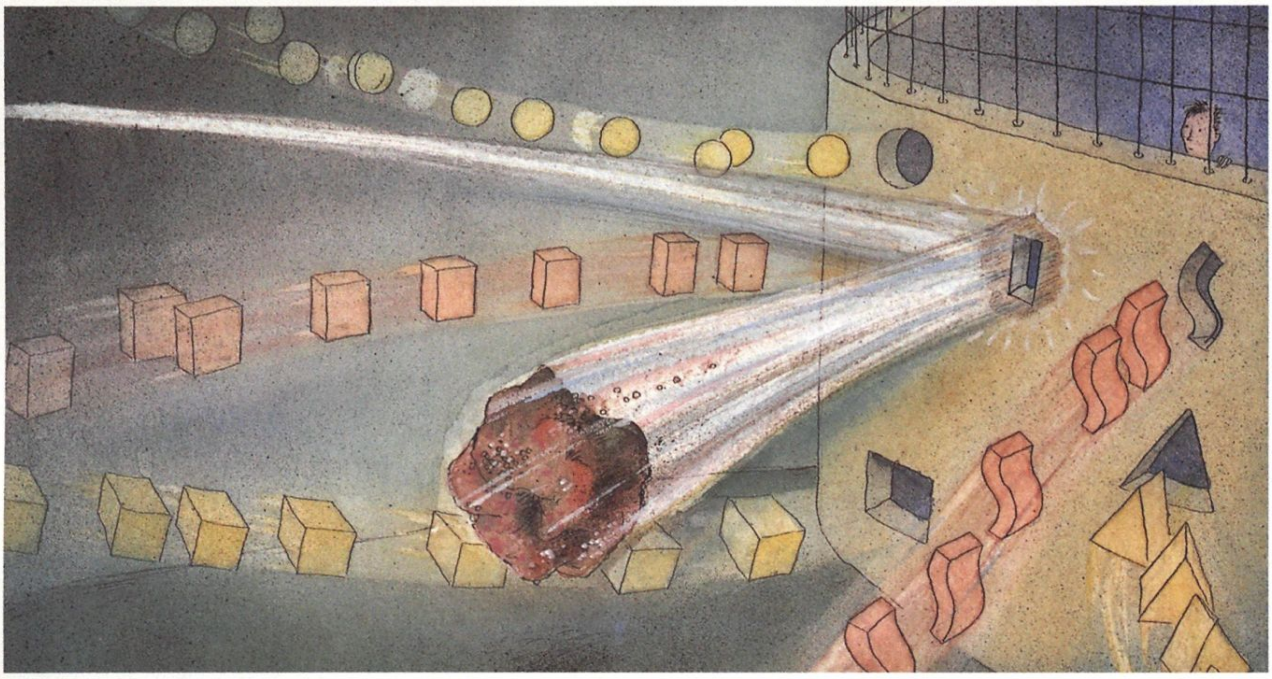
Ames' contention that it is a waste of time to worry about man-made pesticides, air pollution and all the rest is by no means universally accepted by scientists—and certainly not by consumers. But his research on cancer and aging is widely respected. His findings add strength to long-held theories about how well cells repair themselves and offer a better understanding of how we can best evaluate the risks we face.

Right now, the 60 trillion or so cells in your body are going quietly about their business, churning out the chemicals needed to keep you alive. In your pancreas, for example, cells are producing insulin and pumping it into your bloodstream. Your thyroid is producing chemicals that govern your metabolism. Your bone marrow and thymus gland are producing antibodies to ward off

Once a damaged section of the helical DNA strand is removed, specialized enzymes arrive to rebuild it.

Illustrations by John S. Dykes

RISK: the second of a two-part series



The membranes that protect both the cell and the nucleus inside it will not allow strange molecules to pass. Only those molecules with the right shape (and that the cell needs) are permitted to enter.

disease. In all of these cells, the key step in the chemical process is the building up and tearing down of specific molecules to extract energy and useful materials from them. Some of the end products, such as insulin, are exported from the cell to be used elsewhere. Some are used to run the chemical reactions inside the cell, others to replenish and repair the cell itself. In most cells, thousands of these chemical reactions are going on at any given moment, each affecting you in some way.

The facilitators of these life-sustaining reactions are proteins called enzymes. For every one of the thousands of chemical reactions that go on in each cell in your body, there is one specific enzyme—one molecule with just the right intricate shape to bring two other molecules together and let them form bonds. The processes of life depend crucially on the right enzymes being present. Where do they come from? The blueprints for making the enzymes that run the cell's chemistry are contained in the molecules we call DNA. From these blueprints the cells make the enzymes, and the enzymes drive the chemical reactions that make us what we are.

Under normal circumstances, the process of translating the information on the DNA into enzymes goes smoothly. But, life being what it is, this complex machinery sometimes breaks down. If the enzymes are flawed, they can seriously hamper the cell's function, perhaps even kill it. Cells die and are replaced all the time.

If, however, the damage is to the DNA itself, the situation is potentially more serious. Alteration of the DNA will not only affect the cell in which it occurs, but when that cell divides, the defective blueprint will be passed on to all the descendants of that cell. And if that defect changes the shape of an enzyme that drives a crucial chemical reaction, the consequences for the organism can be serious.

By far the easiest way for this damage to occur is for other molecules to interact with DNA and upset its complex structure. Where do these "killer" molecules come from? Bruce Ames' research shows that the overwhelming majority are byproducts of the normal process by which cells turn food into energy. They have been around since life began. If cells couldn't repair damage to their DNA, Adam and Eve would have died when they ate that first apple, and none of us would be here today. Somehow our cells learned to deal with chemical damage to DNA. It is the details of how these mechanisms work—and how *much* they work—that molecular biologists are starting to sort out.

The double-helix shape of the DNA molecule is now familiar to everyone. You can think of this shape as a twisted ladder in which the rungs (which chemists call "base pairs") keep the two sides of the helix from drift-

James Trefil, the Clarence J. Robinson Professor of Physics at George Mason University, eats his fruits and vegetables in Fairfax, Virginia.

ing apart. Here and there along the helix are segments of DNA known as genes, where the information about building enzymes is stored. Each gene carries the information needed to assemble one enzyme and hence the ability to control one chemical reaction in the cell. In humans, there are about 80,000 genes. Every single living thing on Earth uses this same DNA molecule and the same code to carry out the business of living. But just as a single code, like the English alphabet, can be used to write an infinite variety of messages, so too can the genetic code be used to "write" everything from a blade of grass to a Nobel laureate.

By far the most common source of damage to DNA is a class of chemicals known as oxidants. When your cells burn the material in food to supply energy, byproducts are produced, including some familiar substances, such as hydrogen peroxide, and some less-familiar substances with names like "superoxide" and "hydroxyl radical." These are active chemicals—they like to combine with other molecules in reactions chemists call oxidation. It is because oxidants do so much of the damage that scientists such as Ames urge people to eat lots of fruits and vegetables, the foods that contain antioxidants. Ames believes they help reduce the body's risks to not only cancer but cardiovascular disease, immune system diseases, cataracts and brain dysfunction.

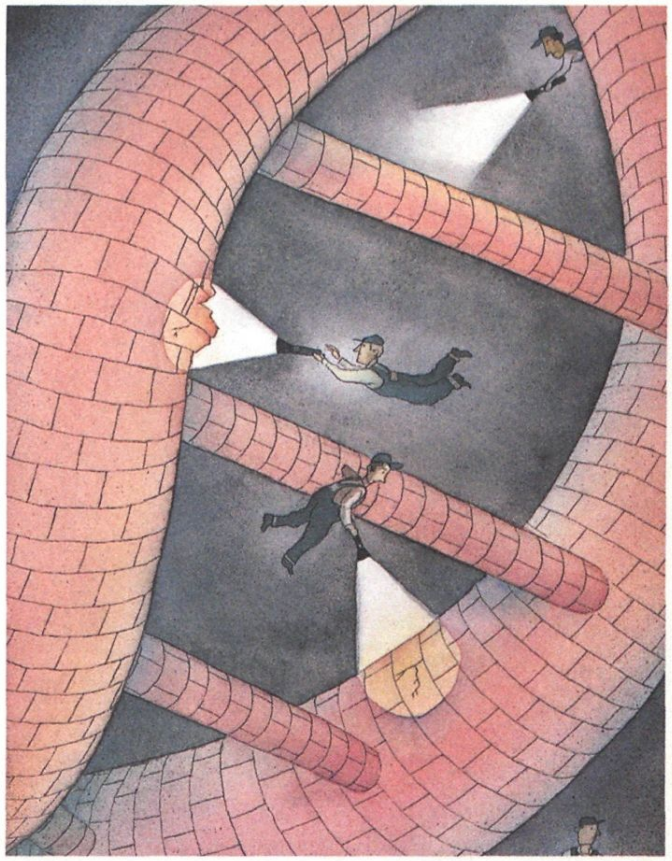
When active molecules attach themselves to the bases in the rungs of the DNA ladder, they change the effective shape of the structure. This means that they introduce the possibility that when the DNA duplicates itself, the base pairs in the copy will be different from the pairs in the original. This is what causes mutation. The DNA in all later generations will have the wrong code, and this could eventually lead to cancer. Cells must have some way of preventing this sort of mistake from being propagated.

The way cells do this illustrates the engineering concept of "defense in depth." First, the places where oxidants are produced tend to be located in the body of the cell, while the DNA is segregated in the nucleus. So damaging molecules have to travel some distance to get at the DNA. Second, our food contains antioxidants (vitamins C and E and beta carotene are the most familiar). Third, damaged or dead cells are routinely sloughed off before they have a chance to multiply, so that damage is confined to a single cell's DNA. Finally, even after the damage is done there are ways that the DNA can be repaired.

Complexes of enzymes move constantly along every strand of DNA, searching for trouble. When they find it, they fix it. There are two general types of DNA repair mechanisms, each suited to a specific kind of problem. The one that concerns us most here is called "excision repair" and serves as a jack-of-all-trades for repairing damaged DNA. It swings into action, for example, when benzo[a]pyrene damages DNA. This is one of the compounds in cigarette smoke that can cause lung cancer. When this very large molecule attaches itself to one side of a rung, it distorts the helix; so when it comes time for the helix to split apart and replicate itself, random bases are edited into the new strand, thus creating mutation. The excision repair enzyme snips out the faulty section of the helix so that the gap can be rebuilt with the correct order of bases.

The other repair mechanism is "mismatch repair," which occurs as the helix duplicates itself prior to cell division. It may be, for example, that the two sides of a rung on the DNA ladder get made from the wrong bases or that one side of the ladder slips down a little bit with respect to the other. When this happens, characteristic lumps of mismatched bases and unpaired bases appear on the helix; these lumps are recognized by the repair enzymes. In most cases the molecule that is creating the new strand of DNA, the polymerase enzyme, is actively correcting its own errors as it works—proofreading, so to speak. When bases are not properly paired, it pulls them apart and fills in the correct base molecules in the new strand.

But when the polymerase misses an error, the mis-



Repair enzymes constantly patrol the six feet of DNA in each of our 60 trillion cells, looking for damage.

By capturing and weighing the debris from damaged DNA, scientists can measure the rate of repair.

match repair enzyme goes to work. Its first order of business is to unwind the DNA strands and determine which strand is the new one and therefore has the incorrect base. It then makes a cut in the new strand and removes all the bases back to the original error. The polymerase enzyme then returns and fills in the gap. To date, scientists have been unable to find any kind of DNA damage that cannot be repaired by these two mechanisms.

The general nature of DNA repair is the key to Ames' arguments. If you eat something that contains a molecule you've never encountered before (a new pesticide, for example), your cells don't have to start from scratch to organize a defense. They will simply react to it as they would to any other molecule that doesn't belong and, as a last resort, repair any DNA that it damages. General defenses give us a great deal of flexibility.

Working at the limits of measurement

Scientists like Bruce Ames monitor DNA repair by analyzing the debris that is discarded when damaged portions of DNA are snipped out. Eventually, many of these fragments are removed from the cell and leave the body by way of the urine. The amount of any given compound will be very small, and it is only in the past decade that scientists have acquired the ability to detect such small concentrations. But the general advance in analytical ability that has allowed us to detect environmental pollution at the level of parts per billion also allows us to measure these infinitesimal quantities of DNA repair byproducts and thereby estimate the volume of repairs going on in our bodies.

It is much easier to describe this kind of work than to actually do it. You need imagination and creativity (to know what to measure) and an almost fanatical attention to detail (to make the measurement). Ames enjoys the reputation he does because he has both qualities to an unusual degree. He is a "scientist's scientist."

When I asked why the cell was able to snip out damaged sections and make repairs, his reply surprised me. Instead of quoting up-to-the-minute biological theory, his answer went back more than a hundred years to Charles Darwin and evolution. Taking his current research on natural plant pesticides as an example, he pointed out: "Every plant has 40 or 50 pesticides it makes to kill off predators and fungi. They couldn't survive if they weren't filled with toxic chemicals. They don't have teeth and claws, and they can't run away. So throughout evolution they've been making newer and nastier pesticides. They're better chemists than Dow and Monsanto."

Human beings and other animals have evolved in a world in which not only do their own bodies produce damaging oxidants, but their main food supply is

loaded with potentially deadly chemicals. The laws of natural selection dictate that in such a situation we would either develop ways of dealing with these toxins or lose the evolutionary battle to someone who did. Furthermore, the defenses would have to be general—otherwise we'd be at risk every time a plant evolved a slightly new version of an old pesticide.

By and large, we've been very successful at countering nature's attempts to kill us off. We've not been completely successful, though, as the occasional newspaper stories about someone dying from eating mushrooms illustrate. So there are some reminders in our daily lives of the long chemical battle between our cells, as they seek energy from plants, and the plants themselves, seeking to keep from being eaten.

Seen this way, the layered defenses of the human cell make sense, as do the busy enzymes patrolling the DNA: we needed them to survive as plants became better at self-defense. But if you're going to invoke Darwin to explain one thing about the cell, you're going to have to follow through and see what he has to say about other things as well. For example, it's true that the human body is a marvelous machine, designed to survive and prosper in a hostile world. In an evolutionary sense, the purpose of this marvelous machine is to reproduce—to place its genes in the next generation. Once this has been done, there is no evolutionary advantage for keeping the organism alive and in good repair. As a middle-aged scientist, I have often brooded on the inequity of this state of affairs, but it remains a basic tenet of evolutionary theory.

The DNA repair mechanisms we've described play a crucial role in keeping us alive. If damage to DNA is allowed to go uncorrected until a cell divides, all succeeding generations of cells will carry the defective blueprint, and the final outcome may be disease or malignant growth. The cell doesn't have forever to effect its repairs, then—it has to do so before the next division. This constraint forces the cell to set priorities in its repair operation, with crucial repairs being done first, others if the opportunity arises.

Repair work is strictly prioritized

First come repairs to genes that are actually being used by the cell. In the pancreas, for instance, the gene that codes for the production of insulin will be first in line. Damage to inactive genes or to other parts of the DNA not in current use will be put off until crucial repairs can be made.

In his studies on rats, Ames finds an interesting pattern to repairs. At any given moment, there may be a million or more damage sites on the DNA in a rat cell. About 100,000 are repaired each day, but a little more than 100,000 new "hits," or lesions, appear. Thus, over time, the uncorrected damage accumulates. There may be, for example, as many as two million DNA lesions in an old rat.

Plants cannot run from those that would eat them, so they have evolved some lethal chemical defenses.

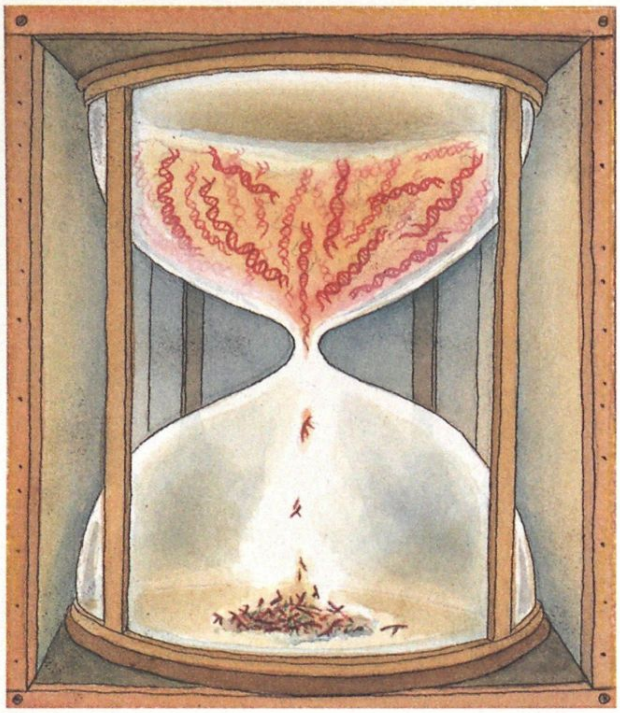
"Is this true in humans as well?" I asked.

"We don't know about humans yet," Ames said. "There are too many variables. You can't put human subjects on a strictly controlled diet. You have to put in a tremendous amount of time to get things worked out in rats first, before you can even think about moving on to humans."

In Ames' view, both the process of aging and the incidence of cancer can be attributed in large part to the accumulation of damage to DNA. "Most [researchers] think that both aging and cancer have something to do with damage to DNA," he says. "Cancer is a disease whose rate increases with age."

There is evidence to back up this view of aging and cancer. Measurements of repair rates show that small mammals have a much higher number of hits to their DNA than do humans. Rats and mice, for example, seem to be making 100,000 repairs to each of their cells per day (versus 10,000 for humans). These rodents live only a few years and are typically full of tumors when they die.

In addition, there is strong evidence that many (if not most) human cancers are related to processes that stimulate the division of cells. The most striking example of this phenomenon is the constant irritation of lung tissue



When the repair forces can no longer keep up with the damage occurring, we experience what we call aging.

from smoking, but there are many others, including the effect of alcohol on the liver and other chronic irritations and inflammations. The more often cells divide, the shorter the time there is for repairs to be made and the more likely it is that a mutation will occur.

DNA repair is more than a fascinating science story. Its ramifications spill over into the politics of our everyday lives, and Ames has never hesitated to make the leap from laboratory to public arena. Back in the 1960s, he developed the Ames test, an elegant, simple way of determining whether a chemical produced mutations in the DNA of bacteria. It has since become a universal screening technique for potential carcinogens. Ames never patented—or made a nickel from—his test. "In those days, people didn't worry about things like that," he says. "Besides, I wouldn't have any way to spend the money. Going to scientific meetings provides all the travel I want." (A new version of the Ames test is about to be patented, however, at the insistence of the University of California.)

When the cancer-causing potential of chemicals was first recognized, attention turned to man-made compounds, such as pesticides. Tests on animals established that about half of the synthetic materials tested could, indeed, produce cancer in rodents. The human race suddenly found itself awash in a sea of apparently carcinogenic chemicals. In the 1970s Ames himself was arguing that humans should not be exposed to even one molecule of any substance that causes mutations in bacteria.

Little attention had been paid to natural pesticides. Ames and his colleagues began to look at the chemicals naturally present in foods from the plant kingdom, and they found that half of them caused cancer in rodents—a proportion similar to that of synthetic chemicals. By the late 1980s Ames had reversed himself, and the group began ranking suspected carcinogens by an index that relates cancer caused in rats to the risk for humans. In the process, he began to question the massive doses given rodents in animal cancer tests. It had become standard to submit animals to the maximum tolerated dose (the most a rodent can ingest without dying). Ames and others now believe that megadoses of anything accelerate cell division, and this in itself leads to cancer. For that reason, they feel, the results from rodent tests cannot be extrapolated to the low, everyday doses to which human beings are exposed.

Today in his lab Ames tells me, "Almost every plant product in the supermarket is likely to contain natural carcinogens." He estimates that an American eats about a gram and a half of these natural pesticides every day—10,000 times more than the residues of man-made agricultural pesticides ingested. In other words, about 99.99 percent of the pesticides we take in every day are natural, only 0.01 percent are man-made. "For example, when you eat cabbage, you ingest 49 different natural pesticides and metabolites," Ames says with that same disarming smile, and goes on to produce a list of 43 foods that contain at least ten parts per million of chemicals that are carcinogenic in rodent tests. Ranging from anise to lettuce, the list even includes parsley, sage, rosemary and thyme. Even a cup of coffee doesn't escape his attention. "There are over a thousand chemicals in a cup of coffee," he says. "We've tested 26 of them, and half of those cause cancer in rats."

"Life is full of 'one in a hundred thousand' risks," Ames states. "If the EPA is spending all its time trying to protect the public against 'one in a million' hypothetical risks—which it is doing to a large extent—it's spending its time on trivia. We're spending $150 billion a year trying to control pollution. Although much of this is useful, I think it will have little influence on cancer rates" (SMITHSONIAN, November 1995).

At bottom Ames, the consummate scientist, wants Americans to recognize *all* the risks in their lives and adopt a rational approach to controlling them. Instead of worrying about a minor (and perhaps even nonexistent) risk, we should think about eliminating major causes of cancer. What are these causes? Ames ticks them off on his fingers: "First, of course, is smoking. Then there is the lack of fruits and vegetables in the diet. And, finally, chronic infections."

Needless to say, Ames' views have not gone unchal-

lenged. One critic is Bailus Walker jr. He is a professor of environmental and occupational toxicology at Howard University Cancer Center in Washington, D.C. He says: "You've got to look at total exposure to everything that the body receives through the air, the food, the water. We can no longer look at these pieces in isolation. We've got to look at the total load."

Others argue that human beings, through the process of evolution, have gotten used to metabolizing natural toxins but haven't yet had time to develop similar defenses against man-made chemicals. Ames responds that there is no chemical difference between the actions of synthetic and natural substances in the cell. An oxidant is an oxidant, regardless of its source, and the general nature of the cell's defenses can handle both. "To a toxicologist, the idea that nature is benign and only man-made things are bad is crazy," he says. To back up this statement, he points out that "most humans are eating plants their ancestors did not—for example, cocoa, tea, potatoes, tomatoes, corn, avocados, mangoes, olives and kiwi fruit." There simply hasn't been time for the human body to adapt to all of the new natural pesticides in these foods, he argues, so the fact that they are considered safe is evidence for the efficacy of the cell's general defenses.

These sorts of arguments have won many scientists over. James Duke, of the National Germplasm Resources Laboratory, part of the U.S. Department of Agriculture, was once one of Ames' harshest critics but changed his view as new information came in. "I have come around to believe him," Duke says, and then goes on to note that his own work on natural pesticides suggests that "Ames may be understating his case." Looking at oregano, for example, Duke finds that there is 100,000 times as much natural pesticide present as there is synthetic pesticide residue.

The new vision of the dynamic, self-repairing cell is going to force not only scientists but policymakers as well to rethink their ideas. But what direction is there for the rest of us? How can we go about controlling the risks in our diet in the face of the sort of media hoopla we encounter all the time? I ask Bruce Ames how he would answer these questions.

"Don't smoke at all," he says. "If you drink, drink moderately. Eat a balanced diet, with lots of fruits and vegetables." Then, with a smile, he adds: "Just do what your mother told you."

For long and healthy lives, biochemist Ames suggests that we just follow the prescriptions of Dr. Mom.

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