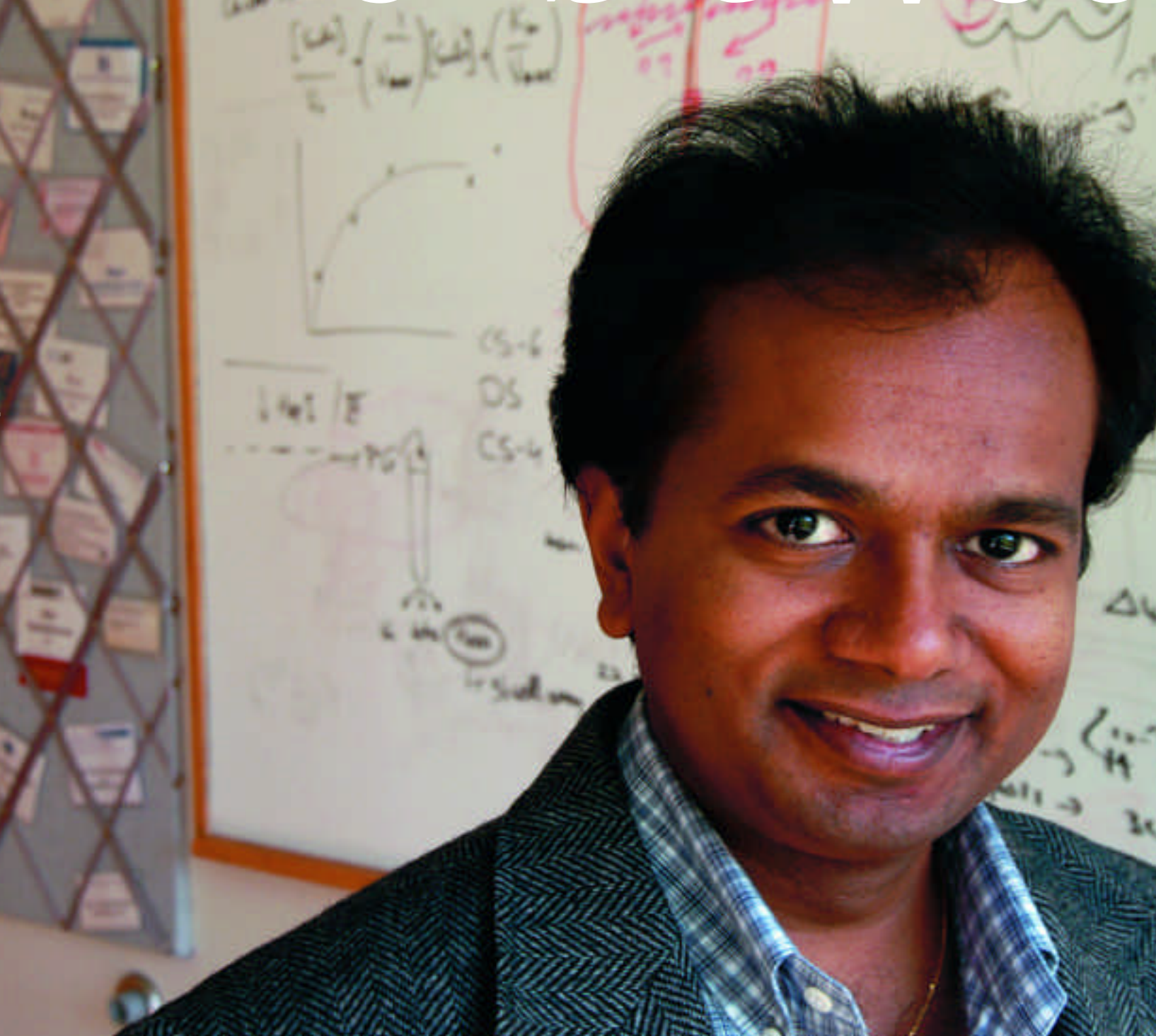
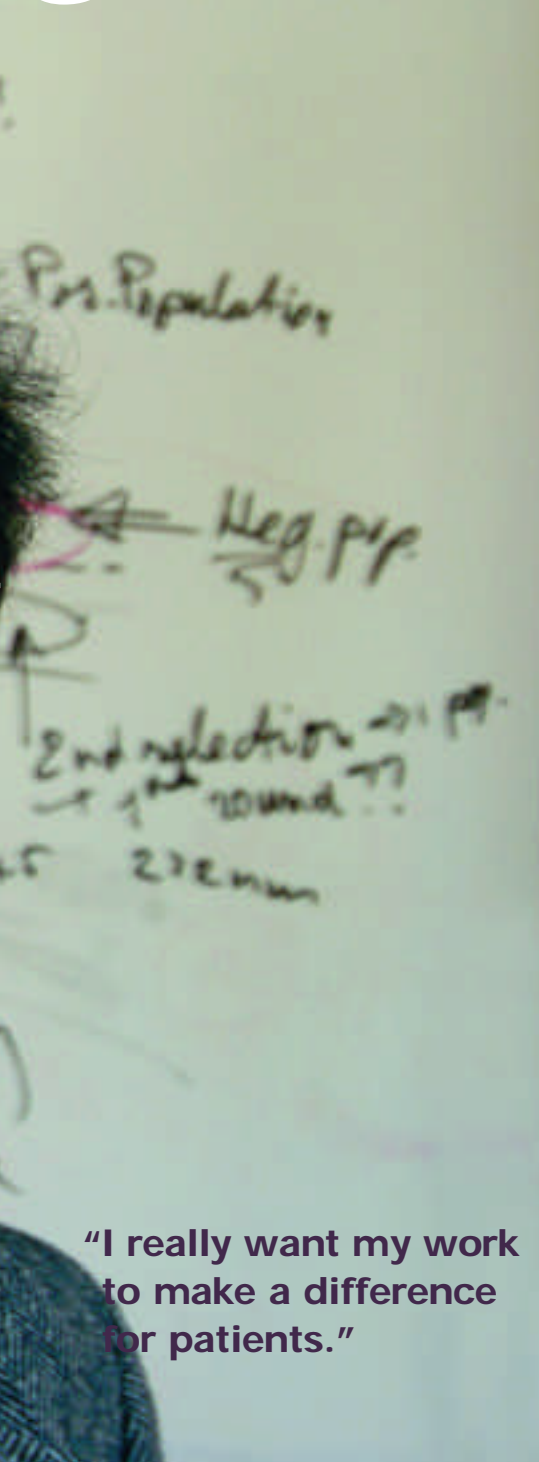


Life Is Sweet



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EMMA SCURINCK

By Alison Davis

Ram Sasisekharan's first experiments with human biology began early. Like most kids, he suffered the "battle wounds" of an active child's growing-up years. Sasisekharan was continually amazed to see his scabs disappear and new skin grow back, over and over again.

"I was absolutely fascinated by how my body automatically healed when I got hurt," he says. "It just seemed too bizarre to be true."

Now 39, and with fewer cuts and scrapes available for scientific analyses, Sasisekharan is still eager to find out what's going on underneath his skin.

How do the cells stitch themselves together to form skin, tissues, and organs?

A professor of biological engineering at the Massachusetts Institute of Technology in Cambridge, Sasisekharan got his bachelor's degree in biophysics and a Ph.D. in medical sciences. His goal is to learn life's basic rules for design.

Knowing how cells come together to form skin, tissues, and organs, he says, will lead to a deep understanding of the language of life and the tools required for editing mistakes that cause disease or the problems that arise from injury. And though Sasisekharan's childhood curiosity has not waned with time, he says that these days curiosity alone is not enough.

"I'm not satisfied with just doing cool stuff in the lab," he says. "While that's what makes science fun, I want to take my science as far as it can go. I really want my work to make a difference for patients."

Sugar Rush

Sasisekharan studies biological sugar molecules called carbohydrates, which are indispensable for life on Earth.

In most life forms, carbohydrates come in many varieties, ranging from simple to complex (see sidebar, page 13). In their simplest form carbohydrates equal energy, and they are sweet. This is the "sugar rush" we all know well. Simple carbohydrates like sucrose, glucose, and fructose are the molecules that give sweetened breakfast cereal, orange juice, candy bars, and many other foods their sugary taste.

L. BARRY HETHERINGTON

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Complex carbohydrates, on the other hand, are made up of simple sugars linked together in various combinations. Complex sugars are not necessarily sweet, and they include substances like the starch in potatoes and pasta and the fiber in apple skins and vegetables.

Complex carbohydrates are part of a healthy diet, and they are also a big part of our bodies.

In fact, complex carbohydrates are among the magical molecules that helped fix Sasisekharan's skinned knees. These gluey substances perform an astounding number of biological roles ranging from holding cells together to communicating messages throughout the body.

Most complex carbohydrates are bundled into packages that also contain proteins and other types of natural chemicals. Scientists refer to these biological mixtures as glycans. Just about every cell in your body has a sugary, glycan coat, and these abundant substances populate the spaces between cells too.

But despite the thousands of important roles carbohydrates play in maintaining our health, they remain poorly understood by scientists.

According to Sasisekharan, researchers know very little about how sugars work in the body because carbohydrates have traditionally been ferociously hard to study. The main reason, he explains, is that complex carbohydrates come in a zillion "flavors."

Unlike a simply organized, linear string of connected units (DNA, for example), complex carbohydrates can be both linear and branched. They look something like trees, with branches big and small extending in every direction.

What's more—unlike our DNA, with its strings of "letters," and our proteins, made of chains of amino acids—carbohydrates are not made from a blueprint. Rather, the body makes complex carbohydrates through a sort of community effort, via the collective work of different enzymes acting in ways that remain stubbornly complicated for researchers to understand or predict.

For many scientists, these characteristics of carbohydrate research spelled "nightmare," not "interesting problem."

Despite years of hard work, many researchers had great difficulty determining how sugars get assembled in nature.

As a graduate student, Sasisekharan saw this as a

challenge and decided to try his hand at it.

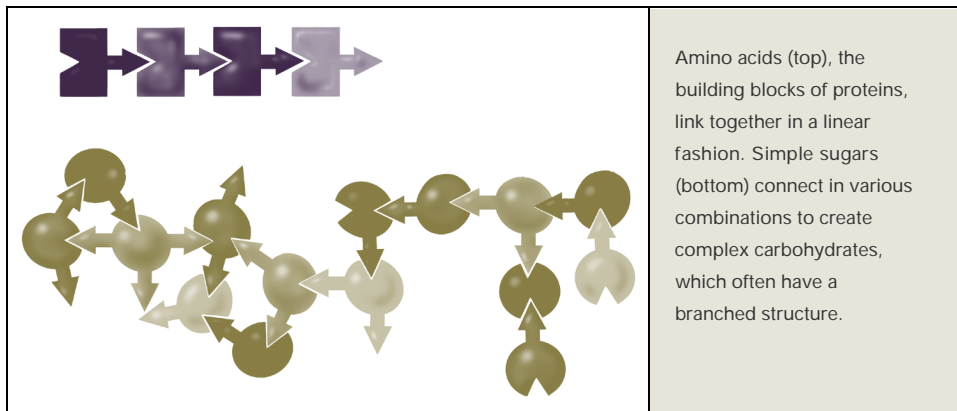
"It was probably a dumb thing to do then, but I was lured by the excitement of the unknown."

He hit the jackpot. Sasisekharan figured out a way to decipher nature's carbohydrate code: how to "sequence," or put in order, the many different constituent parts of a glycan called heparin. In doing so, he opened the door to studying sugar molecules in intricate detail.

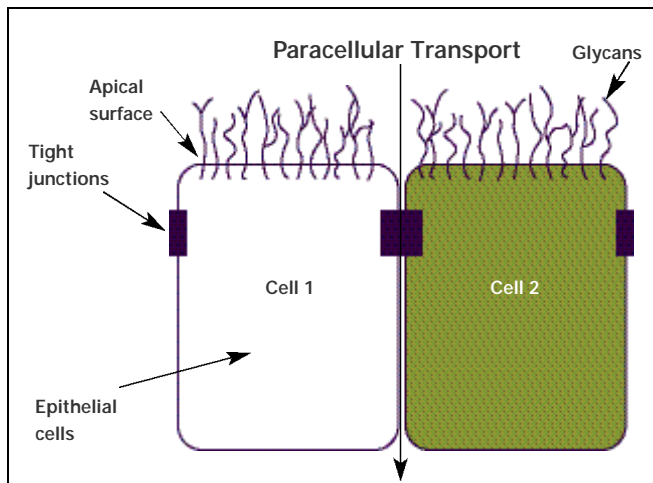
Open, Sesame

Among the many ways sugars affect our health is by policing the gates between so-called epithelial cells. These are the cells all over the body that line organs, such as the stomach, lungs, and brain. The body strictly guards the passage of molecules through epithelial cell gates, a process called paracellular transport.

Simple and complex carbohydrates are present in many different foods.



Amino acids (top), the building blocks of proteins, link together in a linear fashion. Simple sugars (bottom) connect in various combinations to create complex carbohydrates, which often have a branched structure.



Another Dimension

Sasisekharan has lots of projects going on in his lab to investigate the multitude of roles that carbohydrates play in the game of life.

But it's easy to get wrapped up in the details, he notes. While Sasisekharan is undaunted by hard problems, he thinks one of the biggest keys to his own success has been his ability to step back and look at the many dimensions of a research puzzle.

One way he does this is by drawing pictures.

"I love to doodle and sketch," says Sasisekharan, adding that scratching on a pad of paper helps sharpen his thinking and his ability to appropriately gauge the depth of a problem.

If the wrong molecules slip through the gates, "bad things can happen," says Sasisekharan. Asthma, diarrhea, and many other health problems are directly linked to problems in transporting molecules across epithelial cell barriers.

Recently, Sasisekharan's experiments have led him to suspect that the epithelial passages are marked with a sugar code that restricts entry to only the molecules that fit just right. It makes sense that the body would do this, says Sasisekharan, since carbohydrates can be constructed in thousands of subtly different ways. That adds up to many, many different combination locks.

"It's sort of like Ali Baba and the 40 Thieves," says Sasisekharan, explaining that specific sugars only recognize molecules that precisely match the correct code, then respond with the chemical equivalent of "Open, sesame."

"If the code is correct, the cellular trap door can swing open and let certain molecules pass through."

While Sasisekharan needs to do more experiments to fully understand what's going on with sugars and epithelial cells, the practical aspects of the findings jump to his mind almost immediately.

"What if we could learn a way to use the correct sugar as a 'key card' to keep cell doors shut when needed?" he wonders. That type of strategy, he says, would be useful in cases where you know the code is too loose—like in asthma.

And what about the other way around, he ponders. "What if we could use the sugar 'key card' to open the door and get medicines inside?" Precise delivery of medicines to their desired job sites in the body could help alleviate side effects caused by drug molecules acting in the wrong place.

Sasisekharan has discovered that paracellular transport, in which molecules pass between epithelial cells, appears to be gated by a "sugar code." The code is specified by glycan molecules that coat the top, or apical, surface of these cells.

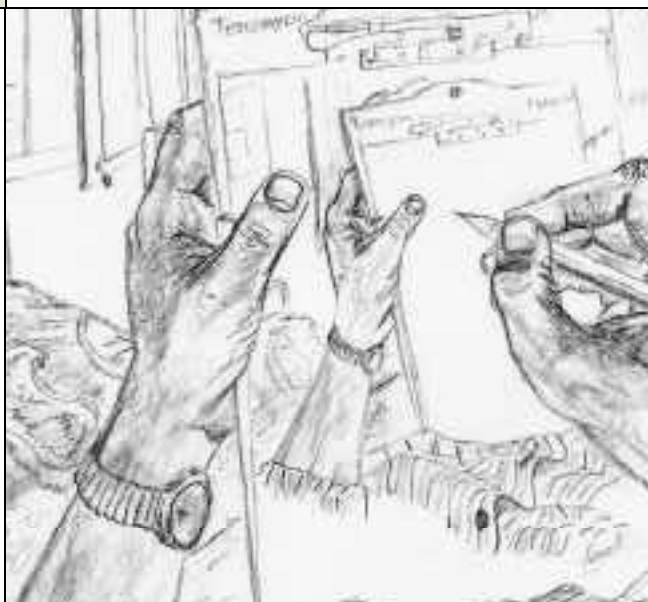
Sasisekharan says that for him, drawing serves as a link between the analytical world and the visual world, bringing new ideas into view.

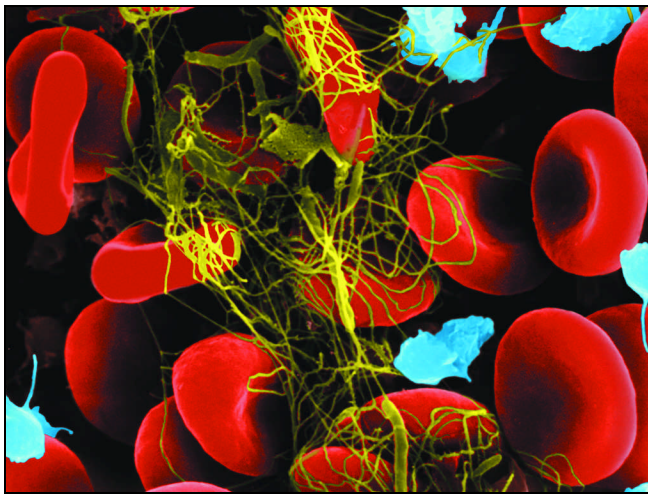
"It's important to zoom in," he says, "but it's also essential to zoom out."

Having the ability to shift focus is absolutely necessary in today's data-rich world of medical research, Sasisekharan believes.

"Biology and science in general are increasingly complex," Sasisekharan says, and making discoveries requires creative approaches to handling large amounts of data.

Sketching helps Sasisekharan visualize research ideas.





Mix and Match

Instead of breaking apart a huge problem into tiny chunks and studying every teensy aspect of a particular chunk, Sasisekharan prefers a different method. He likes to build new models, juxtaposing the individual pieces in many different combinations, and then see what happens.

Sasisekharan did just that when he determined the sequence of heparin, a sugar-based drug and one of the most widely used medicines in the world. Heparin, and a similar, but smaller version called low-molecular weight heparin, are glycans that doctors use during and after surgery to prevent the formation of blood clots that can lead to heart attacks and strokes.

Knowing the overall size and dimensions of a large heparin glycan molecule, Sasisekharan began by asking his computer to generate a master list of all the possible individual sugar pieces that could theoretically connect together to make up the larger carbohydrate. Computers are excellent at crunching through millions of combinations, doing in a few hours what would take a person months.

Many of the potential solutions derived by the computer dropped out immediately when Sasisekharan gave the computer instructions to deal with practical considerations such as the basic rules of chemistry and the natural abundance of specific sugar types.

Through chemical tests and the process of elimination, pretty soon only one possible structure came out at the end of the exercise. Using what he'd learned, Sasisekharan could then custom-make different varieties of heparin with special properties.

Sasisekharan's work is very important medically. While heparin is one of the top-selling drugs in the world, in

many patients it can produce potentially worrisome side effects such as excessive bleeding. The trouble is that there hasn't been a quick and easy way to break the glycan apart and determine how much of the active ingredients are actually present in a given bottle of medicine.

Most commercial preparations of heparin come from pig intestinal lining, and these preparations contain widely varying mixtures of different sizes of glycan molecules. Because the drug is not completely "homogenous," or pure throughout, it is hard to know ahead of time how well a particular batch will work in patients.

Sasisekharan's custom-made, "designer" heparins have the potential to be safer than current preparations because the

molecules work predictably. What's more, the way the molecules are designed enables scientists to neutralize them easily to prevent bleeding in a person's arteries or veins. This has been a hit-or-miss process with the old varieties of heparin.

Commercial preparations of heparin vary widely in their ability to prevent blood clots, in which strands of fibrin (yellow) form a meshwork and trap red blood cells in a clump.

Sweet Treatments

Ever eager to speed his lab discoveries to patients, in 2001 Sasisekharan helped to form a biotechnology company called Momenta Pharmaceuticals, which is located in Cambridge, Massachusetts. According to Sasisekharan, the company's goal is to use the tools he has developed to make new forms of heparin and other sugar-based drugs. Progress is under way, and human tests of Sasisekharan's designer heparins are set to start within a year.

Sasisekharan's basic studies have led in another direction important to public health: fighting cancer. Researchers have known for some time that sugar molecules that "decorate" the surface of cancer cells play a role in how fast the cells grow, and some sugars actually appear to slow tumor growth.

A few years ago, Sasisekharan began experimenting with heparinase, a chemical "scissors" that clips sugary glycan molecules from cell surfaces. He reasoned that by altering the sugar coating on cancer cells, he might be able to control tumor growth.

Studies in mice worked. One particular form of heparinase actually stopped cancer growth in these lab mice, and Sasisekharan is hoping the findings will someday translate to treating human cancer as well.



The possibilities seem endless, and Sasisekharan hopes that novel uses of biological sugars will lead the way not only to new medicines, but also to safer versions of existing drugs.

Research Ecosystem

Looking back in time, Sasisekharan recalls another spark that interested him in the world of science.

“I was spellbound by the space around us,” he says, remembering as a child being in complete awe of subjects like astronomy and geography.

Sasisekharan recalls thinking to himself, “Wow, how does weather happen? How does it contribute to the ecosystem?”

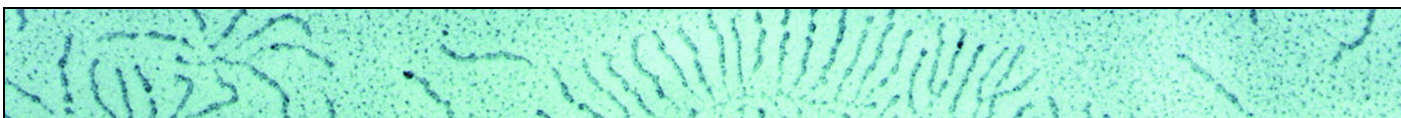
In a sense, those early wonderings were a hint toward Sasisekharan’s future thinking. His approach in the lab is to stay in touch with the ecosystem of science and how it is always changing.

“Science has evolved,” says Sasisekharan. “It is very different now than it was 20 or 30 years ago, and it will be even more different in another 20 or 30 years.”

Future biology labs will be home to mathematicians, computer scientists, engineers, and physicists, Sasisekharan predicts, adding that it will be very important for scientists of all stripes to work together to improve health.

He thinks there’s never been a more exciting time to do research and that science can offer long-lasting impacts to society.

“The number of unanswered questions grows every day,” Sasisekharan says, “and patients are waiting.” ■



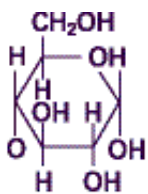
Carbs Made Simple

Carbohydrates are the main energy source for the human body. You probably know that your body converts the carbohydrates from your diet into energy. Plants do the opposite—through the process of photosynthesis, plants take energy from the sun and turn it into carbohydrates, giving off oxygen as a byproduct.

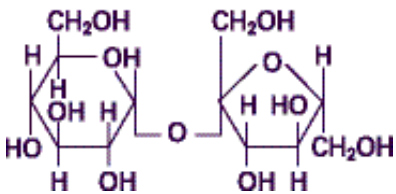
Also called sugars, carbohydrates are indeed the stuff of life. They exist in several different forms: monosaccharides, disaccharides, and polysaccharides. As the prefix “mono” implies, a monosaccharide contains one simple sugar molecule, and glucose is an example. Disaccharides contain two simple sugars linked together, from the prefix “di” for two. Sucrose, or table sugar, is a disaccharide, consisting of glucose and fructose chemically linked together.

Polysaccharides—literally, “many sugars”—are long, interconnected complexes of monosaccharide or disaccharide units that repeat in a pattern. Often, certain atoms within a polysaccharide contain extra “decorations” that add a negative charge to the overall sugar or change its shape. These chemical modifications help customize sugars for their many different tasks.

Nestled together with proteins, polysaccharides form complicated bundles of molecules called proteoglycans, which are everywhere in our bodies. Because of their structure, proteoglycans can twist and bend. They help to thicken the fluid in joints and are key components in cartilage and connective tissue. Proteoglycans also dot cell surfaces and help cells roam around the body.—A.D.



Glucose



Sucrose

