Through the Looking Glass

Glycomics is a brand-new field that is shining a light on the complicated role carbohydrates play in health.

Forget about what's on your plate. Forget everything you've been told about good carbs, bad carbs, and complex carbs.

Instead, prepare to fall down the rabbit hole and feast on this: Carbohydrates may be the key to just about everything that goes right in the human body—and everything that can go wrong.

Enter glycobiology, the study of carbohydrates—and one of the approaches Emory is taking toward transforming health and healing.

"This is a new era where we're connecting the structures of carbohydrates to biologic functions," says glycomics expert Richard Cummings. Less than a year into his tenure at Emory School of Medicine as chair of biochemistry, he has amassed a team of 20 to begin magnifying the connections between carbohydrates and disease.

Since each disease, organism, and type of cell has its own unique carbohydrate structure, the connections are indeed numerous. But the effort of decoding each carbohydrate may well be worth it. After all, Alzheimer's disease has struck more than 24 million worldwide, and 25 million Americans get the flu each year. While the flu and Alzheimer's have little in common besides those numbers, the different carbohydrate structures involved in these diseases may hold the key to locking both away—not to mention hundreds of other diseases.

By Dana Goldman • Illustration by Andy Powell

Taking the glue out of carbs

While the stakes are huge, the science is relatively clear: For bacteria and viruses to take hold in the human body, they have to stick to cells. They have proteins that bind to carbohydrates (also called glycans). These glycan-binding proteins, or GBPs, seek out carbohydrates on the surfaces of the cells of the human host. All human cells also express a battery of different GBPs that are important in human cell biology and cellular interactions—for example, sticking together.

If scientists can block carbohydrates from sticking to proteins, they may be able to block disease from taking hold as well. And the odds are in the scientists' favor. "The GBPs as a kind of group are among the most abundant class of proteins encoded by the human genome," says Cummings. "In addition, every virus we've looked at binds to carbohydrates. So a new paradigm is forming—all glycan structures may be bound by a GBP, either expressed by our own cells or cells of disease organisms."

Cummings's magnifying glass has already shown that the link between carbohydrates and infection extends beyond people. "Even clams have an inducible immune system based on carbohydrate-binding proteins," Cummings says. "This concept of the importance of carbohydrate-binding proteins is evolutionarily an ancient idea. From the original multi-cellular organisms to the most complex organisms that exist today, all have carbohydrate-binding proteins."

Wonderland population: several million, and counting

Forget the clams—cataloguing the entirety of human carbohydrate structures is no small job. "In the human glycome, we're estimating there are several million carbohydrate structures," says Cummings. Unlike DNA, these carbohydrate structures are not stagnant. With an elusiveness worthy of the disappearing and reappearing Cheshire cat, they shift forms when gene expression changes.

The complexity of the human glycome means decoding it may take longer than any one scientist's career. "In my lifetime, I'll never hear the term, 'the end of the glycomic era,'" Cummings says. "We think we're only a small percent of the way there. And since we don't know the total number of structures—or how they change depending on diseases, environmental issues, and health—the numbers could be even larger."

Over the past 10 years, nanotechnology and mass spectrometry have made isolating and analyzing carbohydrates a much quicker process, creating a growing buzz in scientific circles. In fact, the buzz over carbohydrates and those protein-carbohydrate structures called glycoconjugates, is big enough to keep Cummings and his team busy for years to come.

Then there's the Consortium for Functional Glycomics, the hub of the glycomics wonderland. The consortium includes eight core facilities worldwide—including Emory—all magnifying different pieces of the glycomics puzzle. Through that consortium, funded by the National Institute of General Medical Sciences at NIH, Cumming's lab analyzes carbohydrate structures from samples sent from around the world—for free—and then makes the results public. "At any one time, our core facility here is probably working with 50 research laboratories around the world," says Cummings.

Offering Emory's magnifying power gratis is changing the face of science. With the NIH fronting the costs, decisions about who gets access to this cutting-edge science are based on the merit of projects rather than money. An investigator who may have limited experience analyzing carbohydrate structures, or insufficient resources to do so, sends in samples. Emory extracts the data from the samples and makes the results public. The investigator uses those results for a paper in a scientific journal, disseminating information to an even broader audience. In effect, the consortium and Emory are speeding up the transfer of information and offering a new model for how research can be conducted globally.

No longer fantasy

For an idea of how glycobiology may change our view of the world, consider the parasitic disease schistosomiasis. Two hundred million people worldwide are infected with the disease, and its manifestations can be severe: bladder cancer, kidney failure, mental retardation, and muscle weakness.

Cummings and colleagues have discovered that the parasitic flatworm that causes schistosomiasis has carbohydrates bound by proteins in human hosts. "We identified its carbohydrates, and now we can use them to make a vaccine," says Cummings. "For people who are already robustly immunized with antibodies to those sugars, the vaccine should be able to attack and kill that parasite as soon as it shows up."

Targeting carbohydrates to treat a disease was seen as a science fiction fantasy just a few years ago. "Even among vaccine people, this is really novel," says Cummings. But while creating vaccines based on carbohydrates might be novel right now, implications of carbohydrate research go much further: toward healing inflammatory, cardiovascular, and autoimmune diseases as well as stopping heritable ailments and metabolic disorders. "Our work impacts all of those areas," Cummings says.

In fact, one of Cummings's biggest discoveries was the finding that human white blood cells that fight infection express a glycoprotein on their surfaces that is bound by a specific GBP in the cells lining blood vessels. This interaction is key to the inflammatory response and allows people to respond to infections. But in some human diseases, there is inflammation without infection and the white blood cells become activated. They use these GBPs to get into tissues where they can cause tremendous damage, such as sickle cell crisis and inflammatory bowel disease. Cummings and his colleagues are trying to develop new therapies that target these GBPs as a way of treating or reducing the inflammation.

Where to focus the glass

If the results of glycobiology have the potential to be astounding, so too are the sheer numbers of those findings. A single scientific research paper would be unable to encompass the information needed to describe the carbohydrate structures in a single tissue or organ, according to Cummings. Websites are being filled with information that is available from the Consortium for Functional Glycomics. Currently, Cummings is writing the second edition of the textbook, *Glycobiology*, to give an overview of what carbohydrates do and how they function, and it has taken him and co-writers 50 chapters just to do that.

More glycobiology textbooks will surely be coming, as Cummings and other glycobiologists continue to advance the field. "Our glycomics ability now is like a giant magnifying glass. It can burn a hole through a problem," says Cummings. "Where do you want to put this magnifying glass? Do you want to burn a hole through a specific health problem? Do you want to know all the glycans in everybody's blood and in every human condition? It's doable. We've figured out how to do it."

At Emory, Cummings is turning the glass on three major areas. He's forming collaborations to focus on predictive health and disease diagnostics. In these studies, blood and other tissue samples will be screened by mass spectrometry to define the levels and kinds of carbohydrates on different glycoconjugates. Changes in carbohydrate expression and structure are associated with many human diseases, and early detection could lead to new insights into predicting and diagnosing disease. In addition, GBPs and antibodies in human blood recognize carbohydrates. Their expression can be important to the ability to fight infection as a part of "the innate immune system." This type of immunity is inherited and always present rather than being triggered by a specific pathogen or virus.

Following what he learned from schistosomiasis, Cummings also will help create new vaccine-based approaches to human disease, where carbohydrates are coupled to carriers and used for vaccination. This approach, carried out through the Glycomics Center in the medical school, could lead to a new era of preventives for many parasitic diseases.

Then, there are his plans for neurobiology: "The one giant, unexplored universe of glycobiology is the brain," Cummings says. "We know that the most unusual glycoconjugates in the body are found in the brain, and we know the least about them."

All of these projects are a welcome challenge to Cummings, who believes the biggest discoveries are yet to come. With his magnifying glass in hand, he's seeing the influence of carbohydrates everywhere he looks. And to him, that's reason enough to fall down the rabbit hole.

Dana Goldman is a teacher and freelance writer for print and radio in Atlanta.

A Glyco-Glossary

Glycan-binding proteins (GBPs): proteins that bind to carbohydrates secreted by cells or on the surfaces of cells; also called carbohydrate-binding proteins or lectins.

Glycan array: an instrument that enables scientists to put thousands of different carbohydrates on glass slides and then analyze their binding to GBPs expressed by human and animal cells and to bacteria and viruses.

Glycobiology or glycomics: the study of carbohydrates' functions, structures, and purposes.

Glycoconjugate: a complex carbohydrate that is linked to a protein, fat, or polypeptides and proteins containing amino acids.

Glycome: the entire spectrum of carbohydrates in a cell or organism.

Glycosylation: The addition of a carbohydrate or carbohydrates to a protein.

Quantitative mass spectrometry: a tool used to figure out what molecules—and how many—are in a particular compound. By analyzing and quantifying which carbohydrate structures appear in different molecules, scientists can detect different diseases.