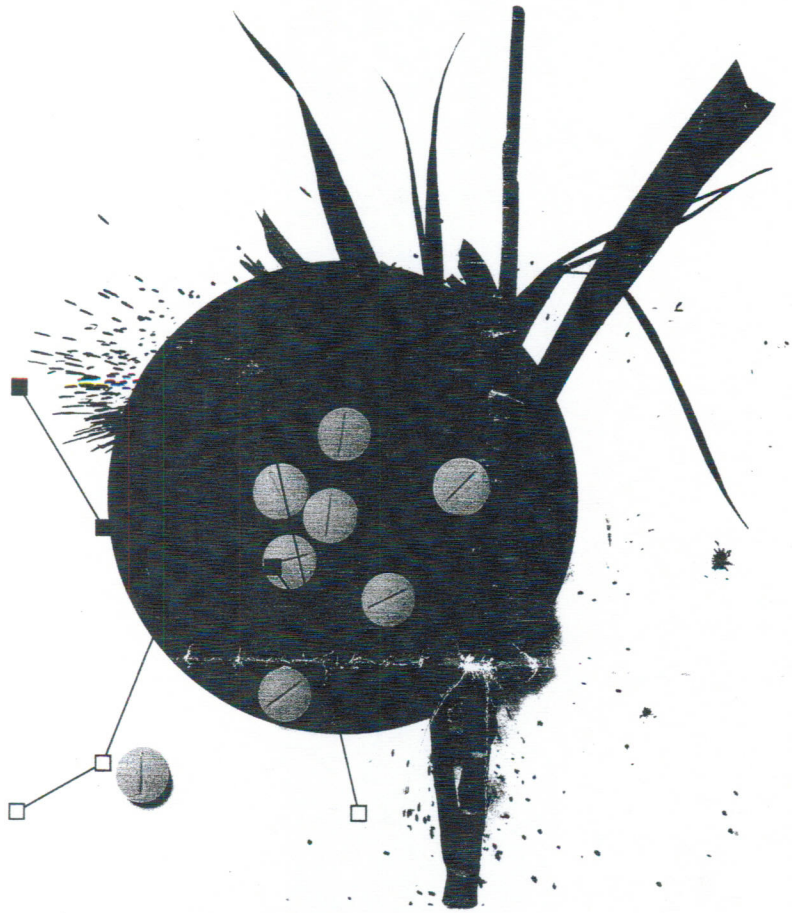
Perhaps it's time to rigorously research what we eat and why — the same way we study other molecules we put in our bodies.



A few weeks ago, I had a minor surgical procedure — the repair of a congenital abdominal hernia. The operation went well. I returned home with a stash of instructions and medicines. There were clear guidelines for which drugs to take for inflammation or pain, in what dose, and in what order and intervals.

But the surgical wound was slow to heal. And so, while continuing the anti-inflammatory medicines, I added an antibiotic, and began to wonder if I should change my diet to aid the healing process. After all, I was pouring molecules into my body. The antibiotic was designed to fight a type of microbe. The anti-inflammatories worked to reduce inflammation. Why not find a different molecule designed to encourage blood-vessel growth, or boost the division of stem cells in the skin — a molecule delivered not in the form of a pill but as a nutrient in my food?

Over my typical Monday-morning breakfast (a bar of chocolate, washed down with a cup of espresso), I began to look for advice about what I *should* be eating to feel better. One website, from the Cleveland Clinic, advised five servings of grains, two servings of vegetables and limited fat to aid with wound-healing. Another article urged quite the opposite: a high-fat, high-protein, low-carbohydrate diet. Yet others suggested zinc, or vitamin D, or enough supplements to clean out the health-foods section of my local grocery.

The smatterings of advice gathered from the internet prompted a thought experiment. What if you went to your doctor with a specific condition, and she prescribed a medicine? But when you asked her *why* you were taking this pill, she said, "Oh, because your ancestors took it." Or "because it tastes good," or, worse, "because it was what the pharmaceutical industry could make most profitably and effectively."

Most of us, I imagine, would find ourselves irate over such answers. Yet we blithely accept these standards for human diet: We are stuck with our diets because our ancestors ate this way, because food tastes good or because agribusiness has persuaded us about dietary compositions. Unlike most medicines, whose effects we sift, measure and scrutinize, often using the most rigorous clinical trials, human diets — the other set of molecules we put into our bodies — have gone relatively unexamined. We are living in a molecular

Photo illustration by Cristiana Couceiro

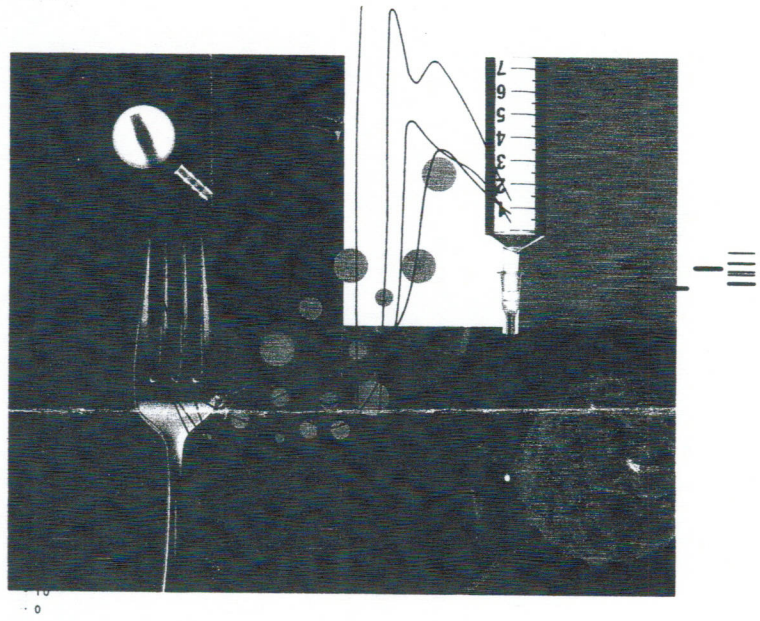
Next Week: On Technology, by John Herrman

age of targeted therapies, in which strategies like immune modulation, genome sequencing and gene editing are used to probe and alter human biology. And yet, while aspects of human diet have undoubtedly changed, we may be eating what we eat for no good reason at all.

Several months before my surgical procedure, a cancer patient asked me whether she should change her diet. She had lost her appetite. One nutritionist had advised her to start consuming highly caloric, sugar-loaded drinks to maintain her body weight. But, she worried, what if the sugar ended up "feeding" her cancer? Her anxiety was built on nearly eight decades of science: In the 1920s, Otto Warburg, a German physiologist, demonstrated that tumor cells, unlike most normal cells, metabolize glucose using alternative pathways to sustain their rapid growth, provoking the idea that sugar might promote tumor growth.

You might therefore expect the medical literature on "sugar feeding cancer" to be rich with deep randomized or prospective studies. Instead, when I searched, I could find only a handful of such trials. In 2012, a team at the Dana-Farber Cancer Institute in Boston divided patients with Stage 3 colon cancer into different groups based on their dietary consumption, and determined their survival and rate of relapse. The study generated provocative data – but far from an open-and-shut case. Patients whose diets consisted of foods with a high glycemic load (a measure of how much blood glucose rises after eating a typical portion of a food) generally had shorter survival than patients with lower glycemic load. But a higher glycemic index (a measure of how much 50 grams of carbohydrate from a food, which may require eating a huge portion, raises blood glucose) or total fructose intake had no significant association with overall survival or relapse.

While the effect of sugar on cancer was being explored in scattered studies, the so-called ketogenic diet, which consists of high fat, moderate protein and low carbohydrate, was also being promoted. It isn't sugars that are feeding the tumor, the logic runs. It's insulin – the hormone that is released when glucose enters the blood. By reducing carbohydrates and thus keeping a strong curb on insulin, the keto diet would decrease the insulin exposure of tumor cells, and so restrict tumor growth. Yet the search for "ketogenic diet, randomized study and cancer" in the National Library of Medicine database returned a mere 11 articles. Not one of them reported an effect on a patient's survival, or relapse.



But, my patient worried, what if the sugar in her recommended diet ended up 'feeding' her cancer?

Siddhartha Mukherjee
is the author of "The Emperor of All Maladies: A Biography of Cancer" and, more recently, "The Gene: An Intimate History."

But what if diet, rather than acting alone, *collaborates* with a drug to produce an effect on a tumor? In the winter of 2016, I had dinner with Lewis Cantley, director of the Meyer Cancer Center at Weill Cornell Medicine. Decades ago, Cantley discovered an enzyme named PI3 kinase, which regulates the growth and survival of cells in the presence of nutrients. By inhibiting this enzyme using novel drugs, researchers had hoped to target the signals used by tumor cells to grow, thus "starving" the cancer. But the drugs designed thus far were only marginally effective. Why, we wondered over salmon teriyaki in a nondescript Upper East Side joint, might blocking such a central hub of growth activity have had only a modest effect on tumor growth?

The trials gave us a crucial, obvious clue that we had missed: Many patients had become diabetic, a phenomenon seen as a side effect of the drug that had been ignored. Perhaps the drug wasn't just providing a "starvationlike" signal only to the tumor cells, we speculated. As most drugs do, the molecule circulated through the entire body of the patient and also acted on the liver, which sensed the same starvationlike signal and, as a reflexive response, sent glucose soaring into the blood. The glucose, in turn, most likely incited insulin release in the pancreas. And some patients treated with the medicine returned to the clinic with sky-high levels of glucose and insulin – in essence, in the throes of drug-induced diabetes.

Cantley wondered whether the additional insulin was reactivating the signals within the tumor cells that had been shut off by the PI3 kinase inhibitor, and so allowing the cells to survive – in effect, undoing all the good being done by the drug. On a paper napkin borrowed from the waiter, he drew out a scheme to outwit this vicious cycle. What if we cut off all extra insulin

Photo illustration by Cristiana Couceiro

released, by putting patients on a low-carb, ketogenic diet while on the drug? It would be a novel kind of trial — one in which diet itself would become a drug, or a co-drug, with the PI3 kinase inhibitors.

Between 2016 and 2018, postdoctoral researchers in Cantley's laboratory and mine established that this strategy worked on several mouse cancers, and on human cancers implanted into mice. By 2019, working with clinicians at Columbia, Cornell and Memorial Sloan Kettering, we hope to begin a study in humans with lymphomas, endometrial cancer and breast cancer, to use ketogenic diets in concert with the PI3 kinase inhibitors. (In the meantime, a host of other studies have also demonstrated that other diets could potently modulate the effects of targeted therapies on cancers in mouse models.)

But the experiments on mice also warned us of an important pitfall of such an approach. While the "drug plus diet" model worked on experimental mouse and human cancers, the ketogenic diet had a limited effect by itself. For some cancers in the mouse models, the keto diet alone kept the tumor growth at bay. But for others, like some leukemias implanted into mice, the diet alone *accelerated* the cancer, while the drug-plus-diet approach slowed it down.

We published this data in the scientific journal Nature early this year. I sent out a tweet with the results, emphasizing that the human trial was about to be started, and that the keto diet alone might have a negative effect on some tumors — in essence, a "folks, don't try this at home" message. The response over social media was unexpected — brisk, vicious, angry, suspicious and, at times, funny. "'Keto' is pure hype," one responder wrote. Another countered: "Who is supporting you? Big Kale?" One writer proposed returning to an ancient diet — "deer, rabbit, river fish" and "wild birds." Yet others blamed me for undermining the effectiveness of the ketogenic diet in cancer.

The vituperative, emotional response to this study illustrates the doubt and anxiety that any conversation about human diets incites in the public realm. A careful scientific examination of diet as medicine is now long overdue in oncology, and in most fields of medicine. There's an interaction of our diets with our gut microbes that remains to be examined, and the impact of diet on longevity, on neurological diseases or even on mental states. Perhaps we need to rebuild the human diet from scratch, much as we built our medical pharmacopoeia: Rather than relying on received knowledge, or on presumed ideas, we might examine our diet molecule by molecule, and trial by trial, probing the aspects of food that incite or treat particular diseases, for particular humans, with particular genetic attributes. In the age of molecular therapeutics, perhaps we might need to rethink diet, too, as a form of molecular therapy. ◆

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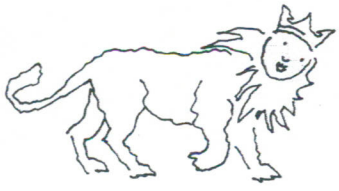
Poem Selected by Rita Dove

Even under the best of circumstances, parenting can feel like navigating a marshland. In the blended family — that alliance of old hurt and new love — heightened vigilance is required; in the search for common ground, the next step could land in quicksand or meadow. In Remica Bingham-Risher's poem, the mother's anxious attention is underscored by dexterous deployment of possessive pronouns. For one afternoon, at least, everything is coming up roses, although not without plenty of cultivation. Enough metaphors: Read this richly layered poem and enjoy the glow.



We See 'The Lion King' on Broadway, I Enter the Pride

By Remica Bingham-Risher

Our girl is telling the boys to pose near the theater doors.
We have traveled to the Minskoff in New York

and the children are finally elated.
They have been trying to teach me

their ways — they wrestle and weary one another,
bending and binding love — but I am useless in my tenderness

until this: I have orchestrated the daytrip of dreams.
Herald Square gleams like a lost enchantress.

As we scuttle and preen, she tries pashminas and caps,
designer shades, everything neon at once. When our tickets have been taken

and they step into the circle, for a flash of moment,
she takes the journey in. It is only a measure

before the music starts, while we head to our seats,
she says *This is amazing —*

all you've done to get us here. It must have taken
hours. Years, I think, years, but she is grateful

and I am finally useful. As the curtain goes up,
everything the light touches is ours.

Rita Dove *is a Pulitzer Prize winner and former poet laureate of the United States. She edited "The Penguin Anthology of Twentieth-Century American Poetry," and her "Collected Poems: 1974-2004" was published in 2016. The director of writing initiatives at Old Dominion University,* **Remica Bingham-Risher** *is the author of three collections of poetry, including "Starlight & Error," published last year by Diode Editions.*

Illustration by R.O. Blechman