LOOK FOR THE POSITIVE

Negative research results can be disappointing, but there are unexpected benefits in scientific 'failures.'

BY BRIAN BUSENBARK

It's the all-too-common scenario that scientists dread. Gleaning insight from previous testing in animals, Brian Shariffi hypothesized that the administration of insulin would increase indices of blood flow in the human brain. Using transcranial doppler (TCD) ultrasound, Shariffi and his team painstakingly performed local and peripheral insulin administration methods on their test subjects. They meticulously collected the ensuing data and found … no change whatsoever in indices of cerebral blood flow levels.

Illustration by Matt Chinworth

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> **—Barbara Alexander, PhD, FAPS**

Although disappointing, Shariffi's unexpected findings came with a silver lining. The negative data led to a collaboration with researchers in Canada who were using a novel analysis technique that could assess cerebral vascular dynamics in a way that TCD measurements alone could not. Applying this method to his data, Shariffi could now see the effects of the insulin administration in his experiments.

"That collaboration has moved our research in a really cool way," says Shariffi, a graduate assistant in the Department of Nutrition and Exercise Physiology at the University of Missouri in Columbia. "It has taken it down another avenue that we probably wouldn't have thought of if we didn't get that negative data."

Of course, not all unexpected research findings turn out so positively. Many lead to frustration and abandoned projects. But why the stigma around negative data?

For some researchers, especially younger scientists looking to advance their careers, findings that don't support their hypotheses and nullify the aims of the research equate to failure. Why invest the time and effort in producing a paper that may highlight the researcher's flawed work? And that's only if it is published at all. As a result, a scientist could have trouble obtaining funding for future research endeavors.

"It can be quite frustrating, especially if we are defining success in our career by the success in our experiments," says Daniel Fehrenbach, PhD, a member of the APS Trainee Advisory Committee and postdoctoral fellow at the Madhur Lab in the Division of Clinical Pharmacology at the Indiana University School of Medicine in Indianapolis. "Though successful scientists often have successful experiments, that's not always the case; we have to acknowledge that to drive our own personal experiments forward, we're going to have to make mistakes along the way."

Mistakes in the lab don't account for all negative data. There are countless variables at play in any experiment—some that are beyond a researcher's control and can skew results. Vendors can change the makeup of test materials without communicating it to the lab. Environmental factors can alter the way test subjects respond. And conducting research with animals is often unpredictable.

"The animal is going to do what they're going to do," says Nick Burgraff, PhD, a fellow at Seattle Children's Research Institute Center for Integrated Brain Research. "I used to work with goats, and if you have a 150-pound animal that doesn't want to be studied that day, it's not happening."

UNINTENDED BENEFITS

Negative data and "failed" experiments are basic elements of the scientific process. "Most of my hypotheses do not come out the way I expect," says Barbara Alexander, PhD, FAPS, professor of physiology and biophysics at the University of Mississippi Medical Center in Jackson. "My trainees and staff often ask what our results should look like, and I always tell them that I don't know; they're just going to be what they're going to be."

Stigmas—and frustration—aside, unexpected findings can actually be beneficial to scientists in a number of ways:

Improved skills. Quite simply, experiencing—and overcoming—unforeseen results makes for better scientists. The process of reviewing a project's data to determine why the results materialized the way they did exercises a researcher's critical-thinking skills, sometimes uncovering hidden gems that produce outcomes far beyond the scope of the original hypothesis. "It seems almost every Nobel laureate says their prize stemmed from an unexpected finding that they were smart enough to figure out its meaning," Alexander says. "Null hypotheses or unexpected outcomes should be considered more the norm—and they can lead to scientific discovery."

Negative data also prompt physiologists to expand their expertise and learn different techniques to better evaluate every part of the human body. "One day you're studying the movement of gases in the lungs and the constriction of the airways and the next thing you know you're doing genetic sequencing," Burgraff says.

"Although you may have never had formal training in any of those topics on their own, you've been trained as a scientist in order to be able to understand how things work."

Better science. When the results of an experiment don't match a researcher's hypothesis, scientists typically explore every aspect of their processes to understand why the data didn't match expectations. When the findings are published, they shore up the overall confidence in scientific research. The scrutiny and retesting that follows negative data also confirm the validity of those results, whereas a false positive that affirms the hypothesis could lead to further errors down the road.

"You may just assume that that result was correct, try to move forward and build upon that result—but unfortunately, it's a shaky foundation," Fehrenbach says.

New opportunities. As the old adage goes, "When one door closes, another door opens." Similarly, the initial disappointment of a null hypothesis can lead a researcher down fresh paths. For Shariffi, it not only blossomed into a fruitful collaboration, but it took his research in an exciting new direction.

Sometimes "failures" can even spark entirely new studies. Alexander began a project researching interventions for preeclampsia in women by studying drug effects on rats. She unexpectedly discovered hypertension among her male rat subjects—their female siblings were not hypertensive. That finding led to two new grants for her to research the causes behind that anomaly. "That turned out to be a positive thing, career-wise," Alexander says. "Sometimes when you have an unexpected finding, it leads to something that is more interesting than what you were expecting."

Guiding others. In many ways, negative data can be just as useful and enlightening as results that follow the hypothesis. The published findings can inform future studies on the topic and prevent other scientists from spending time and money on research that's already been done and hypotheses that have been disproved.

It's not uncommon, Fehrenbach says, for a scientist to chat with colleagues at a conference and discover they had already attempted—unsuccessfully—to prove a hypothesis on which that researcher is currently struggling. The frustration of those wasted efforts, along with a common belief among many of his colleagues for the need for wider outlets for negative data, prompted Fehrenbach to champion a trainee symposium at the 2024 American Physiology Summit titled "Breaking the Mold: Embracing the Unexpected in Physiological Findings."

"We wanted to give trainees who are doing high-quality work an opportunity to show off their really cool science, even though it resulted in negative data," Fehrenbach says.

COPING WITH NEGATIVE RESULTS

Perhaps the best way to ease the sting of encountering unexpected research results is embracing their ubiquity, the key role they play in the scientific process and the myriad benefits they present. Beyond those, our experts shared additional methods and techniques to move past the frustration:

Check the work. A thorough review of your team's processes provides peace of mind in knowing that your results—although unexpected—are accurate. "Be a perfectionist when it comes to data collection and analysis," Shariffi says. "Triple and quadruple check it to ensure everything that you controlled was done to the best of your ability."

Leverage your network. "You can't be an island in science," Alexander says. Cultivating and relying upon a wide group of colleagues, mentors and others will help you work through the stress and provide sound guidance on how best to navigate negative results to a positive outcome.

Be flexible. The ability to pivot in the face of adversity is crucial to success in science. Expect the unexpected and be ready to change course. "Those who do best in science tend to be the ones who are able to handle those pivot points and understand that the results are not what they expected them to be," Burgraff says. "But this is how the science works, and ultimately we're here to understand physiology at its core."

Diversify your studies. Engaging in multiple research projects simultaneously ensures that any one setback won't be too crushing. More active experiments means there are increased possibilities for your work to catch the eyes of reviewers. And it also allows you an opportunity to shift gears and clear your thoughts if negative data on one study bogs you down.

"Beyond that, when we can step back and look at the project on a larger scale, maybe we need to reassess where it is going," Fehrenbach says. "We can identify new ways to look at that problem while we're being productive on something else, which helps us feel confident in what we're doing and why we're there."

Importantly, allow your passion for physiology to provide the resilience you need. Don't forget why you pursued this field in the first place.

"Sometimes, things aren't going to work—that's normal; that's part of the process," Burgraff says. "At the end of the day, what you enjoy doing is understanding how various parts of the human body interact and work. And it can be fun; it doesn't have to be stressful—we're just being scientists, so have fun with it."