



Life Is an N of 1

Michael Rosbash

It is a strange feeling not to anticipate begging, pleading, sweating, or getting angry at a rejection letter/email when crafting a manuscript for *Cell*. This manuscript will presumably escape that torture as it is a brief, personal story invited by the *Cell* editor Marta Koch. I was sorely tempted to tell the tale of my long and colorful history with *Cell*. However, it cannot be brief, so here is a different piece of personal history.

Our Nobel Prize can be seen from several perspectives. It is for making important contributions to the mechanistic underpinnings of circadian rhythms. It celebrates basic science, emphasizes the importance of model organisms to research, and elevates *Drosophila* once again to a starring role. It is the fifth Prize for this remarkable, little beast and its first as a solo performer since 1995. (The metaphor makes me think of Meryl Streep and the Oscars.) Lastly, the Prize can be seen as underscoring the relationship between genes and behavior.

The inheritance of behavioral traits—the “nature” in the nature-nurture debate—has a murky history. Eugenics gave it a bad rap, and it was overtaken in the US by Skinnerism and its emphasis on the environment—or “nurture”—in determining behavior. Twin studies as well as the dubious nature of many of those psychological studies contributed to swinging the pendulum back in the other direction toward inheritance. It has been followed by the current zeitgeist of epigenetics, which takes us back to the nurture camp. Although the word epigenetics has been hijacked by the histone-chromatin field, the term as originally coined by C.H. Waddington can be conveniently viewed in this context as environmental influence or developmental noise, i.e., anything that influences phenotype other than a fixed genetic path. In addition, determinism is generally unattractive, which adds to the appeal of non-genetic influences.

It is against this backdrop that I entered the story. I was studying gene expression and RNA at Brandeis when I met Jeff Hall, also a professor at Brandeis, and began some years later to collaborate on circadian rhythms and the *Drosophila period* gene. Among the many reasons I began this work was the fact that I had always been interested in the relationship of genes and behavior. In particular, why did I always seem to court trouble? Was it nature or nurture, my genes or some environmental event?

Ever since I can remember, mostly since middle school, I had trouble at school. I do not mean academic trouble; I was always a good student. (Good does not mean outstanding, as I was largely indifferent to learning until mid-way through my second year at Caltech when I was bitten by the academic bug. My delayed path was probably not unrelated to my behavioral issues, but this is another story for another time.) However, I had quasi-serious behavioral issues in the Newton Public Schools before Caltech. I had a big mouth, was rowdy, and most importantly, really disliked authority—being told what to do. I also pushed buttons, and limits. Remarkably in hindsight, this caused me little trouble at Caltech as an undergraduate and at MIT as a PhD student. Both institutions were filled with weird characters and were remarkably tolerant meritocracies; if you could perform, everyone ignored all but the worst behavioral issues. And some iconoclastic behavior, a lack of respect for the status quo, is part of doing original research. So I thrived at both institutions.

However, my character traits contributed to some trouble during my post-doc in Edinburgh and especially as an assistant professor at Brandeis. Although a much longer and more complicated story, I really lacked respect for my elders, which was frequently visible if not audible. Although some of this was due to my having been a politically engaged student in the late 60s (“Never trust anyone over 40”) as well as some very different and complicating local factors, my issues from adolescence still existed and were not irrelevant.

Michael Rosbash in his lab

“I had always been interested in the relationship of genes and behavior. In particular, why did I always seem to court trouble?”



Most of the original circadian crew, circa 1985. (L to R) Will Zehring, Tony (A.A.) James, Jeff Hall, Pranitha Reddy, Michael Rosbash, Dave Wheeler.

These conflicts with authority led to my being denied tenure in the Rosenstiel Center, where my laboratory had resided since I had been hired in 1974. The negative recommendation was despite my strong publication and grant record. There were at the time two parallel tenure decisions required for Rosenstiel Center assistant professors: one in the Center and the other in the academic department of the candidate—in my case, Biology. In contrast to the Center decision, the Biology Department voted to recommend me for tenure albeit narrowly. This was a novel conflict, which landed on the desk of the Brandeis President for adjudication. He granted me University tenure but required that my lab vacate the Rosenstiel Center and that I move to Biology. The move was delayed because the University had some trouble finding and then outfitting adequate space, but I finally moved in August of 1982, to the Bassine Biology building. Strictly by chance, my new space turned out to be on the same floor as the lab of my pal Jeff Hall. We even shared a seminar-lunchroom, which was situated between the two labs. About 2 months later, in October of 1982, we began our collaborative work.

As I indicated above, one motivation to begin this gene-behavior work was my own character: how did it come about? For reasons that are too complicated to explain in a short essay. I was always partial to genetic or “hard-wiring” as responsible for human behavior. Our own gene-behavior research on fruit flies reinforced this prejudice, despite the sea of differences between this work and the kind of human question I had been pondering. However, there was one substantial argument in favor of an environmental explanation for my character: my father died of a sudden heart attack in 1954, when I was 10 years old and in 6th grade. This tragedy not only left me without a father and male role model but also shook our nuclear family to its core. I was set adrift and had a hard time finding some emotional center of gravity. Moreover, the world or at least my mother handled this tragedy much differently in the 1950s than one would today; for example, my father was never mentioned in our house again after his death. As the timing coincided roughly with middle school, indeed with my first memories of school troubles, this seemed a good candidate for a major contribution to my character. It was certainly a viable

“There are of course no control experiments in life; everything is an N of 1”

CITIZENSHIP	Excellent	Satisfactory	Unsatisfactory
	Attitudes:		
	Is courteous	✓	
	Is attentive	✓	
	Shows self-control		✓
	Works well with others	✓	
	Work Habits:		
	Follows directions		✓
	Works independently		✓
	Is neat and orderly		✓
Makes good use of time	✓		
Takes care of material	✓		

Third grade Michael seems to be trying to be cooperative at all times. He is not always alert and attentive when directions are given. As a result, he does draw my attention while I'm with another group and so is a very disturbing influence.	Respects the rights and opinions of others Begins work promptly Follows directions accurately	
Fourth grade If Michael makes a request and it is not immediately granted he is inclined to be very insistent. Explanations have been given to help him understand that there are occasions when we must respect the rights and opinions of others.	Respects the rights and opinions of others Begins work promptly Follows directions accurately	
Fifth grade Although he is sincere and well meaning, Michael is rather quick-tempered with the other children.	Respects the rights and opinions of others Begins work promptly Follows directions accurately	
Fifth grade, second term Michael is eager to do everything well but he still needs to share opportunity with others.	Respects the rights and opinions of others Begins work promptly Follows directions accurately	
Sixth grade Has had some difficulty accepting responsibility for his own actions. While it is true that others contribute to the situations, Mike must learn to recognize his part in them.	Respects the rights and opinions of others Begins work promptly Follows directions accurately	

School report cards

explanation, which resonated with a couple of my more-sophisticated friends over the years and even with me from time to time.

Of course I never figured out how to investigate a human character question of this complexity, and therefore I left it behind as our circadian work progressed over the decades. Aging—some would say maturing—also left behind many of those difficult character traits that caused me so much trouble for so long. However, here is a counterargument to the aging or maturing description: my family to this day has been unable to tolerate Larry David because of his similarity to the contemporary Michael Rosbash. The resemblance is not only physical. My daughter said to someone not long ago: “Watch *Curb Your Enthusiasm*? Get real; we live with this kind of behavior all the time.” So maybe the changes over the 35 years since tenure and my laboratory move are more superficial than profound.

Nonetheless, the question of my character and its origins reemerged in 2009. I had a 65th birthday symposium and party for the Biology Department and for my many trainees who returned to campus for the symposium. As my final talk required some reflection, I decided to explore this issue. I also thought it might amuse my trainees and colleagues, all of whom had experienced some version of my unvarnished character.

I was aided in this quest—and not without some irony you will appreciate—by my mother’s death the year before in 2008, when she was 94 years old. (My Lord, would she be kvelling had she lived to see this day!) She had kept all sorts of memorabilia from my childhood, including most notably my report cards and notes from my earliest years. Note that with the possible exception of my 6th grade report card, they all occurred well before my father’s death and therefore provide in my opinion unambiguous data in favor of a hard-wiring explanation.

“Watch Curb Your Enthusiasm? Get real; we live with this kind of behavior all the time.”

There are of course no control experiments in life; everything is an N of 1, so maybe some earlier environmental event strongly contributed to my character. I also note that my preference

for genetics or hard-wiring does not absolve me of responsibility, although I am still not a fan of free will as a biological-philosophical construct. And I tend to doubt almost everything, so all of these issues as well as most others must be associated with probability coefficients; there is no certainty. Or as I like to say in the lab: "I'll give you 5-to-1 odds that it's hard-wiring." And to hedge even more strongly, "I'll give you 5:1 that it's mostly hard-wiring." Don't forget: doubt as well as curiosity is a motive for doing scientific research.