1 Crispr, Cas and Capitalists

> Genuine tragedies in the world are not conflicts between right and wrong. They are conflicts between two rights.
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> – Georg Wilhelm Friedrich Hegel

Derrick Rossi is a stem cell biologist at Harvard Medical School. He studies DNA repair mechanisms, the means by which cells fix themselves when things break down. In the winter of 2013, I worked in his lab on the ground floor in the white marble quadrangle, where I used a computer at a lab space next to a Spanish woman named Paula and a couple of metal chairs with "Rajewsky" written on the back in marker. Rossi has stylish jet black hair, wears a Dr. Seuss watch and sometimes eye glasses with chunky black frames. His ancestors originated from the tiny island of Malta, near Sicily and off the coast of northern Africa; but he completed his PhD in Helsinki, Finland, and married a Finnish woman who was a former scientist at Genentech, making them a sort of scientific power couple. By now, he and his wife had three smallish children with straight hair who looked like they could appear in an LL Bean catalog, and who scrawled upon the four walls of white board, turning his office into a pop-up art exhibition.

Rossi pointed me to one sharp watercolor which his daughter had painted with shafts of skylight in silvers and blues, a few black snakes slinking along a path. "I had a dream in which my youngest daughter was bitten by a black mamba, and I don't know if you know anything about that, but one bite is lethal. It was frightening, of course, but what was odd was that the snake that bit her was wearing a grey woolen sweater. I recounted the dream to my family over breakfast that morning and a few days later my middle daughter had painted her interpretation of this dream of mine in watercolor – complete with snake sweater."

Rossi and his family take adventurous summer trips to Finland, but this year he missed it, too busy with work. But the imagery of his family moved into his office, and at least a little bit of his office into his house. I returned to his office a number of times over the years, and each time I came back there were expanding exhibits of art, so much so, that it

began to be almost comical. In his office, the collection of paintings from his children grew. On large cardboard panels. On acid-free paper stuck to the walls with scotch tape. Comingled with his children's drawings were Rossi's own science scribblings. His drawings appeared as schematics of cell lineages or a logical flow of ideas, ordered and analytical. The realm of art deals with deficit and negative space, and a soul that is churning and evolving. It deals with duty and virtue, and questions of option and purpose. The realm of science deals with cause and effect, and predictable outcomes, and focuses on maximizing those outcomes, while the motives are largely assumed. This tension between these realms continued, as Rossi drew experiments, and his children piled back into his office and overwrote his boards with their probing art. The cycle continued, upon any free space, at all, in his office. Rossi drew a pathway to derive a specific blood cell type on the white boards. His children erased that and drew a forest path. The tension replayed, again and again, over what British scientist and novelist C.P. Snow has called the "two cultures" of arts and sciences. That one of these two cultures is more *real* than the other is a question that has a hold on us.

Not that long ago, it became popular for people to send some biological samples away to learn something about ourselves. As the Nobel laureate Jim Watson noted, regarding the push to sequence the human genome, "How could we not do it? We used to think our fate was in our stars. Now we know, in large measure, our fate is in our genes." We want to know if we have Neanderthal genes, which recently have been linked to small tendencies for depression, or genetic variants in there that suggest we are more intelligent or prone to schizophrenia – there are also studies that do this – or that we may have Viking genes. This is the popular idea of genetics which has been sold to the public. In reality, a single gene often has three or four functions. And, a single genetic variant in one of those genes can be pleiotropic, meaning that it causes unrelated effects in different cells, tissues or systems, or that its effects can be enhancing or diminishing, based on genetic background. To complicate things more, most of the genetic variants that explain a complex disease or trait, such as a cancer, height or intelligence, are weak signal variants, meaning they alone are poor predictors of a trait and only exert their effects in the company of other genetic variants, so a lot of the force of a single genetic variant depends on its background. Complex traits are broadly heritable through genetics, but it's

improbable that we will ever be able to affect traits through scrupulous genetic editing. The temptation to particularize our character in our genes is enormous. We love to put things in boxes. My own father sent away a cheek swab to Family Tree DNA, and learned his Y chromosome, which I also carry, puts us in the haplogroup R-M512 and explains the route some of our ancestors took traipsing through Eastern Europe winding up in the Tatra Mountains in Poland, which we visited. The test reported that I was Austrian, German and mostly Polish, which I knew, but also that there were markers for Ashkenazi, but we are not Jewish, my father said.

My grandfather never graduated past the 6th grade. Surviving the hardscrabble Depression, he was a member of the Army Corp of Engineers, a heavy drinker and amateur boxer who began to lose his memory, probably due to too many punches, a condition called *dementia pugilistica*. My father graduated from Massachusetts Institute of Technology, became a lawyer who helps adjudicated youth and wins contests with his haiku. If I learned anything from this, it is how taxing the 1930s must have been for the immigrant class. One of my instincts is that in our age of neurobiology we rely too much on measured intelligence to decide what our lives should look like and the scope of our horizon. Whenever I talk about intelligence, I am trying to be conscious of what I really mean, which is that I seek to exclude myself as an exception from the drama of life, seeking immunity from social rifts and asylum from nature. In fact, the idea that the street credit of a few outstanding individuals can represent the character of an entire group or that the typecast of a group can define an individual, "Jewish exceptionalism" or "American exceptionalism," is rightly called the exception fallacy. The idea of Jewish identity, or Black identity, for that matter, exists to some extent in our genes and biology, to some extent in our culture and religion, to some extent in our interpretation of our own experience. We all know that identity *emerges* through navigation of layers of substance in these three spheres, the most hardwired of which is our genes. But our genomes are like snowflakes, no two are exactly alike, and which genetic variants – say, a smattering of those on the Y chromosome, or those on 6 chromosome – count as a license to a group, means that ethnicity can often be classified in more than one way. These categories may become all the more flexible, if we were to start slipping snippets of genetic code into our cells, customizing our

genomes at will. And this exposes the unsettling existential reality that we are not part and parcel to the categories which are fundamental to existence, but that nature itself changes – we are each just individuals living dangerous lives. The sphere of culture, by comparison, is even more flexible. "Culture" is a crutch, a means to cohesion – science has culture, this book is a piece of culture – and, importantly, entrance into a piece of culture, implies exclusion. It's therefore not surprising that when some people hear the word culture, they reach for their gun.

One of the ideas that animates this book is that science is not higher in its truths, but rather, science is a component of our broader phenomenology. How we assess and use science is deeply subjective, and often dogmatic. Most US taxpayers probably have little appreciation that much of the science they are funding is of dubious value, due to the "replication crisis" which primarily emerges due to scientific studies that reach conclusions based on incomplete information. In 2012, researchers at Amgen reported they could only reproduce results of 6 of the 53 hematology and oncology studies they attempted to replicate.[5] Around the same time, researchers at Bayer uncovered a similar problem in trying to validate published papers to pursue new drug targets, reporting they could not replicate more than 75 percent of the 67 published studies they examined.[6] A study will typically focus on the effect of a genetic variant taken out of context of its genetic background and other types of biological contributions and environmental stressors, which either counter or enhance its effect. Scientists themselves are quite aware that they are probably submitting false positives to the literature. In the words of Paul Thompson and colleagues, "subtle phenomena such as the 'winner's curse' are well known in quantitative genetics, where the effect size of a finding is often not as strong in a replication sample as it is in the initial discovery sample."[7]

In fact, the field of genetics is struggling to define its facts, in large part, because genetic variants have different effects when sorted into the genetic background of unique people. Daniel MacArthur and colleagues at Harvard working on The Exome Aggregation Consortium, or ExAC, revealed that of 192 high-frequency genetic variants they were fairly certain were pathogenic, only nine are probably harmful to most people. Furthermore, much of the false information that is reported in scientific papers is due to lax standards on publishing. MacArthur and colleagues suggested guidelines on reducing false positives in the literature,

although those guidelines are merely suggestive, certainly not enforceable.[8,9,10] To illustrate one of their points, they described a study on autism in which researchers found four *de novo*, or new, mutations in the gene *TTN*. But, it turns out the *TTN* gene is the largest coding gene in the human genome which builds a protein called Titin, and just by chance, we might expect to find two mutations. Finding four, then, is not so surprising. The researchers in that study dropped that gene as an autism candidate. But these are only best practices. Within statistics sleeps a demon. Genetic and RNA expression data is expensive – often running into the tens or hundreds of thousands of dollars to generate – and researchers who acquire data *always* find something. In truth, every data set usually includes eight to ten plausible stories for publication, and scientists will typically choose one or two of those stories and ignore the rest. And they often make their picks based on their ability to narrate rather than the strength of the statistics. The temptation to spin a good tale is enormous. Goldstein anticipated the sheer wealth of candidate mutations in the human genome and the allure to tell their story on the impact to traits as the "narrative potential of human genomes."[11]

The emergence of one compelling story often ignores competing interpretations, or downplays the reality that a finding is context dependent. The replication crisis in social sciences is even more severe and controversial.[12,13,14] But, while the data-driven culture of science involves evaluation of cause and effect and results-based assessments, it excludes deontic or virtue ethics, characteristics we pursue for the sake of duty or honor or beauty. But I am not the first person to feel that science and technology has the potential to erode our capacity for introspection, and weaken our sense of reality. At the turn of the century, William James complained that "scientific absolutists pretend to regulate our lives," and explained in his dissenting opinion that "science has organized this nervousness into a *regular* technique, her so-called method of verification; and she has fallen so deeply in love with this method that one may even say she has ceased to care for truth by itself at all. It is only truth as technically verified that interests her. The truth of truths might come in merely affirmative form, and she would decline to touch it."[15]

Institutions strive to avoid the "merely affirmative," and strive to be data driven in their decisions under the guise that they're being scientific, and thus more authentic. The repression of intuition and the value of experience is nudging forth today, as the subconscious is

not only thought of as primitive, but tainted. At my workplace, talks are given on "implicit bias," suggestive that intuitive pull not only has little value but jeopardizes our lives and demoralizes our heads. The subconscious is said to lead us astray through preference and bias, but seldom is discussed how it protects and signals against dangers and the wrong choices. But we seek to eliminate it. We evaluate decisions in terms of data science and we extol those who are data-driven. The Yale psychologist Paul Bloom has called empathy a "parochial emotion" and the organizational guru Adam Grant has suggested we find ways to remove "soft" intuition-based influence over our decisions, telling *The Washington Post* "I think we are leaving the age of experience and moving into the age of evidence," he says. "One of my big goals professionally is to get more leaders to stop acting on intuition and experience – and instead be data-driven."[16,17] The allure is obvious: we simultaneously remove our bias and let the data decide for us, removing any existential tension over how to make a decision on who to hire, or fund, or to bring into our lives, a problem I have written about before.[18]

The "modern impulse," which seeks to particularize and monetize, based on data-driven decision science, is often placed in dichotomy with the "romantic impulse," which values soft intuition and experience, although intuition and experience play a large role in science itself. The German chemist August Kekulé solved the structure of benzene after dreaming of a coiled black snake with its tail in its mouth. The neuroscientist Eric Kandel, among others, has called this "night science," a visitation that seems to be a strange remnant from the Romantic Period; as Edgar Allen Poe once professed, "they who dream by day are cognizant of many things which escape those who dream only by night."

The way I read it, the irrational or "romantic impulse" does not refer to unconfirmed beliefs, but finds its more authentic definition in its premise that nature is agnostic to its classification, and that it's ultimately accidental at its core – there is no logic at the basis of reality. "Darwin displaced humanity from the pinnacle of the organic world," Nathaniel Comfort, a historian of science at John Hopkins, astutely wrote recently in *The Atlantic*, while "Cheerleaders for Crispr" and their gene-centric history suggest "when we control the gene, its champions promise, we will be the masters of our own destiny."[19] The "subtler gene," as Comfort calls the "rise of genomics," disabuses us of the inclination that

we can use Crispr to treat modern maladies such as schizophrenia or autism, and control fate and time. Indeed, such a naïve view on the insistence on genetic science as a wellspring of meaning and an illuminated reality is at odds with the existentialists' observation that personality often finds itself foreign – this foreignness is deeply problematic for science. We think if we only had better data, we'd have complete control. Comfort notes the seductive illusion that we might control our genes with "Crispr, the new, revolutionarily simple method of editing genes, foretells designer babies, the end of disease, and perhaps even the transformation of humanity into a new and better species."

Science emerges, as Noam Chomsky noted, through our "science forming faculties." As phenomenologists called it "bracketing," setting aside questions of real existence to focus on the analysis of the phenomenon of experience. Experience is organized into the systems and classifications as science, and is put into frame, as if experience is part of a classification. But categories break down through encounters with nature, and through the other, and the alterity of "otherness," elucidated by such writers as Kafka and Kundera, and by Ralph Waldo Emerson, who wrote, "Other men are lenses through which we read our own minds." That nature is not cohesive, and that it's agnostic to its classification, and that it's ultimately accidental, means that nature defines logic, and fundamantal categories of belonging.

The scientific doctrine of eliminativism even suggests that our folk science, mythologies and general assumptions of how agents operate in nature will eventually be eliminated or rejected by the scientific process, or in Robert Pogue Harrison's words, "what used to be called the soul before it curled up and disappeared from the scene of history." But a brain is a classifier, or, a belief generator, and our kitchen-table psychology is a critical step in developing our expanding and collapsing perspectives. Taken to its fullest extent, eliminativism risks a repression of our sense of agency, development, and a general self-awareness that we are framing every thought and event. Science is not free from the framing of the experience. No scientific paper was ever written without a bit of framing, and any pretense that we are writing without framing data or perception is an act of self-deception.

The modern science view is that intelligence and personality dynamics are particularized in our genes. We can test it and what we see is what we get. The folk science view is that our character is built as

experience seeps into our being. "It takes a while for our experiences to sift through our consciousness," the writer Nathalie Goldberg once observed. "Our senses are themselves dumb. They take in experience, but they need the richness of sifting for a while through our consciousness and through our whole bodies. I call this 'composting.' Our bodies are garbage heaps: we collect experience, and from the decomposition of the thrown-out eggshells, spinach leaves, coffee grinds, and old steak bones of our minds come nitrogen, lead, and very fertile soil. Out of this fertile soil bloom our poems and stories. But this does not come at once. It takes time. Continue to turn over and over the organic details of our life until some of them fall through the garbage of discursive thoughts to the solid ground of black soil."[20] Watson is right, but he is only partly right – our fate is in our genes, but at least as much of the human condition we enter into is a blooming, buzzing confusion.

Genetics contains pieces of who we are. It had only begun to percolate. I had been a journalist for a number of years, when entering the grips of a quarter-life crisis, I went back to school to study genetics – "Be a mensch" my father said. "I think it's funny that you should say that," I said, since that word sounds Yiddish to me. After graduation I was camping on the shore of New Hampshire for six months, which incidentally, was just at the beginning of the "Occupy" movement. I decided science would provide a route to a purer form of knowledge, which was free from the corporate racket. I finally got a job. One of the first people I met in the world of working scientists was Derrick Rossi.

Rossi was still a young scientist at age 45 when he landed on *Time Magazine*'s list of 100 Most Influential People in 2011, just months before demonstrating how to reprogram adult cells into stem cells. That same year, a good year for him, he launched a company, Moderna Therapeutics, which quickly drew more than a billion dollars in investment. Rossi developed the company's core technology, which involves introducing customized RNA molecules into cells to effect a therapeutic outcome. This counts as a "biologic," a means to use biological spare parts to alter or repair a cell signal. Consider that a gene is built from a sticky macromolecule of sugary bases, or nucleotides, which are adenine, guanine, cytosine and thymine, and are themselves composed

of carbon, hydrogen, nitrogen and phosphoric acid, which assemble into rings to make those four nucleotides. This is deoxyribonucleic acid, or DNA, and it is in turn copied into ribonucleic acid or RNA. In fact, the "central dogma" in biology is that DNA is transcribed into RNA, which is translated into protein, and modern drugs, for the most part, target the proteins in our cells, that molecular menagerie of enzymes, antibodies, receptors and cell signaling molecules. What Rossi was doing was to move the drug industry a step deeper to the level of the RNA. In effect, by inserting his own engineered RNA molecule he could instruct the cell to produce any type of protein he wanted from scratch. I wrote to him asking for work. Rossi said Moderna didn't hire many computational people, but he could use help on a separate project in his lab at Harvard to characterize the nature of mutations in stem cells, which concerns his other interest, how cells break down and the machinery that repairs them. That's how I got to work at a bench next to Paula.

I work on the computer. Paula sacrifices mice, which Rossi constantly refers to as "sacking mice" as if we are taking a castle. After Paula sacks the mice and harvests a cluster of stem cells, we dose the cells with a treatment to induce mutations, or DNA damage, and Rossi wants me to look at the data and tell him which genes have the mutations, and whether general purpose stem cells are more or less prone to mutations than differentiated adult cells, which build our blood, bones and immune system. "That's a question I've wanted to know the answer to for a long time," he tells me, later acknowledging that it was one of many questions his lab has posed since its inception. The established dogma in the field is that stem cells are more protected, or "uniquely cytoprotected,"[21] against mutations, and Rossi wants to test his theory that the opposite may be true, that stem cells may be *more* at risk to accruing mutations than differentiated adult cells. This all plays into an emerging concept that mutations arising in stem cells give rise to many different types of cancer, the so-called "stem cell hypothesis."

To me, it looks like the "control" cells are littered with mutations. That might be expected because "we dosed the (expletive) out of those cells," Rossi tells me. But, after a few months, it turns out our data was not sequenced adequately at the core lab, which provides a service for next-generation sequencing, and is not of high enough quality to draw any conclusions from our experiments. The core lab at Tufts says they will do it again, for free. We're going to have to start over from scratch,

and I can tell that Rossi is annoyed and sometimes he walks by without saying anything. "That's just how he is," Paula says. "He's thinking in his head, 'I've got to get things done, I've got to get things done.'" What was going on in his head was more complicated than I knew. That month, a couple of papers had appeared in the journal *Science* on Crispr-Cas9, a powerful new tool which worked like tiny molecular scissors, and could be programmed to edit a specific genetic sequence in a human cell. This system was discovered as an immune system that a microbe has to fight against phages, which are viruses that can invade a single-cell microbe such as a bacterium.[22] It was only later repurposed as a technology. In fact, 50 years ago microbiologists first discovered that bacteria have *innate* immune systems to fight viruses by using "restriction enzymes," proteins which can chop up phage genomes at specific short sequences, thereby restricting their growth. Scientists then repurposed these enzymes to cut and paste DNA, in effect, giving rise to the biotech industry.[23] A decade ago microbiologists discovered that bacteria also have *adaptive* immune systems, meaning they are equipped with a kind of programmable system that will allow them to acquire intelligence on a phage by capturing a bit of code from it. Once the bacterium has a record of the phage on file, it can hack to pieces any invading virus that matches the description. This was the Crispr system. A few small molecular tricks later, scientists had learned to reprogram it as a tool to make precise edits to the genes in human cells, rekindling a debate on what it meant to engineer human cells.

In fact, Crispr stands for "clustered regularly interspaced short palindromic repeat" and it is repetitive genetic code that has nested within it more code, called a "spacer," which records telltale signs of a past invading phage, keeping a record of the phage like a fingerprint or a mugshot. In effect, the spacer captures the code of an invading phage as a genetic download in the genome of the bacterium. If a phage that matches the description enters the bacterium in the future, an expressed molecule senses and detects the phage and guides a special enzyme called a Cas nuclease to chop up the phage like molecular scissors. In 1987, Japanese researchers first reported these strange repeat sequences in the common bacteria *Escherichia coli*, not knowing what to make of them.[24] But a molecular gumshoe was on the case.

Eric Lander, director of the Broad Institute of MIT and Harvard, recounted the tale of Spanish microbiologist Francisco Mojica's