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First Coronavirus Death in U.S. and New Cases Detected as Testing Expands Washington Post

Craig needed three days to start testing.

Akash wanted to start a clinical trial in 10 days.

Melanie needed 32 days to grow antibodies and sequence them.

Franco needed 45 days for his CRISPR test, which would drop the cost of testing to five dollars.

First went the handshakes. Second went travel. Everyone canceled their trips.

Even in a crisis, people want to look smart and rational. There was a compulsion across society to use the little we knew to declare predictions. It took several weeks to recognize the futility of looking into the future. The only honest people were those who admitted, *this is the unknown*.

There was no plan, just a way. We all went home from IndieBio, vacating

the lab so Franco's team from Argentina could take it over and develop their test. After a day, we couldn't stand the feeling of retreat. This was not us. Our philosophy is action.

Then Arvind got the email from Akash.

Akash had a proposal to stop COVID-19. I forwarded it to the team.

Text from my sister, who is an eye surgeon at a major hospital in New York:

> Sad case today. A 17-year-old with a bad injury from yard work. Full corneal laceration, traumatic cataract and retinal detachment. His father was so devastated. When we were talking he collapsed and hugged me out of sorrow. Now I feel like I'm covered in corona.

Akash wrote that he had 735 kilograms of niclosamide on its way to the U.S. They were going to use it for a clinical trial as a form of birth control, as a spermicide. But they wanted to try it for COVID-19. They were in contact with the FDA. Niclosamide was invented by Bayer in the 1950s and was mostly used in the developing world to treat tapeworm. It had been pulled off the U.S. market in 1996, but it was still made elsewhere.

The argument was that niclosamide might work because, even though it had never been used to treat SARS or MERS during an outbreak, long after the fact it was shown

that niclosamide could stop those viruses from replicating inside us. The COVID-19 virus had the same 11 proteins as SARS and MERS, the same arsenal of weapons.

Normally, VCs take weeks or months to study a deal. This took us about an hour to say yes, which was the length of our first phone call. It was a blind bet with no evidence, only theory. Usually those bets bust. We would have been fine with that.

We were worried about Craig. He'd been coming by the lab to borrow our RT-PCR for weeks. He was so frustrated by the lack of testing that he invented an alternative to the CDC's protocol. He took four steps and simplified it into one step. He and Gabe were out on the street, testing random people, including the homeless.

Then Craig got some positive samples from UCSF, and he was able to confirm his test worked. He had a lab space arranged. He could start testing in three days, but he needed money to buy a real-time ABI7500DX PCR to handle the volume. When we tried to wire him $250,000, he realized he hadn't even set up a bank account yet.

Sleep was important. Sleep as much as possible. Roll out of bed, Zoom calls for fourteen hours. Days became a photocopy of the day before. Without the texture of moving around the city, or bouncing around IndieBio, I became forgetful; my memories were unmoored from geography, synthetic, like boring dreams I couldn't wake from.

Arvind wrote a letter to all our alumni:

> "Nobody knows how long this will last. Nobody knows how this will end. I do know this. Nothing is ever as good as it looks or as bad as it feels. We will be fine. We may even be better from it. But first, we must survive it. You are all IndieBio companies. Which means you are already survivors. Born and bred in the basement on Jessie Street in the Tenderloin. Walking into the office meant stepping over the hardships of life just to face it again in the lab. But this shock is different. Covid-19 will test us all."

At least a dozen of our alumni were running into the fire.

In Korea, their Zoonotic Virus Lab tried 3,000 existing drugs, in a high-throughput screen using kidney cells infected with the virus. They found 24 that worked well, and niclosamide was one of the two that stood out above the rest. We called the Gates Foundation to get it on their radar. Around the same time, Akash got great results back on niclosamide from the Galveston National Lab, a Biosafety Level 4 containment facility that worked with live virus. Three medical centers had agreed to start a trial.

Text from my sister in New York:

> I have an emergency transplant to do. She will lose her eye by tomorrow. Patient should be tested for COVID but hasn't. The virus becomes airborne during intubation and can infect the whole operating room for hours. They don't have a mask for me.

I sent an N95 mask to her by FedEx. It arrived three hours late.

We had just opened IndieBio New York. Our team there never even had a chance to visit the lab before being sent home. But they were working with the state, and it became clear we needed to send Craig to the New York Genome Center in SoHo. His ability to do high-volume testing was more needed there than in San Francisco. He started with all 4,000 people at the United Nations.

Working with Sean O'Sullivan, the managing general partner of our firm, we decided to announce publicly that we would fund eight COVID-19 initiatives.

We got drowned in applications. Everybody needed money. Few VCs were open for business. The team did fifteen to twenty Zoom calls a day. Decoy strategies at the heparan sulfate receptor. Protein degraders. Vaccine platforms. Llama antibodies. Antivirals from plants. Sanitizer tech that used nothing but water and charged ions. I've never seen a team absorb so much information, so fast, and make decisions on the fly about what they believed was our best chance.

Exosomes, engineered to rescue lung function in patients who can't breathe. Mickey needs 60 days. We're in.

Some people checked the stock market ten times a day. I checked Nextstrain to follow the mutations and migrations. Both are a kind of Rorschach test.

Message posted on IndieBio Slack:

> Also if you join by video, please dress up. Haha. Theme is that it is the year 3020 and the human race has been in isolation for 1000 years.

Message posted on IndieBio Slack:

> Shit! Ryan Gosling's Butter Sacrifice party is popping! The tunes are crazy!

Franco called from IndieBio. Half his team just tested positive.

Everyone says this started in bats. And that as long as there are bats, there will be viruses spilling over into humans. But parts of that story are missing.

Bats are the only mammal that flies. Flying raises their heart rate so high (up to 1,000 beats per minute), and they burn so much energy, that the DNA damage created would kill anything else. So along with the ability to fly, bats evolved more powerful DNA repair mechanisms. Their genome has a second copy of P53, the guardian of the genome, which patrols their DNA for mutations. They also express far more interferons. These protect and repair the bat genome so well that bats can *also* handle all the genetic chaos that viruses create. The viruses will live in bats, without tearing them apart.

Once these viruses spill over to humans, it's like LeBron James showing up at the local pickup court. It's too easy. The virus has evolved to compete against far superior bat defenses. Against our weaker defenses, the virus carves us up.

But what's missing is this: Bats don't normally infect humans. That's why this happens rarely. Bat genomes are so good at keeping viruses in check, that most of the time, bats are no danger to humans.

It's only when bats suffer immunological stress, and their viral load goes way up, that they get sick and can pass their viruses to humans. One of the most common stresses, recently, is loss of habitat. Deforestation, urban development, and arid wetlands.

So this didn't start with bats. This started with whatever caused the bats to get sick.

Everyone is looking for a drug. But the body is better and faster at designing drugs than any pharma company.

Mutation is normally bad for the body. But we actually have little tiny laboratories in our bodies where we turn on hypermutation when something foreign gets in, like a virus.

We do this in a controlled, safe setting–on a particular stretch of the genome in B lymphocyte cells. This is where the body invents antibodies. The hypermutation is called V(D)J recombination. Variable, Diversity, and Joining.

Every time the B cell divides, short code chunks of Vs, Ds, and Js randomly recombine. The genetic proofreaders don't interfere. The body keeps recombining and recombining until–randomly–one works. If an antibody latches on to the virus, all sorts of signals ramp up, and cells clone the antibody rapidly, like a drug factory. These antibodies mark cells for destruction.

Every single person who gets the virus has to invent their own antibodies. It's a race: Can your body hypermutate a drug to save you before the virus turns your blood vessels into pink slime?

Someone started tailing me. I tried to shake them in the baking aisle. At the grocery store, it was like a zombie film. In the vegan aisle, the shelves were full. I lost him there.

In Iceland, my family was losing their jobs. The government was testing people randomly, calling them out of the phone book. Ten percent of the country had been tested, so the media was reporting how Iceland hasn't sheltered in place. But according to our family, nobody was leaving the house. Except to go out and shoot caribou.

I missed being at IndieBio. And even though I wasn't going to actually leave IndieBio for three more months, being sheltered at home made me aware of what I'd miss the most. It's how the day starts–how almost every day at IndieBio starts.

I park across the street, step over a whiskey bottle and a syringe, give a hug to whoever opens the door, and descend

the steel staircase to the Ivory Basement. The distance to my desk is about the same as a fashion show runway. High fives and more hugs, quick updates, then the team rolls out for coffee. We sit outside on Market Street, the city's raw spectacle rolling in ecstasy at our feet. We tell personal stories. The drama at group houses. The parties we can't unsee, even if we wish to. We triage the companies we're incubating. It feels so good to spend time together. Then we start brainstorming. Maybe it's how plant cells use gravity to know up from down. Or tax policy in India. Or someone declares the amount of joules in the chemical bonds of a pound of body fat. Somehow, the conversation leaps topic to topic with every exchange, and we always end up talking about something we never could have predicted even a minute earlier. It doesn't get better.

Melanie had made antibodies against Zika when she was at IndieBio. She believed she could do it again against this virus. There were 23 companies trying to invent the perfect antibody, and a dozen more trying to design one with a supercomputer. "They're slow," Melanie said. "They start in humanized mice, then hope what they get works in humans. It takes tons of repetition and adjustment. In a computer, you can design an antibody in days. But you have no idea if it will have off-target effects, so that testing takes months and months." Melanie said she could do it in 32 days.

Melanie's approach was truly unique. Her company, Prellis, was the world leader in 3D-printing human organ tissue, using lasers and stem cells. Her goal for Prellis was right out of a science-fiction movie: She wants to print a new

liver for patients when their liver is shot. She was getting close. She'd been making mini-livers.

But this was wartime. "I can make dozens of mini-lymph nodes, little immune systems. I'll inoculate them with the virus. They'll create antibodies just like they would inside a human body. I'll screen the antibodies for which works best."

In a week, the lymph nodes were printed. A week later, inoculated. One more week, and the miracle of V(D)J recombination was generating antibodies to the virus.

Collectively, the search for remedies is like trying to defuse a bomb that you're carrying in your own hands–while simultaneously running a marathon.

Franco says his team is *not* positive. It was a false alarm. All the more need for his far more accurate test.

My daughter asks me how talking on the phone can help stop the virus.

One day we will go back to normal. But I'll fondly remember the girls Zoom-bombing me on my calls, taking family walks in the rain, and losing "name the animal" to my five-year-old.