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SEPTEMBER 2003 $4.95

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SARS CRACKING THE CODE

TENSION AT TELUS

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Deconstruct a killer virus and find out what makes it tick. And do it fast . . .

impossible

Cue the music . . .

It's Saturday evening, April 5, 2003, and Martin Petrie, a senior virologist at the B.C. Centre for Disease Control (BCCDC), is standing in the Vancouver International Airport, waiting to make contact with a courier carrying a tiny package of death. The Severe Acute Respiratory Syndrome (SARS) virus has, by this point, infected more than 1,500 people worldwide and killed nearly 100. Hospitals and schools have been closed from Toronto to Singapore, and in Hong Kong, the SARS hotspot, more than 1,000 people are being held in quarantine – some against their will.

The courier, a senior official from the National Microbiology Laboratory in Winnipeg, Manitoba, is carrying a purified sample of the SARS genetic code – a precious commodity that, in the right hands, might reveal the origin of this new killer. It is, at this point, a race. The virus is straining to break into the general population – there to wreak havoc not seen since the 1919 flu pandemic – and the world health community is hustling to understand and struggling to restrain the SARS threat.

But (and here you can cut the music) if the threat is real and the adrenaline is flowing in agitated torrents, the physical reality of this scene is mundane in the extreme. As the courier disembarks, there are no armed guards, no oxygen masks – not even a stainless steal briefcase dangling from a manacled wrist. There is only a small

» by Richard Littlemore » photographs by Dina Goldstein

Styrofoam container the size and shape of a box you'd get from Birks if you bought a large, expensive bracelet. The handoff is simple, unceremonious, virtually invisible to the other passengers – which is probably good. Given the general state of public concern about SARS, frequent flyers staring daggers at anyone who so much as sniffles or coughs, the airport crowds would likely have panicked if someone had said: "That man over there is carrying SARS in a box."

No need to panic, says Jaswinder 'Jaz' Khattra, coordinator of the Gene Expression Laboratory of the Vancouver-based Genome Sciences Centre (GSC). The sample is pure RNA – ribonucleic acid – a microscopic strand of genetic material that has been stripped from its viral shell. From a safety perspective, there is no reason the sample couldn't have been Fed-Ex'ed. The high-priced Winnipeg courier is honoring protocol and ensuring speed more than protecting anyone's safety.

Still, there is no reason not to be careful. When Petrie arrives at Khattra's lab in the BCCDC building on West 12th, it's after 9 p.m. – but Khattra is waiting. He knew the sample was coming and slept in the afternoon, expressly so he would be ready to begin work the instant it arrived. With Petrie at his side, Khattra moves to the next room, to the large bio-safety cabinet – an open, glass-fronted box that looks like an expensive salad bar. He places the Styrofoam container into the workspace, slits the tape and gently removes the lid. As the mist from the dry ice clears in the cabinet ventilation, they see it: an Eppendorf tube not quite as big as your little finger. In the bottom of the tube – the very bottom – is a drop of clear fluid, a surprisingly, disappointingly, frighteningly small drop.

Khattra's adrenal gland goes into arrest. Such a tiny sample means he has no margin for error. He and the other members of the team at the GSC have waited more than a week for this RNA. It's a sample from the second patient who died from SARS in Canada. It was isolated in Toronto, purified in Winnipeg and passed along for experimentation. The droplet is too small even to measure without special equipment; it is so tiny, it would evaporate instantly if you spilled it on the bench. Even in its container, the slightest contamination will degrade it to the point of uselessness.

Khattra places the tube back in the box, the lid back on the top and the sample into a -80 Celsius freezer – keeping it ultra-cold to ensure there is no biological activity – and retreats to his office to "dwell on the options." Petrie goes home. In such a situation, Khattra says later: "One gets quite anxious."

This race, this measured sprint to an unmarked finish line, began nine days earlier over coffee. Dr. Marco Marra, the young turk (37 years young) who is director of the GSC, and Dr. Caroline Astell, a former UBC biochemistry and microbiology professor who is now the GSC's project leader, were taking a break on March 27 when the conversation turned to SARS.

"We were wondering, 'What is this thing?'" says Astell. Given what they already knew, or had heard, they assumed it was an RNA-encoded coronavirus. But by the time they had finished coffee, they were agreed: the GSC is one of only 10 or 12 facilities in the world capable of sequencing the SARS genome. And because of the centre's high throughput capabilities, SARS would also be 'a very small project for this facility,' Astell says. Even so, there was no budget for the work. The four-year-old facility is well funded by Genome Canada and Genome B.C. and has attracted many millions from the U.S. National Institutes of Health. But virtually all of that money is tied directly to specific experiments.

Marra had applied to the Department of National Defence last year for funding to prepare the GSC to react quickly in assessing

threats from a potential bio-terrorism attack. The funding request was denied – but the SARS project still represented an opportunity to test the GSC's quick-response capacity and to show its worth. Marra and Astell agreed to find the money, and do the work. They initiated contact with the Winnipeg lab . . . and then they waited for the tiny vial to arrive.

"This is the most exotic sample I have ever dealt with," says Jaz Khattra of the SARS RNA. "One is quite anxious"

It's still Saturday night, midnight, and Khattra has charted his course. He will 'amplify' the sample – get it to duplicate itself – using a process called polymerase chain reaction (PCR). It's a matter of manipulating the sample with a mix of enzymes and reagents, thereby convincing it to replicate in whole or in part.

Khattra is hoping to find something familiar, work on an assumed section of the genome, amplify it out, stain it with fluorescent dye and then scan it with a high-end digital scanner to measure its size. This won't produce a gene sequence but if the sample comes up exactly the same size as a known coronavirus, he can be relatively sure of what he has. He works through the night, alone in the building save for the roving security staff. Again, commenting later, he strays into understatement: "One is quite nervous. Even if other people are there, it is not as anxiety ridden. Because this is the most exotic sample I have ever dealt with."

And it doesn't work – at least not conclusively. Khattra identifies a fragment and confirms this killer is a coronavirus, but he cannot establish its exact type. He walks home, sleeps for "four to six hours" and returns, again working through the night to amplify sections of the RNA.

Dawn breaks early and without a cheerful result. Khattra heads off for a meeting with the GSC management group, led by Marco Marra and Caroline Astell. It will become a daily meeting during the entire 16-day course of the project. They decide to change the strategy, to build something called a cDNA library – a sort of full-set encyclopedia of the genome's component parts.

This is neither as difficult as it sounds, nor as easy. In the grand scheme – which is to say whenever you are dealing with a DNA-based genome – DNA begets RNA: DNA is the mother, giving orders; RNA is the offspring, executing the genetic plan – following the DNA code to manufacture the protein building blocks of cellular structure.

RNA viruses do it backwards. The virus invades a cell first and then, using host material in combination with an enzyme called Reverse Transcriptase (RT), creates a DNA copy of itself – a cDNA. The good news, for Khattra, is that these DNA copies are easy to grow – to mass-produce – in bacterial cultures. The bad news is that, unlike the PCR process, RT will chew up big portions of his tiny sample. If it goes wrong more than once, "it's a show stopper."

By noon Monday, six people in Khattra's lab are fully engaged sourcing chemicals and reagents and preparing parts of the process; the Gene Expression Lab is a just-in-time operation in that it doesn't keep a huge store of materials that won't be immediately useful. Khattra's people deal with "hardcore biological life science suppliers" and frequently ask for rush calls, he says. On this occasion, though, "the higher ups in these companies [are] informed of the nature of the project." Call them motivated. One local supplier fills an order in 30 minutes – delivered – and even the bigger supply houses in Ontario

are promising product in less than a day.

Once he is sure everyone is on track, Khattra steals home for a few hours sleep Monday afternoon. Again he returns to work through the night – concluding in the darkness that the whole process is (and here comes that understatement again) "paradoxical."

"Usually," he says, "if you want to do something the fastest way, you don't get the finest product." In this case, everyone wants it fast and it has to be perfect.

But wants and needs don't guarantee immediate success. Khattra and company insert the RNA into a molecular vector and set it up to grow in a harmless strain of e-coli bacteria. They wait 12 hours and they get back, pretty much, nothing. When Khattra goes home Wednesday afternoon, sleep is elusive at best.

Wednesday night. Four days after receiving the vial. Khattra is back to amplifying the sample, worrying that he will induce some sort of bias, but stressing even more about using up what little of the sample he has left. He repeats the RT process, using a different vector and, again, everyone waits.

By now, the news has leaked out that the GSC is on the hunt for the SARS genome sequence. Khattra's phone is ringing, the emails are piling up, the media figuratively pressing its nose against the window. The pressure is on. In such a situation, he says, "you ignore the people who you have to ignore."

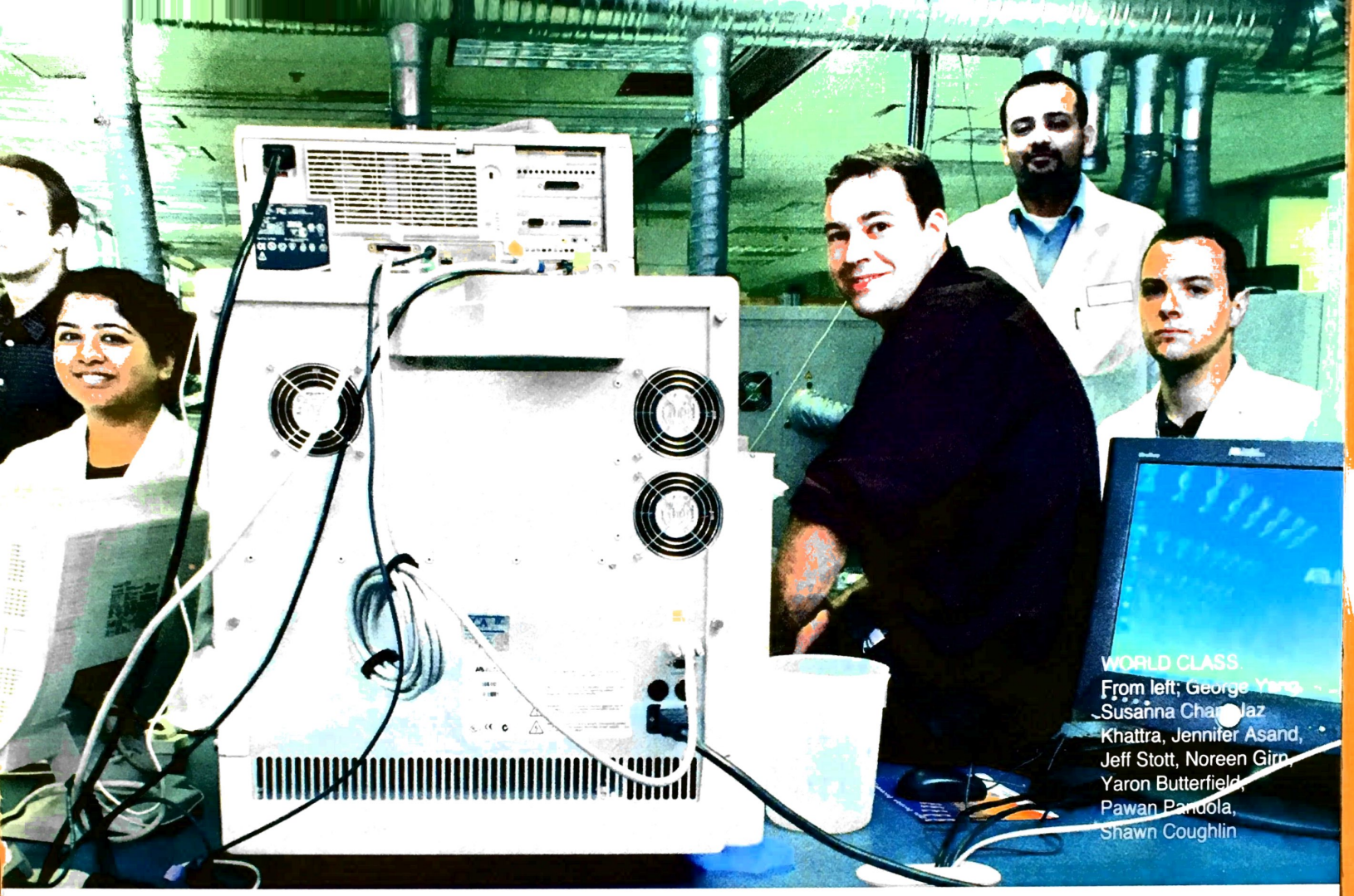
But you don't sleep. Khattra skips his afternoon nap and sets off Thursday evening for a stroll to Granville Island, leaving others to monitor whether the bacterial culture blooms.

Meanwhile, there is a considerable amount of alpha-dog thumb twiddling going on next door. While Khattra's staff has been working in the BCCDC building, the denizens of the actual sequencing centre are waiting – nervously, impatiently – in the BC Cancer Agency building across the alley. (The GSC operates under the auspices of the Cancer Agency.)

The most striking thing about the main part of the GSC is not the $10 million in hardware. DNA sequencers, even if the best of them cost $750,000 plus, still look square and dull; all the interesting stuff occurs inside, robotically and microscopically. Wet lab benches also look the same everywhere – stirrers and shakers, test tubes and trays – but there's nothing that looks as complex or as silly as the simplest laboratory set in a Hollywood movie. Even the monster GSC servers stacked in the bioinformatics room look vaguely like a 1970s-era mainframe computer.

No, the most striking thing about this facility isn't the hardware. It's the people, and particularly their average age – not yet 30. Genome science is so new that many of these 20-somethings couldn't study their specialty during their university careers because the discipline didn't exist, yet.

The most obvious example is bioinformatics – the scientific marriage of biology and computer processing. To some degree bioinformatics has existed since the invention of the calculator. But in genome science, the computational challenges are so huge it would be impossible to organize information without using computers at every stage. Asked how old bioinformatics is as a discipline, Yaron Butterfield, the 29-year-old assistant bioinformatics coordinator, ponders: "Oh, it goes way back, like, a few decades." But when Butterfield did his B.Sc. at



WORLD CLASS
From left: George Yang, Susanna Chan, Diaz Khattra, Jennifer Asand, Jeff Stott, Noreen Girn, Yaron Butterfield, Pawan Pandola, Shawn Coughlin

SFU, there were no bioinformatics courses on the syllabus. He made his own education, studying biochemistry and microbiology and taking computer science courses on the side.

Now he's cruising the internet, downloading genome information on all the known coronaviruses to prepare comparisons for when – and if – they start getting SARS results. He is also gathering gene sequences of everything from mice to men. He can use these to check whether Khattra's sample has been corrupted by the introduction of some other slice of DNA or RNA.

Day five. Thursday evening. Khattra phones from Granville Island for news: "There are tons of bacterial colonies." The tiny sample has recreated itself as available DNA. Khattra is "not jubilant, just relieved." He knows he has something. However, he can't yet be sure that it is an uncorrupted strand of SARS DNA. Still unable, or unwilling, to sleep, he starts culturing a third batch using yet another cloning vector – just to be sure.

In the GSC sequencing centre, the waiting turns to working. They have Khattra's cDNA but (and here again you'll notice a trend) they still don't have enough. A team led by sequencing production coordinator Jeff Stott and assistant George Yang start 'amplifying' again – using the same PCR process on the DNA that Khattra used on the RNA five days earlier. Beginning at 11 p.m. they work through the night, amplifying and then handpicking the clones (the replicated bits of DNA). They do this, basically, by poking a toothpick into the plates where the clones are being cultured and transferring microscopic samples into the tray that will get loaded into the DNA sequencer. It's work usually done by robots, mechanized, multi-armed machines that poke and pick with relentless disinterest. But given the tiny size of the SARS sample, it's quicker – if incredibly more tedious – to do it tonight by hand. Stott and Yang even drag bioinformatician Butterfield into the wet lab to help out.

> By Wednesday, the news has leaked that the GSC is on the hunt. Khattra's phone is ringing, the emails are piling up. When the pressure builds, he says, "You ignore the people who you have to ignore"

By noon on Friday, April 11, they're ready to start loading the sequencers.

This next bit is all connected to the apparent black art that enabled researchers to map the human genome. DNA looks like a twisted ladder – a double helix – with the rungs of the ladder made up of base pairs of nucleotides: adenine is always paired with thymine (or with uracil in RNA) while guanine pairs with cytosine. The order in which these nucleotides appear dictates the nature of the gene, which is why genetic code is written out to look something like this: ACGCC-TAACGTCACT....

To identify the sequence of a particular section, researchers dye the DNA so the nucleotides fluoresce different colors when exposed to light. Then they draw the DNA strand through a tiny tube –

a capillary – and out past a laser beam that 'reads' the colors. Really, there's nothing to it if you have, oh, $750,000 and patience enough to load the machine.

It's 6 p.m. Friday. Day Six. The team has loaded the first 96-well sequencer and started its three-hour run. Now, there is nothing to do but wait – or eat. The whole group troops off to Stott's apartment for spaghetti – maintaining an Italian theme that, for much of the week, has been dominated by pizza. (Stott says they chose his place for dinner because he's the best cook. Everyone else says it's because Stott's apartment is closest.) They're back by 9 p.m., staring into the computer screen, waiting for a result.

Which is where Khattra has been all along. Still unable to sleep, he has been preparing the third batch of cDNA; it has now bloomed successfully and is available. Knowing when the sequencers were loaded, and with access to the computer system that yields the results, he is sitting in front of his own keyboard, not-quite-manically pushing the Enter key every 30 seconds to refresh the screen.

At 9:25 p.m. the first sequences start to pour in. Khattra immediately takes one of the longer sections and begins comparing it to other coronaviruses.

It's definitely a coronavirus – unique but part of the family. Khattra's concern that he might have been dealing with a corrupted sample immediately disappears. He picks up the phone to call the director – "which I would never normally do" – and Marra stabs it on the first ring. Yes!

But they're not nearly finished. With the current state of technology, sequencers can read only 500 to 800 base pairs at once. Given that the human genome has three billion base pairs and that even a simple coronavirus usually has about 30,000 pairs, you can't just stick the whole strand of DNA in one end and get a result out the other. You have to chop up the strand, take 'shotgun' reads of all the samples and then reassemble the partial result into one long string of code. Actually, you get the computer to reassemble the results – that's where the bioinformaticians begin to take over the operation.

But even from Butterfield's first 'build', it's clear they're on track: one section is almost 6,000 base pairs long and another is 7,000 pairs long. For the next five hours, they keep reloading the sequencers and rebuilding results. At 2:30 a.m., Butterfield hits the 'Eureka' moment. Built 28 comes back in one piece, right down to and including the tell-tale polytale – a long string of 'A's that always marks the end of a piece of messenger RNA.

For the wet-lab crew, euphoria gives over

to exhaustion. They file out to get some sleep. Butterfield keeps working – analyzing, verifying, comparing the completed sequence to others on file. When Stott comes back at 4 a.m., he startles Butterfield so badly, he is at risk of being impaled on the pen that Butterfield reflexively flings across the room.

By 7 a.m. Saturday, Day Seven, the place is humming, including Marra, who arrives with the Saturday morning version of a gourmet feast: Egg McMuffins for everyone and the full selection of Safeway orange juice – pulp, no-pulp and low-acid. (Who says scientists don't know how to party?)

Noon brings the overwhelming flow of reporters and by 11:30 p.m. Saturday April 12, 2003, the GSC 'publishes' its results on its website. Within hours they are getting requests from labs and research centres around the world for more information and

for samples of specific sections of the cDNA. On Sunday the renowned U.S. Center for Disease Control in Atlanta, publishes a partial sequence on its website. By Monday the CDC mounts a full sequence: it's 29,751 base-pairs long and only eight of those differ from the GSC version. By genomic standards this is a perfect match – each centre's result is an endorsement of the other as the product of high-quality science.

At its best science is not about ego: it's about understanding.

Everyone at the GSC is remarkably sensitive about depicting the sequencing as some kind of a race for glory. It was not. It was a race against SARS, an act of social and global responsibility. Acting together with Atlanta, the GSC has made the information available to the whole world – at no cost. Had a private lab been first to the prize, it would likely have patented the sequence – as has been done with a type of hepatitis C – and then charged research institutions when they wanted to work on the virus, to look for a vaccine or a diagnostic tool.

But whenever it comes up that the CDC in Atlanta – the biggest, richest, most experienced facility in the world – came a close second to the lab way up there in B.C., the folks at the GSC sit a little straighter. Some even allow themselves a satisfied smile.

There is much more than boasting rights on the line. Success in science breeds success – or more particularly, it attracts the money necessary to take the next step. For example, the full name of the GSC facility is the Michael Smith Genome Sciences Centre, named for the late UBC professor and Nobel laureate whose accomplishment and fame attracted attention, talent (such as Marra) and hard, cold cash. The fastest-growing business sector in B.C. is bio-tech and life sciences. In four years, the GSC alone has ballooned from a staff of 10 tending to one sequencer, to a staff of more than 100 running nine sequencers around the clock.

As immediate evidence of the potential economic, as well as health, dividends available to the research community, the provincial government stepped in soon after the sequencing with $2.6 million to fund the B.C. SARS Accelerated Vaccine Initiative (SAVI) under the auspices of another Michael Smith recruit, UBC microbiologist Brett Finlay. There will be more.

Last word, however, should go to Jaz Khattra as a fitting representative of a growing community of highly trained and accomplished life-science researchers who usually work in comfortable anonymity on projects that can take many years to yield results.

Of this experience, he put it this way: "It breaks the monotony." ■