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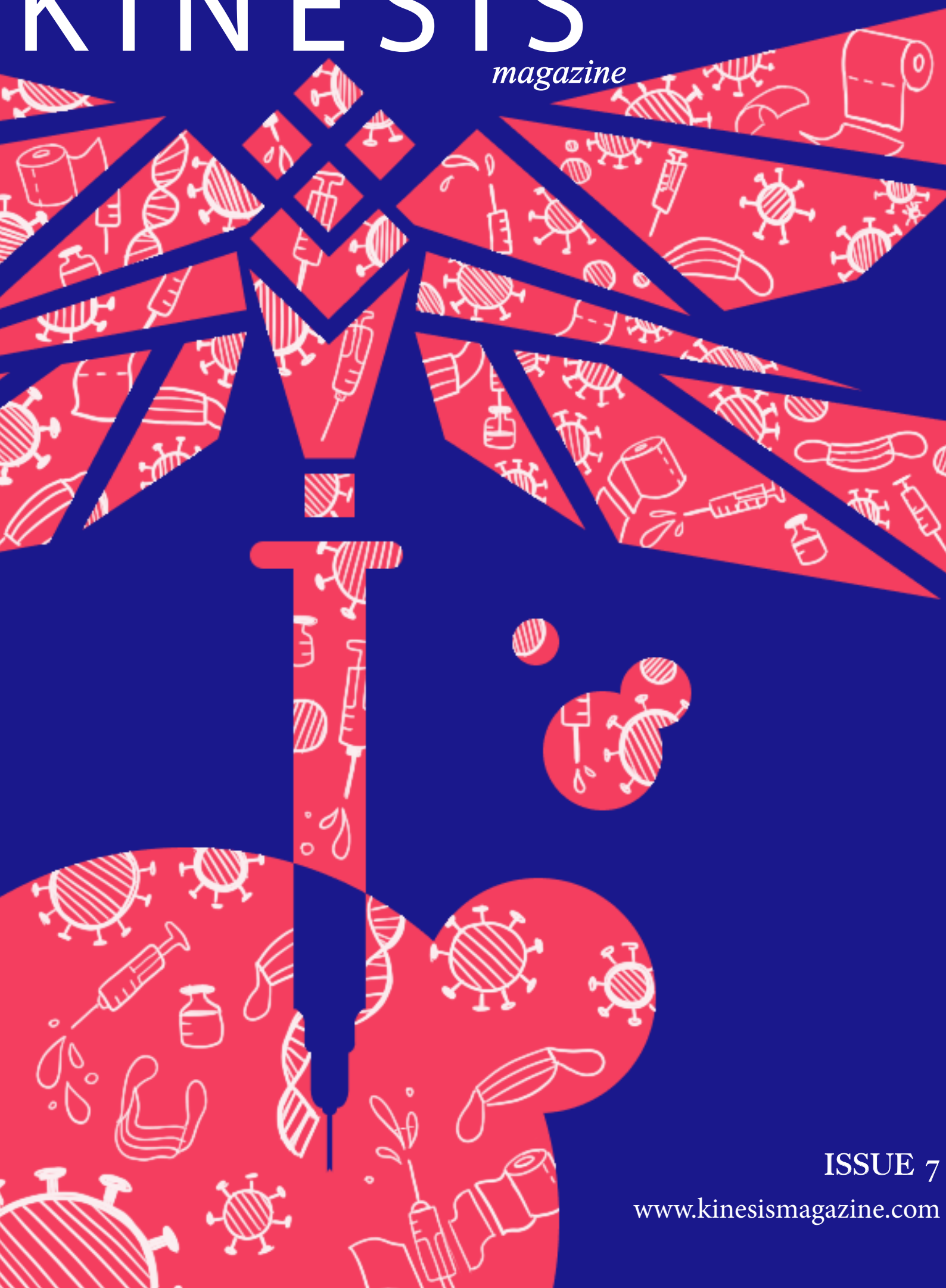

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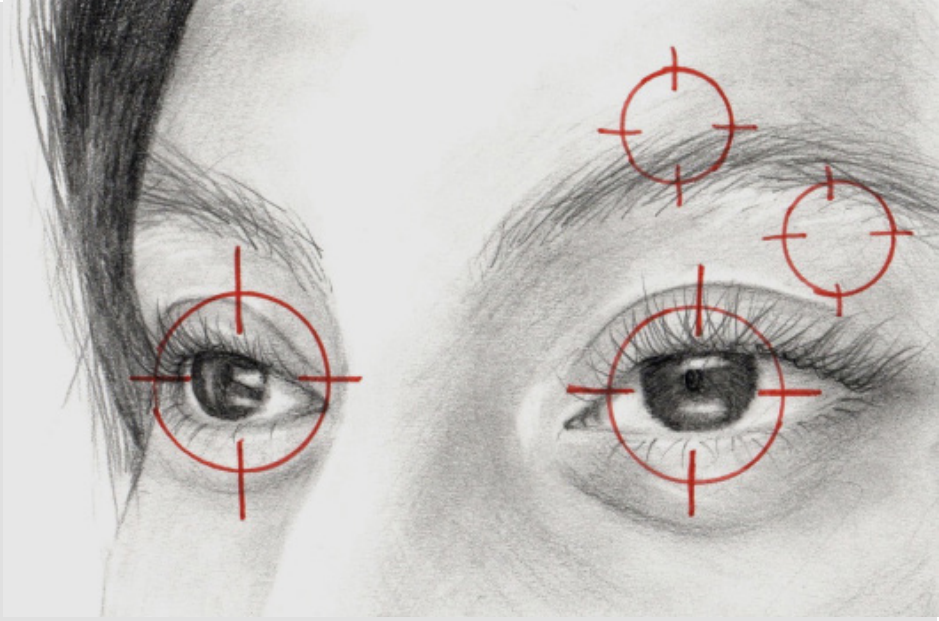
A Note on Eye-tracking and its Research Applications

How your eyes betray your thoughts...

Written by Chrysi Anastasaki
Art by Rosie Jarett



The concept of studying eye movements has been around since the 1800s, when psychologists observed - without advanced technology - how the eyes change position while reading a script or staring at a photo. Today, eye tracking can be used to reveal what people engage with, and what they ignore, during activities that require visual attention. On a daily basis, we spend little time thinking about the position of our eyes, or how many times we blink, but our eye moments can actually give hints about our thoughts to the people who know how to look for them.

The eye is the organ of vision, which responds to the stimulus of light. Eye-tracking technology measures a person's eye movements: where they look, what they see (or do not see), and for how long they gaze at one spot. These eye movements are categorised as either 'saccades' (when the eyes jump quickly from one object to another), 'fixations' (when the eyes stop to rest on an object) or 'smooth pursuit' (when the eyes follow a moving object). By analysing these motions, researchers can gain information about our hidden cognitive processes.

Eye trackers are devices that use a combination of sensory technologies and high-definition cameras to follow and record eye movements. Near-infrared light is projected onto the eye and reflects off the clear outer layer (the cornea). The direction of the reflected light is noted and used by advanced algorithms to calculate the exact position of the eye. This occurs many times per second, so that movements can be captured with high precision. There are various types of eye trackers - screen-based, wearable, webcam - making them versatile tools that can be used in most instances where mental processes are being investigated.

The benefits of eye-tracking technology include the fact that it is safe, affordable, and portable. Furthermore, tests can be carried out on both healthy volunteers and patients, which is not always the case with brain imaging modalities such as functional magnetic resonance imaging (fMRI). On the other hand, it is still a technique that requires laboratory conditions to conduct experiments. This can prohibit observation of the natural behaviour of participants, who might behave differently in a lab setting to the way they would in real life. Another key consideration when using eye tracking is that it cannot explain the reasons behind observations. Therefore, it is worth combining eye tracking with other quantitative and qualitative techniques to maximise its potential for robust and accurate results.

Psychology, neuroscience and other disciplines have endorsed eye tracking in their research. One of the most relevant topics is pupillometry, which measures changes in the pupil diameter. The study of pupil dilation has been connected to factors such as drug use or to cognitive features such as intelligence.

Developmental disorders, such as autism, have been studied with eye tracking - particularly as reduced eye contact is a hallmark of autism. According to a study from 2007, autistic people spend less time looking at the core features of a face such as the nose, mouth and eyes, compared with non-autistic people. This type of study can reveal information about the way autistic people process the world around them, and lead to a better understanding of the disorder.

Another interesting use of eye tracking is in examining human perception of qualities such as beauty. One study measured the perceived beauty of the Great Barrier Reef by asking people to observe pictures of turtles, coral, sand, sea and water contamination and rate their beauty. Eye movements, such as fixations, indicated that subjects spent more time on a beautiful picture, compared to an ugly one. This is useful in a broad range of applications, from social psychology to advertising and marketing.

Recently, eye tracking has been used to examine how people ingest actual news, as opposed to fake news. A team of researchers altered news articles by adding false words into the original headlines. The study participants were found to spend less time looking at the fake headlines compared to the real articles. The results were then used to build an algorithm to predict whether a news headline was fake or not, based on an observer's eye movements. This suggests that in the future, machine learning could be combined with eye tracking to enhance its capabilities, and even to tackle misinformation.

It is clear that eye tracking is a useful tool, with a relatively simple principle: the movement of the eyes can be an indicator of thought and behaviour. So far, this has been used in a wide range of applications ☐ from probing beauty perception and autism to building fact-checking tools. Technological innovation is enhancing eye-tracking capabilities at an astounding rate; it may not be long before its achievements make you doubt your own eyes.

Pandora's problem: Why do we keep reading bad news?

Written by Alexander Hancock
Art by Lia Bote

Given that people are 49% more likely to read an upsetting piece of news compared to an uplifting one, it might be time we start trying to understand our gravitation towards the darker side of life.

Our relationship with the news has often been compared to Pandora's Box, the Greek myth that warns of curiosity and its potential to incite danger. While we plead for uplifting stories to bless our news feed, our exposure to morbid content is unrelenting. That our obsession with the news has grown in the past couple of years is evidenced by its ubiquity: on social media, TV, radio, newspapers or even Alexa's quotidian news coverage. A simple tap of the screen can transport us from the safety of our beds to warzones, crime scenes, and the depths of plastic-ridden oceans. But is our addiction solely rooted in a yearning to be better educated on current affairs, or do we secretly prioritise upsetting news over good news? Can we blame the media for its fixation on tragedies like COVID-19 or are they simply feeding our appetite for them?

Our fascination with the macabre has often been linked to the notion of negativity bias, which suggests that humans are more likely to be affected by a piece of bad news, opposed to a good piece of news. Stories that focus on natural disasters take precedence over stories about environmental sustainability because we respond to negative stimuli more acutely. Psychologist John Cacioppo tested this theory in 1998, when he showed participants photos ranging from 'positive' images (a new car) to 'negative' images (a dead animal). Measuring their behavioural responses, he discovered that upsetting images engendered a far bigger cerebral response, compared to uplifting images. A 2014 study corroborated Cacioppo's theory, measuring higher cognitive activity in the right inferior frontal cortex when volunteers were exposed to negative stimuli. Researchers believe this immediate and intense cognitive response to negative news links to evolutionary adaptive functions, which played a significant role in the survival of our ancestors. Psy-

chologists also discovered that exposure to distressing content stimulated the release of neurotransmitters in the amygdala, which are fundamental in the consolidation of emotional memories. Their research concluded that negative news stories enter our long term-memory more quickly, compared to positive news stories. This may provide an explanation for the philosophical nugget that we learn more from our mistakes than we do our successes.

A more cynical approach suggests humans secretly revel in the misfortunes of others. Reading about the dredging up of an actor's problematic tweets or a politician's failed tax evasion scheme can sometimes provide the boost we need to get through the day. This is what Sigmund Freud discussed in relation to the German term Schadenfreude — the happiness we experience from someone else's failure. Freud posited that this phenomenon begins in young children. Babies laugh — according to Freud — because they feel a sense of superiority when witnessing their parents' mishaps. Subsequent studies indicate that our amusement from watching someone fail relates to social comparison theory, which propounds that our sense of self-worth is contingent on how we view ourselves in comparison to other people. This might explain our fascination with vicious celebrity gossip and petty slandering of political rivals.

Perhaps, accepting that we're all guilty of having a morbid curiosity is the hardest pill to swallow. From gruesome gladiator duels to public hangings, even to the popularity of shows like You, our proclivities towards the macabre have spanned centuries. Aristotle famously declared: "we enjoy and admire paintings of objects that would annoy or disgust us". But where does this curiosity come from? In a study published by Psychological Science, researchers suggested our obsession with morbidity is born from an intrinsic compulsion to eliminate uncertainty. Despite our understanding that finding answers in the unknown may disturb us, our desire to know supersedes these fears.

Yet, an important distinction here lies in the difference between interest and enjoyment. While Freud and Aristotle may have argued that we experience happiness from things that upset us, contemporary researchers — Christopher K. Hsee and Bowen Ruan — purport it is our curiosity that draws us towards the darker aspects of life, not a sense of pleasure. In an experiment with two sets of volunteers, the researchers explained to one group that among a cluster of pens, some would cause an electric shock, but did not specify which ones would produce the jolt. With the second group, they identified the exact pens that would cause a shock and the ones that wouldn't. The first group clicked more pens compared to the second group.

Contemporary scholars have argued that our unyielding fixation on COVID-19, including daily updates on global figures and stories about overwhelmed hospital staff, epitomises this burning curiosity. A report issued by Ofcom revealed UK Internet users spent 26% more time on news sites during lockdown.

If Pandora's Box has been open for centuries, the question isn't so much to do with whether our curiosity is waning, but rather the precarious balancing act that confronts us: are we teetering between being well-informed and being overwhelmed with negativity? Now more than ever, with the relentless output of worrying information and data concerning COVID-19, our mental wellbeing is perhaps at its most vulnerable.

What can your voice say about you?

Now that Zoom has taken away our ability to assess body language, our voices have become the prime agents for detecting one another's emotions.

Written by Anastasiya Kolesnichenko Art by Sophie North

The world as we know it has become digitalitalised. Meetings and classes have moved online, as has the ability to express oneself. Whilst previously, speakers could look their listeners directly in the eyes, walk around the room or even stomp their feet to show their emotions, this is no longer the case online.

So how can we emote in a digital world? Thankfully, back in 2017, Dr. Michael Kraus of Yale University conducted a study addressing this issue. The solution might just surprise you: it is easier to detect someone's emotions when you can hear them, but can't see them.

Kraus asked strangers to discuss difficult work situations over Zoom using either just the microphone or both microphone and video. The results showed that the participants were more empathetic during the voice-only communication.

So if you're trying to communicate something over Zoom, you should probably turn your camera off. The solution sounds easy, but how can we decode emotions from someone's voice?

How do we hear emotions in speech?

The autonomic nervous system is closely linked with the emotion centres in the brain. This connection helps to explain why we can recognise when our loved ones are upset or angry from slight changes in their tone of voice.

When we hear an unfamiliar person talk, we are quick to notice their sex and age. It's not hard for us to determine whether the language spoken is their mother tongue, or where in the country they were brought up. We do this not only by interpreting the words they say but also by how they say it. When we listen, we pay attention to the nonverbal content of the voice; the pitch, the volume, the speed, and the pauses in speech.

In many cases, sounds such as 'woohoo' and 'oops' are enough for us to assess how the person pronouncing them feels. For millions of years, humans have used these wordless vocalisations to communicate feelings that can be understood in seconds. These vocal bursts, the 'oohs', 'aahs' and 'uh-ohs', represent a grand total of 24 emotions, according to a 2019 American Psychologist study.

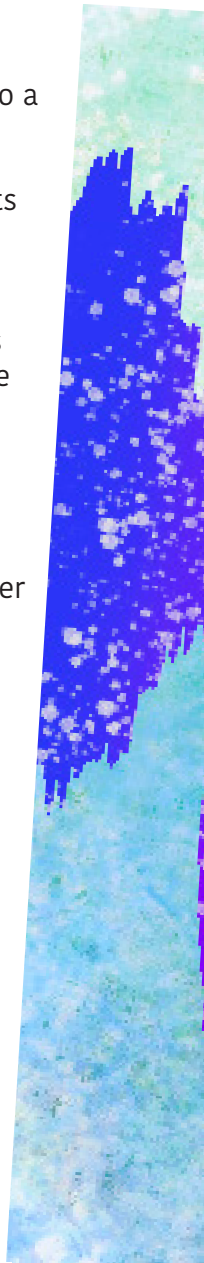
How do our brains react to voices?

In 2017, researchers at the University of Geneva mapped the brain regions involved in interpreting emotions that are communicated orally. They found that the frontal lobes play a critical role, classifying and discriminating between emotions to facilitate productive social interaction.

Video calls, however, can be hard on the frontal lobes. In a gallery view, where all participants appear next to each other with their amusing backgrounds and kids walking by, we are forced to focus on so many things at once that we challenge the brain's central vision and can't fully comprehend the speaker. As a result, people report a similar feeling of exhaustion.

Neuropsychology professors still refer to a famous study from UCLA psychology professor Albert Mehrabian when they explain the condition that has earned its own name, 'Zoom fatigue'. The study, published in 1972, concluded that during face-to-face interaction, our brains pay the least attention to what's being said, instead focusing on the tone of voice and body language. This seems to explain the experiences of online users today.

Video calls take away most body movement cues, but because the speaker is still visible, our brains search for facial expressions to understand their emotions. In this scenario, our brains work harder than usual, leading to fatigue. So in your next Zoom call, you could try joining on your phone and focussing solely on audio.



Why is it important to study oral emotion recognition?

Tuka Alhanai studies depression diagnostics in the Computer Science and Artificial Intelligence Laboratory at MIT. To diagnose depression, clinicians ask questions related to past mental illnesses, lifestyle and mood. “Some of us may be better at this than others,” said Alhanai in an interview with Kinesis, “but we might use patterns in the words they use, for example, if someone says they are ‘feeling sad’, or are struggling with everyday activities, or are speaking more slowly than normal”.

Artificial intelligence (AI) systems may be trained to detect these same patterns by analysing thousands of voices of depressed and non-depressed people. Researchers at MIT, including Alhanai, have created a neural network that can be used to spot the signs of depression in human speech.

Alhanai pointed out the critical importance of interpreting emotions from voice in light of the pandemic. “In the current era, where we wear masks, it might be trickier to inspect someone’s facial expressions and so we might be forced to focus more on their voice and the emotional content contained within”.

The role voices play in emotion recognition has been studied since as early as 1972. Today, with masks covering our faces and Zoom calls taking over in-person communication, we have to largely rely on the vocal cues. What can your voice say about you? Your voice can give away as little as your gender and as much as your level of depression.

Edible vaccines and how tobacco might save your life

What's for dinner? Balanced portions of protein, vegetables, carbs, perhaps some vaccine for dessert?

Written by Tara Spasojevic Art by Rachel Kiss

Edible vaccines, pharming, plantibodies, biologics, plant-made pharmaceuticals; in the face of a media storm of agricultural vocabulary, let's get to the root of it. The term 'edible vaccine' was first introduced in the 1990s by Charles Arntzen. His goal was to induce immunity to infectious diseases by simply eating a modified food item, such as rice or potatoes. This idea was ambitious but fanciful, and as is the way of life, it wasn't quite that simple. Arntzen since said that he has "come to regret coining the term" edible vaccine, as it clouds a brilliant idea behind misconceptions.

Vaccines are used to teach the body's immune system to recognise fingerprints, or 'antigens', of disease-causing microbes. When the antigen is artificially introduced in a vaccine, the body mounts a protective retaliation – and it can therefore respond more quickly in case of subsequent infection by the real pathogen.

Traditional vaccines are created using a weakened, inactivated or dead form of the pathogen. Edible vaccines are genetically engineered plants expressing proteins that mimic antigens of pathogens. These plant-based vaccines avoid the risk of infection. They could be a safe, efficient and cost-effective way of producing vaccines, which would be especially beneficial in developing countries.

The first example of an edible vaccine was presented by Hugh Mason in 1992, in collaboration with Arntzen. Mason and his colleagues expressed the surface antigen of the hepatitis B virus in tobacco plants. Prior to this work, the only way to isolate this protein was time-consuming and costly, so a better option was pursued.

The ideal candidates for edible vaccines are plants that can be eaten raw, because cooking can weaken their immunogenic properties. While rice, potatoes, tomatoes, bananas and carrots have been used as model systems, tobacco has proven most effective. The tobacco plant grows quickly and it is relatively easy to induce expression of an antigen gene, leading to an immune response when ingested. The irony of using a plant which usually has more insidious associations as a potential lifesaver is not lost here.

Unfortunately for Arntzen and his dream of immunisation-by-potato, edible vaccines won't actually be in the form of the food on your dinner plate, as it is difficult to control the dose. There is still hope, however, to use plant tissue directly as vaccines, in the form of a freeze-dried powder inside capsules, or other oral administrations. This would still skip the lengthy and expensive purification step, which can account for as much as 90% of production costs of conventional vaccines.

Capsules of freeze-dried, plant-based vaccine. Source: Plant-derived vaccines and antibodies: potential and limitations

Traditional vaccines have multiple limitations. As you might be painfully aware, they are typically given via an injection, which requires trained staff and sometimes several doses. Not to mention, being poked at with a suspiciously large needle is generally not very popular. How many times have you, or someone you know, felt scared or even avoided getting your jabs? Imagine how much better it would be if you could just swallow a pill.

In 2015, more than half of the deaths in developing countries were attributable to infectious diseases that are preventable with proper immunisation. One of the main challenges for immunisation programmes is widespread distribution and administration. To maintain their protective properties, vaccines need to be kept in the so-called 'cold chain' at temperatures as low as -70°C. This is a problem in areas with poor electricity supply. Edible vaccines, with their superior thermostability, could be the solution.

Orally administered edible vaccines have the added advantage of bypassing a key blind spot of conventional vaccines: mucosal immunity. This refers to the immunity generated at mucosal surfaces like the intestinal lining and airways; these large areas are often where pathogens make their grand entrance and interact with our own cells.

One of the main challenges facing edible vaccines is the stigma surrounding genetically modified products. Some people fear that other plants or food crops could become cross-contaminated, although care is taken to keep the 'pharmaceutical' plants separate, particularly during pollination. There is also concern that these genetically modified plants could take over scarce farmland desperately needed for food crops. However, with the infrastructure already in place, it would be easy to scale up vaccine production quickly. A recent study found that

a mere 200 acres of land could provide edible vaccines for all infants worldwide.

In 2014, the drug ZMapp was developed to fight the deadly Ebola outbreak, and has since become the standard treatment for the disease. ZMapp is a 'cocktail' of antibodies produced in a close relative of the tobacco plant, making it a 'plantibody'. Delivering low-cost oral vaccines is still the stuff of dreams, but plant-made pharmaceuticals show promise in being effective against HIV, hepatitis B, and perhaps even COVID-19.

If scientists can refine dose control, delivery, and reduce development of tolerance, plant-based vaccines may start 'cropping' up a lot more, particularly in developing countries. In the words of Professor George Lomonossoff from the John Innes Centre, edible vaccines are combining science with gardening to save lives.

genetically modified products. Some people fear that other plants or food crops could become cross-contaminated, although care is taken to keep the

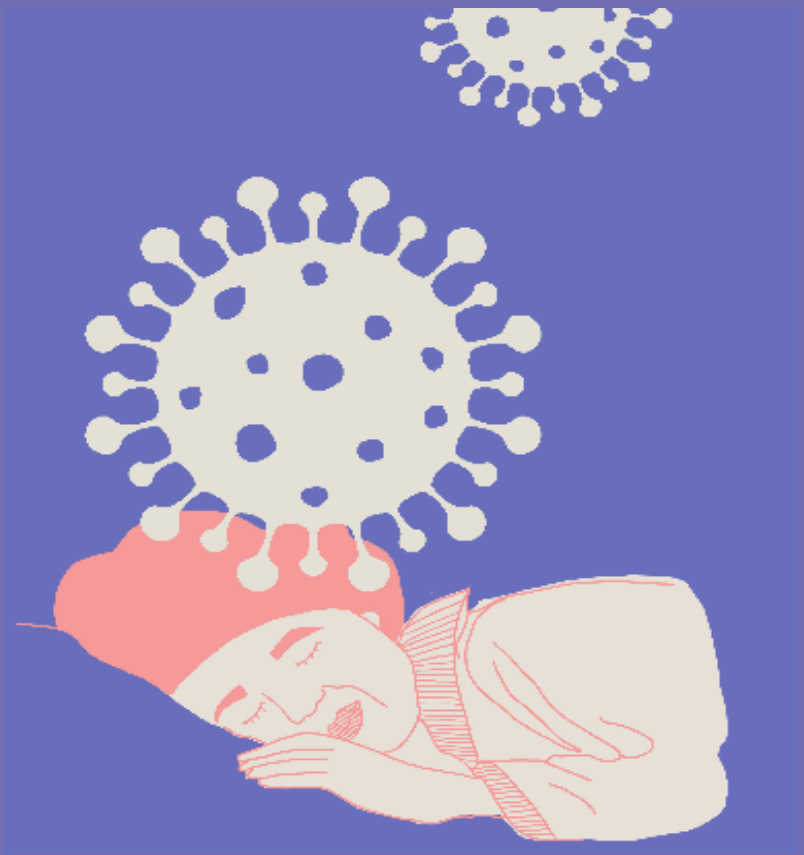
COVID Dreams

Dreaming during a pandemic: how COVID-19 is infiltrating our sleep

Written by Eve Davies Art by Lola Artiles

With COVID-19 an ever-present threat in our lives, the past eight months have been traumatic and anxiety-inducing for many of us. Some have noticed that these daytime stresses have infiltrated their dreams; anxiety has bred weird and wonderful characters who have taken a starring role in the world of their subconscious mind. These nighttime narratives have been becoming more unusual and more memorable, but why? What exactly is the cause of this shift in our sleeping lives?

In April of last year, 62% of people reported a change in their sleeping pattern. With fewer commitments as a result of the enforced inactivity lockdown has brought, many have been getting more sleep than usual. And more sleep means more time to dream.



Dreams typically happen during the rapid eye movement (REM) stage of sleep, and since the periods of REM sleep lengthen over the course of the night, more sleep results in more and longer dreams. Studies also indicate that the periods of REM sleep that occur later in the night are more intense and memorable than those earlier on. Perhaps, therefore, additional sleep is yielding a richer and more plentiful array of dreams.

While this extra REM sleep might explain the increased quantity and memorability of our dreams, the question still arises as to why they are becoming weirder and increasingly in tune with our anxieties. There are two main theories about what the subconscious is doing as we dream: the first is that it is sorting and unravelling a tangled web of emotions, and the second, that it is undergoing preparation for the future.

Sleep specialists from Yale University have suggested that dreams featuring anxieties may provide our brains with space to deal with the difficult emotions associated with the events of our waking lives. als who are infected with the virus or exhibiting symptoms.

Studies show that REM sleep helps people to organise stimuli that have overwhelmed them during the day, allowing important information to be stored. This may include concerns about avoiding individuuals who are infected with the virus or exhibiting symptoms.

Dreaming could also be a way for our brains to prepare us, testing scenarios before we experience them in the daytime. A Harvard study which has been cataloguing recollections of COVID-19-related dreams found that the most common themes related to fears of contracting the virus, anxiety around forgetting masks or other precautions and frustrations over isolation and social distancing. As one researcher said, "nightmares are often reflective of our own effort to avoid threats to our security, our survival, or our physical integrity".

So, what steps can we take if we are currently distressed by our dreams? Scientists suggest that the best way to alleviate these feelings is by talking to others, since sharing dreams stimulates empathy and increases our collective perspective. Talking to friends or finding outlets online are both options. Several online forums have been set up for this very purpose over the last few months. One such forum can be found at lockdown-dreams.com, which was developed by a group of UCL postgraduate students as a part of a study into how "the current pandemic colours the themes, narratives, and imagery that appear in [our dreams]".

If you are currently experiencing bizarre dreams or stressful nightmares, you can take comfort in the fact that your brain is simply doing what it is supposed to do; trying to make sense of difficult emotions and preparing you for the challenges ahead. Chat to a friend or turn to the internet to share your dreams, and you will invariably find that you are not on your own.

More revision, more problems?

Delayed exams: A blessing or a curse for students?

Written by Altay Shaw Art by Louisa Norton

On 12th October 2020, Education Secretary Gavin Williamson announced that most of the A-Level and GCSE exams would be going ahead for the 2021 exam season. The most important update from the press conference was that exams would only be moved back by 3 weeks. Research suggests that 4 in 10 students got little to no contact with their teacher between March and June, and that millions had been left floundering.

So, how is it that students missed an average of 5 months of structured learning, and will have only 3 extra weeks to prepare for exams covering the entire curriculum, despite repeated calls by opposition leaders and teachers?

Psychological impact of the COVID-19 pandemic on students

During the lockdown period, a lot of research was carried out into students' mental well-being. Early results primarily discussed the impact of COVID-19 on students in China and the steps that were taken to tackle mental health concerns. A key recommendation was to encourage children to have as much communication with those around them to stave off prolonged periods of isolation.

The only major pandemic of recent times that can be compared to COVID-19 is the 2009 swine flu outbreak. Over the same period of time, there have been three times as many lab-confirmed COVID-19 cases in the UK as there were cases of swine flu worldwide. During the 2003 SARS epidemic, parents reported a 30% rise in signs of PTSD among children who were forced to quarantine. In addition, the loneliness of self-isolating was stated as the biggest hurdle when trying to address the stigma associated with a positive diagnosis of SARS. Recommendations from this research suggested that further funding was needed to educate healthcare professionals on the early signs of anxiety.

It is also important to clarify students' concerns within the classroom. Before the lockdown, the digital divide between the most and least affluent areas was staggering. The Education Policy Institute estimated the difference in class time experienced by rich and poor pupils to be around 18 months by the time both cohorts had completed their GCSE examinations. This sentiment was backed by David Laws, the Executive Chairman, commenting that "this figure seems to have increased since the closure of school" during the first national lockdown. The Government's failure to supply schools with the laptops required to take learning online has confounded issues, especially as schools are required by law to provide remote setting-based teaching for students when necessary.

The divides, coupled with the typical exam stress and anxiety in schools, have only worsened the situation for many students. According to the Office for National Statistics, 41% of parents reported that home-learning was having a negative impact on their children's well-being. With a potential for there to be even more lockdowns in the coming months, the sombreness of working from home is only likely to increase.

Impact on exam results for students

As a result of the pandemic, there was pressure on the Government to change the way in which students were assessed. After calls to use teacher-assessed grades, the Government opted to have an algorithm determine student grades. In a nationwide fiasco, the algorithm overwhelmingly assigned students from private schools their predicted grades, while many students at state schools were downgraded by 1 or 2 grades.

Particularly hard hit were private candidates, as their lack of previous centre-based assessments and formalised education meant that their predictions were entirely ignored. In total, around 42% of grades were downgraded using the government algorithm, leading to mass calls for a review. Following the initial refusal to change the way in which grades were awarded, Williamson announced on 17th August that teachers' predicted grades would be used for both A-Levels and GCSEs, marking a shift in tone.

Due to the shift in grading systems, there was above-average grade inflation for achieved results, most of which would not have been attainable under normal circumstances. Though this may have benefited the 2019-2020 cohort in the short term, it has also unintentionally created a new challenge for those sitting exams in the 2021 exam period. This cohort will be competing with students who received idealised predicted grades, which at times may only be predicted correctly 16% of the time.

The reprieve from exams may have made a good proportion of students feel relaxed. However, it is also important to consider that students moving forward with their careers would not have had a chance to test their knowledge in a controlled environment for up to three years.

Moving forward - An education in a pandemic

With the ongoing pandemic and the lack of clarity in England for the 2021 exam season, it is understandable that students and staff members are on edge. Given the uncertainty over future lockdowns and an unwavering stance on changing exam material, only time will tell how much students have been affected and what their longer-term prospects will look like.

Migraine:
A prevalent condition with no effective treatment in sight

"I've tried every treatment, and none of them work for me!"
The long search for a solution to migraine continues.

Written by Viktorija Vaitkeviciute and Eugenia Wong Art by Cveta Gotovats

Most of us have had a headache and know that merely functioning with a pulsating pain in your head can be a challenge. Now imagine that headache intensifying to the point of feeling nauseous and becoming acutely sensitive to light and noise, for at least 15 days per month – quite debilitating, isn't it?

That was a short description of chronic migraine, an incredibly common disorder that affects not only the person who experiences it but their family too, who must adjust their day-to-day lives around the condition and provide support. It is a genetic neurovascular disorder that affects around 15% of the population, most commonly between the ages of 22 and 55. It is much more prevalent in women, with a 3:1 female to male ratio. It often begins in childhood and the frequency of attacks increases during adulthood. Some migraine headaches start without warning signs (prodromes), while others have a prodromal phase whose symptoms include irritability, fatigue, and increased sensitivity to sound, smell and light. There could also be an induced aura, which is a group of neurological symptoms including visual disturbances (flashing lights, white spots) and sensory disturbances (numbness and tingling) that begin right before the migraine attack.

Despite the prevalence of migraines and the abundance of existing treatments, there is an increasing number of patients who say that they have tried every medication and that none of them have worked. So, why is that?

Current treatments: not a definitive solution

The leading abortive treatments, which stop a migraine episode once it has begun, are anti-inflammatory drugs and triptans. Triptans inhibit the release of neurotransmitters that transmit pain signals to the brain. Anti-inflammatory drugs, such as ibuprofen, inhibit pain development and inflammation. Since triptans are significantly more expensive, they are used when other therapies fail to provide relief from a migraine attack or if the acute migraine is severe.

Despite the abortive drugs' relative success in diminishing the pain, the relief they offer is short-lived. This leads to an endless cycle of pain and further drug consumption. Excessive use of these drugs can even worsen the headache.

"I've tried so many treatments – none of them work"

There are many patients who think that they have exhausted every possible migraine treatment when they see a doctor. In many cases, treatment failure is a result of the patient having an incomplete or incorrect diagnosis. They could be treating the wrong brain disorder or only targeting one of several comorbid conditions that they may have. It is therefore essential to have a complete diagnosis before commencing treatment.

There may also be some specific, unidentified headache triggers. The most common trigger is the overuse of medications. For example, someone who is taking over-the-counter drugs for pain relief that contain caffeine might be unaware that caffeine can also trigger future headaches once the effect of the drugs wears off.

It is also essential that preventive medications are used correctly. Patients are often quick to say that a drug is not effective after just a few days of use, which might not be enough time for it to work. Unfortunately, the misconception that preventative drugs will stop headaches completely is wrong

since migraine is a chronic disease with no cure; a migraine treatment is considered successful if it reduces headache frequency by 50%.

New therapies: a step closer to an effective treatment

Erenumab is one of the newest drugs for migraine prevention. It is an injection that a patient can self-administer every month. Erenumab inhibits CGRP, a migraine-inducing transmitter that mediates pain perception and relaxes blood vessels in the brain. It seems to be effective in patients for whom other treatments have proved unsuccessful. However, this drug only reduces headache frequency and severity rather than ceasing them entirely. It is also incredibly expensive, costing around £5,000 a year, which limits its availability to patients.

Non-invasive neurostimulation is emerging as a safer alternative in the abortive and preventative treatment of migraine compared to conventional pharmacological approaches. This brings significant help for sensitive patient populations such as pregnant women, as well as those who do not respond to treatment or have overused medications. These therapies work by altering the neural activity of pain pathways in the brain.

As migraine is such a common disorder that affects people in their most productive years, there is a pressing need for new and better treatments. Unfortunately, there is no cure in sight that can solve the condition once and for all, but only drugs that provide symptomatic relief. While some new therapeutics seem promising, the cost and side effects often reduce their availability to the general population. Hopefully, increasing migraine research will offer more solutions to this exhausting condition which affects the lives of many families.

“Mrs Bibi, the doctor will see you now...”

**The NHS was designed to provide treatment at the point of need.
So why are BAME communities still struggling to access the care they need?**

Written by Zara Ahmed Art by Cveta Gotovats

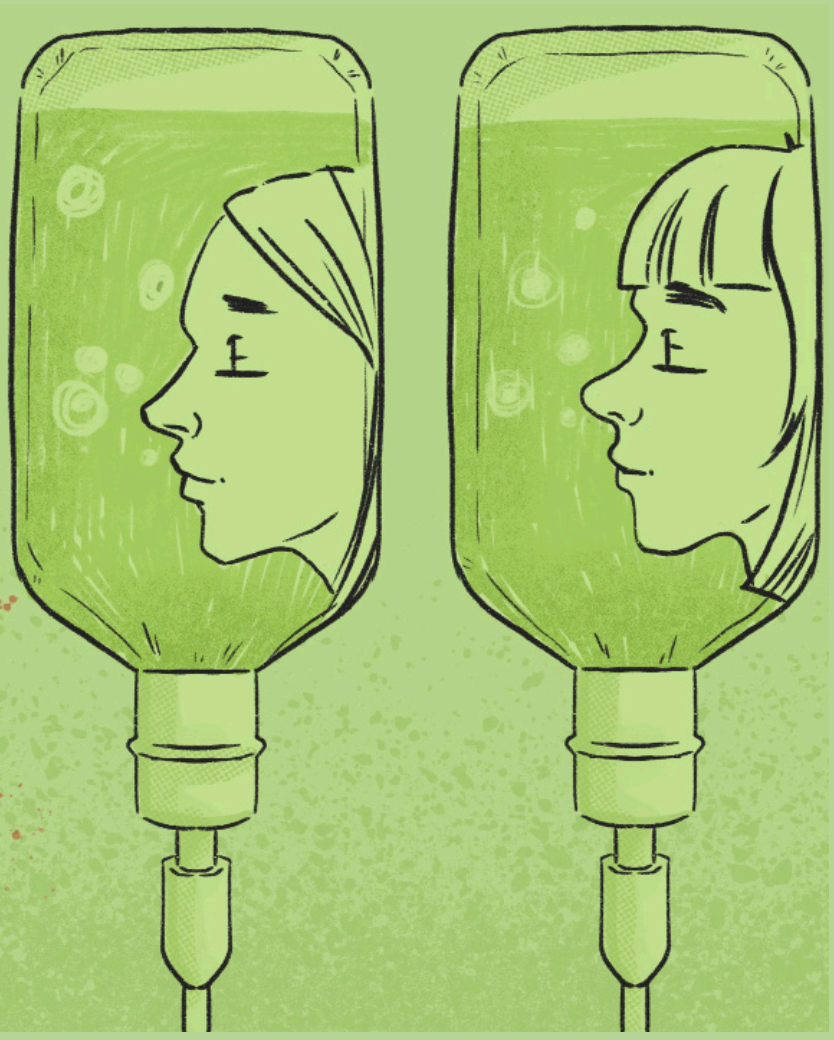
An old, South Asian woman walks into a hospital and starts exaggerating her symptoms. Put this way it sounds like the start of a poor joke. But some doctors would have you believe this is a perfectly plausible situation that goes by the name of Mrs Bibi (or Begum) Syndrome.

This long-standing medical stereotype, derived from Begum and Bibi being common surnames of Pakistani and Bangladeshi women, depicts elderly, ethnic women as ones who dramatise their health complaints. Aside from the obvious racial insensitivities, it serves to alienate other patients from ethnic minorities. They may delay seeking treatment as they believe their conditions will not be taken seriously and to avoid being diagnosed with ‘Bibi-itis’.

Healthcare inequalities are the differences in care received by different groups of patients. Experiences using the NHS, access to treatment and social factors all contribute towards establishing a person’s health status. It is no secret that Black, Asian and minority ethnic (BAME) patients in the UK suffer from poorer health than their White counterparts in many different areas. They are more likely to suffer from underlying health conditions such as high blood pressure and diabetes. South Asian women have a higher risk of suicide and Black women are almost twice as likely to have a stillbirth and five times more likely to die in pregnancy. The idea that doctors and other health professionals

may be widening the gap to healthcare equality with their own bias and microaggressions is even more disconcerting. A study found that Asian dementia patients are 14% less likely to be prescribed anti-dementia drugs than White patients, with researchers suggesting this may be due to “language and cultural barriers”.

Medical education in this country is at the heart of the issue. Although the process of increasing BAME representation in patient case studies, clinical images and textbooks is well under way, the fact remains that generations of doctors were educated in a system that did not represent the population demographics they are now working with. And of course, with medical students shadowing doctors, watching and learning all the time, they may pick up unhelpful



colloquialisms in the clinics. One such example was a doctor who said she first heard the term 'Mrs Bibi' being used as a medical student. Ten years later, as a foundation year doctor, the term was used by her colleague to diagnose a patient who was due to be seen in the Emergency Department. The colleague went as far as to call the patient's surname "the crucial diagnostic clue".

Unwelcome is the thought that this problem may be set to expand further. Despite the perpetual talk of an artificial intelligence (AI) revolution in medicine being on the horizon, it may not be as ready for rollout as we think. These innovations are designed to improve diagnoses, treatment and patient experiences. Yet in 2016, only 19% of patients in AI healthcare trials were of non-European ancestry. If AI is the future of medicine as we are being led to believe, then what confidence can BAME patients have in a system that simply was not designed for their use?

Racial inequality in healthcare has been around for a long time, but fortunately conversation about these disparities at a national scale has certainly increased due to the COVID-19 pandemic. BAME communities were hit disproportionately hard by the virus. Men and women of Black ethnicity, after adjusting for age, have the highest risk of dying from COVID-19. They are four times as likely to die than people of White ethnicity. Furthermore, data released by the Office for National Statistics show that 34% of admissions to intensive care due to the virus were patients of ethnic minorities, despite accounting for only 13% of the population of England and Wales.

BAME patients, particularly the elderly or those with limited English proficiency, on the already-difficult road atra vigilant in trying to navigate the murky waters of healthcare. Everyone should be guaranteed to receive the treatment and advice suitable for their condition, regardless of skin tone, ethnic background or surname.

Opinion on wearing masks against COVID-19

Fighting the pandemic on two fronts: against the virus, and against pseudoscience

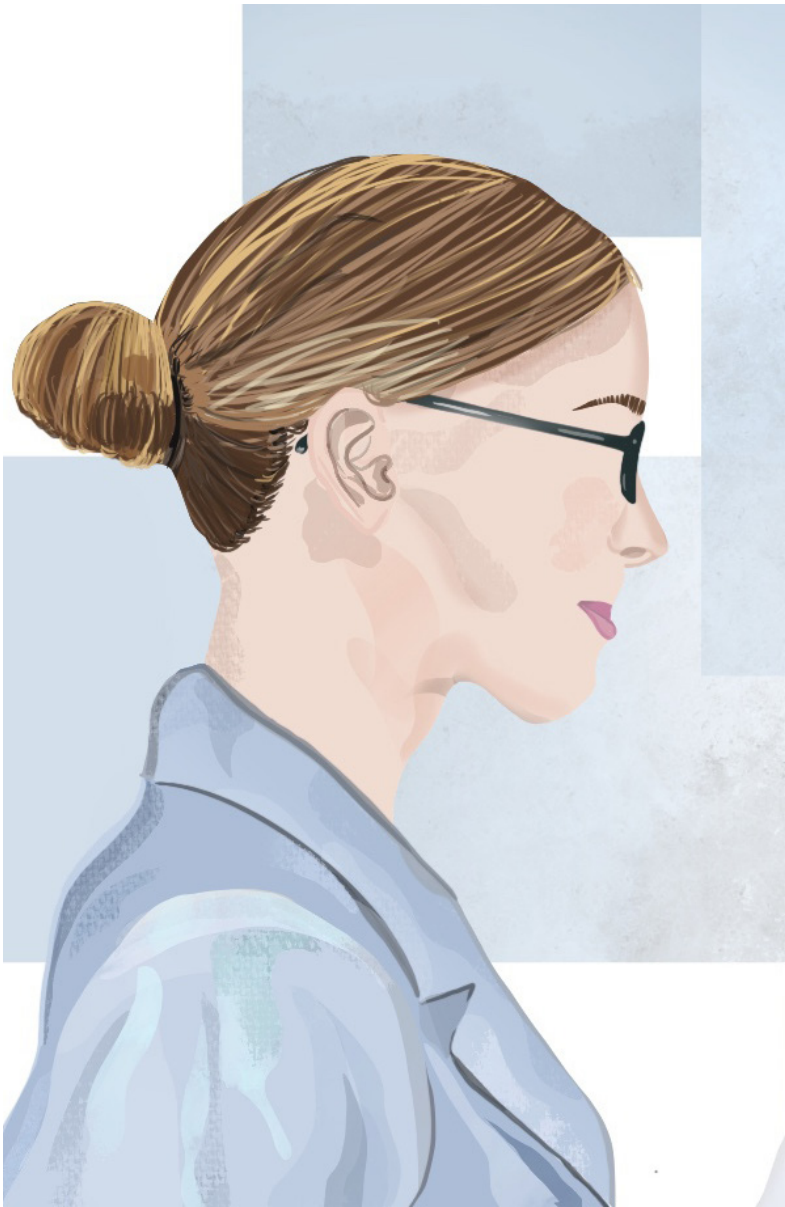
Written by Bence Kover Art by Sophie Maho Chan

The anti-vaccination movement found its little brother in the form of 'anti-maskers', and now stronger than ever, together they are posing a significant threat to public health, evidence-based medicine, and science itself. Ironically, wearing masks is the least economically detrimental non-pharmaceutical intervention, yet it still became the most controversial policy during the coronavirus pandemic. What originally represented a time-tested method for controlling pandemics became politicised; masks are mere symbols of compliance with government guidelines nowadays. However, public health should primarily be a scientific and medical issue, and if we want to act responsibly, we need to rely on scientific evidence when choosing sides in the 'mask debate'.

While SARS-CoV-2, the virus causing COVID-19, can be transmitted via physical contact, it is primarily spread by liquid droplets or aerosols during breathing, talking or coughing. The role of masks is not only to inhibit the inhalation of these viral particles, but also to prevent their emission by an infected individual in the first place. In fact, research shows that while masks are mainly effective in source control, when worn by both the spreader and the receiver, the protective effect is greater. This means that their purpose is not just the protection of the wearer, but mainly the altruistic protection of the community. Historically masks have been shown to be effective against various respiratory viruses, including SARS, MERS, and types of influenza. However, masks are just one of many non-pharmaceutical interventions, including social distancing and frequent hand sanitising, and their success partly relies on public compliance with other public health guidelines.

Masks are generally grouped into three categories in the media and in the scientific literature, namely N95 respirators, surgical masks, and cloth masks. N95 respirators, by definition, filter out 95% of particles that are above 300 nm in diameter, while surgical masks are slightly less effective. There is established literature on the efficacy of these masks, and also a long history of medical usage. Nonetheless, they have two main problems; they are single-use, so create large amounts of waste, and their supply is finite. Therefore, N95s and surgical masks were mainly recommended for healthcare workers, and the general public has been advised to use cloth masks instead.

Government agencies around the world have mostly provided flawed information regarding cloth mask design for the public. Research shows that using only a single layer of cotton or a loose-



ly-woven material (like a scarf) has no effect with regards to filtering airborne particles. Furthermore, reusing cloth masks, or not properly cleaning them, can plausibly increase the chance of infection, which can be exacerbated by their moisture retention. One article raised concerns about cloth masks shedding microscopic particles, which could potentially aerosolise viruses and cause infections. Currently, there isn't sufficient data to support this hypothesis, and as always, further research is necessary.

That said, evidence shows that a design with proper fit, using multiple layers of hybrid cloth, usually tightly-woven cotton with flannel, chiffon or silk, can replicate the filtration efficiency of surgical masks. This is thought to be because the cotton layer provides a mechanical barrier, while the flannel/chiffon layer acts as an electrostatic shield. Other slightly grotesque solutions include wrapping a nylon stocking around the facemask, or stuffing paper towels between the cloth layers. Irrespective of the exact design, having multiple such cloth masks at hand, and washing them after a single day of use, which can just mean putting them in the laundry, can be a sustainable and safe solution.

Furthermore, mathematical modelling found that considerable public compliance with mask-wearing policy can significantly flatten the curve, even if masks were only moderately effective. Masks are also a useful precautionary measure when it comes to the high number of asymptomatic and presymptomatic individuals, reminding us that it is not enough if only symptomatic people wear masks. Observational studies have shown that mask usage did indeed 'flatten the curve' in some areas, such as Hong Kong, which had lower case numbers than countries with similar population densities and healthcare systems.

While masks are clearly effective when used properly and in conjunction with other non-pharmaceutical measures, there is an emerging fear that they can induce feelings of overconfidence and reduce compliance with social distancing and handwashing guidelines. Unfortunately, there isn't any meaningful research on this topic, but being mindful of these caveats is definitely helpful.

Looking at the evidence, we can conclude that wearing face masks is an effective non-pharmaceutical measure against SARS-CoV-2, however the wearer should be aware of the possible design flaws and psychological caveats. On these grounds, we can dismiss the pseudoscientific claims of the anti-mask movement and advise the general public to wear cloth masks, while N95 respirators and surgical masks should be reserved for healthcare workers and the elderly. With all the uncertainty introduced into our lives by COVID-19, there are very few things we can be confident about, but the protective effect of face masks is definitely one of them.

The importance of primary care for COVID-19 and beyond

Primary care is the crucial but severely overlooked answer to managing public health during this pandemic and beyond.

Written by Lia Bote

The fragility of our healthcare system is one of the many long-standing issues highlighted by the pandemic. At the time of writing, there have been over one million COVID-19 deaths around the world, and much of the virus' pathogenicity is still yet to be understood. Recently, it has been shown that pre-existing conditions can double or triple the risk of fatality, with 94% of COVID-19 deaths in the US occurring in patients with other comorbidities. How, then, can we accurately identify and minimise the risk from these pre-existing conditions? The answer lies in primary care.

Primary care acts as a patient's first point of contact with the health system. It encompasses early diagnosis, direct management of both acute and chronic conditions, disease prevention, and health education. Primary care physicians (PCPs) can also refer their patients to secondary or tertiary care for specialist management.

As such, primary care is vital in ensuring that patients can sustainably manage both their physical and mental health, and remain knowledgeable about how best to do this. Unfortunately, it is also often overlooked. In a study led by Professor Stephen Morris from the Department of Public Health and Primary Care at the University of Cambridge, it was found that areas in England with a greater density of general practitioners (GPs) had significantly better quality of healthcare. Despite this, general practice is still severely underfunded, with GPs providing 90% of patient contact but only receiving 10% of the NHS budget.

The need for comprehensive primary care has become even more important during the pandemic. The World Health Organization stresses the role of primary care in early diagnosis of both COVID-19 and pre-existing conditions that contribute to increased risk. PCPs can also help with differentiating COVID-19 from other respiratory symptoms to reduce hospitalisation burden, and with making sure that people are informed about the virus and proper hygiene measures.

However, COVID-19 policy measures both in the UK and globally place a higher focus on secondary care for patients with more severe symptoms. GP consultations have been reduced by about 30%, and diagnostic tests usually administered by PCPs also fell by over 80% during the first wave of infection in the UK. This may relate to a range of factors: GPs being advised to delay routine referrals so hospitals have more capacity for severe COVID-19 cases, patients being worried about visiting GP clinics, or the availability of alternatives, such as telephone consultations, which may be helpful but not always sufficient.

As a result, the severe consequences of the chronic neglect of primary care are especially evident during the pandemic. The comorbidities that contribute to high fatalities can go undetected and untreated, and many COVID-19 patients do not even visit their doctors, resulting in 30% of COVID-19 fatalities in the UK occurring outside of hospitals. Worryingly, these consequences may not just be felt in the present; the poor control of chronic conditions, the rise in mental illness, and the health impacts of widening socioeconomic disparities are only a few of the pandemic's many long-term consequences.

Rebuilding our primary care system to be more robust in the long term involves intervention at every level. Public policy must align with and recognise the importance of primary care in protecting society, for example with mass vaccination programmes and established supply chains for hospital protective equipment. With successes like the eradication of wild poliovirus in Africa just this year, the value of such measures cannot be ignored. Integration at the community level has been a successful practice in many countries, with community health providers working hand-in-hand with GPs in diagnostics and health promotion. Prevention must also be prioritised: GPs work closely with their patients to assess risk factors in relation to long-term outcomes, the importance of which is clearly underscored by COVID-19. Ultimately, strengthening our primary care system is essential not only in curbing this pandemic, but also in helping to ensure that we are equipped for whatever comes next.

Nobel Prize: Are we on the verge of eradicating hepatitis C?

Three scientists' rocky journey from unknown pathogen to Nobel Prize.

Written by Maja Bronowska Art by Zach Ng

Hepatitis C virus, an agent that currently infects over 70 million people worldwide, remained unidentified until three decades ago. The infection can lead to chronic inflammation of the liver, which may eventually progress to cirrhosis or even liver cancer. In some cases, liver damage is so gradual and surreptitious that patients show no clinical symptoms for years. The Nobel Prize in Physiology or Medicine for 2020 was awarded to three scientists who discovered hepatitis C virus – Harvey J. Alter, Charles M. Rice and Michael Houghton.

Hepatitis infections were first identified at the beginning of the 20th century. They were thought to be accounted for by two strains of the virus: hepatitis A, transmitted via contaminated food and water, and hepatitis B, transmitted by blood. In the 1960s and 70s, advancements were made in the field with the development of diagnostic tests for hepatitis A and B infections and a vaccine for hepatitis B. But many patients presenting clinical symptoms of hepatitis appeared not to be infected with the known strains of the virus, leaving those infections unexplained.

Alter and his team, in the mid-1970s, made a breakthrough when they demonstrated that the cryptic infections were caused by an unidentified infectious agent. Originally, he studied hepatitis cases in blood transfusion recipients, and proved that screening for hepatitis B reduced the risk of the infection. However, even with well-developed screening protocols for hepatitis B in place, many transfusion patients still contracted the infection. Hepatitis A couldn't be responsible as it is not a blood-borne infection. Alter transfused plasma of those patients to chimpanzees, who subsequently developed the disease. This experiment proved that the unexplained cases of hepatitis were caused by an infectious agent, very likely a new hepatitis virus.

In the 1980s, knowing that the infection could be induced in chimpanzees, Houghton and his team isolated DNA fragments from infected chimpanzees' blood, which they anticipated would contain unfamiliar sequences of the new hepatitis virus. They then took sera from hepatitis patients, as they believed it must contain antibodies for the virus. After numerous attempts, they successfully cloned the virus by inserting the viral chimpanzee-derived DNA into a bacterial vector and using human antibodies to screen for the virus. This innovative molecular technique had never been used before to search for a new viral genetic sequence. It pioneered the development of effective blood screening for the presence of the virus.

Nevertheless, whether the hepatitis C virus alone could account for the disease was undetermined. The third scientist, Rice (and his colleagues), put considerable effort into answering this question. They attempted to inject the cloned pathogen into animals and induce the disease, but this was unsuccessful as viral replication was not triggered. The scientists conducted a thorough analysis of viral DNA sequences, in which they discovered that the clones had acquired mutations, making the virus defective. After repairing the mutations, Rice demonstrated that hepatitis C virus alone was capable of inducing the disease in host organisms.

The three lead scientists entered the battle against hepatitis C virus and have made a tremendous contribution towards its decline. Their discoveries facilitated the development of highly sensitive blood tests that to this day make blood transfusion safer by eliminating the risk of post-transfusion hepatitis. Moreover, a better understanding of the pathogen and how it works led to the discovery of antiviral drugs targeting the hepatitis C virus. Since 2011, direct-acting antivirals (DAAs) that cure the infection have been made available. In 2016, 86% of patients who started treatment worldwide received DAAs, with Egypt accounting for 40% of these. In 2017, access to DAAs increased, so more low-income countries joined the programme and many more lives have been saved. Although hepatitis C has been present in society for a long time, the identification of the pathogen has given us a real possibility of eradicating the disease.

The World Health Organization set a goal to eliminate hepatitis C as a major threat to public health by 2030. Further development of drugs and screening programmes are promising, and survival rates are significantly increasing. Although the drugs can cure more than 95% of infected patients, they might not be enough to fully eradicate the virus. Ultimately, we need an effective vaccine – but with the COVID-19 pandemic ongoing, priorities have changed, and hepatitis C virus research has taken a backseat. The virus has now been known for 30 years, yet there is still no vaccine. This Nobel Prize victory brings hope that this will change, as hepatitis C has become a focus of attention once again.

The precision medicine promise: A feasible future?

How far are we from the vision of precision medicine that is so commonly presented to us?

Written by Sumayyah Imran
Art by Zach Ng

For the past few years, I have been as captivated by the prospect of precision medicine as the rest of the public and the scientific community. However, upon researching the field I discovered that, as with so many other technologies intended to revolutionise healthcare, there is a significant chasm between the promise of precision medicine and its implementation. So where do we stand? What are the issues, and what does the future hold? Can we still see a future for this approach?

Precision medicine is defined as the adaptation of medical treatment to a patient's lifestyle and genotype. The logic behind it is simple; at present, the 'one size fits all' approach to medical care fails to account for individual variations in genetics and environment. Precision medicine will allow clinicians to match their patients to appropriate treatments on the basis of both clinical factors and molecular biomarkers. This will limit exposure to ineffective and potentially harmful drugs and maximise the time for which patients receive beneficial treatment.

Current applications

Tumour profiling and pharmacogenomics are two avenues that are being explored.

Genetic profiling of tumours focuses on identifying mutations that drive cancer development and can act as potential drug targets. This has created a new buzz in oncology, and since the early 2000s, when trastuzumab was approved for breast cancer expressing HER2 receptors, there has been a race to develop drugs acting on a range of tumour biomarkers.

Pharmacogenomics develops therapies targeted to particular alleles that influence drug uptake, distribution and metabolism. A number of drugs which come with companion diagnostics have been approved by the US Food and Drug Administration (FDA). These are only to be used if patients are genetically compatible with them. For instance, the HIV drug abacavir and the anti-seizure drug carbamazepine are known to cause serious side effects in patients with certain HLA gene variants.

It is clear that precision medicine holds exciting promise for the future. This has been latched onto by the academic community and the public alike, fuelled by media reports and econom-

ic incentives like Barack Obama's $215 million Precision Medicine Initiative. However, the pace of development seems to be outstripping the evidence.

Unreliable evidence

Academic interest in precision therapies for cancer was catalysed by a series of case reports of super-responders to these treatments. However, a systematic review of these reports revealed several shortcomings in the data. It appears that much of the optimistic discourse stems from incomplete evidence which cannot be generalised to the broader population. Furthermore, the few randomised controlled trials which have been conducted into precision cancer therapies have yielded modest results at best and poorer treatment tolerance at worst. These studies demonstrate the need for pragmatism; much of the academic community is jumping the gun before appropriate evidence can be obtained.

Precision pharmacotherapy has three main problems. Firstly, the demand for therapies currently outstrips the available treatments. Secondly, trials target a narrow patient population, which limits drug indications. Finally, there is very little gold-standard testing of the drugs. Considerable amounts of time and funding are required to overcome these issues.

Other barriers to adoption

Practicality and logistics pose the most obvious issue. Precision medicine requires the integration of various streams of data, from blood results to gene profiles, and thus has complex data needs. It is here that artificial intelligence (AI) may play a role. However, this requires high-quality input data, which we don't always have access to.

There are also significant ethical concerns associated with precision medicine. Most research into the discipline is conducted at large academic centres in developed nations, and this does not translate well into rural or resource-deprived settings. Funding and resource barriers, coupled with many clinicians' lack of awareness of the available treatments, will undoubtedly lead to huge inequities in care delivery. The issue of inclusion doesn't end there; the majority of available genetic data has been taken from individuals of Northern European origin and is thus unlikely to account for variants in people of different ethnic groups. Indeed, genetic test results indicating a 'variant of unknown significance' are of greater frequency in ethnic minority women, and this is testament to how under-researched the interests of these patient populations are.

What can be done to make the promises of the past decades a reality?

Firstly, the scientific community must commit itself to collecting evidence through randomised controlled trials just as it would for other therapies. Furthermore, doctors, patients, researchers and funders must all collaborate to allow the smooth implementation of precision medicine into clinical practice. Examples of such collaborations are the IGNITE and CSER2 consortia in the US, which are being funded by the National Human Genome Research Institute (NHGRI).

There will have to be considerable collaboration between stakeholders to allow the aims of precision medicine to be delivered. Even then, it is unlikely that the utopian vision of precision medicine that is so commonly touted will come to fruition; the gaps in our understanding and data processing capabilities place that future somewhat beyond our present reach. However, in small ways precision medicine is becoming one of the tools the clinician has at their disposal, and it is crucial that it is implemented with the aim of improving patient care rather than for the sole benefit of advancing innovation. And finally, as A Cecile JW Janssen writes, the end goal of precision medicine should be whatever the patient desires it to be.

Wolbachia: how the world's most successful insect symbiont is being used to eliminate dengue

A reproductive parasite or humanity's latest public health weapon?

Written by Sophie Maho Chan **Art by Stephanie Chang**

Symbiosis is often presented in a black-and-white manner, categorised into either mutualism (beneficial), commensalism (neutral) or parasitism (harmful). When it comes to bacteria, we are particularly quick to discriminate between friends and foes. We notice no irony as we slather our hands with germ-killing antibiotics and slurp down 'good bacteria'-restoring probiotics. However, in reality, biology is highly contextual. On a spectrum of host-symbiont interactions, a single bacterium can flexibly play the role of mutualist, parasite or even both — nowhere is this better demonstrated than in the bacteria genus Wolbachia.

It would be an understatement to call Wolbachia an evolutionary success. Experts predict they reside in over half of all insect species, making them the most prevalent endosymbiont on Earth. If this does not resonate with you, consider this: it is estimated there are at least two million species and 10 quintillion individual insects (that is 19 zeros) at any given moment.

From nutrient supplementation to antiviral protection, Wolbachia are vital mutualists to some insects. However, a major part of their success lies in their capabilities as reproductive parasites. Dubbed the "master manipulators of invertebrate biology", Wolbachia are notorious for hijacking the reproductive patterns of insect populations in wide-ranging ways. This includes feminising male embryos and selectively killing male progeny. As an extreme example, when an all-female asexual group of wasps was discovered, it turned out that Wolbachia were single-handedly responsible for converting unfertilised eggs that would otherwise harbour males into females; subjected to antibiotics, male populations were restored. The goal of all of this? Ensuring succession. Exclusively inherited down the maternal line, Wolbachia have "evolved many ways of screwing over male hosts to expand its pool of female ones", as described by Ed Yong in his book I Contain Multitudes.

While Wolbachia have long been cast aside as "the bad guys" in evolution, this reputation is changing for the positive. By the late 20th century, scientists had already found that Wolbachia could prevent mosquito eggs from hatching as well as shorten insect lifespan, indicating their potential in disease control. The major breakthrough, however, was in 2008, when Wolbachia were proven to block a range of viruses from growing in Aedes aegypti mosquitoes altogether. Included were chikungunya virus, yellow fever virus, Zika virus and, of most relevance, dengue virus.

The idea of using bacteria to fight a mosquito-transmitted virus seems like a long-winded way to tackle the problem. Nevertheless, desperate times call for desperate measures. Dengue has been on the rise in recent decades, expanding its global reach and amplifying in areas where it was already endemic. In 2019, the World Health Organization recorded 4.2 million cases. Urbanisation, international travel and climate change are all furthering the rise of mosquito-transmitted diseases. With no available cure or treatment, killing A. aegypti mosquitoes has been the only solution — until now.

As A. aegypti mosquitoes do not naturally carry Wolbachia, scientists had to tinker with evolution and forge a new symbiosis in the lab. Working for over a decade, Scott O'Neill and his team discovered a way to artificially infect A. aegypti eggs with a fruit fly-derived strain of Wolbachia. Since infected female mosquitoes pass Wolbachia to their offspring with almost 100% reliability, the bacteria will efficiently spread through wild mosquito populations within a few generations, rendering them virus-free, at least in theory.

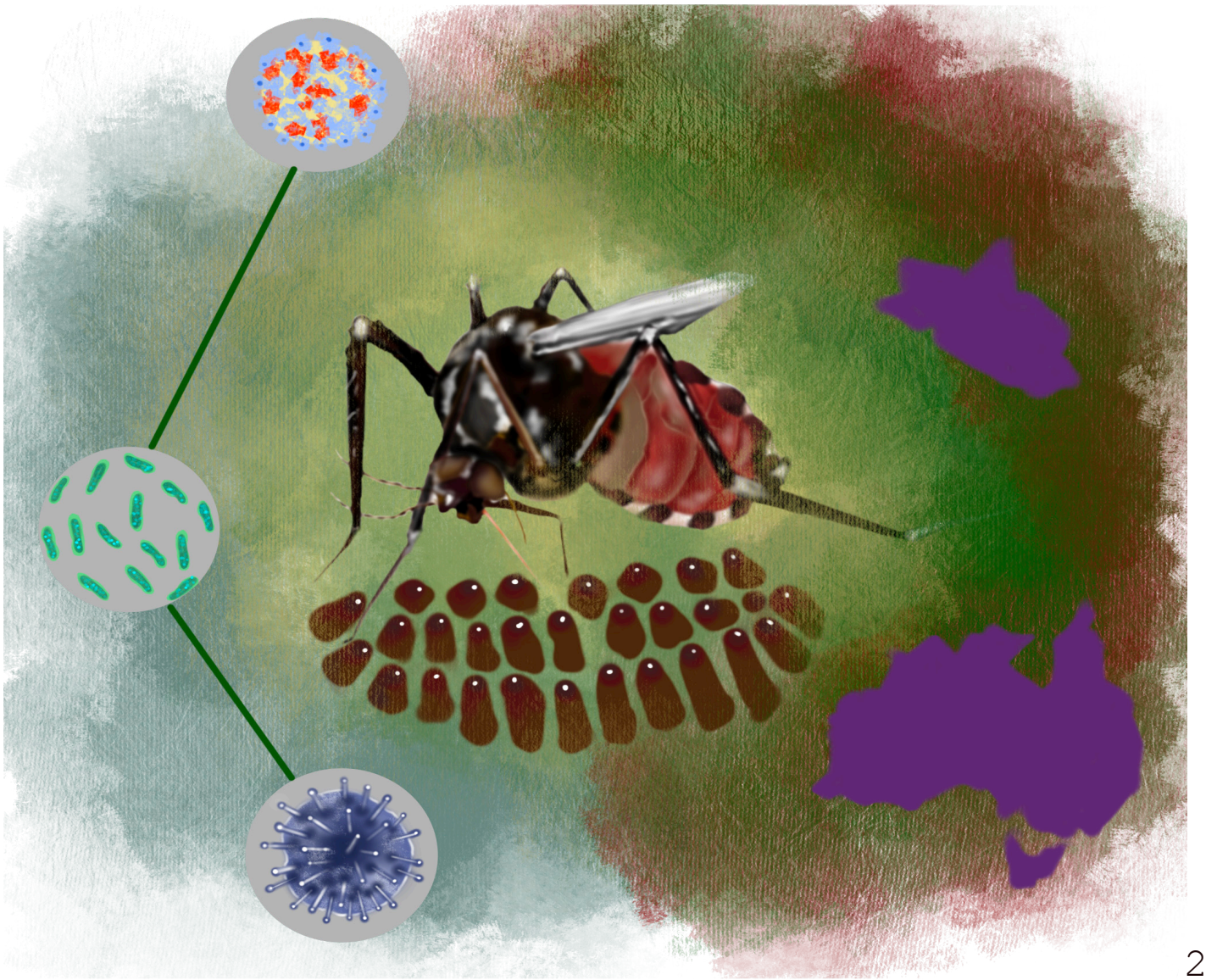
2011 marked the first field trials of introducing Wolbachia-infected mosquitoes in northern Australia. The results were phenomenal. After releasing 10 mosquitoes per house per week for 10 weeks, more than 80% of the wild mosquitoes in the area carried Wolbachia. When further tested

two months later, the local population still all carried Wolbachia and remained 'immune' to dengue. There have been no recorded outbreaks in the region for the last 5 years.

Today, the World Mosquito Program, formerly known as the Eliminate Dengue project and directed by O'Neill, has projects spanning 12 countries. As of December 2019, the programme has successfully colonised areas inhabited by five million people with Wolbachia-loaded mosquitoes. This year saw the first randomised controlled trial conducted in Yogyakarta, Indonesia, where dengue is endemic. Incidence of human infections were found to be 77% lower in regions where Wolbachia-infected mosquitoes were introduced compared to untreated regions.

Risk assessments have confirmed the safety of Wolbachia. Furthermore, they are sustainable and cost-effective in comparison to insecticides which need to be sprayed continuously. Wolbachia also has various mechanisms through which it blocks viral replication, making it difficult for viruses to develop resistance. Nonetheless, experts warn that viral resistance is bound to develop and that we must also prepare for A. aegypti evolving resistance against Wolbachia.

The next step is to expand efforts to other mosquito-transmitted viruses. Ongoing projects in Brazil, previously affected by Zika and chikungunya epidemics, seem to confer positive results. However, since these diseases are periodic and unpredictable compared to dengue, producing reliable data from trials is a challenge. Others suggest that Wolbachia can even fight malaria, which is transmitted by a different species of mosquito. While only time will tell of its true efficacy, Wolbachia-infected mosquitoes offer us an exciting, novel approach to tackling diseases, by harnessing our biological understanding of symbiosis.



The CRISPR Chronology

How to turn a mistake, yogurt and a little research into a Nobel Prize

Written by Priyanka Peres **Art by Patrick Marenda**

1987, Osaka University: Yoshizumi Ishino's team accidentally cloned an unusual repetitive sequence of DNA while investigating E. coli bacteria – and it baffled them. When reporting their findings, they included a short paragraph on the last page of their paper mentioning a confusing repeating section of DNA near the target gene in their experiment. They wrote "So far, no sequence homologous to these has been found elsewhere in procaryotes, and the biological significance of these sequences is not known".

Many years later, scientists would confirm that Ishino's team had serendipitously stumbled upon a CRISPR sequence – a small sequence of bacterial DNA that would go on to launch a gene-editing technology revolution. The ensuing story of the discovery of CRISPR is a tale of meticulous observation of the genetic code, but also of dedication, passion and global collaboration.

Stanford Medicine calls CRISPR "a revolutionary gene-editing tool". It allows scientists to pinpoint specific genes and edit them. It means that, for the first time, the human race is able to not just read and decode but permanently and accurately tinker with the code of life. The system itself is an immune response found in bacteria to prevent viral infections. It contains three fundamental components: the spacer sequence, the Cas protein and the CRISPR sequence.

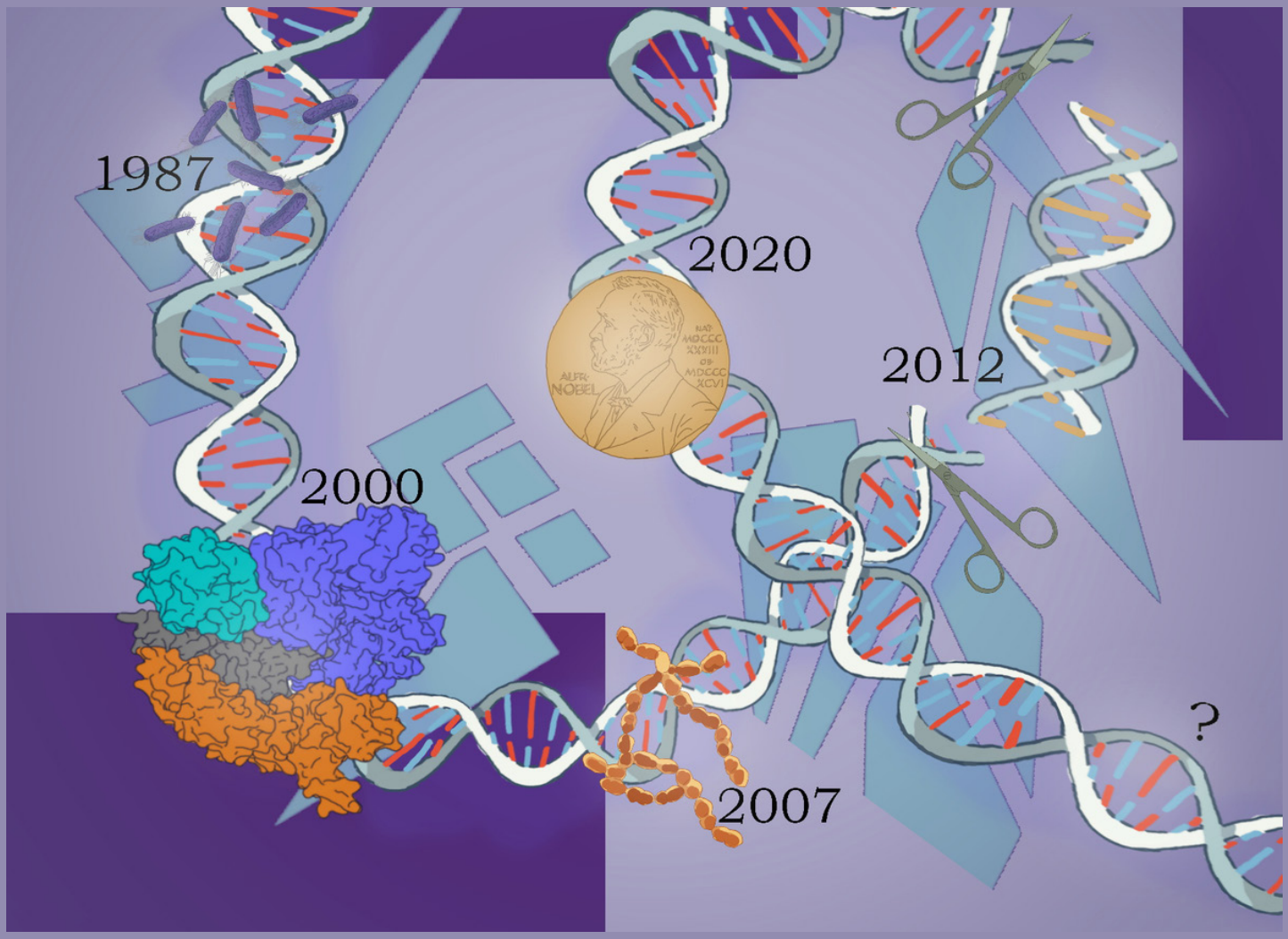
The spacer sequence is a section of a virus genome that is copied and inserted into the bacterial DNA – it helps the CRISPR identify foreign genetic material. Meanwhile, the Cas protein is able to damage or break alien DNA, and the CRISPR sequence codes for a molecule that aligns the components into a single precise killing machine. There are various other components but the discovery of these three were critical in generating an initial understanding of CRISPR systems.

So why was Yoshizumi Ishino so confused by his seemingly simple observation? Repetitive sequences are quite common in DNA. However, the sequences found by Ishino's team were interesting because they were interspaced by non-repetitive sequences (the spacers) that could not be seen elsewhere in the genome. (Hint: it's because they didn't belong to the bacteria E. coli at all).

2000, University of Alicante, Spain: The first real foray into CRISPR research was made over a decade later and halfway across the world. Francisco Mojica and Ruud Jansen coined the term CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) as a unified term for the newly interesting segments. Along with their contemporaries, Mojica and Jansen made some key observations in the next few years that allowed an early picture of CRISPR systems to form. The first of these was identifying the Cas protein sequence in the DNA.

About a year later, teams from Spain, France and the Netherlands observed that the spacer sequences interspersed between CRISPRs do not originate from the organism they are studying, but from viruses. Recounts of the time hail this as a truly head-scratching, but fascinating, addition to the growing body of literature on CRISPR. Additionally, Mojica showed that if a bacterium transcribes a spacer sequence from a virus that infects it, the bacterium is immune to that strain of virus. This information generated much speculation about CRISPR's role as a potential immune system.

After a basic understanding of the components of the CRISPR system was obtained, there was a gap in research. It was hypothesised that all of these components came together to confer immunity, but the exact mechanism remained unknown for a while. This was when an unlikely hero came to save the day – the yogurt industry.



2007, North Carolina State University, US: Danisco, a dairy production company, were looking to protect the bacteria manufacturing their yogurt – Streptococcus thermophilus – from viruses. Through their research with Rodolphe Barrangou, Danisco scientists provided evidence for the role of the CRISPR system as a form of adaptive immunity. From that point on, literature and knowledge in this field continued to grow. However, the team that would go on to put the final pieces of the puzzle together didn't even know each other yet.

2011, US and Sweden: Jennifer Doudna was working at University of California, Berkeley, and Emmanuelle Charpentier, at Umea University, Sweden. Both women were carefully studying CRISPR systems, and slowly reaching similar conclusions on its potential applications. After bumping into each other at a conference, they would go on to join forces – transforming CRISPR from a bacterial immune tool into a gene editing powerhouse. By 2012, Doudna and Charpentier discovered that this natural adaptive immune system could be hijacked. By customising the spacer sequence used to guide the Cas protein, scientists could target virtually any gene in any species with a kind of genetic 'scissors' – which when coupled with additional cellular repair machinery can edit almost any gene.

Doudna and Charpentier would go on to win the 2020 Nobel Prize in Chemistry for their work on CRISPR. Their discovery has altered biological research forever. In its wake, there was an explosion of new research using CRISPR and it has been widely hailed as the technique that will be the basis for the next century of medical and biological research. As it continues to receive recognition for its potential, it is important to remember that CRISPR was discovered through decades of dedicated work, careful observation and international collaboration.

Engage the Phage: A Solution to Antibiotic Resistance?

They've given us restriction enzymes, CRISPR/ Cas9, and now they might just be our answer to antibiotic resistance.

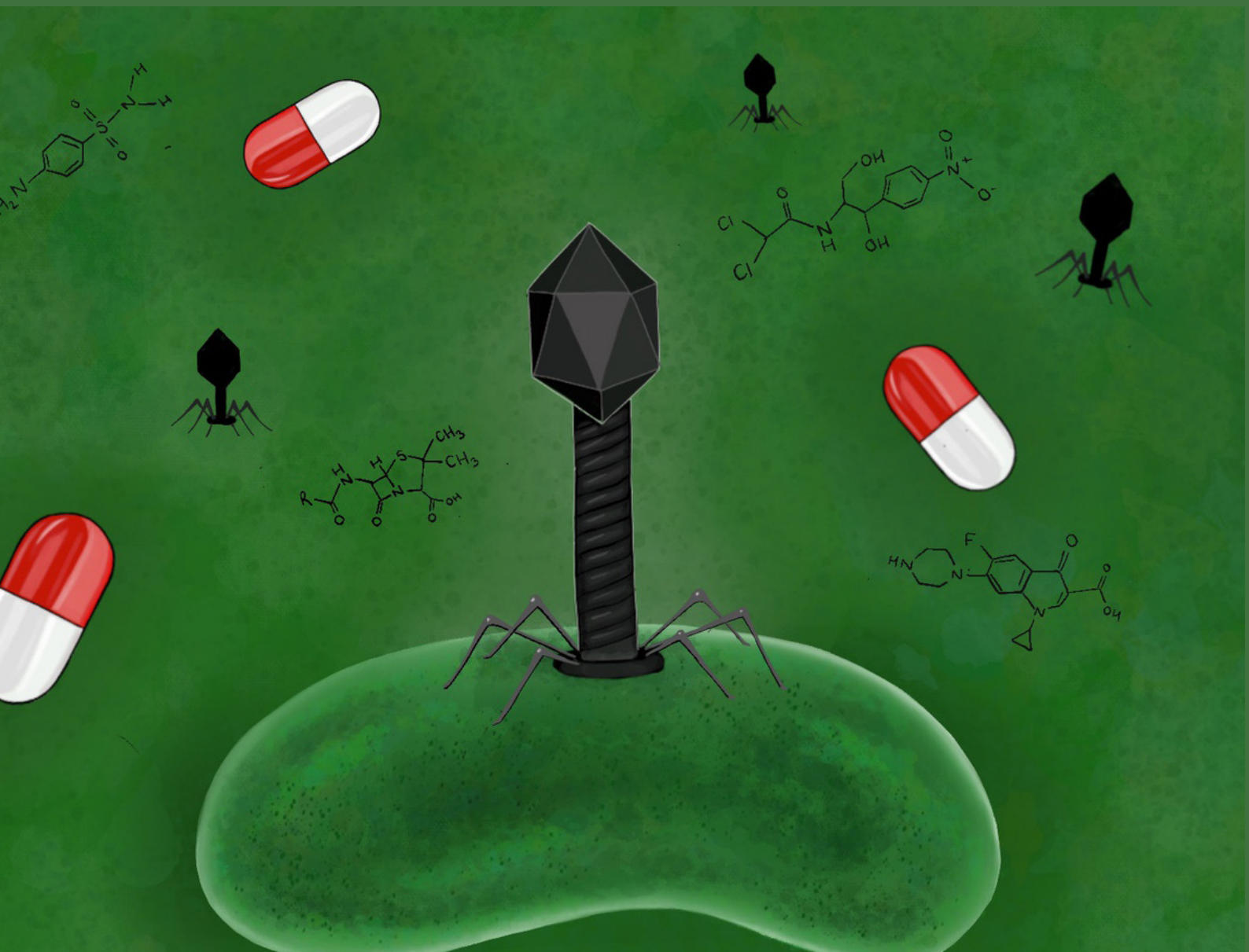
Written by Katie Dale **Art by Kate Morling**

In 2015, doctors found a football-sized cyst in the biliary duct of Tom Patterson, a holiday maker in Egypt who thought he was experiencing a routine bout of food poisoning. But it was far more serious than that. The cyst contained Acinetobacter baumannii, one of the deadliest species of bacteria in the world, due to its extensive resistance to known antibiotics. Tom's infection was resistant to every drug the doctors tested. When it reached his bloodstream, he was put in a medically induced coma, with his family told to prepare for the worst.

As a last resort, Tom was treated with an experimental cocktail of bacteriophages (phages), viruses that specifically infect bacteria, custom-made by scientists to treat his infection. Phages work in similar ways to common human viruses, like HIV and COVID-19. They first interact with a receptor on the surface of the host cell, and once inside they release their genetic material. They then hijack the cellular machinery, using it to make new virus particles. When the host cell can no longer cope, it bursts open, releasing the viral progeny and dying in the process.

Brutal for the bacteria, but the treatment saved Tom's life. Three days after he was given the phage treatment, he awoke from his coma, and the long road to recovery began.

Phages are able to kill antibiotic-resistant bacte-



ria because their mechanism of toxicity is completely different. Antibiotics are small molecule drugs that work by disrupting pathways critical to the survival of bacteria, for example the β-lactam antibiotic penicillin disrupts cell wall synthesis. Bacteria have evolved to evade these effects by producing an enzyme (β-lactamase) that breaks down the drug, actively pumping the drug out of their cytoplasm, or using other less common mechanisms. Antibiotic resistance has developed rapidly because we use tonnes of these drugs in agriculture, to keep our livestock healthy, and in medicine, to keep ourselves healthy, so we have created a strong selection pressure for resistant bacteria. On top of this, bacteria are able to rapidly share resistance genes through horizontal gene transfer, a process where DNA is passed from one bacterium to another.

We have reached a turning point in the past few decades where the pipeline of new antibiotics has dried up, and the number of drug-resistant infections like Tom's is increasing. Just 15 new antibiotics have been put into clinical use in the 21st century, compared to 42 in the 1980s. It's crucial that we find alternative strategies.

Phages offer a promising approach to solving the problem, as it's much harder for bacteria to develop resistance to them. As the most abundant organism on Earth, there are thousands of different types of phage, each recognising a particular species of bacteria. This means that phages can be carefully selected to only kill the pathogenic bacteria causing illness, while leaving our friendly gut bacteria unaffected. It also means that there is likely to be a phage out there for just about any species of bacteria. However, identification of the right phage can be difficult, and isolation from its environmental source can also pose a challenge. Phages are enriched in dirty material such as sewage, requiring a lengthy purification process that is poorly suited to large-scale production.

Researchers are currently developing libraries of characterised phages, as well as cocktails containing multiple types, as resistance can still occur. Bacteria have naturally evolved their own kind of immune system for defence against viral infection, including restriction enzymes and the CRISPR/ Cas9 system, which both function by cutting up the viral genetic material. They can also develop resistance to phages if a spontaneous mutation arises, modifying the receptor that the phage uses to recognise and enter the bacterial cell. This can work in our favour, however, as often it impairs the fitness of the bacterium. For example, one study found that treatment of the potato pathogen Eca with a flagellum-targeting phage caused the emergence of resistant variants with flagellum defects. This resulted in reduced virulence, as the bacteria were less motile and unable to spread to new uninfected areas of potato.

In Tom's case, when the Acinetobacter baumannii infection developed resistance, the fitness cost meant that the infection became sensitive once again to the antibiotic minocycline, which was then added to his treatment regimen. In the clinic, combining antibiotics with phage therapy has been highly successful, as they show a synergistic effect when used together.

So why isn't phage therapy currently being implemented to fight antibiotic-resistant infections across the world? The best results are achieved with personalised cocktails containing different types of phage, but FDA regulations require each phage to go through clinical trials individually before a cocktail can be tested. This has limited pharmaceutical development, as production and testing of personalised therapies represents a substantial investment with little return. Although there have been clinical trials proving the safety of single-agent phage therapy, the future relies on trials that show safety and efficacy of phage cocktails. However, the results from case studies like Tom's suggest we have an ace up our sleeves yet in the fight against antibiotic resistance, we just need to figure out how to play it.

TARDIGRADES: EVOLUTIONARY ADVENTURES AND THE WATER BEAR GLOW UP

Scientists discover another superpower of tardigrades – what does this mean for us?

Written by Elizabeth Jovena Sulistyo

Art by Patrick Marenda

On 10th October 2020, a paper made headlines with the revelation that a species of the tardigrade genus Paramacrobiotus can survive harmful radiation by glowing blue. This discovery, described by Suma and coworkers in the journal Biology Letters, was found while studying the UV radiation tolerance of an unknown species of tardigrade. By lucky chance, the team noticed a tube of them glowing near a UV source, and subsequent experiments revealed that they exhibit a natural fluorescence which acts as a shield to protect them against radiation. Remarkably, during this investigation, the team also managed to transfer the fluorescent extract from this Paramacrobiotus species to both the nematode Caenorhabditis elegans and another tardigrade species Hypsibius exemplaris, protecting them from UV exposure as well.

Fluorescence is the emission of light after temporary absorption of electromagnetic radiation. Despite pervading the animal kingdom – scorpions, parrots, chameleons and frogs can autofluoresce – its functional significance in nature is unknown. Photoprotection against UV radiation is a suspected purpose for a few organisms like comb jellies and corals, with corals demonstrating a strong correlation between fluorescence and susceptibility to bleaching. However, there has been no direct experimental evidence for this in any organism until now.

Tardigrades, also known as water bears or moss piglets, are microscopic, invertebrate animals famous for being nearly indestructible. Discovered in 1773, these tough little creatures are strangely adorable, looking like a cross between a caterpillar and a marshmallow. They form the phylum Tardigrada, which comprises about 1,300 known species split in two major clades, Heterotardigrada and Eutardigrada. Most of them grow to be about 0.5 to 1 mm in length and their eight legs

terminate in either claws or suction discs.

But what makes them so special? Tardigrades can exist in a cryptobiotic or inactive 'tun' state, which is where they are particularly invulnerable and able to endure extremely harsh conditions. This adaptation allows them to survive dehydration in between their periods of activity, when they must be in an aquatic environment. Therefore, as extremophiles, they have been found to occupy an immense range of niches, including marine, freshwater and terrestrial habitats.

Tardigrades only live for 3 to 24 months in their active state, but can have a total lifespan of up to 30 years. For the majority of their existence, they are cryptobiotic; they reversibly suspend their metabolism through anhydrobiosis (desiccation), anoxybiosis (oxygen depletion), chemobiosis (high toxin concentrations), cryobiosis (freezing temperatures) or osmobiosis (excessive salinity). Remarkably, they are the first animals found to be able to survive exposure to the vacuum and radiation of outer space. The tun form curls up, reducing its surface area for evaporation, with lost water replaced by bioprotectants such as trehalose that protect cellular macromolecules and internal organs.

Recently, it was shown that a unique protein called Dsup (damage suppressor) is partly responsible for tardigrades' resilience. This protein binds to nucleosomes and protects chromosomal DNA from reactive hydroxyl radical-mediated cleavage, generated by ionising radiation in water and soil. This is just one of many antioxidant defences that set tardigrades apart.

The incredible resilience of tardigrades has various implications for research. In the medical field, studying the stress mechanisms in tardigrades that protect cells and maintain genome integrity after radiation can advance our understanding of cancer. For instance, the DNA-protecting properties of Dsup would be extremely useful in protecting humans against X-ray-induced damage and extending cell longevity. So far, the transfection of Dsup into human embryonic kidney cells has indeed been shown to increase tolerance to radiotherapy and reduce oxidative stress.

In addition, the protective characteristics of trehalose in cryptobiosis has driven developments in dry-state preservation of cells, bioreagents and organs for both medical and research purposes. As similar defensive compounds are being discovered in tardigrades (TDPs, CAHS proteins), much more progress can be expected, especially for pharmaceutical use, since trehalose can be produced at an industrial scale. From another commercial standpoint, even the fluorescent extract produced by Paramacrobiotus could be a great addition in sunscreen if it can be patented and mass produced.

Moreover, the tardigrade's temperature and radiation tolerance opens up vast prospects for human survival, especially in space. Several programmes, such as TARDIS and Phobos Life Project, have already been launched to study how they react in space, but other possibilities include studying how they react to Martian conditions or travelling cosmic distances via simulations on Earth. In fact, there may already be thousands of tardigrades living on the moon from a spacecraft that crashed in 2019. And who knows? Perhaps, in the far future, we could be living across the universe because of these little water bears.

CRISPR Applications in Medicine

Nature's molecular scissors in the treatment of disease.

Written by Shivaani Iyer **Art by Lucie Gourmet**

'Revolutionary' is a term that has crept its way into modern science and medicine. The birth of scientific revolution as a concept can be traced to philosopher Thomas Kuhn, who put forth his understanding of 'revolutionary science' as an outcome of crisis, through which a discovery emerges almost as a phoenix from the ashes.

Breakthroughs in biology, however, rarely fit the parameters of his definition. Instead, it can be argued that a discovery can only truly be identified as revolutionary when it propagates into a range of different applications. The recent Nobel Prize nomination to Emmanuelle Charpentier and Jennifer Doudna has drawn attention to the trajectory that CRISPR technology has taken into agriculture, transport, and the most striking yet, medicine. And so, we are naturally drawn to the question: what is CRISPR?

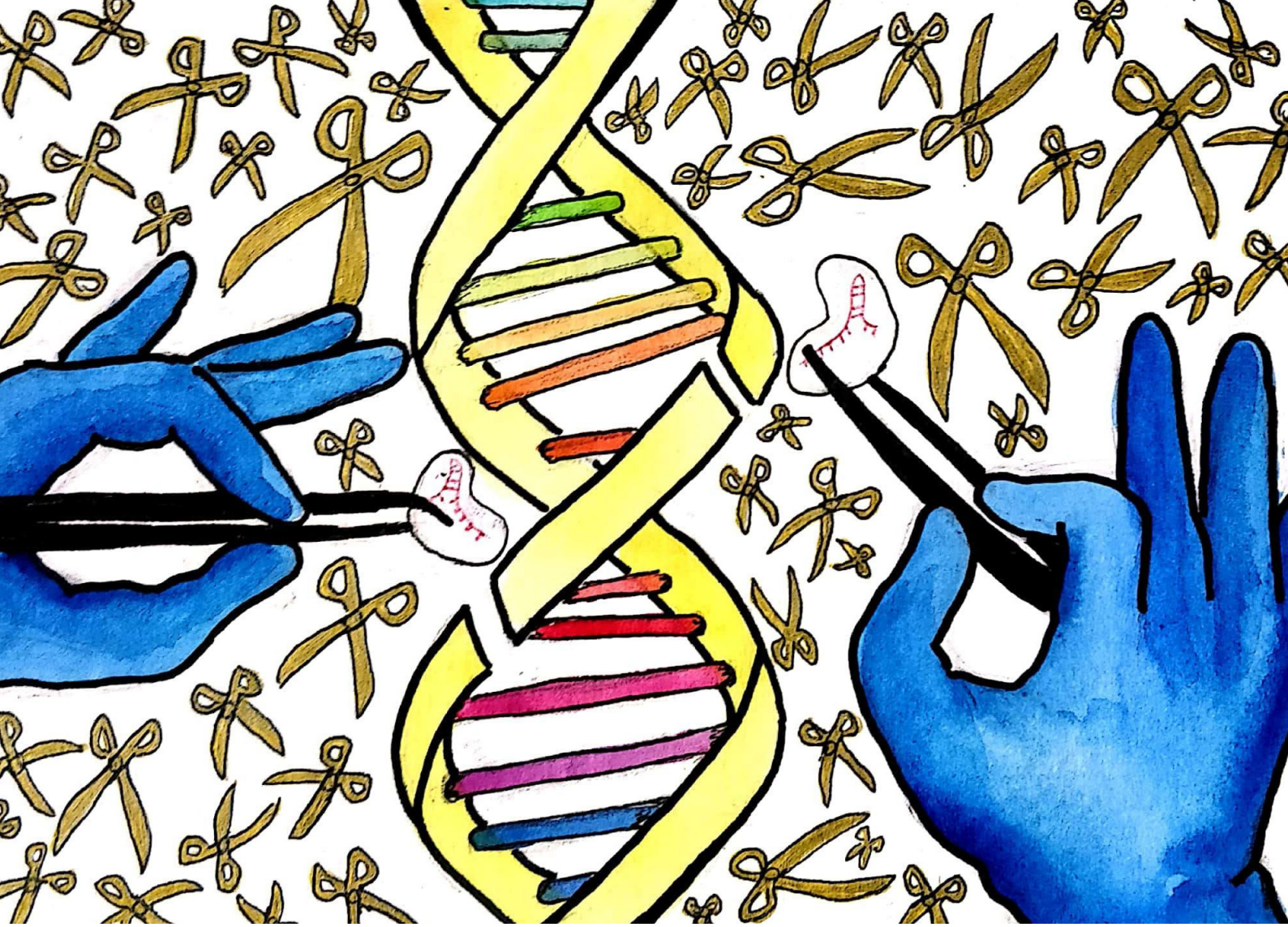
A DNA sequence found in the genome of E. coli shattered the illusion of genome editing as merely a futuristic concept. CRISPR is a bacterial guide RNA (gRNA) component of the prokaryotic adaptive immune system that can recognise viral DNA. When complexed with Cas proteins, it guides the sequence-specific cutting of double stranded DNA to protect against viral infection. In genetic engineering, we can design a gRNA to recognise a specific sequence within the human genome, to direct the Cas nuclease to generate a cut at that site. The cut is then repaired using the cells' own machinery, either via non-homologous end joining, which introduces base deletions or insertions, or by homology-directed repair facilitated by a repair template. The latter pathway is far less error-prone due to the homology, or similarity, required between damaged and repair template sequences. These techniques are the driving force behind the expansion of the CRISPR industry, currently at an annual increase of 24% from $550 million in 2018.

For a genome-editing technology, the most obvious place to start is with potential treatment of genetic diseases. The root problem of hereditary disease lies in the intertwining A, T, G and Cs that form the alphabet of our genetic code. The CRISPR/Cas9 system can facilitate the correction of genetic defects by inducing DNA repair at the desired sequence, thus leading to several therapeutic opportunities.

The treatment of monogenic conditions is currently the most widely explored area of gene therapy with CRISPR. One example can be seen in the treatment of Duchenne muscular dystrophy, a severe condition triggered by the mutation of the X-linked dystrophin gene, causing the degeneration of skeletal muscle. Repair via non-homologous end joining produces an unpaired nucleotide at the point of cleavage, allowing the reframing of the mutated gene. Interestingly, the multinucleate structure of skeletal muscle optimises it for CRISPR editing as studies show that a correction of only 15% of nuclei can completely restore levels of dystrophin.

Another example of a monogenic disease, cystic fibrosis is an autosomal recessive disorder that arises from the mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, resulting in the progressive loss of lung function. Following the successful repair of the CFTR gene in intestinal stem cell organoids, CRISPR research is posed to cure the debilitating disease. Homology-directed repair proves to be an unlikely pathway due to the low division rate of airway epithelial cells, therefore one study investigated the use of the ligase inhibitor enzyme Scr7 in mouse embryos to favour the pathway over non-homologous end joining.

But what about multigenic diseases such as cancer? A recent study employed CRISPR/Cas9-mediated editing of fusion oncogenes, formed from



the joining of two genes, to repress tumour growth and induce genomic deletion exclusively in cancer cells. Researchers have also begun to investigate the deliberate mutation of Cas9 to eliminate its cutting activity in a form called nuclease dead Cas9 (dCas9). dCas9 can be directed to a specific locus, where it binds to its target gene to suppress transcription, and may be used to down-regulate oncogenes.

It goes without saying that scientific revolution of this calibre cannot arise without its complications. In vivo studies use adeno-associated virus to deliver the CRISPR/Cas9 complex to the target cells, but the Cas9 gene must be small enough to fit within the viral capsid. Studies have found use of a smaller Cas9 variant improves the efficiency of delivery to target cells. Off-target gene modification is being battled by experimentation with an alternative form of Cas9 called Cas9 nickase (Cas9n). Cas9n combines two gRNAs for increased accuracy of target site recognition. This, however, is a double-edged sword – the paired gRNAs may prove to be too big to be packaged into a single vector, and the delivery of the complex is once again compromised.

The CRISPR toolbox continues to diversify, reaching new frontiers in diagnostics and treatment. However, it has occurred to many that this is merely the tip of the iceberg. Studies have found that editing of human embryonic cells can result in the loss of a segment or whole chromosome, an exemplification of how germline editing introduces permanent, yet unpredictable effects into future generations. A mere 6 years after Charpentier and Doudna's publication, an uproar surfaced in relation to Chinese scientist He Jiankui's attempt to engineer HIV-resistance in human embryos, which is yet to be confirmed as successful. It will be essential to tread carefully and thoughtfully as we delve deeper into CRISPR-based solutions to disease.
CRISPR. 6 letters.1 revolution. What's next?

Our view of Nature: Humboldts Legacy in Ecology

While climate change makes headlines, the man who shaped our view of nature remains forgotten – it is due time we acknowledge the life and work of Alexander von Humboldt.

Written by Patrick Marendra **Art by Patrick Marenda**

In 1799, Alexander von Humboldt (1769-1859), a German naturalist, arrived in South America. He would spend the next five years travelling thousands of miles to explore, collect and understand the natural world, and change our view of nature up to this day. Though he contributed greatly to biology, he was mostly written out of history and forgotten outside of Germany and Latin America. He represented the epitome of the naturalist, falling out of favour with more specialised modern disciplines. Nevertheless, his view of nature has left traces in society and some contemporary researchers continue his legacy.

His central vision was that everything in nature is interconnected. To show that the water systems from the Andes to the Amazon rainforest were connected, he sailed through the deep jungles of Venezuela, Colombia and Brazil. While crossing the Llanos, a savannah in Venezuela, he observed the ecosystem evolving around the palm tree (Mauritia flexuosa), identifying it as a keystone species, 170 years before Robert T. Paine coined the term. To illustrate these extensive interconnections, he drew the 'Naturgemälde', translated as 'painting of nature'. This image was Humboldt's first depiction of an interconnected web of life. It documented the different vegetal species and placed them at their respective altitudes on the Chimborazo, a volcano that he climbed in 1802. Through this description of the physical and geographical characteristics that stratified vegetation type both by altitude and latitude, he established ecological biogeography. Furthermore, when coining the term 'ecology', Ernst Haeckel was inspired by Humboldt's work. The original diagram of the Chimborazo still plays a role in documenting global warming.

Humboldt's Naturgemälde of the Chimborazo (Geographical Magazine)

Humboldtian heritage continues in the form of research about interconnections in ecosystems, such as the identification of recurrent elements in food systems and higher-order interactions inside communities. After making a new discovery in South America, he would rigorously compare it to what was known about the natural world in Europe, Asia and Africa, to create a global picture. His ambition was so great that his later work was entitled Cosmos: A Sketch of a Physical Description of the Universe.

On his journey, Humboldt met people ranging from Spanish colonists and indigenous populations to African slaves, leading him to study the interactions between humans and the natural spaces they inhabit. Such investigations continue today with research about the uses of palms in indigenous cultures of South America.

He discovered soon after his arrival the slavemarkets of the Spanish colonies; he was shocked and strongly condemned slavery. Furthermore, around Lake Valencia he saw the environmental consequences of the intensive cultivation of cash crops such as cotton, coffee, sugar and tobacco, exploiting both slaves and the soil whilst leaving deep scars in the landscape. Humboldt was the first to highlight the effects of human-induced land-use and climate change on the natural world. He would continue to oppose slavery and colonialism throughout his life, citing them as the main sources of human misery and the destruction of nature. According to Humboldt, only democracy in an agrarian economy could both promote social progress and preserve nature.

He described the fundamental functions of the forest for the ecosystem and climate, such as water storage, enriching the atmosphere with moisture, soil protection, and atmospheric cooling. Today, the concept of a cooling effect has been revitalised with the suggestion that the recent rise in European temperatures is related to the replacement of broad-leaved trees with managed pine plantations. However, his views on nature introduced some biases into our ecological thinking, such as valuing forests over other biomes in Western societies. Indeed, for Humboldt the emphasis lay upon the climate and soils, leading to the neglect of the role of megafau-

na and especially of fire. In reality, fire can fill the role of the megafauna and is a key actor in the sustainable and healthy survival of multiple biomes. Where megafauna has been replaced by livestock, increased grazing prevents fires from spreading, increasing the number of trees and changing the carbon sink. The replacement of the Humboldtian 'balance of nature' by the term 'flux of nature' accounts for a more complex reality in which disturbances play a central role.

His publications, which have been translated into dozens of languages, combine scientific rigour and a captivating narrative, raw data and vivid imagery in a form that gives birth to curiosity and passion for science. His most important contribution might have been the transformation of the traditional notion of nature as separated from humanity and culture into a holistic and ecological worldview. What's more, many of the global challenges that he identified still exist, amongst others in South America. Besides his invention of the isotherms, the notion of climate zones and the first international scientific network (of geomagnetic observation stations), Humboldt was keen to share his knowledge. He was the mentor of many young scientists and inspired more through his writings, including Charles Darwin, George Perkins Marsh and John Muir. Andrea Wulf's biography has tried to restore Humboldt's memory to its rightful place, as a key contributor to the history of the natural sciences.

CRISPR editing to tackle climate change impacts on agriculture

In a world under pressure from climate change, CRISPR-edited crops could be the future.

Written by Alice Ho Art by Lucie Gourmet

In many science fiction blockbusters, gene editing has been responsible for creating some of our most beloved superheroes and supervillains. But what if we have to use it on plants – and not on humans – to save our planet?

Recently, the 2020 Nobel Prize in Chemistry was awarded to scientists Jennifer Doudna and Emmanuelle Charpentier for their work in developing the revolutionary gene-editing tool CRISPR/Cas9, popularly referred to as CRISPR. The technology has been mired in controversy, with many questioning its possible side effects and potential to propagate eugenic ideals (through genetically engineered 'designer babies', for one).

Nevertheless, CRISPR is also highly promising – scientists can now edit plant genomes with unprecedented precision, creating safer and cheaper products than previous gene modification techniques. Hence, CRISPR is being used in the hope of tackling one of mankind's most pressing issues: climate change.

The United Nations has named climate change "the defining issue of our time". It's not difficult to see why – on top of the 821 million people already undernourished, modelling by the Intergovernmental Panel on Climate Change predicts that a further 1 to 183 million will be at risk of hunger due to climate change. Scientists are thus investigating how CRISPR could provide a solution to food insecurity.

First, we must examine CRISPR's fundamental function. CRISPR/Cas9 has two components: CRISPR and Cas9. In nature, they act together as a 'search and destroy' mechanism that allows bacteria and archaea to defend themselves against intruders. CRISPR, a type of DNA, encodes RNA sequences that 'search' for and pair with complementary DNA of invading viruses and plasmids. Cas9, a protein, then cleaves these foreign sequences, destroying the viral invader.

Scientists manoeuvre these same principles to introduce traits to plants, conferring additional resilience towards climate change. First, they identify the target gene which produces the desired trait, such as drought resistance, and reconstitute it in RNA. This 'guide RNA' is inserted into a cell together with Cas9, where it binds to the target gene and allows Cas9 to cut through both strands of DNA. A new DNA sequence can be introduced at the same site. Finally, the guide RNA and Cas9 are removed. To pass on the new desired trait, the mutant plant can be crossed with a native plant, producing a new strain of improved crops.

Currently, global food security faces several threats. Estimates show that by 2100, around 50% of insects, mostly pests or disease vectors, will shift ranges by about 50%. As the distribution of pests and diseases change, many crops are failing to adapt and are becoming devastated. One such crop is Theobroma cacao, commonly known as the cocoa tree.

Imagine Valentine's Day without chocolate truffles or Christmas without hot chocolate. This could soon become a reality if we are unable to stop the myriad of diseases ravaging cocoa plantations. Thankfully, scientists are looking at CRISPR for a solution. In cacao plant tissue, CRISPR has been used to delete the TcNPR3 gene, which suppresses the plant's immune response against pathogens. While ongoing research is still testing this method in whole plants, it could ideally increase the resistance of cacao to diseases that would have previously wiped out entire farms of fruit. Similar techniques have been used in laboratories to make wine grapes, bananas and papayas more resilient to mildew, fungi, and insect-pests, respectively.

Furthermore, abiotic factors such as rising temperatures and changing precipitation patterns are significant stressors to food crops. By increasing plant tolerance to stressors, CRISPR could be key in helping plants adjust to adverse environmental conditions, so that we can maintain our food supply and continue to enjoy the foods we love.

In addition to making agriculture durable, CRISPR is also being used to make agriculture more sustain-

able. Since 1961, the use of nitrogen fertilisers has increased by about 800%, polluting soils and waterways with nitrogenous waste. As a result, researchers are considering how CRISPR can decrease our dependence on them. Start-ups such as Pivot Bio are engineering microbes that can replace the harmful fertilisers. Other research explores the use of CRISPR to enhance the abilities of nitrogen-fixing bacteria in plants, which convert nitrogen in the soil into a form that plants can process.

To lower greenhouse gas emissions from the agricultural sector, one research team is using CRISPR to develop an improved grass species which makes cows burp less – and thus produce less methane. Over at the Salk Institute, the Harnessing Plants Initiative is taking a different approach. It aims to create 'ideal plants', which can absorb more carbon dioxide from the atmosphere as they grow and release less carbon dioxide when they die. Researchers are manipulating genetic pathways that allow plants to grow bigger and more robust root systems, so that they can store more carbon dioxide in soils.

CRISPR-edited crops are estimated to hit the shelves in about 5 to 10 years, and the possibilities are certainly exciting. However, CRISPR isn't the silver bullet to all climate change-related agricultural issues. More mundane forms of action such as converting to veganism and reducing consumption and waste are equally important in deciding our planet's fate. CRISPR still has a lot of rough edges, including potential side effects, inadequate ethical guidelines, and uncertainties about its effectiveness in practice. Until these are ironed out, we will have to wait before the application of this technology becomes the norm.

THE ARCTIC PRISM: WHERE HISTORY DIFFRACTS

Meditations on Arctic ecology, past and future, in relation to Bathsheba Demuth's Floating Coast and the British Museum's Arctic exhibition.

Written by Sacha Fouquay O'Donnell

Art by Louisa Norton

Memories are passed down, across time, across spaces. We transmit against the backdrop of loss. Yet as much as the second law of thermodynamics tells that order is a momentaneous anomaly within the ever-more disordered universe, scribal overarching civilisations are gazing at the potential of their own hell: biodiversity crashing, temperatures soaring, migrants fleeing: chaos multiplies, losses certain.

We are betrayed by our unsustainability. In the face of extinction, we must look at our environment and our relationship within historical and spatial contexts. Circumpolar cultures have, too, faced many losses. Although weakened by colonial purges, they still adapt and have done so for 30,000 years. Contemporary Iñupiaq poet Joan Kane tells us how she writes against her culture becoming the province of anthropology. We too should be more active in fighting loss and it is within the burgeoning works on Arctic cultures, histories, and ecologies, that novel environmental ethics and historical geometries are to be reflected upon.

One of these works is Bathsheba Demuth's book Floating Coast: An Environmental History of the Bering Strait. The author asks how "capitalism, and the attempt to escape it through socialism, function when seen not just as human endeavours but ecological ones". Ideologies are viewed not only through sailors' logbooks and indigenous dwellers but also through the eyes of whales, deers, walruses and foxes.

The Arctic is a prism, onto which history diffracts. As Yankees and Soviets struggled, Demuth argues, in subduing the unwelcoming beringian lands that formerly connected Eurasia to America, succeeding equated to a demonstration of the potency and primacy of the respective political ideology. Yet, in this arms-race, misconceptions of the polar world crystallised to illuminate anthropogenic mischieves.

Blind to population cycles and their fine-tuned and clock-like equilibria, socialist and capitalist sought to bend periodical trends and adjust it to teleological visions: the former assigned by Moscow, the latter by demand. What telos? It was material in kind, and in Beringia, besides minerals, it was a morbid body.

The Arctic colonial machine ingested not only whales but walruses, foxes and caribou if not humans. To settle onto barren lands Russian and Americans needed energy; whales became fuels to power the socialist or capitalist endeavour. Caribou, on the other hand, through herding were viewed as a means to civilise and tame 'locals'. To the incomers' eyes, life's value only materialised when dead, a problem still discussed by economists today.

Concurrently, Nature is as irrespectful of demand; fox populations can plummet in a few months. Grey whales on the contrary are long-lived yet both ideologies contracted their population from 50,000 to 3,000 individuals in the 1920s. In Stalin's words, "One death is a tragedy, a million deaths is a statistic". Death counts hide the severity and immorality of these environmental massacres. Horror penetrates our porous cerebrum and as depicted by Bathesba Demuth, at play is our alienation caused by our illusion that a hermetic membrane separates us from the environment.

The rupture of this membrane is harrowing. Thus, as a Soviet whaler wades through the milk and blood of a butchered mother grey whale, he confesses in the logbook "If whales could scream out in pain like people, we would have all gone mad". Yet cetaceans do not scream and nevertheless the cycle was perturbed, the ecosystem faltered, Arctic people died of hunger. Man went mad, indeed.

Today, foreign dominion is less assertive. Yet, two centuries of extraction and interaction has not left the Arctic and its dwellers unspoilt. Indigenous cultures were deemed heretical, 'pre-historic'. Currently, their grounds are marred as climate change turns the permafrost into slush. But a younger generation of Yupik or Sami are speaking loudly, and their voices are being echoed. You might hear these at the British Museum's timely exhibition, Arctic: Culture and Climate.

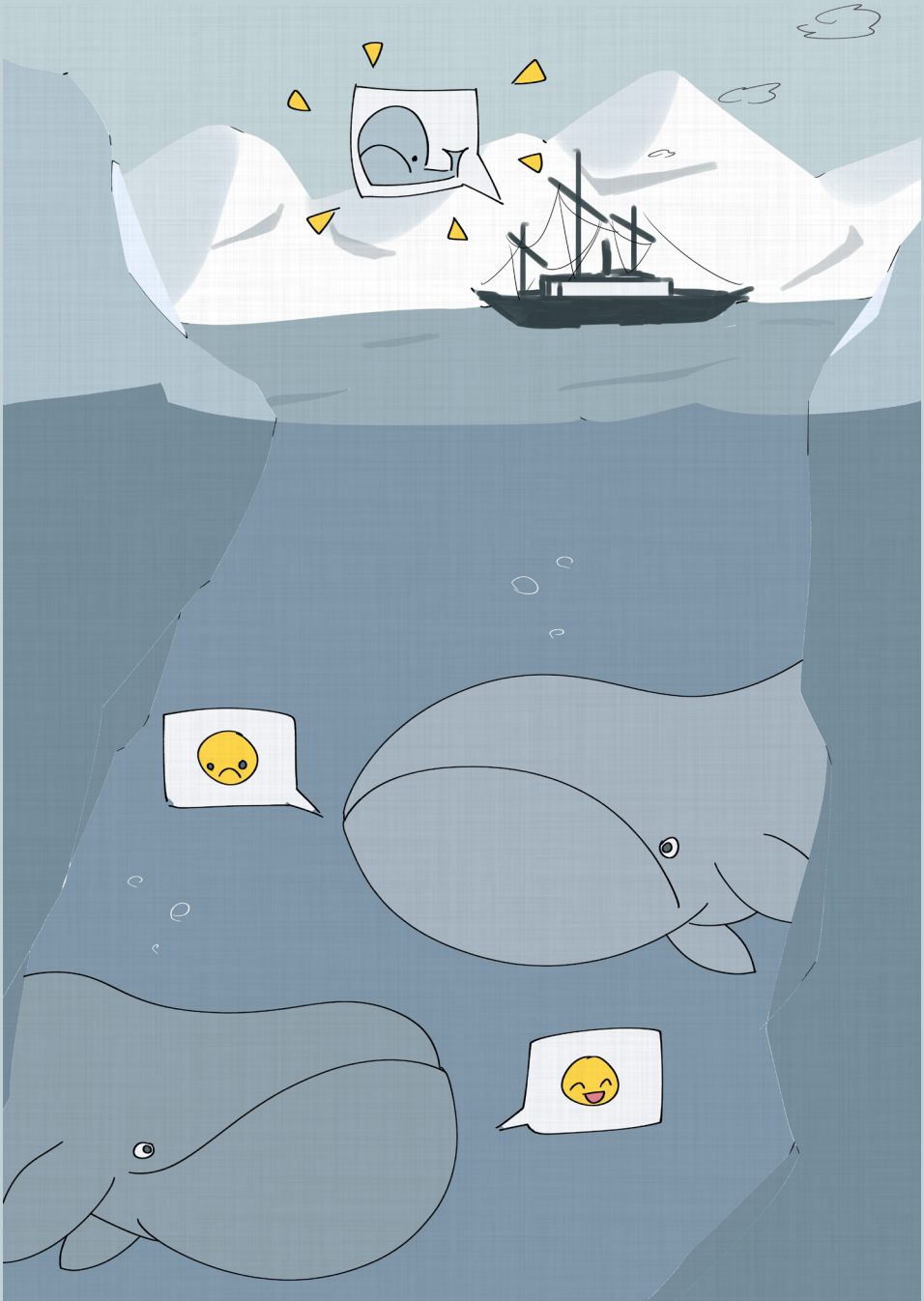
The Native experience occupies a central role

within the museum's display. Their experience and knowledge of the polar world is akin to the Rosetta stone: a translation guide for navigating changing climates. Understanding how Arctic people have survived for more than 30,000 years, coped with many variations and how they fare today on ice-less shores, is vital.

Comprehending Arctic cultures means appreciating animism as a force. Animals, central to Arctic cosmology, are sentient beings – they have agency – and judge whether the hunter is worthy of their flesh. Conversely, the hunter and his family will be as respectful and innovative with the surrendered material if they are to be recompensed by the cycle. Remarkable displays include a seal-gut-skin parka; bags assembled from duck feet; and intricate baskets, by Iñupiaq Marvin Peter, made of baleen, bird quills, and walrus ivory. All these unlikely plush yet practical artefacts originated in leftovers.

The interrelationship between animals and circumpolar culture is that of continuity. Indeed, if respected, organisms are only 'borrowed from an environment to which they will return'. Linear telos is truly foreign therefore, as it does not have any ecological basis. Circular geometries like that of Inuit are exhaustive; they acknowledge man's place in a changing world.

Incidents such as the COVID-19 pandemic have made it clear we are all interlinked, biologically in front of a virus, physically with international transport. The 2020s are said to become less globalised and more virtual. Yet our interconnectedness must not be shunned if we are to fight climate change.



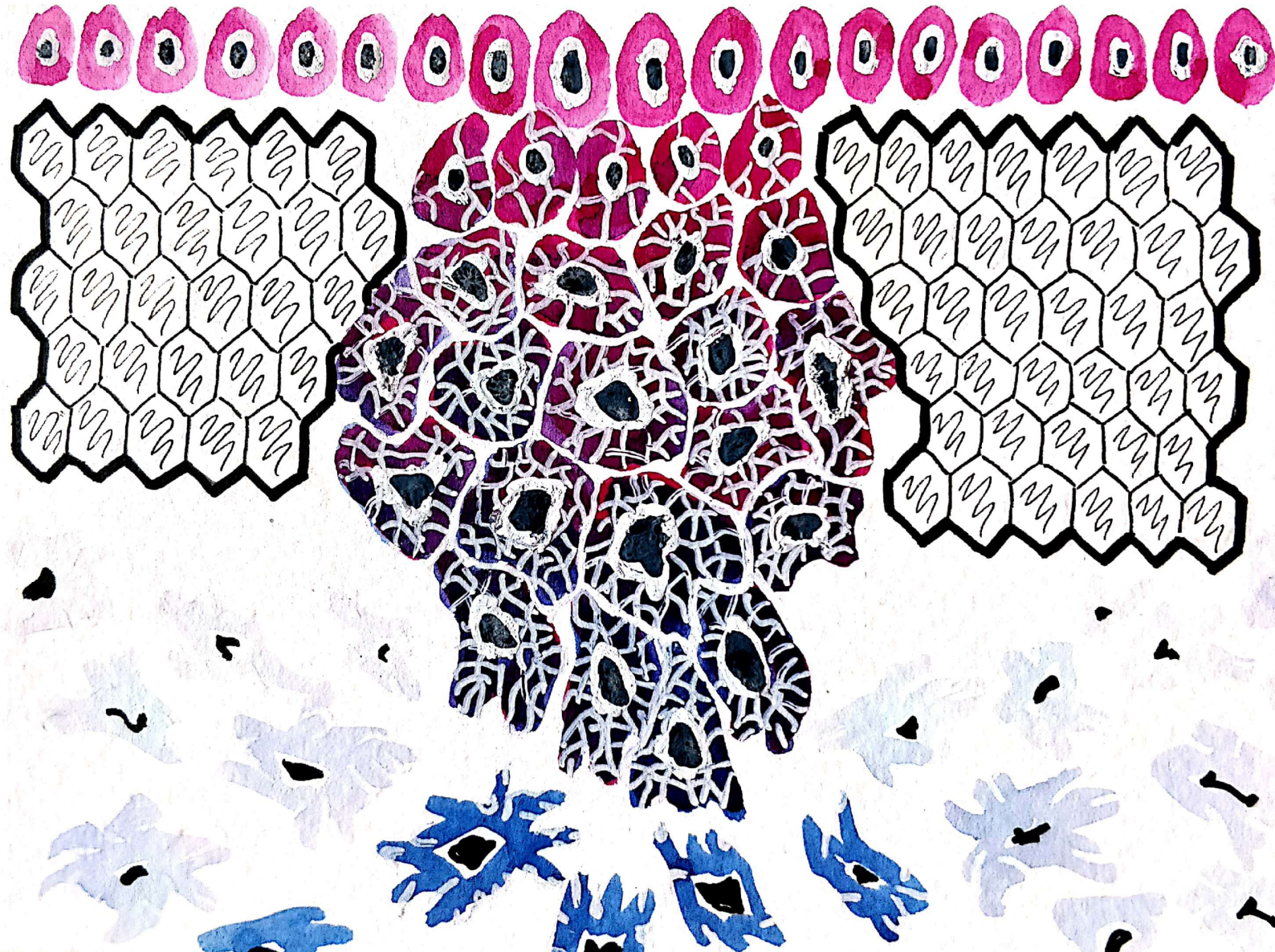
TREATING CANCER IN THE COVID-19 ERA: HOW HAVE THINGS BEEN AFFECTED?

Many of the consequences of SARS-CoV-2 arise not from the virus itself, but

Written by Dan Jacobson Art by Lucie Gourmet

Whilst there are a multitude of ways to measure the world-wide impact of SARS-CoV-2, one of the most telling approaches is to calculate the number of 'excess deaths' during this pandemic. This measure refers to the increase in deaths compared to the same period in previous years. Although many of these can be directly attributed to COVID-19 itself, a significant number are not, and are instead the result of our response to it.

Cancer may end up a key contributor of excess deaths for a variety of reasons, including delayed diagnosis of new cases due to cancelled referrals and limited access to therapy; symptomatic of the enormous stress put on healthcare practices this year. Early diagnosis has always been essential



for combating cancer. A recent review suggested that even a four week delay in treatment can lead to increased mortality across multiple cancer and treatment types.

This early diagnosis has been enabled by a focus on researching early stages of cancer, alongside public encouragement to seek out regular cancer screenings, millions of which may have been missed due to COVID-19. The drive to 'Save The NHS' by not supplying additional burdens undoubtedly prevented individuals from being both treated and diagnosed, with devastating consequences.

In April, researchers at UCL's Institute of Health Informatics used electronic health records to estimate the effects of coronavirus' disruption of cancer treatment. They estimated an additional 18,000 deaths amongst cancer patients, with over 6,000 in newly diagnosed patients over the following 12 months. This was attributed to a combination of late diagnosis, delayed chemotherapy, cancelled operations, and increased risk of COVID-19. According to Public Health England, weekly cancer-associated excess deaths increased by between 10 and 20% during the first month of lockdown.

Following her preprint publication, Dr Alvina Lai, who led the study, stated that "it [is] vital that these [cancer] patients are recognised as being vulnerable and that their care is managed appropriately". During April, Dr Lai also reported a decrease in chemotherapy attendance of 60%, and a 76% decline in urgent referrals by GPs. The question therefore facing medical practitioners is how to treat patients when they are actively discouraged from turning up to medical appointments.

In addition to disruptions in cancer treatment this year, the pandemic has also triggered a paradigm shift regarding healthcare resource allocation, which will have a significant long-term effect on cancer research. Thousands of clinical and drug trials have been paused or scrapped. Millions in cancer research funding have also been lost, or diverted towards coronavirus research, with Cancer Research UK reporting cuts of up to £150 million.

From the beginning, SARS-CoV-2 was aptly described as a 'wicked problem' and, from lockdowns to furloughs, we have become used to talking about our collective response in terms of hindsight. However, cancer-associated excess deaths emphasise the importance of a holistic approach to the pandemic. We know that coronavirus is not disappearing, so the next step is learning to continue with it.

HOW COVID-19 IS DIVIDING SOCIETIES

Once christened as 'The Great Equaliser', the virus is only widening the gap between the rich and the poor.

Written by Pauline Münchenberg

Art by Sophie Maho Chan

Since the first cases were officially reported by the World Health Organisation (WHO) in early January this year, the novel coronavirus disease (COVID-19) has continued to rage across the globe, affecting every country on Earth. Even though it was believed that no matter how wealthy, how well educated or how healthy, COVID-19 would not spare or differentiate between countries and people, the truth is that mainly the poor and weak suffer from the virus. Existing social injustices, inequality and discrimination have worsened since the pandemic began, and the negative consequences experienced by the most vulnerable in society have increased.

The North-South divide describes the global socio-economic and political division between countries. In light of the pandemic, states like India or Brazil have had more difficulties coping with the virus and have struggled with much higher infection and death rates than other, more economically developed, nations. This can be traced back to greater poverty and poorer healthcare systems in low- and middle-income countries. Life often depends on jobs that require close contact with other people and the option to quarantine or practise social distancing is not possible. As developing countries tend to possess cities with greater population density, and multiple generations often live under one roof, the virus spreads more efficiently. Furthermore, poverty goes hand in hand with further restricted financial protections, pre-existing health conditions and poor hygiene, contributing to high

death rates in these countries.

In the favelas in Brazil, for example, access to clean water is limited and areas are overcrowded. Obesity, diabetes and hypertension – increasingly prevalent in countries like India and Mexico – are risk factors for severe illness from COVID-19. This is reflected in the high death and infection rates, with both countries tallying among the ten worst affected nations worldwide. To prevent a catastrophic outbreak of the virus, many developing countries such as Peru or Nigeria have gone into strict lockdowns to limit the strain on weak healthcare systems. However, such drastic restrictions in turn lead to long-lasting economic and educational problems. In Peru, many continue to risk their lives by continuing to work unofficially to feed their families.

However, even in wealthier countries, division in the spread of COVID-19 and its negative consequences between the rich and poor can be found. In the United States, poverty disproportionately affects those from minority ethnic backgrounds or immigrants. In addition to the known circumstances surrounding poverty, for many people remote working is not an option, leading to higher infection rates. As shown by the Centers for Disease Control and Prevention (CDC), ethnic minority groups in the US are significantly more affected by COVID-19. In almost all groups included in the study, case rates were nearly three times higher than in the white population, and hospitalisation rates were around five times higher. In the black population, the death rate was almost double that of the white population. These findings mirror ongoing social injustices, inequality and discrimination in American society.

Additionally, the negative consequences of COVID-19 beyond the disease are far more widespread in disadvantaged communities. Unemployment rates have skyrocketed worldwide, and for many children, severely limited access to online learning materials or home-school resources have led to a significant expansion of social inequality.

Even though everyone has suffered from the pandemic, it is the disadvantaged and ethnic minority communities that have experienced the most negative consequences. It is our obligation to protect the most vulnerable and to face inequalities in our societies, illuminated once again by the pandemic. Despite its many harrowing effects, COVID-19 has provided us with a chance to reassess our priorities, tackle inequality and work on improving life and health standards for everyone.

You Leave More than a Tip at Restaurants

"If you've ever handled a penny, the government's got your DNA. Why do you think they keep them in circulation?" —The Simpsons

Written by Ebani Dhawan

Art by Sophie Maho Chan

When you pay the bill, it seems like the only additional thing you leave behind is a tip. Little do you know that you've left enough genetic material to send off for a 23andMe test. Piecing together the handshakes, the cigarette butts, saliva on the cutlery and more, anyone with the now readily-available technology can identify you.

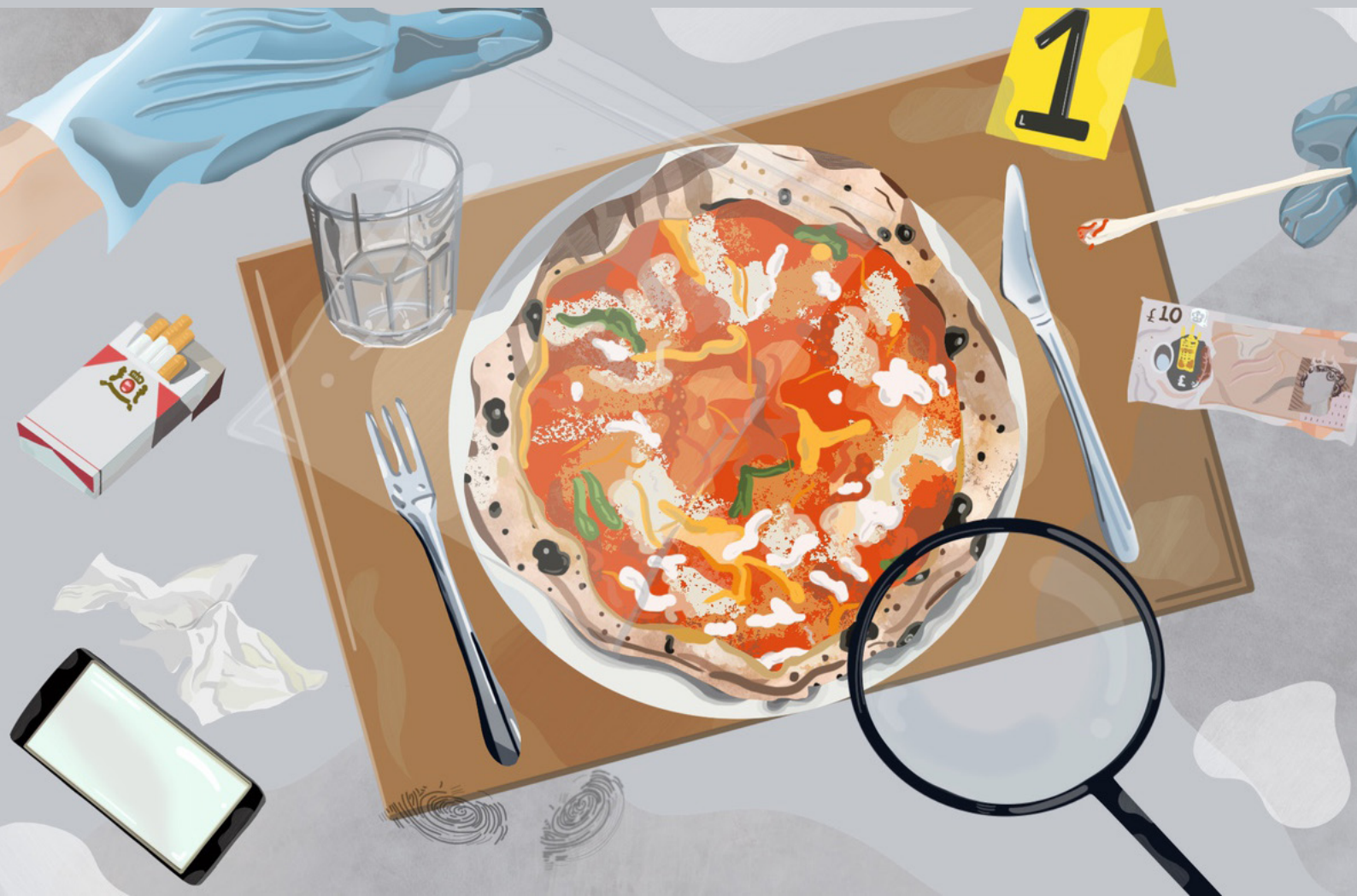
Take the Grim Sleeper case: a southern Californian serial killer who terrorised women from 1985 to 2007. In a pizzeria in Los Angeles, a policeman disguised as a staff member took the utensils, plates, and pizza crusts a customer left behind to a forensics lab. From this 'abandoned' DNA, they identified the customer as Lonnie David Franklin Jr. — the Grim Sleeper.

Thanks to this success and many more, law enforcement agencies look to restaurants and other public places as prime sources for usable genetic material — abandoned DNA. This term refers to any quantity of human material left behind involuntarily or inadvertently that is stable enough for DNA analysis.

Surely this is illegal, you might think.

Non-consensual DNA testing was outlawed in the UK in 2006, whereas the US has failed to pass similar legislation. Previous legal cases have shown some police to "act as passive collectors, waiting for a suspect to discard a smoked cigarette or to spit on the floor". There is no regulation to prevent any law enforcement official from taking advantage of abandoned DNA. In fact, during People v. Ayler in 2004, the judge denied the suppression of incriminating DNA evidence obtained from cigarettes offered to the defendant in a police interview.

This fear of your own DNA betraying you has reached



those at the top of society. It has been said that the Secret Service collects the cutlery and tableware the US President uses when on tour. Even Madonna has a personal sterilisation team, deep-cleaning her dressing rooms to rid them of 'leftovers'.

But, is DNA profiling even accurate?
Heather Dewey-Hagborg's art suggests so. Her 2012 'Stranger Visions' project comprises portrait sculptures from analyses of genetic material collected in public places. With the help of unknowing strangers' abandoned DNA, she shares a glimpse of a future of genetic surveillance, highlighting issues of privacy and bioethics. From just a strand of hair, an entire facial sculpture is created.

So, it makes sense that DNA profiling has always been seen as the infallible forensic technique that would solve crimes. However, what does it really tell us about crime? With its incredibly high rate of transfer, matching DNA samples are not strong enough to prove guilt. In 2012, Lukis Anderson was betrayed by his own DNA as he was convicted for murder. His DNA was found at the crime scene, implicating him immediately. It was considered valid evidence and was used against him in court, but it was only after his public defender detailed his robust alibi that they concluded Anderson was not there.

Despite the inconsistencies in DNA profiling, the current tendency is to elevate genetic data above equally crucial contextual evidence. The first step in collecting genetic evidence is knowing which areas and surfaces to find it. But, current approaches are blighted by inaccuracies, as low-quality DNA is often collected. Next comes extraction. Despite improvements over the years, many tracing kits lose up to 75% of the DNA present found in the sample. Once extracted, the DNA sample is amplified through polymerase chain reaction (PCR) and repetitive sequences called short tandem repeats are analysed. But, this endeavour is often fruitless since contamination is a huge issue.

These nuances of DNA profiling aren't clarified in courtrooms; juries are told that genetic material never lies, which we know is not the case. It is crucial that we view DNA profiles in their context.

The journey of DNA in the legal world has always been a messy one. Until it cleans up, try to make sure to take your genetic leftovers with you.

Three Key Findings from UCL's COVID-19 Social Study

What have we discovered about the psychological and social impacts of lockdown?

Written by Lucy White

Art by Lia Bote

As lockdown was announced across the UK on 23rd March 2020, a UCL study into the effects of the COVID-19 pandemic and social distancing measures on our mental wellbeing was launched.

Currently ongoing, the study is led by UCL's Dr Daisy Fancourt, an associate professor of psychobiology and epidemiology. According to their website, the aims of the study are to track patterns of mental health and loneliness in the UK, pinpoint at-risk groups, and identify activities that support mental wellbeing.

At the time of writing, the questionnaire-based study involved more than 70,000 adults in the UK. The study has been continuously recruiting, so the number of participants in the early stages was significantly smaller.

While it would be impossible to cover in appropriate depth the plethora of statistical information gathered since the study began, here are three key findings from the UCL COVID-19 Social Study.

Anxiety and depression

During the first week following the introduction of the first national lockdown, 22.6% of people showed moderate to severe anxiety and 21.5% showed moderate to severe depression. Although the exact statistics vary depending on the study, these levels are generally accepted to be significantly higher than normal. For example, according to data from the Office for National Statistics, only around 1 in 10 adults showed depressive symptoms before the pandemic (from July 2019 – March 2020).

Although rates remained higher than the generally accepted norm, both anxiety and depression followed a downwards trajectory over the weeks of strict lockdown, suggesting that people were able to adapt reasonably well to the national lockdown and resulting social distancing measures.

Risk factors for higher rates of anxiety and depression were found to include being female, being younger, having a lower income, and living alone or with children. Interestingly, key workers reported similar levels of anxiety and depression when compared to others, with rates being slightly higher only in the first few weeks after the lockdown was introduced.

The study did deliver some cheerier news. People who partook in activities such as exercising, reading, gardening, arts, and spending time with friends and family showed reduced levels of depression and anxiety. This phenomenon is not unique to the COVID-19 pandemic and has been seen in other studies. A common theme in this study's results has been the importance of human interaction, with people living with other adults generally faring better than those living alone.

Public confidence

Confidence in the Government has shifted throughout the pandemic. In England, after a brief rise following the introduction of national lockdown, confidence decreased gradually. It then stabilised in the weeks following the easing of lockdown. The infamous escapades of Dominic Cummings in May – when Boris Johnson's Chief Advisor appeared to break lockdown rules by travelling 425 km while his wife showed COVID-19 symptoms – correlated with a sharp decline. Perhaps unsurprisingly, the number of people who do not have confidence in the Government has increased from 25% to 56% since the study began. The picture is less bleak in Scotland and Wales, where confidence in the devolved governments has been substantially higher since late April.

Similarly, although there had been a gradual decrease in total compliance with social distancing rules since lockdown began, this decrease grew following the reports that one of the most senior government advisors was taking liberties with the rules.

One concern that caused many people anxiety at the beginning of the pandemic was the possibility of losing access to essentials, such as food, water and electricity. After several weeks of memes about

panic-buying toilet paper, confidence in accessing essentials increased following the imposition of lockdown, from 20% in March to 91% in mid-June. This has decreased again since August, to around 85%.

Healthcare

Although UCL's study has not continuously tracked the effects of lockdown on people's access to non-COVID-19-related healthcare, the survey dedicated a week to this issue. 39% of people reported having one or more barriers to accessing healthcare, 26% reported not seeking healthcare when they needed it even if it was available, and 20% didn't contact their GP when they normally would have done. People with a diagnosed mental health condition were almost twice as likely as those without to not report symptoms to a GP when they would have done before.

These statistics highlight an important side effect of social distancing measures. While attempting to mitigate the effects of the virus on people's health and the already overburdened NHS, UCL's study suggests that governments and healthcare providers should be wary of discouraging people from accessing healthcare during the pandemic.

Since March, UCL's study has been critical in tracking the effects of lockdown and social distancing measures on the nation. While the study has noted differences in their findings for many different groups of people – for example, between key workers and non-key workers – their fortnightly reports did not begin stratifying results by ethnicity until week 32. As ethnicity has been identified as a risk factor for COVID-19, this seems like an oversight, although one that is now hopefully being rectified. Nonetheless, the study has provided a wealth of important information about the UK's wellbeing during the pandemic.

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