IF DEPRESSION WERE CANCER

RESEARCH INTO DEPRESSION HAS STRUGGLED, WHILE STUDIES OF CANCER HAVE THRIVED — BUT THE BALANCE COULD BE SHIFTING.

BY HEIDI LEDFORD

If the extent of human suffering were used to decide which diseases deserve the most medical attention, then depression would be near the top of the list. More than 350 million people are affected by depression, making it one of the most common disorders in the world. It is the biggest cause of disability, and as many as two-thirds of those who commit suicide have the condition.

But although depression is common, it is often ignored. Three-quarters of people with depression in the United Kingdom go undiagnosed or untreated — and even if the disorder is diagnosed, today's medications will work well for only about half of those who seek help. "It's unbelievable," says Tom Foley, a psychiatrist at Newcastle University, UK. "If that was the case in cancer care, it would be an absolute scandal."

The comparison between depression and cancer is a common one. Cancer, too, is a terrible blight: it affects more than 32 million people and kills some 8 million a year, many more than depression. But at least in developed countries, the vast majority of people with recognized cancers do receive treatment.

In research, too, depression has failed to keep up with cancer. Cancer research today is a thriving field, unearthing vast catalogues of disease-associated mutations, cranking out genetically targeted therapies and developing sophisticated animal models. Research into depression, meanwhile, seems to have floundered: once-hopeful therapies have failed in clinical trials, genetic studies have come up empty-handed. The field is still struggling to even define the disease — and overcome the stigma associated with it.

Depression research also gets a great deal less funding than that gobbled up by cancer. The US National Institutes of Health pumped about US$5.3 billion into cancer research in 2013 — a stark contrast to the $415 million it spent on depression research and the $2.2 billion on mental-health research as a whole. The same pattern holds elsewhere: in its most recently completed funding scheme, the European Union invested about €54.3 million (US$67.4 million) a year for studies of mental-health disorders, €8 million of which was flagged specifically for depression. The programme allotted €205 million a year for studies of cancer.

No one denies that cancer deserves rich funding and attention, nor do they begrudge the advances made in understanding the disease. Mental-health researchers just wish that they could claim similar advances for their field, and that medical care could offer more.

So why has depression not garnered the same scientific resources and attention as cancer? And had it done so, where would understanding of this disorder stand now? *Nature* put these questions to researchers. Although many said that extra money would have solved some challenges earlier, the technology needed to crack others — by probing the brain and analysing its circuits, for example — is only now emerging. But some scientists hope that a recent explosion of interest in brain studies will at last push mental-health research into a different league. "Cancer's a great inspiration: they've had a lot of investment and they've made big breakthroughs," says Foley. "There's no reason why we can't see the same things in depression."

POWER OF ADVOCACY

Research agendas are rarely set by human need alone. Political, social and economic concerns can all tip the balance in favour of one disease or another — and patient advocates have a major influence on the way that money is handed out. The divide between cancer and depression can be traced back several decades, when strong advocacy helped to spur the United States to declare a 'war on cancer' in 1971. Since then, funding has poured into the field, seeding a huge research enterprise focused on understanding the causes of cancer and finding treatments for it. That war has not

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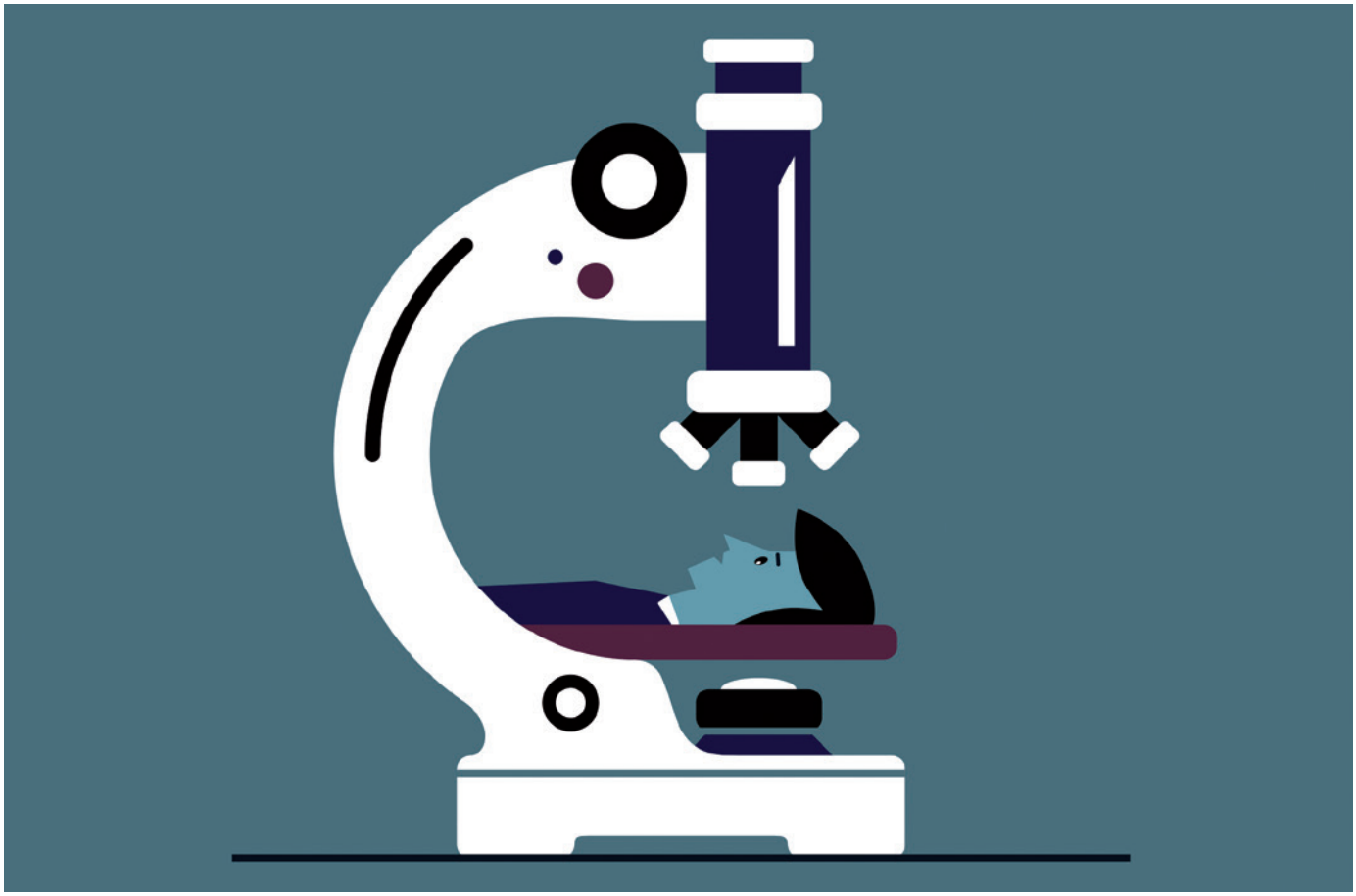

ILLUSTRATION BY DENIS CARRIER

been won — but no world leader ever stood up and declared a war on depression, and that fact is reflected in the more generous funding that cancer still receives. Garen Staglin, co-founder of One Mind, a non-profit organization in Seattle, Washington, that funds mental-health research, estimates that the US public donates about $1 billion a year to support cancer research and patients. Mental-health research typically nets less than one-fifth of that.

Campaigning takes energy and confidence — and the very nature of depression makes it difficult for those with the condition to come forward and campaign for support. But another major factor is the long-standing stigma associated with depression. Many people still do not acknowledge that it is a legitimate condition, says Nelson Freimer, a psychiatric geneticist at the University of California, Los Angeles. "A large proportion of people believe depression is just something that we all feel," he says. "They think you should pull your socks up and get back to work."

Cancer, too, once carried a stigma. "People didn't want to talk about their cancer," says Staglin. "They called it the C-word." That has changed, he says, as treatments improved, advocacy groups raised awareness and more people spoke out about their battles with the disease. It helped, too, that the reality of cancer is easy to grasp: tumours can be seen, monitored and removed. No such certainty exists in depression, where the affected tissue is locked inside the brain, cannot be easily seen and certainly cannot be cut out. A rigorous diagnosis requires a two-hour session with a psychiatrist, and yet two patients diagnosed with major depressive disorder — which is how psychiatrists label depression — can exhibit completely different symptoms. "Even one person can have two depressive episodes and the second time is unrecognizable from the first," says Tim Dalgleish, a clinical psychologist at the MRC Cognition and Brain Sciences Unit in Cambridge, UK.

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All this leaves the concept of depression as a disorder vulnerable to attack. "It's hard for crackpots to say that pancreatic cancer or breast cancer is not real," says Eric Nestler, a psychiatrist and neuroscientist at the Icahn School of Medicine at Mount Sinai in New York City. "Yet somehow they can say that people with mental illness don't have a real illness. It really is awful."

Efforts are under way to change how depression is defined and diagnosed in research. Last year, Thomas Insel, head of the National Institute of Mental Health in Bethesda, Maryland, pushed researchers funded by the institute to eschew classical psychiatric diagnoses, which tend to be indistinct and overlap. Instead, a study might group together patients with specific symptoms, such as anxiety or difficulty with social communication, that are linked to depression as well as to other psychiatric disorders. The hope is that focusing on well-defined traits will reduce some of the experimental noise from artificial diagnostic boundaries, eventually leading to new diagnoses that are grounded in biology. "Ultimately, depression is as biological as cancer and heart disease; it is simply a matter of identifying the relevant molecules," says Nestler. "It just turned out to be a lot harder than any of us thought it would be decades ago."

GENETIC PROMISE

Some researchers hope that genetics will help to define depression and delineate subgroups within the condition. That has been the case in cancer, where in the past few years many countries have poured money into the analysis of genomes from a wide range of cancers. The results are revolutionizing the field: they have generated a huge list of mutations linked to cancers, some of which can now be used to match a patient to a therapy. It is a revolution still in progress, but it has placed cancer at the leading edge of personalized medicine.

Depression studies have not fared as well. The largest study so far — a search through

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the genomes of just over 16,000 patients with major depressive disorder and another 60,000 controls — has turned up just one, as yet unconfirmed, genetic association[1]. Jonathan Flint, a psychiatrist at the University of Oxford, UK, who has been looking for genetic links to depression for nearly two decades, says that some colleagues ask him why he is still working on the problem. "What has held back the entire field is the belief that it's intractable," he says. "What is the point of doing something if you're not going to get anywhere with it?"

The problem stems — yet again — from the disorder's fuzzy definition: grouping everyone with a diagnosis of major depressive disorder into one genetic study is like looking for the genetic risk factors for fever, explains Flint. "You would have lumped together autoimmune disease, infection, cancer and a whole set of different conditions." And it is not clear that more funding a few decades ago would have helped the field to move much faster, he says, because the genomic technologies needed for such studies have become available only in the past ten years. But even since then, cancer studies have far outstripped those for depression. "Surely we can do better," he says. "We have to do better."

Scientists are already doing better in identifying the genes that underlie some other mental-health disorders, such as schizophrenia. Like depression, schizophrenia can be difficult to diagnose accurately, and initial attempts to find genetic risk factors yielded few hits. But an international group of researchers known as the Psychiatric Genomics Consortium worked to ramp up the sample size in the hope of increasing statistical power and helping the signals to rise above the noise. In September, the consortium published an analysis[2] of nearly 40,000 genomes from people with schizophrenia that together highlighted 108 different regions potentially linked to the disorder. The consortium now plans to do the same for depression, aiming to scrutinize up to 60,000 genomes from people with the condition.

ANIMALS ON TRIAL

Results from genetic studies could help depression researchers to clear another major hurdle: the development of better animal models. Scientists studying cancer now have a rich choice of model animals that form a crucial part of their research. These include mice that have been engineered to express cancer-associated genes found in human tumours, and even 'personalized' animal models that have been tailored to study a person's disease by transplanting a piece of their tumour into the mouse. Depression researchers, however, have faced huge challenges in creating mice or other animals that behave in a way that mirrors how people are affected by the disorder (see page 200).

Those who do study depression in animals often use physical stresses to prompt behaviours seen in people with depression. The most common assay is the 'forced swim test', in which mice are plunged into water and timed to see how long they struggle to get out. (Those that give up sooner are taken to have depression-like behaviour.) The assay has been used to screen drug candidates — and many antidepressants on the market do extend the time that a mouse is willing to fight. But it is far from ideal: human depressive episodes are rarely triggered by physical stress, and there are signs that antidepressants act differently in this model compared to humans. In mice, they start to work almost immediately, for example, whereas it can take a month or longer to see an effect in humans.

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In an attempt to mimic what happens in humans more closely, Nestler and his colleagues subject mice to chronic social — rather than physical — stress. In this 'social defeat' model, the researchers place a mouse in a cage with a "bigger, meaner mouse", he says. The bigger mouse starts to beat up the smaller one, and the fighting continues until the researchers separate the mice using a screen. After ten days of fighting, the smaller mouse typically no longer shows interest in pleasurable activities such as sex or drinking sugar water, and avoids social contact, even with litter-mates[3]. This reflects some of the symptoms shown by people with depression. So far, the social defeat model seems to better mimic the action of antidepressants in humans, says neuroscientist Ming-Hu Han, also at the Icahn School of Medicine. Experimental drugs that act quickly in people, for example, also work rapidly to ease responses to social defeat in mice.

Mental-health researchers acknowledge that even the best animal models remain a crude reflection of a complicated human disorder. "To understand human circuitry, it isn't just about whether you will seek out sugar water," says Helen Mayberg, a neurologist at Emory University in Atlanta, Georgia. "There's guilt, there's suicide." It is also difficult to use animals to study the placebo effect, which is particularly prominent in depression studies and complicates clinical trials of potential antidepressants.

Some scientists question whether an animal can ever truly mimic the human condition. "I don't like to say I study depression because I don't think that can be done in animals," says Olivier Berton at the University of Pennsylvania in Philadelphia. "Those representations of disease are hurting the field and we need to forget them." Instead, Berton says that he studies stress responses in mice.

There is one way in which the science of cancer and depression are closely aligned, and that is in the growing appreciation of their complexity. Genetic studies of tumours are showing that they are not just divided into lung, liver and other tissue types, but that each tumour is an intricate mosaic of cells with different mutations and behaviours, and that this mosaic differs from one person to another (see *Nature* **464,** 972–974; 2010).

In depression, an equally complicated picture is beginning to emerge. Researchers always knew that understanding it would be difficult — this is the brain, after all. But as they sort through the thousands of different kinds of neuron in the brain, it is becoming clear that it is important not only to identify the cells, but also to find how they are connected to one another in circuits. Efforts now under way to understand neural circuits may not have happened any earlier, even if depression research had been funded to cancer levels, says Nestler. Picking them apart requires methods that did not exist until recently — for studying single cells, mapping neural connections and activating specific brain circuits. "We lacked some of the basic knowledge and tools of the brain," he says.

CIRCUIT TESTING

Now, with those tools in hand, researchers are deep into dissecting the neural circuits involved in depression and working out how to manipulate them using methods that rely on magnets or electrical current. Such work could point to treatments that go beyond the traditional antidepressant pill, says Noah Philip, a psychiatrist at Brown University in Providence, Rhode Island. "Treating depression isn't as simple as filling up a tank of neurotransmitters," he says. "It's correcting a disorder of different neural networks that are not behaving properly." Mayberg's team, for example, has been testing deep-brain stimulation as a means to relieve depression. Initial studies found a response rate of around 75%, she says, and she hopes to raise that rate using new imaging techniques to guide the surgery.

Nestler and other researchers argue that it would have been premature to declare a war on depression in the 1970s — but that now, with techniques coming online for brain research, could be the right time. "This is still going to take a couple of decades," he says. "But I have complete confidence that it will work."

One of the biggest challenges for the field is to spread that confidence and attract more bright scientists to tackle depression, however thorny the problem may seem. "You don't throw your hands up because it's intractable," says Kelsey Martin, a neuroscientist at the University of California, Los Angeles. "You figure out the best way to find a route into the problem." ■

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1. Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium *et al. Mol. Psychiatry* **18,** 497–511 (2013).
2. Schizophrenia Working Group of the Psychiatric Genomics Consortium. *Nature* **511,** 421–427 (2014).
3. Berton, O. *et al. Science* **311,** 864–868 (2006).

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