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What lies beneath

A focus on specific biological targets rather than constellations of symptoms heralds a more scientific approach to the treatment of neuropsychiatric disorders.

It is difficult to decide which is the more dispiriting statement: that one person in four suffers from a mental-health problem at some point in their lives, or that the sorry state of care for the millions of people affected is often discussed only in the immediate aftermath of the actions of a single mentally ill individual. One can quibble about statistics and diagnostic standards, but the bottom line is that neuropsychiatric disorders account for one of the greatest burdens of disease in the developed world, yet patients are not receiving the help they need.

Part of the problem is that, for many people, the available therapies simply do not work, and that situation is unlikely to improve any time soon. By the early 1990s, the pharmaceutical industry had discovered — mostly through luck — a handful of drug classes that today account for most mental-health prescriptions. Then the pipeline ran dry. On close inspection, it was far from clear how the available drugs worked. Our understanding of mental-health disorders, the firms realized, is insufficient to inform drug development.

With industry pulling out, the burden of developing therapies for mental disorders is increasingly falling on academic researchers. And with its strapped budget, it comes as no surprise that the US National Institute of Mental Health (NIMH) in Bethesda, Maryland, wants to make quick and decisive changes to the way its money is spent.

For several years, the NIMH has been trying to forge a different approach, and late last month institute director Thomas Insel announced that the agency will no longer fund clinical trials that do not attempt to determine a drug or psychotherapy's mechanism of action (see page 288). Without understanding how the brain works, he has long maintained, we cannot hope to know how a therapy works.

According to the NIMH's new grant framework, clinical trials must be designed to yield scientific knowledge as well as to determine whether a therapy works. This will allow researchers to decide quickly whether to proceed with a trial, modify it or end it before too much money is spent on recruiting and testing patients. To receive funding, scientists will have to show how they intend to test whether a therapy targets a particular brain circuit, for instance, or what mechanism a therapy uses to alter a person's behaviour.

The move will certainly ruffle feathers. Insel notes that more than half of the trials that the NIMH currently supports would not receive funding under the new requirements, at least not without modifications. For example, a trial that focuses on changes in attention span as a means of testing a behavioural-intervention therapy in children with a broadly defined disorder such as attention-deficit hyperactivity disorder would not be funded unless researchers could present a controlled way to study how the therapy takes effect. The NIMH would rather see trials that aim to recruit people with a common trait — say, hallucinations — regardless of their specific psychiatric diagnosis, treat them with a drug that acts on a specific brain receptor, and measure changes in brain activity.

The change applies to trials of drugs and behavioural therapies alike: the key is that they are set up in such a way that a single variable can be changed and a single effect seen. An example would be deep brain stimulation (DBS), which has proved an effective treatment for disorders ranging from Parkinson's disease to depression, but whose underlying mechanism is largely unknown. When a major trial of DBS for depression failed last year, scientists were left not knowing whether they had sited the devices wrongly or recruited the wrong group of patients. It is becoming increasingly apparent that the optimal placement of and frequency used by such devices to stimulate neurons may differ from person to person (see page 290).

"Our understanding of mental-health disorders in insufficient to inform drug development."

Critics will argue that the NIMH has exchanged a difficult problem — treating mental illness — for an even more challenging one, understanding the brain. But the institute's new direction on trials may also aid an effort to free research on mental-health disorders from the limits of existing diagnostic categories — an approach for which *Nature* has previously expressed support (see *Nature* **496,** 397–398; 2013).

A project called the Research Domain Criteria, which the NIMH is developing, places patients on a matrix on the basis of both their symptoms and biomarkers such as brain activity. According to the NIMH, more and more grant applicants are using these criteria, although no trials have yet been completed. If this work throws up new targets for possible intervention, industry may once again see psychiatric drugs as a market worth investing in. It is a gamble — and a variety of approaches are still needed — but the potential pay-off is worth it. ■

How to get ahead

The success of the $1,000 genome programme offers lessons for fostering innovation.

Genome technologists are on the verge of fulfilling a goal that was once considered so far off as to be almost fictional: the sequencing of human genomes for US$1,000 apiece. Eleven years ago, when genome sequencing cost tens of millions of dollars, scientists from the US National Human Genome Research Institute (NHGRI) in Bethesda, Maryland, said that, should it be met, the $1,000 goal "would revolutionize biomedical research and clinical practice".

The price of sequencing has indeed dropped — and this development is changing science and beginning to change medicine. In retrospect, it may seem that it was inevitable that the cost would come down from what it was at the close of the Human Genome Project

in 2003. Entrepreneurs and scientists were already working on technologies to replace Sanger sequencing, the workhorse of the genome project. But these entrepreneurs and other genome technologists give at least some of the credit for the precipitous price drop to the NHGRI. In 2003 it launched the $230-million Advanced Sequencing Technology programme, to support research to improve genome technology in academia and industry (see page 294). The programme will give out its final grants this year, but it has provided some key lessons on how to set up similar sponsored innovation efforts.

Set a clear goal. The NHGRI programme — often referred to as the $1,000 genome programme — shares this feature with other successful technological endeavours, including the British government's eighteenth-century Longitude Prize for a practical method to determine a ship's position; NASA's Apollo Moon shot in the 1960s; and even the US Defense Advanced Research Projects Agency's contest to sponsor the creation of self-driving cars, first held in 2004. Stating a tangible goal galvanizes the field, harnessing researchers' collective brainpower to achieve a common aim.

Set the bar high, but not too high. The Archon Genomics X Prize was cancelled last year after only two teams signed up to take on its challenge: the sequencing of 100 complete human genomes in 30 days at unparalleled accuracy and low cost. That test was widely seen as too difficult, dissuading researchers from trying. The NHGRI, by contrast, seems to have set a more reasonable goal; before setting $1,000 as its benchmark, it undertook a broad consultation of scientists in the field.

Spur competition. The 97 groups awarded grants by the NHGRI programme so far are made up of academics and companies working on a diverse range of concepts. Recipients have included a who's who of the sequencing industry past and present, as well as a huge array of people working on speculative ideas. Each grant — ranging from hundreds of thousands of dollars to a few million — is small compared with the amount of funding needed to take an idea all the way to market. But the spreading of money between so many competitors keeps the field lively, and keeps market leaders on their toes.

Foster cooperation. The programme convenes all grant recipients every year for a meeting, where all — including those from industry — are expected to describe their progress. Jeffery Schloss, the amiable head of the programme, deserves much of the credit for coaxing grant recipients to share information, and for promoting an atmosphere of collegiality that has moved the field forward.

"Cheaper sequencing is changing science and beginning to change medicine."

Seed a broad range of ideas. The vast majority of the programme's grants — 75% so far — have gone to academics rather than companies. This has nurtured ideas that are too speculative for industry, ensuring that when the market weeds out less successful companies or throws up a monopoly, there is a nursery of new concepts waiting to keep the field from stagnating.

Be flexible. The NHGRI deserves credit for allowing Schloss to operate the programme differently from most of its schemes. For instance, reviewers were allowed to award small chunks of money to parts of an application that seemed promising, rather than cutting off funding for every project that failed to meet a milestone. This allowed the programme to provide more grants than would otherwise have been possible.

Of course, just incorporating these six elements into a programme does not guarantee success. Entrepreneurs and academic scientists have contributed ideas and drive to genomics advances, and venture capitalists have contributed money. And although the $1,000 goal is within striking distance, it has not yet enabled the depth of understanding needed to make full medical or biological use of the knowledge derived from ever more genomes. Attacking that problem is the next challenge of genomics. But in part because of the $1,000 genome programme, biologists are now in a position to address it. ■

Past wisdom

The recent Nature PastCast *series is instructive as well as entertaining.*

Four decades ago, in August 1975, a short paper on antibodies was published in *Nature*. The findings spawned a multibillion-dollar drug industry: the monoclonal antibody drugs Herceptin, used to treat breast cancer, and Humira, used to treat rheumatoid arthritis, were together worth around US$15.4 billion to the pharmaceutical industry in 2012. But the revolution was nearly stillborn: the published technique to make monoclonal antibodies could not be reproduced. The crisis was such, says historian Lara Marks at King's College London, that the authors considered withdrawing their article from *Nature*.

It was years before the investigations paid off and the huge medical potential of monoclonal antibodies started to crystallize. "Nowadays it seems prophetic," says Greg Winter, who made the first monoclonal antibody for use in humans. "But at that point I don't think anyone had realized the importance."

If those who do not learn from the past are truly doomed to repeat the same mistakes, then *Nature* has done its bit over the past few months to help them avoid that fate.

There are many lessons from history in our archive, alongside nuggets of scientific insight and experience. Some of these — and contemporary reflections on them from experts such as Marks — have been presented in the *Nature PastCast*, a 12-part audio series on the history of science that draws to a close this week. Some stories featured in the series are humbling; others simply entertaining. All are relevant.

Are you navigating a tricky international collaboration? So was astronomer Arthur Eddington, who tried to mount an expedition to view a solar eclipse as the First World War was drawing to a close. He was an Englishman — a pacifist Quaker to boot — trying to find evidence to support a German-born physicist's theory (Albert Einstein's general theory of relativity). Or maybe your desk is piled high with a backlog of data needing analysis? In the mid-1980s, climate scientist Jonathan Shanklin had to sift through reams of the stuff before the evidence for the ozone hole popped out at him.

Or are you having trouble avoiding jargon in your latest write-up? In a November 1919 discussion of relativity, the physicist J. J. Thomson is reported to have 'regretted the very complicated form in which Einstein expressed his theory, and hoped it might be possible to put it into a form in which it would be more generally comprehensible and useful.'

Some of the best stories are those that reflect a simple commitment to doing science. In November 1924, palaeontologist Raymond Dart was getting ready to appear as best man at his friend's wedding when a box of fossils arrived at his home in Johannesburg. Having an inkling of its content, he couldn't resist opening the package. In his diary, Dart recounts how the groom himself had to drag him away. "My God, Ray, you've got to finish dressing!"

Wilhelm Röntgen showed similar mettle. According to Otto Glasser's 1934 biography, in the days after he first discovered X-rays, Röntgen ate and slept in his lab "in order to avoid the distracting influence of daily trivialities, and to be able to continue his experiments immediately in case of a sudden inspiration". Once Röntgen had published his X-ray experiments, a journalist asked him what he thought of his new findings. Röntgen gave a reply that every researcher should consider sticking on their fridge. "I did not think; I investigated." ■

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