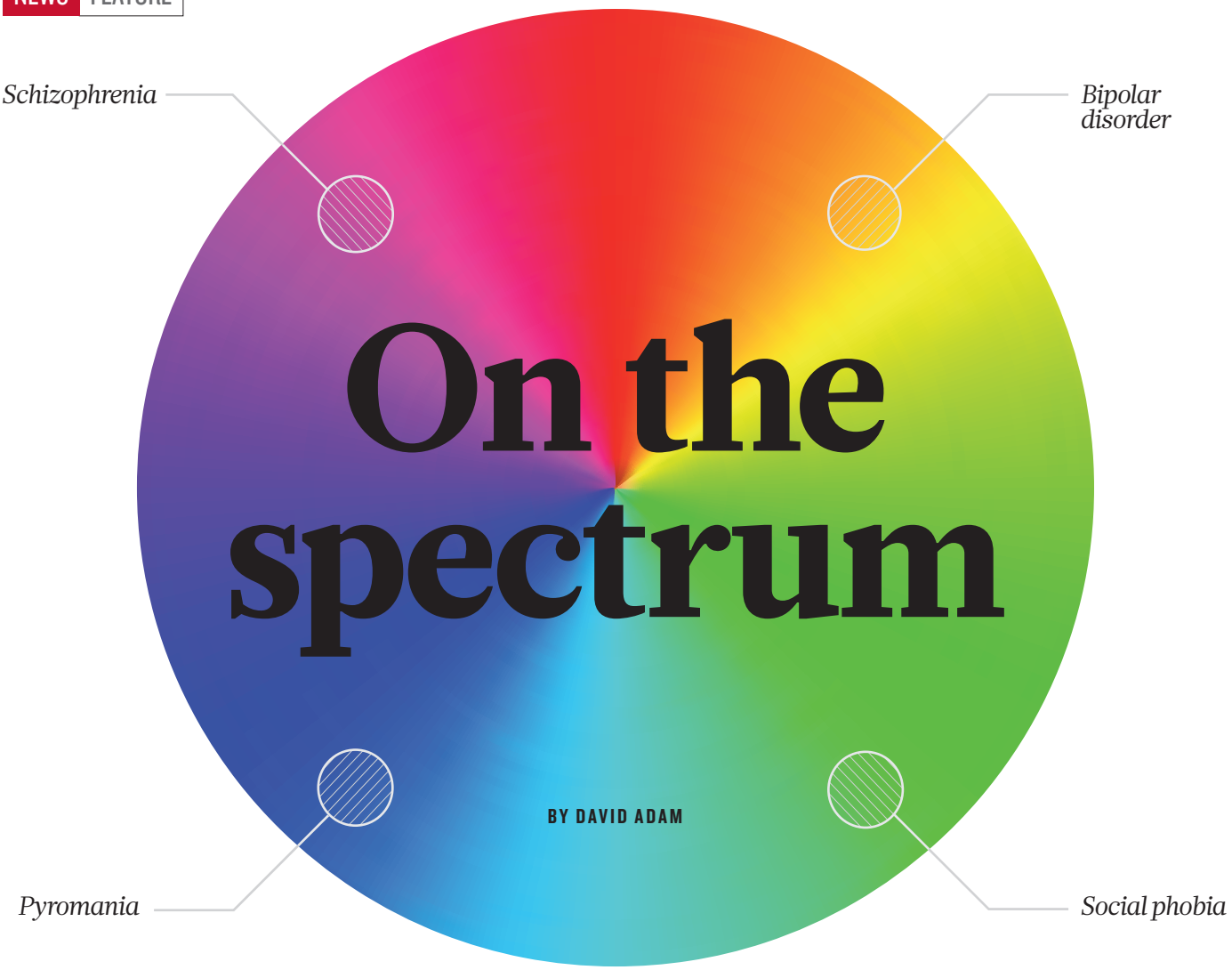

On the spectrum

BY DAVID ADAM

Research suggests that mental illnesses lie along a spectrum — but the field's latest diagnostic manual still splits them apart.

David Kupfer is a modern-day heretic. A psychiatrist at the University of Pittsburgh in Pennsylvania, Kupfer, has spent the past six years directing the revision of a book commonly referred to as the bible of the psychiatric field. The work will reach a climax next month when the American Psychiatric Association (APA) unveils the fifth incarnation of the book, called the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), which provides checklists of symptoms that psychiatrists around the world use to diagnose their patients. The *DSM* is so influential that just about the only suggestion of Kupfer's that did not meet with howls of protest during the revision process was to change its name from *DSM-V* to *DSM-5*.

Although the title and wording of the manual are now settled, the debate that overshadowed the revision is not. The stark fact is that no one has yet agreed on how best to define and diagnose mental illnesses. *DSM-5*, like the two preceding editions, will place disorders in discrete categories such as major-depressive disorder, bipolar disorder, schizophrenia and obsessive–compulsive disorder (OCD). These categories, which have guided psychiatry since the early 1980s, are based largely on decades-old theory and subjective symptoms.

The problem is that biologists have been unable to find any genetic or neuroscientific evidence to support the breakdown of complex mental disorders into separate categories. Many psychiatrists, meanwhile, already think outside the category boxes, because they see so many patients whose symptoms do not fit neatly into them. Kupfer and others wanted the latest *DSM* to move away from the category approach and towards one called 'dimensionality', in which

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mental illnesses overlap. According to this view, the disorders are the product of shared risk factors that lead to abnormalities in intersecting drives such as motivation and reward anticipation, which can be measured (hence 'dimension') and used to place people on one of several spectra. But the attempt to introduce this approach foundered, as other psychiatrists and psychologists protested that it was premature.

Research could yet come to the rescue. In 2010, the US National Institute of Mental Health (NIMH) in Bethesda, Maryland, launched an initiative, called the Research Domain Criteria project, that aims to improve understanding of dimensional variables and the brain circuits involved in mental disorders. Clinical psychologist Bruce Cuthbert, who heads the project, says that it is an attempt to go "back to the drawing board" on mental illness. In place of categories, he says, "we do have to start thinking instead about how these disorders are dysregulation in normal processes".

But that will be too late for the *DSM*. Kupfer says that he now sees how hard it is to change clinical doctrine. "The plane is in the air and we have had to make the changes while it is still flying."

MANUAL EVOLUTION

The Catholic Church changes its pope more often than the APA publishes a new *DSM*. The first and second editions, published in 1952 and 1968, reflected Sigmund Freud's idea of psychodynamics: that mental illness is the product of conflict between internal drives. For example, *DSM-I* listed anxiety as "produced by a threat from within the personality". Symptoms were largely irrelevant to diagnosis.

Things got more empirical around 1980. Shocked by the discovery that patients with identical symptoms were receiving different diagnoses and treatments, an influential group of US psychiatrists threw out Freud and imported another role model from central Europe: psychiatrist Emil Kraepelin. Kraepelin famously said that the conditions now known as schizophrenia and bipolar disorder were separate syndromes, with unique sets of symptoms and presumably unique causes. *DSM-III*, published in 1980, turned this thinking into what is now called the category approach, with solid walls between conditions. When the existing version, *DSM-IV*, came out in 1994, it simply added and subtracted a few categories.

Since then, an entire generation of troubled individuals has trooped into psychiatric clinics and left with a diagnosis of a *DSM*-approved condition, including anxiety disorder, eating disorders and personality disorders. Most of those conditions will appear in the pages of *DSM-5*, the contents of which are officially under wraps until the APA annual meeting — which starts in San Francisco, California, on 18 May — but have been an open secret since the APA published a draft on its website last year and invited comment.

But even as walls between conditions were being cemented in the profession's manual, they were breaking down in the clinic. As psychiatrists well know, most patients turn up with a mix of symptoms and so are frequently diagnosed with several disorders, or co-morbidities. About one-fifth of people who fulfil criteria for one *DSM-IV* disorder meet the criteria for at least two more.

These are patients "who have not read the textbook", says Steve Hyman, who directs the Stanley Center for Psychiatric Research, part of the Broad Institute in Cambridge, Massachusetts. As their symptoms wax and wane over time, they receive different diagnoses, which can be upsetting and give false hope. "The problem is that the *DSM* has been launched into under-researched waters, and this has been accepted in an unquestioning way," he says.

> "We need to give researchers permission to think outside these traditional silos."

Psychiatrists see so many people with co-morbidities that they have even created new categories to account for some of them. The classic Kraepelian theoretical division between schizophrenia and bipolar disorder, for example, has long been bridged by a pragmatic hybrid called schizoaffective disorder, which describes those with symptoms of both disorders and was recognized in *DSM–IV*.

Basic research has offered little clarification. Despite decades of work, the genetic, metabolic and cellular signatures of almost all mental syndromes remain largely a mystery. Ironically, the ingrained category approach is actually inhibiting the scientific research that could refine diagnoses, in part because funding agencies have often favoured studies that fit the standard diagnostic groups. "Until a few years ago we simply would not have been able to get a grant to study psychoses," says Nick Craddock, who works at the Medical Research Council Centre for Neuropsychiatric Genetics and Genomics at Cardiff University, UK. "Researchers studied bipolar disorder or they studied schizophrenia. It was unthinkable to study them together."

"We need to give researchers permission to think outside these traditional silos," says Hyman. "We need to get them to re-analyse these conditions from the bottom up."

In the past few years, some researchers have taken up the challenge — and the findings from genetics and brain-imaging studies support the idea that the *DSM* disorders overlap. Studies with functional magnetic resonance imaging show that people with anxiety disorders and those with mood disorders share a hyperactive response of the brain's amygdala region to negative emotion and aversion[1]. Similarly, those with schizophrenia and those with post-traumatic stress disorder both show unusual activity in the prefrontal cortex when asked to carry out tasks that require sustained attention[1].

And in the largest study yet undertaken to try to pinpoint the genetic roots of mental disorder, a group led by Jordan Smoller at the Massachusetts General Hospital in Boston screened genome information from more than 33,000 people with five major mental-health syndromes, looking for genetic sequences associated with their illness[2]. At the end of February, the team reported that some genetic risk factors — specifically, four chromosomal sites — are associated with all five disorders: autism, attention deficit hyperactivity disorder, bipolar disorder, major depression and schizophrenia. "What we see in the genetics mirrors what we see in the clinic," Hyman says. "We are going to have to have a rethink."

RIVAL APPROACH

At the same time that research and clinical practice are helping to undermine the *DSM* categories, the rival dimensional approach is gaining support. Over the past decade, psychiatrists have proposed a number of such dimensions, but they are not used in practice — partly because they are not sanctioned by the *DSM*.

The frequent co-morbidity between schizophrenia and OCD, for instance, has led some to suggest a schizo-obsessive spectrum, with patients placed according to whether they attribute intrusive thoughts to an external or internal source. And in 2010, Craddock and his colleague Michael Owen proposed the most radical dimensional spectrum so far[3], in which five classes of mental disorder are arranged on a single axis: mental retardation–autism–schizophrenia–schizoaffective disorder–bipolar disorder/unipolar mood disorder (see 'Added dimensions'). Psychiatrists would place people on the scale by assessing the severity of a series of traits that are affected in these conditions, such as cognitive impairment or mood disruption. It is a massively simplified approach, Craddock says, but it does seem to chime with the symptoms that patients report. More people show the signs of both mental retardation and autism, for example, than of both mental retardation and depression.

When Kupfer and his *DSM-5* task force began work in 2007, they were bullish that they would be able to make the switch to dimensional psychiatry. "I thought that if we did not use younger, more-basic science to push as hard as we could, then we would find it very difficult to move beyond the present state," Kupfer recalls. The task force organized a series of conferences to discuss how the approach could be introduced. One radical and particularly controversial proposal was to scrap half of the existing ten

Added dimensions

In the dimensional approach to psychiatry, mental-health conditions lie on a spectrum (example shown here) that has partly overlapping causes and symptoms.

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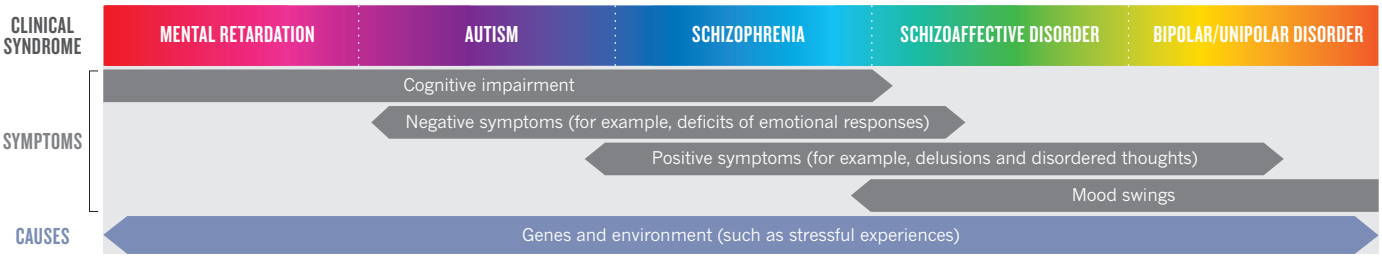

conditions relating to personality disorder and introduce a series of cross-cutting dimensions to measure patients against, such as degree of compulsivity.

But this and other proposals met with stinging criticism. The scales proposed were not based on strong evidence, critics said, and psychiatrists had no experience of how to use them to diagnose patients. What is more, the personality-disorder dimensions flopped when they were tested on patients in field trials of the draft *DSM* criteria between 2010 and 2012: too many psychiatrists who tried them reached different conclusions. "Introducing a botched dimensional system prematurely into *DSM-5* may have the negative effect of poisoning the well for their future acceptance by clinicians," wrote Allen Frances, emeritus professor of psychiatry at Duke University in Durham, North Carolina, in an article in the *British Journal of Psychiatry*[4]. Frances had served as head of the *DSM-IV* task force and was one of the strongest critics of proposals to introduce dimensionality to *DSM-5*.

The proposal was also unpopular with patient groups and charities, many of which have fought long and hard to make various distinct mental-health disorders into visible brands. They did not want to see schizophrenia or bipolar disorder labelled as something different. Speaking privately, some psychologists also mutter about the influence of drug companies and their relationship with psychiatrists. Both stand to profit from the existing *DSM* categories because health-insurance schemes in the United States pay for treatments based on them. They have little incentive to see categories dissolve.

CHANGE OF TACK

In the middle of 2011, the *DSM-5* task force admitted defeat. In an article in the *American Journal of Psychiatry*[5], Kupfer and Darrel Regier, vice-chair of the *DSM-5* task force and the APA's research director, conceded that they had been too optimistic. "We anticipated that these emerging diagnostic and treatment advances would impact the diagnosis and classification of mental disorders faster than what has actually occurred." The controversial personality-disorder dimensions were voted down by the APA's board of trustees at the final planning meeting in December 2012.

The APA claims that the final version of *DSM-5* is a significant advance on the previous edition and that it uses a combination of category and dimensional diagnoses. The previously separate categories of substance abuse and substance dependence are merged into the new diagnosis of substance-use disorder. Asperger's syndrome is bundled together with a handful of related conditions into the new category called autism-spectrum disorder; and OCD, compulsive hair-pulling and other similar disorders are grouped together in an obsessive–compulsive and related disorders category. These last two changes, Regier says, should help research scientists who want to look at links between conditions. "That probably won't make much difference to treatment but it should facilitate research into common vulnerabilities," he says.

The Research Domain Criteria project is the biggest of these research efforts. Last year, the NIMH approved seven studies, worth a combined US$5 million, for inclusion in the project — and, Cuthbert says, the initiative "will represent an increasing proportion of the NIMH's translational-research portfolio in years to come". The goal is to find new dimensional variables and assess their clinical value, information that could feed into a future *DSM*.

One of the NIMH-funded projects, led by Jerzy Bodurka at the Laureate Institute for Brain Research in Tulsa, Oklahoma, is examining anhedonia, the inability to take pleasure from activities such as exercise, sex or socializing. It is found in many mental illnesses, including depression and schizophrenia.

Bodurka's group is studying the idea that dysfunctional brain circuits trigger the release of inflammatory cytokines and that these drive anhedonia by suppressing motivation and pleasure. The scientists plan to probe these links using analyses of gene expression and brain scans. In theory, if this or other mechanisms of anhedonia could be identified, patients could be tested for them and treated, whether they have a *DSM* diagnosis or not.

One of the big challenges, Cuthbert says, is to get the drug regulators on board with the idea that the *DSM* categories are not the only way to prove the efficacy of a medicine. Early talks about the principle have been positive, he says. And there are precedents: "Pain is not a disorder and yet the FDA gives licences for anti-pain drugs," Cuthbert says.

Going back to the drawing board makes sense for the scientists, but where does it leave *DSM-5*? On the question of dimensionality, most outsiders see it as largely the same as *DSM-IV*. Kupfer and Regier say that much of the work on dimensionality that did not make the final cut is included in the section of the manual intended to provoke further discussion and research. *DSM-5* is intended to be a "living document" that can be updated online much more frequently than in the past, Kupfer adds. That's the reason for the suffix switch from V to 5; what comes out next month is really *DSM-5.0*. Once the evidence base strengthens, he says, perhaps as a direct result of the NIMH project, dimensional approaches can be included in a *DSM-5.1* or *DSM-5.2*.

All involved agree on one thing. Their role model now is not Freud or Kraepelin, but the genetic revolution taking place in oncology. Here, researchers and physicians are starting to classify and treat cancers on the basis of a tumour's detailed genetic profile rather than the part of the body in which it grows. Those in the psychiatric field say that genetics and brain imaging could do the same for diagnoses in mental health. It will take time, however, and an entire generation will probably have to receive flawed diagnoses before the science is developed enough to consign the category approach to clinical history.

"I hope I'll be able to give a patient with possible bipolar a proper clinical assessment," Craddock says. "I'll do a blood test and look for genetic risks and send them into a brain scanner and ask them to think of something mildly unhappy to exercise their emotional system." The results could be used to trace the underlying cause — such as a problematic chemical signal in the brain. "I'll then be able to provide lifestyle advice and treatment." He pauses. "Actually it won't be me, because I will have retired by then." ■ SEE EDITORIAL P. 397

David Adam *is* Nature*'s Editorial and Columns editor.*

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