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Interview with Steven E. Hyman

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Steven E. Hyman holds a BA from Yale University, a BA and MA from the University of Cambridge, and an MD from Harvard Medical School, where he became Professor of Psychiatry in 1998. He served as Director of the US National Institute of Mental Health (NIMH) from 1996 to 2001 and Provost of Harvard University from 2001 to 2011. He is currently Harvard University Distinguished Service Professor, Professor of Stem Cell and Regenerative Biology, and Scholar in Residence at the Broad Institute of Harvard and MIT. He is Editor of the Annual Review of Neuroscience, Founding President of the International Neuroethics Society, a fellow of the American Academy of Arts and Sciences, and a member of the Institute of Medicine of the US National Academies. He chairs the International Advisory Group for the revision of the International Classification of Diseases (ICD-11) Mental Disorders Chapter and is a member of the Task Force for the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).

What turned you on to science in the first place?

My infatuation with science started with the natural world. According to my parents, I was relentlessly curious and ever skeptical. One of my earliest personal memories of doubting – memorable, perhaps, because I was so wrong – followed my hearing an authoritative voice at a planetarium intone that in times past people navigated by the stars. From my childhood perch on the West Side of Manhattan, the assertion seemed preposterous – stars were not reliably visible. My view was corrected by a visit to suburban hinterlands.

By my later school years, motivated by bemused observations of my family and my classmates, and my self-reflection, the most compelling questions in science involved the workings of the brain and its relationship to lived experience. It was not at all obvious how I could make a satisfying career of such stuff, although academia seemed to be part of the solution. My parents, however, the children of striving immigrants, hoped that I would forget all this nonsense and become a private practitioner of some respectable branch of medicine (i.e. not psychiatry).

What steered you towards psychiatry in particular?

I did get trained in psychiatry, but arrived by a tortuous path. There was not much to be learned about higher brain function in undergraduate courses of the early 1970s. This was not the fault of the excellent faculty that taught me at Yale, but reflected the dominant approaches to psychology and the early state of neuroscience. I therefore focused on philosophy. While rigorous and enjoyable, however, my undergraduate experience, followed by 2 years studying the history and philosophy of science at the University of Cambridge, convinced me that more penetrating explanations of brain function would lie in biology and psychology after all. Given my intellectual trajectory, however, I was certain that I could not convince the few neurobiology PhD programs that had begun by 1975 that I was either prepared or serious. I therefore decided to enter science via medical school, which in the USA seemed agnostic about prior fields of study.

I found my first-year psychiatry course at Harvard Medical School repellant. The psychoanalysts and psychopharmacologists who taught us proffered, with serene confidence, absolutely incompatible views of the causes of mental illness. What they shared was simplistic determinism. One apparently revered senior psychoanalyst noted the benefits of 'putting schizophrenics and manic depressives' on the psychoanalytic couch, and conceptualized their symptoms as reactions to a 'crazy world'. Meanwhile, the champions of biology ascribed psychopathology to 'levels' of a few monoamine neurotransmitters, all the while ignoring emerging understandings of brain circuitry and experience-based plasticity that were coming from right across the street. Indeed, future Nobel laureates Torsten Weisel and David Hubel were, in the very same semester, teaching in a magnificent course that introduced me to neurobiology.

By now the reader might wonder why I became a psychiatrist rather than heading right to the laboratory or perhaps entering neurology. It was not to fight with colleagues (although for many years that had a certain charm): it was the patients. In my third year of medical school, I was fortunate to observe people with remarkable and moving conditions, including acute mania, deep melancholic depression and florid psychosis. These illnesses struck me as extraordinarily worthy scientific challenges, an understanding of which would help to illuminate higher cognitive function and emotion. At the same time it seemed that research, if successful, could have enormous benefits by relieving terrible human suffering and disability.

How has the landscape of psychiatric research changed in the past 30 years?

Optimism reigned when I began psychiatry residency in 1981. Despite the daunting complexity of the brain, there was reason to believe that important clues to pathogenesis and treatment of severe disorders might be at hand. The serendipitous discovery of lithium, chlorpromazine

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(the first antipsychotic drug) and several antidepressants in the 1950s and of their initial targets in the brain in the 1960s and 1970s promised both therapeutic progress and significant probes of brain function. Looking back, the picture is painfully different. The efficacy of psychotherapeutic drugs plateaued by 1955. Subsequent progress has been limited largely to tolerability. Strikingly, we still do not know how psychotherapeutics exert their desired effects.

Genetics also promised important clues to pathogenesis. Serious mental illnesses were long known to run in families. Twin and adoption studies demonstrated that genes played major roles in schizophrenia, bipolar disorder, alcoholism and other disorders. With the dawn of molecular biology (the field in which I did a 5-year post-doctoral fellowship after psychiatry residency) it seemed that we might soon identify causal mutations. There were concerns that risk could be polygenic and thus very difficult to analyze, but such worries were generally suppressed as the field focused on families in which schizophrenia or bipolar disorder seemed to be transmitted with tragic certainty. Only later were the striking phenotype differences even within such 'high-density' families recognized as significant harbingers of genetic complexity, along with a plethora of other disconcerting observations.

How have your views evolved with respect to the Diagnostic and Statistical Manual of Mental Disorders (DSM)

DSM-III was published in 1980, the year before I began my psychiatric residency. For all its flaws, most seriously the lack of validation, it was an exciting advance central to the optimism of the field. Without the inter-rater reliability (promised by the operationalized, field-tested diagnostic criteria of the DSM), validity could never be achieved. I believed that DSM-III represented a first draft of a modern disease classification that would evolve as science progressed. More than three decades later, this promise has not been realized, partly because the brain, in its complexity, gives up its secrets slowly and grudgingly, and partly because the DSM system quickly became so central to psychiatric research and practice that its diagnoses have gone unquestioned to a striking degree.

Nonetheless, as the DSM approach was applied to clinical practice and research, fundamental flaws began to surface. These flaws were not the sort to be repaired by refining of criteria. As one major example, the authors of DSM-III conceptualized mental disorders as discrete categories, discontinuous from health and from other disorders. Except for mental retardation, they rejected approaches in which disorders might represent a quantitative deviation from health on relevant dimensions (in analogy to hypertension or type 2 diabetes). Much subsequent research demonstrates that dimensional approaches would better represent depression, attention deficit hyperactivity disorder (ADHD), autism, anxiety disorders, personality disorders and many others. This error contributes to much of the disutility of the DSM for research and for setting of defensible treatment thresholds.

Another salient example: Psychopathology is not transmitted in families in the form predicted by the DSM. Symptoms do not segregate across generations in the groupings that define a single disorder. Rather families might exhibit schizophrenia, mood disorders and intermediate states or else multiple different putative anxiety disorders and depression. This observation reflects the fact that the genetic, epigenetic, and other environmental risks of psychopathology are etiologically complex and heterogeneous. For example, the many risk genes that might contribute to schizophrenia are not transmitted together across generations. The categorical DSM approach assumed far simpler causality, in analogy with a single gene (Mendelian) disorder or a disease caused by a single microorganism.

What was your thinking concerning the DSM system as director of NIMH?

When I became director of NIMH in 1996, I was aware of 'DSM troubles', but given a scientific career focused on regulation of gene expression, I had not given these problems deep thought. Indeed, I thought classification a dull topic better suited to medieval scholastics. As I viewed processes for grant review, however, I began to think differently. Indeed, I saw a troubling paradox. As a reliable and widely accepted diagnostic system, the DSM undergirded the replication of research results. As a result, but problematically because the DSM was clearly deeply flawed, grant reviewers, journal referees, editors and regulatory agencies all required DSM diagnoses for disease-related research. Indeed, they acted as if DSM criteria, *mutatis mutandis*, picked out real human diseases. Thus, its wide acceptance meant that a conceptual schema based on the thinking of the 1960s and 1970s exerted control over the scientific questions that could be asked.

Classification now had my attention, but I could not figure out how to facilitate a fundamental transformation without undercutting the diagnostic agreement crucial for clinical practice as well as research. I rejected the idea of commissioning NIMH research diagnoses because they would split researchers from clinicians. If an imaging study or clinical trial were conducted using research diagnoses, how would the results be correlated with DSM-based clinical practice?

What is your role in the revisions that will produce DSM-5 and ICD-11?

I left NIMH in 2001 thinking that I would return to academia, having kept my laboratory functioning during my years of government service. I could not resist an offer to return to Harvard to be provost (chief academic officer) with a special focus on building cross-disciplinary and cross-school science. I did not realize just how long I would stay in post, but that is another story.

Despite my day job, I continued to read, muse and write about issues in neurobiology and psychiatry. In 2007 I published a possible path forward in DSM reform in Nature Neuroscience, with the result that I was invited into the revision processes for DSM-5 and the World Health Organization ICD-11. The idea is simple: diagnostic criteria for individual disorders could be left unchanged in the absence of a compelling scientific reason. However, disorders should be clustered according to our best current hypotheses. For example, high levels of comorbidity and

twin studies would suggest clustering of fear-based anxiety disorders and unipolar depression; similar approaches suggest clustering of antisocial personality disorder, substance use and other impulse control disorders. Neural circuit hypotheses suggest that obsessive–compulsive and related disorders should be a cluster carved out of anxiety disorders. The key to any utility is that scientists, grant makers and journals should be encouraged to ignore individual DSM-5 disorders and to work at the level of clusters or even across related clusters to develop and test new bottom-up disease definitions, including dimensional measures that that cut across diagnoses. Happily, NIMH has a program that will facilitate this scientific transition.

If you knew earlier what you know now, would you have pursued the same career?

I would still pursue much the same career, because I find no other topic as engaging. Despite the heady nature of leadership roles, I find that I am happier surrounded by scientists as I am during my sabbatical year at the Broad Institute of Harvard and MIT. Sometimes I wonder whether it would have been better to have followed a straighter, more focused scientific path through life. In truth, I would not give up the breadth that my education and my various roles have allowed. This is not to say that I would ever recommend my precise path to a young person because it could just as well have been a recipe for failure. I have been very lucky.

What is next for you?

I decided some years before stepping down after a decade as Harvard provost that I did not want another high-level administrative position, but that I was hungry to return full time to science. I am focused on how emerging genetics results in autism, schizophrenia and bipolar disorders can yield incisive neurobiological experiments and how we might as a result accelerate much-needed new therapeutics.

What advice would you give to young people interested in a research career in psychiatry?

By all means enter this exciting field, but make sure that you are well grounded in your chosen area of science. Gain training in the best possible laboratories, not necessarily in your clinical department. Progress will be challenging because the brain is by far our most complex organ. Thus, only deep and effective scientific training is likely to equip a person to make significant – and much needed – contributions.

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