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Wellcome Trust Lecture in Neuroethics, University of Oxford (2010)
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Steven E. Hyman has engaged in basic laboratory investigation in molecular neurobiology; has taught neurobiology to undergraduates, graduate students, and medical students at Harvard; and has served in academic and government leadership roles at Harvard, the National Institutes of Health, and the Broad Institute. Throughout his career, he has maintained a focus on basic neurobiology that has contributed to understanding the mechanisms underlying neuropsychiatric disorders—such as schizophrenia, mood disorders, and addiction—and thus to their treatment.

Steven E. Hyman

Prologue

As I embarked upon my career as an independent scientist in 1989 and set up my lab at Massachusetts General Hospital (MGH), I was anxious but also felt very lucky. I was one of three new investigators working together to start a molecular neurobiology unit at the MGH Neuroscience Center. We had nicely renovated space and startup funds from our department chair and mentor Joseph Martin, and I had obtained two National Institutes of Health (NIH) grants: one to cover my salary and the other to support my first project. The project grant supported analysis of molecular mechanisms—enhancer elements and activity-regulated transcription factors—that controlled expression of genes encoding endogenous opioid peptides. I had clinical duties, which I found highly rewarding, but I also had managed to keep tightly circumscribed. I spent one morning each week making rounds with the psychiatry residents in the MGH emergency room. The patients we saw together often suffered from serious problems, such as drug overdoses, suicide attempts, and acute psychotic episodes. However, I did not have long-term clinical responsibilities for any patients so that I could focus on the lab.

In 1990, Gerald Fischbach returned to Harvard from Washington University to chair the Medical School Department of Neurobiology and direct the MGH Neuroscience Center. Gerry, who was never short of ideas, decided it was time to reimagine the graduate program in neuroscience. I had taken a graduate neuropharmacology course from Gerry in 1979 during his previous time at Harvard, and he had become a mentor and friend. Gerry invited Richard Masland, David Corey, and me to work with him to rethink the required initial neurobiology course for the first-year graduate students that also would be taken by the joint Harvard–MIT (Health Sciences and Technology) students. Developing this new course (Neuro 200/HST 130) was hard work, but it was also stimulating and, importantly, once we began teaching it, brought me into early contact with the Harvard graduate students. Within a few years, I had four very bright doctoral students in my lab along with several postdoctoral fellows, three of whom had MDs and PhDs and had completed neurology residencies. (I had no such luck recruiting young psychiatrists.) Overall, despite intense early career anxieties as occurred when awaiting news of grant reviews and submitted papers, I felt fortunate to be on the path that I had dreamt of and had reached by a long and indirect route. This path, involving research, teaching, and a modicum of clinical engagement was one that I planned to follow for the duration of my career. Clearly, I did not understand myself well.

In fact, by 1996, my path had deviated profoundly from this initial, idyllic vision. My career has been extremely interesting and, in many ways, privileged, but it also has been characterized by many unexpected twists and turns. These included sojourns in government as director of the National Institute of Mental Health (NIMH) and in academic leadership as provost of Harvard University. These opportunities came unbidden, but they proved to be irresistible. I had remarkable experiences, extraordinary opportunities to learn, and interactions with what were to me exotic fauna, such as senators, cabinet secretaries, and the U.S. president and vice president. Most important, I had the opportunity to shoulder significant responsibilities at institutions that mattered to science and more broadly to academia and to exert influence on matters that I cared about deeply.

I was keenly aware that I lacked the usual administrative experience for the directorship of NIMH and later the position of university provost. Thus, I had to navigate in highly visible roles while learning on the job. I was 43 and had not even been a department chair when I found myself in 1996 at the helm of a federal research agency with a budget of approximately $600 million (and by the time I left, $1.3 billion) and more than 1,000 intramural scientific personnel and extramural program officers and administrators. My intense commitment to the success of these institutions, my desire to advance a vision, and my capacity to lose myself in the work all helped me to manage my anxiety and propel me forward. Given my temperament, I was attracted to these leadership positions because they conjured in me a sense of mission. They also permitted me to make significant contributions to science, academia, and ultimately to society that outweighed the losses I would inevitably incur in terms of my own scientific efforts, privacy, and time with my young family. The move to Bethesda came at a time that was incredibly disruptive to my family; without my wife Barbara's resilience and understanding, my tenure at NIMH might have been six months instead of nearly six years. Becoming director of NIMH also meant that I had to make my own lab smaller and that I would not have enough time to spend with my students and postdoctoral fellows. After I moved back to Harvard from NIH, the intensity of my duties as university provost and the beginning of turbulent times at the university led me, with regret but of necessity, to close my lab, which I had been maintaining at NIH with a view toward moving it to Boston. Nonetheless, despite my duties as provost, I remained connected to neuroscience by teaching it to undergraduates, writing review articles and opinion pieces, and serving as editor of the *Annual Review of Neuroscience*. My conscious commitment to stay engaged in neuroscience ultimately made it possible for me to return full time. After a sabbatical in 2011, I was able to take on the directorship of the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard, which now gives me a significant opportunity to influence investigation of genetics, disease mechanisms, and potential therapeutics for mental illness (Hyman 2018).

Notwithstanding my changing job descriptions and titles, my broad scientific goals have remained constant from the beginning of my career. Whether in my lab, in my role as NIMH director, and now at the Stanley Center, I have worked to understand the neurobiological mechanisms that underlie psychiatric disorders with my greatest focus on addiction and schizophrenia and with the ultimate goal of advancing therapeutics. It is frustrating that neurobiological insights into mental illnesses remain modest and that treatment options remain limited for many who are distressed and suffering from significant impairments. The present time offers great promise, however, not because we have become smarter, but as is often the case in science, because of the development of new tools and technologies (Galison 2003). Thus, new tools for genomics, computation, stem cell biology, genome engineering, analyses of single-cell transcriptomes and epigenomes, and system-level neurobiology have made possible real traction on psychiatric disease mechanisms and the hope of achieving meaningful, cumulative progress. I have experienced false dawns before, such as when the genetics of bipolar disorder fleetingly seemed tractable in the late 1980s (Egeland et al. 1987). Thus, my enthusiasm for emerging results (Schizophrenia Working Group 2014) is tempered by the intense skepticism that is a defining aspect of my character.

Education

I was born at St. Albans Naval Hospital in Queens, New York, about a year after my father, a physician trained in hematology, returned from the Korean War. I spent my first four years on the Upper West Side of Manhattan, near my father's extended family and not far from my wonderful maternal grandparents, who lived in the Bronx, both immigrants from Russia. My maternal grandmother, who lived with us after my grandfather died—I was four at the time—had survived the Triangle fire, an important event in American labor history. She had testified at the trial of the sweatshop's owners and subsequently was arrested several times for involvement in labor disturbances and for marching for women's suffrage. She instilled in me an indelible commitment to social justice. Both of my parents had attended New York City Public Schools and were great believers in public education. Like many of their contemporaries, they came to the view that suburban public schools would provide a better and safer education than the schools that they had attended in the city, and so we joined the great migration of the 1950s to the suburbs. In our case, that meant moving a few miles across the Hudson River to Teaneck, New Jersey, where I would remain until I graduated high school and left for Yale in 1970.

I imagine that my elementary and junior high schools offered a perfectly reasonable education, but I could not testify to that because I spent much of my time daydreaming and in the earlier grades, drawing labyrinths (with Minotaur) on my desks with number 2 pencils. Inward pulls generally

overpowered any offerings from the external world, especially when the world outside my head meant the classroom. The few experiences that reliably drew me out of myself were those involving nature. My mother had started a graduate degree in biology before her financial needs pushed her into dull office work. She happily took me with my sister and later, my brother (both younger) to such places as the American Museum of Natural History, which was very close to the apartment of a favorite aunt in New York City. We visited the Central Park Zoo often and the far larger Bronx Zoo on occasion. Once or twice a summer, we drove to various quarries in New Jersey or upstate New York to search for interesting rocks and fossils. I still have large chunks of fluorescent franklinite and willemite that I brought home from a closed zinc mine in Franklin, New Jersey. We also took frequent walks along the nearby Hackensack River and the associated (very stinky) wetlands. I remember ponds and creeks that seemed to be teeming with pollution-tolerant killifish and perch that we could catch in nets or with drop lines, and the thrill of spotting and catching frogs and the occasional newt or their terrestrial juvenile forms, red efts. To this day, I experience something strangely akin to Marcel Proust's description of how the smell and taste of madeleines and tea triggered an involuntary flood of childhood memories—except for me the stimulus is the acrid, eye-watering air that I had encountered on those wetland walks. Because I still have family members to visit in Northern New Jersey, and despite beneficial reductions in pollution over the years, I can still on certain lucky days, enjoy my crypto-Proustian experiences at certain felicitous spots along the New Jersey Turnpike.

A bathtub on the top floor of our house was occupied for a time by a large, admittedly misshapen-looking fish that my brother had netted on one of our walks—we generally brought with us a few nets and the pail that otherwise held our mop. That fish somehow survived several months of bathtub captivity, during which time our Airedale terrier spent periods standing on her hind legs, with her front paws resting on the edge of the tub, watching Alonso (that was the fish's name) swimming endlessly back and forth. Over the years, many wild animals shared our suburban house with us, but the more significant risk to the human inhabitants was my chemistry set. In our intensely lawyered present, children likely suffer fewer burns on their arms and hands than I did, but they miss out on such glorious experiences as dropping small chunks of metallic sodium into toilets—resulting in minor explosions—of tossing copper, cobalt, or iron-containing salts into the fireplace to produce colors (and an early appreciation of spectroscopy), and of burning magnesium ribbon on the driveway. In Teaneck in the mid-1960s, a teen could even purchase a tiny amount of red phosphorus at a shop called Davis Toys on our main street—such chemicals were kept behind the counter, presumably to keep them out of the hands of even younger children. My "experiments" were limited only by my allowance. My mother not only tolerated these experiments, but also even bought me a periodic table

printed on cardboard to hang in my room. I loved that table and loved reading about the different elements listed on it almost as much as I loved the explosions when the metallic sodium hit the toilet.

After puberty had its way with me, the rocks and fossils on my shelves lost some of their salience, and my relentless curiosity turned, inter alia, to what made people tick. I began to read avidly on the topic, but it being the 1960s, I could not find much about the brain that was intelligible to me. The psychology of the time, or at least what I found of it, was Freudian or else behaviorist. I discovered some popular paperbacks by or about the pioneering ethologists, Niko Tinbergen and Konrad Lorenz, but found them disconcertingly dry. I read with no real guidance or even conversation partners—my discussions with high school friends largely focused on football, poker, intoxicants, and similar subjects. In my solitary meanderings at the town library and the occasional well-stocked book store, such as the Strand, when I could get to New York City, I eventually found my way to philosophy, which, seemed to me the discipline that most directly (if not always understandably) addressed my questions about human minds, human identity, the status of scientific knowledge, and the basis of ethics for the skeptical materialist that I had become.

I matriculated at Yale in 1970, just as protests over the Vietnam War reached their apogee. During the spring before my arrival, the Yale president, Kingman Brewster, reflecting on the Black Panthers who were jailed in New Haven awaiting trial for murder, publically expressed doubt as to whether these black revolutionaries could get a fair trial. In response, U.S. Vice President Spiro Agnew (who later was forced to resign over petty bribes he had received) called for Brewster to be fired. Very likely Mr. Agnew spared Yale the violence and disruption that occurred at other colleges by causing the students to rally around Brewster. Against this complex, anxiogenic backdrop, I began my college education.

I had received advanced placement credit in several subjects, including biology and chemistry. I was thus in a position to talk my way out of introductory survey courses and into interesting upper-level science courses. The physical chemistry course with which I started was quite challenging—it was a bracing reminder that I was no longer in Teaneck High School. The biology courses I took in later semesters were enjoyable and not so taxing; a favorite of mine was a well-taught developmental biology course. The odd and opportunistic smattering of science courses that I took would later prove critical in convincing medical schools that I might succeed if admitted.

Against the advice of my parents, I decided to major in philosophy. I was so thirsty for knowledge, however, contrasting the limited intellectual horizons of my high school with the opportunities at Yale that I took a second major as well. This second major, called History, the Arts, and Letters (HAL), was an interdisciplinary program in the humanities, with a competitive application process, that enrolled a cohort of approximately a dozen students.

We were taught in seminar format by stellar faculty members on subjects that included world literature; history; history of ideas; and history of art, architecture, and music. The curriculum, spread over three years, was organized chronologically, so that diverse topics were studied in conjunction with each other, demanding interdisciplinary thinking that was well ahead of its time. Although my philosophy major and my science courses emphasized critical thinking, HAL also put enormous demands on integrative thinking and cognitive flexibility, capacities that later proved extremely useful to me.

From Philosophy to Psychiatry and Neuroscience

I loved my undergraduate education. It introduced me to fascinating worlds that I had not known existed, and it increased rather than slaked my curiosity about anything I could learn. I had the sense that a university would be a good place for me to spend my career, but I never had the discipline to narrow my focus or settle on a sensible plan. Thus, as graduation approached, it became obvious that my only option was to temporize. I applied for fellowships to study in England before selecting a goal for graduate school. Having no realistic alternative plan, I was anxious and then incredibly lucky to receive a two-year Mellon Fellowship to the University of Cambridge. The Mellon fellows became members of Clare College, which is particularly beautiful even among Cambridge colleges, and proved to be both welcoming and supportive of my academic goals. With a view toward exploring areas that I might subsequently pursue for a PhD, I decided on history and philosophy of science, which brought together subjects that I found compelling and that had a strong faculty at Cambridge. Although I was broadly interested in both the history and philosophy components, across diverse areas or science, I developed a special focus on issues related to psychology, neuroscience, and their implications for understanding thought, emotion, human identity, and agency—much in keeping with my longstanding interests.

Although, I did not ultimately pursue a PhD in philosophy, I did become deeply engaged in several questions, some of which continue to excite me to this day. One of these, which might have become the topic of my thesis had I stayed in philosophy, was to investigate causal inference across levels of complexity in the brain—across levels constituted by genomes, molecules, cells, synapses, circuits, cognition, and behavior. A challenge for such analyses lies in the "many to many" mappings across levels of complexity that limit the utility of widely used reductionist experimental approaches. In highly complex multilevel systems, of which the brain represents the *non plus ultra*, functioning at higher levels of integration cannot be explained by the properties of individual components at lower levels. A useful, if anachronistic, illustration of the challenges for experimental design is offered by the frustrating attempts to produce a molecular explanation of long-term potentiation (LTP) and spatial memory in the 1990s by generating scores of transgenic mouse

lines. Generally, in this line of experiments, genes expressed in the hippocampus were knocked out and the resulting mouse lines were studied physiologically for evidence of LTP and behaviorally to evaluate memory using such tests as the Morris water maze. Most of the mouse lines described in published reports (which probably represented publication bias toward expected phenotypes) exhibited deficits in LTP and spatial memory. Taken together, these experiments seemed to implicate more than 100 genes but yielded no useful molecular explanation of mechanisms underlying either LTP or spatial memory (Sanes and Lichtman 1999). Conversely, many neuroscientists and philosophers don't even try to explain cognition in terms of synapses or circuits by declaring cognition to be emergent properties of activity within circuits. Neither approach is satisfactory if neuroscience is to deliver testable explanatory models that will help generate hypotheses leading to therapeutic interventions. It seems necessary, therefore, to develop experimental approaches that, paired with computational models, will permit neuroscientists to follow causal influences across levels of complexity.

Today, my colleagues and I at the Stanley Center face just such challenges of causal inference. We participate in and perform the genomic analyses for several large international consortia that are successfully identifying both common and rare DNA variants (alleles) that confer risk for psychiatric disorders such as schizophrenia, bipolar disorder, and autism spectrum disorders (ASDs). We have found that these disorders have highly polygenic risk architectures, which at the population level, involve thousands of allelic variants associated with many hundreds of genes (Schizophrenia Working Group 2014). Each risk allele exerts only a small additive effect on phenotype. The occurrence of illness, such as schizophrenia or bipolar disorder, in any individual person results from genetic loading for some subset of the risk alleles found in the population, acting together with stochastic developmental events and environmental risk factors. Even if we focus only on the genetic component of risk, causal models are difficult to formulate, yet they are critically important if disease-altering therapies are to be discovered. We must ask how diverse combinations of modestly penetrant risk alleles influence the transcriptomes and proteomes of a subset of neural cell types and their synapses to produce damaging effects on cognition and behavior (McCarroll and Hyman 2013; Hyman 2018). Is there convergence on shared mechanisms across individuals? The development of causal models of polygenic disorders will almost certainly prove critical in guiding the development of therapeutic interventions. Unsurprisingly, most clinical neuroscience remains focused on rare monogenic illnesses, which appear to be far more tractable, but ultimately, neuroscience must address the common polygenic disorders that are so damaging to both individuals and to the public health.

Another problem that gained my interest, and that connected with later periods in my career, was the question of why some scientific fields stagnate. Much attention has been paid by historians to dramatic scientific advances

(such as Newtonian mechanics and relativity) and to catastrophic failures (such as the disastrous application of Lamarckian inheritance to Soviet agriculture in the 1940s), but I became interested in the human factors that can impede scientific progress. As I will discuss later, such issues, which I had considered only theoretically when at Cambridge, became major real-world concerns for me during my tenure as director of NIMH.

Returning to my practical concerns of 1975, however, it seemed that with one year left in my Mellon Fellowship, it was high time to commit to a more focused intellectual trajectory, and perhaps even a career. I thought that I would be intellectually engaged by academic philosophy, but as much as I enjoyed reflecting on problems of mind and brain from that vantage, I realized that I would find it more stimulating to participate in brain research directly. In addition, I incessantly wondered how I might make the greatest positive difference in the world and concluded that it was by becoming a scientist. These thoughts reminded me, however, that I had dug a bit of a hole for myself. Given my academic background, I could not imagine anyone admitting me to one of the few graduate programs that focused on neuroscience in the mid-1970s. Ultimately, I decided on a plan: I could enter into a scientific career via medical school followed by extensive postdoctoral training. This plan had the additional charm that it would temporarily make my parents happy—they had wanted me to be a doctor like my father and his brother—although once I followed through with the plan, I knew that they would be disappointed, which, in fact, they were. My plan was based on the fact that while medical schools in the United States favored science majors, they accepted some students from other disciplines. It helped that I had done well in undergraduate science courses; I realized, however, that there was no way around taking organic chemistry. I did so at Harvard during the summer of 1975 and to my surprise and delight, I enjoyed this highly logical subject enormously.

I applied to several schools and entered Harvard Medical School in the fall of 1976. To my horror, I discovered that the two initial classroom-based years of medical school in the 1970s were intellectually execrable—dreary exercises in rote learning. I was often bored, and in truth, frequently unpleasantly irritable because of the unrelenting intellectual poverty of the curriculum—a notable exception being the glorious neurobiology course taught by Ed Furshpan, David Potter, Ed Kravitz, and David Hubel. One silver lining was that being blessed with a good memory, I did not find the coursework challenging. This allowed me the time I needed to begin working in a research lab, which I did throughout medical school. My research in the lab of Wayne Alexander on regulation of angiotensin II receptors eventually resulted in my graduating with honors. In stark contrast to the first two years, the clinical courses of the third and fourth years were engaging, demanding, and extremely well taught by the remarkable clinical faculty of the Harvard-affiliated hospitals.

I decided to follow medical school with residency training and assumed that it would be in neurology. I was particularly enthralled by a series of evening lectures given by Norman Geschwind, a pioneering behavioral neurologist, who was also a riveting speaker. He started his series by reanalyzing the work of the great 19th-century neurologists Broca and Wernicke who had correlated careful clinical observation with postmortem brain lesions and thus had identified anatomic regions associated with the production and decoding of speech. Geschwind illustrated cases in which Wernicke's and Broca's areas had been disconnected from each other by lesions in the arcuate fasciculus to produce a conduction aphasia. He then elaborated his connectionist model of brain function and illustrated it with fascinating clinical and neuropathological observations made on patients with aphasias, alexia, and apraxias.

During my neurology clerkship, I was not disappointed by the senior neurologists with whom I interacted at the Peter Bent Brigham Hospital (now Brigham and Women's). They possessed encyclopedic knowledge and applied impressive deductive skills to the clinical presentations of the patients we saw. The patients, however, were nothing like the cases that Geschwind had described in his mesmerizing lectures, often the result of small, focal strokes that serendipitously revealed fine distinctions in the functional architecture of the cerebral cortex. In stark contrast, the conditions that afflicted the hospitalized patients on the neurology service were typically devastating hemispheric strokes, spinal cord injuries, advanced Parkinson's disease that was refractory to L-DOPA, and late-stage multiple sclerosis. These patients were severely impaired even with respect to the most basic aspects of self-care and communication, and we had little to offer therapeutically. In the late 1970s, the exquisite neurologic exams we learned and the logical processes by which we deduced the location of the patients' lesions (recognizing that at the time, there was usually no way to confirm these conclusions antimortem) yielded little of benefit to patients and families. Among the older, highly respected clinicians, I also detected an undercurrent of animus directed at neuroscience as a pursuit that was irrelevant to practice but somehow luring talented young people away from the wards.

I had a very different, almost opposite experience in psychiatry. I was deeply moved by the patients, fascinated by talking to them, and recognized that the existing treatments, although far from perfect, were nonetheless often quite beneficial. In contrast to the neurologists, whose rigor and well-grounded anatomic knowledge I admired, many of the psychiatry faculty—of course with notable exceptions—were intellectually off-putting. The largest number of faculty with whom I crossed paths were psychoanalysts or practiced related treatment approaches, such as psychodynamic psychotherapies. They eschewed the idea of diagnosis, which was so fundamental to the rest of medicine, and construed the symptoms of their patients as manifestations of unresolved unconscious conflicts. The brain, or indeed any

consideration of biology, was utterly foreign to many, even those who treated severely ill patients with schizophrenia or bipolar disorder. The majority of the teaching faculty members exhibited calm certainty in describing the theoretical underpinnings of their psychoanalytic practice—something that never failed to elicit outrage in my younger self as I heard a litany of "just-so" stories with scant empirical basis. The exceptions among the psychiatry faculty were often, however, among the most thoughtful and caring clinicians I met during my medical school years, and I have maintained contact with some of them. I believe that these clinicians, most of whom treated patients with very severe illnesses, demonstrated remarkable humility, impressive commitment to this highly stigmatized and marginalized patient population, and effective pragmatism in looking out for their patients that had to extend far beyond the confines of the clinic.

The 1970s and 1980s were characterized by pitched battles between proponents of the still-dominant, but waning, clinical approaches grounded in psychoanalytic theory and the insurgent psychopharmacologists (Klerman 1990). In their zeal to vanquish the psychoanalysts and to be recognized as "real doctors," some of the self-styled biological psychiatrists rather bizarrely discounted the role of environmental factors or lived experience in the pathogenesis and clinical outcomes of mental illness. Many could find no role for talk therapies in treatment—unlike cardiologists, for example, who, implicitly confident in the biological basis of their therapeutics, thought it no disgrace to address diet, exercise, and stress reduction along with medications or surgery in treating cardiovascular disease. I was in full sympathy with the rejection of psychoanalytic theory with its preposterous ideas about the nature of mental illness, but I was unimpressed by the reductive explanations offered as alternatives by the biological psychiatrists who taught my medical school classes. The fetishization of neurotransmitter levels in the brain, as if the brain were an endocrine organ as simple as the thyroid gland, and their seeming ignorance about synaptic plasticity and neural circuit function seemed inexplicably backward given that I had been taught by David Hubel, Torsten Wiesel, and Norman Geschwind at the same medical school. This is not to suggest that disease mechanisms underlying psychiatric disorders could readily have been identified with a bit of better theory—we are still at the very beginnings of mechanistic understandings. What bothered me was that instead of seriously embracing neurobiology, many biologically oriented psychiatrists had walled themselves off intellectually and thus had failed to recognize that there was more to the human brain than could be revealed through pharmacology.

The question of whether to study neurology, psychiatry, or both was challenging and frustrating—after all, these are two disciplines grounded in diseases of the very same organ—but often in unrecognizably different ways. Finally, it struck me that I would be spending the vast preponderance of my clinical hours with patients, not with my colleagues, and decided that

I should weight my choice of specialization based on the patients with whom I would interact and the diseases that would be most compelling to study in the lab. I never regretted my decision to train primarily in psychiatry, although I did complete part of a neurology residency. Indeed, being intellectually cantankerous, I rather enjoyed the many edgy discussions I have had with colleagues in psychiatry over the years. I also imagined that it was an opportune time for a physician-scientist at the beginning of a career to pursue basic neuroscience relevant to mental illness. I believed that the tools were emerging that would elucidate the processes that go awry in the brain to produce disorders such as schizophrenia and depression. I obviously did not recognize the complexities that would stymie attempts to understand psychiatric disease mechanisms for several more decades. Notwithstanding these unforeseen scientific hurdles, the mystery of psychiatric disease mechanisms gained a hold on me, not only because of the terrible effects of these disorders on many people, including some members of my extended family, but also because so much remained tantalizingly unknown. That seemed to offer a great opportunity, assuming that much-needed new tools and technologies would emerge during the course of my career.

After a year of medical internship at MGH, I began psychiatry residency at McLean Hospital, an MGH affiliate that was, at the same time, proudly independent. I spent the first year of my residency on a unit, North Belknap-1, that specialized in treating patients with acute psychoses. In practice, this meant I treated patients with first psychotic episodes of schizophrenia and psychotic relapses; patients with acute episodes of mania; and, less commonly, individuals with severe depression who had psychotic symptoms, such as voices telling them that they were worthless or delusions that they were rotting, emitting a stench, or otherwise debased. The unit was run by two pragmatic young psychiatrists who were skilled psychopharmacologists and excellent physicians. They based their therapeutic approaches on clinical trial evidence when it was available, and eschewed participation in the ideological battles that roiled psychiatry. My year on this unit permitted me to interview a large number of patients with diverse psychotic illnesses and to oversee the treatment of scores of patients (with the gentle oversight of the psychiatrists in charge). I also gained significant experience in the properties of psychiatric medications, including both their benefits and their many side effects.

One powerful example of the way in which my clinical experience further ignited my scientific curiosity came from my caring for a young woman of 19 with acute mania. She was a college student from Maine, said by her family to have been demure, conservative in her behavior, and studious. Over a period of a few weeks, she had undergone a remarkable change that had reached a crescendo in the days before her hospital admission. She had begun sleeping for only about two hours per night but had remarkable levels of energy. She had become uncharacteristically sexually promiscuous and

had started drinking large quantities of alcohol. When I first saw her, she was shouting loudly that she wanted to go bear hunting. She had most of the canonical symptoms and signs of acute mania, including rapid, pressured speech and grandiose ideas.

For the first few days of her hospital stay, I prescribed a benzodiazepine and an antipsychotic drug to help calm her ceaseless motion and yelling and also to help her get some sleep. At the same time, I initiated treatment with lithium, which must be started slowly to minimize side effects, and then takes weeks to exert its antimanic effects. Over about six weeks, the quiet and rather shy young woman who had been described by her family reemerged. By what neurobiological mechanisms, I wondered, did manic-depressive illness cause such dramatic alterations in physiology, thought, speech, and behavior? And how was it that if we brought her to a serum concentration of 1 mM lithium we were able to return this young woman to herself? It seemed to me in 1981 that genetics, molecular biology, and neurobiology would soon provide us with answers. Unfortunately, we still do not know how lithium treats mania, nor do we possess even rudimentary insight into its pathogenesis (Hyman 2012).

My wonderful year on North Belknap-1 came to an end, and I began rotations that were supposed to last several months each on other clinical services at McLean Hospital. I found myself in what seemed a waking nightmare. Depending on the units to which patients were admitted—something partly determined by the chance occurrence of an empty bed—they might receive shockingly different treatments for the same illness at the same stage of life. Had the young woman with mania that I described been admitted to one of the units at McLean that I rotated through, she would have received sedatives and antipsychotic drugs, but not lithium, and her main treatment would have been a version of the psychoanalysis that had been developed at Tavistock Clinic in London. In short, she would have had her manic symptoms interpreted to her by the staff and her therapist as their central therapeutic intervention. Given what we knew at the time about the treatment of bipolar disorder, this seemed unethical and even abusive, a set of conclusions that I shared with peers and with faculty to a decidedly mixed reception.

At one point, I was assigned to spend several months on an inpatient children's unit that was directed by a rigid man who espoused yet another school of psychoanalytic theory. The unit housed children with a range of conditions, including what we would now diagnose as ASDs, psychoses, mood disorders, and borderline and antisocial personality disorders. Treatments were prescribed and administered, not according to diagnoses, which were eschewed except for the purpose of billing insurance. Instead, treatments were based on case formulations grounded in psychoanalytically inspired developmental theories. When medications were administered, it was generally to control anxiety, agitation, or aggressive behavior, rather

than as treatment for the underlying illness. These clinicians were not skillful in psychopharmacologic therapeutics; indeed, typically, drug doses were too high. Thus, excessive sedation and the Parkinson-like motor side effects of first-generation antipsychotic drugs were much in evidence.

Quite upset by what I was seeing on the unit, I complained to the director of the McLean psychiatry residency, Philip Isenberg. This warm and flexible psychiatrist was not at all surprised by what I told him, although that did not assuage the moral outrage I felt at the treatment of ill children based on antediluvian psychoanalytic theories. Indeed, his calm handling of my concerns betrayed a kind of fatalism, as if he had been defeated too many times in trying to intervene in the successful businesses that the individual clinical fiefdoms seemed to be. Surprisingly, however, his response to my litany of complaints about the clinical practices I observed, their risks to the patients, and (in my view) their profound disutility for my training, was "so don't go."

I took him at his word, and from then on Dr. Isenberg allowed me to slip away from putatively required clinical rotations so long as I never shirked my assigned service responsibilities (such as night call) and promised to keep learning psychiatry, so that I would pass the specialty boards—which I later did without much trouble. I used my newfound free time to start working in a laboratory again, and I also took a series of moonlighting jobs at outside clinics. These helped me supplement my very meager salary—my wife and I had a 16.75 percent mortgage, which was better than many on offer in the early 1980s, on our small starter house. Moonlighting gave me independence from theory-ridden supervisors and the intense learning experience conferred by responsibility for sick people. My most interesting experience was a daytime job at an outpatient clinic on the grounds of the old Boston State Hospital in Dorchester, Massachusetts, where once a week, I was the prescribing physician for patients, mostly with schizophrenia, recently discharged from the state hospital.

At the time, the de-institutionalization movement was in full swing, and the campus felt like a ghost town with many red brick buildings dating from the 1930s sitting eerily empty on the enormous, ill-tended grounds. The other staff at this clinic, officially named the "aftercare" clinic, were older, experienced nurses who had seen every possible clinical situation over the years and who were unflappable and often charmingly cynical. True to my promise to Phil Isenberg, I read the clinical literature with ferocious intensity—and learned an enormous amount from these nurses and, above all, from the patients. Looking back, I am amazed by my temerity, but I codified my reading and my moonlighting experiences by writing and editing three clinical manuals that were published by Little, Brown (later merged into larger publishers) as components of a successful medical handbook series (Hyman 1984; Hyman and Arana 1987; Hyman and Jenike 1990). The first two went through multiple printings and several editions and were translated into diverse languages, including not only Spanish but also Japanese,

Turkish, and Croatian. Without doubt, one never learns better than when teaching and explaining—and, in this case, because I knew that clinicians would act on my advice, I obsessively made sure that the advice I gave was as accurate as the literature permitted.

In lieu of a final year of residency at McLean, I received permission to substitute a year of neurology residency at MGH. It was not only informative but also awe inspiring to examine patients with the great neurologists Raymond Adams and C. Miller Fisher and to spend several months in the clinical neuropathology lab with E. P. Richardson. As in medical school, I felt deep respect for the neurology faculty, but I remained frustrated by how little could be done for the patients. Despite the possibility of getting board certification in both psychiatry and neurology with yet one more year of neurology residency, I was not seriously tempted to do so. I had observed and learned about a wide swath of diseases of the nervous system, which had been my goal for residency training, but I was 31 years old and experiencing diminishing returns at the intellectual level. It was high time to embark upon laboratory neuroscience full time. My parents, in fact, had been disappointed when I told them that I would do a residency in psychiatry rather than internal medicine. When I explained to them that I was about to begin a postdoctoral fellowship in molecular biology, they could not fathom what I was up to.

Can Molecular Neurobiology Help Elucidate the Pathophysiology of Psychiatric Illness?

Many of the Harvard Medical School affiliated basic scientists studying aspects of mental illness had their labs in the Mailman Center at McLean Hospital. The center had been built for the arrival of Seymour Kety, who had first moved from Johns Hopkins to MGH in 1967 and then to McLean 10 years later. In the 1940s, he had pioneered methods to study blood flow in the brain, and later he did foundational work in psychiatry by demonstrating genetic transmission of schizophrenia using well-designed adoption studies based on the Danish national birth registry. He found a fivefold greater risk of schizophrenia when the disease was present in an adoptee's biological family than when it occurred in members of an adoptive family. Dr. Kety was in the process of winding down his lab, however, and was not taking new trainees. Other accomplished investigators at the Mailman Center included Ross Baldessarini, who had characterized the ligand-binding properties of several neurotransmitter receptors and also had an encyclopedic grasp of the clinical and translational psychopharmacology literature.

Although I appreciated the work of many of the investigators at the Mailman Center, their commitment to well-established methods grounded in pharmacology seemed too narrow for someone at the start of a career. I was drawn instead by the promise of genetics and the emerging discipline

of molecular neurobiology. The McLean faculty were surprisingly discouraging about the relevance of molecular biology to the problems of psychiatry. I therefore sought the advice of John Potts, chair of the Department of Medicine at MGH, whom I had met during my medical internship. He introduced me to Joseph Martin, chair of the Department of Neurology at MGH. I was delighted and surprised by the fatherly interest both of them showed in my future—surprised because psychiatry ranked low in the academic pecking order—indeed, several professors during my medical school years were unreservedly horrified that I was going to train in that discipline. Years later, it was Joe Martin who provided me with space and startup funds to begin my independent lab, and who made valiant, but unsuccessful, attempts to bring clinical training in neurology and psychiatry closer together.

In contrast to the senior psychiatrists at McLean who had tried to discourage me, Drs. Potts and Martin were optimistic about the tools that molecular biology would provide for understanding brain disease. Joe Martin had already worked together with David Houseman (MIT) to connect Houseman's former postdoctoral fellow Jim Gusella with the human geneticist Nancy Wexler, a collaboration that would eventually lead to identification of the mutation that causes Huntington's disease. Together, Drs. Potts and Martin recommended me to Howard Goodman, who had just arrived at MGH from the University of California, San Francisco (UCSF) to found a department of molecular biology. The MGH department would be a branch of the Harvard Medical School Department of Genetics, which had been started and was chaired by Philip Leder, who had developed the first transgenic mouse cancer model. The MGH Department of Molecular Biology was founded with a then-unprecedented $70 million grant from the German pharmaceutical company Hoechst (which several years and many mergers later, was absorbed into Sanofi). Howard was initially skeptical of accepting a postdoc with an MD, no PhD, and no experience in molecular biology. I committed to staying in the lab long enough, however, so that early investments in getting me up to speed might be repaid with experimental results and publications. The transition to Howard's lab was difficult as I moved from a position of relative expertise in my clinical discipline to the status of basic learner. I was fortunate that a fellow postdoc, Michael Comb, who was talented and experienced in molecular biology, generously helped me get started and then became a collaborator. Mike moved with me later to the Molecular Neurobiology Unit in the Neuroscience Center. He eventually decided that he preferred the biotech industry to academia and founded a successful company, Cell Signaling Technologies.

The Goodman lab had other challenges for me. It was built around molecular technologies rather than core biological questions. Thus, few in the lab were interested in neurobiology. Indeed, by the time I left Howard's lab, more than half the people were working on plant molecular biology. On the positive side, Howard began to recruit junior faculty members, who

were smart and creative, and for the most part, highly collaborative. These included Brian Seed, Robert Kingston, and the future Nobel Laureate Jack Szostack. Brian Seed, on learning of my interests, would share papers with me related to the neurobiology of psychiatric disorders as well as providing much appreciated scientific advice.

On the basis of his graduate work with Ed Herbert at the University of Oregon, Mike Comb brought an interest in endogenous opioid peptides to the Goodman lab and had set out to understand the regulation of their synthesis at the level of gene transcription. Endogenous opioid peptides are cleaved from precursors encoded by three separate genes (i.e., proenkephalin, prodynorphin, and proopiomelanocortin), each of which had been cloned. I was happy to be offered the opportunity to collaborate with Mike on regulation of proenkephalin gene expression, partly for the intrinsic interest of the problem and partly because of the potential relevance of endogenous opioids to emotion, reward, and analgesia. However, investigation of gene expression in brain reward circuitry would have to come later. Little was known yet about the basic mechanisms by which neurotransmitters, second messengers, or pharmacologic agents influenced gene expression (Comb et al. 1987). It was exciting to be involved in working on relevant aspects of signaling to the nucleus, and the identification of enhancer elements that mediated gene regulation by second messengers and their associated protein kinases. I stayed in the Goodman lab for five years, and I learned much from members of the lab and others in the department. As Howard grew more interested in plants and less in animal systems, I was forced to become increasingly independent, which was frustrating at times, but ultimately helped me learn the necessary skills to develop my own lab.

In 1989, after publishing several papers on gene regulation (and working on a side project helping Elizabeth (Betsy) Ross, who had recently joined the Goodman lab, clone the gene encoding phenylethanolamine-N-methyl transferase, the enzyme that converts norepinephrine to epinephrine, I felt that I had reached a natural transition point. MGH was in the process of renovating a vast amount of lab space in a former torpedo factory in the nearby Charlestown Navy Yard with an entire floor dedicated to a new Neuroscience Center. Joe Martin offered me space and startup funds. Moreover, my wife Barbara Bierer had the opportunity to establish an independent immunology lab at the Harvard-affiliated Dana Farber Cancer Institute in Boston. Given the challenges of searching together for positions in the same city and given the attractive offers we both had in Boston, we decided to stay. Over the years, we have both been offered interesting positions at other universities, but Harvard had the attraction of talented colleagues, wonderful students, and good positions for both of us. Except for the years when I was at NIMH in Bethesda, and Barbara served in several positions, including acting clinical director of the intramural research program at the National Heart Lung and Blood Institute, we have stayed in the Boston area.

Regulation of Gene Expression by Dopamine

As I thought about projects for my lab, I focused on connecting my scientific trajectory studying gene regulation to mechanisms involved in psychiatric disorders. Psychiatric disorders clearly are not cell autonomous; to the contrary, their symptoms and functional impairments represent abnormal functioning of synapses and distributed circuits underlying cognition, emotion, and behavioral control. Such considerations already had led me to focus on transsynaptic and drug-regulated gene expression, which could be studied initially in cell culture but later was applied to studies in laboratory animal brains. A challenge was to select experimental paradigms that would credibly have relevance to psychiatric illness but remain tractable to mechanistic analysis.

I have long been skeptical of putative animal models of psychiatric disorders. I was even more skeptical of the traditional criteria for validation of such models, especially of "face" validity, which invites anthropomorphic fantasies, and ill-advised follow-up studies focused on traits that might reflect convergent evolution rather than shared mechanisms. Another problematic "validator" was predictive validity, that is, a model in which drug modification of a trait in the animal predicted drug efficacy in humans. This type of correlation is hardly a validator of underlying mechanisms in the model, but rather the use of an animal as a kind of black box assay system. I later published these ideas with my friend Eric Nestler (Nestler and Hyman 2010), but since then, we have both grown further skeptical of the third traditional validator, construct validity. My skepticism is based on the recent discovery that risk of psychiatric disorders is highly polygenic and often involves regulatory regions of the genome that are not well conserved across evolution (Hyman 2016, 2018). My philosophy, as I chose my first projects, was to consider what I did, including work in animals, to be basic science that would inform research on psychiatric disorders by providing intellectual building blocks, such as potentially relevant molecular mechanisms.

Even if I considered my research to be basic, it was still difficult to make it relevant to psychiatric disorders because I would have to find appropriate systems in which to perform studies that involved living brains. I can illustrate my concerns as follows. Lesions of midbrain dopamine neurons with 6-hydroxydopamine or MPTP do not produce a veridical model of Parkinson's disease. The neuronal loss is acute rather than insidious as it is in humans, and the deficits are only in motor systems, whereas in humans, sleep, mood, cognition, and other functions are affected. It is possible, however, to learn much of relevance from living animals that lack dopamine neurons as a result of such lesions and thus, even if imperfectly, gain insights into motor aspects of Parkinson's disease. However, no such compelling approximation existed for depression, bipolar disorder, or schizophrenia. For example, putative models of depression most often were based on chronic stress. These resulted in behaviors that could (with some imaginative effort) be analogized

to those of depressed humans; however, there was no evidence that these behaviors shared underlying mechanisms with human depression. Credible animal models of schizophrenia and bipolar disorder simply do not exist.

I came to the view that of all psychiatric conditions, addiction was the best candidate for studies of molecular mechanisms because the critical causal factors were known—the addictive drugs themselves. The transition from voluntary drug administration to compulsive use, which is central to understanding addiction, could not be fully captured in animals given the important role in humans of cognitive control implemented by a human prefrontal cortex as well as the vast contextual differences under which human versus experimental 'addiction' occur. In analogy with dopamine lesions to study aspects of Parkinson's disease in animals, however, an extensive literature demonstrated the importance of associative learning in reward-related behavior in animal models and of cue-dependent drug-seeking and relapse in drug-addicted humans. I hypothesized that if addiction involved abnormal synaptic plasticity in reward circuitry, then drug-induced changes in gene regulation could play a critical role in initiating and maintaining the relevant synaptic changes. In addition, the long-lived nature of addiction, with its protracted risk of relapses was also consistent with a role for associative memory in pathogenesis and thus, potentially, with altered regulation of gene expression.

As the lab grew, we focused largely, but not entirely, on the actions of increased and decreased dopamine release and dopamine receptor activity using a variety of pharmacologic agents and 6-hydroxydopamine lesions in rats and in both transgenic and wild-type mice. We studied phosphorylation of the cyclic AMP and Ca^{2+} regulated transcription factor cAMP response element binding protein (CREB) in response to such manipulations and the induction of immediate early genes. We also began to discover dopamine-inducible genes in the dorsal and ventral striatum that were potential candidates for roles in altering behavior. I was able to obtain the needed levels of grant funding, and my MD-PhD postdoctoral fellows were almost universally successful in obtaining individual career development awards—that is, K08 awards from the National Institute of Neurologic Disorders and Stroke (NINDS). On the basis of my frequent scientific interactions with him, Gerry Fischbach proposed that I move my lab from MGH to the Harvard Medical School Department of Neurobiology, and started renovations for me in the Medical School Quadrangle in the Longwood Medical Area. Then, literally out of the blue, NIH came calling and everything changed.

NIMH

In 1994, the director of NIMH, Frederick Goodwin, was forced to step down by the secretary of health and human services at the behest of Congress. Goodwin's departure eventuated from public remarks that he made in the context of a "violence initiative" that he had championed as a way of

mitigating high rates of youth violence then occurring in cities. Goodwin drew an analogy between violence observed in young male monkeys and violence perpetrated by inner-city youth. He also pointed to research that had been performed in rhesus macaques that reported associations between low levels of serotonin metabolites in cerebrospinal fluid and high levels of aggression—an association similar to one that had been reported in Finland in a study of suicidal humans. Some members of Congress took umbrage at Goodwin's seeming to equate inner-city youth, interpreted as code for minorities, with nonhuman primates and saw him as favoring the kinds of deterministic biological explanations that previously had inspired eugenics.

Harold Varmus had become NIH director in 1993, and it fell to him to replace Goodwin, which under the circumstances was an even greater challenge than usual, given that issues concerning mental health and human behavior seemed always to draw scrutiny from diverse advocates and from members of Congress. Varmus had shared a Nobel Prize with Michael Bishop in 1989 for discovering that oncogenes arose from mutations in normal cellular genes. Of particular note, he had almost no administrative experience before becoming a very successful and influential NIH director. Perhaps generalizing from his own (exceptional) experience, Harold decided that he wanted to replace retiring NIH institute directors, who typically had been career administrators, with working scientists who like himself would continue to run labs while directing their institutes.

Varmus appointed a search committee with instructions to identify a psychiatrist—a qualification that was demanded by members of the mental health community—with an active laboratory research program. The committee identified a short list that included a plausible senior psychiatrist, but before the process finished, he unfortunately died while jogging at a scientific meeting. The other candidates, as I heard the story later, were prominent psychiatrist, including department chairs, whose work did not pass muster with Harold. He decided, therefore, that a new search was necessary, and after that one failed to identify a candidate that could meet his expectations, he asked for a third search. As my wife reminds me, I was the product of the third failed search. By the time the third search was initiated, Zach Hall, Harold's colleague from the UCSF had arrived to lead the neurology institute, NINDS. Zach Hall, now retired, was a superb basic neuroscientist who had chaired the Department of Physiology at UCSF. He and Alan Leshner, then Director of the National Institute on Drug Abuse (NIDA) cochaired the third search for an NIMH director.

Federal searches have very formal procedures, including clearly specified start and end dates. As Zach Hall later told me, he had looked through the candidate's CVs on a day before the search was to close. He saw that once again, there would be no candidate acceptable to Harold Varmus, and therefore started calling a few younger neurobiologists with psychiatry training who would not have imagined applying for such a role, but whose research

might appeal to Harold. I was traveling when Zach called my office—he reached me at home a few days later during the weekend to explain what he had done. On the Friday on which the search was to close at 5 p.m., my tricky friend had managed to convince my assistant to fax my CV to him; he then used my CV to enter me into the search. I was flabbergasted and flattered—I had enormous respect for Zach, whom I had gotten to know from writing a chapter for his book, *Introduction to Molecular Neurobiology* (Hall 1992). That said, I had little idea of how NIH worked despite reasonable success in obtaining grants from NIMH, NIDA, and NINDS, and no sense at all of what institute directors did.

I then learned I was to be interviewed on the NIH campus in Bethesda, and soon, a stack of paper and brochures arrived that described current intramural and extramural personnel and programs, and also contained recent program announcements, press releases, and reports. I was troubled by what I read, although based on my familiarity with the science relevant to mental illness, I confess that I was not surprised. Although I had not published in psychiatry journals—my lab's work belonged in neuroscience and molecular biology journals—I did keep up with the psychiatry literature. Based on the materials I received, it was clear that NIMH supported some excellent basic neuroscience that ranged from the molecular to the neural circuit levels of analysis; there was even a small, but superb, portfolio of computational neuroscience. However, the basic neuroscience portfolio represented a surprisingly small fraction of the NIMH investment, and indeed, the percentage of its extramural funds spent on investigator-initiated (R01 grant funded) basic science was among the lowest among all NIH Institutes. The NIMH portfolio was dominated by large and often intellectually amorphous center grants. The largest expenditure in the portfolio went to center grants that supported research in psychiatry departments. The funds were largely expended on departmental infrastructure and internally selected pilot projects—skating fairly close to the Platonic ideal for slush funds. Most of these center grants had been renewed many times over the years and had devolved very nearly into an entitlement.

There was also a portfolio of individual projects and four large center grants focused on the prevention of mental disorders. The most troubling feature of this costly investment was the complete lack of any empirical basis on which to base primary prevention of any serious mental disorder. Lacking any insights into pathogenesis, these centers largely focused on epidemiological risk factors, such as a childhood history of abuse, neglect, poverty, and stress. These are all bad things to be sure, indeed already known to exert broad negative effects on health. Not forthcoming, however, was any evidence of specific, actionable mechanisms associated with any of the mental disorders to be prevented. As a result, most of the recommendations coming from this research program argued for large-scale social and economic policy interventions well outside the remit or expertise of NIH.

Within the large and costly intramural program, many of the clinical branches, like a large number of extramural grants, purported to be translational in nature. As in the case of the prevention grants, there were no credible, replicated basic research findings on which to base such an extensive translational investment. At best, the research projects seemed premature; many relied on questionable animal models or on human studies, most often underpowered, that enrolled subjects according to *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria, and therefore were studying a heterogeneous grab-bag of conditions.

I have little capacity or desire to suppress my honest views in the service of diplomacy, although I do often soften confrontations with humor. In any case, it seemed preposterous to me that I might be a serious candidate for the directorship, and I assumed that the committee would agree. I therefore saw my interview as an opportunity to share my concerns with influential leaders in the field of mental health and related disciplines, such as neurology. I was critical, but also clear about what I would do if selected (and later did do). I described the goals that I would pursue to the committee and later to the science press (Marshall 1996). These included increasing investment in basic neuroscience and basic cognitive and behavioral science relevant to the NIMH mission, scrutinizing the center grants with a view toward eliminating those that were unproductive, investing in the technology and computational tools to advance the analysis of genetically complex disorders, rolling back support for weak and premature translational research investments, and recasting the clinical trials program to involve fewer but better-powered trials—and in the absence of interesting new compounds—using our trials program to address questions that could significantly inform clinical practice. I also noted that given the low quality of intramural research compared with the possibilities extramurally, I would commission an in-depth review of intramural research at NIMH.

I reassured my wife Barbara, pregnant with our third child, happy with her lab and clinical work (pediatric bone marrow transplantation) at the Dana Farber Cancer Institute, and very much against a move, that after my *enfant terrible* performance I was sure I would never hear from NIH again. Once again, I was wrong. A few weeks later, Harold Varmus invited me to interview with him, after which he began a process of recruitment. From my first interactions with Harold, I was deeply impressed with him, and initially intimidated by his breadth of understanding and penetrating intellect. It mattered to me that he had successfully recruited Zach Hall to NIH, which indicated that it was possible for there to be a new generation of institute directors who were different in scientific acumen, taste, and rigor than some of the prior generation. Nonetheless, I was happy at Harvard, and a move seemed to promise only disruption with no benefit for my family.

I was in the midst of planning new space at the Medical School with Gerry Fischbach and it was early enough in my career that I worried about what would become of me if I were to become NIMH director. I certainly did

not intend to remain an institute director for life, which seemed a recipe for growing stale and bureaucratic, and I also recognized that my personal laboratory would have to take a back seat to the serious work I would be taking on. I talked to Zach Hall, Alan Leshner, and Harold Varmus about my uncertainties for four months—my angst must have grown wearying to them. By March 1996, it was past time for me to decide, and I was leaning against moving to NIH for all of the rational reasons I have adduced. However, my temperament was brewing a different outcome for me. I felt growing within me an intense drive to fix what was broken at NIMH. I would wake up at night thinking about what I would do. I suspect that Harold recognized this as my Achilles' heel. More than once he told me that my ability to influence the science I cared about would be far greater from the vantage of NIMH than from my lab at Harvard. He reeled me in by acknowledging how weak the NIMH portfolio was, saying something to the effect that NIMH was broken, that it had to be fixed, and looking right at me, said that it was my job to do it.

There is a Jewish concept of Tikkun Olam, which can be translated as a duty to repair the world. In Reform Judaism (and in my atheist, materialist version of secular Judaism), this can be interpreted as a call to act constructively, but it can also mean that some things in the world are broken and thus in need of repair. I was definitely not thinking about such Jewish concepts during that conversation in Harold's office in Bethesda, although I have often returned to them when reflecting on why I disrupted my family and risked my long-term career as a laboratory scientist. In any case, Harold hit the mark, and I accepted. He then added that he needed me to start in two weeks since Congressional budget testimony was in the offing, and he was unwilling for the acting NIMH leadership to represent NIH. Over the years, Harold more than held up his end of what was a powerful implicit bargain. He was a great mentor to me, invariably supporting me when, after the appropriate consultations, I made the changes that NIMH needed. Harold was himself an exemplar of fearlessness in the defense of high scientific standards and academic freedom and, while I am no shrinking violet, his example gave me courage when I told furious incumbents that NIMH programs on which they had long relied were coming to an end.

After arriving at NIMH, I spent much time analyzing the portfolio and trying to understand how funding decisions were made. I was curious about variations in the functioning of study sections (initial review groups) that rank grants by scientific and technical merit. I also wondered whether NIMH slavishly followed study section rankings or whether the staff and the advisory council—more properly the National Advisory Mental Health Council or NAMHC—made alterations in the ordering of grants based on such criteria as mission relevance, portfolio balance, or demonstrable errors by a reviewer. With regard to mission relevance, I quickly learned that the defense of basic science was a consuming and never-ending effort.

Patient advocates often confronted me at meetings, wrote critical op-eds, and complained to Congress about what they saw as wasteful distractions from discovering new treatments but that I saw as the critical foundations for progress, albeit unpredictably so and in the long term. Making matters worse, a small but vociferous fraction of clinical and translational scientists publically agreed with my critics, arguing that if only they had the resources being diverted to basic science, there might have been cures already. The well-known advocate E. Fuller Torrey kept recycling attacks on the basic research that NIMH funded, with a special venom reserved for behavioral science. A favorite target for Fuller was research on bird song as the epithet of "bird-brains" seemed irresistible to him (Torrey 2001). I had to respond to multiple Congressional inquiries over the years—indeed, I proactively visited key members of Congress who I learned were susceptible to the denigration of basic science—educating them, albeit very respectfully, about such facts as that the mechanisms by which birds learn their songs were our best window into the relationship between learning and brain plasticity.

Returning to peer review and decision making, I learned that NINDS had a history of funding grants strictly in percentile order coming from study sections. NIMH intervened, albeit modestly, in setting the order in which grants were paid, but I was surprised to learn that there were no formal criteria for doing so. Based on my sitting as an observer at some study sections and reading many summary statements, I was concerned by the significant variation in the quality of judgments. Many peer review groups exercised appropriate rigor, acted as good stewards of their disciplines, supported reasonable risk taking, and even tolerated occasional heresy if proposed by credible investigators with well-reasoned proposals. At the other extreme were peer review groups that seemed like closed-minded sects on a mission to protect the funding of their members. Like any human endeavor, the quality of peer review depends on many factors, including its overall organization, assignment of applications, instructions provided to reviewers, the strength and competitiveness of the field being judged, and the people participating in the review process.

Over time and based on discussions with colleagues at the weekly 90-minute meetings of institute directors, I concluded that the strength and vitality of the fields supported by NIMH had unusually large variance. Important factors included historically based intellectual commitments of fields (e.g., in some areas of psychology and other areas of social science, the idea that genes contribute to human behavior was treated as anathema, notwithstanding much compelling evidence from twin and adoption studies). Other important factors included the maturity and power of the technologies available to the field, the tractability of the field's problems, and the number of well-trained scientists engaged in that research area. Large fields supported by NIMH for which significant weaknesses were apparent during the 1990s included neuroimaging to identify correlates of mental illness

(in contrast with robust, replicable results achieved when neuroimaging was applied to well-defined questions in cognitive neuroscience), biological candidate gene studies of various disorders, investigations of disease mechanisms that relied on the putative face validity of animal models, and studies that employed pharmacologic or hormonal perturbations of patients to probe disease mechanisms or identify biomarkers. It was apparent that too many studies were based on surmise rather than strong prior evidence; many were poorly designed (in some cases, because investigators were forced to rely on DSM criteria to select their subject populations); essentially all lacked power calculations; and most did not test any crisply stated hypotheses. What was apparent was that practitioners within such fields seemed to have blind spots for such weaknesses (many would have been addressable if recognized). Especially in the clinical branches of the intramural program, I was struck by the number of intelligent, well-trained, and well-intentioned people who had devolved into a state of torpid incumbency within scientifically stagnant communities. In the intramural research program, the risk factors were clear: generous funding year after year, along with relaxation of the competitive selection pressures that characterized extramural science. This is not to say that the extramural research portfolio was immune to such problems, but they were far less common.

These observations reminded me of my studies at the University of Cambridge and, in particular of Thomas Kuhn's *The Structure of Scientific Revolutions* (1962). Although much attention and debate focused on Kuhn's analysis of scientific revolutions, such as that engendered by Copernicus, I was more interested in his analysis of what he called "normal science." Kuhn's view was starkly different from Karl Popper's heroic view of science as an ongoing process of hypothesis testing. According to Popper (1959), hypotheses could never be proved, only falsified; however, falsification served to clear out the intellectual underbrush making way for better hypotheses. In contrast, Kuhn described normal science as being typified by long periods of incrementalism constrained by the need to fit new observations and theories within a settled explanatory framework or, in his terminology, paradigm. When working within a paradigm, Kuhn argued, scientific communities behave conservatively. They do not boldly test hypotheses with a view toward discarding them, but rather, resist falsification. Scientists tend to explain away or turn a blind eye to evidence that does not fit the accepted framework. A classic example of this phenomenon was the addition of epicycles to models of planetary orbits to preserve the Ptolomeic understanding of the solar system in the face of otherwise highly destabilizing observations.

In Kuhn's view, only when anomalous observations and negative evidence accumulate to a breaking point might a revolution occur, precipitating a wholesale replacement of the old paradigm, such as the replacement of Ptolemaic with Copernican astronomy. Kuhn's dichotomy is too simplistic and Procrustean to capture much of the history of science, including the

history of biology. Although there are instances when his concept of a revolutionary paradigm shift fits, it is also true that normal science often exists for many years in parallel with clear-eyed hypothesis testing. Kuhn's views combined with more recent work, such as that of Kahneman and Tversky documenting such cognitive distortions as confirmation bias, help explain this strange phenomenon by which scientific communities insulate themselves and resist needed change.

In any case, Kuhn might not have been surprised by what I observed. Several large scientific communities in the NIMH orbit ignored well-established methodologic advances, especially if they were developed within another discipline and violated their consensus explanatory frameworks. For example, from before my time at NIMH to the present, scientists who study psychopathology within psychology or psychiatry continue to accept candidate gene by environment (G X E) interactions as an established truth; within these fields, investigators still attempt to extend existing findings. Yet the population and statistical genetics communities that represent the sophisticated stewards of the relevant methods have definitively rejected candidate G X E approaches to psychopathology as conceptually confused (excessively reductive and positing more than additive effects for which there is no evidence), guilty of reliance on vaguely defined and ascertained environmental effects, and statistical sins such as failure to correct for multiple testing or attain reasonable statistical power (reviewed in Duncan and Keller 2011).

I came to the view that the only way to reprogram resources from backward, entrenched scientific communities was through structural reorganization and changes in policy. Rational discourse is no match for the powerful incentives that affect the worldview and actions of well-funded incumbents. Fortunately, when I arrived at NIMH, I was given a mandate from Harold Varmus to integrate the review of NIMH neuroscience and behavioral science grant applications into the larger NIH review system. NIDA and the National Institute of Alcohol Abuse and Alcoholism (NIAAA) had received similar mandates. Like NIMH, they had been overseeing the review of their own grants—a most unhealthy practice—as a result of a prior bureaucratic separation of our extramural grant-making into a now defunct Alcohol, Drug, and Mental Health Administration (ADMHA) that also made block grants to the states for service provision. Now extramural review was to be integrated into the broader NIH system. Instead of tinkering at the margins, I was able to convince my open-minded colleagues Zach Hall, Alan Leshner, and Richard Hodes (National Institute on Aging) to rethink the review of neuroscience and behavioral science proposals at NIH and start entirely afresh. NIAAA, which in those days exerted great efforts to separate itself from NIDA, based on considerations of turf instead of the needs of science, opted out and decided to integrate with a liver toxicology study section.

The reforms entailed much analysis, work, and engagement with investigators who served on the many committees that had been invited to design

the new study sections. As would be expected from such a complex reform, the result needed adjustments when put into practice. This reorganization, however, permitted us to recognize the emergence of new fields and methodologies, to take account of newly formed intellectual connections, to break up groups that previously had acted like protective guilds, and to ensure that no study section was dominated by any one institute. The reform successfully created a larger and more open marketplace of ideas—for a time. Like any such human activity, the benefits waned over time as new self-regarding groups coalesced. It would have been ideal to renew such a process every decade or so, building in better evaluative tools than we did. The amount of work for everyone and anxiety for investigators was simply too great, and thus changes in review organization since that time have tended to be more piecemeal.

As promised before I took up my post, I commissioned an in-depth analysis of NIMH intramural research by a "blue ribbon" panel. One of their foremost observations was that there had been similar reviews in the past, but that the recommendations had not been acted on seriously. I did not disappoint this panel. The panel found some great strengths such as the primate neuropsychology program led by Mortimer Mishkin and the basic neuroimaging program, both world leaders. It also made many trenchant criticisms not only of individual basic laboratories and clinical branches, but also of governance processes. In response I strengthened the periodic reviews of the laboratories and branches (many of which had budgets of several million dollars each year) and gave them teeth. These subsequent reviews were organized and led with integrity by the two scientific directors who led the intramural program in succession, Susan Swedo and Robert Desimone. While recognizing the difficulties created for some investigators, we closed many of the irretrievably weak programs over the years, and I reprogrammed much of the money to extramural grant-making, with the greatest beneficiary being the extramural division that funded basic neuroscience.

I doubt that I would have wanted to start an intramural program if it had been up to me many years before; but the decision had been made long ago and I was responsible for the program and the more than $100 million in taxpayer funds that it spent. An important question was how to maximize the program's strengths, which in many areas, were considerable. I worked on this issue together with my old friend and colleague Gerry Fischbach, who had replaced Zach Hall as director of NINDS—I had cochaired the search. We asked ourselves how we could lower barriers to collaboration across the two institutes, share expensive equipment, and increase cooperation on recruitments in a manner that would enrich the community intellectually. I give Gerry full credit for recognizing that the optimal solutions would require a new building.

The idea was to replace the old and incommodious Building 36 shared by our neuroscience programs with a modern building designed to maximize

collaborative interactions. Building 36 seemed to have been constructed on the plan of a medieval monastery. The walls between the small, often depressing lab spaces were constructed of cinderblocks so that renovations required a jackhammer. Ultimately, we convinced Harold Varmus, Donna Shalala (then secretary of health), the White House Office of Management and Budget, and finally the U.S. Congress of the need for an upgraded neuroscience facility at NIH. The plan was a building large enough to bring together as many of the neuroscientists at NIH as possible and to configure the space to maximize collaboration. Although the full construction took years longer than planned, and was finished long after I left, the John Porter National Neuroscience Center seems to have accomplished what Gerry and I had envisioned. I worked closely and happily with Story Landis who replaced Gerry as NINDS director when he left to become vice president of Columbia University and dean of its Medical School. We ensured implementation of our vision of interdisciplinary collaboration, open collaborative spaces, and shared core facilities and equipment. After I left NIH at the end of 2001, Story shouldered the burden of fighting the human tendency to prioritize administrative silo-building over scientific collaboration.

I initially worried that some judgments I was making might be unfairly severe. However, discussions over many months with Harold Varmus, Zach Hall, Alan Leshner, Rick Klausner (National Cancer Institute), Tony Fauci (National Institute of Allergy and Infectious Disease), and other colleagues convinced me that the problems I had perceived were quite real—and that there was a strong expectation that I would take them seriously. From my savvy colleagues, I also got the good advice not to take on too many issues at once and not to assume an excessively confrontational stance. At the same time, however, I was intensely aware that NIMH received significant public funds and that I had been entrusted to oversee the allocation of those funds to the best science that would contribute to our mission of elucidating the pathogenesis of mental illness in the service of making much-needed advances in diagnosis and treatment—critical public health needs that had been languishing for decades. It helped me that I had no desire to remain an institute director for life. I mused that if I were somehow forced out of my position for acting on my convictions, my "punishment" would be a speedier return to academia.

That said, scientific groups that detect threats to their funding—and thus to their livelihood and sense of dignity—often react with fury, and I was, on more than one occasion, the object of such anger. For example, a group from the American Psychiatric Association (APA) complained to members of Congress and to Harold Varmus when I terminated the mechanism that awarded large, indefinitely renewable center grants to psychiatry departments. My recollection is that Harold declined to meet with the APA delegation. I did create a new, far smaller center program aimed at incentivizing interdisciplinary research, and named it for Silvio Conte, a

congressional appropriator who had been a champion of NIH research. I insisted that the program permit only one renewal, on the assumption that after 10 years of funding, it would be time for members of a collaborative network to find other partners with new technologies and new questions. Overall, however, I preponderantly ended centers programs, thus creating a large infusion of money into investigator-initiated grants with a significant focus on basic neuroscience. Given that NIMH was one of the few institutes with no Mendelian disorders in its purview, I also supported investment in the development of genomic and computational tools to advance the analysis of polygenic disease.

A few other surprises awaited me. For example, I discovered that the lion's share of NIMH career and training funds went toward the salaries of the most senior scientists in the field—despite their access to many other sources of funding—through a renewable career award mechanism (K05). After far more consultation and analysis than was really necessary to enact a just and sensible policy change, I terminated this mechanism and reprogrammed the funds to junior investigators. There was a campaign of outraged editorial writing (Holzman et al. 1998) and complaints. These did not change my view or the new policy, but they did reinforce my dark Augustinian-Hobbesian view of human nature.

There was no shortage of areas in need of attention, and on occasions in which there were topics of significance to the institute, I appointed a group from my advisory council (NAMHC) to work along with NIMH staff and extramural scientists to devise new policy recommendations. I made sure to provide clear charges to these groups, with encouragement to be bold, and made myself available for questions they might have. One example was a Genetics Workgroup that I commissioned in 1997. It was chaired by Sam Barondes (USCF) and included as members, Aravinda Chakravarti, Mary Claire King, Eric Lander, Robert Nussbaum, Ted Reich, Joe Takahashi, and Steve Warren.

This group was constituted in recognition of the failure of candidate gene and linkage studies in psychiatry, and in light of the growing recognition of the polygenic nature of these disorders, signifying that extremely large samples would be needed for genomic analysis. The workgroup recommended, and I implemented policies to establish, a repository to store DNA samples and associated phenotype data with the goal of facilitating large-scale genetic studies that would become feasible as genomic technologies matured. In concert, the workgroup recommended that NIMH require sharing of these banked DNA samples after a proprietary period of 12 to 18 months (which in retrospect was excessively long).

I also implemented the recommendation of a strong requirement for data sharing (one of the earliest such policies at NIH) with the goal of facilitating meta-analyses needed to achieve adequate statistical power as well as secondary analyses. The workgroup also recommended that informed

consents be redesigned to permit wide sharing of data, encouraged international studies and studies of diverse populations, and recommended that NIMH genetics studies attain the scale necessary to investigate genetically complex disorders. This last recommendation militated against the inefficient and inevitably underpowered "biological candidate" gene studies common at the time. With the agreement of the NAMHC, no extramural grant applications with candidate gene designs were subsequently funded. However, within the intramural program, projects are reviewed retrospectively, not prospectively. For an intramural program this is the right procedure because prospective review could focus too much on feasibility and impede risk-taking. In this instance, however, it meant that several intramural clinical branches ignored the best advice of professional geneticists and NIMH policy and continued to perform wasteful and unscientific candidate gene studies. This had the further ill effect of influencing the work of neurobiologically oriented translational scientists worldwide who did not have the training to reject such false leads. Indeed, failures of translation across the yawning interdisciplinary gulf that lies between human genetics and neurobiology continue to trouble psychiatry research to this day (Hyman 2018).

In addition to my deep engagement with NIMH science, there were opportunities to engage through Congressional testimony in policy discussions on such issues as fighting for parity of health insurance coverage of mental disorders with general medical disorders, pushing for the broader adoption of evidence-based treatment of mental disorders, and advancing the idea that many juveniles in the criminal justice system deserved diagnostic workups for potentially treatable neuropsychiatric disorders. In June 1999, I participated in a White House mental health conference with President Bill Clinton, Hillary Clinton (who introduced me to the audience), and Al and Tipper Gore. Beyond the heady nature of such interactions, the conference had important practical results, most importantly, the president extended parity of mental health insurance to all federal employees. Many ethical issues also arose during my years at NIMH. Some related to the knotty problem of standards for informed consent when people suffered a severe mental illness. Other raised concerns that extended beyond traditional bioethics, touching on issues such as the effects of illness and treatment interventions on personal identity, moral agency, and other human characteristics dependent on the functioning of our brains. These considerations rekindled my interest in philosophy and ethics that contributed to my later becoming a founder of the International Neuroethics Society.

Given the rapidly changing technologies relevant to neuroscience and genetics, the remarkable advances in computing, and my unfinished business with respect to modernizing the scientific outlook and investments of NIMH, I could have fruitfully spent 10 years as director, but I did not. One piece of unfinished business for me was the system of disease definitions and classification in mental illness that were systematized in the American

Psychiatric Association's DSM, then in its fourth edition. Although knowledge of etiology and pathophysiology that would be necessary for a valid diagnostic system were clearly lacking at the turn of the 21st century, and is only very slowly emerging today, there was already much evidence that the DSM was grounded in conceptual errors. The major errors, about which I subsequently wrote (Hyman 2010) are (a) conceptualizing mental illnesses as discrete, discontinuous categories (like smallpox—either you have it or you don't), instead of quantitative deviations from health (like diabetes mellitus); and (b) the elaboration, without evidence, of a large number of narrowly defined disorders so that many patients who receive a single DSM diagnosis receive many.

The problem for research was that the DSM system had been adopted as a shared language with the false view that it would enhance replicability—in fact, inter-rater reliability is quite poor using DSM definitions for many disorders. Moreover, major depression, the most common serious brain disorder afflicting humanity, is diagnosed by a person having to meet five of nine criteria for at least two weeks. This gives 256 different ways of meeting criteria, and some individuals in a study cohort might overlap on a single criterion. Because study sections and journal referees had come to demand DSM criteria in the selection of patients for study cohorts, many studies have been vitiated by enrolling extremely heterogeneous populations but imagining them as a valid class.

I had thought of initiating the development of a new set of research diagnostic criteria for 10–15 serious, common disorders. I never initiated such an effort because the state of the science seemed too premature. In particular, genetics had yet to yield useful results that might provide some partial grounding of diagnostic groupings in nature, instead of committee consensus. Perhaps if I had stayed at NIMH longer, I would have initiated such an effort, but even now, 17 years after my departure, it seems too early scientifically for a wholesale overthrow of existing diagnostic manuals, even though some such efforts have been made, and despite the fact that the DSM system remains a millstone around the necks of investigators.

In December 1999, Harold Varmus resigned from NIH to become the president of Memorial Sloan Kettering Cancer Center in New York City. NIH was left with indecisive acting leadership and thus much greater vulnerability to the whims of the Congress. I had gotten to know Al and Tipper Gore quite well. She was particularly committed to mental health issues, and it was clear that if Mr. Gore were elected, NIH and NIMH would flourish. Of course, George W. Bush was elected, and although he supported rapid growth of the NIH budget in the first years of his presidency, life at NIH quickly became difficult.

President Bush has a complex legacy in health care. His powerful support for the President's Emergency Plan for AIDs Relief (PEPFAR) to distribute antiretroviral drugs to treat individuals with HIV/AIDS is arguably one of

the most important large-scale medical interventions in history. It saved countless lives in the developing world, especially in sub-Saharan Africa, and President Bush deserves enormous credit. However, notwithstanding early acquiescence to Congressional plans to increase the NIH budget in his first three years, there was no evidence that the new administration supported science as an activity and, indeed, substantial evidence of hostility. Best known are the severe limitations the Bush administration placed on investigations of climate change and on federal funding of stem cell research.

For NIMH, this significantly impeded our ability to support development of much needed human cellular models with which to study molecular mechanisms that contribute to psychiatric disease. In addition, the administration exhibited profound distrust of scientists and science agencies. They instructed the NIH institutes that they were not to have their own press officers, who had long served to share discoveries and important health messages with the public. Instead any communication to be externally released was to be overseen by the Department of Health and Human Services, which was not staffed to understand biomedical research, and which was politicized. Most institute directors had developed close relationships with some members of the House and Senate and with their staffs, as I certainly had. Members were often interested in diseases that affected their own families and their constituents—matters unrelated to partisanship—and also wanted to understand the manner in which we spent the considerable discretionary funds that the Congress had entrusted to NIH and the peer review system.

The Bush administration instructed us that we could no longer have a Congressional liaison on our staffs and that we were no longer permitted to initiate meetings with the Congress. Furthermore, if a member of Congress requested a meeting, we were to inform the Department of Health and Human Services. The department would then send a watcher to sit in on our meetings to ensure our loyalty on matters such as budgets, stem cell research, and other topics that they deemed controversial. After about six months, I concluded that I could not, in good conscience, work in such an administration and quietly began thinking about alternatives.

As I thought about leaving NIMH, I was struck by how much I valued the staff, many of whom I had recruited, and how guilty I felt that I would not stay longer to watch out for them during a difficult time for science. I also began to realize that my personal scientific goals had evolved. For more than five years, I had worked flat out to advance the science of mental disorders. My personal lab was doing well, but it still focused on dopamine and second messenger regulation of gene expression. As I contemplated a move, I realized that I would want to change my personal scientific focus, so that I could help make progress on diseases, such as schizophrenia and mood disorders, to which I had dedicated myself as NIMH director. These thoughts were accompanied by a sense of despair because there was not an

iota of scientific traction on disease mechanisms in 2001. Based on the high heritabilities of these disorders, it was clear that genetics would eventually yield molecular clues to pathogenesis, but not yet.

Based on the advice of the Genetics Workgroup of 1997 I had begun to put programs in place to maximize the likelihood of eventual success. The technology did not yet exist, however, that would permit genotyping and DNA sequencing inexpensive enough and accurate enough to identify specific alleles that conferred risk for highly polygenic conditions, such as schizophrenia and mood disorders. Without molecular clues that would eventually come from genetics, I saw no basis on which neurobiological investigation could proceed. It was during my period of scientific pessimism that Lawrence Summers, the new president of Harvard University, and U.S. treasury secretary during the last years of the Clinton administration, called me about the possibility of serving as provost (chief academic officer) at Harvard.

A Decade in the Scientific Time-out Box

Just as I had never imagined becoming NIMH director, it had never crossed my mind that I might become a university provost. In truth, when Larry first called me, I was not sure what a provost was. Yet Larry Summers' vision for Harvard was compelling. One of his most important goals was to promote cross-disciplinary academic inquiry with a focus on science and engineering. He was thus seeking a scientist, ideally one who knew Harvard, who had experience in the leadership and administration of a large enterprise. If I took this position, it would permit Barbara and me to return to Boston with our three children—although once again, it would disrupt Barbara's work and, for a second time, her local social networks.

Larry began recruiting me by stating that he saw interdisciplinary life sciences as perhaps the most important intellectual venture of the early 21st century. He recognized that Harvard had a strong faculty in diverse areas of biology as well as a large and accomplished clinical faculty based at the affiliated hospitals—in 2001, the hospitals had approximately 11,000 faculty members and currently about 14,000 of which approximately 2,000 are principal investigators with grants. Despite Harvard's strengths, Larry thought that the university was not living up to its potential in the life sciences primarily because the different labs and departments across the Faculty of Arts and Sciences, Harvard Medical School, the Harvard School of Public Health, and the hospitals were highly balkanized. The possibility of taking on an entrepreneurial institution building role in light of Harvard's resources was quite attractive.

There were negative aspects to the position as well. Most obviously, the provost position was relatively new at Harvard with poorly established responsibilities. Compared with essentially all other major research universities, the Harvard provost's office was small and weak. Larry supported the idea of a

strong provost and building a modern provost's office at Harvard because he recognized that some central authority would be necessary to pull together scattered and often fractious elements of the university. That said, I was well aware of the skepticism of the faculty and the antagonism of many of the deans toward a stronger central administration. In considering the options, I increasingly felt alienated from the Bush administration—I had spent considerable time with the secretary of health and human services and with Bush administration staffers who were no friends of science. As Larry and I talked further, the prospect for strengthening science and engineering at Harvard seemed to outweigh the worrisome aspects of academic administration.

I began at Harvard at the end of December 2001. I did build a strong and effective provost's office. More gratifying was the broad intellectual engagement that came from such diverse roles as chairing ad hoc committees that were the final step in tenure decisions across schools and disciplines, overseeing deans, hiring and supervising the director of a great art museum, reorganizing the world's largest private library system, and finding some time to teach bright undergraduates. In terms of enhancing the life sciences, I negotiated the Harvard side of the agreement with MIT (represented by their provost Bob Brown) and the philanthropist Eli Broad that established the Broad Institute of MIT and Harvard, where I now spend the preponderance of my time. I worked with another philanthropist, Hansjoerg Wyss, to create an interdisciplinary and cross-school institute that works at the boundaries between science and engineering. I also helped create the first department at Harvard that spans the Faculty of Arts and Science and Harvard Medical School.

The plan was for me to serve as provost for about five years, and to make the kind of progress that I described. But plans do not always survive contact with reality. Larry was brilliant and visionary but also brusque and—I think that he would himself agree—remarkably impolitic. By the spring of 2006, he was on his way out of the Harvard presidency, and the university was in turmoil. A new president, Drew Faust, begin in 2007 but soon thereafter markets crashed, and the great recession began. My hopes of moving on were impeded by the circumstances: I did not think it ethical to abandon the university and a new president at such a troubling time. In the end, I served for nearly a decade, far longer than I had planned.

I was repaid for these extra years because the Broad Institute, which I had been deeply involved with early in its history, had matured and was a wonderful place for collaborative science. Most unexpectedly, during my decade as provost (and from a scientific perspective, my decade in the "time-out" box), genomic technology and computing resources had advanced to the point at which psychiatric genetics could succeed. In addition, stem cell technologies and genome engineering had come of age and single-cell transcriptomics was on the horizon. New approaches to systems-level neurobiology were also moving ahead quickly, later to be accelerated by President Obama's

BRAIN Initiative in the United States and by diverse national and international brain projects across the world. There was no longer reason to despair about psychiatric research. Although still exceedingly difficult, it was now possible, beginning with genetics, to gain traction on disease mechanisms.

I was particularly fortunate that a psychiatric disease program had been initiated at the Broad Institute by Ed Scolnick, who had retired after many years as president of Merck Research labs. The plan for the center was to attack the biology of serious mental illness beginning with insights gleaned from genetics, but the main goal was to use emerging knowledge to advance therapeutics. Thanks to the philanthropy of Ted and Vada Stanley, the program was renamed the Stanley Center for Psychiatric Research at the Broad Institute. Ed Scolnick wanted to be able to focus on therapeutics research in the years before his second retirement. Thus, in spring 2012, I became director, the start of a new adventure.

I have had to learn a great deal about the design, implementation, and analysis of large-scale, unbiased human genetic studies. Because these studies are yielding results (with nearly 100,000 schizophrenia patients studied by genome-wide association, and nearly 30,000 by whole exome sequencing), I have had the opportunity, along with brilliant colleagues, to advance the development of model systems that permit us effectively to interrogate hundreds of allelic variants of small effect (McCarroll and Hyman 2013; Hyman 2018). These include thousands of patient-derived pluripotent cell lines that increasingly can be differentiated into specific neural cell types and studied in massively parallel experiments that minimize technical variability while permitting examination of genome-engineered variants against large numbers of human genetic backgrounds. In addition, emerging model systems include human brain organoids with diverse genetic backgrounds and engineered mutations, and marmosets genetically engineered with CRISPR-Cas 9. The interrogation of polygenic human brain disease will be extremely challenging. Nonetheless, especially in light of the despair that I felt upon leaving NIMH, I now feel quite fortunate to have great colleagues, remarkable philanthropic and federal funds, and access to the technologies that are beginning to elucidate the mechanisms of schizophrenia, bipolar disorder, ASDs, and other dreadful illnesses.

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