Brave New Brain:
Conquering Mental Illness in the Era of the Genome
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Report by Bob Pignatti

This book is an excellent introduction to what scientists and researchers know about the human brain and the human genome. Doctor Andreasen shows us how molecular genetics, molecular biology, and neuroimaging of the brain are converging in an effort to conquer mental illnesses such as schizophrenia, bi-polar disorder, anxiety disorders, and dementia. In the first of four sections, the author introduces us to the major topics: the personal and economic burden of mental illnesses, the internal experience of those who suffer from them, and the various ways that they are often misunderstood by the public. The second section provides a "mini-tutorial" on neuroscience and molecular genetics. This is a rather technically challenging section, but it offers a valuable resource to learn more about the mind and how it relates to the tiny inner chemical workings of the brain. The third section talks about scientific advances in the four major groups of mental illnesses mentioned above, going into detail for specific illnesses and defining the symptoms and the effects on patients' lives. The last section addresses moral and economic implications of our knowledge of mental illness. Throughout the book Dr. Andreasen presents case studies that give us a feeling for the impact of mental illness in a person's life. This book is a much-needed plea to improve our understanding of these tragic and wide-ranging diseases.

The author likens the message of this book to one of Shakespeare's last plays, *The Tempest*, suggesting that the play looks at pain and suffering and expresses a conviction that they can be conquered through enlightenment and knowledge. She says this book is about building a "brave new brain" and discusses a group of illnesses that humans are heirs to—illnesses that arise from the brain and are expressed through the mind. There are many reasons why we cannot afford to ignore mental illnesses. They are among the most common of all diseases that afflict human beings. They are very costly both economically and psychologically. The global burden of mental illness will continue to increase until we can identify ways to improve treatments or develop preventative measures. But at the same time, we are in the midst of a golden age of biomedical research—both mapping the human brain and the human genome. The achievements on these two developments will meet one another in time. We hope to understand how cells in our brain go bad—specifically, what this does to systems like memory and attention, and how it leads to the development of diseases such as schizophrenia and depression.

We look at a case study about Jim, a man who slowly discovers that he suffers from depression. As we hear his story, we realize that this can happen to any one of us. It starts out innocently enough, with little things like having difficulty getting up in the morning and anxiety over things that would normally not bother him. But as he gets progressively worse, he sees several doctors and, with the help of his understanding wife, gets the treatment he needs—a combination of medication and counseling. This study shows how important it is to have good doctors to prescribe the proper medication. Some medications can have adverse effects for the patient, which happened in Jim's case, where he actually felt worse after taking a particular medication.

Dr. Andreasen now explores the differences between analysis and synthesis. To analyze means to break a thing down into its parts. Synthesis puts the parts back together again and restores the wholeness of things. Synthesis allows us to see things free of boundaries and barriers, as they are in the natural world. Over the years we have invented false dichotomies and arbitrary categories such as mind and brain, or drugs vs. psychotherapy. "Brain" refers to a physical organ and "mind" refers to an abstract concept—not palpable—so, the mind is sometimes considered less real. When we think of mental illnesses we must synthesize and understand them as mind/brain disorders. False reasoning says that if these illnesses are mental, then they should be treated with support and counseling of some sort; if physical, then medications should be used. Unfortunate consequences can result when medications and counseling are polarized and pitted against each other. The best advice is not "either-or," but "neither-or-both, as needed." Both counseling and medication affect mind functions by changing brain functions. A third false dichotomy is genes vs. environment; are mental illnesses due to genes or the environment? If caused by genes, mental illness is physical, biological, a "real illness and less stigmatized." If caused by environmental factors, then it is mental, psychological, less real, and easily criticized by arguing that the illness is due to an inability to cope with problems. Very few things in human life are due entirely to genes or to environment. Almost all mental illnesses are caused by a mixture of genes and environmental factors; such illnesses are called "multifactorial." People often do not know that genes are not rigid, but "plastic." They are influenced by the environment, and their behavior is changed by it. When we abandon these false dichotomies it gives us a much better grasp on how life actually works—we see a much more complex and richly textured world. Mental illnesses usually arise from multiple interacting causes, many of which we do not fully understand yet. Using synthesis rather than analysis can help us to avoid unwanted false polarization and open our minds to learning about mental illness in a more objective and natural way.

At this point we look at the brain and its physical make-up and what we currently know about how it functions. The brain is composed of three kinds of tissue: gray matter—densely packed cell bodies of neurons; white matter—neuron connections called "axons"; and cerebrospinal fluid (CSF), which contains nutrients and the by-products of brain activity. The surface of the brain looks very wrinkled, evidently in order to pack enough neutrons inside our skull and still keep our head relatively small. Genetic blueprints coded in our DNA provide the basic instructions that tell the brain how to grow correctly. These are shaped and modified by the experiences that the mind/brain encounters as we navigate our way through life. This concept, known as "brain plasticity," emphasizes that the brain is dynamic—it changes rapidly from moment to moment in response to challenges from the world around it. People who read this review will have slightly different brains as they absorb its contents and implications. We *can* change who we are by what we see, hear, and do.

The brain can be divided into functional systems that correspond to what we think of as "the mind," such as remembering, communicating with language, and focusing our attention. We are introduced to how the mind functions with the language system, the memory system, and the attention system. In addition, there are filtering mechanisms that mediate a variety of human functions and a variety of areas that are considered seats of executive, emotional, and cognitive functions. There is a fascinating look at how nerve cells of the brain send chemical messages to

one another. The neurotransmitters are the chemical couriers by which these messages are sent. Several common neurotransmitters relevant to mental illness are discussed here along with their locations and functions. Research now shows us multiple distributed circuits of the brain, showing that our brains are "multitasking experts." We almost never do only one "mental activity" at a time, but frequently use many systems to perform a single act; these are parallel circuits of complex mechanisms like a large orchestra playing a symphony.

Every cell in our bodies has exactly the same genes and DNA, which act as a blueprint for our basic human structure. Genes, however, are not as rigid as we tend to think, but a "responsive group of legislators that need to listen to biological messages and respond." One common question is how traits get passed on from parents to children. In order to answer this, we can use Gregor Mendel's remarkable observations to categorize four major types of transmission. Autosomal recessive transmission occurs in diseases like cystic fibrosis; autosomal dominant transmission in cases like Huntington's disease; sex-linked recessive transmission in diseases like muscular dystrophy; and sex-linked dominant transmission, which is extremely rare, occurs in some forms of rickets. A major breakthrough was the discovery of DNA by James Watson and Francis Crick in 1953. The role of DNA is often referred to as the Central Dogma in that it specifies a pathway for the flow of genetic information. DNA contains the genetic code that dictates the structure and development of all living things. Understanding the regulation of gene expression will likely give us clues to how diseases are caused and treated. Genetic mutations occur as a consequence of some disruption in DNA replication. There are two broad types of mutations: gene mutation and chromosome mutation. Cancer and many mental illnesses are probably examples of disorders that have high mutation rates since they sometimes occur in individuals with no known family history and then recur in later generations. Searching for disease genes is a daunting task because most common genetic diseases are "complex illnesses" and may be caused by nongenetic factors as well as genetic ones. Another complication is that not all people who carry the genetic abnormality will manifest the illness.

We now discuss the latest tools available to researchers for studying the brain. Mapping the mind using neuroimaging techniques provides researchers with important information as to how the human brain functions. When we discuss mapping and measuring the brain anatomy (structural techniques), we talk about CT (computerized tomography) and the newer MR (magnetic resonance). These tools are structural (anatomical) techniques. The second group of tools includes functional techniques (physiological/neurochemical). These include single photon emission computer tomography (SPECT), functional magnetic resonance (fMR), and positron emission tomography (PET). With these methods we can observe the brain while it is actually functioning as a mind—thinking, seeing, hearing, etc. In MR technology the brain is divided into a series of slices. These slices are then divided into tiny cubes called "voxels," which allow us to see the brain in very fine, three-dimensional detail. This allows researchers to study mental illness using MR as a probe to address some very basic questions about the brain's structure. We can also use MR to measure brain function and chemistry; functional MR methods can be used to study working memory, spatial attention and many other complicated activities by observing increased blood flow to specific brain areas. PET images are also used as functional imaging techniques, but the images are similar to MR. PET has shown that large parts of our brains are busy most of the time. With functional imaging techniques, we are learning about planning, recognizing, feeling pain, and brain aging. What has PET taught us about functional activity, of

the brain in mental illness? While performing a variety of mental tasks, patients with schizophrenia are unable to activate their frontal cortex as much as healthy volunteers. The story is more complicated than a single brain region malfunction, but it is a good start and, hopefully, we can continue to identify other brain regions involved with schizophrenia as well. We also hope to use PET to help identify and monitor the effect medications and psychological treatments have on the brain. PET studies have provided scientific evidence about the effect of higher and lower doses of medications to help us determine the correct dose for each patient.

The book explores a brief history of how misunderstandings and stigmas of mental illness arose throughout the ages. Then we meet some of the vital scientists and researchers who have contributed to our understanding of mental illness. A very influential but little-known German psychiatrist, Emil Kraepelin, with help from his now legendary team of researchers, including Alois Alzheimer, created the medical structure that we continue to use today, defining three groups of disorders including dementia, schizophrenia, and mood disorders such as depression and bi-polar disease. Alzheimer, for instance, identified a specific neural mechanism that serves as a marker for the disorder we now call Alzheimer's disease. Kraepelin and Alzheimer noted that these findings tended to occur in older people with dementia. While these discoveries were being made in Munich, a Viennese psychiatrist focused on another group of disorders known as neuroses or anxiety disorders. Sigmund Freud was intrigued by the exciting new techniques of neuropathology. He examined the effects of drugs on the brain and behavior and explored hypnosis to treat physical complaints. Sigmund Freud's work complimented Kraepelin's work, which emphasized dementias and psychotic disorders. Many of Freud's patients suffered from the illnesses we now call anxiety disorders.

The book explains the four stages of understanding mental illness: identifying a specific syndrome; identifying its pathophysiology; finding a treatment; and finding a way to prevent it from arising. Today most mental illnesses are still defined at the syndrome level—i.e., they are defined by a clustering of signs and symptoms in combination with a long-term course. The syndrome definitions are created in the Diagnostic and Statistical Manual (DSM), which is the standard diagnostic method for teaching medical students and psychiatric trainees. The first DSM (DSM1) was published in 1952 and evolved over time to result in the latest edition (DSMIV), which was published in 2000. The main goals of the DSM were to increase reliability and consistency in psychiatric diagnosis. The reliability levels of agreement between two clinicians who are evaluating the same information have increased considerably since the first publication of DSM1. Patients have also benefited from the increased objectivity provided by the diagnostic criteria. Anyone who is interested can buy a copy of DSMIV or look up the definitions on the Internet. However, there are some downsides to these DSM definitions. People can take these definitions too seriously. Also, the scientific basis of this information is credible but not infallible. Another criticism is that DSM definitions may tend to dehumanize clinical care—because of the easy and fast checklist it provides—and overlook the unique economic and social situation each person brings with him.

Now we go into an actual case study of Scott, a nice-looking seventeen-year-old boy who develops schizophrenia. When he first starts neglecting his appearance and showering infrequently, his parents get worried. He begins withdrawing into his room and spending lots of time alone when normally he used to enjoy time with his family and friends. The internal mental

dialogue presented in the book presents a chilling description of how disconnected and overwhelmed Scott feels without knowing why he feels this way. He deteriorates as he becomes increasingly suspicious of people and jumps off a bridge, attempting to take his life. With hospitalization and medication, Scott eventually recovers and is stabilized, for the most part, but he never returns to his old sunny self.

Schizophrenia primarily strikes during the late teens and early twenties. This is a complex disease that can be difficult to define because it has many different signs and symptoms, both active and passive. Passive symptoms, such as withdrawal and loss of interest in friends, are often the first sign of the illness. Active symptoms, such as hallucinations and delusions, may develop later and tend to respond to treatment more rapidly than the passive ones. The following are some basic problems expressed by patients with schizophrenia: *My thinking is confused; my ideas don't seem to connect quite right; I have trouble filtering out unimportant information; I feel bombarded by stimuli.* Schizophrenia is a brain/mind disease where, in most cases, several causes can contribute to injure the brain and mind. The pattern of family transmission suggests a role for genes and not for bad parenting. Most experts think that schizophrenia is multifactorial, involving multiple genes and, maybe, different genes in different individuals, as well as other environmental influences such as head injuries at birth, viral infections and hormonal changes. Studies by the National Institute of Mental Health (NIMH) show that during critical teenage years, brain growth and change occur in both healthy people and those with schizophrenia, but the developmental curves are quite different. The ill people show a decline in total brain volume and an increase in the volume of gray matter. To pinpoint the critical time window for the development of an illness is a vital step in figuring out how to prevent it. This disease seems not to originate in any specific brain region, but is a disease of functional connectivity between distributed regions. Newer medications have raised hopes to improve both the active symptoms such as psychotic episodes, as well as the passive symptoms such as loss of interest in life and loss of the ability to enjoy things and to think clearly and logically. Patients with schizophrenia also need help learning how to organize everyday activities. Cognitive re-learning treatment programs can help patients learn to focus attention more precisely, to solve problems more efficiently, and to improve both motor and mental coordination. These treatment programs can gradually rewire their brains so that new connections are found and patients learn to think and function more clearly and effectively.

Mood disorders such as bi-polar disease can be an emotional roller coaster. We will now look at the story of Hal, a successful developer in Santa Fe who recently began acting strangely—he became hyperactive, started talking faster, and was sexually obsessed; he acted like a domesticated animal who was turning wild. When Hal got a speeding ticket and then uncharacteristically punched the police officer, Marcia, his wife, got scared and sent him to a psychiatric unit for testing. He had symptoms of mania and was given medication to even out his excesses in moods. Over the next several years they both learned to cope with the highs and occasional bouts of depression Hal experienced. Mood disorders are illnesses that affect the emotional coloring with which a person perceives the world. In Hal's case he suffered from bi-polar disease—alternating between mania and depression—poles opposite one another. Depression is a miserable condition where the core abnormality is emotional, but there can also be problems with motor activity and cognition in more severe cases. Mania is the pole opposite depression: patients with this illness are cheerful, enthusiastic, and very talkative, but can

sometimes lapse into irritability when contradicted or when their plans are thwarted. Boundless self-confidence is a key aspect of mania. Patients can be convinced they have special powers, e.g., predicting personal experience; this is most likely produced by brain chemistry. Rates of depression among baby-boomers have risen sharply due to unexpected conditions they found in the world, intense competition due to large numbers and idealistic aspirations. Mood disorders tend to run in families with about twenty percent of the parents of people with mood disorders also suffering from a mood disorder. The tendency to be creative and to have mood disorders also co-occurs in families. Statistics from a thirty-writer study showed strong tendencies for mood disorders among them. Furthermore, their relatives also suffered from mood disorders. Common treatments include mood stabilizers, antidepressants, electroconvulsive therapy, and psychotherapy. Mood stabilizers such as lithium are used mostly to treat bi-polar disorder. Antidepressants, including tricyclic antidepressants and monoamine oxidase inhibitors, have some side effects, and careful prescription is necessary in each application. ECT is a very effective treatment for severe depression, although it has been given bad press by movies like "One Flew over the Cuckoo's Nest." And, finally, psychotherapy may be the treatment of choice for people who would benefit from this type of interaction and prefer not to take medication.

Now Dr. Andreasen discusses dementias that are diseases of aging. The hallmark of all types of dementia is impairment in memory and cognition, which leads to general decline in the ability to relate or function in life. Major forms of dementia are Alzheimer's disease and vascular dementia and other less common forms such as Huntington's disease and the dementia associated with Parkinson's disease. The brains of patients with Alzheimer's disease have nerve cells that look as if they had exploded and turned into a messy tangle of string. There are also areas that looked as if puddles of sludge (called "plaques") had accumulated. This disease is partially hereditary and occurs in adults from the forties through the eighties or nineties. Alzheimer's disease is the most common of the dememtias and accounts for about fifty percent of all cases of dementia, affecting about 2.5 million Americans. Vascular dementia is also called "multi-infarct dementia" and is the second most common cause of dementia. People with vascular dementia develop their symptoms because they have had a series of "small strokes." Depression is quite common in vascular dementia, as it is for stroke victims. Alzheimer's disease progresses with a slow, downhill deterioration, while vascular dementia has a stepwise deterioration, with increasing cognitive impairment after each stroke. Huntington's disease—unlike the complex Alzheimer's disease—is very simple and is probably the most genetic of all the metal illnesses. This illness is due to a single genetic mutation located on the short arm of Chromosome 4. This abnormal gene affects the caudate nucleus in the brain, which controls motor function. The first symptoms may be outbursts of anger or prolonged periods of despondency; later, people with this disease develop writhing and squirming movements with facial grimacing and speech impairment and typically die between five and twenty years after onset. How can dementias be prevented or treated? At this point there seem to be more questions than answers. Some basic ways to lower our risk are good physical and mental health. Engaging in a good exercise program keeps the heart pumping well to deliver an adequate blood supply to the brain. A healthy diet will give the brain the food it needs, balancing out fats, which are useful to the brain, although too much is not good for one's arteries. It seems that mentally active people may be less prone to dementia; so, keeping our mind exercised will also help to reduce risk.

Dr. Andreasen now focuses on anxiety disorders. Anxiety disorders are a group of conditions that share a pathological anxiety that jumps in and attacks us when we don't want it, or when it makes no sense at all. Anxiety can be useful to us in the right amounts and at the right times. The trick is finding just the right level of anxiety to do well; too much or too little are both bad. Anxiety disorders occur when our anxiety regulator gets reset to too high a level, so that we experience pathological anxiety rather than adaptive anxiety. Since the early twentieth century, several scientists have contributed to the understanding of anxiety and fear. Ivan Pavlov discovered the process we now call "conditioning"; John Watson applied Pavlov's ideas on animals to the study of humans' anxiety; Walter Cannon is famous for describing the "fight or flight" response; James Papey hypothesized that emotion tended to build up in the limbic system. The central theme in all of these experiments is a paradigm called "fear conditioning," which permits scientists to examine brain functions and responses that are common to most species. In us human beings, fear conditioning is most likely the mechanism that explains anxiety disorders. Frightening, anxiety-provoking images seem to stimulate the more primitive "limbic brain." On the other hand, using PET studies, we see that pleasant images shown to people stimulate the cerebral cortex, or the "higher" part of our brain. There are several types of anxiety disorders. Panic disorder is basically having a "panic attack"—an abnormal, intense fear reaction to a perceived danger. Phobic disorder is the intense fear of a social situation or a specific thing. Posttraumatic Stress Disorder (PTSD) is a repeated stress reaction to memories of a severe trauma such as during a war. Generalized Anxiety Disorder (GAD) is a disorder in which people feel anxious and worried most of the time, on edge, restless and tense, and may have trouble falling asleep. Obsessive-Compulsive Disorder (OCD) produces compulsive and repetitive acts that people perform for no obvious reason or to an extreme degree. These disorders are treated by medical and behavioral therapy and psychotherapies. One, or often a combination, of these treatments can be useful to patients with anxiety disorders.

The author explains that scientists once hoped to find a single gene or two for a specific mental illness. But now it is believed that most major mental illnesses are caused by more than one gene, or "multiple genes of small effect." Each of us has a genetic fingerprint totally unique to us. As these "fingerprints" sharpen with our increased understanding of the human genome, we can identify people with high risk for certain mental illnesses and choose a drug and dose suited to that person. We are in a race to create new and better drugs to treat mental illness, although it is a long and difficult road to obtain FDA approval. There are four phases in drug development; phases one through three are trials. It takes about ten or more years to complete all three trial phases, and ninety percent fail the phase-one trial. The long-term goal of psychiatric research is early intervention and prevention of mental illness, but that is difficult to achieve. We do not have the tools to identify high-risk individuals; the pharmacological treatments used to intervene are relatively crude; and the ethical problem of treating young people who are not yet ill may adversely affect their self-esteem and may have adverse side effects. The question of genetic determinism, as presented in Aldous Huxley's haunting futuristic vision in *Brave New World*, is not likely to happen, according to the author. Although genes play an important role in human development, they interact with many nongenetic factors, ruling out the notion that we are predestined and have no sense of autonomy. Several fascinating questions are addressed here: What about medication of the mind—is it humane treatment, cosmic surgery, or self-indulgence? Will the growth of biomedical technology dehumanize psychiatry (consider, for example, HMOs that may be dictated more by saving money and increasing profits rather than emphasizing the

patient's welfare)? If the mind and brain are different facets of the same thing, where is the soul or sense of self? Where are *we* after our brains cease to exist? What is the role in psychiatry—to cure people or cure society? There are no simple answers to these questions, but thoughtful opinions are given by Dr. Andreasen to provide a starting point for further discussion.