Brain and Mind  
May 13, 2004  

Richard Mayeux, MD  
Introduction to Session II  

Four Vignettes  

Richard Mayeux: Good afternoon. Welcome to the afternoon's session. My name is Richard Mayeux. I'm going to be your moderator and host. 

Just as I was coming up here I was handed a memo. There seems to be an electrical problem with the lights, and if you have a cell phone or a beeper, and it happens to go off you'll be electrocuted. So I'm going to ask everyone to turn your cell phones and beepers off. Thank you very much. 

This afternoon's session will deal with brain function and disease. I'd like to start off by giving you a couple of vignettes. 

Charlie had been an ambassador until he retired at age 76. He read biographies. His main complaint on the days that I visited him was that he had to reread several pages to remember where he was the night before. Every day he asked me if I had a cure for that problem, and he died about a year after that while sailing off the coast of Nantucket. He had Alzheimer's disease. 

During her twenties, while working as a broker in a prestigious firm in New York City, Deborah began to experience periods of severe depression accompanied by a loss of interest in her family and her friends and in her work. She found it increasingly difficult to concentrate. She experienced a loss of energy, difficulty sleeping, and eventually lost that job. By age 30, these bouts of depression were interrupted by periods of excitement, irritability, insomnia, and rare hallucinations. And she's still out of work, although she's functioning somewhat better under treatment. Deborah and her husband Matt are now trying to decide whether to have a child. Deborah has bipolar or what's called manic depressive illness. 

Michael's birth was very much anticipated by Janet and David. However, from an early age Michael's parents found him to avoid eye contact, to engage in meaningless, repetitive behaviors, didn't play with other children in the nursery, nor did he seem to have any desire to be contacted by anyone, even his parents. His speech was limited and he spent many hours focused on a particular piece of
furniture in the house. Michael is now 6, he’s in a special school, and he’s been diagnosed with autistic disorder.

Joe is an outdoorsman. He built his home for his family with his brother, [and] he’s a construction worker in Westchester County. He had a big passion for fishing and for extra-long camping trips in upstate New York. He and his family would often go for long walks in the Adirondacks. At age 68, though, he began to slow down, he was beginning to look older, stooped, he developed a postural tremor. Once a diagnosis was made and his treatment was started, he resumed many of these activities, although Joe was never quite the same person that defined him in those early years. Joe has Parkinson’s disease.

The Burden of Brain Disease

These are just a couple of examples of the devastating effects that diseases of the nervous system have on the lives of people. The burden of brain disease—and by that I mean all neurologic, psychiatric, and neurosurgical diseases—is high, one in seven people have a disorder of the brain. According to the Global Burden of Disease 2000 study, 20 percent, a fifth, of the years of life lost by premature death or lives lived with disability in the population can be attributed to stroke, depression, alcohol abuse, and Alzheimer's disease. Notably, after heart disease, those are the top four, so in the top five, four of them are neurological disorders or psychiatric disorders.

Studies of most brain and nervous-system disorders, such as these in twins, suggest that at least 50 percent of the societal burden is likely to be genetically influenced. But most of these common neuropsychiatric disorders are genetically complex. They can present as a Mendelian disorder where they follow the predictable rules of genetics, or they can be non-Mendelian, in which the signs and symptoms occur in what seems like a sporadic fashion, although there is this tendency to aggregate in families. Variations in several genes can lead to the same overall disease manifestation, but there are also disorders in which different types of mutations in the same gene result in different or unique manifestations and sometimes even different diagnoses.

Over the past two decades we've learned a great deal about Alzheimer's disease, Parkinson's disease, ataxia, depression and schizophrenia from the study of genetic variation in families. For example, inherited variations in four genes cause Alzheimer's disease differing only by the age at which you develop the condition, ranging anywhere from 20 to 80. Similarly, variations in four genes cause Parkinson's disease. But both sets of abnormal genes affect a common metabolic pathway that leads to regional brain degeneration. Family studies currently in progress indicate that variations in several additional genes will be identified in the next year or so, and each is expected to contribute to the complex story.
Recent studies of families of depression and schizophrenia have also identified promising leads to abnormalities in the brain that contribute to the cause of these disorders. Early-childhood trauma may trigger depressive episodes in later life among people who have a particular variation in the serotonin-transporter gene. At least four of the five susceptibility genes for schizophrenia appear to be involved in synaptic plasticity, signaling, and possibly glutamate neurotransmission.

Mutations in five different genes cause the most common form of hereditary neuropathy or nerve damage. It's called Charcot-Marie-Tooth. Duplication of a base pair or the presence of an extra segment of DNA in a gene called the Peripheral Myelin Protein, or PMP22, leads to the dominantly inherited form of the disease, which is most common and in adult years can be quite disabling. However, if you're missing a segment, if there's a deletion of the segment in the same gene, it leads to a disorder that's much less disabling called Hereditary Liability to Pressure Palsies. It was first discovered in tulip growers in the Netherlands, who after spending long hours on their knees working would develop a foot drop with subsequent complete or partial recovery. And on the other hand, if you delete a single base pair from that same gene, you call a devastating disease of childhood called Dejerine-Sotas, which is an inflammatory demyelinating neuropathy.

**Introducing Session Speakers**

The speakers for this afternoon's session on brain function and disease are going to take you through their own series of fascinating discoveries about the diseased brain. Using modern imaging techniques as a window into the unknown, Dr. Rapoport will discuss developmental alterations in children with hyperactivity and psychosis that are leading her team to a better understanding of the causes of these diseases.

Huda Zoghbi is going to discuss her work on Rett syndrome as a neuropsychiatric disorder in which a mutation on the X chromosome can alter gene expression, chromatin composition, and chromosomal architecture. Understanding this disorder will probably shed light on the fundamental properties of nerve cells, but also on the spectrum of autistic disorders. Continuing in this discussion will be Dr. Rutter. Autistic disorder, Asperger's syndrome, Rett syndrome, [and] pervasive developmental disorders represent a complex of developmental disabilities that occur early in life. Sir Michael Rutter will discuss his work on the genetic basis of these disorders and their pathogenesis.

Substance abuse is a massive public-health problem affecting individuals of all ages. Advances in brain imaging have allowed Nora Volkow to visualize and quantify the deleterious effects of drug abuse on the brain. Using this information she and others hope to develop strategies to prevent this deadly affliction.
More importantly, I think what you're going to hear this afternoon should give you hope, the hope that someday devastating diseases of the brain and nervous system will be detected earlier in life, perhaps even before birth, and effectively treated before the onset of disability, [and] the hope that our neurologic and psychiatric hospitals can become centers for prevention of disease rather than for the treatment of chronic and progressive disorders. Progress, though, takes place in carefully planned steps. The scientists that will share fruits of their efforts with you this afternoon are making great strides and are well on their way to satisfying our hopes and dreams for a better quality of life, perhaps someday free of the most common disorders of the brain and nervous system.