INTRODUCTION TO THE STANLEY BRAIN COLLECTION

The Stanley Brain Collection, part of The Stanley Medical Research Institute, is the most widely used brain collection in the world for researchers trying to find the causes of, and better treatments for, schizophrenia and bipolar disorder (manic-depressive illness). These disorders are the most severe and disabling of all psychiatric disorders, affecting approximately 4 million Americans at any given time. Schizophrenia and bipolar disorder, when untreated, are major contributors to the problems of homelessness, overcrowding of jails and prisons, episodes of random violence, and family tragedies. The public cost of these two disorders is estimated to be approximately $100 billion per year (in both direct and indirect costs). Finding the causes of and better treatments for these disorders is thus a national priority.

Between 1994 and 2005, The Stanley Medical Research Institute collected over 600 brains for this research. With the permission of next-of-kin, the brains were collected under agreements with selected medical examiner offices and tissue transplant banks. In many cases, the families making the donations also donated corneas or other body parts to other organ banks for transplantation. Since it is known that schizophrenia and bipolar disorder involve many areas of the brain, the whole brain was required for research. Detailed pathological examinations were carried out on these tissues at the Stanley Laboratory, and the reports were sent back to the medical examiners.

At the time the Stanley Brain Collection was started in 1994, there was a great shortage of brain tissue available for research on schizophrenia and bipolar disorder. The National Institutes of Health had funded two brain collections, at Harvard and UCLA, that had successfully collected brains from individuals with Alzheimer's diseases, but it had had limited success in collecting brains from individuals with psychiatric disorders. A few individual researchers had collected brains for their personal research, and the National Institute of Mental Health had begun making a limited number of brains from individuals with schizophrenia available, but the worldwide shortage of brains available for research was a major reason why so little was known about the causes of schizophrenia and bipolar disorder.

Since 1996, the Stanley Brain Collection has sent over 200,000 sections and 10,000 blocks of brain tissue to 240 researchers in 23 states and 20 foreign countries. All tissue has been provided to the researchers without charge. All costs for collecting, processing, and storing the brain tissue have been borne by The Stanley Medical Research Institute as a public service. All reasonable requests for brain tissue (over 90 percent of applications) have been honored.

A primary measure of scientific advancement is publication in peer-reviewed medical journals. To date, the availability of brain tissue from the Stanley Brain Collection has produced 183 research publications. This has resulted numerically in a sharp increase in research publications per year on the neuropathology of both schizophrenia (50% increase) and bipolar disorder (300% increase). It has resulted substantially in important new information on the causes and treatments for these diseases, as illustrated by the following examples:

- Until recently, schizophrenia and bipolar disorder were assumed to be diseases of brain neurons. Although there are ten times more glia than neurons, the glia had been relatively neglected. Cotter et al. (London), Ongur et al. (St. Louis), and Uranova et al. (Moscow) all found glial abnormalities in the brain tissue (schizophrenia, bipolar disorder, and depression); this has led to a new research interest in glia.

- Prior to 1990, most researchers assumed that schizophrenia was caused primarily by abnormalities of dopamine. The introduction of second-generation antipsychotics threw some doubt on this. Research based on our brain collection has substantiated and increased this doubt. Most of the dopamine studies have shown no abnormalities in brain tissue. Instead, abnormalities in the GABA and other neurotransmitter systems appear to play an important role in both schizophrenia and bipolar disorder.

- A major research question has been what areas of the brain are abnormal in schizophrenia and bipolar disorder. Our brain collection has played a major role in increasing interest in this question. The hippocampus and prefrontal cortex are certainly involved, but it is now clear that other areas are also

involved, including the thalamus and cerebellum. One study using our brain tissue also found abnormalities in the thalamus in depression (Young et al., Dallas).

- Prior to about 1995, most researchers believed that schizophrenia and bipolar disorder were different diseases. Many of the results from our brain collection have found much overlap of abnormal findings between the two diseases, e.g., 15 out of 23 neurochemical abnormalities overlapped in one study. These findings have contributed to an ongoing re-evaluation of the traditional dichotomy. Bipolar disorder with psychotic features may be closely related to schizophrenia.

- When chlorpromazine was first introduced in the 1950s, there were reports of some liver toxicity. In recent years, almost no research has been done on that question. Using small samples of liver collected from many individuals who donated brains, a detailed analysis is being carried out to determine if the newer (second-generation) antipsychotics cause liver toxicity.

- To develop new drugs to treat schizophrenia and bipolar disorder, it is necessary to first identify the neurochemical abnormalities. A summary of 100 studies done on brains in the Stanley Collection identified some likely targets for drug development in schizophrenia. Similarly, a meta-analysis of multiple microarrays has identified some previously unknown neurochemical abnormalities in bipolar disorder that may be good drug targets (Torrey et al., 2005; Elashoff et al., 2006).

Finally, it is important to point out that all of the research has been possible only because of the generosity of the families who agreed to donate the tissue of their deceased family member. All of us who have family members affected with schizophrenia or bipolar disorder, and all of us who do research on these diseases, are grateful to them.

In 2000, *Schizophrenia Research* published an article describing the Stanley brain collection:

> Torrey EF, Webster MJ, Knable MB, Johnston N, and Yolken RH. The Stanley Foundation brain collection and Neuropathology Consortium. *Schizophr Res* 2000;44:151-155.

Single copies of the article may be downloaded and printed for personal research by linking to: brain-collection.pdf.

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