Preface

This volume of *Advances in Neurobiology* deals with the neurochemistry of disease. Included are chapters on both human diseases and animal "model" diseases.

Sources of human tissue.
The three main sources of human neural tissues for chemical studies have been:

Brain obtained at autopsy
Brain obtained at biopsy or incidental to neurosurgery
Nonneural tissues containing molecules identical to those in clinically affected brain or nerve

In theory, peripheral nerve is more available than brain, but chemical analyses of peripheral nerves are relatively limited.

A major problem in doing chemistry on brain obtained at autopsy is the possibility of artifacts arising during the process of dying or in the interval between death and chemical analysis: agonal or postmortem artifacts. During the first decades of modern neurochemistry, this problem was considered so severe that few studies were done on autopsy material. Over 30 years ago, Davison and Bowen and their coworkers at Queen Square in London recognized that it was possible to study meaningfully in autopsy brain those molecules that were stable agonally and postmortem (Bowen et al., 1976). Their recognition that one of these proteins was the enzyme choline acetyltransferase allowed them to make major discoveries about the vulnerability of the cholinergic system in Alzheimer disease; that discovery has led to the only available treatments for this common and devastating condition.

Davison and coworkers did extensive control experiments to ensure that they were studying properties of the brain rather than artifacts that arose during the process of dying or after death. Unfortunately subsequent workers have not always adhered to those meticulous standards. It is relatively easy to obtain pieces of human autopsy brain in a hospital or medical school from people who had a variety of diseases of the brain as well as from "controls" free of brain disease detected clinically during life. These are, of course, not truly "healthy controls." They are, after all, dead; they have to have died of something. The ease with which samples of human brain can be obtained has, unfortunately, allowed publication of studies

where control of sample quality has been sloppy. Interpretation of neurochemical data obtained from autopsy brain must *always* take into account the possibility of the agonal or postmortem artifacts that so worried earlier neurochemists.

Chemical measurements have also been made on human brain tissue obtained from biopsies or from therapeutic surgery (Smith et al., 1983). Here, agonal and postmortem artifacts are not a problem. However, the tissue available is limited. Patient welfare rather than scientific utility must determine the amounts of tissue available and the anatomical sites from which it comes.

An experimental approach that avoids concerns about the quality of brain tissue is to study in available peripheral tissues genes or gene products that are identical to those in neural tissues. Examples include blood cells and cultured skin fibroblasts, and to a lesser extent biopsies of other tissues such as muscle (Bubber et al., 2005). Most workers assume that genes are identical in all tissues examined from an individual but worry about epigenetic modifications, to DNA as well as to post-translational and posttranscriptional products. However, extensive data indicate that study of proteins in peripheral tissues can often give critical information about those molecules in the brain: the standard A striking example is the use of white blood cells and cultured skin fibroblasts to elucidate enzyme defects in inborn errors of metabolism. A well-known example is Tay–Sachs disease (GM_2–gangliosidosis) (Roe and Shur, 2007).

Animal tissues.
Brain and other tissue from sick experimental animals is as readily available as from healthy animals. That includes transgenic and other animals with "model human diseases." But, it is vital to remember that mice are not men, nor are rats or other experimental animals. For instance, triple transgenic mice have been crafted that develop light microscopic lesions that mimic those of Alzheimer disease (AD). (Pietropaolo et al., 2009). However, direct molecular studies document that such triple gene mutations are not the cause of human AD (Tanzi et al., 1991). Treatments have been identified that benefit "Alzheimer mice" (Sung et al., 2004) but not human patients with this illness. (Petersen et al., 2005; Tabet et al., 2000)

Disease.
Neurochemical studies of illness of the brain typically involve comparing a set of samples classified as "disease" versus a set of samples labeled "control." Clinicians or pathologists do the classification, not chemists. At the extremes of health or illness, it may seem easy to decide who is sick and who is not. In fact, the line is hard to draw. If bizarre and often self-destructive behavior is a sign of mental illness, do we classify adolescence as a form of madness? Are intestinal parasites found in the majority of people in a population "normal" or a form of disease? We have been treating hookworm even though this "germ of laziness" was once endemic in the states of the old Confederacy. Social consensus is particularly important in labeling as "sick" behaviors that are odd but not harmful. Certain sexual variants are considered worth treating in the United States but are thought of as harmless eccentricities in England. (That shocked some of my fellow Americans who went for additional

training in psychiatry at the Maudsley Hospital in London.) Soldiers who sacrifice their lives intentionally for their comrades are not classified as suicidally insane. Instead we give them medals.

Specific diseases.
For the last three centuries, it has been conventional to classify sick people as having one or another specific disease. That includes illness of the nervous system, psychiatric as well as neurological. In fact, the concept of specific diseases is a useful but fundamentally unrealistic abstraction. It is one of those approximations that comes out of the English Enlightenment, that are too useful to be discarded even though they do not stand up to close analysis. Grouping patients according to their "disease" helps to provide guidelines for their care, even though in fact every sick person is different from every other sick person. Skilled care requires individualization of care. The British psychiatrist R. E. Kendall has developed the logic of this conundrum with great clarity (Kendall, 1975).

An historical aside may clarify the issues. In the medical tradition that went from the ancients (Hippocrates and Galen) through the Middle Ages until the Enlightenment, physicians basically thought about disease in terms of mechanism. The conventional "theory of humors" was a crude attempt to describe illness in terms of imbalances in body composition, before the invention of modern chemistry and biochemistry.

The modern theory of "specific diseases" was developed in the 1600 s by an English physician, Thomas Sydenham (Haas, 1996). His Latin was too weak for him to study the medical literature of his time, but the professoriat at Oxford granted him a medical degree anyway: his brother was one of Oliver Cromwell's colonels. Came the Restoration, and Sydenham had to make a living. Fortunately, he was a genius. He recognized that specific patterns of signs and symptoms could define clinical entities that typically responded to specific medications. His model was the use of quinine to treat malaria, to treat "tertian and quartan fevers." His concept of specific diseases responding to specific medicines was so powerful that it has come to dominate medicine.

In the later nineteenth and early twentieth century, German-speaking neuropsychiatrists ("alienists") defined neuropsychiatric diseases for which they could not find a neuropathological substratum in terms of the aberrant behaviors. Although sensible enough for the state of knowledge at that time, this approach has been breaking down in recent decades. It is now clear that the same gene mutation can lead to different psychiatric syndromes, to different "diseases" as they are now defined. One classic example is the gene *DISC 1,* which can predispose to "schizophrenia" as well as to "bipolar disease" (manic-depressive psychosis) and "depression" (Chubb et al., 2008).

Perhaps more important, behavioral patterns alone do not predict response to chemicals that act on the nervous system, that is, to medications (Blass, 2006). Thus, behavioral manifestations do not identify specific diseases in the sense originally defined by Sydenham. That is true even of the detailed behavioral classifications created by the committees that write the *Diagnostic and Statistical Manual* of

the American Psychiatric Association (the successive versions of *DSM*) (American Psychiatric Association, 2000).

Neurobiology and specifically neurochemistry may—one hopes—give rise to more biologically based and therefore presumably more clinically useful definitions. The editors hope that this volume on the neurochemistry of disease will further that aim.

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