1. PHARMACOGENOMICS

R. Weinshilboum
Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Medical School-Mayo Clinic, Rochester, MN USA

A therapeutic revolution took place during the latter half of the twentieth century—a revolution with profound implications for psychiatry. The development of a series of powerful therapeutic agents during that time transformed all of medicine, but it also increased the need to individualize drug selection and dosage to maximize therapeutic efficacy and minimize toxicity. That same period witnessed the emergence of the discipline of pharmacogenetics—the study of the role of inheritance in individual variations in drug response. Pharmacogenetic studies have demonstrated clearly that inheritance represents an important factor responsible for large, clinically significant individual variations in both drug toxicity and therapeutic efficacy. “Pharmacogenomics” represents the convergence of these pharmacogenetic observations with the rapid and striking advances that have occurred in human genomics during the past decade. Advances in genomic knowledge and the development of new genomic techniques have opened the way to translate the promise of pharmacogenetics into clinical reality. This presentation will provide an overview and examples of the current state of pharmacogenomics—with an emphasis on both the promise and the reality of this rapidly emerging medical discipline.

2. NEUROIMAGING IN THE POSTGENOME ERA

D.R. Weinberger
Clinical Brain Disorders Branch, National Institute of Mental Health/IRP, NIH, Bethesda, MD 20892-1379

Neuroimaging in the last quarter of the twentieth century was a cornerstone of the brain science revolution in psychiatry. In the first decade after completion of the human genome project, it is liable to have a very different “phenotype.” While 20th century functional neuroimaging studies were aimed at finding patterns associated with mental and cognitive states and with psychiatric disorders, studies in the 21st century will target biological characteristics related to genetic effects that underly risk for psychiatric disorders. Physiological phenotypes will be defined at the level of information processing patterns and dynamics defined with MRI and MEG. Pharmacological imaging will identify genetically determined responses to specific drugs and the expression characteristics of specific proteins. It may be possible to use neuroimaging to quantitate gene expression in the brain in vivo, and to monitor the effect of stem cell transplantation for the treatment of brain disease. Neuroimaging in the post genome era will be a cornerstone of clinical functional genomics.

3. SEQUENCING AND COMBINING TREATMENTS: CAN THE ART BECOME A SCIENCE?

A.J. Rush
The University of Texas Southwestern Medical Center, Dallas, Texas

Over the past 15 years, a wider range of medication options for the treatment of psychiatric disorders has become available. These options have different presumed mechanisms of action. Some agents are effective for some patients, while other medications are effective for different patients. Thus, recent efforts have focused on how to best organize (i.e., sequence or, when needed, combine) these options. As a consequence, practice guidelines, treatment algorithms, or disease management protocols have been developed, disseminated, and evaluated. While common in general medical practice over the last 2 decades, such efforts are new to psychiatry. This presentation focuses on the conceptual and practical issues in developing, implementing, and evaluating various practice guidelines for the mentally ill. The types of evidence needed to form an empirically based treatment plan, and how to use available data sources, clinical consensus, and patient preferences to address guideline relevant questions will be discussed, as will the kinds of studies needed to provide information on what to do (strategies) and how to do it (tactics). The Texas Medication Algorithm Project (TMAP) and Sequenced Treatment Alternatives to Relieve Depression (STAR*D) will be used to illustrate the development, evaluation, and evolution of these guidelines.

4. A 20-YEAR LONGITUDINAL STUDY OF RISK FACTORS FOR ALCOHOLISM

M.A. Schuckit
Univ. of Calif., San Diego and VA San Diego Healthcare System, Dept. of Psychiatry, 3350 La Jolla Village Dr., San Diego, CA 92161

Alcohol dependence is a complex genetically-influenced disorder where all genetic factors together explain 60% of the variance of risk. One genetically-influenced characteristic that appears to contribute to the development of severe and repetitive alcohol problems is a low level of response (LR) to alcohol. This presentation reviews the series of studies that have established a low LR as a characteristic in about 40% of the sons and daughters of alcoholics. This characteristic predicts alcoholism 10- and 15-years later, explaining approximately half of the relationship between a family history and an alcoholic outcome. Based on findings from the successful ten-year follow-up of 99.3% of an original sample of 453 sons of alcoholics and controls, candidate gene analyses and sibling-pair genome scans have been developed and have identified several areas of chromosomes and several specific genes that appear to contribute to a low LR. While searching for genetic material that contributes to this phenotype, our group is also developing, implementing, and evaluating various practice guidelines for the treatment of brain disease. Neuroimaging in the post genome era will be a cornerstone of clinical functional genomics.