1. PHARMACOGENOMICS

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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

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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 underlie 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 quantify 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

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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*ED) 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

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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 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*ED) will be used to illustrate the development, evaluation, and evolution of these guidelines.
This presentation will review recent findings in these studies, and discuss the potential implications of this work for prevention and treatment.

5. PSYCHIATRY IN THE NEW MILLENNIUM

S.E. Hyman

National Institute of Mental Health, Bethesda, Maryland

Psychiatry enters the new millennium grappling with complexity at many levels. Gone are many simple ideas, for example, that there is “a gene for schizophrenia” or “a gene aggression”. Gone are simple ideas that related single neurotransmitters to mental disorders. Gone too are the ideas that correlated circumscribed brain regions with particular cognitive or emotional functions. Instead behavioral tendencies and risk of mental disorders turn out to be genetically complex, involving the interaction of multiple genes and nongenetic factors—indeed our comfortable picture of genes acting in simple additive ways, and of their product, proteins, acting in simple linear signaling pathways has proven woefully inadequate. At the same time, it is clear that the brain must be understood in terms of distributed information processing, with its cellular components being remarkably plastic. Not only is it the case that synapses are constantly being physically remodeled by the environment, but contrary to old dogmas, neurogenesis in the mature brain is now an established fact. Even clinical trial design must adapt to the need to be generalizable to a complex “real world”. These new views introduce new needs for computation and informatics, and for new models to replace the old. Ultimately, however, with our new ideas and new technologies, we will be on track to answer the central age-old questions of psychiatry: How is the human brain built? How does it change over the life span? What are the pathophysioligies that produce the symptoms and disabilities? How do our treatments, including psychotherapy work? What objective markers can we discover to monitor the progression of the pathophysiology and the effects of treatment? How will we discover preventive measures and cures that will be effective in diverse populations and settings?

6. AN UPDATE ON NEW SOMATIC TREATMENTS FOR DEPRESSION—ECT, TMS, VNS, DBS

M.S. George (1), H.A. Sackeim (2), A.J. Rush (3), R. Kumar (4)

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Recently, several new brain stimulation methods have been introduced with reported antidepressant effects. These improvements in older technologies (ECT), or invention of new approaches (TMS-transcranial magnetic stimulation, VNS—vagus nerve stimulation, DBS—deep brain stimulation) build on advances in functional neuroimaging and improved knowledge of the brain circuits involved in regulating mood and anxiety. This workshop will involve brief presentations of recent data in each of these fields, although full presentation of the findings with each tool are also presented at other parts of the Biological Psychiatry Meeting (Drs. Sackeim (ECT) and Kumar (DBS)-Sat. Morning). Following the brief presentations of the newest findings in each field, the workshop will focus critical discussion on common issues across these fields. These include but are not limited to the following:

- the effects of different frequencies, pulse widths and dose on brain function,
- relative invasiveness and known side effects of each approach, the potential for studies in normal subjects as opposed to pathology,
- future use of the techniques in informed algorithms of clinical treatment (what to use when and in what order, if and when they are approved for clinical use),
- progress in using animal models of depression to understand these new tools,
- and using imaging techniques to understand the brain effects of the technologies and measure effectiveness.

7. GABA/GLUTAMATE DYSREGULATION IN DEPRESSION

H. Murck (1), I.A. Antonijevic (1), F. Petty (2), P. Skolnick (3), R.S. El Mallakh (4)

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Robust biological markers of depression are endocrine changes, especially hypercortisolism, and changes in the sleep EEG, especially a more disrupted