2009 in Review

The Editors are pleased to offer personal selections of some of the articles they found particularly interesting and important in this year's *Journal.*

Early Change in Negative Bias After Antidepressant Treatment

Harmer et al. (1) advocate a new strategy for drug discovery in depression. Their article illustrates how the use of intermediate phenomenology outcomes could expedite drug discovery for depression; moreover, the report demonstrates how basic cognitive neuroscience can be useful in understanding and treating brain diseases. Cognitive neuroscience developed the concept of "negative bias" in information processing, a situation where more negative than positive emotional information is extracted from a stimulus. The authors used three sophisticated emotional tasks developed within cognitive neuroscience to demonstrate several different aspects of negative bias in a set of depressed and comparison volunteers. The depressed subjects expressed performance deficits in these tasks consistent with their negative bias. This bias has been shown before, but it was particularly striking in this data set because of its consistency across tasks. All volunteers, depressed and healthy, received a single administration of the antidepressant reboxetine at a dose of 4 mg. When the volunteers were retested after drug administration, it was clear that the single dose of reboxetine had normalized negative bias in the depression group in all three of the cognitive emotion paradigms, even though their subjective mood as reflected in the Beck depression score had not changed. We all know that it can take 2 weeks or longer to see a positive effect of an antidepressant drug on ratings of depressed mood. Moreover, there is great variability in this symptomatic outcome. Harmer et al. posit that subjective mood is a downstream phenomenon, whose response to treatment may potentially be modeled by an earlier alteration of a more basic underlying cognitive characteristic of depression, such as negative bias, with greater sensitivity and reliability. This interpretation still needs to be rigorously tested. If the model is validated by more examples of early response, then initial human testing of antidepressant drug candidates would be significantly more time-efficient and would have greater reliability than occurs with evaluation of subjective mood as the primary treatment outcome. A related clinical point is that psychiatrists may want to look more closely for changes in cognitive bias early in the course of treatment of patients with depression.

CAROL A. TAMMINGA, M.D.

Systematic Studies of Psychotherapy

The systematic study of psychiatric treatment has catalyzed the discipline's transformation from folklore to science-based practice. This has largely been achieved in psychopharmacology, although problems persist in measuring clinically relevant outcomes and obtaining long-term follow-up. However, the systematic study of psychotherapy, particularly dynamic psychotherapy, has lagged behind. As articles by Bateman and Fonagy (2) and McMain et al. (3) demonstrate, it is now catching up.

The earliest efforts in psychotherapy research focused on relatively "simple" disorders (phobias, depression) and on behavioral or cognitive-behavioral treatments. The articles by Bateman and Fonagy and by McMain et al. study more complex clinical challenges and in one case a psychodynamic treatment.

Their titles suggest their similarity—"randomized trial" (the gold standard in treatment assessment), a specific disorder (borderline personality), and the comparison of a carefully defined treatment with a carefully designed, clinically appropriate alterna-

tive. They employ experienced therapists, large numbers of patients (134 and 180), and reasonable durations (18 months in one case, 1 year with a 2-year follow-up planned in the other). Both monitored therapists' adherence to protocol.

The results are not startling. One shows no significant difference, the other a small advantage for the dynamic therapy. However, far more important, they demonstrate that the methodologic rigor that many thought impossible in psychotherapy research is not only possible but well under way, and they promise advances in the therapy that only research can provide.

ROBERT MICHELS, M.D.

Molecular Signature of Depression in the Amygdala

This year's collection of articles provides an unusual opportunity to celebrate diversity: diversity of research focus, methods, findings, and impact on clinical thinking. One article foreshadows the exciting future of psychiatry by harnessing diverse methods to embody broader themes in the *Journal*. Sibille and colleagues (4) used postmortem brain tissue to examine the molecular signature of major depression in the amygdala and compare this signature to that of chronic stress in rodents. Findings suggest that stress-related plastic amygdala perturbations represent a primary pathology in depression.

In some ways, the study is a virtual tour de force through widely discrepant methods; it integrates clinical data with work in human neuroanatomy, comparative physiology, and molecular genetics. In other ways, the study adopts a singular focus central to other important papers in clinical neuroscience. Diverse methods are focused on the singular goal of identifying an underlying pathological substrate that might be targeted by novel prevention and treatment approaches. Perhaps no other feature of translational neuroscience generates more enthusiasm than the field's potential for generating novel therapeutic ideas. While earlier work focuses on relevance for therapeutics in schizophrenia, Sibille and colleagues provide an early voice pertinent to comparable issues in depression.

DANIEL S. PINE, M.D.

Suicide From the Golden Gate Bridge

A Clinical Case Conference by Blaustein and Fleming (5) offers compelling insights into the lives and thoughts of individuals who chose to jump from the Golden Gate Bridge, through first-hand interviews with survivors and families of victims. The power of this article lies in these vivid accounts, which aptly reflect the different facets of suicide in each individual tragedy. The cases include an adolescent boy, a chronically mentally ill woman, and a middle-aged married man. Their stories may not be discerned in research studies of epidemiological risk factors or the neurobiology of suicide. Yet they bear scrutiny, as the problem of suicide becomes a more urgent public health problem. The authors depict the remarkable attraction of "suicide magnets," such as the Golden Gate Bridge, which facilitate obsessional beliefs that suicide there lends a special meaning to the death. Yet it is also noteworthy how quickly the survivors regretted their action, in one case as soon as the fall from the bridge began. Access to lethal means is something that clinicians consider daily in the assessment of the at-risk patient. Although we might not expect that case reports, such as those described in this Clinical Case Conference, would be capable of effecting change in public policy, a task force established by the Psychiatric Foundation of Northern California has used these and other case histories to convince the municipal authorities to authorize a safety net below the bridge, an initiative that they had long resisted despite the number of victims. The individual portrayals of affected people served a crucial role in compelling action.

SUSAN K. SCHULTZ, M.D.

Prenatal Infection Exposure and Schizophrenia

A major challenge in understanding any psychiatric disorder is knowledge of how the etiological factors that are operative in the illness unleash pathogenetic mechanisms that produce a pathological entity, a conserved set of molecular and cellular disturbances in the brain. This pathological entity then alters the normal circuitry and function of the brain, producing a characteristic pathophysiology that gives rise to the recognized clinical features of the disorder. In the case of schizophrenia, complex genetic factors are known to play a major role in the etiology of the illness. In addition, a number of epidemiological studies have demonstrated replicated associations between a range of environmental events, occurring from gestation through adolescence, and an elevated risk for the illness. Less common, however, are studies that address the intermediate processes between a given environmental exposure and the clinical illness that might point to the pathogenetic mechanisms linking etiology and pathology. Consequently, one of my favorite *Journal* articles of 2009 is the study by Brown and colleagues (6) that evaluated the relationship between serologically documented prenatal exposure to influenza or toxoplasmosis and cognitive function in individuals with schizophrenia. The authors found that patients who were exposed to infection in utero were more likely to have impaired performance on tasks that require cognitive set shifting. Although the neural substrate for this pattern of cognitive abnormalities was not evaluated, the results of this study help constrain the search for the types of pathogenetic mechanisms that might arise from prenatal infection and produce pathological alterations in the brain circuits that subserve cognitive set shifting.

DAVID A. LEWIS, M.D.

New Conceptualization of Posttraumatic Stress Disorder

A Reviews and Overviews article on validation of the diagnosis of posttraumatic stress disorder (PTSD) by North et al. (7) made me think about how an illness is the interaction between a cause and a reaction. Tumor, rubor, color, and dolor—the classic signs of inflammation—cause patients to seek treatment. These same signs help physicians identify a wide range of pathogenic causes, from acquired infection to inherited autoimmunity. North and colleagues argue that we need to conceptualize PTSD the same way. The significance of the causes, which range from the Holocaust to minor automobile accidents, can only be assessed in the context of the patients' stress disorders, their reaction to the putative cause. As we approach DSM-V and we long for illnesses that have defined causes, like viruses or gene mutations, these authors remind us that we have much to learn by inquiring of our patients what distresses them. This conceptualization of PTSD encountered some resistance from the article's reviewers, who pointed that this new approach to diagnosis could become circular: a disorder originally conceived as a reaction to a trauma now defines the trauma by the reaction. However, North and colleagues cogently present the case that we cannot assume that as psychiatrists we are able to divine independently what the pathological significance of events in their lives should be, without considering their reactions. They further point out that their approach mandates a new rigor in the diagnosis of PTSD, because careful symptomatic and biological assessment of the reaction and full understanding of the circumstances of the patient are necessary to pinpoint the cause.

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