

Editor's Note: We believe our readers will benefit from knowing about the annual ASENT (American Society for Experimental Neurotherapeutics) meeting and having available the abstracts from this meeting. Emphasizing therapy in neurology is the objective of ASENT and thus this information is both timely and important.

Roger N. Rosenberg, MD

Abstracts from the Program of the Fourth Annual Meeting of the American Society for Experimental NeuroTherapeutics, Washington, DC, March 14-16, 2002.

Setting Standards to Avoid Conflict of Interest in Clinical Trials

Marcia Angell, MD

The financial connections between academic clinical researchers and their institutions, on the one hand, and private companies with interests in the outcome of clinical research, on the other, are more extensive than ever before. Increasingly, academic medical centers and private industry see themselves as partners in a common endeavor.

This trend gives rise to a number of serious concerns. When researchers and their institutions have financial interests in companies whose products they are evaluating, it undermines public confidence in their objectivity and commitment to the welfare of human subjects. The case of Jesse Gelsinger was a powerful wake-up call in that regard. There is also good evidence that researchers with such ties are more likely to publish work favorable to the companies, suggesting widespread bias. In addition, the type of research undertaken at the outset may be skewed toward clinical trials that serve the marketing interests of industry, at the expense of more important research into the causes and pathophysiology of disease.

Financial conflicts of interest are not an inherent part of the research enterprise. They are largely optional, despite current rhetoric to the contrary, and nearly all of them could be eliminated. Instead, the academic community seems bent on accommodating or "managing" them. Even the most stringent of current academic guidelines permit researchers to maintain certain financial ties to industry and provide for exceptions to prohibitions.

Instead of wasting time and energy worrying about how to manage conflicts, we should be working to eliminate them whenever possible. Just as judges may not have financial interests in cases they are hearing, so clinical researchers should not have interests in products they are evaluating, other than grant support administered at arm's length. Academic medical centers, for their part, should have no equity in the drug and device industry, so they are not compromised in overseeing their faculties.

The mission of investor-owned companies is quite different from the mission of academic medical centers. The primary purpose of the former is to increase the value of their shareholders' stock, which they do by securing patents and marketing their products. Their purpose is not to educate, nor even to carry out research, except secondarily or as a means to their primary end. There is no doubt that academic/industrial collaborations can lead to important advances, but their missions should not be blurred by financial ties.

Conduct of Clinical Trials: The Pharmaceutical Perspective

Roger J. Porter, MD

The objectives of clinical research in the industry are identical to those in academia or government. The pharmaceutical industry seeks the truth about its compound or invention, and it seeks to find this truth as soon in the development process as is possible; such knowledge permits the company to make early decisions about increased support or abandonment of an individual compound.

All of our abilities to "know" the truth about any object are based on our powers of observation. We have been aware of the limitations of our observational powers since the time of Plato¹ who noted that "the body disturbs . . . and hinders the soul from getting possession of the truth." Aristotle carried the concept further by noting, "we have the power to imagine things whenever we please, seeing them in our mind's eye."¹ We have learned, however, to better control our powers of observation by a manipulation of the observational process—an experiment. It has taken us about 2000 years to learn how to create meaningful experiments, and clinical trials are among the most recent kinds of experiments to be accepted as an improvement of our observational powers. Yet even today we find that the "pure" experiment can be denigrated by inadequate control, either by sloppiness or by design, though only rarely by conscious design. To understand the reasons for improper, and less objective, experimental plans, we must

examine the motivating factors that drive scientists to accomplish their tasks and then relate these motivations to the conflicts of interest in clinical trials.¹

The major pharmaceutical companies of the world are concerned with everything from the conceptual foundations of drug discovery to post-marketing development of additional indications. From the time of first discovery to the time of clinical testing and beyond, industry scientists are dependent on a "chain of truth" from every department that contributes to the knowledge about the potential drug. This truth-seeking effort will hasten the day when better drugs will be available to the patients who need them.

1. Porter RJ, Malone TE. *Biomedical Research: Collaboration and Conflict of Interest*. Baltimore, Md: Johns Hopkins University Press; 1992.

Conduct of Clinical Trials: The Principal Investigator's Perspective

Karl Kiebertz, MD

Research investigators have unique responsibilities to protect human subjects participating in clinical trials. Investigators must use their clinical and professional judgment in areas that are not readily reviewed by institutional review boards (IRBs).

The investigator must be able to respond affirmatively to 3 questions regarding the research protocol: (1) Does the protocol ask an important enough scientific question to justify the required resources of the investigators and research participants? (2) Is there a reasonable likelihood that the study can be completed as designed? and (3) Is it likely that the completed study will answer the research question?

In the special setting of a randomized intervention study, the investigator must be certain that there is clinical equipoise regarding the alternative treatment assignments. Clinical equipoise implies that the scientific community is in a state of genuine uncertainty regarding the relative merits of different interventions, including, in the special setting of placebo-controlled trials, no intervention. Only the investigator can make an educated assessment of this situation. Even if clinical equipoise exists, if the investigator has a deeply held personal bias regarding treatment alternatives, participation as an investigator is unwise.

During the conduct of the study investigators also have important initial and ongoing responsibilities regarding the consent of research participants. Although IRBs review consent forms, the process of consent is seldom overseen. The investigator must determine whether, in his or her best judgment, the potential research subject has made a voluntary and informed decision to participate in the study. If the investigator feels that this condition is not met, even if the person is willing, the person should not be enrolled. In addition, the investigator is responsible for advising research participants of study developments that may bear on continued consent to par-

ticipate in the research. This is not merely a factual reporting of events but requires providing the information in an individualized context.

Although IRB review of protocols enhances the likelihood that research subjects will be protected, investigators continue to need to exercise thoughtful judgment in areas that are not easily reviewed by oversight groups.

The Place of Placebos/Sham Surgery in Clinical Trials

Stanley Fahn, MD

In clinical trials of pharmaceutical agents, comparison of the agent being tested with a placebo is a time-honored, accepted method to evaluate the efficacy and safety of the agent. But this methodology has not become standard in the evaluation of a new surgical procedure being proposed as improved therapy. Yet, expectations by patients undergoing a surgical procedure are at least as great as in those willing to try a new medication. A common rationalization is that the greater the perceived risk, the greater the expectation that the procedure must be more rewarding. Thus, it is logical to anticipate that surgical procedures could result in a greater placebo effect than that encountered with drug testing. In spite of such reasoning, placebo-controlled surgery (ie, utilizing sham surgery controls) is rarely employed. Typically, new surgical procedures are open-label trials that never proceed to a rigorous controlled surgical trial in which sham surgery is the comparator. Admittedly, a major justification to avoid sham surgery is that such surgery may incorporate the inherent risks of any surgical procedures, such as anesthesia, infection, blood loss, incision errors, pain, discomfort, time for healing, and even the emotional stress of hospitalization. This has led to the alternative of comparing a new surgical procedure with the best medical treatment available. But open-label controls such as these cannot account for the mental mechanism of rationalization (ie, a satisfactory outcome would justify the ordeal of a surgical procedure). Thus, open-label best-medical comparison trials are less than ideal. Even the ingenious temporal-lobe controlled surgical trial,¹ in which blinded raters reviewed subjects' written statements about epileptic seizures, still cannot account for the fact that subjects knew that they either had the surgical procedure or were still in the 1-year medical treatment waiting phase of the study. A placebo effect could have influenced their statements.

Another limiting fact is that some surgical procedures require observing immediate results during the operative procedure before the operation can be completed. This is the typical situation for functional stereotaxic neurosurgery employed to arrest abnormal involuntary movements or bradykinesia on awake patients. Such operations are not suitable candidates for a comparative sham surgical procedure. Thus, only operations that are expected to produce delayed benefit would

be the candidates for sham surgery controls. Still, these have rarely been performed.

Transplant surgery for Parkinson disease is an ideal procedure for having sham surgical controls. Probably hundreds of operations have been performed for adrenal medulla autografts, with varying degrees of reported success. It was only after several years went by and autopsies showed no tissue survival that those performing and evaluating the procedure realized that these operations were failures. Motor improvement in patients with Parkinson disease is seen regularly in the clinic and in controlled clinical trials evaluating medications, and thus a placebo effect should have been anticipated. Transplants of fetal dopaminergic tissue have also been performed in dozens of trials, typically showing benefit. The benefit could be explained by the increase in [¹⁸F]fluorodopa uptake in positron emission tomographic scans. The first sham-controlled surgical trial for such procedures² confirmed success in reducing Parkinson disease signs and symptoms in the practically defined "off" state, but only in subjects aged 60 years or younger. Older subjects had the same degree of positron emission tomographic scan improvement but without clinical benefit, indicating that [¹⁸F]fluorodopa uptake alone is insufficient to account for clinical benefit. The study also showed that approximately one third of the sham-operated group, both younger and older subjects, rated themselves as moderately to markedly improved. This points out the powerful placebo effect from simply having the operation, and this must be taken into account when trying to evaluate any open-label surgical procedure.

1. Wiebe S, Blume WT, Girvin JP, Eliasziw M, and the Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med.* 2001; 345:311-318.
2. Freed CR, Greene PE, Breeze RE, et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *N Engl J Med.* 2001;344:710-719.

Prefrontal Neurons and the Genetics of Schizophrenia

Daniel R. Weinberger, MD

Studies of prefrontal neurocognition and functional neuroimaging of prefrontal information processing consistently reveal abnormalities in patients with schizophrenia. Both the physiologic abnormalities and the cognitive deficits are predicted by a cellular measure in dorsolateral prefrontal cortex—low *N*-acetyl-aspartate signals from magnetic resonance spectroscopy. In pharmacologic imaging studies, patients manifest excessive dopamine release induced by amphetamine, an abnormality also predicted by low *N*-acetyl-aspartate in the dorsolateral prefrontal cortex. These findings suggest that abnormal function of the working memory cortical system (associated with positive symptoms) represents emergent properties of specific dorsolateral prefrontal cortex neuronal pathology. Abnormali-

ties of prefrontal information processing also are found in unaffected individuals who are genetically at risk for schizophrenia, suggesting that genetic polymorphisms affecting prefrontal function may be susceptibility alleles for schizophrenia. One such candidate is a functional polymorphism in the catechol-*O*-methyltransferase (*COMT*) gene that markedly affects enzyme activity and that appears to uniquely impact prefrontal dopamine. *COMT* genotype predicts performance on prefrontal executive cognition and working memory tasks. Functional magnetic resonance imaging confirms that *COMT* genotype affects prefrontal physiology during working memory. Family-based association studies have revealed excessive transmission to schizophrenic offspring of the allele (*Val*) related to poorer prefrontal function. These various data provide convergent evidence that the *COMT Val* allele increases risk for schizophrenia by virtue of its effect on dopamine-mediated prefrontal information processing, the first plausible biologic mechanism by which a specific allele affects variation in normal human cognition and risk for mental illness. These findings have implications for the development of novel treatments aimed at the prefrontal dopamine signaling cascade.

The Neurobiology of Mood Disorders

Dennis S. Charney, MD

There have been major advances in our understanding of the neurobiology of depression. The roles of the monoamines, serotonin, and norepinephrine have remained a focus. However, given the complexity of these systems, more refined hypotheses have been developed. In addition, it has become more clear that other neurotransmitter systems, neuropeptides, and intracellular molecular mechanisms may be equally or even more important in the etiology and treatment of depression. This presentation will update the audience on recent findings pertaining to these areas. Possible new approaches to the treatment of depression based upon this work will be presented.

Development of Atypical Neuroleptics

Richard C. Meibach, PhD

It has been 12 years since the first atypical neuroleptic was approved for use in the United States. Since that time, 4 additional drugs have entered the marketplace. Several more are in the late stage of clinical development and should be submitted for approval in the near future. All of these compounds have in common qualities that differentiate them from first generation neuroleptics. They all share affinity for

the dopamine (d2) receptor, but they bind with much lower affinity. They are all less selective in that they also bind with high affinity to serotonin receptors. All of these new compounds were developed in schizophrenic patients but because of their effects on improving positive symptoms were approved for the broader claim of treatment of the “manifestations of psychotic disorders.” New rating scales such as the Scale for the Assessment of Negative Symptoms (SANS) and the Positive and Negative Syndrome Scale (PANSS) were employed to further elucidate the effects on the negative symptoms, and product labeling includes mention of these effects in the clinical trial section. Although it has been debated whether these new drugs offer greater efficacy, it is well accepted that this class has significantly fewer extrapyramidal adverse effects than typical neuroleptics. Because of this greater safety margin, atypicals are being used in much broader patient populations today, resulting in a \$5 billion market.

This presentation will highlight the clinical development of these compounds. Strengths and weaknesses of the individual study designs will be reviewed, as well as hurdles of using new rating scales in drug trials. Discussion will also include attempts to differentiate these drugs on the basis of both efficacy and safety. Clinical results in other areas, including neurological uses, will be presented. Finally, preclinical research is already exploring the next generation of antipsychotic medica-

tions. Some thoughts on how these may be developed in the clinic in order to differentiate them from our current medications will be outlined.

Advances in Neuropsychiatry

K. Ranga R. Krishnan, MD

Two problems in trials of psychotropic medications are the use of placebos and the high placebo response. Both lead to ethical concerns and a number of failed trials. The ethical issue with regard to use of placebos has been well addressed for trials in depression and panic disorders where the risk with the placebo arm is small and there is a need for placebos to demonstrate that a drug has efficacy. Another issue is the potential use of surrogate markers in designing trials. In this presentation, I will discuss the use of novel trial designs to minimize placebo exposure and the use of surrogates in Alzheimer disease. I will discuss “play the winner” as an example of a design that could be used to reduce the number of subjects exposed to placebo and also its potential as a design for proof of concept. The limitations and problems with this type of design will be discussed. The use of magnetic resonance imaging and spectroscopy as a surrogate in Alzheimer disease trials will be discussed. Results from clinical trials will be presented to illustrate their use.