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THE ACNP AT 50: LIVING UP TO THE VISION OF OUR FOUNDERS

Eric J. Nestler, M.D., Ph.D.
President

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President-Elect

The American College of Neuropsychopharmacology (ACNP) was formed 50 years ago by a visionary group of leaders. At a time when psychoanalysis dominated American psychiatry, these scientists asserted that advances in psychopharmacology and neuroscience could alleviate the suffering of people with mental illness. They created this organization as a College, implying that it would educate its participants and through this mechanism transform the fields from which its membership was drawn. Fifty years later, the ACNP is one of the world's most prominent biomedical organizations. Successive presidents and Council members have passed the leadership of the College to those who were children at the time of the College's founding. Now that the College and its leadership are of a similar age, it is timely to reflect on the ACNP legacy and consider its future.

Where do we stand with respect to the scientific vision of our founders? Progress in generating new treatments for psychiatric disorders has been disappointing. The ACNP was founded at a time of naïve optimism, which reflected the startling early progress in the field. At the time of the founding of the ACNP, nothing mechanistic was known about the etiology of mental illnesses and the field had only superficial insight into the remarkable new treatments (imipramine, chlorpromazine, chlordiazepoxide) and other powerful psychopharmacological tools (LSD, amphetamine, phencyclidine) of that era. Even today, enormous gaps remain in our understanding of the mechanisms underlying the efficacy of the landmark achievements of those early days: even though we have a far better understanding of important pharmacological effects of psychotherapeutic agents, we still do not know the ultimate mechanisms by which antidepressant, antipsychotics lithium and certain anticonvulsants produce behavioral improvement. But the initial progress was built on serendipity rather than knowledge of the brain, and the initial progress could not be sustained. Our field repeatedly underestimated the complexity of the brain and the etiology and pathophysiology of psychiatric disorders. With each successive advance, treatment breakthroughs seemed imminent but did not materialize. And the situation for neurological disorders was similar: despite genetic breakthroughs for rare familial forms of illnesses, advances in understanding common forms of the disorders and in developing new treatments have been similarly limited.

In parallel with these clinical frustrations, each successive ACNP Annual Meeting provided further testimony to exciting breakthroughs in neuroscience and genetics. We also have learned more about the enormity of the challenge of understanding the brain and its diseases. We recognize that psychiatry may never again see a period

that so radically and rapidly transformed the treatment of mental illness as that of the founders. However, today, it seems possible once again that we are approaching a new type of "tipping point" where genetics and neuroscience may at long last offer real insights into the etiology, pathophysiology, diagnosis, and treatment of brain diseases. These advances highlight the common aims and approaches employed by several fields, erasing historical distinctions between psychiatry and neurology, and strengthening new bridges with genetics, immunology, endocrinology, neurosurgery, and other areas of medicine. Meanwhile, the evolving explanatory science, which has been impressive, is the hallmark of a mature field. Thus, at middle age, the ACNP can take credit for its role in nurturing the growth of our field and celebrating the remarkable achievements in fundamental science at successive meetings.

Have we succeeded as a College? In some ways, the ACNP and the fields that it has nurtured have succeeded in developing far beyond what could have been anticipated at the formation of the College. While the ACNP was founded in 1961, it would be another 8 years before the creation of the Society for Neuroscience, which illustrates the contribution of neuropsychopharmacology as one of the founding disciplines of neuroscience. The ACNP decisively maintained its intimate and "collegial" educational focus, and developed a reputation for elitism that reflected its focus on a modestly-sized annual meeting that showcased the members' best science. In contrast, the Society for Neuroscience grew into a large representative body with a commensurately broad agenda and a vast annual meeting. The ACNP is now but one of several organizations addressing the opportunities and challenges in translational neuroscience. In addition, over the years, issues arose as to the optimum size of the College, its unique role and mission, how to incorporate important new areas of science in the College, and how to attract and engage younger and more diverse members. In response, the recent ACNP leadership prescribed diet, exercise, and a little cosmetic surgery: focusing on the core priorities of the College as a strategy for preserving its impact. Its leadership has simplified the structure and function of the College and focused its priorities accordingly. As a result, although somewhat larger than in the era of its founders, the ACNP retains its focus on modern science, great presentations, and plenty of room for informal discussions. We are proud that, in its fiftieth year, the ACNP continues its strongest commitment to young scientists and nurtures its culture of collegiality.

Looking ahead, the ACNP seems headed toward a second childhood rather than to old age. There are abundant challenges to this vitality, including concerns about NIH funding, the withdrawal of pharmaceutical companies from neuroscience discovery, and remaining ethical issues that challenge our public credibility. Transformative advances in neuroscience necessitate a parallel revolution in the training of medical students, psychiatrists, and neurologists. Even though neuroscience-related majors are among the most popular at many colleges, instruction in molecular, cellular, systems, and cognitive neuroscience, including introductions to neuropsychiatric genetics and neuroimaging, are inadequate at all levels of medical and professional education. This training impediment is a threat to the long-term vitality of the ACNP and the clinical neurosciences.

But the ACNP has overcome similar challenges in its history. The science is more exciting than ever in the history of the College. Keeping up with the new science is challenging, but it will keep us young. In turn, the Annual Meeting is still the place where young scientists encounter their scientific heroes around every corner and get a chance to present their ideas to the pioneers in their respective fields who laid the groundwork for their research. It is an honor and privilege to serve the College at this historic moment. The 50th Annual Meeting is a wonderful celebration of a very special organization, whose best days are yet ahead.

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Creating a Social Environment for Science: A History of the Evolving Influence of the American College of Neuropsychopharmacology

Nancy D. Campbell, Ph.D.

"Like a modern Rosetta stone, psychopharmacology holds the key to much that is puzzling today."[1] —*Joel Elkes*

INTRODUCTION

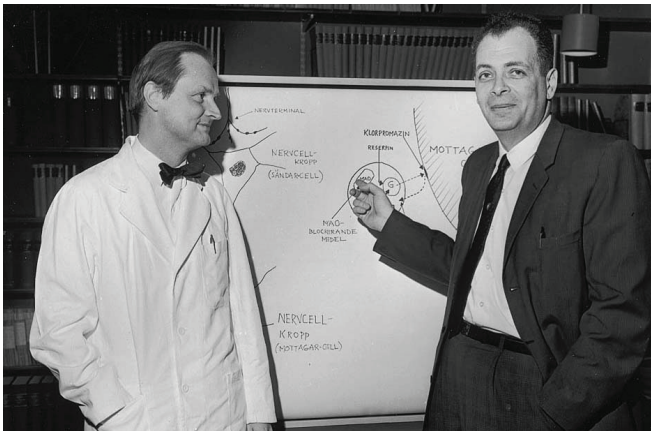
For the past 50 years, the American College of Neuropsychopharmacology (ACNP) has helped create social acceptance necessary for sustained research on brain disorders. The ACNP has provided scientific leadership within the National Institutes of Health, and prior to that within the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). As an elite scientific society, the ACNP has had only a limited impact on the outcome of any individual science policy campaign. Major social, political, and economic changes impact the ability of the scientific communities contributing to neuropsychopharmacology to conduct research relevant to the brain and evolve effective and humane treatments for brain diseases. A major conceptual shift in public understandings of psychiatric illness and addictive disorders as "brain disorders" occurred during the 1990s, designated the Decade of the Brain by President George H. W. Bush. The ACNP helped create conditions that made possible the Decade of the Brain. By allying with patient advocacy organizations in educating key congressional leaders and policy makers from the mid-1980s into the present, the ACNP reinforced the message that brain science had much to contribute to the society's responses to brain disease and disorder. This article is based on archival evidence of how the ACNP has responded to major issues of societal relevance in the past. Many of these issues—particularly those concerning how those who suffer from brain disorders will be treated in U.S. society—remain unresolved.

Science alone is unlikely to be sufficient for solving social problems, including mental health parity; the cyclic vicissitudes in federal and state funding for research and treatment; the consequences of deinstitutionalization, including increased populations of homeless and incarcerated mentally ill; and contentions over how the social costs and benefits of animal research will be distributed. As the following history demonstrates, the ACNP has been selective and strategic in choosing when and how to engage its expertise in scientific research, technological innovation, and drug evaluation as a basis for commentary and action on political and economic issues, particularly those of the federal research apparatus. The overarching societal value of the organization rests ultimately on its members' ability to translate scientific knowledge into treatments that positively affect the lives of those living with brain disorders and neurodegenerative diseases as patients, parents, partners, and providers of compassionate care.

Given the organization's emphasis on remaining a place where only science is spoken, it may surprise many fellows to learn that the ACNP was not founded solely as a scientific society. In the initial meeting where the need for such an organization was discussed, clinical researcher Anthony Sainz drew attention to the "other and more important factors in the research situation at the present time beyond the merely scientific. There are economic considerations. There are material considerations, and there are political considerations with which I believe the society has to [concern itself] if it is going to make any definite contribution to research."[2] The social significance of the ACNP must be judged on grounds that transcend the scientific contributions of its members—such an assessment

of the historical value of the organization must be couched within the economic, material, and political considerations that enable it to exercise power and influence on questions of major relevance to its membership not only in the past but in the future.

Mental health policy has changed greatly during the time in which the ACNP has existed, moving from a state institution-based model to a far-flung system no longer overseen by any single state or federal agency, but by a decentralized public



Arvid Carlsson and Sidney Udenfriend

and private insurance industry and mainstream healthcare institutions.[3] While discontinuation of ineffective and inhuman practices has resulted in treatment improvement, overall prevalence and characteristics of the severely mentally ill population remain relatively constant. Practice streamlining has come about from innovations in pharmacotherapy.[4] Treatment of brain diseases as an "exceptional" area of health has declined since the mid-1950s, when the Federal Mental Health Study Act (1955) created the Joint Commission on Mental Illness and Health, an ambitious effort to survey the then-current state of the field involving 20 organizations.[5] In 1963, President John F. Kennedy stated his support for community-based care and the goal of halving the institutionalized population. Later that year Congress passed the Mental Retardation and Facilities Community Mental Health Centers Construction Act (1963), which propelled deinstitutionalization.[6] By the time President Jimmy Carter's Commission on Mental Health surveyed the nation's mental health needs in the late 1970s, the federal system was regarded as dysfunctional.[7] The ambitious Epidemiological Catchment Area (ECA) study, based on diagnostic interviews with 20,000 Americans, was hailed by ACNP fellow Daniel X. Freedman as an "unprecedented atlas" of *Psychiatric Disorders in America* (1991) that had been produced by a "modern-day *Voyage of the Beagle.*"[8] Freedman was influential in directing the priorities of the President's Commission on Mental Health towards increased resources for mental health research.[9] The costs of non-partisan political involvement were debated "more or less constantly" by the ACNP Council, but by the late 1980s, President Arthur J. Prange argued that there was a consensus that "this activity is in fact worth the time, work, and money it costs. We are heard and heard clearly."[10] This amplified voice for neuropsychopharmacology research contributed to create the political consensus leading to 1990s being declared the Decade of the Brain.

While the Decade of the Brain was the outcome of work by a broad coalition of federal agencies, patient advocacy organizations, and scientific organizations, by the time Congressman Silvio Conte (R-Mass) and the National Foundation for Brain Research (NFBR) began proposing a congressional resolution on the Decade of the Brain, the ACNP Council had met with Conte's office on numerous occasions in the mid-to-late 1980s. Conte noted in a letter to ACNP counsel his "own belief in the incredible opportunities in research on the brain.... [F]or several years now, I have been talking about the extraordinary gains being made in this area as the 'Decade of the Brain.'"[11] His proposal during the 1987-1988 Congressional appropriations process that the National Institute of Neurological Diseases

and Stroke (NINDS) develop the broad-ranging neuroscience research plan that became known as the 'Decade of the Brain'[12] was received warmly in the neuropsychopharmacological research community. NIMH, then under the direction of Lewis L. Judd, seized the opportunity to remake itself as the preeminent federal research institute for the neurosciences and offered its own research plan for the Decade of the Brain. As the research community had migrated towards neuroscience in the 1980s and 1990s, the ACNP and patient advocacy groups had begun to speak of the conditions with which they dealt as "brain diseases." The research community had long called for the end of stigma and funding levels comparable to those of other diseases. However, as Frank and Glied (2006) found, the integration of mental health treatment into mainstream medical practice had advantages and disadvantages, producing new challenges. While much new knowledge has been produced about the brain and how it works, President George W. Bush's New Freedom Commission on Mental Health Report (2003) found a mental health services system in disarray. How the results of brain research are translated into clinical practice, in other words, must be contextualized within the political and economic policies and structures that shape the nation's response to people who suffer with brain diseases. This article locates the American College of Neuropsychopharmacology within the historical changes that have enabled or constrained its political and economic influence as the premier representative of the sciences of neuropsychopharmacology.

Founding Moments: The Emergence of ACNP and the New Science of Neuropsychopharmacology (NPP)

I. The social environment and political context within which ACNP was formed

The 'new science' of neuropsychopharmacology (NPP) emerged in the 1950s at the confluence of several scientific disciplines and areas of clinical practice. Signal events prepared the ground for the emergence of NPP in the United States. Chief among these were a series of annual meetings on Neuropharmacology from 1954 to 1959 convened by the Josiah Macy, Jr. Foundation, which brought prominent early ACNP fellows such as Bernard Brodie, Joel Elkes, and Seymour Kety into annual contact in the decade preceding the organization's inception.[13] In 1953 neuroendocrinologist Hudson Hoagland organized a meeting at Battelle Institute in Columbus, Ohio, on "socio-pharmacology," the role of social setting in relation to drug effects, which Joel Elkes, destined to become the ACNP's first president and an eloquent spokesperson for the discipline, called "a new and strange concept to the orthodox pharmacologist."[14] Nathan Kline organized a Symposium on Psychopharmacology for the American Association for the Advancement of Science (AAAS) and the American Psychiatric Association (APA) late in 1954.

This ferment was not confined to the professional enclaves in which labored the scientists and clinicians who came to call themselves "neuropsychopharmacologists," but spilled into the popular press. The fledgling international and national infrastructure for brain research, neuroscience, and NPP was built in a time of great optimism about what pharmacology could offer an anxious public. Meetings of professionals responsible for researching and treating mental illness occurred alongside enthusiastic media

portrayals of the new science, such as Aldous Huxley's 1958 article, "Drugs That Shape Men's Minds" in *The Saturday Evening Post*. As Ralph W. Gerard wrote in a 1957 invited report for *Science*, "Drugs for the Soul: The Rise of Psychopharmacology," so much conversation about psychopharmacology was occurring among the lay public and professional press that no one person could digest it all. "The gossip and symposia and publications have become prodigious. I personally have been asked to attend well over a dozen special symposia on psychopharmacology in the past year (most of which have or will burst out in monographs), have actually participated in half of them, and have been guilty of organizing one."[15] He co-chaired a Conference on Evaluation of Pharmacotherapy in Mental Illness (1956) with psychiatrist Jonathan Cole, then staffing several National Academy of Science / National Research Council committees. The 1956 conference was sponsored by the U.S. Public Health Service, the National Institutes of Mental Health (NIMH), the NAS/NRC, and the American Psychiatric Association. Gerard also reported on the 1956 Conference on Meprobamate and Other Agents Used in Mental Illness co-chaired by James G. Miller and Frank Berger at the New York Academy of Sciences.

Established scientific organizations began to take notice of the new science and seek out its spokespersons. The 1956 annual meeting of the APA catalyzed a major event in the consolidation of the emergent science, as it led to Frank Ayd, Henry Brill, and Nathan Kline to testify on Capitol Hill on behalf of forming an NIMH Division on Psychopharmacology. The outcome was the NIMH Psychopharmacology Service Center (later known as the Psychopharmacology Research Branch), which operated from 1956 to 1965 under direction of Jonathan Cole. According to an interview with Cole, the PSC/PRB "fed" the ACNP by supporting its

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annual conferences and serving as an institutional home for psychopharmacology within the U.S. federal research apparatus that had been evolving since the end of World War II. The PRB ran the NIMH's first large-scale, comparative clinical drug evaluation programs in state hospitals. Cole clearly saw the ACNP as an important meeting ground for the emerging neuroscience research infrastructure—one that included among its ranks scientists from industry as well as academic scientists and clinicians.

This ferment of national and international activities culminated with the founding of the Collegium Internationale Neuro-Psychopharmacologicum (CINP) in 1957, a banner year for neuropsychopharmacology by all accounts. In addition to the above developments in the United States, Joel Elkes, then at the University of Birmingham in England, where he had founded the Department of Experimental Psychiatry in 1951, convened four International Neurochemical Symposia in 1955. The idea for the CINP arose at the International Symposium on Psychotropic Drugs (1957), organized by Silvia Garattini at the University of Milan, Italy. Several American researchers associated with the Laboratory of Chemical Pharmacology, Bernard Brodie's laboratory at the National Institutes of Health (NIH), were at the Milan meeting. The decade closed with unsettled questions about how to define this new science. The disciplinary identities of its practitioners included both researchers and clinicians who were seeking to narrow the knowledge gap between chemistry and behavior.[16] The core ideas and intertwined goals of NPP and its close relative biological psychiatry were deeply bound together in the mid-20th century, a story now told so often that there is no need to repeat it here.[17] As Elkes noted in accounts of the early days of NPP, "experimental psychiatry is clinical, or it is nothing," for the field acts not simply as a "catalyst for bringing into being whole new areas of science, but also as a binder and as a relater of these sciences to each other."[18]

B.B. Brodie

The ACNP played a central role in legitimating biological psychiatry, while displacing the psychoanalytic and psychodynamic approaches to major mental illness, substance abuse, and alcohol abuse that prevailed before it. Scientists, clinicians, and clinical researchers convinced that mental disorder had a molecular, neurochemical, or biogenetic basis joined together to create the ACNP, which has for five decades provided a cross-disciplinary meeting ground for the scientific and clinical communities involved in biological psychiatry. Constrained by the blunt instruments available to them in the 1950s, they set about doing clinical research in mental institutions just as these were beginning decades-long transformations under the combined pressures of fiscal crises of the state and the clinical advances portended by the new drugs, particularly chlorpromazine. Yet in the early days of neuropsychopharmacology, researchers spent much time refuting biological studies and hypotheses, discovering that many of the differences between disordered patients and controls were artifacts of institutional care.[19]

Neuropsychopharmacology (NPP) has been defined as a new discipline that emerged to study the "relationship between neuronal and mental processing in the brain,"[20] using drugs that act upon the central nervous system as probes to understand the molecular changes involved in neural processing. Elkes and Ban credit U.S. Public Health Service researcher and early ACNP fellow Abraham Wikler with recognizing that NPP opened up a new perspective not only upon psychiatric illness

or mental disorder, but also upon the biochemical mechanisms of non-pathological brain function. Writing from the NIMH Addiction Research Center in Lexington, Kentucky,[21] Wikler published *The Relation of Psychiatry to Pharmacology* (1957), which was recognized as a "prescient vision" that foretold the "true dimensions of our field"[22]:

> [W]hat are called "behavioral effects" are not isolated, elementary changes in "consciousness," "perception," "emotion," "ideation," or "learning," which are simply increased or decreased by "stimulants" or 'depressants," but complex *patterns* of change, proceeding in time, involving all of these aspects of behavior to varying degrees, and dependent not only on the drug administered, but also on biographical and environmental factors as well as on the activities of the observer. . . . Eventually, our "compartmentalized" thinking about the dynamics of behavior will have to give way to a "transactional" point of view. This is a problem for the future."[23]

As the relationship between psychiatry and pharmacology unfolded, the process enabled neuropsychopharmacology to be launched as a common enterprise of researchers working both in clinical and laboratory settings. While the available techniques and technologies were limited in the 1950s, the urge to produce an integrated knowledge of biochemical, neurophysiological, and psychological mechanisms involved in the specific patterns by which drugs modified behavior was strong in the field's pioneers.[24] Predicting that drugs with well-studied therapeutic effects were the key to understanding molecular-level changes involved in mental processing and mental illness, Wikler was chosen as the first co-editor of *Psychopharmacologica*, one of the first major journals that helped define the field.

The number of effective drugs available in the therapeutic armamentarium widened dramatically during the 1950s, and technologies such as the spectrofluorometer had been introduced by 1955 at Brodie's NIH lab.[25] New technologies gave researchers ways to measure drug-induced changes in neurotransmitters and metabolites—important preconditions for NPP's conceptual basis.[26] Ideas about 'the brain' and 'mental disease' and disorder underwent great change; Gerard heralded the 'emphatic reentry of the brain into the mental arena' as these new tools became available.[27] As the brain became more accessible to scientific investigation, a "triumph of biological thinking" overtook the prevailing view that the brain had little to do with mental illness and consequently did not matter within Freudian psychoanalysis and within a psychiatry that insisted on the mind's independence from the brain.[28] However, in the 1950s the idea that research on neurophysiology and neurochemistry would lead to new knowledge about how the brain worked was young. The small cadre of researchers, clinicians, and state hospital administrators who comprised the core of the ACNP shared the view that the gap between brain and behavior would be narrowed through the use of drugs as analytic tools and chemical probes. This drew them into drug development and evaluation—and into conversation with others doing similar work in similar settings.

II. Conference for the Advancement of Neuropharmacology (1960)

"Before we lay any eggs, it will be necessary that we have a chicken."[29]

Even before the ACNP's inception, its principal founders had been actively interested in setting regulatory standards for clinical investigation of new drugs used to alter or treat mental states. If neuropsychopharmacologists were to "regulate before the government does," as Frank Ayd put one of the explicit purposes of the 1960 meeting

that led to the establishment of the ACNP, they would need a permanent group structure. For this reason, the Conference for the Advancement of Neuropsychopharmacology, which led to the founding of the ACNP, was held on November 12-13, 1960 at the Hotel Barbizon-Plaza in New York City. The meeting's stated impetus was to create an organization modeled on the American College of Physicians for those involved in producing and testing the efficacy of new drugs. Clinician Theodore Rothman was the convening secretary and the meeting was chaired by Paul H. Hoch, the Hungarian-born Commissioner for Mental Health in New York State. At the time Hoch was serving as president of the CINP, but he and other North American investigators (who, it should be noted, included more than a few recent émigrés from Europe) were motivated to gather in part because they felt they had been treated as "orphans" in CINP.[30] Those assembled pointed out the irony that although most psychopharmacology work was done in the United States, the first question the nascent organization faced was whether or not to affiliate with its European counterpart. They held two votes: the first established an American Society or Association on Neuropsychopharmacology, and the second affiliated with the international Collegium.

The questions before the Conference for the Advancement of Neuropsychopharmacology concerned whose responsibility testing in animals and early human studies should be, as well as what kinds of human subject populations should be considered. Those gathered raised questions about whether drug evaluation—both animal toxicity testing and clinical investigation—should be undertaken differently in psychiatric patients than in other clinical domains. Many had experience with the two-step approval process put into place by the U.S. Food and Drug Administration (FDA) as a result of meetings held from 1956 to 1958. This process preceded the 1962 amendments to the FDCA (1938) requiring clinical trials and proof of efficacy as well as safety. In the early 1960s, there was palpable reluctance on the part of NIH to oversee or coordinate large-scale clinical trials design, a situation prevailing throughout the Kefauver hearings and the controversy over thalidomide that led to the current regulatory scheme.[31] Many researchers shared Frank Ayd's disapproval of government involvement or "policing" in the early stages of drug discovery and feared that regulation by the FDA would hamper future pharmaceutical innovation.[32] While FDA oversight of clinical trials expanded the agency's regulatory responsibilities, opportunities for clinical trialists and academic researchers funded by NIMH also expanded at this time and pharmaceutical innovation remained strong.

Concerns arose from two sources: one was that the climate of serendipitous discovery arising from novel, clearly 'off-label' clinical uses of psychoactive compounds that prevailed in the 1950s would be shut down, and the other was that pharmaceutical companies would be deterred from supplying research compounds to neuropharmacological investigators. The need for an expert body to set standards for clinical investigation in the field of mental illness was clear to the conference. The gathering was keenly sensitive to the differences between psychiatry and other fields of medicine in terms of the patient population and accepted therapeutics. Such differences came up that first afternoon, which was devoted to a discussion of dissemination of information about the new drugs by pharmaceutical companies and their "field men," advertisements, and commercial brochures. Already there were concerns that the nascent organization might be perceived as allying too closely with the drug industry, but the consensus was that "research men" needed to convey solid information about

the new drugs to psychiatrists and general medical practitioners, who were thought to be unnecessarily deterred from prescribing "good drugs" by too much attention to side effect profiles.

The expertise of basic and clinical researchers was focused on how best to go about screening and evaluation of psychoactive drugs.[33] Director of the NIH Laboratory of Chemical Pharmacology, Brodie, who spoke of himself as representing the basic sciences, defined psychopharmacology's goal as "know[ing] how the drugs we are using alter mental states by modifying in some way the activity of the neurophysiologic and biochemical functions in the central nervous system." Reaching this goal, he admitted, was far distant given the impossibility of describing drug influence in terms of gross neural pathways, much less explaining exactly how drugs exerted their more subtle effects. He was concerned with how psychopharmacologists were going to screen drugs that acted only on abnormal states and speculated that such states could be induced with one compound, and then blocked with another. Similarly, Abram Hoffer encouraged the association to be concerned with drugs that produce abnormal mental states or "strained states" similar to psychotic states, such as pyridine, LSD, and mescaline—and indeed many of the early ACNP fellows worked with these drugs to explore so-called psychotomimetic states.[34] The difficulty of knowing whether such states really modeled the mental conditions that psychiatrists were trying to treat or not was raised by Paul Hoch, who pointed out the difficulty of knowing whether such a state was identical or just similar to mental illness.

The excitement pervading this meeting extended to the organizational session that was held in what Joel Elkes recalled as the "proverbial smoke-filled room in which some of us, years ago, planned the creation of the American College of Neuropsychopharmacology."[35] The final organizational session stabilized the structure that would be used to continue the conversations begun in 1960 in the Organizing Meeting of the American College held October 7-8, 1961 in Washington, DC.[36] The 105 attendees became the Founders of the ACNP and they elected Joel Elkes as its first President. The early meetings preceding the first annual meeting were striking in the degree of camaraderie, enthusiasm, and consensus as attendees ranged freely across issues confronting them in the regulatory domain, the clinical arena, and in the basic research questions to which the field sought to reply.

III. ACNP's Inaugural Year Culminated in the First Annual Conference

The ACNP's first annual meeting was held January 24-27, 1963 at the Woodner Hotel in Washington, DC. The meeting included nine informally organized study sections, most held in the individual hotel rooms of their conveners. Proposed by President Joel Elkes in his first presidential report of June 1962, the initial 123 members recalled the study sections fondly:

> "It is the responsibility of the College to develop the science of psychopharmacology and the application and dissemination of the science. The Group comprising the College is small; Members know each other through their respective work, and with the passage of time will get to know one another even better. There is thus a ready opportunity to clarify some issues through frank debate in small groups. With this in view, Council has accepted my suggestion for the formation of Study Groups within the College. Groups are intended to examine topics which are either vague or controversial; to summarize the status (including the gaps) within a given field, and to provide guidelines for its future development." [37]

This forward-looking vantage point became a hallmark of the organization, which from its earliest days allowed frank debate on many vague and controversial topics in which neuropsychopharmacology was implicated during the first 50 years of the ACNP.

In 1965, the site of the annual meeting was moved to Puerto Rico with three consecutive meetings held there and the fourth somewhere on the mainland or in Hawaii. This arrangement stopped in 1996.

As the organization matured, the early focus on self-regulation became moot. That focus makes clear that the ACNP was not founded simply as a scientific organization: as Kline put in his 1967 ACNP Presidential Address, "because of our relatively modest size and cohesiveness it has been possible to react rapidly and with general unanimity to some of the legislative, administrative and other events which seriously concerned us. Many of us feel that it is our responsibility to contribute not only research findings but to help create the social environment whereby new knowledge in our field can be safely acquired and maximally applied."[38] Creating the kind of social climate in which the findings of neuropsychopharmacology would be accepted and implemented in socially beneficial ways was the goal. That goal has been an ongoing commitment of the ACNP: the redefinition of many so-called social problems once understood as socioeconomic in origin as behavioral, mental and mood disorders best understood as originating in the brain. The ACNP was positioning itself to deliver this message to the American public and federal agencies, while consolidating the scientific basis of American neuropsychopharmacology.

First Study Sections of the ACNP

(Followed by meeting place)

1. Individual Variation in the Metabolism of Psychoactive Drugs
2. Analysis of the Effect of Drugs on the Electrical Activity of the Brain
3. Individual Animal Differences in Drug Responses: Determining Factors (Sam Irwin's room)
4. Social Factors and Individual Expectation in Relation to Drug Responses in Man
5. Advantages and Limitations of the Controlled Clinical Trial in Psychopharmacological Investigation
6. Effects of Drugs on Communication Processes in Man, with Special References to Problems of Verbal Behavior (Joseph Zubin's room)
7. Pharmacology of Memory and Learning (Murray Jarvik's room)
8. Unification of Reporting of Data of Drug Trials in Hospital Settings and in Office Practice (Paul Feldman's room)
9. Toxicity of Psychoactive Drugs (Klaus Unna's room)

Section One

Evolving Social Responsibility: The Maturing Organization Evolves a Structure to Respond to Problems of Public Concern

I. Clinical Interventions

Serendipitous discovery led to most of the major drugs used in clinical treatment of major mental illness. Clinical use of these compounds helped hasten a process of deinstitutionalization underway since the late 1940s due to fiscal crisis in the state hospital systems. Among the work of the founding fellows were some legendary breakthroughs in psychopharmacology, such as Nathan Kline's early work on the use of reserpine (Rauwolfia) to treat psychosis and schizophrenia; the early work of Heinz Lehmann, Frank Ayd, Joel Elkes, and others on chlorpromazine; the serendipitous discovery of MAO inhibitors such as isoniazid working as antidepressants; the work of Donald F. Klein on imipramine in panic and phobia; and attempts to study schizophrenia and psychosis using psychotomimetics such as LSD by many early members of the ACNP. These serendipitous discoveries led to hypotheses about how the brain and brain chemistry worked, in addition to altering the clinical climate and making community-based care seem a realistic prospect.

While the idea that altering brain chemistry could have salutary effects on behavior and mood was not confined to the ACNP membership, which was purposely kept to 160, the founding fellows were influential in widely diffusing this notion. The atmosphere of the early meetings was electric as a result. As Albert A. Kurland recalled in his ACNP interview, "In those very heady days at the ACNP meetings, everybody was on the verge of a major discovery of one kind or another. But the interesting thing is, over the years that we carried on our research, and everything we were involved in . . . went along in a very carefully calculated way." The first decade of the ACNP's existence was witness to a dramatic change in understandings of what psychopharmaceuticals could do for patients inside and outside of mental institutions.

As Kline put it in his 1967 presidential address, "These dramatic results reflect not only the action

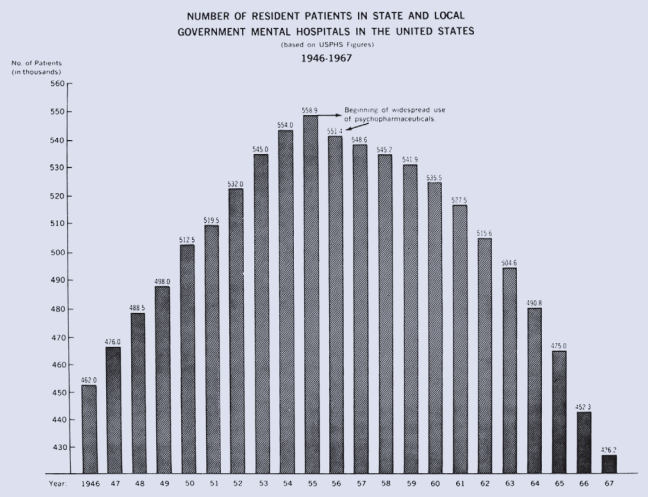

Fig. 1—Number of resident patients in state and local government mental hospitals in the United States (based on USPHS Figures) 1946-1967.

of the drugs themselves but improved staff-patient ratios, newer concepts of treatment such as the 'open' hospital and increasing acceptance of psychiatric disorders as diseases rather than manifestations of demons, defiance or debility."[39] Noting increased popular acceptance of both institutional and pharmacological treatment, Kline pointed out one of the most "impressive confirmation[s] of the effectiveness of treatment"—this era witnessed both a doubling of hospital admissions and a better than two-fold increase in the discharge rate.

Changing patterns of psychiatric care affected communities in ways that were by no means restricted to changes in psychoactive prescribing patterns. In the early days of ACNP,

there was attention to clinical practice in community psychiatry through a Study Group on Psychopharmacology and Social Therapy, chaired by clinicians Theodore Rothman and Else Kris. The study group heard regional reports on community psychiatry in major cities such as Boston, New York, and Baltimore, and considered the transitions underway in large mental hospitals and the shift towards community mental health centers, after-clinic care, and day hospitals. The majority of early fellows were clinically inclined, even if they thought of research as 'basic', and thus the emerging therapeutic armamentarium was greeted within the context of potential practice improvements. In his ACNP interview, Irv Kopin credits ACNP with bringing clinical and basic research together into a "biochemical pharmacology applied to the nervous system." This unique aspect of the organization brought clinical trialists—who were then in the process of refining methodology and research design—together across diagnostic categories, disciplines, and research location.

Attempts to place assessment and treatment of neuropsychiatric disorders on a rational footing—and to derive more reliable diagnoses and new therapies from basic science and feed them back into clinical practices[40]—was an important condition of possibility for fruitful interactions between clinicians, researchers, and epidemiologists. The process leading to the publication of the DSM-III (1980) was viewed as 'revolutionary' by the small cadre who advanced it, and it was crucial for development of psychiatric epidemiology. Although psychiatric assessment tools proliferated, psychiatric diagnosis was far less reliable prior to the 1980 third edition of the *Diagnostic and Statistical Manual*. Early ACNP fellow Joseph Zubin, a psychometrician working closely with Paul Hoch and British psychiatrist Morton Kramer to explain diagnostic discrepancies between the U.S. and the U.K. in the 1960s, said in the ACNP 25th anniversary publication, "Biometrics became an important element in the development of NPP because it provided means for testing the hypotheses raised by drug research" and also provided NPP "with a yardstick and a language as well as a conscience."[41] Refinements in diagnostic tools enabled productive relationships between psychiatric epidemiology and research in psychiatry and psychopharmacology.[42] As ACNP fellow and Washington University psychiatrist Samuel B. Guze put it in *Why Psychiatry Is a Branch of Medicine* (1992), "Psychiatric illnesses, like all illnesses, are most comprehensively conceptualized within a broad epidemiological framework, where health and disease are seen as varying aspects of the organism's efforts to adapt to its environmental circumstances and history."[43] Arguing that psychiatric disease is best situated in a "medical model" closely intertwined with biological psychiatry, Guze saw the medical model as embedded "within the matrix of our knowledge about evolution, neurobiology, cognitive science, and genetics."[44] As views on prevalence, social distribution, and clinical response to psychiatric disease changed, so did ideas about which disorders counted as 'brain diseases'—and the widespread democratization of this evolving idea is perhaps the ANCP's chief legacy.

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II. Early Involvement with 'Social Problems' and Abuse of Psychoactive Substances

The fledgling ACNP was prominently involved with one issue widely considered to be a 'social problem' until the late 20th century when it was redefined as a 'brain disorder'—that of substance abuse, 'addiction,' or 'drug dependence.'[45] According to Jonathan Cole's interview, one of the main organizational models for ACNP was the National Academy of Sciences (NAS) Committee on Drug Addiction and Narcotics (CDAN), which changed its name to the College on Problems of Drug Dependence (CPDD) in 1965. Cole had staffed CDAN before moving to NIMH to assume directorship of the Psychopharmacology Research Branch. Cole was well aware of the excellent working relationship between CDAN/CPDD, the National Institutes of Health (NIH), the NIMH Addiction Research Center, the Federal Bureau of Narcotics (then the "regulator" for opioid analgesic development), and pharmaceutical industry representatives innovating in the analgesic area.[46] At the time CDAN/CPDD was essentially a small steering committee that coordinated efforts to develop a non-addicting analgesic and an effective pharmacotherapy for addiction treatment.[47] While CDAN/CPDD involved a wider set of scientific disciplines than neuropsychopharmacology, it was focused the narrower set of problems involved in opiate addiction.

Heinz Lehmann with President Johnson

Given the emphasis on drug probes and the theoretical interest devoted towards induction of psychotomimetic states in early neuropsychopharmacology, drugs of abuse were a major focus for the early ACNP, although these were typically considered in relation to mental illness.[48] Substance abuse researchers had worked hard to overcome the notion that addiction was an outcome of psychopathology, and to set their research enterprise on scientific footing. They found in neuropsychopharmacologists ready allies in efforts to find out what was going on in the brains of addicted persons and to use that insight to learn about brain function. For neuropsychopharmacologists, work on drugs of abuse offered an entrée to issues of public concern, governmental import, and national politics.

During the 1970s significant federal attention was devoted to drugs and alcohol due to the formation of the National Institute on Drug Abuse (NIDA) in 1973 and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in 1970. ACNP often devoted plenaries to drug abuse, as in the 11th annual meeting, held in October 1972 on "Psychosocial and Pharmacological Aspects of Opiate Addiction," chaired by Daniel X. Freedman. This meeting was the high-water mark for the focus on addiction. Wikler gave the Daniel Efron Memorial Lecture on "Dynamics of Drug Dependence: Implications of a Conditioning Theory for Research and Treatment," and Stephen Szara and William [Biff] E. Bunney, then head of the NIMH Department of Narcotic Addiction and Drug Abuse (DNADA), soon to be absorbed into NIDA, presented "Recent Research on Opiate Addiction: Review of a National Program." There was a continuing education program on clinical approaches to treatment and control of opiate

addiction chaired by Elkes that included Jerome H. Jaffe, Freedman, and other prominent addiction researchers. While the ACNP focus on drug addiction peaked in 1972, the organization assisted CPDD with an organizational crisis stimulated by changes in the committee structure at the National Academy of Science later in the 1970s. Alcohol researchers also had a separate organization, the Research Society on Alcoholism (RSA). Several high-profile neuropsychopharmacologists whose research centers on substance abuse and alcoholism have taken leadership roles in ACNP. Although the organization's focus on 'social problems' faded from view after the first two decades, reemphasis on substance abuse research reemerged as conditions formerly viewed as mental illnesses were no longer considered 'social problems' but 'brain diseases.'

III. Ethics Committee as Conduit for Social Issues Leads to Formation of Ad Hoc Committee Structure

Early in its life as an organization, ACNP dealt with other policy questions construed as 'social problems'—but its main purview was how society responded to those suffering from major mental illness. Until the late 1960s all social issues formally taken up by the ACNP generally entered through the Ethics Committee. For instance, late in the 1960s Kline suggested this committee consider the ethics of wide "public use by society of psychotropic drugs." He and Wayne O. Evans chaired an ad hoc study group on the "Effects of Psychotropic Drugs on Normal Humans," which published *Psychotropic Drugs in the Year 2000: Use by Normal Humans* (Springfield, IL: W. I. Thomas, 1971). Their forward-looking orientation foreshadowed today's debates on neurocognitive enhancement, and led the ACNP Council to consider whether setting up ad hoc committees, rather than running societal issues through the Ethics Committee, might not be a better approach for "various issues that the society may wish to consider and take a stand on."[49] The Ethics Committee, Council suggested, could be a "watch dog" for "public issues of a moral and ethical nature" that should be brought to the attention of Council and membership. Ultimately, Council approved the "watch dog" approach, a structure that has led to the formation of many ad hoc committees over the years. These are addressed below.

By the mid-1970s the ACNP Ethics Committee was concerned with societal issues involved in protecting human subjects of biomedical research. The ACNP's original "Statement of Principles of Ethical Conduct for Neuropsychopharmacologic Research in Human Subjects" was written in response to a presidential request for universal standards governing "all human research, federally funded or not, and regardless of the source of funds,

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[which] should be subject to the same principles of ethical conduct."[50] The first principles were approved by the membership in June 1976. This document provided the organization a useful starting point at a time when the current regulatory regime was being institutionalized and implemented. In the mid-1980s when ACNP's legal counsel, Paul Perito, updated the original statement, he wrote, "[W]e are impressed with the degree to which the basic ethical principles have stood the test of time."[51]

Charged with expanding the utility and modernity of the statement, Perito compared it favorably to federal regulations and expanded its "legal comfort" for neuropsychopharmacologists facing unique issues not fully addressed in federal law due to their working with "patients with diminished capacity or residing in inherently coercive environments,"[52] both conditions rendering human subjects part of the most vulnerable classes according to the President's National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

Avoiding unnecessary encumbrances in the research process and maximizing scientists' autonomy remained one of the ACNP's primary advocacy goals and one to which the Ethics Committee has been devoted. As an honorary society, the organization consistently represents its members as a scientific elite that mainly needed to be left alone in order to accomplish good scientific work for the benefit of humanity.[53] The ACNP has played up its role as an "organizational setting for the discussion of regulatory and administrative issues" and its collaborations with FDA and NIMH.[54] Portraying the goal of research as "provid[ing] relief of distressed human beings," the ACNP has promoted human and animal experimentation as essential along with the view that IRBs should be given the "autonomy necessary to fit the degree of 'protection' to the circumstances of the research."[55] The 1979 document read in part, "The ACNP does not believe that either real 'protection' or a viable research atmosphere would result from detailed, mandatory procedures which substitute regulations for good judgment."[56] Concerned that clinical researchers might be deterred by the regulatory burdens thrust upon them by the emerging human subjects protection regime, the ACNP advised the federal government to "counter the discernible trend away from committing resources, human and financial, to clinical research in the United States."[57] The concern was not only about a potential decline of clinical research, but the extent of scientists' moral responsibility to contribute to human welfare. Recent incarnations of the ACNP "Statement of Ethical Conduct for Neuropsychopharmacologic Research in Human Subjects" (1996) state that researchers should not only minimize risk and safeguard the welfare of individuals who participate in research, but contribute to "present and future welfare" by reconciling "society's needs for advancing knowledge and for conducting research in an ethically informed and regulated manner." The 1996 revision served as an important model for further interactions at a number of universities dealing with the ethical issues relevant to neuropsychopharmacology.

IV. Social Responsibility and the Committee on Problems of Public Concerns

While the Ethics Committee initially provided a conduit for issues, the ACNP also created a Committee on Problems of Public Concern (CPPC). During the 1970s, when the organization devoted its resources to legal cases (see below), this committee was perceived as weak. This decade was one of great upheaval in the research climate and the regulatory structure within which neuropsychopharmacologists conducted their work due to several high-profile events that drew attention to research ethics and moved Congress to create the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[58] In the wake of the National Commission's recommendations, which were binding upon the Department of Health, Education, and Welfare, *all* scientific communities involved in using human subjects for research underwent profound change, but these changes were greatest for those who worked with the institutionalized. In 1975 the CPPC got the ACNP Council to co-sponsor a conference by

Donald F. Klein to explain the impact of the National Commission's recommendations to science writers and legislative aides. There was also a proposal for the organization to sponsor meetings on the "Right to Refuse Treatment" and the "Right of Competent Treatment," which paralleled the court cases in which the organization had become involved. ACNP officers and members organized a letter campaign in support of the Addiction Research Center (no longer an NIMH laboratory but the intramural research program of NIDA), which was by then the sole remaining *federal* correctional institution at which research was conducted on prisoners. Indeed the minutes of the December 1976 ACNP Council meeting left participants with a dismal picture of the problems besetting the research community with respect to "anti-scientific sentiment." The disarray left the CPPC in a weak position, but the committee rallied to craft a stance on several matters of pharmaceutical regulation such as the then-common practice of supplying unsolicited drug samples through the mails and what should be done about the proposed "patient package inserts" designed to accompany prescribed drugs.

While the CPPC took a backseat to the focus on the legal and judicial arena encouraged by the ACNP's increasing traffic with its Washington law firm and its participation in the Boston State Hospital case (see below), some members urged that this committee be strengthened so that it could take on more activity in formation of government policy and regulation.[59] The actions of the ACNP toward excessive bureaucratic standards and unnecessary changes to human subjects protection must be interpreted in light of the organization's earliest stance on the matter, which was that scientists and clinicians were in the best position to regulate themselves. While this stance made turning to law and policy contentious, the historical record indicates that the ACNP *has* worked on multiple fronts to evolve an ethical framework to expand funding in ways that would enable ethical conduct of socially responsible neuropsychopharmacological research using both human and animal subjects. Efforts to increase the organization's political clout took myriad forms. "We were political animals at one point," as one former ACNP President put it.[60] ACNP Council and the CPPC located champions of mental health research in Congress in order to use the ACNP's clout to leverage bipartisan interest in mental health.

By the late 1970s Frederick Goodwin chaired the CPPC and suggested organizing a "series of 'shock troops' that could act in key states" when issues pertinent to research advocacy arose. He suggested the ACNP should build closer relationships with public bodies and the "more responsible consumer groups" such as the venerable state Mental Health Associations, and make a more consolidated effort to promote research within APA task forces.[61] Goodwin remained optimistic about the College's potential impact on the federal government, citing recent positive response to the rewriting of human subject regulations and those for the Institutionalized Mentally Ill in ways more palatable to researchers and clinicians than those of the National Commission. Issues concerning cost effectiveness of the regulations had arisen; Goodwin expected ACNP to be active in rewriting of regulations.

Increasingly, through a variety of mechanisms in addition to the CPPC, the College sought to influence the federal research infrastructure and relevant regulatory bodies. While it is difficult to gauge the success of these often behind-the-scenes efforts, many of the positions taken by the College did in fact come to pass. By the mid-1980s the ACNP Council had also begun to consider how to use broadcast media to better reach the general public in order to translate advances in psychopharmacology

for the lay public. The organization began thinking about educational programs for physicians, an effort that led to formation of a Model Curriculum and a series of continuing education seminars. The broadcast media issue arose in response to a CBS report on tardive dyskinesia that some felt might deter patients from taking prescribed drugs, as well as perennial concerns about electroconvulsive therapy (ECT). While Klein reported that the committee had been "comatose" at the December 1983 Council meeting, he remained optimistic that the CPPC provided a vehicle for addressing myriad issues ranging from Forced Medication of Patients to the Addiction Liability of Benzodiazepines and their scheduling by the World Health Organization, in addition to animal care legislation.

The events of the early to mid-1980s laid the groundwork for the ACNP leadership to establish and maintain more formal relationships with patient and consumer advocacy groups. At the July 1985 ACNP Council meeting, Roger Meyer, then chair of the CPPC, was asked to make that committee the principal liaison from ACNP to NAMI and other advocacy groups. The CPPC in turn proposed inviting patient/consumer advocacy groups to annual meetings, adding plenaries such as a 1986 session on "The Delicate Balance Between Discovery and Action," and co-hosting events such as a 1986 show-and-tell program on Capitol Hill titled "A New Partnership for Hope and Progress: Advocacy for Research on Brain and Behavior." Such events showcased an evolving relationship between ACNP and the advocacy groups, which will be revisited below.

In the late 1980s the CPPC migrated towards matters of scientific misconduct, fraud, medical malpractice, and over-prescription of psychoactive drugs to children. By the 1990s issues of public concern were increasingly folded into discussion of relations with advocacy groups and the CPPC chair expressed concern about the vagueness of the committee charge and overlap between the CPPC and the Committee on Relations with Advocacy Groups. In the February 1989 Council meeting, Roger Meyer commented that the CPPC had the least clear mandate and was most responsive to initiatives generated by the ACNP president. While it is clear from the archives that the interests of the CPPC chair also mattered in terms of steering the committee, the overlap perceived between the CPPC, the Advocacy Committee, and the Liaison Committee with Governmental Agencies and Pharmaceutical Industry was increasingly expressed in negative terms. The role of the latter committee was unclear; it, too, was supposed to "respond to relevant issues and problems identified by Council, individual committee members, and ACNP members," but the CPPC was generally regarded as a 'committee in waiting' without a fixed charge, agenda, or area of responsibility. The confusion over which committees had jurisdiction led to a certain sense of gridlock, and the CPPC became a casualty of this malaise. At the same time, the CPPC may also be seen as having served its purpose and giving way to the Advocacy Committee in part because advocacy groups were becoming better-situated to tackle some of the "problems of public concern" as they arose.

In the mid-1990s, the so-called Decade of the Brain, there was a brief attempt to resuscitate the CPPC to better face challenges arising in Washington, DC. Under co-chairs Don Gallant and David Kupfer, the committee convened a day-long seminar on "Problems of Federal Funding for Brain Research" in the summer of 1993. That year research funding was cut in the Veterans' Administration and no new investigators were to be funded in fiscal year 1994; NIH was also short-changed. Roger Meyer and Thomas Detre wrote a brief paper, "But Will It Be Remembered as the 'Decade of the Brain'?" Informally, a joke circulated that the "Decade of the

Brain" had become "more like Secretaries' Week," as brain-related issues were trumped by AIDS, breast cancer, women's health, and the Human Genome Project. The ACNP Council met regularly with legislators and staff to discuss the social costs of "brain disorders" and the necessity of basic research for preventing and treating them. Council repeatedly pointed out funding discrepancies between conditions like heart disease or cancer, and the "ADAMHA-type diseases" (substance abuse, alcoholism, and mood and other mental health disorders were then the province of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). They argued that neuroscience research was a health and economic investment in the future. While their arguments seemed to go unheard at the time, the doubling of the NIH budget for 4-5 years starting in 1998, a period during which there was considerable drug development and a rapid expansion of neuroscience, indicate that someone was listening to the arguments on behalf of basic research.

It became increasingly apparent to the ACNP Council that concerns once addressed by the CPPC had been taken on by the Advocacy Committee. In December 1996 Council proposed to abolish the CPPC on grounds that it had become inactive for two main reasons: "One is the belief by many on Council that effective political and/or legislative action can only be accomplished at the local level, and a national committee such as the CPPC will not serve an effective purpose. A second reason is that much of the work done in previous years by this committee is now accomplished by and through the Committee on Relationships with Advocacy Groups. For that reason, Council voted to recommend to the membership that the CPPC be discontinued."[62] The vast majority of members agreed. Another factor in retiring the CPPC was the emergence of other important groups that could speak to the kinds of issues typically the CPPC's purview, such as the Society for Neuroscience.

Section Two

The Politics of Neuropsychopharmacology: ACNP Involvement with Ethical, Legal, and Social Issues in the 1980s

I. Public Policy and Law

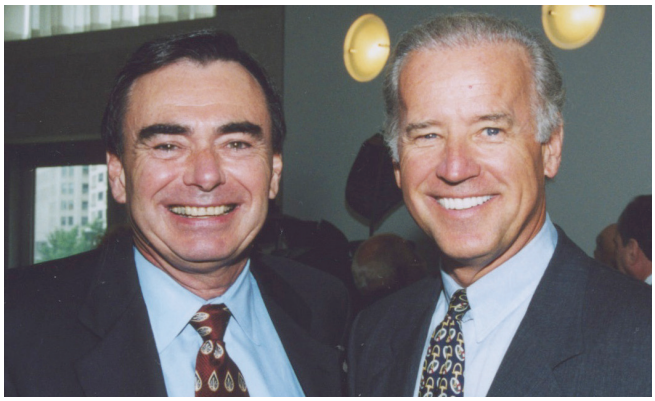
The ACNP's role in public policy gradually expanded in the 1970s and 1980s. In 1973 both ACNP and CPDD retained the same Washington, DC, law firm, Neil Chayet and Michael Sonnenreich, to examine the implications of the Psychotropic Substances Act (1973).[63] Jonathan Cole facilitated the relationship. Five years later, Sonnenreich suggested ACNP move its offices to Washington, DC, so as to be better situated for advocacy work. ACNP Council emphatically rejected the College's locating in the nation's capital on grounds that the College was not a political organization, and moved the offices to Vanderbilt University in Nashville, Tennessee. While rejecting a course of action that would have placed it inside the Beltway, the ACNP became significantly more involved with science policy and law. The College became more active in offering commentary to the Drug Enforcement Administration (DEA), the FDA, and the National Commission on specific drugs and revisions to the rules governing clinical research, particularly with the institutionalized mentally ill. The College took up a variety of legal issues and public policies bearing upon the work of its scientific community. Increased visibility in the regulatory arena was coupled with

many members of the College playing roles in government. ACNP entered the Washington health policy decision-making arena, keeping its activities consistent with the objectives of a prestigious scientific association.

A. Influencing Allocation of Federal Research Funds and Direction of Health Policy

During the 1980s and well into the 1990s, the ACNP Council met twice yearly in Washington, DC, often with key people in the federal government and Congress arranged by legal counsel to further the College's interests and foster influence. While the College's effectiveness and visibility rose as a result, the ACNP remained relatively unknown to the press and to the public.[64] The initial impetus for the increased political presence was an announcement in mid-February 1981 that the Office of Management and Budget planned to reduce funding for "ADAMHA-type research" by more than half of the current outlay.[65] ACNP Council worked behind the scenes to reverse the threatened cuts. As a result of these and other efforts some $12 million was restored to the mental health research budget that year.

During this era, many high-profile legislators and legislative aides, including H. Westley Clark, then working for Senator Edward Kennedy (D-Mass), and Senator Al Gore (D-) attended ACNP's Washington meetings. Leadership took on active role on appointments to such posts as administrator of ADAMHA and the directorships of NIDA, NIAAA, and NIMH. With varying results, ACNP weighed in on the periodic reorganizations to which the federal research apparatus has been subject. When circumstances called for ACNP action at the state level, typically in states like New York with longstanding mental health research capacities, letter-writing campaigns were organized. For instance, in 1983 the College took an active interest in New York State budget cuts affecting the Department of Mental Hygiene, writing letters to then-Governor Mario Cuomo and state legislators urging them to reconsider a 28% proposed cut to a department that had an international reputation for making great contributions to the understanding of mental health. The College noted that it was "inexcusably shortsighted" from the perspective of chronically ill mental patients and for future state budgets, "with their staggering bills for mental health care," for which the "only hope lies in psychiatric research."[66] While this claim can be debated—states in that era were responding to federal cuts in mental health services, support for the disabled, and Social Security that profoundly impacted the newly deinstitutionalized mentally ill[67]—it was clear that ACNP argued on behalf of research as the best route to compassionate and humane treatment of the nation's mentally ill.



Charles O'Brien and Joe Biden

Healthcare policy, treatment services, and mental health policy take place at a distance from science policy oriented towards research. For the past 20 years, the ACNP has tried to close the gap between research and services. The Washington meetings were often designed to draw attention to this gap, but the ACNP always emphasized the translation of research into treatment as the pathway to improved treatment. As Perito wrote to ACNP President Seymour Fisher in 1984, "It has been our

experience that both members and staff genuinely appreciate having the scientists and doctors who have done, for example, actual drug-related research or reassembled genes, make a live presentation to them so they can have a hands-on and eye-to-eye understanding of the breadth of interest and contribution of neuropsychopharmacologists."[68] He pointed out that a relatively small organization could only rely on the strength and integrity of its members without Political Action Committee (PAC) funding or a large membership by which to raise funds to donate to political campaigns. This planted the germ of the idea that the ACNP should form a PAC, which was actually formed in the 1980s but never utilized.

Various members of the ACNP leadership have felt that the organization should attempt to garner greater political influence with the goal of "increasing the total amount of monies available in the general area of neuroscience, biological psychiatry, and psychopharmacology" by encouraging foundations to target money for research in the general area of neuropsychopharmacology.[69] The ACNP inhabits a competitive environment dominated by increasingly professional lobbyists from multiple special interest groups both friendly and unfriendly to science. As patient and consumer advocacy groups gained in sophistication, the ACNP could mainly contribute by throwing the weight of its scientific prestige and expertise behind patient advocacy groups. Many individual members serve on scientific advisory boards and were able to observe the growing effectiveness of citizen action campaigns. As this gradually became apparent, some members began to push for stronger ties to advocacy groups taking shape in the mental health arena. This relationship-building turned out to be fortuitous, given the tumultuous times ahead in the area of animal welfare and animal research.

B. Animal Welfare/ Animal Research

Contentions over the use of animals in research occur cyclically in the American polity. Periods of intense concern arose both early and late in the 20th century. Animal researchers were already involved in self-regulation before the ACNP's inception through the National Research Council's Institute for Laboratory Animal Research (ILAR), which was established in 1952, and the Animal Care Panel, which was the precursor to the American Association for Laboratory Animal Science (AALAS) Committee for the Consideration of Animal Regulatory Activities established guidelines for care and use of laboratory animals in 1963. In 1965, the name of the accrediting organization was changed to the American Association for the Accreditation of Laboratory Animal Care (AAALAC). By the time Congress passed the Laboratory Animal Welfare Act (1966), laboratories voluntarily sought accreditation through AALAC. For the first two decades of the ACNP's existence, attention to animal research issues was scant. The organization did not become deeply involved in the animal research issue until the early 1980s, when the issue ignited with the Silver Spring monkey incident in late 1981. The ACNP took a supportive stance towards behavioral researcher Edward Taub, who was exonerated by the Maryland Court of Appeals. In March 1983, the ACNP Council approved an Ad Hoc Committee on Animal Rights Legislation to be chaired by Keith Killam and in 1986 it formed a Task Force on the Use of Animals in Neuropsychopharmacology, also chaired by Killam. Working in concert with citizens' groups in a number of states, the Task Force was successful in "preventing the passage of unwise legislation."[70]

Provoked by what ACNP legal counsel called "unlawful messianic actions" and laboratory break-ins by the animal rights movement mobilizing in the 1980s, the organization closely monitored federal regulation of animal research and encouraged

members to become involved in testifying in the early stages of local and state level efforts. Researchers were urged to counter the animal rights movement by emphasizing the benefits of biomedical research in terms of patient care and healthcare cost-cutting. Perito wrote, "Do not underestimate adversaries. They have been very effective using the emotional appeal that researchers harm pets."[71] For instance, he suggested that an "effective position to take in the support of funding for research on Alzheimer's disease is that 'research reduces hospital care in the long run'." The ACNP was far from the only scientific society that felt vulnerable to attacks from animal rights groups, while simultaneously working to improve standards of animal care, methodologies for animal research, and the quality of veterinary medicine.[72] The ongoing nature of the dispute over the societal value of animal research led the ACNP to look into making greater contributions to other research advocacy efforts.

Indeed when the ACNP celebrated its 25th anniversary in Washington, DC, there was great concern that animal rights activists, then actively picketing several campuses and research facilities, might disrupt the 1986 annual meeting. Such concerns helped cement the ACNP's relationship with advocacy groups seen as having shared interests in ensuring that appropriate animal-based research continued without disruption.[73] The advocacy groups were reportedly willing to assist the ACNP with the animal welfare issue, and "may be of help as buffers with those who strenuously object to animals' use in research."[74] In 1987 the ACNP formed a Task Force on the Use of Animals in Neuropsychopharmacology, which became a standing committee in 1990. The task force responded to several specific issues: Animal Rights Mobiliziation! (ARM!), also known as TransSpecies Unlimited, an organization led by George Cave, had targeted substance abuse researcher Michiko Okamoto at New York University Medical Center, and deterred her from accepting a NIDA grant. There were ongoing questions about what to do with Taub's deafferented Silver Spring monkeys, used in neuroplasticity experiments to study cortical remapping. In response the NIH convened a group of scientists to evaluate these animals, which had been part of a study at the Institute for Behavioral Research in Silver Spring, Maryland. The monkeys had been confiscated by police after a 'tip' from Alex Pacheco, a founder of PETA, who was then working as a lab assistant while Taub was on vacation. The monkeys were recovered and maintained at the Delta Primate Center after the incident. Although the NIH advisory group recommended that the animals be "terminated," some immediately and others later, they were maintained by a consortium of scientific and professional groups, including the ACNP, which supported the "scientific aims and rational scientific termination of the experiments" by collecting funds to defray NIH costs.[75]

Advocacy groups were felt to be best-positioned to counter animal rights advocates with emotive appeals based on the experiences of patients or parents struggling with behavioral, mood, and brain disorders. In 1991 the animal committee recommended that the ACNP Council encourage members of advocacy groups to seek seats on institutional animal care committees across the country.[76] Secretary Oakley Ray wrote to the advocacy affiliates: "One of the easiest, yet most important ways in which the ACNP and Advocacy Groups can help each other is reflected in this memo and its enclosures. The need to protect patient rights and confidentiality while ensuring a continuous flow of good preclinical and clinical research aimed at a greater understanding of mental illness and the development of new treatments is a project on which the ACNP and Advocacy Groups can readily

cooperate and collaborate."[77] The memo included tips on addressing Chairs of Psychiatry in hopes of facilitating committee appointments, a bottom-up strategy reflecting the College's attempt to widen the base of its influence by working in tandem with influential advocacy groups willing to take a stand on animal research controversies. As Ray himself did not regard this strategy as successful, the ACNP Council sought to ally with other scientific associations and coalitions working on the issue, becoming members of the National Association for Biomedical Research (NABR) and the Incurably Ill for Animal Research (iiFAR) in the 1990s. During this decade, the ACNP Committee responded directly to the U. S. Department of Agriculture (the agency that enforces the Animal Welfare Act) and to regulations promulgated in the Federal Register concerning inclusion of rats and mice.[78] While there was no ACNP legislative committee, ACNP Council continued to take quite seriously the committee's reports on "The Animal Rights Movement: A Threat to Progress in Neuropsychopharmacology."[79] Council also voted to join Americans for Medical Progress (AMP) at the Committee's suggestion, and in 2001 joined AAALAC International.

C. Influencing the Location and Direction of NIMH/ NIDA/ NIAAA

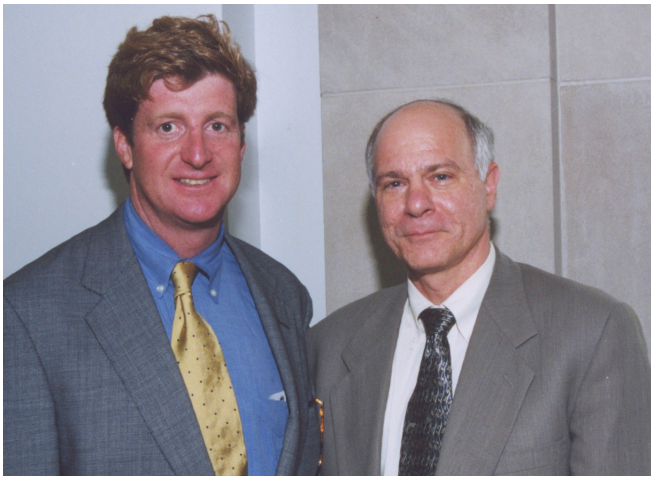
During the 1980s, the ACNP cultivated its influence over federal resource allocation within a broader policy framework that directed attention to the particular interests of researchers in neuropsychopharmacology. By mid-decade, the idea that substance abuse, alcoholism, and mental health were matters of 'brain disease' or 'brain disorder' began to surface in the health policy arena. Against the backdrop of this reconceptualization, there were proposals to move or merge the research institutes that once made up ADAMHA. Some felt they should be moved out of ADAMHA and back into the fold of NIH. For instance, in 1981, Senator Daniel Inouye's office proposed to transfer NIMH[80] back to NIH, which it had been part of for its first two decades. NIMH was then made part of the U.S. Public Health Service; briefly rejoined NIH in 1973; and then in 1974 became one of the three institutes composing ADAMHA. Despite predictions that ADAMHA would be short-lived, the ADAMHA Reauthorization Act was passed by unanimous consent on August 2, 1991, but soon after its research functions were reorganized and moved to NIH. The former ADAMHA institutes--NIMH, NIDA, and NIAAA -- finally rejoined the NIH formally in 1992.

Louis Sullivan, Frankie Trull and Oakley Ray

There had been several attempts to move the institutes to NIH before one actually took. Inouye's 1981 proposal was intended to garner more support for NIMH and provide the nation's "mental health leaders . . . with a much more efficient vehicle for interacting in depth with the other leaders of our nation's health care programs."[81] The senator's office was important in the gradual societal transition towards viewing research on mental health and illness as 'brain research,' and mental health disorders, alcoholism, and substance abuse as 'brain disorders.' Psychologist and APA activist Patrick DeLeon served as a legislative aide and chief of staff for Senator Inouye from the 1980s on. Inouye often acted as a friend to ACNP. At the July 12-14, 1987 Council meeting, a Task Force on ADAMHA was appointed to study the pros and cons of the

proposed move of NIMH back to NIH, the move that was finally accomplished in 1992.

The ACNP leadership has taken various positions on these proposed and actual moves depending on the science and funding climate at the time. Another perennial issue has been periodic proposals to merge NIDA and NIAAA, (and which is again a current issue in 2010-2011). The ACNP has taken an abiding interest not only in the location of the research institutes but in their relationship to services and clinical research, and in their leadership (an issue that was at times a proxy for perceptions that the ADAMHA institutions were stigmatized due to the nature of the disorders they investigate). For instance, alcohol and addiction researcher



Patrick Kennedy and Bob Swift

Nancy Mello urged the organization to protest a job description circulated for a new director of NIAAA that did not include "research expertise and a national reputation for scientific excellence in basic or clinical investigation" as a criterion for selection. ACNP president Leonard Cook argued that NIAAA should have a director of the same high scientific caliber as the other research institutes.[82] For the ACNP, concerns about institute leadership, research trajectory, or funding can be seen as safeguarding an institutional home for neuropsychopharmacology research within the federal government. Given the transdisciplinary nature of NPP and the convergence of basic research on the brain, the College has often sought to head off proposed reorganizations that might result in a loss of a place for biological psychiatry, which "represents the integration of basic and clinical science," an integration that is considered the very basis of the ACNP.[83]

II. Growing Pains: Science Policy Becomes an Issue

On the eve of the ACNP's 25th anniversary, which was celebrated in Washington, DC in December 1986, ACNP President Roger Meyer testified before the House Committee on Appropriations and the Subcommittee on Labor, Health and Human Services and Education on behalf of ACNP and CPDD (May 1986). At the 25th anniversary meeting, there was a panel chaired by Gerald Klerman titled "Marshalling and Governing Resources for Biomedical Research and Research Training—Strategies for the 1990s." While the ACNP leadership demonstrated a growing interest in science policy, there was pushback from members who opposed granting more time to policy problems at annual meetings, with one letter stating, "I would rather catch the interest of the public by our science. If we want to influence policy makers, isn't there a more direct way?"

In due course the ACNP evolved a more direct lobbying strategy aimed at the House and Senate Committees on Appropriations, and the Subcommittees on Labor, Health, and Human Services, and Education.[84] However, the appropriate degree and extent of the ACNP's "Washington involvement" has remains contentious. Many members have held federal government positions at some point in their careers and are legally barred from lobbying; others prefer to stay out of politics; still others find it difficult to imagine research advocacy without seeming self-serving.[85] One of the

ways that the organization has influenced law and policy governing treatment and research on mental health has been to act in an amicus curiae capacity.

II. Compelled Medical Treatment Cases: ACNP as Amicus Curie

The first case on which the ACNP acted as an amicus curiae occurred in the 1970s when Al DiMascio was secretary from 1972 to 1979. During this time DiMascio was director of psychopharmacology for the Massachusetts Department of Mental Health at Boston State Hospital. Boston State was involved in a 1975 case involving allegations that staff physicians and psychiatry residents at that hospital had committed medical malpractice by using short- and long-term seclusion and short- and long-term medication. The case was heard in three parts, and in 1978 the ACNP weighed in on the question of whether or not malpractice had occurred due to improper use of medication or seclusion. Concerned that this case, combined with a New Jersey case, *Rennie v. Klein* (1979),[86] represented a new judicial willingness to intrude upon medical decisions to medicate the mentally ill, the ACNP closely followed the case.

One of the fundamental legal questions posed by the case concerned whether there was a constitutional right to refuse psychotropic medications prescribed for treatment of mental illness. ACNP was active on the issue of compelled medical treatment, submitting an Amicus Curiae brief in *Rubie Rogers v. Robert Okin (1980)* to the U.S. District Court for the District of Massachusetts, a case heard as *Mark Mills v. Rubie Rogers (1980)* in the U.S. Supreme Court in 1980. ACNP supported the lower court's finding with regard to a right to refuse treatment but differed with the lower court as to how that right should best be implemented. The ACNP amicus brief addressed to the U.S. District Court for the State of Massachusetts stated:

> "The ACNP believes that the rights of the mentally ill and the responsibilities of the physician can and must coexist within the institutional setting. The system implementing such coexistence, however, must be fashioned in such a way as to recognize the realities noted above. It is the purpose of this brief to focus the court's attention upon these realities, to emphasize the special nature of the role of the physician in the institutional setting, and to furnish some insight into the types of problems which will result if physicians are removed from first line responsibility for treatment decisions."[87]

The College sought to preserve "maximum flexibility" for physicians while also protecting patients' rights, and preserving the practice of medicine from incursions from the judiciary.

> "[T]he ACNP believes that a realistic balance can and should be reached between the rights of the patient and the responsibility of the physician to provide necessary care and treatment. The creation of such a balance, however, requires an understanding on the part of the court of both the critical role of the physician in day-to-day decision-making with regard to care, the need for prompt response to patients' needs, and the limited ability of the patient to assist in the decision-making process."[88]

Direct court monitoring or supervision, in other words, was viewed as an undesirable imbalance of power between physician and patient. Despite the ACNP's efforts, that was the outcome of the Supreme Court's 1983 opinion, which encouraged several states to require a cumbersome process by which court-mandated "Rogers orders" were required to overrule patient refusals.

Ongoing concern about tying too many resources up in legal cases made the ACNP selective about which cases to engage, and it tended to enter the legal fray where members were directly

affected. In the summer of 1997, a case arose in New York, *T.D., et al v. New York State Office of Mental Health* (1998). In the January 1998 decision, New York's highest court issued a narrow decision nullifying the power of the lower court's lengthy constitutional rulings on surrogate consent, saying the lower court's findings were "inappropriate" and "unnecessary." By confining itself to technical issues, the high court set aside the lower court's broader constitutional rulings, which ACNP and other amici had argued were thoroughly flawed. To write this brief, the ACNP had contracted with Pepper, Hamilton & Scheetz and the resulting brief was "probably the determining factor in 'winning the case,' i.e. preventing an appeal which, if successful, would have extended greatly the lower court's constitutional restrictions on research into mental illness."[89] While the outcome of this case aligned better with the ACNP position, it became evident to many that organizational resources were strained in the legal arena, and the College left these to the larger professional organizations such as the APA, with which most members were affiliated. In retrospect this seems a wise decision, given the lengthy and tortuous process and equivocal outcomes of cases into which the ACNP has entered.

Section Three

The 'Pharmacy Within'[90]: Transforming Mental Disorders into Brain Disorders

I. Shifting Relations Between Basic and Clinical Researchers in ACNP

Since the 1960s the climate and conditions of clinical research ethics and practice have undergone profound change. As an organization specifically founded to bring basic and clinical researchers together for mutually beneficial conversations, the ACNP and its members have had to keep pace not only with changes in the regulatory regime but changes in societal views towards the value of their work. They have also had to keep pace with each other. By the mid-1970s, the numbers of individual members in the ACNP who were interested in clinical work were roughly equal with those interested in more basic investigations. The program committee was asked to maintain balance in study groups, plenary sessions, and open communication sessions.[91] Yet a decade later, high-profile members such as Gerald Klerman had become concerned about an "anticlinical bias" in the ACNP, although Floyd Bloom assured him that the entire program was "rich in clinical content, with more than half of the sessions dealing almost exclusively with clinical studies."[92] Although the organization tried to maintain balance between basic and clinical research, the balance of power in the larger scientific community had shifted towards those who studied the cellular, molecular, and even submolecular bases of disease.

Another issue impacting this relative balance of clinical and research interests was the organization's decision to avoid panels structured around any single drug, direct comparisons between drugs, or the products of a single pharmaceutical firm. Distaste for such panels increased during the 1980s. There was more enthusiasm for treatment-oriented panels when a drug's mechanisms of action could be hypothesized as related to possible cellular mechanisms of action and sources of pathophysiology inferred on that basis. There was also a strong drive to incorporate more preclinical data into annual meetings. Recently, however, the field has shifted towards an emphasis on the translation of basic research findings into clinical

advances, once again allowing clinical researchers and clinicians pride of place. In an organization with the longevity of the ACNP, these cyclic reconfigurations are to be anticipated, and even heralded as signs of the times signaling the larger social, political, and economic contexts within which scientific and clinical work takes place.

II. Practicing Clinical Psychopharmacology: Educating Clinicians and the Debate over Extension of Prescribing Privileges

ACNP has sought to influence the field of clinical practice by offering regional meetings structured as continuing education seminars. For instance, in 1996 two such meetings were held, one an "Update on Practical Clinical Psychopharmacology" focusing on treatment of mood and affective disorders in mid-life and elderly patients on the west coast, and the other on "Psychiatric Disorders and Women: From Diagnosis to Treatment" on the east coast. Earlier in the 1990s, the ACNP Nonphysician Prescribing Task Force, chaired by Louis Lasagna, became involved in evaluating an American Psychological Association pilot project called the Department of Defense Psychopharmacology Demonstration Project (PDP). Working on behalf of the APA, and through a legislative aide who was a psychologist, Patrick DeLeon, Senator Daniel Inouye's office persuaded Congress and the DOD to allow psychologists a limited experiment in training military psychologists who were members of the Armed Forces (and thus not subject to state licensure) to prescribe psychotropic drugs. Two years of postdoctoral training in psychopharmacology, in additional to supervised clinical training, took place at the Uniformed Services University Medical School in Bethesda, Maryland. ACNP was awarded a contract to evaluate the training program, through which ten military psychologists were certified to prescribe.[93] The ACNP team recommended improvements to both the didactic and clinical portions of the program. While this pilot program was discontinued in 1997 due to its resource-intensiveness, it helped lay the groundwork for extending prescribing privileges to psychologists through state licensing programs, with New Mexico becoming the first state to allow such privileges in 2002. The PDP helped provide an evidence base for the movement to expand psychologists' privileges in 12 states or more.

Louis Lasagna

III. Caring for Patients: The ACNP's Impact on Clinical Practices

The ACNP has had its greatest impact on patient care through the scientific advances made by its members. Since the mid-20th century, conditions that once consigned those suffering from brain diseases to the category 'untreatable' have become tractable to drug treatments emerging from the neuropsychopharmacological research community during the decades in which the organization has been in existence. Many ACNP members recall the changing landscape of clinical practice in their interviews; their careers began at a time when psychoanalysis or psychodynamics were still the dominant approaches to the treatment of mental illness. They witnessed how patients were 'treated' in the days before medications for managing mental illness were accepted within the walls of mental institutions. While prominent ACNP fellows such as Eric Kandel, Roger Meyer, or Daniel X. Freedman were trained in psychoanalysis, they saw its limits and embraced neuropsychopharmacology as an alternative. They were in turn welcomed by the ACNP, an invitation to which often served as a rite of passage signaling the newcomer's membership in

the most elite ranks of the science. Schizophrenia researcher Herb Meltzer recalled an informal group characterizing psychoanalysis as insufficient for the treatment of mental illness; 'The Stagecoach Club,' headed by Yale social psychiatrist Fritz Redlich, who mentored Freedman and Thomas Detre, met throughout the country in the days when critics of psychoanalysis were still marginalized and biological psychiatrists far from triumphant. However, due to its small size and elite status, the ACNP's was a unique voice among treatment-oriented researchers in the field of psychiatric disorders. Clinical practice has changed a great deal in response to the realization that schizophrenia is not one condition but many; and in response to both first- and second-generation neuroleptics. Similarly, treatment of depression has undergone a sea change since the SSRIs were put on the market. The shift from inpatient, residential care in large-scale institutions to outpatient pharmacotherapy regimens has occurred, for the most part, during the life of the College and the careers of many of its members. Such changes are based on changing disease theories and hypotheses about how the brain works that are produced in the search for explanations of drug actions and effects.

The ACNP has also played a useful role in evaluating pharmacotherapy in areas lacking an FDA-approved treatment but experiencing such widespread off-label use that it can be considered the prevailing standard of care. For instance, the ACNP Task Force on Use of Anti-Psychotics in Elderly Persons with Dementia considered the necessity of treating psychosis and agitation in elderly persons with dementia and recommended shared decision-making between caregivers, families, and clinicians. After finding that clinical success rates and improved quality of life for both drug treatment and nonspecific interventions were likely higher than implied by large-scale trials, the ACNP affirmed clinical judgment and shared decision-making.

IV. Evaluating Drug Safety: A Perennial Concern

The transdisciplinary arena of NPP co-evolved with the drugs that enabled its practitioners and theorists to probe the brain. Thus the College has always been concerned with translation to the clinic and thus with drug safety and effectiveness in the area of mental illness. Psychoactive drugs were used as tools in the early days, as 'chemical probes,' in the words of Elkes, for understanding and mapping brain function and dysfunction before the days of neuro-imaging. Given the organization's history, participating in the important social function of evaluating drug safety and efficacy has been central to the careers of almost all fellows. In the 1970s the ACNP Task Force on Drug Safety, chaired by Herb Meltzer, faced a variety of controversies over particular agents. In 1978 the FDA called for a precaution statement in the patient package insert for all neuroleptics elevating prolactin, despite lack of direct clinical evidence supporting the need for such action. Meltzer had recently written a review on the putative implication of prolactin in breast cancer.[94] He attended the FDA hearing on behalf of the ACNP task force and executive committee, and the FDA withdrew its proposed precautionary statement in the face of these objections.

ACNP worked to create a mechanism for drug evaluation that would allow the College to appear as an impartial, honest broker rather than endorsing or not endorsing any particular drug or pharmaceutical company. Various task forces and committees have been set up to consider specific drug safety issues: the threatened withdrawal of barbiturates from the market, issues of lithium toxicity, and combinations of tricyclic antidepressant-MAO inhibitors. At the October 15-16, 1984 Council meeting, Herb Meltzer

was again designated to form two task forces that would sunset in three years—one to consider the safety of clozapine, and the other to determine whether there were adequate inpatient and outpatient settings for controlled clinical research. The task force mechanism proved well-suited to issues with a narrow purview and delimited time horizon.

One of the most important drug evaluation issues in the College's history arose in the area of the management of depression and schizophrenia, given controversy over the side effect profiles of first-generation drugs such as reserpine and chlorpromazine, two drugs deeply bound to the history of the ACNP. The five decades of the organization's existence have been regularly punctuated by the advent of loudly heralded advances in the treatment of depression, and principal fellows have been involved in the controversies attendant to these (see below synopses of task forces). In addition to changes in clinical and research practices, political and economic structures aligned to produce a much broader population on antidepressants and anxiolytics. This alignment has in turn produced wide uptake and common acceptance of the view that depression, anxiety, and other mood disorders are indeed 'brain disorders' that can be modulated through medications.

Pharmacotherapy's impact has been considerable in most areas of clinical practice in which ACNP members are interested. The ACNP has provided such a crucial meeting ground for the ascendance of biological psychiatry that some claim there has been no major psychotherapeutic drug on the market where an ACNP member was *not* intimately involved in the development or clinical trials of that drug.

Section Four
Drug Discovery and Drug Development: Serving as an 'Honest Broker' Organization

"[O]ne of the main purposes for which [the College] was established [was to] constitute a scholarly forum for the development of new means to treat mental illness and affective disorders, and to learn through investigations into the actions of such drugs the nature of the disease process… We must not relinquish our past essential roots."[95]

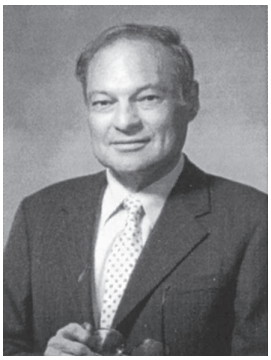
Almost all compounds in current use for psychiatric disorders were serendipitously discovered—rather than intentionally developed—to act upon mood disorders. For instance, isoniazid, a drug in use for tuberculosis, was discovered to act as an antidepressant, paving the way for the introduction of the MAO inhibitors. Serendipitous discovery, however, is insufficient for getting a drug through the regulatory process and into clinical practice. Initially, the ACNP served as an organization designed to bring clinicians who were doing research into professional relationships with basic researchers and with the scientists working in pharmaceutical houses. Convergent interests served to make for convivial meetings, but also for important informal discussions and easy relationships that so many members recall from their own earliest days of attendance.

Over time, relationships between industry, government, and academia have been perceived as more fraught with potential for corruption and conflict of interest than they were in the early days of the organization. According to Herb Meltzer, ACNP once possessed the "optimal model…[for] "managing the minefield"[96] by "having the expertise and the resources of the pharmaceutical industry

blended with NIMH and academic science." Many researchers stress the way in which ACNP has served as an unrestricted and noncommercialized space—because ACNP is the "place where you get the doers and shakers of the world to try to influence how they think." While the social worlds of industry, government, and academia sometimes overlap, ACNP members often move between these locations at various points in their careers. As Roger Meyer put it in his ACNP interview, "We've done it *with* industry, not *to* industry," arguing that truly translational research requires a "setting in which industry, academia, and government can civilly engage in discussions that are principally scientific." While these relationships are not without both perceived and, at times, actual conflict, it is clear that the ACNP provided 'networking terrain'.

I. Working the Triple Helix: Industry, Government, and Academia

The role of the U.S. government, principally NIMH, in supporting the growth of neuropsychopharmacology cannot be overestimated. In the heady early days of the new science, the Psychopharmacology Research Center was a conduit for prominent academic scientists as well as those at NIH laboratories. The changing nature of relationships and knowledge flows between industry, government, and academia and how these are in turn related to wider changes in the pharmaceutical innovation system has been the subject of recent work in science and technology studies (STS). The so-called "triple helix"—industry, academia, and government—offers a more accurate picture than a bipolar construction of industry and academia. The federal research apparatus has been very important to the ACNP—not only by way of employing members or funding their laboratories through contracts and grants, but the NIMH PRC supported the organization for many years until pharmaceutical companies began to make unrestricted educational grants supporting teaching days at the annual meetings, and the organization found other ways to sustain itself.



Gerald Klerman

Back in the 1970s, an FDA-ACNP Task Force chaired by Gerald Klerman called the Committee on Evaluation of Antidepressant Drugs had proposed guidelines for clinical evaluation of antidepressants in 1974. The FDA Division of Neuropharmacological Products requested ACNP to help develop guidelines for evaluating new therapies for treating anxiety and depression. At the time a seeming lack of scientific and clinical consensus created ambiguity within the scientific community and "considerable confusion in the pharmaceutical industry and the FDA" just when so many such agents were being manufactured and marketed that it was referred to as the "gold rush." This arrangement placed the ACNP in a unique relationship with the FDA, which found itself in the midst of a "therapeutic cacophony."[97] Two subcommittees were formed—one under Gerald Klerman to consider antidepressants and one under E. H. Uhlenhuth to take a hard look at antianxiety medications. Task forces were coordinated by former ACNP president J. R. Wittenborn. The College set about collecting the bewildering number of psychiatric rating scales for diagnosis and evaluation of anxiety and depression that then existed, and collating determinations of therapeutic efficacy for both disorders.[98] These efforts were laboriously summarized and guidelines prepared. Ultimately, the work of the two subcommittees was combined in a report entitled the "ACNP-FDA Guideline Materials for the Clinical Investigation of Anxiolytic and Antidepressive Substances" (1974),

which also considered drugs for mixed states of anxiety and depression. The ACNP acted as an "honest broker" between government and industry, suggesting a convergence between professional and scientific interests and public need for specific criteria by which new drugs would be judged safe and efficacious.

By late 1990s there was an emerging consensus that ACNP had helped to usher in a collapse of distinctions between basic and clinical sciences, and a characterization of the organization as 'translational' from its outset. It was clear that clinical research was not declining but expanding as pharmaceutical development became a global enterprise that simply could not have been envisioned in the early days of the organization. The U.S. Food and Drug Administration (FDA) has become a central player in the globalizing clinical trials industry, and many ACNP members have evolved a variety of relationships with FDA.

II. Relations with Industry: Beyond Conflicts of Interest?

One of the real issues in drug development, of course, is *where* it takes place and who foots the bill. At the 1982 annual meeting, the ACNP adopted its first Conflict of Interest Policy Statement, which had been drawn up by the Washington law firm. Its outline was simple and payment of annual dues was considered an affirmative statement to the effect that the member has read the COI policy and was declaring no conflicts. If a member felt he or she did have a conflict, the ACNP secretary was to be informed. This relatively casual approach worked well until the 1990s, when the issue surfaced again. Concerned with corporate membership and COI issues, the organization confronted changes in the clinical research environment. Previously, corporate membership had been restricted to pharmaceutical companies performing in-house scientific research. A novel request involving a Contract Research Organization (CRO) was complicated by the fact that members of the ACNP Council were in the process of setting up such a company themselves to conduct clinical trials. Such entities were new on the scene, representing creative responses to the regulatory regime and economic pressures within the industry. This situation led President Huda Akil to convene a Corporate Membership Task Force in 1998 due to her concern that "such an entity could use the ACNP meeting, not so much as a place of scientific and intellectual exchange, but as a site to make deals, or conduct business."[99] These considerations illustrate how much the clinical research environment had changed since the early days of the ACNP, when state hospital psychiatrists came to meetings to interact with basic scientists.

In the College's early days, interactions between those working in industry and those working elsewhere were interwoven into the very fabric of the organization. Jonathan Cole emphasized that by contrast to other scientific organizations such as the American Society for Pharmacology and Experimental Therapeutics (ASPET), there was little incentive for the ACNP to exclude scientists based in the pharmaceutical industry.[100] Approaching the end of the 20th century, Cole viewed the heightened awareness of Conflict of Interest with skepticism. Indeed it has become clear that medications development in the area of complex brain disorders requires interaction between several different kinds of expertise. Public-private partnerships have evolved as a means for bringing industrial developers together with

Jonathan Cole

academic expertise in disease biology and patient symptomatology in order to contribute to the search for innovative treatments, which requires industry to provide ongoing access to drugs and government to provide public access to data.[101] The ACNP nurtured some of the earliest collaborations between government, industry, and academia.

Given the pride members take in this history, attempts to preserve ACNP meetings as places where "only science is spoken" have been ongoing. Despite perennial concerns about keeping business off the scientific program, by the late 1980s, drug development was seen as languishing and there was a perceived need to reinvigorate the "traditional ACNP focus on new drug development, evaluation, and investigation."[102] Several parties believed the College had lapsed into a "near-listless state in this critical area of discourse." To them that meant the College had "lost one of the main purposes for which it was established, namely to constitute a scholarly forum for the development of new means to treat mental illness and affective disorders, and to learn through investigations into the actions of such drugs the nature of the disease process."[103] The concern led in 1989 to the formation of a "Task Force on Coordinating Academic-Industrial-Government Efforts in Psychopharmacology" charged with determining whether the College had ceased to play a useful role in drug development. If the task force determined that the ACNP had become irrelevant to medications development, it was supposed to figure out how to "resume a more effective and constructive role in this area of our field."[104] Many felt that members' experience with discoveries in clinical diagnostics and signaling mechanisms could help move drug development and assessment issues forward scientifically. This task force later became the Liaison Committee, emphasizing the shared goals and mutual dependence of the organization and industry. The Liaison Committee has waxed and waned in terms of whether its charge was interpreted as one of *monitoring* national-level developments, or playing a more *activist* role at the interface between the ACNP, federal agencies, and the pharmaceutical industry.[105]

The ACNP also attempted, somewhat awkwardly, to involve consumer advocacy groups in drug development efforts. In the fall of 1989, the Committee on Relations with Advocacy Groups hosted a workshop on "Drug Development" in Alexandria, Virginia. According to a scientist who attended, "The advocates are not quite ready in my perspective to be allies with regard to anything research-wise; I was more than slightly taken aback by their very aggressive stance and more than modestly irritated attitude at science for not doing more to speak to them, and with them, publically." This attendee found the spokespersons for the advocacy groups too demanding in requesting more sessions at the annual meeting and more scientists to accompany them in lobbying sessions. "My guess is they would not be satisfied that a fair sharing of the burden is that we do research and they talk to funders to get us more funds to do our research." Conflict over the proper division of labor demonstrated the gulf between the two cultures of science and advocacy—but also the growing clout and large-scale access to patients enjoyed by the advocacy groups.

While the ACNP saw its purpose in engaging advocacy groups as a way to broaden *advocates*' exposure to mainstream science and join with them in research advocacy, the advocacy groups saw the ACNP as a source of expertise that could legitimate the disease conditions from which their constituencies suffered, as well as possible funding for educational outreach efforts. Given this evolving relationship, the 'triple helix' might be broadened to include relevant publics as powerful fourth partners and as fellow advocates who speak in a different voice. As a former chair of the Committee on Relations with Advocacy Groups put it in a

panel at the 2009 annual meeting, "Part of the ideal relationship between the ACNP and our advocacy affiliates is that our members represent rational voices regarding scientific and medical issues related to these disorders. Because there is so much misinformation out there, . . . it is incumbent upon the ACNP membership to provide voices strongly based in science to our advocacy affiliates." As the next section demonstrates, the College has taken up its social responsibilities with enthusiasm although the outcomes of such efforts are not always clear even to those who take part in them.

Section Five

Going Public with Research Advocacy: Advocacy During and Beyond the 'Decade of the Brain'

I. The Evolving Patient/Consumer/Survivor Advocacy Movement

During the 50 years in which the ACNP has served as meeting ground for preclinical and clinical researchers interested in mental health and illness, the patient advocacy movement in mental health has matured.[106] From its earliest days, ACNP has had relationships with advocacy groups, most famously the National Mental Health Association, whose executive director, Michael Gorman, a contemporary of Mary Lasker, attended the 1956 APA meeting in Atlantic City, New Jersey, where he heard physician and "accidental psychiatrist" Frank Ayd give a talk. A consummate lobbyist, Gorman got Ayd, Brill, and Kline, all soon to become active in the early days of the ACNP, to testify before a congressional committee headed by Senator Lister Hill. This triumvirate of pioneers in American neuropsychopharmacology suggested the formation of an NIMH division of psychopharmacology. Their suggestion sparked the PSC/PRB. Although this story is buried in the origin of the ACNP, it testifies to the power of patient advocacy for paving the way for science. The need to foster a common agenda between ACNP and relevant advocacy groups has become more compelling in the last two decades.

By the mid-1980s, ACNP moved toward formalizing relationships with advocacy groups under the leadership of Roger Meyer and Bob Rose. In 1986 the ACNP Council established a Task Force on Relations with Citizens' Advocacy Groups.[107] In 1988 this body became the Ad Hoc Committee on Relations with Advocacy Groups. Becoming a constitutional committee made the committee's status with the College more solid and assured continuity of the relationships. Council charged the committee to "work with those citizen organizations who share a common concern about the advancement of research on major mental illness and affective disorders."[108] The committee structures the relationship between ACNP leadership and that of the advocacy groups. Once the ad hoc committee was made a permanent constitutional committee, the ACNP President became an ex-officio member. Co-chairs and membership represent the breadth of advocacy for substance abuse and major mental illness.

The advocacy groups work on multiple, sometimes competing, issues; have multiple, sometimes competing interests; and do not work from the same assumptions or for the same policy outcomes as each other. Among those working with the ACNP have been the aforementioned National Mental Health Association, founded by Clifford Beers in 1909, and now called Mental Health America! Another major player has been the National Alliance on Mental Illness (NAMI), which grew out of organizing efforts by California patients, consumers, and parents. In the early 1990s these two organizations had a highly public disagreement over a report issued by Public Citizen

Research Group and NAMI, which NMHA found to be an anecdotal, subjective, and "emotionally-charged account of difficulties facing community mental health agencies." The NMHA denounced this report because it was concerned that it would erode funding for research and services at a time when institutional care was already inadequate. Yet the ACNP established and maintained relationships with both NMHA and NAMI; in the fall of 1990, the NMHA was so positive towards the ACNP that it went so far as to title a press release on the evolving relationship, "One Night Stands Are Over."

In forging relationships with advocacy groups, the ACNP clearly saw itself becoming more responsive to the public but through the narrow role of providing technical assistance and expertise. When chairing the committee, Rose wanted to improve ACNP's responsiveness to media, to Congress, and to the public on issues relevant to drug development, neuroscience, and genetics.[109] Through the 1990s there was an effort to create a more "grassroots" effort on behalf of the membership, particularly in their home districts. Advocacy affiliates met with the Committee on Relationships with Advocacy Groups a few times a year in Washington, DC, and at the ACNP annual meeting. Meeting more frequently increased the strength and utility of the alliance between the ACNP and the advocacy groups. The Washington meetings also brought the directors of the federal agencies concerned with mental health, alcoholism, and substance abuse (NIMH, NIDA, and NIAAA) to roundtable discussions with members of key advocacy groups. They were designed to foster development of a common agenda among scientists and advocacy groups. Despite these efforts, some ACNP members felt the relationship between the organization and the advocacy groups was best characterized as an "uneasy marriage."

Sometimes the interests of the advocacy groups converge with those of ACNP on specific concerns. For instance, the advocacy groups brought the state of New York's 1989 implementation of a triplicate prescription rule, which included benzodiazepines, to the attention of the ACNP.[110] The advocacy organization was worried that requiring triplicate prescriptions would make physicians reluctant to prescribe. There was much concern that the triplicate system might become nationwide since it had the backing of law enforcement and the stated intent of these laws was to reduce prescription drug abuse. The ACNP Council opposed such laws but urged the Committee on Problems of Public Concern to study the issue before taking a position.[111] Ultimately, the College recommended in 1991 a moratorium on additional laws because it was concerned that such regulations might reduce access to care and "contribute to stigmatizing patients suffering from mental and addictive disorders."[112] "Public policy should be influenced by scientific evidence wherever possible and in this case reliable methodology exists for determining the actual impact of the prescribing restrictions." This incident shows an organization becoming more sure-footed in the science policy advisory role, but confining itself to issues on which it had clear technical expertise.

However, the larger context provided by the "Decade of the Brain" stimulated the organization to think in terms of broadening the focus of its research advocacy efforts. The Committee on Relationships with Advocacy Groups planned a nationwide campaign to encourage membership and members of advocacy groups to invite state and federal legislators to visit clinical research programs in an effort to secure continued support. A packet of material on "Grass Roots Activities" was prepared with talking points on mental health parity; the need for health care reform with a specific emphasis on mental health coverage; and the need to end the "historic discrimination in insurance coverage that now confronts persons with mental illness or substance abuse disorders and their families"

for the 1993 annual meeting.[113] More recently, educational outreach has proved an efficient and engaging mechanism for reaching patients and their advocates. In the early 2000s some ACNP members worked closely with advocacy groups to produce roundtables and videos on psychopharmacology such as those put out by the Depression and Bipolar Support Alliance, which were supported by a mini-grant from the ACNP, with the involvement of Ellen Frank. Delivered in a conversational format, the basic message of these materials was that treatment works as well for mental as for physical illness, and that combinations of pharmacological and non-pharmacological treatments are effective. The video format allowed engagement with local chapters without straining organizational resources.

Ellen Frank

Reflecting shifts in a field beginning to differentiate between neuropharmacology and psychopharmacology, the committee added the American Foundation for Suicide Prevention (AFSP) and Alzheimer's Foundation to its list of advocacy groups. This helped spur wider involvement with NIH institutes beyond the "traditional ADM institutes" to include the Child, Neurology, and Aging institutes. Committee chair Thomas Detre urged the committee to broaden its efforts beyond "our somewhat parochial lobbying efforts."[114] While ACNP should remain focused on the clinical and basic research agenda, Detre argued that the organization should support all neurobiological research regardless of where it took place. "Taking any other position would not only be considered parochial by our many allies in the fields of neurobiology and neuroscience but would be counterproductive vis-à-vis the leadership of the HIH, which is in the process of mounting a major effort to encourage the institutes of the NIH to collaborate in interdisciplinary research programs."[115] Detre spearheaded the above mentioned grassroots efforts, which culminated in some education of committee members in the legislative process and possible ways to approach and influence legislators.[116] The organization seemed to be at a crossroads when it could increase its public visibility on behalf of research advocacy, or, as the alternative was put bluntly in a letter from Oakley Ray, "continue our *laissez faire approach to Washington legislation and legislators"* (emphasis mine). Increasingly, at the outset of the 21st century, efforts to broaden the social impact of the organization took the form of task forces composed of a small subset of ACNP fellows positioned to speak authoritatively on topics of public interest.

II. Broadening Societal Impact: Task Forces on Hot-Button Issues

The College has experimented with several different ways to advocate for the science of neuropsychopharmacology and for those whose lives are touched by its benefits. The College has evolved several different mechanisms for enabling its membership to act on matters of consequence. Several current ACNP standing committees began life as task forces through a structure that allows the ACNP to move nimbly when social issues of relevance to their science arises. Task force activity has also resulted in the rise of new scientific trajectories within the College, as glimpsed in those on suicide or responses to terrorist attacks. Task force reports are pitched in the rational language of science and are designed to present the press, the public, and organizations of the state and federal governments with state-of-the-art scientific thinking achieved through a consensus-based process.

A. A New Public Relations Model: The Media Task Force

Perceptions that the ACNP could potentially

increase its societal impact were shared by its members. In a 2000 survey, the strongest single response affirmed that the College should "become more active in trying to influence public policy makers and decisions."[117] A majority of members thought that College should keep its finger on the pulse of the Beltway; the leadership looked to create a body along the lines of the Society for Neuroscience's Rapid Response Network. In 1999 the ACNP Media Task Force, chaired by Roger Meyer, met for the first time with the Committee on Relationships with Advocacy Groups, and developed fact sheets on specific issues that created a more unified response from scientists to press queries. The group searched for a Washington media advocacy firm to represent it on ongoing issues such as protection of human and animal subjects and appropriate relationships between academia and industry. Policy Directions was hired in 2001 to facilitate the Council's access to a variety of issues during the first few years of the 21st century. The College also joined the APA and other groups in the Consortium for Proposed Public Relations Activities on Behalf of Psychiatric Research," whose goal it was to increase public awareness and acceptance of the positive contributions of psychiatric research, as well as public recognition of psychiatry as a science-based medical specialty dedicated to improving care of people with mental illness including substance use disorders."

B. Task Forces on SSRIs and Suicide

One advantage of task force efforts is that they can be rapidly assembled to analyze a broader evidence base than do agencies responsible for governmental oversight. This attribute is useful in moments of high scientific uncertainty. Task forces can run parallel to or catalyze similar efforts within FDA or industry; by helping shift the climate around a particular issue, they can have effects beyond the narrow purview for which they were convened. For instance, a focus on the neurobiology of suicide and suicidal ideation emerged in the ACNP in the early 1990s, when the concern first surfaced that a certain antidepressants might be implicated in that most adverse event of all—suicide. Similar concerns arose in 2003, this time focused on youth and following on the expansion of adolescents and children diagnosed with depressive disorders and prescribed antidepressants. The ACNP Task Force reports were timely, thorough, evidence-based documents that served the needs of the public; the relevant professions, particularly child psychiatry; and the regulatory agencies involved.

Fred Goodwin with Steve and Constance Lieber

Chaired by John Mann, the first task force found little or no pharmacological evidence supporting the claim that the SSRIs were implicated in suicide rather than the underlying conditions they were supposed to treat. However, the ACNP task force's 1992 report did not lay the issue to rest as the FDA, through a parallel effort, mandated black-box warnings and changes to the labeling language on all SSRIs. In the wake of the ACNP task force report, which was focused on adults, similar issues arose as more and more children were prescribed SSRIs. An unintended consequence of the FDA process was the realization that many drugs—not just the SSRIs—were being prescribed to children and adolescents without an adequate evidence base concerning safety or efficacy. The FDA launched an incentive

program designed to encourage industry to conduct pediatric clinical trials. When the FDA took a hard look at research on phenomena involved in suicide, the agency found that many of the studies lacked agreed-upon definitions, methods, and analysis. To remedy this problem, the FDA created a new data set that demonstrated its value the next time the question came up.

In spring of 2003, youth suicide-related adverse events surfaced in the United Kingdom. The British Medical and Healthcare Products Regulatory Agency (MHRA) warned physicians not to prescribe most SSRIs to children until the issue was further studied. This catalyzed activity in the US FDA. The ACNP formed a second task force focused on youth chaired by John Mann and child psychiatrist Graham Emslie. This second ACNP report was released and publicized shortly before the FDA committee released its results. Upstaging the FDA was not the ACNP's intent; the timing brought to the surface tensions between those who argue that the ACNP should have a prominent public profile, and those who see "backstage" activity as a more fruitful or legitimate mode of civic engagement for scientists working on controversial or uncertain issues.

C. Terrorism Task Force

One indication of the organization's desire to take on a more public research advocacy role occurred in the wake of the events of September 11, 2001. After measured consideration, the ACNP constituted the Terrorism Task Force, chaired by Steve Hyman and Dennis Charney, which produced a white paper on "The Impact of Terrorism on Brain, and Behavior: What We Know and What We Need to Know." Citing troubling gaps in knowledge and a significant lack of knowledge about psychological and behavioral effects following traumatic events such as terrorist attack and/or disaster, task force members felt that as scientific researchers they should have been in a better place to inform policy than they were at the time. Prior to this moment, Post-Traumatic Stress Disorder (PTSD) had not been a major focus of the ACNP, although there had been token representation of researchers working on the neurobiology of PTSD at ACNP meetings from the late 1980s on. The task force strengthened the constituency for such scientific interests within the College. Members of the task force credit the College with seeing the need for rational responses that come from a basis in empirical evidence and are informed by scientific research meeting standards for peer review.

D. Moving from Insularity to Public Engagement?

Many ACNP task forces deal with matters internal to the organization or the profession, and the College has sometimes been perceived as insular as a result. The task force efforts described above, however, have sought to add something unique and different to the public dialogue, broadening the College's reach through emphasis on its scientific contributions. Task forces have provided a vehicle for demonstrating how scientists could fulfill a sense of social responsibility, reaffirming the ACNP's position as a "place where only science is spoken," yet navigating the partisan shoals of politics. Currently, the ACNP has joined the American Brain Coalition (ABC), which strives to provide a unified umbrella for research advocacy groups, neuroscientific societies, and medical associations seeking to "reduce the burden of brain disorders to individuals, families, and society." Such coalitions offer the benefits of a Washington presence without the proliferation of redundant efforts and steep costs. As the ACNP faces its next 50 years, a question remains unresolved—will the ACNP elect to move quietly in the background, or will it come to play a more prominent and public role than it has to date? From the vantage point of the early 21st century, the high-profile nature of the recent task forces indicate that the College may assume a more visible research advocacy role.

Conclusion

Tracing the Travels of a Big Idea: From Psyche to Brain

Writing a history of the societal impact of this relatively small, yet highly prestigious, honorary scientific society requires inquiring deeply into why ideas about the causes, consequences, and treatment of mental disorders shift when they do. The social organization of scientific and clinical research designed to understand and remedy such disorders has changed over time, as have the methodologies, technologies, and funding structures used to address them. The College was conceived at a time when ideas about the molecular, neurochemical, and neurophysiological basis of mood and mental disorders, alcoholism, and substance use were young. Over the five decades of its existence, that idea has been refined, reinforced by evidence, and become widely shared not only within the scientific elite but by policymakers and the public. While it is always hard to measure the impact of a relatively small group of elites whose members are active on many fronts, the ACNP's widening and deepening involvement with the advocacy groups and its behind-the-scenes political work suggest that the organization has been crucial to redefining mental and mood disorders, substance abuse, and alcoholism as brain diseases that can be safely and effectively treated.

Recalling Kline's sense that the ACNP was responsible for creating the "social environment whereby new knowledge in our field can be safely acquired and maximally applied,"[118] we see that the College has acted in myriad ways to accomplish this. The College has incorporated new and changing understandings of the purview of psychopharmacology under the theme of 'scientific diversity." A new emphasis on neurodegenerative diseases, including Alzheimer's, Parkinson's, Traumatic Brain Injury, epilepsy and other seizure disorders, migraine, cognition/memory/learning, and obesity/appetite regulation has brought increased representation of those who study these and other areas formerly considered "neurological" into the organization. Neurogenetics—rarely mentioned in the early days of the College—has come to the fore as technologies have evolved in the context of the Human Genome Project. Indeed, the broadening research purview means that the organization is now poised to play an even greater role in communicating how the research efforts and accomplishments of its members have been translated into treatments that benefit millions of patients and their families.

By reinforcing the modern idea that mental illness is a physical disease that can be treated, and innovating technologies and research practices to study the human brain *in situ*, ACNP fellows have contributed to the new knowledge base for psychology, psychiatry, and the neurosciences. They have revolutionized pharmacology in the process and expanded into new areas with translational value for the clinic. Teaching days have been important for relatively senior members of the field to learn emergent fields and techniques from the ground up. As one relatively young researcher said in a 2009 interview, "The field of science has moved very quickly from understanding everything there is about peripheral biochemistry and neurochemistry, to the brain. A lot of things had to be learned by people very quickly – neuroimaging techniques, how do you look at the brain, how do you understand those images, how do you understand neurogenetics."[119] Given the rapidity with which neuroscience developed in the last decades of the 20th century, it has been crucial for neuropsychopharmacologists to keep pace. At the same time, the historical interests of the College and its ties to biological psychiatry offered opportunities for neuroscientists seeking to translate

basic science into clinical advance. However, as the ACNP leadership has astutely recognized, science alone is unlikely to be a sufficient basis for responding to the kinds of health conditions with which researchers in this area deal. The organization has made it a priority to stabilize the federal research apparatus wherever possible; to expand or better target funding; to create an ethical framework that enables ethical scientific research with clinical populations; and to address issues brought to it by patient advocates, including mental health parity, compelled medical treatment. As this history has shown, the ACNP has carefully chosen its issues and allies in the ongoing struggles to create a social climate of respect for the role of the brain in brain disorders. By bringing to the table a scientific elite engaged in the national leadership of all of the federal agencies involved in research on mental health and brain disorders, the ACNP has expanded the conversation far beyond what its progenitors could have envisioned as the purview of neuropsychopharmacology.

Long ago in reference to his studies of cerebral circulation in the human brain, which provided a basis for today's neuro-imaging technologies, Seymour Kety said: "[I]t is the human brain, which is heir to disorders that one cannot produce in lower animals like schizophrenia and other mental illnesses, it is the human brain that experiences profound sorrow, laughter, jests, incites, and it is the human brain that can speak and reveal its inner workings to some extent."[120] As he walked through the construction site destined to become the NIMH Clinical Research Center, Kety recalled Robert H. Felix, founding director of NIMH, recruiting him for the "challenge of directing the greatest program for the study of brain and behavior that the world had ever seen." Neither could foresee that theirs was but a modest beginning. Today, with the luxury of hindsight, we recognize the transdisciplinary science of neuropsychopharmacology as a meeting ground from which has grown insights about myriad brain diseases. The American College of Neuropsychopharmacology has provided a capacious and hospitable ground for the flourishing of a new science, one that has continued to expand vigorously as the discipline evolved thicker and richer connections between disorders, drugs to probe or treat them, and the workings of the brain.

Endnotes

1 Epigraph from Joel Elkes, First Presidential Lecture, 1963.

2 Remarks of Anthony Sainz, "Origins of the ACNP," C-13. Quotations are from transcripts in "ACNP: In the Beginning…The Origin of the American College of Neuropsychopharmacology." The session held on the morning of November 12, 1960 was labeled 'A'; the afternoon session 'B'; the session held on the morning of November 13, 1960 'C', and the organizational session held on the following day 'D'.

3 See Richard A. Frank and Sherry A. Glied, *Better But Not Well: Mental Health Policy in the United States Since 1950* (The Johns Hopkins University Press, 2006); Gerald N. Grob and Howard H. Goldman, *The Dilemma of Federal Mental Health Policy* (Rutgers University Press, 2007); Gerald N. Grob, *From Asylum to Community: Mental Health Policy in America* (Princeton University Press, 1991).

4 Frank and Glied 2006.

5 See Jack R. Ewalt, "Goals of the Joint Commission on Mental Illness and Health," *American Journal of Public Health* 47.1 (1957): 19-24.

6 Frank and Glied 2006, 7.

7 Grob and Goldman 2006, 68.

8 In his introduction to the final report, which was authored by Lee N. Robins and Darrell A. Regier, Freedman credited the cartographic impulse to the Carter commission. However, the project capitalized on the field's decades-long shift towards objective diagnostic methods and the standardized diagnostic criteria of the DSM-III (1980).

9 Correspondence dated April 1, 1979 from ACNP President Fridolin Sulser to the ACNP Membership (ACNP Collection 1090, Box 4, F7).

10 Correspondence dated February 1987 from ACNP President Arthur J. Prange to the ACNP membership (ACNP Collection 1090, Box 4, F7).

11 Correspondence dated December 9, 1985 to Fred Graefe (ACNP Collection 1090, Box 18 F1).

12 Lewis L. Judd, "NIMH During the Tenure of Director Lewis L. Judd (1987-1990): The Decade of the Brain and the Four National Research Plans," *American Journal of Psychiatry* 155.9 Supplement (1998): 25-31.

13 The Macy Foundation also hosted three annual conferences on the Central Nervous System and Behavior (1958-60) and Brain and Behavior (1961-63). International meetings such as the 1958 Moscow Colloquium on Higher Nervous Activity led to the 1961 formation of the International Brain Research Organization (IBRO), an organization with ties to the Scientific Command of the U.S. Air Force and UNESCO.

14 Joel Elkes, "Psychopharmacology: Finding One's Way," *Neuropsychopharmacology* 12.2 (1995): 93-111. Elkes founded one of the world's first experimental facilities dedicated to psychiatry and psychopharmacology at the University of Birmingham Hospital in England, shortly before founding the NIMH Behavioral and Clinical Studies Center at St. Elizabeth's Hospital in Washington, DC in 1957. He later directed the NIMH Clinical Neuropharmacology Research Center.

15 Ralph W. Gerard, "Drugs for the Soul: The Rise of Psychopharmacology," *Science*, 125 (1957): 201-203.

16 "At that time, there were two anchoring points for our work in the mental disease field: neurochemistry, at the bench level, and human behavior, as influenced by drugs. There was nothing in between, no indicator that could relate the effects of drugs on the brain in the conscious animal to behavior, nor any correlation between behavior and chemistry of the brain" (Elkes 1995, 97).

17 See Joel Braslow, *Mental Ills and Bodily Cures: Psychiatric Treatment in the First Half of the Twentieth Century* (University of California Press, 1997); David Healy, *The Creation of Psychopharmacology* (Harvard University Press, 2002); Horace W. Magoun, *American Neuroscience in the Twentieth Century: Confluence of the Neural, Behavioral, and Communicative Streams* (A.A. Balkema Publishers, 2003); and Edward Shorter, *A History of Psychiatry: From the Era of the Asylum to the Age of Prozac* (John Wiley, 1997).

18 Elkes 1995, 108.

19 Irv Kopin's ACNP interview described Seymour Kety's work on schizophrenia and their 1958 refutation of the adrenochrome hypothesis. Transcripts of all ACNP interviews are housed in the ACNP Archives at the Louise M. Darling Biomedical Library at UCLA. My thanks to Joel Braslow, Marcia Meldrum, Russell Johnson, and Theresa Johnson for help in accessing the archives, and to all those who participated in creating this exceptional resource for the history of science.

20 Thomas A. Ban, *The First Fifty Years: An Oral History of Neuropsychopharmacology: Peer Interviews*, Preface and Introduction, mss. 4.

21 At its inception in 1948, the NIMH inherited the Addiction Research Center in Lexington, Kentucky, which was operated by the U.S. Public Health Service from its opening in 1935. According to Donald F. Klein, who spent several years at Lexington in the 1950s, the ARC was at the time the "most advanced center for human psychopharmacological experimentation in the world" (see Donald F. Klein, "The Loss of Serendipity in Psychopharmacology," *JAMA*, 299.9 (March 5, 2008): 1063-1065).

22 Elkes 1995, 101.

23 Abraham Wikler, *The Relation of Psychiatry to Pharmacology* (Williams and Wilkins, 1957), 267-268.

24 Wikler 1957, 126.

25 Healy 2002, 205.

26 See Thomas A. Ban, Helmut Beckmann, and Oakley S. Ray (eds.), CINP International Photo Archives in Neuropsychopharmacology (2000).

27 Gerard 1957, 201.

28 Shorter 1998.

29 Remarks of Anthony Sainz, "Origins of the ACNP," A-23.

30 "Origins of the ACNP," A-24.

31 "Clinical Trials in CND Drugs," John A. Talbot, *The Handbook of Psychopharmacology Trials: An Overview of Scientific, Political, and Ethical Concerns*, eds. Marc Hertzman and Douglas E. Feltner (New York University Press, 1997), p. xviii.

32 See ACNP Origins, A-12-13. Ayd underlined the need to self-regulate by voluntarily raising the standards for clinical investigation from within the field itself (ACNP Origins B-8; B-11).

33 This was the topic of the morning session on the second day, which was chaired by Brodie. All material in this paragraph is taken from pages C-1, C-10, and C-19.

34 For an archival account of Hoffer's research program in Saskatchewan, see Erika Dyck, *Psychedelic Psychiatry: LSD from Clinic to Campus* (The Johns Hopkins University Press, 2008). Although Hoffer and Humphrey Osmond's initial experiments were, like many in early 20th century pharmacology and psychiatry, conducted on themselves, family, colleagues, friends, and graduate students, they also recruited broadly in the mental health community. By the late 1950s they theorized that schizophrenia had a biochemical basis; that LSD enabled mental health professionals to gain a more empathic understanding of major psychotic symptoms; and they, like others, used their theoretical work to put psychoanalysis to rest.

35 Elkes, "Letter to a Young Colleague Considering a Career in Psychopharmacology," *Principles of Psychopharmacology* (Academic Press, 1978), p. 753.

36 According to J. R. Wittenborn's unpublished history of the early college, 90 people attended this meeting, electing Elkes as president, Hoch as president-elect, and Theodore Rothman as secretary-treasurer, adopting the constitution and by-laws, and planning for the first annual meeting. ACNP Archives, Box 4, F5.

37 Joel Elkes 1962, 5.

38 Kline 1967, 2. Nathan S. Kline, "Presidential Address," *Psychopharmacology: A Review of Progress*, *1957-1967*, edited proceedings of the ACNP's sixth annual meeting. The volume was co-published by ACNP and the NIMH Psychopharmacology Research Branch. Kline's address opens the volume (pp. 1-3). The ACNP published periodic reviews of progress in the field, which were important to the organization's educational mission. See Efron, D. H, ed., *Psychopharmacology, A Review of Progress*, *1957-1967* (U.S. Government Printing Office, 1968); Lipton, M.A., DiMascio, A, Killam, K.F., eds., *Psychopharmacology: The Second Generation of Progress* (Raven Press, 1978); Meltzer, H., ed., *Psychopharmacology: The Third Generation of Progress* (Raven Press, 1987); Bloom, F.E., Kupfer, D.J., eds., *Psychopharmacology: The Fourth Generation of Progress* (Raven Press, 1995); Charney, D., Coyle, J.T., Davis, K.L., et al., eds., *Neuropsychopharmacology: The Fifth Generation of Progress* (Lippincott Williams & Wilkins, 2002).

39 Kline 1967, 2.

40 Much of this paragraph was derived from group interview conducted by Alan Frazer with Paula Clayton, Kenneth Davis, Chris Fibiger, Irv Kopin, Herb Meltzer, Roger Meyer, and Fridolin Sulser in preparation for the ACNP's 50th anniversary celebration. According to Kopin, "The idea of bringing basic scientists, . . . to meet with people who were clinicians and realize that they had common ground [and] that the questions that they were asking in the basic area could be answered from the clinical area and the big questions that the clinicians had could contribute to . . . new therapies from the basic scientists was a brand new concept. [It] was at that time a revolutionary thought in the early 1960's."

41 Joseph Zubin, "ACNP Observed," Prepared for the 25th Anniversary Anthology, ACNP, 1986, 130.

42 I am indebted to James C. Anthony for this point.

43 Samuel B. Guze, *Why Psychiatry Is a Branch of Medicine* (1992), p. 14.

44 See Samuel B. Guze, "Biological psychiatry: Is there any other kind?" *Psychological Medicine* 19 (1989): 315-323 and Guze, 1992, 54.

45 See Nancy D. Campbell, *Discovering Addiction: The Science and Politics of Substance Abuse Research* (University of Michigan Press, 2007).

46 Cole was not the only connection between ACNP and CDAN/CPDD. Wikler worked at the ARC, where most of CDAN/CPDD's human testing protocols were carried out; ARC Director Harris Isbell was the first chair of the ACNP Credentials Committee. CPDD did not become the large membership organization it is today until the 1980s.

47 On the project to develop a non-addicting analgesic in the United States, see Caroline J. Acker, *Creating the American Junkie: Addiction Research in the Classic Era of Narcotics Control*. (The Johns Hopkins University Press, 2002).

48 See ACNP Collection 1090, Box 14, F11; ACNP Bulletin, October, 1966, Program for 5th annual meeting, to be held at the Sheraton in San Juan, Puerto Rico. Most of the program was devoted to drug addiction, the only exception being an afternoon plenary on use of Dilantin (diphenylhydantoin) in psychiatric conditions.

49 ACNP Collection 1090, Box 1, F13, council meeting minutes, June 21, 1969, pp. 5-6.

50 Correspondence from President Philip R. May to Donald M. Gallant, chair of the Ethics Committee, December 1974. See ACNP Council meeting minutes, December 15-16, 1975.

51 Correspondence from Paul Perito to ACNP President Seymour Fisher dated April 23, 1984.

52 ACNP Collection 1090, Box 17, F3.

53 For instance, in the summer of 1979, the College submitted "Comments of the ACNP on Proposed Regulations Amending Basic HEW Policy for Protection of Research Subjects" to the Office of the Secretary of the Department of Health, Education, and Welfare (ACNP Collection 1090, Box 11, F12).

54 ACNP Collection 1090, Box 11, F12, 2.

55 ACNP Collection 1090, Box 11, F12, 4.

56 ACNP Collection 1090, Box 11, F12, 4.

57 ACNP Collection 1090, Box 11, F12, 5.

58 See Campbell 2007, 143-177; Susan M. Reverby, *Examining Tuskegee: The Infamous Syphilis Study and Its Legacy* (University of North Carolina Press, 2009).

59 Correspondence from Donald F. Klein to ACNP President Fridolin Sulser, Collection 1090, Box 26, F10.

60 Personal Communication with David Kupfer, January 4, 2011.

61 ACNP Collection 1090, Box 11, F12, p. 4.

62 ACNP Collection 1090, Box 34, F3.

63 ACNP Collection 1090, Box 25, F7.

64 ACNP Collection 1090, Box 18, F2. Council meeting minutes, July 13-14, 1984, p. 6 and 11.

65 Memo to membership from ACNP President Donald F. Klein, Oakley Ray, and Paul Perito, dated November 19, 1981: "On October 5, 1981, the ACNP Council decided to fight legislative efforts to reduce federal funding for research in mental health, drug abuse and alcoholism. This decision entailed ACNP undertaking its first active lobbying of Congress on the issue. ACNP should be aware of the facts that went into this decision and the status of this legislative advocacy project" (ACNP Collection 1090, Box 18, F18, p. 2).

66 ACNP Collection 1090, Box 18, F10.

67 The context of this fiscal crisis is explained in "Mental Health in the Present Era, 1977-1998 at http://www.archives.nysed.gov/a/research/res_topics_health_mh_hist_present.shtml. For the authoritative national overview, see Grob 1991.

68 ACNP Collection 1090, Box 17, F1, p. 2.

69 Correspondence from William E. Bunney, Jr., to ACNP President Seymour Fisher, dated Aug. 8, 1984 (ACNP Collection 1090, Box 17, F1).

70 According to Arthur J. Prange's President's letter dated February 1987. ACNP Collection 1090, Box 4, F7.

71 ACNP Collection 1090, Box 17, F1.

72 This latter point is drawn from the ACNP interview with Keith and Eva Killam (1994), both of whom described becoming involved in animal research issues for scientific and ethical reasons: "It is disturbing to both of us that funding for what we would consider research that encompasses multi-levels of discourse from the cell to the behaving organism [is] not being funded; what is being funded almost entirely are molecular approaches and the ability to take receptors and clone them and predict from the flask. . . . Grants now being funded for primate research in neuropsychopharmacology are almost zero. . . . Being people who are in a university with a prominent veterinary school, we see that our work has contributed directly to the rapidly growing field of medicine for animals. . . . [But] we believe the future looks dim…[for studies] where you can have this interplay from anatomists to molecular biologists through whole animal groups to physiologists and psychologists through translation into the clinic.

73 ACNP Collection 1090, Box 19, F17.

74 ACNP Collection 1090, Box 15, F8.

75 See correspondence from Joseph V. Brady (ACNP Collection 1090, Box 16, F3).

76 By law such seats must be made available to persons outside of the institution to judge experimental animal protocols.

77 ACNP Collection 1090, Box 19, F17.

78 Memorandum from Chris-Ellyn Johanson on behalf of the committee for the use of Animals in Neuropsychopharmacology to Louise Gallant dated December 7, 1999. ACNP Collection 1090, Box 49, F4.

79 Co-chaired by Thomas Insel and Chris-Ellyn Johanson, this committee reported in November 1998 on the animal rights movement's "successful conflation of the issue of animal rights with the cause of animal welfare" (p. 3) and the appeal of its message to women and youth. The committee pointed out that the "USDA now openly admits that the animal rights community is one of its 'major constituents'" and the major lobby for the regulation of rats and mice in the Animal Welfare Act (p. 5).

80 But not NIAAA or NIDA.

81 Correspondence from Inouye's Washington office to Donald F. Klein dated Oct. 28, 1981.

82 Correspondence from President Leonard Cook to William Mayer, Administrator of ADAMHA dated October 4, 1982. Mayer provided examples of USPHS and ADAMHA directors who were not themselves researchers, "but under whose stewardship very high quality research programs have developed." For instance, NIMH was then directed by Herbert Pardes, who "is not a laboratory scientist per se, but who has helped to build and direct the most prestigious research institute on mental health and mental illness in the world." Mayer also noted that "Although research is the principal program of the Institute, its role also includes important national activities which reach far beyond the laboratory" (ACNP Collection 1090, Box 17, F6).

83 Council meeting minutes July 14-16, 1985, p. 3 (ACNP Collection 1090, Box 15, F8). After the ACNP Council relayed its concerns to Dr. Shervert Frazier, he noted that the reorganization was meant to emphasize the importance of basic research and upgrade neuroscience to a branch of its own, and that the disorders orientation was designed to answer the fiscal questions of Congress. ACNP Council responded to Frazier by pressuring for a division that would include psychopharmacology and biological psychiatry.

84 Correspondence from Michael F. Cole of Washington, Perito & Dubuc to Oakley Ray dated March 10, 1988 (ACNP Collection 1090, Box 17, F9 Legal Interests, 1984-88).

85 Memo to ACNP Council from Oakley Ray dated 1989 (ACNP Collection 1090, Box 16, F4).

86 Judge Brotman, the judge who ordered creation of a mechanism for independent administrative review of a patient's decision to refuse treatment in the New Jersey case, was invited to attend the 1979 ACNP meeting in Puerto Rico, where Louis Lasagna chaired a plenary session on the implications of the two decisions for care of the institutionalized mentally ill. The cases were similar. As stated in a detailed synopsis mailed to all ACNP members, the court held that there was a constitutional right to refuse treatment grounded in the emerging right to privacy (Memo from ACNP Council to membership, November 27, 1979, ACNP Collection 1090, Box 25, F15).

87 1980, p. 3.

88 1980, 31-32.

89 Letter from Oakley Ray to sign-on organizations dated June 1998 (ACNP Collection 1090, Box 30, F5).

90 Term drawn from David Healy's interview with Joel Elkes, p. 209.

91 Report of the ACNP 1975 Program Committee submitted by William E. Bunney, Jr.

92 Correspondence from Floyd Bloom to Gerald Klerman dated August 11, 1987 (ACNP Collection 1090, Box 15, F16).

93 Biographies of the 10 graduates are at http://www.apa.org/monitor/feb03/prescribers.aspx.

94 "Neuroleptic-induced Prolactin Elevation and Breast Cancer: An Emerging Clinical Issue," Paul M. Schyve, Francine Smithline, and Herbert Y. Meltzer, *Archives of General Psychiatry* 35.11 (November 1978): 1291-1301.

95 "We must not relinquish our past essential roots" (ACNP Collection 1090, Box 16, F4).

96 Term used by Alan Frazer interviewing Herb Meltzer (2009) in order to document the importance of annual meetings at the Caribe Hilton in San Juan, Puerto Rico.

97 ACNP Collection 1090, Box 11, F14, Wittenborn, Draft, October 1, 1973, p. 3.

98 These were the days before the DSM-III set psychiatric diagnosis on firm footing; there was considerable disagreement about how diagnostic criteria should be presented.

99 ACNP Collection 1090, Council meeting minutes, February 1998.

100 At its founding in 1908, ASPET excluded pharmacologists employed in industry "in order to avoid every external influence inimical to the scientific interests of pharmacology." The decision was contentious throughout the first three decades of the Society and it was changed in 1941. On the history of ASPET, see John Parascandola, "A Brief History of ASPET on Its Centennial Anniversary," *Molecular Interventions* 7.6 (December 2007): 288-302.

101 Author's interview with Drug Development Panel, 2009.

102 Oakley Ray asked Robert Prien of the NIMH Affective and Anxiety Disorders Research Branch to chair a special ACNP Task Force on Coordinating Academic-Industrial-Government Efforts in Psychopharmacology. Correspondence from Oakley Ray to Robert Prien, December 2, 1988.

103 ACNP Collection 1090, Box 16, F4.

104 From the Committee Charge, 1989.

105 Memorandum from Donald F. Klein, Chair, to members of the Liaison Committee, dated January 24, 1996. (ACNP Collection 1090, Box 40, F36).

106 See Nancy Tomes, "The Patient as a Policy Factor: A Historical Case Study of the Consumer/Survivor Movement in Mental Health," *Health Affairs* 25, no. 3 (2006): 720–729.

107 ACNP Collection 1090, Box 15, F8.

108 ACNP Collection 1090, Box 16, F3.

109 In a May 24, 1990 memo, Bob Rose asked the membership to indicate willingness to speak at meetings or to the media on topics ranging from the animal rights controversy to improved science-based education.

110 ACNP Collection 1090, Box 10, F10.

111 Charles P. O'Brien, chair of the Committee on Problems of Public Concern, solicited information and received a letter from the Upjohn Company stating there was no evidence that triplicate prescriptions decrease abuse (the reason the New York State legislature had acted to mandate triplicate prescriptions).

112 ACNP Collection 1090, Box 19, F27.

113 During the 1990s the issue of mental health parity in insurance coverage was one on which several influential Congressional representatives such as Paul Wellstone and Pete Domenici, both of whom had affected family members and ties to some of the same advocacy groups as ACNP, had built a bipartisan coalition to overcome the traditional Congressional reluctance to act in this arena. See Deborah Sontag, "When Politics Is Personal," *New York Times*, September 15, 2002.

114 In June 1994 Thomas Detre, chair of the Committee on Relationships with Advocacy Groups, urged the committee to "change our somewhat parochial lobbying efforts" (ACNP Collection 1090, Box 22, F31).

115 ACNP Collection 1090, Box 22, F31.

116 Material from ACNP Council meeting minutes from the December 7-8, 1997 (ACNP Collection 1090, Box 30, F5) included Roger Meyer's Memo on Action in Washington, in which he recapitulated a brief history of the College's efforts "toward impacting the federal government's spending habits for research and training. . . We became active in Washington in Don Klein's term. . . Tom Detre later introduced the grass roots-politics concept to the ACNP. . . . The Grass Roots approach culminated in a program at the 1996 Annual meeting." Meyer's diagnosis: "Our grass roots programs have not succeeded because those who know how to do it, already are doing it—and the College has never committed the funds to educate those who should and could, but don't do it."

117 ACNP Collection 1090, Box 49, F7.

118 Kline 1967, 2. Nathan S. Kline, "Presidential Address," *Psychopharmacology: A Review of Progress, 1957-1967* was the edited proceedings of the ACNP's sixth annual meeting. The volume was co-published by ACNP and the NIMH Psychopharmacology Research Branch. Kline's address opens the volume (pp. 1-3). The ACNP published periodic reviews of progress in the field, which have been important to the organization's educational mission but also for first consolidating and then diversifying the field itself: see Efron, D. H, ed., *Psychopharmacology, A Review of Progress, 1957-1967* (Washington, DC: U.S. Government Printing Office, 1968); Lipton, M.A., DiMascio, A, Killam, K.F., eds., *Psychopharmacology: The Second Generation of Progress* (New York: Raven Press, 1978); Meltzer, H., ed., *Psychopharmacology: The Third Generation of Progress* (New York: Raven Press, 1987); Bloom, F.E., Kupfer, D.J., eds., *Psychopharmacology: The Fourth Generation of Progress* (New York: Raven Press, 1995); Charney, D., Coyle, J.T., Davis, K.L., et al., eds., *Neuropsychopharmacology: The Fifth Generation of Progress* (Philadelphia, PA: Lippincott Williams & Wilkins, 2002).

119 Author's interview with Rachel Yehuda, 2009.

120 Seymour Kety, ACNP interview, p. 4.

1961 FOUNDING MEMBERS

We especially want to salute those individuals who were around "at the beginning." Their names are listed below and we acknowledge their energy and wisdom which started the organization of which we are honored to be members.

Even more, the names listed here are the toilers, the conceptualizers, the integraters who provided the strong scientific base of brain-drug-behavior interactions and insisted on maintaining and emphasizing the critical link between basic research and clinical issues. Their insistence on these two components when combined with their focus on excellence have given us a solid foundation on which to build the American College of Neuropsychopharmacology.

Leo G. Abood
Julius Axelrod
Frank J. Ayd, Jr.
Lauretta Bender
Ivan F. Bennett
Lorraine Bouthilet
Joseph V. Brady
Henry Brill
Bernard B. Brodie
John J. Burns
Enoch Callaway III
C. Jelleff Carr
Lincoln D. Clark
Mervin L. Clark
Bertram D. Cohen
Jonathan O. Cole
Leonard Cook
Erminio Costa
Jose M.R. Delgado
Peter B. Dews
James M. Dille
Alberto DiMascio
Edward F. Domino
Daniel H. Efron
Joel Elkes
David M. Engelhardt
Guy M. Everett

Paul Fe1dman
Max Fink
Barbara Fish
Seymour Fisher
Herbert Freed
Alfred M. Freedman
Daniel X. Freedman
Harry Freeman
Fritz A. Freyhan Arnold
Arnold J. Friedhoff
Ralph W. Gerard
Bernard C. Glueck, Jr.
Douglas Goldman
Louis A. Gottschalk
Milton Greenblatt
Paul Greengard
Thomas E. Hanlon
Robert G. Heath
Harold Edwin Himwich
Paul H. Hoch
Ebbie C. Hoff
Abram Hoffer
Leo E. Hollister
Samuel Irwin
Harris Isbell
Murray E. Jarvik
Samuel C. Kaim

Alexander G. Karczmar
Seymour S. Kety
Eva King Killam
Keith F. Killam, Jr.
John Kinross-Wright
Gerald D. Klee
Gerald L. Klerman
C. James Klett
Nathan S. Kline
Werner P. Koella
Conan Kornetsky
Else B. Kris
Albert A. Kurland
Heinz E. Lehmann
Stanley Lesse
W.T. Liberson
Sidney Malitz
Lester H. Margolis
Amedeo S. Marrazzi
Philip R.A. May
Roger K. McDonald
Sidney Merlis
James Grier Miller
Benjamin Pasamanick
Carl C. Pfeiffer
Albert J. Plummer
Benjamin Pollack

Lowell O. Randall
Max Reiss
Karl Rickels
Sherman Ross
Theodore Rothman
Anthony Sainz
Gerald J. Sarwer-Foner
Burtrum C. Schiele
Jurg Schneider
Charles Shagass
Ernest B. Sigg
R. Bruce Sloane
Joseph M. Tobin
James E.P. Toman
William J. Turner
E.H. Uhlenhuth
George A. Ulett
Klaus R. Unna
Heinrich Waelsch
Louis Jolyon West
N. William Winkelman, Jr.
John Richard Wittenborn
Arthur Yuwiler
Joseph Zubin

KNOWN PARTICIPANTS AT THE ORGANIZATIONAL MEETING OF THE AMERICAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY

(THE CONFERENCE FOR THE ADVANCEMENT
OF NEUROPSYCHOPHARMACOLOGY)

Barbizon-Plaza Hotel
New York, New York
November 12-13, 1960

Frank Ayd

Henry Brill

Bernard Brodie

Eugene Caffey

Dr. Carpenter

Jonathan Cole

Erminio Costa

Wilfred Dorfman

Edwin Dunlap

Joel Elkes

Dr. Falmonic

Paul Feldman

James Ferguson

Danny Freedman

Bernard Glueck

Douglas Goldman

Milt Greenblatt

Paul Hoch

Abram Hoffer

Leo Hollister

John Kinross-Wright

Nathan Kline

Lou Lasagna

Joseph Lazerte

Heinz Lehmann

Nolan Lewis

Sidney Malitz

Sidney Merlis

Ted Rothman

Anthony Sainz

John C. Saunders

Arnold Scheibel

Joe Tobin

Jim Toman

Bill Turner

Klaus Unna

Dr. Von Munger

Joe Zubin

American College of Neuropsychopharmacology

First Organizational Meeting
October 7-8, 1961
Woodner Hotel – Washington, DC

1. Seymour Kety
2. Paul Feldman
3. Fritz Freyhan
4. Mrs. Cole
5. Jonathan Cole
6. Ted Rothman
7. Paul Hoch
8. Joel Elkes
9. Mrs. Elkes
10. Frank Ayd
11. Danny Freedman
12. Thomas Hanlon
13. Mrs. Kurland
14. Al Kurland
15. Jelleff Carr
16. Carl Pfeiffer
17. Keith Killam
18. Peter Dews
19. Lowell Randall
20. _____
21. Klaus Unna
22. Bob Burlew
23. James Dille
24. Karl Rickels

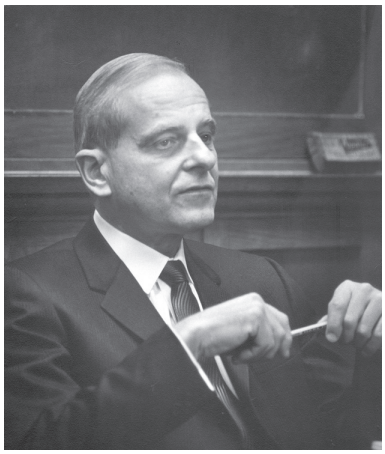
25. Joe Zubin
26. Sy Fisher
27. Murray Jarvik
28. Sam Irwin
29. Ernest Sigg
30. Lincoln Clark
31. Al DiMascio
32. Bud Veech
33. Erminio Costa
34. Mrs. Costa
35. Guy Everett
36. Alex Karczmar
37. Sid Malitz
38. Stan Lesse
39. Mervin Clark
40. Len Cook
41. Conan Kornetsky
42. Lorraine Bouthilet
43. Charles Shagass
44. Dick Wittenborn
45. Max Rinkel
46. Jim Toman
47. Hussain Azima
48. Mrs. Winkelman
49. Bill Winkelman
50. Burt Schiele
51. Elsie Kris
52. Doug Goldman
53. Max Fink
54. Gerry Klerman
55. _____
56. Sherman Ross
57. Mrs. Ross
58. Herb Freed
59. Mrs. Freed
60. Max Reiss
61. Mrs. Reiss
62. John Pearse
63. Al Freedman
64. Mrs. Hines
65. Len Hines
66. _____
67. Werner Koella
68. John Burns
69. Abe Wikler
70. Rita Ayd
71. N.D.C. Lewis
72. Henry Brill
73. Barbara Fish
74. Heinz Lehmann
75. Arnold Friedhoff
76. Eugene Roberts
77. Paul Greengard
78. Henry Beecher
79. Mel Sabshin
80. Ivan Bennett

Fifty Years Through the ACNP Science Retrospectoscope

Floyd E. Bloom • The Scripps Research Institute • La Jolla CA

Introduction: In the Beginning

When the Founders of the American College of Neuropsychopharmacology met for their organizational meeting in the fall of 1960, the field they were striving to launch had already been recognized with a Lasker Clinical Medical Research Award to Deniker, Kline, Laborit and Lehmann for their introduction of chlorpromazine and reserpine into the treatment of major psychoses, and the demonstration that these drugs could influence the clinical course of psychiatric disease. Before the ACNP had formed, monoamine oxidase inhibitors and imipramine had been shown to treat depression. As a result, the organizers, virtually all experienced clinical investigators in the new field aware of double blind and cross-over treatment studies, were motivated by an anticipated onslaught of more new medications for the treatment of serious psychiatric diseases. Their chief concerns were the perceived lack of standards by which to perform, analyze and disseminate their research findings to the rest of the medical community. The 4 sessions of that organizational meeting were largely devoted to these clinical research needs, and focused on the active sharing of concepts of how the drugs might be working between laboratory and clinical scientists.



Heinz Lehmann

Only one of the 4 organizational sessions dealt with the preclinical science of how the drugs then being used in practice might be acting in the brains of experimental animals to produce in patients the early anti-psychotic, sedative, and anti-depressant actions. The highly selective presentation of the biochemical explanation for reserpine's behavioral actions avoided already published data that norepinephrine and dopamine were present in the brain in equal amounts and were both also depleted by reserpine. The desirability of improved dialog between basic and clinical investigators was obvious to all. A rough approximation of the key advances in our field in the subsequent 50 years can be seen in the differences between the stated purposes of the College at the time of its incorporation in 1961 and the current Mission statement of the College as of 2010 (see box below).

MISSION STATEMENT

The principal function of the College is to further research and education in neuropsychopharmacology and related fields by: a) promoting the interaction of a broad range of scientific disciplines of brain and behavior in order to advance the understanding of causes, prevention and treatment of diseases of the nervous system including psychiatric, neurological, behavioral and addictive disorders; b) encouraging scientists to enter research careers in fields related to these disorders and their treatment; and c) ensuring the dissemination of relevant scientific advances in these disorders.

ADOPTED BY COUNCIL
JULY 1997 (amended June 2010)

From the starting goal of simply convening experienced investigators to educate and disseminate research results with a rather unspecified definition of the field, we have now a

highly specified call to promote "the interaction of a broad range of scientific disciplines of brain and behavior in order to advance the understanding of causes, prevention and treatment of diseases of the nervous system including psychiatric, neurological, behavioral and addictive disorders". In this article, I will offer my personal perspectives on the series of scientific evolutions in our preclinical and clinical research that have brought us to our present understanding of neuropsychopharmacology, and briefly indicate some of the outstanding questions that still confront our ability to treat or prevent these diseases of the nervous system.

Brain Knowledge at the Founding

Although one would not know it from reading the discussions between the clinicians and basic scientists at the organizational meeting, brain research in late 1960 was far more than a black box. The general field, not yet dubbed 'neuroscience' was thriving in each of its main domains to lay the foundations for today's neuropsychopharmacology. John Eccles had been converted from electrical transmission between neurons to an acknowledgement that at least in the spinal cord, like the neuromuscular junction, transmission was by chemical mediators. However, the only widely accepted neurotransmitter was acetylcholine, and then only for one spinal cord synapse between motoneurons and their local inhibitory interneurons the Renshaw cell. Although belief that inter-cellular communication in the brain must be mainly electrical was widespread in textbooks of the time, early electron microscopy had proven that Cajal was correct in asserting that neurons were discrete contiguous elements and not the continuous syncytium predicted by Golgi. The ultrastructural evidence had shown that the presynaptic elements contained vesicles then conceptualized as containing the unknown chemical substances that could act as synaptic transmitters. The EEG was being employed to detect 'brain' responses to systemically injected drugs. Golgi impregnations had already revealed the large, long axon neurons of the reticular formation, that Magoun and Moruzzi had shown capable of affecting cortical EEG rhythms. Kety had recently reviewed the biochemical theories of schizophrenia, finding none convincing, but having no data to eliminate almost any of them except perhaps the ascorbic acid deficiency leading to a toxic

ABOUT THE AUTHOR

Floyd E. Bloom is presently Professor Emeritus in the Molecular and Integrative Neuroscience Department at The Scripps Research Institute, where he was formerly Chairman of the Department of Neuropharmacology. He has been involved in neuroscience research since the mid-60's, was the Secretary and seventh President of the Society for Neuroscience, as well as an elected President of the American College for Neuropsychopharmacology, and the Research Society for Alcoholism. With more than 600 original peer reviewed publications, Dr. Bloom has also co-authored or co-edited several textbooks of neuroscience including the ACNP's Fourth Generation of Progress and Introduction to Neuropsychopharmacology (2009), first edition with Iversen, Iversen and Roth. A member of the National Academy of Sciences and the Institute of Medicine, he has received a number of honorary degrees from major universities, and was the Editor-in-Chief of SCIENCE, 1995-2000.

adrenochrome intermediate. Marthe Vogt had shown that the measurable amounts of norepinephrine in the brains of cats and dogs varied by brain region and were responsive to drug manipulation. Olds and Milner had demonstrated that experimental animals found electrical stimulation of their lateral hypothalamus rewarding. Evarts and Landau had demonstrated that LSD and related compounds could depress visually evoked responses at the first visual synapse in the lateral geniculate. Hubel and Weisel were already recording single units and mapping out the connections between elements of the cortical visual system, while Mountcastle was mapping the units of the somatosensory system.

Psychiatry at the Founding

On the clinical side by 1960, it is important to understand that psychiatry was entangled in the aftermath of a relatively recent shift in the conceptualization of psychiatric disease. Before World War II, psychiatry had been a relatively minor component of the medical community, focused largely on state and private "insane" asylums with almost no individuals in private practice. The existing concept had been the 'medical model' of psychiatric disease (mental disease is a brain disease) as proclaimed by Emil Kraepelin. The new perspective was the psychodynamic, psychoanalytical view. Adolph Meyer, a distinguished protagonist of the psychodynamic position (he coined the term 'psychobiologic' to describe it), held that mental disorders arose from the life history of the individual, and that simple one word diagnostic terms, or indeed any attempt to diagnose groups of patients, were meaningless.

But clinical experiences during the war fueled these changes. Military doctors found that while serious mental health problems arose frequently under battlefield conditions, these problems were not the severe mental illnesses of the civilian population, but rather a wide variety of so-called personality problems. In fact, about 1 million of the 11 million plus individuals serving in the military during the war had been admitted to hospitals for 'neuropsychiatric' problems, a sizable fraction considering that this figure did not include those diagnosed with 'combat exhaustion' and those who were successfully treated as outpatients before returning to duty (see below) or being dismissed from the ranks.

At the beginning of 1944, psychiatry became a division within the Office of the Surgeon General and was placed on an equal organizational level with medicine and surgery. William C. Menninger, (of the Menninger Clinic) directed the division and was the first psychiatrist promoted to general. In order to account accurately for all instances of morbidity among the service personnel, the military psychiatrists needed a system of nomenclature of diseases that covered what they were facing and that included far more categories than those ordinarily seen in mental hospitals. The result was the Armed Forces Nomenclature, also known as "Medical 203", employed by Army and Navy psychiatrists, and later adopted with minor changes by the Veterans Administration.

By the end of the war, about 2,400 military physicians had been assigned to psychiatry of whom less than a third were previously trained in the specialty. In 1940, by way of comparison, the APA had a total membership of only 2,295. The idea that mental-health problems could befall normal individuals, and at a much higher rate than had been believed to be true before, set the stage for the post-World War II growth of the mental-health professions. This finding fit well with Meyer's 'psychobiological' view. During the war, military psychiatrists had made major contributions to dealing with the neuropsychiatric casualties with supportive forms of psychotherapy that combined

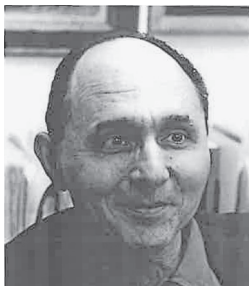
with rest, sleep, and food, were successful in returning servicemen to active duty. A therapeutic optimism arose among these physicians who carried it back into civilian life. The adverse experiences of service personnel returning to civilian life after the war strongly confirmed the need for neuropsychiatric adjustments, increasing the scope of the societal needs for psychiatric interventions. At the end of the war, the APA developed the DSM-I largely from Medical 203, and was heavily influenced by Menninger who had by then been elected President of the American Psychoanalytical Association before being elected President of the American Psychiatric Association.

The emphasis placed on the concept of mental disorder as a reaction to adversity struck a responsive chord in the spread of psychodynamic thinking within psychiatry, and led to the formation of the National Institute of Mental Health in 1949 and the Veterans Administration both of which poured training funds into the training of psychiatrists. Between 1948 and 1962, NIMH training increased nearly 50-fold, from $1.1 million to $38.6 million, while research grants increased nearly 150 fold, from less that $0.5 million to more than $40 million.

These psychodynamic influences held sway throughout the 1960's despite the emergence of the new therapeutic medications, which the psychodynamicists, that then included virtually all academic departments of psychiatry, found quite threatening and generally discounted. The number of hours in the curriculum devoted to psychiatry also quadrupled between 1940 and 1969. Virtually every department of psychiatry was aligned with the psychodynamic perspective (as contrasted with the descriptive or organic). DSM-II, retained this perspective when it was published in 1968, the same year that the ACNP published its first comprehensive assessment of the achievements and needs of the field of neuropsychopharmacology to reveal the gaps in knowledge that future work might fill.

A Second Transition in Diagnostic Perspective

However, well before 1968, two groups of psychiatric researchers, one at Washington University in St. Louis and one at the New York Psychiatric Institute began to promulgate a psychiatric diagnostic nomenclature designed to set boundaries for the major clinical conditions that began to usher in a new medical model, or 'Neo-Kraepelinian' perspective. They were motivated to improve the reliability of diagnostic categories and establish their natural history, allow for an objective differential diagnosis and epidemiology, although there was no stated application to the assessment of psychopharmacological agents. This shift in perspective expanded in the early 1970's, and resulted in the Research Diagnostic Criteria (RDC) for 15 major categories of mental disorder. The RDC served with refinement as the basis for a major part of the DSM-III, which then led to the virtually complete erosion of the psychoanalytical-personality from the psychiatric nomenclature. This second transition within psychiatry serves as the background against which the scientific growth of neuropsychopharmacology flourished over the past 4 decades. Let us now examine the growth and evolution of this science.



Eli Robbins

Jean Endicott

Emergence of the Neurosciences Underlying Neuropsychopharmacology

When the Society for Neuroscience was founded in 1971, three years after the ACNP's first Review of Progress in Psychopharmacology, there was a recognized need to accelerate progress by breaking

down the technical and investigative partitions between the chemistry, anatomy and physiology of the brain, and in no endeavor was this more constructive than in neuropsychopharmacology. Several questions were of immediate concern-- how many other synapses outside of the motoneuron-Renshaw Cell system were chemically operated, what were the neurotransmitters that operated there, and could the actions of the existing psychopharmacological agents be explained in terms of discrete effects on specific synaptic systems?

Rules for identifying a specific chemical agent as 'the' transmitter for a given synapse had been applied to the autonomic nervous system to establish that acetylcholine was the transmitter for nicotinic junctions at the neuromuscular junction; that within autonomic ganglia, muscarinic junctions at parasympathetic terminals were also mediated by acetylcholine; and that norepinephrine was the transmitter for post-ganglionic sympathetic nerves on the their smooth muscle and glandular targets. However, the complicated anatomy of the brain made detection of synaptic release virtually impossible given the methods then available, even if one knew which tracts to stimulate to evoke release.

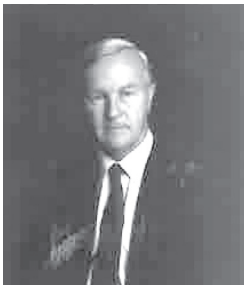
Microiontophoresis, using multiple capillary pipets fused to an extracellular recording electrode allowed for a glimpse at whether neurons were responsive to any of the 'putative' neurotransmitters that initial biochemistry detected in abundance in the brain besides acetylcholine and norepinephrine, namely serotonin, dopamine, histamine, and the as yet chemically uncharacterized "Substance P". Gamma-amino butyrate (GABA), which Roberts had found to be uniquely expressed in brain did not receive serious attention as a mammalian transmitter until it was shown to be the transmitter for a lobster nerve in 1967. Despite a mountain of published observations on various putative transmitters in various regions of the brains in numerous experimental conditions, the results were not definitive for any transmitter in any given region or synaptic circuit.

Biochemically, tritium-labeled monoamines were shown to be accumulated first by peripheral autonomic nerve terminals, a property confirmed by ultrastructural autoradiography. However, the electron microscopic evidence for small dense core vesicles in the brain as seen in the same peripheral sympathetic nerve terminals proved elusive. Nevertheless, the accumulation of H^3-norepinephrine and serotonin after intraventricular injection soon established this previously unforeseen property of monoamine neurons, an active re-uptake mechanism, and -- importantly--a property that tricyclic antidepressant drugs could selectively block. Using the methods of differential centrifugation by which cell biologists had been able to separate the main organelles of liver and pancreas, it was determined that the putative transmitters norepinephrine, dopamine, serotonin, and histamine resided in fractions of brain homogenates enriched in synaptic vesicles while the evidence for acetylcholine in this fraction was initially more contentious.

Neurotransmitter Discovery and Mapping

The early 1960's saw the evolution of the first biochemically characterized histochemical method, the condensation of formaldehyde vapor with norepinephrine, dopamine and serotonin led to the unique fluorescent end-products by which these substances could be mapped to cell bodies and axons in freeze dried materials. At last it could be determined where the terminal fields of catecholamine axons were located, and the effects of norepinephrine in cerebellum and hippocampus, and of dopamine in the striatum strengthened their establishment as neurotransmitters. The severe reduction of dopamine content in the striatum of patients dying with the diagnosis of

Parkinson's Disease led to the first attempts to treat this disease with the established precursor of dopamine, L-dihydroxy-phenylalanine (L-DOPA); these early therapeutic attempts were, unfortunately, unsuccessful.



Les Iversen

Neurophysiological observations indicated that the effects of monoamines on their presumptive synaptic target neurons did not fit the then standard expectations of the nicotinic excitatory transmitter or the eventual properties of GABA and glycine which had received support for inhibitory transmitters in the spinal cord. The catecholamine responses were contextual, speeding some responsive neurons and slowing others. The case for the inhibitory amino acid transmitters were strengthened further when strychnine was found to selectively antagonize glycine mediated responses, and picrotoxin and bicuculline blocked GABA responses.

Evidence then emerged that at some sites, the catecholamines acted at their receptors to stimulate the synthesis of cyclic adenosine monophosphate (cAMP), and that the amine actions could be augmented in the presence of a phosphodiesterase inhibitor, indicating that the post-synaptic response involved formation of an intracellular second messenger. Staining for the acetylcholine catabolic enzyme, cholinesterase was less clear cut, but terminal fields in the hippocampal formation suggested that responses of pyramidal neurons here could be either nicotinic or muscarinic. As the categories for neurotransmitter responses became sub-divisible for the catecholamines, alpha adrenergic receptors and dopamine D2 receptors were found to inhibit synthesis of cAMP, suggesting some basis for the diversity seen in post-synaptic responses.

A major transition in electrophysiological neuropharmacology emerged with the development of the brain slice technology in the late 1970's. No longer was it necessary to perform cellular level studies in anesthetized animals, and the brain circuitry worked out through elegant mapping methods of anterograde and retrograde tracers allowed for the activation under visual control of specific circuits in slices of hippocampus or neocortex, and long-lasting plastic changes in synaptic physiology that have bridged cellular events to behavioral phenomena, such as presumptive memory. Neurons in such slices could also be probed with still finer electrodes to isolate ion channels and receptors and determine drug events occurring presynaptically on the vesicle-transmitter release process, or post-synaptically on the receptor.

The 1970's introduced further tools for transmitter identification including selective toxins for catecholamine circuits, and others for 5-HT circuits, enhanced ability to obtain fluorescent mapping data on non-freeze dried, vibratome sections of partially fixed brains, and the development of antibody localizations directed against synthetic enzymes in the case of acetylcholine and the monoamines, as well as the enzyme dopamine-β-hydroxylase to distinguish fibers containing norepinephrine from dopamine. The development of immunocytochemical mapping coincided nicely with the chemical identification of families of neuropeptides.

A Focus on Transmitter Discovery

To place the discovery of the neuropeptides into a more general perspective deserves a brief digression that illuminates the whole transmitter discovery process. As the list of consensus transmitters grew, two strategies of discovery were shown to be successful: either the chemical factor was discovered 1) before or 2) after the biological actions for which it is now recognized. In the "factor first-function later" strategy are substances that bear mainly chemical names: acetylcholine,

gamma-amino butyrate, dopamine, glutamate, aspartate, glycine or taurine. They earned chemical names because it was their chemical structure for which they were exclusively identified as biological products, without functional inferences.

In the "assay first-factor later" strategy, the development of a bio-assay for an unknown regulatory factor became the starting point for a purification-isolation process. This was the classical approach of Starling and the early gastro-intestinal regulatory peptides, for insulin and glucagon, and for the "sympathin" era of Cannon and colleagues. All of the peptidic messengers resulting from this approach carry functional names rather than chemical names: gastrin, cholecystokinin, substance P, angiotensin, oxytocin, vasopressin, as well as more conventional small molecules like the biogenic amines, adrenaline, histamine, serotonin-- also identified as 5-hydroxytryptamine-- and the prostaglandins; one could include in the latter group the intercellular signaling peptides found in the immune system, the chemokines and cytokines.

Sol Snyder

This methodology reached its zenith under the skilled prodding of Guillemin, Schally, McCann and others who pushed their colleagues to identify the hypophysiotrophic factors conceived by Geoffery Harris in the mid-1940's and early 1950's, requiring the development of sensitive new methods for peptide isolation, purification, and sequence analysis, as well as very large amounts of freshly dissected cattle brains. From this effort came the "assay first", functional names for thyrotropin-releasing hormone, somatostatin, gonadotropin-releasing hormone, and prolactin, and including the last two of the originally postulated hypophysiotrophic factors, corticotropin-releasing factor and growth hormone releasing factor. The identification of the corticotropin releasing factor was molecular completion of the final circuit by which the brain controls the response to stress. That finding established the brain as the master regulator of the endocrine system, and an inroads into the intricacies of 'stress' in normal and dysfunctional brains. Corticotropin Releasing factor was also a key insight into the study of neuroendocrine regulation in brain disease. Furthermore, this neo-classical approach (isolation, purification, chemical characterization) proved its value time and time again as others used the methods to isolate factors based on rather unpredictable assays: the loss of blood pressure that produced neurotensin, the gut vascular effects that lead to vasoactive intestinal polypeptide and gastric inhibitory peptide, and the opiate-like effects in *in vitro* assays that produced the opioid peptides.

The discovery of the opioid peptides deserves more attention because it represented a major development in the search for new neurotransmitters. While the ability of opiate drugs to treat pain and produce dependence had been recognized since the great wars of the 19th century, very few investigators had considered the question of how the drug worked and what receptivity to such a powerful medication might imply. The identification of stereoselective binding sites for opiate antagonists motivated some to ask whether the site of opiate action might represent the receptor for an as yet unknown transmitter, much in the way that the alkaloid nicotine acted through the receptor for acetylcholine. Although an endogenous opiate transmitter was once unimaginable, Liebeskind and colleagues had demonstrated convincingly that there were endogenous systems using unknown transmitters that could regulate responses to painful stimuli. The eventual confirmation that at least three gene families could produce opioid peptides confirmed the value of this line of thinking and unquestionably helped fuel the search for the natural

ligands whose receptors provided the molecular receptors for the benzodiazepines and for the endogenous cannabinoids (or endocannabinoids).

That glimpse aside, the 1970's were also epitomized by attempts to map the distribution of neurotransmitter receptors using ligand binding autoradiography, a molecular approach soon outmoded by the development of methods to isolate, purify, and sequence the receptors themselves, allowing for the development of synthetic peptide fragments against which receptor mapping antibodies could then be developed and applied, and through which new agonists and antagonists could be synthesized. The successes with the receptors for the nicotinic cholinergic receptor, the glycine receptor and the GABA receptor was followed by similar structural information for three types of glutamatergic receptors, all of which fit the generic picture of receptors that were also ion channels, and whose transmembrane structure adapted to binding of their endogenous ligands by increasing selectively the flow of ions into or out of the neuron.

Molecular Biology Meets Neuropsychopharmacology

As we entered the 1980's, another new approach to neurotransmitter identification and peptide family completion emerged This second new approach is based on the central dogma of molecular biology - all peptides are synthesized under the direction of a specific messenger RNA (mRNA) encoded by the gene for that peptide. With the emergence of recombinant DNA technologies, it became possible to determine the amino acid sequence of the single pro-hormone that could yield, depending on the cell type in which it was expressed, either β-lipoprotein, and its end product, β-endorphin, or the adrenocorticotropin hormone (ACTH). When that pro-hormone sequence was completed, it was found to contain an unanticipated third biologically relevant peptide, deduced solely from the mRNA sequence on the basis of its structural analogy to alpha and beta melanocyte-stimulating hormone (MSH). Subsequently, the recombinant DNA approach was employed to obtain the pro-hormone structural sequences, and some of the genomic sequences for almost every one of the previously identified neuropeptides of the endorphin family, somatostatin, VIP, Neuropeptide Y, oxytocin, vasopressin, corticotropin-releasing factor, growth hormone-releasing factor, substance P, cholecystokinin, and gonadotropin- releasing hormone. Moreover, pursuit of the pro-hormone for calcitonin, led Rosenfeld and Evans and their collaborators to the recognition that rearrangements of parts of the mRNA domains of the pro-calcitonin, could give rise to a "calcitonin-gene related peptide" which in fact was found in special segments of the rat CNS and had unsuspected biological activity.

A somewhat modified approach seeking genes expressed in hypothalamus but not elsewhere in the brain identified hypocretin (also called orexin for one of its functional properties) as a hypothalamic member of the secretin family, whose functions include not only appetite, but also sleep, and blood pressure regulation. Mutations of this peptide or its receptor have been found in heritable forms of narcolepsy. Peptide sequencing was accelerated when mass spectrometry advanced to the point of peptide fragment identification, reducing the amounts of material required to determine a complete sequence, and allowing quantitation of non-peptidic brain agents such as the endocannabinoids, other fatty acid amides, and the retinoic acids.

Aside from the discovery of new potential signaling agents in the brain, the continued evolution of molecular biological technology has provided neuropsychopharmacology (as well as the broader neurosciences) additional tools. Among them are the ability to create transgenic mice expressing the apparently etiologic mutated genes of heritable

neurological diseases. These mouse models of human brain disease have provided a means to develop medications that are already undergoing late phase clinical trials in Alzheimer's Disease, Parkinson's Disease and Huntington's Disease. The same molecular discovery tools that identified multiple molecular partners of the transmitter receptor proteins clustered at synaptic junctions, have also identified down stream regulators of G-protein receptor function and their ultimate ionic mediators. These newly discovered proteins represent opportunities for new forms of therapeutic interventions, although as of yet, these have yet to appear. The mouse transgenic models have already provided for means to control. both spatially and temporally, the genes associated with disease vulnerability, as well as the means to identify and activate the pathways in which selected receptors or mediators are expressed.

Brain Imaging Joins Neuropsychopharmacology

A very major part of the evolution of neuropsychopharmacology in the past decade has been the simultaneous rise in brain imaging with functional magnetic resonance imaging revealing cortical networks of clustered locations that on a several second time span seem to be co-active. Such analyses have revealed systems linked functionally to different qualities of sensory, motor, and cognitive functions, including a default mode network that is active when the brain is not actively engaged in inspection of the external or internal world. These functional connectivity paradigms offer, for the first time, the ability to search for abnormalities of circuit function as well as abnormalities of spatially defined brain regional volumes in the brains of patients with neurologic or psychiatric diagnoses, and may find its greatest utility initially in those families with highly heritable forms of disease vulnerability. For example, the default mode network correlates with the cortical regions of the highest glucose utilization, and also with those regions that are most vulnerable to the pathophysiology of Alzheimer's Disease.

As with all new methodologies, one can raise questions about the analysis of functional connectivity MRI in which all brains analyzed are spatially transformed to a consensus 3-dimensional atlas. Such transformations blur inter-individual differences in brain shapes and other properties but define commonalities across large populations of subjects and imaging centers. Yet for neuropsychopharmacology those very inter-individual differences may be a major part of metal illness or the vulnerability to mental illness. Variations such as cortical folding patterns, the almost certain variability in the location of functional cortical areas relative to these surface folds, the unknown relationship between the boundaries of cortical areas defined by cellular architectonics and gyral/sulcal landmarks could be critical variables. Furthermore, the inter-individual variations in the size of cortical areas defined by function or cytology, and the consequential variations in the degree to which these areas may be interconnected, must all be dependent on physical activity, age, gender and other factors yet to be resolved, including life experiences. The latter factor may, in fact, offer a biological base for psychotherapeutic intervention. Presumably these issues will begin to be resolved by the recently announced NIH sponsored Human Connectome Project.

The Gaps Neuropsychopharmacology Now Faces

Taking all these developments together, it is my view that we must begin to rise above the level of individual molecules that transmit information from one neuron to another and look for attributes of the behavioral function of those chemically identifiable brain systems. Such higher level functions and

then paths to achieve them have already been formulated for the 2 brain systems which presently seem the most likely substrates for the actions of anti-psychotic and anti-depressant drugs. Thus, in the last decade we have seen the demonstration that the post-synaptic actions of specific dopaminergic and noradrenergic neuronal circuits can be linked to the behavioral repertoire of the firing patterns of the source neurons of these circuits, and to the formulation of more profound system explanations for what such circuits do in the healthy brain and how loss of these functional properties may lead to emotional and cognitive dysfunctions.

The questions of when do the catecholamine neurons fire, and what functions do the catecholamines released at these synapses perform have been under study for more than three decades, but have recently become relevant to clinical neuroscientists. The nigro-striatal and meso-limbic dopaminergic systems and the coeruleo-cortical noradrenergic systems were once quite controversial pathways to study physiologically because there were no prior strategies for defining the functions of neurochemically identified pathways. As noted above, the body of physiological data that was produced indicated that catecholamine neuron systems had properties that differed dramatically from those of "classical" central systems that were either excitatory or inhibitory. Moreover, further mapping of these systems demonstrated that the distributions of these aminergic afferent systems were far more complex and regionally selective in the primate brain than in the rodent brains where they were first studied in depth.

Similarly, subsequent studies suggest that DA neuronal firing is not 'simply' a signal that a reward to a behavioral response has been generated, but rather that the fluctuating output (tonic or phasic discharge patterns) of the primate DA neuron signals changes or errors in the predictions of future salient and rewarding events.

Recent observations on cellular synaptic actions in the mouse striatum, profiting from years of tract-tracing and transmitter receptor localizations in both primate and rodent brains, led to the recognition that the output circuitry of the caudate consists of two principle pathways, a striato-nigral projection to the substantia nigra and entopeduncular nucleus (referred to as the external pathway), and a striato-pallidal to the globus pallidus (referred to as the internal pathway). Although all striatal medium spiny neurons are GABA-containing, their associated neuropeptides and dopamine receptor subtype differ depending on which output pathway to which they are localized: by immunocytochemistry and in situ hybridization, the striato-nigral neurons express the neuropeptides Substance P and dynorphin, as well as the D1 receptor, while the striato-pallidal neurons express pro-enkephalin and the D2 receptor.

By developing transgenic mice in which the expression of D1 or D2 receptors was molecularly reported by the co-expression of green fluorescent protein, it was possible for Surmeier and colleagues to investigate 2 forms of striatal synaptic plasticity, long term potentiation (LTP) and long term depression (LTD). To greatly simplify a complex experimental protocol, these investigators observed that D2-expressing neurons could express either LTP or LTD according to the stimulation sequences, and that D2, but not D1, antagonists could block both potentiations. These observations indicate that DA 'is critical for the induction of the plasticity' acting in concert with GLU, adenosine, and activity in the external world. In conditions in which there are few if any behaviorally interesting stimuli, DA neurons fire slowly to keep high affinity D2 receptors activated, but not activating the lower affinity D1 receptors; when DA neurons fire in bursts, raising extracellular DA levels briefly, the lower affinity D1 receptors activate. Thus, the direction of the plasticity shaped by the same transmitter under different conditions has distinct

but consistent modulatory effects. Do these insights offer opportunities to anticipate how anti-psychotic drugs can be therapeutic for some patients with schizophrenia, but not all?

Similar investigations of the primate noradrenergic system have led to similar, and more profound functional insights. When the discharge patterns of LC neurons were recorded in freely behaving rats and monkeys, LC neurons exhibited a more general and subtle pattern of activity: a slow, tonic, basal discharge rate, but with brief phasic responses to novel sensory stimuli of all kinds—visual, auditory, somato-sensory and gustatory. Furthermore, these neurons showed an interesting correlation between neuronal firing rate and wakefulness, with progressive diminution of already slow basal activity as the animals engagement with its environment decreased, and complete silencing of activity as the animal entered rapid eye movement sleep.

Aston-Jones and Cohen have taken these observations to a further refined interpretation with an integrative theory of locus coeruleus-norepinephrine function, that they term 'adaptive gain and optimal performance' invoking a more complex and specific role in the control of behavior than was previously thought. In their view, phasic LC activation is driven by the outcome of task-related decision processes and is proposed to facilitate ensuing behaviors and to help optimize task performance (exploitation). The slow tonic rates of discharge would be expected to activate high affinity alpha receptors, while the phasic discharge would be expected to activate lower affinity beta receptors. Do these observations suggest insights into the psychobiological basis of depression and how it is possible for antidepressant medications to improve the emotional status of some, but not all, depressed patients? It is perplexing that similar spatial,functional and behavioral information has not yet been reported for the serotonin and acetylcholine neuronal circuits. It is also frustrating that more than 30 years after Hökfelt and colleagues first reported that neuropeptides were present in neurons already characterized as having an amino acid or amine transmitter that we do not understand how these signaling systems work together at their central synapses and whether the functional importance of co-existing transmitters is implemented pre-synaptically or post-synaptically, or is frequency of activity-dependent as in the autonomic nervous system.

The past decade has also seen studies by several US and French-based investigators establish the validity of animal models of drug addiction, and the discrete chemically defined circuits that underlie the major forms of drug dependence. These animal studies have established a basis for therapeutic agents (methadone, buprenorphine, naltrexone, acamprosate, and varenicline) that have been shown to reduce the burdens of addiction and that have been approved by the FDA for this purpose (see box on page 58). The pioneers in the field of addiction therapy, Dole and Nyswander had in the mid-60's proposed the treatment of opiate addicts with a long acting oral morphine substitute on the premise that addicts were deficient in some substance that could be compensated for by an opiate. They would perhaps be surprised at the success of longer lasting opiate antagonists in the treatment of alcoholism, a disorder that many do not recognize as medically treatable. Of very recent appearance are the elements of this field that have demonstrated that when neurons in regions critical for drug dependence adapt to their imposed chronic drug administration, (either self-administered or passively received), the adaptive activity emerges not only from changes in the genes expressed and proteins synthesized in those neurons, but in the manifestations of those proteins in terms of clusters of receptors, recycling of synaptic vesicles, and even the shape and temporal profiles of dendritic spines, all of which changes load the critical circuits for

pathological activity. Of great surprise to me has been the elegant quantitative studies on the plasticity of dendritic spines in hippocampal formation and cortex and the ability to relate these changes to parameters of synaptic efficiency and timing. The recent example from the neuroscience of substance abuse clearly documents the dynamic alterations in the molecular basis for dendritic spine morphologies during drug dependence and withdrawal.

One last development, still in its early days of application to our field is the extremely high throughput analytical capacity to examine the non-protein coding parts of the genome, the intronic segments, once ignored, that now seem capable of regulating networks of genes in either their transcriptional or translational steps, and may well obviate most of the presently recognized clues to vulnerability or resilience to mental disease.

All these tools, including newer ways to visualize and control circuits on the basis of gene expression manipulations such as optogenetics, BrainBows and those tools not yet known may help us at last answer the original questions posed by our founders and their drug development colleagues:

• beyond their molecular effects on receptors and transporters,how do antipsychotics and anti-depressants achieve their therapeutic results?

• what is the mechanism by which lithium treats not only the mania of bipolar disease but also reduces the frequency of the depressive episodes?

• what is different about the diseased patients who do not respond to these medications?

• how many molecular and cellular pathways are there to these symptomatic diagnostic end-points?

• how essential is genetic vulnerability to psychosis, addiction, or stress induced dysfunction, and is there a definable basis for resilience to these conditions?

• how can we at least learn enough about the pathophysiological mechanisms of these brain diseases to devise more effective medications or prevent their onset or recurrence?

These are the substantial questions that the College may be able to answer in its second 50 years.

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50 Years of Clinical Therapeutics in Neuropsychopharmacology

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The masterful chronology of ACNP-relevant trends and discoveries in neuroscience, written, as it could only be, by Floyd Bloom, details disease-related "scientific evolutions in our preclinical and clinical research" over the last 50 years. The history of Psychiatry as a discipline, its structured diagnoses, and the emerging biology of its diseases, puts the youthfulness of the field into perspective. Dr Bloom's review reminds us of the critical role of basic neuroscience in the discovery of treatments for human brain diseases, where a rational approach to drug discovery relies on mechanistic targets, something we have not had enough of in psychiatric disease. The task of linking the molecular targets in human brain systems with their behavioral functions, then with the manifestations of psychiatric syndromes and their treatments, is the modern goal of disease-oriented research as it was envisioned by ACNP founders, albeit increasingly complex. Most of the therapeutic agents discovered for psychiatric diseases,

have been serendipitous *and* highly influential, as only first-in-kind treatments can be. Dr Bloom identifies a poignant reason in 1960 that the founders of the ACNP formed the College: founders "were motivated by an anticipated onslaught of more new medications for the treatment of serious psychiatric diseases." It is, therefore, timely to look specifically at what new clinical advances in treatments and disease understanding that have emerged over the last 50 years.

It was everyone's hope that the anticipation of an onslaught of new medications—ie, of categorically new medication—would have been as vast as the ACNP quotation implied. While we have many new medications, the true categorical advances have been more modest, but striking when they have occurred and these have increasingly brought psychopharmacology to the attention of our medical colleagues and to the public. One of the most influential and popular of these new medication families, based on tricyclic antidepressant efficacy, was the selective serotonin/norepinephrine reuptake inhibitors (SSRIs, SNRIs), introduced by fluoxetine in 1987. The SSRI/SNRIs filled some (but not all) of the existing indications for tricyclic antidepressants and had lower side effects with lower toxicity risk in overdose. This allowed the use of SSRIs/SNRIs to spread broadly to mild depression conditions, into children and adolescents and to depression's co-morbid conditions. Many additional SSRIs have been developed with somewhat modified effect- and side-effect profiles but with roughly equal efficacy to fluoxetine. As antidepressants, the MAO inhibitors were effective but always used as secondary treatments; the introduction of reversible MAO inhibitors were novel and useful developments for depression. Although ketamine, the NMDA receptor antagonist used experimentally for depression, cannot be expected to become a treatment option, its characteristic of fast-onset antidepressant action and sustained effect has made it an important scientific probe for discovering a new family of fast-onset antidepressant drugs. We can expect that this observation will be able to guide depression research to new treatment mechanisms.

Likewise, benzodiazepines were launched into clinical practice in 1960s with chlordiazapoxide, a drug which represented the first in a family of antianxiety agents that have been gradually refined. These are still are used as first-line treatments for serious anxiety disorders, most closely represented by generalized anxiety disorder and panic disorders.

Although lithium was discovered prior to ACNP's launch, the discovery of the efficacy of anti-epileptic medications for mood stabilization has been a more recent phenomenon. Depakote was the first in this family of new medications to show a therapeutic action on unstable affect in bipolar disorder and is widely used as well in psychotic disorders where mood instability exists.

For addiction treatment, the introduction of buprenorphen for opiate addiction, varenicline for smoking and naltrexone for alcohol addiction, pioneered the subsequent application of these addiction drugs to other addictive disorders, with significant therapeutic advantage. This strategy of testing a therapeutic agent in similar addictive disorders, once efficacy is demonstrated in one, has supported the more speculative idea that rewards of all kinds, not only drugs of abuse, but also food, sex and gambling, can be addictive in excess and these addictions can be treated dimensionally, with similar medications. The rise and fall of rimonabant, the CB1 antagonist rationally indicated for smoking and obesity, illustrates the grave difficulties of CNS drug development.

The treatment of diseases in children became easier as safer medications became available for

depression, bipolar disorder and even schizophrenia. Attention deficit hyperactivity disorder (ADHD) has emerged as a diagnosis characterized by its positive response to stimulant treatments, beginning with methylphenidate. While many criticize excesses in treatment, especially in the area of childhood disorders, it would be hard to underestimate the benefits of ADHD treatment to affected children.

Antipsychotic medications were introduced and already in broad use when ACNP formed, and indeed, were partially responsible for the optimism around pharmacological treatments in psychiatric illness. Clozapine was identified as a uniquely effective antipsychotic, an action widely discussed but not understood even today. While the marketed antipsychotic treatments of today remain within the same family of anti-dopaminergic medications, there are novel approaches in development, including an mGluR2/3 agonist and candidates for cognition enhancement in schizophrenia.

Neurodegenerative diseases, including the dementias, demand treatments which will modify cell loss and these approaches have eluded us. Nonetheless, symptomatic treatments which enhance acetylcholine function, rationally developed based on known cholinergic degeneration in Alzheimer's disease, do provide disease benefit even without remission. Early approaches tested cholinergic agonists but found acetylcholinesterase inhibitors to have greater efficacy. While these acetylcholine enhancing medications have sufficient potency to increase cognition to a significant degree in dementia, they have not been potent enough for cognition enhancement in other diseases.

The exponential growth in the diagnosis of autism, which is thought to reflect both a phenomenon of diagnostic substitution and development of new cases, has not experienced a parallel growth in treatment options for the primary symptoms of the illness. Nonetheless, treatments for the co-morbidities of autism, including treatments for OCD (eg, clomipramine), ADHD (eg, clonidine and atomoxetine) and epilepsy (ie, mood stabilizing anticonvulsants) provide significant benefit to children and adults with autism.

The driving technologies for developing novel treatments for human brain diseases, are grounded in basic neuroscience discovery and aim to define functional brain systems for normal behaviors and the mechanisms within which pathology can occur along with animal models to develop drugs for those dysfunctions. The explosive growth in clinical and basic genetics will surely be the basis for disease and treatment advances in the near future. In addition, modern clinical therapeutics utilizes evolving technologies in clinical diagnosis, trial design, and novel approaches for determining drug action in human brain. Methodologies to more precisely assess drug action on neural systems include human brain imaging techniques for drug occupancy at target proteins, to measure drug actions on cerebral transmitter systems like glutamate, GABA and dopamine, and functional imaging to demonstrate predicted effects of drug treatment on brain function. It is not inconceivable that gene therapy will provide an avenue for ameliorating symptom manifestations in treatment-resistant conditions in the future, a technique even more strongly dependent on defining molecular targets in human brain diseases. Progress is evident; tools for discovery exist; the field is even better poised now than 50 years ago to take advantage of new cellular and molecular mechanisms for brain diseases with the goal of generating truly rational therapeutics.

Fifty Years of Clinical Research in Neuropsychopharmacology

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In parallel with advances in neuroscience and preclinical neuropsychopharmacology, a dramatic evolution in the design, conduct and interpretation of clinical trials has also taken place. In addition, advances in ethics, computer science, information technology, telecommunications and the development of the internet have all contributed to modern-day clinical research in ways that could never have been imagined 50 years ago.

Developments in nosology and epidemiology have played critical roles in clinical research. A DSM was first published in 1952, but it was not until the Research Diagnostic Criteria in 1978 and DSM III in 1980 and a variety of structured diagnostic interviews (e.g. The Schedule for Affective Disorders and Schizophrenia) that a rigorous effort was made to achieve both validity and reliability to the extent possible. Differences between the US and UK in epidemiology and ultimately diagnostic prevalence contributed to the enhancement of these efforts.

The development of rating scales, which could be administered by trained clinicians with demonstrated inter-rater reliability, became another principle on which trial methodology was based. In addition, patient self-report and informant observations have become an important component of assessment in some trials.

The field continues to struggle with diagnostic validity as etiology and pathophysiology remain poorly understood and objective tests to confirm clinical diagnostic perspectives remain few and far between. As a result, debate continues about relative under – and over-diagnosis of some conditions amid accusations of the overmedication of emotional and behavioral problems.

This debate has been particularly fierce in the area of child and adolescent psychiatry. Despite growing recognition that many serious psychiatric disorders of adulthood begin before age 18 and that pediatric onset disorders are often more severe and less treatment responsive, the diagnosis of psychiatric disorders and prescription of psychotropic medications in the vulnerable pediatric population has been highly controversial. Concerns have focused on the prescription of psychostimulants for youth with attention deficit-hyperactivity disorder, the limited effects of antidepressants in RCTs in youth, the increased diagnosis of autism spectrum disorder

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conditions and of bipolar disorder in youth with chronic mood instability, and on the sharp rise in antipsychotic prescriptions in children and adolescents, mostly for non-psychotic, aggressive spectrum disorders and often without adequate provision of non-pharmacologic treatments. The NIMH responded to this situation with the funding of several trials that compared stimulants or antidepressants with a psychosocial intervention, the combination of medication and the psychosocial intervention and pill-placebo or usual care. Together, these trials showed that combination treatment and medication treatment alone were superior to the psychosocial intervention and to pill placebo or usual care, with some advantages in the combination therapy group. Moreover, responding to the Children's Mental Health Parity Act in 2007, the FDA incentivized pharmaceutical companies to conduct pediatric studies with select drugs by granting a 6-month patent extension for adequate safety data in at least 100 youth followed for 6 months. This initiative has contributed to a substantial and much needed increase in the placebo-controlled efficacy data base in youth combined with medium-term, open label extension studies contributing important safety and tolerability data. Additionally, companies studying new drugs with a likelihood of use in the pediatric population have recently been required to conduct pediatric trials either prior to FDA approval or as a part of a post-approval commitment. Nevertheless, despite this progress, longer-term studies that assess the developmental effects of psychotropic medications are still needed.

Because of the enormous body of clinical trial data in neuropsychopharmacology, we have been able to establish the efficacy and effectiveness for many psychotropic medications, which compare favorably with routine treatments for many major medical illnesses. Beyond the simple lists of symptoms and behaviors that currently constitute the diagnostic paradigm, a great deal of effort has gone into finding biomarkers (including genetic parameters) that could define more homogeneous subtypes that, in turn, could lead to personalized treatments. Peripheral markers, structural and functional neuroimaging findings, and, of course, genetics and pharmacogenomics have been advancing at a rapid pace, but are not yet developed enough for routine application in clinical trials, let alone clinical practice. Current efforts, such as the Research Domain Criteria (RDoCS) initiative, spearheaded by the NIMH, are attempts to tie nosology more closely to potential pathophysiologic mechanisms, but will require years of concerted effort by many groups of investigators.

It is also important to recognize that a more systematic and long-term assessment of adverse effects has also played a critical role in the evolution of both trial design and regulatory requirements. Adverse effects, such as tardive dyskinesia or diabetes and stroke and cardiovascular illness or death, are relatively infrequent or evolve over long periods of time and serve as examples for pharmacovigilence. Concerns about Qt prolongation and its potential consequences have led to the largest randomized pragmatic trials ever conducted in psychiatric populations (18,000 subjects).

The design and analysis of trials in psychopharmacology has progressed appreciably over six decades. The initial trials were small, uncontrolled case series that used non-standardized clinical observation as outcomes. Cade's 1949 lithium case series involved just 10 patients. Three years later the initial

chlorpromazine series included 20 patients. Kuhn reported on an open case series of 40 patients in the first evaluation of imipramine in depression.

Randomized controlled trials were introduced into psychopharmacology through crossover designs, which became popular in the 1950s and 1960s. The first controlled study of lithium involved a crossover trial with placebo. Similarly, the initial placebo-controlled trial of chlorpromazine was a crossover study. Although this design provided comparison data, carryover effects and uncertainty as to time course of response and exacerbation created problems in study implementation and interpretation.

The Kefauver Harris Amendments to Federal Food, Drug, and Cosmetic Act was passed by Congress in 1962. This Congressional act had a profound influence on clinical trial methodology in psychopharmacology. For instance, it required a manufacturer to provide substantial evidence of effectiveness from adequate and well-controlled studies. It also strengthened the safety of available medications by requiring FDA approval before marketing of a drug. Furthermore, Kefauver Harris required that informed consent be obtained from all human research subjects in trials that are submitted in applications to the FDA.

There was remarkable progress in clinical trial design, assessment, and statistical analyses during the decades following Kefauver Harris. Double-blinding and placebo controls became the norm and standardized instruments were developed. The randomized withdrawal design was used in 1970s to examine maintenance therapies for schizophrenia, recurrent depression and mania. In the 1980s and 1990s, the randomized double-blind parallel group, placebo-controlled clinical trial became the standard design for psychopharmacology and was used to support numerous regulatory approvals of antidepressants, antipsychotics, and anticonvulsants. Fixed-dose trials gained more popularity during this period.

RCTs in psychopharmacology that are conducted for regulatory submission tend to have strict inclusion and exclusion criteria and, as a consequence, their results are not applicable to many patients with mental disorders. They are generally considered to be efficacy or explanatory in nature. To deal with these inherent limitations, there has been an effort to conduct more pragmatic (effectiveness) trials, which seek to evaluate interventions in real world settings. In the 1990s NIMH initiated support for several pragmatic trials that had more broadly generalizable samples and involved longer periods of treatment than had been seen in previous studies. These included two large, comparative effectiveness trials: Sequenced Treatment Alternatives to Relieve Depression (STAR*D) and Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) for schizophrenia. These trials also reinforced the appreciation of the potential pitfalls of any single trial design and highlighted the differences between methods necessary to test superiority and non-inferiority. STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) another NIMH initiative included over 4,000 outpatient participants treated for up to 2 years using open treatment to assess outcomes and with embedded randomized trials to address specific questions.

Statistical techniques used in psychopharmacology in the 1950s and 1960s included t-tests, chi-square tests, and analysis of covariance. These were acceptable when trials were limited to chronically ill inpatients who seldom terminated from trials prematurely. However as trials expanded to the outpatient

realm, none of these approaches sufficiently adapted to the ubiquitous problem of attrition, which introduces bias and decreases statistical power, precision, and generalizability. The principle of intention to treat was described in 1961 by A. Bradford Hill, a clinical trials pioneer, as including all randomized participants in the analyses, not just those who adhere to treatment. Last observation carried forward (LOCF) was first used in the 1950s and 1960s as a method of imputing missing values. However, LOCF assumes that a participant's rating would not have changed if he or she had completed the trial. LOCF is not based on statistical theory and does not estimate a population parameter. If an imputation technique is to be used, multiple imputation is more appropriate.

Survival analysis and mixed-effects regression models are data analytic approaches that include participants with incomplete data. Survival analysis, which accounts for censored cases, was initially applied in psychopharmacology for a trial of treatments for mania. Mixed-effects models were employed in psychopharmacology shortly after being introduced in 1982.

Adaptive design trials have seldom been used in psychopharmacology, yet, if implementation is feasible, they have advantages over conventional designs. These multistage trials evaluate accumulating data in real time to modify features of the design. For example, in a dose-finding study, after the initial 15% of planned subjects have completed the study, the least effective dose could be dropped. Decisions to modify design in an ongoing study must be based on pre-specified criteria otherwise the validity and integrity of the trial could be undermined. Equipoise randomization has also been applied in some clinical trials to address issues of patient preference and shared decision-making.

Archival RCT data can serve as a very rich source of information. Meta-analyses, which aggregate such information from multiple trials, can be used for either hypothesis testing or hypothesis generation, but only if assumptions are carefully examined. For example, the recent meta-analyses of antidepressant data resulted in an FDA-mandated boxed warning for suicidality. Nevertheless, meta-analyses need to be evaluated carefully too, as their quality and the validity of their conclusions rest on the selection and caliber of the included studies.

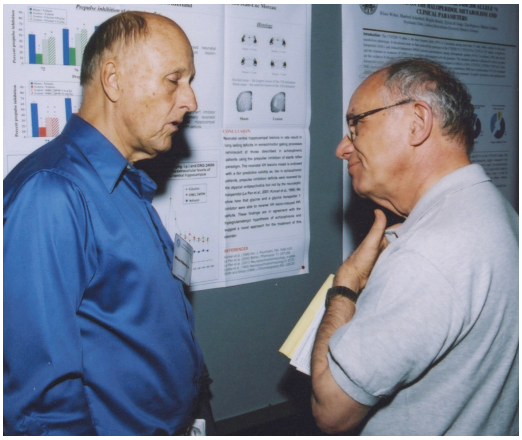
As therapeutic development has advanced over the decades, the field has seen tremendous progress in design and analysis of clinical trials. Many of the advances were motivated by the Kefauver Harris Amendments in 1962. The movement from case series to crossover studies to randomized double-blind parallel group placebo-controlled clinical trials, the adoption of statistical methods that accommodate attrition, and the enhanced assessments procedures have all contributed to the progress in psychopharmacology. The next decades of psychopharmacology research can take advantage of these developments. However, to move the field forward and to forge the way for true personalized medicine in psychiatry, several additional steps are needed. These include the dissection of the underlying biology of specific disorders and of response to treatments, discovery of novel mechanisms of drug action, closer interaction between basic and clinical science to achieve true translation, and more sophisticated efforts at implementing existing evidence into broad based clinical care. All of these developments are currently underway, stimulating hope that the next 50 years will provide at least as many breakthroughs and achievements as did the last 50 years.

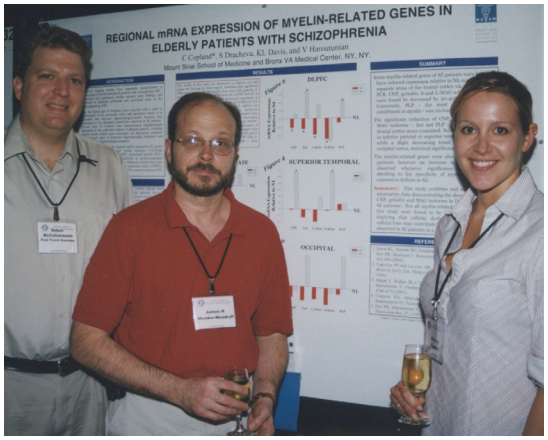

AMERICAN COLLEGE
OF
NEUROPSYCHOPHARMACOLOGY


Caribe Hilton


45
A dopamine


Caribe Hilton




REGIONAL mRNA EXPRESSION OF MYELIN-RELATED GENES IN
ELDERLY PATIENTS WITH SCHIZOPHRENIA
SUMMARY
DLPFC
SUPERIOR TEMPORAL
OCCIPITAL

Paul Hoch Distinguished Service Award

Paul H. Hoch, M.D. (1902-1964) was one of the founding members of the College and played an active role in its early development. He served as President in 1963. Dr. Hoch was an active researcher, teacher, and administrator and served as Commissioner of the New York State Department of Mental Hygiene for many years. At the time of his sudden death he was also Clinical Professor of Psychiatry at the College of Physicians and Surgeons, Columbia University.

In 1964, Council established a committee to develop an award to be given when a Member made unusually significant contributions to the College. The emphasis of the award is on service to the College, not for teaching, clinical, or research accomplishments. In 1965, the award was named for Paul Hoch in recognition of his contributions to the College. The award is given aperiodically, and nominations are solicited each year from the membership for consideration by Council.

The award is presented to the recipient at the Annual Meeting. It is acknowledged by a plaque and monetary award. The following individuals have been honored by the College with the Paul Hoch Distinguished Service Award.

1965	Jonathan O. Cole
1968	Richard Wittenborn
1973	Theodore Rothman
1974	Burtrum C. Schiele
1978	Alberto DiMascio
1980	Leo E. Hollister
1982	Daniel X. Freedman
1983	Oakley Ray
1986	David M. Engelhardt
	Morris A. Lipton
1988	Frank J. Ayd, Jr.
1989	Leonard Cook
1990	Keith F. Killam, Jr.
1991	Donald F. Klein
1993	J. Christian Gillin
1995	Arthur J. Prange, Jr.
1996	Arnold J. Friedhoff
1998	Floyd E. Bloom
	David J. Kupfer
1999	Roger E. Meyer
2000	Herbert Y. Meltzer
2002	Eva King Killam
2003	Thomas Ban
2004	Irwin J. Kopin
2005	Ira D. Glick
2007	Kenneth L. Davis
2008	William T. Carpenter, Jr.
2009	Charles P. O'Brien
2010	Huda Akil

Daniel H. Efron Research Award

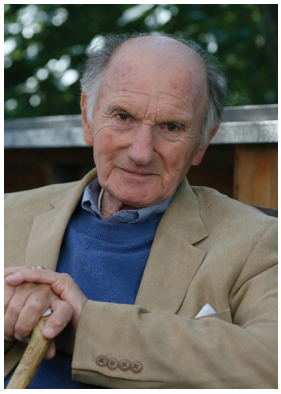
Daniel H. Efron, M.D., Ph.D. was Program Director of the Pharmacology Branch of the Psychopharmacology Service Center from 1964 to 1967. From 1967 to his untimely death in 1972, Danny was Chief of the Pharmacology Section of the Psychopharmacology Research Branch of NIMH. Within NIMH he was a forceful spokesman for all of neuropsychopharmacology and a strong defender of the pursuit of excellence in research. He was a good friend and active supporter of the ACNP. Shortly before his death he was elected Secretary-Treasurer of the College.

In 1974, the College established the Daniel H. Efron Research Award to honor Dr. Efron and recognize his contributions to neuropsychopharmacology. The award is presented by the College to a young investigator who has made distinguished basic/translational research contributions to neuropsychopharmacology. The recipient of the Efron Research Award must be forty-five (45) years of age or younger. He/she does not need to be a member of the ACNP or a citizen of the United States.

The award, given for excellence in basic research, is marked by a plaque and monetary award presented at the ACNP Annual Meeting. The following individuals have been honored by the College with the Daniel H. Efron Research Award.

1974	Solomon Snyder
1975	George Aghajanian
1976	Ross J. Baldessarini
1978	Jack D. Barchas
1979	David J. Kupfer
1980	Herbert Y. Meltzer
1982	Joseph T. Coyle
1983	Benjamin S. Bunney
	Richard J. Wyatt
1984	Michael J. Kuhar
1985	Robert M. Post
	Elliot Richelson
1986	Steven M. Paul
1987	Charles B. Nemeroff
1988	Roland D. Ciaranello
1989	Salvatore J. Enna
1990	Kenneth L. Davis
1991	George F. Koob
1992	Dennis S. Charney
1993	Stephen J. Peroutka
1994	Eric J. Nestler
1996	Peter W. Kalivas
1997	Errol B. De Souza
1998	Robert C. Malenka
1999	Randy D. Blakely
	Anthony A. Grace
2000	Emmanuel Mignot
2002	Bita Moghaddam
2003	David Bredt
2004	Athina Markou
2005	Joseph Buxbaum
2006	David Self
2007	Akira Sawa
2008	William A. Carlezon, Jr.
2009	Antonello Bonci
2010	Karl Deisseroth

Joel Elkes Research Award

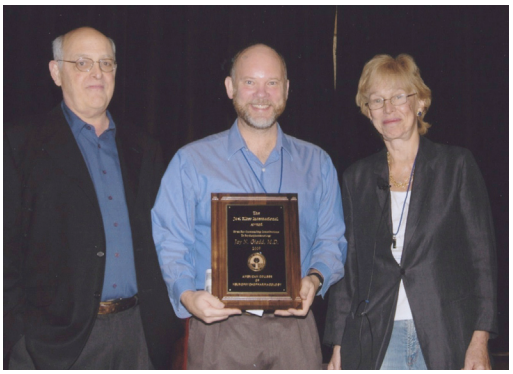


Joel Elkes joined the ACNP in 1961 and is a Founding Member of the College. In 1962 he was elected the ACNP's first President. Between 1946 and 1950, he created a program on "Drugs and the Mind" at the University of Birmingham, England. This program led, in 1951, to the creation of the first Department of Experimental Psychiatry in the world.

The Joel Elkes Research Award was established in 1986, to recognize exceptional clinical/translational contributions to psychopharmacology. The award is given to a young scientist (under 45 years of age) for clinical studies and may mark an empirical advance or a theoretical construct, based on laboratory findings. The contribution may be based on a single discovery or a cumulative body of work. Of particular interest in selecting the awardee are contributions which further our understanding of self-regulatory processes as they affect mental function and behavior in disease and well-being. The award may be given annually to an individual selected from nominations submitted by the international community of scientists. The recipient does not need to be a member of the ACNP or a citizen of the United States.

The award, given for outstanding clinical studies, is marked by a plaque and monetary award presented at the ACNP Annual Meeting. The following individuals have been honored by the College with the Joel Elkes Research Award.

1986	Kenneth L. Davis	1999	Nora D. Volkow	2006	Andreas Meyer-Lindenberg
1989	Daniel R. Weinberger	2000	Susan Swedo	2007	Shitij Kapur
1993	Thomas R. Kosten	2001	John H. Krystal	2008	Daniel S. Pine
1994	Harold A. Sackeim		Marc Laruelle	2009	Jay N. Giedd
1995	Jack M. Gorman	2002	Daniel C. Javitt	2010	Joseph D. Buxbaum
1996	Robert W. Kerwin		Neal R. Swerdlow		
1997	Alan Breier	2003	Husseini Manji		
1998	Stephanie O'Malley	2004	Scott L. Rauch		
	Joseph R. Volpicelli	2005	Paul Jeffrey Harrison		



ACNP Media Award

In 2002, the ACNP Media Award was established to honor a member of the print or electronic media who has made a major contribution to the education of the public about mental illness and substance abuse research and the positive impact of research on treatment. The award is intended to be an expression of appreciation from the College toward outstanding leaders in the media who provide complete, accurate, and unbiased information to our society about brain diseases. Furthermore, as a result of attending the ACNP Annual Meeting and interacting with members, the honoree will further develop his/her own knowledge of the field and will expand his/her network of expert contacts.

The Media Award consists of an expense paid trip to the ACNP Annual Meeting and a plaque to be presented at the ACNP Annual Meeting during the President's Plenary. The Award winner must attend the Annual Meeting.

2002 Ellen Levine, Editor in Chief
Good Housekeeping Magazine

2003 Tim McCann
Exile Productions

2004 Michelle Trudeau, Science Correspondent
National Public Radio

2005 Marianne Szegedy-Maszak
U.S. News and World Report

2006 Bill Lichtenstein
Lichtenstein Creative Media

2007 John Hoffman & Susan Froemke
HBO Producers, *Addiction*

2008 P. Michael Conn & James V. Parker
The Animal Research War

2009 Brian Shanahan, CEO
MediSpin Inc.

Julius Axelrod Mentorship Award

Julius Axelrod, Ph.D. (1912-2004) joined the ACNP in 1961 and was a Founding Member of the College. He received the Nobel Prize for Physiology or Medicine in 1970. In his illustrious career, he served as a mentor to many young scientists who later became distinguished researchers in their own right.

In 2004, the ACNP Julius Axelrod Mentorship Award was established to honor an ACNP member who has made an outstanding contribution to neuropsychopharmacology by mentoring and developing young scientists into leaders in the field.

The award is marked by a plaque and monetary award presented at the ACNP Annual Meeting during the President's Plenary Session.

2004	George Heninger
2005	Solomon Snyder
2006	George Aghajanian
2007	Joseph T. Coyle
2008	Bruce M. Cohen
2009	Dennis S. Charney
	Eric J. Nestler
2010	David J. Kupfer

2011 Eva King Killam Research Award

As part of the 50th Anniversary year, the American College of Neuropsychopharmacology (ACNP) announced a new award, the Eva King Killam Award, to an individual on the basis of outstanding **translational research** contributions to neuropsychopharmacology. The contributions of the awardee will focus on translating advances from basic science to human investigations. The selection of the awardee is based on the quality of the contribution and its impact in advancing neuropsychopharmacology. Award recipients receive a monetary award and a plaque. The first award will be given at the ACNP Annual Meeting in Waikoloa, Hawaii, December 4-8, 2011.

This new award is named for Eva King Killam, who served as the first female President of the ACNP in 1988.

Exceptionally Prestigious Awards

Throughout the years, many of our members have been the recipients of many awards. Those that have received some of the highest awards in biomedical science are shown below.

The Lasker Award

Year	Member	Award Type
1957	Deniker, Pierre	Clinical Medical Research
1957	Lehmann, Heinz E.	Clinical Medical Research
1957	Kline, Nathan S.	Clinical Medical Research
1964	Kline, Nathan S.	Clinical Medical Research
1967	Brodie, Bernard B.	Basic Medical Research
1978	Snyder, Solomon H.	Basic Medical Research
1981	Sokoloff, Louis	Clinical Medical Research
1983	Kandel, Eric R.	Basic Medical Research
1987	Schou, Morgens	Clinical Medical Research
1999	Kety, Seymour S.	Special Achievement in Medical Science

President's National Medal of Science Award

Year	Member	Award Type
1968	Brodie, Bernard B.	Biological Sciences
1988	Kandel, Eric R.	Biological Sciences
2000	Andreasen, Nancy C.	Biological Sciences
2001	Graybiel, Ann M.	Biological Sciences
2003	Snyder, Solomon H.	Biological Sciences
2009	Fowler, Joanna S.	Chemistry

Nobel Laureates

Member
Axelrod, Julius
Carlsson, Arvid
Greengard, Paul
Kandel, Eric

Institute of Medicine Members

Aghajanian, George K.
Agranoff, Bernard W.
Akil, Huda
Andreasen, Nancy C.
Appelbaum, Paul S.
Barchas, Jack D.
Barondes, Samuel H.
Benes, Francine
Blazer, Dan G.
Bloom, Floyd E.
Brent, David A.
Bunney, Benjamin S.
Bunney, William E.
Burns, John J.
Carpenter, William T.
Charney, Dennis S.
Choi, Dennis W.
Cloninger, C. Robert
Coyle, Joseph T.
Davis, Kenneth L.
Deisseroth, Karl
Dement, William C.
Detre, Thomas
Dews, Peter B.
Frank, Ellen
Freedman, Robert
Gibbons, Robert D.
Goodwin, Frederick K.
Graybiel, Ann M.
Greengard, Paul
Gur, Raquel E.
Hyman, Steven E.
Insel, Thomas R.
Jeste, Dilip V.
Judd, Lewis L.
Kandel, Eric R.
Kleber, Herbert D.
Kraemer, Helena Chmura
Krishnan, Ranga R.
Krystal, John H.
Kupfer, David J.
Lerman, Caryn
Lewis, David A.
Li, Ting-Kai
Lieberman, Jeffrey A.
Manji, Husseini K.
Mayberg, Helen S.
McEwen, Bruce S.
Mignot, Emmanuel
Milad, Mohammed R.
Mobley, William C.
Nemeroff, Charles B.
Nestler, Eric J.
O'Brien, Charles P.
Pardes, Herbert
Paul, Steven M.
Rakic, Pasko
Rapoport, Judith L.
Reiss, Allan L.
Robins, Lee N.
Rubenstein, John
Schatzberg, Alan F.
Schuster, Charles R.
Sedvall, Goran C.
Shooter, Eric M.
Snyder, Solomon H.
Sokoloff, Louis
Tamminga, Carol A.
Tsuang, Ming T.
Vale, Wylie
Volkow, Nora D.
Watson, Stanley J.
Weinberger, Daniel R.
Weissman, Myrna M.
White, Raymond

National Academy of Sciences Members

Akil, Huda
Amara, Susan G.
Axelrod, Julius
Bloom, Floyd E.
Brodie, Bernard B.
Burns, John J.
Costa, Erminio
Fowler, Joanna S.
Gerard, Ralph W.
Goldman-Rakic, Patricia
Goodman, Louis S.
Graybiel, Ann M.
Greengard, Paul
Iversen, Leslie L.
Jones, Edward G.
Kandel, Eric R.
Kaufman, Seymour
Kety, Seymour S.
Malenka, Robert C.
McEwen, Bruce S.
McGaugh, James Lafayette
Rakic, Pasko
Schultes, Richard
Shooter, Eric M.
Snyder, Solomon H.
Sokoloff, Louis
Takahashi, Joseph S.
Udenfriend, Sidney
Vale, Wylie
Wender, Paul H.
White, Raymond

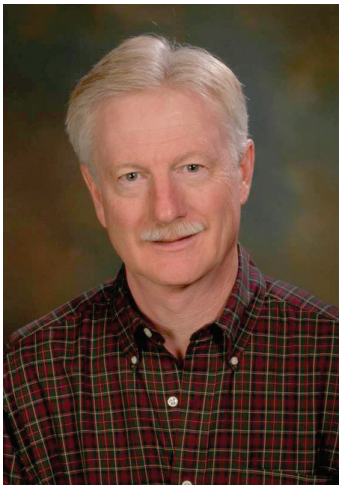
Brief Introduction to Publication History of the American College of Neuropsychopharmacology

George F. Koob • June 15, 2011

The tremendous growth of the interdisciplinary science of neuropsychopharmacology both from scientific and practical points of view formed the basis not only for the formation of the American College of Neuropsychopharmacology but also the need to disseminate the rapid growth in this emerging knowledge. To this end, a series of compendia were commissioned that resulted in the ***Generation of Progress*** series. By 1967-1968, the College felt that an assessment of all the achievements and needs in the field of neuropsychopharmacology was indicated, not only to review what was already achieved, but to identify gaps in knowledge and to show future directions for the development of neuropsychopharmacology.

The American College of Neuropsychopharmacology with the support of the National Institute of Mental Health organized a meeting at which all facets of psychopharmacology in the last 10 years were discussed. In addition to members of the College, a number of other scientists were invited to present papers. The presented papers were of two types - those of newer experimental findings of the authors and review papers. The First Generation of Progress volume (*Psychopharmacology: A Review of Progress, 1957-1967*, edited by the Daniel H. Efron) was published in 1968 by the U.S. Government Printing Office. It contained 116 papers, which constituted the proceedings of the sixth annual meeting of the ACNP.

Continuing the theme that one of the primary concerns to the founders of the College was the active sharing of concepts, data, and problems between laboratory and clinical investigators, the Second Generation of Progress volume (*Psychopharmacology: A Generation of Progress, 1976*, edited by Morris Lipton Albert DiMascio and Keith Killam) was organized and sponsored by the American College of Neuropsychopharmacology. The timing of this publication seemed particularly appropriate since 1976 marked the 15th year of the American College of Neuropsychopharmacology and the 20th year of the Psychopharmacology Research Branch, and it appeared singularly fitting that a second major review of the field be organized. The book was 1,731 pages long and contained 149 chapters prepared by 249 contributing authors, most of whom were members or guests of the ACNP.



George F. Koob, Ph.D.
Professor and Chairman
The Scripps Research Institute
Committee Neurobiology
Addictive Disorders

In the early 1980's a psychopharmacology curriculum was prepared by the Education and Training committee of the American College of Neuropsychopharmacology (members: Richard Schaeder, Carl Salzman and Ira Glick) with the objective to improve the teaching of Psychopharmacology. The curriculum was distributed in the 1980s at no cost to both ACNP members and to departmental chairs (nationally) (A Model Psychopharmacology Curriculum for Psychiatric Resident. The American College of Neuropsychopharmacology, 1984 editors Ira Glick, David Janowsky, Carl Salzmann et al.). Although not used extensively, it was well received by those that used it and was translated into several languages for use abroad. The curriculum subsequently has been

redone, updated and published by the American Society for Clinical Psychopharmacology.

The explosion of information in neuropsychopharmacology, reflected in the exponential growth of original and review publications in refereed journals, led to the commissioning of the Third Generation of Progress volume (*Psychopharmacology: The Third Generation of Progress*, *1987*, edited by Herbert Y. Meltzer and Morris A. Lipton). The third edition contained 184 chapters prepared by 345 contributors and was 1,780 pages long. The editors reported that this edition could have been much longer, but its length was restricted by the editorial decision to limit the contents to a single volume. This volume was divided into sections on Basic Neurobiology, Biological Psychiatry, Clinical Psychopharmacology, and Psychopharmacology to reflect the growth and breadth of the field.

The accelerated pace of research in the field of neuropsychopharmacology reduced inter-publication interval and the arbitrarily designated the length of a scientific generation to considerably less than the classic two decades. Thus, the history of the Generation of Progress series has been one of progressively shorter and shorter intervals of assessment of the progress within our field. The Fourth Generation of Progress volume (*Psychopharmacology: The Fourth Generation of Progress*, *1995* edited by Floyd E. Bloom and David J. Kupfer) differed from its predecessor volumes in the attempt to provide a more comprehensive overview of the clinical and preclinical arms of the field. Here, an approach was employed first to provide new scholars with overviews of preclinical and clinical psychopharmacology, and then more detailed coverage to understand the methods by which data in each of these arms are assessed in research. The fourth edition contained 163 chapters prepared by 317 contributors and was 2002 pages long.

After the 4th generation was published, it was recognized that the field was changing rapidly, and the collective wisdom of the leadership of the college at the time was to update a subset of chapters with a greater frequency than was possible with a book, and exploiting digital/electronic media. Accordingly, a decision was made to reissue an updated version of the book but on a CD ROM, inviting chapter authors to update existing material if necessary, and to add additional chapters. Stan Watson led this CD ROM Update project, publishing a first CD in 1996.A second CD came out in 1998 that updated 24 original chapters and added 18 totally new chapters to the book. A third CD was undertaken, however the CD version of that update was abandoned in favor of updating the material on the ACNP Website. This became the first scientific content to be published on the ACNP website, and that material can still be viewed there now.

In 1996, an Anthology was prepared by Oakley Ray for the 35th Anniversary of the College. Enclosed were statements and caricatures of all the past Presidents, and also special sections where some past-presidents were challenged as to what the future would be like. At the end of the Anthology, the minutes of the first 2-day meeting in New York in December 1959 were reproduced that led to the College's formation as an independent society not a branch of CINP.

In 1998, the college started the process of identifying editors for the 5th generation book. Given the success of the CD ROMs that were issued with the Fourth Generation of Progress, the vision was to publish a book, continue the tradition of issuing a CD ROM update every year or two to continue what Stan Watson had done, but to also launch a scientific website to be able to update content even more frequently, all as a bundled package. Later, the decision was made to drop the CD project because it was recognized

that CD ROMs were going to become obsolete and that the future was web-based. The CDs were put on the ACNP scientific website where they are still accessible under the 4th generation tab. James Meador-Woodruff was selected as the inaugural editor of the website, a position he held from 1999 until 2007 when he was selected as editor of *Neuropsychopharmacology*. David Sibley was selected as the editor of the web site and he remains the current editor.

The Fifth Generation of Progress volume (Neuropsychopharmacology: The Fifth Generation of Progress 2002 edited by Kenneth L. Davis, Dennis Charney, Joseph T. Coyle, and Charles Nemeroff*)* appeared at an important moment in the history of psychopharmacology as the decade of the brain ended, a decade that witnessed enormous progress in understanding fundamental physiology of the central nervous system.

This edition in the *Generation of Progress* series detailed advances in both the basic science and clinical application of recent research in psychopharmacology which included fundamental discoveries that were acknowledged by the awarding of the Nobel Prize in Psychology or Medicine to three members of the College, Arvid Carlsson, Paul Greengard and Eric Kandel for their discoveries on neuronal signaling. The fifth edition contained 134 chapters prepared by 292 contributors and was 2010 pages long.

The second major publication sponsored by the American College of Neuropsychopharmacology was the founding and subsequent establishment of the journal *Neuropsychopharmacology*. The editors of the journal have been distinguished members of ACNP and include: J.C. Gillin, 1987-1993, R.D. Ciaranello, 1994, H.Y. Meltzer, 1994-1998, H.C. Fibiger, 1995-1998, R.H. Lenox, 1999-2001, C.B. Nemeroff, 2002-2006, and J.H. Meador-Woodruff, 2007-present. The first editor J. Christain Gillin wrote in 1987 Volume 1: "*Neuropsychopharmacology* will encompass the biologic and psychological sciences related to both preclinical and clinical neuropsychopharmacology", "The inaugural issue of *Neuropsychopharmacology* comes near the end of a generation of unprecedented progress in psychopharmacology", and "We have no doubt that neuropsychopharmacology and its related fields will continue to be among the most exciting areas of scientific inquiry and clinical application in the future". The journal was created as the official journal of *ACNP* with the following mission statement:

"Neuropsychopharmacology is an international scientific journal and the official publication of the **American College of Neuropsychopharmacology (ACNP)**. This journal focuses upon clinical and basic science contributions that advance our understanding of the brain and behaviour, especially as related to the molecular, cellular, physiological and psychological properties of agents acting within the central nervous system and the identification of the new molecular targets for the development of the next generation of drugs. "

By all accounts the journal *Neuropsychopharmacology* has been an outstanding success. Each successive editor has improved the journal significantly by reducing review time, reducing the time to publication, balancing the preclinical and clinical publications, expanding and balancing the editorial board, raising the bar on quality of papers accepted, instituting an editorial triage process, and more recently incorporating the Neuropsychopharmacology Reviews component.

Publication of *Neuropsychopharmacology* moved from the publisher Elsevier to the Nature Publishing Group (NPG) in 2002**.** The relationship between ACNP and NPG has been quite successful. The revenue generated for the College has increased substantially since entering into this new agreement.

With NPG's cooperation, we were able to be one of the early adopters of delayed open access for NPP; i.e. articles are open for free access one year after their publication. With NPG's success at getting articles posted in Advanced Online Publication (AOP) very quickly and ACNP's initiative of sending a weekly email with links to new AOP articles, ACNP members now have access to journal articles within approximately 25 days from acceptance. The staff at NPG and the ACNP editorial team is now working together on ideas to improve the number of clinical papers submitted to the journal.

Neuropsychopharmacology has an impact factor of **6.993** and now ranks **6/117** among Psychiatry journals, **18/230** among Neuroscience journals and **1/236** among Pharmacology journals. Currently, 14 % of papers submitted are ultimately accepted for publication. Total # of submissions >1200 per year. The mean time to initial editorial decision=18 days, and the mean time from acceptance to Advance Online Publication in final form=23 days. Time to print varies depending on inventory of accepted manuscripts but currently is about 3 months. In short, the journal has been on an asymptotic trajectory of scholarship and ranking in the field and is the jewel that reflects the progress of our field and the success of ACNP.

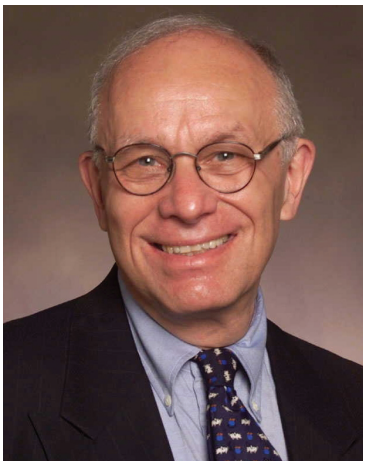
In December 2005, the Council of the American College of Neuropsychopharmacology at the recommendation of the publications committee commissioned the journal *Neuropsychopharmacology Reviews* to replace the *Generation of Progress*. While the *Generation of Progress* served for decades as a major reference work, a single large volume became an increasingly difficult mechanism for promulgating new data given the pace of research, developments in information technology, and the time needed for authoring, editing, printing, and distributing such a massive work. After considering several alternatives, it was decided that a yearly publication of review articles would be more easily managed, and allowed for more timely coverage of critical topics than is possible with a major reference work. To help ensure timeliness, the work includes a Hot Topics chapter that is prepared just prior to the production deadline. The volume also features downloadable graphics that can be used as a teaching resource. The aim is to provide coverage of all aspects of clinical and basic neuropsychopharmacology every five years or so, however, no limits are placed on how often a particular subject may be reviewed since selection of material is driven by developments in the field.

Preparation of *Neuropsychopharmacology Reviews* is overseen by members of the College, two of who serve as Series Editors and the editor in chief of Neuropsychopharmacology, James Meador-Woodruff. The editors are assisted by an Editorial Board comprised of individuals who will serve as Volume Editors on subsequent editions of the work. The College was fortunate in having Husseini Manji and Peter Kalivas as the initial Series Editors. The Nature Publishing Group handles production and publication.

Former Editors of *Neuropsychopharmacology*

J. Christian Gillin, 1987-1993

Roland D. Ciaranello, 1994



Herbert Y. Meltzer, 1994-1998

H. Christian Fibiger, 1995-1998

Robert H. Lenox, 1999-2001

Charles B. Nemeroff, 2002-2006

James H. Meador-Woodruff, 2007-present

NEUROPSYCHOPHARMACOLOGY 1987 – VOL. 1, NO. 1 (Elsevier)

NEUROPSYCHOPHARMACOLOGY: GOALS AND AIMS

Neuropsychopharmacology will encompass the biologic and psychologic sciences related to both preclinical and clinical neuropsychopharmacology. The interplay between basic and clinical sciences has been a hallmark of the American College of Neuropsychopharmacology (ACNP) since its inception in 1961. This journal will continue that tradition and further it.

The audience and the contributors will be multidisciplinary, including psychologists and psychiatrists, pharmacologists and physiologists, neuroanatomists and nosologists, epidemiologists and endocrinologists, and practitioners in other disciplines concerned with the understanding and use of neuropsychopharmacologic agents. Relevant topics will include the effects of these drugs and the physiologic and psychologic bases of their action. Appropriate areas of interest include the biologic substrates of normal and pathologic behavior; the nature, etiology , and pathophysiology of neuropsychiatric disorders; biologically relevant aspects of epidemiology, diagnosis, and treatment of these disorders; and the basic mechanisms -molecular, cellular, physiologic, and psychologic - by which psychopharmacologic agents exert their effects.

The inaugural issue of *Neuropsychopharmacology* comes near the end of a generation of unprecedented progress in psychopharmacology. During this time, a great deal has been learned about the nature, structure and function of the nervous system, and much of this new knowledge has been profitably applied to the understanding of normal and abnormal behavior. In addition, the introduction of the major and minor tranquilizers, antidepressants, lithium, L-DOPA, and other new drugs has transformed clinical practice, stimulated basic and clinical research, and led to new conceptual models about the pathophysiology of the major neuropsychiatric disorders. Moreover, many new methodologic advances have been made, including a renewed rigor and interest in clinical diagnosis, assessment, and the evaluation of treatment outcome; new brain-imaging technologies; the use of biologic measures in clinical research; and the introduction of molecular biology into the preclinical and clinical neurosciences.

We have no doubt that neuropsychopharmacology and its related fields will continue to be among the most exciting areas of scientific inquiry and clinical application in the future. Unfortunately, we also have no illusions that the abuse and misuse of mind-altering agents-alcohol, nicotine, cocaine, opiates, hallucinogens, and others-will soon cease to plague society. Certainly, new concerns will also arise about both the appropriate use of psychopharmacologic drugs and the significance of their unwanted consequences. We anticipate, therefore, that *Neuropsychopharmacology*, like the ACNP, will long have the opportunity to serve researchers and clinicians, and, through their scientific contributions, policy makers, patients, and the public.

J. Christian Gillin, M.D.
Editor-in-Chief

NEUROPSYCHOPHARMACOLOGY 1994 – VOL. 10, NO. 1 (Elsevier)

Letter from the Editors – Our Goals, Our Challenges

As we begin our respective terms as coeditors of *Neuropsychopharmacology*, we want to share with our readership our thoughts about the Journal, and in particular our goals. As the official Journal of the College, *Neuropsychopharmacology* enjoys a singular status among scientific journals, reflecting the stature of the College and its membership. Much of this we owe directly to Chris Gillin and the standards he set. The Journal is what it is today in large part because of Chris.

As we look to the future, it is easy to articulate our goals. We want the Journal to be the best in the three fields it represents: psychiatric research, neuropharmacology, and psychopharmacology. We want the outstanding people in the field to think first of *Neuropsychopharmacology* when they are preparing their very best work for publication, and for their students to dream of seeing their names in our pages.

No one begins a new task by celebrating mediocrity or laying a clear path to the middle. How do we propose to accomplish our goals? We think we have two major tasks: to convince the very best people to send us their best work when they could send it anywhere they choose and to make certain there are no impediments to publishing their work.

Attracting the best scientists is a circular process; it is achieved by having the best scientists publish in our Journal, so that others who do not know us become attracted. It is a bit like priming the pump, and we are fortunate in that the College is a rich source of priming material. The College membership embodies the very best in our fields: simply put, if you publish your best work in *Neuropsychopharmacology*, then the Journal's .success is guaranteed. Thus we are actively soliciting each of you to send us your best work; we are asking you to think of us first. From there, it is a short distance to the next step, attracting outstanding scientists from outside the College to send us their work.

To begin this process, we have increased the membership of the Editorial Board and have secured commitments from each of them to send us one or two of their best papers yearly. They have agreed enthusiastically, and if we can achieve the same commitment from each of you, the next problem we face will be the need to expand our page numbers. We are looking forward to facing that problem.

Rapid review, response, and publication are important in science and, in our fast-moving field, particularly important. We recognize that without fast turnaround, top scientists will not publish in *Neuropsychopharmacology.* Continuing a process started by Chris, we will assign reviewers to each manuscript the day it arrives in our offices, fax the title page and abstract to prospective reviewers and obtain commitments from them within 24 to 48 hours. We will follow up with them to ensure that reviews are received back within 2 weeks. Our goal is to publish accepted papers within 4 months of their submission. But these are mechanics: in themselves, they do nothing to elevate quality. Quality comes from you.

Both of us are honored to be holding our positions and committed to achieving success. But we need your help: specifically, we need your best papers. We want the members of the College to take button-popping pride in their Journal. To borrow from Abraham Lincoln: without your support, we cannot succeed, with it we cannot fail.

Roland Ciaranello
Herbert Y. Meltzer
Editors-in-Chief

NEUROPSYCHOPHARMACOLOGY 1999 – VOL. 20, NO. 1 (Elsevier)

EDITORIAL

A changing of the guard has provided us the opportunity to contemplate the past and project into the future. Chris Fibiger and Herb Meltzer have not only very ably led this journal over the past three years, but have left us with big shoes to fill as they have eloquently set forth in their editorial in the last edition of the journal for 1998. The most recent impact factor (4.1) for the journal as determined by the Institute for Scientific Information places us well within the top 10% of both psychiatric and pharmacological journals and in the top 15% of neuroscience journals as well. In accepting the position, Editor-in-Chief of N*europsychopharmacology*, I well understand the responsibilities of building upon this momentum and the challenges that face this journal as we move into the millennium. As the official journal of *ACNP*, and as described in our mission statement, *Neuropsychopharmacology* should represent a forum for publication of the best science that bears upon identifying the biological basis of neuropsychiatric disorders and the discovery of new pharmacological strategies for their prevention and/or treatment. The juxtaposition of the finest clinical and basic scientists in our field has served to create a most dynamic setting for scientific interaction for both the college and the journal. While we endeavor to create the bridges that will take us from the bench to the patient and back, our field is clearly dependent upon using the most creative and advanced experimental strategies in both the clinical and laboratory setting. Thus the journal must attract the best scientists to submit their best science.

It is in this light that I have reorganized the editorial , include Field Editors in six major areas of scientific pursuit to emphasize our commitment to publishing the highest quality research across these scientific disciplines. I am pleased to welcome Ron Duman (molecular/cellular), Irwin Lucki (behavioral pharmacology), Raquel Gur (imaging), Jeff Lieberman (clinical psychopharmacology), Gary Aston-Jones (neurophysiology),and Wade Berrettini (Genetics). While we certainly have competition from specialty journals in each of the scientific areas of interest, *Neuropsychopharmacology* provides a unique venue for reaching a readership that reflects the most outstanding scientists across these various disciplines with a research interest in neuropsychiatric disorders. I can not agree more with Chris and Herb that the quality and creativity of the science must prove to be the criteria by which we determine publication priority. Each of our Field Editors is an accomplished working scientist with significant experience, and together with a newly appointed Editorial Board, will assure us the quality within the review process that is worthy of our constituents within the scientific community. It is also important to note that this editorial office has established procedures that will prove to streamline the review process and provide both timely yet high quality review of manuscripts that will assure rapid publication. Over the next six months each of these Field Editors will have the opportunity to provide an editorial reflecting upon their field of interest and its impact upon the future direction of the journal.

We also have appointed three senior editors to provide additional guidance and perspective to the journal in concert with the Editor-in-Chief. I am delighted that Bruce McEwen, Biff Bunney and John Tallman have agreed to accept my invitation to play such a role within our editorial team. The selection of these Senior Editors has been carefully crafted to bring to the journal the finest expertise from both a clinical and basic science perspective. While

I am sure that I need not justify the qualifications of these scientists, it is important to note that John Tallman is also a respected representative of the pharmaceutical industry. Given the foundations of the ACNP and the mission of the journal, we have the opportunity of engaging the pharmaceutical industry at both a scientific and academic level. For it is in the pharmaceutical setting that some of the biggest advances in drug discovery strategies are occurring, and where issues including pharmacogenetics and pharmacoepidemiology are on the front burner. Over the coming year we will also look to each of our Senior Editors to provide a perspectives article that I am sure will enrich and awaken us to new scientific questions being addressed in their respective areas of expertise. In addition, together with the Editor-in-Chief, we will be providing perspective articles from noted scientists that will serve to not only provide an overview of important scientific advances for our readership but will hopefully signal new directions for both scientific interactions and composition of our college.

Together with Elsevier, *Neuropsychopharmacology* is also taking advantage of opportunities for enhancing our use of the electronic media and as of this month will not only have table of contents on line but access to full manuscripts. In addition I am most pleased to welcome Stan Watson who will serve as Electronic Media Consultant to the journal and will help coordinate the most effective integration of the journal into electronic publishing in concert with the ACNP and Elsevier. I am highly optimistic regarding the future of *Neuropsychopharmacology*, and look forward with enthusiasm to working with my respected colleagues.

Robert H. Lenox, M.D.
Editor-in-Chief

From the Editor

Charles B. Nemeroff, Editor-In-Chief
ACNP Bulletin, August 2002, Volume 8, Number 3

There have been many changes in Neuropsychopharmacology in the last six months - some have undoubtedly been evident to you, as for example, the change in the cover. Others are less evident but no less important in attaining our goal of being ranked as the best journal in our field.

The move of Neuropsychopharmacology to Nature Publishing Group is an exciting evolution for the Journal and the American College of Neuropsychopharmacology. The addition of our journal will enhance Nature Publishing Group's cluster of high quality Neurology, Neuroscience, Psychiatry and Pharmacology titles.

Neuropsychopharmacology will continue to publish the highest quality original research in areas of clinical and basic science that advance our understanding of the brain and behavior, especially as related to the molecular, cellular, physiological and psychological properties of agents acting within the central nervous system and the identification of new molecular targets for the development of the next generations of psychotropic drugs. In view of the interdisciplinary nature of the field, particular emphasis is placed on studies that address the biological substrates of normal and pathological behavior, the nature, etiology and pathophysiology of neuropsychiatric disorders, biologically relevant aspects of the epidemiology, diagnosis, and treatment of these disorders, and the basic mechanisms by which psychopharmacological agents exert their effects. With a remarkably energetic team of field editors and new publishing arrangements, this

internationally successful journal will continue to publish the leading research in this rapidly evolving field.

One of the reasons we are so delighted with Nature, is the ability to transition almost immediately to a fully electronic and web-based peer review system. This will allow for both submission of manuscripts and review to occur electronically, which will ultimately markedly reduce the time to publication.

Clearly the view of the journal by both ACNP members and non-members is on the rise, as evidenced by a marked increase in the number of manuscripts submitted for publication. Moreover, the journal's impact factor increased in 2001 from 4.579 to 4.715; it is ranked by the Scientific Citation Index as 6 of 81 (top 7.5%) psychiatry journals, 11 of 186 (top 6%) pharmacology journals and 28 of 198 neuroscience journals (top 14%). My goal is to further improve these rankings over the next few years.

At the summer meeting of the field editors, several changes in the journal were discussed and ultimately adopted. First, the large increase in manuscripts submitted has necessitated an increase in the size of the journal. We plan on publishing 170 pages per issue in a new, more efficient page layout. The net result will be a 33 percent increase in the amount of material we can publish. We will therefore maintain our high quality without incurring an unwanted delay in time to publication. Second are changes in the categories of manuscripts submitted. Our mainstay is, of course, primary research reports. We have eliminated the Brief Report section. If you wish to submit a short report, please do so – it will be reviewed and placed with the other research reports. We will continue to publish state of the art reviews (Perspectives). We wish to add two new categories of manuscripts: (1) Controversial Topics in Neuropsychopharmacology will be brief, point-counterpoint papers published together on cutting-edge topics in the field. Each author will provide a 3-4 printed page manuscript summarizing their position. Please send recommendations for authors and topics that would be suitable for this section; (2) complicated case studies – in response to the view expressed by several of our members that the journal was very neuroscience/basic science focused and not as clinically based as it should be, we have introduced this series in which complicated cases are described and then discussed in detail. Please consider contributing to this section.

I have received a large number of gratifying positive comments from many ACNP members about the new cover of the journal. Nature has agreed to keep the format similar. The cover illustrations are not linked to an article published in the journal. As such, I would be delighted to receive your best illustrations for use of the journal cover. Please consider sending me brain imaging, immunocytochemistry and any other illustrations you consider appropriate. The Emory faculty would appreciate your help here as I have relied heavily upon them for cover illustrations.

On a troubling note, several ACNP members and even a few members of the editorial board have declined our requests to review manuscripts for the journal. This is an absolute requirement for editorial board membership – it is not honorific in any way. Moreover, ACNP members should recognize that reviewing manuscripts for our journal is part of the requisite service to our college.

I have been privileged to have a superb managing editor, Jen Mahar, nine talented and hard-working field editors and the support of the ACNP President and Council. I am even more enthusiastic about Neuropsychopharmacology than I was when I accepted the Editor-in-Chief position and hope that you, the membership, are equally enthusiastic. Feel free to contact me at any time concerning the journal.

Neuropsychopharmacology Vision and Goals

James Meador-Woodruff, Editor, Neuropsychopharmacology

ACNP Bulletin, February 2007, Volume 13, Issue 1

I am honored to have been selected by the College as the next editor of *Neuropsychopharmacology*. The journal is now in its 20th year, and is one of the most prestigious journals in the various fields in which we all work. For 2005, the journal's impact factor was 5.369, placing it 5th of 94 journals in psychiatry, 19/198 in neuroscience, and 14/187 in pharmacology. We are likely on track this year to reach 1000 annual submissions for the first time. The journal is by all means healthy, having steadily improved on each of my predecessors' watch. My pledge to you is that I will continue to build on this impressive base and take the journal to the next level.

In the short term, the new editorial team has assumed responsibility for the journal, and hopefully this process has gone smoothly for any of you that have papers under consideration. For those of you that had submitted papers prior to the change in editorship which effectively took place during our 2006 annual meeting, rest assured that your papers have been and are being handled by the field editor that you originally submitted through, although we are near the end of that transition.

We have made a number of changes around how manuscripts are handled centrally, including assignment of handling editors. We have begun a process of identifying manuscripts unlikely to be publishable in the journal, and have started a triage process to not delay authors from seeking a more appropriate or more likely place to publish, and importantly to be maximally efficient when requesting our reviewers' time by only sending to them those manuscripts that are more likely to eventually be in contention for our limited number of pages. I have rapidly discovered that the most limited resource we have at our disposal is reviewers. My personal thanks to those of you to whom I have already turned repeatedly for your thoughtful (and speedy) reviews.

I have instituted a weekly editorial conference call for the deputy editors and our managing editor, Jen Mahar, where these triage decisions and other issues are discussed. We are also implementing changes to reduce the time a manuscript is in review. My goal is to further decrease the time from initial submission to an author being notified of an editorial decision, to carve additional days from the already relatively short time the last editorial team had been able to accomplish. Many of these changes should be behind the scenes for authors, but the outcome is that authors will get ever faster reviews and decisions.

Longer term, a number of new initiatives are under discussion. One area that is evolving for all of medicine is the issue of disclosure of potential conflicts of interest. This is clearly an area of intense interest and is a changing landscape. With the guidance of the Publications Committee, I feel we have streamlined the journal's disclosure policy as much as we can given current trends and mandates from the College, and that what authors need to provide should be relatively straightforward.

We are one of the few top notch journals in any of our fields that does not have word limits: while our average paper runs 8 or so pages in print, we have some considerably longer than this but not many shorter. Given our fixed number of pages, we will need to institute policies on manuscript length in the near future.

I am particularly interested in developing an electronic-only eNeuropsychopharmacology website, hopefully in collaboration with Nature, our publishers, to publish negative studies. We all have well designed studies that result in negative

data that should be published but are often given low priority at journals simply because they are negative. Hopefully we will be able to implement something along these lines this year.

Much of what has made *Neuropsychopharmacology* great has not and will not change on my watch. We will keep the current cover layout, so please send us any attractive figures that you would like considered as a cover illustration. Over the past 20 years, I have personally heard every editor of the journal ask the membership to keep *Neuropsychopharmacology* in mind as a place to send some of your best work. I now ask you to do the same: this is our journal, and as we continue to develop, be increasingly prominent, and grow our impact factor, submissions from our membership can and should lead the way. I am always happy to hear from you and get feedback on what we are doing well as well as what we could do better. Again, I am honored to have been selected for this position, and look forward to continuing to serve the ACNP in this role.

Psychopharmacology: A Review of Progress, 1957-1967

Daniel H. Efron, M.D., Ph.D., Jonathan O. Cole, M.D., Jerome Levine, M.D., J. Richard Wittenborn, Ph.D.

Preface

In the last 10 years we have witnessed a tremendous growth of psychopharmacology both from scientific and practical points of view. Psychopharmacology has become a vigorous interdisciplinary science. Most of the medical and biological sciences have contributed to its development. One of the signs of this development was the organization of the American College of Neuropsychopharmacology. The proceedings of a meeting held in 1956 on the evaluation of psychopharmacotherapy in mental illness was published in 1959 in a volume entitled, "Psychopharmacology, Problems in Evaluation," edited by Jonathan O. Cole and Ralph W. Gerard. After a lapse of more than 10 years it was felt that a new assessment of all the achievements and needs in the field of psychopharmacology was indicated, not only to assess what was already achieved, but gaps in knowledge and future to show directions to go for the development of psychopharmacology.

The American College of Neuropsychopharmacology with the support of the National Institute of Mental Health organized a meeting at which all facets of psychopharmacology in the last 10 years were discussed. In addition to members of the College, a number of other scientists were also invited to present papers. The presented papers were of two types - those of newer experimental findings of the authors, and review papers. This volume contains the proceedings of this meeting.

The editors had substantial difficulties in preparing this volume because of the many ways the material could be presented. Finally, it was decided to present to the reader a set of papers with as few deletions and editorial changes as possible, so that the volume is not only a collection of papers presented at the meeting, but a type of psychopharmacology encyclopedia and a permanent handbook for everyday use. This sometimes resulted in very extended tables, literature references, etc. We have even included some appendices (Cole's paper) which present a reproduction of official documents on the regulation requirements of the Food and Drug Administration for new drugs. Because of the multidisciplinary nature of the meeting, problems of terminology,

extent of the material and possible readers with different backgrounds who may use this volume, no restrictions were imposed on the participants with regard to nomenclature used, order of material, or uniformity of presentation and reference lists. The diversity of form and style of the various presentations was not altered for publication and remain in their original form.

Generally, discussions after every paper or session were not recorded and are not presented. The only exceptions are as follows: (1) Session IV where invited discussants and members of a panel presented their views, (2) Session V where invited participants presented papers discussing the main presentations, and (3) Session VI where the chairman and the secretary of the session have prepared a summary of the discussion. The reader will probably find errors in this volume. This is largely due to the haste with which this volume was prepared for publication in order to put it in the hands of the reader while the material was still very current. If the book is a success, it is most certainly due to the caliber of the authors of the papers and the amount of work they extended in preparing them. At this point we would like to thank them for their efforts. We also feel that special thanks should be extended to the chairmen of the sessions and especially to the ones who helped in reviewing papers, to Dr. J. R. Wittenborn, the Secretary-Treasurer of the College and Mrs. Gloria Light of his staff for their efforts in preparing the meeting and in assembling the papers, and to members of the staff of the Psychopharmacology Research Branch of the National Institute of Mental Health, Dr. Albert A. Manian and Mrs. Lillian Altman, for their help in the preparation of the manuscript.

Psychopharmacology: A Generation of Progress

Morris A. Lipton, M.D., Ph.D., Alberto DiMascio, Ph.D., Keith Killam, Ph.D.

Introduction and Historical Overview

This volume was organized and sponsored by the American College of Neuropsychopharmacology. The timing of such a publication seemed particularly appropriate in the light of the utility and favorable reception of the tenth-anniversary publication of *Psychopharmacology: A Review of Progress, 1957-1967*, edited by the late Daniel H. Efron. Moreover, 1976 marked the 15th year of the American College of Neuropsychopharmacology and the 20th year of the Psychopharmacology Research Branch, and it appeared singularly fitting that a major review of the field be organized.

Such a book seems especially needed at this time because neuropsychopharmacology has grown enormously in the 20 years since it emerged as a discipline. Many journals have been created and tens of thousands of papers have been published. Many books have been written that touch on one facet or another of neuropsychopharmacology, but none covers it comprehensively. Hundreds of students have been trained in neuropsychopharmacology and hundreds more are in training. Thousands more are exposed to neuropsychopharmacology as a significant part of their training in the neurosciences as well as in psychology, neurology, and psychiatry. All of this testifies amply to the vigor of this young hybrid science.

Of primary concern to the founders of the College was the active sharing of concepts, data, and problems between laboratory and clinical investigators. A stress on active participation, as evidenced by the high attendance at annual meetings and the level of intense scientific exchange, has been a continuing hallmark of the College. The format of the meetings, and thus the flavor of

the presentations, has reflected the leadership of each President and has varied from study groups to formalized meetings such as this one. Again, the focus has been intimate, pluralistic exchanges rather than a theater or medium for showcase productions. At periodic intervals, the College has presented position volumes such as this which review and organize thinking. As the College entered its 16th year, a time in a person's lifespan generally recognized as entry into maturity, the Council felt it appropriate to put into this single volume much of the breadth and depth of knowledge that had been developed over the past generation. Such a volume, it is hoped, will communicate the unity and diversity of those goals that led to the births of the discipline and the College.

These goals had been the fusion of several existing disciplines into a new hybrid for problem solving through research and, thereafter, the codification of a body of knowledge to be taught. Psychotropic drugs had been used for thousands of years for medical, religious, aesthetic, and recreational purposes, but their use was empirically rooted in folklore. (Carl Sagan in the *Dragons of Eden* notes that a primitive pygmy tribe that obtains its food from hunting and fishing uses marijuana to increase is patience during these tedious activities. The only crop this tribe cultivates is marijuana, to ensure its supply. He suggests humorously that this may have been the transition crop that converted man from a hunter to a farmer.) The accidental discovery of LSD-25, the introduction of reserpine into Western medicine, and the accidental discoveries of the clinical utility of phenothiazines, tricyclic antidepressants, and MAO inhibitors, all within approximately 10 years, were catalytic in establishing a new scientific discipline. Together, they generated a revolution in research and practice the consequences of which are not yet entirely clear. For example, the dramatic hallucinogenic properties of LSD-25 catalyzed the interest of research psychiatrists who were struck by its capacity to simulate some aspects of psychosis and of basic neuroscientists impressed by its extraordinarily high potency in altering some aspect of brain metabolism. Simultaneously, it attracted the interest of a young generation and their gurus who promised new experiences, expanded consciousness, and novel solutions to existential problems. The explosion in usage among the young stimulated the Federal Government to simultaneously enlarge research funding and impose legal controls.

The discovery of chlorpromazine-and soon after of other antipsychotics, tricyclic antidepressants, and MAO inhibitors-also had multiple consequences. To psychotic patients, their families, and their physicians there was new hope for rapid improvement, de-institutionalization, and even cure. To many psychiatrists trained in Freudian psychodynamics, and with therapeutic skills limited to psychotherapy, it was a threat; they had apparently forgotten Freud's prediction that psychoanalysis was a temporary milestone in the treatment of mental illness that would someday be replaced by the results of advances in biochemistry and endocrinology. They initially ignored these drugs and then were skeptical of their utility. To become accepted, clinical psychopharmacologists shifted from the practice of a medical art to science. They conducted research-generating hypotheses and then rigorously testing them. To do so, they developed rating scales to access initial states and degrees of change. They used double-blind studies in controlled clinical trials to obviate the possibility of placebo effects. These efforts have generated more hard data about the effectiveness of a therapeutic modality than have ever before existed in the field of psychiatry.

To basic scientists, the psychotropic drugs were quantifiable and reversible variables that could be used as chemical probes to study specific aspects of brain metabolism and the relationship between these

aspects and behavior. From the study of their mode of action in animals and humans, there have emerged new insights into the operations of the normal brain and a major therapeutic advance in the treatment of Parkinson's disease. There have also emerged hypotheses about the pathogenesis of schizophrenia and of depression that, although incomplete, are almost certainly not incorrect because they are based on sound data. Furthermore, the hypotheses are testable as science demands and modifiable as new information is generated.

To the pharmaceutical industry, a new potential market emerged. To achieve its share of the market, virtually every major drug company developed a division of psychopharmacology with basic science to develop and test new drugs.

To the social and community psychiatrists interested in de-institutionalizing patients and reintegrating them into their families and community, the psychotropic drugs offered a means for attenuating psychotic symptoms to the point where patients could be rapidly discharged from hospitals. It is doubtful whether the community mental health movement could have developed without them.

To the psychiatric theorist, the advent of psychotropic drugs represented a major blow to Cartesian mind-brain dualism. That drugs could influence mood, thought, and perception without altering consciousness was revolutionary. Drugs are chemicals that act on chemical systems in the brain and not on psychological abstractions like the mind or metapsychological constructs like the id. To the extent that they influence these systems, they do so by altering chemical events in the brain. The mind, then, is now generally accepted as a behavioral manifestation of the anatomy, physiology, and biochemistry of the living brain. The artificial distinction between functional and organic illness is becoming blurred.

All of these events, and more, occurred in an optimistic economic and legislative climate where research and research training were highly valued and appropriately funded. When these attractions were added to the existing discoveries that were being made almost daily, basic scientists began to recognize opportunities and enlarged research activities. Without giving up their identity in their parent disciplines, they acquired a new and comfortable identity in which they could lend and borrow thoughts and skills from each other while they interacted in the conduct of interdisciplinary research and teaching. The training of clinical psychiatrists began to be more biologically oriented and that of neurologists began to consider behavior. This trend, which continues, began to generate physicians trained to be neuropsychiatrists with concerns about mind and brain similar to those of Charcot, Janet, and Freud at the beginning of the century.

It is a tribute to the foresight of the National Institutes of Health and the National Academy of Sciences that in the mid-1950s they sponsored a meeting to examine the state of the art and to project the needs for what emerged as neuropsychopharmacology. The concerned guidance from the National Institutes of Health was provided by Jonathan Cole. Major influence and enthusiasm in the scientific sphere was provided by Ralph Gerard, and the clinical drive was promoted by Paul Hoch, Henry Brill, Nathan Kline, and Heinz Lehmann. By 1960, the dimensions and form of neuropsychopharmacology had stabilized to the point that Theodore Rothman and Paul Hoch organized a meeting in New York City to stimulate discussion and to suggest proposals for the advancement of neuropsychopharmacology. A committee was formed, proposing the superstructure that emerged as the present College. Membership in the College was limited to those individuals who were active in research and scholarship and who were already leaders in the field, or showed promise of becoming so. They were drawn from

government, industry, academia, and private practice. This amalgam of talents, the small size of the College, and the stress on participation, not only at meetings but throughout the year, have made the College synonymous with the development of neuropsychopharmacology. Its membership has not only contributed to the major advances in knowledge, but it has also addressed itself to the social problems that that revolutionary advances have created.

After 20 years, neuropsychopharmacology may be considered a vigorous young adult with problems commensurate to its age. The earliest meetings of the College attempted to highlight clinically relevant and methodological issues. As the clinical potentials and limitations of drugs became more well established and known, the later meetings began to emphasize biochemical, pharmacological, or neurophysiological inquiry and observations in an attempt to understand the etiology of mental illness and the mechanisms of action of the psychotropic drugs. As the field began to grasp the impact and import of the findings thereof, theories were generated and expounded and hypotheses were tested and reported at such meetings. Simplistic concepts that were the subjects of discussion of some sessions at the early meetings, such as the "neurotransmitter of the year" and its role in schizophrenia, or that drug X would cure all depression, began to give way to multidimensional concepts and comprehensive therapeutic programs. At more recent meetings, the College has provided a forum for discussing the pharmacodynamics or clinical pharmacology of drugs as a means for better understanding individual variability of response. What is not known, or what has not been accomplished, is as likely to be presented at meetings as are the successes and new findings. The breadth and flexibility of the College and its members made such a transition desirable and feasible.

But it is not only the scientific changes within the field that have caused changes in College activities. As the fruits of laboratory and clinical research have been translated into therapeutic success, and the fundamental understanding of higher nervous function has progressed, there has been a continual shift in the expectations of government and of society. The responsibilities of the neuropsychopharmacolgy community have enlarged. From its very inception, the College has considered the need to respond in these areas, as well as in those reflected in our scientific and clinical contributions. The responsiveness is reflected in the Constitutional Committees established for liaison with government agencies and industry, or other learned societies, for review of ethical matters, or for education and training.

Under the direction of one of these Committees (the Government/Industry Liaison Committee), a book was prepared in collaboration with the Psychopharmacology Research Branch of the National Institute of Mental Health, entitled *Principles and Problems in Establishing the Efficacy of Psychotropic Agents* that would hopefully be of use to the Food and Drug Administration in their reviews of drug efficacy. As a consequence of this endeavor and others, a unique and responsible partnership among the investigative community, government, and industry has developed.

The Education Committee has spent immeasurable time considering who is to be given training in psychopharmacology, how it is best accomplished, and what material is known and can be taught. Their work is really in an embryonic stage. For example, the magical expectations associated with the introduction of psychotropic drugs must be eliminated. Hopefully, this will diminish self medication and inappropriate medications for many patients. The hazards of prolonged psychotropic drug use must be taught. The limitations of the benefits that can be achieved

when drugs alone are used for the treatment of chronic anxiety and schizophrenia must be recognized and the need for integration of drug treatment with other treatment modalities must be emphasized. Research in this area remains sadly lacking.

Furthermore, as society involved itself with drug misuses, advocacy pursuits, and patient rights, the need for establishing guidelines and principles for human drug research became evident; the College responded by assigning the Ethics Committee to prepare such guidelines. The product of this Committee was voted on and overwhelmingly accepted by the members of the College. But new ethical problems constantly arise. What, for example, should be done about informed consent for psychiatric patients who require prolonged treatment with neuroleptic drugs and who thereby face a significant risk of irreversible neurological damage?

Many problem-oriented scientific societies have been formed but have had limited impact on the particular field. In the College, the leadership of each of the Presidents, the support from the Council and the Constitutional Committees, and the concerned participation of the membership have been important factors in the many accomplishments achieved. The backbone or stabilizing factor for the College, however, has been the Secretariat. The College has been blessed by the talents of three able men who have served *ad seriatum:* Theodore Rothman, J. Richard Wittenborn, and Albert DiMascio. Much of the success of the College has been attributed to the untiring service put forth by these men and their devoted staffs. It has been they who translated the ideas and programs of the presidencies into action and provided the continuity that has made the College an effective professional organization.

It is both tempting and risky to predict the future of the field of neuropsychopharmacology. The riskiness becomes evident when one considers that less than a quarter of a century ago it was beyond the limits of the imagination of most of us to conceive that drugs would be developed for the relatively specific treatment of mania, depression, and psychoses without altering consciousness. These drugs were, of course, discovered by accident and serendipity. Only later were hypotheses developed as to their mode of action, and these, in turn, gave further insights into pathogenesis of mental illness.

As drugs lose their magical qualities, we may more realistically assess their benefits, their hazards, and their limitations. In the process, we may learn to better understand the biological substrates of behavioral states, feelings, and emotions. The biological substrates can and increasingly will be modified with drugs-especially when they are associated with illness-but it seems beyond comprehension to imagine that we shall someday have drugs that will specifically and selectively modify each and every feeling and behavioral state that seem so uniquely to be part of the human repertoire. In particular, we will probably learn that drugs are not, and can never be, a total substitute for the interpersonal relationships and the social support systems upon which we all depend. As this is recognized, a more effective integration of pharmacotherapy with other forms of treatment and support will likely ensue.

The College and its members have much to do. The challenge facing them and the field is establishing new frontiers, while continuing the resourceful investigation of brain function and treatment of the abnormalities of mental function from whatever the source. If one reflects on the fabric of the College proposed by the founding committee, the emphasis was on pluralism and constant refreshment of new ideas by dedicated investigators and clinicians. If these ideals are carried forth, the next 15 years will see an expansion of productive research, teaching, and therapeutics.

Psychopharmacology: The Third Generation of Progress

Herbert Y. Meltzer, M.D.

American College of Neuropsychopharmacology and the History of This Edition

The American College of Neuropsychopharmacology (ACNP) has grown in its 25 years of existence from a membership of about 50 to approximately 400. From inception, its members recognized that psychopharmacology was a dynamic field that would need to incorporate as well as catalyze developments in diverse areas of clinical and basic neuroscience were it to fulfill its inherent mission.

The common bond of the pioneering, as well as subsequent ACNP members, is an active research or administrative interest in understanding the structure and function of the central nervous system and its behavioral output in health and illness. Publication of symposia from its annual meeting as well as periodic review volumes has been a key function of the ACNP.

This edition is a product of the college membership. The Editor and Associate Editors identified the major areas of psychopharmacology and chose Section Editors to oversee the writing of chapters by contributing authors who were agreed on by all three editorial levels. Most, but not all, first authors are ACNP members.

The first edition of *Psychopharmacology, A Review of Progress* 1957-1967 was published in 1968 by the U.S. Government Printing Office. The 116 papers included in it constituted the proceedings of the sixth annual meeting of the ACNP. Eight sessions were held at that meeting, and in each of these, either original work or reviews of a significant area of psychopharmacology, were addressed. The second edition, entitled *Psychopharmacology: A Generation of Progress* was prepared in 1976 to mark the twentieth year of the National Institute of Mental Health's Psychopharmacology Research Branch and the fifteenth year of the ACNP. The book was 1,731 pages long and contained 149 chapters prepared by 241 contributing authors, most of whom were members or guests of the ACNP. This, the third edition contains 184 chapters prepared by 271 contributors and is 1,840 pages long. The explosion of information, reflected in the exponential growth of original and review publications in refereed journals, is evidence that this edition could have been much longer. Its length has been restricted by the editorial decision to limit the contents to a single volume.

Comparison of the two preceding editions with the present one reveals that the major concerns of both basic and clinical psychopharmacology have not changed, but the sophistication of the methods with which these problems are addressed has been enhanced in many areas. The basic neuroscience addressed in the first edition described the key outlines of the chemical neuroanatomy and biochemical pharmacology of the central nervous system, electrophysiological indicators of drug action, the biology of memory and learning and central nervous system toxicology. Clinical sections were devoted to the anxiolytic agents, the antidepressants, antipsychotic agents, and psychotomimetics. A section was devoted to alcohol and drug addiction. In still other sections, considerable attention was paid to research methodology in human psychopharmacology and to ethical and legal considerations of research in the area of brain and behavior.

The Second Edition updated newer research findings in these areas and added the emerging areas of research with receptors, the neuropeptides, neuroendocrinology, and animal models. Clinical sections dealing with the psychopharmacology of neurological, pediatric, and geriatric disorders were introduced. The major outlines of some of the

current theories of the etiology of schizophrenia and depression were described.

This edition will help to prepare the current generation of psychopharmacologists to understand the contributions of molecular biology.

Introduction

The first section of *Psychopharmacology: The Third Generation of Progress*, Basic Neurobiology, provides extensive consideration of the anatomy, biochemistry, and physiology of monoaminergic systems, including excitatory amino acids. Key findings in receptors of monoamines and other neurotransmitters as well as ion channels are thoroughly reviewed. This area has made enormous progress in the past decade, influencing psychotropic drug development and contributing greatly to the understanding of the mechanism of action of psychotropic drugs and the role of neurotransmitters in neuropsychiatric disorders. Neurotoxins, which have emerged as potential etiological agents in Parkinson's disease and schizophrenia as well as research tools are emphasized.

Molecular biology, like neuroscience, at the cutting edge of modem medicine, is systematically considered for the first time in the section on Neuropeptides. The focus is on the biosynthesis of peptides from prohormone precursors. Molecular biology has already provided important information about receptor structure and the identification of the genes involved in Huntington's chorea and Alzheimer's disease. The search for the genes that cause mental illnesses is well underway. Success in this endeavor will clarify the crucial nosological questions that continue to elude definitive resolution. Identification of the genes that predispose to mental illness is likely to eventually transform the professional lives of psychopharmacologists even more profoundly than the discovery of the currently available psychotropic drugs, by assisting in diagnosis and, possibly, by permitting novel approaches to prevention and treatment by manipulation of genes. Molecular biology has enabled us to begin to understand how genes, acting

in concert, lead to the development of the brain we so indelicately perturb with drugs, how genes, when required, guide the remodeling of the brain, and how genes ultimately orchestrate the complex sequence of biochemical events that underlie our thoughts and feelings.

The emphasis of this volume on the Biological Psychiatry section reflects the value placed by modern psychopharmacology on the pathophysiology of mental illness as well as normal brain functioning, in order to understand and monitor drug action, to identify predictors of drug response, and to help in the search for clues as to new strategies for drug development. This section provides overviews of the biological theories of the etiology of affective disorders (and aggression), schizophrenia, childhood behavioral disorders (including mental retardation), dementia and anxiety, and the somatic treatments that have proven to be most effective, including mood-altering therapies, such as carbamazepine and light therapy. A molecular biological approach to mental retardation is also described. For now, the genetic, biochemical, neuroendocrine, electrophysiologic, neuroanatomic, and brain imaging studies appear best organized along disease lines. This is true even though many of the biological markers thus far identified appear to be nonspecific vulnerability factors, and that key neurotransmitters, such as dopamine, serotonin, norepinephrine, and γ-aminobutyric acid (GABA), appear to have crucial roles in a wide range of neuropsychiatric disorders.

The chapters in this section reveal steady progress in translating the new knowledge of basic science (described in the first part of this edition) into clinical studies. Thus, the relevance of

receptor subtypes, neurotransmitter interactions, neuropeptides, and new information about the structural organization of the brain for biological hypotheses have begun to be tested by clinical neuroscientists in both pre- and postmortem studies. Clinical tools, such as ligand binding procedures, receptor assays, high-pressure liquid chromatography, and positron emission tomography that have emerged from the basic scientist's laboratory have been developed rapidly. Advances in the techniques of PET scanning will no doubt provide knowledge about normal and abnormal brain functioning not possible through other means. When coupled with other brain imaging techniques, such as magnetic resonance imaging and, perhaps, brain electrical activity mapping, it may be possible to discern the abnormal interactions of regions of the brain that lead to pathological behaviors.

The section on Clinical Psychopharmacology is the largest component of the triad that comprises psychopharmacology. The state of the art of developing new psychopharmacologic means to treat the affective disorders, schizophrenia, geriatric psychiatric disorders, anxiety, childhood psychiatric disorders, and eating disorders is considered. Subsections consider pharmacokinetics, major drug side effects, the effects of psychotropic drugs on various functions in normal humans and infrahuman species, alcohol and drug abuse, and the development of new drugs from the viewpoint of industry and federal regulators. The importance of assessment methods using standardized interviewing schedules and explicit diagnostic criteria is highlighted throughout the clinical psychopharmacology section. Thirty years ago, psychiatric theory and practice were dominated by psychodynamic psychoanalytic thinking. Psychopharmacology emerged empirically, and its demonstrable results quickly made it competitive. Early debates between the advocates of the two schools of thought were often acrimonious. Psychoanalytic practitioners called psychotropic drugs "chemical straight jackets," and some psychopharmacologists predicted the demise of psychological approaches. Over the past 30 years, both extremes have been proven to be wrong. This edition demonstrates much of the change in psychopharmacology. Less evident (in this edition) are the changes in psychosocial treatments, which now include group, family, and social modalities, as well as cognitive therapy, desensitization, and behavioral shaping. Although some degree of competitiveness will continue to be inevitable, it becomes increasingly clear that both modalities will continue to be necessary: psychotropic drugs to reduce vulnerability and psychological treatments to enhance coping skills. Currently, both have limitations. Fortunately, the therapeutic armamentaria of both types of treatment modalities are constantly increasing. It seems likely that the future will bring more precise and powerful drugs. It is equally likely that improving

clinical and laboratory skills will permit the development of biological and behavioral markers that will permit early detection and intervention. Biological and psychological approaches should no longer be competitive but, rather, cooperative in the interest of the mentally ill. The issue for the future should no longer be one of pharmacotherapy versus psychotherapy but rather, which of the large number of available drugs should be employed for what conditions and with which of the increasing number of psychosocial interventions to enhance prevention and treatment.

The Psychopharmacology section presents the steady progress that has been made in developing new drug strategies in many conditions, even though truly novel approaches that are of dramatic therapeutic advantage have not yet been developed. Alprazolam and buspirone for the treatment of anxiety, carbamazepine for the treatment of affective disorders, clonidine for the treatment of opioid

withdrawal states and perhaps other addictions are examples of novel drugs that were not present a decade ago, but have since gained some measure of acceptance in clinical practice. The use of lithium to potentiate antidepressant action in nonresponders is an excellent example of the application of basic neuroscience knowledge to a therapeutic problem. Progress in treating schizophrenia has been least impressive. Some of the reasons for this are discussed by Hollister and Klerman in the introductory and final subsections. The novel approaches to drug treatment of schizophrenia described by Tamminga and Gerlach in Chapter 116 are not without benefit for some patients. Atypical neuroleptic drugs, such as clozapine and the benzamides, may yet find their way into broader clinical use for schizophrenia. This decade has been one of fine tuning our ability to use already-available drugs discovered in affective disorders, anxiety disorders, childhood disorders, schizophrenia, eating disorders, and sleep disturbances. The chapters concerning these topics describe the results of important studies that target predictors of response, duration of treatment, dosage schedule, side effects, withdrawal effects, etc., that are of great importance for safe and optimal drug utilization.

The tremendous importance the ACNP attaches to the understanding of all aspects of substance abuse for the well-being of our society is evidenced by the attention given in this edition to biological and psychopharmacologic studies of ethanol, cocaine, opioids, marijuana, phencyclidine, tobacco, and the phenylisopropylamines. There has been a vast increase in our knowledge of opioid mechanisms and how phencyclidine acts at a basic level. Clinical studies of alcohol, cocaine, and tobacco abuse as documented here have become much more sophisticated and have produced important data on risk factors and reward mechanisms.

This edition includes a chapter on teaching psychopharmacology. The ACNP has developed a model curriculum to facilitate educating medical students, residents, and mental health professionals of all disciplines in psychopharmacology. The philosophy behind this curriculum and its major elements are described.

Psychopharmacology began as an empirical science that quickly demonstrated clinical utility. Ultimately, its progress will be judged on the basis of its capacity to prevent and to treat neurological and psychiatric illnesses effectively. Both the prospects for and the impediments to rapid progress are impressive. We have much reason to believe that insights offered by the new technologies of neuroscience and molecular biology will lead to better and more specific diagnosis and treatment. New discoveries about multiple receptors for the monoamine neurotransmitters and the mechanisms involved in the regulation of their sensitivity and number will likely lead to new drugs with greater specificity and fewer adverse side effects. Methods probably will be developed for introducing neuropeptides or smaller molecules, which possess their activity, into the brain. Linkage studies and the methods of the molecular biologist may well permit the identification of absent or aberrant genes that predispose people to genetic vulnerability to the major mental illnesses. Environmental factors that convert the genotype to the phenotype will likely be better understood. Scientifically, prospects for the future are rosy.

Yet, impediments are formidable. Clearly, the major mental illnesses differ from the simple illnesses that are caused by the toxic or deficiency states in which medicine has had its greatest successes. Rather, they resemble those illnesses, like hypertension and some forms of diabetes or cancer, in which appropriate regulation of physiological processes is either inadequate or overwhelmed by environmental events. Animal models for the major human mental illnesses are still inadequate, and even these are threatened by political movements

that oppose animal experimentation. Uncertain economic forecasts and fragile international relationships make for an unstable economy and national priorities that compete with those of health-related research. Even in the health research area, there is competition between mental health research and the physical illnesses that are still a burden to society. Along with the brilliant advances in science, there is emerging an antiscience manifested by a resurgence of creationism, fundamentalism, and intense nationalism.

Given these opposing forces and the intense competition among them, it is hazardous to predict where we will be a decade from now. On the optimistic assumption that all will go well in the basic and clinical neurosciences, we may confidently predict that in the next decade there will be very many surprises.

Psychopharmacology: The Fourth Generation of Progress

Floyd E. Bloom, M.D. & David J. Kupfer, M.D.

Preface

The accelerated pace of modern scientific research has inevitably reduced the length of a scientific generation to considerably less than the classic two decades. In fact, the history of this series has been one of progressively shorter and shorter intervals of assessment of the progress within our field. Like its predecessors, this volume seeks to redefine the scientific field of neuropsychopharmacology for its parent organization, The American College of Neuropsychopharmacology. In this iteration, the field's definition has been constructed from the two interrelated bodies of work that comprise the major working arms of the College: the *clinical* investigation of psychiatric and neurological disorders in terms of their biologically defined mechanisms of pathogenesis, treatment and prevention; and the *preclinical* foundations of neuropsychopharmacology in terms of the essential signaling mechanisms by which neurons interact to perform the behavioral level operations of the brain and mental activity. In these parallel tracks of effort, drugs are a tool to dissect the chemical signaling systems of the brain, as well as a means to restore functions disrupted by brain diseases. The better the characterization of the chemical signaling systems, the more insightful will be the analyses of the drugs in their therapeutic assessment.

A slight departure of this book from its predecessor volumes is the attempt to provide a more comprehensive overview of the clinical and preclinical arms of the field. Here the approach is designed first to provide new scholars with overviews of preclinical and clinical psychopharmacology, and then more detailed coverage to understand the methods by which data in each of these arms are assessed in research. The introductory sections provide a basis for the detailed coverage of the enormous amounts of progress that have been achieved since the previous volume. Finally, the coverage builds upon these foundations with assessments of the most recent cross-cutting issues. There is intentionally extensive cross-referencing between clinical and preclinical subjects. The text is designed to allow experts in both spheres to find the latest assessments of progress, while also permitting the less experienced readers to increase their appreciation of the work underway. The cast of authorships is broad and international, by design going beyond the boundaries of the College's current membership. By providing a road map to the linkages between the major topics of today's research, the editors and authors hope to illuminate critically the most exciting discoveries, as well as to indicate the important gaps that need attention, while allowing room for the unexpected discoveries that will almost certainly emerge. We close this preface with our sincere appreciation to all those who worked with us on this effort.

Neuropsychopharmacology: The Fifth Generation of Progress

Kenneth L. Davis, M.D., Dennis Charney, M.D., Joseph T. Coyle, M.D., Charles Nemeroff, M.D., Ph.D.

PREFACE

Neuropsychopharmacology: The Fifth Generation of Progress appears at an important moment in the history of psychopharmacology. We have recently ended the decade of the brain, a decade that witnessed enormous progress in understanding fundamental physiology of the central nervous system. The fruits of these basic science discoveries have already resulted in important progress in the treatment of mental illness. The importance of these fundamental discoveries has recently been acknowledged by the awarding of the Nobel Prize in Psychology or Medicine to three members of the College, Arvid Carlsson, Paul Greengard and Eric Kandel for their discoveries on neuronal signaling. This edition in the *Generation of Progress* series details advances in both the basic science and clinical application of recent research in psychopharmacology. It also demonstrates the prospects for even greater advances in the future.

-Charles P. O'Brien, M.D., Ph.D.
ACNP President, 2001

-Joseph T. Coyle, M.D.
ACNP President, 2002

Neuropsychopharmacology Reviews: The Next Generation of Progress

Salvatore J. Enna, Ph.D.

This volume represents the inaugural issue of *Neuropsychopharmacology Reviews.* As an annual publication, the offering is designed to provide authoritative and timely coverage of contemporary topics in the field. As subscribers to *Neuropsychopharmacology*, members of the College have early access to these reports both on line and in print.

Neuropsychopharmacology Reviews replaces the *Generation of Progress*, which consisted of five volumes published intermittently between 1968 and 2002. While the *Generation of Progress* served for decades as a major reference work, a single large volume is an increasingly difficult mechanism for promulgating new data given the pace of research, developments in information technology, and the time needed for authoring, editing, printing, and distributing such a massive work. After considering several alternatives, it was decided that a yearly publication of review articles is more easily managed, and makes possible more timely coverage of critical topics than is possible with a major reference work. Timely because the reviews are written shortly before the publication, and topical in that it will be possible to publish updates and perspectives on the same subject as often as warranted. To help ensure timeliness, the work includes a Hot Topics chapter that is prepared just prior to the production deadline. This section contains summaries of some of the most recent developments in the field. The volume also features downloadable graphics that can be used as a teaching resource. It is anticipated that the regular publication of this high-quality review journal will build a recognizable franchise, further establishing the College as the most authoritative source for information in the discipline.

While the primary audience for this offering is clinical investigators and neuroscientists, authors are encouraged to prepare reports that are informative for practicing physicians and the lay public as well. Although the aim is to provide coverage of all aspects of clinical and basic neuropsychopharmacology every five years or so, no limits are placed on how often a particular subject may be reviewed since selection of material is driven by developments in the field.

Preparation of *Neuropsychopharmacology Reviews* is overseen by members of the College, two of whom serve as Series Editors. The editors are assisted by an Editorial Board comprised of individuals who will serve as Volume Editors on subsequent editions of the work. The College is fortunate in having Husseini Manji and Peter Kalivas as the initial Series Editors. Production and publication is handled by the Nature Publishing Group.

The College is indebted to many individuals for the timely production of this first issue of *Neuropsychopharmacology Reviews.* Besides Drs Manji and Kalivas, others deserving special recognition are Ronnie Wilkins and his associates in the ACNP office, in particular Jennifer Mahar and Diane Drexler, and to Joyce-Rachel John and Elizabeth Durzy with the Nature Publishing Group. Thanks to their extraordinary efforts, less than a year elapsed between recruitment of the Series Editors and receipt of the final manuscript for this volume. During this interval the theme was selected, authors recruited, and the manuscripts written, peer reviewed and revised. Thus, as intended, this offering is timely and current.

Neuropsychopharmacology Reviews will serve not only as an information source, but also as a showcase for work performed by ACNP members and as a stimulus for research in the field. To these ends, readers are encouraged to recommend topics for consideration by the Editorial Board. Please do not hesitate to communicate directly with Drs Manji or Kalivas. We look forward to your comments and trust you will enjoy and benefit from this latest offering from the College.

Sam J Enna, PhD
Chair, ACNP Publications Committee
The University of Kansas, School of Medicine,
Kansas City, KS, USA

Snapshots

Alan Frazer, Ph.D., ACNP Secretary, 2011

The following pages provide snapshots of the growth and evolution of our College over the past 50 years. Shown initially are the programs for the organizational meeting of the ACNP in 1961, its first Annual Meeting in 1963, and the meetings leading up to the 50th Anniversary Meeting. The growth in size of the College and its Annual Meeting limits the detail given for the last two meetings. Nevertheless, these programs are a testament to the growth of the field, as are the listings of the plenary sessions that follow. Finally, our past presidents were invited to write their personal perspective of the development of the field of Neuropsychopharmacology. As you browse your way through these reflections, the broad and sometimes divergent views of our leaders will become apparent and one appreciates the wisdom that has guided our College.

AMERICAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY
PROGRAM FOR THE FIRST ORGANIZATIONAL MEETING:
WOODNER HOTEL, WASHINGTON, D.C.
OCTOBER 7TH AND 8TH, 1961

Organizing Committee:
Frank Ayd, Jr., M.D.
Bernard Brodie, M.D.
Jonathan O. Cole, M.D.
Paul Feldman, M.D.
Paul H. Hoch, M.D.
Theodore Rothman, M.D.

OCTOBER 7TH, 1961

Morning:

8:30 to 9:00 A.M. Registration in front of the meeting room.

9:00 to 1:00 P.M. Business Meeting.
Chairman, Theodore Rothman, M.D.

1. Introduction

   a. "The Present Need For A College"
      Jonathan O. Cole, M.D.

   b. "Proposed Objectives For The College"
      Paul H. Hoch, M.D., and
      Bernard B. Brodie, Ph.D.

2. Report of the Organizing Committee

3. Election of Charter Fellows

4. Adoption of Constitution and By-Laws

5. Report on Contributing and Sponsoring Memberships

6. Election of Ad Hoc Committee for Nomination of Officers

Afternoon:

2:30 to 5:00 P.M. "Contributions of Basic Research to Clinical Neuropsychopharmacology"
Moderator: Joel Elkes, M.D.

Evening:

7:30 P.M. Banquet

"Current Program of the Psychopharmacology Service Center, NIMH"

Speaker: Jonathan O. Cole, M.D.

OCTOBER 8th, 1961

Morning:

9:00 to 10:30 A.M. Symposium of Membership

"Contributions of Clinical Neuropsychopharmacology to Basic Research"

Moderator: Fritz A. Freyhan, M.D.

10:30 to 1:00 P.M. Business Meeting

1. Report of Ad Hoc Nominating Committee
2. Election of Officers by Charter Fellows
3. Organization Proposals by the Membership

Program for 1st Annual ACNP Meeting
January 25-27, 1963

PLENARY PROGRAM – FIRST ANNUAL MEETING
WOODNER HOTEL – WASHINGTON, D.C.

Friday, January 25

12:30 p.m. to 2:00 p.m. – Group Luncheon

2:00 p.m. to 5:00 p.m. – Study Group Meetings

8:15 p.m. to 10:15 p.m. – Top of the Park
Words and Meaning in Psychopharmacology
A discussion to be opened by:
B.B. Brodie
D. Mck. Rioch
H. Waelsch
H. Lehmann
J. Zubin
Joel Elkes (Moderator)

Saturday, January 26

Morning Plenary Session
Chairman, Paul Hoch

1. 9:00 a.m. to 9:30 a.m.
Genetic Factors in Relation to Pharmacological Research
B. Ginsburg

9:30 a.m. to 9:45 a.m.
Discussion to by opened by
B.B. Brodie

2. 9:45 a.m. to 10:05 a.m.
Inherited Sensitivity to Pentobarbital in Mice
C. Kornetsky
R. Bickham

3. 10:05 a.m. to 10:25 a.m.

The Effect of Psychotropic Drugs on Exploratory and Adaptive Behavior: A Critique on the Use of Activity Cages
G. Everett

4. 11:05 a.m. to 11:45 a.m.

Studies on Conditioning of Physical Dependence and Reinforcement of Opioid Drinking Behavior in Morphine Addicted Rats
A. Wikler

11:45 a.m. to 12:00 noon

Discussion to be opened by:
Joel Elkes

12:00 noon to 1:30 p.m. – Group Luncheon

Afternoon Plenary Session

Chairman, Milton Greenblatt

5. 1:30 p.m. to 1:50 p.m.

Drugs and Placebo: A Model Design
S. Ross
A. Krugman
S. Lyerly
D. Clyde

6. 1:50 p.m. to 2:10 p.m.

Comparative Behavioral Effects of Imipramine and Desipramine
A. DiMascio
M.A. and G. Heninger

2:10 p.m. to 2:25 p.m.

Discussion of papers 5 and 6 to be opened by:
S. Fisher

7. 2:25 p.m. to 2:45 p.m.

The Milieu as a Factor in Response to Medication: A Reappraisal
G. Grosser
H. Wechsler
H. Freeman

8. 2:45 p.m. to 3:05 p.m.

The Effect of Psychotherapy and Ataraxic Drugs on Length of Hospital Stay and Readmission Rate of Schizophrenic Patients
P. May

3:35 p.m. to 5:00 p.m.

Reports of Study Group Chairmen

Sunday, January 27

9:00 a.m. to 10:45 a.m.

Annual General Business Meeting

11:00 a.m. to 1:00 p.m.

The Implications of the New FDA Law and Regulations for Research in Psychopharmacology – Panel Discussion
I. Siegel
H. Beecher
H. Brill
L. Lasagna
J. Cole (Moderator)

TUESDAY, December 14, 1976

9:00 a.m. – 12:30 p.m.
Welcoming Remarks: Keith F. Killam, President
Alberto DiMascio, Secretary-Treasurer

Presentation of Daniel H. Efron Memorial Award

PLENARY SESSION
10 YEARS OF PROGRESS IN PSYCHOPHARMACOLOGY

Historical Overview
Keith F. Killam, Ph.D.
President, ACNP
Department of Pharmacology
University of California Medical School
Davis, California 95616

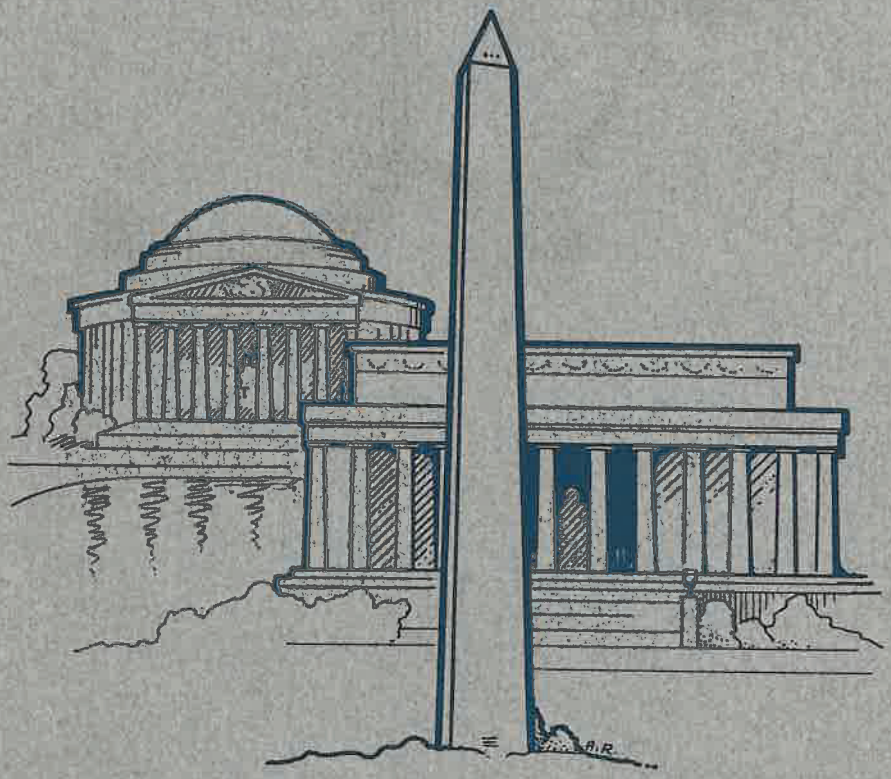
Strategies of Basic Research
Seymour S. Kety, M.D.
Psychiatric Research Laboratories
Harvard Medical School
Boston, Massachusetts 02114

Giving and Taking Drugs: Social, Political and Ethical Consequences in the Past Decade
Daniel X. Freedman, M.D.
Department of Psychiatry
University of Chicago
Chicago, Illinois 60637

Strategies of Clinical Research
Heinz Lehman, M.D.
Department of Psychiatry
McGill University
6875 LaSalle Boulevard
Verdun, Quebec, Canada

In the Service of Psychopharmacology Research:
The PSC-PRB NIMH Program 1956-1976
Jerome Levine, M.D.
Psychopharmacology Research Branch
NIMH
Rockville, Maryland 20852

American College of Neuropsychopharmacology



General Program

25th Annual Meeting

December 8-12, 1986
The Mayflower Hotel
Washington, D.C. U.S.A.

President: E. H. Uhlenhuth, M.D.
Program Chairman: Philip A. Berger, M.D.

President's Plenary Session 1986
25th Anniversary of ACNP

Welcoming Remarks and Announcements

E. H. Uhlenhuth, President

Research Strategies in Neuropsychopharmacology

Co-Chairs: Herbert Y. Meltzer
E.H. Uhlenhuth

Strategies for Research in Basic Psychopharmacology and Neurobiology

Solomon H. Snyder

Future Directions, Goals in Basic Psychopharmacology and Neurobiology

Floyd E. Bloom

Strategies for Research in Biological Psychiatry

Daniel X. Freedman

Future Directions in Biological Psychiatry

Frederick K. Goodwin

Strategies in Clinical Psychopharmacology

Leo E. Hollister

Future Prospects for Clinical Psychopharmacology

Gerald L. Klerman

PLENARY PROGRAM – TWENTY-FIFTH ANNUAL MEETING
MAYFLOWER HOTEL – WASHINGTON, D.C.
DECEMBER 8-12, 1986

25th Annual Meeting
The Mayflower Hotel
Washington, D.C. U.S.A.
December 8-12, 1986

Scientific Sessions

Teaching Psychopharmacology in the 1990's
Co-Chairs: Ira D. Glick
Robert D. Myers

The Delicate Balance Between Discovery and Action
Moderator: Roger E. Meyer

Research Strategies in Neuropsychopharmacology
Co-Chairs: Herbert Y. Meltzer
E.H. Uhlenhuth

Amino Acids and Acetylcholine
Chair: H.C. Fibiger

The Neuropsychopharmacology of Daytime Alertness
Chair: William C. Dement

Ethanol, Membranes, and Neurotransmitters: Novel Approaches to Modifying the Behavioral Actions of Alcohol
Co-Chairs: Steven M. Paul
Roger E. Meyer

Neurotoxins
Chair: Israel Hanin

Methodologies for Assessing Central Dopaminergic Function: Plasma and Urinary Homovanillic Acid Following Debrisoquin Administration
Co-Chairs: James Leckman
James Maas

Consent Issues in Human Research: Innovative Approaches
Co-Chairs: Burr Eichelman
Magda Campbell

The Onset and Therapeutically-Specific Actions of Anti-depressant Drugs
Co-Chairs: Alan Frazer
Martin M. Katz

Recent Developments in the Regulation of the Mesolimbic and Mesocortical Dopamine Systems: Basic and Clinical Implications
Co-Chairs: George F. Koob
Charles B. Nemeroff

Quantitative Neuropathology in Schizophrenia
Chair: Dilip V. Jeste

Eye Movement Dysfunctions in Schizophrenia
Chair: Seymour S. Kety

Pharmacokinetics in Psychiatry: An Update
Co-Chairs: David J. Greenblatt
Richard I. Shader

Science Policy and the Addictions: 1966 – 1986
Chair: Daniel X. Freedman

Human Electrophysiology in Psychiatry
Chair: Enoch Callaway

Biology of Psychiatric Disorders of Childhood
Chair: Roland Ciaranello

Peptides and the Endocrinology of Affective Disorders
Chair: Arthur J. Prange, Jr.

Zeitgebers, Biological Rhythms, and Depression
Co-Chairs: David J. Kupfer
Cindy L. Ehlers

Post-Marketing Surveillance of Psychotherapeutic Drugs II
Co-Chairs: Leo E. Hollister
Mitchell B. Balter

Neurotransmitters in Affective Disorders and Aggression
Chair: Dennis L. Murphy

Mechanism of Action of Treatments of Affective Disorders
Chair: Robert M. Post

The Psychopharmacological Effects of Light in Seasonal Affective Disorder
Co-Chairs: Alfred J. Lewy
Norman E. Rosenthal

Biology of Dementia
Chair: Richard C. Mohs

Treatment of Childhood Disorders
Chair: Judith Rapoport

Marshaling and Governing Resources for Biomedical Research and Research Training - Strategies for the 1990's
Chair: Gerald L. Klerman

Sensitization to Psychoactive Drugs: New Perspectives
Co-Chairs: Peter W. Kalivas
David S. Segal

Design and Analysis Issues
Chair: John E. Overall

Clinical Psychopharmacology of Schizophrenia
Chair: John J. Kane

Neuroanatomy, Neurochemistry, and Neurophysiology of the Aminergic Systems I
Chair: George Aghajanian

Neuroanatomy, Neurochemistry, and Neurophysiology of the Aminergic Systems II
Chair: George Aghajanian

Biology of Schizophrenia I
Co-Chairs: Malcolm B. Bowers
Monte S. Buchsbaum

Biology of Schizophrenia II
Co-Chairs: Malcolm B. Bowers
Monte S. Buchsbaum

Alcohol and Drug Abuse I
Co-Chairs: Roland R. Griffiths
Nancy K. Mello

Alcohol and Drug Abuse II
Co-Chairs: Roland R. Griffiths
Nancy K. Mello

Alcohol and Drug Abuse III
Co-Chairs: Roland R. Griffiths
Nancy K. Mello

What is the Function of Central and Peripheral Epinephrine?
Co-Chairs: William Z. Potter
Ivan N. Mefford

Clinical Psychopharmacology of Affective Disorders
Chair: Gerald L. Klerman

New Developments in the Psychopharmacology of Personality Disorders
Co-Chairs: Larry J. Siever
S. Charles Schulz

New Advances in the Psychopharmacology of Excitatory Amino Acids
Co-Chairs: Stephen M. Stahl
Leslie L. Iversen

Problems in Neuropsychopharmacologic Drug Evaluation: Perspectives of FDA, Academia, and Industry
Chair: Louis Lasagna

Biology of Anxiety
Chair: Donald F. Klein

Geriatric Psychopharmacology: Treatment Update
Chair: Lissy F. Jarvik

The Unipolar/Bipolar Dichotomy: A Re-Evaluation
Chair: Paula J. Clayton

Neuropeptides
Co-Chairs: Stanley J. Watson
Huda Akil

Effects of Psychotropic Drugs on Major Functions in Normal Humans and Infra-Human Species
Chair: E.H. Uhlenhuth

Associations among Phencyclidine Receptors, Sigma Receptors, and Excitatory Amino Acid Antagonists
Chair: James H. Woods

MA-ergic Regulation of Aggression and Impulse Control I
Co-Chairs: Herman van Praag
Markku Linnoila

MA-ergic Regulation of Aggression and Impulse Control II
Co-Chairs: Herman van Praag
Markku Linnoila

Receptors I
Chair: Elliott Richelson

Receptors II
Chair: Elliott Richelson

Side Effects
Chair: Richard J. Wyatt

Treatment of Anxiety
Chair: Donald F. Klein

Neuropsychopharmacology of Eating Disorders
Chair: Katherine Halmi

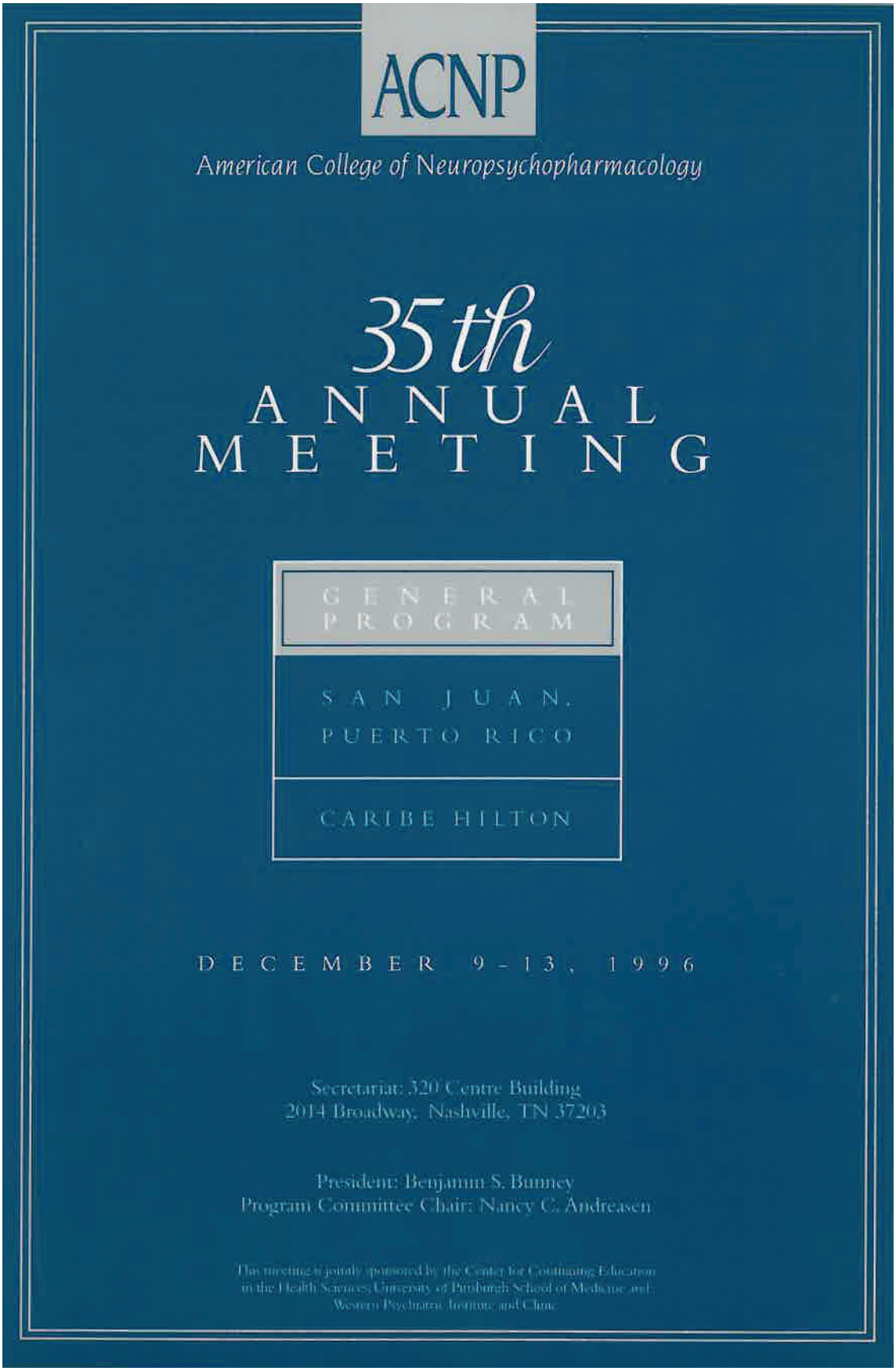
The Biology of Affective Disorders
Chair: J. Christian Gillin

Environmental Factors Influencing Drug Action
Chair: Leonard Cook

The Process of CNS Drug Development and Acceptance: Is it Rational or Even Intelligent?
Co-Chairs: Morton E. Goldberg
Bernard Dubnick

Discussion of Pertinent Topics in the Use of Animals in Neuropsychopharmacologic Research
Chair: Keith Killam

Selected Topics in Clinical Psychopharmacology
Chair: Richard I. Shader


ACNP
American College of Neuropsychopharmacology
35th
ANNUAL
MEETING
GENERAL
PROGRAM
SAN JUAN,
PUERTO RICO
CARIBE HILTON
DECEMBER 9-13, 1996
Secretariat: 320 Centre Building
2014 Broadway, Nashville, TN 37203
President: Benjamin S. Bunney
Program Committee Chair: Nancy C. Andreasen
This meeting is jointly sponsored by the Center for Continuing Education
in the Health Sciences, University of Pittsburgh School of Medicine and
Western Psychiatric Institute and Clinic

December 9 - 13, 1996
Caribe Hilton
San Juan, Puerto Rico

President's Plenary Session

Welcoming Remarks
Moment of Silence
Benjamin S. Bunney, President

Presentation of Awards
David Kupfer, Chair
Honorific Awards Committee

Beyond Molecular Biology

Chair: Benjamin S. Bunney

Logistics of Brain Development: From Molecules to Brain

Pasko Rakic

Activation of c Fos by Psychotropic Drugs: Does the Brain Care?

Steven E. Hyman

Beyond the Dopamine Receptor

Paul Greengard

Huntington's Disease: From Molecules to Mind?

Christopher A. Ross

Panels

University-Industry Collaborations: Problems, Challenges and Promises
Chair: Charles B. Nemeroff

Amyloid Protein Receptors
Co-Chairs: Emmanuel M. Landau
Steven M. Paul

Anatomical Correlates of Positive Symptoms in Schizophrenia
Chair: Alan Breier

Drugs of Abuse Alter Intracellular Signaling in the Ventral Striatum: From Genes to Behavior
Co-Chairs: Eric J. Nestler
Ann E. Kelley

Neurotensin, Antipsychotic Drugs and Schizophrenia: New Insights
Co-Chairs: Daniel M. Dorsa
Charles B. Nemeroff

New Paradigms for the Enduring Effects of Stress
Co-Chairs: Larry J. Siever
Paul Plotsky

Nitric Oxide in the Brain: Molecular Biology Behavior and Novel Pharmacologic Opportunities
Co-Chairs: Ted M. Dawson
Paul Greengard

Apolipoprotein E in Alzheimer's Disease
Co-Chairs: D.P. Devanand
Gary W. Small

Evolving Molecular Targets for Cocaine Pharmacotherapy
Co-Chairs: Thomas R. Kosten
Eric Nestler

Immune Dysfunction and the CNS: Recent Findings
Co-Chairs: Jack M. Gorman
David Strauss

New Drugs with Novel Mechanisms
Co-Chairs: Nancy C. Andreasen
Dorothy W. Gallager

Pre- and Post-Synaptic Imaging of Dopamine Transmission in Schizophrenia: Convergences and Controversies
Co-Chairs: Marc Laruelle
Robert B. Innis

Working Memory and Schizophrenia
Co-Chairs: David Braff
Richard Keefe

Atypical Antipsychotic Drug Treatment of First Episode and Recent Onset Schizophrenia
Chair: Jeffrey A. Lieberman

Controversies in Nicotine and Tobacco Smoking Actions
Co-Chairs: Edward F. Domino
Edythe D. London

Dynamic Organization of the Brain During Sleep
Co-Chairs: Alexander A. Borbély
Mircea Steriade

Obesity: Molecular Mechanisms Regulating Food Intake and Its Disorders
Co-Chairs: Steven M. Paul
Theresa A. Branchek

Oxytocin in Neuropsychiatric Illness: From Gene to Behavior
Co-Chairs: Eric Hollander
Thomas R. Insel

The Relationship Between Local Circuit Dysfunction and Cognitive Impairment in Schizophrenia
Co-Chairs: Daniel C. Javitt
Robert W. McCarley

Approaches to Assessing and Understanding Thalamic Pathology in Schizophrenia
Co-Chairs: William Byne
Monte Buchsbaum

Clinical Trials in Depressed Patients: Differences Between Europe and the United States
Co-Chairs: Manfred Ackenheil
Yves Lecrubier

Genetic and Epigenetic Factors in the Development of the CNS and the Implications for the Etiology of Mental Disorders
Co-Chairs: Douglas L. Meinecke
Stephen H. Koslow

The Interrelationship of Cardiovascular Disease, Mood and Anxiety Disorders
Co-Chairs: Charles B. Nemeroff
K. Ranga R. Krishnan

The Role of Glutamate in the Acute and Chronic Actions of Psychomotor Stimulants
Chair: Charles Bradberry

Presenilins and Alzheimer's Disease
Co-Chairs: Kenneth L. Davis
Nikolaos Robakis

Inflammatory Mechanisms in Neurodegeneration and Alzheimer's Disease
Co-Chairs: Giulio Maria Pasinetti
Kenneth L. Davis

Beyond Hypofrontality in Functional Brain Imaging of Schizophrenia
Co-Chairs: Daniel R. Weinberger
Karen Faith Berman

Gut Feelings: Brain-Gut Interactions in Psychiatric Disorders
Co-Chairs: Rita J. Valentino
Yvette Taché

Human Brain Development: *In Vivo* Brain Imaging
Chair: Judith L. Rapoport

Is Clozapine a Cost-Effective Treatment for Refractory Schizophrenia?
Chair: Dennis S. Charney

New Insights in Receptor Regulation Mechanisms and Implications
Co-Chairs: Mark W. Hamblin
Bryan L. Roth

The Continuity Between Childhood and Adult Depression: Clinical and Biological Findings
Co-Chairs: Myrna M. Weissman
Judith L. Rapoport

Dopamine in the Prefrontal Cortex: What Does It Do?
Co-Chairs: Susan R. Sesack
Terry E. Goldberg

Neuroanatomical and Physiological Basis of Late-Life Depression: An Integrative Approach
Co-Chairs: Harold A. Sackeim
Anand Kumar

Schizophrenia Cognition, Clinical Symptoms and Pharmacologic Treatment
Co-Chairs: William T. Carpenter Jr.
Richard C. Mohs

Slowing Neurodegeneration: Is Selegiline a Paradigm and What Might Its Mechanism Be?
Co-Chairs: Pierre N. Tariot
Steven Ferris

Molecular Biology and Genetics of Mental Disorders
Co-Chairs: Elliot S. Gershon
John I. Nurnberger Jr.

Molecular Biology and Genetics of Mental Disorders
Co-Chairs: Wade Berrettini
Lynn DeLisi

Alcoholism from Genes to Imaging
Co-Chairs: Nora D. Volkow
Markku Linnoila

Brain Imaging of Bipolar Disorder
Co-Chairs: Bruce M. Cohen
Alan F. Schatzberg

CNS Effects of Reproductive Endocrine Change
Chair: David R. Rubinow

Dopamine Receptor Circuits in Human Brain Neuroanatomy, Ontogeny and Neuropsychiatric Illness
Co-Chairs: James H. Meador-Woodruff
Joel E. Kleinman

Schizophrenia: A Developmental Perspective
Co-Chairs: Judith L. Rapoport
Alan S. Brown

Study Groups

Genetic Linkage Studies in Panic Disorder: Defining the Phenotype
Chair: Jerrold F. Rosenbaum

Is Glutamatergic Transmission Altered in Schizophrenia? Clinical Evidence
Chair: Carol A. Tamminga

Medication Compliance in Substance Abuse Treatment Trials:
Is It Important, How Can It Be Measured and What Can Be Done to Improve It?
Chair: Henry R. Kranzler

Melatonin: Current Issues and Controversies
Chair: Alfred J. Lewy

A Psychopharmacologic Jam Session: A Dialogue on Mood and Anxiety Disorders
Chair: David S. Janwosky

Tracking the Next Generation of Antipsychotic Drugs
Chair: David Pickar

Are TCAs More Effective than SSRIs in Severe Depression?
Chair: Harold A. Sackeim

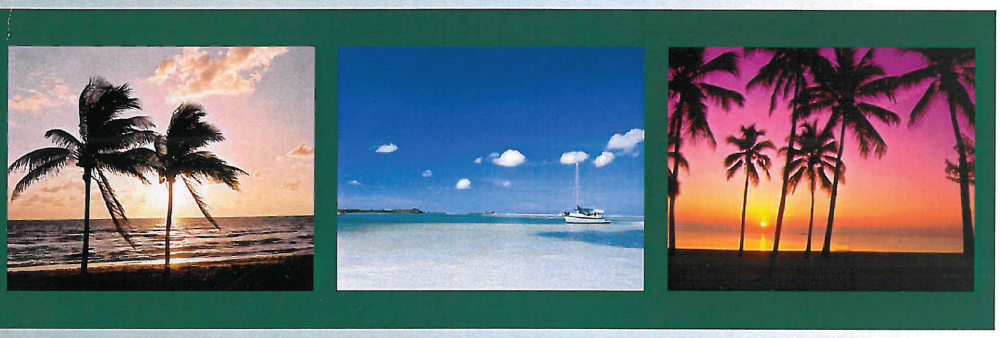
Migraine: Preclinical Substrates for Novel Therapeutic Intervention
Chair: J. David Leander

New Approaches to Medications Development for the Treatment of Cocaine Abuse
Chair: Jack H. Mendelson

Quantitative Trait Loci Mapping in Animal Models of Substance Abuse
Chair: Wade Berrettini

Repetitive Transcranial Magnetic Stimulation (rTMS): A Novel Probe of Mood
Chair: Robert H. Belmaker

Strategies for Defining a More Homogeneous Phenotype of Autism for Family/Genetic Studies
Chair: Eric Hollander



ACNP

45th Annual Meeting Program Book

December 3-7, 2006
Hollywood, Florida

President:
Kenneth L. Davis

Program Committee Chair:
Larry Siever

This meeting is jointly sponsored by
the Vanderbilt University School of Medicine Department of Psychiatry and
the American College of Neuropsychopharmacology.

ACNP 45th Annual Meeting
Hollywood, Florida
The Westin Diplomat
December 3-7, 2006

President's Plenary

Welcoming Remarks and Moment of Silence
Kenneth Davis
President

Presentation of Honorific Awards and Media Award
Daniel Weinberger
Chair, Honorific Awards Committee

Beyond Linkage: Psychiatric Genetics in the Age of Functional Genomics

Chair: Kenneth Davis

9:00 a.m. Mechanisms of Chromatin Remodeling in Neuropsychopharmacology
Eric Nestler

9:45 a.m. Genetics: The Gorgon's Head of Schizophrenia Research
Michael O'Donovan

10:30 a.m. The Genetic Architecture of Autism Spectrum Disorders
Joseph Buxbaum

11:15 a.m. Beyond Linkage: Whole Genome Association
Wade Berrettini

Distinguished Lecture

Dissection of Complex Traits in the Era of High-Throughput Genomics

Chair: Kenneth Davis

Presented By
Jonathan Pritchard

Professor, Department of Human Genetics
University of Chicago

PANELS

Co-Morbid Pain and Addiction: Novel Treatments
Chair: Charles O'Brien
Co-Chair: Petra Jacobs

Determinants of Vulnerability to Nicotine Addiction in Schizophrenia
Chair: Tony George
Co-Chair: Sherry Leonard

New and Differing Roles for Brain-Derived Neurotrophic Factor in Cocaine Addiction
Chair: David Self
Co-Chair: Jacqueline McGinty

Drug Development
New Medication Development for Schizophrenia and Mood Disorders: Academia, Industry and FDA Perspectives
Chair: Husseini Manji
Co-Chair: William Carpenter

RNA Splicing and Processing in Neuropsychiatric Disease
Chair: Vahram Haroutunian

The Fragility of Phases of Memory: Reactivation and Reconsolidation
Chair: Jack Gorman
Co-Chair: Cristina Alberini

The Neuroscience of Affiliation: From Basic Science to Experimental Therapeutics in Autism and Related Disorders
Chair: Eric Hollander
Co-Chair: Jennifer Bartz

Unravelling Sources of Genetic Complexity of Complex Disorders: Lessons from Neurologic Disorders
Chair: Kathleen Merikangas

Cellular Mechanisms of Stress-Induced Atrophy of Prefrontal Cortex
Chair: Ronald Duman

Conducting Treatment Research in Decisionally Impaired Subjects: Problems and Possible Solutions
Chair: Dilip Jeste
Co-Chair: Trey Sunderland

Genetics of Cognitive Deficits in Schizophrenia: What Is Inherited and How?
Chair: Michael Davidson

Insulin Signaling in the Forebrain and Its Relevance to Cognition and Schizophrenia
Chair: C. Anthony Altar
Co-Chair: Konrad Talbot

Drug Development
Pharmacology and Molecular Genetics of Nicotinic ACh Receptors: Relevance for Treating Nicotine Addiction
Chair: Stephen Stahl

Psychiatric Diagnosis Revisited in the Era of Molecular Genetics
Chair: Fritz Henn

Treating Affective Disorders - Moving from Resetting Chemical Imbalance to Targeted Neuromodulatory Interventions
Chair: Thomas Schlaepfer
Co-Chair: Hilary Blumberg

Bipolar Disorder: What is the Core Deficit?
Chair: Ellen Leibenluft
Co-Chair: Mary Phillips

Large Scale Pharmacogenetics in Large-Scale Trials
Chair: David Goldman

Drug Development
New Experimental Approaches to Treatment of Schizophrenia
Chair: P. Jeffrey Conn

Prefrontal-Accumbens-Amygdala Circuitry in Impulsive Aggression:
Implications for Treatment Development
Chair: Eric Hollander
Co-Chair: Antonia New

Synapse Failure in Dementia: How Much is Functional?
Chair: Ralph Nixon
Co-Chair: William Mobley

Drug Development
The Vesicular Monoamine Transporter (VMAT) as a Target for Novel Therapeutics
Chair: Irwin Lucki
Co-Chair: Wade Berrettini

Transcriptional Regulation of Synaptic Function
Chair: Lisa Monteggia
Co-Chair: Eric Nestler

Drug Development
Emerging Tools for Alzheimer's Disease Modification Trials
Chair: Gary Small
Co-Chair: Trey Sunderland

Genes and Convergent Molecular Pathways in Schizophrenia Pathogenesis
Chair: Daniel Weinberger

Intracellular Mechanisms for Regulating Cell Sensitivity to Corticotropin-Releasing Factor and Stress
Chair: Rita Valentino
Co-Chair: Dimitri Grigoriadis

Mechanisms of Substance Abuse Risk in ADHD
Chair: Scott Kollins
Co-Chair: James M. Swanson

Recent Findings from the STAR*D Trial
Chair: A. John Rush
Co-Chair: Myrna Weissman

Role of Cardiovascular Drugs with Anti-Hypertensive Properties in the Treatment of Alzheimer's Disease Dementia
Chair: Vahram Haroutunian
Co-Chair: Giulio Pasinetti

Salvinorin A: From Natural Product to Validated Molecular Target for Mood-Related Disorders
Chair: Bryan Roth
Co-Chair: William Carlezon

5HT2A Receptor as a Potential Therapeutic Target for Depression
and Suicide: Evidence from the Bench
Chair: Maria Antonia Oquendo
Co-Chair: Zubin Bhagwagar

Can Correcting Cognitive Deficits Improve Treatment Responses in Substance Abusing Patients?
Chair: Frank Vocci

Epigenetics of Psychiatric Disorders
Chair: Ted Abel
Co-Chair: Christine Colvis

Kynurenic Acid: A New Player in the Pathophysiology of Schizophrenia
Chair: Robert Schwarcz

New Frontiers in Imaging Phasic Dopamine Release in Humans
Chair: Dean Wong
Co-Chair: Rikki Waterhouse

Treatment of Frontotemporal Dementia: Identifying Pathophysiologic Targets
Chair: Bruce Pollock
Co-Chair: Tiffany Chow

VMAT2 in Health and Disease: Individual Differences, Imaging and New Therapeutics
Chair: George Uhl
Co-Chair: Kathleen Clarence-Smith

Evaluating the Efficacy and Safety of Antidepressants for Depression and Suicide Risk in Youth and Adults
Chair: J. John Mann

Integrative Genomics of Alcoholism
Chair: David Goldman
Co-Chair: Marc Schuckit

Mechanisms of Stress-Induced Modulation of Prefrontal Cortex Circuitry and Function
Chair: Susan Sesack
Co-Chair: Lois Winsky

Drug Development
Molecules, Methods and Memory: Research Update on Alzheimer's Disease Therapeutics from the ADCS
Chair: Mary Sano

New Bioinformatics Approaches for Neuropsychopharmacology
Chair: Robert Harris

Drug Development
Time Course of Drug and Placebo Response: Implications for Clinical Trials and Drug Discovery
Chair: William Carpenter
Co-Chair: Shitij Kapur

Translating Research on the Metabolic Effects of Antipsychotics into Public Health and Treatment Guidelines
Chair: John Newcomer

An Insular View of Anxiety
Chair: Murray Stein
Co-Chair: Martin Paulus

Causes and Consequences of Inhalant Abuse
Chair: Stephen Dewey

Drug Addiction: A Disorder of Pathological Learning and Memory
Chair: Nora Volkow
Co-Chair: David Shurtleff

Mechanistic Convergence of Cortical GABA and Glutamate Theories of Schizophrenia
Chair: David Lewis
Co-Chair: Bita Moghaddam

Drug Development
Molecular Libraries Roadmap: Small Molecules, Big Science
Chair: Linda Brady
Co-Chair: Glen Hanson

Neuroimaging and Genetics Across the Lifespan in Health and Illness
Chair: Nitin Gogtay

Psychotropic Treatment During Pregnancy: Doing Good or Harm (or Both) on Which and Whose Outcomes?
Chair: Katherine Wisner

Study Groups

Research with Prisoners: Ethics and Opportunities
Chair: Charles P. O'Brien

Comparing the Cost-Utility of Psychopharmacological vs. Psychosocial Treatments for Schizophrenia: Why and How
Chair: Daniel J. Luchins

Identifying and Characterizing Drug-Induced Risks: Can We Improve upon Current Strategies for Assessing Drug Safety?
Chair: Donald S. Robinson

Drug Development
Fostering Collaborations Across Academia, Industry, and Government to Develop Biomarkers for Decision-Making in Drug Development
Chair: Dean F. Wong

Comparative Effectiveness of Antipsychotic Drugs: Complete Results of the CATIE Study
Chair: Jeffrey Lieberman

ACNP 50TH ANNUAL MEETING

FINAL PROGRAM

December 4-8, 2011
Hilton Waikoloa Village
Waikoloa, Hawaii

President: Eric J. Nestler, M.D., Ph.D.
Program Committee Chair: William A. Carlezon, Jr., Ph.D.
Program Committee Co-Chair: Anissa Abi-Dargham, M.D.

This meeting is jointly sponsored by the Vanderbilt University School of Medicine Department of Psychiatry and the American College of Neuropsychopharmacology.

50th Annual Meeting – December 2011

Plenaries:

Distinguished Lecture: Insights into Circadian Clock and Sleep from Human Genetics
Chair: Eric Nestler

Institute Director's Plenary: Institute Status of Funding / Strategic Plan
Chair: Eric Nestler

Neuropsychopharmacology Reviews Plenary: Neurotherapeutics Teaching Day Panel
Chairs: Gwenn Smith
Xiaohua Li
Jeff Conn

History Lecture: Progress in Neuropsychopharmacology: 1961-2011 and Beyond
Honorary Chair: Joel Elkes
Chair: James C. Anthony
Moderator: Alan Frazer

President's Plenary: Brave New World for Brain Therapeutics
Chair: Eric Nestler

Special Session for Associate Members: "Ask the Experts" Career Development Program
Chair: Marlene Freeman
Co-Chair: Linda Carpenter
Moderators: Linda Carpenter
Paul Holtzheimer

Teaching Neuropsychopharmacology Plenary
Chair: Mark Rapaport

The Perils and Pitfalls of Biomedical Research Historical and Contemporary Perspectives on the Ethics of Research
Chair: Ellen Frank
Co-Chair: Jeffrey Lieberman

Panels:

A Convergence in Autism and Schizophrenia Genetics: The Conundrum of Shared Risks and Divergent Outcomes
Chair: Matthew State
Co-Chair: Thomas Lehner

Adolescent Brains: The Constancy of Change
Chair: Ruben Gur

APOE and Alzheimer's Disease: Neurosusceptibility, Neuroprotection and New Treatments
Chair: Terry Goldberg
Co-Chair: Steven Paul

Beyond Genome-Wide Association Studies: New Approaches to Risk of Psychiatric Illness
Chair: Robert Freedman

Circadian Rhythms, Sleep Deprivation and Mood Disorders
Chair: Ted Abel
Co-Chair: Colleen McClung

Contribution of Genetic Epidemiology to Identifying Genetic and Environmental Risk Factors for Neurologic and Psychiatric Disorders
Chair: Kathleen Merikangas
Co-Chair: Emmanuel Mignot

Cortical Dopamine in Schizophrenia: Quantifying Levels, Understanding Function
Chair: Anissa Abi-Dargham
Co-Chair: Holly Moore

Downstream Effects of Visual and Auditory Perceptual Impairment in Schizophrenia
Chair: Michael Green

Drug of Abuse during Adolescence: A Development Period of Vulnerability or Resilience?
Chair: Susan Andersen
Co-Chair: Patricio O'Donnell

Emerging Methods to Examine Fear Regulation
Chair: Kerry Ressler

Panels Cont:

Enhancing Cognitive Performance: Molecular, Pharmacological, and Experiential Strategies
Chair: Robert Bilder

Enteric Hormone Modulation of Cerebral Neurotransmission and Eating Behaviors in Obesity
Chair: Robert Kessler

Epigenetic Modifications in Development, Aging and Mental Illness
Chair: Barbara Lipska
Co-Chair: Joel Kleinman

Feast or Famine: Is Disordered Eating Related to Disordered Reward?
Chair: Kathryn Cunningham
Co-Chair: Ralph DiLeone

From Genome to Macro-Connectome: Integrating High-Dimensional Genetic, Imaging and Behavioral Data, with Application to Large-Scale Studies of Alzheimer's Disease, Schizophrenia, and Substance Abuse
Chair: Vince Calhoun
Co-Chair: Godfrey Pearlson

From Transcription to Oscillations: How Sick Interneurons Create a Schizophrenia-like Phenotype
Chair: James Meador-Woodruff
Co-Chair: Rita Cowell

Functional Connectivity in Neural Systems as a Developmental Abnormality in Creating Risk for Bipolar Disorder
Chair: Kiki Chang

GABA, Glutamate and Neural Synchrony in Schizophrenia
Chair: Lawrence Kegeles
Co-Chair: Steven Siegel

Genes, Fear and Anxiety: From Mice to Humans
Chair: John Neumaier
Co-Chair: Larry Zweifel

Genetic and Molecular Mechanisms of Normal Cognitive Aging
Chair: Venkata Mattay
Co-Chair: Terry Goldberg

Panels Cont:

Gimme Another Hit of Chocolate. Is Food Addictive?
Chair: Walter Kaye
Co-Chair: Guido Frank

Glutamate Targets for CNS Therapy: Insights Obtained from a Potential Dynamic Duo
Chair: Dean Wong
Co-Chair: Rikki Waterhouse

Is Love Epigenetic? Transformative Effects of Social Experiences and of Oxytocin
Chair: James Harris
Co-Chair: James Leckman

Medication Discovery for Addiction: Translating the Dopamine D3 Receptor Hypothesis
Chair: Amy Newman

Memory Erasure: Mechanisms and Potential Utility in Psychiatry
Chair: William Carlezon
Co-Chair: Michael Davis

Molecular Mechanisms Informing PTSD Risk, Treatment and Prophylaxis
Chair: Rachel Yehuda
Co-Chair: Eric Vermetten

Neural Mechanisms of Environmental Risk for Psychiatric Disorders
Chair: Andreas Meyer-Lindenberg
Co-Chair: Charles Nemeroff

Neuroactive Cytokines: Critical Therapeutic Targets for Depression and Treatment Resistant Depression?
Chair: Husseini Manji
Co-Chair: Andrew Miller

Neurodevelopmental Pathology of Cortical Interneurons in Schizophrenia: Is it the Journey or the Destination that Matters?
Chair: Cynthia Weickert

Neuroimaging Genomics: Discovering a Signal in the Complexity of Genes, Brain and Behavior
Chair: Raquel Gur
Co-Chair: John Blangero

Panels Cont:

New Directions in Understanding the Neurocircuitry of Choice, Value, and Decision-Making
Chair: Suzanne Haber
Co-Chair: Steven Grant

NMDA Receptor Complexes: A Point of Convergence for Schizophrenia Candidate Pathways
Chair: Raquel Gur

Novel Approaches to Therapeutic Development in Alzheimer Disease
Chair: Ralph Nixon
Co-Chair: Mary Sano

Novel Functions of Prefrontal Cortex Regions in Motivated Behavior: Implication for Psychiatric Disorders
Chair: Peter Kalivas

Novel Synaptic Targets in Depression Emerging from Clinical, Biochemical, and Circuit Based Approaches
Chair: Lisa Monteggia
Co-Chair: Lois Winsky

Optogenetic Dissection of Cortico-Limbic Circuit Function and Dysfunction
Chair: Lorna Role

Progress in Understanding the Role of GABA and GABAA Receptor Biology in Psychiatric Disease
Chair: Nicholas Brandon

Rapid Acting Antidepressants Increase Synaptogenesis
Chair: Ronald Duman
Co-Chair: Wayne Drevets

Role of Phagocytes in Synaptic Plasticity and Remodeling of Tissues in the Nervous System
Chair: Lei Yu
Co-Chair: Jonathan Pollock

Serotonin Signaling during Development: Unexpected Sources, Large Neuron Heterogeneity, Limited System Plasticity and Big Impact on Physiology and Behavior
Chair: Sheryl Beck
Co-Chair: Mark Ansorge

Panels Cont:

Sex Differences in Brain and Behavior: Emerging Genetic and Cellular Mechanisms
Chair: Rita Valentino
Co-Chair: C. Neill Epperson

Striving for the Correct Diagnosis of Mental Health Disorders
Chair: Alan Schatzberg
Co-Chair: Stephen Koslow

Synaptic Plasticity: From Adaptive Molecular Mechanisms to Dysregulation in Psychiatric Disorders
Chair: R. Suzanne Zukin
Co-Chair: Carol Tamminga

The Autism Sequencing Consortium (ASC): Unraveling the Genetic and Functional Architecture of Autism Spectrum Disorders
Chair: Thomas Lehner
Co-Chair: Matthew State

The Development of Novel Pain Therapeutics: New Strategies to Overcome Drug Discovery Barriers
Chair: Robert Lenox
Co-Chair: Frank Porreca

The Noradrenergic System as a Therapeutic Target for Drug Dependence
Chair: Bernard Le Foll
Co-Chair: David Weinshenker

The Putative Role of ER Stress in Neuropsychiatric Illnesses
Chair: David Bredt
Co-Chair: Guang Chen

The Use of Intraoperative Techniques to Assess the Physiology of the Anterior Cingulate Cortex
Chair: Darin Dougherty

Toward A Neuroimmune-Mediated Subtype of Autism Spectrum Disorders
Chair: Christopher McDougle

Translating Pharmacogenetics into Clinical Utility: Optimizing the Phenotype
Chair: Thomas Schulze
Co-Chair: Anil Malhotra

Panels Cont:

Translational Approaches to Understanding Negative Symptoms
Chair: Stephen Marder

Vaccines, Viral Vectors, and Cocaine Addiction: Neutralizing Cocaine before it gets to the Brain
Chair: Marilyn Carroll

Will We Have New Drugs or Not? Addressing the Crisis in Neuropsychiatric Drug Discovery
Chair: Eric Nestler
Co-Chair: David Michelson

Study Groups:

Assessing Brain Developmental Trajectories from Infancy to Adulthood
Chair: James Swanson

Can Vulnerability Markers Identify Informative Neurodevelopmental Abnormalities across the Spectrum of Early Psychosis?
Chair: Kristin Cadenhead
Co-Chair: Diana Perkins

Crisis in Psychiatric Drug Discovery: Solutions from Academia, Government and the Advocacy Community
Chair: Mark Rasenick
Co-Chair: William Potter

Ethical, Legal, and Social Challenges in Research on Psychiatric Genetics
Chair: Paul Appelbaum

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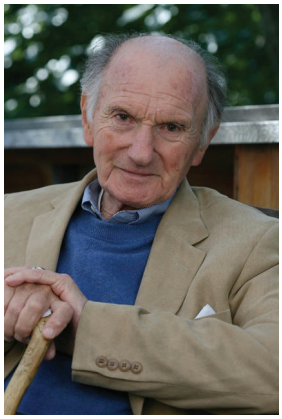
Chair: Raymond Anton
Co-Chair: Henry Kranzler

Utilizing the NIH's CTSA Network to Advance Neuropsychopharmacology Research
Chair: Anantha Shekhar
Co-Chair: William Potter

Joel Elkes – ACNP Past President, 1962



I hope you will forgive an old man for trying to piece together a few fragments of his life, as he attempts to establish continuities. For example, I remember sitting in the library of St. Mary's Hospital School in London 75 years ago, reading my beloved Charles (Sir Charles) Sherrington, a giant in Neuroscience, and coming upon this passage:

> *"The body of a worm and the face of a man alike have to be taken as chemical responses. The alchemist dreamed of old that it might be so. The dream, however, supposed a magic chemistry. There they were wrong. The chemistry is plain everyday chemistry. But it is complex. Further, the chemical brew in preparation for it time has been stirring unceasingly throughout some millions of years in the service of a final cause. The brew is a selected brew."*[1]

A chemistry of Thought, a chemistry of Feeling: Sherrington said it was plain everyday chemistry, but it is "complex" and speaks of stirring the pot of chemical evolution. Interesting!

Some twenty plus years later, my late wife, Charmian, and I sit at the Inagural Dinner of our College.[2] You had done me the honor of electing me the First President of the College. There is no honor in my life that has meant more to me. And future Nobel Laureates are at the table. [Page 44] After my first year of service, having reviewed our progress, I had this to say:

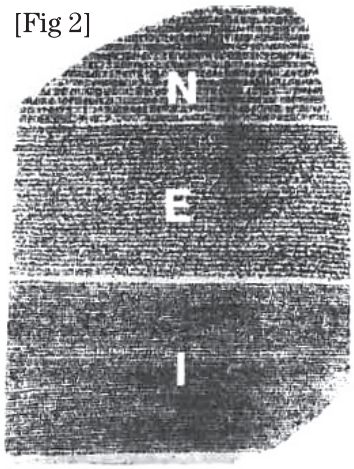
> *"It is not uncommon for any one of us to be told that Psychopharmacology is not a science and that it would do well to emulate the precision of older and more established disciplines. Such statements betray a lack of understanding for the special demands made by Psychopharmacology upon the field, which compound it. For my own part, I draw comfort and firm conviction from the history of our subject and the history of our group. For I know of no other branch of science which, like a good plough on a spring day, has tilled as many areas in Neurobiology. To have, in a mere decade, questioned the concepts of synaptic transmission in the central nervous system: to have emphasized compartmentalization and regionalization of chemical process in the unit cell and in the brain; to have given us tools for the study of chemical basis of learning and temporary connection formation; to have resuscitated that oldest of old remedies, the placebo response for careful scrutiny; to have provided potential methods for the study of language in relation to the functional state of the brain and to have encouraged the Biochemist, Physiologist, Psychologist, Clinician, Mathematician and Communication Engineer to join forces at bench level, is no mean achievement for young science. That a chemical text should carry the imprint of experience, and partake in its growth, in no way invalidates the study of symbols, and the rules among symbols, which keep us going, changing, evolving, and human. Thus, though moving cautiously, Psychopharmacology is still protesting; yet, in so doing, it is, for the first time, compelling the physical and chemical sciences to look behaviour in the face, and thus enriching both sciences and behaviour. If there be discomfiture in this encounter, it is hardly surprising; for it is in this discomfiture that there may well lay the germ of a new science. In our branch of science, it would seem we are as attracted to soma as to symbol; we are as interested in*

1 Sherrington, C.S. (1941), Man on his Nature, Cambridge University Press, England, p. 104
2 Elkes, J. (1962), The American College of Neuropsychophannacology, A Note on its History, and Hopes for the Future

overt behaviour as we are aware of the subtleties of subjective experience. There is no conflict here between understanding the way things are and the way people are, between the pursuit of science and the giving of service. So we must go on along lines we began: talk to each other, and keep talking. Psychopharmacology could prove a template for a truly Comprehensive Psychiatry of the future. We must train colleagues who do good science and, above all, who also listen: for, like it or not, our humanity will never leave us in our molecular search. Morality is at the very center of our field."[3]

In sum, we must seek, see and connect: connect to fields congruent with our own. Whether we like it or not, it would appear that we've become a Rosetta Stone, [Fig 2] linking the languages of the Nervous, the Endocrine and Immune System to each other, and, more generally, linking the languages of the Life Sciences to the Sciences of the Mind. In these three fields, we already see significant affinities. The Nervous System, the Endocrine System and the Immune System share neurotransmitters. This is very significant, but our inquiry must be pursued more deeply. We must ask what molecular attributes, what features and characteristics do the neurotransmitters share as a group to make them so persistent and successful in evolution? What makes them so fit for the storage, affective labeling and retrieval of the memory trace? Should we look for analogies in the Silicon networks, which nowadays proliferate like algae across the planet? In short, should we start conversations with our brethren in the computer field? We have a mechanism for such conversations, it was established it in this college 50 years ago. The mechanism is that of Study Groups. I suggest that we create a series of Transdisciplinary Conversations in Neuropsychopharmacology. We could do this with the Computer Sciences and we could do this with other fields. Evolutionary Molecular Biology comes to mind. Are we looking at macromolecules the right way? Are there Quantum Properties in their shapes? Do macromolecules create or exist in Electromagnetic Fields? Could this information be useful in constructing nanorobots and thus open a wealth of practices and opportunities? Should we have a Study Group on Alzheimer's Disease? To function optimally, such groups should be truly collaborative, leave the armor of the Ego at the door and distill the wisdom of the group in free discussion. New ways of Incentives and Rewards would have to be invented. And while we are talking in this manner should we move beyond the concept of "Cure" of "Disease" to the concept of "Healing" – inquiring into the ancient, autonomous chemistry of the body, promoting the healing processes of tissues and organisms. Such inquiries could bare some of natures most deeply held secrets and give us new leads in the chemical engineering in which we are engaged.

[Fig 2]



The Rosetta Stone, deciphered by Champollion in 1821, opened up the hieroglyphics. Neuropsychopharmacology holds the key to an understanding of the shared languages of the Nervous System (N), the Endocrine System (E) and the Immune System (I)

Myriads of opportunities present themselves. Common Languages (possibly new Mathematical Languages) are needed, replacing the present cacophonies of our modern tower of Babel. We must, to say it again, seek, see, and connect. New languages will develop and take their own time; old/new answers will emerge, leading us back to old/new Beginnings.

3 Elkes, J. (1995), Psychopharmacology, Finding One's Way, Neuropsychopharmacology 12. 93-111 Closing remarks, Elsevier Science

Alfred M. Freedman, M.D. – ACNP Past President, 1972

Congratulations to the ACNP on its 50th birthday! This occasion makes us all proud and joyous. For me, it is particularly evocative. As I reflect upon the past, I have many warm memories of being a charter member of an organization marking the development of a pioneering movement in the history of psychiatry as well as Science in general.

As I think back to the early days of the ACNP, I recall the annual meetings at the Caribe Hilton Hotel in San Juan, Puerto Rico. We were really a small society of limited membership at that time, so it was easy to get to know one another and be stimulated by the exchange of information about new developments. It was an occasion to get to know outstanding leaders in the development of psychopharmacology. Paul Hoch, Jonathon Cole, Joel Elkes and Joe Zubin among others come immediately to my mind. I had such admiration for the leaders as well as the members of the ACNP that I. was indeed surprised and honored to be elected President for a 1972 term. We had no central permanent office in those days. While Daniel Ephron had been elected to be Secretary Treasurer, he was ill and regrettably died later that year. Dick Wittenborn, who had been our perennial Secretary Treasurer for several previous years stepped into the breech and nobly served as Secretary Treasurer during my term. Dick Wittenborn was elected President for the following term, and still with no permanent office, the business of the ACNP was principally carried in Dick's briefcase and the files in my Medical School office. The meetings of officers of the ACNP were held either around the table in a restaurant during lunch, or in my office at the Medical School.

I need not review the impressive developments that have taken place in the ACNP since those early days. The ACNP not only established a permanent office in Nashville under the direction of Oakley Ray, but has been playing a major role in many areas such as legislation, judicial action, ethical principles, working out relationships with pharmaceutical houses, education and particularly encouragement to minority aspirants or those already in junior positions. Of course the major thrust remained a concentration on Neuropsychopharmacology.

In regard to the future, I see the major trend as a progression toward Integration. Integration has become a frequent area of concern by many in our field as well as other areas of Science. The ACNP is in an excellent position to tie in a multitude of complex variables in an integrated whole. The ACNP could become a catalyst for the integration of these variables leading to a new paradigm of normal and abnormal behavior.

The first step in enhancing the progress toward integration is the final elimination of concepts of dualism and reductionism that block the development of an holistic view of behavior, but by integration we differentiate it from "interactionism" a mechanical notion that admits the influence of, for example, biology and experience, but insists on dividing total variances into percentages. Thus, it may be said, that 77.5% of intelligence is due to biology and 22.5% to experience or environment or vice versa. This becomes another form of dualism and reductionism, that is, analyzing the whole in terms of the underlying properties of its parts.

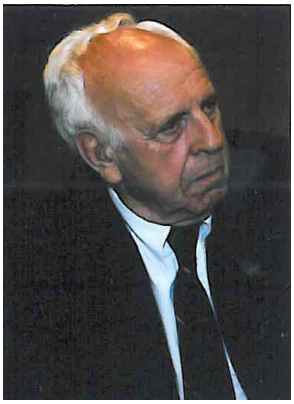
One must go beyond reductionism to a concept of wholeness that biology and experience interdigitate and interpenetrate in an inextricable manner. One variable is not basic and essential and the other derivative and superimposed. Each builds upon the other, neither is separable. In the words of the late Professor

S.J. Gould: "The solution must be in properly melding the themes of inborn predisposition and shaping through life experiences… When two ends of such a spectrum are commingled, the result is not a separable amalgam but an entirely new entity that cannot be decomposed. The best guide to a proper integration lies in recognizing that nature supplies general ordering rules and predispositions, often strong ones, to be sure, while nurture shapes specific manifestations over a wide range of outcomes."

To cope with such an approach, we need a new way of thinking. I have been attracted for many years to the biopsychosocial model as defined by George Engel. Engel inveighs against the fractionation of nature into bits of matter to be dealt with one by one. He terms this the hallmark of the Newtonian model that is characterized by reductionism, linear causality, dualism and factor analysis. Engel's paradigm is holistic, transactional, probabilistic, and analogical. He bases much of his thinking on the concepts of modern physics, including Einstein's Theory of Relativity, Heisenberg's Law of Indeterminacy and Planck's Quantum Theory. Engel looks at variables such as cause and effect, biology and experience, and nature and nurture as components of an ever changing dynamic whole that demands a complex model to account for any eventual behavioral state.

Such an effort to utilize concepts of moderate physics to comprehend behavior may seem quite exotic and way out. However, many of us have been attracted to this new way of thinking in medicine in general and neuropsychopharmacology in particular. As a matter of fact, I organized several workshops at the annual meetings of the APA dedicated to discussing and making contributions to the relationship of modern physics and behavior. These workshops attracted a considerable number of participants and continued for a few years until I became involved in other areas. However, there are many who are interested in behavior and modern physics and have been holding meetings worldwide. There are several groups, from whom I receive e-mail, announcing meetings in various countries including the United States but, unfortunately, I have been unable to travel. But I expect that there will be a steady stream of contributions of innovative thinking currently and in the future. It is noteworthy that Niels Bohr, the great physicist, speculated on the relationship of Quantum theory and psychology. All this work reinforces notions of integration leading to a fresh and innovative model of conceptualizing and utilizing such thinking to a new level of comprehending Neuropsychopharmocology, Psychiatry and Medicine. Our entire conception of the Biological Sciences will be enhanced and bring us to a new level of knowledge.

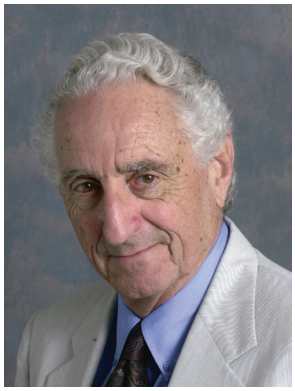
Fridolin Sulser – ACNP Past President, 1979



Being one of the 3 oldest surviving Past–Presidents, I love to reflect on the historical perspective of our field, neuropsychopharmacology, by being cheerful, patient and realistic and skeptically detached. Looking back over 50 years, I have witnessed the epochal progress in neuropsychopharmacology and neuroscience. The Oral History of the ACNP -10 volumes – expertly edited by Tom Ban, is a unique tribute to this progress. Methodology drives science and this Oral History is testimony of how new methodologies have catalyzed this progress: The invention of the spectrofluorimeter by Bowman and Udenfriend, fluorescence histochemistry developed by Hillarp and his pupils, the availability of radioactive isotopes, leading to the discovery of receptors and subtypes of receptors, the discovery of second messengers and their role in protein kinase activation and slow synaptic transmission, coupled with the revolution in molecular biology have been responsible for this spectacular progress. The membership of our college has been crucial in this revolution with 4 Nobel Laureates – Julius Axelrod, Arvid Carlsson, Paul Greengard and Eric Kandel – leading the field. I am very, very proud of the ACNP and I hope that our membership will study the Oral History when it becomes available at our 50th Anniversary. It is a source of enlightenment and inspiration. Accolades to Tom Ban!

Have these spectacular advances in our understanding of basic brain function at the cellular and sub-cellular level translated into equal advances in the pharmacotherapy of mental disorders as we all predicted at the 25th Anniversary of the ACNP in 1986? Unfortunately, the answer is NO. We have begun to recognize that molecular biology per se – no matter how technically sophisticated – operating in a functional vacuum, will not contribute substantially to our understanding of emotional and cognitive functions of the brain. But, as future research is shifting its emphasis to the elucidation of the functional relevance of changes in programs of gene transcription and scientists emerge who can, as Louis Lasagna said in his Presidential Letter, “synthesize as well as analyze”, new targets for psychotropic drugs will emerge, targets for drugs which promise to treat the disease rather than the symptoms of the disease. I am, once again, optimistic!

Donald F. Klein, M.D. D.Sc. – ACNP Past President, 1981



During the early 1950s through 1975, the most critical, fruitful, generative psychopharmacological events were the serendipitous discoveries that lithium, the anti-psychotics (including clozapine), the anti-depressants (TCAs and MAOIs), and the anti-convulsants, were uniquely powerful psychotropic agents. ACNP was founded in the early 1960's by clinical scientists, hoping to transcend serendipity by rational drug design. This effort, now labeled "translational research", assumes that basic biology will inform the production of new therapeutic agents while extending the range of indications.

However, about 1975, these discoveries stopped, despite enormous increases in investment by industry and NIMH in translational research aimed at drug discovery.

Unfortunately, new agents that achieved marketing were essentially me-too modifications with no effective gain. At best, there was some modification in the side effect profile. However such slightly modified winners produced a very favorable profit to cost ratio since all the basic work was unnecessary.

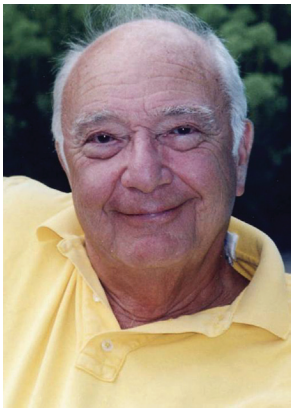
The proof of the pudding is in the eating. So far these efforts (over 35 years) have produced much interesting biology but no useful novel therapeutics. My inference is that the, by now conventional, "translational research" program vastly underestimated our ignorance of brain functions, their disorders and the difficulty with remediation.

There was great success at the production of novel psychoactive substances but these regularly proved toxic or useless. This should not be surprising since most bioactive agents interfere with a finely tuned homeostasis. However, therapeutic agents either normalize or compensate for deranged adaptive functions. Since our knowledge remains primitive of just what functions became maladaptive, it is not surprising that new agents, developed in ignorance of their goal, miss their target.

Unfortunately serendipity has not been transcended. Indeed, the changes in our clinical system towards short hospitalizations and short patient contacts have been anti-serendipity, by preventing fortuitous observation of benefit. The setting for serendipity (long term clinical observation) has been demolished. What substitute can be found? One inflaming public health issue has been the frightening perception of rare, late, toxicities during long term treatment. Since randomized controlled trials address acute effects, are of relatively short duration and insufficient size to reliably discern rare toxicities, it is clear that another approach is necessary to deal with these issues. Further, it goes relatively un-remarked, that current trials are inadequate to affirm long-term benefit.

One safety directed possibility is the development of reliable, interlinked, computerized, longitudinal, medical (prescription, practice, hospital, laboratory, autopsy, etc.) records. These could form the data-base for serendipitous observations of unsuspected toxicities from already marketed agents. Such a plan goes far beyond the current FDA Sentinel plan which is restricted to occasional inquiries regarding the conclusions already found from each, of multiple, data bases. Further, these are not systematically monitored regarding data entry or analysis. Perhaps of equivalent, or more importance, is that such a well developed network allows for prospective computerized serendipitous discoveries of unanticipated benefit. Clearly, this will not happen without educated public demand and legislative action. This affords ACNP a new leading role in the scientific promotion of therapeutic drug discovery—especially since the failure of the last approach has become distressingly (and economically) obvious.

Leonard Cook – ACNP Past President, 1982



During the past six decades I have observed the impressive advances in scientific methodology relevant to understanding mental disease and those useful in identifying new therapeutic agents. It has been a privilege to have participated in the field of neuropsychopharmacology from its beginning in the 1950s.

The decade of 1950-1960 was an amazing period during which antipsychotics and anxiolytics were identified and developed as important therapeutic agents. Among the laboratory tools available at that time to study these agents were electrophysiology, biochemistry, and behavioral procedures. Significantly, the most dependable and useful was the array of behavioral procedures, developed to a large extent in the pharmacological laboratories, to identity the new psychotherapeutic agents. Procedures such as Conditioned Avoidance and Conflict-Punished behaviors (employing rodents and primates) were very valuable as well as many other Skinnerian procedures.

The Conditioned Avoidance procedure specifically identified antipsychotic agents (e.g. the phenothiazenes and butyrophenones), and the Conflict-Punishment procedure very specifically identified the anxiolytics (e.g. benzodiazepines).

The data from these behavioral procedures was shown to be highly correlated with clinical results. Conditioned Avoidance potency data correlated highly with the clinical efficacy potency of the antipsychotics, as did the data from the Conflict-Punishment tests with their anti-anxiety efficacy potency in the clinic. Several publications supported these findings.

In the very critical decisions made by the companies' pharmaceutical research boards in their decision as to which compounds they should invest in regarding the very expensive development process towards a marketable product, the behavioral data was the most critical data in this selection process.

Tremendous advances have been made in molecular biology in this field, particularly elaborating and understanding the disease processes. The usefulness of behavioral techniques in the discovery phase of psychotherapeutics, recently, seems to have been very much ignored. I recommend that consideration of the applicability of the many proven behavioral techniques found to be so useful in the 1950s and 1960s be reconsidered regarding their value in the drug discovery process and for more complete understanding of the drugs' pharmacological profiles.

Recent scientific articles have attempted to correlate sophisticated molecular biology data with overly simple, non-specific behavioral data (e.g. gross motor activity). These attempts ignore the more useful and meaningful data which is derived from the very specific behavioral procedures available, which better define psychopharmacological effects.

The value of highly specific molecular biological data may tend to lose focus with regard to the overall integrated pharmacological actions in the whole animal.

William E.Bunney, M.D. – ACNP Past President, 1983

I am honored to be a Past President of the ACNP. Throughout my membership in the ACNP, the meetings have continued to include presentations of research at the cutting edge of neuropsychopharmacology, neuroscience, psychology and neurology. The ACNP has, over the years, maintained its reputation as the leading scientific society in our field. The broad areas of science represented by the expertise of the members of this society have, in my view, an extraordinary exciting future. I want to comment on a few areas involving current conceptual and methodological advances which I believe could lead to major breakthroughs, and to note some challenges for future generations of ACNP members.

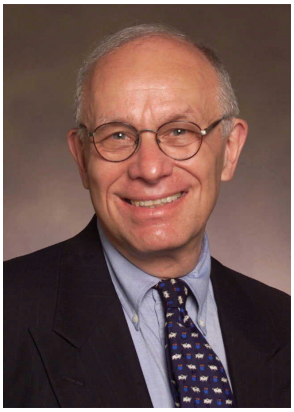
First of all, there is a great deal of evidence that we are on the verge of a revolution in diagnosis, treatment and prevention involving nanomedicine. Nanoprobes are 10,000th the diameter of a human hair. The disease progression in many neuropsychiatric disorders is initiated years to decades prior to the emergence of overt symptomatology. Nanoprobes have already been utilized for the early detection of cancers and it is predicted that as we develop a more thorough understanding of specific genetic and epigenetic risk factors, nanoprobes will be important in identifying early disease processes in psychiatric and neurological illnesses. It has also been predicted for a number of years that nanotweezer probes, which can function at the level of actin filaments, will be capable of DNA repair. Of interest to our field is that fourteen compounds have recently been nano-reformulated and approved by the FDA.

Second, emerging optical technologies are improving the ability to use light for the study of normal and diseased neuronal systems including the activation of specific brain circuits in behaving animals. These technologies include extremely high resolution imaging with 2-photon microscopy and optogenetics of cellular function in awake animals and humans. Continuing advances in immunofluorescence microscopy have made it possible to measure profiles in the size ranges of synapses. When coupled with automated methods that can sample billions of synapses, these developments open the way to the first quantitative analysis of how drugs and experience modify connections across the multiple stages of brain networks. The ability to image and use time-lapse photography to follow molecular events has added a critical new research tool.

Third, there has been an explosion of our knowledge concerning clock genes which control all circadian rhythms in lower animals and man. It has been known for decades that depression is associated with circadian abnormalities affecting sleep, behavior, temperature and cortisol. In the future we will discover the molecular mechanisms which link antidepressant compounds, signaling clock machinery and chromatin remodeling.

To advance our understanding of the brain diseases in psychiatry and neurology, we face a number of future challenges: develop a standard model of the cortex wiring and functioning, build the first memory maps and formulate a neurobiological theory of memory retrieval. With these advances, we may even have the first glimmerings of a brain-based theory of consciousness. One suspects that meeting these challenges will require breakthroughs that will be as revolutionary to the life sciences as quantum mechanics was to physics.

Herbert Meltzer – ACNP Past President, 1985



The ACNP is the world's best forum for basic and clinical neuroscientists interested in the basic sciences of brain and behavior and their application to understanding behavior in all species, especially man, and alleviating mental illness. This dualism parallels my career-long engagement in both basic and clinical research and my work as a clinician, concentrating on patients with schizophrenia. My engagement with the ACNP began in the very early stages of my career due to the fortunate happenstance of joining the Dept of Psychiatry at the University of Chicago in 1968 at the behest of its then new chairman, Daniel X Freedman, the doyen of the ACNP of that era. That early exposure which the ACNP provided to the best and the brightest of our field in the 1970's contributed greatly to what I later achieved with regard to the treatment of schizophrenia through my clinical and basic research with clozapine, and to the development of other atypical antipsychotic drugs which ensued from those investigations.

The early years of the ACNP, the 1960s and 1970s, were characterized by intense efforts by many of its members, especially Jerry Klerman, George Simpson, Leo Hollister, and Steve Bunney, to explore the efficacy, side effects, and mechanism of action of antipsychotic drugs. The huge advances in both areas they and others made provided the impetus for me to commit myself to a career in both preclinical and clinical research, with the goal of applying that knowledge to help patients with severe mental illness, especially schizophrenia. At the same time, the research and demeanor of ACNP founders, including Bernard Brodie, Julie Axelrod, Joel Elkes and Jonathan Cole greatly stimulated me to attempt to contribute to both basic and clinical research.

With such iconic figures as role models, I readily made the decision, in 1962, as a third year medical student at Yale, to pursue psychopharmacology, biological psychiatry and clinical trial research, the combination of translational research I have pursued for almost 50 years. This fateful decision, probably the best I ever made, occurred during my clerkship on the famous Tompkins 1 Psychiatric Ward of Grace-New Haven Hospital, directed by Tom Detre, ACNP president in 1994, and the architect of the development of the Dept of Psychiatry at the University of Pittsburgh into the top echelon of world psychiatry. My passion for serotonin research was kindled during the preceding two years at Yale, as part of the research I did during the first two years of medical school with Dan Freedman and Jack Peter Green, in the pharmacology department which was then the leading Dept of Pharmacology in the country. Arnold Cooper, the chairman of Pharmacology, and the founding editor of the journal *Biochemical Pharmacology* took great pains to edit my first primitive efforts to publish original research. During that time, I also had the opportunity to work with and learn from George Aghajanian and Floyd Bloom. How lucky could a medical student be?

I was elected ACNP President in 1985, an honor and privilege I remain most grateful for and along with the two endowed Professorships I have held and the Presidency of the CINP, among my highest honors. The tension over the balance between basic and clinical research in the annual program in San Juan, which was the highlight of the year for most of us, was particularly intense. Many of the early ACNP members were primarily clinical investigators. They were far from shy in expressing their belief that their scientific interests were no longer reflected in the program and that the neuroscience of that era, which was by the standards of today, very elementary, was nevertheless, overrepresented. As chair of the program committee for two years

before becoming President, and as President, I made major efforts to include panels and workshops, as well as a teaching day that was accessible and meaningful to both camps. The Poster session was an innovation which I started as Program Committee chair. The Caribe Hilton hunted all over San Juan for those first poster boards, which did give more of an opportunity to present clinical research, especially clinical trials. The hybrid nature of ACNP makes the balance of basic and clinical research an ongoing challenge. Only time will tell if the best scientists in both areas continue to see the ACNP as the arena they come together to show their latest discoveries and learn from each other. I hope that is the case.

Dualism was also evident in the discussions during my presidency about whether the ACNP should have its own journal and if so, what should be its mission. Volume 1 of *Neuropsychopharmacology* was published in 1987. I recall no conflicts about the decision that it should publish both basic and clinical papers produced by ACNP members and the rest of the field. The choice of the late Chris Gillin as the first editor proved an excellent one and clearly reflected the desire of the leadership of that time to reassure the membership that clinical research was still highly esteemed. As I was also completing editing *Psychopharmacology, The Third Generation of Progress* (1987) at that time, I made every effort to have that volume also provide an integrated approach to basic and clinical science. With the aid of many able section editors, the consensus was that we succeeded. Many people have told me that that volume was the one of that series which succeeded best at explicating and integrating basic and clinical research. I can think of no higher complement.

It is my hope that the leadership in the ACNP will continue to focus their energies on integrating basic and clinical research as a primary goal of its activities, not merely as a by product of the effort to present the best of each. I think, for example, of a current controversy I am engaged in: the value of the typical and atypical antipsychotic drugs relative to each other, and, in particular, about the controversy as to whether the atypical agents are more effective to improve cognition. Having published the first study which showed an advantage for the atypical antipsychotic drugs, I am puzzled by the difficulty some have had in replicating these findings. So I have used basic research to help clarify the issues. Preclinical rodent data from many labs, including mine, and primate data from others, show a decisive advantage for the atypical antipsychotic drugs related to clozapine in a wide variety of models that are believed to be clinically relevant to schizophrenia, e.g. the ability of the atypical antipsychotic drugs but not typical drugs to reverse and prevent the effects of sub-chronic administration of the NMDA antagonists, phencyclidine (PCP) and MK-801 to improve novel object recognition, working memory and social cognition. It is now necessary for clinical and basic scientists to understand why translation of these basic studies is so difficult. Is it the models? Is it the way we test patients? Is it the disease process(es) which make it impossible for these drugs to achieve much benefit in patients? There is no better forum than the ACNP to discuss such complex and important issues. I have every faith the answers will be forthcoming at a not too distant ACNP meeting. I hope I am not only around to hear them but to contribute them as well. After all, I have been attending ACNP for only 40 years.

Arthur J. Prange, Jr., M.D. – ACNP Past President, 1987

Many months ago each past president of the ACNP was invited to write a note to help celebrate the fiftieth birthday of the College. I decided to decline because I had nothing to say that was either original or especially insightful. But as autumn approached it came to me that silence might be mistaken for lack of interest, and I would not have it so. The invitation specified that whatever I wrote would be published under the rubric "reflections." After reflecting I decided to address three themes.

The first theme is merely the citation of some events that I know about or have experienced, events, or their telling, that have occurred in the last fifty years and pertain to the purview of the ACNP. To wit: my first analyst told me that, as a boy, he saw a young woman whipped nearly to death in the public square of his native central European village. She had had wrong thoughts. Early in my career I administered ECT, unmodified by a muscle relaxant or an anesthetic, unmodified because full motor expression of the fit was deemed necessary to confer benefit, vertebral fractures a common price to pay. I was the last psychiatrist in North Carolina, I think and I hope, to administer insulin coma therapy. A bit later I was party to the notion that if chlorpromazine failed to produce full remission from schizophrenia, such failure was prima facie evidence that more of the drug should be prescribed, and so forth, until something happened. Finally, the late Morrie Lipton, first among my mentors and himself a past president of the ACNP, and I strolled one noon to the UNC general campus to see the computer. Occupying most of the basement of a new building, the computer was a wondrous thing. Disks whirled; lights flashed. If you had enough grant money you could join the waiting list to use it. So, attitudes, treatments and technology do change. Sometimes the rate of change seems glacial, but a hundred years or so is not even a blink of the historical eye.

Every organization, whatever its goals, functions in a worldwide context, and a quick characterization of that context is my second theme. While the accomplishments of the ACNP have been remarkable, the context of the past fifty years has had its grim side. Even as their levels rise, our oceans are over-fished, perhaps critically so, and ocean water is turning acidic from deposition of carbon dioxide. Mercury (remember the Mad Hatter?) mainly from coal-fired power plants (the Chinese create a new one, on average each week) falls from the sky. As for fresh water fish, south of Alaska many if not most male fish are developing female characteristics, presumably from the estrogenic properties of the myriad of molecules that are thrown but not away. Enough of such horrors. My point is that many unintended or unattended, consequences of human activity bear upon all aspect of life, certainly including the central nervous system.

If the environmental side of our context is grim, another side is propitious–and robust. I refer to human relationships. Race relationships, though still erratic, have improved beyond what a few years ago would have seemed an absurdly sanguine prediction. But just as important as that is what I think of as "the rise of women." Women seem to be everywhere and doing just about everything. This serves the common good. In the modern world maybe upper body strength is not what it used to be; maybe patience is more valuable than aggression. But here's the rub: the rise of women has been severely limited to the industrialized world. If it doesn't spread to the rest of the world, and spread quickly, I see little hope for population control, and without population control I see little hope. The race is on.

My third theme consists of recommendations. (If you invite an elder to write, prepare for some recommendations.) As I have suggested, the ACNP never has, and never will, exist in a vacuum. Members should be citizens as well as scientists. Politicians are far and away in the strongest position to directly affect our social-environmental context, so they ought to be chosen carefully and once chosen they should be watched and (if they pass the watching test) supported diligently.

As for recommendations within the purview of the ACNP-- the study of the nervous system, its disorders and treatments-- members as always will be guided first by opportunity and second by personal interest. In fact, if you explore an opportunity you are very likely to discover an interest.

It is prosaic to say so, but if I were to rejoin the research fray, I think I would take a stab at genetics. What little I know about modern genetics I can formulate in three ways. First, it provides an elegant explanatory system; in a new way, it can sometimes tell us what went wrong (or right) and how. "Junk" DNA is a puzzle. Either evolution is incomplete (examples, anyone?) or/and some bits of junk are sly adjectives or/and they really are junk. Try figuring this out.

Second, genetic discoveries can suggest treatments. For example, I am fascinated by reports from our British colleagues that quite a few people for genetic reasons have brains that are not good at deiodinating thyroxine to make the more potent triiodothyronine. This surely suggests a treatment. But because these people are not grossly, but only subtly, compromised, the finding also suggests that for any genetic fault there may be potential compensations. I am in good company if I suggest that there probably are not many diseases like cystic fibrosis, wherein a genetic change is both necessary and sufficient for the disease to become manifest. Instead, genetic changes may only contribute, in varying degree, to the demonstration of disease. Think of the pathways of a single neurotransmitter—synthesis, storage, release, use, disposal—and the possible compensations, and then think of the array of neurotransmitters that may be involved in an illness. Then ask how many "kinds" of, say, schizophrenia may exist.

The third thing about genetics that attracts my attention is that genes can be changed. They can be knocked out or inserted. Even a large animal can be cloned. And invented forms of life, such as disease resistant seeds, can be patented legally and corporately owned. This makes me uneasy.

I have a final recommendation. Every member of ACNP has some degree of authority, be it large or small. With authority comes the opportunity to provide opportunity to others. I think you should do this if the aspirant shows even a trace of promise. Find him or her some bench space and some of the tools that go with it. To do so may be the best deal you will ever make. Most people will astonish you, and if they don't, you haven't lost much.

In the more likely case you may contribute to the development of scientists, chairs, even deans. If you do, then in your later career they may invite you to "give a talk." If this happens, do not take slides, not even the new 2x2 cardboard and celluloid ones. No. Put everything you know on a plastic and tin gadget about the size of a large cockroach and try not to lose it in an airport.

Good luck.

Floyd Bloom – ACNP Past President, 1989

My 1989 statement at the end of my year as President concentrated on four specific issues. Re-reading that statement today, I am hard pressed to think of newer issues that are more important to the continued enhancement of the College.

First, a continued focus on new drug development and evaluation for which the College has been the central scholarly forum for new means to treat mental illness and addictive disorders, and to learn through investigations into the mechanisms of action of such drugs the nature of the disease process. From that focus came a new session at the Annual meeting devoted to promising new drugs under development, and a revision of the College's Guidelines for Clinical Trials of Psychotropic drugs.

Second, at the 1988 Annual Meeting, the College was faced with two especially bothersome problems that have not gone away. The first of these issues is that of animal experimentation. And the second being of scientific fraud and other forms of unethical conduct by scientists (to the latter of which we did not anticipate the degree to which conflicts of interest from experts covertly paid as consultants to Pharma would intrude on the integrity of the College). This concern led the ACNP Council to develop our first Code of Ethical Conduct and was applied to information exchanges at the Annual meeting and in the College journal.

Third, a new Ad Hoc Task Force chaired by Don Klein was appointed to examine the advisability of creating a neutral (i.e., neither government-based nor university-based) professional organization. This organization could serve to advise both research institutions and scientists on appropriate and responsible measures of response when charges of misconduct are made.

My final recollection of significant accomplishment was the appointment of a new Task Force on Credentialing, chaired by Steve Koslow. The three goals of this task force were to: a.) establish criteria by which the accomplishments of pre-clinical, clinical, or corporate neurospychopharmacologists could be compared to each other on reasonable standards, commensurate with their fields of endeavor, and not be restricted exclusively to scientific journal publications; b) challenging senior members of the College employed in corporate research laboratories to identify prospective candidates for membership; c) creating a new category of membership, the Associate member, to provide a means for the young and promising candidates to be formally inducted into College membership with criteria commensurate for their time since graduation from graduate or medical schools. I believe this category has proven its utility for the College to acquire the new blood and energy that such junior members have traditionally added to our discussions.

Irwin J. Kopin, M.D. – ACNP Past President, 1992

I have been a member of the ACNP for over 40 years and had the privilege of being President in 1991. I remained on Council for the following 13 years, as Past President and Treasurer. When I reflect upon my memories of these years, what is forefront in my mind are the people: Seymour Kety, my mentor at NIH who urged me to come to the first of the many ACNP meetings I attended, Julie Axelrod with whom I published my first 18 papers, Morrie Lipton, Danny Freedman, Oakley Ray and a host of others that I so admired and came to have as friends through the ACNP meetings, as well as about three dozen ACNP members who were, or are still, at NIH.

Then come thoughts of the spectacular changes that I have witnessed in basic neuroscience; biochemical pharmacology and drug development, molecular genetics, brain imaging, etc. Many times, plenary presentations at the ACNP have alerted the membership to landmark discoveries that have had a major impact on understanding the bases for the underlying mechanisms and potential treatments of mental illness, addictive disorders and neurological disease. For example, when I was President, the theme of Teaching Day was "Update on Human Genetics." At that session, David Housman discussed the newly discovered trinucleotide repeats responsible for Muscular Dystrophy and Nancy Wexler's presentation on Huntington's Disease was a prelude to the publication only 3 months later of trinucleotide repeats in that genetic disorder. These advances, which could be used to predict high risk for development of disease, highlighted the many ethical, moral and economic issues and logistical dilemmas related to genetic privacy. Particularly sensitive issues include disclosures…to insurers, to genetic counselors and to individuals with a family history of a disease without known treatments or means of prevention. The early promise that discovery of the gene would rapidly lead to means of correcting the genetic abnormality, or at least facilitate development of means for preventing the progression of such disorders, has yet to be realized. However, the teaching day presentations and the presidential symposia admirably fulfill the educational opportunities for the membership and their guests and remain popular today.

Perhaps the most enjoyable and satisfying time that I have spent at the meetings has been at the poster sessions…not only for the wine and cheese, but also for the opportunity to meet the young people who were showing their work and were eager to discuss their findings. I still enjoy that! My preference for poster sessions may have resulted from having to miss many of the panel sessions: I was attending Council meetings for a total of 18 years, most as Treasurer. The discussions at Council reflected the desire of the leadership to facilitate interdisciplinary research and provide professional educational opportunities at the annual ACNP meeting, but also there were concerns about the membership. The members of Council recognized the need to foster ethnic and gender diversity in the membership, to obtain a balance between limiting the number of members and the need to recruit and admit to membership young rising stars in our field and to obtain adequately wide representation of the disciplines that encompass studies of brain function and disorders. Other major concerns included means to favorably influence public opinion, to have an impact on federal funding of psychopharmacology, to meet challenges to research (such as antagonism of animal rights groups), to deal with the issues of the appearance of conflicts of interest and to reduce dependence of the College upon funds obtained from pharmaceutical industry. We have made significant advances through task forces

and committees to address specific issues, e.g., to initiate and promote growth of our travel award programs for young investigators, to develop and maintain contacts with advocacy groups, and to resolve ethical issues of transparency and appearance of conflicts of interest.

One of our major successes has been the development of the ACNP as a widely recognized authoritative source of information about our discipline. This began over 40 years ago with the publication of "Psychopharmacology, A Review of Progress, 1957-1967" and continued with subsequent (Second, Third, Fourth and Fifth) "Generation of Progress" volumes published at 7-10 year intervals. In 1987, Neuropsychopharmacology, the official Journal of the ACNP, was launched and has flourished. Adaptation and application of the developments in electronic publication and access became a means to update chapters of books and as a means for journal submissions, searches and access. Today members have electronic access to the journal and can even see papers before hard copy publication.

As a relatively small organization with limited financial resources and a membership that is largely occupied with clinical and/or laboratory research, our ability to have an impact on federal policy and funding of research has been limited and our efforts have varied over the years. Our best course appears to have been to join other, much larger, kindred societies and advocacy groups in joint efforts.

The more recent ACNP officers, Journal Editors, Program Committees and our Executive Director, Ronnie Wilkins and his Deputy, Sarah Timm, have continued to guide the ACNP in accomplishing the goals of excellence of our meetings and, between meetings, engaging in useful activities that support and advance the field of Neuropsychopharmacology.

A particularly special memory of ACNP meetings that Rita and I cherish is the welcoming manner in which many members of the College and their spouses received and befriended Rita's mother, Sarah, over many years.

The ACNP has been, and continues to be, an exciting adventure for me. The meetings have been a source of intellectual stimulation and social interactions for which I will always be grateful.

Roger Meyer – ACNP Past President, 1993

Since 1993, the challenges and opportunities, and the crises and satisfactions, within neuropsychopharmacology and our College have continued. The promise of a new generation of antidepressant and antipsychotic drugs was greeted with much enthusiasm; while the subsequent comparative effectiveness studies supported by NIMH raised questions for policy makers and fueled controversies within the field. Many questions remain unresolved, and in need of further research to inform public policy at a time of imminent change in our health care system.

The great promise of basic research in neuroscience continues at an extraordinary pace, but its immediate relevance to the development of new drug targets for psychiatric treatment is constrained by the need for new validated models of translational research in patient populations and in whole animal analogues of pathophysiology. In its youth, the ACNP provided the venue for critical consideration of patient assessment tools and clinical trials methodology that became the "gold standard" for psychotropic drug development. But these tools, or their derivatives, are now nearly a half century old. The ACNP needs to again take the lead in advancing translational research, and the development of new assessment tools that will be sensitive to the development of novel therapeutics.

Finally, the ACNP (like other scientific societies) has been buffeted by the controversies at the interface of industry, academic and government. Our codes of conduct have been recognized for their responsiveness to public good, as well as their sensitivity to the need for fruitful and non-conflict of interest laden interaction and collaboration among scientists from each of these three sectors. In the years ahead, our College and its membership will be challenged if we fail to live up to the ideals that we have made clear to our industry and non-industry members, and that we have put forward into the public space. If we fail to live up to the ethical standards that we have set for the College and its members, we will lose the support of the public for our science. We must not let that happen!

Thomas Detre – ACNP Past President, 1994

Between 1977, when I became a member of the ACNP, and 1994 when I was elected president, it became painfully clear that the neuropharmacologic agents we use to treat our patients were far less effective than we originally thought. We also learned that the mode of action of so-called antianxiety, antidepressant and antipsychotic drugs is not that specific, and our hypotheses on the pathogenesis of mental illnesses based on how these drugs impact the uptake of certain neurotransmitters could not be proven. The final blow to this era came recently when it was shown that variation in the serotonin transporter gene, even when compounded by stressful life events, does not increase the risk for depression.

The initial and rather naive expectation that mapping the human genome would rapidly improve our understanding of the etiology, pathogenesis and treatment of human maladies was also not fulfilled. Fifteen years after the identification of the gene for Huntington's chorea, we still do not have any effective treatment. The current research which shows that seven or more genes are likely to contribute to the vulnerability of Alzheimer's disease, that as many as 90 genes may be involved in the proclivity to substance abuse, or that there are a number of shared "candidate" genes for schizophrenic and bipolar disorders, led to the view that the majority of neuropsychiatric and other medical disorders are multigenic. It is quite possible however that this is not true either and that the collection of clinical signs, symptoms, and laboratory findings, which today define what we call diseases or syndromes, are phenomenologically deceptively similar, but are quite heterogeneous and actually represent as yet an unknown number of definable biologic entities. It is also a reminder that no amount of tinkering with our phenomenologically based diagnostic systems is likely to be productive.

All of the above serves as a preamble to the question past presidents were asked to respond, namely, what were the most conceptual advances in our lifetime? My answer is that thanks to the enormous advances in basic neuroscience, we have a better grasp than ever before of what we do not know. And, since progress is likely to continue and even accelerate, as ACNP celebrates its 50th anniversary, each of us will have to make painful choices about who we are, since very few of us have the ability to be up to date on preclinical, translational and clinical research. This topic is worthy of future discussion.

David J. Kupfer, MD – ACNP Past President, 1995

Our 50th anniversary is indeed a special moment in our history, so I am very pleased to add a Past Presidential reflection to this compendium. While many things have changed over these 50 years, many other things have not. In my statement included in the 35th anniversary update, I commented that neuropsychopharmacology was experiencing the best of times and the worst of times. That is still true. The opportunities to advance our science in relationship to both health and disease are unprecedented. The plethora of replicable scientific findings will unquestionably change the face of biomedicine within the next decade or two. However, we still are not sufficiently proactive in terms of public concern and advocacy for neuropsychopharmacology. We continue to need to make a stronger case for the virtues of translational neuroscience and the importance of education as well as for the implementation of such findings in the diagnosis and treatment of disorders that have enormous public health impact.

It is not easy to determine the best course for the College, but we must seek to influence how its future unfolds. Part of our difficulty relates to the stigma attached to the disorders we study and the problems inherent in working with disorders that have rarely been accorded the respect of serious scientists in other areas of medicine. Our increasing alliance with our important partners, the advocacy groups, represents one strong component of an overall mission. Working together, we should be able to clarify the scientific vision of the ACNP and its members, a vision of the enormous potential of research in our field, of our role as scientists as we move into the next century and of our role as clinicians who can provide the best possible care for our patients and their family members. I am hopeful that the next 50 years will allow us to achieve that vision and thus, ensure a healthier future for all individuals who suffer from neuropsychiatric disorders.

Benjamin Bunney – ACNP Past President, 1996

In my "Presidential Statement" written on the occasion of the ACNP's 35th anniversary, I concluded:

> *"Assuming continued funding, what will the field of Psychopharmacology look like 35 years hence? By then we should know enough about the brain and its diseases to rationally design therapies which are highly efficacious and lack serious side effects. The optimistic can hope that around that time, or shortly thereafter, some therapies will become available for correcting identified underlying genetic predispositions and/or specific environmental manipulations will be known that prevent the emergence of symptoms in those at risk. Last, but equally important, because the biological basis of mental illness will been proven, stigmatization of the mentally ill will all but have disappeared."*

Although only 15 years have past, we have made significant progress toward these goals. The human genome has been mapped and techniques developed for rapid genetic analysis that has greatly speeded up our ability to search for "disease genes" and to understand both the genetic underpinnings of individual variations in the therapeutic response to a given drug and its side effects. The dream of developing treatments designed to fit an individual's genetic profile is rapidly becoming a reality. Although complex genetic trait diseases like schizophrenia have not yet yielded their secrets to us, we are much closer than we were 15 years ago.

Totally new fields have emerged during these last 15 years as well. In 1996 no one talked about nanotechnology. Today it is an exploding field which carries the promise of revolutionizing many other fields, not the least of which are the fields of neuroscience and neuropharmacology. For example, whole new classes of drugs based on peptides will be enabled in hitting their targets by nanotechnology.

Lastly, we have made great strides in educating the public about mental illness, and in so doing greatly decreased its stigmatization. Hardly a day passes now that there isn't an article on some aspect of mental illness in one of our major newspapers. More and more TV shows are devoted to it and Congress has finally passed a parity law. The ACNP played a significant role in bringing about this change through its lobbying efforts and through its members educating the public about the fact that mental illness is a brain disease. However, there is still more to be done, especially in the area of substance abuse. I have no doubt the ACNP will continue to be one of the leaders in these efforts.

One discipline that has not kept up with the science in our field and needs a lot of attention is ethics. I am not referring to the ethics of our interactions with pharmaceutical companies or of publication but the ethics associated with use of the power over people's lives that science is increasingly wielding. When we can identify the person who carries the genes that can lead to a mental illness, who gets access to that information? Will employers and insurance companies want to screen for these probabilities? When we can prevent a mental illness through expensive genetic manipulations, who will decide who benefits and who doesn't? A start was made on these issues when the Genetic Information Nondiscrimination Act was passed onto law in 2008. However, much remains to be done.

There are a myriad of theses issues that if not addressed, preferably before they become a scientific reality, will threaten to make populations of citizens second class or create a back lash against the science itself. Scientific knowledge is expanding exponentially and will continue to do so, funding permitting. But the fruits of discovery will never be realized unless we address the ethical issues surrounding the transition of discovery to practice. If we can make the development of ethical standards a priority which keeps pace with our increasing knowledge of the biological underpinnings of mental diseases, the next 15 years will be very exciting indeed.

Steven M. Paul, M.D. – ACNP Past President, 1995

As I write this statement, well over a decade since my term as ACNP president ended, I am still struck with a profound sense of appreciation (and gratitude) for having been selected by our College to serve as its president. Serving as ACNP president remains one of the most rewarding experiences of my professional career.

I first became aware of the ACNP as a young postdoctoral fellow in Julie Axelrod's lab at NIMH where I had the good fortune to meet many of Julie's former fellows (Julie's "boys" - many of whom were ACNP members) and to attend my first ACNP meeting in San Juan. To this day, attending our annual meeting remains one of the most exhilarating, rewarding and intellectually stimulating experiences of my academic life. I am pleased that our meetings, if anything, have only gotten better over the years. They represent a terrific opportunity to share (formally and informally) one's latest research findings, but most importantly, to learn (and apply) new approaches to one's own "science" and thus, to be challenged to grow both scientifically and professionally. I suspect all of my ACNP colleagues share this sentiment.

During my term as ACNP president, there were at least two issues (challenges and opportunities as I like to say) that I vividly recollect and that I believe were critical to the College's evolution and future success. The first was the successful recruitment of our first executive director, Ronnie Wilkins, who I am pleased to say as I write this statement, is still our executive director (and doing a splendid job!).

The decision by Council to recruit an executive director was not an easy one by any means. Our *beloved* college secretary, Oakley Ray, had effectively served in this capacity for longer than any of us could remember. Oakley, truth be told, embodied our College's collegiality and friendship, and was singularly responsible in my view, for the College's tremendous growth and success as a preeminent scientific organization. Personally, Oakley was a dear friend, wise advisor and even "father figure" to many of us. Stilt we (Council) felt, given the College's rapid growth and complexity as both a scientific organization and not-for-profit business, that a fulltime executive director was in the best long-term interests of the College. With the leadership of Huda Akil, Chuck O'Brien and Alan Schatzberg, and, of course, the blessing of Council (and especially Oakley), we successfully recruited Ronnie to be our executive director. While I have not been as intimately involved in the College's leadership for quite some time, it is my impression that our decision to recruit a fulltime executive director, while difficult at the time, was in hindsight the right decision. Importantly, the successful transition from Oakley's leadership to Ronnie's was a true testimony to both their professionalism and love for the ACNP.

The second issue or challenge to arise, somewhat ironically, during my tenure as president, concerned the potentially nefarious role of the pharmaceutical industry in our College's scientific mission and annual meeting. At the time I served as president, I was leading the Neuroscience (CNS) R&D efforts of Eli Lilly and Company, arguably one of the more successful programs in the industry and with several CNS products that comprised a large (and growing) percentage of our company's revenues. Importantly, in my view, our College almost by definition (we are of course neuropsychopharmacologists) needed to have a close working relationship with scientists from industry. Moreover, for better or worse, our College's financial well being depended in good measure on the financial support of industry. Still, it was clear to Council and me that

"things had gotten out of hand". Our meetings were being used by pharmaceutical companies to announce (via press releases) the latest findings on their drugs (often somewhat dubious comparative studies versus their competitors' drugs), and to separately meet (via satellite meetings) with ACNP members (their so-called "thought leaders") to "review" and be "educated" about these latest findings - and all under the imprimatur of the ACNP. Of course some of our members (including myself) worried that the increasingly influential role of the pharmaceutical industry in our annual meeting might erode our image and the unbiased and stellar scientific reputation of the ACNP in the eyes of the public, and worse yet, its current and future members. Consequently, Council mandated a number of new rules which prohibited such unauthorized press releases and satellite meetings. These new rules, along with enhanced policies on full disclosure of potential financial conflicts of interest among our membership and meeting participants, have had again in my view, a very tangible impact in reducing the potential trust-eroding influence of the pharmaceutical industry's commercial enterprise on our College's scientific and educational missions. Moreover, we also managed to navigate these delicate and potentially controversial issues in a manner that solidified the important working relationship with industry and especially their superb neuropsychopharmacologists (many of whom have subsequently been elected to membership in our College). Nonetheless, this "issue" and ongoing concerns about financial conflicts of interest with industry will continue to require close and thoughtful monitoring and attention by current and future ACNP leadership.

In my opinion, one of the most important roles of the ACNP is to literally serve as a catalyst for scientific progress in our field, and importantly, progress that will ultimately result in better treatments for our patients. In this regard, never before has the ACNP's mission been so critical. Clearly, there have been many advances in neuropsychopharmacology (broadly defined) over the past 50 years, and especially over the past 20 years. We have at our disposal, a host of "effective" and relatively safe medicines to treat mood disorders, anxiety disorders, schizophrenia and some forms of substance abuse. Those of us who are also trained as psychiatrists know that it would be almost impossible to treat severe mental illness without the current armamentarium of psychiatric medicines. On the other hand, virtually none of the current medicines we routinely use to treat for example, depression or schizophrenia, are really any more effective than the ones that were initially discovered and introduced in the 50's and 60's (and most by sheer accident!). Far too few patients respond adequately to even our current genre of "second generation" medicines, and true remissions for the more severely afflicted patients are rare. Without sounding too cynical or pessimistic, I am quite concerned about the rather slow progress we have collectively made of late, in discovering that "next generation" of medicines for depression, schizophrenia and other disabling neuropsychiatric disorders. In fact, very recently, several large pharmaceutical companies have announced that they are no longer going to invest in R&D for psychiatric disorders, in particular, a worrisome and in my view, ill-conceived and hopefully temporary decision on their part (fortunately, this is not the case with a number of companies including Lilly). The reasons for this malaise are multifactorial, but the solution is simple. We need a much better understanding of the neurobiological substrates, etiology and pathophysiology of the very disorders we desire new treatments for, especially severe mood and anxiety disorders, schizophrenia, autism and substance abuse. For those highly heritable disorders, we need to discover their exact genetic etiologies and we need much more information on the disordered brain circuitry (pathophysiology) for each of these disorders. In my opinion, advances in next generation DNA sequencing (whole genome sequencing)

and functional neuroimaging (fMRI) to find disease-causing genetic variants (etiology) and dysfunctional neurocircuitry (pathophysiology), respectively, are the two most promising methods to provide the necessary neurobiological substrates for drug discovery, we so desperately need. I am confident that has been the case for other eNS disorders; such scientific advances will catalyze (rejuvenate and reenergize) public and private sector investments both intellectual and financial to find new and better treatments. Finally, let me also confess (as heretical as it may sound coming from this die-hard neuropsychopharmacologist), that I believe non-pharmacological (and noninvasive) methods for "treating" the neurocircuitry dysfunction underlying the major mental disorders (depression, anxiety disorders and schizophrenia) are also on the horizon; treatments that are not unlike those we currently use for certain forms of heart disease (cardiac dysrythmia). The mission of our College, therefore, has never been more relevant and critical to making such scientific progress a reality.

Charles O'Brien – ACNP Past President, 2001

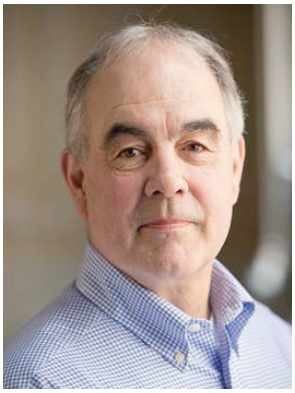
As I look back on my time on Council and as President, I have largely very happy memories and a feeling of satisfaction. My presidential year was 2001, and it was a great year for many reasons. The most important reason was that three of our members Paul Greengard, Eric Kandel and Arvid Carlsson received the Nobel Prize. We held a major celebration in Washington, DC and included our fourth Nobel laureate, Julie Axelrod. The symposium consisting of Nobel lectures at the Reagan Building was quite memorable and was attended by both politicians and scientists. We then had a gala dinner at the Library of Congress.

2001 was also memorable for another reason in that the ACNP had just moved to a system of having a professional Executive Director rather than using an elected scientist for administrative affairs. This has proven to be an excellent system with an outstanding Executive Director, Ronnie Wilkins, and college members as Secretary, Treasurer, and of course, monitoring by Council and President.

Although the future looks bright for our field and for the College, it is important to keep in mind the dangers involved in our relations with the pharmaceutical industry. On the one hand, it is a distinct advantage for progress in the field to have a close working relationship between scientists in academia and scientists in industry. In fact, some great industry scientists are also members of the College. At the same time, this working relationship carries with it the risk that we will be seen as biased toward industry and influenced by financial concerns. We must always remember that we have to earn the trust and respect of society if we are to influence the development of funding for science. Trust is based on the belief that we are independent and honest. By reducing our financial dependence on dues from pharmaceutical companies, we have reduced the risk that we will be perceived as merely spokespeople for industry. We also should beware of the myth that we have to have a huge treasury in order to protect us from losses in case there is some form of natural or terrorist initiated catastrophe that causes cancellation of a meeting. Indeed a serious financial loss will never happen because our contracts with hotels protect us against that. We really don't need a large reserve in the treasury. We should continue as Council has done in the past to keep dues relatively low and to spend our money on worthy projects such as training of young scientists and informing lawmakers by our efforts in Washington.

It is a privilege to be members of this wonderful society and I anticipate an exciting and productive future as the science in our field progresses.

Joseph Coyle – ACNP Past President, 2002



I can still remember from 30 years ago a tap on my shoulder and the whispered remark that "you made it". This was great news, as I was elected a member of the College that my mentors, Sol Snyder and Julie Axelrod, had touted as having the best scientific meeting of the year. It was a great honor and continues to be, participating in an organization that defines the cutting edge of research in psychiatry.

Some 20 years later, while on Council, I was invited to run as President of the College, and I was greatly honored to be elected by the membership to serve in this position. This occurred at the beginning of a new century that, in retrospect, heralded important changes and challenges for the College.

During my Presidency, concerns were raised about the conflicted nature of the College's relationship to the pharmaceutical industry. Funds provided by the industry in various ways underwrote nearly 80 percent of the College's operating budget. Complaints were registered about "marketing of drugs" in the poster sessions and in symposia. As a consequence, Council decided that the number of attendees from industrial sponsors was to be restricted. Poster authorship responsibilities were clarified, and access to the scientific sessions was limited to registered attendees. Subsequent initiatives have seen a steady reduction in the College's reliance on funds from the pharmaceutical industry, although participation by scientists from industry continues to represent an important aspect of the scientific program.

With the growth of the annual meeting and creation of its own journal, it was clear that the College could no longer rely on the secretary, Oakley Ray, Ph.D., to bear the administrative load alone. The position of the Executive Director was created, leading to the recruitment of Ronnie Wilkins, Ed.D., who has had a tremendous impact on the operations of the College. Limitations in the ability of the Caribe Hilton, the historical default site for the annual meeting, to house most of the meeting participants prompted the decision to hold the annual meeting primarily at larger mainland sites.

With concerns over the modest royalties generated by Elsevier, the publisher of the College's journal, the publishing contract was subject to an open search at the time of its renewal. Because of favorable terms and synergy with their other journals, Nature Publishing Group (NPG) was selected during my term. Subsequently, as co-Chair of the Publications Committee, Sam Enna and I proposed that a new annual issue of the *Neuropsychopharmacology* be dedicated to invited reviews focusing on particular research topics in psychiatry. Thus, *Neuropsychopharmacology Reviews*, came to replace the "Generation of Progress" books with much more timely, accessible and citable review articles. Even with rapid electronic publication of accepted manuscripts and the decision not to accept pharmaceutical advertising, the revenues from these publications grew nearly ten-fold over the last decade, to make a substantial contribution to its bottom line for the College.

Thirty years after that tap on my shoulder, I am still awed by the College and the commitment of its membership to scientific excellence. The annual meeting remains ***THE*** place to learn about the most current and innovative research that informs psychiatry and neuropsychopharmacology. The tradition of inviting first-rate non-member scientists to participate in the symposia educates the membership on emerging areas of science relevant to its mission. Today's basic research should inform tomorrow's clinical research, and the College stands as the premier forum for translational research in psychiatry.

Carol Tamminga – ACNP Past President, 2004

The ACNP was begun by basic and clinician-scientists who were motivated by curiosity over the mechanisms of psychotropic drug action as they acted on the manifestations of cognitive and affective diseases. At the time, these diseases were only partially conceptualized as diseases of the brain with a molecular and cellular basis. In a prescient action, the founders of the ACNP organized themselves, a few dedicated scientists, to examine the biology of these diseases, including both their molecular basis in brain and the clinical implications: this group did translational neuroscience from the beginning. Of course, this was (and still is) all much more complex than any had imagined. The ACNP has grown both in the number of its scientist-members and in the scope of its science, but has never strayed from its dedication to understand the disease and treatment neuroscience of its diseases, diseases that modern medicine has left behind. This focus defines my esteem of the ACNP.

For me the ANCP has been an organization that has collected the best of the translational, basic and clinical scientists (academic and industry) into a loose but goal-oriented consortium, which has been able to get its members together at least once a year to talk with each other and has encouraged us to achieve educational and political goals ('community service') within our scientific and educational areas. The growth of neuroscience has been explosive over that last half century; the perspectives and motivations of ACNP members has kept a steady pressure for application of these methodologies to human brain disease research. Whereas, only 20 years ago, our disease formulations (while we made them) were simplistic and superficial, now we have real basic neurobiology as the foundation to build our disease formulations. It is the ACNP where many of these formulations are initially vetted and edited by discussion and commentary. All of us can remember specific examples of vigorous vetting, loud discussion and new insights. It is the intellectual excitement of discovery that has most characterized ACNP interactions for me, especially at the Annual Meeting, over the years.

What has been amazing to me over the last several decades has been the relentless, sometimes paradigm shifting and always clever advance of knowledge about basic neural structure, chemistry, systems and function. It is less about any single discovery or single methodology that has brought the field forward, in my opinion, than the continual acquisition of novel insights from different perspectives and methodologies and their application to human mental function that has incrementally clarified our conceptualizations about brain function. With little sophisticated knowledge about basic brain biology (as was the case in early ACNP days), clinical pathophysiologic formulations of psychiatric conditions were based on rarified interpretations. But, over the last half century, neuroscience research has developed a rich and integrated knowledge base on which clinical hypotheses of disease mechanisms can realistically be constructed. It is not that we know the mechanisms of our illnesses today, because we still do not, but we at least have the knowledge to pursue and test rational hypotheses. And, the situation provides the promise for future discovery. The ACNP will be a force in this progress.

It is hard to dismiss the importance of a community of scholars with such a dedicated focus and a specialization on the brain and psychiatric illness. I realize its importance every time I receive a "Death of a Colleague" announcement and get to personally reflect on my interactions and discussions with the person, down to specific work assignments, shared concepts and advances in understanding that accompanied motivated discussions. Members of the ACNP are a combination of neuroscientists, colleagues, friends, golfing partners, wine aficionados, and science politicians. It is a precious conglomerate, delicate in its balance, contributing to our intellectual and psychosocial wellbeing, I believe.

Daniel Weinberger – ACNP Past President, 2005

It is hard to believe that I was president of the ACNP at all, let alone that it was only five years ago (seems much longer!). I first attended an ACNP meeting as a resident and guest of Dick Shader. That was sometime around 1977 and it was in New Orleans. I remember having almost no idea what everyone was talking about. My next time as an attendee was as an NIMH fellow and guest of Richard Wyatt. That was in the early 1980s. I had a slightly better idea at that time of what everyone was talking about, but not much. I have not missed a meeting since, and I have become increasingly comfortable with what everyone has been talking about. After several stints on the council, I was honored by the ACNP membership by being elected its president. The time on the council and my year as president were memorable and very meaningful. It is a gross understatement to say that the work of being president, which is of course fun and challenging at times, was mostly tedious and repetitive and would not be tolerable were it not for the extraordinary ACNP staff, particularly Ronnie Wilkins and Sarah Timm. I owe them an enormous debt of gratitude. They helped not only with details and organization, but with their good spirit and dependable encouragement.

When I ran for president, I said in my campaign statement that the two developments in biomedical science with the greatest impact on the ACNP membership would be the molecular biology of neuroplasticity/neurodevelopment and human genetics. I still endorse this view and believe that the fields of research encompassed by the ACNP membership have been advanced immeasurably by these dramatic scientific developments. As compelling as this new science has become, we have a major challenge in making it relevant to the clinical practitioner. The gap between the basic science of psychiatry and clinical practice is probably greater than in any other field of medicine. This is an important area for the ACNP to tackle in the coming years.

Looking back on my year as president, there are several lessons that I learned and memories that stand out. First, as is said by every past president, the College is an historic achievement with unique value in the landscape of psychiatry research. The cornerstones of the College - its collegiality, diversity, scientific standards, and informal meeting environment - are its indelible signature. Sitting on top of this structure as president is a singular lifetime experience for anyone in our field. I was deeply honored and very happy to have had this opportunity.

During my presidency there were two major events that shaped much of what we did during that year. First, we had invested a huge amount of time and money in fashioning a “strategic plan” for the College. There were many meetings, discussions, letters to the membership, and more discussions and letters to the membership. We constructed a detailed document of many pages. In retrospect, this seems now mostly to have been a waste of time and money. We have not followed the strategic plan in any structured way, and one of the principal goals for me, to reduce the dependence of the College on support from Industry to less than 40%, has in fact, moved in the exact opposite direction. This, I believe, is an unfortunate misstep on our part. The other major event involved ethics investigations of members of the College. This, I also believe, got way out of control and was not handled as effectively and appropriately as it should have been. Regrettably, these are the kind of circumstances that develop a life of their own, particularly in public organizations who

become overly concerned with their image, press notices and become overly defensive. Thus, it becomes impossible to stop the tide. If I have one message for the College from my experience with both of these events, it is: the College takes itself a bit too seriously.

One of the privileges of being president is planning plenary talks and themes for the annual meeting. I was very delighted to take on that challenge and invited speakers from diverse areas of genetics and developmental neurobiology who had not previously been to the ACNP. I also had a great party in my presidential suite overlooking the Pacific Ocean that I, and hopefully those who attended, will never forget. All in all, it was a year that I treasure and that I hope added meaning to the history of the ACNP. Thanks to all for being there with me.

Kenneth Davis – ACNP Past President, 2006

It was my privilege to be president of ACNP in 2006, and although I wish my memories from that year and our annual meeting would be crowded with scientific breakthroughs, they are not. Instead the year was most memorable for the turmoil surrounded by the perception that our field was wracked with bias stemming from the inappropriate involvement of prominent members with the pharmaceutical industry. Newspapers with national circulations wrote articles and editorials highly critical of our field and the appearance of conflict of interest among some of the College's membership. Indeed the credibility of our own journal, Neuropsychopharmacology, was under attack, due to allegations that a "ghost written" article had appeared in the journal. It was suggested that this article was largely authored by employees of a device company, and that the article had received inadequate peer review. All these faults were purported to be the fault of our journal editor who was also the senior author on the paper in question.

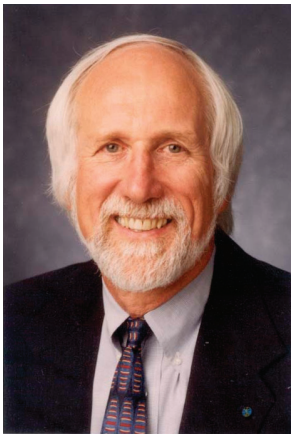
It would be unfair to say that ACNP leadership had not been aware of the potential for there to be the appearance of conflict of interest between the College and the pharmaceutical industry for some time. Indeed for all the years I served on Council, leadership had been aggressively addressing this issue. During the presidency of Carol Tamminga, a strategic plan was developed to substantially reduce the dependence of the College on revenues derived from the pharmaceutical industry. A series of restrictions had also been imposed on the uses of donations from corporate members, and the prominence of corporate activities at the meetings. Indeed, these reforms had already substantially lowered the percentage of our College's revenues that derived from industry, as well as the ambience of the annual meetings. However, these efforts were dwarfed by the avalanche of negative publicity surrounding the publication in the ACNP's journal of the paper in question.

Our membership was mobilized by all this negative press. Some thought we were being inappropriately targeted, while others felt the members involved in the suspect paper should be removed from the College. Most distressing was how colleagues, and even members who had been friends for decades, engaged in bitter debates, and even personal attacks. The camaraderie that was so valued in our College was in jeopardy.

Daily, I received letters and e-mails with suggestions, or just lamenting our situation. With the help of Council, the Ethics Committee, the Publications Committee and Ronnie Wilkins we took a number of forceful measures. Ultimately our College was cited by other professional organizations as having a model code of conduct and rules of engagement around academic industry relations. Policies and procedures around our journal were modified and far better enforced, and a new journal editor was appointed.

These were all the matters I reviewed at the annual business meeting. What is still most salient in my memory of that address was my call for a more civil tone among our members. That we should never lose sight of the fact that we were not just bound together by our interest in brain science, but we were also bound together by years of friendship. That we not only share in each other's scientific accomplishments, but in the milestones of our lives including births, deaths, marriages, and celebrations. Our College's strength is its membership, and the strength of that membership depends on our caring for each other.

William T. Carpenter, Jr. – ACNP Past President, 2007



My year as president of the ACNP was a wonderful experience with colleagues and staff and a deeply meaningful honor. It was also a time of paradox. Neuropsychopharmacology is an amazing enterprise, vastly interesting and pushing knowledge forward at an incredible rate. On the other hand, use of that knowledge to advance therapeutics for our major disease syndromes has been disappointing.

In 2007 anti-psychotic drugs were based on the same mechanism introduced with chlorpromazine 55 years earlier, lithium continued to keep pace with newer drugs in the treatment of bipolar disorders, and the efficacy of anti-depressant medications was not much advanced over the original tricyclic medications. Adverse effects have been modified, but novel mechanisms and significant therapeutic advances are rare.

My interest is in schizophrenia, and here methods and concepts have evolved and an alternative paradigm is taking hold for the purpose of etiological and therapeutic discovery. The field has gradually recognized that schizophrenia is a heterogeneous clinical syndrome and, as such, was not a robust target for drug development. Deconstruction of the syndrome into more specific and homogeneous domains of pathology represents a paradigm shift resulting in more specific targets for research. Domains of pathology can be translated into animal models with greater validity than attempts to model a syndrome. Domains also provide more robust targets for investigations ranging from neuroimaging to genetic influences.

The FDA has accepted this paradigm shift as illustrated by their recognition of impaired cognition and negative symptoms in schizophrenia as potential drug indications. Previously, psychosis was used as a proxy for schizophrenia and resulted in anti-psychotic medication, not anti-schizophrenia drugs. The methodology required to test for efficacy in these domains was developed through a collaboration of academia, NIMH and the FDA. For cognition, the methodology was published by Buchanan et al in the January, 2005 Schizophrenia Bulletin; for negative symptoms by Kirkpatrick et al in the April, 2006 Schizophrenia Bulletin.

I have been interested in this development since we put forward domains of pathology as an alternative to syndrome-based investigation (Strauss, Carpenter and Bartko) in the winter, 1974 issue of the Schizophrenia Bulletin. The paradigm gained traction at the turn of the century with the NIMH MATRICS and TURNS initiatives. It now appears likely that the domains of pathology paradigm will form a dimensional assessment component in DSM-V (scheduled for publication in 2012).

In 2009, NIMH initiated a formal process for identifying basic behavioral traits associated with the major disease syndromes. The aim of this initiative is to define the neurobiological underpinning and neural systems associated with domains of pathology. This process, initiated by NIMH Director Tom Insel and chaired by Bruce Cuthbert, promises to link the domains of psychopathology used to deconstruct syndromes to the basic biological processes common to mammalian species. This will provide an integrated construct to support the creative acquisition of new knowledge relevant to the etiology, pathophysiology and treatment of major mental illness. And this translational science is central to the interest represented by the ACNP.

Judith L. Rapoport, M.D. – ACNP Past President, 2008

For child and adolescent psychopharmacology, the most useful and interesting discoveries have been: the striking short term efficacy of stimulant drug treatment for ADHD, the efficacy of SRIs and SSRIs for OCD, and low dose antipsychotics for Tourette's Disorder. More limited data suggests the usefulness of immunosuppressant treatment and glutamatergic agents for selected cases of childhood onset OCD/tics.

The ACNP has been particularly supportive of training and research in the field of Pediatric Psychopharmacology over the past 35 years. As with the field in general, however, the treatment pipeline has faltered. The focus has been more on toxicity such as suicidality with SSRIs and rare cardiac deaths with stimulants, in pediatric populations. These preoccupations have been misused to discourage use of medication.

One promising avenue of research across virtually all psychiatric disorders has been the systematic study of very early onset patients. These are proving to be more homogeneous for some disorders, or cases with distinctive subgroups in others. This approach to clinical research is revealing more salient physiological and genetic factors. The therapeutic implications of this research remain, however, a promissory note.

David L Braff, M.D. – ACNP Past President, 2009

As we approach the ACNP's 50th Anniversary, there is good reason to be proud of our past, live fully in the moment and to be excited about nurturing young scientists for a challenging and promising future. There is also good reason to prepare for continuing significant challenges in these current somewhat difficult times. As the last Past President to contribute to this Volume, I know that our immediate future is in the hands of two exceptional Presidents-To-Be: David Rubinow and Eric Nestler. We could not ask for two better scientists and human beings to guide us through our 50th Anniversary. Plus, they have our exceptional staff, led by Ronnie Wilkins and Sarah Timm to help them navigate through our increasingly complex world of economic and social challenges. As Sam Barondes frequently says: "Who is the Wealthy Person? S/He who rejoices in his portion." We are truly lucky to have each other, our emerging science and our patients willing to help others via their participation in research. Now we must continue to unravel the complex neural and genomic substrates of disabling neuropsychiatric disorders as we strive to do our best to relieve the suffering of others.

The Past: The ACNP was founded in the cauldron of the scientifically unsound, anecdotal mid-20th century psychiatry that focused on myths and the elusive search for even minor parenting errors that allegedly left indelible and severe scars on the psyche. Thus, almost 50 years ago, the ACNP was established based on the promise of a new "scientific psychiatry" reflecting the optimistic belief that in using strong inference to delineate brain-behavioral abnormalities we ultimately could find cures for seriously disabling mental disorders. Although most biological therapies resulted from serendipity, it was a good start.

The Present: Our College is in the midst of dealing with profound scientific and societal transformations. The Human Genome Project, advances in brain imaging and the use of neural circuits, genetic circuits and advanced clinical trials has borne some fruit, but there is a long way to go. For example, the impact of genetic variation on key neurodevelopmental and neural substrate functions, allow us to begin to understand the mysteries of neuropsychiatric disorders. We have the potential to use novel genomic and neurobiological findings to create a more efficacious generation of psychotropic medications. Yet, treatment is more complex than just giving a patient some pills, it involves the therapeutic alliance and psychosocial and vocational rehabilitation, which in themselves likely change the organization of the brain's neural connectivity. Per the NIMH Strategic Plan, we need to use our resources to not only treat common and disabling mental disorders, but to identify the biomarkers of risk that will enable us to create and implement "early" detection and treatment of these disorders: to perhaps even cure them.

We face challenging societal expectations and responsibilities to our patients and their families. Alfred Adler called for "Gemeinschaftsgefühl" (community spiritedness) at the beginning of the 20th century, we will be wise to adopt such a spirit in our work in our 21st century. From the "outside", patients and society expect and deserve increased vigor in delineating how we handle conflicts of interest and other ethical issues. One vexing issue is how to address conflicts of interest (COIs). A COI represents the potential for misbehavior. Many COI's do not constitute violations of ethically acceptable behavior. It is only when the conflict leads to unethical behavior that wrong doing has occurred. The ACNP has developed proactive polices regarding our core values and our ethics rules for academic members, which also are excellent models of establishing

a moral center from which we can lead our "Triple Helix" of Academia, Pharma (Big and Small) and the NIH and other Governmental entities. We will also continue the efforts started by previous Councils and Officers to clarify the boundaries of acceptable behavior for both academics and industry in our converging interests in helping psychiatric patients, their families and Society as a whole. While it is clear that the optimal solution to the conundrum of the control of clinical trials would be a purely unbiased NIH or IOM based clinical trials entity, such a solution is not realistic in the near future. So we need to move to fully utilize and monitor existing structures and develop new medication evaluation entities. But we should not take on too many sometimes tangential regulatory or ethical tasks; this is time consuming and reflects the type of "Mission Creep" that can drain our energy and resources.

2009 Accomplishments: Within the ACNP this past year we created a clear, transparent and more easily understood path to Membership with Bob Freedman and the Credentials Committee acting in concert with our Council, this will be posted on our Website. Neal Swerdlow and the Program Committee have also created a clear and transparent path to showing how meeting submissions are scored. We have also moved the Annual Meeting Planning in-house (Sarah Timm strikes again) lowering our per person meeting costs dramatically. We also established a Meeting Planning Company (Parthenon) from the efforts of Ronnie Wilkins and Sarah Timm. This will provide an income stream since Parthenon, as well as our new office building, is wholly owned by the ACNP. We have also increased women's participation in the College and have more young people attending than ever before as we prepare for the inevitable change in overall leadership as older Founding Members are less active. Luckily we have a first rate staff, led by Ronnie Wilkins and Sarah Timm, to help us in all these endeavors.

The Future: We all hope to nurture the next generation of psychiatric neuroscientists. The ACNP is an honorific College, and we hope that Travel Awards, Associate Members and Invitees, will facilitate our scientific growth. The rapid expansion of information about genomics, proteomics, signaling pathways and neurodevelopment and our ability to influence these and other neural processes offer a rich palette of possibilities for advancing our science. But like the God Janus, who looked in multiple directions simultaneously, we must be sensitive to both good science and society. We should help a new generation of leaders to integrate vast arrays of information wisely and to use strong inference to demythologize mental disorders and apply the best new science to treating seriously disabling mental disorders. Right now our knowledge (facts) sometimes runs ahead of our integrative wisdom about how all the brain's "moving parts" work together in their in their rich tapestry of amazing synchrony, conducted by the thousands of genes and environmental vectors that impact brain function and dysfunction.

In the near future, we hope to embrace the emerging idea of an equitable "Sunshine Law" that, while respecting individual rights, will create a central repository of information about funds that are received by biomedical researchers from our Industry. We have an obligation to be agents of positive change, to foster research into the cause and treatment of psychiatric disorders and to focus on key new research. I remember the excitement (and a bit of 'newcomer anxiety') I felt at my first ACNP Meeting. Now we must all create a continued exciting and balanced College and welcome and encourage our young colleagues as we advance our basic and clinical science. I thank you for the opportunity of serving and leading the College, it is a singular honor. I believe that our members are still the "best and brightest" and tapping into our wealth of talent and good will offers a unique opportunity to advance our field and to help alleviate the suffering of our patients and their families.

David Rubinow – ACNP Past President, 2010

The theme that comes to mind as I am about to assume the role of president is borrowed from a marriage ceremony –"something old, something new." The "something old" is obvious – the tradition of the ACNP, one characterized by a unique combination of superb science and warm collegial interactions. Indeed, I feel privileged in being able to help run this organization that from the earliest phases of my research fellowship represented the best that our field had to offer.

As my term is about to begin – "something new"- my thoughts are directed to the future of our organization and our field. From the vantage point of technology, the future (not surprisingly) has never been brighter. We have an arsenal of spectacular new tools: tools for real time imaging of neuronal function in relation to behavior, for detection of acute and long term changes in gene expression, as well as the chemical modulators of expression, for delineation of critical signaling pathways and for identification of new molecular targets for therapeutics. Accompanying this unparalleled and very real technological promise are the need for new conceptual and computational tools and the danger of reductionism.

First, we are facing enormous computational and combinatorial complexity – huge numbers of variables and absolutely staggering numbers of combinations – e.g., 20,000 genes, the expression of which is modified by 300 possible coregulators existing in multi-subunit complexes with approximately 250,000 possible distinct post-translational modifications per complex yielding 10^{13} possible functionally distinct coregulator complexes; or, consider this: the number of two gene pairs with 20,000 genes is greater than the calculated number of elementary particles in the universe! These are big numbers, and we need the statistical tools that will permit the detection of meaningful signals that otherwise might be drowned out by efforts to control for the large numbers of variables and comparisons. The successful exploitation of current and future discoveries will clearly require dramatically improved bioinformatics.

Second, it appears that our ability to identify relevant molecules – growth factors, chaperones, adaptor proteins, kinases, coregulators, G-proteins, micro-RNAs, etc - has outstripped our ability to make sense of the myriad ostensibly relevant factors in even a single psychiatric illness. We are very good at identifying molecules; we need, however, to be good at integrating findings, at developing a systems approach (whether at the level of cell signaling or neural circuitry) so that we are not left with lots of candidate molecules but little understanding of how these molecules talk to each other, of the "spatial" and temporal roles of these molecules in the development of susceptibility or resilience to emergent behavioral disturbances. The framing of discovery in terms of systems biology will diminish the risk of molecular myopia.

Third, no matter how sophisticated our biological lexicon or how detailed our mapping of neural circuitry, our abilities to translate our knowledge into new treatments will ultimately depend upon the sophistication of our phenomenology. Consequently, we must be as diligent in advancing the precision of our clinical phenomenology as we are in our biological dissections, ready to abandon old nosologies in favor of component-driven categories that may more closely reflect physiological processes known to be disturbed in more than one psychiatric illness.

The "something new" also characterizes the four challenges we face as an organization if we are to assure the continued vitality and preeminence of the ACNP. The first is our need to identify and recruit bright

young scientists who will both enrich our ranks and benefit from their interaction with our members. We are starving our future - that of the ACNP and that of our country's scientific excellence - if we (and the nation) fail to invest in the early careers of our young scientists. Second, we must be vigilant in keeping the ACNP relevant for new members; the honor of being elected to ACNP membership will simply not be sufficiently compelling unless we recognize and address the different generational expectations and needs of those young scientists whom we would want as members. Third, we need to promote the development of multi-threat scientists – those who are trained in multiple disciplines (e.g., psychiatry/psychology, immunology, pharmacology, genetics, proteomics, ecology, bioinformatics). These are the individuals who will take brain sciences and the ACNP to the next level. Finally, and perhaps gratuitously, we must remember that our scientific efforts are in the service of understanding and treating mental illness and addictive disorders. This mission, which entails the attendant obligation to unceasingly combat the ignorance and stigma surrounding mental illness, is one that we can all justifiably take pride in, and one that for the foreseeable future will continue to require and deserve our dedication.

Eric J. Nestler, M.D., Ph.D. – ACNP President, 2011

Great Progress, True Frustration

1986 marked the 25th Anniversary of the ACNP. It also was by chance my first ACNP meeting, where I was hosted by my postdoctoral advisor, John Tallman, to present a poster on our recent findings of the role of G proteins in long-term adaptations to opiate drugs of abuse. My first impression of the ACNP was that it truly was an old-boys club; at age 32, I felt like a toddler. The ACNP also struck me as more of a secret society than a scientific organization, since there was virtually no cutting edge, modern neurobiology presented at the annual meeting.

The 25 years that have passed since have brought some striking changes, yet sobering realizations. The ACNP today is very different from the one I first met. We now have far better representation of young investigators, and an increasing number of women, in the College. Today's annual meetings offer a far more impressive representation of the best basic and clinical neuroscience that the field has to offer. While there is still more we can do to achieve the proper diversity for the College (age, gender, race, geographic), and to optimize the quality and state-of-the-art science that underpins it, we should be proud of the real progress attained, while we strive to do still better.

The last 25 years, with the advent of molecular biology, have brought revolutionary advances in our knowledge of the nervous system. We now have a broad and ever more complete understanding of the diverse array of molecules that serve neurotransmitter and related functions in the brain, and the wide range of receptor proteins that mediate neurotransmitter actions. Mechanisms, underlying neurotransmitter synthesis, release, reuptake and degradation are known with exquisite detail. We also have an increasingly complete view of the complex post-receptor signaling cascades that make nerve cells able to adapt and respond over time, including the role of gene expression and, more recently, chromatin remodeling, in mediating such processes. The sophistication of our experimental tools, from inducible and cell type-specific mutations in mice to viral-mediated gene transfer, advanced confocal and two-photon microscopy, and high throughput DNA sequencing, among many others, have matched our growing base of knowledge.

Strikingly, however, this extraordinary list of achievements has not yet had a significant impact on the treatment of psychiatric and neurologic disorders. In 1987, Ron Duman and I first coined the term *Molecular Psychiatry* when we formed our Laboratory of Molecular Psychiatry at the Connecticut Mental Health Center. Looking back to those heady days, the field correctly anticipated the great advances in neurobiology emanating from molecular biology, listed above. However, we also boldly expected that those advances would easily and naturally spin off fundamental advances in the diagnosis, treatment and prevention of brain diseases. Despite everything we have learned about the nervous system, virtually all of today's treatments for brain diseases were available in 1986 (and, for most treatments, decades earlier). Despite advances in genetics, we still have not yet identified genetic variations that are responsible for the considerable genetic risk for virtually all psychiatric disorders as well as common neurologic disorders. And we have seen, in recent years, several large pharmaceutical companies abandon drug discovery in psychiatry because it has proved too difficult and too expensive to develop new medications with truly novel mechanisms of action.

Despite this lack of progress in translating basic advances to the clinic, I remain optimistic that we will

get there. Humbled yes, but still optimistic. In retrospect, we were very naïve 25 years ago in thinking that tackling the nervous system will proceed at the same pace as for cancer, heart disease and metabolism. Unlike all other organ systems, which face a complex molecular network of many thousands of gene products, the nervous system has the overlaid complexity of neural networks involving many billions of nerve cells and many trillions of synapses. We are now only beginning to overlay those two dimensions of daunting complexity. It also has dawned on us that new diagnostic tests and treatments will not flow easily, but will require directed hard work and require increased collaborations between academia and industry at a time when such collaborations have been unfairly demonized.

I would like to believe that, at the 75th Anniversary of the ACNP, when I will be a young 82 years of age, the field will have continued its remarkable track record in understanding the nervous system, but also achieved the crucial clinical translation that has thus far eluded several generations of research.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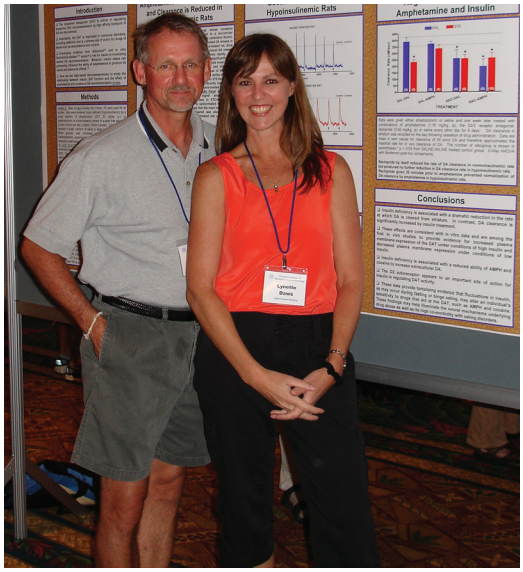
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