

Archives
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SUMMARY OF SELECTED SCIENTIFIC & ADMINISTRATIVE WORK OF WILLIAM E BUNNEY

William E. Bunney, M.D.

A. Service to Society and the Profession of Medicine

Dr. William Bunney served the scientific community in leadership roles in major societies, on Editorial Boards and on NIH Study Sections. Dr. Bunney was elected to and served as President of three societies.

Elected Positions In Scientific Societies

1974- 1975	President, Psychiatric Research Society
1983 - 1984	President, American College of Neuropsychopharmacology - the top national society in the field of psychiatry and psychopharmacology
1986 - 1988	President, Collegium Internationale Neuropsychopharmacologicum (CINP), the largest international society in neuropsychopharmacology and neuroscience.

Dr. William Bunney has held a number of administrative positions during his career including:

Director of the Division of Narcotic Addiction and Drug Abuse

As head of the division*, Dr. Bunney restructured the Federal Drug Abuse program in the United States. Historically, in the 1960s and 1970s, there was a strikingly inadequate health care delivery system for narcotic addicts and drug abusers, and there was relatively little research in this critical area. In 1971 Dr. Bunney was appointed by the Secretary of the Department of Health and Human Services to the position of Director of the Division of Narcotic Addiction and Drug Abuse. This included rehabilitation, training, education, research and international drug abuse health programs. The position further involved administratively supervising the Lexington Research Center, preparing and testifying before Congressional committees concerning requests for budget appropriations and legislation related to drug abuse. During his time as Director of the Division, Dr. Bunney increased treatment facilities, research, and training efforts in the U.S. A national health care delivery system for the narcotic addict and drug abuser was established with an increase in treatment centers from 23 to 140 centers. Eight university-based research centers in drug abuse were created and the number of individual clinical investigators receiving grants increased from 44 to 130. The budget of the Division during his three-year tenure increased from \$60 million to \$244 million dollars. The permanent staff size of the Division in 1973 was 793.

*See "Adventures" Section

Establishment of the First Childhood Psychiatric Disorders Branch at the NIMH

At the NIMH, Bunney advocated for and established the first Branch of the Intramural Program dedicated to the biological and genetic studies of childhood psychiatric disorders. The Branch is internationally recognized as an important contributor to child mental health and includes studies of ADHD, autism, depression and childhood onset schizophrenia.

Service on Editorial Boards and to Society

In the past and currently, Dr. Bunney served in various Editorial positions on 19 scientific journals. He served on and chaired Study Sections for the NIMH, served on three International Prize Committees, and on the Scientific Advisory Boards of National and International organizations.

Service to the National Academy of Medicine

Dr. Bunney chaired and organized projects for the National Academy of Medicine, including a study titled, "Reducing Suicide: a National Imperative". One recommendation from the study was to establish national centers for the prevention and investigation of suicide. Five new Centers were funded by the NIMH as a direct result of this recommendation.

Service to the Brain and Behavior Research Foundation

Dr. Bunney currently serves on the Scientific Council for the Brain and Behavior Research Foundation, which since 1987 has awarded over 3,497 grants for an overall investment of \$204.4 million, to Young Investigators conducting research across 100 institutions in 13 countries. Serves on the Committee on Membership/Nominations; on the *Colvin Prize for Outstanding Achievement in Mood Disorders Research*. Committee; and serves as Chair of the *Lieber Prize for Outstanding Achievement in Schizophrenia Research* Selection Committee.

Service on National Scientific Advisory Boards

1987 - Present	National Alliance for Research in Schizophrenia and Depression (NARSAD), (Brain and Behavior Research Foundation)
1987 - 2003	Depression and Bipolar Support Alliance DBSA (formerly the National Depressive and Manic-Depressive Association NDMDA)
1993 - 1995	Extramural Science Advisory Board, National Institute of Mental Health
1997 - 2004	Nancy Pritzker Depression Network Scientific Advisory Board
1997 - 1998	NIMH Scientific Advisory Group for the Extramural Research Division
1997 - 2003	Scientific Advisory Board for the National Autism Society
1997 - Present	Scientific Advisory Board for the Harvard International Brain Repository
2012 – 2013	National Action Alliance for Suicide Prevention (NAASP) Research Prioritization Task Force (RFP), Overview Expert Panel

Service to International Scientific Community

1984 - Present	Appointed Member of the World Health Organization (WHO) Expert Panel on Mental Health
1984 - 1995	University of California, Irvine, Department of Psychiatry selected by the World Health Organization as the U.S. Collaborating Center for Research and Training in Biological Psychiatry (co-Director)
1986 - 1989	Appointed to Scientific Advisory Board, Max Planck Institute for Psychiatry

B. Notable Accomplishments in Biomedical Research

Selected Investigations from 447 Peer-Reviewed Papers

Initiated Patient Research Ward at NIMH

Early in his career Dr. Bunney developed an Intramural Program at the NIMH, under the mentorship of Dr. David Hamburg. The ward, the first of its kind, included 24hour behavioral ratings of patients and daily collection of body fluids. The unit set an internationally acclaimed model for the intensive study of neuropsychiatric disorders, and provided the ability to obtain a new quality of behavioral and biological data (*Archives of General Psychiatry*, 1963).

Lithium and the Treatment of Bipolar Disorder

Research made possible by the methodology in this unit involved early double-blind studies of lithium treatment where placebo was substituted for lithium in an on-off longitudinal design. Over 5 days, the blind daily ratings documented the time-course of a consistent step-wise decrease in manic ratings in patients on lithium and an increase in manic ratings on placebo. This work provided irrefutable evidence of the efficacy of lithium during a manic episode.

Dr. Bunney's research helped launch the use of lithium in the United States. He played a role in the FDA approval of the use of lithium in bipolar disorder, and was a member of the APA Task Force report on the status of lithium which was a key document in the FDA approval process (*Am J Psychiatry* 1975). Now more than 4 decades later, lithium is one of the most widely used treatments for mood disorders and has benefited millions of patients.

Investigations on the Mode of Action of Lithium

Ongoing research has contributed significant data concerning potential mechanisms of action of lithium treatment. Below are listed four papers which contributed to this body of knowledge. Research on Lithium was shown to alter the uptake of noradrenaline by synaptosomes (*Nature* 1967). Follow-up pre-clinical investigations under the supervision of Bunney at the NIMH reported lithium's effects on subjective functioning and morphine-induced euphoria (*Science* 1977). Further research showed that lithium blocked haloperidol-induced presynaptic dopamine supersensitivity (*Nature* 1978) and also that chronic lithium prevented dopamine receptor supersensitivity (*Science* 1978).

- a) Colburn RW, Goodwin FK, Bunney WE Jr, Davis JM. Effect of lithium on the uptake of noradrenaline by synaptosomes. *Nature* 215.1395-1398, 1967.
- b) Jasinsky DR, Nutt JG, Haertzen CA, Griffith JD, Bunney WE Jr. Lithium. Effects on subjective functioning and morphine-induced euphoria. *Science* 195.582-584, 1977.
- c) Gallagher DW, Pert A, Bunney WE Jr. Haloperidol-induced presynaptic dopamine supersensitivity is blocked by chronic lithium. *Nature* 273.309-312, 1978.
- d) Pert A, Rosenblatt JE, Sivit C, Pert CB, Bunney WE Jr. Long-term treatment with lithium prevents the development of dopamine receptor supersensitivity. *Science* 201.171-173, 1978.

Biomarkers for Suicide

Dr. Bunney made significant contributions to research for biomarkers of suicide. In the United States 42,000 individuals commit suicide each year. The World Health Organization estimates that 1 million commit suicide worldwide each year. Thus the accurate identification of risk of suicidal behavior is a critical global imperative. The NIMH research ward facilitated the investigation of suicidal patients.

Over 200 severely depressed, intensely suicidal patients were evaluated longitudinally throughout their hospitalization. Behavioral ratings using the Bunney-Hamburg rating scale were completed hourly. Daily evaluations of urinary 17-hydroxycorticosteroids (17-OHCS), the major breakdown product of cortisol, were obtained. Extreme elevations of 17-OHCS were found to be a reliable biomarker of severe suicidal behavior including completed suicides (*Archives of General Psychiatry*, 1965; More recently, Dr. Bunney published a scale to assess psychological pain as a reliable predictor of suicidal intent. Bunney's research team also published data showing that 2 additional biomarkers, metallothioneins and polyamines represent risk factors in the evaluation of suicidal behavior.

In 2012-2013 Bunney was selected to serve on an Overview Expert Panel for the National Action Alliance for Suicide Prevention, Health and Human Services (HHS) National Action Alliance for Suicide Prevention, Research Prioritization Task Force. This task force produced a comprehensive publication and recommendations, which were approved by HHS and by the White House.

Innovative Norepinephrine Hypothesis

Bunney published a report presenting evidence that norepinephrine was critical in the pathophysiology of depressive reactions (*Arch Gen Psychiatry* 1965). This landmark high-impact paper was labeled a Citation Classic and has been cited over 1200 times, including recent citations. Along with a review by Schildkraut (1965), the norepinephrine hypothesis stimulated hundreds of scientific efforts.

One of these scientific studies involved MHPG (3-methoxy-4-hydroxyphenylglycol), the major metabolite of norepinephrine. MHPG was assayed in cerebrospinal fluid of mood disorder patients and was found to be lower in depressed patients compared to controls, which is compatible with altered norepinephrine metabolism (*Science* 1973). Research on alpha-methyl-para-tyrosine, the rate limiting step in the synthesis of dopamine, and on L-Dopa provided evidence implicating norepinephrine in depressive disorders.

- a) Bunney WE Jr, Davis JM. Norepinephrine in depressive reactions. *Arch Gen Psychiatry* 3:483-494, 1965.
- b) Post RM, Gordon EK, Goodwin FK, Bunney WE Jr. Central norepinephrine metabolism in affective illness. MHPG in the cerebrospinal fluid. *Science* 179:1002-1003, 1973.

First Direct Evidence of Circadian Patterns of Gene Expression in Human Brain and Abnormal Patterns in Major Depressive Disorder

A subset of patients with major depressive disorder (MDD) frequently experience abnormal 24 hour rhythms in sleep, temperature, hormonal secretions, and mood. These rhythms are all controlled by circadian clock genes. In 2000 Bunney (WE) and Bunney (BG) reviewed molecular clock gene machinery in man and hypothesized that core circadian clock genes could be disrupted in depressive disorders.

In 2013, a major collaborative study on which Bunney was one of the PIs was supported by the Pritzker Neuropsychiatric Disorders Research Fund. The study reported the first direct evidence of significant sinusoidal rhythms that varied in synchrony over 24 hours across six human brain areas in non-psychiatric controls. These rhythms were significantly disrupted in major depressive disorder patients, most significantly in the anterior cingulate.

Dr. Bunney's role in this research involved an ongoing focus on circadian clock genes, participation in the analysis of the data, and in the preparation of the manuscript. Findings from this research provide clues for potentially important and unique molecular targets for the treatment of MDD. Bunney was recently informed that the Proceedings of the National Academies of Science journal (PNAS) tracks downloads of its publications, has published approximately 18,600 papers since its inception, and that the paper listed below (Li JZ) on which Bunney was the senior author, ranked in the top 98% of all papers published by the PNAS journal.

First evidence to suggest that rapid-acting antidepressants may act on Clock Genes

Bunney and Bunney also proposed that rapid treatments for depression including sleep deprivation therapy and low dose IV ketamine might function in part by resetting abnormal circadian clock genes. The first paper to support this suggestion was published in 2011, where it was shown that ketamine significantly altered clock genes in neuronal cell culture (Bellet, et al. 2011).

- a. Bunney WE, Bunney BG. Molecular clock genes in man and lower animals: Possible implications for circadian abnormalities in depression. *Neuropsychopharmacology*, 22 (4): 335-345, (2000).
- b. Bellet MM, Vawter MP, Bunney BG, Bunney WE, Sassone-Corsi P. Ketamine Influences CLOCK:BMAL1 Function Leading to Altered Circadian Gene Expression. *PLoS ONE* 11:13223R1 10.1371/journal.pone.0023982. Aug 2011.
- c. Li JZ, Bunney BG, Meng F, Hagenauer MH, Walsh DM, Vawter MP, Evans SJ, Choudary PV, Cartagena P, Barchas JD, Schatzberg AF, Jones EG, Myers RM, Watson SJ, Akil H, Bunney WE. Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. *PNAS* / doi:10.1073/PNAS 1305814110, May 2013.

- d. Bunney BG, Li JZ, Walsh DM, Stein R, Vawter MP, Cartagena P, Barchas JD, Schatzberg AF, Myers RM, Watson SJ, Akil H, Bunney WE. Circadian dysregulation of clock genes: clues to rapid treatments in major depressive disorder. *Molecular Psychiatry* (2015) 1 - 8;1359-4184/14.

C. Relevant Awards for National and International Recognition

National Academies

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| 1988 | Elected to the National Academy of Medicine |
| 2001 | Designated by the President of the National Academies, the honorific title of "Lifetime National Associate of the National Academies" |
| 2003 -- 2007 | Appointed Executive Vice President, National Academies Corporation |
| 2009 – 2010 | Appointed Chairman of the Interest Group for Neuroscience, Behavior, Brain Function and Disorders |

National Awards

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| 1970 | First Place Research Award from the Division of Psychopharmacology of the American Psychological Association |
| 1971 | APA Hofheimer Research Award -- First Place |
| 1971 | DHEW Superior Service Award |
| 1976 | The McAlpin Mental Health Association Research Achievement Award |
| 1977 | Public Health Service, Distinguished Service Medal |
| 1997 | Exemplary Psychiatrist Award, (NAMI) |
| 2001 | Nola Maddox Falcone Prize for Outstanding Achievement in Affective Illness Research (NARSAD) |
| 2008 | 1st Annual Chair Achievement Award at the Psychiatric Chairs Summit |
| 2013 | Yale Psychiatry Distinguished Alumni Award |
| 2014 | Paul Hoch Award, American College of Neuropsychopharmacology |
| 2015 | The Payne Whitney Clinic Award for Extraordinary Public Service, The Department of Psychiatry, Weill Medical College of Cornell University |
| 2016 | The 2016 Distinguished Graduate Award from the Perelman School of Medicine, University of Pennsylvania |

International Awards

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| 1971 | International Anna-Monika Award for Psychiatric Research First Place |
| 2011 | Awarded the Highly Prestigious <i>Rhoda and Bernard Sarnat International Prize in Mental Health</i> , from the National Academy of Medicine / National Academy of Sciences (NAM/NAS). Previous honorees include two scientists who went on to receive the Lasker Award; two researchers who received the Medal of Freedom, the highest civilian honor, from the President of the United States; and one investigator who was knighted by the Queen of |

England for his research. Bunney received this award for his lifetime contributions to research. It was announced to the Membership of the National Academy of Medicine at their annual meeting and was presented to Bunney by the President of the National Academy of Medicine at a special ceremony.

2012 The Pioneer Award, Collegium Internationale Neuro-Psychopharmacologicum (CINP)

D. Additional Pertinent information

Scientific Recognition

Listed as one of the 1,000 most frequently cited researchers from all fields of science from 1965 to 1980. Only four other psychiatrists were listed among the 1,000 researchers.

Listed as one of 250 of the most cited researchers in the world in the field of psychiatry/psychology (2000-2005) by ISI Thompson Scientific, the independent firm which catalogs and distributes scientific literature worldwide and compiles the index.

2016 - Total citations of all papers 35,884 (Source: Google Scholar)

H-Factor score of 105

(105 papers cited over 105 times, 55 of which were cited between 200 and 1228 times.)

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