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Andrew C. Heath

Washington University School of Medicine in St. Louis

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MIDWEST ALCOHOLISM RESEARCH CENTER: AN OVERVIEW

Andrew C. Heath, D. Phil.

Director, Midwest Alcoholism Research Center

Spencer T. Olin Professor of Psychiatry

Department of Psychiatry

Washington University School of Medicine

GOAL

- ◆ To conduct a collaborative program of community-based research on the etiology and course of alcohol problems and associated comorbidity, with an emphasis on prospective high-risk, behavioral and molecular genetic, genetic epidemiologic and experimental perspectives, and with a particular focus on adolescents and youth, to address three etiologic models and five major research questions.
- ◆ **Etiologic Models for Alcohol Dependence**
 - **Behavioral undercontrol** – what is the role of impulsive traits, attentional problems, and adolescent conduct problems (or problem behaviors) in the etiology of alcohol dependence?
 - **Negative affect regulation** – what is the role of negative affect, depression and anxiety disorders and early onset suicidality in the etiology of alcohol dependence?
 - **Pharmacologic vulnerability** – what is the role of innate differences in metabolic, subjective, psychomotor and physiologic responses to alcohol, and to nicotine, in the etiology of alcohol dependence?

Major Research Questions

- ♦ **Gene discovery**
Can we use genetic linkage or association approaches to identify novel genetic risk factors for alcohol dependence or associated substance use disorders (e.g., tobacco dependence)?
- ♦ **Developmental course/natural history**
Can we identify stage-specific risk factors (genetic or environmental), e.g., different risk or protective factors for initiation of adolescent drinking versus transition to problem drinking versus remission of alcohol problems?
- ♦ **Risk Modifiers**
What modifiers/vulnerability factors, genetic or environmental, interact with known risk factors to exacerbate or diminish risk (e.g., under what environmental conditions is the effect of genetic risk increased or diminished – genotype x environment interaction)?
- ♦ **Human experimental paradigms**
What sociodemographic, personality, psychiatric, or other individual difference variables account for genetic (or environmental) influences on risk of alcohol dependence?
- ♦ **Micro-level (ecological) analysis of human behavior**
How do real-time recording method, (e.g. Palm-Pilot-based methods) confirm or disconfirm findings based on more global self-ratings of behavior.

Approach

- ♦ Bring together expertise in diverse areas of alcohol research, represented principally at the three major research universities of the state of Missouri:
 - Washington University School of Medicine—expertise in biological psychiatry, genetic and epidemiologic aspects of alcoholism
 - University of Missouri–Columbia—expertise in psychosocial, psychobiological approaches to understanding alcoholism etiology and consequences
 - Saint Louis University School of Public Health—expertise in public health, epidemiologic aspects of alcoholism research

- ♦ Five other institutions collaborate in our research program:
 - Queensland Institute of Medical Research, Brisbane, Australia—provides access to a large number of families with adult twins (>10,000 families), permitting cross-cultural comparisons with a heavy drinking society
 - Palo Alto Veterans Administration, Palo Alto, California—expertise concerning psychosocial and family study approaches in alcoholism research
 - Brown University, Providence, Rhode Island—expertise in behavior genetics, and quantitative psychology and longitudinal methods
 - University of Iowa, Iowa City, Iowa—expertise in psychological disorders and psychosocial research pertaining to adult and adolescent alcoholism
 - Arizona State University, Tempe, Arizona—expertise in the development of substance abuse/dependence in adolescents and adults and associated mental health disorders



Center-Affiliated Research Projects, Science Cores, and Training Programs

- ♦ The Center's alcoholism research program is much broader than the scientific cores and three research projects directly funded through the NIAAA Center grant.
- ♦ Table 1 (later panel) summarizes (most of) the Center's relevant research and training portfolio that is supported through other research mechanisms. Five research areas/approaches are represented:



Center-Affiliated Research Projects, Science Cores, and Training Programs (*con't.*)

A. Methodologic Research Projects

Methodological projects involving original theoretical work, computer simulation, and secondary data analysis, that are designed to develop improved methods of collecting and analyzing data on genetic influences on risk of alcoholism and related phenotypes, and their interactions with environmental risk factors.

B. Gene-Mapping Projects

The emphasis here is on projects using community-based rather than clinic-based sampling schemes, and using a Quantitative Trait Locus approach. One funded project is focused on smoking and nicotine dependence, but is included here because it is also assessing alcohol-related phenotypes, to take advantage of the overlap of genetic risk factors for alcohol and nicotine dependence. Three are using both diagnostic and quantitative indices of alcohol dependence and consumption patterns. Another project is using a mutation screening approach to identify genes that contribute to risk of co-occurring alcohol and nicotine dependence.



Center-Affiliated Research Projects, Science Cores, and Training Programs (*con't.*)

- C. **Conventional Prospective Epidemiologic & Genetic Epidemiologic Projects**
Because of the relative maturity of the field of genetic epidemiologic research on alcoholism, these are primarily focused on comorbid phenotypes such as gambling where mediators and modifiers of genetic influence are less well understood, as well as other laboratory-based molecular genetic studies (e.g. mutation screening, candidate gene studies). There are several projects focused on children, adolescents or young adults and their parents. These include (i) an African-American family study, focused on adolescent siblings and their parents, with oversampling of high-risk families where there is paternal history of alcohol dependence and/or recurrent drunk-driving convictions; (ii) twin-family studies of childhood Attention Deficit Hyperactivity Disorder (ADHD), a disorder of particular interest because it is observed much more commonly in the children with an alcoholic biologic parent; (iii) a prospective adolescent male twin study of adolescent smoking and nicotine dependence which is coordinated with the MARC adolescent twin project; (iv) a mentored clinician scientist award focused on parental alcoholism and adolescent suicidality; (v) a longitudinal study of drinking and high-risk sexual behavior which is following a panel of subjects first assessed as young adults; (vi) and an adolescent twin project focused on adolescent and young adult alcohol problems and dependence, with follow-up assessments at ages 17-25 of participants first assessed at ages 13-19.



Center-Affiliated Research Projects, Science Cores, and Training Programs (*con't.*)

D. Human Experimental Projects

One project collects data on the children of a comparison group of drug-dependent twins and their cotwins, and will be especially powerful for detecting the environmental influences of parental alcoholism, including those whose effects may depend upon offspring genotype (genotype x environment interaction). A 20-year project has completed repeat assessments of student drinking and alcohol dependence, and comorbid problems, through the college years, with follow-up in adulthood. A new cohort is now being recruited, with assessment prior to entry to college, and planned follow-up through the same age range. Another project is using electrophysiological approach using nicotine challenge to define heritable dimensions of response to nicotine and/or alcohol, which may be associated with differences in alcohol dependence risk.

E. Human Micro-Assessment Studies

A new direction of the MARC, these studies use moment-to-moment assessment of behavior (via electronic diary [ED, i.e. Palm Pilot] assessment) with the goal of bridging the gap between association found in genetic epidemiology (including molecular genetic) studies, and findings from studies investigating these associations in the human experimental laboratory.

Table 1: Research projects and training programs (including grants pending funding or pending review) of MARC personnel.

| <i>PI</i> | <i>Funding Agency</i> | <i>Mechanism</i> | <i>Title</i> | <i>Project Period</i> |
|---|------------------------|------------------|--|-----------------------|
| A. Methodologic Research Projects | | | | |
| 1. Cooper, M. | NIH/NIMH | K02 | Functional Perspectives on Health and Risk Behaviors | 05/04-04/09 |
| 2. Fu, Q.J. | NIH/NCI | K07 | The Genetics of Smoking: The Transtheoretical Model | 09/05-08/10 |
| 3. Heath, A. | NIH/NIAAA | R37 | Genetic Epidemiologic Models of Alcohol Abuse | 07/89-06/08 |
| 4. Jackson, K. | NIH/NIAAA | K01 | Longitudinal Methodology and Alcohol Use | 08/03-07/08 |
| 5. Lessov-Schlaggar, C. | NIH/NIDA | U01 | Core--Statistics | 09/05-06/10 |
| 6. Trull, T. | NIH/NIMH | R21 | Characterizing Affective Instability Using EMA | 09/04-08/07 |
| B. Gene-Mapping Projects | | | | |
| 7. Heath, A. | NIH/NIAAA | R01 | Molecular Epidemiology of Alcoholism 3--EDAC Families | 09/01-08/07 |
| 8. Madden, P. | NIH/NIDA, NCI | R01 | Genetics of Vulnerability to Nicotine Addiction | 05/00-04/07 |
| 9. Price, R. | NIH/NIDA | R01 | Disentangling Substance Use & Psychiatric Disorder Comorbidity for Future HuGE | 09/05-08/10 |
| 10. Todd, R. | NIH/NIAAA | R01 | Molecular Epidemiology of Alcoholism 2--Big Sibships | 04/03-03/08 |
| 11. Todd, R. | NIH/NIMH | R01 | Molecular Genetics of Inattention in Australia | 09/05-06/10 |
| 12. Todd, R. | NIH/NIAAA | R01 | Mutation Screening of Nicotine and Alcohol Dependence | 08/02-07/07 |
| C. Conventional Prospective Epidemiologic & Genetic Epidemiologic Projects | | | | |
| 13. Anokhin, A. | NIH/NIAAA | R01 | College Drinking: A Twin Study | 09/02-08/07 |
| 14. Bucholz, K. | NIH/NIAAA | R01 | Alcoholism: Epidemiologic High Risk Family Study | 07/01-06/07 |
| 15. Dick, D. | NIH/NIAAA | R01 | Gene-Environment Interplay in Adolescent Alcohol Use | 09/05-08/10 |
| 16. Glowinski, A. | NIH/NIMH | K08 | Familial Transmission of Youth Suicidal Behavior | 05/02-04/07 |
| 17. Heath, A. | NIH/NICHD | R01 | GxE in Early Childhood: Twin Mothers | 01/05-12/09 |
| 18. Heath, A. | NIH/NIAAA | R01 | Parental Alcoholism & Child Environmental Risk | 09/04-08/09 |
| 19. Jacob, T. | NIH/NIAAA | R01 | Offspring of Twins: G, E and GxE Risks for Alcoholism | 03/98-01/10 |
| 20. Jacob, T. | NIH/NIAAA | R01 | Alcoholism Course Throughout Midlife | 09/06-08/10 |
| 21. Knopik, V. | NIH/NIDA | K01 | Externalizing Behavior: Genetics x Prenatal Nicotine | 07/04-06/09 |
| 22. Lynskey, M. | NIH/NIDA | R01 | Cannabis and Other Illicit Drug Use: A Twin Study | 09/05-08/10 |
| 23. Lynskey, M. | NIH/NIDA | R01 | Cannabis Use, Abuse and Dependence: Exploring Penotypes | 09/04-06/09 |
| 24. Nelson, E. | NIH/NIAAA, NIMH, NICHD | R01 | Childhood Trauma, Parental Alcoholism, and Comorbidity | 09/02-08/07 |
| 25. Nelson, E. | NIH/NIDA | R01 | Opioid Dependence: Candidate Genes and GxE Effects | 09/03-06/08 |

Table 1 (con't.): Research projects and training programs (including grants pending funding or pending review) of MARC personnel.

| <i>PI</i> | <i>Funding Agency</i> | <i>Mechanism</i> | <i>Title</i> | <i>Project Period</i> | |
|--|---------------------------|------------------|--------------|---|-------------|
| C. Conventional Prospective Epidemiologic & Genetic Epidemiologic Projects (con't.) | | | | | |
| 26. | Pergadia, M. | NIH/NIDA | K08 | Refining Phenotypic Measures of Nicotine Withdrawal | 08/05-07/10 |
| 27. | Philibert, R. | NIH/NIDA | R01 | Genetic Studies of Substance Abuse in Iowa Adoptees | 07/04-06/09 |
| 28. | Price, R. | NIH/NIMH, NIDA | R01 | Follow-Up of Vietnam Veterans at Risk for Suicide | 09/01-08/07 |
| 29. | Slutske, W. | NIH/NIMH | R01 | Genetic Epidemiology of Pathological Gambling | 04/03-03/08 |
| 30. | Todd, R. | NIH/NIMH | R01 | Molecular Epidemiology of Inattentive ADHD | 01/04-11/08 |
| 31 | Todd, R. | NIH/NINDS | R01 | Mutation Screening of ADHD | 06/02-05/07 |
| 32 | Todorov, A. | NIH/NIDA | R01 | Genetic Epidemiology of Opioid Dependence in Bulgaria | 08/06-04/11 |
| D. Human Experimental Projects & Human Micro-Assessment Projects | | | | | |
| 33. | Anokhin, A. | NIH/NIDA | K01 | Biobehavioral Markers of Risk for Nicotine Addiction | 07/01-06/07 |
| 34. | Anokhin, A. | NIH/NIDA | R01 | Neurocognition, Genetics, and Adolescent Substance Abuse | 09/04-07/09 |
| 35. | Bucholz, K. | NIH/NIDA | R01 | Gene-Environment in Outcomes of PSuD Twins' Offspring | 06/01-05/07 |
| 36. | Chassin, L. | NIH/NIDA | R01 | Substance Use Among Children of Alcoholics | 09/87-06/11 |
| 37. | Constantino, J. | NIH/NICHD | R01 | Autistic Traits: Life Course and Genetic Structure | 04/02-03/08 |
| 38. | Sher, K. | NIH/NIAAA | R37 | A Prospective Study of College Students | 06/87-06/07 |
| 39. | Sher, K. | NIH/NIAAA | R01 | Long Term Consequences of Collegiate Alcohol Involvement | 09/02-08/07 |
| 40. | Sirevaag, E. | NIH/NIDA | R01 | Behavioral Genetics of Nicotine Dependence | 08/01-05/07 |
| 41. | Bucholz, K. | NIH/NIAAA | U13 | A New Annual Alcohol Research Forum: Guze Symposium | 05/02-04/07 |
| 42. | Chassin, L. | NIH/NIMH | T32 | Research Training--Child Mental Health/Primary Prevention | 07/87-06/10 |
| 43. | Cicero, T | NIH/NIDA | T32 | Biomedical Research Training in Drug Abuse | 09/91-06/06 |
| 44. | Heath, A. | NIH/NIAAA | T32 | Biomedical Training in Alcoholism Research | 07/00-06/10 |
| 45. | Sher, K. | NIH/NIAAA | T32 | Psychology of Alcohol Use and Dependence Training | 07/02-06/07 |
| G. Midwest Alcoholism Research Center | | | | | |
| 46. | Heath, A. | NIH/NIAAA | P50 | MARC: Genetic Epidemiology of Alcoholism & Comorbidity | 06/04-05/09 |
| 47 | Piasecki, T. and Sher, K. | NIH/NIAAA | P50 | Conjoint Alcohol and Tobacco Use: An Ecological Study | 06/04-05/09 |
| 48 | Slutske, W. | NIH/NIAAA | P50 | Australian Children of Alcoholic Female Twins | 06/04-05/09 |
| 49 | Todd, R. | NIH/NIAAA | P50 | Molecular Epidemiology of Alcoholism/Comorbid Disorders | 06/04/05/09 |

Organization:

1. Scientific Cores

- ◆ **Administrative Core (PI Heath)**

Responsible for coordinating the MARC research program, facilitating communications among the eight participating sites, monitoring project productivity and human subjects protections, and arranging oversight by the External Scientific Advisory Board and Community Advisory Committee.

- ◆ **Pilot Project Core (PI Bucholz)**

Provides pilot project support for junior investigators and others who are trying to develop new directions in alcoholism research.



Organization:

2. Center-Based Research Projects

Project 4: Australian Children of Alcoholic Female Twins (PIs Slutske, Treloar)

This ongoing project examines the role of genetic and family environmental influences, and their interaction, in the development and course of alcohol use disorders (AUD) by studying Australian women who are mothers and twins and their offspring as young as 7 years old.

Our research will enable us to confirm or disconfirm our emerging data based on retrospective reports of twin mothers about their adolescent and young adult offspring on disorders with early childhood onset (ADHD, Oppositional Defiant Disorder [ODD], conduct disorder [CD]). And by the end of the renewal period, samples will be sufficiently large so that complex cross-sectional and longitudinal analyses will be firmly based.

The research strategy incorporates:

- use of the children of twins (COT) design involving twins who are concordant or discordant for AUD as well as control pairs
- assessment of children of alcoholic mothers
- use of a prospective design which allows for description of offspring development from preadolescence through the late twenties

This prospective study is coordinated with two R01 projects focused on U.S. national samples of alcoholic and control Vietnam-era veteran male twins and their cotwins, spouses, and offspring.



Organization:

2. Center-Based Research Projects (*con't.*)

Project 5: Molecular Epidemiology of Alcoholism & Comorbid Disorders (PIs Todd, Trull)

This project builds upon gene-discovery projects such as COGA (Collaborative Study on the Genetics of Alcoholism: PI Begleiter) and similar projects which are studying treatment-ascertained alcoholics and their relatives, and the MARC-affiliated Alcohol-QTL IRPG consortium (PIs Heath, Martin, Madden, Todd), which is studying community-ascertained alcoholics and heavy smokers and their adult relatives, by incorporating a molecular genetic component into 4 mature, prospective longitudinal studies (PIs Chassin, Cooper, Heath, Sher) spanning the age-range from early adolescence into young adulthood, with 3-7 waves of prospective assessment. In addition to collecting DNA from the target samples (years 1-3), this project combines secondary data-analysis and genotyping, proceeding in 4 stages:

- i. behavioral genetic analyses using existing twin data sets (MOAFTS, the former MARC Project 1, or other US and Australian data-sets to which we have access through the MARC) to confirm heritability of phenotypes defined at stage (i), determining whether that phenotypic operationalization is optimal for understanding genetic effects (years 1-3);
- ii. longitudinal and other phenotypic analyses to establish consistent phenotype definition across informative data-sets (years 1-3);
- iii. Genotyping for a limited number of candidate genes (years 3-5); and
- iv. genetic association analysis (years 4-5).



Organization:

2. Center-Based Research Projects (*con't.*)

Project 6: Conjoint Alcohol & Tobacco Use: An Ecological Study (PIs Piasecki, Sher)

This study uses the Ecological Momentary Assessment (EMA; Stone & Shiffman, 1994) to investigate hypothesized mechanisms that may motivate joint use of alcohol and cigarettes, assessing alcohol use and smoking, their subjective antecedents and sequelae, and environmental contexts allowing comparisons to be made between (i) drinker-smokers, (ii) only drinkers, (iii) only smokers, and (iv) neither drinkers or smokers.

- Via handheld electronic diary (ED, i.e. Palm Pilot), subjects enter ED recordings, including morning assessments, drinking episode assessments, and smoking episode assessments, as well as random prompts, over a 3-week period.

This study examines:

- i. the unique effects of conjoint alcohol-smoking, relative to smoking alone and drinking alone, on both positive and negative affective states;
- ii. the relation between individual differences in conjoint alcohol-smoking and substance-specific changes in positive/negative affect and subsequent drinking and smoking behavior;
- iii. the extent to which individual difference variables condition the magnitude of conjoint and substance-specific effects on alcohol and/or tobacco seeking behavior;
- iv. the association between smoking level and acute and delayed aversive (punishing) effects of alcohol; and
- v. the extent to which individual differences in these aversive consequences predict subsequent drinking behavior

Investigators

- ◆ A multi-disciplinary team of faculty investigators is taking part in this research program, many with primary appointments in the Department of Psychiatry at Washington University, which has a long history of trans-disciplinary research on alcohol, tobacco, and other drug dependence; but with other investigators drawn from departments as diverse as Neurology and Otolaryngology at Washington University, the Department of Psychological Sciences at University of Missouri–Columbia, the Department of Psychiatry at the University of Iowa, the Family Study Center at the Palo Alto VA, the Center for Alcohol & Addiction Studies at Brown University, the Prevention Research Center at Arizona State University, and the Department of Community Health at Saint Louis University School of Public Health. Eight post-doctoral fellows also participate in this research program. Fourteen faculty investigators are also former graduates from our training program.
- ◆ Because foreign populations may offer particular advantages for genetic research, foreign collaborators from Australia are included in our team of investigators, with other collaborations with investigators in Japan, China, Finland, and the Netherlands under active development.

Table 2. Faculty Investigators

| Investigator | Department, Institution | Expertise |
|--------------------------|---|--|
| A. Agrawal, PhD | Psychiatry, Washington University | Psychiatric disorders, statistical genetics |
| A. Anokhin, PhD | Psychiatry, Washington University | Psychology, behavioral genetics |
| K. Bucholz, PhD | Psychiatry, Washington University | Epidemiology, genetic epidemiology, adult assessment |
| L. Chassin, PhD | Psychology, Arizona State University-Tempe | High-risk longitudinal research |
| J. Constantino, MD | Psychiatry, Washington University | Child psychiatry, epidemiology |
| L. Cooper, PhD | Psychological Sciences, University of Missouri-Columbia | Social and developmental psychology |
| N. Cowan, PhD | Psychological Sciences, University of Missouri-Columbia | Memory and attention in human cognition |
| D. Dick, PhD | Psychiatry, Washington University | Behavioral and psychiatric genetics |
| Q. Fu, MD | Community Health, Saint Louis University | Health psychology |
| A. Glowinski, MD | Psychiatry, Washington University | Child psychiatry, child assessment |
| J. Goebel, MD | Otolaryngology, Wash University | Dynamic posturography |
| J. Grant, PhD | Psychiatry, Washington University | Developmental psychology, behavioral genetics |
| R. Haber, PhD | Family Study Center, Palo Alto Veterans Administration | Clinical psychology, family studies |
| A. Heath, DPhil | Psychiatry, Washington University | Behavioral genetics, genetic epidemiology |
| K. Jackson, PhD | Community Health, Brown University | Quantitative psychology, longitudinal methods |
| T. Jacob, PhD | Family Study Center, Palo Alto Veterans Administration | Clinical psychology, family studies |
| V. Knopik, PhD | Community Health, Brown University | Psychology, behavioral genetics |
| C. Lessov-Schlaggar, PhD | Psychiatry, Washington University | Genetic epidemiology, twin methodology |
| C. Lewis, MD | Psychiatry, Washington University | Addiction psychiatry |
| P. Madden, PhD | Psychiatry, Washington University | Behavioral genetics, genetic epidemiology |

Table 2. Faculty Investigators *(con't.)*

| Investigator | Department, Institution | Expertise |
|-----------------------|--|--|
| N. Martin, PhD | Genetic Epidemiology, Queensland Institute of Medical Research | Genetics, longitudinal studies |
| E. Nelson, MD | Psychiatry, Washington University | Psychiatry genetics, alcohol and anxiety |
| R. Neuman, PhD | Psychiatry, Washington University | Mathematics, statistical genetics |
| M. Pergadia, PhD | Psychiatry, Washington University | Behavioral genetics |
| R. Philibert, MD, PhD | Psychiatry, University of Iowa | Psychiatric genetics |
| T. Piasecki, PhD | Psychological Sciences, University of Missouri-Columbia | Psychology of addiction |
| R. Price, PhD | Psychiatry, Washington University | Sociology, psychiatric epidemiology |
| J. Rohrbaugh, PhD | Psychiatry, Washington University | Psychophysiology, challenge studies |
| J. Romeis, PhD | Community Health, Saint Louis University | Public health, behavioral genetics |
| J. Scherrer, PhD | Psychiatry, Washington University | Behavioral genetics, epidemiology, longitudinal research |
| K. Sher, PhD | Psychological Sciences, University of Missouri-Columbia | Clinical psychology, high-risk longitudinal research |
| E. Sirevaag, PhD | Psychiatry, Washington University | Psychophysiology, nicotine challenge |
| W. Slutske, PhD | Psychological Sciences, University of Missouri-Columbia | Behavioral genetics |
| R. Todd, PhD, MD | Psychiatry, Washington University | Child psychiatry, molecular neurobiology |
| A. Todorov, PhD | Psychiatry, Washington University | Biometrics, statistical genetics |
| S. Treloar, PhD | Genetic Epidemiology, Queensland Institute of Medical Research | Population studies, human genetics |
| W. True, PhD | Community Health, Saint Louis University | Public health, behavioral genetics |
| T. Trull, PhD | Psychological Sciences, University of Missouri-Columbia | Clinical psychology, personality & personality disorder |
| P. Wood, PhD | Psychological Sciences, University of Missouri-Columbia | Quantitative psychology |
| M. Waldron, PhD | Psychiatry, Washington University | Clinical psychology, family studies |