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Genetic and Environmental Influences on Alcohol Drinking Behavior

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National Institutes of Health
Department of Health and Human Services**

Guze Symposium

**Washington University in St. Louis
February 19, 2004**

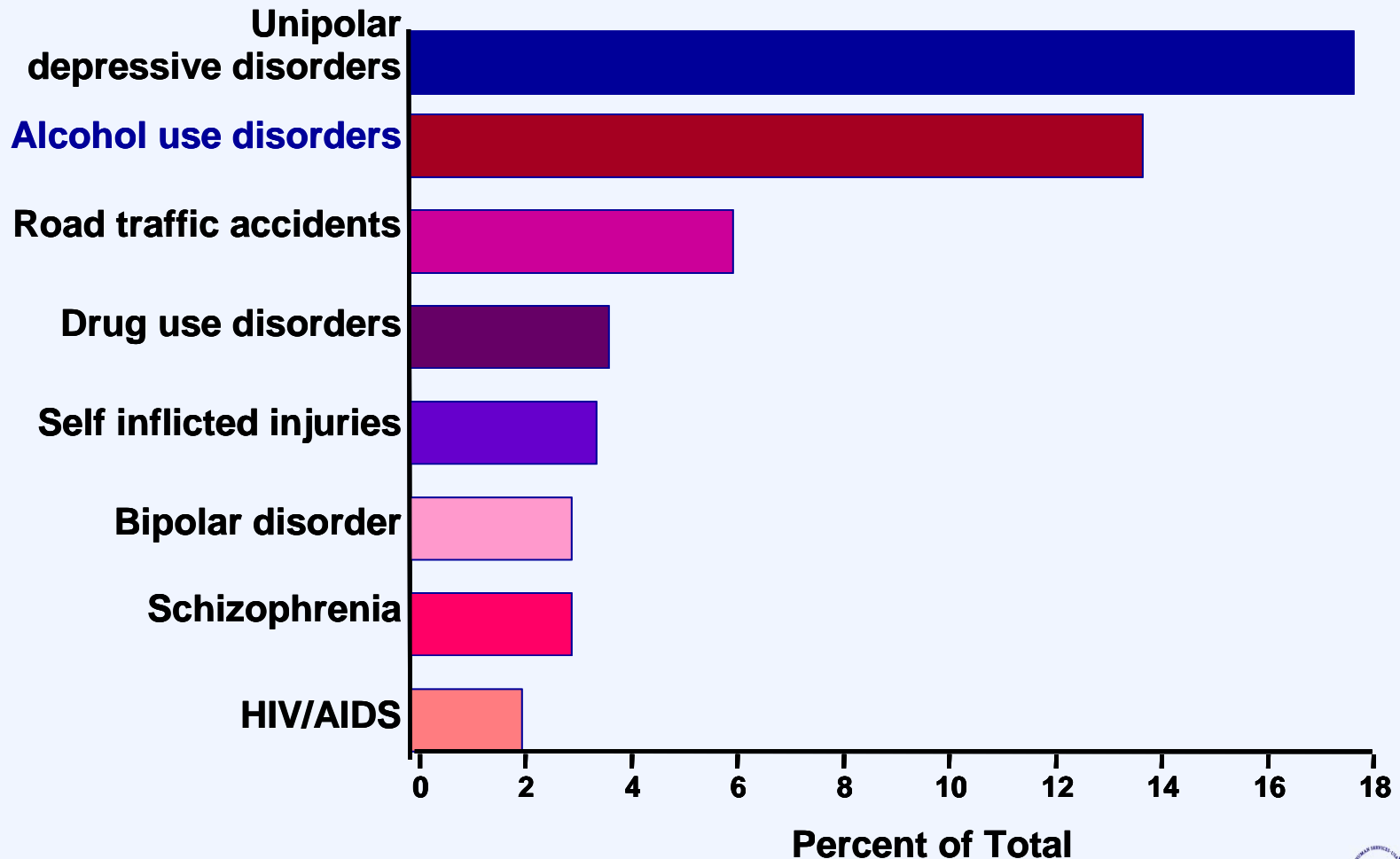
Quantity-Frequency of Drinking: relationship to alcohol abuse and alcoholism

Predisposing and Protective Factors

Animal Models for Study of Alcoholism

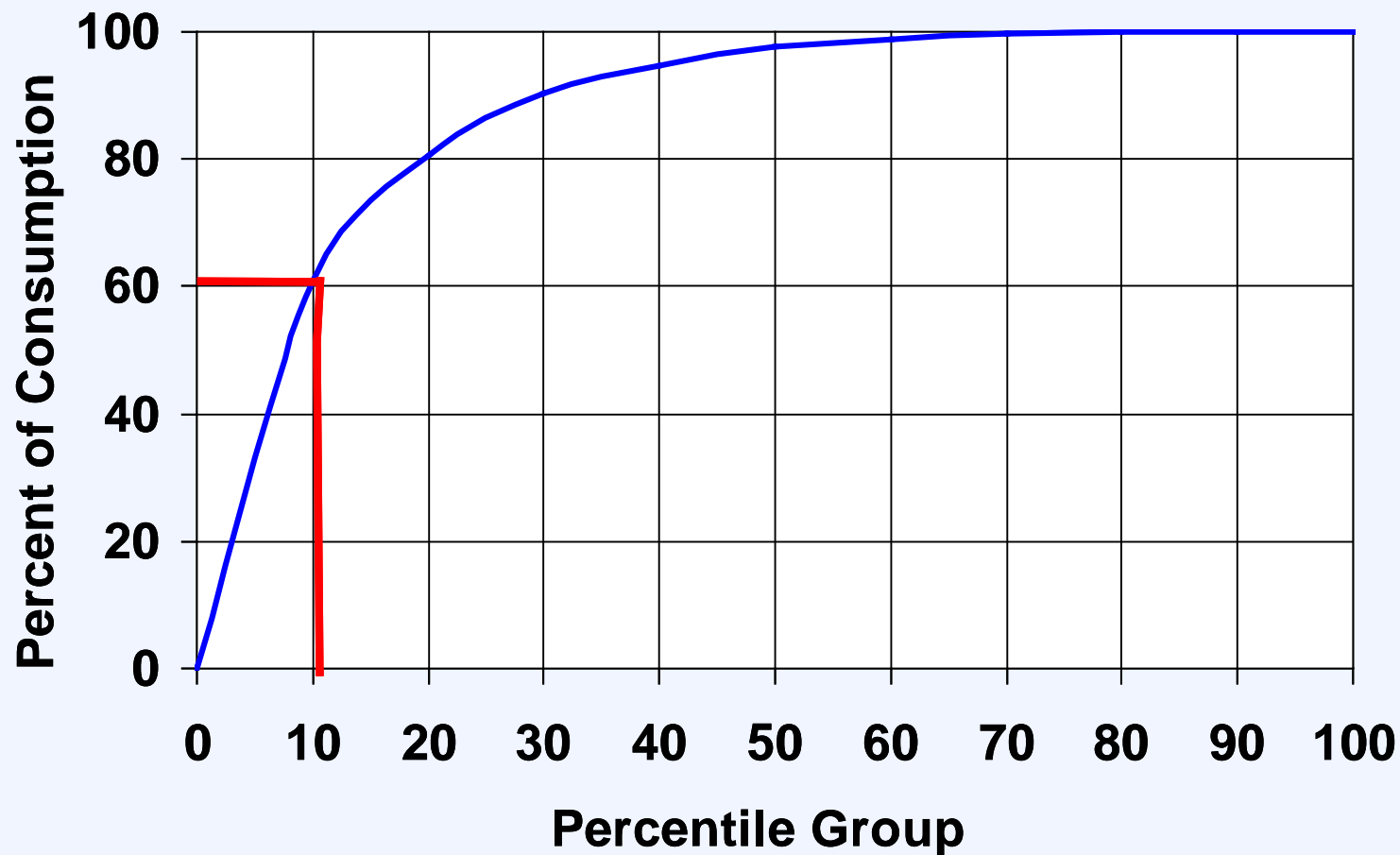
Disease Burden by Illness - DALY United States, Canada and Western Europe, 2000

15 - 44 year olds



Source: WHO – Burden of Disease Statistics, 2001

Cumulative Distribution of Alcohol Consumption in the United States



Source: Greenfield and Rogers; *J. Stud. Alcohol* 60:; 79-89, 1999

***Alcohol-related health,
personal, and social
problems arise from drinking:***

- **too much too fast**
- **too much too often**

Drinking Patterns: Rates and Risks

Moderate Drinking

Most people abstain or drink **moderately** placing them at low risk for alcohol use disorders. In general, **Moderate Drinking** is defined as 2 drinks/day for men; 1 drink/day for women (USDA/HHS dietary guidelines)

(One drink: one 12-ounce bottle of beer or wine cooler, one 5-ounce glass of wine, or 1.5 ounces of 80-proof distilled spirits)

Alcohol Abuse

A pattern of *high-risk drinking* that results in adverse outcomes, including:

- **Personal problems:** impact on memory and cognition; loss of employment, family, friends, and other significant relationships; increased risk for health problems and organ damage
- **Problems to others:** homicides, sexual assault, and other forms of interpersonal crime and violence; property damage; risk for injury and death
- **Problems for society:** illegal underage drinking; increased health care costs; loss of economic productivity; balancing economic, health, and social benefits, and risks of alcohol consumption

Drinking Patterns

	Percent of U.S. adults aged 18+	Abuse without dependence	Dependence with or without abuse
Exceeds the <i>daily</i> limit <i>less than once a week</i>	16%	1 in 8 (12%)	1 in 20 (5%)
Exceeds the <i>daily</i> limit <i>once a week or more</i>	3%	1 in 5 (19%)	1 in 8 (12%)
Exceeds <i>both</i> weekly & daily limits	9%	1 in 5 (19%)	1 in 4 (28%)

Source: NIAAA National Epidemiologic Survey on Alcohol and Related Conditions, 2003

Drinking Patterns: Rates and Risks

Binge Drinking

The National Advisory Council on Alcohol Abuse and Alcoholism has recommended the following definition of **“Binge Drinking”**:

A “binge” is a pattern of drinking alcohol that brings blood alcohol concentration (BAC) to 0.08 gm% or above. For the typical adult, this pattern corresponds to consuming 5 or more drinks (male) or 4 or more drinks (female) in about 2 hours. Binge drinking is clearly dangerous for the drinker and for society

Alcohol Dependence ***(Alcoholism)***

A *common complex disease* characterized by a persistent and progressive pattern of abnormally intense **alcohol-seeking behavior** that, over time, results in:

- **loss of control over drinking**
- **a preoccupation with drinking**
- **the development of tolerance and dependence**

Alcohol and Dependence

Genetic Susceptibility

- **personality/temperament**
- **alcohol pharmacokinetic and pharmacodynamic responses**

Environmental Exposure

- **Quantity/Frequency**

Why Some People Drink/Do Not Drink

- **Reinforcing Effects**

Positive

Negative

- **Aversive Effects**

- **Peer/Cultural Influences**

Why Some Drink More Than Others

Individual differences in:

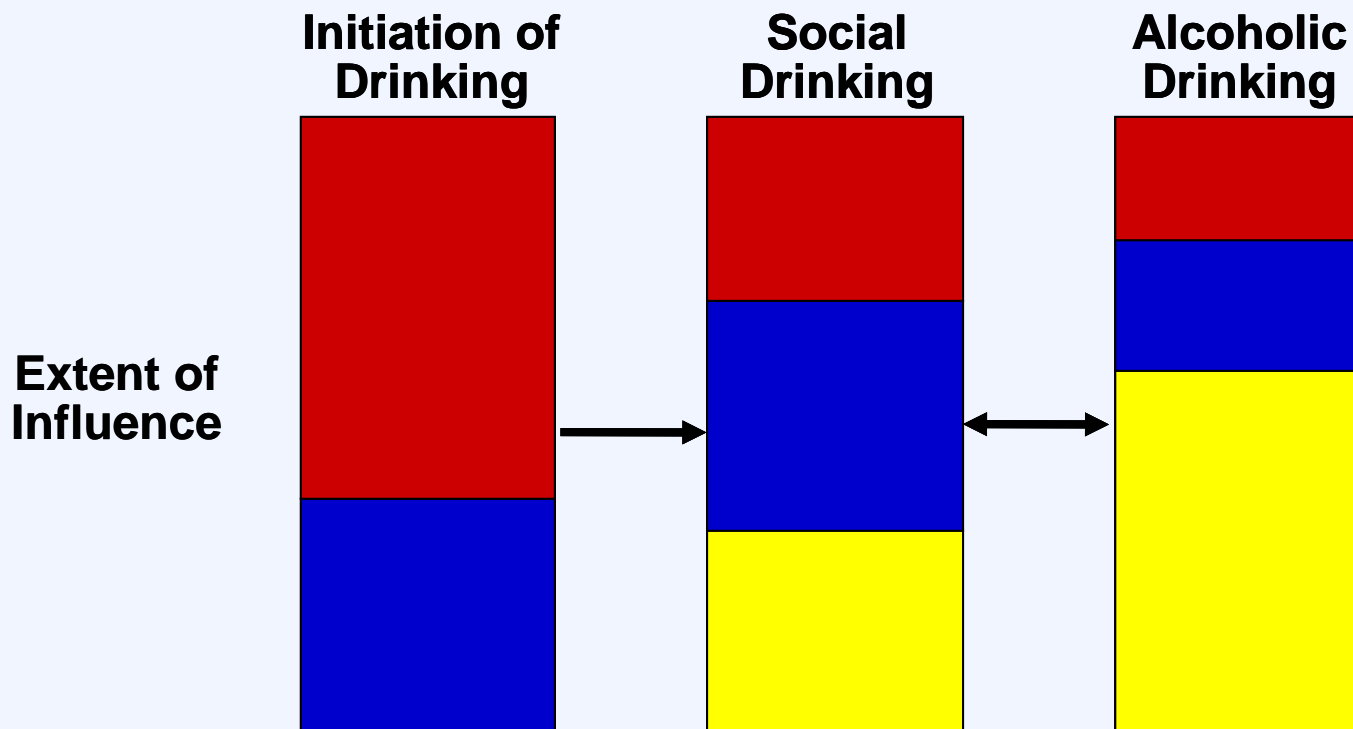
- **metabolism**
- **“level of response” to alcohol**
- **neuroadaptation (tolerance and/or sensitization with chronic drinking)**

Why Some Drink Despite Negative Consequences

- **Physical dependence (withdrawal)**
- **Psychological dependence (addiction)**

Predisposing and Protective Factors

Initiation and Continuation of Drinking



- Environmental (familial and non familial)
- Personality/Temperament
- Pharmacological effects of ethanol

Between Individual Variations in Responses to Alcohol

- **Pharmacokinetics: absorption, distribution, and metabolism of alcohol**

3-4 fold

- **Pharmacodynamics: subjective and objective responses to alcohol**

2-3 fold

Protection Against Alcohol Dependence by $ADH2^*2$ and $ALDH2^*2$ (Han Chinese Males in Taiwan)

	$ADH2^*2$	$ALDH2^*2$
Nonalcoholic (n=50)	0.73	0.30
Alcoholic (n=50)	0.48 [†]	0.06 [†]

[†]p < 0.001

Interaction Between the Functional Polymorphisms of Alcohol and Aldehyde Dehydrogenase in Protecting Against Alcoholism

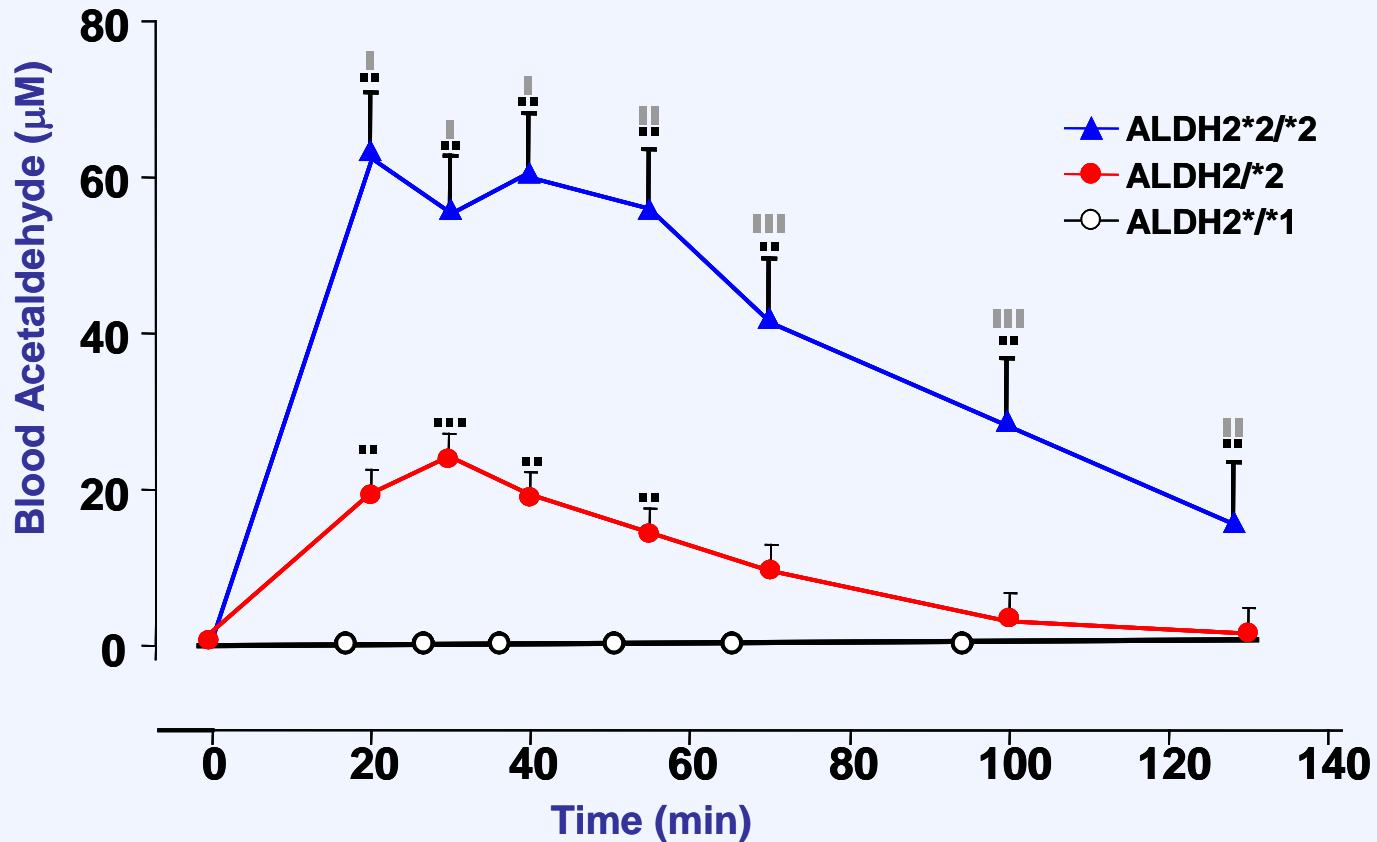
***Chen CC, Lu RB, Chen YC, Wang MF, Chang YC, Li T-K, and Yin SJ
Am.J. Hum. Genet. 65: 795-807, 1999***

1/Odds Ratio of Risk*

ADH1*1/*2 - ALDH2*1/*1	4.5
ADH2*1/*1 - ALDH2*1/*2	3
ADH2*1/*2 - ALDH2*1/*2	17
ADH2*2/*2 - ALDH2*2/*2	100

***Reference Group is ADH2*1/*1 - ALDH2*1/*1**

Blood Acetaldehyde Concentrations After 0.2 g/kg Dose of Ethanol in Men with Different ALDH2 Allelotypes



Significant differences are seen between the homozygous groups and between them and the heterozygous group at almost all time points (n = 6 per group)

Aldehyde Dehydrogenase Genotypes in Japanese Alcoholics Over Time

ALDH2 Genotypes	1979	1986	1992
ALDH2*2/*2	0.0	0.0	0.0
ALDH2*1/*2	2.5	8.0	13.0
ALDH2*1/*1	97.5	92.0	87.0

From: Higuchi et al. Lancet 343: 741-742, 1994.

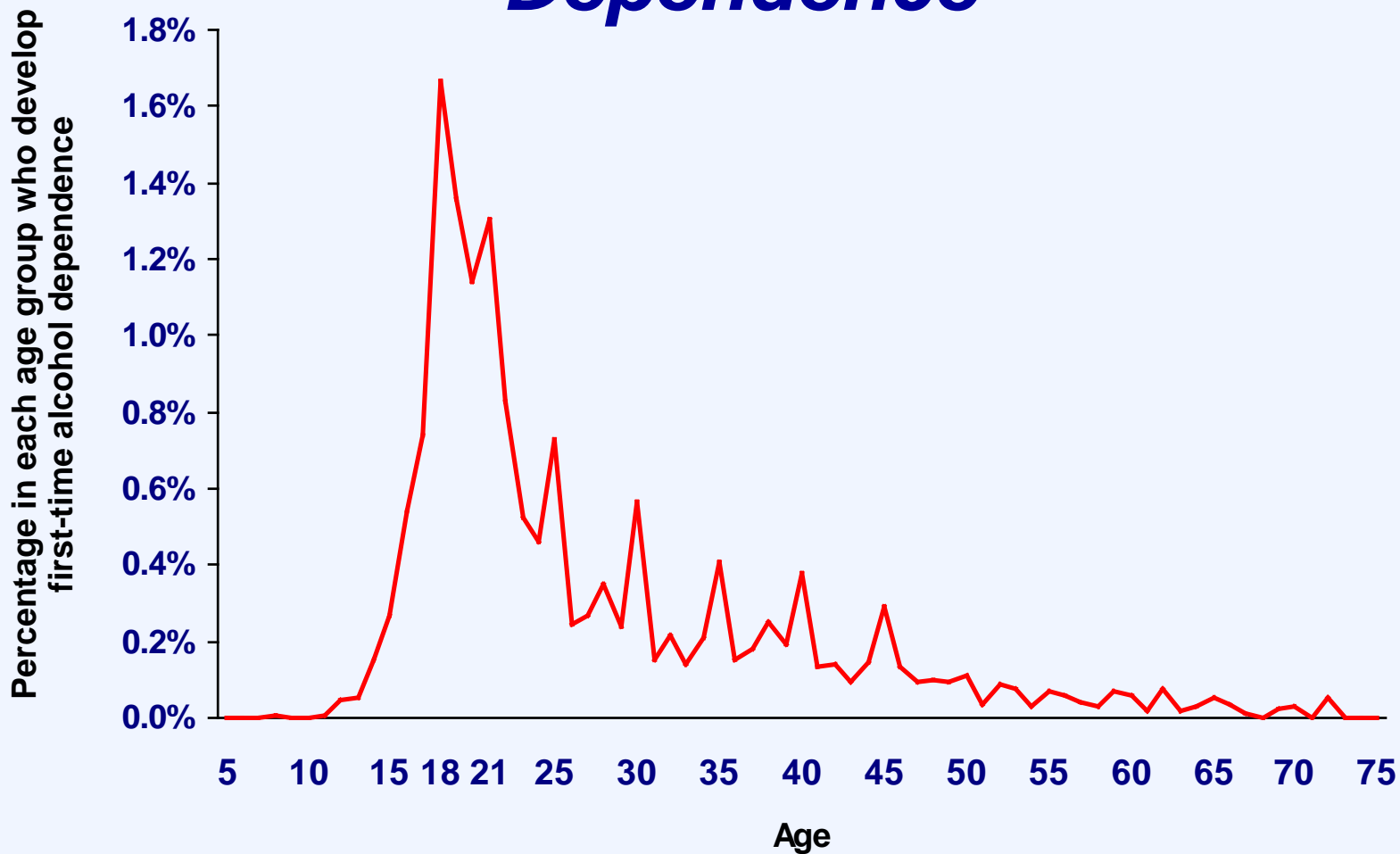
ADH2 Allele Frequency in Jews and Drinking Behavior

- **ADH2*2 frequency is 0.02 in Israeli population (36% have at least one copy)**
- **ADH2*2 allele is associated with lower quantity and frequency of drinking**

From: Neumark, Friedlander, Thomasson and Li. *J. Stud. Alcohol* 59:133-139, 1998.

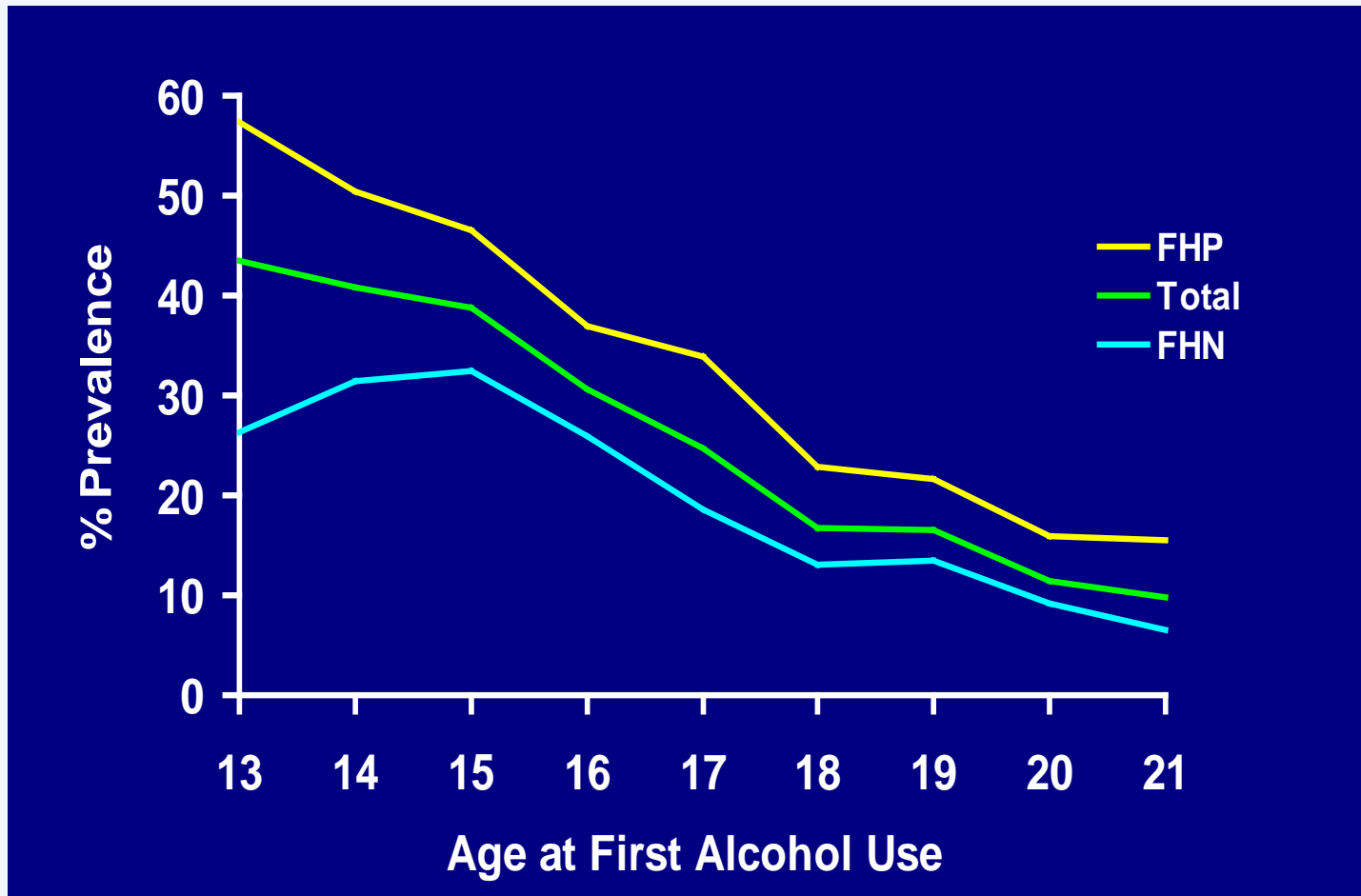
Age of Onset of Brain Disorders

Age at Onset of DSM-IV Alcohol Dependence



NIAAA National Epidemiologic Survey on Alcohol and Related Conditions, 2003

Prevalence of Lifetime Alcohol Dependence by Age of First Alcohol Use and Family History of Alcoholism



Grant and Dawson. *J Subst Abuse*. 1998;10(2):163-73.

Genes That Predispose to and Protect Against Alcoholism

Genes Specific to Alcoholism

ALDH2

ADH2

alcohol metabolism

Genes for Endophenotypes and/or Disorders Co-occurring with Alcoholism

COMT
Val158met

schizophrenia, alcohol dependence, heroin addiction, cognitive dysfunction, lower frontal P300 amplitude, diminished response to pain and stress

SERT
Ile425Val
(chr 17)

OCD and cluster of neuropsychiatric disorders including alcohol and other substance abuse/dependence, social phobia, anorexia

GABRA2

alcohol dependence and beta frequency of the EEG

Involvement of Cholinergic Muscarinic Receptor Gene (CHRM2) on Chromosome 7 in COGA* Families

- **Significant linkage and linkage disequilibrium for frontal theta event-related oscillations that underlie P3 on chromosome 7 at CHRM2 (Jones, Porjesz, Almasy et al., *Int'l J. of Psychophysiology*, in press)**
- **CHRM2 gene may contribute to development of major depressive disorder in COGA families (Beirut, Wang, Hingrichs et al. Abstract Presented at World Congress of Psychiatric Genetics, 2003)**
- **Significant linkage and linkage disequilibrium for CHRM2 with alcohol dependence (Washington University COGA Group)**

Animal Models

Rodent Lines Selected for Ethanol-Related Traits (Mice)

Line/Species	Selection Phenotype
Long/Short Sleep (LS/SS)	Duration of loss of righting reflex after EtOH
Cold/Hot	Acute EtOH hypothermia
Fast/Slow	EtOH stimulated activity
Severe/Mild Ethanol Withdrawal (SEW/MEW)	Severity of withdrawal on a multivariate index
Withdrawal Seizure Prone/Resistant (WSP/WSR)	Severity of handling-induced convulsions after chronic EtOH
High/Low Alcohol Preference (HAP/LAP)	Preference for 10%EtOH solution

Rodent Lines Selected for Ethanol-Related Traits (Rats)

Line/Species	Selection Phenotype
ALKO Tolerant/Nontolerant (AT/ANT)	EtOH impairment of tilting-plane performance
High/Low Alcohol Sensitive (HAS/LAS)	Duration of loss of righting reflex after EtOH
ALKO Alcohol/Nonalcohol Preference (AA/ANA)	Preference for EtOH solutions
Preferring/Nonpreferring (P/NP)	Preference for 10% EtOH solution
High/Low Alcohol Drinking (HAD/LAD)	Preference for 10% EtOH solution
High/Low Alcohol Drinking (HARF/LARF)	Preference for 12% EtOH solution - limited access conditions

Selectively Bred Alcohol-Preferring Rats as Animal Model to Study Alcoholism

- **Voluntarily consume 6-8g ethanol/kg/day**
- **Attain BACs of 0.05 – 0.25 g%**
- **Work to obtain the ethanol**
- **Consume ethanol for its pharmacological effects (not taste, smell, or calories)**
- **Develop tolerance with chronic drinking**
- **Develop physical dependence with chronic drinking**

Propensities of Animals with High Alcohol-Seeking Behavior

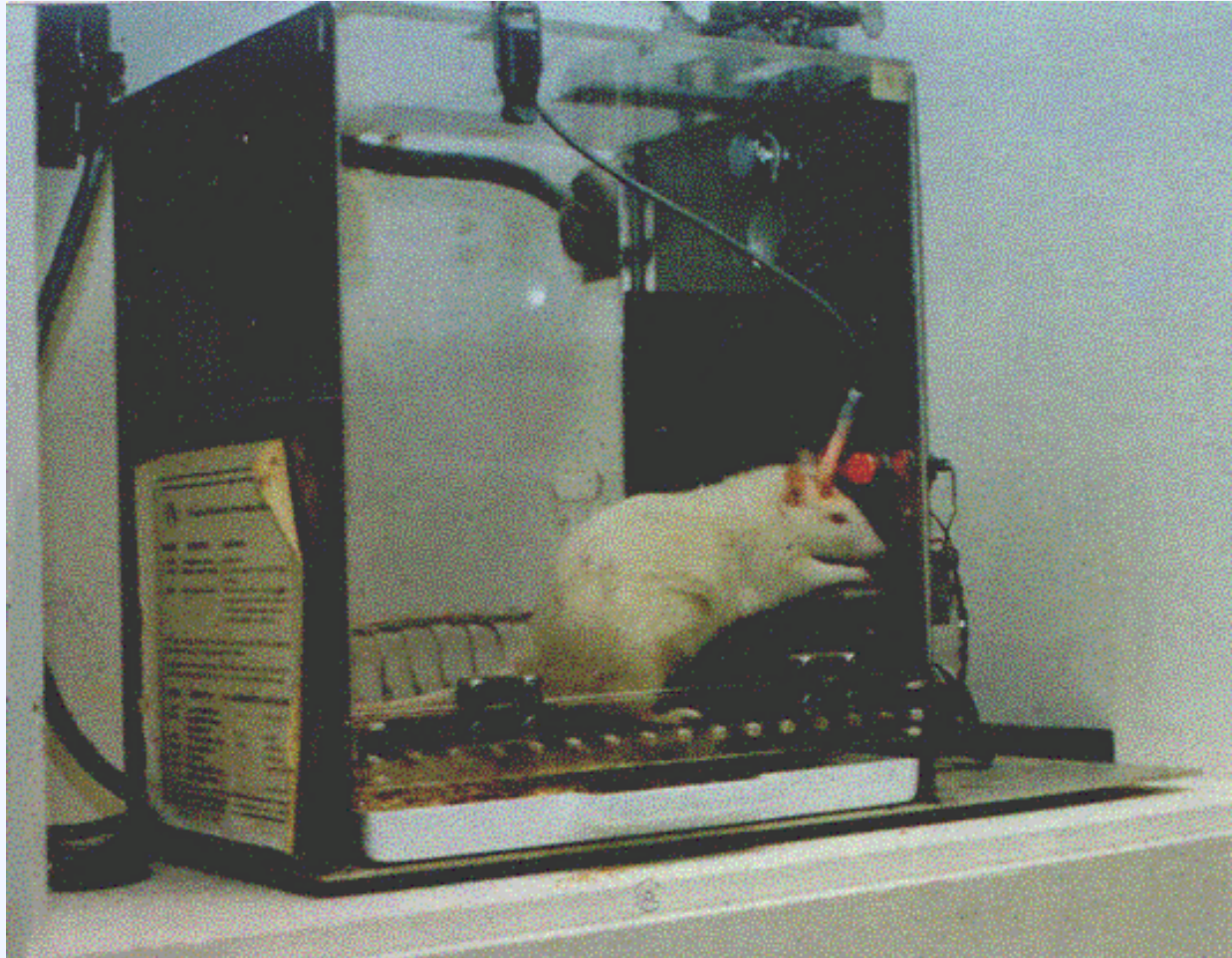
Sensitive to the reinforcing/activating effects of ethanol (low/moderate dose)

Resistant to the aversive/impairing effects of ethanol (high dose)

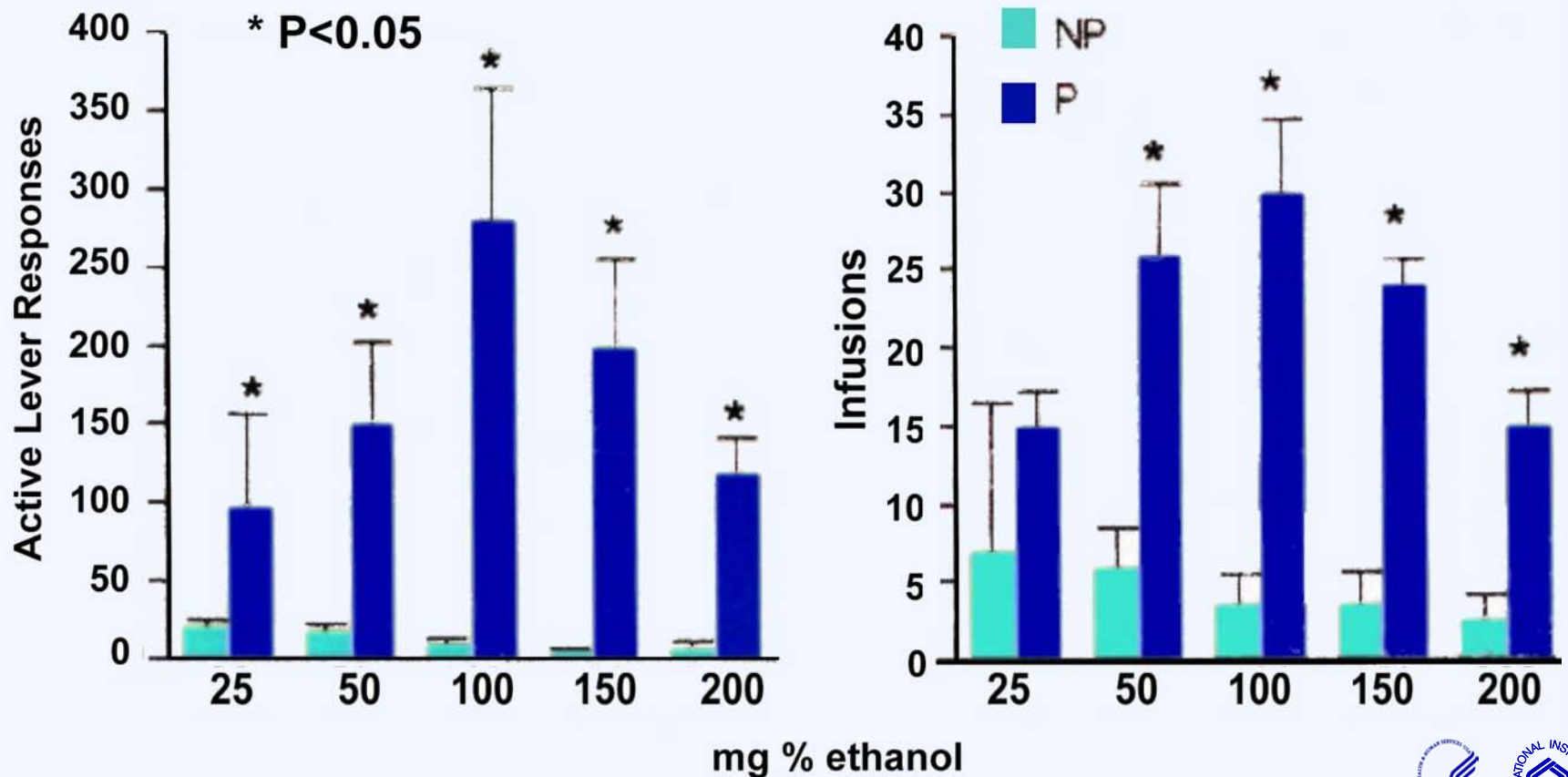
Rapid development of tolerance to the high dose impairing effects of ethanol

Retains tolerance developed to the aversive impairing effects of ethanol

Intracranial Self-Administration



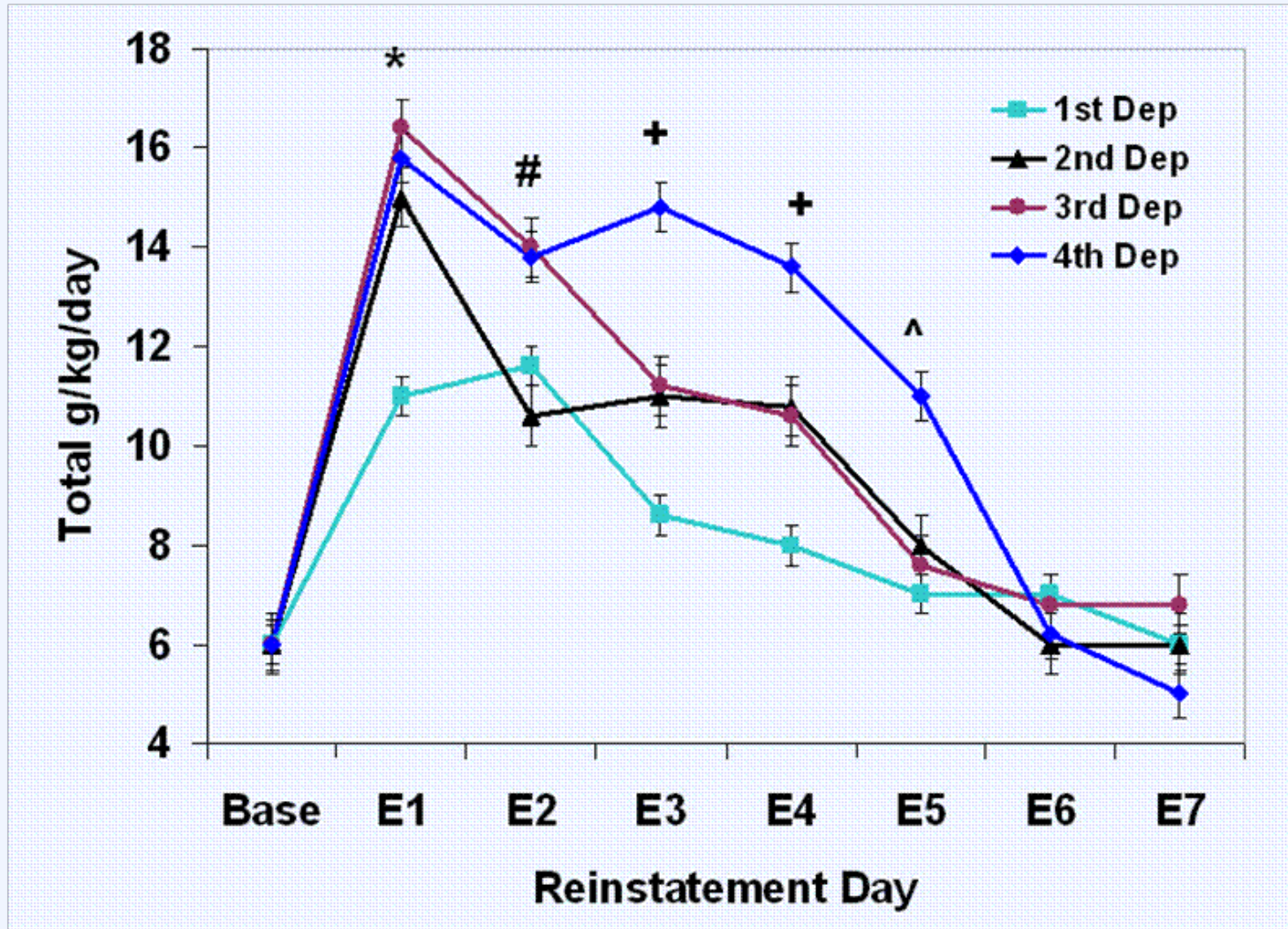
Lever Responses and Reinforcements for the ICSA of 25-200 mg % Ethanol by P and NP Rats



Alcohol Deprivation Effect (ADE)

- **Temporary increase in alcohol consumption following a period of alcohol deprivation**
- **Observed in rats, mice, monkeys, and humans**
- **Animal model for studying relapse**

Repeated Deprivations – Concurrent EtOH Concentrations



Comparison of Alcohol Consumption in Alcohol Preferring Rats and Humans

- The AER for the rat (400 mg/kg/h) is about **4x** that for humans (100 mg/kg/h)
- Rats drinking 6 g/kg/d would be equivalent to humans drinking
 - 1.5 g/kg/day *or*
 - 105 g/70 kg person/day *or*
 - 8-9 drinks/day
- Rats drinking 16g/kg/d would be equivalent to humans drinking
 - 4g/kg/day *or*
 - 280 g/70kg person/day *or*
 - 23-24 drinks/day

Animal Models in Alcohol Research

Rodents: (Rats)

QTL	Candidate Gene	Transgenic/ Knockout
P/NP		
Alcohol Preference (4:57 cM)	α -synuclein	KO: ↓ consumption
Alcohol Consumption (chr 4)	Neuropeptide Y	KO: ↑ consumption; less sensitivity to sedative/ hypnotic effects Tg: ↓ preference; greater sensitivity to hypnotic effects
HAD/LAD		
Alcohol consumption (chr 10)	CREB	KO: ↑ consumption

ALCOHOLISM

Heterogeneity of Phenotypes

- **Multiple environmental factors influence drinking behavior**
- **Multiple genes affect host susceptibility**
 - **Personality/mental function (antisocial behavior; CD; depression)**
 - **Ethanol pharmacogenetics (metabolism; CNS action; neuroadaptation)**
- **Different persons have different sets of susceptibility genes and experience different kinds of environmental provocation**

