Evolution of NIAAA and NIDA: Science, Structure, and Function

Scientific Management Review Board

April 28, 2009

Lawrence A. Tabak, D.D.S., Ph.D.

Acting Deputy Director, NIH

Director, National Institute of Dental and Craniofacial Research

Overview

- Issue at hand
- Impetus
- Prior organizational frameworks
- Science supported by NIAAA and NIDA
- Specific charge to the SMRB

Issue

- **Neuroscience research has revealed that addictive substances, including drugs and alcohol:**
  - Differentially affect brain receptors and can result in unique neuropathologies
  - Similarly activate certain physiological pathways including the brain's reward circuit, which can result in compulsive substance use
- **Considering both biological differences and similarities, does the current organization separating research institutes on drug and alcohol use, abuse, and addiction provide optimal infrastructure for supporting these areas of scientific research?**

Impetus: *Why consider this particular organizational change at this particular time?*

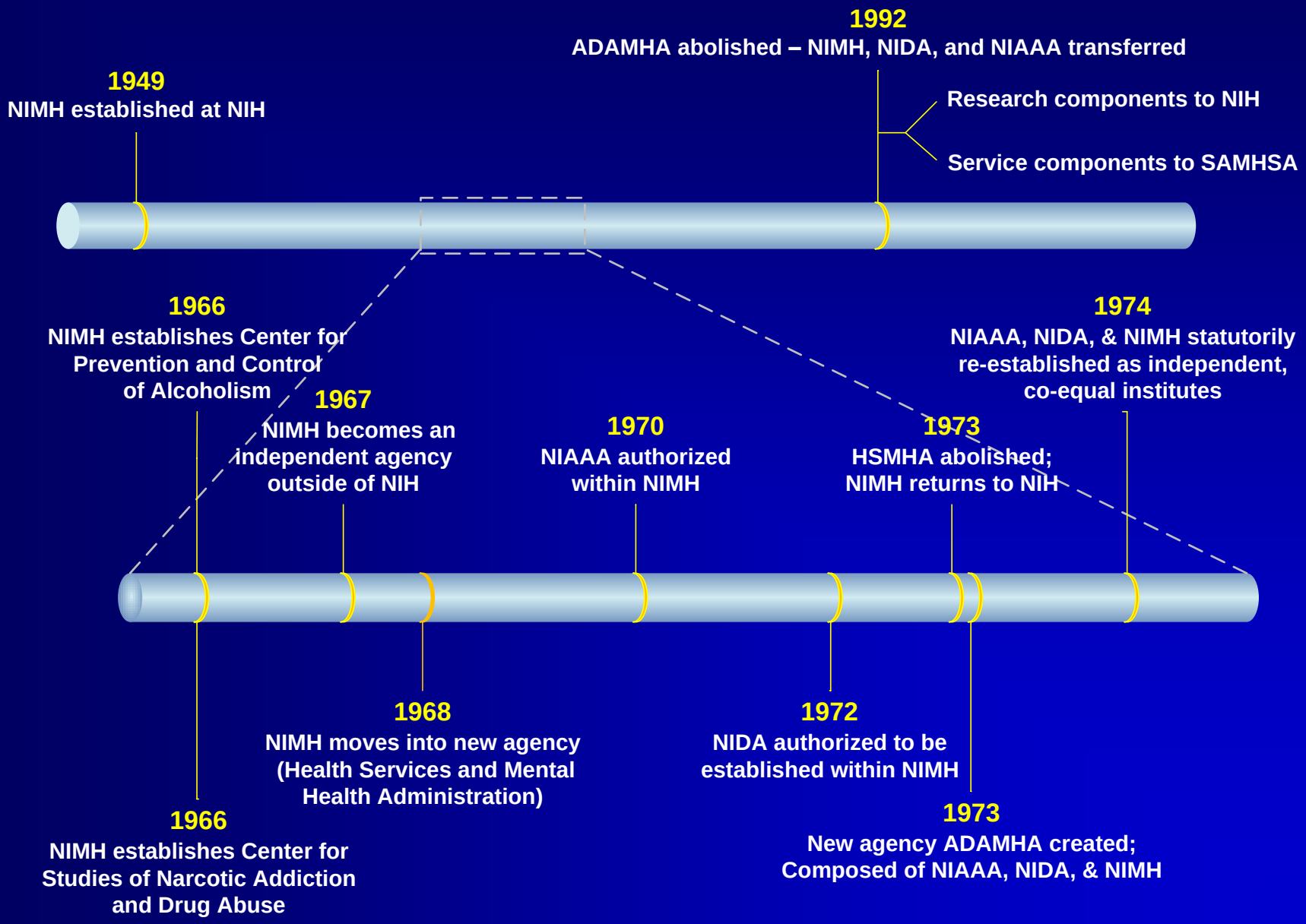
- **Scientific:**
  - Research is revealing that diverse addictive substances including alcohol and numerous drugs affect people through both unique and common pathways.
- **Social-Political:**
  - The NIH Reform Act of 2006 highlighted the authority of NIH to make organizational changes and established the SMRB to advise NIH on the use of those authorities.
  - In 2003, the National Academies recommended considering merging NIAAA and NIDA. The option of a combined institute of addiction was also identified by the Lewin Group in 1988.
  - The Drug Abuse Education, Prevention, and Treatment Act of 2001 (S.304) required the DHHS Secretary to request an IOM study to determine whether combining NIDA and NIAAA would strengthen scientific research efforts and increase economic efficiency.

Past as Prologue: Observations on Prior Organizational Structures

- The precursors to NIAAA and NIDA were established within the National Institute of Mental Health (NIMH), but grew into separate entities with the increasing recognition of biological underpinnings for alcohol addiction and drug abuse.
- Tension between research and services components of NIAAA's and NIDA's earlier missions resulted in multiple transfers of these organizations and/or component offices.
- Today, substance abuse treatment is within the mission of a separate agency within HHS, the Substance Abuse and Mental Health Services Administration.
- *Any lessons learned?*

Issue
Impetus
Structure
Science
Charge

Organizational History of NIAAA, NIDA, and NIMH



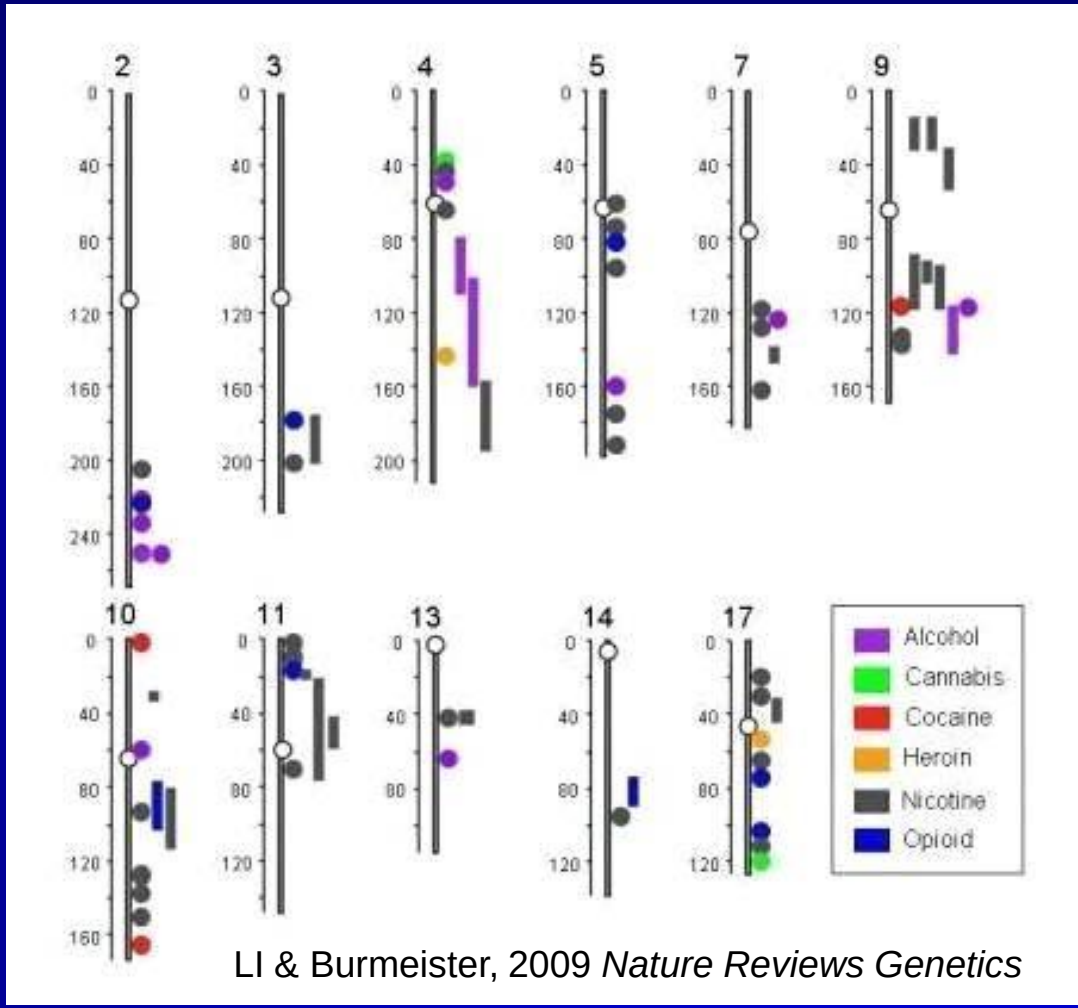
Current Understanding of the Science of Alcohol and Drug Use Disorders

- **Many substance users suffer from multiple drug dependencies, "co-morbid conditions":**
  - Prevalence of alcohol use disorder among those with a cocaine use disorder is 79%; Prevalence of cocaine use disorder among those with an alcohol use disorder is 2.5%
  - Smoking rate is 3x higher among alcoholics than in the general population
- **Some data suggest that treating one disorder without concurrently treating the other can lead to higher relapse rates for either substance.**
- **While drugs and alcohol have different mechanisms of action, common pathways are involved in addiction. This finding has implications for potential therapeutic strategies.**

Stinson et al., 2005 *Drug & Alcohol Dependence*

Current Understanding of the Science of Alcohol and Drug Use Disorders *(cont…)*

Unique genetic sites associated with risk for specific disorders related to alcohol and several other drugs



LI & Burmeister, 2009 *Nature Reviews Genetics*

Current Understanding of the Science of Alcohol and Drug Use Disorders *(cont…)*

- **While different drugs (alcohol, opiates, cocaine, nicotine, marijuana) activate different receptors in the brain, they all directly or indirectly elevate dopamine levels in the limbic system, the brain's endogenous reward system.**
- **Stimulation of the brain's reward system produces euphoria:**
  - Motivating behaviors necessary for survival, such as eating
  - Resulting in learned association of substance and pleasure, leading to repeated behaviors
- **Understanding addiction as usurpation of normal reward-related learning suggests prevention and treatment strategies may be transferable across addictions.**

NIAAA and NIDA Support for Science

- **Collaborative funding**
  - 2008: 13 grants co-funded by NIAAA and NIDA
  - 2009: 8 grants co-funded by NIAAA and NIDA to date
- **Common principal investigators**
  - 2008: 112 investigators received awards from both NIAAA and NIDA
- **Comparable success rates**
  - 1992 – 2004: Rates were comparable
  - 2004 – 2008: NIAAA success rates were 26-31%; NIDA success rates were 20-27% (Could be due to a number of issues, including focus and portfolio balance)

From Science to Structure

What organizational structure within NIH best supports scientific inquiry investigating fundamental pathways underlying substance use, abuse, and addiction, helps develop new treatments for addiction, and helps develop therapeutic applications of these substances?

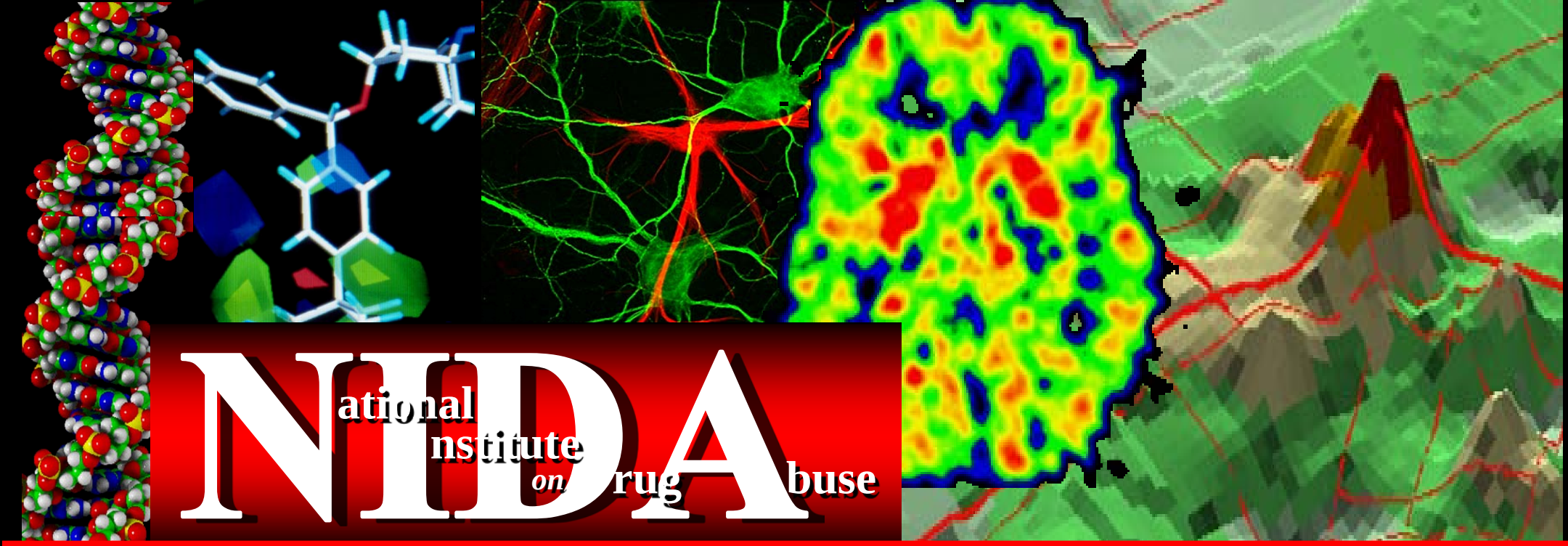
e.g., the National Academies suggested considering a merger of NIAAA and NIDA

From Science to Structure *(cont.)*

- **Issues to consider:**
  - How can NIH increase the synergy among researchers studying different facets of substance use, abuse, and addiction?
  - How can NIH best promote development of treatments for multiple addictions/co-morbidities?
  - How can NIH ensure that all areas of addiction, including addictive behaviors such as gambling, receive appropriate scientific attention?
  - How can organizational structure advance research on fundamental pathways underlying substance use and abuse, help develop new treatments for addiction, and help develop therapeutic applications of these substances?
  - What are the pros and cons of various organizational options?

Specific Charge to the SMRB

- **Should the SMRB consider organizational change within NIH to optimize research into alcohol and drug use, abuse, and addiction to better understand fundamental pathways, develop new treatments for addiction, and identify potential therapeutic uses for these substances?**
  - No
  - Yes
    - Process to inform decision
    - Timeline
    - Next steps



NIDA

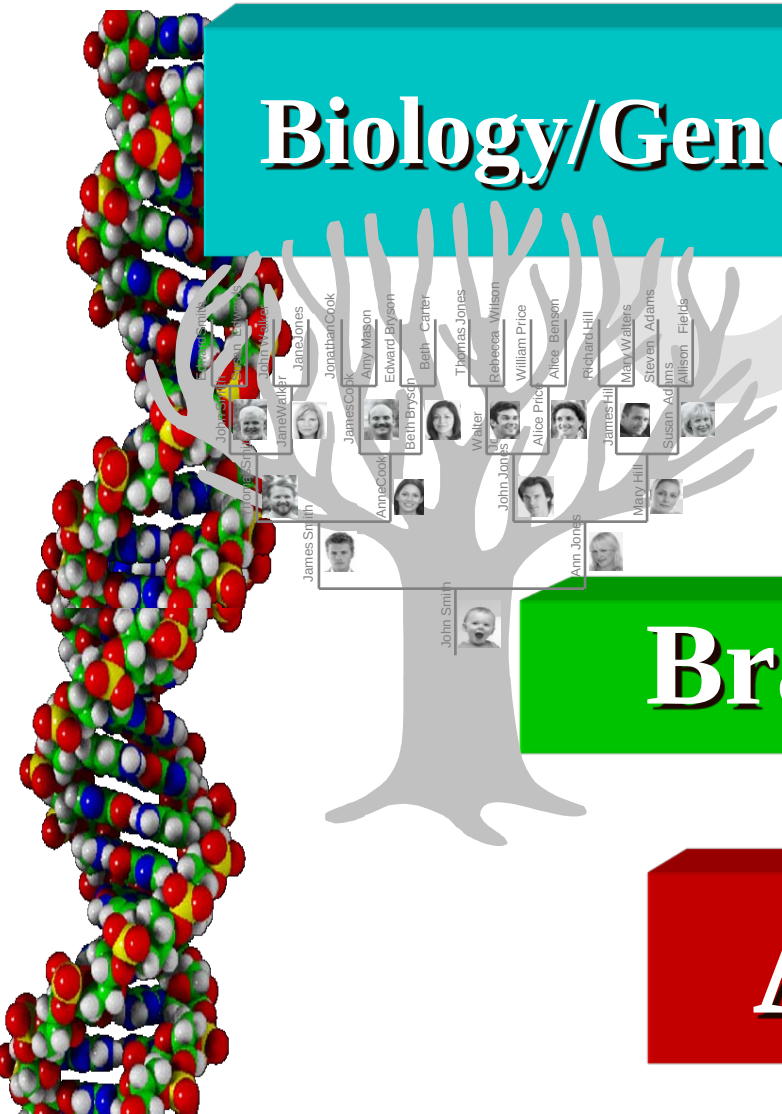
National Institute on Drug Abuse

… Bringing the full power of science to bear on

Drug Abuse & Addiction

Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse

ADDICTION INVOLVES *MULTIPLE FACTORS*



Biology/Genes ⟷ **Environment**

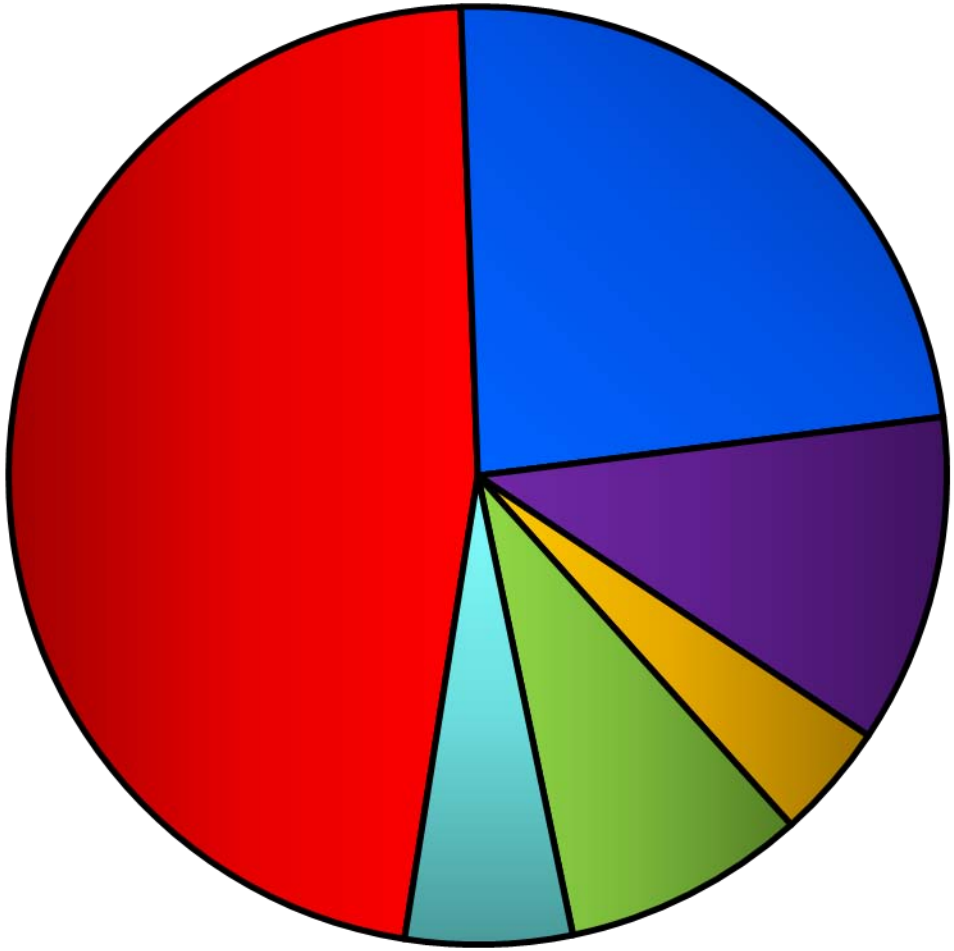
DRUG

Brain Mechanisms

Addiction

National Institute on Drug Abuse Portfolio

FY 2008 Actual



- Basic & Clinical Neuroscience & Behavioral Research -- 47%
- Epidemiology, Services & Prevention Research -- 24%
- Pharmacotherapies & Medical Consequences -- 11%
- Clinical Trials Network -- 4%
- Intramural Research -- 8%
- RM&S -- 6%

Priority Areas for NIDA

Prevention Research

(Children & Adolescents)

- genetics/epigenetics
- development
- environment
- co-morbidity

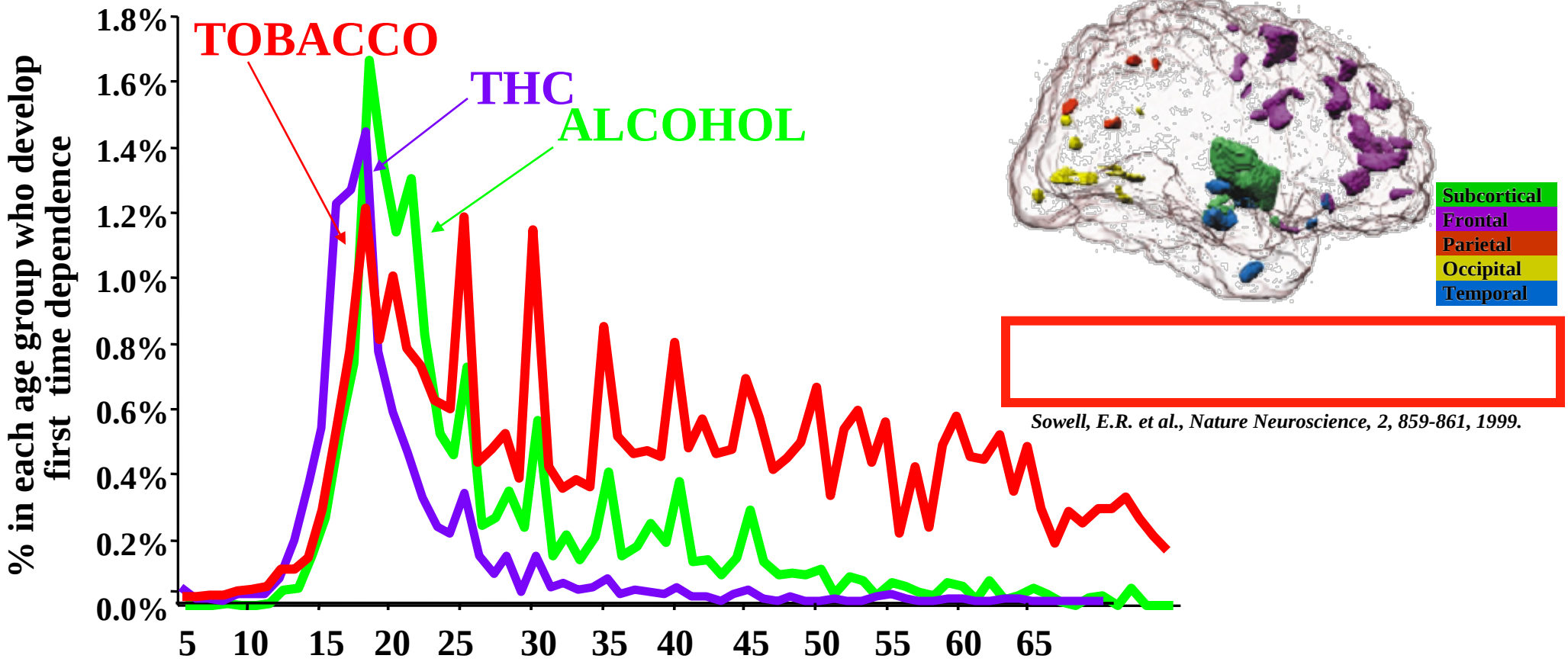
Treatment Interventions

(New Targets & New Strategies)

HIV/AIDS Research

ADDICTION IS A *DEVELOPMENTAL* DISEASE

starts in adolescence and childhood

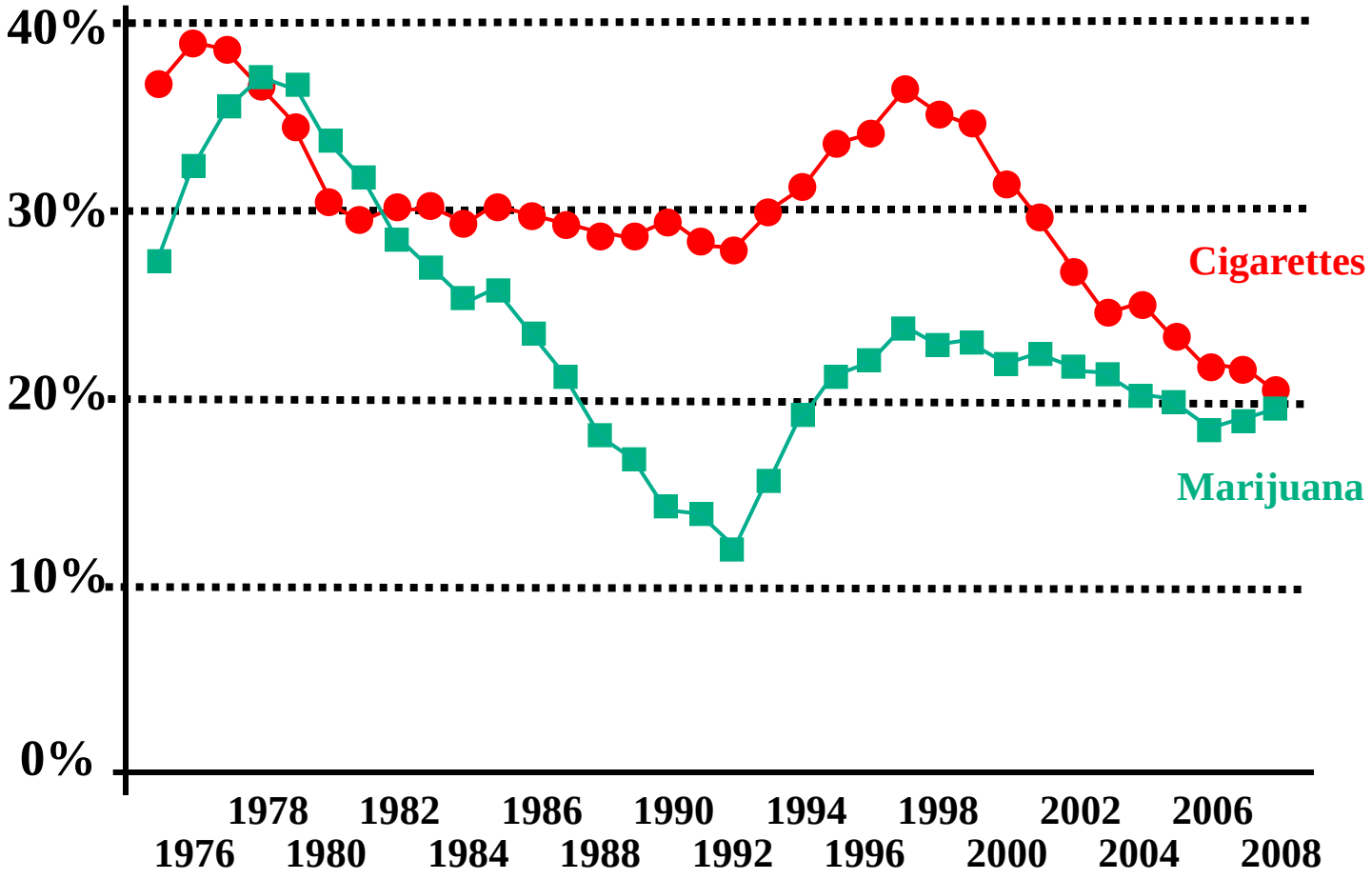


Sowell, E.R. et al., Nature Neuroscience, 2, 859-861, 1999.

Age at tobacco, at alcohol and at cannabis dependence as per DSM IV

NIAAA National Epidemiologic Survey on Alcohol and Related Conditions, 2003.

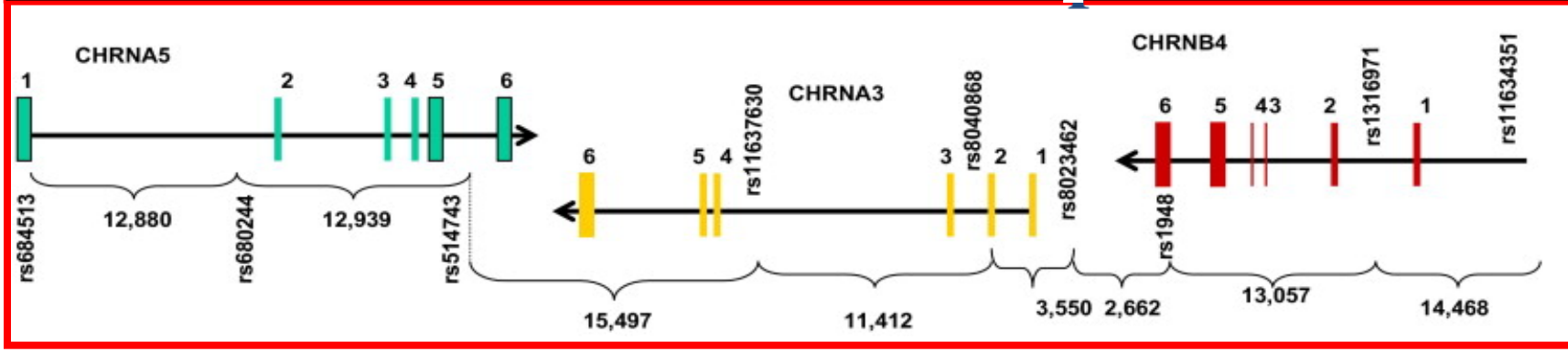
Percentage of U.S. 12th Grade Students Reporting Past Month Use of Cigarettes and Marijuana, 1975 to 2008



CESAR *FAX* January 19, 2009, Vol. 18, Issue 2.

Adapted by CESAR from University of Michigan, "Trends in 30-Day Prevalence of Use of Various Drugs in Grades 8, 10, and 12,"Monitoring the Future study, 2008.

Convergent Results Support CHRNA5/A3/B4 Gene Cluster Association with Nicotine Dependence



Human Molecular Genetics, 2007, Vol. 16, No. 1 **24–35**
doi:10.1093/hmg/ddl441
Advance Access published on December 7, 2006

Novel genes identified in a high-density genome wide association study for nicotine dependence

Laura Jean Bierut[1,*], Pamela A.F. Madden[1], Naomi Breslau[2], Eric O. Johnson[3],

Biological Psychiatry

The CHRNA5/A3/B4 Gene Cluster Variability as an Important Determinant of Early Alcohol and Tobacco Initiation in Young Adults

Isabel R. Schlaepfer, Nicole R. Hoft, Allan C. Collins, Robin P. Corley, John K. Hewitt, Christian J. Hopfer,

Molecular Psychiatry (2008), 1–6

www.nature.com/mp

IMMEDIATE COMMUNICATION

α-5/α-3 nicotinic receptor subunit alleles increase risk for heavy smoking

W Berrettini[1,2,3], X Yuan[2,3], F Tozzi[2,3], K Song[2,3], C Francks[2,3], H Chilcoat[4], D Waterworth[2,3], P Muglia[2,3,5] and V Mooser[2,3]

nature

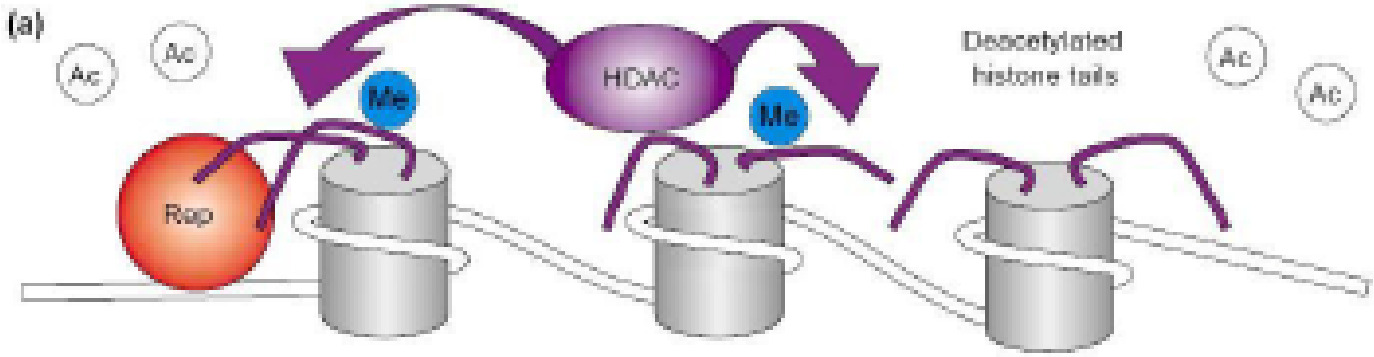
LETTERS

A variant associated with nicotine dependence, lung cancer and peripheral arterial disease

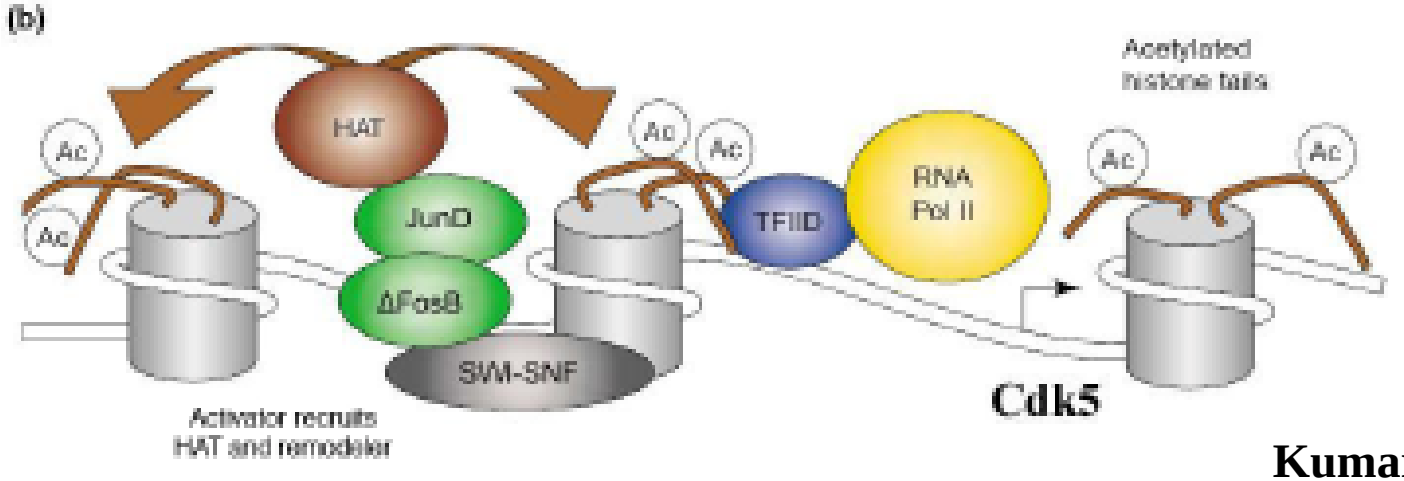
Thorgeir E. Thorgeirsson[1]*, Frank Geller[1]*, Patrick Sulem[1]*, Thorunn Rafnar[1]*, Anna Wiste[1,2], Kristinn P. Magnusson[1], Andrei Manolescu[1], Gudmar Thorleifsson[1], Hreinn Stefansson[1], Andres Ingason[1], Simon N. Stacey[1], Jon T. Bergthorsson[1], Steinunn Thorlacius[1], Julius Gudmundsson[1], Thorlakur Jonsson[1], Margret Jakobsdottir[1], Jona Saemundsdottir[1], Olof Olafsdottir[1], Larus J. Gudmundsson[1], Gyda Bjornsdottir[1], Kristleifur Kristjansson[1], Halla Skuladottir[3], Helgi J. Isaksson[4], Tomas Gudbjartsson[5], Gregory T. Jones[8], Thomas Mueller[9], Anders Gottsäter[10], Andrea Flex[11], Katja K. H. Aben[12,13], Femmie de Vegt[12], Peter F. A. Mulders[14], Dolores Isla[15], Maria J. Vidal[15], Laura Asin[16], Berta Saez[17], Laura Murillo[18], Thorsteinn Blondal[19]

…and with the risk of such smoking-related diseases as lung cancer and peripheral arterial disease

Epigenetic Marks Are Altered by Repeated Exposure to Drugs of Abuse

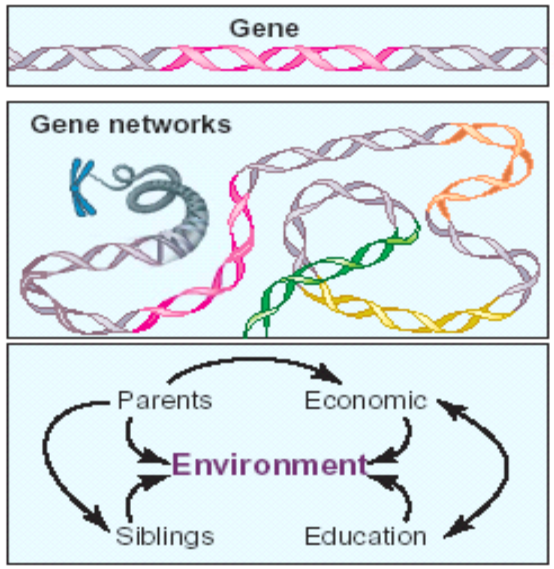


Cocaine induces the transcription factor • FosB, which co-activates HAT leading to sustained acetylation of histones and activation of genes, such as Cdk5, involved in addiction

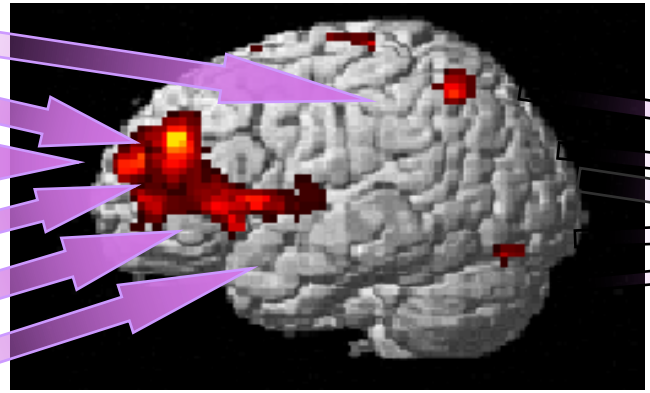


Kumar et al Neuron 48: 303-314 2005

How Do Genes Influence Brain Development, Behavior and Disease?



Risk for Disease



BRAIN FUNCTION

Protein expression
Neurotransmission
CBF
Metabolism
Electrophysiology

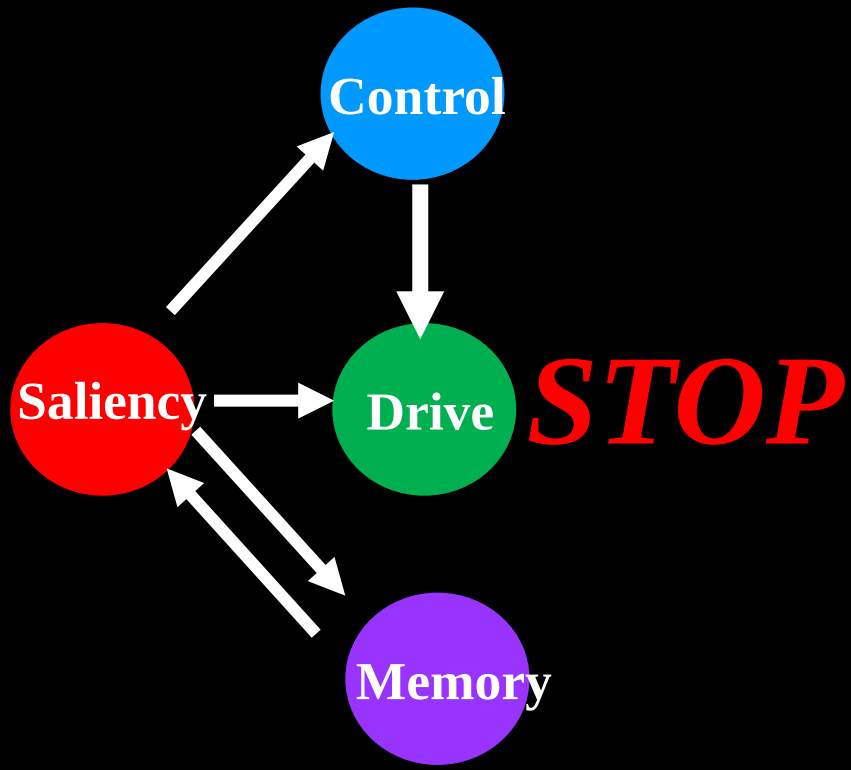
Behavior*

Symptoms and DISEASE

***Adapted from Hamer, *Science*, 2002; MAO A genotype studies from Caspi et al., *Science*, 2002.**

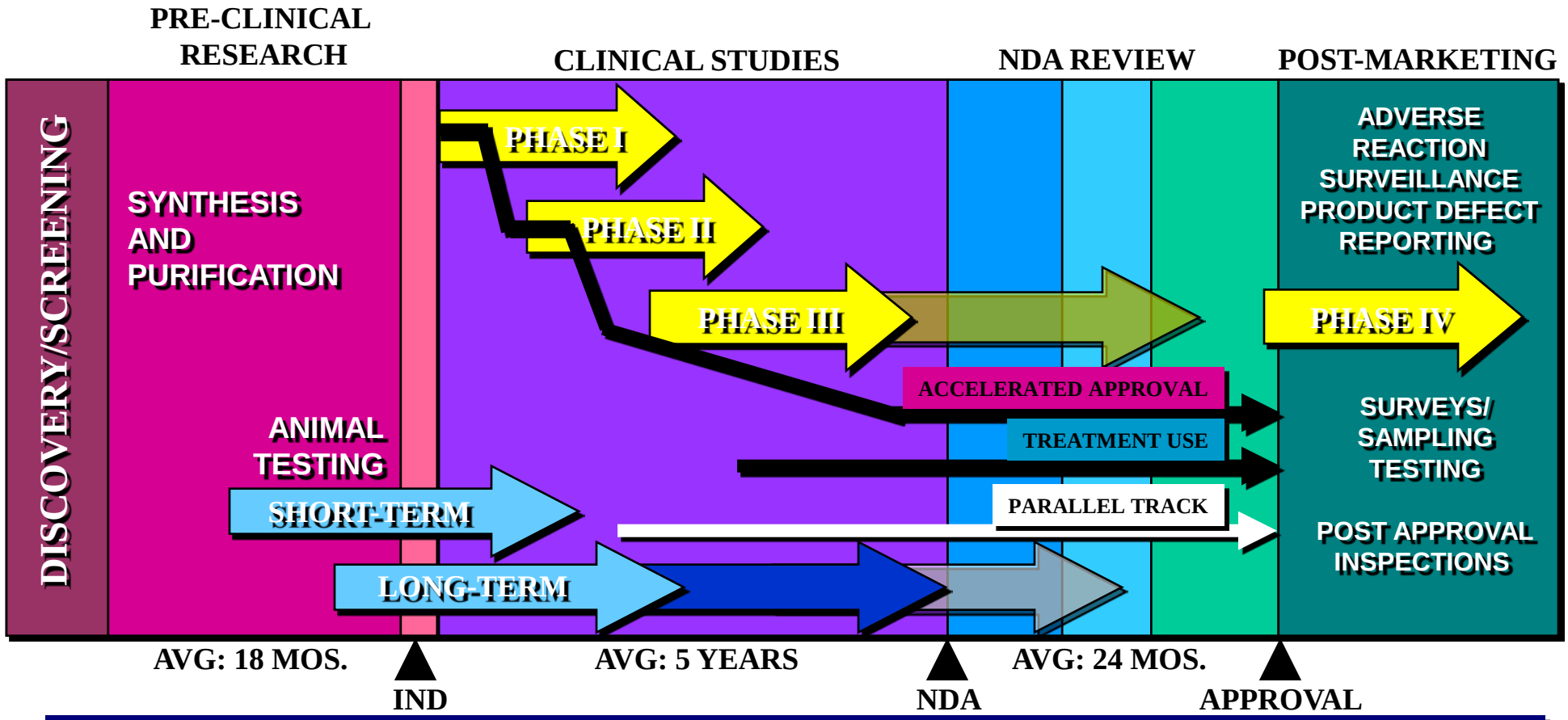
Medications for Relapse Prevention

Non-Addicted Brain



Interfere with drug's reinforcing effects	*Vaccines* *Enzymatic degredation* *Naltrexone* *DA D3 antagonists* *CB_1 antagonists*
Executive function/ Inhibitory control	*Biofeedback* *Modafinil* *Bupropion* *Stimulants*
Strengthen prefrontal-striatal communication	*Adenosine* *A2 antagonists* *DA D3 antagonists*
Interfere with conditioned memories (craving)	*Antiepileptic GVG* *N-acetylcysteine*
Teach new memories	*Cycloserine*
Counteract stress responses that lead to relapse	*CRF antagonists* *Orexin antagonists*

ROADBLOCK #1: Lack of Pharmaceutical Industry Interest in Developing Medications to Treat Addiction



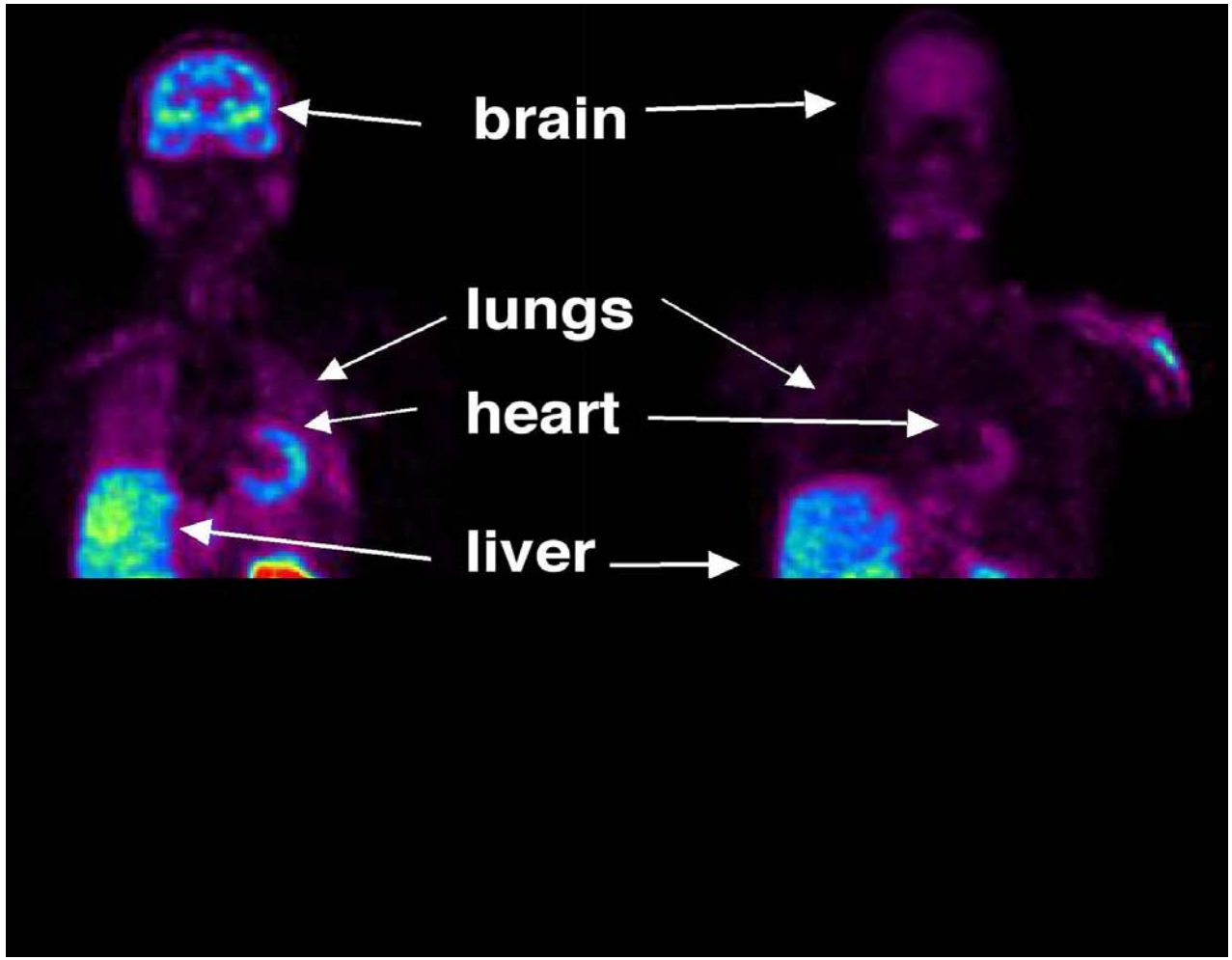
The Process of NEW DRUG DEVELOPMENT Is Long…and Expensive

ROADBLOCK #2: Erosion of the Medical Community's Involvement in Preventing and Treating Drug Abuse and Addiction

Primary Care Physicians Are Often Reluctant To Treat Substance Abuse or Fail to Link This With Their Patients' Other Medical Conditions

ADDICTION CONTRIBUTES TO MANY SERIOUS *MEDICAL CONSEQUENCES*

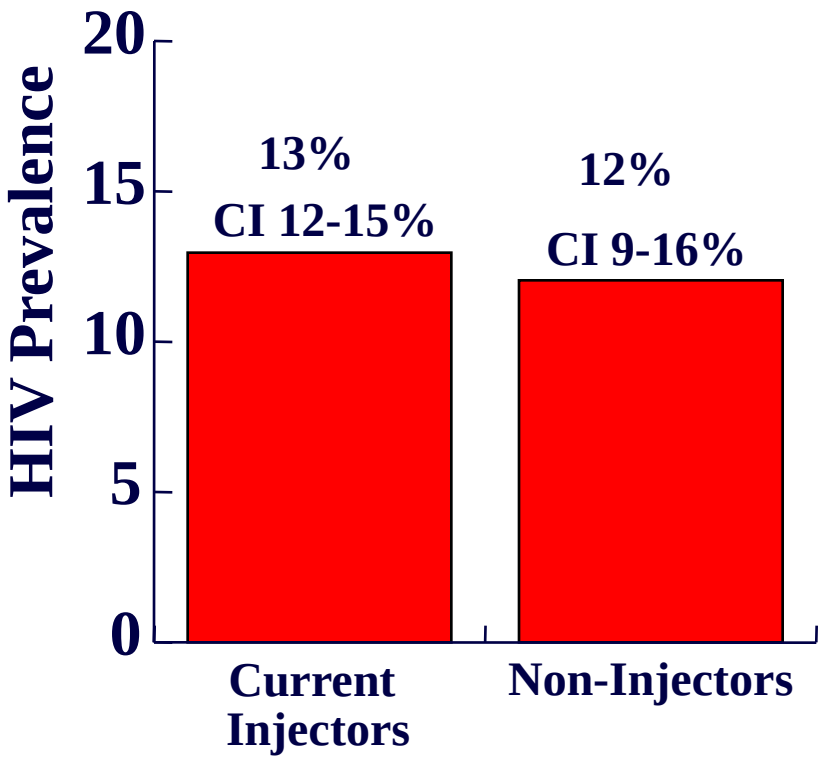
- Mental Illness
- Cancer
- Infectious Diseases (HIV/HCV)
- Cardiac
- Pulmonary
- Learning Disorders
- Obesity
- Cerebrovascular (strokes)
- Trauma (accidents)



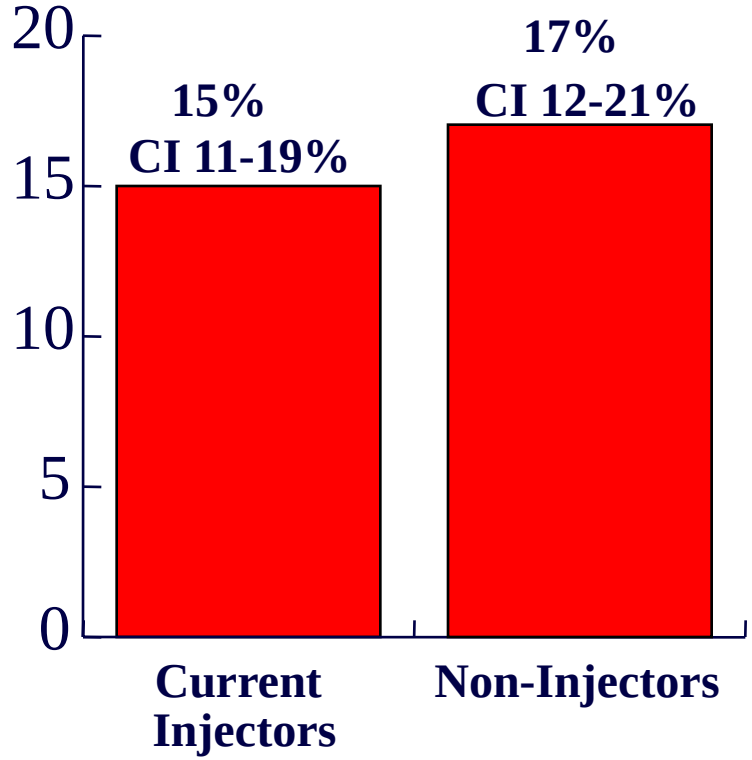
Source: Fowler JS et al., PNAS. 2003;100(20):11600-5.

Convergence of HIV Seroprevalence Among Injecting and Non-injecting Drug Users

Drug Treatment Program (n=2121 2001-2004)



Respondent-Driven Sampling (n=448 2004)

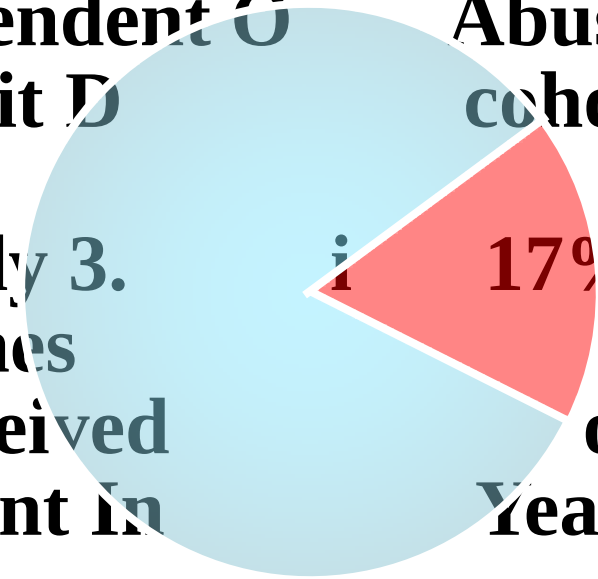


Source: Des Jarlais et al AIDS, 21: 231-235, 2007.

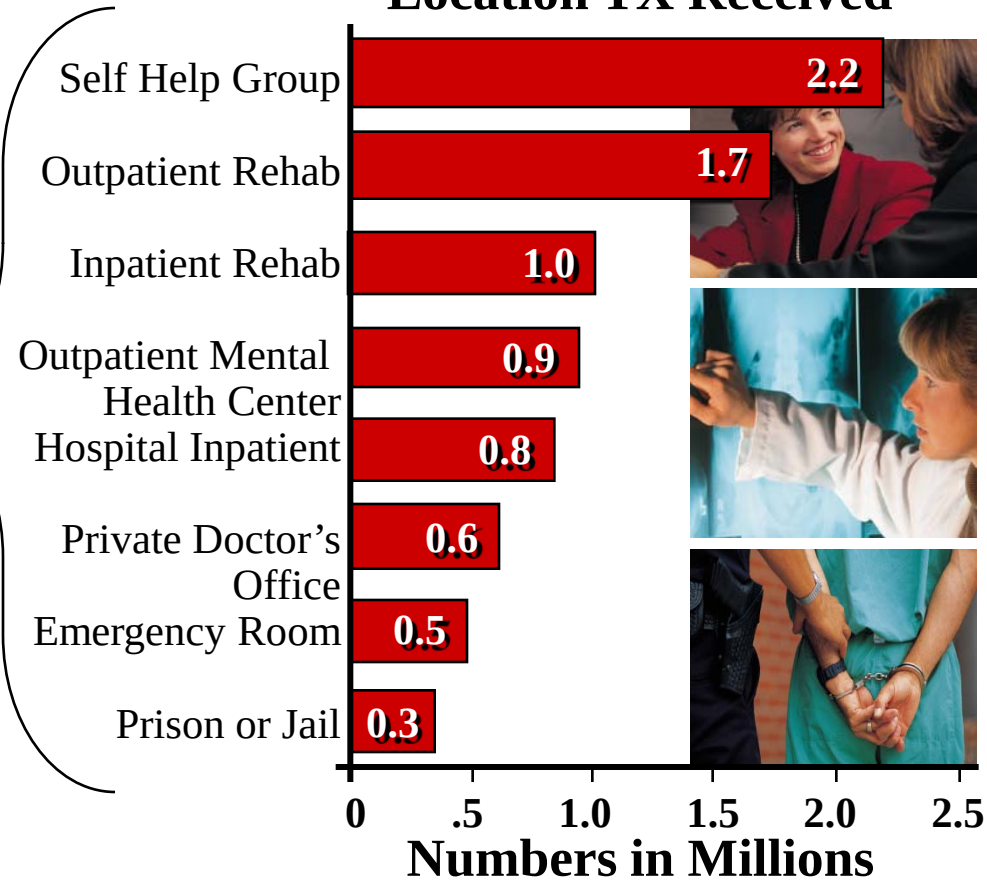
ROADBLOCK #3: Although Treatments For Addiction Are Available, They Are Not Being Widely Used By Those Who Need Them

In 2007 An Estimated 22.3 Million Americans Were Dependent O Abused Any Illicit D cohol

But…Only 3. i 17%) of Thes of Had Recei ved Treatment In Year

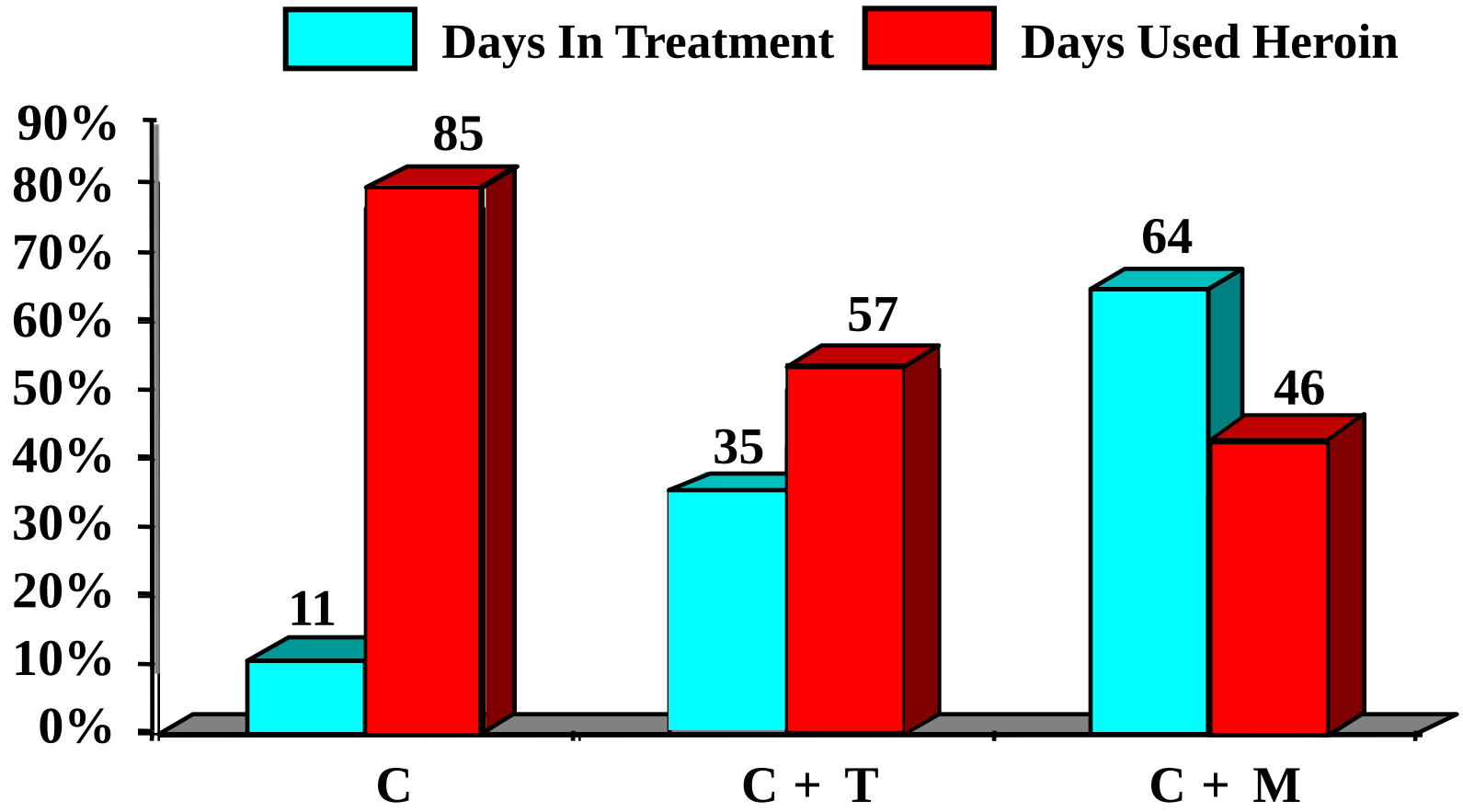


Location TX Received



Source: 2007 NSDUH, National Findings, SAMHSA, OAS, 2008.

Treatment Linkage & Days Used Heroin
6 Months Post-release



C = Counseling Only
C+T = Counseling & Treatment Referral
C+M = Counseling & Methadone Started in Prison

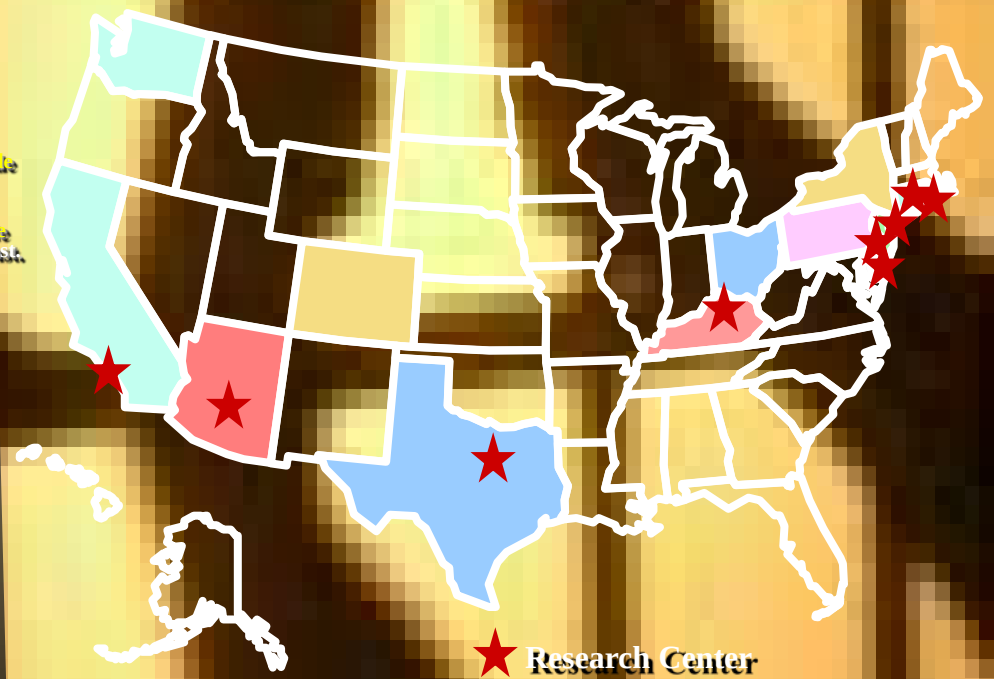
Source: Gordon, MS et al., Addiction 103:1333-1342, 2008.

Blending Research and Practice

National Drug Abuse Treatment Clinical Trials Network (CTN)

NIDA Criminal Justice Drug Abuse Treatment Studies (CJ-DATS)

Research Centers & CJ Partner Sites



presentation to the

NIH Scientific Management Review Board

on

The National Institute on Alcohol Abuse and Alcoholism

Kenneth R. Warren, Ph.D.
Acting Director

April 27-28, 2009

National Institute on Alcohol Abuse and Alcoholism

Mission: To understand how alcohol use impacts normal and abnormal biological functions and behavior across the lifespan and at all levels of drinking including:

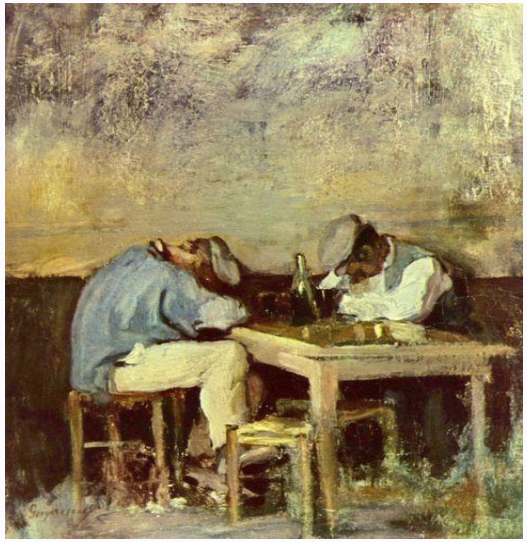
- Alcohol-associated disease (including alcohol dependence)
- Alcohol-derived organ pathologies
- Public health problems resulting from acute and chronic alcohol use (e.g., alcohol poisoning, accidental injury and death)

Thereby improving the health and well-being of the nation

- Alcohol is legal, widely used, and easily obtained
- It is a part of the social context in many countries and cultures and is used in ceremonial occasions such as marriages, and births, and to enhance the enjoyment of social gatherings

"Wedding Toast"
Erik Henningsen
https://www.allposters.com/-sp/Wedding-Toast-Posters_i2829204_.htm

Pierre-Auguste Renoir The Luncheon of the Boating Party (1880)

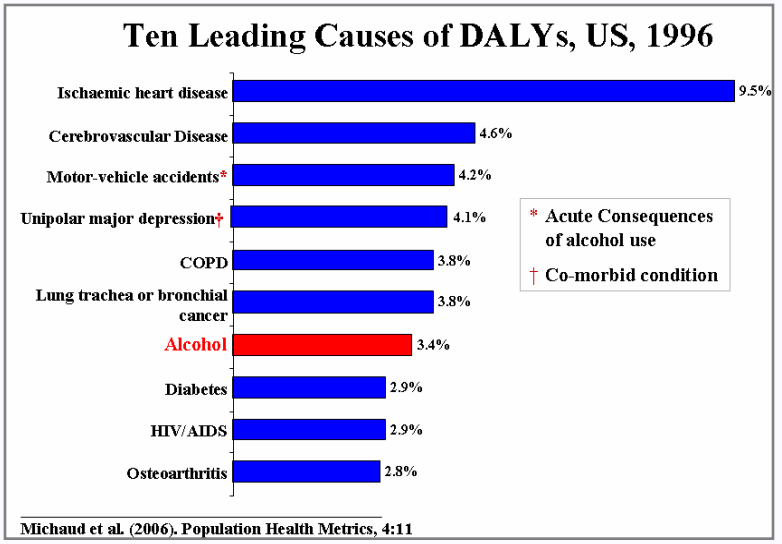


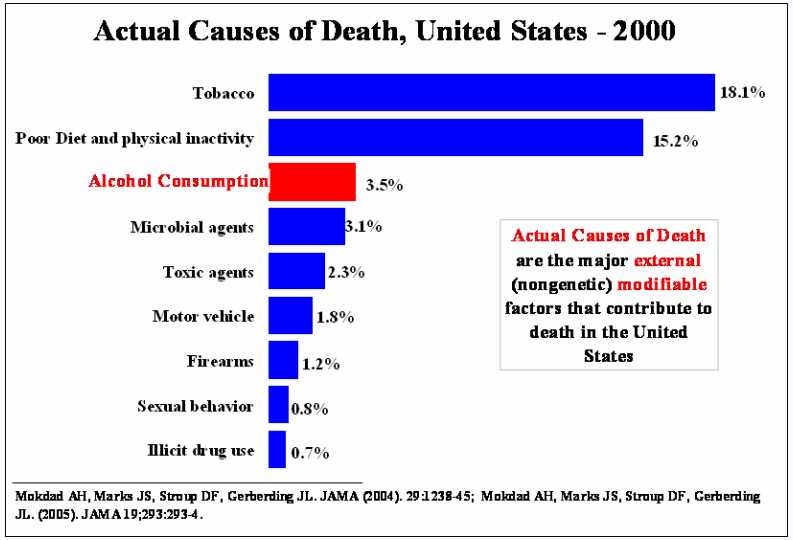
Nicolae Grigorescu

- Alcohol has both beneficial and harmful health effects, and it is used by most individuals without causing harm to themselves or others
- However, alcohol interacts with the whole body, and risk drinking produces intoxication and other impairments to the CNS, and harm to organs and body systems
- Indeed, alcohol is a leading risk factor for morbidity and mortality in the United States and worldwide

- 18 million Americans (8.5% of the population age 18 and older) suffer from alcohol abuse or dependence
- Alcohol problems cost U.S. society an estimated $185 billion annually
- Alcohol consumption is among the top ten leading causes of DALYs*
- Among Actual Causes of Death Alcohol ranks 3rd with an estimated 79,000 deaths annually for 2001-2005

*Disability-adjusted life years (years of potential life lost due to death plus years of healthy life lost to disability)





Binge Drinking
(too much, too fast)
5+/4+ drinks/2 hours

Heavy Drinking
(too much, too often)
frequent 5+/4+ drinks/day

acute consequences including:

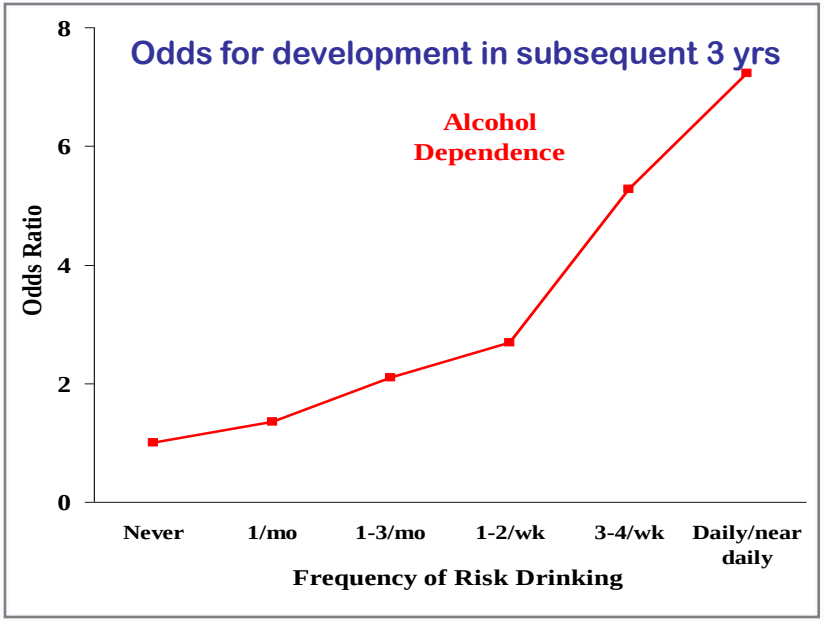
- unintentional death and injury
- homicide and violence
- suicide attempts

particularly prevalent among adolescents and young adults

chronic consequences including:

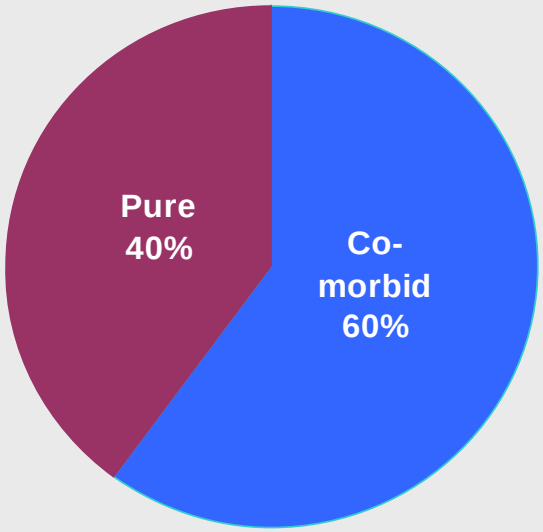
- liver cirrhosis
- cardiovascular diseases
- pancreatitis
- dementia
- alcohol dependence

- NIAAA has defined risk drinking as exceeding 5+/4+ per day (14+/7+ per week) based on epidemiologic data from the NESARC and probabilities of an adverse outcome at various drinking levels
- 65% of the U.S. adult population are current drinkers
- 59% of current drinkers do not report risk drinking



- 55% of Individuals with Drug Use Disorders have an Alcohol Use Disorder; 13% of individuals with Alcohol Use Disorders also have a drug use disorder
- Research on the pharmacology and treatment of drug and psychiatric disorders co-morbid with AUDs is an important part of our agenda

Pure and Comorbid Past-Year Alcohol Use Disorders in the U.S. Population

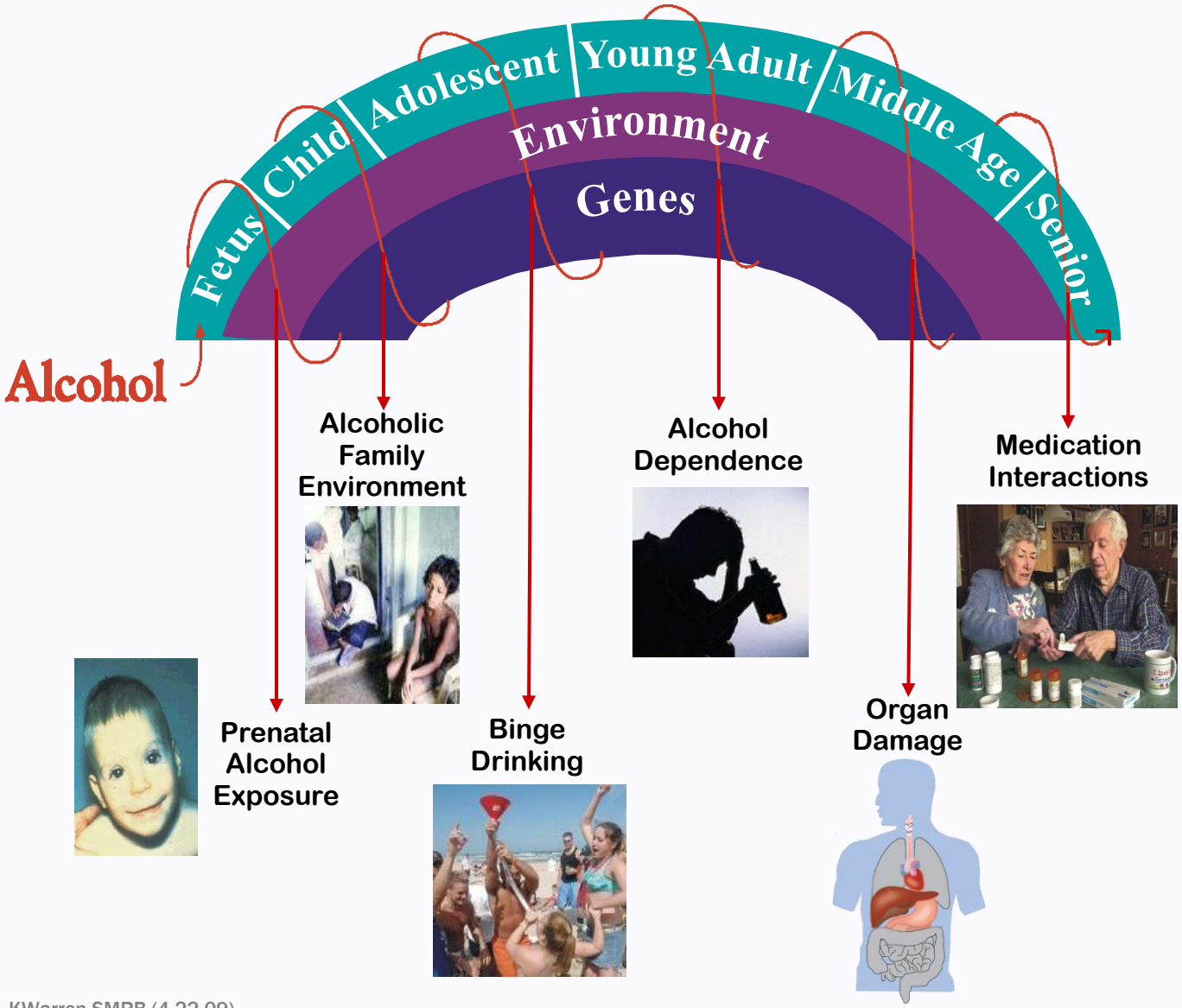


NIAAA NESARC. NIAAA Laboratory of Epidemiology and Biometry

Co-morbidity Rates for 12-month DSM-IV Psychiatric and Drug Disorders Among Individuals with Alcohol Use Disorders in the U.S. Population

Disorder	Rate
Nicotine Dependence	33.8%
Personality Disorders	29%
Mood Disorders (including major depression)	19%
Anxiety Disorders	17%
Drug Use Disorders	13%

NIAAA's Broad Mandate Requires Research Programs To Address Alcohol Issues Throughout The Lifespan...



Lifespan Transcending Themes

- Metabolism
- Genetics
- Epigenetics
- Epidemiology
- AUD Diagnosis
- Neurobiology
- Health Services Research

Brain

- Multiple Neurotransmitter System Targets
- Dependence
- Structural Damage
- Cognitive Deficits
- Dementia

Peripheral Neuropathy

Cardiovascular System

- Cardiomyopathy
- Hypertension
- Stroke
- Arrhythmias
- Blood platelet dysfunction
- Moderate drinking & CAD

Liver

- Hepatic steatosis
- Fibrosis
- Cirrhosis
- Hepatocellular carcinoma

Skeletal Muscles

- Myopathy

Blood Platelet Dysfunction

Lungs

- Acute Respiratory Distress Syndrome

Gastrointestinal Tract

- Esophageal Cancer
- Gastritis

Pancreas

- Pancreatitis

Fetus

- FAS/D

Immune System Deficiency

Endocrine System

- HPA/HPG/ HPT Dysfunction

Bone

- Osteoporosis

Metabolic Syndrome

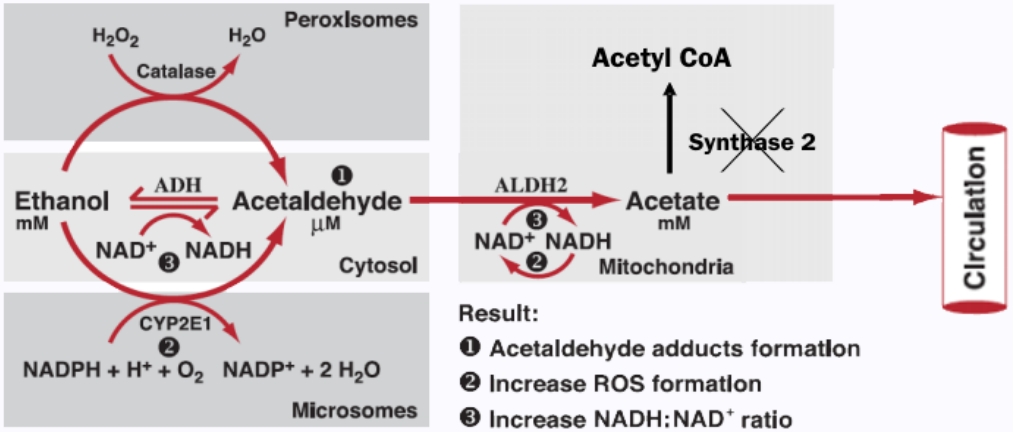
- Decreased Risk of Coronary Artery Disease
  - HDL⬆; LDL ⬇
  - Decreased platelet aggregation
  - Increased fibrinolysis
  - Ischemic/reperfusion
- Decreased risk of Ischemic Stroke
- Metabolic Syndrome and Type 2 Diabetes
- Decreased Osteoporosis
- Decreased risk of dementia
- Improved cognitive function in women

The wide range of physiologic and pathologic effects of alcohol on many organs requires that alcohol research be conducted from a broad systems approach, where the effects of alcohol on one organ elicits metabolic changes that affect other organs, for example:

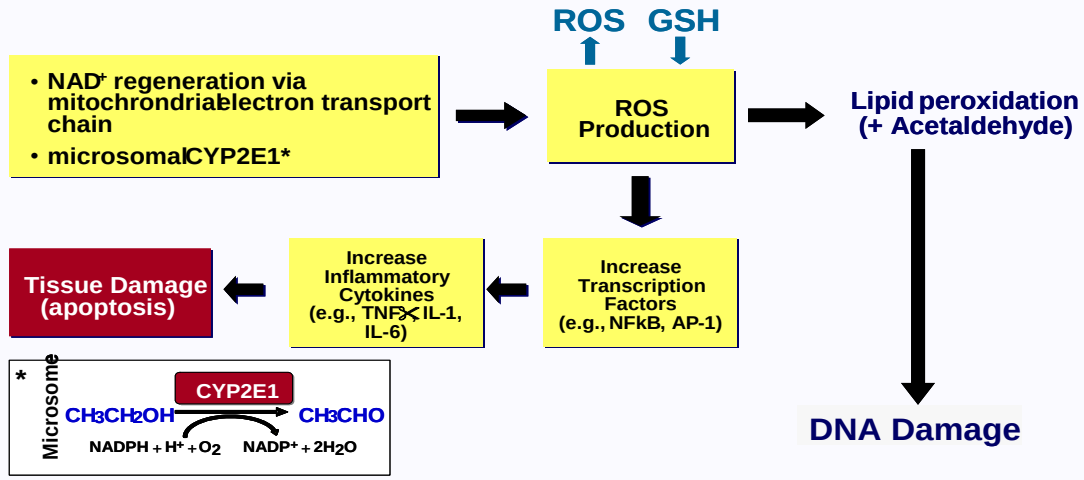
- Increased permeability on intestinal mucosa resulting in an increase in LPS which affects liver and brain pathology
- Alcohol's metabolic effects on liver lipid metabolism affecting vascular system, CHD risk (- and +), dementia risk (- and +)
- Hormones from gut, pancreas, adipose tissue affecting drinking behavior: e.g., CCK, ghrelin (?); PYY (?)

- Another key factor that may contribute to alcohol's broad effects is that it is consumed at levels more typical of a food than a pharmacologic agent
- A standard alcoholic beverage (12 oz beer, 5 oz wine, 1 ½ oz distilled spirits) has 14 grams of ethanol
- An individual consuming 6 drinks is ingesting 84 grams of ethanol; 588 calories from ethanol
- Consequently, alcohol can have profound metabolic effects

Oxidative Pathways of Alcohol Metabolism

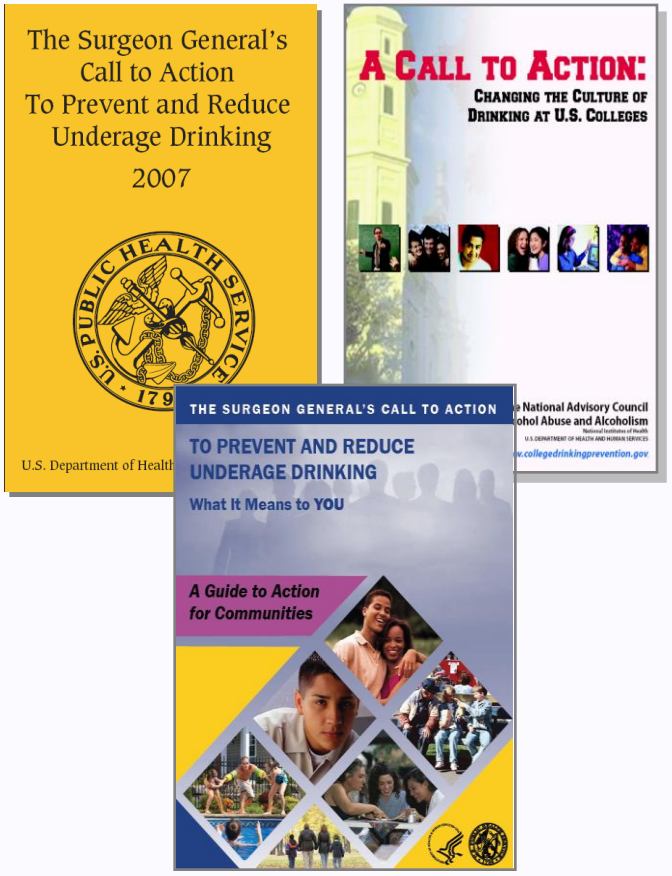


Alcohol Metabolism, ROS Production, and Tissue Damage



Alcohol also inhibits methionine synthase impairing biosynthesis of SAMe and potentially leading to hypomethylation in epigenetics (DNA, histones)

- NIAAA has a Major Public Health Focus on Underage Drinking
  - Goal: Delaying the Onset of Drinking to reduce risks for development of AUDs later in life (4x greater risk to develop dependence with drinking onset <15 years).
  - NIAAA provided the research base for the Surgeon General's Call to Action on Underage Drinking.
  - Research on the impact of Enforcement of Underage Drinking Laws (EUDL)



- College Drinking Initiative included translating research to campus and community prevention initiatives
- Community research on price, zoning, outlet density, hours of operation, merchant and server intervention
- NIAAA research on the effect of 21 drinking age, 0.08% BAC limit, and zero tolerance for <21 drinking/driving led to implementation of these laws

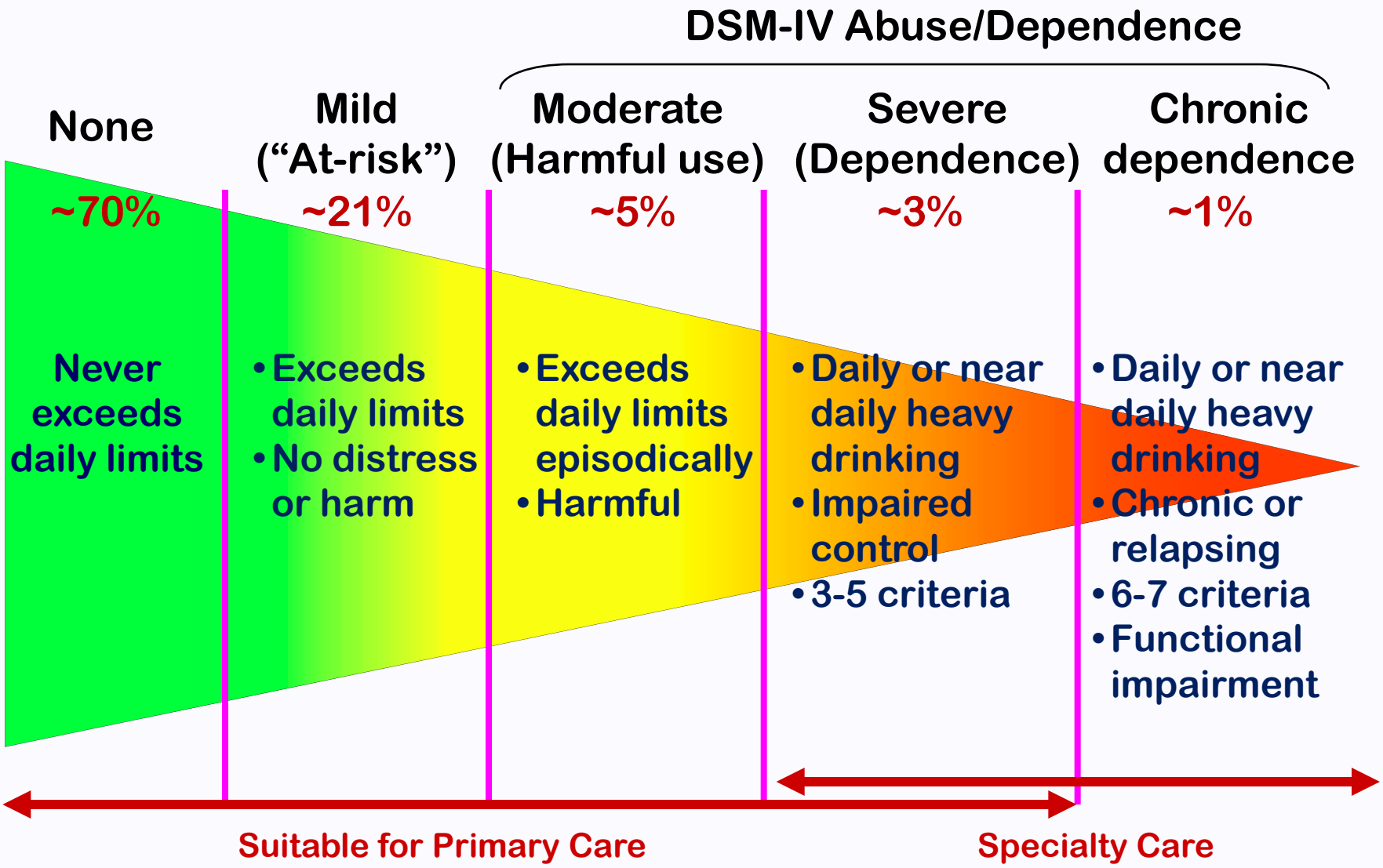
- NIAAA research established that several Behavioral Treatments are effective in the treatment of alcohol dependence:
  - Cognitive Behavioral Therapy
  - 12-Step Facilitation
  - Motivational Enhancement
  - Community Reinforcement
  - Marital Behavioral Therapy
- Screening and Brief Intervention for Alcohol Problems has been established as both effective and economical in:
  - Trauma Centers
  - Prenatal Practice
  - Primary Care (Now a recommendation from the U.S. Preventive Services Task Force)
- In 2006, NIAAA launched a major initiative to understand the mechanisms of behavior change
  - Precursor to NIH Roadmap developmental initiative on Science of Behavior Change

NIAAA Research – Science in Support of Practice

Developing Medications

Medications with Proven Efficacy	
Medication	**Target**
Disulfiram	Aldehyde Dehydrogenase (FDA approval 1949)
Naltrexone	Mu Opioid Receptor (FDA approval 1994)
Acamprosate	Glutamate and GABA-Related (FDA approval 2004)
Naltrexone Depot	Mu Opioid Receptor (FDA approval 2006)
Topiramate (AD)	GABA/Glutamate (off-label)
Examples of Potential Therapeutics Under Investigation	
Medication	**Target/Type**
Valproate (AD)	GABA/Glutamate
Ondansetron (AD)	5-HT_3 Receptor
Nalmefene (AD)	Mu Opioid Receptor
Baclofen (AD)	$GABA_B$ Receptor
Antalarmin (AD)	CRF1 Receptor
Rimonabant (AD)	CB1 Receptor
Refanalin (liver fibrosis)	heptic-growth-factor-mimetic
NAPVSIPQ and SALLRSIPA (FAS/D)	neuroprotective peptides/L1 receptor
Choline (FAS/D)	ACH (?)

Extended Continuum: From Low to High Risk to AUD



- The NIAAA Clinician's Guide, was developed as the first fully evidence-based guide for primary health care to provide screening for all patients, provide brief intervention for risk drinkers, diagnose DSM-IV alcohol use disorders and provide treatment or referral to specialty treatment services
- The *Guide* has penetrated primary and mental-health care with the extensive help of the AMA and other professional organizations
- The guide makes it is easier for clinicians to address alcohol use with their patients and de-stigmatizing alcohol treatment

CME credit available at:
www.niaaa.nih.gov/guide

- Our goal for the Consumer Guide *Re-Thinking Drinking* (as with our Clinician's Guide) is to help facilitate a healthy relationship with alcohol for those many adults who choose to drink thereby helping them to avoid the adverse health and personal consequences associated with harmful alcohol use

RethinkingDrinking.niaaa.nih.gov

- For those individuals with Alcohol Use Disorders, our goal is to develop a range of treatment options (behavioral and pharmacologic) that are accessible, acceptable, affordable, and appealing to clients, and thereby close the treatment gap for alcohol use disorders

Kenneth R. Warren, Ph.D.
Acting Director
National Institute on Alcohol Abuse and Alcoholism

NIAAA National Institute on Alcohol Abuse and Alcoholism
of the NATIONAL INSTITUTES OF HEALTH

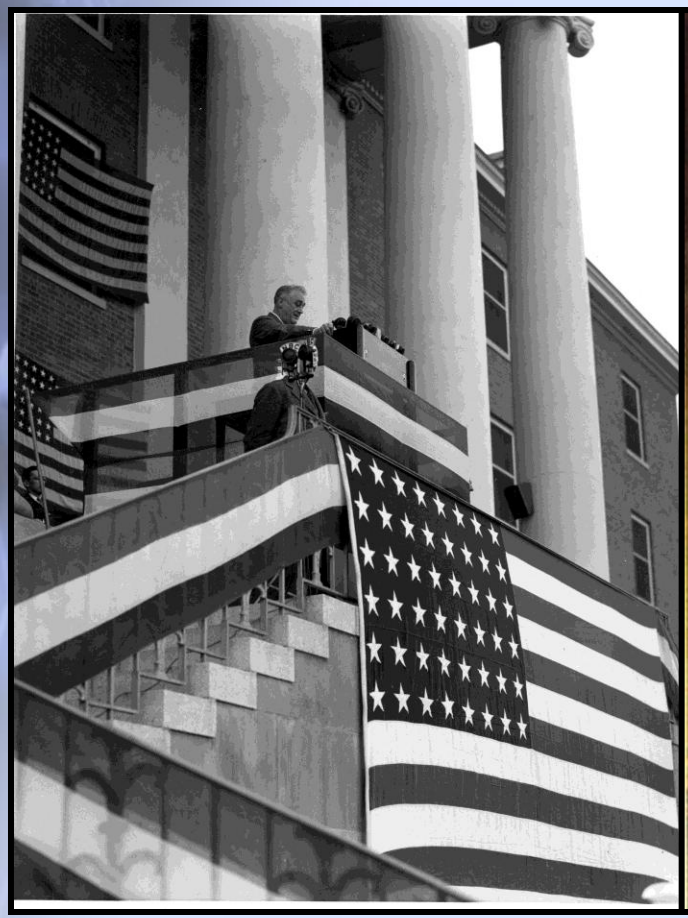
http://www.niaaa.nih.gov

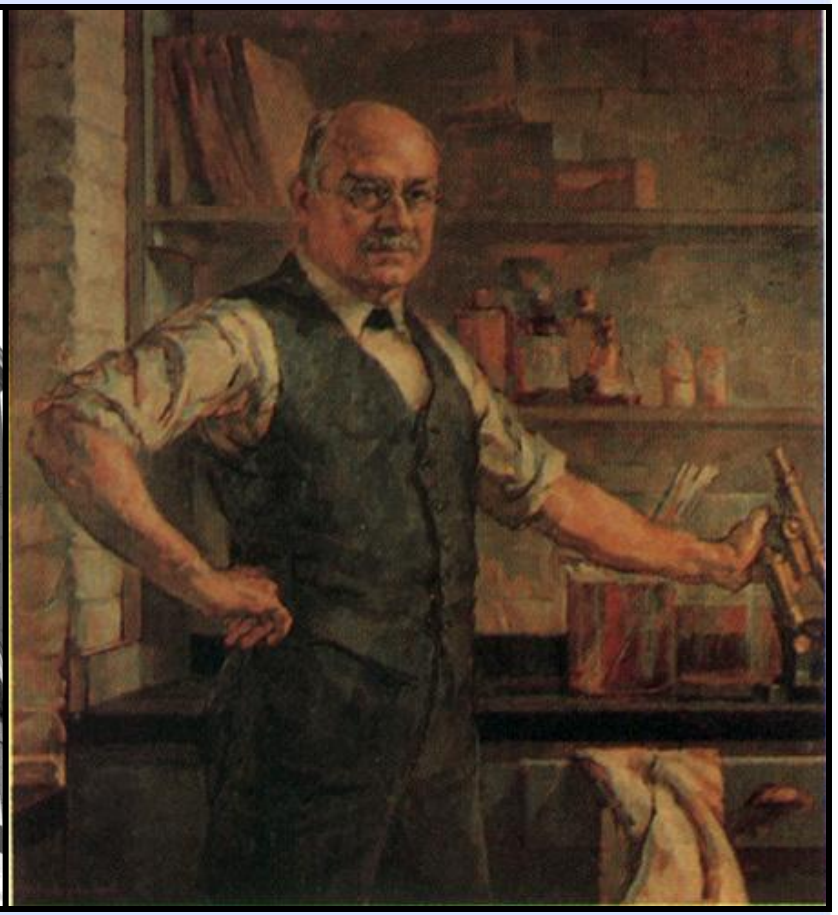
The NIH Intramural Research Program: Taking Its Place for the Future

Presentation to the Scientific Management Review Board
April 28, 2009

Michael Gottesman, M.D.
Deputy Director for Intramural Research

The NIH Intramural Research Program: Past and Calls for Change





Historical Perspectives

- Derived from a one-room lab in 1887 to its present configuration on 5 major campuses
- Has conducted research that transformed biomedicine and trained investigators who lead academic health centers; trusted source of medical information and facilitator of collaborative interactions
- Has provided a research environment distinct from most others
- Called a “social invention for human betterment” (Lewis Thomas--1984)
- Described as a “rallying point of the Nation’s overall biomedical research effort” (IOM--1988)

The NIH Intramural Research Program: Present

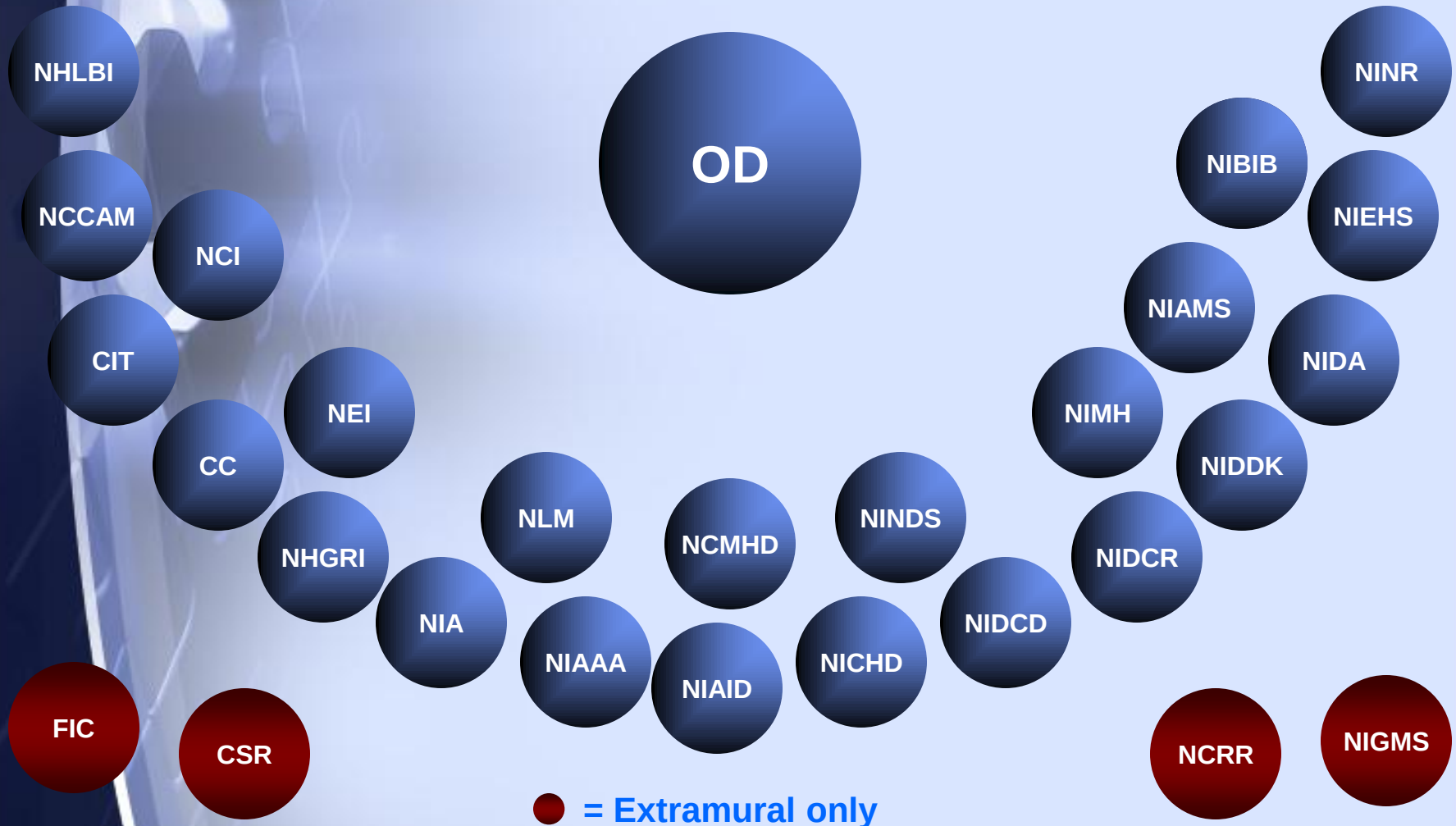
Key Underpinnings of the NIH Intramural Research Program

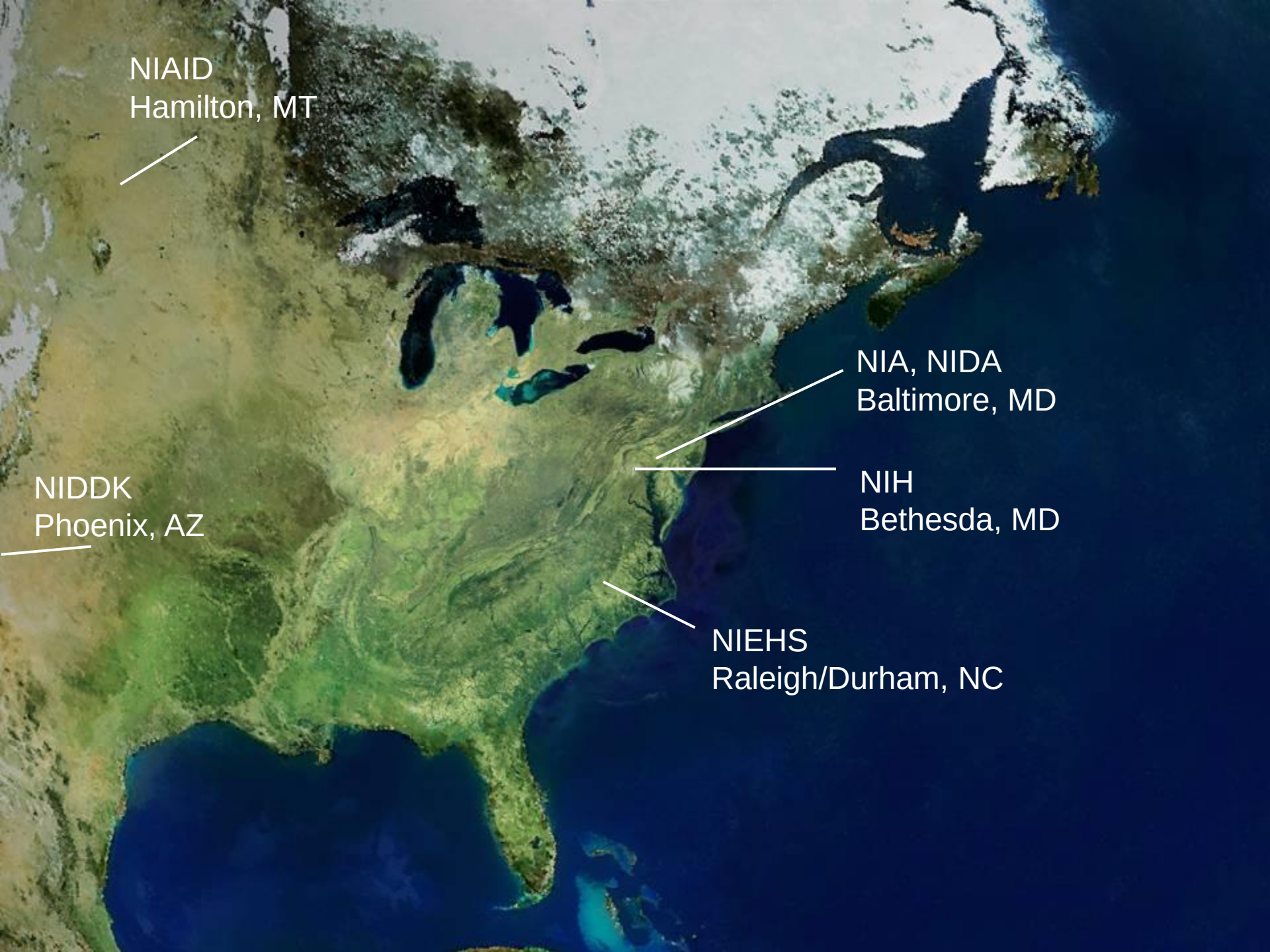
- **Mission and vision of the intramural research program to provide a distinct environment to support the overall NIH mission**
- **Intellectual freedom: ability to do high-risk, high-impact science mainly because of a largely retrospective review system**
- **Long-term resources and funding for new technology and high-risk long-term projects**
- **A critical mass of talent engaged in collaborations and partnerships**
- **Supportive leadership that recognizes the unique environment of the NIH intramural program**

Structure and Oversight of the NIH Intramural Research Program

- 23 of the 27 ICs participate in the intramural research program
- Office of Intramural Research and Deputy Director for Intramural Research oversees hiring of PIs, external review process for science, tech transfer, intramural training programs, human subjects research, and animal care and use to assure uniformity and quality of the overall intramural research program
- IC Directors allocate resources from IC budgets to intramural within envelope established by the NIH Director; Scientific Directors of each intramural program manage within allocation to set scientific priorities and support shared resources

NIH consists of 27 Institutes and Centers of which most have intramural programs




NIAID
Hamilton, MT
NIA, NIDA
Baltimore, MD
NIH
Bethesda, MD
NIDDK
Phoenix, AZ
NIEHS
Raleigh/Durham, NC

Scientists and Trainees at NIH

- 1,000 summer students (high school, college, graduate and medical)
- 600 post-baccalaureate trainees
- 100 medical/dental students
- 500 graduate students
- 3,800 post-doctoral fellows
- 300 Staff Clinicians
- 900 Staff Scientists
- 240 Tenure-track Investigators
- 900 Senior Investigators

Distinguishing Features of Intramural Research

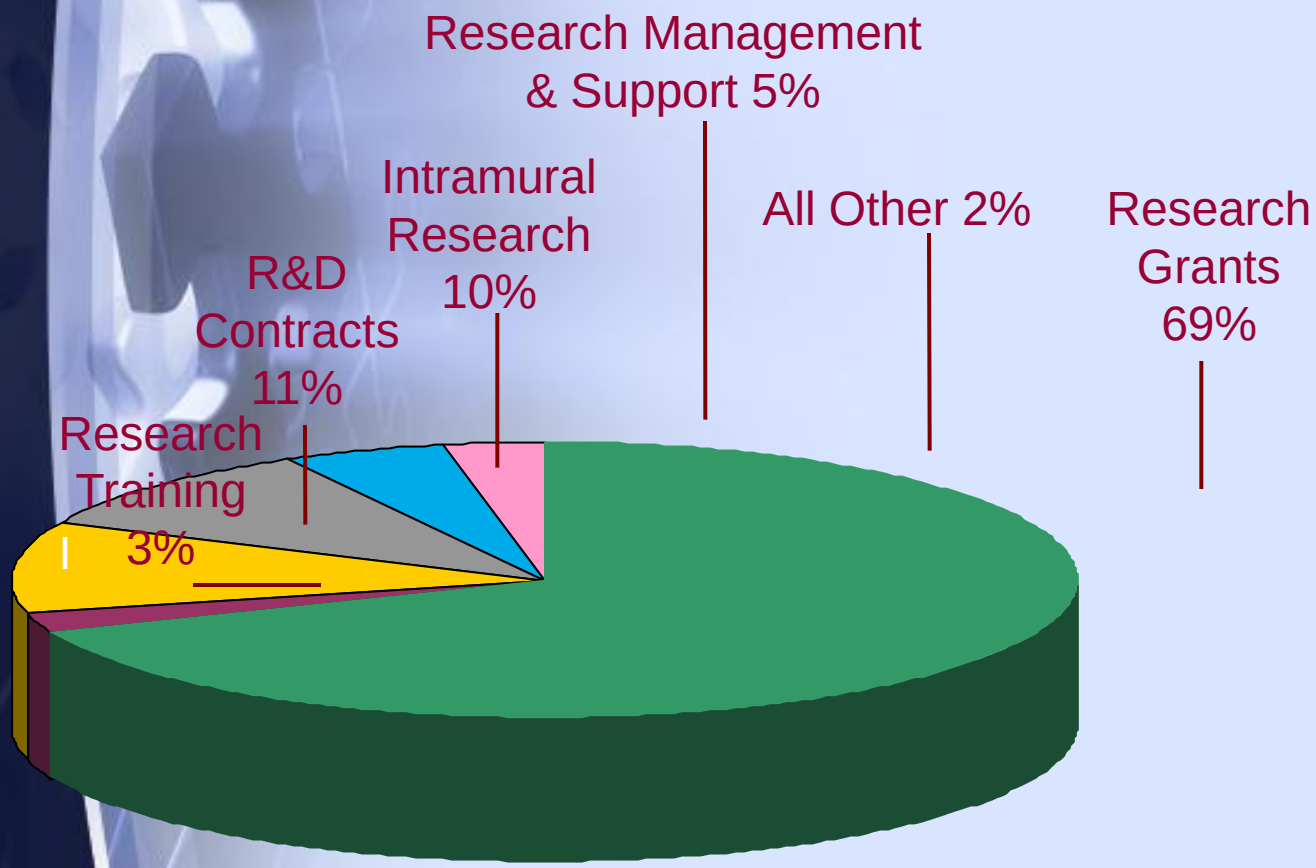
- SDs assign funds for high-impact, long-term, innovative research--Board of Scientific Counselors review process emphasizes this
- Emphasis on rigorous retrospective peer review
- Ability to build and support stable infrastructure (i.e., facilities and equipment)
- Research risk mitigated by optimizing research support
- New directions and research areas are common, easy to do and encouraged

Distinguishing Features of Intramural Research

- Bedside to Bench to Bedside in the Clinical Center--close proximity of lab and clinical investigators
- Scientific leaders interact directly with PIs
- Researchers focus on research and mentoring, not on grant proposals
- Emphasis on post-doctoral rather than graduate training
- Financial conflicts of interest minimized by government ethics rules

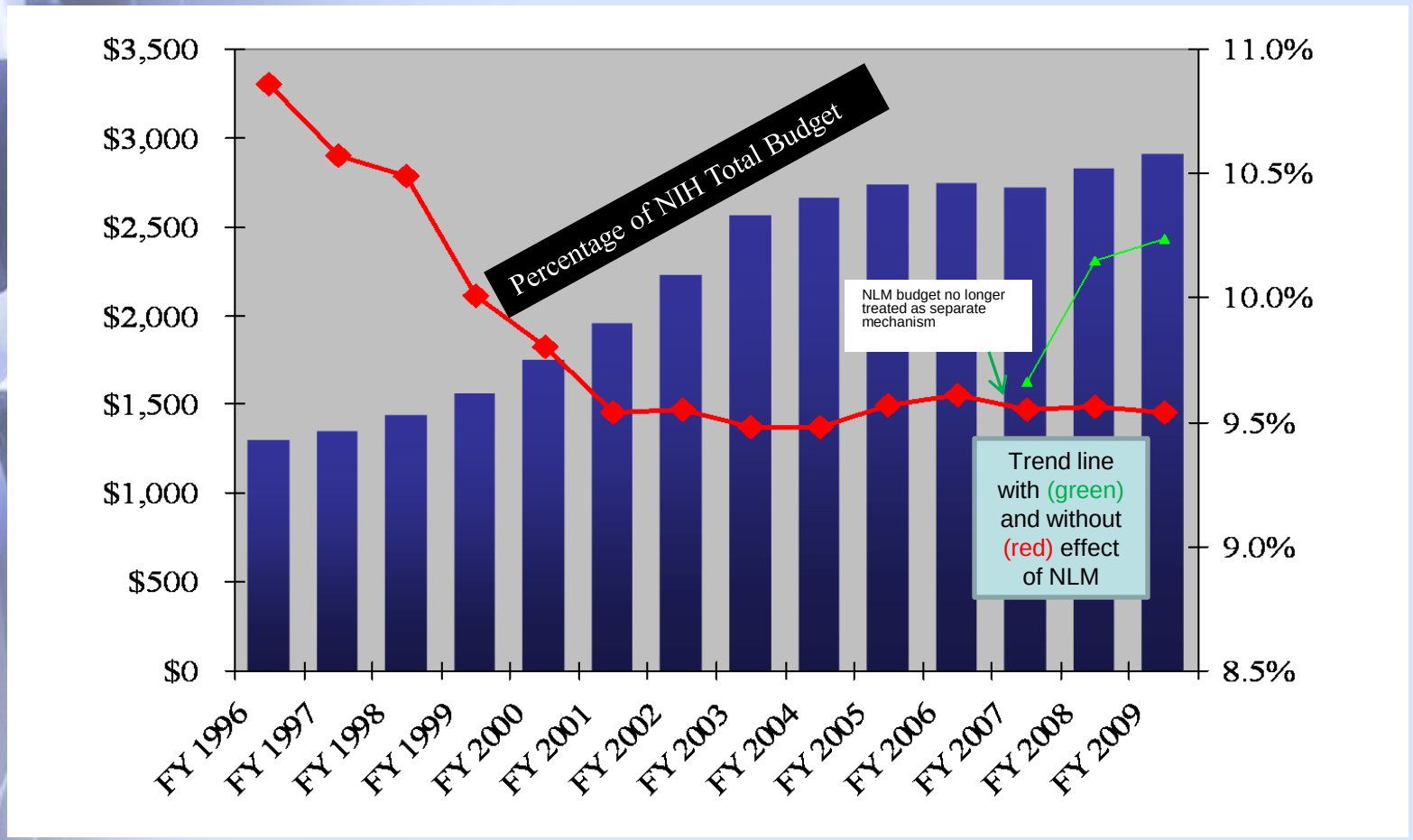
National Institutes of Health

FY 2009 Enacted $30.6 billion

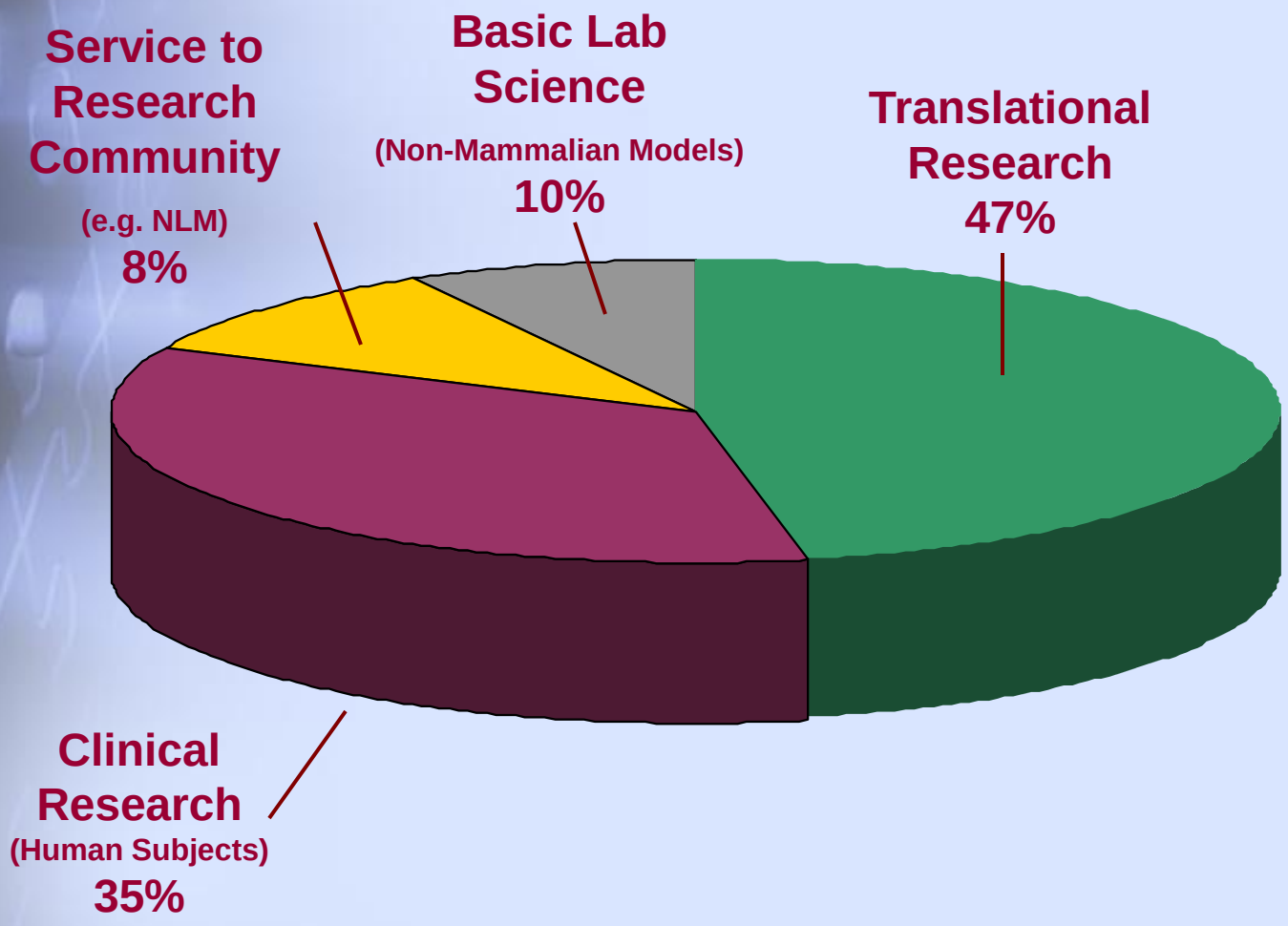


Over 80% of NIH funds support extramural research

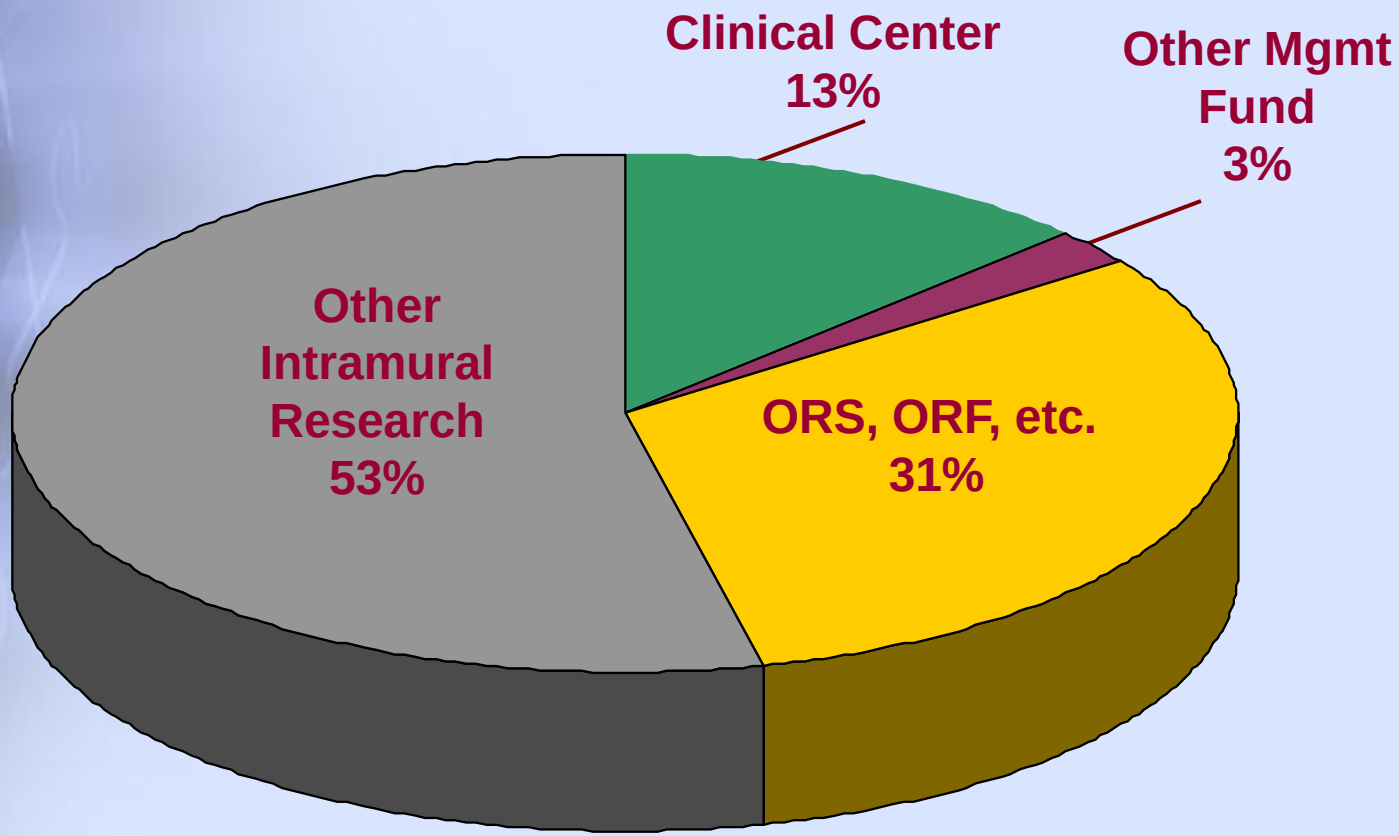
Intramural vs. Total NIH Funding over Time (FY 1996-2009)



Approximate Distribution of NIH Intramural Resources by General Subject Area



Distribution of Intramural Budget by Accounting Categories—FY 2008



Managing with Flat Budgets, FY 2004-FY 2009

- Rising administrative and personnel costs mean research operating budgets are a smaller percentage of total
- Ongoing dollar stretching exercises result in increased operating efficiencies
- Healthy turnover of PIs with approx. 300 leaving NIH in past 5 years and 180 new hires
- Trans-NIH initiatives to encourage shared resources and stimulate innovation

Trans-NIH Scientific Initiatives

- Imaging: molecules to man (lead NIBIB)
- Center for Human Immunology (lead NHLBI)
- Systems Biology (leads NCI, NIAID, NHLBI, NIDDK)
- Stem cells (hES and iPS, adult bone marrow mesenchymal)(leads NINDS, NIDCR)
- Undiagnosed diseases program (lead NHGRI)

- Epigenomics
- Biomarkers
- Intramural AIDS targeted anti-viral program
- Biodefense
- Bench-to-bedside proposals

Challenges and Goals

1. In concert with the NIH leadership, refine the mission and vision of the Intramural Research Program
2. Build a translational research continuum from laboratory, to target validation and pre-clinical pharmaceutical development, including animal models, to early phase clinical research
3. Maintain the preeminence of the NIH Clinical Center and increase productive intramural-extramural interactions in translational and clinical research areas
4. Establish and encourage new trans-NIH initiatives to leverage talent and resources across the NIH Institutes and Centers
5. Change demographics and enhance the diversity of scientists and trainees at the NIH

Questions for the SMRB about the Clinical Center

- **Can we create a business model that makes the CC viable for the foreseeable future?**
- **How can we align the research requirements of the intramural research program with the new business model for the CC, and encourage intramural-extramural interactions?**

The NIH Clinical Center

NIH Scientific Management Review Board
April 28, 2009

John I. Gallin, M.D.
Director, NIH Clinical Center

Outline

- **Overview**
- **Key Challenges**

CC Vision

**As America's research hospital,
we will lead the global effort
in training today's investigators
and discovering tomorrow's cures.**

The NIH Clinical Center Profile

- More than 350,000 patients since opening in 1953; currently follow ~86,000 patients
- A national hospital
- 234 beds
- 1,850 CC employees and ~4,000 IC employees
  - 1,222 credentialed MDs
- 1,449 active protocols

“There’s No Other Hospital Like It” So What Makes Us Different?

- **Every patient is enrolled on a protocol**
- **Care is free**
- **Highly educated nurses familiar with clinical research**
- **A hospital surrounded by research labs with gifted investigators**
- **1st in human clinical trials**
- **Unique cohorts of patients with rare diseases**
- **Long term and high intellectual/economic risk studies**
- **Rapid response to public health emergencies and scientific opportunities**

Selected Accomplishments

- Chemotherapy and immune therapy for cancer
- 1st platelet transfusions; 1st continuous flow blood cell separator
- Lithium for bipolar disorders
- Blood tests for AIDS, hepatitis
- 1st gene therapy (ADA Deficiency)
- Pathogenesis and treatment of AIDS
- 1st fluoride gels to treat dental caries as an infectious disease
- Cardiac MRI for chest pain to identify high vs low-risk pts.
- Technology for human papilloma virus vaccine
- PET scans to clarify some abnormalities in schizophrenia

Specialized Services and Facilities

- GMP facility for producing candidate drugs
- Imaging equipment
  - 3 cyclotrons
  - MRI center
- Biomechanics laboratory
- Blood products; stem cell
- IT Tools for clinical resea
  - ProtoType
  - BTRIS
- Phenotyping

Multi-modality minimally-invasive procedural suite

Alex Witchel: Rupert Everett, Out and About Jon Mooallem: The Great Whooping-Crane Con

The New York Times Magazine

FEBRUARY 22, 2009

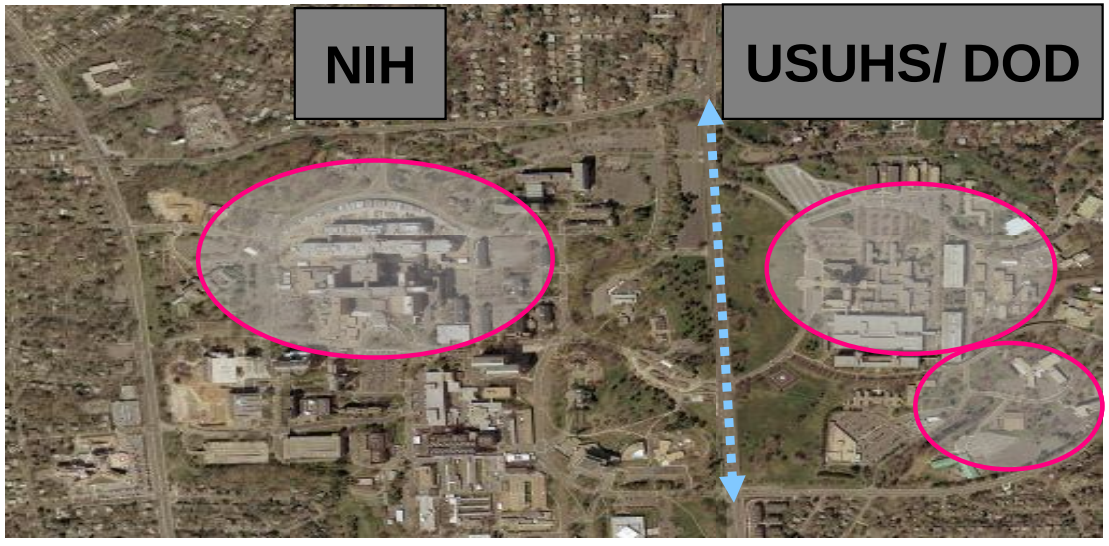
The Medical Detectives

Some patients have spent their lives suffering from mysterious diseases that no one can conclusively diagnose. A team of N.I.H. researchers is working against time to find answers where other doctors are not equipped to go. BY ROBIN MARANTZ HENIG

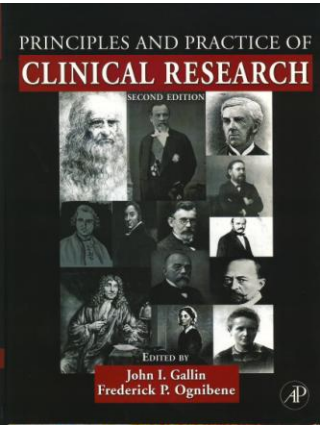
TBI/PTSD Initiative-2009

Partnership with USUHS & DOD

- **$70M**
  - **~$8.8M expected to CC**
    - **~$800K Rehab Med**
    - **~$8M Radiology**
- **Soldier and civilian participants**

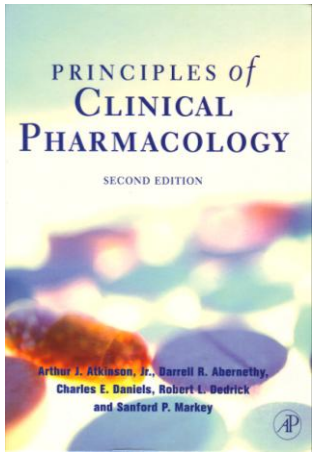


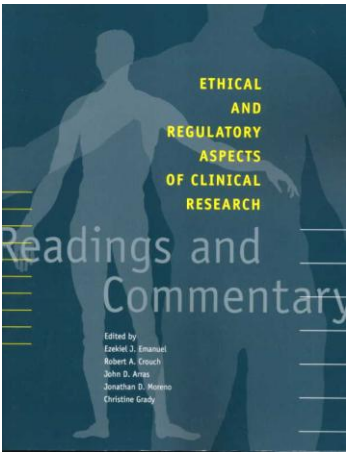
NIH Training Curriculum In Clinical Research



Introduction to the Principles & Practice of Clinical Research
>7,600 participants since course introduced in 1995

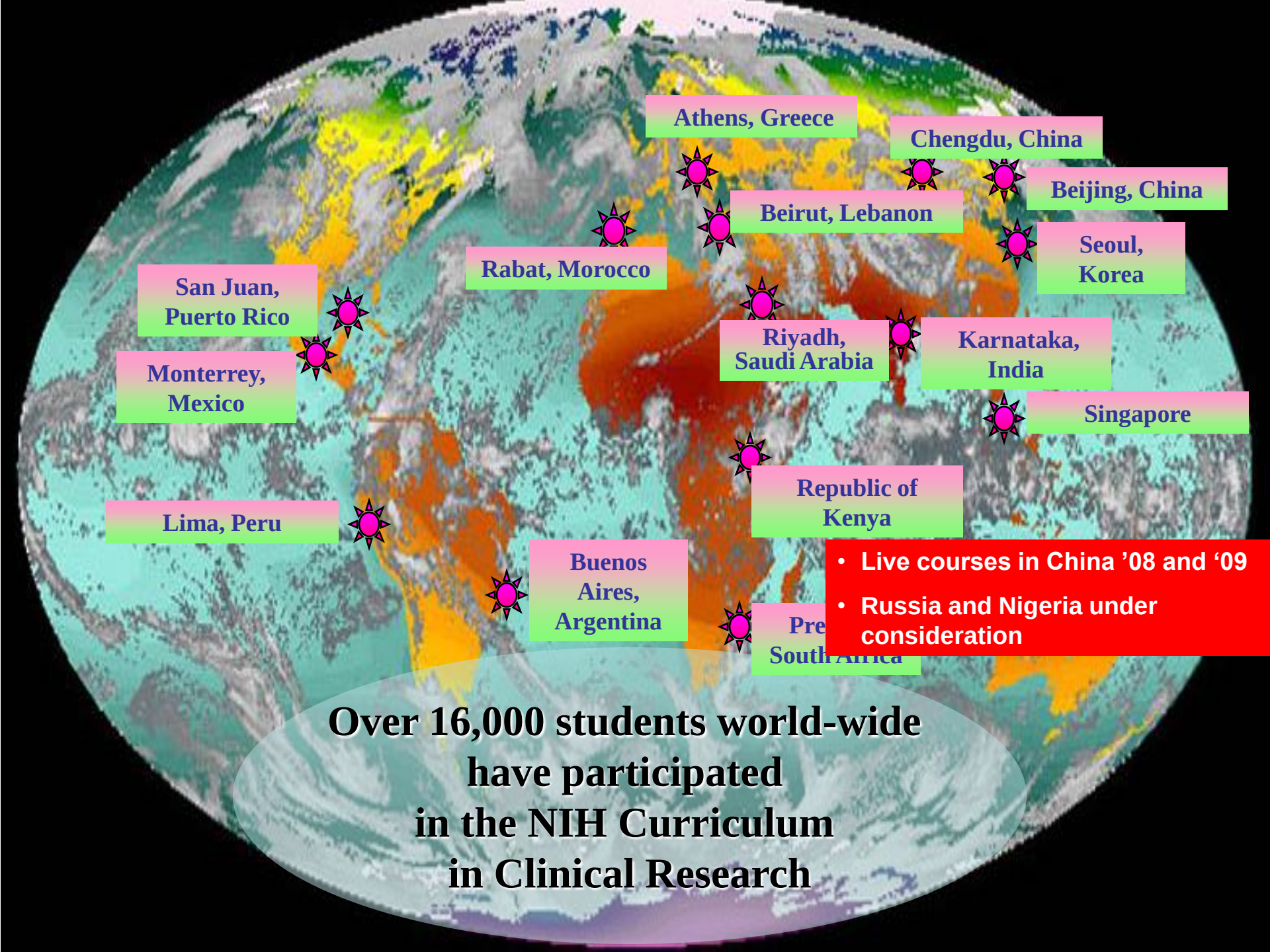
Principles of Clinical Pharmacology
>4,500 registrants since course began in 1998





Ethical and Regulatory Aspects of Human Subjects Research
>3,400 participants since course began in 1999

April 2009


Athens, Greece
Chengdu, China
Beijing, China
Beirut, Lebanon
Seoul, Korea
Rabat, Morocco
San Juan, Puerto Rico
Riyadh, Saudi Arabia
Karnataka, India
Monterrey, Mexico
Singapore
Republic of Kenya
Lima, Peru
Buenos Aires, Argentina
• Live courses in China ’08 and ‘09
• Russia and Nigeria under consideration
Over 16,000 students world-wide have participated in the NIH Curriculum in Clinical Research

2009 Training Initiatives to Support Extramural AHCs

- **Sabbatical in clinical research management**
- **Inventory and build virtual clinical research "university" within CTSA network**

Barrier: Prohibition of co-mingling intramural and extramural $

Bench-to-Bedside Awards Promote Intramural/Extramural Partnerships

$4.5 M/year from:

- **NIH offices/centers**
- **FDA**
- **intramural programs**

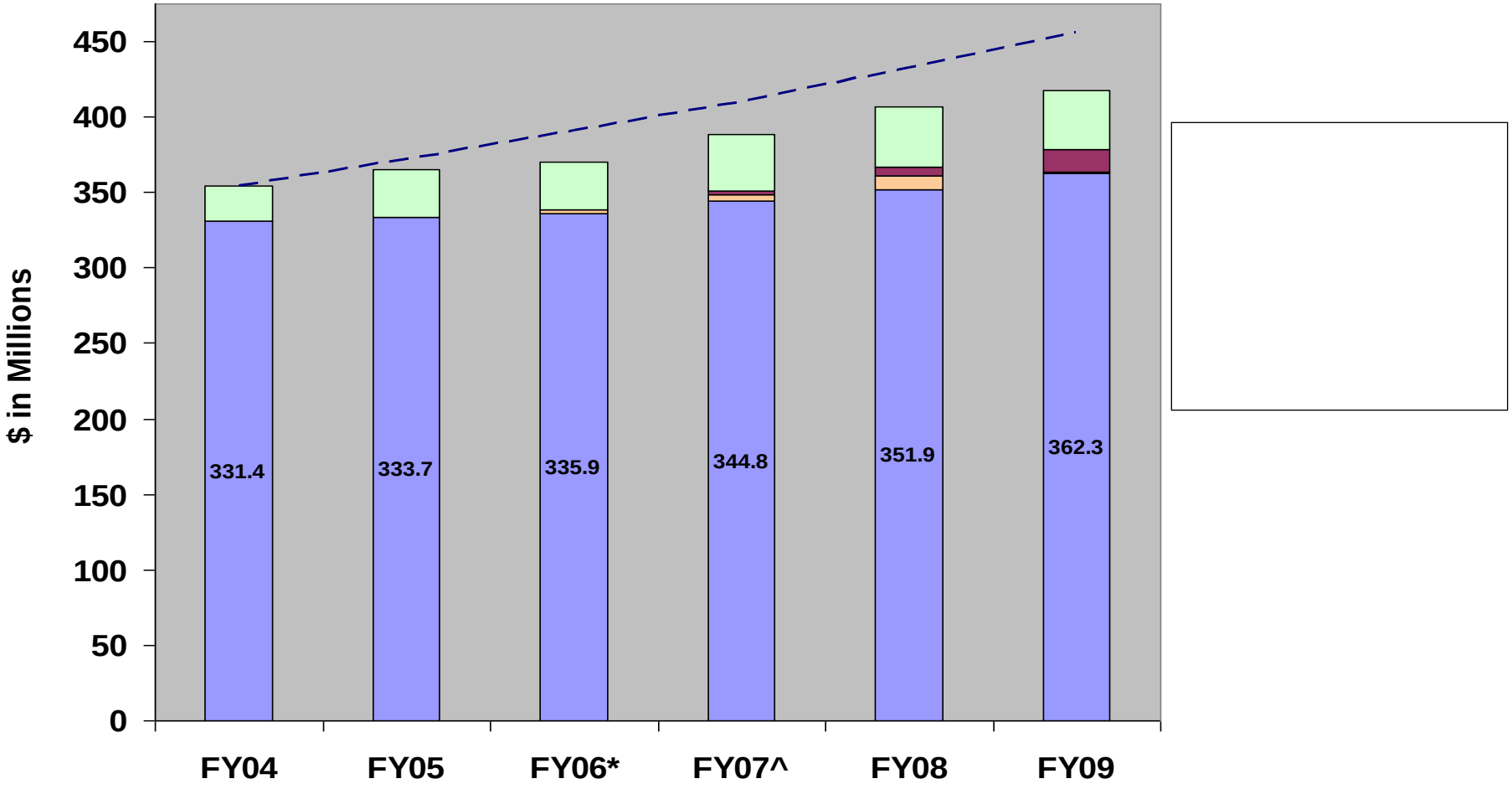
- **Supports ~17 awards/year; 47 AHC partnerships**

Next Steps: Secure stable long-term funding

The Key Challenges

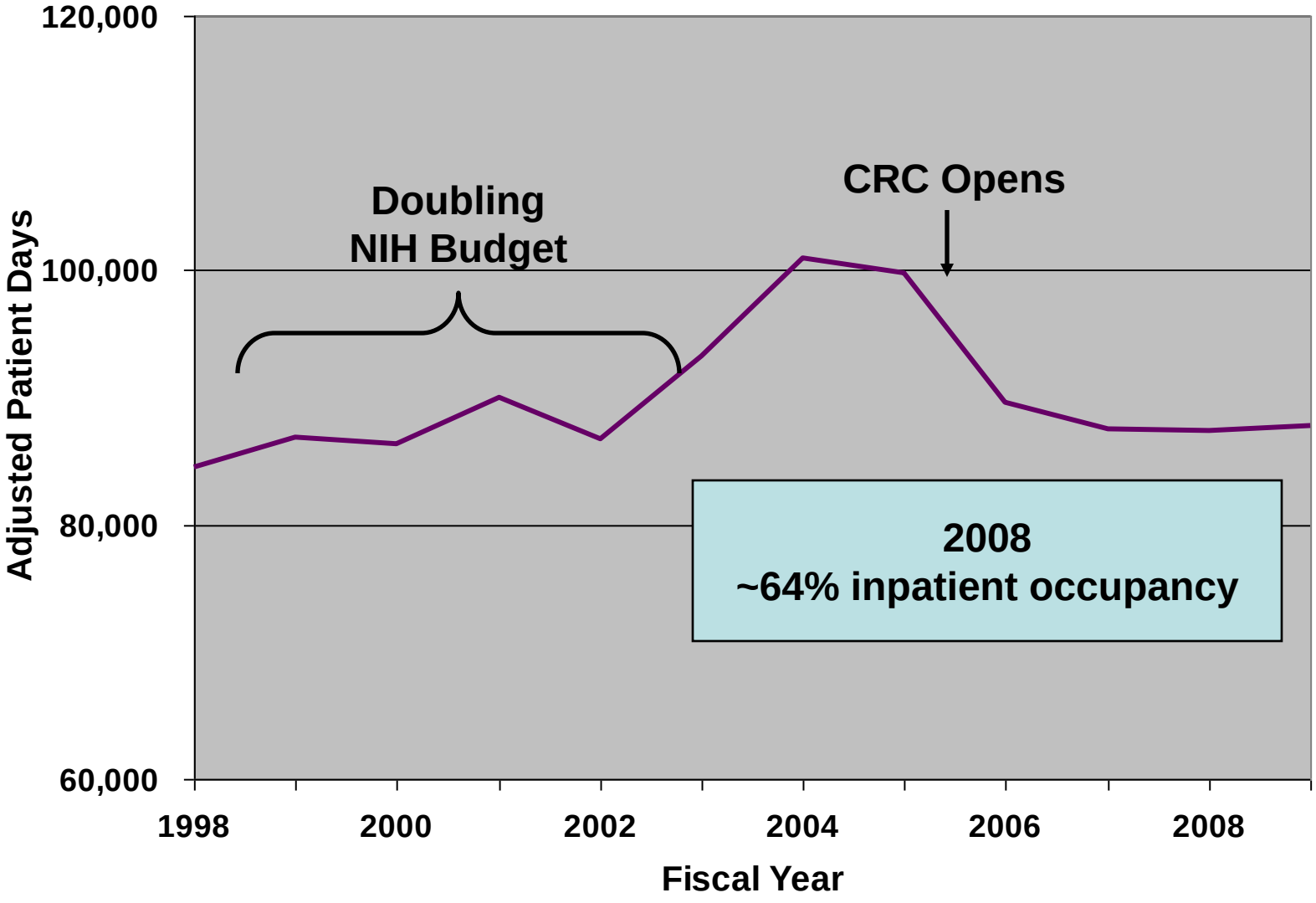
- **Budget**
- **Patient Activity**
- **Protocol Activity**
- **PIs**

CC Budget FY 2004-FY 2010



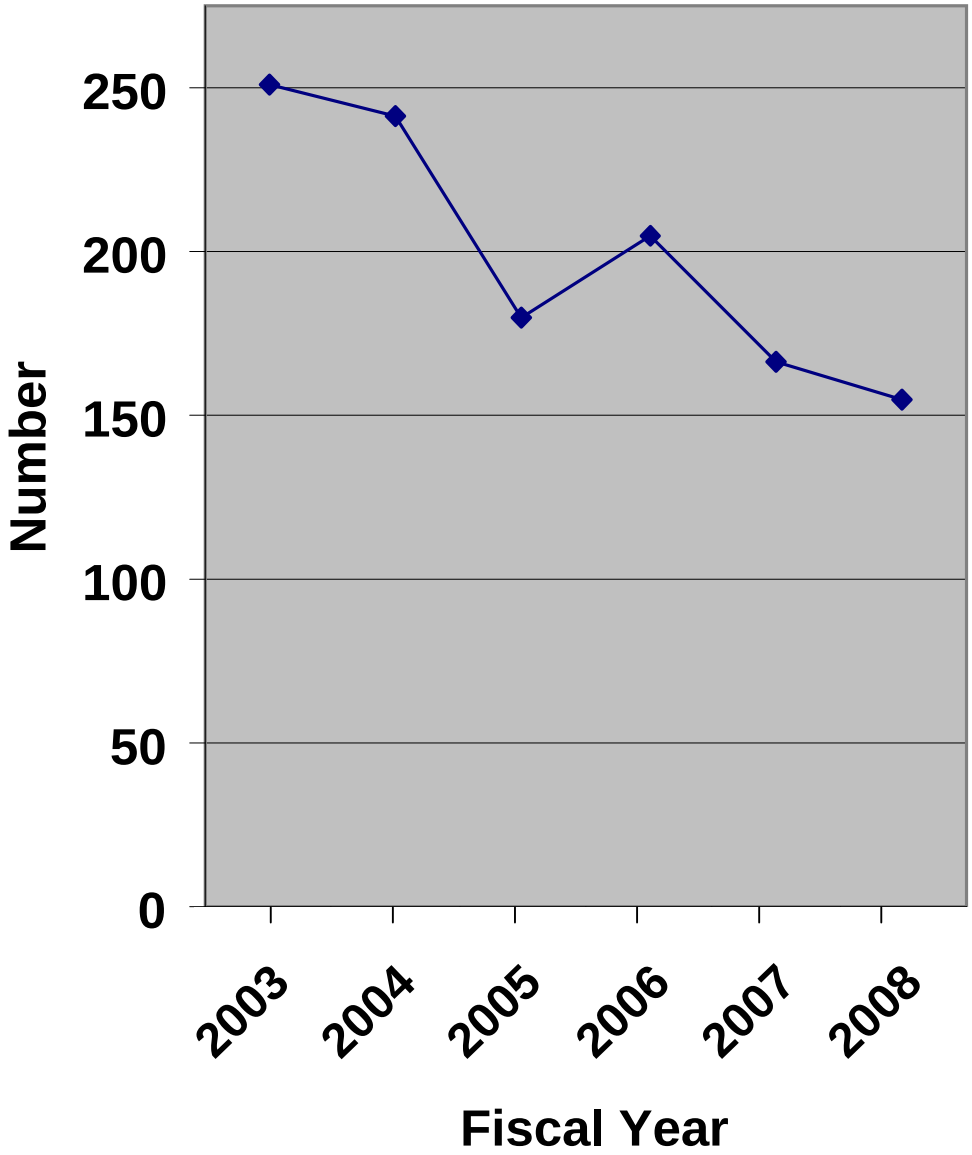
*FY06 includes budget neutral adjustments for security ($2.2M) and NIBIB transfer (-$1.5M).
^FY07 includes budget neutral adjustment for CRIS ($6.5M)
Hospital inflation rate source: R-C Healthcare Management (Feb 12, 2008)/HFMA

Adjusted Patient Days*
(FY 1998 – 2009)

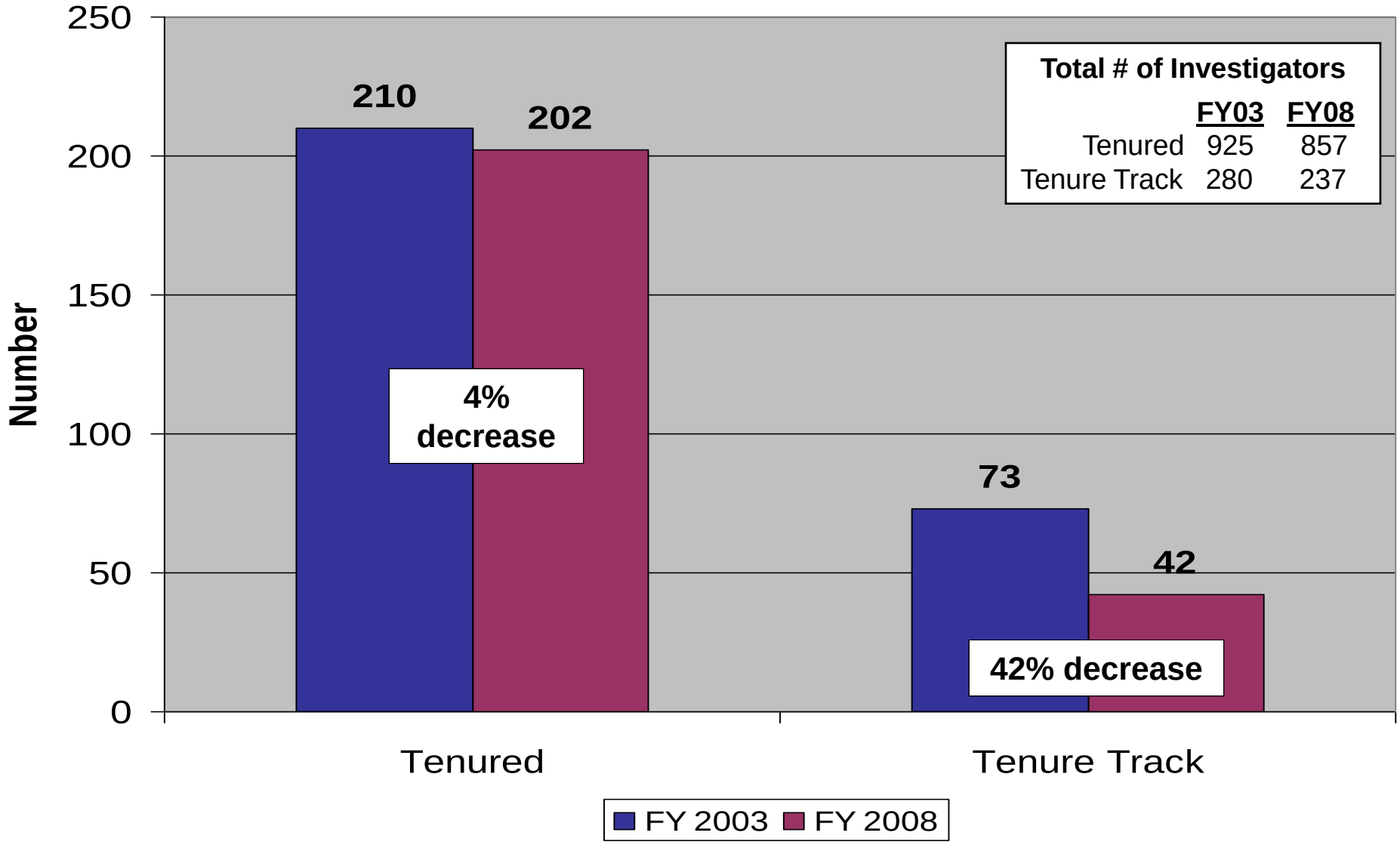


* Adjusted Patient Days = Inpatient Days + (Outpatient Visits x 0.4)

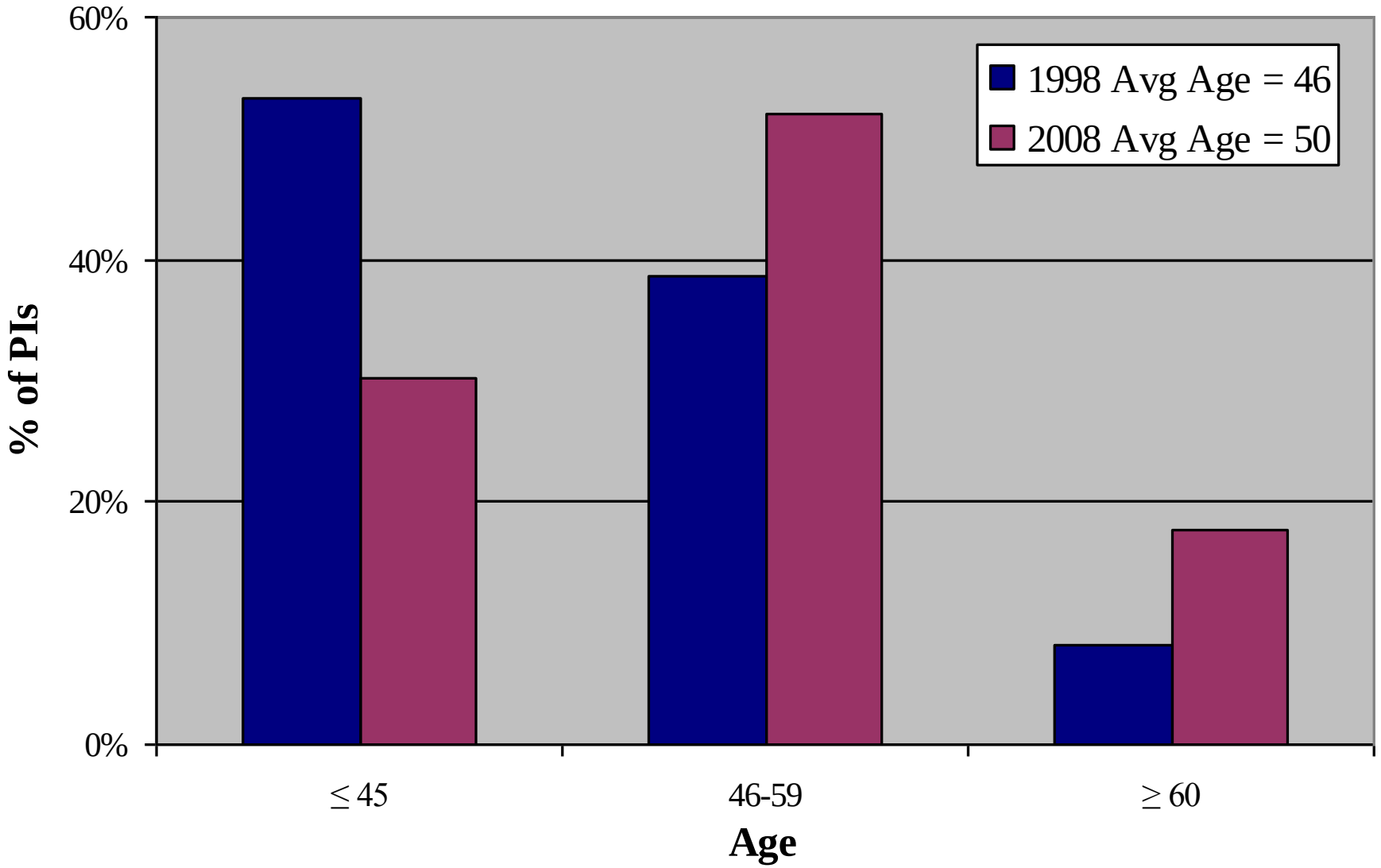
New Research Protocols



PIs on Clinical Protocols



Aging of Clinical PIs



Recruitment Challenges

- **Conflict of interest**
- **Expensive housing/childcare**
- **Salaries**

Summary

Key Challenges

- **Budget – 5 yr. relatively flat; prohibition of co-mingling intramural and extramural $**
- **Patient Activity – untapped capacity**
- **Protocol Activity – # new protocols ↓**
- **Principal Investigators – ↓ tenure track; aging; recruitment challenges**

Opportunity

- **Strong infrastructure for clinical research, model for the nation, opportunity for future accomplishments**

Questions for the SMRB about the Clinical Center

- **Can we create a business model that makes the CC viable for the foreseeable future?**
- **How can we align the research requirements of the intramural research program with the new business model for the CC, and encourage intramural-extramural interactions?**

SMRB Next Steps

- **Proposal to form working group on "Deliberating Organizational Change"**
- **Decisions on whether to deliberate:**
  - **Science of Substance Use, Abuse, and Addiction and the roles of NIDA and NIAAA**
  - **NIH Intramural Research Program and its Clinical Center**
- **Future meetings**
  - **Series of "foundational briefings"**
  - **Workgroup teleconferences and roundtables: Summer/Early Autumn**
  - **Full SMRB meeting: October/November**
- **Website under construction for committee working documents**

Deliberating Organizational Change Workgroup DRAFT Charge

- **The Deliberating Organizational Change (DOC) workgroup of the SMRB would be convened to provide input to the full SMRB on:**

  1. **How a national biomedical research enterprise could be organized *de novo* today to optimize scientific advances and address public health needs;**
  2. **How the organizational strategies identified in item (1) may need to be adapted in considering the structure of NIH given the agency's substantive historical evolution and existing organization;**
  3. **Fundamental principles and strategies for contemplating, implementing, and evaluating the consequences of changes in the organization of the nation's biomedical research enterprise.**

Deliberating Organizational Change Workgroup DRAFT Charge

- ***In addressing these aims, the DOC workgroup will consider:***
  - **Scientific opportunities, public health needs, and new research technologies**
  - **Circumstances motivating organizational change**
  - **Likelihood of intended results following organizational change**
  - **Measures used to optimize implementation of organizational change**
  - **Metrics for evaluating successes and any untoward consequences of organizational change**

QUESTION

- **Does the SMRB wish to form a Deliberating Organizational Change Workgroup that could gather information and data as well as draft overarching principles for consideration by the entire Board ?**

SMRB Next Steps

- **Proposal to form working group on "Deliberating Organizational Change"**
- **Decisions on whether to deliberate:**
  - **Science of Substance Use, Abuse, and Addiction and the roles of NIDA and NIAAA**
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- **Website under construction for committee working documents**

QUESTION

- **Does the SMRB wish to consider whether changes within NIH could further optimize research into substance use, abuse, and addiction?**

QUESTION

- **Does the SMRB wish to consider whether any changes to the NIH Clinical Center and/or the NIH Intramural Research Program could further optimize the opportunities available in a central research program at NIH?**

SMRB Next Steps

- **Decisions on whether to deliberate:**
  - **Science of Substance Use, Abuse, and Addiction and the roles of NIDA and NIAAA**
  - **NIH Intramural Research Program and its Clinical Center**
- **Future meetings**
  - **Series of "foundational briefings"**
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Overarching Initial Goals of Potential Briefings

- **Equip SMRB with overview and data regarding NIH's strategies and tools for:**
  - **Staying abreast of emerging areas of science/scanning scientific horizon**
  - **Analyzing whether portfolio is responsive to current and emerging scientific opportunity and public heath needs**
  - **Assessing short and long-term outcomes of NIH funded research**
  - **Analyzing effects of polices and funding mechanisms on sustainability of a vibrant and cutting edge scientific workforce**
  - **Coordinating and collaborating with other Federal agencies to enhance the application of biomedical science in addressing public health needs**

SMRB Next Steps: Potential General Briefing Topics

- **Agency Capacity for Analysis and Evaluation of Scientific Enterprise:**
  - **NIH Portfolio Analysis: Strategies, Mechanisms and Processes**
  - **Outcome Analysis: Conceptual framework, mechanisms, and metrics for assessing short and long-term outcomes of NIH funded research**
- **Fostering Interdisciplinary Science**
  - **Capacity of Current paradigm for peer review and funding mechanisms to foster interdisciplinary science**
  - **Criteria and processes for making decisions regarding the Common Fund**
  - **Other mechanisms that ICs use to coordinate and collaborate on scientific opportunities and public health needs that transcend the mission of any single IC**

SMRB Next Steps: Potential General Briefing Topics

- **Development of Scientific Workforce**
  - **Shifting demographics of scientific workforce and any implications for regeneration of scientific leadership in the future**
  - **Tenure policies for intramural investigators**
- **Legal and policy framework for SBIR grants**
- **Trans-Federal coordination and collaboration**
  - **Goals, mechanisms and processes for enhancing the application of biomedical science in addressing public health needs**
- ***Other potential topics? (ideas from SMRB members and public)***

SMRB Next Steps

- **Future meetings**
  - **Series of "foundational briefings"**
  - **Workgroup teleconferences and roundtables: Summer/early Autumn**
  - **Full SMRB meeting: October/November**
- **Website under construction for committee working documents**