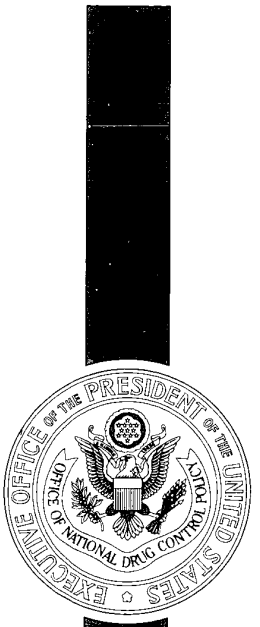

Proceedings

The 1995 ONDCP International Workshop: Drug Abuse Treatment Technology

August 15–16, 1995

Baltimore, Maryland

Sponsored by

Executive Office of the President

Office of National Drug Control Policy

Counterdrug Technology Assessment Center

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Introduction

The Office of National Drug Control Policy (ONDCP) is pleased to have hosted this First International Workshop on Drug Abuse Treatment Technology. The workshop was organized by the Counterdrug Technology Assessment Center (CTAC) to promote technical information exchange on current issues and developing opportunities in advancing technologies for drug abuse treatment and prevention. Attendees to this workshop were drawn from the demand reduction, drug abuse treatment, and associated law enforcement communities.

Demand reduction of illicit drugs incorporates the disciplines of biochemistry, psychology, physiology, and social sciences to improve drug abuse detection and therapeutic treatment for drug users within the law enforcement and criminal justice processes. Workshop presentations explored the effective application of innovative technology to all aspects of drug abuse treatment and prevention. Promising areas of associated research and applied drug abuse treatment technology were highlighted in two separate workshop panel presentations.

The Innovative Treatment Approaches panel focused on current and emerging developments in drug immunization and treatment research and applications within the criminal justice processes. Several new technical approaches were presented. Among these, an interim report by a Columbia University research team described how artificial enzymes could be employed to provide catalytic antibodies that destroy cocaine molecules in the bloodstream before they reach the brain. Other panelists discussed the medical, legal, and ethical issues raised by the application of such technology within the law enforcement and criminal justice systems.

The Drug Testing/Monitoring Technology panel considered current and emerging developments for the noninvasive detection of illicit drug use through the analysis of hair, sweat, urine, and saliva. The presentations described the employment of advanced analytic technology for detecting drug use within the respective matrices to extend the window of detection and provide more effective drug abuse testing. Several field testing activities were described, including the interim results from an ongoing study of first-time offenders in the New Orleans Parish, Louisiana.

These proceedings contain the record of those technical presentations provided by the participants on the two workshop panels.

ONDCP and CTAC gratefully acknowledge the excellent technical contributions provided by the various panelists at this workshop, as well as the thoughtful and useful comments developed by the many workshop participants attending these presentations. An incredible wealth of information was shared among the attendees and has been taken back to their respective communities in criminal justice, industry, and academia.

Dr. Albert E. Brandenstein
Office of National Drug Control Policy
Counterdrug Technology Assessment Center
November 1995

Overview

Exploring New Paradigms for Substance Abuse Treatment

The Counterdrug Technology Assessment Center (CTAC) of the Office of National Drug Control Policy (ONDCP) sponsored a technical workshop on drug abuse treatment technology on August 15 and 16, 1995, at Baltimore, Maryland. Experts in the field gathered to discuss the latest in innovative treatment approaches and drug testing technology. The workshop began with some sobering facts from the Maryland Secretary of Public Safety and Correctional Services Bishop Robinson and Assistant Baltimore Police Commissioner Leon Tomlin on the adverse effects substance abuse has on our community. For the past 20 years, they have seen crime increase tenfold, entire neighborhoods destroyed, and new prisons become overcrowded before they can be completed. It is time to find the cure rather than only treat the symptoms.

World-class experts, such as Dr. Alan Leshner, Director of the National Institute on Drug Addiction (NIDA), Dr. Herbert Kleber, Center for Addiction and Substance Abuse, and Dr. Jerome Jaffe, Department of Health and Human Service, then guided technical discussion on the nature of drug addiction and the latest breakthroughs in technology for the treatment of substance addiction.

Dr. Leshner set the central theme for the gathering with NIDA's goal to "replace *ideology* in the treatment of drug addiction with *science* by the year 2000." A review of the CTAC-sponsored research program focused the workshop on some opportunities for using advancements in science and technology to improve our drug abuse treatment programs. While many differing approaches were expressed, one common problem among *all* researchers was the lack of relevant clinical data to support their research.

For example, CTAC's project with NIDA's Addiction Research Center will provide a state-of-the-art brain scanning facility and radiochemistry laboratory dedicated to measuring the interaction of cocaine and other drugs of abuse with neuroreceptors in the brain. CTAC also sponsors a project called the Drug Evaluation Network (DENS) to link treatment centers and research facilities on a common computer network. Both of these projects will increase the availability of and expand access to relevant clinical data for researchers *and* treatment providers alike. CTAC's plans for next year include establishing a node on the DENS network to serve as a "model" treatment center.

In the area of innovative treatment approaches, Dr. Donald Landry, from the Columbia University College of Physicians and Surgeons, discussed progress on a CTAC-sponsored project to develop artificial enzymes as a therapeutic drug to "immunize" addicts against cocaine. The highly specific catalytic antibodies bind with the cocaine molecules in the bloodstream and deactivate the cocaine before it reaches the brain. An immunization drug would have the potential to render the cocaine serum levels in the blood stream harmless for up to 6 months per treatment.

To complement Dr. Landry's work, CTAC is exploring new ideas for agonists to *replace* abused drugs in the brain or antagonists to *block* drugs in the brain. This year, CTAC expects to begin developing cocaine agonists and antagonists.

Breaking the Cycle

The second day of the workshop went beyond treating drug effects and addressed the entire spectrum of factors known to contribute to drug dependence and abuse: social, environment, employment, family, and physiological. It was shown that the highest success was achieved from in-patient treatment programs where all aspects of the patient's environment were controlled. Since everyone cannot and does not enroll in an in-patient regime, the importance of having noninvasive means to remotely monitor and test patients for relapse was stressed.

For improving noninvasive drug testing and monitoring, a CTAC project with the Jet Propulsion Laboratory uses technology previously developed by NASA to monitor an astronaut's bodily functions in space to remotely monitor the sweat and hair of parolees and inmates for signs of drug abuse. The New Orleans District Attorney's Office described its Diversionary Program for first-time offenders and how it is being used in conjunction with CTAC's efforts to serve as a "testbed" for evaluating new appliques for drug monitoring and testing as they are developed.

In all, the technical workshop was a success and focused the resources of our corrections officers, research scientists, and treatment professionals on exploring those improved drug treatment opportunities available from advancements in technology. The broader spectrum of the underlying causes of drug dependence and abuse is now understood by those scientists and researchers who can make a difference.

Dr. Albert E. Brandenstein
Office of National Drug Control Policy
Counterdrug Technology Assessment Center
November 1995

Opening Presentation

New Approaches to Understanding Drug Abuse

Dr. Edythe London
National Institute for Drug Abuse (NIDA)

Positron Emission Tomography Research - Demand Reduction

Efforts to reduce the demand for illicit drugs of abuse require knowledge of the biological mechanisms that support addiction. Because drug abuse is a chronic disease of the brain, identification of long-term neurochemical abnormalities in affected individuals can help target the development of effective therapeutic agents. The Counterdrug Technology Assessment Center, ONDCP has therefore initiated a research program to use positron emission tomography (PET) scanning, a noninvasive nuclear medicine procedure, to assay brain function in individuals who suffer from addictive disorders and normal control volunteers in order to delineate abnormalities in brain function that are associated with addiction. Scientists at the Intramural Research Program of the National Institute on Drug Abuse (NIDA) are focusing on such differences in brain function with the use of PET and a radiolabeled tracer for measuring consumption of glucose by the brain. Regional rates of glucose metabolism can be mapped, and they provide an index of local brain function.

Persistent Abnormalities in Brain Function in Drug Abusers. In a recent study comparing the patterns of brain activity by PET, NIDA investigators have demonstrated that individuals with histories of polydrug abuse, including injection of heroin and cocaine, show abnormalities in brain function even when detoxified from illicit drugs of abuse. When compared with normal volunteers, matched for age, sex, and socioeconomic status, detoxified subjects who actively use illicit drugs of abuse show deficits of glucose metabolism in the visual association cortex in brain (Fig 1). It is not known to what extent this and other abnormalities in brain function of substance abusers predates or is a consequence of illicit drug abuse.

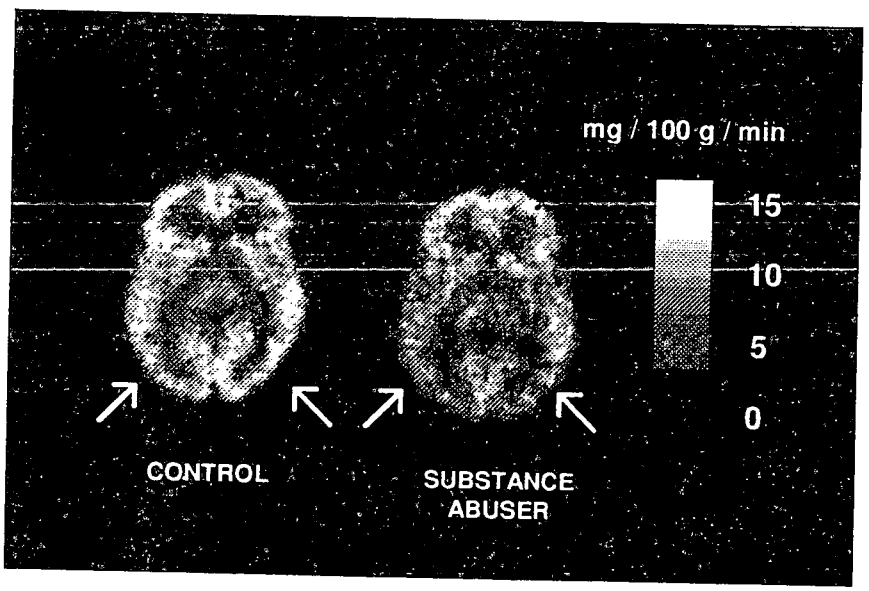


Figure 1: PET scans showing rates of glucose utilization (mg/100g/min) in a normal volunteer (left, control) and a participant with a history of polydrug abuse. Arrows indicate visual association area of the cortex. where the substance

Craving for Cocaine - A target for Therapeutic Intervention. Environmental stimuli that are regularly associated with drug use are thought to elicit behavioral and physiological responses that contribute to drug craving and, thereby, to the perpetuation of addiction. As curbing craving for cocaine has been identified as a target for therapeutic intervention, knowledge of the brain mechanisms that underlie craving is needed. NIDA investigators are addressing this problem by pairing PET scanning with self-report assessments in cocaine abusers during two experimental sessions. In one test session, neutral stimuli, including a videotape on arts and crafts, are presented. In another session, research volunteers are presented with a drug-related stimulus complex (videotape of cocaine-related activity, paraphernalia, and a small amount of cocaine). In subjects with a history of cocaine abuse, the cocaine-related stimuli produce craving, quantitatively reported by the subjects (Fig. 2). In the drug abusers, but not in normal volunteers, activity in cortical regions implicated in processing of memory is increased during the presentation of cocaine-related cues. Increases in the medial temporal lobe and the dorsolateral prefrontal cortex (Fig. 3), brain areas implicated in declarative memory, are correlated with self-reports of cocaine craving (Fig. 4). The findings indicate that a neuroanatomical network related to the processing of explicit memory links exposure to relevant environmental cues with the genesis of cocaine craving. Further studies are required to delineate the neurotransmitters responsible for linking the activation of these areas with the feeling of craving.

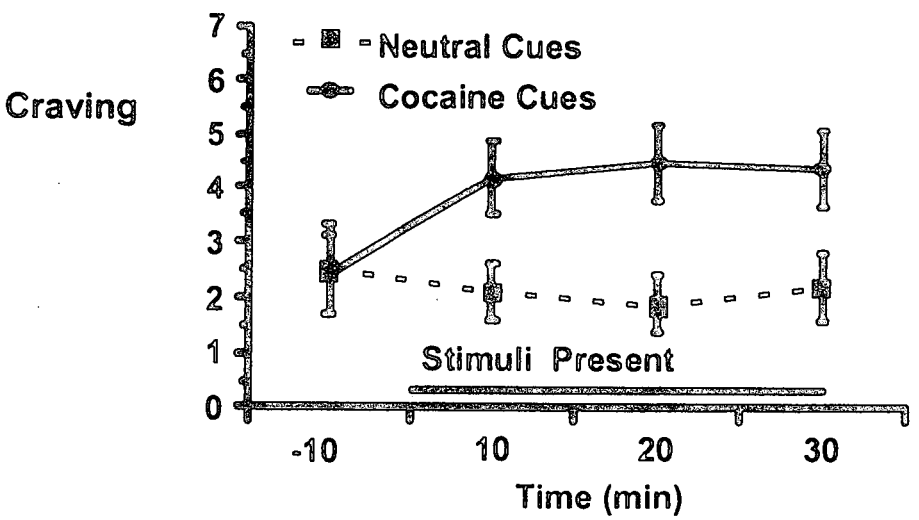


Figure 2: Self-reports of craving when research volunteers are presented with neutral or drug-related environmental stimuli. Human subjects who actively use cocaine report feeling craving when the cocaine-related stimuli are present.

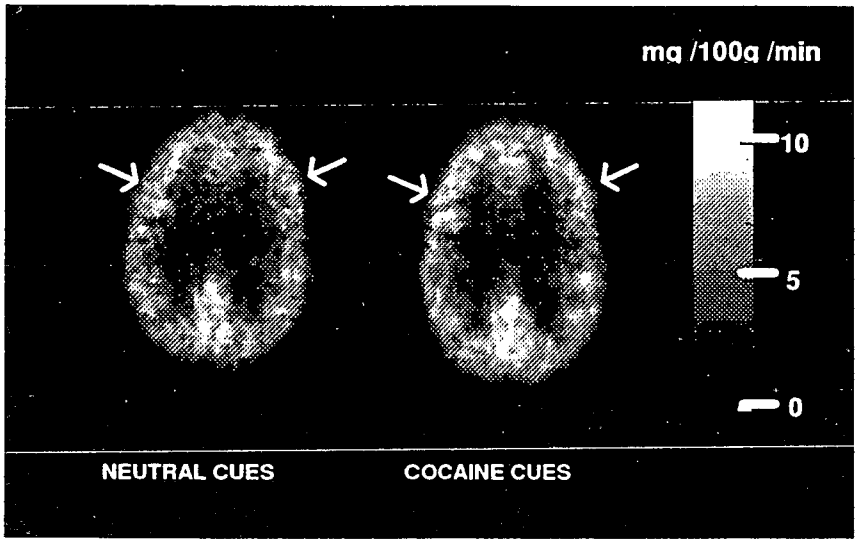


Figure 3. PET scans showing activation of the dorsolateral prefrontal cortex by cocaine-related cues. When human volunteers with histories of cocaine abuse were presented with cocaine-related cues, they reported craving for the drug and showed a stimulation of glucose utilization (mg/100 g/min) in the dorsolateral prefrontal cortex (arrows), a brain area involved in episodic memory.

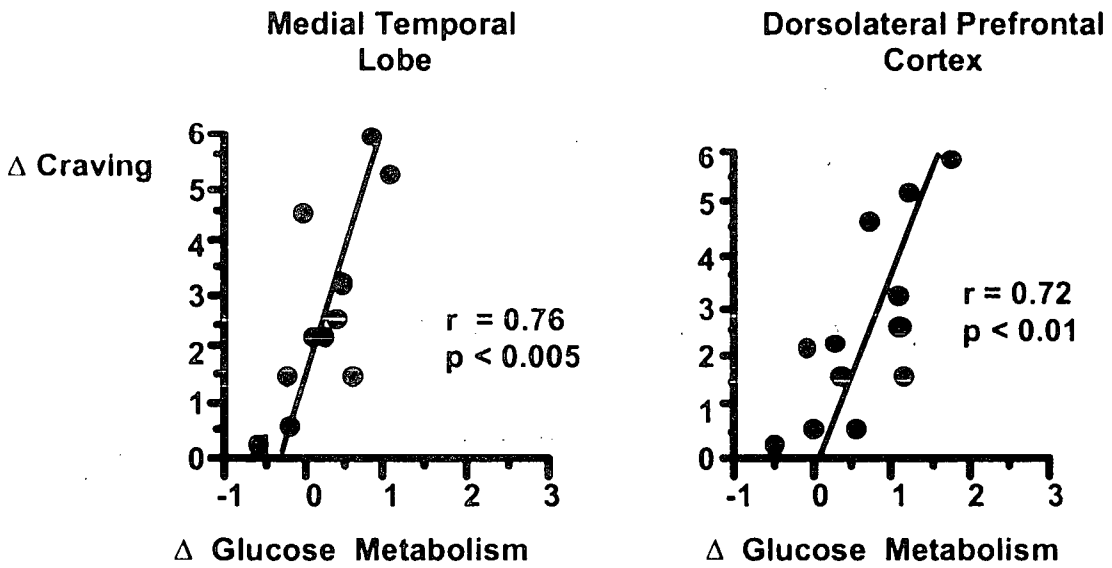


Figure 4. Correlation of craving with glucose utilization in medial temporal lobe and dorsolateral prefrontal cortex. Regression lines show the relationship between the change in craving and the change in regional brain activity in two test sessions (cocaine-related cues minus neutral cues). Brain activity was assessed as the rate of glucose utilization in individual brain regions, measured by PET. The change in activity in two regions important in episodic memory, the medial temporal lobe and dorsolateral prefrontal cortex, was highly correlated with craving.

Workshop I:
Innovative Treatment Approaches

163298

Innovative Treatment Approaches

Dr. Herbert Kleber
CASA/Columbia University

NATIONAL EVALUATION of SUBSTANCE ABUSE TREATMENT

Size of Problem

18,000,000 alcoholics/problem drinkers

2,000,000 cocaine addicts

750,000 to 1,000,000 heroin addicts

2,500,000 multi-drug, hallucinogens, inhalants, etc.

TOTAL (non-alcoholic) = 5.5 to 6 million in need of treatment

NATIONAL EVALUATION of SUBSTANCE ABUSE TREATMENT

Treatment (Drug)

Available: 600,000 "slots" that can treat 1,400,000 (approx) individuals per year

Needed: 1,000,000 "slots" to treat 2,500,000 individuals per year

Why the gap? Widespread belief that treatment doesn't work.

NATIONAL EVALUATION of SUBSTANCE ABUSE TREATMENT

Need for this Study

There is inadequate information on which substance abuse treatment modalities work and for which populations.

There is a reluctance on the part of policy makers, insurance companies and businesses to invest resources in treatment without clear evidence that shows what works and for whom.

NATIONAL EVALUATION of SUBSTANCE ABUSE TREATMENT

Study will Provide

National data that answers the questions:

How and why do different people come into treatment?

What services do they receive in treatment?

What are the outcomes of their treatment?

A study method that can be used as a national "scorecard" to monitor the effectiveness of all substance abuse treatment.

A pilot study of a computer-linked network of treatment programs that could provide data on treatment characteristics/efficacy on an ongoing basis.

NATIONAL EVALUATION of SUBSTANCE ABUSE TREATMENT

Methodology

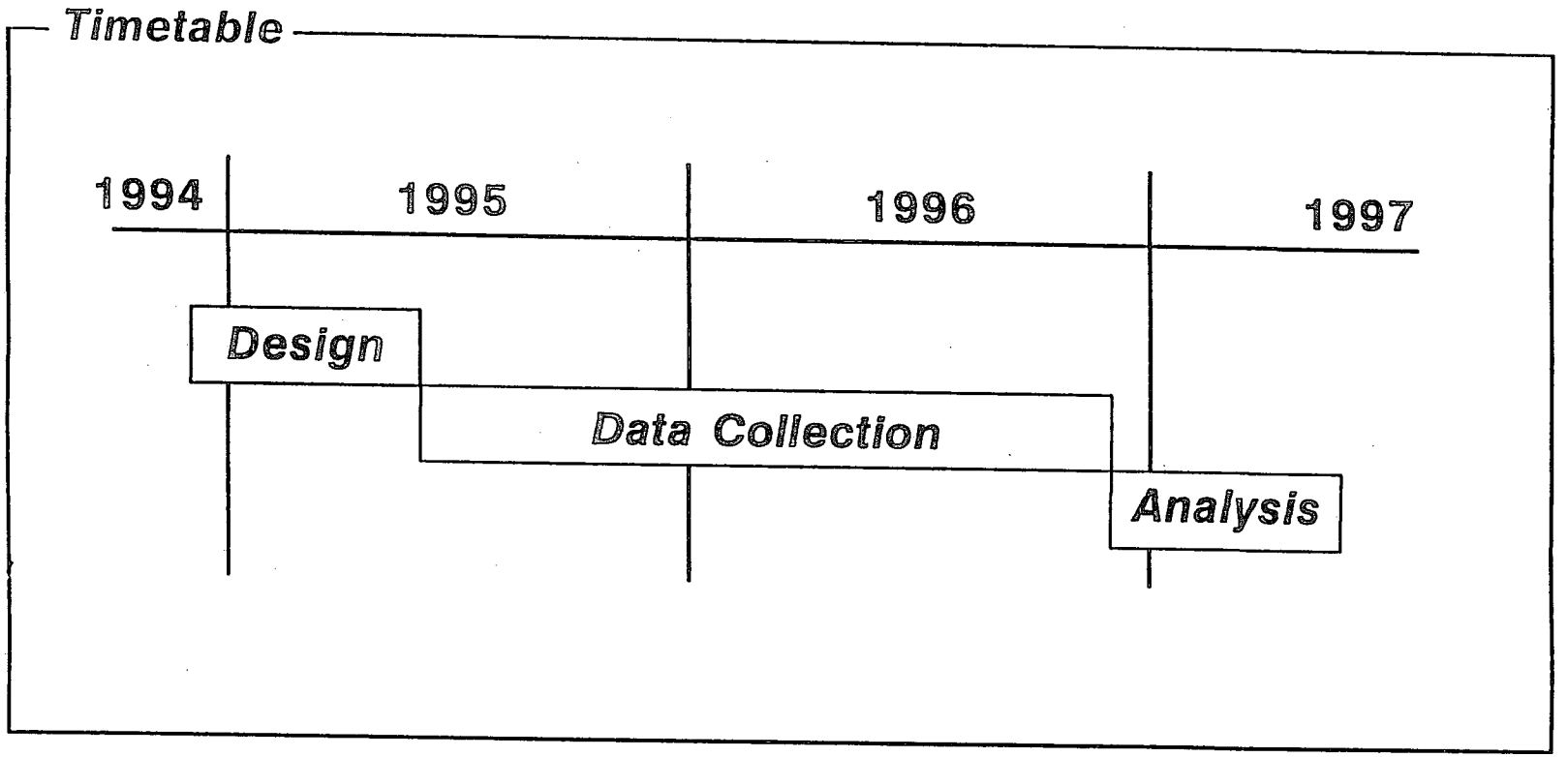
Data collection will include:

- *intake interviews and assessment of treatment sites*
- *assessment at 3 and 12 months after intake*
- *collection of urine specimens and breathalyzer tests to verify self-report data*

A pilot study of a computer-linked network of treatment programs:

- *select 20 programs in the Northeast as pilots*
- *use main study to determine instruments*
- *will provide data on changes in treatment, patients & outcome in very short time frame*

NATIONAL EVALUATION of SUBSTANCE ABUSE TREATMENT



NATIONAL EVALUATION of SUBSTANCE ABUSE TREATMENT

Design

December 1994 -- May 1995:

Convene Advisory Board to resolve research design issues.

Identify random sample for treatment units and clients.

Work with government to select subcontractor.
(Note: Both CASA and TVA have veto power.)

NATIONAL EVALUATION of SUBSTANCE ABUSE TREATMENT

Data Collection

June 1995 -- November 1996:

Carry out field interviews.

Monitor collection of data and develop statistical programs for analysis.

NATIONAL EVALUATION of SUBSTANCE ABUSE TREATMENT

Analysis

December 1996 -- May 1997:

Analyze data on groups and subgroups of patients in each treatment modality.

Analyze data on the treatment units' characteristics that are associated with outcomes of the patients.

Release a final report.

COCAINE INTERVENTION PROGRAM

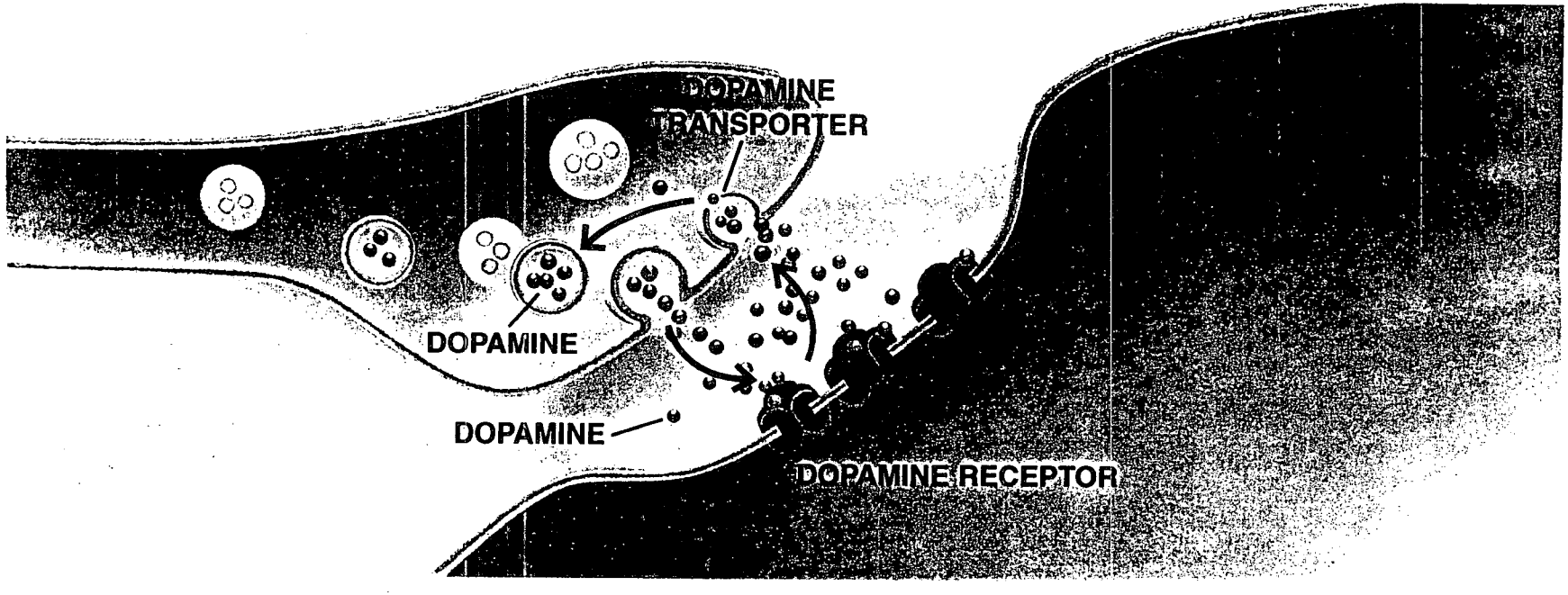
Guilford Pharmaceuticals Inc.

Magnitude of Problem

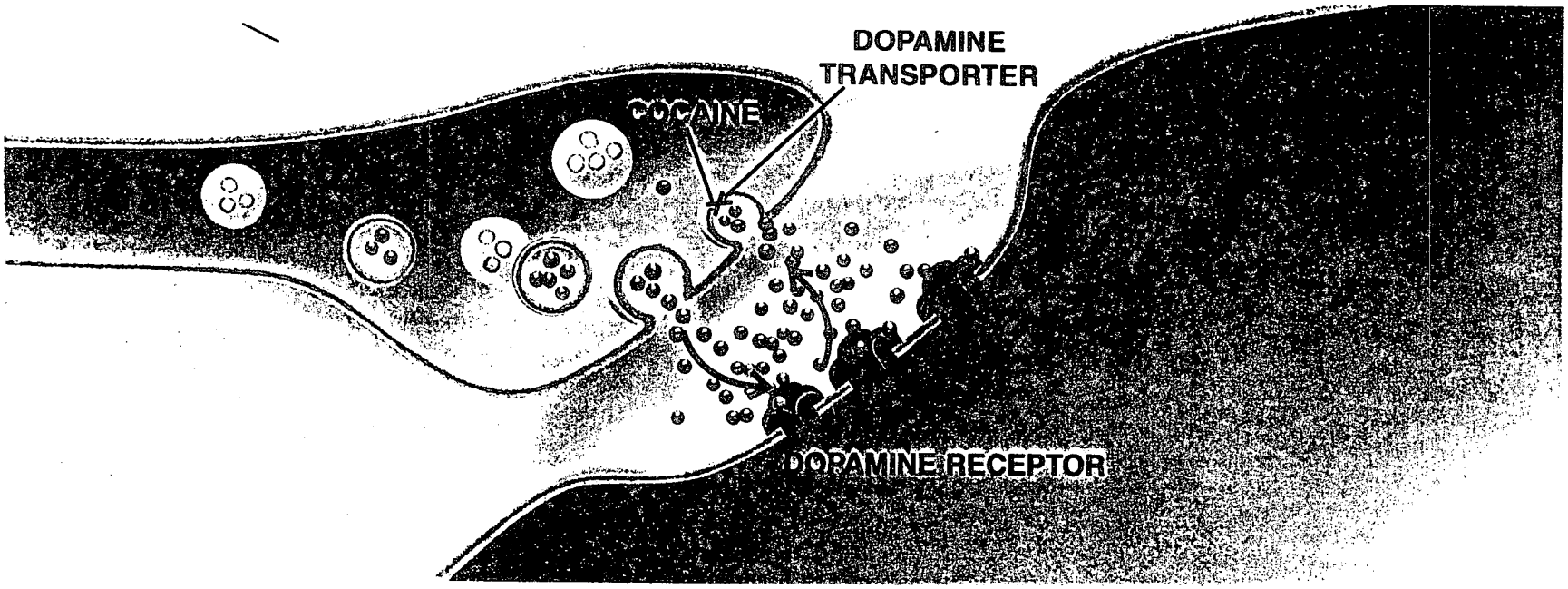
- 2.1 million people use cocaine on a weekly basis
- Measurable economic costs of illicit drug abuse were more than $67 billion in 1990
- Violence and drug related crimes

There are currently no medications which effectively treat cocaine addiction

NORMAL CELL COMMUNICATION



EFFECT OF COCAINE

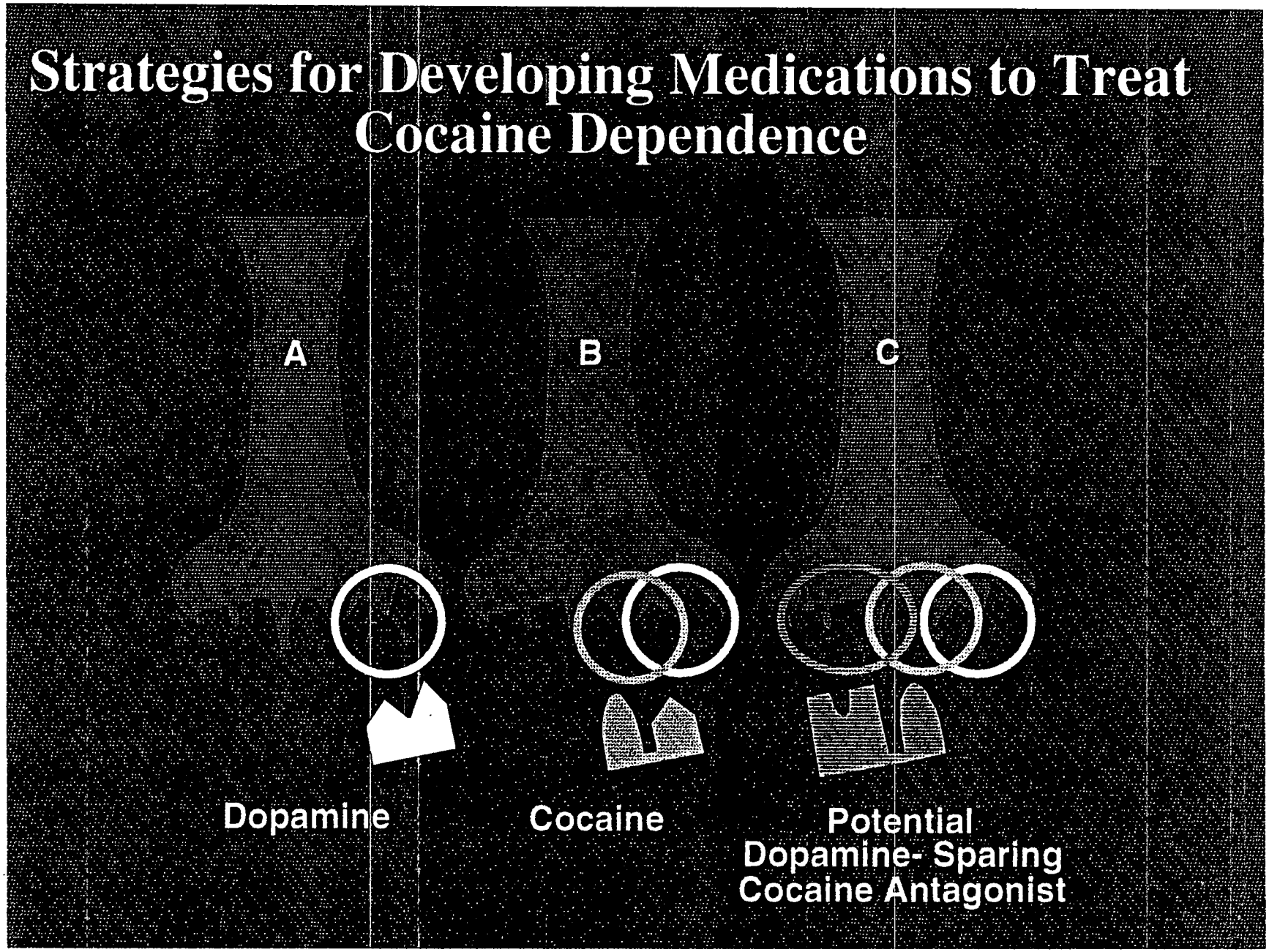


The addictive properties of cocaine are related to its ability to inhibit the dopamine transporter protein

Dopamine Transporter Protein

- Dopamine transporter was cloned in 1992
- Elucidate the primary structure of the protein
- Allows for the direct examination of a drug's interaction with the human dopamine transporter

Strategies for Developing Medications to Treat Cocaine Dependence



Therefore, it is now possible to design drugs which will block cocaine binding but will not interfere with the normal dopamine uptake process.

D
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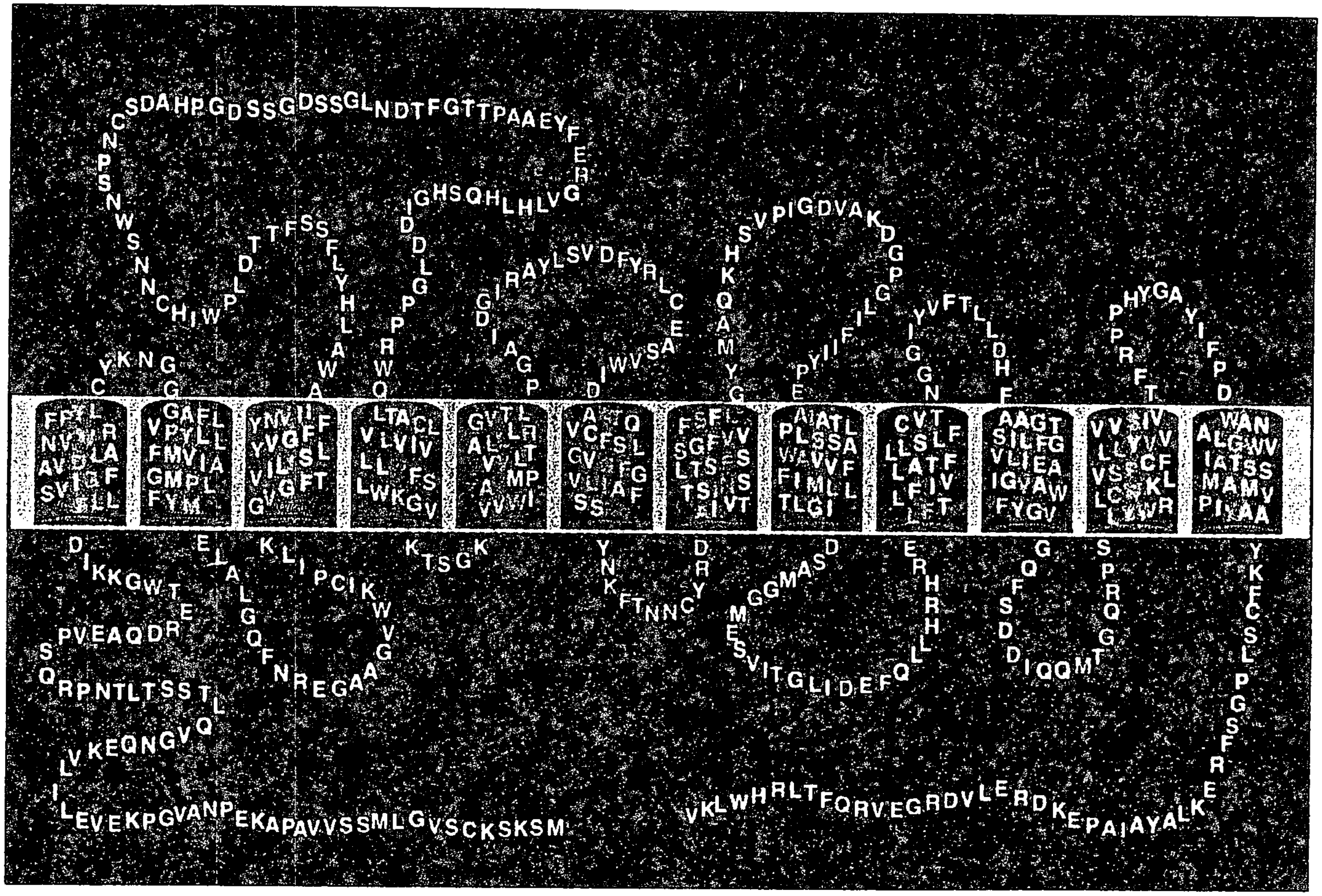
DOPAMINE AND
COCAINE
DOPAMINE



Dopamine Transporter Protein

- Dopamine transporter protein was cloned in 1992
- Elucidate the primary structure of the protein
- **Allows for the direct examination of a drug's interaction with the human dopamine transporter**

Guilford's Cocaine Intervention Program

- Cooperative Research and Development Agreement with NIDA (CRADA)
- High Throughput Screening
- Rational Drug Design

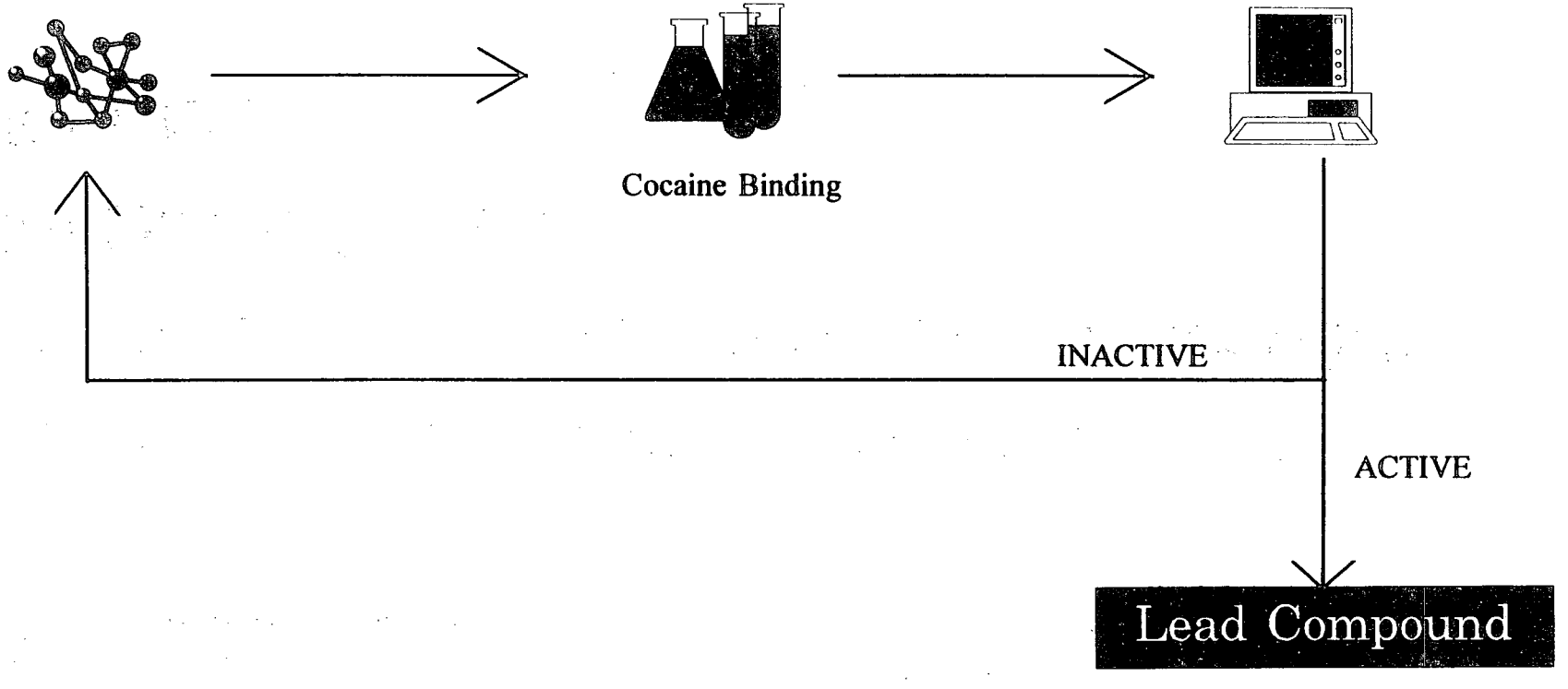
CRADA

- Guilford has established a collaboration with Dr. George Uhl at NIDA

- Access to cell lines expressing the human cloned dopamine transporter protein

- Access to proprietary compounds

Testing of Potential Anti-Cocaine Drugs



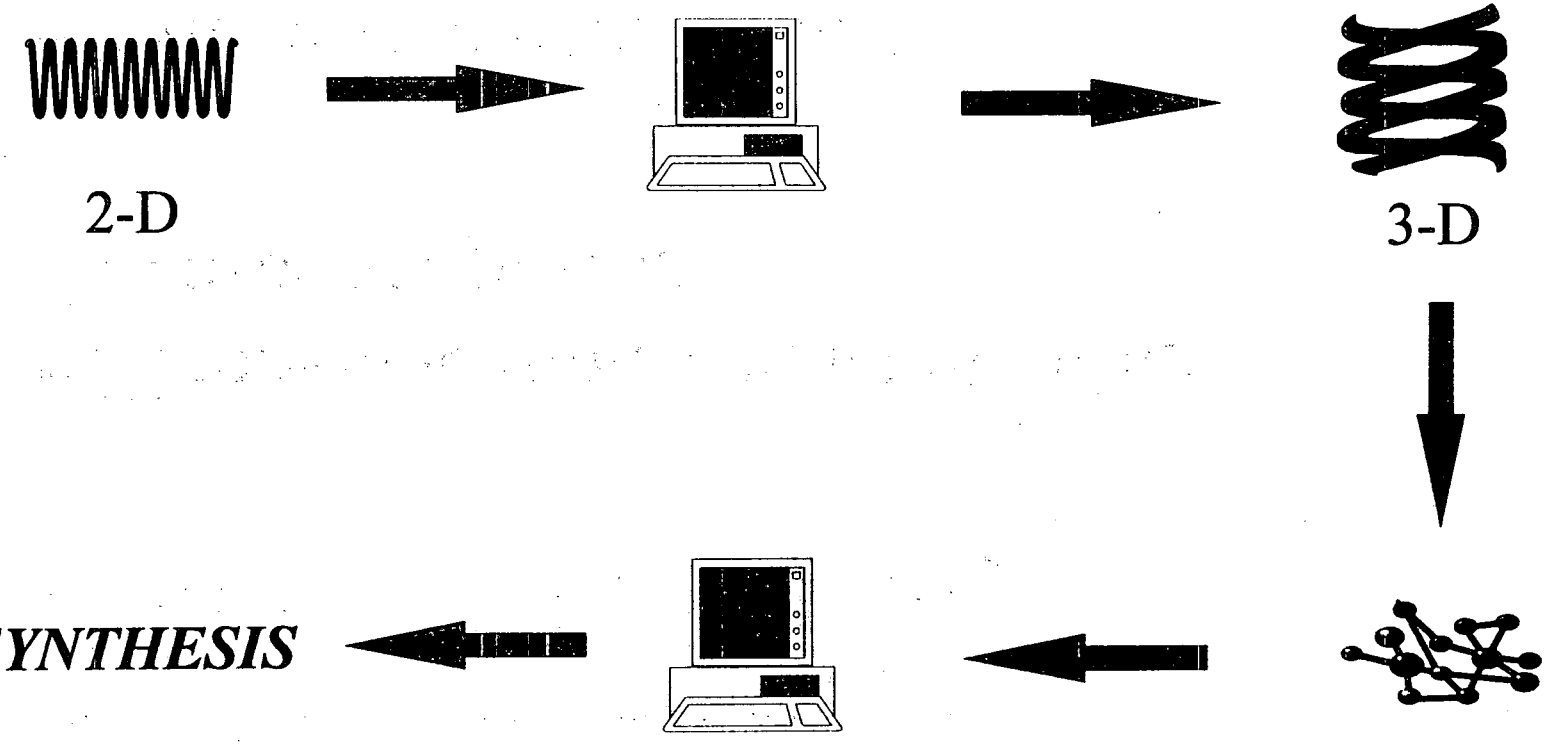
High Throughput Screening

- Previous methods -250 compounds per week
- Guilford's Method - 3500 compounds per week
- Molecular Cloning
- Robotics

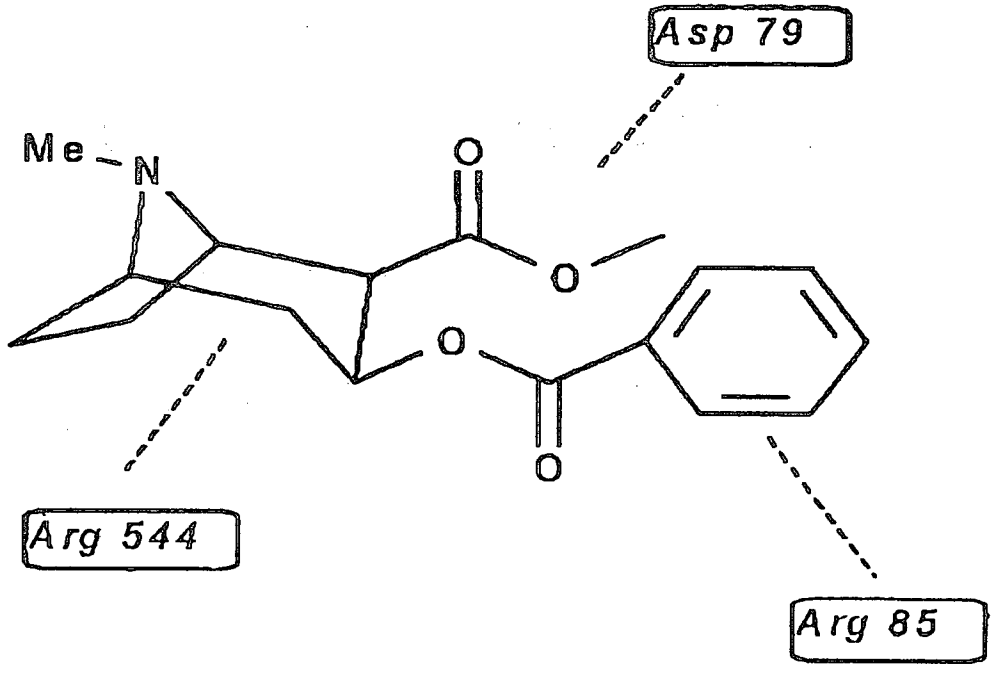
Rational Drug Design

- Computer-Aided drug design
- Three-dimensional structure of the transporter protein
- Synthesis of compounds

Computer-Aided Drug Design

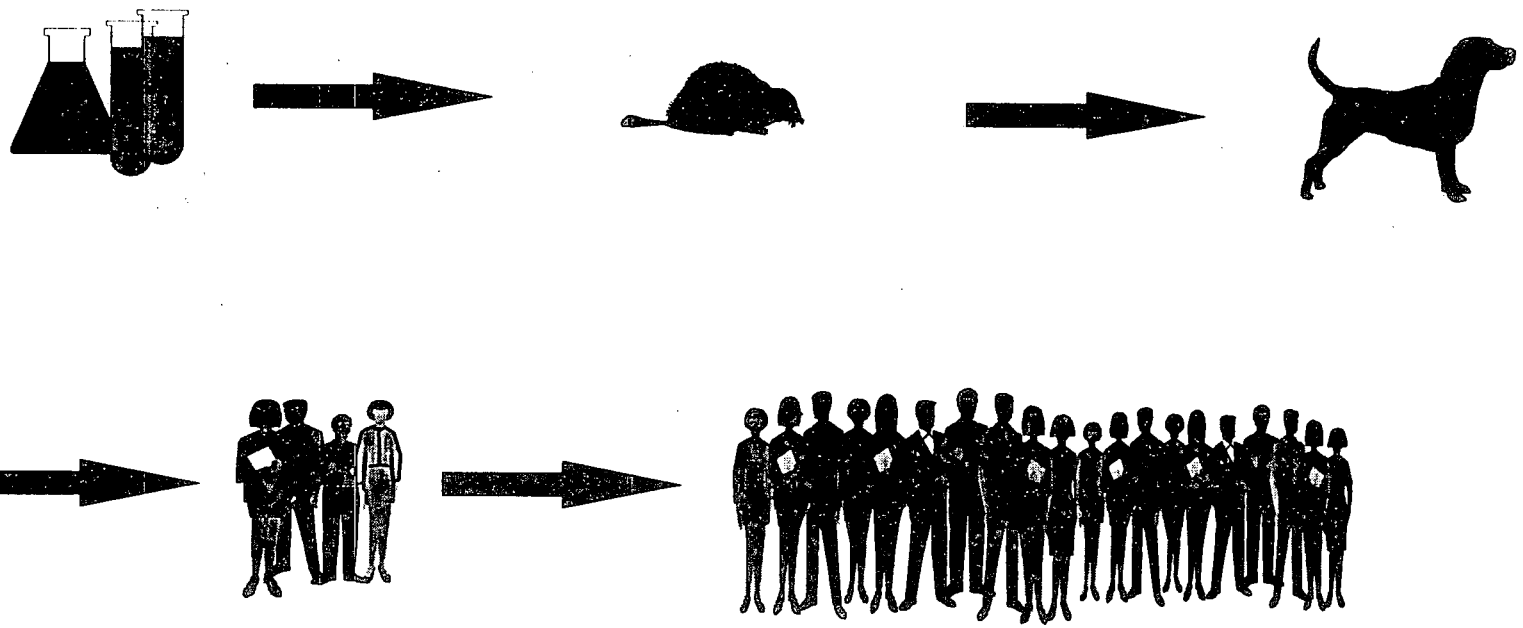


Molecular Modeling



Guilford has identified several lead molecules which exhibit desirable pharmacological properties

Test Tube to Humans



Medications Development Division

- Established in 1990
- Animal Models of Addiction
- Toxicology
- Clinical Trials
- Expedited Review

Summary

- Guilford has established a comprehensive program to develop medications useful for the treatment of cocaine addiction
- Collaboration with NIDA
- High Throughput Screening Capacity
- Rational Drug Design

Acknowledgments

The Abell Foundation, Inc.

Anti-Cocaine Catalytic Antibodies

Dr. Donald W. Landry
Columbia University, Department of Medicine

STIMULANT EPIDEMICS

1890's

1920's

1950's

1960's

1980's

Clinical Characteristics of Cocaine Abuse

Magnification of pleasure
Dose dependent euphoria
Progressive social isolation
Transition to binge use
Cravings

Abstinence

Crash
- hypersomnolence
- dysphoria (mild for 12-96 hrs)

Withdrawal
- anergia
- anhedonia
- craving (relapse)

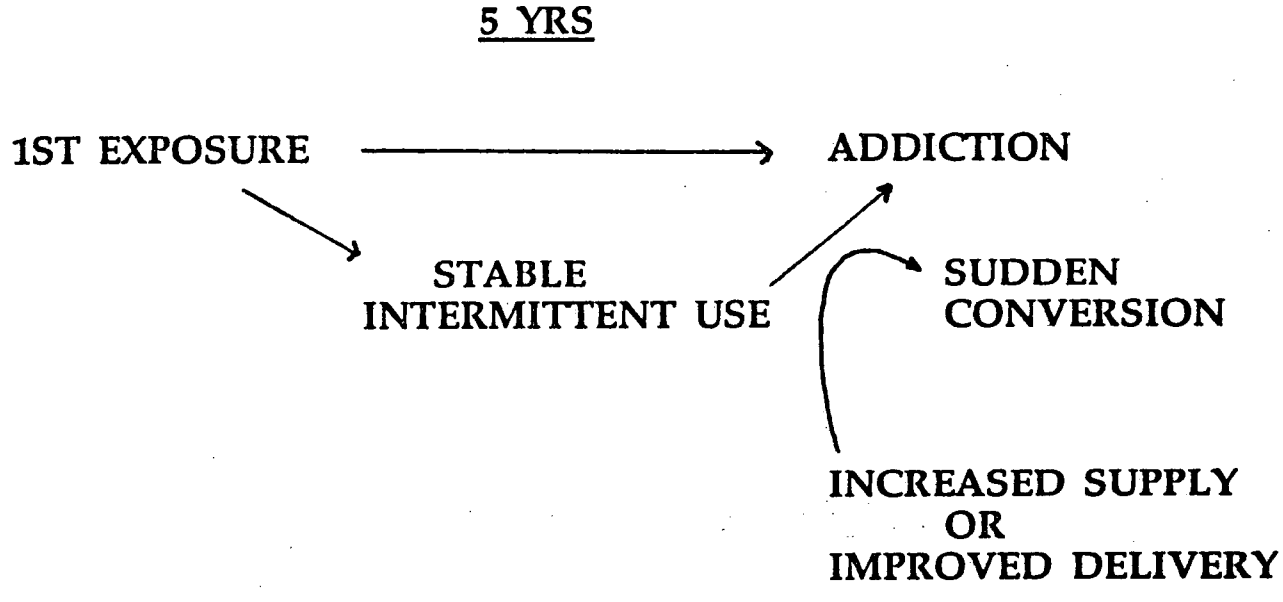
Extinction
- gradually diminishing cravings

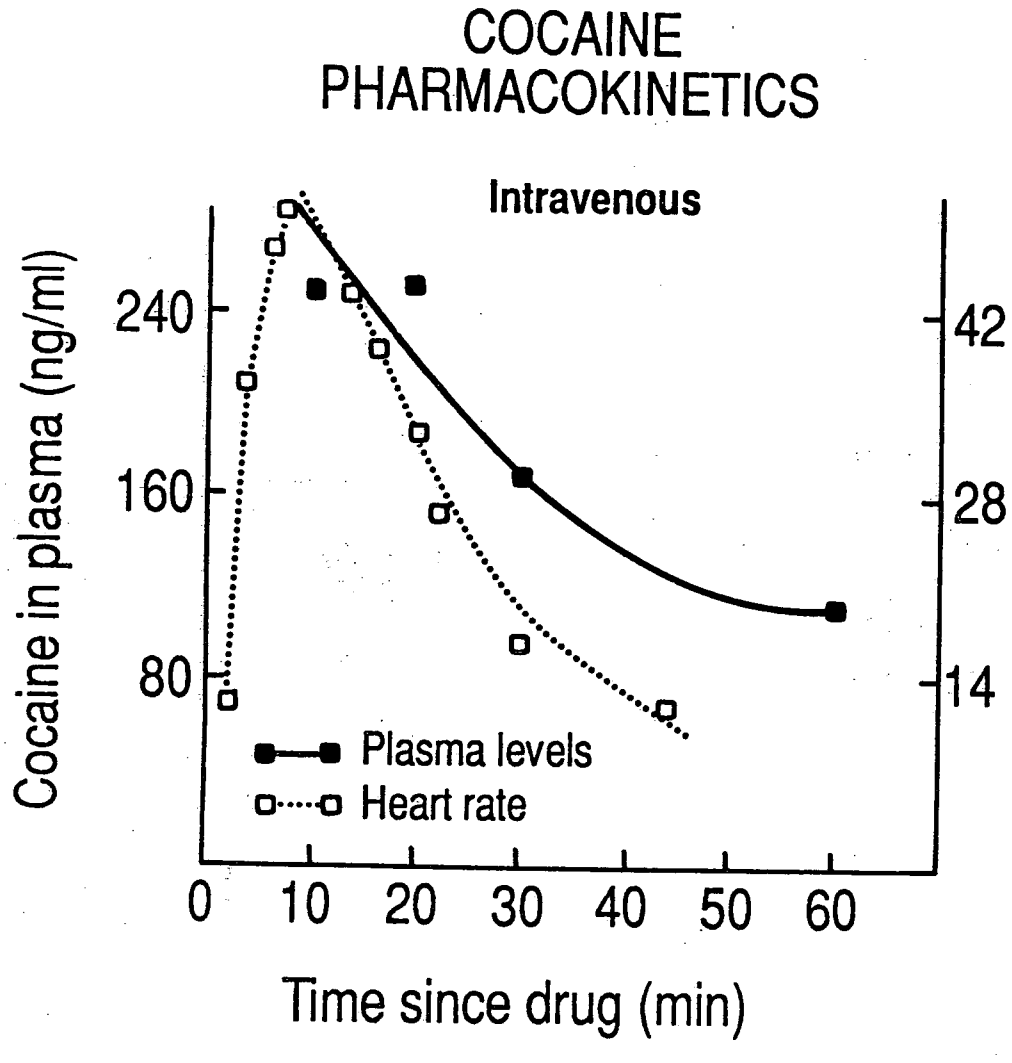
INTOXICATION vs ADDICTION

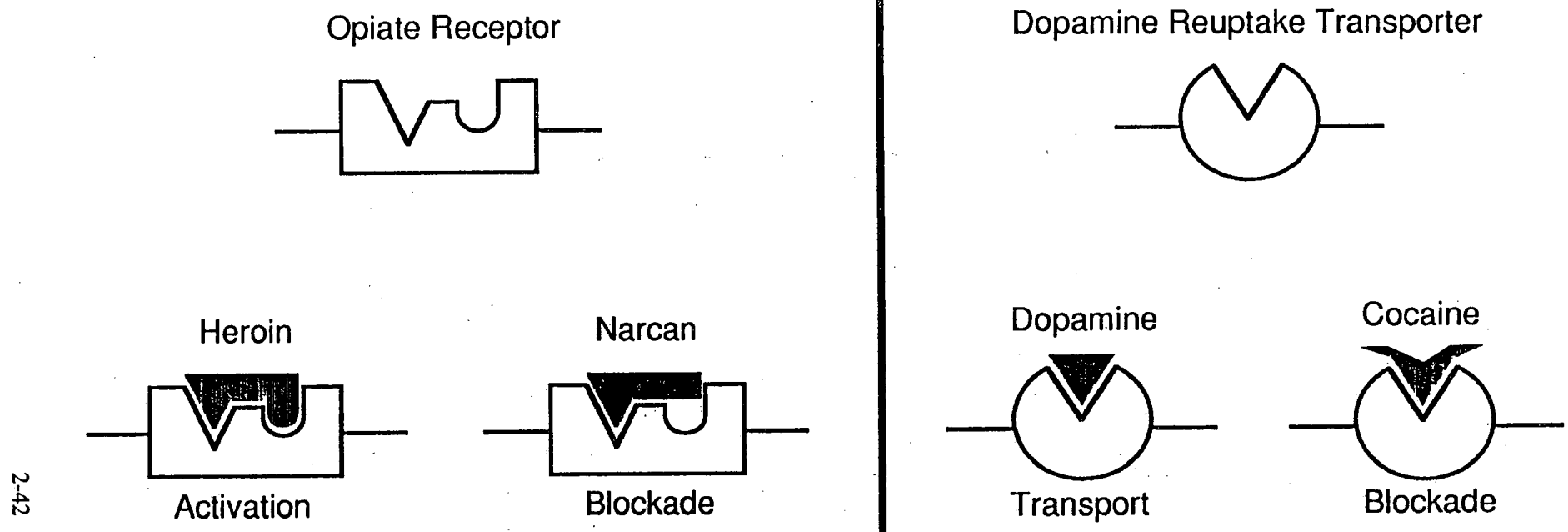
40,000,000 EXPOSED

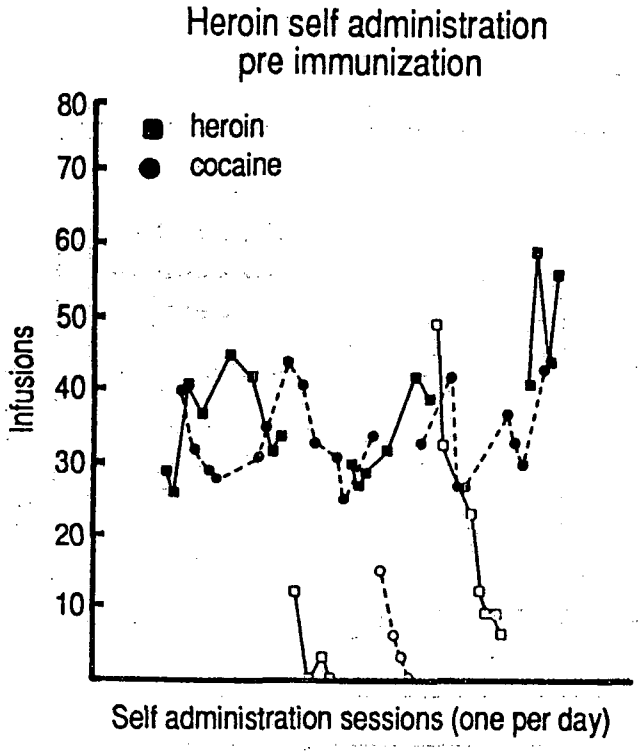
6,000,000 REGULAR

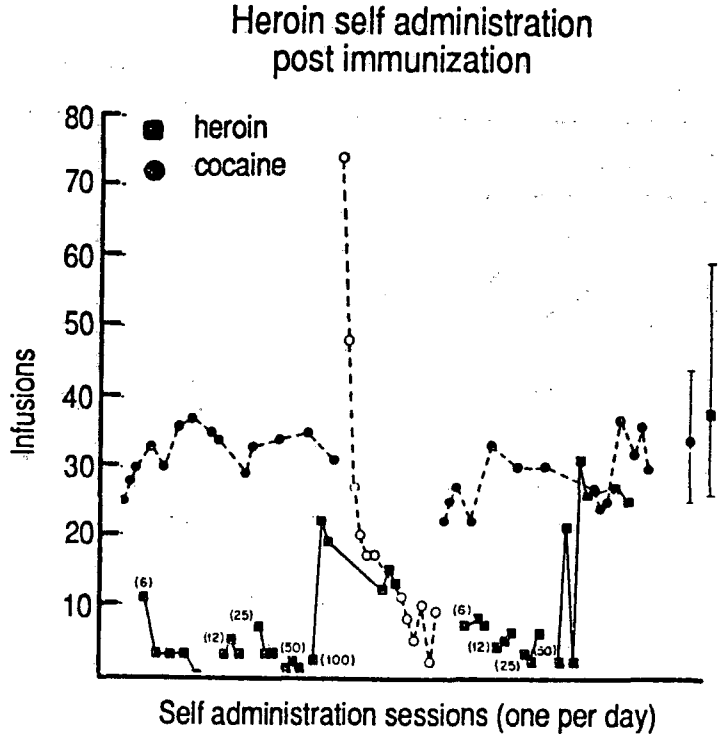
2,000,000 ADDICTED

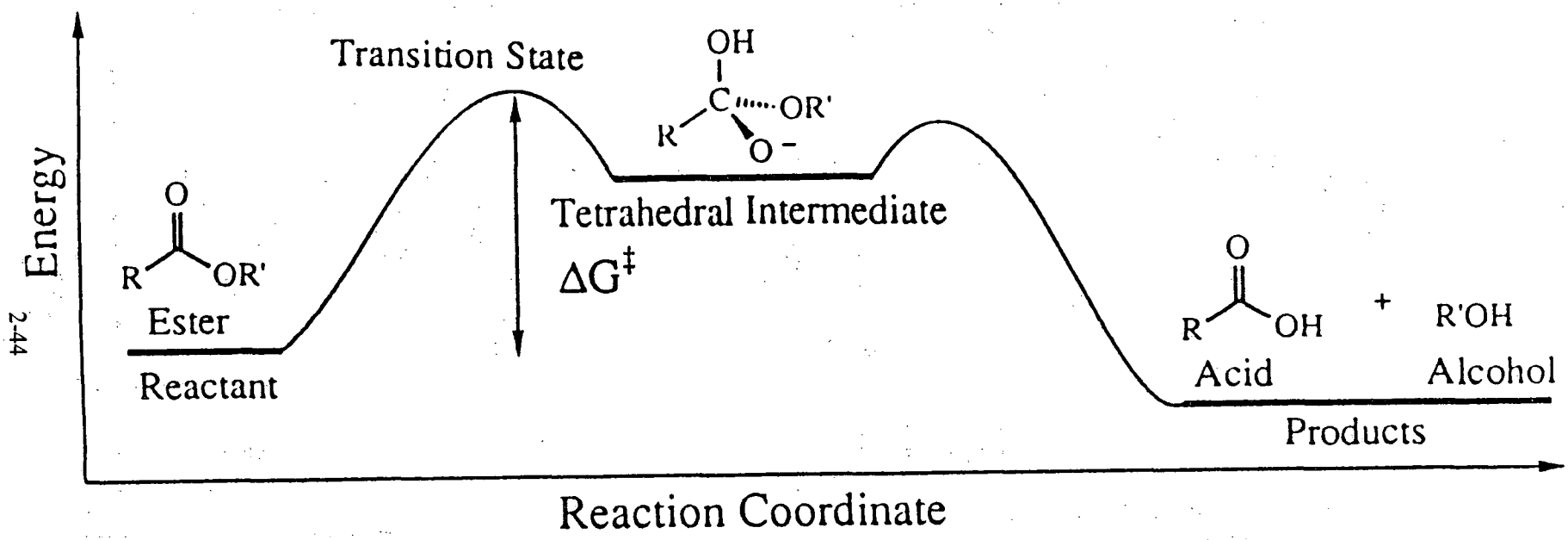

5 YRS
1ST EXPOSURE
ADDICTION
STABLE
INTERMITTENT USE
SUDDEN
CONVERSION
INCREASED SUPPLY
OR
IMPROVED DELIVERY

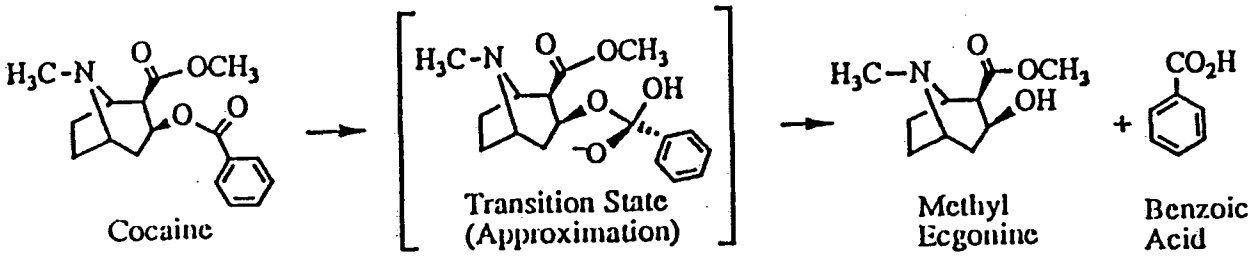

COCAINE
PHARMACOKINETICS
Intravenous
Cocaine in plasma (ng/ml)
240
160
80
42
28
14
Plasma levels
Heart rate
0
10
20
30
40
50
60
Time since drug (min)

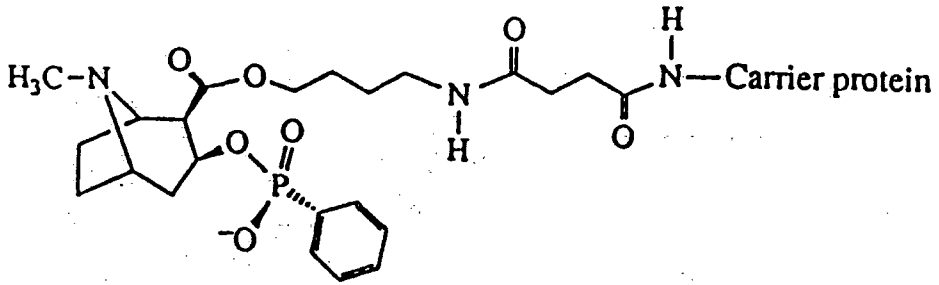

Opiate Receptor
Heroin
Activation
Narcan
Blockade
Dopamine Reuptake Transporter
Dopamine
Transport
Cocaine
Blockade


Heroin self administration
pre immunization
heroin
cocaine
Infusions
80
70
60
50
40
30
20
10
Self administration sessions (one per day)

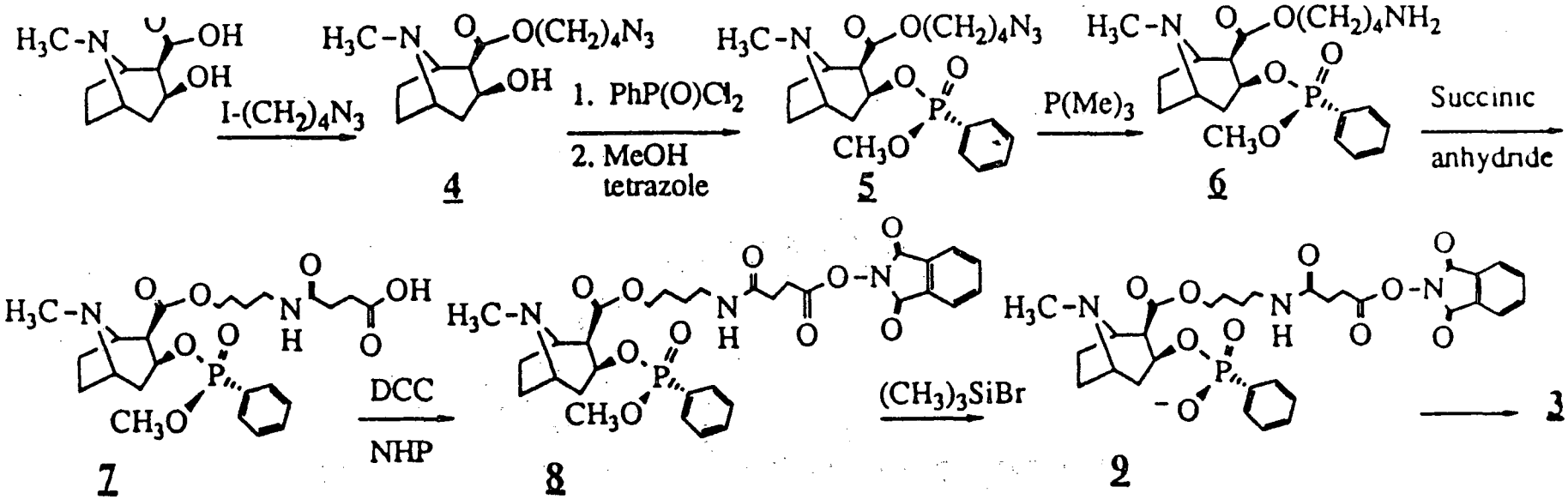

Heroin self administration
post immunization
heroin
cocaine
Infusions
80
70
60
50
40
30
20
10
(6)
(12)
(25)
(50)
(100)
(6)
(12)
(25)
(50)
Self administration sessions (one per day)


Energy
Transition State
OH
C
OR'
R
O –
Tetrahedral Intermediate
$\Delta G^{\ddagger}$
O
R
OR'
Ester
Reactant
O
R
OH
+
R'OH
Acid
Alcohol
Products
Reaction Coordinate

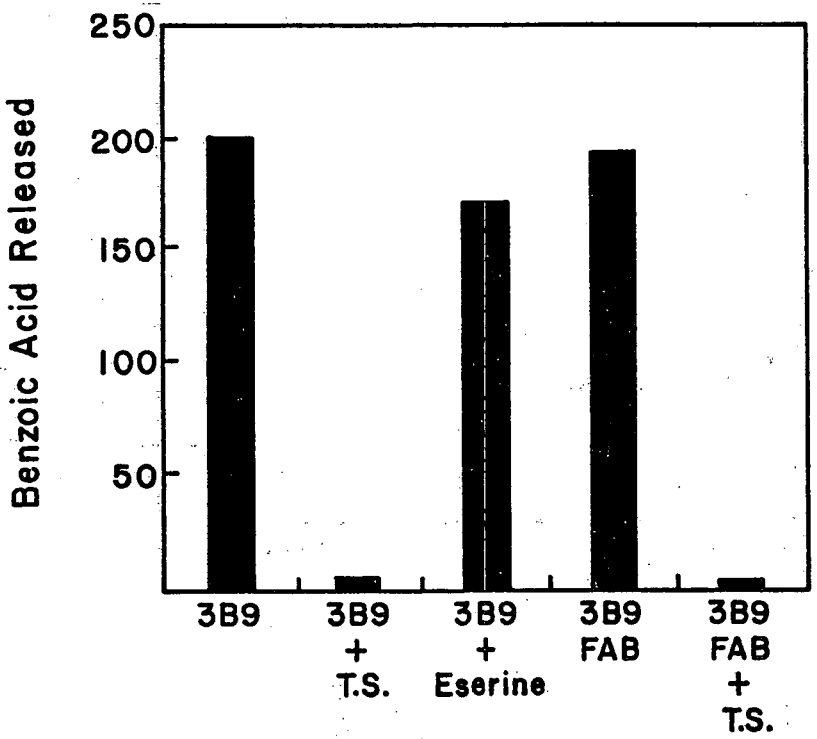


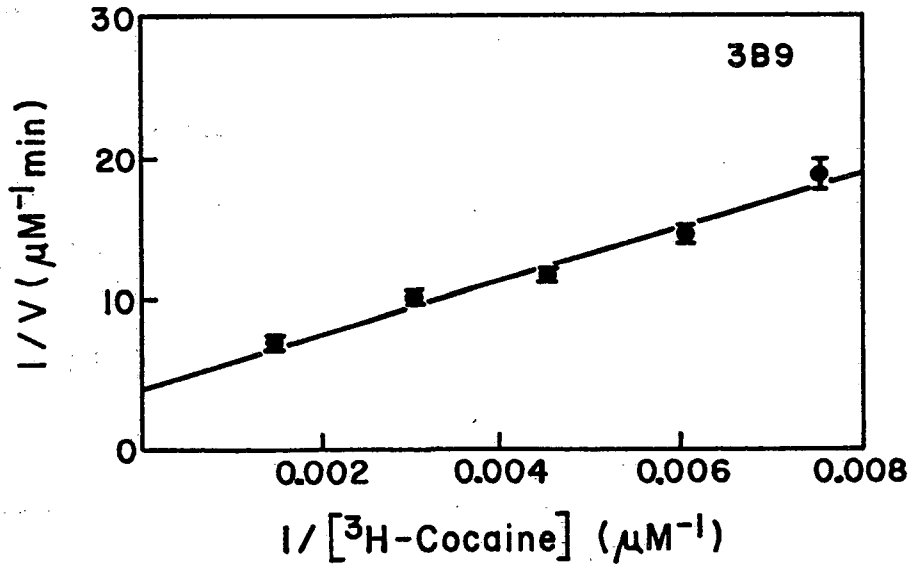


Phosphonate mono-ester
Transition State analog


I-(CH2)4N3
1. PhP(O)Cl2
2. MeOH
tetrazole
P(Me)3
Succinic
anhydride
DCC
NHP
(CH3)3SiBr
4
5
6
7
8
9
3

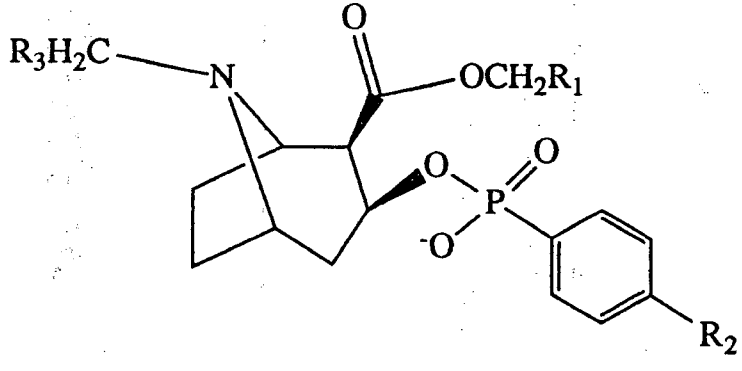
Artificial Esterase Activity





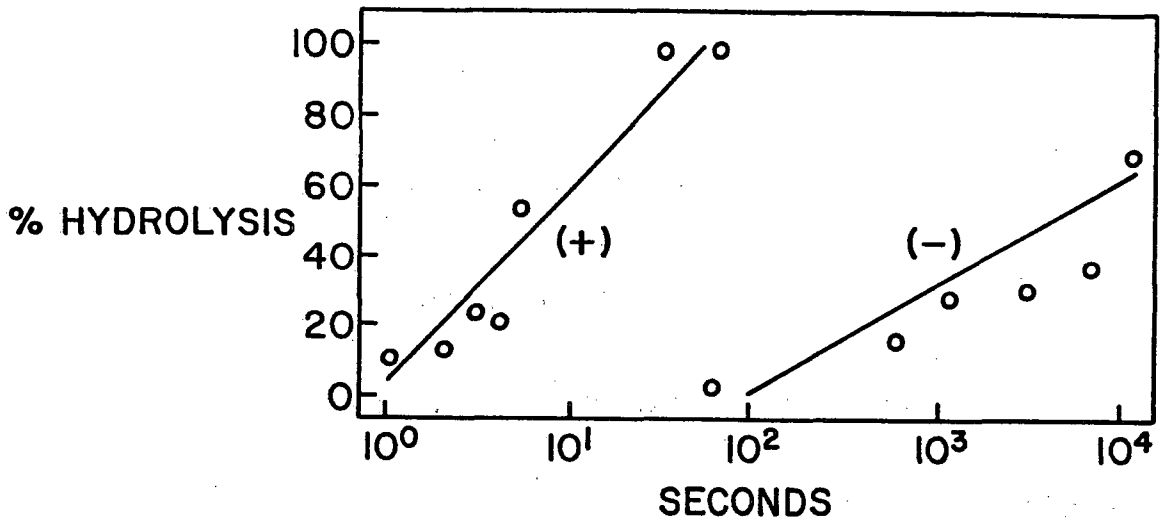
Catalytic Antibodies Against Cocaine

mAB	TSA	Km (uM)	K_{cat} min^{-1}	K_{cat} / K_o
3B9	I	490	0.11	1100
6A12	I	1017	0.072	710
15A10	I	251	0.47	5000
2A10	I			
19G8	I			
9A3	I			
12H1	II	82	0.064	660
8G4G	III			
8G4E	III			

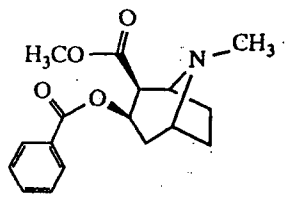


TSA I R_1 = tether, $R_2 = R_3 = H$
TSA II R_2 = tether, $R_1 = R_3 = H$
TSA III R_3 = tether, $R_2 = R_1 = H$

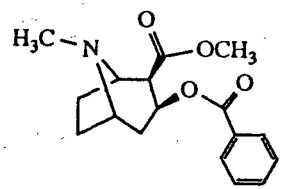
HYDROLYSIS OF (+) AND (−) COCAINE IN PLASMA



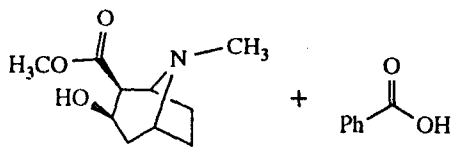
(+) Cocaine

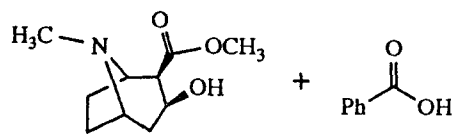


(-) Cocaine



RR > 2000 butyryl cholinesterase RR = 1





Kinetic Model

Transit time: 15-20 sec

Doses of cocaine: 100 mg (0.3 mmol)

Dose of enzyme: 500 mg (0.003 mmol)
(0.006 meq)

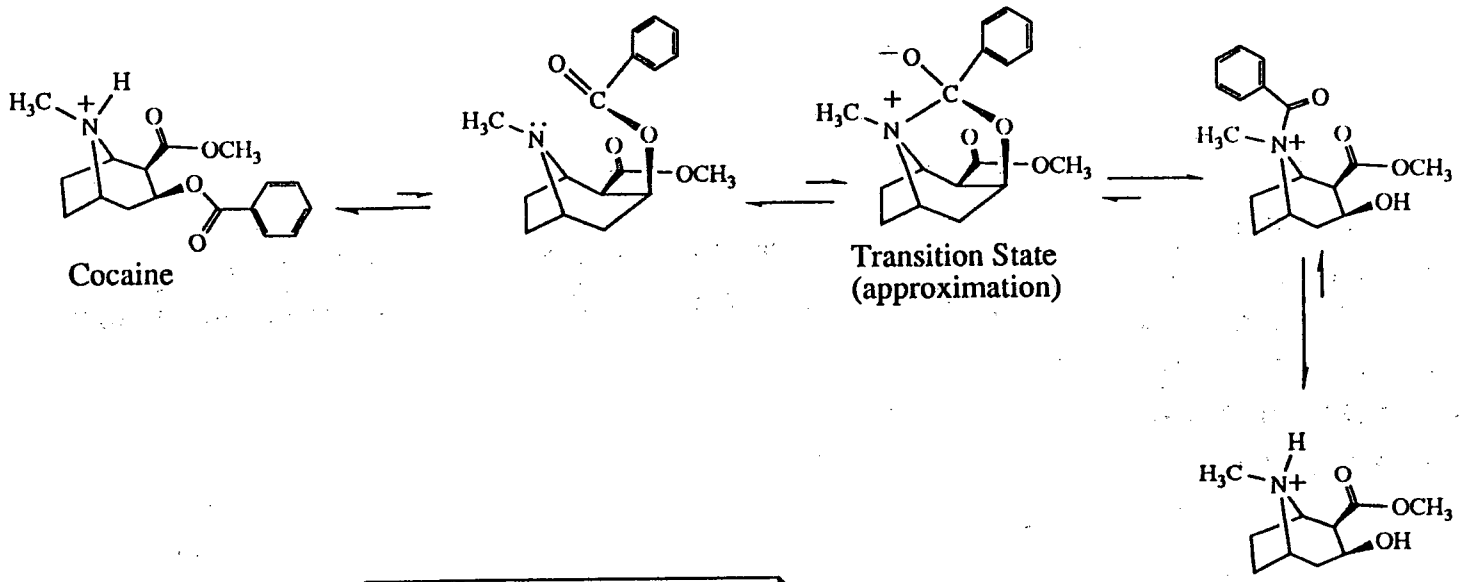
Turnovers required: 50

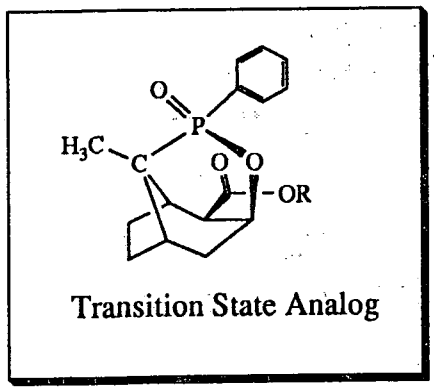
Turnover rate: 2-3 sec^{1}

$[Cocaine]_{pulm\ art} = 30\ \mu M$

Optimization of Cocaine Esterase Activity

Organic Synthesis	Hybridoma Screening	Protein Engineering
$Analog_1 \rightarrow$	Catalytic $mAB_{1,1} \rightarrow$	$cmAb_{x1}$
	$cmAb_{1,2}$	$x2$
	$cmAb_{1,3}$	$x3$
$A_2 \rightarrow$		
$A_3 \rightarrow$		
$A_4 \rightarrow$		Co-crystallize cmAb:$Analog_x$
		Site directed mutagenesis
		Phage display mutagenesis
		Random replacement
		HC/LC hybrid with metallo binding site
Analogs based on substrate-assisted antibody catalysis	Immunologic screening of active enzymes	


Cocaine
Transition State
(approximation)
Ecgonine methyl
ester


Transition State Analog

Effect of Treatment on Drug-Related Behavioral Problems

Dr. Thomas McLellan
University of Pennsylvania

COMPLIANCE AND "RELAPSE" IN SELECTED MEDICAL DISORDERS

- **INSULIN DEPENDENT DIABETES**
  COMPLIANCE WITH MEDICATION REGIMEN - **<50%**
  COMPLIANCE WITH DIET AND FOOT CARE - **<30%**
  RE-TREATED W/IN 12 MO. *(by phys, ER, or Hosp)* **30-50%**

- **MEDICATION DEPENDENT HYPERTENSION**
  COMPLIANCE WITH MEDICATION REGIMEN - **<30%**
  COMPLIANCE WITH DIET - **<30%**
  RE-TREATED W/IN 12 MO. *(by phys, ER, or Hosp)* **50-60%**

- **ASTHMA (Adult)**
  COMPLIANCE WITH MEDICATION REGIMEN - **<30%**
  RE-TREATED W/IN 12 MO. *(by phys, ER, or Hosp)* **60-80%**

Factors Associated With "Relapse"

#1 - LACK OF COMPLIANCE WITH MEDICATIONS, DIET AND BEHAVIOR CHANGE (**50%***)
#2 - LOW SOCIOECONOMIC STATUS
#3 - POOR FAMILY AND SOCIAL SUPPORTS
#4 - PSYCHIATRIC CO-MORBIDITY

SCOURCES Nat Ctr Health Stats; Harrison 13th Ed., More than 30 other studies

TABLE 1
PRE TO POST TREATMENT CHANGE IN THREE GROUPS OF TREATED SUBSTANCE ABUSERS

PROBLEM MEASURE^	OPIATE BASELINE N = 195	t	OPIATE 6 MONTHS N = 195	COCAINE BASELINE N = 212	t	COCAINE 6 MONTHS N =212	ALCOHOL BASELINE N =242	t	ALCOHOL 6 MONTHS N =242
OUTCOME DOMAIN #1: REDUCTION IN ALCOHOL AND DRUG USE									
Drug Composite Score	.336	***	.256	.228	***	.081	..022	**	.011
Days Opiate Use	11	***	6	1	*	2	1		1
Days Stimulant use	5	***	3	11	***	2	1		1
Days Depressant use	6		6	1		1	2	*	1
Alcohol Composite Score	.109		.093	.209	***	.080	.642	***	.158
Days Alcohol use	6	*	5	8	***	3	17	***	4
Days drank to intoxication	3	*	2	6	***	2	16	***	3
OUTCOME DOMAIN #2: INCREASED PERSONAL HEALTH AND SOCIAL FUNCTION									
Medical Composite Score	.349		.311	.230	*	.168	.229		.223
Days Medical Problems	8		8	6	.08+	4	7		6
Psychiatric Comp Score	.309	*	.268	.222	***	.089	.220	***	.115
Days psych problems	12	***	8	9	***	3	9	***	4
Employment Comp Score	.675		.641	.621	*	.571	.552		.487
Days worked in past 30	8		10	12	*	14	11	**	14
Employment Income	$417	*	$537	$613	*	$783	$697	*	$841
Family Composite Score	.268	*	.225	.250	***	.136	.198	***	.094
Days family conflicts	4		3	3		2	2	**	1
Days social conflicts	2		2	2	*	1	2	*	1
OUTCOME DOMAIN #3: REDUCTION IN PUBLIC HEALTH AND PUBLIC SAFETY PROBLEMS									
Shared Needle/Syringe	23%	***	3%	3%		3%	<1%		0%
Had Unprotected Sex	14%	*	9%	22%	*	13%	19%	**	7%
Legal Composite Score	.133		.102	.064	**	.024	.051	***	.006
Days illegal activity	4	*	2	2	**	1	1		1
Illegal Income	$289	**	$109	$105		$83	$26		$1

^ All measures derive from ASI interviews covering the 30 day periods prior to baseline and 6-month follow-up.

*=p <.05, **=p<.01, ***=p<.001 by paired t-test

TABLE 2

Drug Related Risk Behaviors by Treatment Status

	In-Tx	Out-Tx
Weekly Injections during prior month:		
Heroin	33% (40)	69% (61)**
Cocaine	22% (27)	61% (54)**
Combined ("Speedball")	32% (39)	45% (40)*
Been to "Shooting Gallery"	33% (41)	55% (48)**
Been to "Crack House"	11% (13)	28% (25)**

** p<.05 ** p<.01 by Chi-Square*

TABLE 3

Three Year HIV Infection Rates by Treatment Status At Time of Enrollment

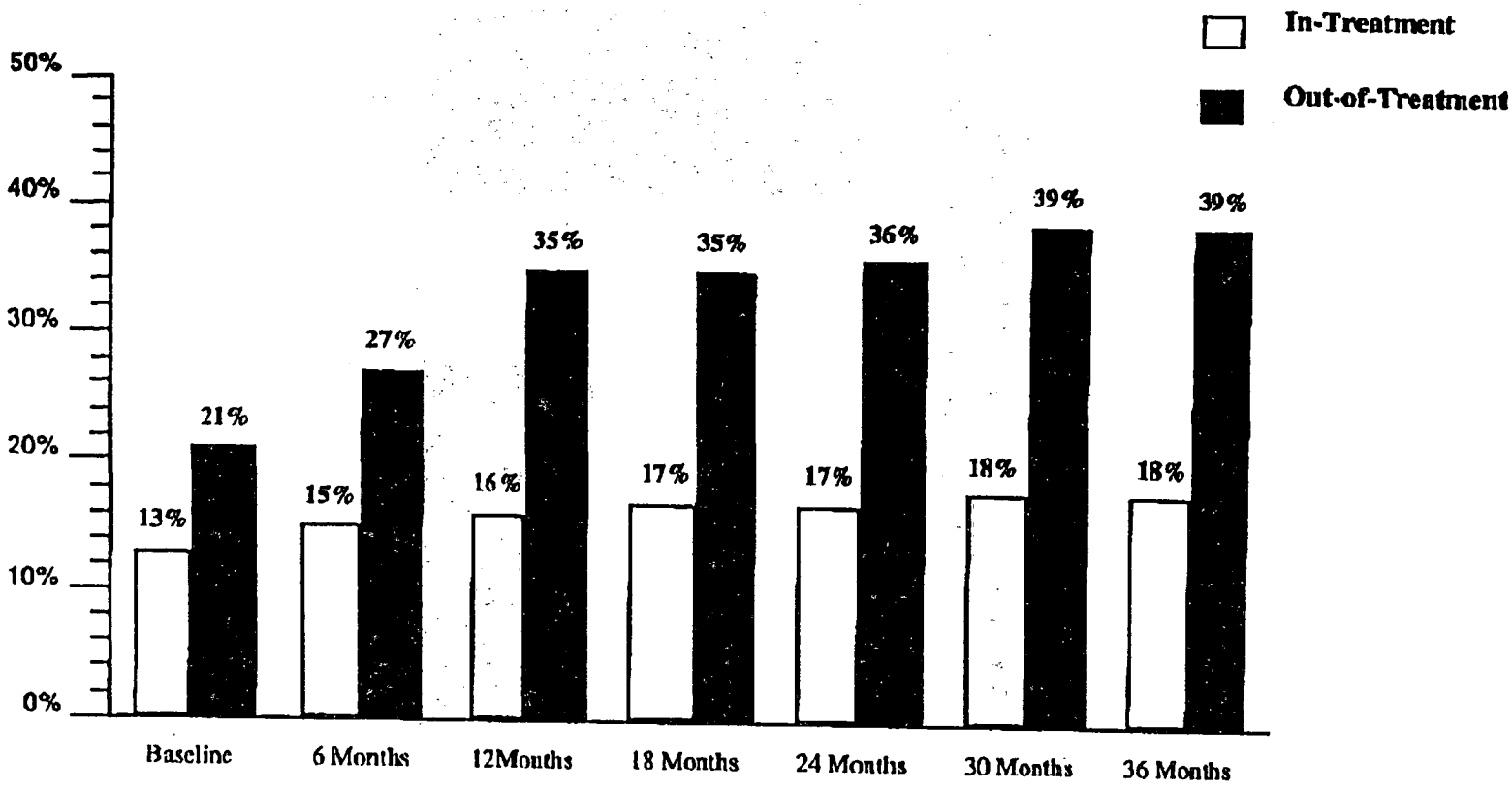


Table 4

Six-Month Re-Incarceration Rates for Two Groups Opiate Dependent, Federal Probationers

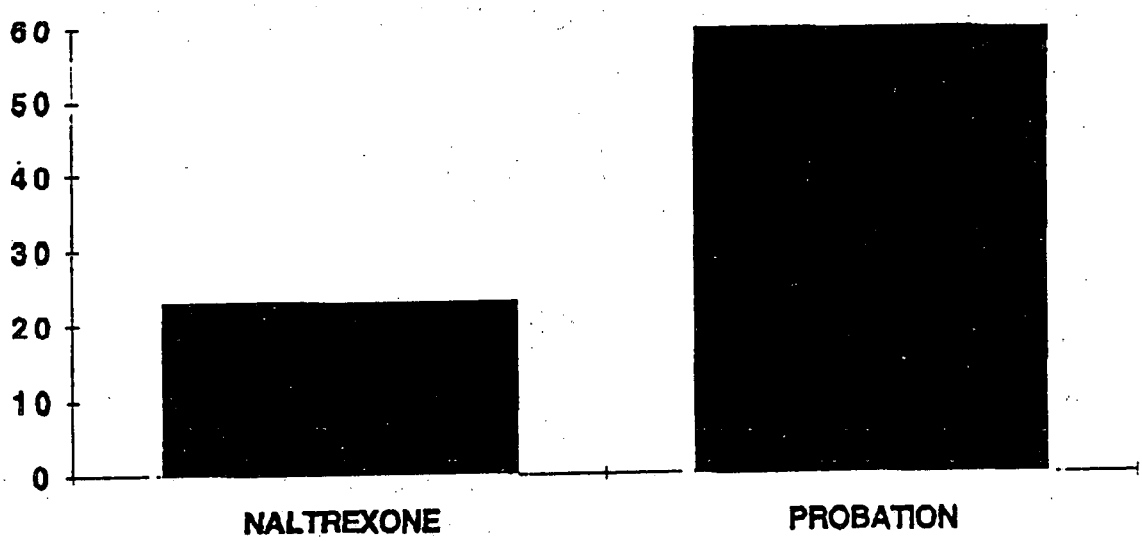


TABLE 5

SIX-MONTH OUTCOME STATUS COMPARISONS AMONG PROGRAMS

During the 30 Days prior to follow-up, what proportion of patients were:

Treatment Program	Average for All Programs	OPT-1 N=45	Sig. Dif.	OPT-2 N=53	INPT-1 N=54	Sig. Dif.	INPT-2 N=46
Abstinent from Alcohol	59%	51%		45%	78%	*	63%
Abstinent from all Drugs	84%	80%	*	71%	87%	*	98%
Working >30 hrs/ week	77%	80%	*	72%	74%	*	83%
Receiving welfare income	11%	2%	**	28%	9%		4%
Committing crimes	3%	0%	*	7%	4%		0%
Experiencing serious psych symptoms	32%	33%		34%	27%	*	35%
Experiencing serious family conflicts	25%	24%	*	31%	22%		24%

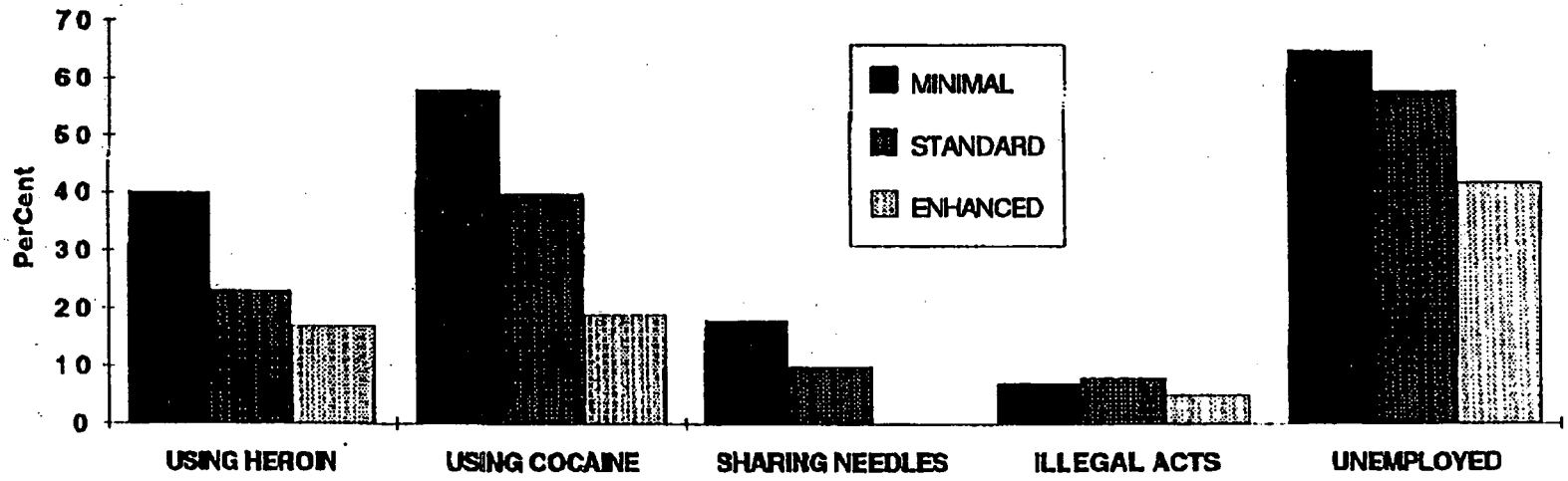
During the 6 months since leaving treatment, what proportion of patients were:

Re-treated for Alcohol problems	12%	15%	*	9%	9%	*	15%
Re-treated for Drug problems	10%	10%		15%	9%		7%
Hospitalized for Medical problems	9%	11%		8%	9%		9%
Hospitalized for Psych problems	7%	4%		7%	7%		9%

All figures express as percentage.

*=p<.05, **=p<.01 by Z test for differences between proportions

METHADONE SERVICES
Target Behaviors at Six-Months By Level of Service



Clinical Approach to Medications Development for Addiction

Dr. George Woody
University of Pennsylvania

Define objectives

Define primary and secondary measures

Secondary measures could be:

- **"craving" or "wish to use"**
- **psychiatric symptoms**
- **illegal activity**
- **employment & family adjustment**
- **decreases in morbidity & mortality**

WORK DERIVES FROM
"WAR ON DRUGS"

SUPPORTED BY NIDA MEDICATIONS
DEVELOPMENT PROGRAM

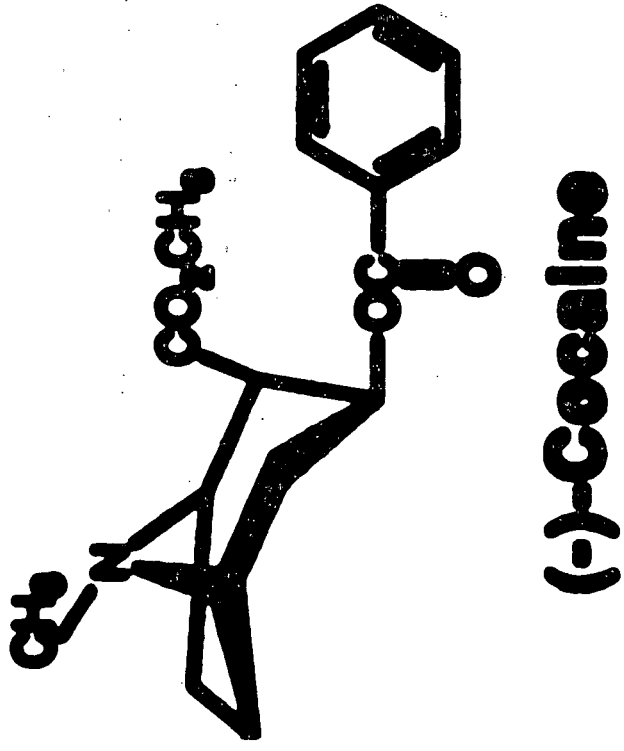
"IF THIS IS A WAR, IT'S MORE LIKE
THE 100 YEARS WAR THAN THE
INVASION OF GRENADA"

HERBERT KLEBER, M.D.

KEY ISSUES

MUCH KNOWN ABOUT EFFECTS OF COCAINE

NOT MUCH KNOWN ABOUT WHAT IS WRONG WITH COCAINE ADDICTS


(-)-Cocaine

DOPAMINE TRANSPORTER

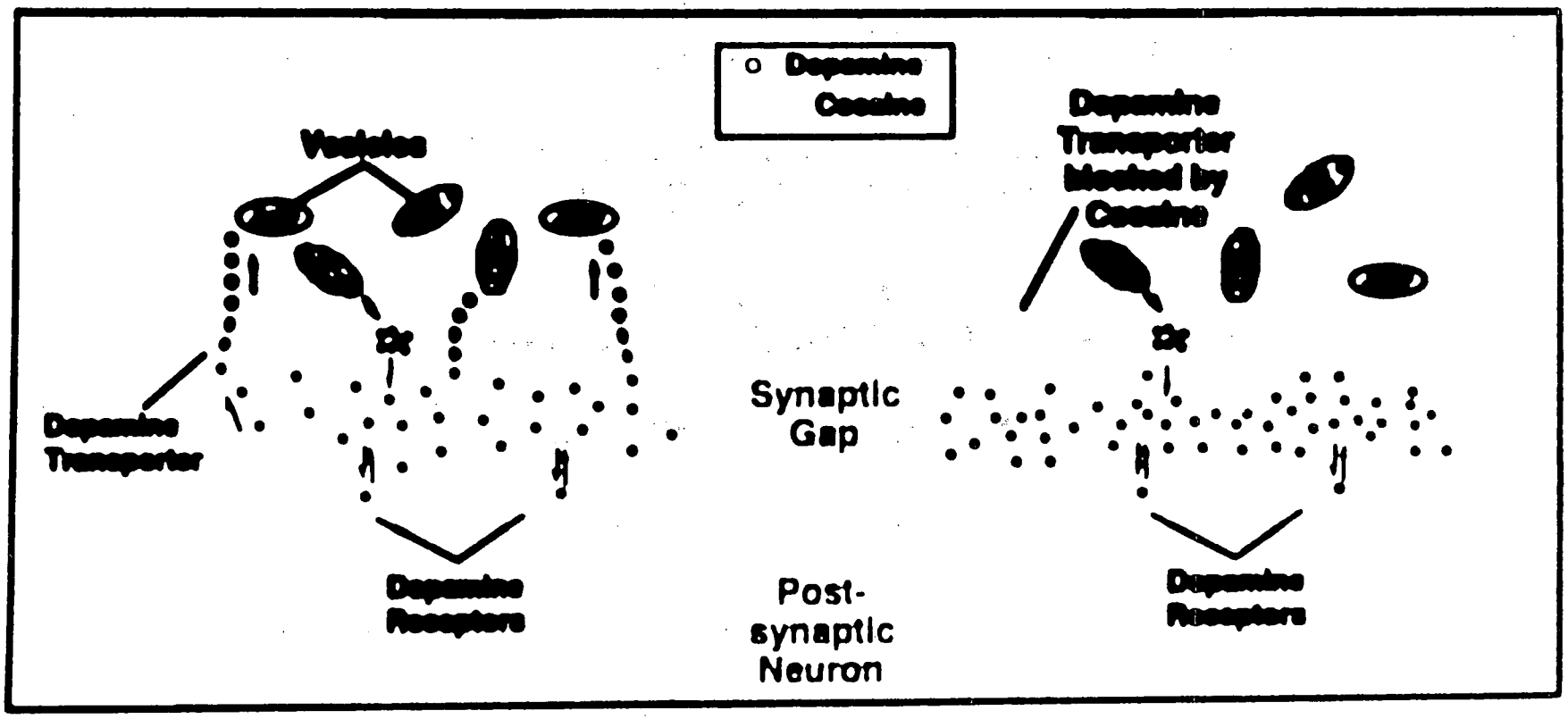
MAY MEDIATE REINFORCING PROPERTIES OF COCAINE

COCAINE BINDING BLOCKED BY MAZINDOL, GBR 12395, WIN 35,428, BUPROPION

MAZINDOL AND BUPROPION REDUCED "COCAINE CRAVING" IN METHADONE PATIENTS (OPEN TRIAL)

RECENT DOUBLE-BLIND STUDY OF BUPROPION IN METHADONE PATIENTS SHOWED NO EFFECT

The Dopamine Hypothesis of Cocaine Reinforcement



D1 ANTAGONIST: SCH 23390

STUDIED IN ANIMALS; NO CLINICAL DATA

REPORTED TO BLOCK OR AUGMENT COCAINE-INDUCED HYPERACTIVITY IN THE RAT WITH A U-SHAPED DOSE RESPONSE CURVE

DOSE-FINDING WOULD BE DIFFICULT

ANTAGONISE COCAINE EFFECTS; MIGHT LEAD TO INCREASED USE IN ORDER TO ACHIEVE "HIGH"

D2 ANTAGONISTS

USED IN SCHIZOPHRENIA; MOST ALSO BLOCK D1, 5-HT AND ADRENERGIC RECEPTORS

TEND TO BLOCK EFFECTS OF COCAINE BUT INCREASE ITS SELF-ADMINISTRATION IN ANIMALS, POSSIBLY DUE TO PARTIAL MASKING OF COCAINE'S EFFECTS

FLUPENTHIXOL - OPEN TRIAL BY GAWIN REPORTED REDUCTION IN CRAVING & USE CONTROLLED STUDY NEEDED

PROLOXIN PATIENTS USE COCAINE

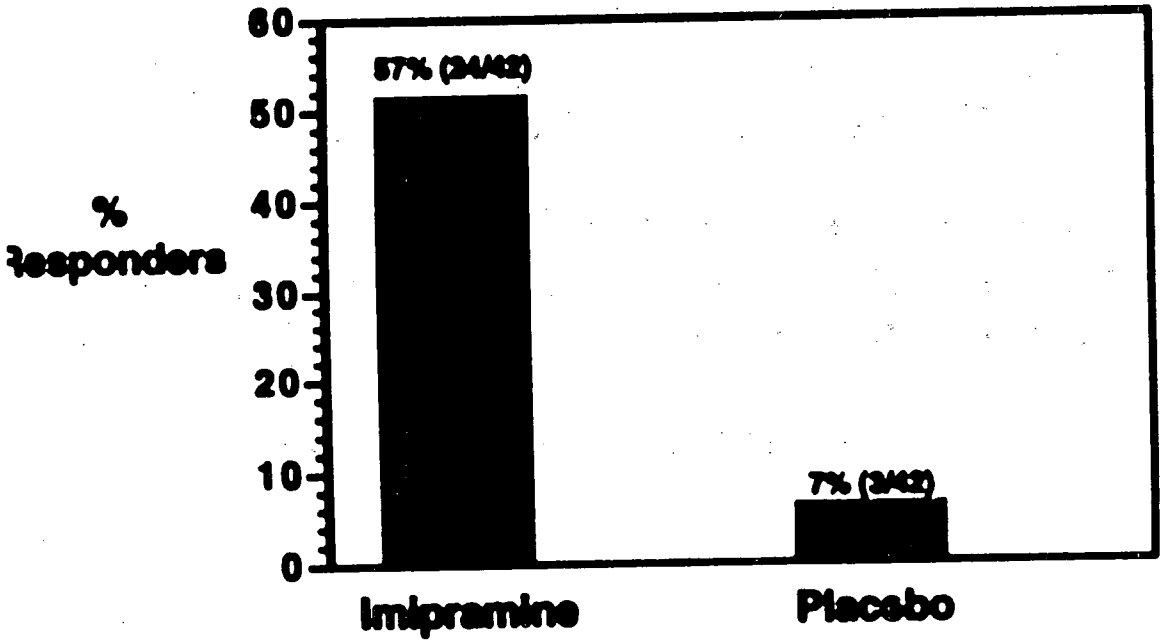
5-HT3 ANTAGONISTS: ONDANSETRON

**PRECLINICAL - REDUCED MESOLIMBIC DA ACTIVITY;
PREVENT WITHDRAWAL EFFECTS FOLLOWING
COCAINE, ALCOHOL AND NICOTINE**

**CLINICAL - NO ABUSE POTENTIAL;
REDUCED ALCOHOL CONSUMPTION IN ALCOHOL
USERS (APPLICABILITY TO DEPENDENCE UNCLEAR);
BLOCKED RUSH & FEEL OF COCAINE
NO CLINICAL TRIALS
ONLY PARENTERALLY AVAILABLE
EXPLORATION OF MECHANISMS MAY BE VALUABLE**

Global Response

(much improved depression **and** 75% reduction in self-report drug use)



Primary could be:

Drug use as measured by:

- **urine tests; breathalizer**
- **self - report**
- **observer report**
- **money spent on drugs**

Retention

Physician or patient asssessment of severity

5-HT1a AGONISTS

PRECLINICAL - INCREASE DA SYNTHESIS IN NUCLEUS ACCUMBENS & CONDITIONED PLACE PREFERENCE

BUSPIRONE - NO WITHDRAWAL OR SELF-ADMINISTRATION - NO CLINICAL DATA ON ADDICTS

GEPIRONE - NO EFFECT IN RECENT STUDY

Are Substance Use Disorders Moral Problems, "Diseases", or "Conditions"?

It may depend on the diagnosis:

Abuse - may be behavioral:

DSM - IV & ICD - 10 disagree

Dependence - more like a disease:

agreed-upon definition: ICD-10 and DSM-IV agree on criteria for dependence

has a course; tendency to relapse

DESIPRAMINE

META-ANALYSIS

Characteristic of randomized desipramine (DMI) studies

Study	No. pat.	Treat*	Days of study	Reten. in tr.	Abstin. in treat.
Tennant & Tarver, 85	11 11	DMI Plac	12 15	55% 55%	64% u.cl 70% u.cl
Giannini et al., 87	10 10	DMI Plac	45	80% 80%	NA
Arndt et al., 92 !Methadone M.	36 23	DMI Plac	84	NA	70% u.cl-25%* 70% u.cl-70%*
Gawin et al., 89	24 24	DMI Plac	84	38% 31%	59% abst 17% abst
Kosten et al., 89	21 18	DMI Plac	56	NA	38% abst 55% abst
Kosten et al.,92 !Methadone M.	30 31	DMI Plac	84	73 87	28% u.cl 24% u.cl
McElroy et al, 89	9 6	DMI Plac	168	50% 50%	78% abst 50% abst
Weddington et al., 91	17 21	DMI Plac	84	53% 75%	6.3 wk c free 4.6 wk c free

* 6 month follow-up

CARBAMAZEPINE

EFFECTS OPPOSITE COCAINE: INCREASE DA CONTENT IN BRAIN SLICES

ANTI KINDLING HYPOTHESIS

OPEN STUDY SHOWED SIGNIFICANT EFFECT (HALIKAS)

NO EFFECT IN CONTROLLED STUDIES

EXISTING PHARMACOTHERAPY FOR SUBSTANCE USE DISORDERS

METHADONE
NALTREXONE
BENZODIAZEPINES FOR ALCOHOL DETOXIFICATION
DISULFIRAM
LAAM
BUPENORPHINE (IN FINAL TESTING STAGE AND LOOKING GOOD)

WHAT ABOUT COCAINE?

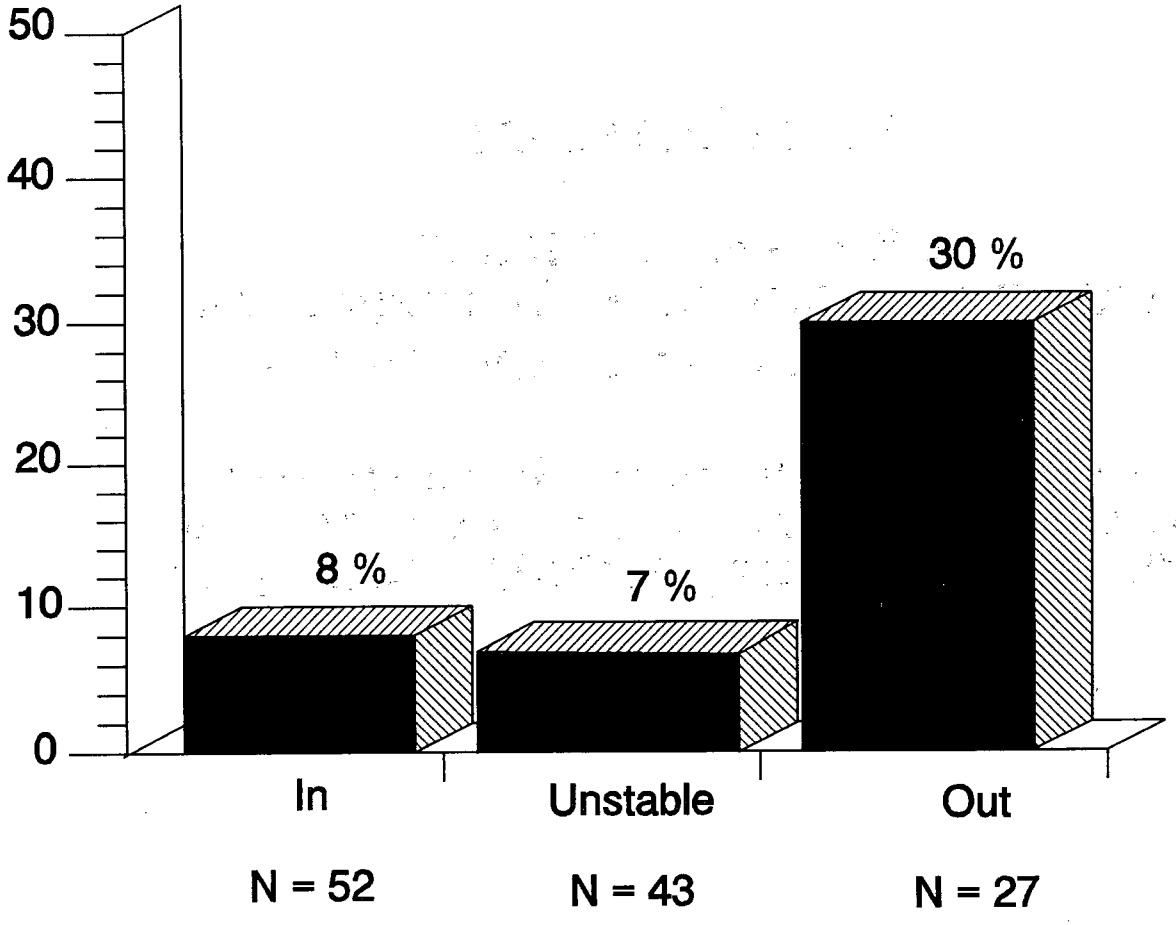
INCREASE COCAINE CATABOLISM

LANDRY (SCIENCE, MARCH, '93); CREATED A MONOCLONAL ANTIBODY THAT BINDS TO COCAINE AND THEN BREAKS IT DOWN

ANTIBODIES AS A FORM OF PASSIVE IMMUNIZATION; COCAINE METBOLIZED BEFORE IT CAN WORK

TEST-TUBE STAGE

Seroconversion by 48-Month Treatment Patterns



Potential Approaches to Drug Abuse Treatment

- **Reduce Relapse to Drug-Taking Behavior**
- **Reduce Craving**
- **Attenuate Withdrawal Symptoms**
- **Antagonize Acute Overdose Toxicity**
- **Reduce Drug-Taking and Drug-Seeking Behavior**

Pharmacotherapies For Substance Abuse Drug Status

- New Chemical Entity (NCE) – PRE – IND
- IND Drug – Being Developed for Another Indication
- Marketed Drug – For Another Indication

5-HT TRANSPORTER

MAY CONTRIBUTE TO EUPHROIC AND REINFORCING EFFECTS OF COCAINE AND OTHER SUBSTANCES

FLUOXETINE: (BATKI, 1993) -2 STUDIES, BOTH GOOD DESIGNS

METHADONE (N=52): LESS COCAINE USE & CRAVING IN FLUOX. GROUP; FEW ACHIEVED ABSTINENCE

PRIMARY COCAINE (N=32): FLUOX. GROUP HAD LOWER DROPOUT RATE; NO DIFFERENCES IN USE

OPIATE AGONISTS, PARTIAL AGONISTS, & ANTAGONISTS

METHADONE: HIGH DOSES (120 MG) SUPPRESS "SPEEDBALL" (Kosten); OPEN TRIAL NEEDS CONTROLLED STUDY

BUPRENORPHINE:
SUPPRESSES COCAINE IN RHESUS MONKEYS (Mello)
POTENTIATION OF COCAINE IN SQUIRREL MONKEYS (Kamien)
NO EFFECT IN LARGEST CLINICAL STUDY (Johnson)

NALTREXONE - MIXED DATA

LITHIUM

NO PRECLINICAL RATIONALE

FEW STUDIES

NO OVERALL BENEFIT

A FEW CASES OF PERSONS WITH CYCLOTHYMIA OR BIPOLAR ILLNESS WHO IMPROVED

CONCLUSIONS

PSYCHOSOCIAL TREATMENTS HELPFUL BUT MUCH ROOM FOR IMPROVEMENT

DESIPRAMINE HAS WEAK EFFECT
AMANTADINE AND FLUOXETINE MAY HAVE EFFECT

NOTHING IDENTIFIED WITH STRONG EFFECT

AGENTS WITH WEAK/MODEST EFFECTS MAY BE USEFUL IF COMBINED WITH PSYCHOSOCIAL TREATMENT

CONCLUSIONS

MANY FALSE LEADS, PRIMARILY DUE TO USE OF OPEN, UNCONTROLLED TRIALS

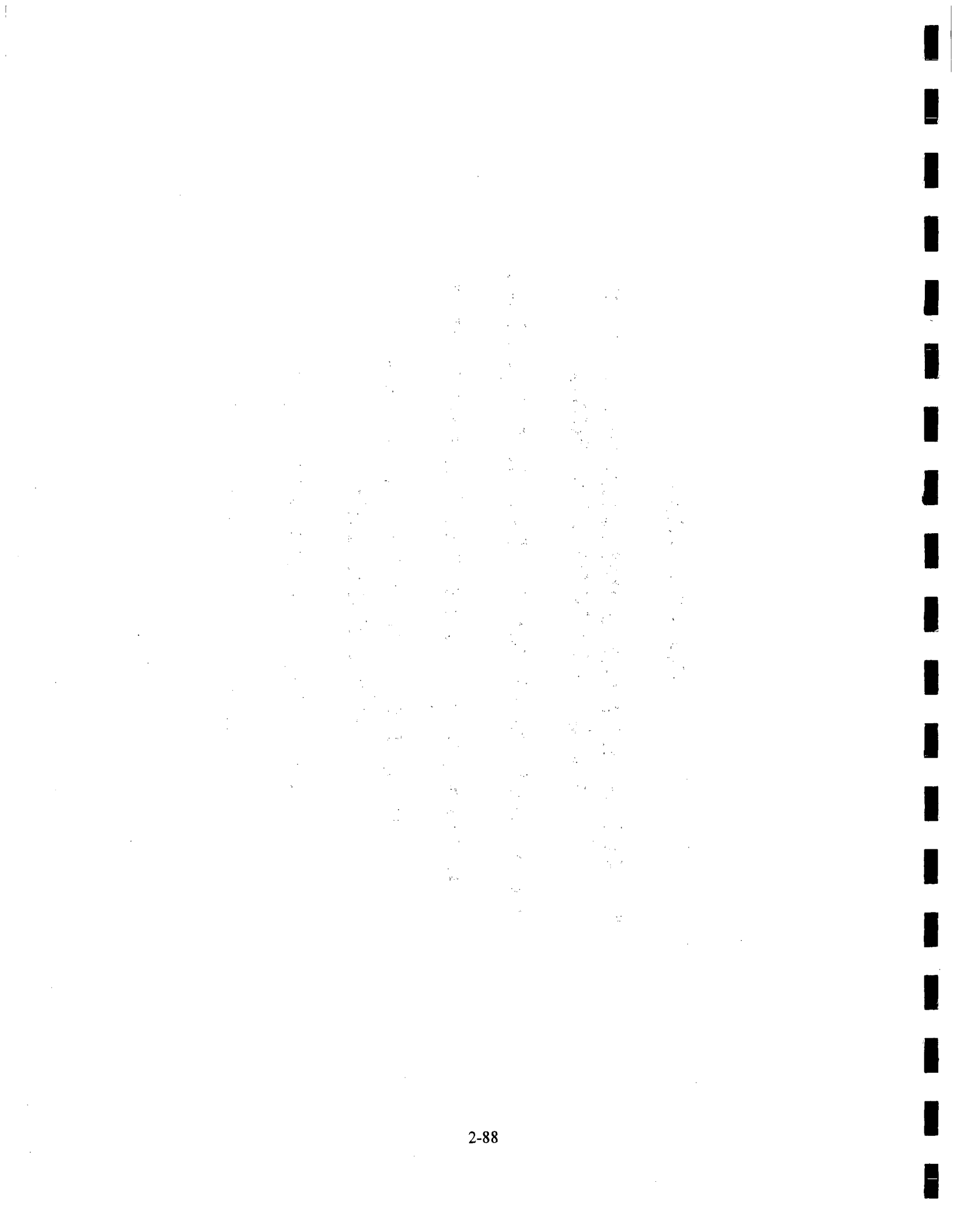
APPROACH HAS BEEN TO TEST EXISTING DRUG

EASIEST, LEAST EXPENSIVE THING TO DO?

SPOILED DUE TO BEING LUCKY WITH OPIATE RESEARCH?

MORE UNDERSTANDING NEEDED

BACK TO THE BENCH



The Development of Medications for the Treatment of Drug Addiction

Aimee Friedman Jocelyn Lehrer
Counterdrug Technology Assessment Center
Office of National Drug Control Policy

INTRODUCTION

This paper discusses the primary reasons for the current reluctance of pharmaceutical companies to invest in the research, development, and marketing of medications for the treatment of opiate and cocaine addiction. Recent developments in federal processing and clinical trial procedures which should stimulate company interest in anti-addiction efforts are elaborated. The report draws heavily from the Institute of Medicine's The Development of Medications for the Treatment of Opiate and Cocaine Addictions: Issues for the Government and Private Sector.

PROBLEM STATEMENT

There has long been limited pharmaceutical research, development, and marketing in the field of addiction treatment. Only three substances, methadone, levo-alpha-acetylmethadol (LAAM), and naltrexone, have ever been marketed specifically for the treatment of opiate addiction. Methadone became successful in the 1960's, and the latter medications were developed in the late 1960's and early 1970's. With the exception of the 1993 approval of LAAM, no drugs to treat opiate addiction have been approved since over a decade ago. Currently, no approved medication for the treatment of cocaine addiction exists (IOM, 1995).

It is estimated that there are 2.1 million cocaine-dependent persons and 750,000 to 1 million opiate-dependent persons in the United States (Hunt and Rhodes, 1992; Kreek, 1992). Substantially greater pharmaceutical activity has been documented in areas with afflicted populations of comparable or substantially smaller size. About $400-500 million is spent yearly on the marketing and development of medications to treat the 2.1 million epilepsy patients in the U.S., and three new drugs have been approved or are in the process of approval (IOM, 1995). Also, several pharmaceutical companies have products in various phases of development for the treatment of amyotrophic lateral sclerosis (Lou Gehrig's Disease), which currently afflicts approximately 25,000 individuals in the United States (IOM, 1995).

There are several reasons for the current lack of pharmaceutical interest in the development and marketing of anti-addiction medications. Primary obstacles are in the area of treatment financing, and include issues of funding methods, patient population size, and the regulatory policies of state governments and federal agencies. Other disincentives include liability concerns, the degree of current knowledge of mechanisms of addiction and relapse, lack of trained specialists for the treatment of drug addiction, difficulties in conducting clinical research, and societal stigma (IOM, 1995).

The financing of treatment is a major focus of concern. Few opiate- or cocaine-dependent individuals have private insurance or the private means to pay for treatment. Of those who do have insurance, only a fraction use it, due largely to the stringent limitations most private insurance plans place on treatment nature and duration. Fear of employer notification is a hindrance as well.

For instance, while approximately 10% of methadone treatment recipients have private insurance, only 5.2% use it to finance their treatment (SAMHSA, 1994). Due to the difficulty associated with using private insurance, fiscal responsibility is left mainly to federal, state, and local governments. For instance, 80% of methadone treatment in 1993 was financed through these means. The primary problem with public financing is that policy is seen by companies as having little guarantee of stability. Additionally, public subsidy and Medicaid carry substantial restrictions on treatment amounts and time periods that notably decrease the potential market for medications, by cutting down on the supply-demand aspects of free enterprise (IOM, 1995). State Medicaid programs are not required by federal law to cover drug abuse treatment; when offered, treatment coverage is often quite limited (GAO,1991; CRS,1993b).

The market size for anti-addiction medications is also limited. First, while the population of cocaine- and opiate-dependent individuals is already small, only a fraction of these individuals are expected to seek treatment and be consistent in recovery efforts. For example, while a 1992 census indicated that there were an estimated 500,000-1 million opiate-addicts in the U.S. (Kreek, 1992), 117,000 received methadone treatment and an additional 80,000 were enrolled in other types of treatment programs in 1993 (Harwood, et.al., 1994). It is important to note, however, that a 1992 National Drug and Alcoholism Treatment Survey found an 85.3% utilization rate for methadone treatment programs (IOM, 1995).

Second, any anti-addiction medication developed is likely to be useful for only one indication within addiction (e.g., reduction of withdrawal symptoms), restricting the range of its use. A single medication would probably also be usable for only a portion of the patient population, as the narcotic-dependent group is a heterogeneous one that differs along a variety of dimensions (e.g., pregnancy, psychiatric status, multi-drug use, HIV, socioeconomic supports) (IOM, 1995). However, it has been suggested that the potential applications of new anti-addiction medications are broader than commonly perceived, in that a single drug can have more than one use in the medical spectrum. For example, in "Lives Saved by Naloxone Hydrochloride" (NIDA, 1992), Henrich Harwood documents the variety of uses for Naloxone, a drug originally created for the treatment of overdose and the harmful side effects of heroin and other opiate abuse. For example, over three million patients yearly are given Naloxone in operating rooms to counteract the analgesic effects of high dosages of opiates given during surgery. Methadone was also commonly used as an analgesic at one point, and clonidine, an agent initially marketed for high blood pressure, has been administered for the treatment of heroin and nicotine withdrawal symptoms (H. Kleber, Center on Addiction and Substance Abuse-CASA, personal communication). Therefore, it is clear that a medication developed for one specific purpose may have wider medical usage. Such is likely to be the case for new medications developed for drug-dependent individuals.

Third, a substantial portion of treatment providers firmly embrace the concept of drug-free treatment. Many of these individuals view pharmacotherapy as the substitution of one drug for another (H. Kleber, CASA, personal communication).

The likelihood of disease and pregnancy in the patient population also raises concerns regarding research and product liability. Lawsuits are an issue with the potential for harm due to unforseen effects of the medication in combination with drugs of abuse, illness, or pregnancy (IOM, 1995). However, it should be noted that the possibility of subjects' poly-drug abuse or sensitive physical conditions were not a major liability concern in the LAAM and buprenorphine clinical trials conducted through Medications Development Division (MDD) of NIDA. Also, the adverse effects of trials for AIDS or other diseases are probably higher that those perceived for LAAM. Additionally, a Data Safety Monitoring Board for multi-center NIDA-sponsored trials is utilized to

insure safety of the subjects (C. Grudzinskas, Medications Development Division-MDD, personal commun

The state of scientific knowledge as well as difficulties associated with attracting researchers to the addiction field also inhibits company interest. As is the case with scientific understanding of most diseases, there are presently gaps in the knowledge of addiction processes. The mechanisms of cocaine action and drug craving have not been fully elucidated, and companies are deterred from becoming involved in an area where they perceive the basic knowledge base as weak IOM, 1995). However, it is important to note the conclusions of a report requested by the Senate Committee on the Judiciary and done by Pharmaceutical Manufacturers Association (PMA), which involves the survey of companies that had and had not been involved with research and development in the drug abuse field. Companies that had been involved in related research and development did not view the state of neuropharmacological knowledge as a problem. It was only companies which had not pursued this work that insisted the scientific base was too narrow to enter the field (PMA letter, 1989). Additionally, Dr. Herbert Kleber (CASA) has noted that the scientific community has far more information on cocaine and heroin's effects on the brain than on neurological mechanisms in other illnesses, such as depression and schizophrenia; numerous companies are pursuing costly projects in these areas. Also, as of 1994, all recognition and receptor sites for the major drugs of abuse have been identified and cloned; this major advance will allow scientists to design and test chemical compounds which act at drug receptor sites within the body (C. Grudzinskas, MDD, personal communication).

Scientists and treatment specialists face numerous disincentives to entering the addiction treatment field, including "the perceived low prestige, low-paying positions, difficulties in conducting clinical research, personal health risks of working with patients who often have serious illnesses, uncertain treatment reimbursement, a stigmatized patient population, and the involvement of many patients with crime and the criminal justice system" (IOM, 1995). These obstacles have led to an increased reluctance on the part of clinicians to enter the field of addiction treatment. Physicians are the individuals that the industry works with in research and development, the relative paucity of clinical activity in addiction treatment development leads companies to believe that there may be little clinical interest in new anti-addiction medications (H. Kleber, personal communication).

Societal stigma is a deterrent to involvement for pharmaceutical companies as well as researchers and clinicians. Companies fear that a drug used to treat addiction will be unpopular for other indications, due to negative public sentiment toward drug addiction and the associated population (IOM, 1995).

Some companies also believe that the process of clinical research to develop anti-addiction medications would be problematic, due to difficulties with subject reliability, accessibility, and follow-up interviews. Assessment of test-drug effects could be easily confounded by patient conditions and illnesses such as multi-drug abuse, pregnancy, HIV, and tuberculosis. There could also be difficulty in conducting adequate control trials and delineating appropriate efficacy goals or standards (IOM, 1995). However, NIDA conducted successful clinical trials for LAAM and buprenorphine, enrolling almost 1400 subjects in 38 centers over the course of fourteen months. The above factors were not major impediments to conduction of clinical trials, and should not be of concern (C. Grudzinskas, MDD, personal communication).

Finally, clinical research on a controlled substance is cumbersome due to DEA and state regulations. If a drug is labeled by DEA as a Schedule II substance, it is subject to DEA determination of yearly production quotas. While quotas are enforced in order to prevent drug diversion, they ultimately lead to a significantly restricted market for the manufacturer. Manufacturing costs may be adversely affected by the quotas, as optimal production batch sizes

may exceed quota limitations. Scheduling also places notable restrictions on physicians who would otherwise prescribe the medications more widely (IOM, 1995).

The DEA scheduling process commonly takes from several weeks to two months after the approval of a New Drug Application (NDA) by the FDA. There is a perception among companies that the scheduling process takes too long; this is probably because scheduling comes at the time when manufacturers are ready to move forward with marketing.

If a potentially marketable drug is a narcotic, it must go through additional procedures imposed by individual states once the federal screening process has been completed. Currently, these state processes frequently take over two years. Dr. Frank Vocci, Deputy Director of MDD, suggests that the sluggish process in many states, due to their individual policies and processes, acts as a primary obstacle to anti-addiction medication development for pharmaceutical companies (personal communication).

While the DEA determines scheduling on a federal level, each state has its own separate scheduling process. State scheduling standards may differ from those of the DEA. Many states cannot begin their process of new screening and scheduling until after completion of the DEA evaluation. In states with linkage between federal and state agencies (New Jersey, Texas and Illinois), the scheduling process can be completed in thirty days. In states that require their own scheduling to be enacted (New York and California), action by a state regulatory agency or legislature must be taken. The possibility of significant delay at the state level is increased as many state legislatures convene in widely spaced sessions (IOM, 1995).

The problem of drug scheduling is not the only obstacle preventing medications from being incorporated into state treatment programs. Compliance with federal and state guidelines by the state narcotic treatment programs are the responsibility of that specific state. In fact, federal approval of any treatment program is dependent of the state's approval of that program first. Every program must abide by federal regulations as well as state specifications, which can be even more stringent.

Differing state jurisdictions make it difficult for a particular drug to reach the entirety of its predicted recipient population. While the federal prerequisite for an addict to be admitted to a methadone maintenance treatment program is a documentable history of narcotic dependence (L. Cummings, MDD, personal communication), some states have much stricter policies regarding program participation. For example, Californians must have a two year history of addiction in order to receive treatment in state programs; this then allows for only two years of treatment. New York State requires proof that a prospective patient has undergone treatment at least twice previously, before allowing the individual into a state program (IOM, 1995). In addition, by federal standards, all clinics must have a licensed physician as the designated medical director. Alternatively, California requires one physician for every 200 patients and a case worker to counsel every 40 patients. New York State insists on one physician for every 300 patients, two full-time nurses for the first 300 patients, and one for every hundred thereafter, along with one counselor for every 50 patients. Any center not up to these standards and others will be prevented from administering the new medication (IOM, 1995). Thus, companies are deterred by the complexities of state regulations when considering the feasibility of acceptable return on investment.

The history of the development and marketing of LAAM all too well portray the difficulties of the entire licensing process. July 9, 1995 was the two year anniversary of the approval of LAAM. In those two years, it has only been approved in approximately 60 clinics in 24 states. The majority

of drug-dependent individuals reside in New York State and California, where LAAM has yet to be approved (IOM, 1995).

BioDevelopment Corporation, the LAAM manufacturer, cites the long nature of the state approval process as the single most unfavorable factor in the development and distribution of anti-addiction medications. However, the FDA, DEA, ONDCP and NIDA collectively suggested that BioDevelopment complaints were overstated. It was concluded that if BioDevelopment had notified state legislators and regulatory agencies earlier, LAAM could have gone through the process of state approval and scheduling in a shorter time span (IOM workshop, 1994). Therefore, although state policies are still problematic, the approval process can be facilitated. If this is the case however, one wonders why New York and California have still not approved LAAM in spite of having two years to do so (H. Kleber, CASA, personal communication).

PROGRESS

In the years from 1989 to the present, several problems related to federal processing, approval, clinical trials and other areas of concern have been addressed on the federal level.

1 - NIDA formally established the Medications Development Division in 1990, with the specific goal of helping addiction treatment medications to be brought to market. Dr. Charles Grudzinskas, with twenty years of experience in the pharmaceutical industry, was chosen to be Director (L. Cummings, MDD, personal communication). MDD now works with the industry "to perform the research and development necessary to secure FDA marketing approval" (IOM, 1995).

2 - The FDA Food, Drug and Cosmetic Act provides financial incentives to pharmaceutical companies through accelerated approval, rolling New Drug Applications (NDA), and treatment Investigational New Drug programs. These provide for faster FDA review, as well as patient access to medications before final FDA approval. Company products can now be moved through the system more quickly, allowing the generation of revenue to begin before approval and possible scheduling are completed (IOM, 1995).

3 -In May 1991, the FDA classified drug dependence as a severe, life-threatening illness. As a result, the FDA now utilizes an expedited review process for all potential anti-addiction medications. The employment of rolling NDA and accelerated approval processes led to the approval of LAAM in eighteen days from NDA submission (IOM, 1995). Naltrexone also received a new indication for adjunctive treatment for alcoholism in an expedited manner in late 1994. Buprenorphine is currently undergoing a rolling NDA for the treatment of opiate dependency (L. Cummings, MDD, personal communication).

4 - The User Fee Law, as part of the FDA Prescription Drug User Fee Act of 1992, mandates a fee for all companies pursuing an NDA. (H. Davis, FDA, personal communication) funds generated as a result of the law allowed for three new hires at FDA, with expertise in the review of potential anti-addiction medications, to facilitate the NDA approval process (C. Grudzinskas, MDD, personal communication).

5 - The issue of recognizable clinical endpoints was addressed as a concern by pharmaceutical companies. In late 1992, coordinated specifically for anti-addiction medications, efficacy endpoints and approval requirements for most aspects of clinical trials were established by the FDA Advisory Committee and NIDA. Called, "Guides for Development and Evaluation of Drugs for the Treatment of Psychoactive Substance Use Disorders," they are still in draft form; however, Dr. Vocci, MDD, suggests that the "non-institutionalized format is not a deterrent to companies."

These primary outcome measurement standards have been very helpful to the heads of R & D and potential sponsors in the formulation of drug development programs (IOM, 1995).

6 - NIDA is actively considering funding an additional several VA sites where clinical trials would take place, from protocol design to data collection and preparation for statistical analysis. Emphasis would be placed on anti-cocaine medication development, with a focus on the elimination of craving and the blockage of cocaine from its receptor (C. Grudzinskas, MDD, personal communication).

7 - LAAM's approval involved the rolling NDA process, and NIDA-sponsored centers were used for clinical trials. DEA cooperation led to registration of the clinical sites in six months; there is usually a higher time variable as to when site registration can be completed (L. Cummings, MDD, personal communication). The communication and cooperation of NIDA, FDA, DEA and ONDCP from the start of its development in 1990 until its approval in 1993 brought about an 18 day NIDA/FDA approval. Only another 60 days were needed for rescheduling and treatment regulation guidelines to be established by the DEA and ONDCP. LAAM's development and approval are not quite as impressive when histories of other public health important medications are considered. However, "if the industry, the research community and regulatory agencies can all act with mutual respect in their common duty to public health, each will benefit" (Grudzinskas and Wright, 1994).

8 - In April of 1995, it was announced that the "reasonable pricing" clause introduced in 1989 to National Institute of Health's (NIH) Cooperative Research and Development Agreement (CRADA) was removed (NIH, 1995). The deletion of this clause is a significant step toward long-term, productive partnerships between the NIH and the pharmaceutical industry, as it allows for independent company digression in the pricing of developed medications. Additionally, there have been an increased number of material transfer and screening agreements since the repeal of the clause, allowing NIDA to screen more compounds for anti-addiction medications and increasing the prospect for NIDA-industry partnerships in the development of anti-addiction medications in the near future (L. Cummings and F. Vocci, MDD, personal communication).

CONCLUSION

Even with recent progress in federal policy and clinical trial facilitation, it is evident that further effort is required to facilitate pharmaceutical involvement in the addiction treatment field. It is largely the responsibility of federal and state governments and agencies to streamline and coordinate their processes so as to enhance the probability that pharmaceutical companies will become invested in both the well-being of drug-dependent individuals and our nation as a whole.

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Workshop II:
Drug Testing/Monitoring Technology

163299

THE ORLEANS PARISH DISTRICT ATTORNEY'S

DIVERSIONARY PROGRAM

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Presentation at the:

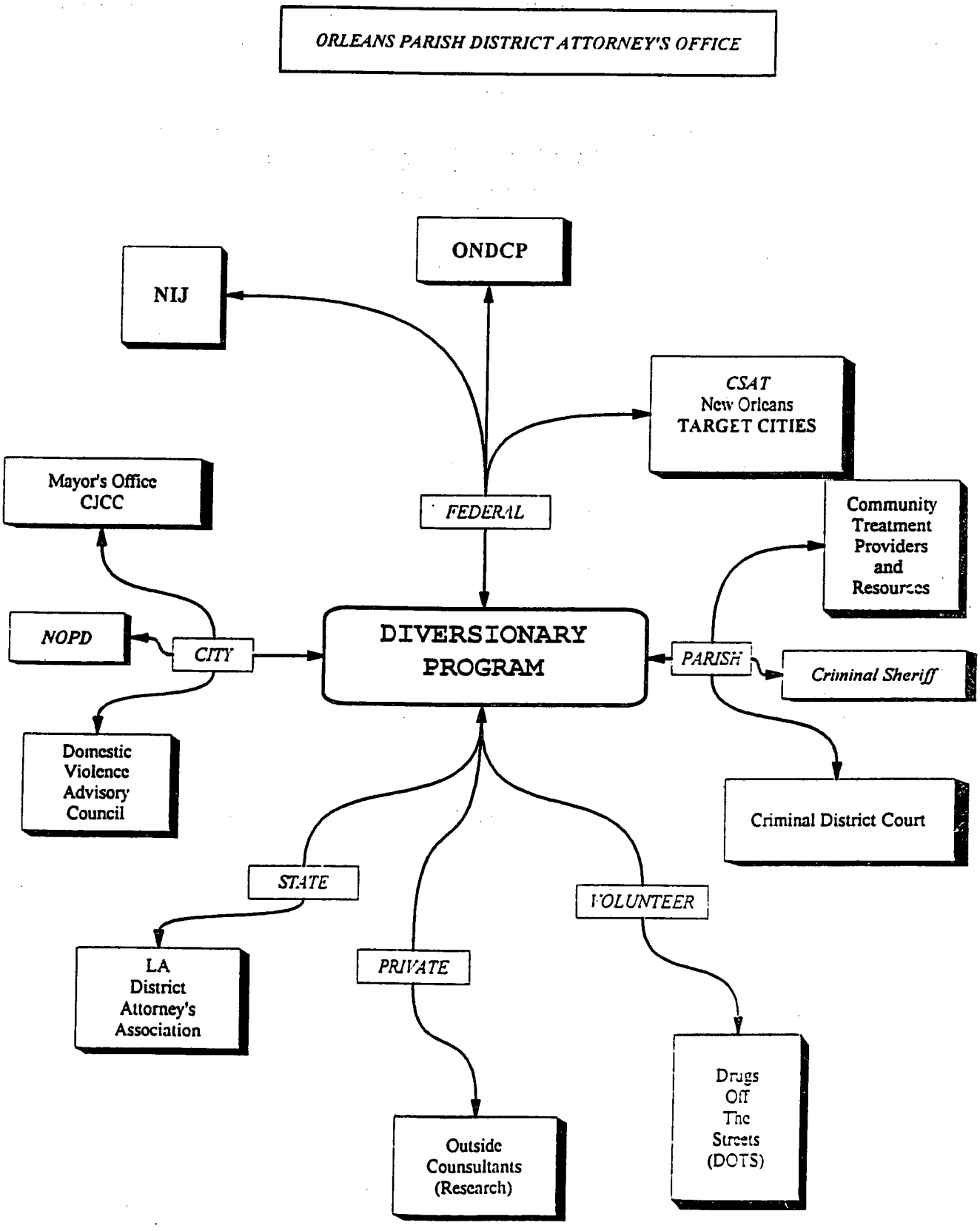
ONDCP/CTAC DRUG ABUSE TREATMENT TECHNOLOGY WORKSHOP

August 16, 1995

COMPREHENSIVE APPROACH TO DRUG TREATMENT IN CRIMINAL JUSTICE SYSTEM

1. Identification of drug users
2. Assessment and Classification
3. Referral to appropriate treatment
4. Supervision in treatment
5. Frequent drug testing
6. Relapse prevention training
7. Aftercare planning
8. Continuous monitoring

(from 'National Drug Control Strategy", The White House 1992)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PARISH
Criminal Sheriff
Domestic
Violence
Advisory
Council
Criminal District Court
STATE
VOLUNTEER
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Attorney's
Association
PRIVATE
Drugs
Off
The
Streets
(DOTS)
Outside
Counsultants
(Research)

ONDCP
COUNTERDRUG TECHNOLOGY ASSESSMENT CENTER

AND

ORLEANS PARISH DISTRICT ATTORNEY DIVERSIONARY PROGRAM

* Demand Reduction Technology

* To evaluate the use of noninvasive drug testing using the biological matrices of:

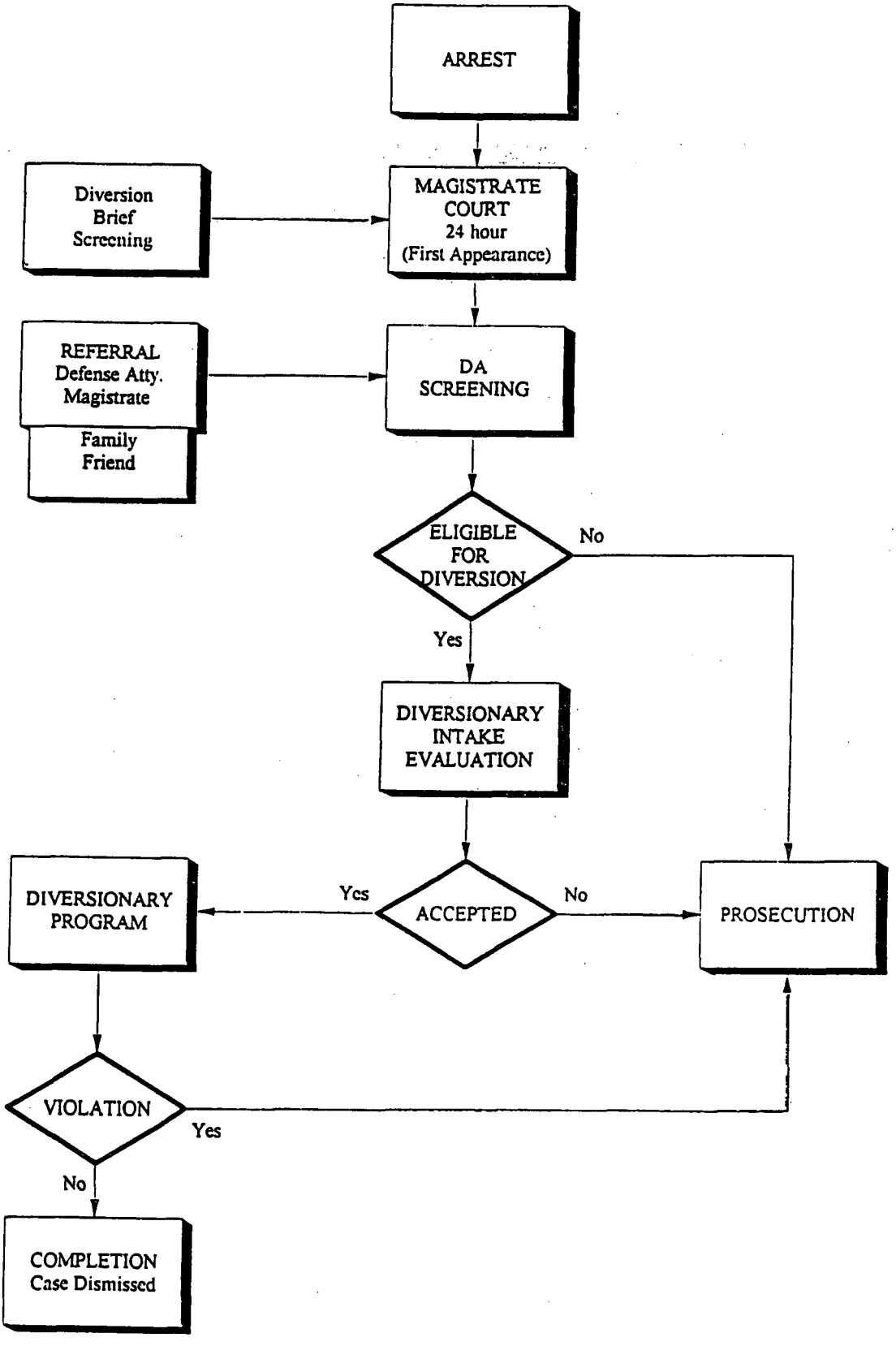
  Hair

  Sweat

  Saliva

* Testbed: currently operating Diversionary Program for drug-involved, first-time offenders

ORLEANS PARISH DISTRICT ATTORNEY
ENTRY INTO DIVERSION PROGRAM



DIVERSIONARY PROGRAM

PARTICIPANTS BY CRIMINAL CHARGE:

FELONY	69%
MISDEMEANORS	31%
NARCOTICS	82%
NON-NARCOTICS	18%

TOP 3 CHARGES

1)	POSSESSION OF CRACK/COCAINE	44%
2)	POSSESSION OF MARIJUANA	30%
3)	PRESCRIPTION BY FRAUD	5%

DIVERSIONARY PROGRAM REQUIREMENTS

- **Misdeameanor = Average 3.8 months**
  Felony = Average 7.6 months

- **Meetings with Diversion Counselor**
  2 - 4 times per month

- **Abstinence**

- **Community Substance Abuse Treatment**

- **Random Urine Testing**

- **Periodic Hair Testing**

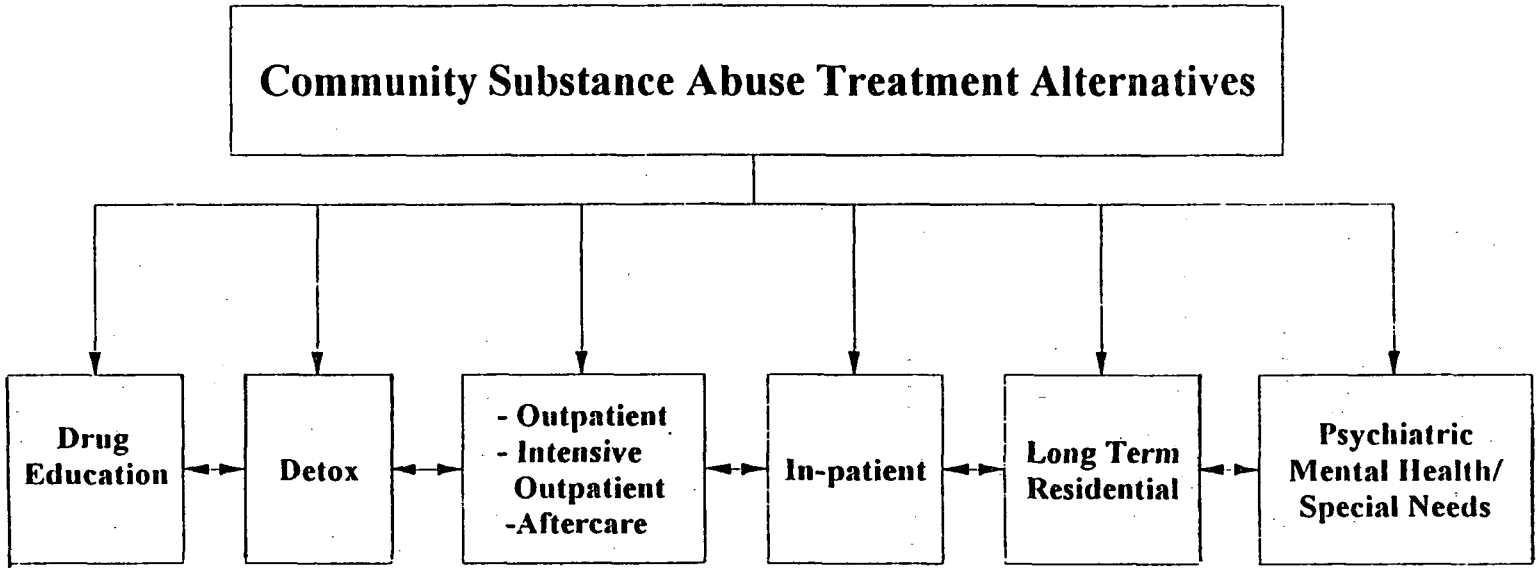
- **12 Step Groups**

- **Payment of Restitution and Program Fees**

- **Family Involvement**

- **Referral to Community Resources**

  - Vocational/GED/Job Search
  - Health/Medical
  - Housing/Homelessness
  - Financial Needs


Community Substance Abuse Treatment Alternatives
Drug Education
Detox
- Outpatient
- Intensive Outpatient
-Aftercare
In-patient
Long Term Residential
Psychiatric Mental Health/ Special Needs

FEATURES OF HAIR AND URINE TESTING

Hair detection:

- Wider "Window" of Detection
  providing an historical view of drug use

  30, 60 or 90-day samples standard, depending upon hair length and period to be analyzed

- Non-invasive collection and easy storage
- Resistant to tampering/adulteration
- If challenged, a second sample can be submitted

Urine detection:

- Reflects recent drug use, 2 - 3 days for many drugs
- On-site testing capabilities
- Wider range of drugs for volume, broad-based testing

USE OF DRUG TESTING
IN THE DIVERSIONARY PROGRAM

HAIR TESTING:

Collection at program intake (on-site) and every 2 months throughout program duration

- assessment of drug involvement
- monitoring drug abstinence
- reduces frequency of urine testing
- provides backup for missed urine tests
- enhances initial and revised treatment planning
- provides a sense of security for program skeptics
- deterrence of drug use since "you can't beat it"
- results reveal highly contaminated samples

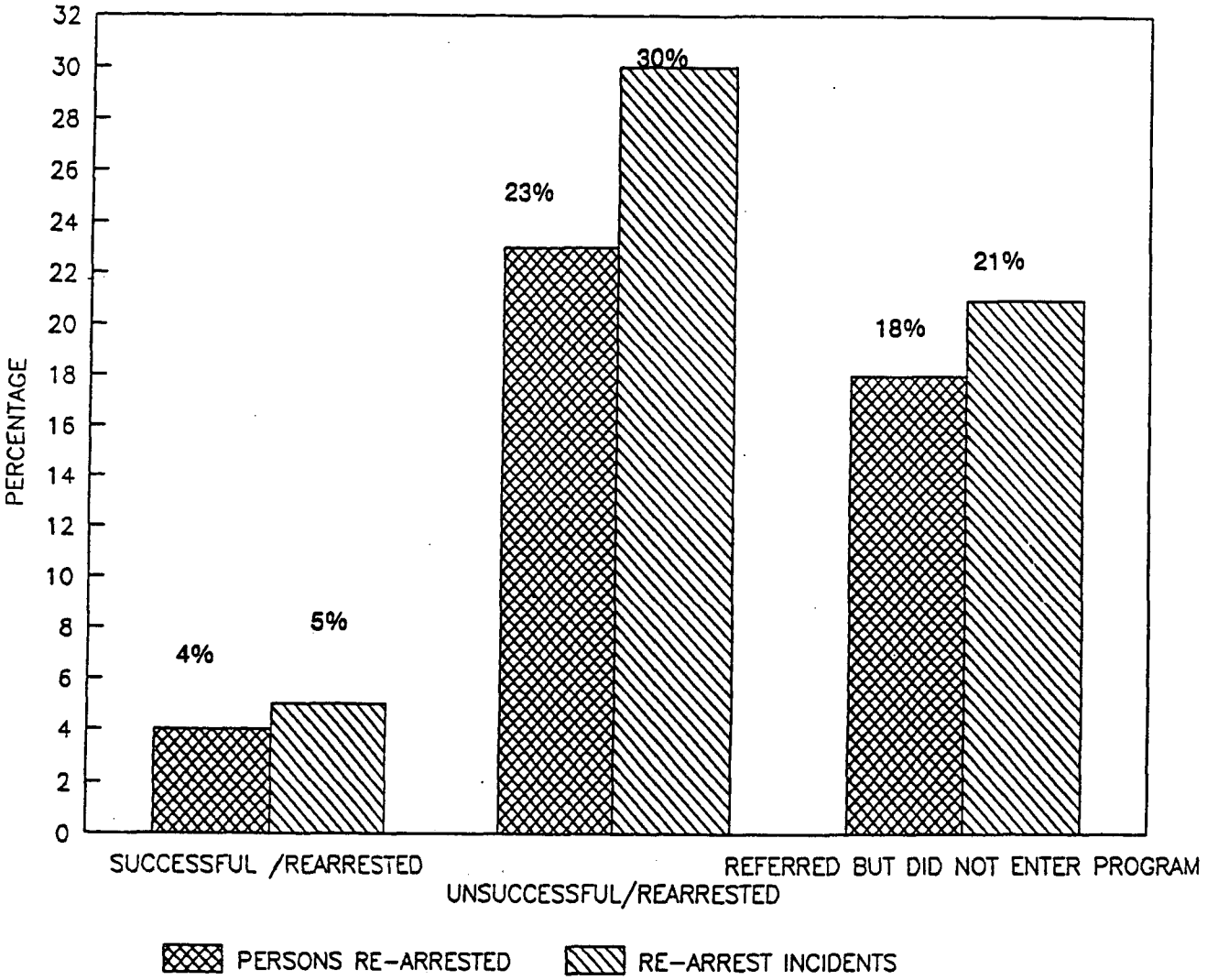
URINE TESTING:

Collection at intake (off-site) and randomly throughout program duration (2-3 times per month)

Daily call to a recorded message line to receive notification (365 days a year)

- provides immediate feedback on most recent drug use
- deterrent effect more frequent
- tests for drugs other than the NIDA 5

RECIDIVISM



(As of 7/25/95)

The Alternative Matrix Program
for Drug Abuse Detection and Deterrence

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3-13

August 16, 1995

Drug Testing/Monitoring Technology

Outline

- Overview of the program
- Issues uncovered with hair analysis any potential consumer should consider
- Example of technology application
  - Tandem mass spectrometry

Focus of the Alternative Matrix Program

Examine the application of other matrices besides urine to deter drug use

- **Hair:**
  - Samples easily obtained
  - Longer window of detection
  - Before widely employed -
    - Examine passive exposure issues
    - Provide better analysis technology

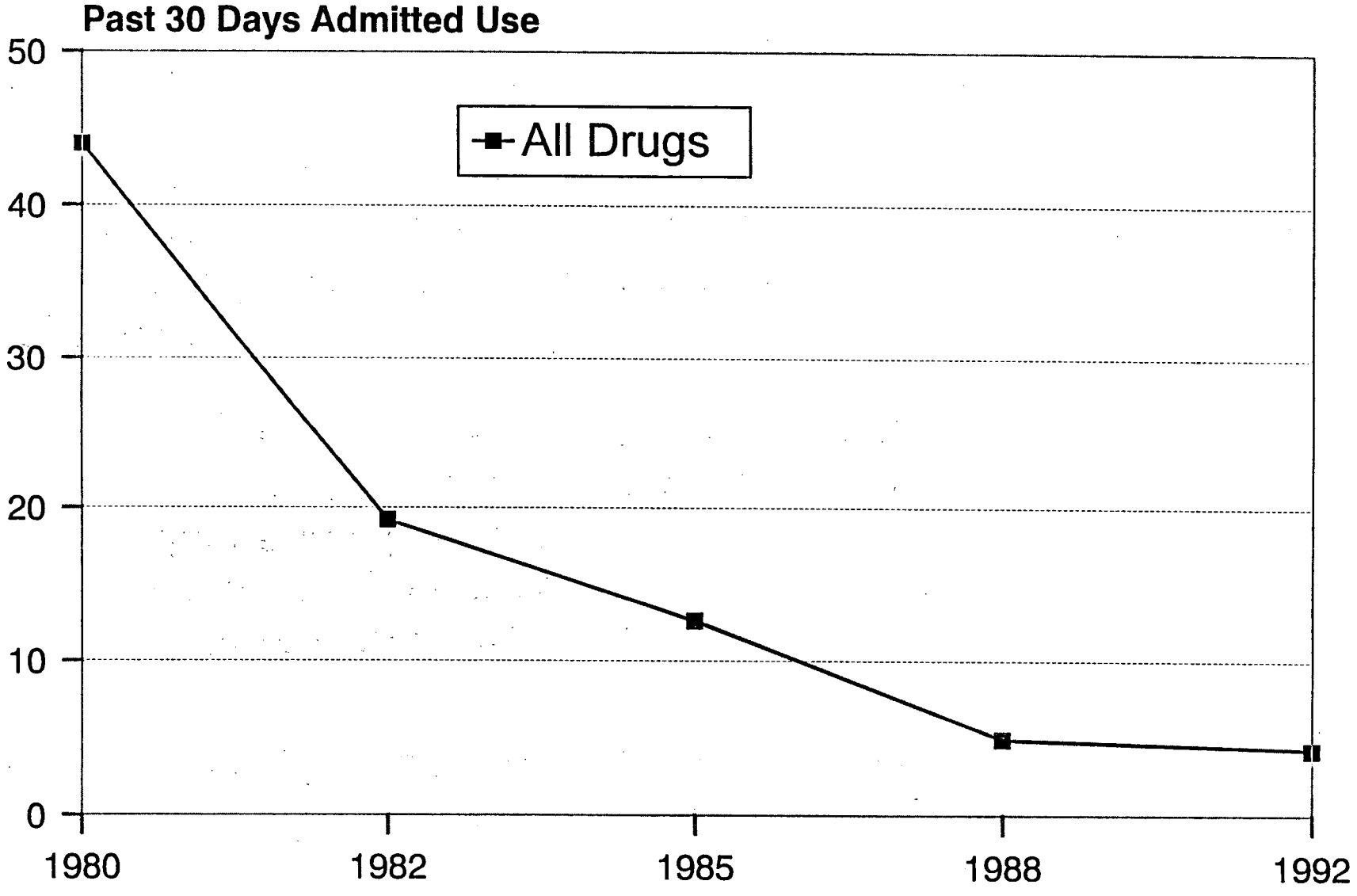
- **Sweat:**
  - Applicability just being investigated
  - Potential for long-term, remote monitoring of high-risk individuals in criminal settings

- **Saliva:**
  - Easily collected
  - Possibility for DWI - Levels correlated with intoxicated state

Does Drug Testing Deter Drug Use?

Percent Reported Drug Use

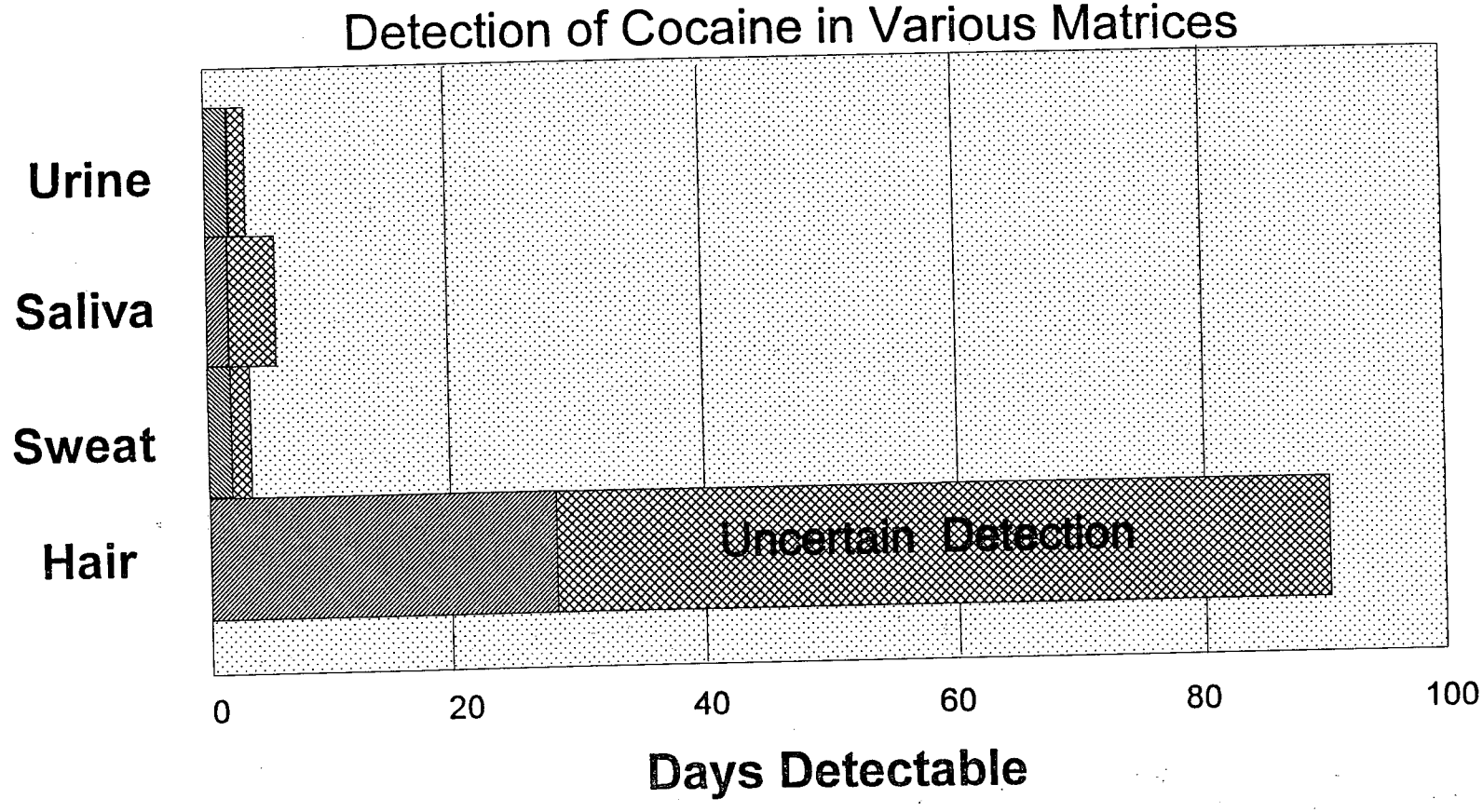
Data from DoD World Wide Surveys



Why Perform Research in Testing Technology?

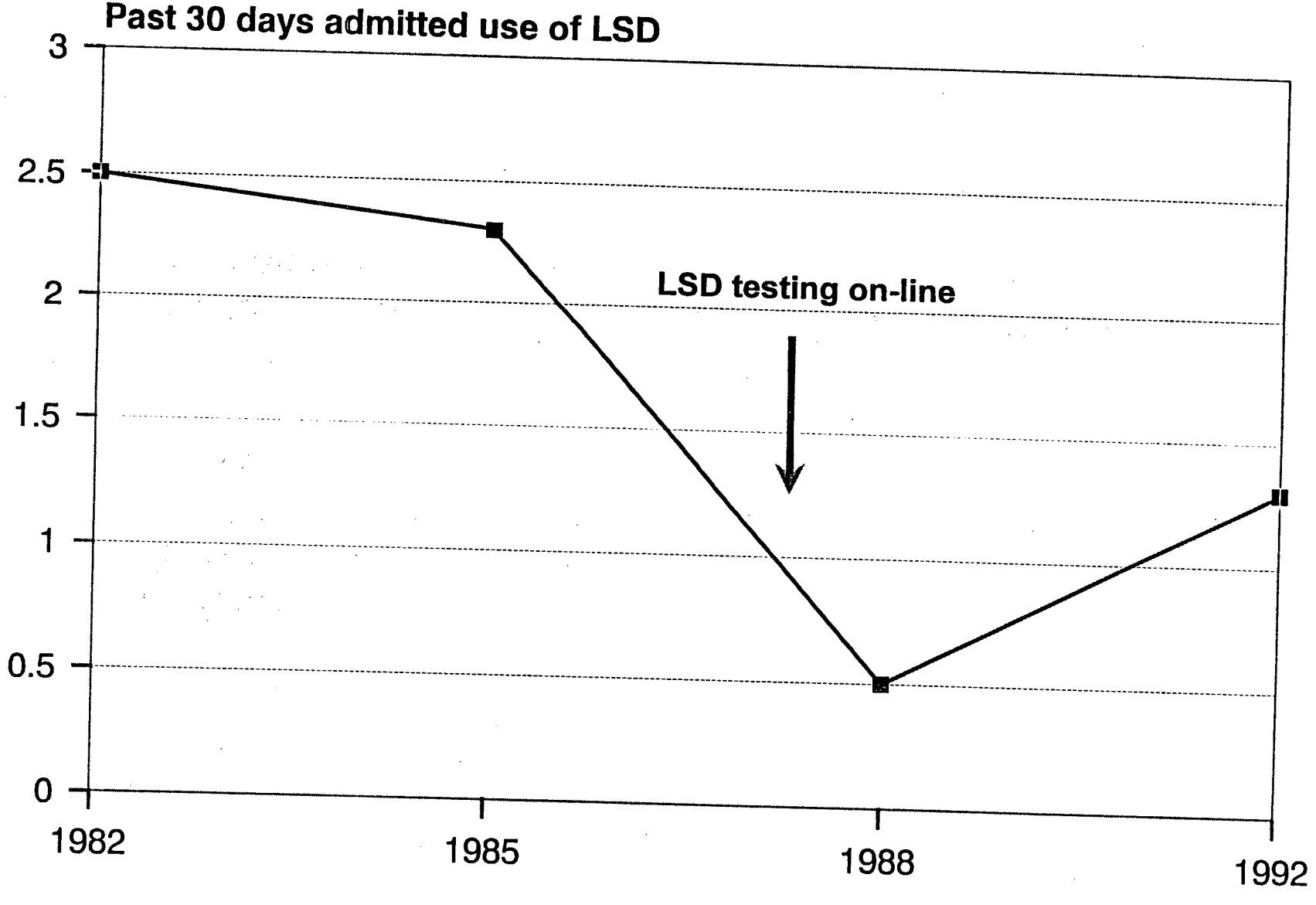
- Main historical matrix was urine
- Urine can:
  - Provide a large sample
  - Drugs present in high concentrations
  - Testing cheap
- Urine disadvantages:
  - Messy to collect properly
  - Can be easily adulterated/substituted
  - Short window of detection for many drugs

Window of Detection Influences
Testing Rate, Convenience, Cost, and Gaming of System by User



Does Impression of Detection Influence Use?

Data from DoD World Wide Surveys



Most Pressing Issue

False Accusation of an Individual as a Drug User

- Depends upon the testing scenario

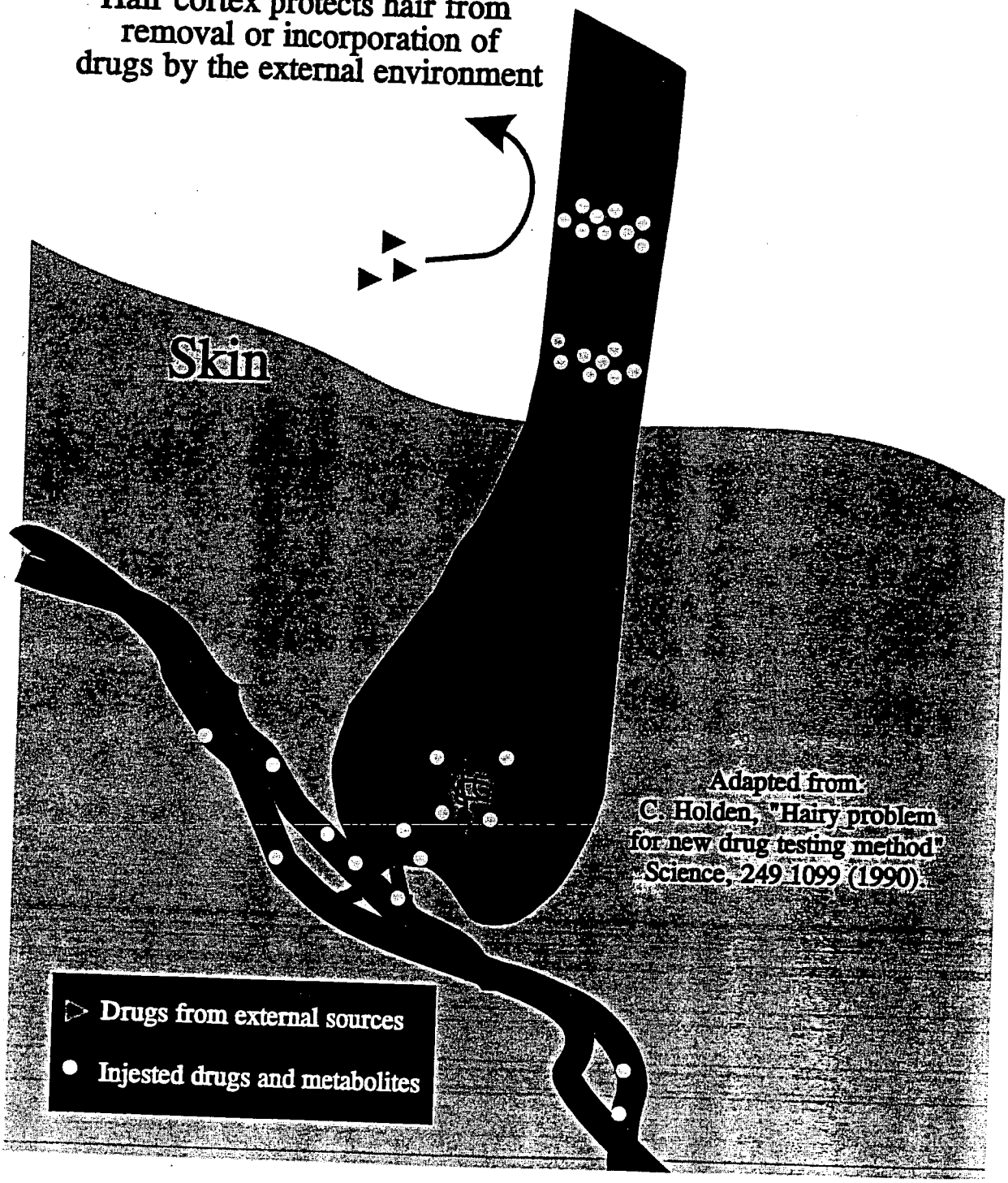
- Legal AND employment purposes
  - Beyond a reasonable doubt
  - Don't want to incarcerate or fire an individual based on faulty science

- Screening or survey purposes
  - False positives must be considered but weight depend upon the consequences

Example is ingestion poppy seeds producing a Heroin positive for urinalysis

Older Hypothesis for Incorporation of Drugs (Growth Model)

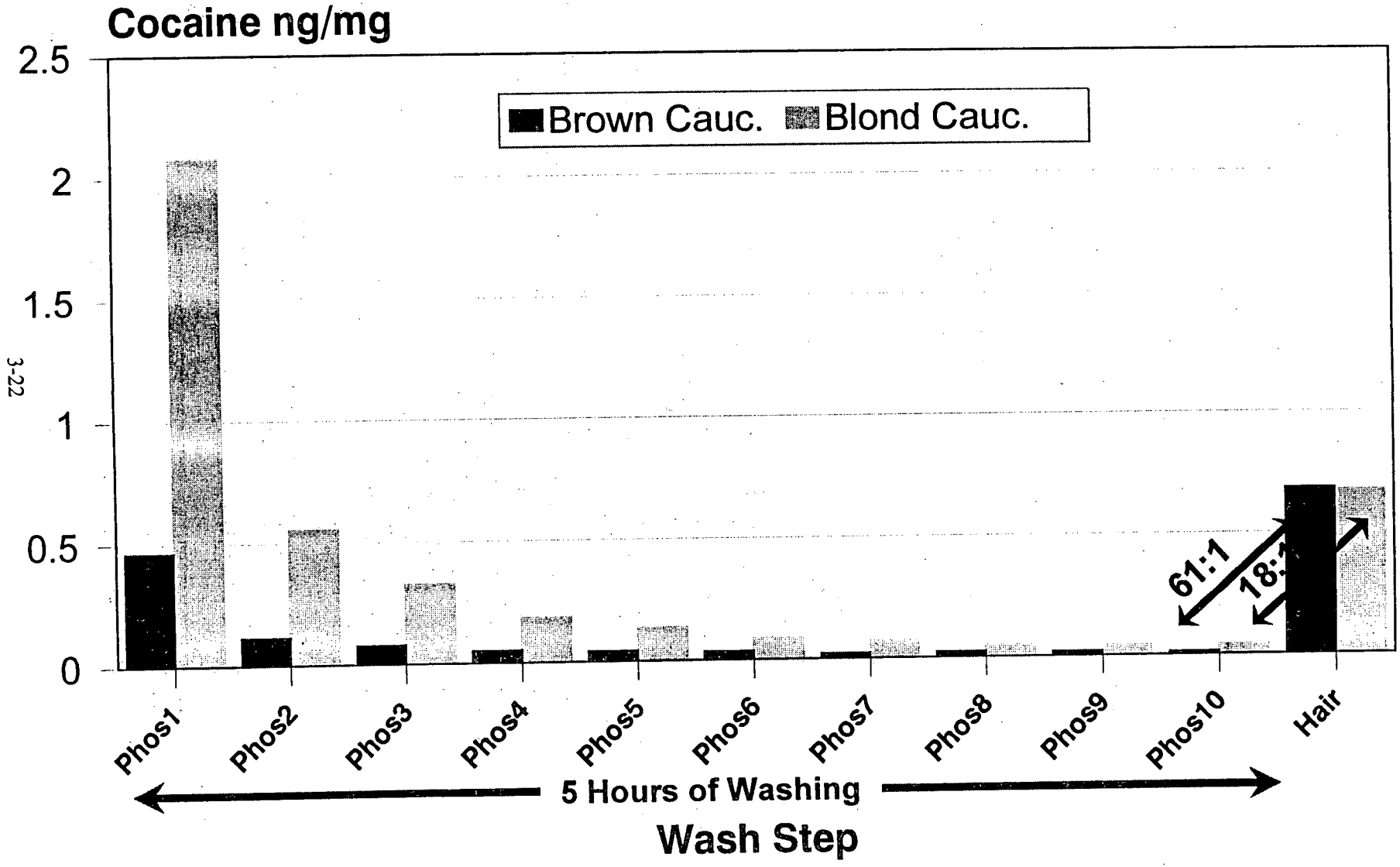
Dogma:
Hair cortex protects hair from removal or incorporation of drugs by the external environment



Can You Remove All External Exposure?

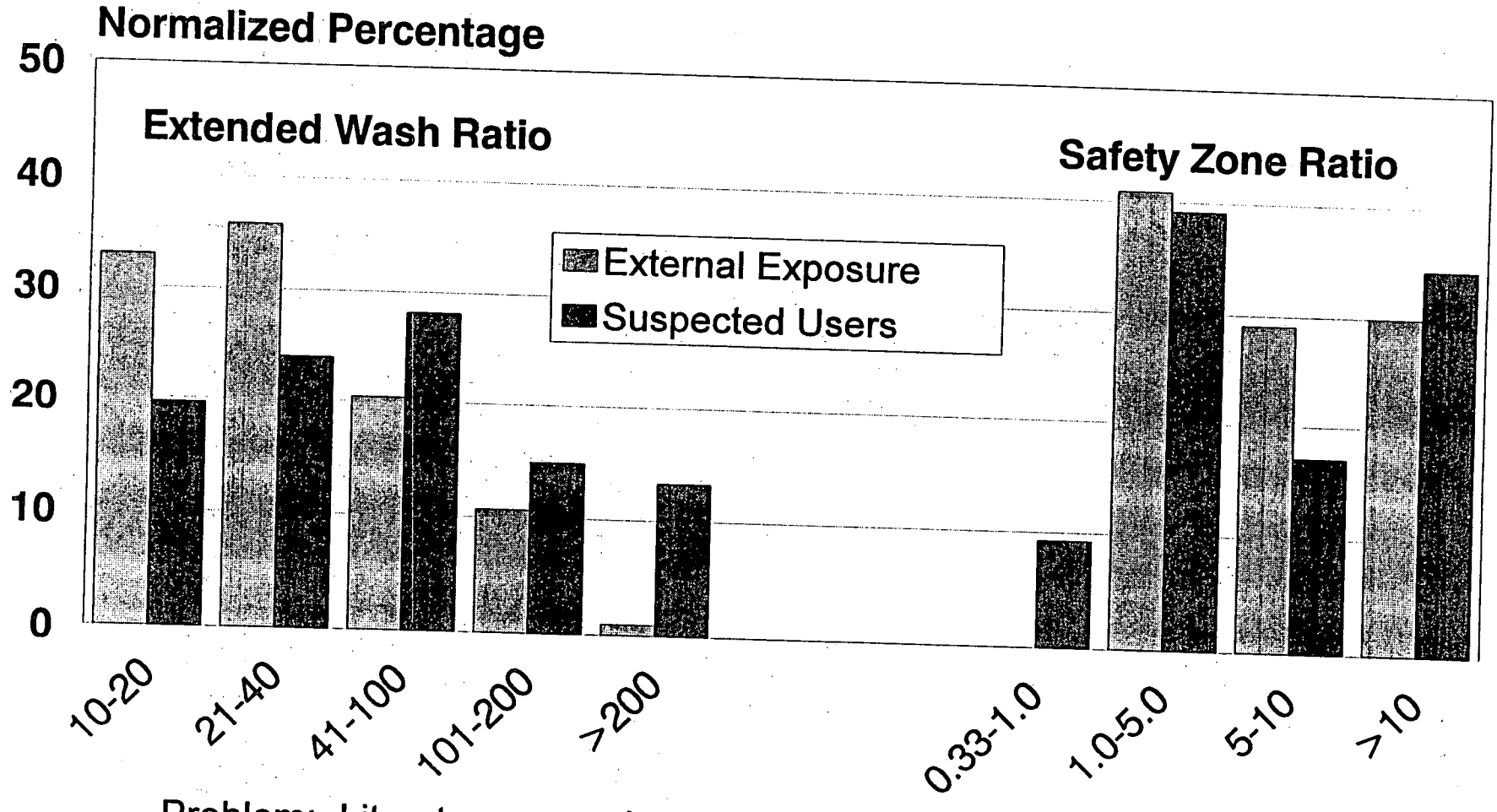
Removal of Externally Applied Cocaine

Exposed to 5 µg/mL Cocaine, 1 hr, 37C, Phos 5.6



Can Laboratory Procedures Distinguish Exposure from Use?

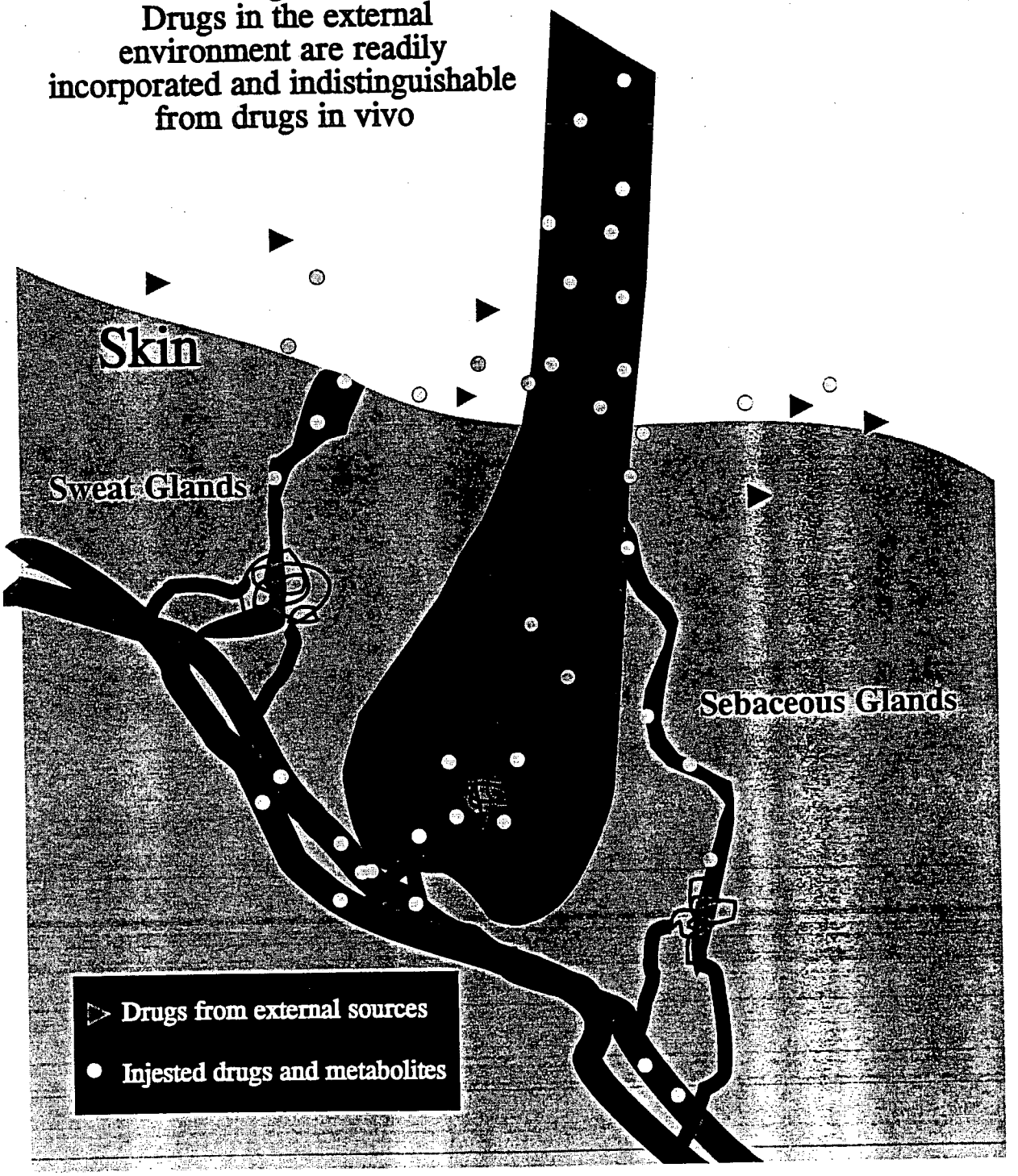
Example of two literature methods purported to be useful



Problem: Literature procedures ignore that people wash their hair. Hair care removes external contamination leaving tightly bound drug introduced from external sources and confuses the laboratory analysis.

Current Model for Incorporation of Drugs (Sweat Model)

Dogma:
Drugs in the external environment are readily incorporated and indistinguishable from drugs in vivo



Why is the Means of Incorporation of Drugs into Hair Important?

Why should sweat be of interest?

- **Drugs in sweat can come from two sources:**

- **Drug user -**
  - Ingestion of the drug and then excreation into the sweat
  - Contact of the drug with drug-free sweat effects determination of drug use

- **Non-drug user**
  - Contact of the drug with drug-free sweat
  - Contact with the drug in the past and then sweating
  - Contact with sweat of another drug user

Only need to consider passive exposure questions if contact with a drug, through past or present use, is possible.

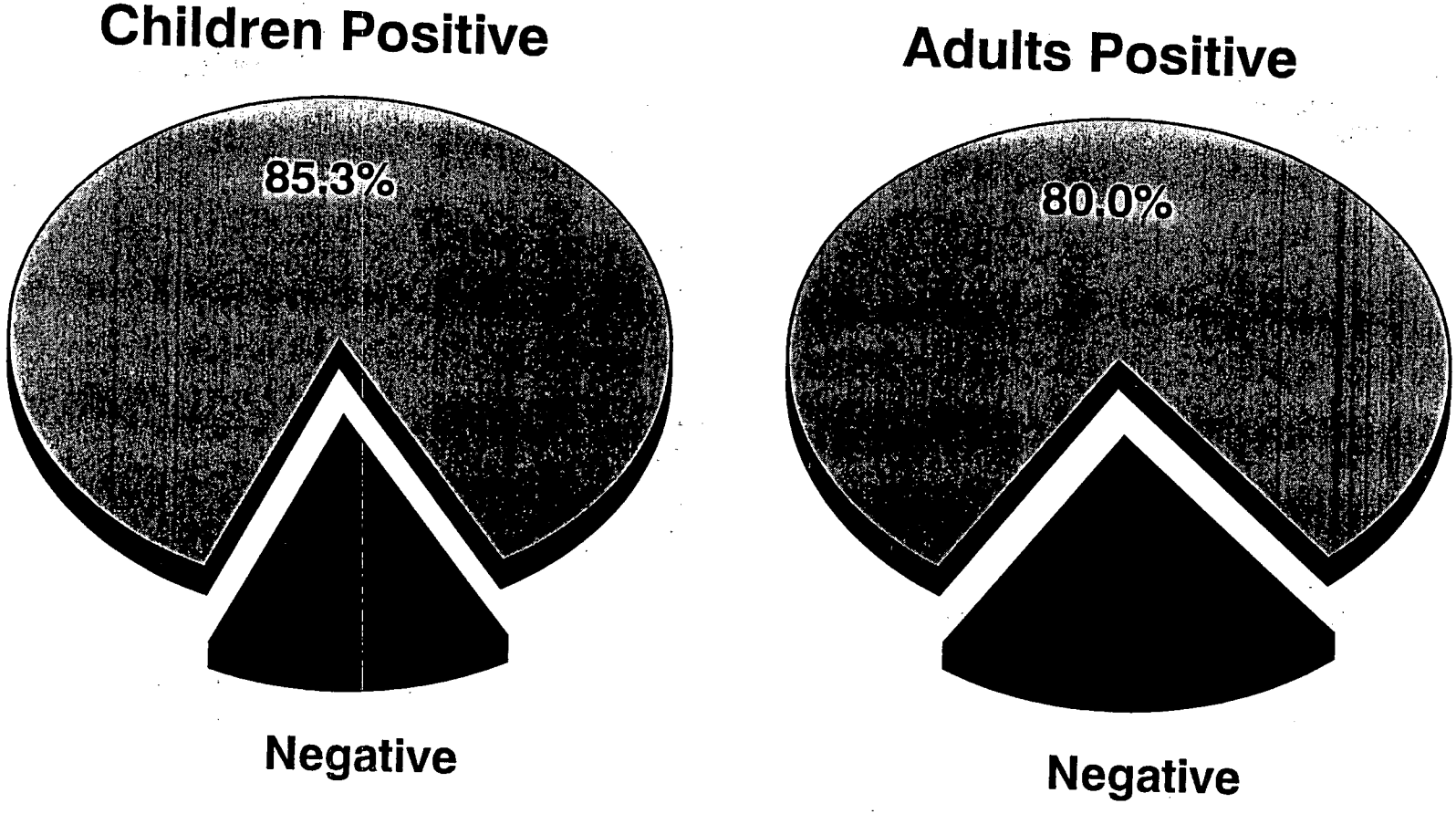
Are the Laboratory Experiments Real?

- Hair testing is becoming widely employed for civilian preemployment screening
  - Being used in numerous court cases

- Laboratory studies showed potential for passive exposure and false accusation of drug use

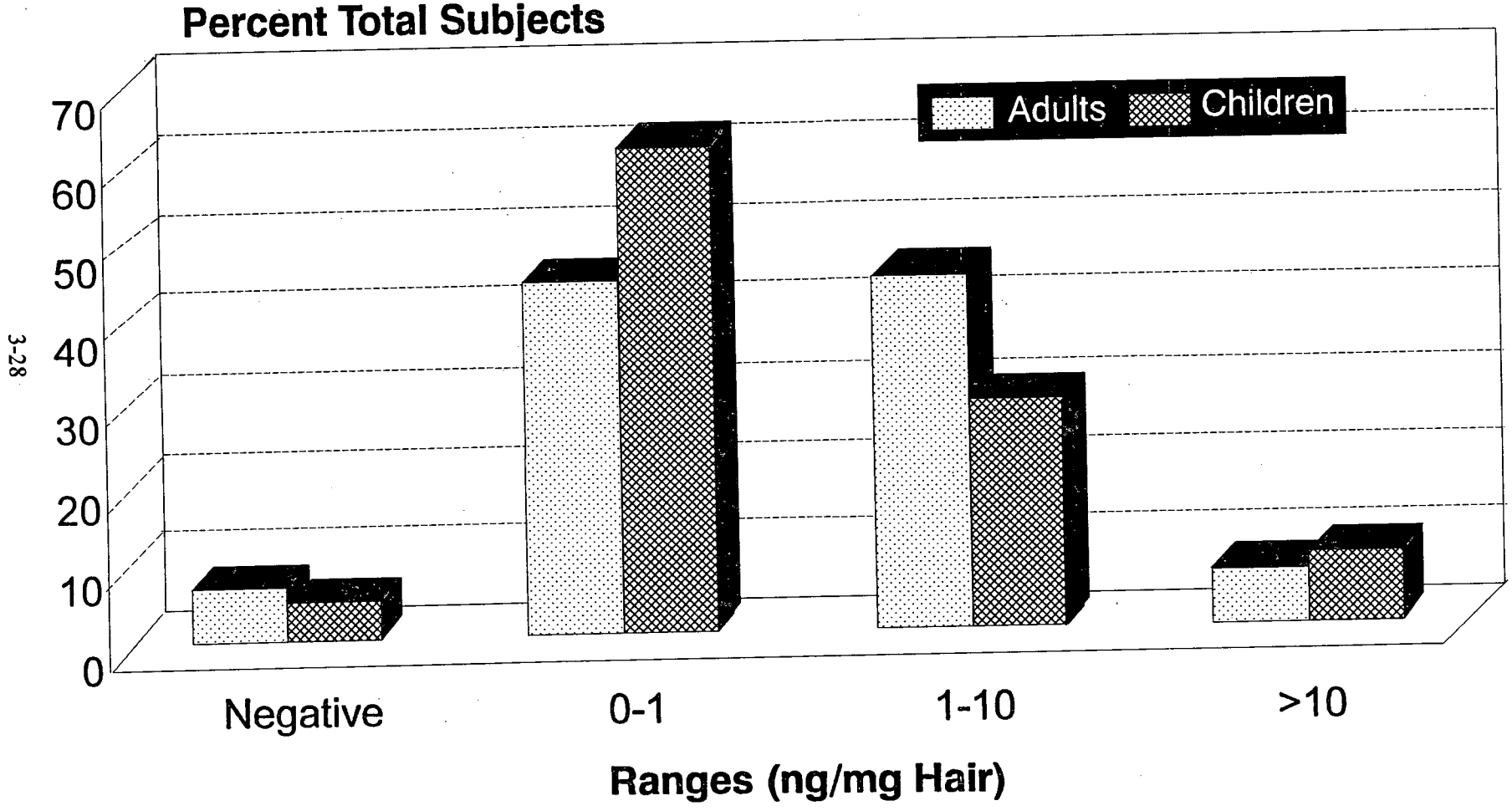
- Does this occur in real-life situations?
  - Examined children living in a cocaine using environment

Positive Rate of Cocaine Users and Their Children

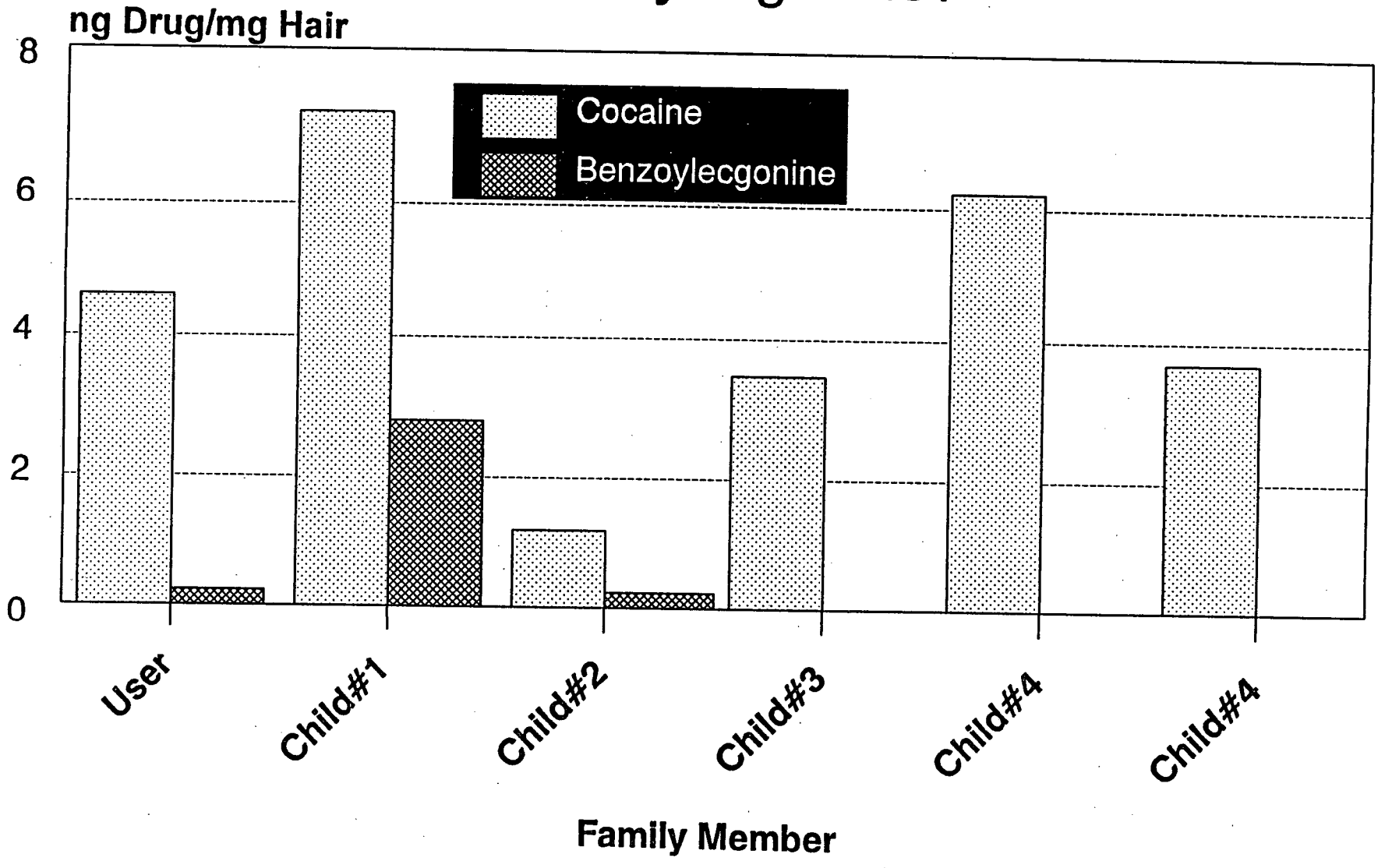


Can We Distinguish Passive Exposure from Use by the Amount of Drug Found?

Distribution of Cocaine in the Hair of Users and Their Children



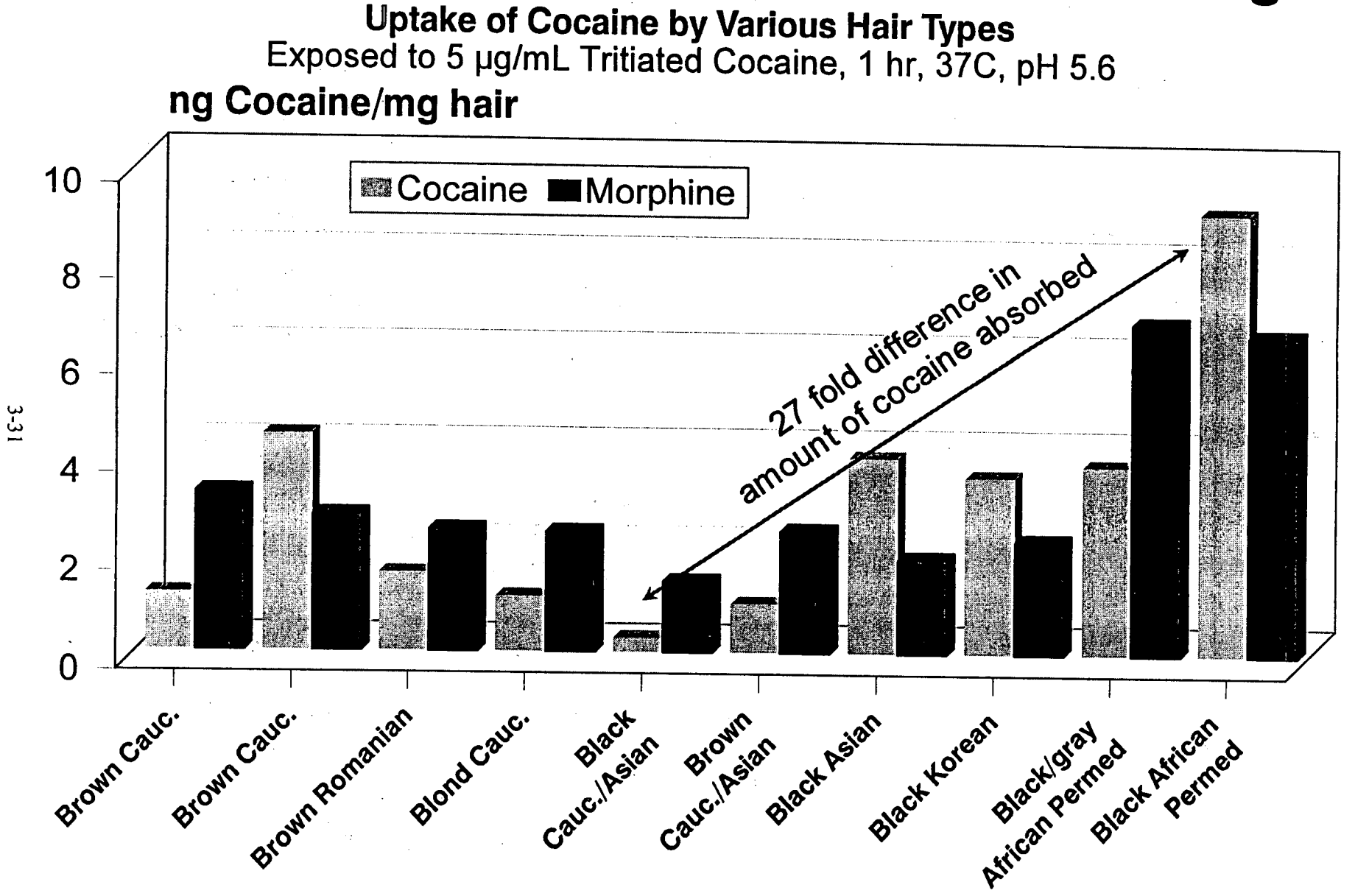
Are Metabolites a Marker of Cocaine Use?
Benzoylecgonine?



Hair Type Bias

- Hair is a complex matrix
- Mechanism for drug incorporation not clear
- Often poor correlation of use and amount in hair
- Black African hair appears to have more drugs than Caucasian hair

Does All Hair Behave the Same Towards Drugs?



What are the Implications for the Use of Hair Analysis?

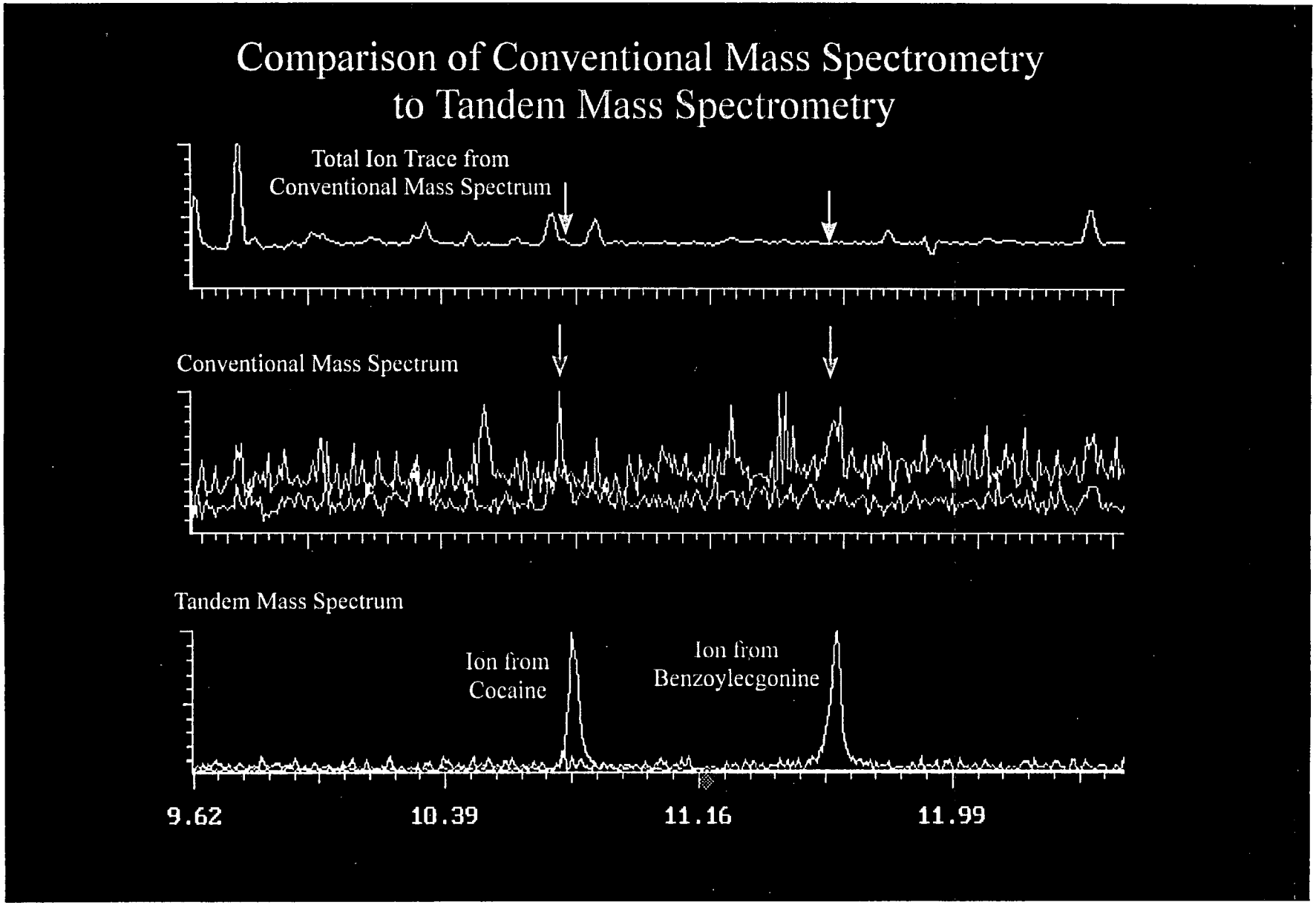
How much proof is necessary for exposure/use?

- Interpretation of hair analysis in forensic cases depends on the circumstances
  - Forensic setting
    - Interpret results cautiously
  - Preemployment testing
    - Inform customer of caveats
  - Survey
    - Possible support for other data

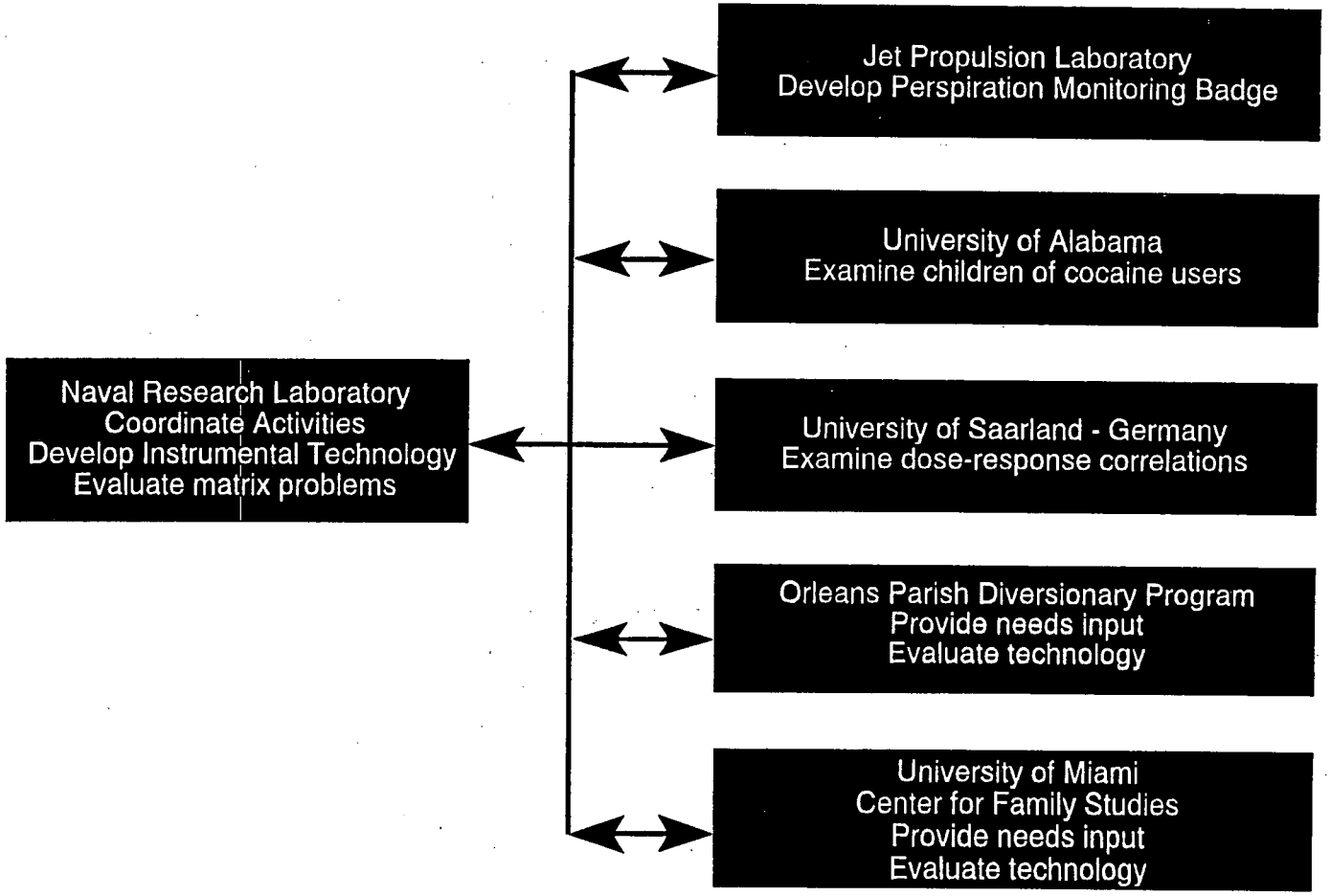
- Keep in mind -
  - Negative results not very meaningful
    - Differences in uptake of drugs vs. hair type
    - Negative results prove nothing - may be too low of dose
  - External exposure hard to differentiate from actual use
    - Drugs are present in many environments
    - Drugs enter hair by a number of different routes
    - Once present, route of entry lost and no removal procedure will distinguish endogenous drugs from external contamination
  - Patterns of drug use may be mimicked by external exposure

Technology Needed for Testing of Other Matricies

- Like urine other matrices contain drugs
- However:
  - Concentrations lower than in urine
  - Sample size limited
- Technology must be pushed for accurate identification and confirmation


Comparison of Conventional Mass Spectrometry to Tandem Mass Spectrometry
Total Ion Trace from Conventional Mass Spectrum
Conventional Mass Spectrum
Tandem Mass Spectrum
Ion from Cocaine
Ion from Benzoylecgonine
9.62
10.39
11.16
11.99

Participants in the Alternative Matrix Program



Summary

- Working with drug treatment personnel to:
  - Gather baseline data for saliva, sweat, and hair
  - Compare to urine
  - Disseminate information to the drug testing community
  - Test and address concerns of passive exposure

- Working with Law Enforcement personnel to:
  - Develop advanced technology

The 1995 ONDCP International Workshop:
Drug Abuse Treatment Technology
August 15-16, 1995, Baltimore Maryland

Telemetered Drug Detection System: A Demand Reduction Tool

Gil F. Richards, JPL/CalTech

JPL Device Development Team

- Biochemistry:
  - Gil Richards and Roger Kern, Chemical and Biological Technologies Group, Science and Technology Development Section
  - Gregory Kampa, Kampa Consulting
- Electronics and Telemetery
  - Conrad Foster, Communications Ground System Section

Goal: Real-Time Detection of Cocaine Abuse in at Home Detainees and Out-Patients

- The device should:
  - Be non-invasive
  - Expand upon existing drug detection techniques to minimize research and development time
  - Be an extension of current electronic sensor technology
  - Have remote capability and rugged design compatible with normal daily activities
  - Contribute to the development of a generic technology to detect substances of abuse

Benefits

- Criminal Justice System
  - Real time remote drug abuse monitoring coupled to at home detention
- Drug Abuse Treatment
  - Monitoring out-patient compliance
  - Rapid overdose screening
- General Medical Community
  - Ethical pharmaceutical dose monitoring in hospitals, at home and in remote emergency settings

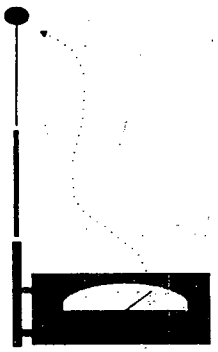
NASA Applications

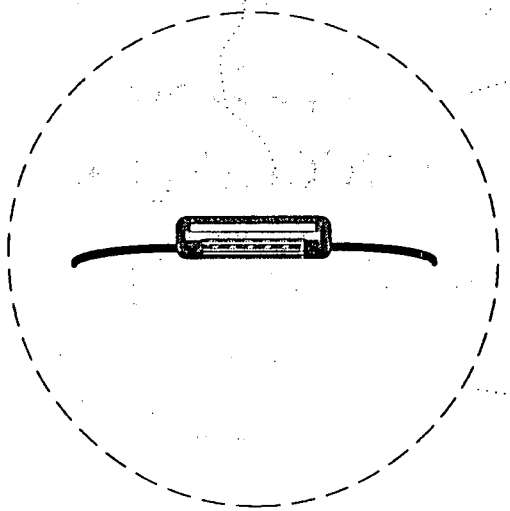
- Remote data acquisition for life science experiments
- space flight medical assessment
- EVA muscular fatigue monitor

Approach: Monitor Sweat for Presence of Cocaine

- Cocaine is detected by a chromogenic antibody competition assay
- Signal is converted by photodiode illumination array matched to antibody reporter dye
- Device is attached directly to skin as a transdermal patch
- Transmitter and Interface Electronics are coupled to a reusable at home detention bracelet or anklet system

Drug Badge





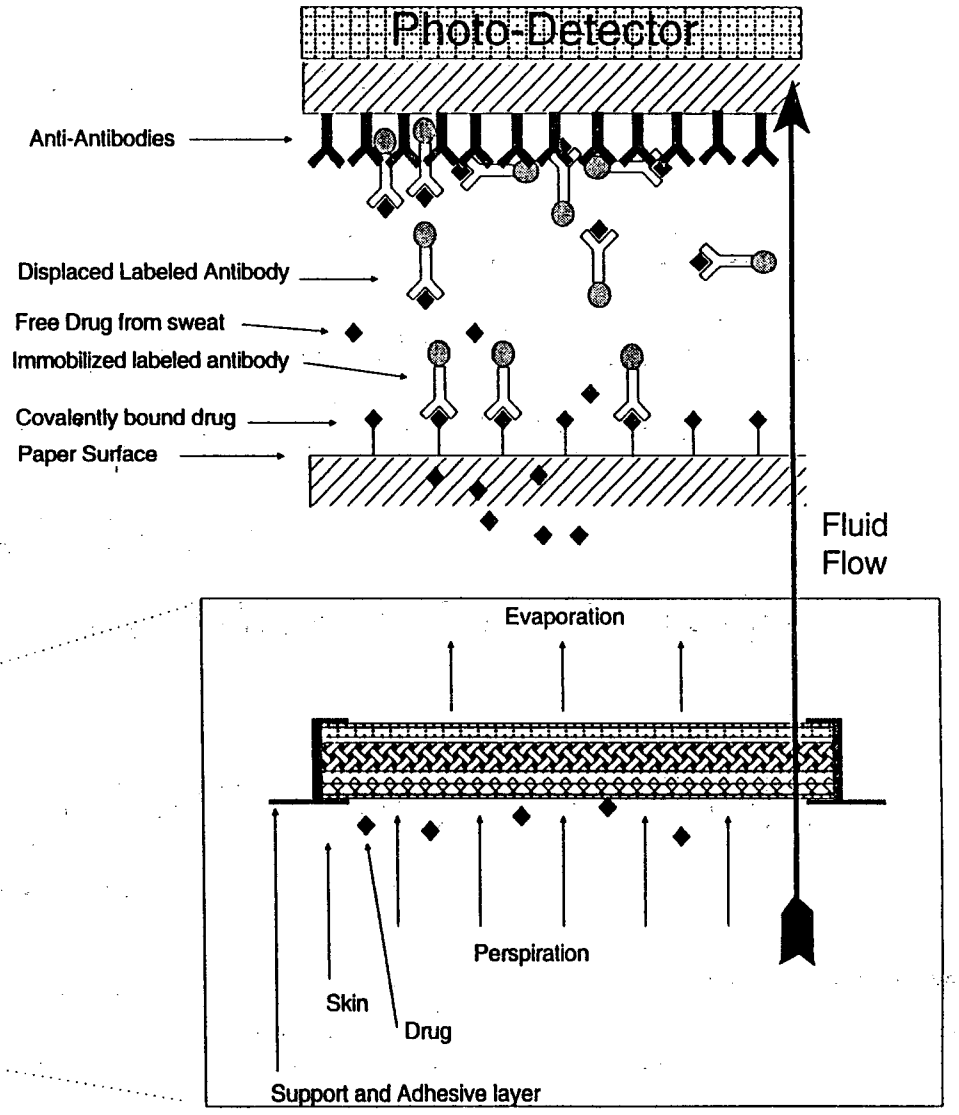


Photo-Detector
Anti-Antibodies
Displaced Labeled Antibody
Free Drug from sweat
Immobilized labeled antibody
Covalently bound drug
Paper Surface
Fluid Flow
Evaporation
Perspiration
Skin
Drug
Support and Adhesive layer

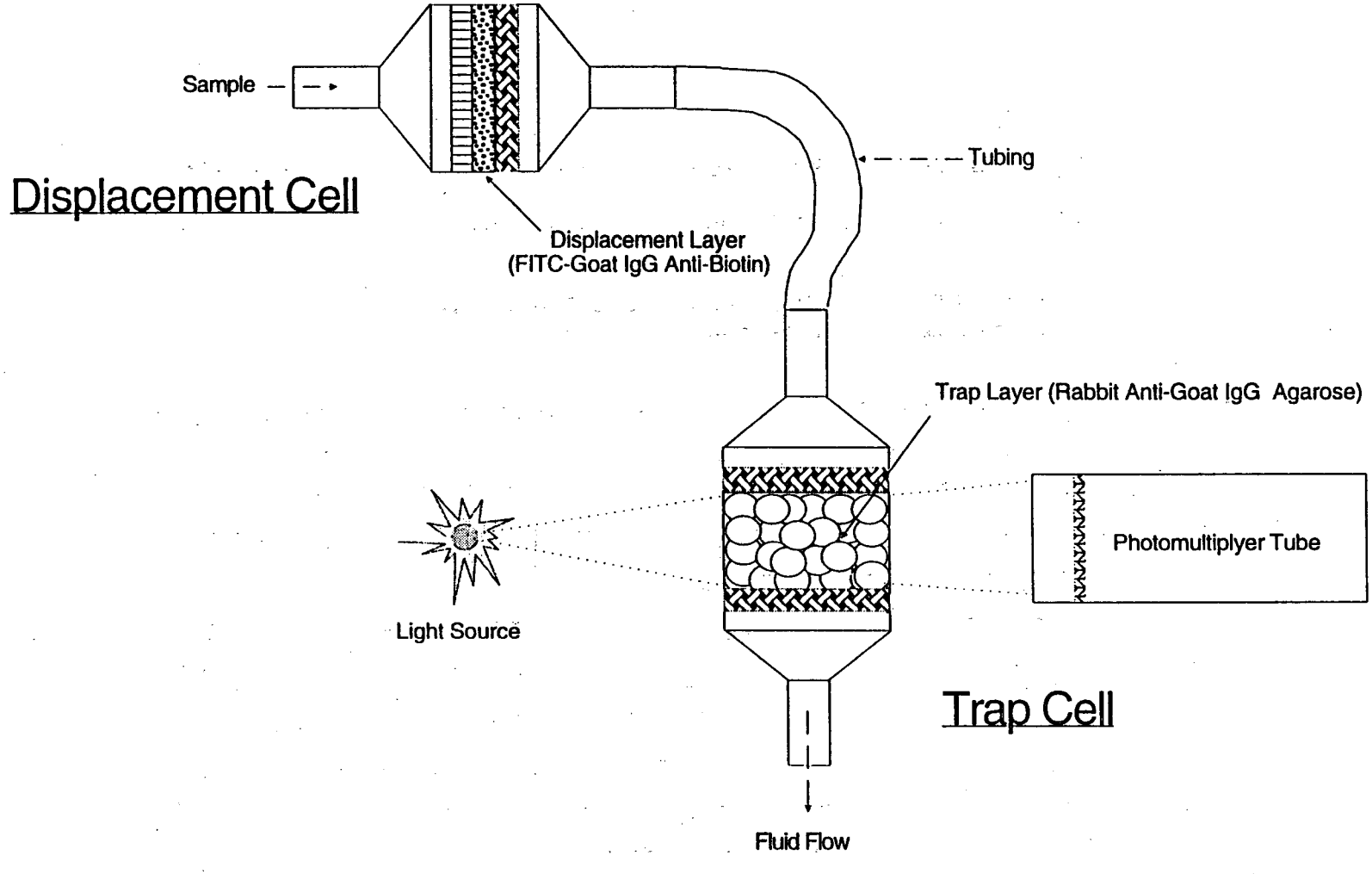
Steps in Device Development

- Demonstrate Drugs in Sweat
- Demonstrate Ab's displacement is a suitable detector
- Demonstrate sufficient sweat can be made available to operate device
- Demonstrate biochemical signal can be presented to match with electronic interface
- Demonstrate transdermal patch operation on human subjects
- Integrate electronics, telemetry and packaging

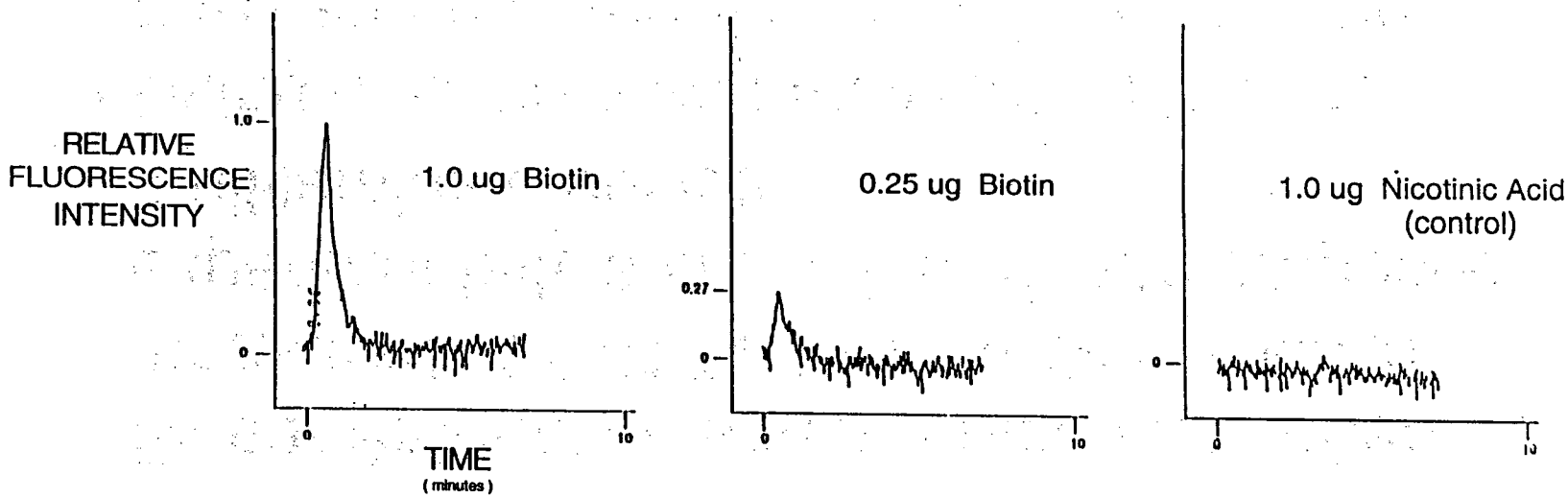
MEASURED DRUG CONCENTRATIONS IN PERSPIRATION

Drug	Concentration (µg/ml)	Range (µg/ml)
Methamphetamine	1.4	0.88-1.42
Morphine	1.5	0.31-2.7
THC	0.32	0.034-1.0
Benzodiazepine	0.19	0.14-0.33
Cocaine	50	3.4-317
Barbiturate	70	66-74
Methadone	0.48	0.31-0.86
Cotinine (nicotine metabolite)	0.51	0.10-0.93

	Rest (w/o exercise)	Endurance exercise	Exhaustive exercise
Lactic Acid:	1990 µg/ml	3940 µg/ml	10,400 µg/ml
Ammonia:	153 µg/ml	463 µg/ml	1630 µg/ml


Sample
Displacement Cell
Tubing
Displacement Layer
(FITC-Goat IgG Anti-Biotin)
Trap Layer (Rabbit Anti-Goat IgG Agarose)
Photomultiplyer Tube
Light Source
Trap Cell
Fluid Flow

BDC DISPLACEMENT LAYER FLOW TEST WITH DRUG ANALOG (Biotin) *



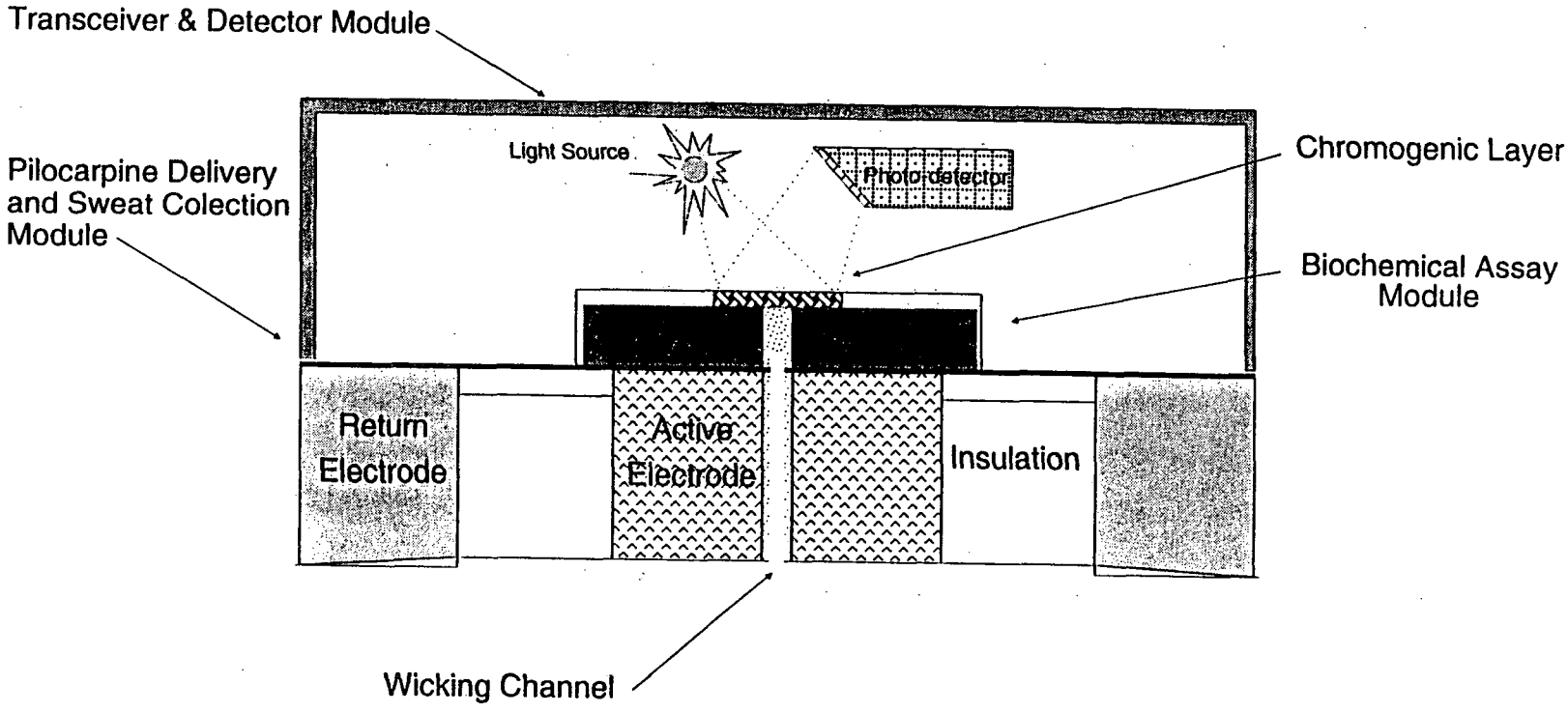
*
Injection Volume = 50 ul
Flow Rate = 1ml/min
Excitation Wavelength = 490 nm
Emmission Wavelength = 520 nm

Sweat Production

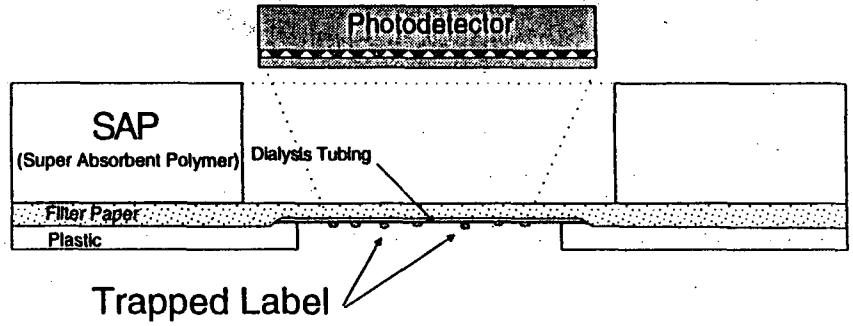
- Normal Rate of Sweat Production ranges from near 0 to 0.5 ml/ sq.cm/day
- Sweat Production under a patch has been measured at 0.017 ml/sq.cm/day which is experimentally sufficient to run the proposed multilaminate device
- Using passive area amplification the flow rate can be further enhanced several fold
- Incorporation of an active Pilocarpine iontophoresis element into the patch can produce 0.050 ml/sq.cm in 10 minutes

SAMPLE ON DEMAND :

Pilocarpine Sweat Enhancement



Detector Layer Geometry



Steps in Device Development

- ✓ Demonstrate Drugs in Sweat
- ✓ Demonstrate Ab's displacement is a suitable detector
- ✓ Demonstrate sufficient sweat can be made available to operate device
- ■ Demonstrate biochemical signal can be presented to match with electronic interface
- ■ Demonstrate transdermal patch operation on human subjects
- ■ Integrate electronics, telemetry and packaging

Commercialization

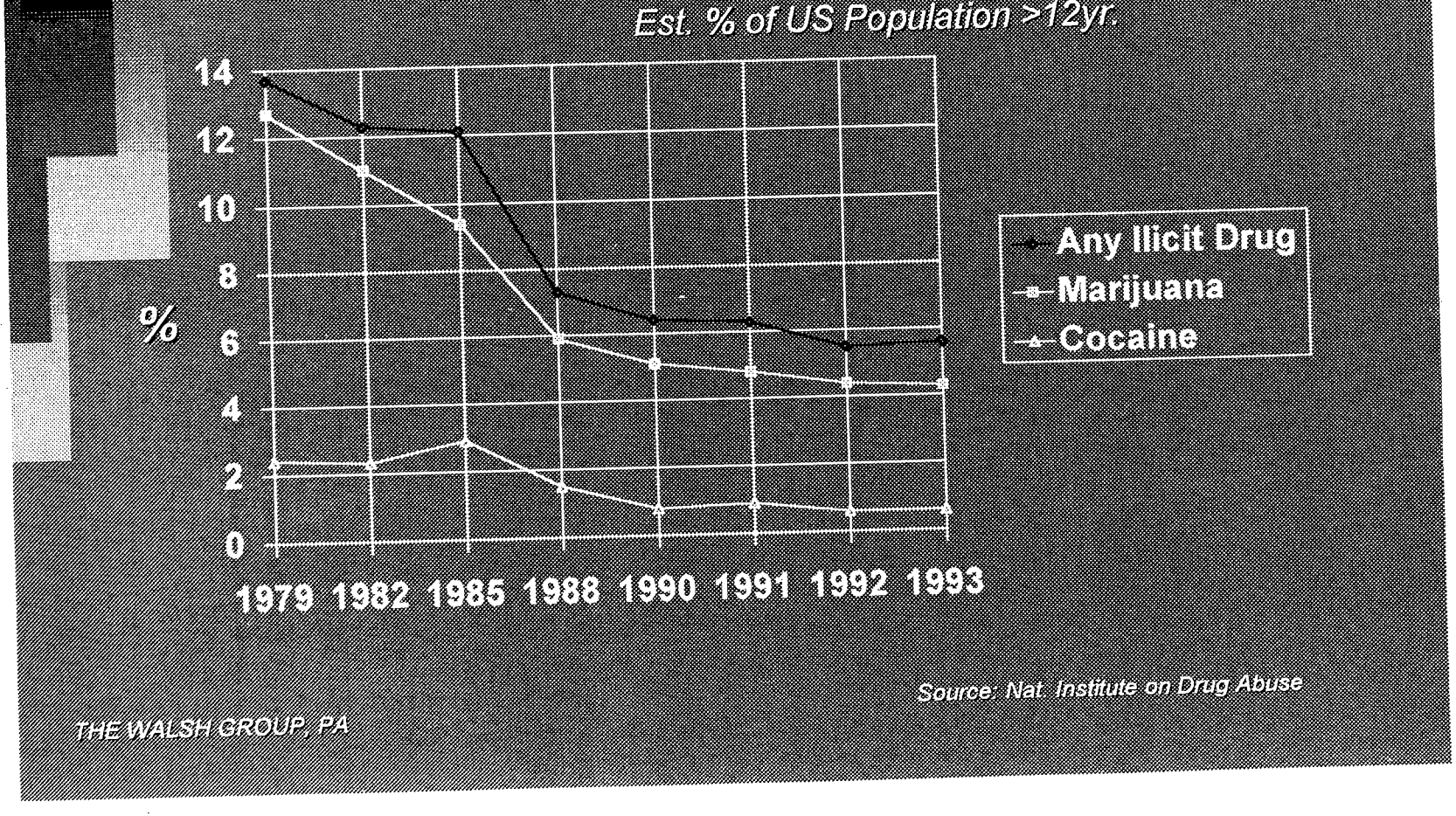
- Merle McKenzie, JPL Technology Transfer and Commercialization Office
  - James Rooney, Technology Affiliates
  - Steve Prusha, Targeted Commercialization
- JPL Commercialization Workshop for Industry, July 26, 1995

ALCOHOL & DRUG USE IN THE WORKPLACE

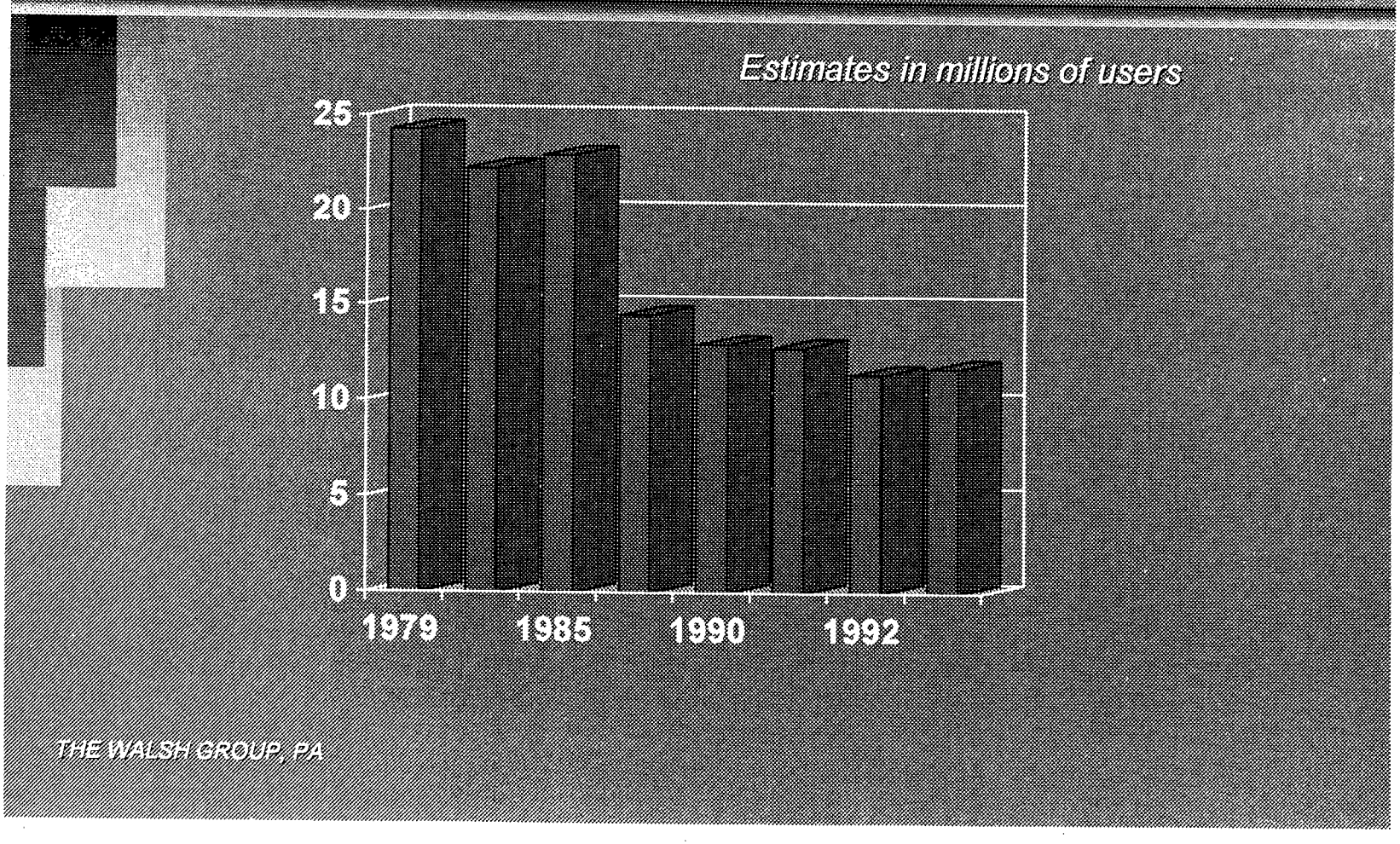
J. MICHAEL WALSH, Ph.D.

THE WALSH GROUP, PA

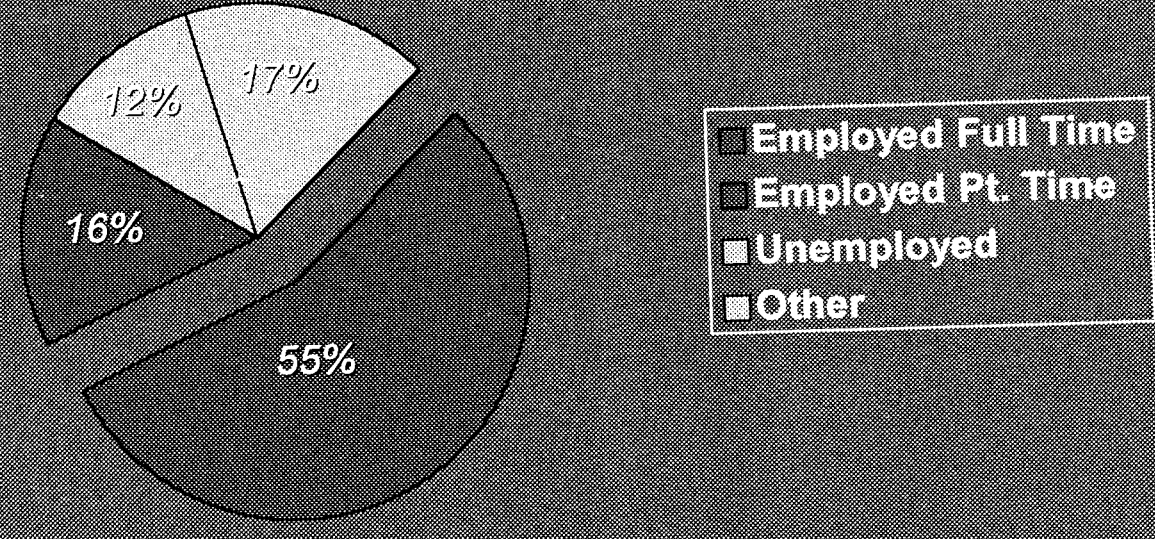
Current Use any Illicit Drug, Marijuana, Cocaine [1979-1993]



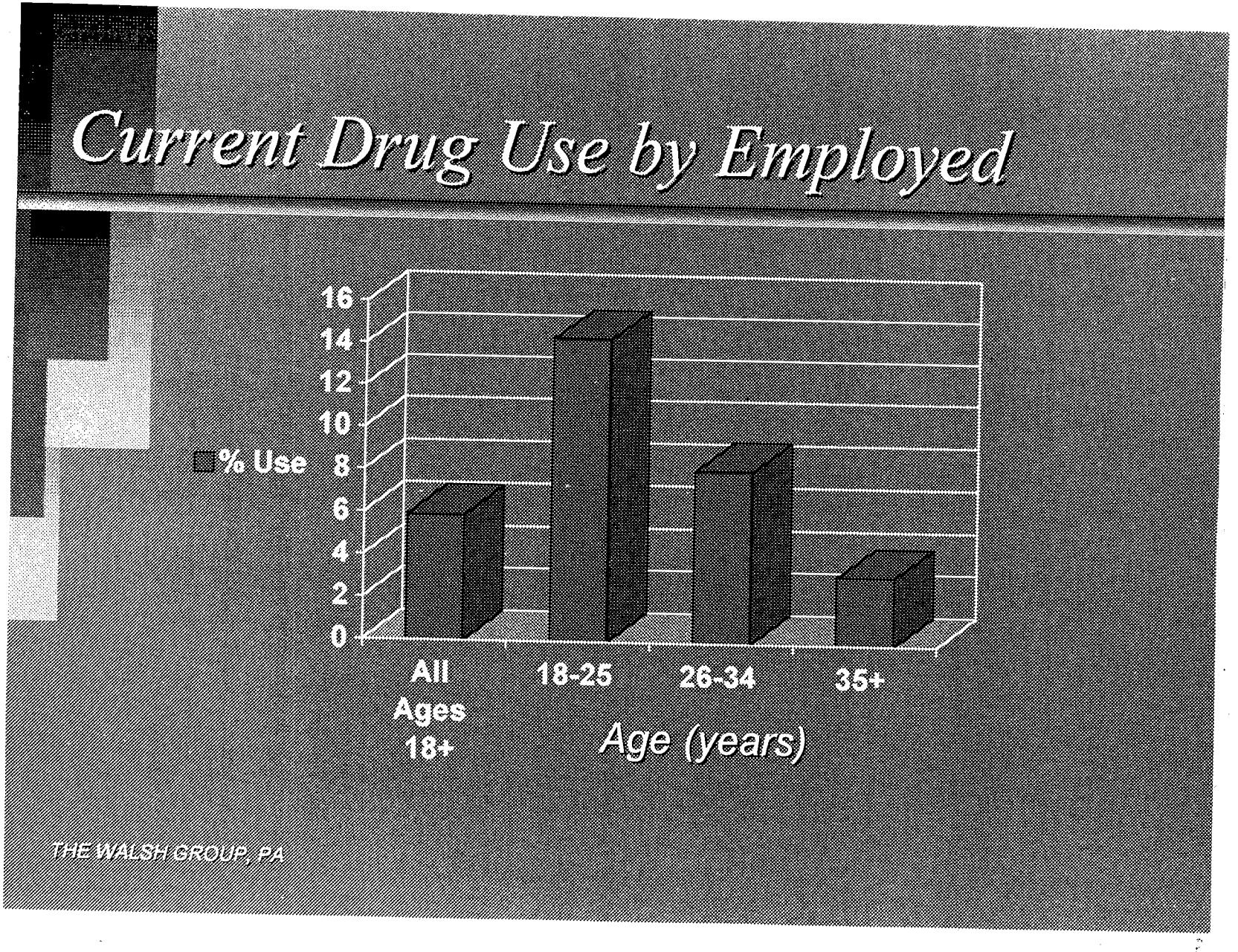
Current (Past Month) Use of any Illicit Drug



CURRENT USE ILLICIT DRUGS



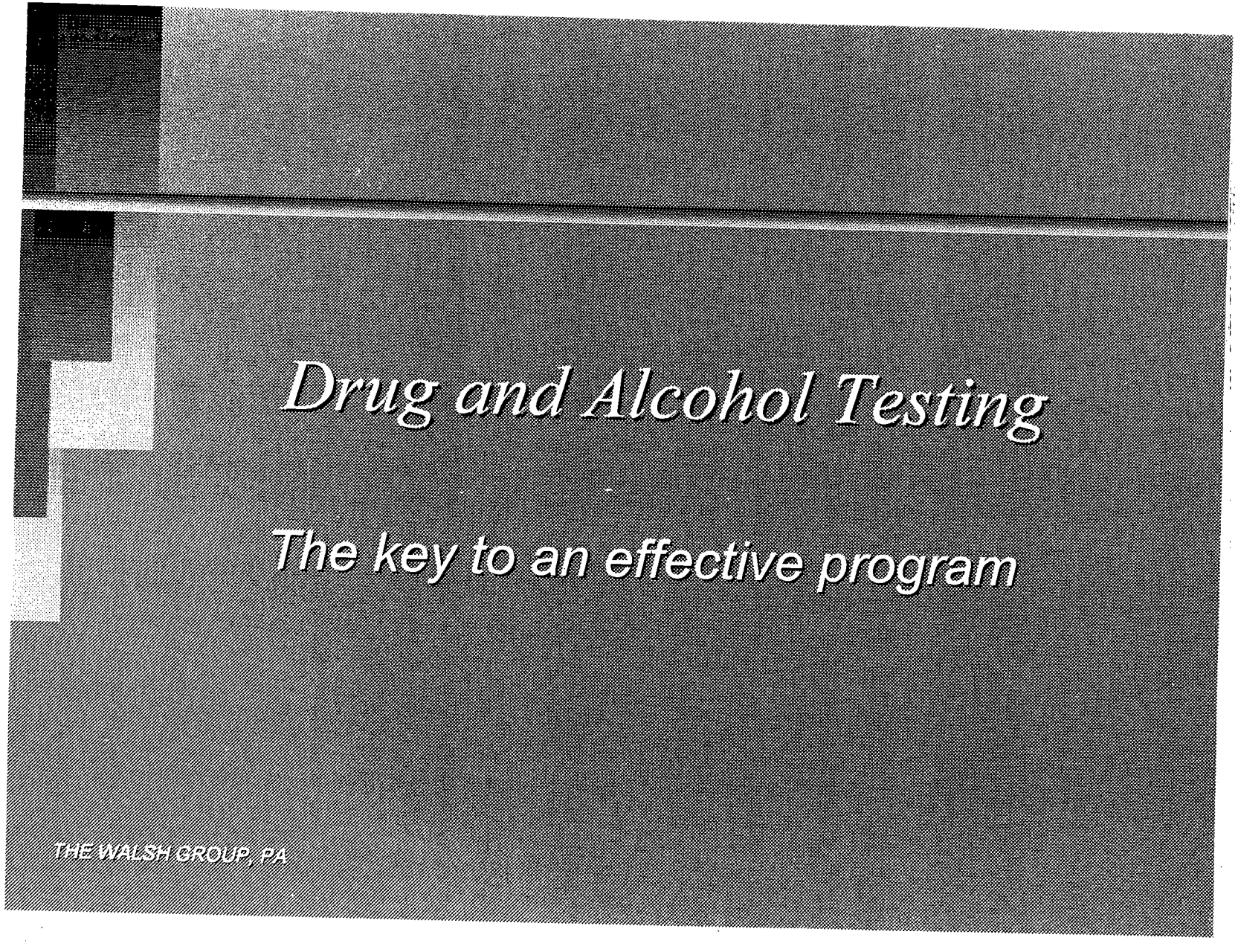
THE WALSH GROUP, PA


Current Drug Use by Employed
16
14
12
10
% Use
8
6
4
2
0
All Ages 18+
18-25
26-34
35+
Age (years)
THE WALSH GROUP, PA

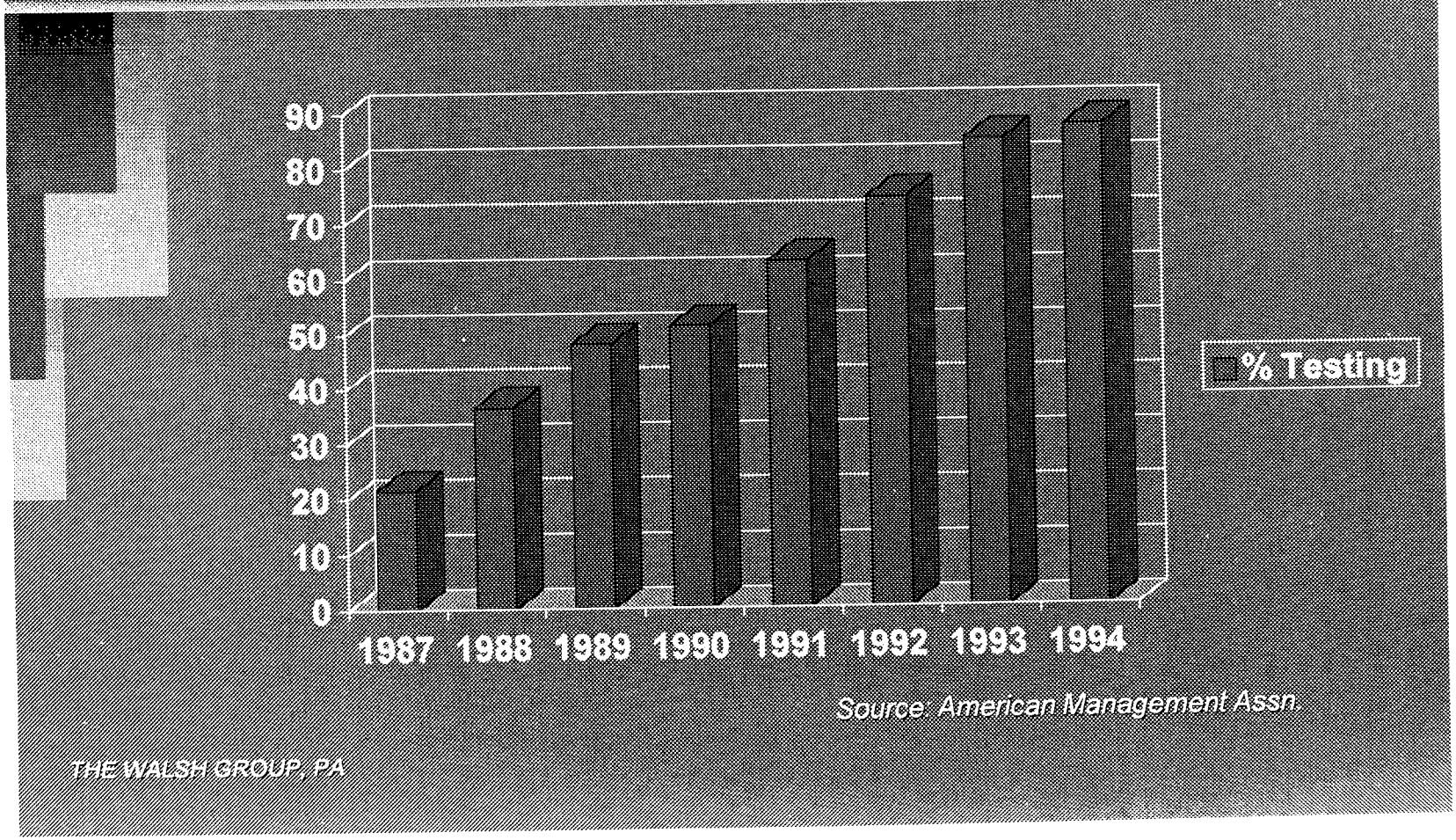
Alcohol Use

- In 1993--approximately 103 million Americans used alcohol in last month
- About 11 million are classified as "heavy" drinkers
- 25% Heavy drinkers use illegal drugs

THE WALSH GROUP, PA

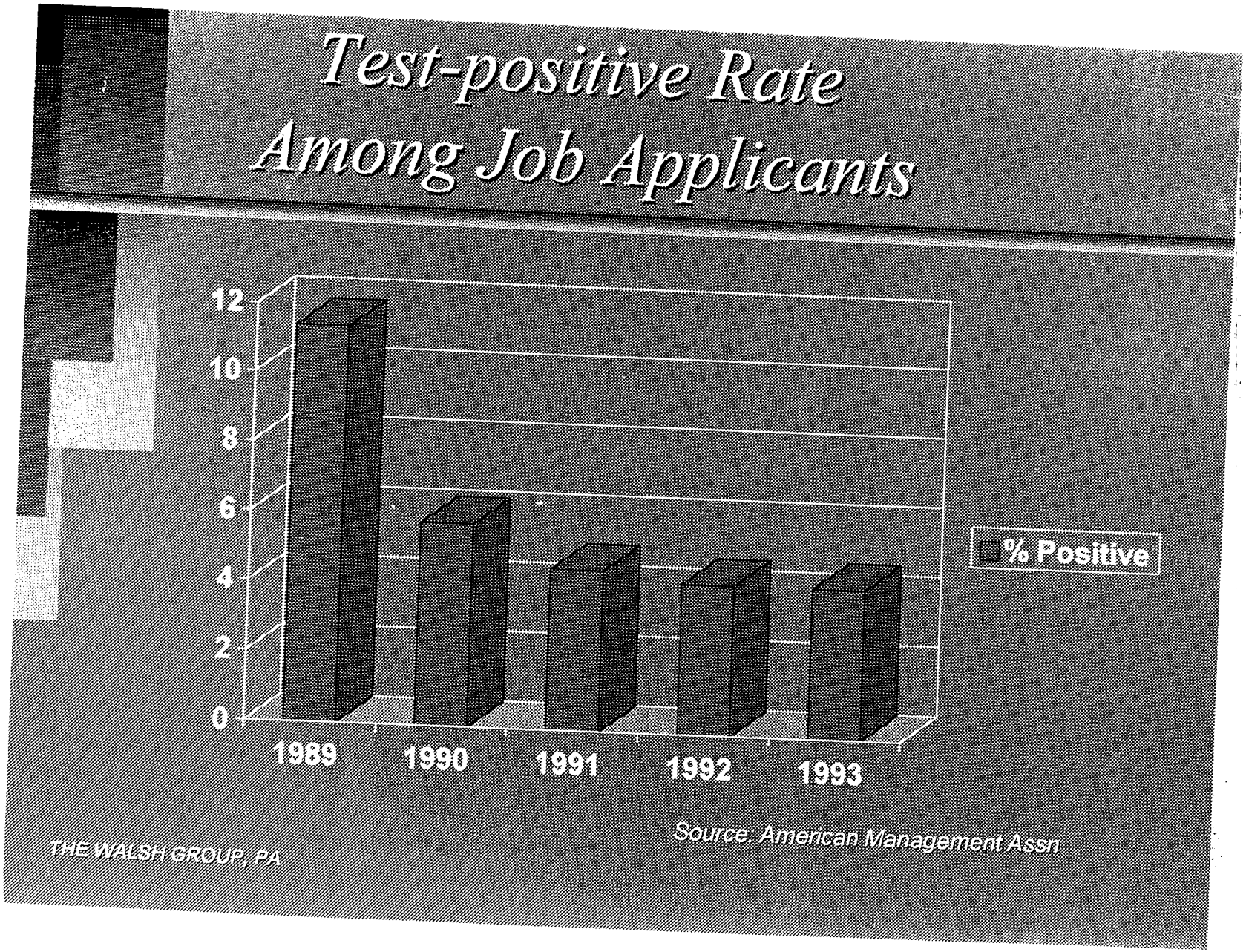

Drug and Alcohol Testing
The key to an effective program
THE WALSH GROUP, PA

Percentage of US Companies Conducting Employee Drug Tests

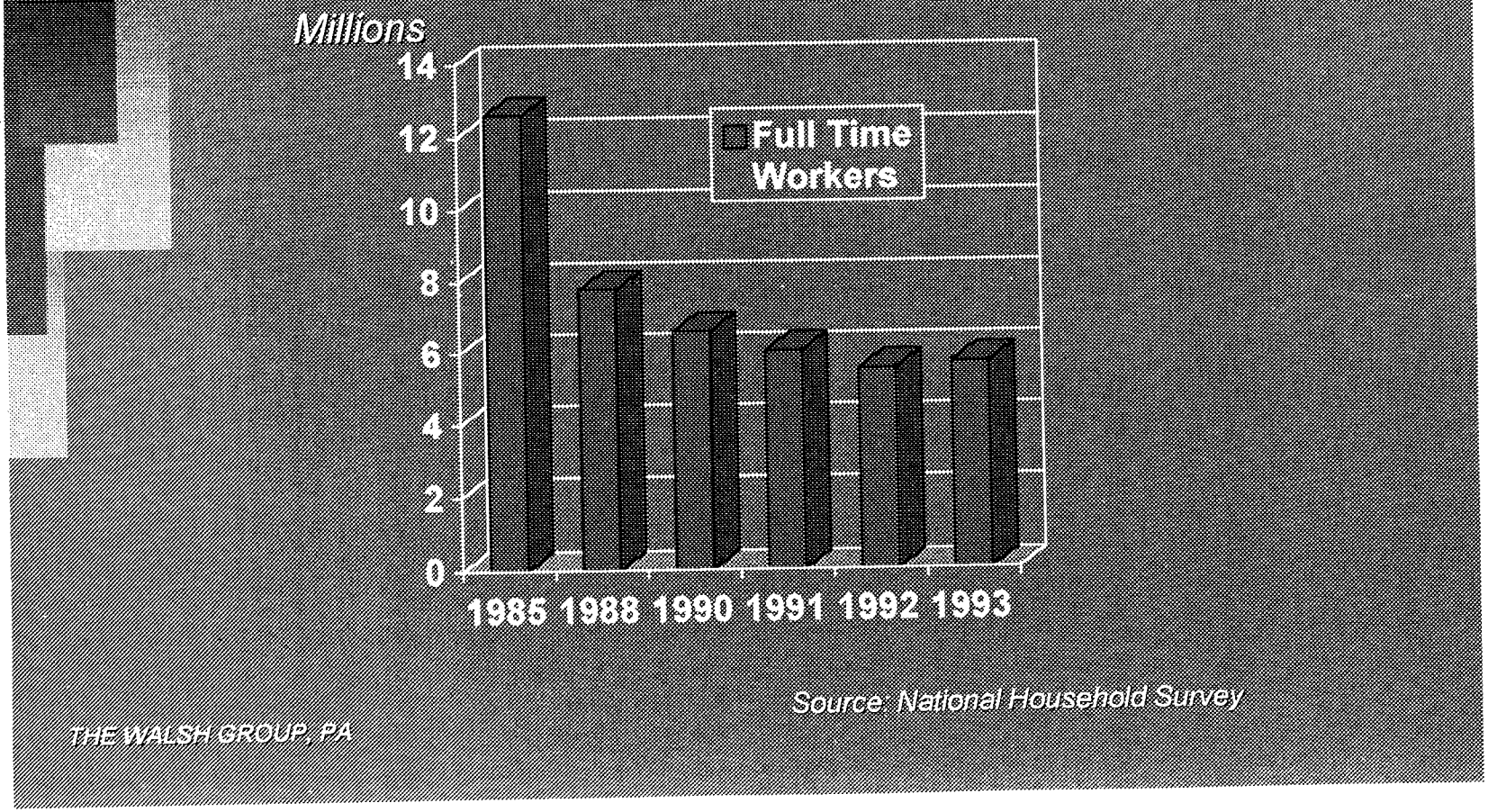


Source: American Management Assn.

THE WALSH GROUP, PA


Test-positive Rate
Among Job Applicants
12
10
8
6
4
2
0
1989
1990
1991
1992
1993
% Positive
THE WALSH GROUP, PA
Source: American Management Assn.

Signs of Success: Decrease in Current Drug Use Among Full Time Workers



Triage™ The Laboratory in the "Cassette"

Step 1

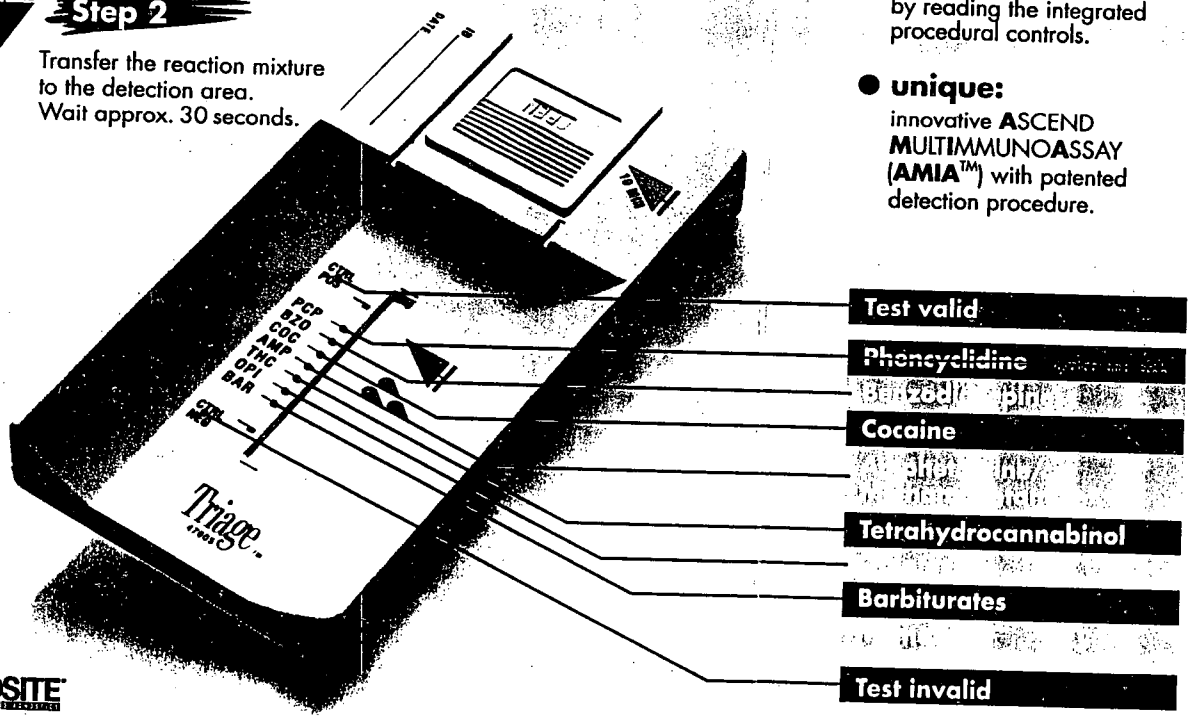
Remove the cap from the reaction cup. Add urine. Incubate for 10 minutes.

Step 2

Transfer the reaction mixture to the detection area. Wait approx. 30 seconds.

Step 3

Add 3 drops of wash solution to the detection area and read test results.



- **fast:** results in 10 minutes.
- **reliable:** test results are assured by reading the integrated procedural controls.
- **unique:** innovative **A**SCEND **M**ULTI**M**MUNO**A**SSAY (**AMIA**™) with patented detection procedure.
- **specific:** 21 selected monoclonal antibodies.
- **simple:** only 2 pipetting steps.
- **visual:** precise, readible results without additional equipment.
- **present:** ease of use, anywhere.
- **complete:** no additional reagents required.

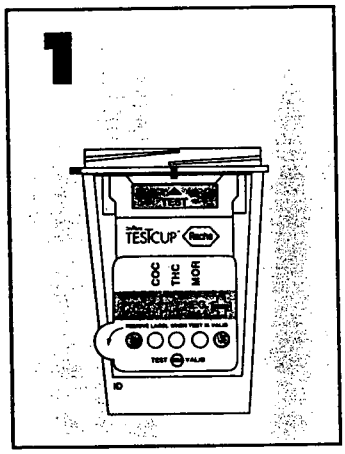
BIOSITE

MERCK

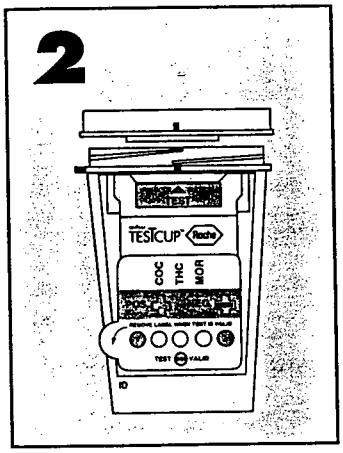
Roche

Helping solve the problems of drug abuse

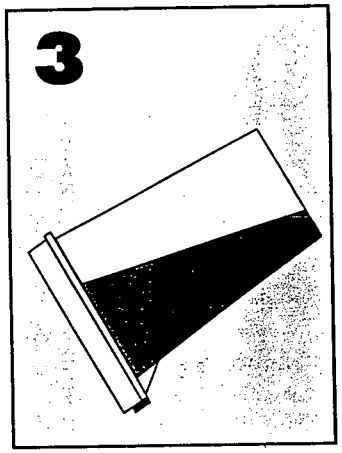
ONTRAK TESTCUP INSTRUCTIONS...



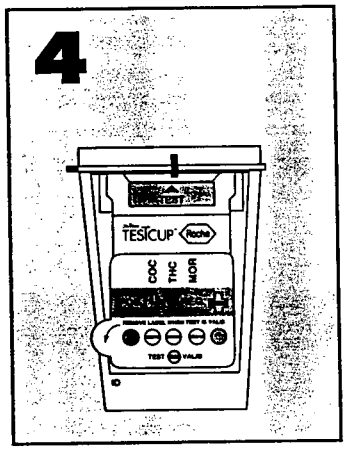
1. Add specimen to cup.



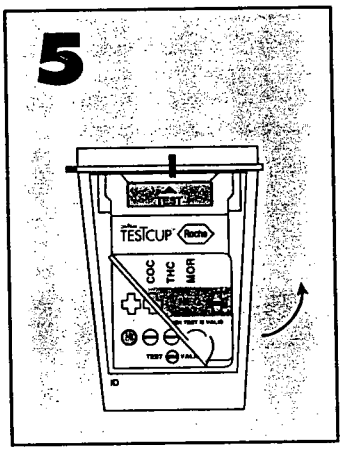
2. Close lid by turning to "TEST" position.



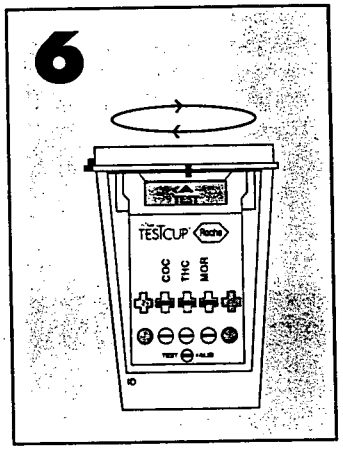
3. Tilt cup *forward* for 3 – 5 seconds.



4. Wait for "test valid" lines to appear. Timing is not required.



5. Peel off label and read each result.



6. Close lid by turning to "stop" position for storage.

Please refer to the package insert for full details on the use of ONTRAK TESTCUP.
For immediate technical assistance, contact the Roche Response Center® at 1-800-526-1247.

ONTRAK
TESTCUP™
Collection / Urinalysis Panel

Plandex 12258-0795

Roche **Roche Diagnostic Systems**
A Member of the Roche Group

Roche Diagnostic Systems, Inc.
Branchburg Township
1080 US Highway 202
Somerville, NJ 08876-3771
1-800-526-1247; in Canada 1-800-268-0482

FINALLY, AN ALCOHOL TEST THAT'S ...

- Simple
- Accurate
- Reliable
- D.O.T. Approved* & F.D.A. Cleared

Q.E.D.®

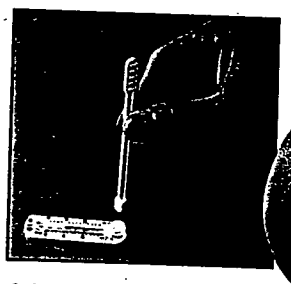
SALIVA ALCOHOL TEST

THE DISPOSABLE Q.E.D.® SALIVA ALCOHOL TEST IS A REVOLUTIONARY BREAKTHROUGH IN QUANTITATIVE ON-SITE ALCOHOL DETECTION.

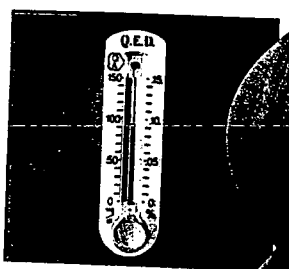
AVAILABLE IN TWO TESTING RANGES.

Three easy steps:

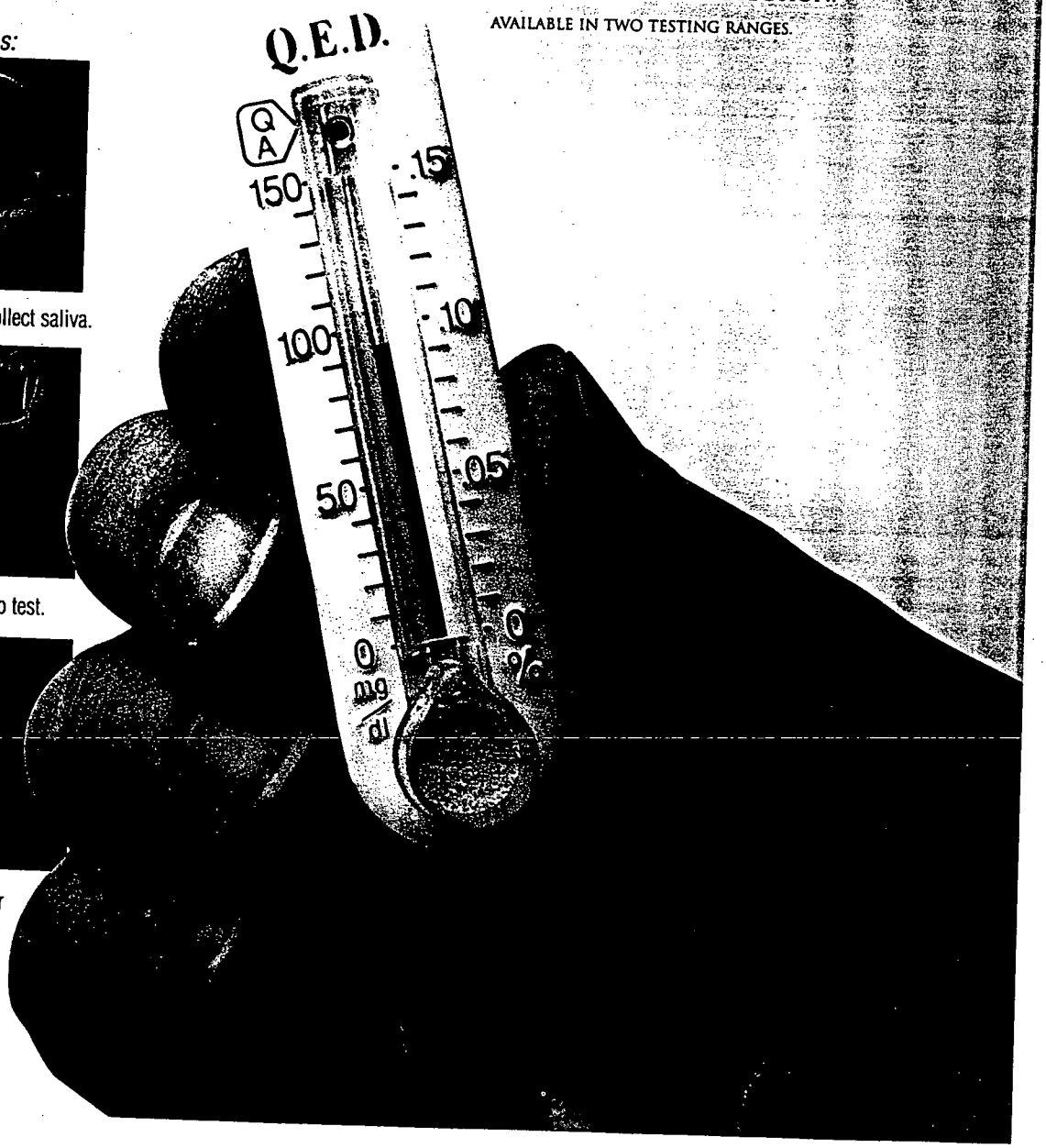
1. Swab mouth to collect saliva.



2. Insert collector into test.



3. Read color bar after several minutes.

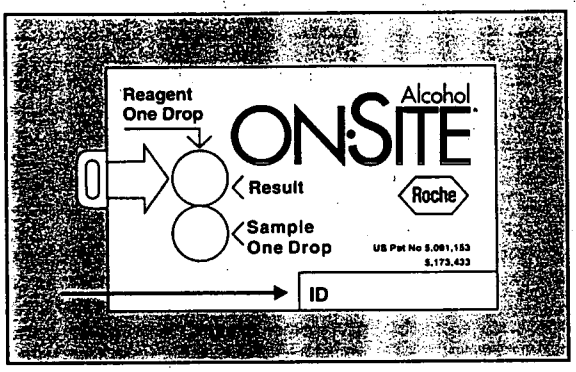


* A150 test only

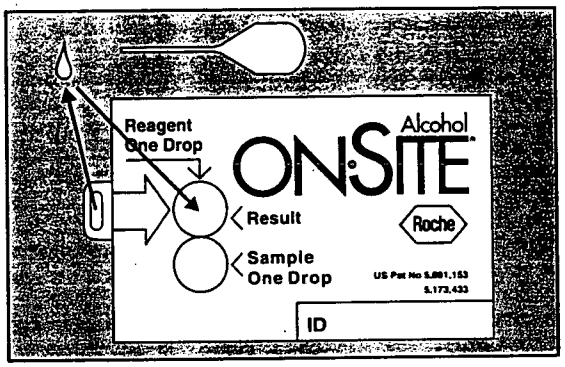
Roche

Helping solve the problems of drug abuse

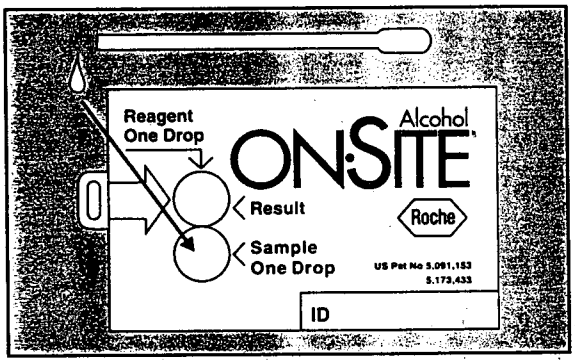
Alcohol ON•SITE®



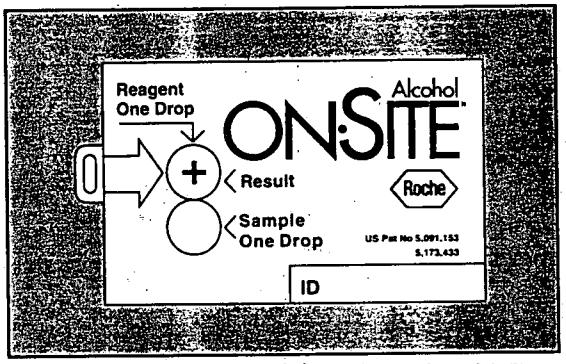
1. Place ON•SITE Alcohol test card on a flat surface and peel off protective cover. Remove contents and discard desiccant. Record specimen I.D.



2. Using small transfer pipet, transfer only one drop of reagent from reagent well to detection reagent pad in the Result well.



3. Using large transfer pipet, transfer one drop of specimen to the Sample well.



4. Read results 2 minutes after sample addition. Purple "positive" sign at ≤2 minutes indicates ethanol concentration ≥0.01% w/v. Negative specimen (<0.01%) does not produce a positive sign (+) in ≤2 minutes.

Results

Positive test results are presented by a purple positive sign (+). Negative results are presented by the reagent pad remaining pale yellow.

Ordering Information

To add a "plus" to *your* alcohol testing program, call the Roche Response Center℠ at 1-800-526-1247.

	Package Size	Order Number
ON•SITE Alcohol Test	50 tests	00302

Manufactured for:

Roche

Roche Diagnostic Systems

a subsidiary of Hoffmann-La Roche Inc.

Roche Diagnostic Systems, Inc
1080 US Highway 202
Branchburg, NJ 08876-1760
1-800-526-1247; in Canada 1-800-268-0482

Plandex 12242-0593R

EVALUATION RESEARCH IN DEMAND REDUCTION PLANNING

Jerome J. Platt, Mindy Widman, and Victor Lidz

Division of Addiction Research and Treatment
Medical College of Pennsylvania and Hahnemann University
Department of Psychiatry
Philadelphia, Pennsylvania

PROGRAM EVALUATION DEFINED

A process of making reasonable judgments about program

- Effort
- Effectiveness
- Efficacy
- Adequacy

Based on systematic data collection and analysis

Designed for use in

- Program management
- External accountability
- Future Planning

Includes special focus on

- Accessibility
- Acceptability
- Comprehensiveness
- Integration of services
- Awareness
- Availability
- Continuity
- Cost of Services

Source: Attkisson and Broskowski (1978).

Appendices

TYPES OF EVALUATION RESEARCH

- Formative Evaluation (Exploratory Research)
- Process Evaluation
- Outcome Evaluation*

TYPES OF EVALUATION RESEARCH

FORMATIVE EVALUATION (Exploratory Research)

- Provides information to guide planning, development, or implementation of a specific program.
- Always prospective.
- Includes: Needs Assessments.
- Examples:
  - Study tracking incidence of substance abuse among New Jersey correctional admissions to inform program planning
  - Early bleach distribution studies which evaluated the most appropriate packaging.

TYPES OF EVALUATION RESEARCH

PROCESS EVALUATION

- Examines whether or not the services which should have been provided, were provided. Also explores who received these services.
- Can be prospectively or retrospectively designed.
- Example: Studies of who accepts bleach for needle disinfection.

TYPES OF EVALUATION RESEARCH

OUTCOME EVALUATION*

- Explores the effect of the program on the participants, on society, or on others. Can be prospectively or retrospectively designed.

- Includes:

    - evaluation of program's success in meeting its outcome goals
    - cost-effectiveness (or cost-benefit) analysis
    - impact evaluation, that ist evaluation, that is, effect of program on the rates of "ill designed to treat

- Example: DATOS

METHODS USED IN OUTCOME RESEARCH

- True Experimental Designs

- Quasi-Experimental Designs

METHODS USED IN OUTCOME RESEARCH

TRUE EXPERIMENTAL DESIGNS

Must be prospective

Includes:

- Randomized Control Trial
- Cross-over Design

METHODS USED IN OUTCOME RESEARCH

TRUE EXPERIMENTAL DESIGNS (continued)

RANDOMIZED CONTROL TRIAL

- Subjects are randomly assigned to a treatment and a control group. Assignement can be blind (unknown to the participants) or double blind (unknown to the participants or those giving the treatment). In drug treatment research, likely to be blind only.

- Example: Clinical trials of drugs as treatment for disease.

METHODS USED IN OUTCOME RESEARCH

TRUE EXPERIMENTAL DESIGNS (continued)

CROSS-OVER DESIGN

- Subjects are randomly assigned to receive a treatment or a placebo. After the passage of time, those in the control group receive the treatment and those who have received the treatment receive the placebo. Can also be blind or double blind.

- Example: Patients receive carbamazepine for manic-depression for 4 weeks, while another group of patients receive a placebo. After 4 weeks, the "treatments" are switched.

METHODS USED IN OUTCOME RESEARCH

TRUE EXPERIMENTAL DESIGNS (continued)

MAJOR STRENGTHS

- Most likely to truly measure the impact of the program, since subjects are randomly assigned to a treatment or control condition
- In cross-over design, subjects act as their own controls

MAJOR WEAKNESSNES

- Can be expensive, because study must continue long enough for its effect to be measured
- Denies subjects in control group the benefit of the treatment or drug being offered.
- Conversely, subjects in the experimental group may be exposed to a dangerous intervention.
- May not be replicable in the real world.
- Those agreeing to participate may be very different from the general population

METHODS USED IN OUTCOME RESEARCH

QUASI-EXPERIMENTAL DESIGNS

Can be prospective or retrospective

Lacks Random Assignment

Includes:

- Cohort Studies
- Prospective Survey
- Before-After Design

METHODS USED IN OUTCOME RESEARCH

QUASI-EXPERIMENTAL DESIGNS (continued)

COHORT STUDIES

- Examines two groups (cohorts) who have been assigned to interventions by luck or chance. Assignment not in hands of researcher.

- Example: Comparison of two cohorts of drug abusers entering different treatment settings during the same period of time

METHODS USED IN OUTCOME RESEARCH

QUASI-EXPERIMENTAL DESIGNS (continued)

PROSPECTIVE SURVEY

- Long-term study of individuals who may become assigned to interventions.

- Example: Study of individuals with alcohol problems who may or may not, due to the passage of time, enter a particular treatment program(s) for these problems.

METHODS USED IN OUTCOME RESEARCH

QUASI-EXPERIMENTAL DESIGNS (continued)

BEFORE-AFTER DESIGN

- Examines the effect of an intervention on only one group of individuals.

- Example: DARP studies

METHODS USED IN OUTCOME RESEARCH

QUASI-EXPERIMENTAL DESIGNS (continued)

MAJOR STRENGTHS

- Can be much less expensive (exception is Prospective Study)

- Reduces the chance that individual will be eliminated from participating in a desired program

- Occurs in the real world

METHODS USED IN OUTCOME RESEARCH

QUASI-EXPERIMENTAL DESIGNS (continued)

MAJOR WEAKNESSNES

- Since there is no random assignment, groups may not be comparable. This can be somewhat controlled by subject matching.
- If treatment has become the "gold standard," it may become difficult to find untreated or "other treated" controls
- In the Prospective Study, one group may end up with too few people for an accurate statistical assessment
- Lack of control group in the Before-After design does not allow researchers to accurately assess if the observed change is due to the intervention or to some other factor, for example the passage of time.

PROBLEMS ENCOUNTERED IN TREATMENT OUTCOME STUDIES:

THE SPECIAL CASE OF DRUG TREATMENT

- Variables usually measured may not actually reflect treatment improvement
- Varying definitions can be applied to the same term
- Standards of success may be highly variable for different types of drug users
- Research has consistently assessed short-term, rather than long-term, outcome

PROBLEMS ENCOUNTERED IN TREATMENT OUTCOME STUDIES:

THE SPECIAL CASE OF DRUG TREATMENT (continued)

- Variables usually measured may not actually reflect treatment improvement

For example, <u>retention in treatment</u> is usually believed to be highly related to treatment success. However, some studies have shown that retention is reflective of characteristics which usually predict a poor outcome, such as severity of psychological involvement (Carroll, Power, Bryant, and Rounsaville, 1993).

PROBLEMS ENCOUNTERED IN TREATMENT OUTCOME STUDIES:

THE SPECIAL CASE OF DRUG TREATMENT (continued)

- Varying definitions can be applied to the same term

For example, retention in treatment has been variously defined as lasting in treatment for 1-4 weeks after entry (Agosti, Nunes, Stewart, and Quitkin, 1991), attending half of required treatment sessions (Gainey, Wells, Hawkins, and Catalano, 1993), or completing a number of sessions over a certain period of time (Carroll, Rounsaville, and Gawin, 1991).

PROBLEMS ENCOUNTERED IN TREATMENT OUTCOME STUDIES:

THE SPECIAL CASE OF DRUG TREATMENT (continued)

- Standards of success may be highly variable for different types of drug users

  For example, abstinence from all drugs may not be a standard applicable to those in methadone maintenance treatment. In another example, cocaine abusers who are also alcoholics may not be able to completely control both addictions, at least without the addition of services during their treatment (Carroll, Rounsaville, and Bryant, 1993).

PROBLEMS ENCOUNTERED IN TREATMENT OUTCOME STUDIES:

THE SPECIAL CASE OF DRUG TREATMENT (continued)

- Research has consistently assessed short-term, rather than long-term, outcome

  For example, most studies measure outcome for only 6 months to 1-year following treatment. This time period may be insufficient to assess the actual impact of treatment, both positive and negative. However, the costs per subject for prospective longitudinal studies may be prohibitive. Likewise, memory, which is relied upon for retrospective longitudinal studies, may be faulty.

RECOMMENDATIONS FOR EVALUATION STUDIES I

Research on Populations

- Types
  - General Population Studies
  - Client Population Studies
- Examine
  - Demography
  - Psychopathology
  - Natural history
  - Treatment-seeking behavior
  - Patient needs
  - Availability for treatment
  - Diagnostic subtypes
  - Diversity
  - Differences in natural contingencies (such as employment or social networks)

- Example: National Survey of American Attitudes on Substance Abuse (1995).

Source: Adapted from Leukefeld and Tims (1993)

RECOMMENDATIONS FOR EVALUATION STUDIES II

Treatment Modalities and Therapy Research

- Studies of the effectiveness of interventions, including treatment modalities such as inpatient versus outpatient care
- Studies evaluating the effectiveness of pharmacological agents, including field testing
- Systematic evaluation of nontraditional or experimental interventions, such as acupuncture
- Assessments of self-help treatments, including 12-step program
- Theory-based studies

Example: l-glutamine study, Jerome J. Platt, P.I.

Source: Leukefeld and Tims (1993)

RECOMMENDATIONS FOR EVALUATION STUDIES III

Research Design Issues

- Documentation of the training and experience of treatment providers in treatment outcome studies
- Inclusion of both behavioral and intrapsychic outcome measures
- Inclusion of survival rates in outcome analysis
- Reconciliation of differences among studies, including standardization of outcome terminology and definition

Example: Drug Evaluation Network System, Herbert Kleber, P.I.

Source: Leukefeld and Tims (1993)

RECOMMENDATIONS FOR EVALUATION STUDIES IV

Other Issues

- The importance of diagnosis and comorbidities in drug treatment
- The value of treatment planning in assessing outcome
- Matching patients to treatment
- Drug testing and drug testing methodologies as integral to treatment
- The role of legal issues and legal involvement in drug treatment outcomes
- HIV/AIDS
- Relapse to drug use and relapse prevention
- The role of training in the effectiveness of counselors and other treatment personnel

Examples: Alternative Matrix Technology Program, David Kidwell, P.I.; PET study, Edythe London, P.I.; and Cocaine Analytic Antibodies Research, Donald Landry, P.I.

Source: Modified from Leukefeld and Tims (1993)

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Appendix B
Program

The 1995 ONDCP International Workshop

Drug Abuse Treatment Technology

Sponsored by:
The Counterdrug Technology Assessment Center
Office of National Drug Control Policy
Dr. Lee P. Brown, Director
Executive Office of the President

August 15–16, 1995
Sheraton Inner Harbor Hotel
Baltimore, Maryland USA

Program

Monday, August 14

Time/Place	Event	Presenter
5:00–7:00 p.m. Chesapeake Gallery	**Registration**	
7:00–10:00 p.m. Camden Yards	**Baltimore Orioles vs. Cleveland Indians (Optional)**	

Tuesday, August 15

Time/Place	Event	Presenter
8:00 a.m. Chesapeake Gallery	**Registration**	
9:00 a.m. Chesapeake I & II	**Plenary Session:**	
9:00–9:10 a.m.	Introduction/Workshop Overview	Dr. Albert Brandenstein Director, ONDCP/CTAC
9:10–9:30 a.m.	State Perspective	Hon. Bishop Robinson Secretary, MD Dept. of Public Safety and Correctional Services
9:30–10:15 a.m.	ONDCP Demand Reduction Perspective	Mr. Fred Garcia Deputy Director, ONDCP
10:15–10:30 a.m.	**Break**	
10:30–11:00 a.m.	NIDA Perspective	Dr. Alan I. Leshner Director, NIDA
11:00–11:20 a.m.	Local Law Enforcement Perspective	Col. Leon Tomlin Ass't Commissioner, Baltimore City Police
11:20 a.m.–12:00 Noon	"New Approaches to Understanding Drug Abuse"	Dr. Edythe London NIDA