

## National Institute on Drug Abuse Director's Report to the National Advisory Council on Drug Abuse

May, 1995

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## Director's Report to the National Advisory Council on Drug Abuse May, 1995

### Research Findings

#### Basic Research

#### Cocaine and Amphetamine Sensitization and NMDA Receptors

Sensitization, defined as the progressive enhancement of the locomotor stimulatory effects of drugs such as amphetamine or cocaine during their repeated administration, is often considered to model processes contributing to (1) drug addiction, and (2) certain drug-induced and spontaneous psychotic symptoms. Dr. Marina Wolf and others have previously shown that the development of sensitization in rats to effects of amphetamine and cocaine is prevented by co-administration of antagonists of the *N*-methyl-D-aspartate (NMDA) receptor complex, a result which is consistent with the demonstrated role of NMDA receptors in other forms of neuronal and behavioral plasticity. Several experiments recently performed by this group have contributed to our understanding of sensitization. (1) Lesion studies indicate that sensitization requires a neuronal circuit involving prefrontal cortex, amygdala, and ventral tegmental area. (2) The response of ventral tegmental area dopaminergic neurons to glutamate was increased in amphetamine and cocaine-sensitized rats, while nucleus accumbens neurons were less sensitive to glutamate. Thus, sensitization appears to be associated with changes in glutamate transmission at both the origin and termination of the mesoaccumbens dopaminergic pathway (White FJ, Hu X-T, Zhang X-F & Wolf ME: Repeated Administration of Cocaine or Amphetamine Alters Neuronal Responses to Glutamate in the Mesoaccumbens Dopamine System. *J. Pharmacol. Exp. Ther.*, in press).

#### Neurobiology Of Sensitization

NIDA has several grantees studying various aspects of stimulant-induced behavioral sensitization in animals. Among them are Dr. Terry Robinson from the University of Michigan (Ann Arbor) and Dr. James Steketee from LSU (Shreveport). Sensitization is a common effect whereby the repeated administration of a psychomotor stimulant results in an increased, rather than a decreased, drug effect over time. The clinical relevance of sensitization is that repeated exposure of the stimulant often results in a drug-associated paranoid psychosis that is clinically similar to paranoid schizophrenia. This increased effect is thought to be due to a neural adaptation produced by repeated exposure.

Of particular significance are the findings by Dr. Robinson that there is stimulus control of amphetamine sensitization (both development and expression). These studies are of particular relevance to drug craving induced by environmental cues (eg, an addict sees an old drug supplier, which makes him return to his drug-seeking ways).

Dr. Steketee is a young investigator who is studying the role of the ventral tegmental area in the development and expression of behavioral sensitization of cocaine in the rat. He is examining the potential role that changes in intracellular signal transduction play in the development of behavioral sensitization to cocaine. In his initial studies, Dr. Steketee determined the role of GABAB receptors in the A10 region of the rat brain by the direct injection of the antagonist 2hydroxysaclofen alone or in combination with cocaine, with measurement of locomotor activity as the endpoint. The antagonist did not alter the spontaneous locomotor activity or the cocaine-induced hyperactivity. These data suggest that blocking the activation of the GABAB receptor may not be important in the development of sensitization.

## **D1 Receptorless Mice Do Not Show Motor Stimulation In Response To Cocaine**

The brain mesoaccumbens DA system is involved in the psychomotor stimulation activities of cocaine. However, the extent to which different DA receptors mediate these effects is not clear. This study used a DA D1 receptor mutant mice produced by gene targeting to investigate the role of this receptor in the effects induced by cocaine. Wild-type mice, showed a dose-dependent increase in locomotion, D1 mutant mice exhibited a dose-dependent decrease. Electrophysiological studies of DA sensitive nucleus accumbens neurons demonstrated a marked reduction in the inhibitory effects of cocaine on the generation of action potentials. Also, the inhibitory effects of DA as well as D1 and D2 agonists were nearly completely abolished, whereas those of 5HT were unaffected. D2-like DA receptor binding was also normal. The results indicate the essential role of the D1 receptor in the locomotor stimulant effects of cocaine and in DA-mediated neurophysiological effects within the nucleus accumbens. Xu, Ming, Hu, Siu-Ti, Cooper, D., Moratalla, Rosaria, Graybiel, A., White, F., and Tonegawa, S. Elimination of Cocaine-Induced Hyperactivity and Dopamine-Mediated Neurophysiological Effects in Dopamine D2 Receptor Mutant Mice. *Cell*, 79: 945-955, 1994.

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## **An Opioid-like Brain Derived Chemotactic Factor**

During normal brain development macrophages are targeted to areas of degeneration, including sites where cell death naturally occurs, and glial scaffolds are eliminated. Similarly, macrophages also are targeted to sites of neuronal injury. What molecular mechanisms control this specific migration? Some investigators have proposed release of a chemotactic signal by degenerating neuronal elements, and, indeed, numerous chemotactic factors (including growth factors and cytokines) have been identified outside the central nervous system. Now, NIDA grantee Dr. Pat Levitt of the Robert Wood Johnson Medical School in New Jersey and coworkers report identifying an injury-induced brain derived chemotactic factor (BDCF) whose activity appears to be opioid-like. The factor attracts both brain and resident peritoneal macrophages. In tests with the latter, delta receptor antagonists naltrindole and ICI174,864 blocked chemotaxis, but mu and kappa antagonists failed to show an effect; however tests with five opioid ligands failed to induce chemotaxis, indicating that the factor is not one of those conventionally known. The investigators report that their results "...suggest that opioids are released as a response to neuronal injury and have critical roles in recruiting phagocytic cells and subsequent immune modulation." Carolanne E. Milligan, Linda Webster, Elmer T. Piros, Christopher J. Evans, Timothy J. Cunningham, and Pat Levitt. 1995. "Induction of Opioid Receptor-Mediated Macrophage Chemotactic Activity After Neonatal Brain Injury. *The Journal of Immunology*, in press.

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## **Transgenic Mice Model of Endogenous Opioid Gene Regulation by Exogenous Opioid**

Stress strongly induces proenkephalin gene expression in the hypothalamus. Using a transgenic mice model, NIDA grantees Steven E. Hyman, David Borsook and their coworkers at Harvard Medical School observed that acute or subacute morphine administration prior to stress produced marked superinduction of transgene expression compared with stress alone. In contrast, chronic morphine administration decreased basal expression of the transgene, and inhibited stress-induced expression of the transgene. The endogenous proenkephalin mRNA and c-fos were induced in parallel with the transgene. These data suggest that acute or subacute morphine administration sensitizes proenkephalin neurons within the hypothalamus to stress and that chronic morphine administration desensitizes this response. With special reference to mechanisms of opioid dependence, this model appears to be a useful tool to investigate the mechanistic aspects of the regulation of endogenous opioid genes by exogenous opioids.

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## **Effects of Prenatal Cocaine Exposure**

Clinical case reports have described cerebral vascular insults in fetuses born to cocaine abusing mothers. Fetal hypoxemia is thought to be one of the mechanisms involved in the patho-physiology of abnormal cerebral growth and neurodevelopment in newborns. Findings from in vivo fetal sheep studies reveal that cocaine causes fetal hypoxemia but does not affect fetal brain oxygen delivery probably due to enhanced compensatory blood flow and oxygen delivery to the heart. Increases in cerebral vascular resistance were also observed following cocaine and its metabolites, benzoylecgonine and cocaethylene; however, the magnitude of change in vascular resistance seen with cocaine metabolites was different from that of the parent drug.

Data from in vitro studies indicate that cocaine affects fetal cerebral vasculature probably through its direct inhibitory effect on neurotransmitter uptake and sodium channels as well as through its major metabolites. Thus, the development of fetal cerebral vasculature and its response to physiological or pathophysiological stimuli may be

altered by prenatal cocaine exposure. (Covert, Schreiber et al., J Pharmacol. Exp. Therap. 270:1-9, 1994; Schreiber et al., J. Dev. Physiol. 20:141-147, 1994; Schreiber et al., J. Applied Physiology 77:834-839, 1994; Pena, Burchfield and Abrams, Pediatric Research 35:248A, 1994)

## Effects of Prenatal Morphine Exposure

Dr. Vathy and her associates have reported recently that prenatal morphine exposure produces long-lasting, sexually dimorphic alterations in norepinephrine (NE) content and turnover rate in specific brain regions. This may indicate altered firing of NE cell bodies of origin or modification in local mechanisms regulating NE utilization at the level of terminals. Morphine also induced postsynaptic alterations in the brains of female rat offspring as mu opioid receptor binding was reduced in females but not in males. Like morphine, prenatal cocaine exposure in modest doses also produced long-lasting, sexually dimorphic alterations in adult sexual behavior and brain catecholamines in rat offspring; however, the alterations in the magnitude of behavioral changes were different than after morphine exposure. (Vathy et al., Dev. Brain Res. 73:1115-1122, 1993; Vathy et al., Brain Res. in press, 1995; Rimanoczy and Vathy, Society for Neurosci. 20:504A, 1994).

## Opioid Regulation of Calcium Channels

Using specific antibodies directed at the G protein *alpha* subunits (*alphao*, *alpha1*, *alpha2* and *alpha3*) to block G protein coupling of  $\mu$  receptors to calcium channels, Dr. Robert L. Macdonald and his colleagues at The University of Michigan Medical School have demonstrated that  $\mu$  opioid induced inhibition of calcium current in acutely dissociated rat primary afferent neurons occurs through activation of a Gi or Go-type G protein and that the reduction is independent of changes in adenylate cyclase activity. Intracellular dialysis with an antiserum specific for Go attenuated calcium current inhibition by a  $\mu$  agonist in 5 of 6 neurons but no alteration of responses to the  $\mu$  agonist were produced when neurons were dialyzed with an anti-Gi1*alpha*/Gi2*alpha* antiserum or antibody specific for the  $\alpha$  subunits of Gi proteins. Thus, **in rat DOG neurons,  $\mu$  opioid receptors coupled to calcium channels via the pertussis toxin sensitive Go subclass of GTP binding proteins**

Furthermore, studies were conducted to examine the regulations of voltage dependent calcium channels, using whole cell patch clamp recordings, on acutely isolated rat dorsal ganglia neurons by  $\mu$  and K opioid agonists. The results indicated that inhibitory response to one agonist was occluded when tested in the presence of the other, suggesting that  $\mu$  and K opioid receptors are co-expressed on at least some primary afferent neurons and appear to be functionally coupled to a common pool of calcium channels. The effect of  $\mu$  agonists was studied on high threshold calcium currents recorded from these neurons. Using selective blockade (a combination of omega-conotoxin, omega-agatoxin IV A and nifedipine), they demonstrated the presence of N type, L type and possibly P type calcium currents. These data demonstrated that  $\mu$  agonists reduced N type and possibly P type calcium currents but did not reduce currents mediated by L calcium channel currents. Thus,  **$\mu$  opioid receptors were negatively coupled to several pharmacological distinct types of high threshold calcium channels in rat primary afferent neurons, probably N type and P type calcium current channels.**

Studies were also conducted to investigate the effects of direct intracellular application of a constitutively active form of protein kinase (PKC), PKM, on whole cell calcium currents recorded from acutely dissociated rat primary afferent neurons to determine which high threshold calcium currents are regulated by phosphorylation by protein kinase A (PKA) or PKC. **PKM enhanced high threshold voltage activated calcium currents. This enhancement was blocked by the synthetic PKC inhibitor peptide (PKC-I) confirming that this was a specific PKC mediated effect. The enhancement of high threshold calcium current appeared to involve both N and L calcium current components.**

Additionally, Dr. Macdonald and his colleagues **have succeeded in co-expressing mouse brain  $\beta$  subunit isoforms with a neuronal class C *alpha1* subunit in HEK 293 cells.** Whole cell voltage clamp recording demonstrated that **addition of mouse brain  $\beta$  subunit isoforms with the *alpha1* subunit produces a marked enhancement of calcium current amplitude.**

Finally, the effect of PKM on K opioid receptor agonist mediated inhibition of N type current in primary afferent neurons was investigated. In the presence of intracellular PKM, the dynorphin A, a K opioid agonist, was less effective in decreasing N type calcium current. This reduction in efficacy was blocked by co-introduction of the inhibitory peptide PKC-I. These data demonstrate that **PKC mediated phosphorylation decreases the coupling between opioid receptor activation and N type calcium current reduction. The target for this phosphorylation remains uncertain and could represent phosphorylation of either K opioid receptor, G protein or calcium**

**channel.**

These studies have demonstrated the feasibility of determining the type of G protein which couples  $\mu$  and K opioid receptors to calcium currents and of identifying the calcium current target. They show the coupling of  $\mu$  and k opioid receptors to the same calcium channel target via the same G protein and reveal a role for protein kinase C mediated phosphorylation in regulating this coupling. Moreover, with the ability to express recombinant calcium channels and opioid receptors in an heterologous expression system, it will become possible to determine the sites of phosphorylation mediated regulation of this coupling and to examine the signal transduction mechanism occurring between G proteins and calcium channels in these cells. ( Moises, Russin and Macdonald, J. Neurosci. 14: 3842, 1994; Moises, Russin and Macdonald, J. Neurosci. 14: 5903, 1994; Hall, Browning, Dudek and Macdonald, J. Neurosci, in press; Massa, Kelly, Yule, MA, Macdonald, and Uhler, in press; Kelly, Esmail, and Macdonald, Soc Neurosci Abstr, 20:899, 1994; Hall, Browning, Dudek, and Macdonald, Soc Neurosci Abstr, 20: 902, 1994.

**NMDA Elevation of Extracellular Dopamine and Serotonin in the Nucleus Accumbens**

A property common to addicting drugs, including opiates, ethanol, nicotine, amphetamine and cocaine, is the ability to increase extracellular concentrations of dopamine in the nucleus accumbens. Many of these drugs also elevate extracellular serotonin in the n. accumbens. Although MDMA increases in extracellular dopamine measured by *in vivo* voltammetry in the accumbens have been demonstrated, it was not clear whether MDMA also increases serotonin *in vivo* in this nucleus. Susan White and colleagues at Washington State University used microiontophoresis combined with extracellular recording to determine the effects of MDMA on glutamate-evoked firing of neurons in the n. accumbens *in vivo*. Then they used *in vivo* microdialysis to determine whether local infusion of MDMA into the accumbens alters extracellular levels of DA and/or serotonin.

These investigators found that local application of MDMA inhibited glutamate-evoked firing of n. accumbens neurons, and that this effect was mediated partially by dopamine and partially by serotonin. Extracellular levels of both of these monoamines were elevated in the n. accumbens following local application of MDMA. These results permit MDMA to be added to the list of abused drugs that have been demonstrated to elevate extracellular levels of dopamine and serotonin in the nucleus accumbens (White et al., Neuroscience **62**: 41-50, 1994).

In even more recent (unpublished) experiments, they found that repeated exposure to MDMA decreased inhibitory effects of dopamine on accumbens cells that were tested 2 weeks after the last MDMA injection. This observation suggests that chronic MDMA, like chronic cocaine, causes long-term changes in dopamine neurotransmission in the accumbens, an effect which may underlie the addictive property of these drugs.

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## Director's Report to the National Advisory Council on Drug Abuse May, 1995

### Research Findings

#### Behavioral Research

#### Effects of Caffeine on Decrements Produced by Benzodiazepines or Alcohol

Researchers at the University of Vermont (Drs. Rush, Higgins, Bickel, and Hughes) have demonstrated in humans that caffeine can attenuate the behavioral performance decrements produced by benzodiazepines or alcohol. Caffeine attenuated learning and performance decrements on the Repeated Acquisition and Performance Procedure and the Digit Symbol Substitution Test produced either by lorazepam, triazolam, or alcohol. Caffeine administered alone did not enhance performance or learning. Caffeine also decreased self-ratings of sedation produced by the benzodiazepines. (Behav. Pharm. 5, 245-254 (1994), Exp. & Clin. Psychopharm. 2, 211-22 (1994), Behav. Pharm. 4, 562-572 (1993) )

#### Amphetamine and Feeding Behavior

Amphetamine produces marked stereotypy that may interfere with feeding behavior. Dr. David Wolgin of Florida Atlantic University has investigated the factors contributing to the development of tolerance to amphetamine-induced hypophagia. Rats learned to suppress stereotyped head movements produced by amphetamine in order to receive sweetened milk reinforcement. Further analysis of head movements revealed residual behavioral effects of amphetamine even in "tolerant" amphetamine-treated rats. These studies demonstrate that behavioral tolerance may maintain drug abuse by decreasing the disruptive effects of stimulant drugs. Behavioral Pharmacology, in press, 1995.

#### Concurrent Cocaine/Alcohol Abuse

Dr. Elinore McCance-Katz of Yale University School of Medicine has conducted a placebo-controlled, double-blind study examining the behavioral and physiological effects and pharmacokinetics of intranasal cocaethylene administration in humans using cocaine as a comparator. Cocaethylene is an active metabolite formed as a result of simultaneous use of cocaine and alcohol, a common occurrence which constitutes a major public health problem. The results showed that the concurrent ingestion of cocaine and alcohol is associated with enhanced subjective euphoria, increased heart rate, and increased plasma cocaine concentration. Slow disposition could result in accumulation of cocaethylene and increase the toxic effects of binge use of cocaine and alcohol in humans. These findings suggest that cocaethylene may play a role in the morbidity and mortality associated with concurrent cocaine/alcohol abuse.

#### Locomotor and Rewarding Effects of Amphetamine in Enriched Social and Isolated Rats

The interactions of novel environments and behavioral responses to drugs have been investigated by Drs. Bowling and Bardo from the University of Kentucky. They examined the influence of environmental enrichment on the behavioral response to amphetamine. Rats were raised in one of three different environmental conditions: a) an enriched condition (EC), b) a social condition (SC), c) an isolated condition (IC). At 53 days, animals were assessed for amphetamine-induced changes in locomotor activity and reward using the conditioned place preference (CPP)

paradigm. EC animals exhibited more horizontal and vertical activity following amphetamine than both the SC and IC animals. Similarly, EC animals exhibited a greater magnitude of amphetamine-induced CPP than both the SC and IC animals. It is hypothesized that the EC environment may sensitize the dopaminergic mesolimbic pathway in much the same way as low doses of amphetamine have been shown to; thus, explaining the enhanced effect of amphetamine in these animals. Bowling, S.L., Bardo, M.T. Locomotor and Rewarding Effects of Amphetamine in Enriched, Social and Isolate Reared Rats. *Pharmacology, Biochemistry and Behavior*, 48, 459-464, 1994.

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### **Conditioned Place Preference Using Opiate and Stimulant Drugs**

Bardo and his colleagues conducted a meta-analysis on data obtained from published articles that have used the conditioned place preference (CPP) paradigm to assess the rewarding effects of morphine, heroin, amphetamine and cocaine in rats. Using a histogram analysis of the data, significant dose effect curves were evident with all of the drugs examined except for cocaine. One surprising outcome was the failure to find any significant differences in effect size based upon the number of drug conditioning trials used. The meta-analysis indicates that researchers must consider the risk of introducing variables which confound interpretations of CPP as a measure of drug reward. Bardo, M.T., Rowlett, J.K., Harris, M.J. Conditioned Place Preference Using Opiate and Stimulant Drugs: A Meta-Analysis. *Neurosciences and Biobehavioral Review*, 18, 1-12, 1995.

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### **Effects of Ethanol on the Acoustic Startle Reflex in Humans**

A substudy of research on the specificity of genetic transmission of risk for substance abuse indicates human sensorimotor reactivity among healthy normal subjects (N=12) was significantly affected by the effects of ethanol. The amplitude of the acoustic startle response in a procedure in which a placebo or ethanol were given on separate days was dramatically reduced by acute ethanol. The effects of ethanol on prepulse inhibition could not be assessed because the startle response was too small in the ethanol conditions. The report helps to describe the risk to normal subjects under acute effects of ethanol in terms of safety and other risks, such as continued drug use. (Grillon, C, Sinha, R, and O'Malley, SS. Effects of Ethanol on the Acoustic Startle Reflex in Humans. *Psychopharmacology* 114:167-171, 1994).

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### **Cocaine and Cigarette Smoking**

In a letter in the December issue of JAMA, Dr. Steven Higgins and colleagues at the University of Vermont described data suggesting that cocaine and cigarette smoking may be correlated. For example, they found that cocaine had a facilitative effect upon cigarette smoking in a laboratory study. Further, a study of cocaine-dependent outpatients revealed that the cigarette smokers in this group used more cocaine than nonsmokers and were more likely to use i.v. or smoked cocaine. This finding is of great concern because the cocaine plus nicotine combination produces greater cardiac risk than either drug alone. [Higgins, S.T., Budney, A.J., Hughes, J.R., Bickel, W.K., Lynn, M., & Mortensen, A. (1994), Influence of Cocaine Use on Cigarette Smoking, *JAMA*, 272, 1724.]

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### **Social Cooperation During Abstinence From Nicotine**

In a study conducted by Dr. Ralph Spiga at the University of Texas, Houston Health Science Center, heavy smokers who had abstained from smoking were brought into the laboratory to investigate their level of cooperation in a shared laboratory task. After the 1st daily session subjects smoked ad libitum, received 0, 2, or 4 mg nicotine gum, or abstained from smoking. Indices of cooperation were significantly greater following ad libitum smoking or acute administration of 4 mg nicotine gum. Nicotine abstinence did not alter "independent", non-cooperative responding, but did reduce cooperative responding. Results suggest nicotine use may increase social cooperation during a shared work task, thus potentially motivating relapse in abstinent heavy smokers. *Behavioural Pharmacology*. Vol 5(3) 337-343, June 1994.

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### **Chronic and Acute Tolerance to Subjective, Behavioral, and Cardiovascular Effects of Nicotine in Humans**

In the first study of its kind, Dr. Perkins and his colleagues (Western Psychiatric Institute, Pittsburgh) measured the

dose-related subjective, behavioral, cognitive, and cardiovascular effects of acute or chronic exposure to nicotine in smokers and non-smokers. The subjective (e.g., tension, confusion, vigor, fatigue) and cardiovascular measures (heartrate, blood pressure) were obtained over the first 5 min, followed by behavioral (e.g., finger-tapping speed, handsteadiness, tremor), and cognitive tasks (memory recognition, numerical Stroop task) during the next 10 minutes after the exposure to nicotine (administered at 0, 5, 10, or 20 ug/kg, via measured-dose nasal spray, with different doses presented on different days to male and female smokers [n=17] and nonsmokers [n=18]). The acute tolerance was clear and substantial for subjective measures, but was less clear for behavioral or cardiovascular effects. There was substantial chronic tolerance for subjective responses, less for behavioral task performance and little for cardiovascular responses. The regular use of nicotine was associated with chronic functional tolerance, and repeated nicotine exposure during a single episode produced acute tolerance. According to the authors, the differential development of tolerance across response domains suggests differential mechanisms responsible for the different effects of nicotine. (Perkins KA, Grobe JE, Fonte C, Goettler JL, Caggiula AR, Reynolds WA, Stiller RL, Scierka A, and Jacob RG. Journal of Pharmacology and Experimental Therapeutics, 270: 628-638, 1994).

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## Director's Report to the National Advisory Council on Drug Abuse May, 1995

### Research Findings

### Clinical and Services Research

### Nosology, Diagnosis and Clinical Assessment

Since her project began in 1988, Dr. Linda Cottler and her colleagues, Washington University School of Medicine, have been examining the inter-rater reliability and clinical validity of substance use disorder diagnoses according to the criteria of the Diagnostic and Statistical Manual, Third Edition, Third Edition Revised, and Fourth Edition [DSM-III, -III-R, and -IV] (American Psychiatric Association) and the International Classification of Diseases, Tenth Edition [ICD-10] (World Health Organization). The Substance Abuse Module (SAM), an expanded version of the substance use disorder sections of the Composite International Diagnostic Interview (CIDI), is the structured diagnostic assessment used in this study. Validity measures have included urine, informant interviews, and clinician interviews using the semi-structured WHO Schedules for Clinical Assessment in Neuropsychiatry (SCAN). Comparisons of DSM-III, -III-R, -IV, and ICD-10 have shown good agreement for dependence diagnoses among alcohol, nicotine, cannabis, and cocaine users, but less agreement between systems for abuse (DSM) and harmful use (ICD). Comparison between the lay-administered SAM and the clinician-administered SCAN has indicated good agreement for ICD-10 alcohol, opiate, and cocaine dependence and poor agreement for cannabis. (Cottler, LB; Robins, LN; and Helzer, JE. Agreement Between DSM-III and DSM-III-R Substance Use Disorders. **Drug and Alcohol Dependence**, 29:17-25, 1991; Cottler, LB. Comparing DSM-III-R and ICD-10 Substance Use Disorders. **British Journal of Addiction**, 88:689-696, 1993. Cottler, LB et al. Subjective Reports of Withdrawal Among Cocaine Users: Recommendations for DSM-IV; **Drug and Alcohol Dependence**, 33:97-104, 1993; Cottler, LB et al. The Discrepancy Interview Protocol: A Method for Evaluating and Interpreting Discordant Survey Responses. **International Journal of Methods in Psychiatric Research**, 4:173-182, 1994.

### Identification of Subtypes of Antisocial Personality Disorder

In a study focused on high risk behaviors, comorbidity and drug use conducted by Dr. Linda B. Cottler and her colleagues, new subtypes of Antisocial Personality Disorder (ASPD) were identified among 405 adult drug users admitted to treatment. To meet criteria for ASPD, a person must have exhibited irresponsible, socially non-conforming behaviors as an adult as well as a pattern of childhood conduct disorder (CD). Results of the study showed that a substantial proportion of injecting drug users met criteria for Adult Antisocial Behavior (AAB) without the childhood trajectory of CD. Using the Diagnostic Interview Schedule, a fully diagnosed ASPD group (with history of CD) was distinguishable from an AAB-only group (without history of CD). The findings identify a distinct subtype of ASPD, especially among women, and suggest a modification in the concept of ASPD.

### Pattern Shift VEPs in Abstinent Cocaine Dependent, Alcohol Dependent, and Codependent Patients

Bauer and Easton (1994, submitted) of the University of Connecticut Health Center evaluated pattern shift evoked potential (PSVEP) amplitudes and latencies in four groups of subjects (controls, 10; cocaine-dependent, 10; alcohol dependent, 11; and cocaine+alcohol codependent, 11). The subjects were given two psychiatric interviews (the Semistructured assessment for the Genetics of Alcoholism and the Addiction Severity Index) and these met the DSM-

IIIR criteria for drug dependence. Drug use or abstinence was verified by urine toxicology. There were abnormal PSVEPs evoked by checkerboard reversal among cocaine abusers abstinent for an average of 3 months. The abstinent alcoholics and those with codependency, also abstinent for 3 months, did not exhibit this abnormality. Data suggest that cocaine may impair visual nervous system function at the level of retina, optic nerve, lateral geniculate, and/or primary visual cortex (Bauer LO and Easton C. Submitted for Publication, 1994).

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### **Neuropsychological Correlates of Urine Toxicology Results**

Easton and Bauer (1994) report neuropsychological decrements associated with cocaine use. Four groups of men and women, aged 15 to 61 years, who had used drugs recently [cocaine (n=12), cannabis (n=14), multiple drugs (n=7) or no drug (n=21)], were assessed for neuropsychological function. The use of drugs was confirmed by standard urine toxicology. The battery of tests included the Wechsler Adult Intelligence Scale (WAIS), the Trail making Tests, and Porteus Maze Test. The cocaine positive group exhibited statistically significant impairments in verbal IQ, and on information, comprehension and vocabulary subtests. These individuals also exhibited decrements on the Trail B and Picture Completion subtests, implying impaired cognitive flexibility and attention/concentration. The other experimental groups did not differ from the urine negative group (Easton C and Bauer LO, submitted for publication, 1994).

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### **Pharmacodynamic Effects of Supraphysiologic Doses of Testosterone Enanthate on the Pituitary-Testicular Axis of Young Healthy Male Volunteers: Preliminary Report**

Dr. Perry and colleagues at the University of Iowa report that follicular stimulating hormone (FSH) is more sensitive to exogenous testosterone (TE) pituitary-testicular axis (PTA) suppression than luteinizing hormone (LH) in healthy male volunteers. TE was administered intramuscularly at doses of 100 mg (n=4), 250 mg (n=4), or 500 mg (n=2) once weekly for 14 weeks after baseline studies and 2 weeks of placebo. Serum LH, FSH, free and total testosterone, and markers of spermatogenesis were measured at 1 or 2 weeks intervals during and up to 12 weeks after dosing ceased. Dose-response curves showed that FSH was more rapidly sensitive to the effects of supraphysiologic doses of TE than LH, and the effect on sperm count varied markedly between subjects. The time to maximal effect (9-11 weeks) on LH and FSH secretion was delayed compared to maximal free and total testosterone (Scott SD, Perry PJ, MacIndoe JH, Yates WR, Holman TL, and Ellingrod VL. Presented at the European Conference on Specificity and Variability in Drug Metabolism, Besancon, May 1995).

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### **Smoking Cessation for Depressed Patients**

Smokers with a history of major depressive disorder constitute a significant proportion of smokers who present for cessation treatment. These smokers experience more frequent and intense depressive symptoms upon initial cessation and relapse at higher rates than other smokers. New and innovative interventions are needed to address the needs of these more recalcitrant smokers who may be unable to quit with standard interventions which are not matched or tailored to their particular needs.

Dr. Richard Brown, a NIDA investigator in Providence, Rhode Island, examined whether adding cognitive-behavioral treatment for depression to a standard smoking cessation protocol will enhance the achievement and maintenance of smoking cessation in smokers with a history of major depressive disorder. Preliminary results suggest that the addition of cognitive-behavioral treatment for depression (to standard smoking cessation treatment) results in superior rates of abstinence for smokers with a history of major depressive disorder, relative to standard smoking cessation treatment alone.

Dr. Arthur Garvey of the Harvard School of Dental Medicine found depressed smokers given nicotine gum were more likely to remain abstinent compared to depressed smokers receiving placebo gum. Although nicotine replacement appears to aid depressed smokers in their attempts to quit, this population may require a combination of nicotine replacement with other methods (antidepressants, mood management therapy) to elevate abstinence rates.

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### **Acute Thermogenic Effects of Nicotine Combined with Caffeine During Light Physical Activity in Male and Female Smokers**

Perkins et al. (1994) studied the thermogenic effects of nicotine (15 ug/kg) and caffeine (5 mg/kg) alone or in

combination, during physical activity (lowintensity cycle ergometer riding) compared with rest in male and female smokers (n=10 each). The energy expenditure was measured by indirect calorimetry while subjects engaged lowintensity cycle ergometer riding (activity) or were in quiet rest. There were significant thermogenic effects of nicotine and caffeine individually, while the combination of both produced additive effects. The energy expenditure attributable to nicotine, caffeine, or the combination significantly increased during activity compared with rest, but only in males. These differences in energy expenditure were not explained by the increased plasma levels of nicotine and caffeine during activity. The gender differences in the thermogenic effects of nicotine and caffeine during casual physical activity explained some of the apparent individual variability in expenditure due to tobacco smoking. In addition, eating played a more substantial role in the influence of nicotine on body weight in women than in men (Perkins KA, Sexton JE, Epstein LH, DiMarco A, Fonte C, Stiller RL, Scierka A, and Jacob RG. American Journal Clinical Nutrition, 60: 312-319, 1994).

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## Director's Report to the National Advisory Council on Drug Abuse May, 1995

### Research Findings

#### AIDS Research

#### Drug Use, Ethnicity, and the Course of HIV Infection

A ongoing study of progression of HIV infection compared a seroprevalent cohort of predominantly African-American, active IDUs with a cohort of predominantly white homosexual and bisexual men. Comparisons of changes in T-lymphocyte subsets following seroconversion indicated that prior to seroconversion the predominantly African-American IDUs had lower CD4% and higher CD8% as compared with the homosexual men. In the first two years after seroconversion, larger changes for both CD4% and CD8% were observed in the cohort of homosexual men as compared with the IDU cohort. After two years, the CD4% levels of the two cohorts converged and then declined at similar rates. These results suggest that drug use and ethnicity do not appreciably alter the course of HIV infection, at least through four years of post-seroconversion follow-up, and that observed differences between the two risk groups prior to seroconversion greatly diminish following seroconversion (Galai, Vlahov, Margolick, Chen, Graham & Munoz, *JAIDS*, 1994; 8:66-74). Furthermore, it was found that membership in either cohort risk group was not a factor in the relationship between clinical outcome and CD4 level. Subgroups in both cohorts who remained asymptomatic had similarly high levels of CD4 at baseline and identically slow rates of CD4 decline. Those in both cohorts who developed thrush or clinically defined AIDS had lower levels of CD4 at baseline and higher rates of CD4 decline. Distributions of these variables were similar in both cohorts (Margolick, Munoz, Vlahov, Astemborski, Solomon, He, Nelson & Saah, *Arch Int Med*, 154:869-875, 1994).

#### Effects of HIV on Immune Function in Humans

Researchers at the Cornell University Medical College have demonstrated that the HIV-1 envelope glycoprotein gp160 significantly reduced the mitogen-induced secretion of interferon- gamma and interleukin-2 but augmented secretion of interleukin-4 by peripheral blood mononuclear cells in vitro. These effects were not observed, however, when target cells were depleted of either CD4- or CD2-positive cells or were incubated with CD4-immunoglobulin chimeric molecules, suggesting that interaction between CD4 and gp160 molecules is necessary for the observed effects. Studies are in progress to further characterize these effects and their significance in HIV infection (Hu, R., Oyaizu, N., Kalyanaraman, V.S., and Pahwa, S. HIV-1 gp160 as a Modifier of Th1 and Th3 Cytokine Response: gp160 Suppresses Interferon-gamma and Interleukin-2 Production invitro. *Clin. Immunol. Immunopathol.* 73:245-251, 1994).

#### HIV Infection in Women with Injection Drug Using Partners

Dr. Stephanie Tortu and colleagues at the National Development and Research Institute examined the risk of HIV infection among a national sample of 5,162 heterosexual women with IDU partners recruited through street outreach and local networks of drug users. Three groups of women were distinguished and compared: those that had single sex partners, those with multiple partners, and those with multiple partners who also exchanged sex for drugs and/or money. Women with multiple partners who exchanged sex for drugs and/or money were at the highest risk for HIV, even when demographic variables were controlled. Tortu, S., Beardsley, M., Deren, S., and Davis, W. *The Risk of HIV*

Infection in a National Sample of Women with Injection Drug-Using Partners. *Am J Public Health*. 84:1243-1249, 1994.

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### **HIV Risk Behaviors Among Injection Drug Users in San Juan, Puerto Rico**

In a study investigating the effects of a community outreach program in reducing HIV risk behaviors among IDUs in San Juan, Puerto Rico, Dr. Colon of the Puerto Rico Department of Anti-Addiction Services, and colleagues at the University of Puerto Rico School of Public Health modeled pre- and post-intervention trends in risk behavior levels from successive cohorts of IDUs. While major portions of reported risk reductions were accounted for by secular trends, the outreach intervention was found to have significant partial effects in lowering risk behaviors related to the shared use of cookers and needle disinfectant practices. However, the intervention did not have an effect on high risk sexual behaviors which underscores the importance of focusing on these behaviors in HIV prevention interventions. Colon, H., Sahai, H., Robles, R., and Matos, T. Effects of a Community Outreach Program in HIV Risk Behaviors Among Injection Drug Users in San Juan, Puerto Rico: An Analysis of Trends. *AIDS Education and Prevention*. 7(3):192-209, May/June 1995.

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### **Women at High Risk for HIV**

Dr. Sherry Deren and colleagues in the AIDS Research Consortium evaluated data on behavioral change among women IDUs and sexual partners of IDUs relative to pregnancy. Baseline and follow-up data were analyzed from a national sample of women who were pregnant at baseline, became pregnant between baseline and follow-up, or who were not pregnant at all during the study. Both pregnant and not pregnant high risk women reported significant levels of risk reductions at follow-up. IDUs who were pregnant or became pregnant reported greater reductions in drug injection rates, were more likely to report entering drug treatment, and reported the greatest reduction in sex risks compared to IDUs who remained non-pregnant. The findings indicate that the period of pregnancy provides an opportunity for changes in risk behaviors of women. Deren, S., Davis, W., Tortu, S., Beardsley, M., Ahluwalia, I., and the National AIDS Research Consortium. Women at High Risk for HIV: Pregnancy and Risk Behaviors. *Journal of Drug Issues*. 25(1):57-71, 1995.

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### **Cognitive Readiness of Drug Injectors to Reduce AIDS Risks**

Dr. Camacho and others from the Institute of Behavioral Research at Texas Christian University examined the impact of motivational factors on AIDS high risk behavior after participation in an AIDS intervention program. As part of NIDA's research program to educate out-of-treatment IDUs and their sexual partners about HIV, the researchers developed measures of motivation to predict which IDUs would alter their risk behaviors following AIDS intervention and to what extent. They found that concern about AIDS was not related to risk levels at the start of an intervention, but that not having concerns about AIDS was a significant barrier to behavioral change at a 6-month follow-up. Further, the rate of risk reduction was greater for individuals reporting high risk and motivation baseline levels, particularly on measures of use of dirty works and injections. Risky sexual behaviors were found to be more resistant to change than drug-related risks. The findings indicate that psychoeducational AIDS interventions will be most effective with persons who have sufficient cognitive readiness to address AIDS-related issues at the personal level. Camacho, L., Williams, M., Vogtsberger, K., and Simpson, D. Cognitive Readiness of Drug Injectors to Reduce AIDS Risks. *Am J on Addictions*. 4:49-55, 1995.

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### **Injection Drug Users' Needle-Cleaning Practices**

Dr. Harvey Siegel and associates at Wright State University observed the needle cleaning practices of 77 injection drug users as part of the Community-Based Outreach/Intervention research project operating in Columbus, Ohio. They observed how, when, and where IDUs cleaned their needles at baseline and 3 weeks later, at a postintervention follow-up session. The intervention included instruction on needle cleaning practices, with emphasis on exposing needles to bleach for at least 30 seconds in the rinsing process. The researchers conclude that prevention messages that target IDUs about their disinfection practices must contain explicit instructions on minimum bleach exposure times. Siegel, H., Carlson, R., Falck, R., and Wang, J. Injection Drug Users' Needle-Cleaning Practices. *Am J Public Health*. 84:1523-1524, 1994.

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## Effectiveness of HIV/AIDS Risk Reduction Interventions Targeting IDUs

Drs. Booth and Watters reviewed published studies for the years 1987 to 1994 to examine the effectiveness of HIV/AIDS risk reduction interventions that target IDUs. The authors identify several major weaknesses that researchers should address when conducting evaluations of risk reduction interventions: a need to control for historic or temporal effects with pretest-posttest control group designs; a need to measure and incorporate intervention dose into the analysis; a need to disentangle exposure effects due to research setting (e.g., treatment clinic vs. street outreach) from intervention effects; and a need to improve problems with small sample sizes, differential attrition, and confounding factors like group differences in years of injection. The authors note that most of the studies they reviewed were implemented and evaluated under adverse conditions which do not lend themselves to more elegant and controlled research designs. Booth, R. and Watters J. How Effective Are Risk-Reduction Interventions Targeting Injecting Drug Users? *AIDS*. 8:1515-1524, 1994.

## Needle Use Practices and HIV Risk-Reduction Among IDUs in the Midwest

Dr. Carlson and colleagues at Wright State University conducted a 2-year ethnographic study of needle use patterns among IDUs in Dayton and Columbus, Ohio. The researchers assert that the term "needle sharing" implies a social bonding or altruistic motive among IDUs who share their needles. They argue that a more appropriate term would be "needle transfer or circulation" because IDUs share works out of economic necessity, from a relative scarcity of syringes. In fact, the researchers found that IDUs were reluctant to use needles previously used by others. This practice was viewed as unhygienic and subordinating because it meant "shooting up behind someone." IDUs who had to wait to use another's needle were more likely to rinse the needle quickly and skip the second bleaching/rinse cycle in their hurry to take the drug. Carlson, R., Siegel, H., and Falck, R. *Ethnography, Epidemiology, and Public Policy: Needle Use Practices and HIV-1 Risk Reduction Among Injecting Drug Users in the Midwest*. In: Feldman, D. (ed.) *Global AIDS Policy*. Westport, CT: Greenwood Publishing Group, Inc., pp. 185-214, 1994.

## Psychosocial Risk Factors and Condom Use in Intravenous Drug Abusers

A study of psychosocial risk and protective factors in HIV transmission among male intravenous drug abusers (N=300 patients in AIDS or methadone clinics in a large city hospital) indicates parental and peer factors and coping measures were associated with more condom use (Brook et al.). Family factors were associated with good coping skills and with selection of friends who support condom use. The findings supported a mediational model for planning to use and actually using condoms. (Brook, DW, Brook, JS, Whiteman, M, Masci, JR, de Catalogne, J, Amundsen, F, Wynn, PS, & Roberto, J. *Psychosocial Risk Factors and Condom Use in Intravenous Drug Abusers*. *American Journal on Addictions* 3:106-114, 1994).

**Effects of Personality Factors and Social Support on Patterns of Coping With AIDS.** Psychological and social measures were used to study the effects of personality factors and social support on patterns of coping with AIDS or the threat of AIDS by male intravenous drug abusers. The pathways by which psychosocial factors affected coping differed in HIV-positive and HIV-negative subjects. A mediational model best depicted the interrelation of personality, family, and peer factors among HIV-positive subjects. Anger and rebelliousness interfered with coping among HIV-negative subjects but not among HIV-positive subjects. This provides insight into the interplay of inner personality factors and external support factors and their effects on coping ability. (Brook, JS, Brook, DW, Wynn, PS, Whiteman, M, Masci, JR, de Catalogne, J, Roberto, J, and Amundsen, F. *Coping with AIDS and the Threat of AIDS in Intravenous Drug Abusers*. *Journal of Genetic Psychology* 155(2):147-159, 1994).

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## Director's Report to the National Advisory Council on Drug Abuse May, 1995

### Research Findings

#### Epidemiology, Etiology and Prevention Research

##### Profile of New York City Homicides

Results of toxicological testing of homicide victims reveals recent cocaine use by 19.0 percent of victims killed in the street (n=1,466 after exclusion of those whose survival time would have permitted elimination of assayed substances) and 15.8 percent of those killed in their own home (n=438, same exclusion). Rates of ethanol involvement were 21.4 and 16.0 percent, respectively, for victims in street and home homicides. Compared to those killed in their homes, homicide victims killed in the street were more likely to be male, to be 15-24 years of age, and to be African American. They also were more likely to be killed by a firearm. This study was based on medical examiner files for 4468 homicides that occurred in New York City in 1990 and 1991; results of primary interest pertain to homicides that occurred in the street or other outdoor places (50.1 percent of the 4468 cases) and in the victim's home (19.3 percent). Tardiff, K., Marzuk, P., Leon, A. Hirsch, C., Marina, S. Portera, L, and Hartwell, N. A Profile of Homicides on the Streets and in the Homes of New York City. Public Health Reports, 110(1): 13-17, 1995.

##### Feasibility of Half-Sibling Designs for Detecting a Genetic Component to a Disease

In genetic epidemiology, adoption and twin study designs are the most commonly used designs to identify genetic and common environmental components underlying familial aggregation but such families are not typical of families in drug abuse research. The feasibility of half-sibling designs for detecting a genetic (single-locus or multifactorial) source of familial aggregation of a disease were studied and compared to both adoption and twin study designs. Results for two types of design where the sample units were relative pairs reared apart (I) or reared together (II) indicated that the half-sibling designs were feasible but required more observations to achieve the same power. Designs involving half-siblings may be more feasible in situations in which greater availability exists of these relatives. This approach broadens opportunities for genetic research in nontraditional families. (Tierney, C, Merikangas, KR, and Risch, N. Feasibility of Half-Sibling Designs for Detecting a Genetic Component to a Disease. Genetic Epidemiology 11:523-538, 1994).

##### Co-morbidity and Co-transmission of Alcoholism, Anxiety, and Depression

Familial transmission analyses confirm findings regarding the specificity of transmission of alcohol and anxiety disorders. Relatives of probands with substance abuse/dependence showed increased rates of drug abuse/dependence and alcohol dependence (not alcohol abuse) compared to relatives of probands with alcohol abuse/dependence, anxiety disorders or normal controls. Specificity of transmission of drug abuse and alcohol abuse and specificity within specific drug classes also occurred. Results suggest that relatives of probands with substance abuse have more than a 2-fold increased risk of developing a substance abuse problem themselves. The rate of disruptive disorders was significantly elevated in offspring (age 7-18) of fathers with diagnoses of both substance abuse and antisocial personality disorder (44.4%) compared to offspring of fathers with anxiety or affective diagnoses (19.2%), both higher than rates of offspring of substance abusers without antisocial personality disorder (9.1%) and normals (7.1%). Analysis of subset of children (age 11-18) indicates that more than 27% of children of fathers with

both antisocial personality disorder and substance abuse met diagnostic criteria for substance abuse or dependence whereas the risk for substance abuse was highest for offspring of mothers with a substance abuse diagnosis (30.8%), a 2-fold increase over offspring of mothers with anxiety or affective disorders and a 10fold increase over offspring of normals. (Merikangas, KR, Risch, NJ, and Weissman, MM. Comorbidity and Co-transmission of Alcoholism, Anxiety and Depression. *Psychological Medicine* 24:69-80, 1994).

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### **Differential Gender-Related Treatment Needs of the Homeless**

The historical status of the homeless as being primarily older white men with alcohol problems is changing as the proportion of women in this population increases. In a 19-site Los Angeles County study comparing homeless men (n=386) and women (n=145), researchers found that homeless men, compared to homeless women, reported more substance use, longer periods of homelessness, poorer housing quality when not literally homeless, and greater criminal involvement. Homeless women were more likely than homeless men to have children living with them. Homeless men, compared to homeless women, showed stronger relationships between mental illness and prior institutionalization, between mental illness and drug use, between drug use and victimization. Homeless women, on the other hand, showed stronger relationships between drug use and alcohol use and between criminal involvement and drug use than did homeless men. Among all the homeless, men were more likely to use drugs and alcohol than were women, but among the homeless who are substance abusers, women were more likely than men to use multiple substances. These results underscore the differences in substance abuse treatment needs between homeless men and women. Stein, J. and Gelberg, L. Homeless Men and Women: Differential Associations Among Substance Abuse, Psychosocial Factors, and Severity of Homelessness. *Experimental and Clinical Psychopharmacology*, 3(1): 75-86, 1995.

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### **Substance Abuse Involvement Among Juvenile Murderers**

In order to determine the extent to which juvenile offenders, convicted of murder or manslaughter, were involved with substance abuse at the time of offense, Fendrich et al., interviewed incarcerated juveniles to determine patterns of substance involvement among them as compared with patterns found in older offenders. Irrespective of age, close to one third of all homicide perpetrators reported that they were affected by alcohol prior to the offense. Alcohol was the substance showing the highest rate of "regular" lifetime use and the highest rate of ingestion in the week preceding the homicide. In many respects, the reported substance use patterns of the 16-17 year old age group were closer to the patterns demonstrated by the oldest (36+) age group than they were to the adjacent 18-20 year old group. Most of the juveniles who were using illicit drugs other than alcohol prior to the homicide attributed the homicide to the effects of those substances. Narrative accounts suggest that substances escalated impulsive, spontaneous violent outbursts. Fendrich, M., Mackesy-Amiti, M.E., Goldstein, P., Spunt, B., Brownstein, H. Substance Involvement Among Juvenile Murderers: Comparison with Older Offenders Based on Interviews with Prison Inmates. *International Journal of the Addictions*, in press, 1995.

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### **Inconsistencies in Self-Reported Drug Use**

Self-report information, in general, but particularly when provided by substance abusers, has traditionally been plagued with inconsistencies. Fendrich and his colleagues evaluated discrepancies in responses to questions about lifetime cocaine and marijuana use asked of nearly 10,000 respondents in the National Longitudinal Survey of Youth, a study that began in 1979. When examining responses from 1984 and 1988, they found that one in seven responses regarding cocaine use were inconsistent in some way, such as when it was first used or how often; one person in six did not tell the truth about marijuana use; African-Americans underreported drug use at higher rates than whites which Fendrich believes may have to do with how much the questions have done to enhance the level of trust. The types of inconsistencies varied according to the substance; cocaine reports yielded more inconsistencies with regard to timing of first use while for marijuana, most of the inconsistencies were with respect to disclosure. Fendrich, M., Mackesy-Amiti, M.E. Inconsistencies in Lifetime Cocaine and Marijuana Use Reports: Impact on Prevalence and Incidence. *Addiction*, 90, 111-118, 1995.

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### **Validity of Self-Reported Drug Use Among Injection Drug Users and Crack Cocaine Users**

Norman Weatherby, Ph.D. and associates at the University of Miami School of Medicine examined the validity of self-reported drug use as a measure of behavior change for the evaluation of drug use prevention and HIV risk reduction

programs. They recruited not-in-treatment IDUs and crack cocaine users through street outreach in four U.S. cities and compared self-reports of drug use in the past 48 hours from the Risk Behavioral Assessment questionnaire (developed by NIDA in 1991) with data from urine tests. Very high agreement was found between self-report and urine test results (86 percent agreement for recent cocaine use; 85 percent agreement for recent heroin use). The results suggest that self-reported drug use in not-in-treatment populations is accurate enough for measuring changes in risk behavior practices. Urinalysis may not be necessary if respondents are asked about their drug use in a nonthreatening manner, and if they are assured of the confidentiality of their results. Weatherby, N., Needle, R., Cesari, H., Booth, R., McCoy, C., Watters, J., Williams, M., and Chitwood, D. Validity of Self-Reported Drug Use Among Injection Drug Users and Crack Cocaine Users Recruited Through Street Outreach. *Evaluation and Program Planning*. 17(4): 347-355, 1994.

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### **Symptom and Substance Use Reporting Consistency**

To investigate accuracy of recall, and factors that potentially affect recall, Drs. Fendrich and Warner from the Institute for Juvenile Research, University of Illinois at Chicago, examined 2-year recall reports of lifetime symptomatology and substance use questions on the K-SADS-E. Comparisons were made between those who forgot and those who remembered reports of screening symptoms made at an initial interview. In general, individuals with externalizing disorders (conduct disorder and substance use) recalled more of their presenting symptomatology than did those individuals suffering from internalizing disorders (depression and anxiety disorders). Conduct disorder and substance use symptoms were characterized by the highest overall median kappa and recall percentage statistics; median kappa values for symptoms constituting both disorders were well above .40. One explanation supported by the findings suggests that consistent retrospective reporting may depend on the extent to which symptoms and behaviors (e.g., drug use) create a lasting impression on the young respondent reporting them. Fendrich, M., Warner, V. Symptom and Substance Use Reporting Consistency Over Two Years for Offspring at High and Low Risk for Depression. *Journal of Abnormal Child Psychology*, 22, 425-439, 1994.

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### **Etiology Research**

#### **Criminal Activities and Drug Using Behaviors**

Dr. Richard Dembo and colleagues of the University of South Florida examined criminal activities and drug using behaviors among a sample of juvenile detainees. They found that familial drug use, mental health problems, involvement in crime, and sexual victimization or physical abuse were stronger predictors of initiation of alcohol and marijuana use compared to family socioeconomic status, composition, and size. Continued use of alcohol and marijuana among these youth was significantly related to the severity of early childhood psychological problems, physical and sexual abuse, and low self-esteem. Dembo, R., Williams, L., and Schmeidler, J. Key Findings of the Tampa Longitudinal Study of Juvenile Detainees: Contributions to a Theory of Drug Use and Delinquency Among High Risk Youth. In: Roberts, A. (ed.) *Juvenile Justice: Policies, Programs, and Services*. 2nd edition. Chicago, IL: Nelson-Hall (in press).

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#### **Problem Behavior Syndrome**

The existence of a Problem Behavior Syndrome or clustering of deviant behaviors has been demonstrated in numerous research studies of a variety of populations. A very clear depiction of the hypothesized pattern was found in a study of 695 African American and 637 Puerto Rican adolescents. For both ethnic groups, the sequence of sexual behavior and its relationships to other problem behaviors were unidimensional, cumulative, and significantly related to the level of drug use and to the frequency of delinquent behaviors thereby suggesting an underlying problem behavior syndrome. (Brook, JS, Balka, EB, Abernathy, T, Hamburg, BA. Sequence of Sexual Behavior and Its Relationship to Other Problem Behaviors in African American and Puerto Rican Adolescents. *Journal of Genetic Psychology* 155(1): 107-114, 1994).

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#### **Influences on Adolescent Smoking Initiation and Escalation.**

Friends' smoking exerts a stronger influence on adolescents' smoking initiation than does parents' smoking. Friends' smoking has both direct and indirect influences on adolescent initiation of smoking but only indirect effects on escalation. Parental smoking has only indirect effects on initiation and escalation, channelled through perceived approval. Parental approval of smoking mediated smoking initiation among females but not among males. Pathways were found to be somewhat different by race/ethnicity, with friends' smoking having both direct and indirect effects on initiation among white and Hispanic adolescents but only direct effects among African American, Asian and other adolescents. These findings are derived from a longitudinal study of 6,695 seventh-grade students recontacted as eighth graders (73.1 percent retention rate). Flay, B.; Hu, B.; Siddiqui, O; Day, L.; Petratis, J.; Richardson, J.; and Sussman, S. Differential Influence of Parental Smoking and Friends' Smoking on Adolescent Initiation and Escalation of Smoking. *Journal of Health and Social Behavior*, 35(3): 248-265, 1994.

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### **Gender Differences in the Pattern and Progression of Substance Use in Conduct Disordered Adolescents**

Conduct disordered adolescents tend to initiate drug use earlier than other adolescents, and, among those with conduct disorder, females are more likely to have experimented with nonprescription diet pills and caffeine while males are more likely to have experimented with snuff or chewing tobacco. Women are at greater risk for qualifying for a diagnosis of nicotine dependence than were men. Although women start drinking alcohol at a later age than men, the latency from initial alcohol use to diagnosis of alcohol abuse/dependence is shorter for women than men, and the age at which males and females qualify for a diagnosis of alcohol abuse/dependence does not differ. Compared to the men, women also show a shorter latency from cannabis use to diagnosis of cannabis abuse/dependence. These findings are based on a sample of 40 female and 42 male adolescents qualifying for a conjoint diagnosis of conduct disorder and substance abuse disorder. The findings suggest that although the prevalence of substance abuse is higher in men, the liability to develop a supra-threshold disorder is greater in women when they do initiate drug use. Mezzich, A., Moss, H., Tarter, R., Wolfenstein, M., Hsieh, Y-C., and Mauss, R. Gender Differences in the Pattern and Progression of Substance Use in Conduct-Distorted Adolescents. *The American Journal of Addictions*, 3: 289-295, 1994.

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### **Social and Developmental Correlates of Tobacco and Alcohol Use Among Elementary School Students**

To test the predictive strength of multiple risk profiles which could expand understanding of "high risk" youth and which could indicate program objectives for earlier intervention for substance use prevention, Jackson and Henriksen from the University of North Carolina report on baseline data for Kids FIRST -- a four year panel study of relationships between child initiation of alcohol and tobacco use. A significant finding related to the differences in rates of initiation of tobacco and alcohol use across gender and ethnic subgroups, and variation in substance use reported across students' levels of development. Also of interest were the findings of the associations between children's initiation of use and their parents' rule setting about tobacco and alcohol use, their parents' modeling of use and other family socialization variables. Jackson, C., Henriksen, L. Tobacco and Alcohol Use Among Elementary Grade Students: Social and Developmental Correlates in a Rural North Carolina Sample. Paper presented at APHA 122nd Annual Meeting, 1994.

**Genetic Pathways to Drug Abuse.** The hypothesis that genetic factors are etiologically important in drug abuse/dependency and that psychiatric problems in adoptive parents are associated with drug abuse/dependency was tested by Dr. Remi Cadoret and his colleagues. A sample of male adoptees, separated at birth from their biologic parents, were followed up as adults to determine their substance use/abuse and their psychiatric diagnosis. Half of the adoptees came from biologic parents known to be alcohol abuse/dependent and/or to have antisocial personalities (determined by hospital and/or prison records). The adoptive home environment assessment included psychiatric evaluations of adoptive parents. This study confirmed the involvement of two independent genetic factors in drug abuse/dependence. It also confirmed the previous finding that environmental factors defined by psychiatric conditions in adoptive families independently predicted antisocial personality disorder in adoptees. Adoptees born of alcohol-abusing mothers showed evidence of fetal alcohol syndrome, but this did not diminish the evidence for a direct genetic effect between an alcohol-abusing biologic parent and drug abuse/dependency in offspring. Cadoret RJ; Yates WR; Troughton E; Woodworth G; Stewart MA. Adoption Study Demonstrating Two Genetic Pathways to Drug Abuse. *Archives of General Psychiatry*, January, 52(1): 42-52, 1995.

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### **Early Onset of Alcohol and Tobacco Use**

Since early onset of alcohol and tobacco use is associated with continued use of both substances, risk of use of other substances and unresponsiveness to substance use prevention programs, Jackson and colleagues collected drug use prevalence and timing data directly from elementary grade children. These data included estimates of alcohol use onset and provided estimates for children living in rural areas. Of the 27% of 5th grade initiators of alcohol use, 59% first had a drink with alcohol while in 1st, 2nd or third grade; of the 21% of 5th grade initiators of tobacco use, 48% first smoked tobacco in 3rd grade or earlier. This study supports the recommendation that primary prevention of substance use begin in the primary grades. Jackson C., Dickinson, D. Early indeed: Onset of Alcohol and Tobacco Use in a Sample of Rural Elementary School Children. *Journal of Drug Education*, in press, 1995.

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### **Impact of Parental Substance Use on Adolescents**

Parental substance abuse increases the likelihood of adolescents' substance abuse both directly and through its association with mediating factors including heightened tolerance for deviance, lower behavioral control, increased perceived coping function of substance use, more negative life events, and greater affiliation with peer users. As an example of these relationships, children who observe parents smoking or drinking may be more likely to engage in these behaviors with age peers, and parental multisubstance use impacts deviance-related attitudes, behavioral control, expectancies about substance use, and stressful life events. These findings are based on a study of 1,775 urban adolescents (mean age 13.3 years) designed to test a mediational model including constructs from stress-coping theory (Cooper, Russell, & George, 1988), the problem behavior (deviancy) model (Jessor & Jessor, 1977), and social learning theory (Bandura, 1977). The findings underscore the need to consider parental substance use history in planning treatment for adolescents. Several treatment strategies are implied by the study, including replacing perceptions of substance use with more acceptable coping methods that also reduce the probability of affiliation with deviant peers. Wills, T., Schreiban, D., Benson, G., and Vaccaro, D. Impact of Parental Substance Use on Adolescents: A Test of a Mediational Model. *Journal of Pediatric Psychology*, 19(5):537-556, 1994.

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### **Stability in Adolescent Friendship Group Context Across the School Year**

The initiation and use of alcohol and cigarettes among adolescents is, to some extent, dependent on membership in friendship groups. Urberg and colleagues investigated the extent to which adolescents are in similar friendship group contexts in the Fall and Spring of a school year, and whether or not they are a member of the same friendship group. Gender and grade differences in the tendency to remain in the similar context were examined. Correlations across a range of variables between Fall and Spring were calculated separately for individuals who changed groups and for those who remained in the stable groups. For all but academic values, there was significant similarity in the group context from Fall to Spring, for both those who changed groups and those who remained in stable groups. The researchers conclude that adolescents who change peer groups do not dramatically change their peer context and that peer context is more stable for those who remain in the same group compared to those who change groups. Urberg, K., Rao, P., Mack, F., Stability in Adolescent Friendship Group Context Across the School Year. Paper presented at the Meeting of the Society for Research in Child Development, Indianapolis, March 1995.

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### **Friendship Influence, Selection, and Deselection in Adolescent Substance Use**

To untangle the often intertwined effects of friend selection versus influence in adolescent substance use, Urberg and colleagues followed Billy and Udry's model to ascertain which might be important processes in adolescent substance use. Students completed surveys in the Fall and Spring terms in which they named their best friend (BF) as well as other friends. Those students who listed a BF were matched with that BF so that the BF's data would be used. Variables of lifetime drug use and current drug use were dichotomized and both were found to increase with grade and prevalence of use was similar across waves. To determine whether influence was operating, nonusers with and without user friends were compared. Controlling for grade and gender, BF use did not make a significant contribution in predicting Spring use for the adolescent. To determine whether selection was operating, those who chose a new BF were examined. Those who had tried drugs before were most likely to chose a BF who had also tried, followed by the student who made his/her transition to use. The researchers conclude that there is more evidence for BF selection rather than BF influence on the basis of substance use. Degirmencioglu, S., Urberg, K., Friend Influence, Selection and Deselection in Adolescent Substance Use Over the School Year: A Two-Wave Analysis. Paper presented at the Meeting of the Society for Research in Child Development, Indianapolis, March 1995.

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## Structure of Adolescent Peer Networks

In order to study the effects of peers on any aspect of adolescent development, but particularly on the initiation of drug use, the most comprehensive data to date on the structure of school-based peer networks has been collected by Urberg and colleagues from Wayne State University. Their database consists of 90% or more of the population of three school systems with each subject naming up to 10 friends. Because subjects are matched to friends, mutuality could be assessed, and data from multiple sources could be used to assess friendship groups. The most robust finding was that females are more integrated into school social networks than males and that numeric minorities usually are less connected to school peer networks than the majority group. Of interest, few group effects replicated across the three schools. This strongly suggests that in order for programs to be maximally effective, attention must be given to school and community level differences that may substantially impact the organization of peer networks. Urberg, K., Degirmencioglu, S., Tolson J., Halliday-Scher, K., The Structure of Adolescent Peer Networks. *Developmental Psychology*, in press, 1995.

## Reciprocal Relations Between Perceived Parenting and Adolescents' Substance Use

Deficits in parental support and control prospectively predict adolescent substance use, and adolescent substance use, in turn, is prospectively related to lower levels of parental support and control. These findings are based on data from a community sample of 441 adolescents (average age of 12.7 years at initial contact) and their parents; half of the adolescents were at risk for problem behavior because of parental alcoholism. The study highlights the need for early prevention efforts and suggests that manipulating parenting practices during childhood, before problem behaviors become ingrained, would be the most effective approach. Stice, E. and Barrera, M. A Longitudinal Examination of the Reciprocal Relations Between Perceived Parenting and Adolescents' Substance Use and Externalizing Behaviors. *Developmental Psychology*, 31(2): 1-13, 1995.

## Attitudes and Health Behavior in Diverse Populations

Five different health behaviors (cigarette use, alcohol use, binge eating, illicit drug use, and drunk driving) were studied prospectively in 5 different groups of subjects. Associations between attitudes toward these behaviors and the behaviors themselves were investigated. Findings revealed that attitudes predicted behavior in 2 instances: alcohol use and marijuana use. Attitudes did not predict drunk driving, binge eating, or smoking behaviors. Past behavior predicted attitude in the domains of binge eating and smoking, but not in the domains of alcohol use, drunk driving, or marijuana use. Stacy, A., Bentler, P. and Flay, B. Attitudes and Health Behavior in Diverse Populations: Drunk Driving, Alcohol Use, Binge Eating, Marijuana Use, and Cigarette Use. *Health Psychology*, 13(1): 73-85, 1994.

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## Director's Report to the National Advisory Council on Drug Abuse May, 1995

### Research Findings

### Prevention Research

#### **Culturally Focused Skills Training Approach to Alcohol and Drug Abuse Prevention Among Minority Adolescents**

A two year follow-up study of 456 inner-city seventh grade minority adolescents from New York City public schools has been completed by Drs. Gilbert J. Botvin and Steven P. Schinke. Three separate preventions (a) generic skills training prevention approach, (b) a culturally-focused prevention approach, and a (c) information-only control were compared. Students in both prevention approaches engaged less in current alcohol behavior and had lower intentions to engage in future alcohol use relative to students in the control group. Students in the culturally-focused group also engaged less in current alcohol behavior and had lower intentions to drink beer or wine than those in the generic skills group. Both prevention programs influenced several mediating variables in a direction consistent with non-drug use and less alcohol use. This study is the first to demonstrate the effectiveness of school-based approaches to alcohol abuse prevention with inner-city minority adolescents and because prevention effects were present two years after the conclusion of the primary year of intervention. The results of this study are also noteworthy because the two prevention approaches were contrasted with a comparison group receiving an information intervention rather than a "nocontact" control group as in most previous prevention studies. Although the results of this study suggest that it may be possible to develop a preventive intervention that is effective with a relatively broad range of students, tailoring interventions to specific populations appeared to increase prevention effectiveness. Botvin, G., and Schinke, S. Effectiveness of Culturally Focused and Generic Skills Training Approaches to Alcohol and Drug Abuse Prevention Among Minority Adolescents: Two-year Follow-up Results. *Psychology of Addictive Behaviors*, in press, 1995.

#### **Long-term Efficacy of a School-based Prevention Approach**

The results of a six year followup of a randomized drug abuse prevention trial evaluating the long-term efficacy of a school-based approach to drug abuse prevention have just been published by Dr. Gilbert J. Botvin and colleagues. The research design was a randomized trial involving 56 public schools that received the prevention program with annual provider training workshops and ongoing consultation, the prevention program with videotaped training and no consultation, or "treatment as usual" (i.e., controls). Follow-up data were collected 6 years after baseline using school, telephone, and mailed surveys. The participants were 3,597 12th grade students. The intervention consisted of 15 classes in seventh grade, 10 booster sessions in eight grade, and five booster sessions in ninth grade. The prevention taught general "life skills" and skills for resisting social influences to use drugs. Measures included six tobacco, alcohol, and marijuana use self-report scales that were recorded to create nine dichotomous drug use outcome variables and eight polydrug use variables. Significant reductions in both drug and polydrug use were found for the two groups that received the prevention program relative to controls. The strongest effects were produced for individuals who received a reasonably complete version of the intervention--there were up to 44% fewer drug users and 66% fewer polydrug (tobacco, alcohol, and marijuana) users. The findings demonstrate that drug abuse prevention programs conducted during junior high school can produce meaningful and durable reductions in tobacco, alcohol, and marijuana use if they (1) teach a combination of social resistance skills and general life skills, (2) are properly implemented, and (3) include at least 2 years of booster sessions. Botvin, G. et.al. Long-term Follow-up

Results of a Randomized Drug Abuse Prevention Trial in a White Middle-Class Population. *JAMA*, (April 12), 273, (14), 11061112, 1995.

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### **Reaching At-Risk Populations in a Mass Media Prevention Campaign**

The relationship of sensation seeking to both drug use and preferences for highly novel, arousing and/or unconventional messages and TV programs have been investigated by Donohew et al. In a five-month televised anti-drug PSA campaign, targeted at high sensation seeking young adults, data from several sources demonstrated the success in reaching the target population members with drug prevention messages and motivating them to call a hotline featuring alternatives to drug use. The authors conclude that the results illustrate the effectiveness of drug prevention strategies based on a sensation seeking model of drug use.

Palmgreen, P., Puzles Lorch, E., Donohew, L., Grant Harrington, N., Dsilva, M., Helm, D. Reaching At-Risk Populations in a Mass Media Drug Abuse Prevention Campaign: sensation seeking as a targeting variable. *Drugs and Society*, in press, 1995.

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### **Attention, Need For Sensation, and Health Communication Campaigns**

Noting that sensation seeking has been strongly related to early trial and use of drugs and other activities involving risk taking in numerous research reports, Donohew, Palmgreen and Lorch of NIDA's Prevention Research Center at the University of Kentucky, are studying the factors and co-factors of attention to novelty as it relates to the need for sensation and health communication campaigns. In their efforts to produce public service announcements (PSA) as a vital part of a drug prevention intervention campaign, they have found that the sensation value of the programming in which PSAs are embedded is a critical factor. Donohew, L., Palmgreen, P., Puzles Lorch, E. Attention, Need for Sensation, and Health Communication Campaigns. *American Behavioral Scientist*, 38, 310-322, 1994.

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### **Influence of Sensation-Seeking, Message Sensation Value and Program Content on the Effectiveness of Anti-Cocaine PSAs**

In order to determine if sensation seeking and message sensation value interacted to affect recall, attitude, behavioral intentions and perceived recall of televised anti-cocaine Public Service Announcements (PSAs), a study was conducted by Everett and Palmgreen at the Prevention Research Center. 120 participants (half high-sensation seekers - HSS and half low sensation seekers - LSS) were randomly assigned to one of four experimental conditions where the sensation value (SV), high (H) or low (L), of the PSA context was varied. After observing the PSAs, participants completed questionnaires dealing with free/cued recall, attitude toward cocaine, behavioral intention to use cocaine, and perceived effectiveness of the PSAs. HSSs tended to recall more, have more negative attitudes toward cocaine, cite less likelihood to use cocaine and perceive messages as more effective after viewing HSV PSAs. LSSs tended to recall more, have more negative attitudes toward cocaine, cite less likelihood to use cocaine, and perceive messages as more effective after viewing LSV PSAs. Everett, M., Palmgreen, P. Influence of Sensation Seeking, Message Sensation Value, and Program Context on Effectiveness of Anti-Cocaine PSA. *Health Communication*, in press, 1995.

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### **The A.T.L.A.S. Prevention Program**

The use of anabolic steroids (AAS) among athletes continues to rise. Researchers from the Oregon Health Sciences University have developed and are testing a school-based intervention to prevent AAS use among high risk adolescent athletes. Eight weekly, one hour classroom sessions delivered by the coach and adolescent team leaders and eight weight room sessions delivered by research staff were part of the intervention. Other components were sports nutrition and strength training as alternatives to AAS use, drug refusal role play and anti-AAS media campaigns. Results indicate that compared to controls, experimental subjects were significantly less likely to want to try AAS after the intervention, less likely to want to use AAS even if their friends used, less likely to believe AAS use was a good idea, believed AAS were more dangerous, had better knowledge of alternatives to AAS use, had improved body image, increase their knowledge of diet supplements, had less belief in these supplements as beneficial and improved their knowledge of other drugs. Significant beneficial effects were found despite a small sample size, suggesting that the effect of the intervention was large. Goldberg, L., Elliot, D., Clarke, G., Zoref, L., MacKinnon, D., Moe, E., Green, C., Wolf, S., Schoenherr, D. The Adolescent Training and Learning to Avoid Steroids (A.T.L.A.S.) Prevention Program: Background and results of a Model Intervention. *JAMA*, in press, 1995.

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## Coaches' Perceptions About Patterns of Drug Use Among Their Teams

Women's sport teams provide a strong peer group and influential coaches to deter drug use and channel students' athletic goals into healthy behaviors. To investigate coaches' perceptions about patterns of drug use among their teams, Drs. Elliot, Wolf and Goldberg surveyed women coaches from Oregon high schools. Regardless of sport, they each estimated their team's prevalence of drug use as follows: Alcohol (25%), cigarettes (4%), anabolic steroids AS (0.1%), other teams' use AS (1.9%), women pro athletes use AS (11-20%), and eating disorders (5-10%). However, although the coaches felt they knew about nutrition and strength training, they demonstrated significant knowledge deficits in both areas. Despite overestimating their knowledge and underestimating prevalence of drug use and eating disorders, coaches strongly agreed with the need for coaching staff and team programs about ergogenic drugs, eating disorders, nutrition and strength training. Elliot, D., Goldberg, L., Moe, E. Health promotion/drug prevention for young women athletes: coaches' assessments of needs and behavioral norms. *Medicine and Science in Sports and Exercise*, 27(5), 1995.

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## Assessment of a Health Promotion Program's Nutritional Curriculum Component

In order to deter high school athletes from using anabolic steroids (AAS), effective behavioral alternatives need to be established. As appropriate nutrition is a major contributing factor to overall athletic ability, Goldberg and colleagues assessed the nutritional curriculum component of a comprehensive 8-week (1-hour/week) health promotion program for high school football players. As expected, baseline data indicated that habits were not optimal. Following the program, students indicated increased satisfaction with their weight and greater awareness of foods' caloric content. However, no changes were observed in meal or food frequencies or in student's self-assessment of their diets. Diet habits are resistant to modification and influenced by many peer and environmental factors. The authors postulate that longer programs, involvement of the school environment or more attention to explicit behavioral goals are needed to alter teen athletes' eating habits. Wolff, S., Elliot, D., Goldberg, L., Moe, E., Clarke, G., Foref, L., Green, C. Evers, C., MacKinnon, D. High School Football Players' Nutrition Knowledge and Behavior: Effects of a Prevention curriculum. *Medicine and Science in Sports and Exercise*, 27(5), 1995.

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## Preventing Drug Use Escalation and Problem Behavior

To evaluate the impact of the Adolescent Transitions Project (ATP) on problem behavior and drug use, analysis of project data was conducted by Drs. Thomas Dishion and David Andrews of the Oregon Social Learning Center. Data revealed that the parent and teen interventions both reduced family conflict and negative interaction. The long term effect of each component is different. The parent intervention reduces escalation in tobacco, alcohol and marijuana use in the one year period following the families' involvement. In contrast the teen condition had an iatrogenic effect on tobacco use and problem behavior up to a year following the intervention. These findings suggest that parent interventions are needed for high risk youth to reduce escalation and that repeated booster sessions are needed throughout the period of risk. Also, high risk youth should not be placed in groups as this seems to contribute to their problem behavior. Dishion, T. and Andrews, D. Preventing escalations and problem behavior. *Journal of Consulting and Clinical Psychology*, in press, 1995.

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## Director's Report to the National Advisory Council on Drug Abuse May, 1995

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### Research Findings

#### Intramural Research

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Work from Dr. George Uhl's laboratories and his collaborations with Drs. Ivy Carroll, RTI, and Shigeo Kitayama, Hiroshima, Japan, have been broadly cited in the press as one of the principal bases for establishment of Gell Pharmaceuticals, a small Baltimore company dedicated to work with anticocaine pharmacotherapeutics. Collaborative research arrangements between Gell and the NIDA IRP Molecular Neurobiology Branch to allow pursuit of Dr. Uhl's observations that dopamine transporter mutagenesis can dissect cocaine recognition from dopamine uptake, and his identification of lead compounds with potencies 30-40-fold greater in blocking cocaine analog recognition than in inhibition of dopamine uptake are being actively pursued.

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#### Medications for Cocaine Abuse and Dependence

Desirable properties of medications for treating cocaine abuse that will substitute for cocaine include long duration of action, slow entry into the brain, and potency. Scientists in the Molecular Pharmacology Section have recently shown, in a series of studies (some in press), that many cocaine analogs studied by our group have these properties. Thus these may be potential medications. Compounds continue to be characterized with this goal in mind.

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#### Lesch-Nyhan Disease Exhibits Loss of Dopaminergic Neurons

Using a PET scanning probe developed for studying cocaine receptor sites in brain, scientists in the Molecular Pharmacology Section, in collaboration with Dr James Harris and Dr Dean Wong from Johns Hopkins, recently showed that the brains of patients with Lesch-Nyhan Disease have severely reduced dopaminergic nerve terminals in the nigro-striatal tract. This supports some earlier observations and suggests a focus for future studies of the disease.

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#### Cocaine Binding Sites on the Dopamine Transporter

By using cocaine analogs that are irreversible and radiolabeled as probes for binding to the dopamine transporter, and by treating the probe-transporter complex with specific proteases, scientists in the Molecular Pharmacology Section are identifying binding domains of the transporter for cocaine. This knowledge will help us understand how the transporter is structured in the membrane, and possibly how to develop cocaine-like agonists and blockers.

Using volumetric magnetic resonance imaging (MRI) assessment, investigators in the Neuroimaging and Drug Action Section (NDAS) have demonstrated that the ventricle-to-brain ratio, a index reflecting cerebral atrophy, is not larger in physically healthy polysubstance abusers than in control subjects, without even a tendency toward ventriculomegaly in the drug abuse group. The results indicate that drugs of abuse may not produce generalized abnormalities in brain anatomy or that potential cerebral structural deficits associated with illicit substance abuse, if any, would be regional. High resolution volumetric MRI studies focusing on specific brain regions which may contribute to vulnerability to or specific effects of drug abuse are in progress. X Liu, RL Phillips, SM Resnick, VL Villemagne, DF Wong, JM Stapleton, and ED London.: No evidence of ventriculomegaly in polydrug abusers: A

volumetric magnetic resonance imaging study. *Acta Neurologica Scandinavica*, in press.

The development of agents to image *sigma* receptors *in vivo* by positron emission tomography (PET) or single photon emission tomography (SPECT) would aid the assessment of the mechanism by which drugs that bind to *sigma* receptors alleviate symptoms of schizophrenia and some neurodegenerative disorders. For this purpose, intramural investigators evaluated radiolabeled 4-phenyl-1-(4-phenylbutyl)piperidine (4-PPBP), a potent and selective ligand for *sigma* receptors, as an *in vivo* ligand for the *sigma* receptor. The regional distribution of its uptake in mouse brain parallels the distribution of *sigma* receptors as assayed by *in vitro* binding. These results and the finding that ligands which bind to *sigma* receptors block its uptake into mouse brain suggest that 4-PPBP would be a suitable radioligand for *in vivo* imaging of *sigma* receptors. K Hashimoto, U Scheffel, and ED London: *In vivo* labeling of sigma receptors in mouse brain with [3H]4-phenyl-1-(4-phenylbutyl)piperidine. *Synapse*, in press.

Although subtypes of *sigma* receptors (*sigma* 1 and *sigma* 2) have been identified, their functional roles are unclear. To date, only ligands that are non selective or demonstrate high (nanomolar) affinity for *sigma* 1 sites have been identified. Intramural investigators compared isomers and analogues of ifenprodil as potential *sigma* 2 ligands. Their results suggest that *threo*-ifenprodil is a relatively selective ligand for the *sigma* 2 site and may be useful for delineating the functional roles of sigma 2 receptors. K Hashimoto and ED London: Interactions of erythro-ifenprodil, threoifenprodil, erythro-iodoifenprodil, and eliprodil with subtypes of *sigma* receptors. *European Journal of Pharmacology*, in press.

Although the nicotinic acetylcholine receptor is thought to be the site where nicotine acts to produce tobacco dependence and this site has been implicated in various neuropathological and physiological states, no suitable radioligand for *in vivo* imaging of this receptor is presently available. The recent discovery that epibatidine, an extract of frog skin, is an extremely potent ligand for central nicotinic acetylcholine receptors *in vitro* led intramural investigators to study the *in vivo* binding properties of [3H]epibatidine in mice. The time-course and regional distribution of its uptake in brain and its sensitivity to blockade by nicotinic drugs suggest that radiolabeled analogs of epibatidine hold exceptional promise for the study of nicotinic acetylcholine receptors *in vivo*. ED London, U Scheffel, AS Kimes, and KJ Kellar: *In vivo* labeling of nicotinic cholinergic receptors in brain with [3H]epibatidine. *European Journal of Pharmacology*, in press.

The Molecular Neuropsychiatry Section was the first group to demonstrate that the neurotoxicity of methamphetamine, MDMA (Ecstasy), and MDA involves the production of superoxide radicals. The section accomplished this by using a combination of molecular and neurochemical techniques. We used transgenic mice that overexpress the human gene CuZn-superoxide dismutase (SOD-Tg) and tested these animals for possible toxic and lethal effects of these drugs. The transgenic mice were protected against the toxic effects in a dose-dependent and in a gene dosagedependent fashion.

The Section was also the first to show that the toxic effects of METH also involves nitric oxide (NO) production. These studies were done by using primary cultures of fetal mesencephalic areas. Investigators also showed for the first time that *in vitro* application of methamphetamine can cause gliosis and this process also involves NO production. These results raised the intriguing possibility that NO and the superoxide radicals might cooperate to cause the toxic effects of amphetamine analogs and that cellular redox status might play a role in the plastic changes that are associated with the administration of drugs of abuse.

This idea has been tested by assessing the effects of METH on the regulation of transcription factors in SOD-Tg mice. Recently it has been demonstrated that the activation of AP-1 is differentially regulated in these mice when compared to non-transgenic animals. Since these results suggest that the hypothesis might be correct, these observations are currently being extended to other drugs of abuse.

The results listed above are providing for the first time a coherent picture for a role of cellular redox state in changes associated with drugs of abuse. These results have application beyond the field of drugs of abuse because some of these plastic changes might be related to memory and motivational behaviors.

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## Psychobiology Section, Preclinical Pharmacology Branch

Scientists in the Psychobiology Section have prepared a series of benzotropine analogs as probes for the dopamine transporter. Several of these analogs, most notably the 4',4"-dihalogenated compounds, demonstrate high affinity binding ( $K_i < 30$  nM) to the dopamine transporter that is selective (>100-fold) over the other monoamine transporters. These compounds block dopamine uptake *in vitro* and yet are not efficacious locomotor stimulants nor are they recognized as being cocaine-like in a drug discrimination paradigm. This series of compounds has recently been extended to include those that have, as well as those that do not have cocaine-like behavioral activity. This recent

development will allow for the development of structure-activity studies that will reveal the pharmacophore for cocaine-like behavioral effects. Further, studies of the interaction of these drugs with the dopamine transporter will provide models of specific sites on the transporter that are responsible for cocaine-like behavioral effects.

Both *in vitro* binding studies and studies of dopamine uptake have indicated that there is a heterogeneity of action of cocaine and cocaine analogs. Both high- and low-affinity binding sites have been identified. Some drugs that bind to the dopamine transporter show both high- and low-affinity components while others do not. Behavioral studies have indicated that the high-affinity component appears to be the one most directly involved in the actions of cocaine related to abuse. These conclusions are based on correlations of affinities and psychomotor stimulant effects and subjective effects determined with cocaine discrimination techniques. In addition, tolerance to the psychomotor stimulant effects of cocaine occurs with a concomitant change in only the high-affinity component for dopamine uptake. Certain dopamine uptake inhibitors appear to have only actions mediated by the low-affinity component. These drugs bind to the dopamine transporter and inhibit dopamine uptake, however, they do not have behavioral effects like those of cocaine. This finding is a critical point of inquiry for the dopamine hypothesis because, based on the neurochemical data, these drugs should have behavioral actions like those of cocaine. In contrast, some of these drugs antagonize the behavioral effects of cocaine, suggesting that the low-affinity site somehow modulates the actions mediated by the high-affinity site. Continuing research is directed at: 1) a better characterization of the heterogeneity of the dopamine transporter and functional endpoints, 2) the development of pharmacological tools that will allow independent manipulation of high- and low-affinity components, 3) a characterization of how these components are regulated by, for example, chronic drug exposure, and 4) a better understanding of mechanisms for interactions among the components.

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## Treatment Branch

Scientists in the Treatment Branch of NIDA's Intramural Research Program, in collaboration with colleagues at the Department of Radiology, Johns Hopkins University, have recently demonstrated increased binding to opiate receptors in certain brain regions of cocaine addicts, using trace amounts of a radioactive synthetic opiate and the technique of positron emission tomography (PET). This finding confirms animal studies that found chronic cocaine exposure increased brain opiate receptor binding, and suggests a possible role for endogenous opiate systems in cocaine addiction. The increased opiate binding persisted over 4 weeks of abstinence in the majority of subjects, and was positively correlated with self-reported cocaine craving and negatively correlated with urine levels of the cocaine metabolite benzoylecgonine. Ongoing research is aimed at confirming and extending these findings, including their implications for long-term changes in the brain of cocaine addicts and for predicting relapse to cocaine use.

Scientists in the Treatment Branch of NIDA's Intramural Research Program have recently evaluated the safety and efficacy of the combination of two dopamine medications, bromocriptine plus bupropion, in the treatment of cocaine dependence. In an open-label study, they found the combination was well tolerated by outpatients, with some evidence of efficacy in terms of better treatment retention and decreased cocaine use. These findings suggest that this approach, which has been used successfully in other areas of neuropsychiatry (e.g., obsessive-compulsive disorder, Parkinson's disease), can help improve the treatment of drug abuse. Future studies will evaluate this combination more definitively with a double-blind clinical trial, and evaluate other medication combinations which influence brain neurotransmitter activity by different mechanisms, with the goal of enhancing efficacy while minimizing side-effects.

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## Director's Report to the National Advisory Council on Drug Abuse May, 1995

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### Program Activities

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#### NIDA HIV/AIDS Counseling and Testing Policy

The policy, which strongly encourages grantees and contractors who have ongoing contact with persons at risk for HIV infection provide HIV risk reduction education and counseling, will be published in the NIH Guide later this month. The policy reads:

Researchers funded by NIDA, who are conducting research in community outreach settings, clinics, hospital settings, or clinical laboratories, and have ongoing contact with clients at risk for HIV infection, are strongly encouraged to provide HIV risk reduction education and counseling. HIV counseling should include offering HIV testing available on-site or by referral to other HIV testing services. Persons at risk for HIV infection include injection drug users, crack cocaine users, and sexually active drug users and their sexual partners.

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#### Planning for FY 1997 HIV-Related Research

NIDA staff participated in the planning process for FY 1997 with the Office of AIDS Research, NIH, to identify programmatic initiatives for 1997 in the areas of etiology and pathogenesis, epidemiology and natural history, behavioral and social science research, therapeutics, and information dissemination. The proposed initiatives represent an opportunity to capitalize on recent advances in research on the drug abuse and HIV/AIDS link, emphasizing those areas that have the most promise for rapidly impacting the AIDS epidemic and for which NIDA is well prepared to take scientific leadership. Dr. Leshner, along with NIDA staff, met with Dr. William Paul, Director, Office of AIDS Research, on April 10 to discuss NIDA's proposed initiatives to respond to the NIH plan.

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#### Medications Development

The Department of Veterans Affairs solicited proposals from the VA system for potential clinical trial sites to be utilized by MDD. Sixteen (16) responses were received by the closing date of April 3. Peer review evaluation took place on May 9-10.

RFPs for two components of an MDD clinical operations contract (clinical trials and regulatory affairs support) have been issued. Responses were due by May 10.

The NIDA Medications Development Database now has over 100 subscribers, including some universities and pharmaceutical companies in Western Europe. The database represents a resource for researchers working in the area of drug abuse and neuroscience. It is a tool which allows researchers to study relationships between structure and activity in the search for new and improved compounds to be targeted as treatment medications. The database now contains nearly 6,000 compounds and biological data consisting of receptor binding data and drug discrimination and self-administration studies, as well as toxicology. All data is preclinical. The database is available on a dial-up basis through an "800" number at no cost to the user. Individual training is also available at no cost to the user.

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## Program Announcements and RFA's

On December 9, 1994, NIDA co-sponsored a Program Announcement (PA-95-030) with NIMH "**Prevention of Relapse to High-Risk Behaviors**" to solicit proposals for theoretically grounded research applications focusing on behavioral strategies for relapse prevention. This program announcement is critical because prevention efforts must be developed to sustain the changed behaviors over time and prevent relapse.

A Program Announcement # PA-95-022 "**Drug Abuse Services Research and HIV/AIDS**" was issued in January 1995. The purpose of this PA is to support a program of research on health services to drug abusers at high risk for HIV/AIDS at the client, program, and services system level.

On February 3, 1995, NIDA released a Program Announcement (PA-95-026) soliciting proposals for "**HIV Disease Progression in Drug Users**" to stimulate research on the biological and behavioral factors influencing HIV disease progression in populations of drug users in and out of drug abuse treatment in order to facilitate prevention and treatment efforts.

A Program Announcement entitled "**Studies on the Linkage of Drug Abuse Treatment and Medical Care**" was published in the NIH Guide on February 3, 1995. The purpose of this announcement is to stimulate research on various models and strategies for linking drug abuse treatment with medical care, with special attention to effects on the prevention, incidence and progression of medical (including psychiatric) disorders in drug abusing populations and the cost and effectiveness of linked treatment. "Linkage", in the context of this research program is defined as including at least the following components: (1) drug abuse treatment and (2) medical care, including at least (a) primary and/or acute care, (b) care related to mental disorders, and (c) public health aspects of medical care, e.g., screening for sexually transmitted diseases, immunizations.

A new Program Announcement, "**Neuroscience Research of Nicotine and Nicotine Abuse**" (PA 95-038) was published March 22, 1995. The announcement emphasizes studies on the addictive properties of nicotine.

A Request For Applications (RFA) # DA-95-005 "**Health Services Research Centers**" was issued on May 9, 1995 to support a program of Health Services Research Centers to conduct interdisciplinary research on financing, organization, access, and utilization of health services for drug abusers.

NIDA has joined the National Institute of Mental Health (NIMH), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the National Institute on Aging (NIA) in issuing a Request for Applications (RFA) entitled "**Family Interventions and HIV/AIDS.**" The term "family" here refers to the breadth of family configurations, including biological kin networks and nonrelated persons who consider themselves to be family through a "network of mutual commitment."

The purpose of the RFA, issued on April 14, 1995, is to encourage research on family interventions intended to enhance the ability of families to prevent the spread of HIV/AIDS and/or its consequences. Drug abuse is a key element of the RFA. Applications are due in June and funding of projects is expected by September.

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## Director's Report to the National Advisory Council on Drug Abuse May, 1995

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### Congressional Affairs

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#### NIDA's Appropriations Hearing for the House Labor/HHS Subcommittee

On March 22, Dr. Leshner testified before the House Labor/HHS appropriations subcommittee (John Porter, R-IL, Chairman). During his presentation, Dr. Leshner declared NIDA's Year 2000 goal to have science replace ideology as the foundation for drug abuse prevention, treatment and policy strategies. (The President's FY 1996 Budget Request for NIDA totals \$452,069,000, a 3.3% increase over the FY 1995 appropriation.)

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#### FY 95 Rescissions -- Senate

The Senate passed its version of H.R. 1158, the rescissions/emergency supplemental appropriations bill, on Thursday, April 6, by a vote of 99-0. After a week of negotiation and compromises, the bill emerged with \$16.1 billion in cuts. Senate action has resulted in \$9 million in additional cuts for NIH, with the cuts totalling \$79 million. All of the cuts are to be taken from NIH's intramural construction account. The House bill included rescissions to NIH intramural and extramural construction projects. The House cut was divided into two parts: \$20 million from the National Center for Research Resources for FY 95 extramural facilities grants program and \$50 million from an NIH account designated for intramural construction projects -- according to NIH sources these funds had been allocated for the new primate center in Frederick, Maryland and the second phase for the Natcher building.

Differences between the two versions of the bill have to be worked out. Senate Minority Leader Tom Daschle (D-SD), includes the \$100 million for drug-free schools as an essential element of the package. President Clinton has said that he would sign H.R. 1158 as passed by the Senate as it removed some of the cost-cutting elements of the \$17.4 billion House rescissions bill.

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#### Tax-Cut Bill

A major tax-cut bill [H.R. 1215] passed the House on April 5 in which tax cuts are paid for by cutting discretionary spending by \$100 billion over five years, increasing the contribution by Federal employees to their pension fund, and cutting Medicare. The Senate has said it will not take up this bill, but the Senate Budget Committee may include some tax cuts in its budget resolution later this Spring. Senate Republicans are preparing to unveil a plan to balance the budget by 2002. As drafted, the \$1 trillion, seven-year proposal gets most of its savings from reductions in Medicaid [about \$160 billion], Medicare (about \$250 billion), other entitlement programs (about \$250 billion including savings from changes to the Federal retirement system); discretionary appropriations for domestic programs (about \$200 billion); and debt interest (about \$160 billion). The plan was prepared by Senate Budget Committee Chairman Pete Domenici (R-NM).

#### Health Care Reform

H.R. 1455 was introduced by Representative Peter Stark (D-CA) and James Hansen (R-UT). The bill would earmark 9% of the revenues from a proposed \$2 per-pack tax on cigarettes--estimated at about \$1.5 billion annually--to fund research supported by NIH. About 88% of the money generated by the bill would be earmarked for the Medicare Part

A Hospital Trust Fund. A newlycreated National Fund for Medical Research would receive 9% of the funds generated by the bill or approximately \$1.5 billion a year.

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## **CRADAS**

Dr. Harold Varmus, Director, NIH, announced on April 11 that cost containment will no longer be an issue in the cooperative research and development agreements (CRADAs) that govern NIH partnerships with industry. This action, which was taken by Dr. Varmus along with top officials at DHHS, stemmed from concerns that the reasonable pricing clause had driven industry away from potentially beneficial collaborations with NIH. It is not clear whether there will be opposition to the removal of the pricing clause from Congress.

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## **Surgeon General Nomination**

A confirmation hearing was held on May 2nd and 3rd before the Senate Labor and Human Resources Committee for Dr. Henry Foster, the nominee for U.S. Surgeon General. Committee Chairman Nancy Kassebaum (R-KS) had stated that only Dr. Foster and members of Congress would testify. Senate Majority Leader Bob Dole (R-KS) said that he might use his power over the schedule to prevent the full Senate from ever considering Foster's nomination. Senator Barbara Boxer (D-CA) stated that she would retaliate by objecting to unanimous consent requests on other Senate business.

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## **Congressional Departures To-Date**

The following congressional members have announced their retirement -- Senators Hank Brown (R-CO); Jim Exon (D-NE); Howell Heflin (D- AL); J. Bennett Johnston (D-LA); Paul Simon (D-IL); and Representative Mel Hancock (R-MO) - each will finish out his term. Senator David Pryor (D-Ark) is expected to announce his retirement soon, bringing to 5 the number of Senate Democrats not seeking another term.

Ed Long, formerly Minority staff on the Senate Labor/HHS appropriations subcommittee, is now vice president of congressional relations with Capitol Associates. No replacement has yet been named.

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## **Bills of Interest**

The amended version of H.R. 4 passed the House on March 24 by a vote of 234-199 with the three elements of welfare reform [H.R. 1157, H.R. 999, and H.R. 1135] reincorporated into H.R. 4. Title VI, Supplemental Security Income, Section 601(d) states, in part, "for carrying out the medication development project to improve drug abuse and drug treatment research (administered through the National Institute on Drug Abuse), \$5,000,000 for each of the fiscal years 1997 through 2000". It would also provide \$95 million for the drug abuse treatment capacity expansion program as provided under section 1971 of the Public Health Service Act.

This legislation [H.R. 4] gives broad authority over a wide range of social services, including welfare checks and school meals. It would replace 44 programs with five block grants, giving States unprecedented authority over cash welfare, child welfare programs such as foster care; child care; school meals; and special nutrition programs for pregnant women and young children. The Senate Finance Committee, chaired by Senator Bob Packwood (R-OR), has talked about replacing the entitlement for welfare checks, and possibly other social services, with block grants to the States. Democrats, led by Senator Daniel P. Moynihan (D-NY), generally oppose the concept. One of the first questions Senate leaders must resolve is whether to include welfare in the reconciliation bill, an omnibus budget package designed to reconcile taxes and spending with deficit-reduction goals [reconciliation bills cannot be filibustered]. Meanwhile, Democrats are trying to develop a strategy -- whether to draft their own bill or simply oppose anything the Senate GOP proposes. President Clinton reportedly urged Senators Moynihan and Tom Daschle (D-SD) to start working on a welfare reform bill during the recess.

The House passed H.R. 1271, Family Privacy Protection, on April 4. It would require any Federal department or agency to obtain "written consent" before a minor could submit to a survey or evaluation that reveals certain information (including illegal, anti-social or self incriminating behavior). During markup by the House Government Reform and Oversight Committee, the term "written consent" was deleted and "prior consent" was substituted. However, prior to House floor consideration, Representative Mark Souder (R-IN) asked the leadership and committee

staff to include an amendment to require "written consent." His request came as the result of a survey given to his child at school. He objected to the questions in the survey and his consent was not requested. Representative Cardiss Collins (D-IL) had expressed strong support for the committee approved language requiring "prior consent" rather than "written consent."

Crime legislation was passed in the form of six separate bills by the House in February. H.R. 728 concerns anti-crime-block grants which would combine last year's grants for police hiring and crime prevention into a block grant program that would give localities more choice in how they spend the money. The Senate Judiciary Committee, chaired by Senator Orrin Hatch (R-UT), is expected to conduct at least one more hearing on crime legislation in late April or May, then begin marking up one or more bills. The key proposal is S. 3, sponsored by Majority Leader Bob Dole (R-KS) and Senator Hatch which would shift last year's funds as authorized under the anti-crime law [P.L. 103-322] from crime prevention programs to prison construction and law enforcement. Sec. 105 of S.3 includes a provision which would amend the Violent Crime Control and Law Enforcement Act of 1994 to require the Bureau of Prisons to include in an annual report to congress "a full examination and evaluation of the effectiveness of the [substance abuse] treatment [provided in accordance with the Act] in reducing drug use among prisoners." Debate is expected in both chambers over repealing the 1994 ban on certain semiautomatic assault style weapons. President Clinton has threatened to veto any measure that undermines last year's police hiring grants, such as the House block grant legislation [H.R. 728].

On March 22, H.R. 1289, the Newborn Infant Notification Act, was introduced by Representative Gary Ackerman (D-NY). It would require, in certain circumstances, States to disclose HIV status of newborn infants to legal guardians of the infants. While there is no mention of research in the bill, the CDC believes that it could effectively halt their survey involving use of about-to-be-discarded blood from samples collected for routine newborn health screening. The CDC met with Representative Ackerman on March 30 to discuss the impact the proposed legislation would have on the agency.

The conference report to S. 244, the Paperwork Reduction Act, no longer includes provisions to change the date of the health services research report or to terminate all statutorily mandated reports to Congress within five years.

S. 555 was introduced on March 14 by Senator Nancy Kassebaum (R-KS) to amend the PHSA to consolidate and reauthorize health professions and minority and disadvantaged health education programs. The bill would, in part, require a Deputy Assistant Secretary for Minority Health to coordinate PHS activities. Also, PHS agencies would be required to submit reports summarizing the agency's minority health activities, and serve as ex officio members of the PHSA advisory committee.

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## **National Drug Control Strategy Hearing**

On April 6, ONDCP Director, Dr. Lee Brown testified before the House Government Reform and Oversight Subcommittee on National Security, International Affairs and Criminal Justice. The hearing was a continuation of the one held on March 9 at which Nancy Reagan and former Drug Czar Bill Bennett were among the witnesses.

Members continued the theme of criticizing the Administration's lack of leadership on the issue of drug abuse and the need to shift resources from demand to supply reduction. Dr. Brown responded to vigorous assaults on everything from failure to provide leadership to questions about his honesty in using travel funds. Dr. Brown continued to defend the Administration's focus on hard core drug users. He mentioned CALDATA and RAND findings emphasizing that money spent on treatment is a good investment. He challenged the chart the committee used which plotted reductions in drug interdiction funds against rises in marijuana use. He defended the effectiveness of the drug free schools program and stressed the importance of drug courts. He also supported random drug testing of all federal employees, Members of Congress and their staff. The Chairman agreed.

At the end of the hearing the Chairman, William Zelliff (R-NH), said the Subcommittee plans to continue efforts to focus attention on this important issue. He also said that they are planning to meet with major CEO's around the country and will be looking at the issue of random drug tests for all Federal employees.

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## **Senate Hearing on Supplemental Security Income (SSI)**

On March 27, Dr. Herb Kleber, Executive Vice President and Medical Director of CASA at Columbia University, testified before the Senate Finance Committee on the SSI program. Dr. Kleber told the committee that benefits should be for

the use of treatment, and that cash benefits for alcoholics and drug addicts are not an incentive for them to receive treatment. Prior treatment should be used as a condition of eligibility for SSI. He also stated that more funds should be used for drug abuse research, specifically for medications development.

Senator Larry Pressler (R-SD) was the only member present to ask about alcoholics and drug addicts eligibility under SSI. He was concerned as to whether an alcoholic or drug addict could simply quit working, declare themselves a drug addict or alcoholic and collect SSI. He was also concerned about the length of time an alcoholic or drug addict continues to receive SSI. In response, Dr. Carolyn Weaver, American Enterprise Institute, indicated that there would have to be documentation that the disability was severe enough to collect SSI. Also, Dr. Kleber explained that there are effective treatment programs and that effective methods currently exist to identify the right treatment program depending on the individual. Senator Pressler asked if we have evidence that the SSI program is successful (that when someone is given treatment they no longer receive SSI) Dr. Kleber responded that the SSI program is not the place to look for effectiveness. However, the majority of outcomes from alcohol and drug abuse treatment are in general very successful.

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## Director's Report to the National Advisory Council on Drug Abuse May, 1995

### International Activities

Dr. Jack Blaine (DCSR) and Dr. Zili Sloboda (DEPR) represented NIDA at the U.S.-Mexico Addiction Research Development Workshop and Symposium on **"The Role of Risk-Taking Behavior in Alcohol and Drug Use"** in Mexico City during March. Dr. Blaine served as U.S. cochair for the treatment working group; Dr. Sloboda was U.S. cochair for the working group in social-behavioral epidemiology. The workshop was one of a series to launch a new U.S.-Mexico Cooperative Biomedical and Behavioral Research Program under an agreement between NIH and the National Science and Technology Council of Mexico (CONACYT). Dr. M. Patricia Needle, International Program, will continue to serve as liaison with the Fogarty International Center in the further development of training and research collaboration between NIDA and Mexican scientists.

Mr. Nicholas Kozel (DEPR) participated in the meeting of the National Coordinators for Epidemiologic Surveillance of Drug Use in Central America, Panama, and the Dominican Republic during April. Dr. Patricia Needle, International Program, also met with the group to discuss opportunities for the development of research collaboration with NIDA scientists. The meeting was sponsored by the Organization of American States and the Pan American Health Organization.

Dr. Robert Battjes, Acting Director, DCSR, attended the **6th International Conference on the Reduction of Drug Related Harm** in Florence, Italy, March 26-30, 1995. On March 25, he also represented NIDA at the opening ceremony of an exhibition on **"Drugs and the Brain,"** sponsored by Professor Pietro Corsi, University of Cassino. This exhibition, for which NIDA staff and grantees provided technical guidance, was held in Florence from March 27 to April 29.

A series of collaborative studies on the **"Action of Thyrotropin Releasing Hormone on Morphine-Induced Analgesia and Preference in Two Inbred Rat Strains"** between the Preclinical Pharmacology Laboratory, Behavioral Pharmacology and Genetics Section of the IRP (Drs. Steven Goldberg and Gregory Elmer) and the Laboratory of Pharmacology of Narcotic Drugs and Experimental Therapy of Drug Abuse, State Research Center of Addictions, Moscow, Russia have been completed and published.

As part of the collaborative research projects between the Institute of Psychiatry, London, and NIDA's Intramural Research Program on properties of drugs and drug mixtures, a report titled **"Evaluation of the Discriminative Stimulus Effects of Midazolam and Morphine Alone and in Combination Using 2- and 3-Lever Drug Discrimination Procedures in Rats"** was published in NIDA Research Monograph 291, 1994. Authors are C.A. Sannerud, J.A. White, S.R. Goldberg, and I.P. Stolerman.

Dr. Amy Newman (IRP Psychobiology Section) has been working with Dr. Yuri P. Belov of Russia. Dr. Belov's stay is funded through the Fogarty International Center. Dr. Belov's research has focused on the separation of enantiomers of chiral compounds that have affinity for the dopamine transporter and compounds that have affinity for dopamine D1 receptors.

With sponsorship from the U.S.-India Fund, Dr. Richard Needle (DEPR) represented NIDA at the Indo-U.S. Workshop on **"Behavioral Research Priorities: Developing Effective Strategies for the Prevention of HIV in India,"** in Bombay from April 24-27. Dr. Clyde McCoy (University of Miami School of Medicine) also participated in the workshop. Following the workshop, Dr. Needle also conferred with U.S. Embassy Science Attache F. Gray Handley and Dr. S.D. Sharma, Director of the Institute of Human Behavior and Allied Sciences in New Delhi, on agenda preparation for an Indo-U.S. workshop on drug abuse research methodologies to be held in New Delhi in early 1996.

Mr. Nicholas Kozel (DEPR) participated in the Thai Epidemiology Work Group meeting on March 1-3 and cochaired the East Asian Multi-City Epidemiology Work Group meeting on March 6-10. Both meetings were held in Bangkok, Thailand, and were funded by the U.S. Department of State.

Dr. Mario de la Rosa met with staff of the Narcotics Matters Section at the U.S. Embassy in Bogota, Colombia, during March. The purpose of the meeting was to discuss the feasibility of conducting workshops in 1995 on the use of quantitative and qualitative methods for assessing drug use patterns and trends. This workshop would be the first in a series with Andean country researchers and will be supported through a Letter of Agreement with the Department of State.

Dr. Rebecca Ashery (DEPR) presented a paper "**The WHEEL Project: Assessing a Community-Based Model for Preventing HIV/AIDS Among Women**" at a February meeting of the World Health Organization in Geneva, Switzerland.

Dr. Steven Goldberg, Chief of the Preclinical Pharmacology Laboratory, Division of Intramural Research, was invited to give a presentation entitled "**Preclinical Evaluation of Drug Abuse Liability**," at the Jikei University School of Medicine, Tokyo, Japan, April 19-21, 1995.

NIDA's **INVEST Research Fellowship Program** has received 12 applications from 10 countries for the 1995-96 fellowship year. The International Program office will announce the awards by June 1, 1995.

The selection panel for the review of applicants for the **1995-96 NIDA Hubert H. Humphrey Drug Abuse Research Fellowship** has taken place, and recommendations have been forwarded to the United States Information Agency for review and concurrence. Humphrey Fellowship awards will be announced in early June.

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## Director's Report to the National Advisory Council on Drug Abuse May, 1995

### Meetings/Conferences

The biannual meeting of the [Community Epidemiology Work Group \(CEWG\)](#), chaired by Mr. Nicholas Kozel, DEPR, was held in New Orleans on December 13-16, 1994. The CEWG is composed of researchers from 20 selected metropolitan areas of the United States who meet semiannually to report on patterns and trends of drug abuse in their respective areas; emerging drugs of abuse; vulnerable populations and factors that may place people at risk of drug use and abuse; and, negative health and social consequences. Reports are based on drug abuse indicator data, such as morbidity and mortality information, treatment data and local and State law enforcement data. Additional sources of information include criminal justice, correctional, medical and community health data, local and State survey information and research findings from ethnographic studies.

Highlights from findings from the most recent CEWG meeting include:

- Cocaine is the drug of primary concern in terms of numbers of users and consequences in the communities represented in the CEWG. However, indicator data for cocaine appear to be levelling off or declining in many areas.
- Indicators of heroin use continue a pattern of general increase that began several years ago. Treatment data from several cities, including Chicago, Boston, Newark, New York City, Minneapolis/St. Paul and St. Louis reflect an increase in younger users. Preliminary indications of a new cohort of younger users also is being noted in Atlanta, Miami, New Orleans, San Francisco and Washington, D.C. Injection is the primary route of use in the West, intranasal use continues to replace injections in New York City, Chicago and Detroit. The emergence of heroin smoking is reported in Atlanta, Chicago and Minneapolis/St. Paul, especially among young users.
- A variety of opiates other than heroin are abused in various CEWG sites. Specific drugs which have been identified as problematic include among others: propoxyphene in Seattle and Minneapolis/St. Paul; Hydromorphone in Atlanta, New Orleans, New York City, Phoenix, St. Louis and in certain areas of Texas; and codeine-based drugs in Chicago, Detroit and Phoenix.
- Marijuana indicator data, primarily from treatment programs, emergency rooms and arrestee urinalysis, continue to show increases in many of the CEWG sites. Use of blunts (gutted cigars refilled with marijuana) is reported in diverse areas of the country, including Chicago, Minneapolis/St. Paul, New York City, Philadelphia, San Francisco and Washington, D.C.
- Abuse of methamphetamine appears to be a regional problem, principally in the Western area of the country, including San Diego, Honolulu, Phoenix and San Francisco. Primary route of administration is by injection in San Francisco and by intranasal or smoking in the other areas. Among other stimulants, availability and use of MDMA (ecstasy) is reported in Atlanta, Dallas, Honolulu, Miami, St. Louis, San Francisco and in Texas, while methcathinone (cat) is reported in Detroit.
- A variety of illegally diverted or smuggled barbiturates, sedative/hypnotics, tranquilizers and antidepressants are available and abused in many CEWG sites. Of note are recent increases in indicators of flunitrazepam (Rohypnol) reported by treatment program staff and information hotline personnel in Florida and Texas. Increased use of Rohypnol originating in Colombia and Mexico have been reported among adolescents in the South Florida and Texas border area and is frequently used in combination with alcohol. In addition to the CEWG reports, abuse of Rohypnol by heroin addicts, cocaine and other stimulant abusers, and adolescents who use it in combination with alcohol have been noted, thus far, by epidemiologic surveillance networks in other parts of the world, including

Western and Eastern Europe, Southeast and South Asia, Australia, North Africa and Central America.

- Among hallucinogens, an outbreak of jimson weed use was reported in the Northeast, specifically New York and New Jersey and in Texas and resulted in two deaths in El Paso and numerous emergency episodes in Texas and New Jersey. An increase in PCP indicators was reported in Philadelphia and is thought to be combined with marijuana and used in blunts. Information from schools and hotlines in several CEWG sites, including Atlanta, Detroit, Miami and San Francisco suggest an increase in LSD use among youth. LSD use among youth and young adults in increasingly being reported in association with "raves".

NIDA, together with CDC, SAMHSA, and Johns Hopkins University co-sponsored a workshop on February 15-16, held at Johns Hopkins, to review issues related to sterile needles and syringes for drug users who continue injecting.

On February 16-18, 1995 NIDA cosponsored the North Carolina Governor's Institute regional conference "**Advancing Substance Abuse/Addiction Treatment: Applying Current Research**" in collaboration with the NIDA Center for the Neurobiological Investigation of Drug Abuse at the Bowman Gray School of Medicine, and the NIDA Center for Community-Based Treatment Research Methods at Research Triangle Institute. Dorynne Czechowicz M.D., Treatment Research Branch, DCSR, was on the conference planning committee and presented on NIDA research priorities at the conference; Gerald Soucy, Ph.D., presented on NIDA's research dissemination program, Timothy Condon, Ph.D., and Lula Beatty, Ph.D., presented on researcher training and development. This meeting brought together basic and clinical researchers, clinicians from different disciplines, teachers and administrators and consumers of services as well to address strategies for disseminating new knowledge and exploring ways in which research can be used to improve treatment services, and to identify future research and research training needs.

On February 22-24, 1995, NIDA co-sponsored a conference on "**HIV Infection in Women**" in Washington, D.C., which was the first national scientific meeting on HIV infection in adult and adolescent women.

On March 6-7, 1995 NIDA's new Behavioral Sciences Research Branch (DBR) sponsored a workshop entitled "**Basic Behavioral Sciences Research in Drug Abuse: New Directions**". Fourteen eminent behavioral scientists participated, representing diverse areas of basic behavioral, neurobehavioral, social and cognitive science research, including a researcher from NIDA's Intramural Research Program. The participants spent a day and a half at NIH discussing new ideas and promising research directions that have the potential to improve our understanding of drug abuse. New directions included research into stress and psychopathology, basic social and cognitive processes, issues of resiliency and vulnerability, and potential application of research in other addictions such as overeating and alcoholism to drug abuse research. Particularly highlighted was the need for development of theoretical behavioral models that span both animal and human research.

On March 7, 1995 an Ad Hoc review of the NIDA Medications Development Program (encompassing all activities in various components of NIDA) was held. Representatives of academia, the pharmaceutical industry, FDA and NIMH attended as well as key NIDA personnel. The review was forward focussed, i.e., it was not a retrospective review and critique but an assessment of where NIDA should be headed in the future, given the state of science and the respective strengths and interests of industry, academia, and government.

On March 8, 1995 a meeting was held to present and review the latest preclinical and clinical information available concerning ibogaine. Non-government speakers presented current data to a group of non-government consultants, who will provide their input to NIDA for consideration. FDA and NIDA personnel were also in attendance.

NIDA sponsored a conference on March 14-15 at the University of Maryland Conference Center on the "**Impact of HIV Risk and Infection on the Delivery of Drug Abuse Treatment Services**" to discuss treatment and research issues.

A NIDA-sponsored workshop entitled "**HIV Disease Progression: Opiates and Immune Function**" was held on April 3-4, 1995 in Gaithersburg, MD. Nineteen clinicians, epidemiologists, and basic scientists discussed the effects of opiates on various parameters of immune function and on disease progression in animals and humans. The workshop was organized by Drs. Harry Haverkos, Lynda Erinoff, Paul A. Coulis and Ms. Katherine Davenny.

On Friday April 7, 1995 a sharing and exchange meeting was held with NIDA staff and the American Academy of Child and Adolescent Psychiatry (AACAP) as a follow up to the Constituent Organization meeting held in Chantilly, VA last November. This meeting was organized by Dr. Dorynne Czechowicz in collaboration with the NIDA Child and Adolescent Workgroup, Chaired by Dr. Vince Smerglio. NIDA staff presented information regarding current research efforts, funding mechanisms, research training opportunities and strategies for promoting education on the identification, treatment and prevention of drug abuse and addiction in children and adolescents. A number of collaborative activities are being planned as a result of this productive interchange between NIDA staff from all Divisions and the AACAP members. For example, NIDA will hold a day long Institute on Substance Abuse at the

AACAP Annual Meeting in New Orleans in October as well as a workshop on grant writing.

On Friday April 28, 1995, a day long NIDA **Symposium on New Approaches to Drug Abuse Treatment** was held at the American Society of Addiction Medicine annual Medical-Scientific Conference in Chicago, Illinois. The NIDA session was organized by Dorynne Czechowicz, M.D., Treatment Research Branch, DCSR, in collaboration with NIDA Divisions and the American Society of Addiction Medicine. The Symposium was chaired by Richard Millstein, Deputy Director of NIDA. The session addressed behavioral therapies, health services research, pharmacotherapies, and integrating behavioral and pharmacotherapies with emphasis on application of the research to current clinical practice.

NIDA's Services Research Branch/DCSR sponsored and participated in a meeting on **"The Impact of AIDS on Drug Abuse Treatment,"** co-chaired by Dr. Barry Brown of the Friends Medical Science Center, University of Maryland and Dr. Frank Tims.

**NEURON: NIDA's Extramural Unique Research on Neuroscience-** The Neuroscience Workgroup at NIDA has initiated a neuroscience speaker series for the purpose of (1) selfeducation of the latest work in neuroscience, (2) information dissemination to the NIH community of NIDA's progress in neuroscience, and (3) forging closer ties with NIDA's neuroscience researchers. Invitees include recent recipients of a grant in response to the Clinical Neuroscience RFA, and NIDA's MERIT award winners. The guests spend a day meeting with NIDA program, review, and budget staff followed by giving a seminar on the work they have proposed and are undertaking under the neuroscience program. The first guest was Perry Renshaw, M.D., Ph.D. of McLean Hospital who spoke on the latest brain imaging techniques and their direct application to drug abuse research. The next guest (scheduled for June 1) is Laure Buydens, M.D. of the Brooklyn VA Medical Center who will present research on cocaine's effect on the serotonergic system.

Dr. David Johnson, DBR, participated in a panel on **"Federal Funding Opportunities for Nicotine Research"** at the first annual meeting of The Society for Research on Nicotine and Tobacco on March 25, 1994 in San Diego, CA.

On April 3, 1995, Mr. Joel Egertson of the Medications Development Division attended the **Second Southeast Regional Narcotic Treatment Conference** in Orlando, Florida. During this 3 day conference, representatives of 11 States formulated a draft set of standards to govern the delivery of narcotic treatment services in the region, and explored the feasibility of developing a central registry of patients being served by programs in those States. The meeting, sponsored by the Center for Substance Abuse Treatment (CSAT), is one in a series of activities NIDA/MDD is working closely with CSAT on relating to the effective use of pharmacotherapy in drug abuse treatment. Additional policy symposia meetings jointly sponsored by CSAT and NIDA were held for the Northeast States (Boston, April 28) and are scheduled for a group of Mid-Atlantic States (Princeton, New Jersey on June 15).

Dr. Frank Vocci of MDD attended the National Conference on **"Smoking Cessation: Alternative Strategies"** in Washington, D.C., April 10-11, and participated in the session of harm reduction as an alternative goal for cigarette smoking.

On April 12, Dr. Harry Haverkos spoke at the **ARC Clinical Case Conference** on NIDA's extramural AIDS program.

On May 15, Dr. Haverkos attended the 1995 Council of State and Territorial Epidemiologists Meeting in Austin, TX and spoke on **"HIV Prevention-Needle Exchange"** in a point/counterpoint format.

On April 6-7, Dr. Robert Battjes, Acting Director, DCSR, participated in a meeting, **"Building Bridges Between the Health Maintenance Organization and Health Services Research Communities,"** held in Coronado, CA. The meeting was co-sponsored by the Group Health Association of America and the Agency for Health Care Policy and Research.

Drs. Rebecca Ashery, DEPR, and Robert Battjes, DCSR, participated in a conference, **"Advancing Knowledge for Human Services: A National Conference of Social Work Researchers,"** held in Arlington, VA, April 9-11. They were discussants to a presentation by NIDA grantee, Dr. David Nurco, on drug abuse research, and also conducted a round table discussion for social work researchers interested in support for drug abuse research. On April 11, Dr. Battjes also presented a poster, **"Trends in HIV Infection and AIDS Risk Behaviors Among Injecting Drug Users,"** as part of the Conference's poster exhibition at the U.S. Capitol.

Dr. Paul A. Coulis, Program Officer, Division of Clinical and Services Research, Clinical Medicine Branch, was appointed to represent NIDA on the Trans-NIH Sleep Research Coordinating Committee.

Dr. Pete Delany made a presentation to the National Association of Deans and Directors of Social Work Programs on

**"Research Opportunities at the National Institute on Drug Abuse"**, San Diego, CA on March 2, 1995.

Dr. Pete Delany participated in a panel presentation at the Annual Program Meeting of the Council on Social Work Education **"Social Work Research in Substance Abuse,"** San Diego, CA on March 3, 1995.

Dr. Pete Delany presented a paper entitled **"Drug Abuse Research and the Criminal Justice System: Where Are We and Where Are we Going?"** at the Association of Criminal Justice Sciences, Boston, MA, on March 11, 1995.

Dr. Mac Horton, presented on **"Drug Abuse Treatment Research"** at the Spring Grove Hospital Center's Psychology Lecture Series on March 3, 1995.

Dr. Timothy P. Condon, Acting Deputy Director, OSPC, spoke February 17, 1995 in Greensboro, North Carolina to the North Carolina Governor's Alcohol and Drug Abuse Institute on research and training priorities at NIDA.

Dr. Timothy P. Condon, Acting Deputy Director, OSPC gave a presentation on the **"Research Training Opportunities in Neuroscience"** to the Annual Meeting of the Association of Neuroscience Departments and Programs on April 24, 1995 in Washington, DC.

J.C. Comolli, SPB/OSPC was invited to **"The Role of Alcohol and Other Drugs in Child and Family Violence"** meeting sponsored by The Johnson Institute Foundation. Other invited participants included researchers, practitioners and advocacy leaders brought together to discuss research and policy issues, and public awareness regarding this topic. The meeting was held in Orlando, Florida February 23-25, 1995.

Dr. Lula Beatty presented a session on **"Proposal Development"** at the conference of the North Carolina State University Association for the Concerns of African-American Graduate Students in Raleigh, NC, February 25, 1995.

Dr. Lula Beatty presented a session on **"Making Our Families Stronger Again"** at the conference of the Washington Alliance of Black School Educators in Seattle, WA, on March 17, 1995.

Dr. Lula Beatty presented a seminar on research opportunities at NIDA for faculty and students in psychology at George Washington University in Washington, DC, on March 30, 1995.

Dr. Lula Beatty participated in a meeting on African American males, violence and substance abuse sponsored by the Office of National Drug Control and Policy, in Washington, DC, on April 5, 1995.

Dr. Lula Beatty participated in a focus group on **"The Maafa, the Media and the Mind"** sponsored by the Association of Black Psychologists on April 22, 1995.

Dr. Lula Beatty attended a conference on grant development for minority scholars at the University of MD, College Park on April 21, 1995.

Pamela Goodlow presented a session on research opportunities at NIDA at the **National Association For Equal Opportunity in Higher Education** in Washington, DC, on March 17, 1995.

Dr. Coryl Jones ERB/DEPR, Dr. Vince Smeriglio CMB/DCSR, and Dr. Elizabeth Rahdert TRB/DCSR, NIDA representatives to the Steering Committee of the NICHD/NIDA/ACYF/CSAT Maternal Lifestyle Study, met April 4, 1995, to review the progress on the interagency agreements and cooperative agreements with Brown University, University of Miami, University of Tennessee, and Wayne State University. Recruitment has been completed (N = 2,300 of 19,000 mother/infant dyads screened by meconium assay and verification, medical history, and interview to establish cocaine exposure, heroin exposure, and matched control groups); the oldest infants have reached 12 months of age; developmental assessments and maternal batteries are on schedule with approximately 7% of infants not being reared by their biologic mother at the time of 4, 8 or 12 month assessments. Recruitment objectives had to be changed due to changes in drug use patterns (reduction in prenatal cocaine exposure) and the impact of managed care in some settings (geographic dispersion of patients formerly seen in public and university teaching hospitals). One outcome already accomplished by this study has been the refinement of procedures for meconium assay and verification for use in epidemiologic studies.

Richard H. Needle, Ph.D., M.P.H. gave a presentation on HIV-related findings from NIDA-sponsored research at the University of Washington Alcohol and Drug Institute in Seattle, Washington on February 23, 1995.

Richard H. Needle, Ph.D., M.P.H. gave a presentation on HIV prevention research at the Henry M. Jackson Foundation Friday afternoon seminar series, on March 3, 1995.

Helen Cesari, M.Sc. represented DEPR's Community Research Branch at the **"HIV Risk Assessment Outcome Measures Meeting"** in New Orleans, LA on April 25 - 26.

Elizabeth Lambert, M.Sc. gave a presentation on the local impact of drug abuse in the Washington, D.C. metropolitan area, at the George Washington University Symposium, "**Substance Abuse '95: Progress in Policy and Practice**," on March 25, 1995.

Elizabeth Lambert, M.Sc. represented DEPR's Community Research Branch at the **Maryland State Epidemiology Work Group** at the University of Maryland in College Park, on May 12, 1995.

Peter Hartsock, Ph.D. represented DEPR's Community Research Branch at the April 6 Yale University colloquium in recognition of the first NIDA-funded research program on needle exchange, in New Haven, Connecticut. Others participating in the Yale colloquium were researchers from Harvard University's International AIDS Program and the Director of the Epidemiology and Prevention Office in Rome, Italy.

Peter Hartsock, Ph.D. represented DEPR's Community Research Branch at the **Florida State Epidemiology Work Group (SEWG)** in Tallahassee, on March 1. A major aim of the SEWG was to develop a joint Florida and related area (e.g., Caribbean) surveillance and research capability for drug abuse and drug-related correlates, including HIV/AIDS, violence, and crime, with special focus given to substance abuse in rural areas and among minorities.

Mario De La Rosa, Ph.D. served as a panelist on the lack of drug abuse research among Hispanic populations at the **NIDA Conference on Hispanic Issues** in January, in Rockville, Maryland.

Mario De La Rosa, Ph.D. participated in NIDA's **Minorities in Drug Abuse Research Workshop** on January 18-19, in Bethesda, Maryland.

Mario De La Rosa, Ph.D. participated in an **American Psychological Association meeting** to review the current status of research on violence held in February, in Washington, D.C.

Dr. James Colliver met with the **Epidemiology Subcommittee of the Interagency Methadone Policy Review Board** which was formed at the request of the DHHS Counsel to the Secretary for Drug Abuse Policy to discuss the interpretation of data on methadone-related deaths reported by medical examiners and to make recommendations regarding future research into the topic. Dr. Colliver is providing methodological advice regarding mortality data, record linkage, and other research issues.

Dr. James Colliver of DEPR represented NIDA at a workshop on data disclosure issues related to the ADD HEALTH Survey, a major, prospective longitudinal study of the health and health-related behaviors of adolescents being conducted by grantees of the National Institute on Child Health and Human Development with input and support from other NIH ICDs including NIDA. Dr. Colliver assisted in defining approaches to providing access to the survey data for research purposes while preventing inappropriate disclosure of data on particular individuals, schools, and communities.

Dr. James Colliver and Andrea Kopstein of DEPR assisted in developing drug questions for the National Longitudinal Survey of Youth (NLSY). They recently represented NIDA at a Technical Review Meeting on the planned NLSY 1996 Cohort (NLSY96) sponsored by the Bureau of Labor Statistics. Discussion at the meeting focused on the survey sample and the questionnaire design and contents.

Dr. Coryl Jones ERB/DEPR participated as discussant in the **Federal Forum on Childhood Research on Child Abuse and Neglect** sponsored by the U.S. Interagency Task Force on Child Abuse and Neglect of which she is a member.

On March 27, 1995 Arthur Hughes gave a presentation titled: "**Overview of Drug Use Among African Americans**." to the "African American Materials Development Meeting, How to Reach African Americans with Research Results."

Sari Izenwasser was invited to present a seminar entitled: "**Neurochemical Mechanisms of Tolerance and Sensitization to Cocaine**." Department of Pharmacology, Boston University School of Medicine.

Amy H. Newman was invited to present a seminar as a participant in the 27th Annual Mardi Gras Symposium in Chemistry "**Drugs of Abuse: Recent Advances in Chemistry and Pharmacology**." held in New Orleans, Louisiana, in February, 1995. Her topic: Novel Benztrapine Analogs are Potent Dopamine Uptake Inhibitors without Cocaine-like Behavioral Profiles.

Amy H. Newman was invited to present a seminar entitled: **Novel Benztrapine Analogs Are Potent Dopamine Uptake Inhibitors Without Cocaine-Like Behavioral Profiles** for the Department of Medicinal Chemistry, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia in March, 1995.

Dr. Toni Shippenberg of the Behavioral Pharmacology and Genetics Section, Preclinical Pharmacology Laboratory, Division of Intramural Research, was invited to speak about therapeutic potential of opioid ligands in the treatment of cocaine abuse at a NIDA Medications Development Meeting, held in Rockville, MD, in March 1995.

Dr. Edythe D. London presented a lecture entitled, "**PET Studies in Substance Abuse**" at the School of Hygiene and Public Health, Johns Hopkins Medical Institutions, on Jan. 9, 1995.

Dr. Edythe D. London presented a lecture entitled "**PET Studies of Drug Abuse**" at the National Heart, Lung and Blood Institute, National Institute of Health, Bethesda, MD, on February 10, 1995.

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## Director's Report to the National Advisory Council on Drug Abuse May, 1995

### Media and Education Activities

NIDA is the lead agency in the development of the Secretary's Marijuana Initiative, to be launched in the late summer/early fall. We are producing:

- A National Conference on Marijuana
- Two companion booklets for parents and children on **Facts About Marijuana**
- A video for parents on the science-based facts about marijuana, how it fits into their children's lives, and what parents can do
- Television PSAs developed by the Partnership for a Drug Free America
- NIDA and the Advertising Council are now producing the next phase of the **Get High, Get Stupid, Get AIDS** national media campaign. There will be new TV PSAs for young teens, produced by cutting edge animators The Brothers Quay. There will also be new PSAs for young adults, based on the characters in the current successful ads. In addition, award winning singer Melissa Etheridge will appear in a music video singing her hit song, "All American Girl," which will be visually combined with the PSA.

### Liaison with National Organizations Update

- DeafPride, Inc. is developing a 2-tape videotape package entitled, "**A Second Chance.**" One tape is designed to inform deaf substance abusers of what they can expect when they enter an inpatient treatment program. The other tape is designed to help service providers understand the special needs of deaf substance abusers and enable them to provide linguistically and culturally appropriate treatment for their clients.
- Minority Materials Development Meetings  
NIDA convened two meetings of substance abuse and communications experts in March to determine the substance abuse information needs and media preferences of Hispanics and African-Americans. A contract will be awarded this fiscal year to develop culturally appropriate information products based on the information gathered at these meetings.
- DEPR's Community Research Branch, through NIDA's Office of Public Affairs, has contributed to the development of a videotape on "**Drug Abuse and HIV: Reaching Those at Risk**" (NIDA Videotape Series, April-May 1995; NCADI VHS 74; 17 minutes). The videotape is an extension of three HIV prevention field manuals published by the Community Research Branch in 1994.

### Press Releases

NIDA has participated in the following Press Conferences/Briefings in recent months:

- April 11, 1995 **School-based Prevention Program Reduces Teens' Drug Use Through the End of High School** NIDA issued an NIH News Release on publication of an article in JAMA by Dr. Gilbert Botvin, Institute for

Prevention Research, Cornell University Medical College. The results of a long-term study showed that drug abuse prevention programs, when conducted with 7th-grade students and reinforced with subsequent booster sessions, can produce lower levels of tobacco, alcohol, and marijuana use by teenagers over a sustained period of time.

- April 3, 1995 **NIDA Seeks New Scientific Director** NIDA issued a Media Advisory announcing the recruitment of a director for the Division of Intramural Research.

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## Press Conference

- April 12, 1995 **Public Education Campaign on Inhalant Abuse** NIDA participated in a press conference sponsored by the Partnership for a Drug-Free America to announce a new public service campaign on inhalant abuse. NIDA Director, Dr. Alan Leshner spoke regarding the extent of inhalant use by teenagers and the harmful consequences of inhalant abuse.

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## Exhibits

NIDA has sponsored exhibits at the following conferences held recently:

- AMSIE'95: The 1995 Annual Meeting and Scientific Innovation Exposition; February 16-21; Atlanta, GA.
- National Asian Pacific American Families Against Substance Abuse (NAPAFASA); March 29 - April 1; Los Angeles, CA.
- Annual Meeting of the American Society of Addiction Medicine (ASAM); April 27-30; Chicago, IL
- **Prevention 2000: HIV, Violence, and Alcohol, Tobacco and Other Drug Use . . . A Community Responsibility**; May 5-9; Orlando, FL.
- American Cities Against Drugs; May 14-16; Atlanta, GA.
- Development of a new NIDA logo and a new portable NIDA exhibit are also in progress.

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## Planned Meetings

NIDA is sponsoring a conference on "**AIDS and Drug Abuse**" which will be held at the Princess Hotel in Scottsdale, Arizona on June 9-10, 1995, prior to the opening of the College on Problems of Drug Dependence, Inc. annual meeting. The purpose of the AIDS and drug abuse meeting is to bring together investigators from the biomedical and behavioral sciences to review the state of research on AIDS and drug abuse, to discuss future research priorities, and to foster scientific collaboration. Approximately 100 scientific presentations will be given over the 2 day conference.

NIDA is delighted to recognize the 60th anniversary of the opening of the Lexington, Kentucky facility which occurred on May 25, 1935 and played such a central role in the development of drug abuse research. This anniversary will be celebrated by a symposium and dinner on Sunday, June 11 at the CPDD meeting in Scottsdale, AZ.

Philippe Bourgois, Ph.D., of the Department of Anthropology at San Francisco State University, will be visiting NIDA on June 19 to discuss his field research among a network of homeless intravenous drug users in San Francisco.

On June 22, 1995, NIDA's Behavioral Science Working Group and the Treatment Working Group will sponsor a **Roundtable Discussion on Drug Craving** at the Gaithersburg Hilton. A small group of behavioral scientists, neuroscientists and treatment researchers will be discussing diverse approaches to studying drug craving and importantly, the experiential and phenomenologic underpinnings of craving in drug abusers.

In collaboration with Northern Arizona University and with the co-sponsorship of other PHS agencies and institutes, NIDA will hold its third science symposium: "**Current Status and Future Prospects of HIV Prevention Research**," on August 16-18 in Flagstaff, AZ. The theme of the symposium will be on the efficacy of HIV prevention: What works? For whom? Under what circumstances? At what cost? NIDA and other symposium co-sponsors will host plenary sessions that feature their HIV prevention research portfolios, and funded researchers will be invited to present findings from their HIV prevention research. The final plenary will address priorities for future HIV prevention

research as viewed by the co-sponsoring PHS representatives. A number of journal editors will be invited to cover the symposium and to facilitate publication of papers in the refereed literature.

A research symposium entitled "**Systematic Innovation in Drug Abuse Treatment**" is scheduled for August 18-19, 1995, in San Diego, CA (co-located with the 37th International Congress on Alcohol and Drug Dependence).

NIDA has several plenaries and major sessions scheduled in the **37th International Congress on Alcohol and Drug Dependence**, San Diego, California August 20-25, 1995.

NIDA will be one of the sponsors of a workshop on "**Molecular Biology and Genetic Approaches to Sleep Control.**" The workshop, organized by the Trans-NIH Sleep Research Coordinating Committee, which includes a member of the NIDA professional staff, will be held on September 6-7, 1995 in Bethesda, Maryland.

DEPR's Community Research Branch, in collaboration with NIDA's Office on AIDS, will be holding a meeting in September on the current status and future directions of needle exchange research.

A satellite meeting on nicotine addiction is planned for November 11, 1995 at the annual Society for Neuroscience meeting in San Diego. The meeting is entitled "**Advances in Drug Abuse Research on Nicotine**".

NIDA's neuroscience representation is enhanced by broad planned participation of intramural scientists in the upcoming Society for Neuroscience meeting in San Diego, CA. A great many abstracts for this meeting have been submitted from the Intramural Research Program, with 14 from the Molecular Neurobiology Branch.

Dr. Larry Seitz of NIDA's Prevention Research Branch in the Division of Epidemiology and Prevention Research is co-chairing a one half day session at the Society for Prevention Research's third annual meeting on "**Issues Related to the Integration of Prevention Intervention and Managed Health Care.**"

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## Director's Report to the National Advisory Council on Drug Abuse May, 1995

### Publications

#### **Diagnosis and Severity of Drug Abuse and Dependence** NCADI BKD166

Provides clinicians and researchers summaries of the latest information, techniques and procedures regarding the diagnosis and severity of drug abuse and dependence.

### Research Monographs

#### **Discovery of Novel Opioid Medications--Research Monograph 147** NCADI M147

Reviews the pharmacology, neuropharmacology, and molecular biology of potential pharmacotherapies for opioids, novel opioids, and non-opioids.

#### **Epidemiology of Inhalant Abuse: An International Perspective--Research Monograph 148** NCADI M148

Describes the epidemiology of inhalant use and abuse in the United States and in selected countries around the world. Discusses unique problems associated with investigations of inhalant abuse and suggests methodologies that might be utilized to investigate the high risk, difficult-to-reach groups who abuse inhalants in various countries.

#### **Medications Development for the Treatment of Pregnant Women, Infants, and Children Born to Drug Abusing Mothers--Research Monograph 149** NCADI M149

Reviews the current treatment strategies and approaches for the development of pharmacotherapeutic agents for the treatment of pregnant addicts and their children/infants.

#### **Integrating Behavioral Therapies with Medications in the Treatment of Drug Abuse--Research Monograph 150** NCADI M150

Latest research findings including state-of-the-art techniques and procedures regarding the integration of psychosocial and pharmacological treatments.

#### **Problems of Drug Dependence, 1994: Proceedings from the 56th Annual Scientific Meeting--Volume I: Plenary Symposia and Annual Reports; and, II: Abstracts--Research Monograph 152 & 153** NCADI M152/NCADI M153

These two monographs contain the presentations from the 56th Annual Scientific meeting of the College on Problems of Drug Dependence, Inc. which includes the comprehensive, up-to-date reviews of research in progress from many disciplines in drug abuse and dependence.

### New Videos

#### **Drug Abuse Treatment in Prison** NCADI VHS72 \$8.50

Portrays two comprehensive drug abuse treatment approaches that have been effective with men and women in State and Federal prisons.

#### **LAAM: Another Option for Maintenance Treatment of Opiate Addiction** NCADI VHS73 \$8.50

Shows how LAAM can be used to meet the opiate treatment needs of individual clients from the provider and patient

perspective. Compares and contrasts LAAM with methadone.

**Drug Abuse and HIV: Reaching Those at Risk** NCADI VHS74 \$8.50

Shows how three intervention models educate out-of-treatment injection drug users about AIDS, about the behaviors that transmit the disease, and about strategies that reduce the risk of contracting AIDS. Focuses primarily on indigenous leader community outreach.

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## Other Publications

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A **Conference Report: "Biological Mechanisms and Perinatal Exposure to Abused Drugs"** edited by Pushpa V. Thadani and conference participants was published in the March 1995 issue of SYNAPSE 19:228-232, 1995. This Conference report resulted from a Technical Review held in June, 1994.

The Washington, D.C. Metropolitan Area Drug Study (DC\*MADS) final report, **Prevalence of Drug Use Among DC Women Delivering Livebirths in DC Hospitals: 1992**, will be printed and distributed by NIDA in May. The report examines the prevalence of illicit drug, alcohol, and cigarette use among DC resident women who delivered livebirths in DC hospitals, using data from interviews, medical record abstraction, and anonymous urine drug testing results. The report also provides information on demographic and household characteristics, prenatal care services received, infant birthweight and gestational age, and medical problems experienced by drug-using and drug-free mothers and their newborn infants. It also describes the relationship between drug use during pregnancy and infant birthweight.

Dr. Haverkos co-published an article in *Genetica* [95:157-164, 1995] on **"Measuring Inhalant Nitrite Exposure in Gay Men: Implications for Elucidating the Etiology of AIDS-Related Kaposi's Sarcoma."**

Dr. Mac Horton, with Jack Blaine MD, Chief of the Treatment Research Branch, and Lee Towle, former Director of International and Intergovernmental Affairs at the National Institute on Alcohol Abuse and Alcoholism, edited the publication **Diagnosis and Severity of Drug Dependence**.

Fletcher, B.W., Inciardi, J.A., and Horton, A.M. (editors). **"Drug Abuse Treatment: The Implications of Innovative Approaches,"** published by Greenwood Press.

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## Director's Report to the National Advisory Council on Drug Abuse May, 1995

### Staff Highlights

NIDA Director, Dr. Alan Leshner was presented with a special recognition award by the Society for Social Work and Research and the Institute for the Advancement of Social Work Research at their first national meeting held in April. This award acknowledged Dr. Leshner's "scientific leadership in addressing the serious human and social problems confronting our nation" and his "enabling vision and support of social work's contribution to building scientific knowledge for human services."

Susan Coyle received her Ph.D. in Sociology from George Washington University in March.

Peter Hartsock, Ph.D. received a letter of appreciation from the German Embassy for technical assistance on issues in drug abuse research.

Dr. Rosemarie Nemeth-Coslett was on detail from the National Institute on Drug Abuse to the Food and Drug Administration for the period September 23, 1994 to April 1, 1995. The purpose of the detail was to provide expert advice to the Commissioner of FDA on issues relating to nicotine and tobacco and to review and research published articles, abstracting and summarizing them for the Tobacco Task Group. During this period of detail, Dr. Nemeth-Coslett continued to perform her regular full time duties at NIDA.

David Shurtleff, Ph.D. joined the Division of Basic Research in April as a Health Scientist Administrator in NIDA's new Behavioral Sciences Research Branch. Dr. Shurtleff came to NIDA from the Naval Medical Research Institute in Bethesda MD, where he conducted research on the effects of environmental stress on behavior and cognitive performance.

The following NIDA staff have been selected to receive the NIH Director's Award for outstanding accomplishments:

#### Individual Awards:

Richard Harrison  
Syed Husain, Ph.D.  
Constance Latzko  
David McCann, Ph.D.  
Audrey Thomas, M.S.

#### Group Award (members of the NIDA Equal Opportunity Advisory Committee):

Lula Beatty, Ph.D.  
Mona Brown  
Arturo Cazares, M.D., M.P.H.  
Carol Cushing  
Mary Custer, Ph.D.  
Richard Harrison  
Arthur M. Horton, Ed.D.  
Davey Jones  
Theresa Kopajtic  
Rao Rapaka, Ph.D.  
Rita Liu, Ph.D.

Charles W. Sharp, Ph.D.  
Nancy Soulen, J.D.  
Jewell Webb

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## Grantee Honors

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NIDA grantee Robert Carlson, Ph.D. received the 1994 AIDS and Anthropology Research Group Annual Paper Award for the chapter he, H. Siegal, and R. Falck contributed to Global AIDS Policy, entitled "**Ethnography, Epidemiology, and Public Policy: Needle Use Practices and HIV-1 Risk Reduction Among Injecting Drug Users in the Midwest.**" In: Feldman, D. (ed.) Global AIDS Policy. Westport, CT: Greenwood Publishing Group, Inc., pp. 185-214, 1994.

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