National Institute on Drug Abuse

Director's Report

to the

National Advisory Council on Drug Abuse

September, 1996

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National Institute on Drug Abuse

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

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Research Findings

Basic Research

Chronic Morphine and Cocaine Produces Sustained Activation of The Extracellular Regulated Signal Regulated Kinase (ERK) Pathway

The laboratory of Eric Nestler at Yale University reported in the August 1 issue of *The Journal of Neuroscience*, Vol 16, pages 4707-4715 that chronic, but not acute, morphine or cocaine treatment selectively increases extracellular signal regulated kinase (ERK) activity in the ventral tegmental area (VTA) but not in substantia nigra, frontal cortex, or nucleus accumbens. The increase in ERK activity and associated induction of tyrosine hydroxylase (TH) produced by chronic morphine or cocaine treatment is prevented by brain derived growth factor (BDNF) and glutamate antagonists. To determine whether ERK kinases play a direct role in the increases in tyrosine hydroxylases in the VTA, antisense ERK1 oligonucleotides were infused into the VTA. Intra-VTA infusion of ERK1 antisense, like BDNF and glutamate antagonists prevented increases in both ERK activity and tyrosine hydroxylase. These findings suggest that sustained increase in ERK phosphorylation and activity contributes to drug induced increases in tyrosine hydroxylase (TH), and perhaps other drug-induced adaptations, elicited selectively in the VTA.

Opiate Exposure Leads to Increase in Synapsin I mRNA in Defined Central Nervous System Regions

Previous research has shown that chronic opiate exposure of spinal cord-dorsal root ganglion (SC-DRG) co-cultures leads to a time- and dose-dependent increase in the immunoreactive levels of synapsin I (a synaptic vesicle-associated protein important for neurotransmitter release). More recently, it was found by Dr. Zvi Vogel and colleagues at the Weizmann Institute of Science that chronic opiate treatment also affects the expression of synapsin I in the CNS of intact animals. A 3-fold increase in synapsin mRNA was observed (by Northern blots) in SC of rats chronically treated for 4 days with morphine. In situ hybridization with digoxygenin-labeled selective antisense cRNA probes revealed an increase of 3-7-fold in synapsin mRNA in selective areas of the CNS, including SC, locus coeruleus and amygdala (areas known to be involved in opiate activity and dependence), but not in most other brain areas, including the hippocampus and cerebellum. These findings raise the important question of the role of synapsin in opiate actions, tolerance and dependence.
Matus-Leibovitch et al., Mol. Brain Res. 34: pp. 221-230, 1995.

Opiate Regulation of Potassium Channel mRNAs

K+ channels are important synaptic proteins which regulate membrane potential of nerve terminals. Opiates affect the activity of various K+ channels (both activation and inhibition of K+ channels have been reported). Utilizing in situ hybridization, RNAse protection, reverse transcriptase-polymerase chain reaction (RT-PCR), Western blotting and immunohistochemical techniques, it was found that motor neurons are highly enriched in the mRNAs of Kv1.5 and Kv1.6 voltage-gated K+ channels, and in Kv1.5 channel protein. A significant increase (2-2.5 fold) in the mRNA and protein of these channels was observed in spinal cord of morphine-treated rats, compared to controls. These results suggest an important role for opiate neurotransmission and for Kv1.5 and Kv1.6 K+ channels in regulating motor activity. Matus-Leibovitch et al., Mol Brain Res, In Press.

Ligands for the Cannabinoid Receptor

Pravadoline, a "non-classical" cannabinoid receptor ligand, is an alkylindole that displays antinociceptive activity. In a recent study, Yamada et al., reported that a naphthyl derivative of this compound which contains the electrophilic isothiocyanate group binds to the cannabinoid receptor with high affinity, and after "washing out" the ligand, it produces an irreversible loss of the receptor binding capacity, possibly by chemical reaction between the isothiocyanate group and nucleophilic amino groups such as lysine or histidine within the binding site. It remains to be shown whether the binding site or sites for this class of compounds is the same as for classical cannabinoids. Yamada, K., Rice, K.C., Flippen Anderson, J.L., Eissenstat, M.A., Ward, S. J., Johnson, M.R., and Howlett, A.C. Journal of Medicinal Chemistry, 39, pp. 1967-1974, 1996.

New Peptidomimetic

It has been previously reported that the peptides FMRFamide (isolated from mollusk) and NPFF (isolated from bovine brain) have antiopiate pharmacological action, possibly via specific NPFF receptors. In a recent NIDA-funded study, a conformationally constrained peptidomimetic analog of FMRF containing E-2,3 methanomethionine and E-2,3 methanophenylalanine proved to be approximately 200 times more potent in a morphine abstinence model, principally because of its enhanced resistance to peptidase degradation as compared to FMRF. Malin, D.H., Lake, J.R., McDermitt, L.S., Smith, D.A., Witherspoon, W.E., Jones, J.A., Schumann, M.D., Payza, K., Ho, K.K., and Burgess, K. Peptides, 17, pp. 83-86, 1996.

Tolerance Development Reduced to Opioid Receptors

DPDPE in animal models results in a tolerance to this delta receptor ligand's analgesic capability. A NIDA-funded study has recently provided evidence that this development of tolerance may be reduced by the chronic administration of MK-801 (a competitive NMDA antagonist) or LY 235959 (a noncompetitive NMDA antagonist). The antagonists may be activating the opioid systems or regulating the processing of opioid peptides. Zhao, G.M., and Bhargava, H.N. Peptides, 17, pp. 233-236, 1996.

Cellular Trafficking of Opioid Receptors

Mark Von Zastrow's laboratory at the University of California, San Francisco reported in the August 9 issue of *The Journal of Biological Chemistry*, Vol 271, pages 19021-19024 that morphine activates opioid receptors without causing their rapid internalization. In this report the authors examined the endocytic trafficking of epitope tagged d and m receptors expressed in human embryonic kidney (HEK) 293 cells. These receptors are activated by enkephalins as well as by the alkaloid agonist drugs etorphine and morphine. Enkephalins and etorphine cause opioid receptors to be internalized rapidly in transferin-containing endosomes. Remarkably, morphine does not stimulate the rapid internalization of either d or m opioid receptors, even at high concentrations that strongly inhibit adenylyl cyclase. These data indicate that agonists ligands which have similar effects on receptor-mediated signaling, can have dramatically different effects on the intracellular trafficking of a G-coupled receptor.

Opioid Peptide Biosynthesis: Regulatory Mechanisms

Enkephalins and endorphin like other biologically active peptides are cleaved from a larger poly-peptide by intracellular processing enzymes. The intracellular processing enzymes responsible for the formation of biologically active opioid peptides in nervous tissue are the new PC1 and PC2 subtilisin processing enzymes. NIDA Grantee Iris Lindberg of Louisiana State University Medical Center and her coworkers recently identified the first endogenous inhibitor of PC enzymes called 7B2. They have now obtained evidence using site-directed mutagenesis that the proline-rich region (residues 888-95, PDPPNPCP) is responsible for the binding of the 21 kDa portion of 7B2 to PC2. This region bears similarities to src homology 3 (Sh4) domain, known to mediate protein-protein interactions. Four different assays were used to assess the functional aspects of mutated 7B2s and the roles of the prolines in the proline-rich region (coimmunoprecipitation, facilitation of proC2 activation, protection from thermal inactivation, and acquisition of enzymatic activity).

Since proteolytic cleavage represents the first step of the enkephalin biosynthetic pathway, it is likely that regulatory mechanisms which control opioid peptide production may involve these crucial proteolytic enzymes. Deficiencies in the biosynthetic capacity for opioid peptides may be responsible for the addictive properties of opiate drugs in certain individuals; thus the study of enzymatic mechanisms regulating endogenous opioid production is of extreme importance. A thorough understanding of regulatory mechanisms in opioid peptide synthesis might one day lead to enzyme-based drugs serving as therapeutic agents in opiate addiction. J. Biol. Chem., In Press.

The Role of Opiate Systems in Immune System Regulation

Expressing the "neural" opiate receptor at high levels in a prototype human immune cell, this group was able to demonstrate a link between opiates and the basic Calcium transport system function. Until recently, functionality as well as binding for these receptors has been difficult to measure due to the low level of expression of these receptors in immune cells. Information gained from this research should enable scientists to better evaluate the importance of opiate systems and immunity regulation. Sharp, B.M., Shahabi, N.A., Heagy, W., McAllen, K., Bell, M., Huntoon, C., and McKean, D. J. Dual Signal Transduction through Delta Opioid Receptors in a Transfected Human T-Cell Line. Proc Natl Acad Sci USA, 93, pp. 8294-8299, 1996.

Opiates are known to function as immunomodulators, in part by effects on T cells. However, the signal transduction pathways mediating the effects of opiates on T-cells are largely undefined. To determine whether pathways that regulate free intracellular calcium ([ca2+]I) and/or cAMP are affected by opiates acting through delta type opioid receptors (DOR), a cDNA encoding the neuronal DOR was expressed in a stably transfected Jurkat T cell line. The DOR agonists, deltorphin and [D-Ala2~D-Leus]-enkephalin (DADLE), elevated [ca2+]I, measured by flow cytofluorometry using the calcium sensitive dye, Fluo-3. At concentrations from 10-11to 10-7 M, both agonists dose-dependently increased [ca2+]I from 60 nM to peak concentrations of 400 nM within 30 sec (ED50 of approximately 5xl0-9 M). Naltrindole, a selective DOR antagonist, abolished the increase in [ca2+]I and pretreatment with pertussis toxin was also effective. To assess the role of extracellular calcium, cells were pretreated with EGTA which reduced the initial deltorphin-induced elevation of [ca2+]I by more than 50% and eliminated the second phase of calcium mobilization. Additionally, the effect of DADLE on forskolin-stimulated cAMP production was determined. DADLE reduced cAMP production by 70% (IC50 of approximately 10-11 M) and pertussis toxin inhibited the action of DADLE. Thus, the DOR expressed by a transfected Jurkat T cell line is positively coupled to pathways leading to calcium mobilization and negatively coupled to adenylate cyclase. These studies identify 2 pertussis toxin-sensitive G-protein mediated signaling pathways through which DOR agonists regulate the levels of intracellular messengers that modulate T-cell activation. Sharp, B.M., Shahabi, N.A., Heagy, W., McAllen, K., Bell, M., Huntoon, C. and McKean, D.J. 1996 Proceeding of the National Academy of Sciences, USA, In Press.

Effects of Cocaine on Pharmacodynamics and Pharmacokinetics

Drs. Charles Mactutus and Rosemary Booze at the University of Kentucky have been studying the effects of cocaine on pharmacodynamics and pharmacokinetics in adult Sprague Dawley rats. They have reported that repeated cocaine administration (0.5 to 3.0 mg/kg/day IV) resulted in a significant dose-dependent increase in striatal D3 receptors and a significant decrease in D3 receptors in the nucleus accumbens. Sensitization to cocaine was also seen, with the time to peak being dose dependent following the rank order of 0.5>1.0>3.0 mg/kg. D2 receptors were unchanged in both striatum and nucleus accumbens. These data suggest that the D3 receptors in the striatum and nucleus accumbens may be differentially involved in the locomotor stimulation (striatal D3) and reinforcing aspects (nucleus accumbens D2) of repeated cocaine administration. Synapse 23: pp. 152-163, 1996. In aged Fisher-344XBrown

Norway rats, these investigators reported that D3 receptors in the striatum and the nucleus accumbens were significantly increased. European J. Pharmacology, In Press.

In other studies, Drs. Mactutus and Booze have concentrated on the pharmacokinetic effects of a single injection of cocaine at 0.5 to 3.0 mg/kg, IV. Arterial plasma concentrations of cocaine and metabolites (benzoylecgonine [BE], ecgonine methyl ester [EME], and norcocaine [NC]) were determined in adult Sprague Dawley rats. Peak plasma concentrations of cocaine occurred at 30 seconds (the first time point measured) and were dose dependent. The distribution half-life (T1/2a) was less than 1 minute for all groups, but inversely related to dose. More importantly, the elimination half-life (T1/2ß) (12-13 minutes), the mean residence time (MRT) (14.5-16 minutes), the volume of distribution at steady state (Vdss) (2.8-3.3 L/kg), and total clearance (Cltot) (195 204 ml/min/kg) were all independent of dose. Although the metabolic profile of IV cocaine was similarly ordered for all dose groups (BE>EME>NC), a quantitative shift in metabolite profile was evident as a function of increasing dose. This metabolic shift, perhaps attributable to saturation of plasma esterases, suggests that the recently reported pharmacodynamic effects positively correlated with IV cocaine are unlikely attributable to norcocaine. In summary, the IV pharmacokinetic profile of cocaine in adult rats is distinct from that observed via the IP, PO, or SC routes of administration. Neurotoxicology and Teratology, In Press.

Effects of NMDA Receptor Antagonists on Opioid Tolerance and Withdrawal

Dr. Tony Yaksh and colleagues at the University of California have studied the effects of administration of NMDA receptor antagonists on opioid tolerance and withdrawal in rats and have found that infusion of MK-801 in combination with morphine resulted in the development of considerably less tolerance of morphine's analgesic properties. MK-801 had no effect on pain processing by itself. These data suggest that activation of NMDA receptors may serve a permissive action in the development of tolerance to morphine's analgesic properties. Similar findings were observed when a different class of spinal analgesics (alpha-2 agonists) were studied, demonstrating broad generality of the involvement of NMDA receptors in tolerance. Anesthesiology, In Press.

THC and Pregnancy

NIDA supported research to be published soon reports that the mouse uterus during early pregnancy has the capacity to synthesize and degrade anandamide. These findings coupled with earlier findings of cannabinoid receptors in the preimplantation mouse embryo and uterus suggest that these tissues could be targets for cannabinomimetic ligands. The researchers also observed an inverse relationship between the synthase and amidase activity at the implantation or inter-implantation sites in the uterus during the peri-implantation period suggesting embryonic influence in regulating these activities. Although the physiological significance of these findings is not yet clear, it is possible that aberrant synthesis of anandamide and/or expression of the cannabinoid receptors in the uterus and/or embryo could contribute to early pregnancy. Paria, B.C., Deutsch, D.D., and Dey, S. K. Molecular Reproduction and Development, In Press.

Renal Function and Drugs of Abuse

The most predominant renal lesion seen in heroin addicts as well as in patients with HIV infection is glomerulosclerosis; however, the mechanism underlying this injury is not understood. A recent report from Dr. Pravin Singhal's laboratory showed that morphine-induced macrophage secretory products stimulated proliferation of mesangial cells derived from rats and mice. Synthesis of extracellular matrix components, laminin and collagen was also enhanced. Furthermore, these actions of morphine on mesangial cells appeared to be mediated through TGF-ß. These findings suggest a possible role for macrophages in the development of glomerular lesions in patients with drug addiction. Singhal, P.C., et al., Kidney Intl. 49: pp. 94-102, 1996.

In another recent paper, these researchers report that macrophage gp-160 interaction products enhance matrix synthesis as well as modulate mesangial cell proliferation which may contribute to expansion of the mesangium. These results, according to the investigators, support the hypothesis that HIV-1 proteins have the potential to cause expansion of the mesangium, and that replication of virus in renal cells is not a prerequisite for the development of glomerular lesions in patients with HIV infection. Singhal, P.C., et al., Amer J. Pathology 147: pp. 1780-1789, 1995.

Potential Treatment for PCP Toxicity

NIDA grantee Dr. Michael Owens from the University of Arkansas College of Medicine has recently published work in the Journal of Pharmacology and Experimental Therapeutics in which he reports having produced anti-PCP monoclonal antibody fragments (Fab) which can clear 90% of injected PCP from rat brain within 10 minutes. Rat behavior returns to normal within 30 minutes of treatment with anti-PCP Fab. This makes anti-PCP Fab a candidate for development as an emergency room treatment for PCP toxicity.

Activation of Limbic Regions During Cue-Induced Cocaine Craving

Using PET, Dr. Anna Rose Childress from the University of Pennsylvania showed that participants with histories of cocaine use demonstrated significant increases in regional cerebral blood flow (rCBF) in temporal pole, amygdala, and anterior cigulate when shown a video with cocaine-related stimuli but not when shown a neutral video. Systematic activation did not occur when shown a neutral video. Results suggest that limbic activation may underlie certain aspects of cue-induced craving. d and m receptors expressed in human embryonic kidney (HEK) 293 cells. These receptors are activated by enkephalins as well as by the alkaloid agonist drugs etorphine and morphine. Enkephalins and etorphine cause opioid receptors to be internalized rapidly in transferin-containing endosomes. Remarkably, morphine does not stimulate the rapid internalization of either d or m opioid receptors, even at high concentrations that strongly inhibit adenylyl cyclase. These data indicate that agonists ligands which have similar effects on receptor-mediated signaling, can have dramatically different effects on the intracellular trafficking of a G-coupled receptor.

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Research Findings

Behavioral Research

Airway Sensory Factors Alone Produce Positive Mood Effects In Cigarette Smokers

In a recent experiment, investigators at Duke University compared the mood effects produced by a standard 1-mg nicotine cigarette versus a denicotinized cigarette. As other studies have shown, subjects reported feeling more calm and less irritable after smoking the cigarette containing nicotine. However, subjects reported many positive subjective effects after smoking the denicotinized cigarette, effects which were in fact comparable in magnitude to the nicotine cigarette. The authors conclude that the airway sensory effects of cigarette smoke alone contribute to the positive subjective effects of smoking. These results further suggest that airway sensory replacement therapy may be useful for smoking cessation. Westin, E.C., Frederique, M.B., and Rose, J.E. Pharmacology Biochemistry and Behavior. 53, pp. 309-315, 1996.

Mechanisms Mediating the Actions of Caffeine

Dr. Stephen Holtzman's research is using behavioral measures to characterize the receptor subtypes and neuronal substrates mediating caffeine's actions. A number of studies from his laboratory have used locomotor activity and the 6-hydroxydopamine unilateral nigral lesion model of rotational behavior to study caffeine's actions. A recent paper "Comparison of the Effects of Prototypical Behavioral Stimulants on Locomotor Activity and Rotational Behavior in Rats", Pharmacology, Biochemistry, and Behavior, 54, pp. 469-477, 1996, demonstrated differences in potency and efficacy of four stimulants, apomorphine, caffeine, d-amphetamine, and cocaine and a D1 agonist SKF-38393 on these two behaviors. Caffeine-induced rotation occurred over a narrow range of doses whereas the dose range for caffeine induced stimulation of locomotor activity was much broader. By contrast, SKF-38393 was more potent and effective in increasing rotational behavior than it was in increasing locomotor activity. The differences in drug effects on rotational behavior compared to locomotor activity suggest that these two behaviors involve different neuronal substrates.

Stress Modulates the Effects of Opiates

Researchers at the University of Chicago are studying how stress or pain modulate the analgesic and reinforcing effects of the opioid analgesic fentanyl, in normal volunteers. Dr. James Zacny's data show that the effect of opioids on mood and pain relief are modified by environmental context. The degree of stress and pain in the context in which opiates are self-administered determine the actual euphoric and analgesic effects of the drugs. During stress, fentanyl is chosen at above chance levels, and for its analgesic properties. With no stress present, fentanyl is not chosen more often than chance.

Behavioral Effects of Inhalants

Ongoing work being conducted at the Medical College of Virginia by Dr. Robert Balster is examining the behavioral teratology of abused inhalants in mice with use of various behavioral testing procedures. The project is specifically examining the neurobehavioral effects of the alkylbenzenes (e.g., benzene and toluene). Dr. Balster has found that many of the abused solvents and volatile anesthetics have a profile of behavioral and pharmacological effects similar to depressant drugs (barbiturates) and alcohol. In particular, the well-known anti-anxiety effect of depressants was also found in the solvents (e.g., lengthened time to enter arms of a plus maze).

Dr. Balster also has found that the volatile anesthetics produce ethanol-like discriminative effects in mice. These findings have led to his recommendations that volatile anesthetics be classified along with abused solvents as having depressant-like abuse potential. Finally, Dr. Balster has demonstrated fetal effects of trichloroethane when administered in utero to mice. This is evidence, with use of an animal model, of "fetal solvent syndrome". European Journal of Pharmacology, In Press; Pharmacology, Biochemistry and Behavior, In Press.

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Research Findings

Clinical and Services Research

Contribution of ADHD Symptoms to Substance Problems and Delinquency in Conduct-Disordered Adolescents

Researchers examined adolescents with conduct disorder (CD) and substance abuse problems to determine if those with attention deficit hyperactivity disorder (ADHD) symptomatology had more severe delinquency and substance involvement. The study sample consisted of 171 adolescent boys, 13-17 years of age, enrolled in a residential program for substance abusers with behavioral problems. ADHD symptomatology was assessed by self-reports using the Diagnostic Interview Schedule for Children (DISC) and by the use of DISC plus reports of others (parents, program staff, and program teacher). Results showed that boys with either self- or multi-source ADHD had more conduct disorder symptoms, earlier age of conduct disorder onset, more substance dependence diagnoses, and more co-morbid depression and anxiety. Thompson, L.L., Riggs, P.D., Mikulich, S.K., and Crowley, T.J. Journal of Abnormal Child Psychology, 24(3): pp. 325-347, 1996.

An Open Trial of Pemoline in Drug-Dependent Delinquents with Attention-Deficit Hyperactivity Disorder

Research shows that adolescents with conduct disorder and substance use disorders have high rates of co-morbid attention deficit hyperactivity disorder (ADHD). Further, ADHD may contribute to the severity and persistence of substance use disorders and antisocial behaviors. A study was conducted to examine if adolescents with ADHD and substance use disorders could be successfully treated. The study sample consisted of 13 male adolescents with CD, substance use disorder, and ADHD, in a residential program. Patients were treated with pemoline, schedule IV stimulant medication but with a known low abuse potential, at a standard daily dose of 37.5 mg, that was increased over the subsequent 3 weeks to a total of 112.5 to 185.5 mg (=1.2-3.3 mg/kg maximal dosing). All patients took this maximal dose for at least 1 week prior to post-treatment assessment of motility, CHI (Connors Hyperactivity Index), and CPT (Continuous Performance Score). Results showed that hyperactivity and motility declined significantly by 13.9% and 7%, respectively, with pemoline treatment. However, the continuous performance scores did not change. These data indicate that pemoline may be a useful treatment for ADHD in substance-dependent delinquents. Riggs, P.D., Thompson, L.L., Mikulich, S.K., Whitmore, E.A., and Crowley, T.J. Journal of American Academy of Child and Adolescent Psychiatry, 35(8): pp. 1015-1024, August 1996.

Frontal P300 Decrements, Childhood Conduct Disorder, Family History, and the Prediction of

Relapse Among Abstinent Cocaine Abusers

Antisocial personality disorder is a frequent co-morbid diagnosis in cocaine dependent patients. A study was conducted in 49 cocaine dependent patients, abstinent for 1-5 months, to examine the following: (1) the neurophysiological effects of pre-morbid antisocial personality symptoms (ASPD; e.g., conduct disorder) occurring before age 15 versus co-morbid or post-morbid ASP symptoms occurring after age 15, (2) comparison of ASPD in patients with a family history of alcoholism and in cocaine dependent patients, (3) to examine the usefulness of P300 in predicting relapse, and (4) examine the time course of P300 decrements in cocaine abusers, with or without ASPD. Patients were assigned according to the presence/absence of a DSM-IIIR diagnosis of ASPD. Analysis of P300 recorded during a visual selective attention task revealed reduced amplitudes at frontal electrode sites among patients with ASPD, relative to the ASPD negative patient and control groups. The frontal P300 decrement was significantly correlated with the number of childhood conduct disorder symptoms, but not with the presence/absence of a family history of alcoholism. Further, discriminant function analysis revealed that P300 amplitude alone accurately identified 71% of the patients who later relapsed, and 53% of the patients who did not. Bauer, L.O., Drug and Alcohol Dependence, In Press.

Safety Dose-Response Study on Lofexidine

Elmer Yu, M.D., from the Philadelphia Medications Development Research Unit, has initiated a safety dose-response study on the alpha-2-noradrenergic agonist, lofexidine, for the alleviation of opiate withdrawal symptoms in opiate dependent individuals. The potential importance of this study is that lofexidine, unlike clonidine, has not historically been associated with decreases in blood pressure that limit the usefulness of clonidine. Other preclinical researchers are determining if lofexidine binds to a different set of receptor subtypes than clonidine.

Impaired Regulation of Arousal in Infants Prenatally-Exposed to Cocaine

Researchers at Yale University have provided evidence of impaired arousal regulation in 3-month old infants prenatally-exposed to cocaine and other drugs. Behavioral state, affective expressiveness, and attention to novel stimuli were the measures of arousal. There were no differences in baseline behavioral state or affective expression prior to stimulus presentation across two groups of 3-month old infants (36 infants prenatally-exposed to cocaine and other drugs, and 27 not exposed to cocaine prenatally). However, the exposed infants were more likely to exhibit a crying state and to display negative affect when novel stimuli were presented. There was no difference in looking time between the two groups. These group results were found when sociodemographic and perinatal factors were controlled. The investigators discuss these findings as to possible sources of differences in arousal regulation, and relative to predictive implications for social and cognitive development. Mayes, L.C., et al., Development and Psychopathology, 8: pp. 29-42, 1996.

Prediction of Treatment Success in Alcohol and/or Cocaine Use Disorders by qEEG

NIDA-funded researcher, Dr. Henry D. Abraham, from the Butler Hospital in Providence, Rhode Island has assessed the ability of quantitative electroencephalography (qEEG) to predict relapse following inpatient treatment for alcohol and/or cocaine use disorders in 27 subjects. Subjects were studied in a drug-free state following treatment and were followed for an assessment of sobriety. At one year after discharge, 39.3% of the subjects had maintained abstinence, and 60.7% had relapsed. Three qEEG variables derived a year earlier predicted relapse with 88.2% sensitivity and 90.0% specificity ($p < .0001$). Dr. Abraham hypothesized that these preliminary findings may lead to markers for diverse etiologies of relapse.

Changes in Brain Metabolism in Chronic Marijuana Users

Dr. Nora D. Volkow of the Brookhaven National Laboratory and her colleagues recently reported on the effects of chronic marijuana use on brain glucose metabolism. Eight chronic marijuana abusers were evaluated with positron emission tomography (PET). At baseline, the marijuana abusers had significantly lower baseline cerebellar metabolic values than normal subjects. Metabolic response to THC administration revealed an increase in relative cerebellar

metabolism in all subjects, but only the marijuana abusers showed metabolic increases in prefrontal cortex, orbitofrontal cortex, and basal ganglia. For the normals, THC either did not change or decreased metabolism in these areas. These results suggest that the lower baseline cerebellar metabolic activity in chronic marijuana abusers could reflect changes in cannabinoid receptors in the cerebellum (a brain structure rich in cannabinoid receptors). Also, the THC-induced activation of the orbitofrontal cortex and basal ganglia in abusers could be one of the underlying neural mechanisms leading to the drive and compulsion to self-administer the drug in addicted individuals. Volkow et al., Brain Glucose Metabolism in Chronic Marijuana Users at Baseline and During Marijuana Intoxication. Psychiatry Research, 67, pp. 29-38, 1996.

Sex Differences in Plasma Cocaine Levels and Subjective Effects after Acute Cocaine Administration

Scott Lukas and colleagues at the Alcohol and Drug Abuse Research Center, McLean Hospital and Harvard Medical School reported that male occasional cocaine users achieved significantly faster peak plasma cocaine levels after an intranasal dose of cocaine hydrochloride. They also reported a greater number of intense effects. Women also differed in their menstrual cycle where peak plasma levels of cocaine were lower in the luteal compared to the follicular phase; subjective reports did not differ. However, heart rates did not differ between males and females, suggesting that females with the lower plasma cocaine had more sensitive cardiovascular sensitivity. These data demonstrate differential effects between the sexes for use of cocaine. Psychopharmacology, 125, pp. 346-354, 1996.

Sleep Improvement by Low Doses of Buprenorphine in Recovering, Dual Dependent (Cocaine and Opiates) Drug Abusers

Dr. Lukas and colleagues have also been studying the disturbed sleep of recovering dual-dependent drug abusers. Findings indicate delays in sleep onset, multiple awakenings and reduced total sleep time with little or no Stage 3 or Stage 4 sleep. Low dose (4 mg/day) significantly increased sleep time, reduced latency, and increased Stage 3 sleep whereas only sleep latency was significantly reduced with a larger dose (8 mg/day).

Cocaine-Associated Agitated Delirium

An increasing number of deaths due to cocaine are characterized by delirium and seemingly violent behavior requiring restraint. NIDA grantee, Dr. Deborah Mash of the University of Miami School of Medicine, together with colleagues in the medical examiners office, are studying the underlying causes of delirium-associated deaths which constitute about 10% of the deaths due to cocaine overdose. They describe in a recent report that victims are most often male, succumbing in the warmer months. Work so far has shown that these psychotic victims have marked reduction of D2 dopamine receptors within the temperature regulatory centers of the hypothalamus and no increases in dopamine recognition sites on the striatal dopamine transporter. It was also pointed out that cocaine per se may not be the sole cause since a similar syndrome was described nearly 150 years ago. Also cocaine-induced changes of dopamine sites may not be the sole cause; other factors such as stress of restraint may exacerbate the situation. American Journal of Emergency Medicine, In Press.

Increase of D3 Dopamine Receptors in Human Cocaine Fatalities

Dr. Mash has also recently reported a 1 to 3 fold increase in the number of D3 receptor binding sites over particular sectors of the striatum and substantia nigra in cocaine overdose victims compared to age-matched and drug-free controls. This receptor has been shown to play a pivotal role in the reinforcing effects of cocaine in, for example, self-administering but not naive, rhesus monkeys. Since this receptor is such an integral part of the brain's reward circuitry in chronic cocaine abusers, it may be a potential site for therapeutic intervention. Journal of Neuroscience, In Press.

Treatment Effects of Acupuncture for Cocaine Abuse

Dr. Milton Bullock and colleagues at the Hennepin County Medical Center in Minneapolis conducted two linked studies to evaluate the potential usefulness of auricular acupuncture (Ac) in the treatment of cocaine addiction. In Study I, residential clients were randomized to true Ac, sham Ac and conventional treatment without Ac. Sham acupuncture consisted of needles in ear points considered to be non-specific for the treatment of substance abuse. Subjects in the specific and non-specific acupuncture groups were blinded to their treatment assignment. In Study II, day treatment clients received conventional psychosocial treatment and were randomized to one of three dose levels of true Ac (28, 16, and 8 treatments). Sham points were not used in Study II. Data were collected from research assistants blinded to the subjects' treatment assignment. Multivariate analyses were performed both to determine outcomes related to placebo and sham treatment factors and to the various Ac conditions. Outcomes examined included cocaine use and craving, treatment effect sizes, treatment attrition rates and health, psychological and social status. The results of this study indicate that Ac did not provide any significant therapeutic benefit for any of the parameters tested over the improvement obtained by conventional psychosocial therapy.

Marijuana Use and Treatment Outcome in Cocaine-Dependent Patients

Dr. Budney and associates at the University of Vermont assessed marijuana use in 186 persons seeking cocaine dependence treatment. Comparisons were made between clients who did and did not report using marijuana, and between marijuana users who did and did not meet diagnostic criteria for marijuana dependence. A high rate of current marijuana use (59%) was observed at intake and the majority of the marijuana users (74%) used marijuana at some point during treatment. Marijuana use at intake was associated with increased psychosocial impairment and substance-use severity. However, no significant adverse relations were observed between marijuana use and any of the treatment outcome measures. That is, regular marijuana use did not interfere with cocaine abstinence during or following treatment. These findings challenge the common assertion that drug-dependent patients must simultaneously cease use of all drugs of abuse to succeed in treatment. Alternative treatment strategies for addressing polydrug use warrant consideration. Budney, A.J., Higgins, S.T., and Wong, C.J. Experimental and Clinical Psychopharmacology, In Press.

Matching Patients to Smoking Treatments

Relatively little is known about individual variation in withdrawal, or the determinants of such variation. Dr. Baker and colleagues at the University of Wisconsin reported findings showing that the course of smoking withdrawal symptoms varies greatly across smokers. Results from two studies reveal that 35-50% of smokers in cessation programs experience withdrawal that follows an "atypical" course over the first 2 months after a quit attempt. Dynamic cluster analysis revealed two clusters of subjects that experienced either a late exacerbation of withdrawal, or a prolonged maintenance of withdrawal symptoms. Women were more likely than men to belong to an atypical cluster, and membership in such a cluster was associated with a higher risk of relapse. This research may identify an important individual difference that predicts relapse vulnerability and may also reveal an important target for future treatments. Piasecki, T.M., Fiore, M.C., Baker, T.B. Profiles in Discouragement: Two studies of Variability in the Time Course of Smoking Withdrawal Symptoms, Submitted to Journal of Abnormal Psychology.

Economic Evaluation of Drug Abuse Treatment Programs

Dr. Michael T. French at the Community-based, Health Services Research Center has published an important review article for the drug abuse treatment field. This study presents a simplified economic evaluation methodology that can be followed by program staff and researchers. The evaluation methodology includes aspects of cost-and-outcome analysis, cost-effectiveness analysis, and benefit-cost analysis. Methods and findings from most of the major economic evaluation studies of drug and alcoholism treatment are discussed. Guidelines for conducting future economic evaluations are presented along with suggestions for how the results can be used for policy purposes and program planning. French, M. Economic Evaluation of Drug Abuse Treatment Programs: Methodology and Findings. Am J Drug Alcohol Abuse, 21: pp. 111-135, 1995. Relatively little is known about individual variation in withdrawal, or the determinants of such variation. Dr. Baker and colleagues at the University of Wisconsin reported findings showing that the course of smoking withdrawal symptoms varies greatly across smokers. Results from two studies reveal that 35-50% of smokers in cessation programs experience withdrawal that follows an "atypical" course over the first 2 months after a quit attempt. Dynamic cluster analysis revealed two clusters of subjects that experienced either a late exacerbation of withdrawal, or a prolonged maintenance of withdrawal symptoms. Women were more

likely than men to belong to an atypical cluster, and membership in such a cluster was associated with a higher risk of relapse. This research may identify an important individual difference that predicts relapse vulnerability and may also reveal an important target for future treatments. Piasecki, T.M., Fiore, M.C., Baker, T.B. Profiles in Discouragement: Two studies of Variability in the Time Course of Smoking Withdrawal Symptoms, Submitted to Journal of Abnormal Psychology.

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Methadone Dosing Practices

An important finding from a long-term study by Thomas D'Aunno concerns methadone dosing practices. Preliminary results, which have not yet been published, indicate that average methadone dose levels have improved in comparison to data from 1988 and 1990. The average dose increased from 46 mg/day in 1990 to 59 mg/day in 1995, and the upper dose limit increased from 82 mg/day in 1990 to 94 mg/day in 1995. Consistent with earlier findings (D'Aunno and Vaughn, 1992), treatment programs more likely to have lower dose levels and shorter times in treatment treat higher percentages of clients who are unemployed, African American, young, and male. Units staffed with more physicians are likely to have higher dose levels.

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National Institute on Drug Abuse

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

September, 1996

Research Findings

AIDS Research

Maternal Drug Use and Mother-to-Infant HIV Transmission

Multivariate analyses in a recent report from the Women and Infants Transmission Study (WITS) indicate an almost three fold increase (Odds Ratio 2.77) in the risk of mother-to-infant HIV transmission associated with prenatal drug use (i.e., a measure combining use of cocaine, heroin/opiates, methadone, and/or injecting drug use), for women with duration of membrane rupture greater than 4 hours. The increased risk observed in this subsample was greater than that seen in univariate analysis for the total sample of 530 HIV-infected women and their infants (Odds Ratio 1.89). These results not only document a prenatal drug use-perinatal transmission relationship, but also provide a basis for further hypotheses as to the timing (intrapartum, intrauterine) and mechanisms of transmission. WITS is an ongoing study of HIV-infected pregnant women and their infants conducted at pediatric and obstetric settings in Illinois, Massachusetts, New York, Puerto Rico, and Texas. NIDA collaborates with the National Institute of Allergy and Infectious Diseases and the National Institute of Child Health and Human Development in supporting WITS. Rodriguez, E.M., et al., Association of Maternal Drug Use During Pregnancy with Maternal HIV Culture Positivity and Perinatal HIV Transmission. AIDS; 10: pp. 273-282, 1996.

Mycobacterial Disease in a Cohort of Active Injection Drug Users

A cohort study of trends and risk factors for mycobacterial disease (M. tuberculosis, M. avium complex (MAC) and other atypical mycobacteria) and the effect of expanded access to isoniazid prophylaxis on tuberculosis (TB) incidence among active injection drug users found that HIV infection is the strongest risk factor for TB, M. avium complex and other mycobacterial disease (relative risk 3.8, 17.2, and 6.9 respectively). After institution of directly observed therapy (DOT), TB incidence fell from a peak of 6 cases/1000 person years in 1991 to one case in 1992 and no cases through 1994. During this time, the number of PPD positive patients who received DOT tripled, indicative of the effectiveness of this mode of therapy delivery. During this same period, however, the incidence of MAC increased significantly, reflecting the increasing disease burden among HIV-infected IDUs with progressive immunosuppression. Other atypical mycobacteria were also observed to increase among HIV-infected IDUs over the same time period. Graham N, Galai N, Nelson K, et al., Arch Int Med, 156: pp. 889-894, 1996.

Successful Tuberculosis Screening at a Syringe Exchange

A study of tuberculosis (TB) screening at a syringe exchange found a high success rate of consent and return rates

for skin test (PPD) reading and follow-up. TB screening was conducted during syringe exchange sessions, at which PPD and anergy testing, TB education, and HIV testing and counseling were offered. Of 493 exchange participants approached, 96.5% consented to TB screening. Of these, 91.5% returned for PPD reading and 78% have completed follow-up TB screening, including chest radiographs if indicated. Of those who consented to screening, 39% were homeless or unstably housed, 35% had no health insurance, and 60% were not in drug treatment. Data indicate that participating IDUs were aware of their TB risk, frequently confused TB infection with active TB, and were receptive to availability of TB services at a syringe exchange. More than 60% reported using the syringe exchange two or more times per week and 52% reported using the exchange for six months or more, suggesting that the population of IDUS at this syringe exchange may be sufficiently stable to allow administration of twice weekly directly observed therapy for those identified with TB infection. Perlman D., Perkins M.P., Solomon N. et al., American Journal of Public Health, In Press.

Transmission Behaviors and Self-Protective Health Acts Among HIV Youth

The level and consistency of HIV related sexual and substance use risk acts, health status and medical adherence were examined among 102 HIV+ youths aged 14 to 23. Current risk behaviors were assessed twice over two 3-month periods. During these periods almost a third had been sexually abstinent. Among youths who were currently sexually active, most had multiple sexual partners (M=4). Almost half used condoms consistently with 72 percent of encounters being protected by condoms. Use of alcohol (63%), marijuana (41%), hard drugs (36%) and injecting drugs (12%) was substantial and remained consistent over 3 months. Youths were relatively healthy. Medical adherence rates for appointments was 66 percent over the 3 months. The data suggest the need for more intensive interventions that must be consistently implemented over time as youths encounter new challenges associated with their disease status. Rotheram-Borus, J.J., Murphy, D.A., Coleman, C.L., et al. Risk Acts, Health Care, and Medical Adherence Among HIV+ Youths in Care Over Time. AIDS and Behavior. In Press.

Reductions in Needle Sharing

In an experimental study of the effects of a risk reduction intervention, researchers found that HIV-negative participants were significantly less likely (on the order of three times or more) to report needle sharing 18 months post-intervention than drug users who did not participate in the intervention. No significant differences were obtained for the HIV positive drug users. Latkin, C.A., Mandell, W., Vlahov, D., et al. "The Long-Term Outcome of a Personal Network-Oriented HIV Prevention Intervention for Injection Drug Users: The SAFE Study." American Journal of Community Psychology, 24,3, pp. 341-364, 1996.

Barriers to Condom Use and Needle Cleaning Among Impoverished Women

Sexual behaviors and drug use factors that inhibit condom use and needle cleaning were assessed among 378 homeless African-American and Latino women. The most highly rated barriers to condom use with partners included believing the partner did not have AIDS (69%), lack of skills in using condoms (52%), inability to get condoms (52%), lack of skills in negotiating condom use with partners (49%), personal dislike of condoms (47%) and discomfort in discussing condoms (46%). African-American women were more likely than Latino women to report barriers related to lack of skills in using condoms, inability to get condoms, discomfort and lack of skills in discussing condoms with partners, not thinking about condoms when high, a belief that their partner did not have AIDS, and a belief that they could not transmit HIV to their partners. On the other hand, Latino women, as compared with African American women, were more likely to report partner's dislike of condoms. This barrier was found among almost three-quarters of the less acculturated Latinos. The most pervasive barrier to needle cleaning among women who shared needles was not having their own needle (62%). This was closely followed by a need to hide needles (60%), being high and not interested in cleaning (59%), and not having disinfectant available (57%). Nyamathi, A., Lewis, C., Leake, B., Haskerud, J., Bennett, C. Barriers to Condom Use and Needle Cleaning Among Impoverished Minority Female Injection Drug Users and Partners of Injection Drug Users. Public Health Reports, 110, pp. 166-172, 1995.

Relationship Characteristics Influence Both Syringe-Sharing and Consistent Condom Use

In a study of 767 street-recruited drug injectors, this study examined how social relationships and perceived peer group culture are related to consistent condom use and receptive syringe sharing. Whether IDUs used condoms consistently or not was found to be relationship specific rather than an individual characteristic; i.e., IDUs used condoms consistently with one partner but not necessarily with another. Independent significant predictors of consistent use of condoms were relationship characteristics, peer norms, personal and partner characteristics, and seropositivity of the IDU whose partner is a non-IDU. Receptive syringe sharing was also found to be relationship-specific, predicted by social characteristics of the drug use network, peer norms, and individual risk behaviors (e.g., injecting speedball). Since sexual and injecting events which pose a risk of HIV transmission occur between two or more people in a particular context, prevention projects should focus on promoting relationship-specific norms about safer sexual practices and injecting behaviors rather than on individual risk characteristics. Friedman, S.R., Neaigus, A. Perlis, T., Jose, B., et al. Personal, Relationship-Specific, and Event-Specific Influences on Risk Behaviors by Drug Injectors. Seisida, 7 (4), pp. 184-186, April 1996.

Syringe Sharing Combined with High-Risk Personal Networks Increases HIV Infection Risks in New IDUs

This study explored the question of whether "new" IDUs who both shared syringes and had personal risk networks that included high-risk injectors were any more likely than other new IDUs to be infected with HIV. A cross-sectional study of 174 IDUs in NYC who had injected for no more than six years were recruited and interviewed about their risk behaviors. They were also tested for HIV serostatus. Compared to new IDUs who did not have these combined risk factors, those who shared syringes within high-risk personal networks were significantly more likely to be HIV positive (40% were HIV positive compared to 14% for others). The interaction of syringe sharing and having a personal risk network member who injected more than once a day was found to be independently and significantly associated with being HIV seropositive, in addition to Latino race/ethnicity and exchanging sex for money or drugs. These findings suggest that interventions to reduce the spread of HIV among new IDUs should focus on their risk networks as well as their risk behaviors. Neaigus, A., Friedman, S.R., Jose, B., Goldstein, M.F., et al. High-Risk Personal Networks and Syringe Sharing as Risk Factors for HIV Infection Among New Drug Injectors. Journal of Acquired Immunodeficiency Syndrome, 11, pp. 499-509, 1996.

Four-Year Study Finds Declines in HIV Seroincidence Among IDUs in Chicago

Six waves of survey and serologic data were analyzed for 641 HIV seronegative not-in-treatment IDUs participating in the Chicago Community Outreach Intervention Project (COIP). One of the first NIDA-funded National AIDS Demonstration Research (NADR) projects, the Chicago COIP used a street-based outreach intervention which was guided by the Indigenous Leader Outreach Model, in which ex-addicts deliver HIV-prevention services targeting IDU social networks in community settings. The cumulative percent lost to the study over the four year period was 32 (208 IDUs); the cumulative percent seroconversion was 13 (83 IDUs); and the number of IDUs at the end of the study who remained seronegative was 308. The observed incidence of HIV infection in the sample decreased from 8.4 to 2.4 per 100 person-years; the prevalence of drug use risk behaviors decreased from 100 to 14 percent; and sexual risk behaviors decreased, but less dramatically, from 71 to 45 percent. Seroconversion was significantly correlated with injection risk behaviors, but not with sexual risk behaviors. Wiebel, W.W., Jimenez, A., Johnson, W., et al. Risk Behavior and HIV Seroincidence Among Out-of-Treatment Injection Drug Users: A Four Year Prospective Study. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, 12, pp. 282-289, 1996.

Sharing of Drug Preparation Paraphernalia is More Common than Sharing of Needles/Syringes

Researchers undertook observational studies in Miami to catalogue risky injection practices by IDUs beyond the direct sharing of needles/syringes. They also examined epidemiologic data from 19 sites participating in NIDA's Cooperative Agreement for AIDS Community-Based Outreach Intervention Research Program. Of 12,323 IDUs, 41 percent used needles/syringes previously used by another, 49 percent shared cookers/cottons/ rinse water, and 32 percent shared both used syringes and drug preparation paraphernalia in the 30 days before the interview. Fewer than 30 percent engaged in none of these high risk behaviors. The authors discuss the implications of these findings on the potential transmission of HIV and in terms of the challenges they pose for HIV prevention. McCoy, C.B., Metsch, L.R., Chitwood, A.D., Shapshak, P., et al. HIV Transmission Potential Through Person-to-Person Blood Transfer During Drug Preparation and Injection: A New Challenge for HIV Prevention. Journal of Acquired Immune Deficiency

Syndrome and Human Retrovirology, In Press.

Drug Injecting Behaviors May Facilitate HIV Transmission Even When Syringes Are Not Shared

Researchers in Denver, Colorado assessed the prevalence of injection-related behaviors other than direct sharing of syringes among 585 IDUs. The IDUs were classified into three groups: those who directly and indirectly shared syringes, those who indirectly shared only (i.e., by sharing water to mix drugs or rinse syringes, by sharing the cookers and spoons used to dissolve the drug before filling the syringe, by sharing the drug solution itself, and by sharing cottons to filter adulterants from the solution at the time of injection), and those who did not share either directly or indirectly. The researchers found that IDUs who injected heroin or speedballs were less safe in their injection behaviors than those who did not. In addition, while indirect sharing behaviors were twice as prevalent as direct sharing of syringes, many IDUs do not recognize the potential link of their behaviors to HIV transmission. Koester, S., Booth, R.E., and Zhang, Y. The Prevalence of Additional Injection-Related HIV Risk Behaviors among Injection Drug Users. Journal of Acquired Immunodeficiency Syndromes and Human Retrovirology, 12 (2), pp. 202-207, 1996.

Evaluating the Effect of Needle Exchange on the Spread of HIV and Other Viral Infections

Needle testing and syringe tracking methods have demonstrated that the New Haven needle exchange program (NEP) effectively reduces the spread of HIV by as much as one-third. NIDA grantees in New Haven extended and elaborated these methods to hepatitis B (HBV) and hepatitis C (HCV). The investigators used polymerase chain reaction (PCR) to test returned (used) syringes at the NEP for HBV DNA and HCV RNA, and the EIA method to test for antibodies to each. Both methods were effective in detecting either hepatitis viruses or antibodies in used syringes. The researchers conclude that syringe testing for hepatitis can inform studies of the efficacy of NEPs in reducing the transmission of syringe-born infections. Because they found a significant decline in the percentage of used needles containing hepatitis B virus, they also conclude that, in addition to their effects on the spread of HIV, NEPs can slow the spread of HBV transmission. Heimer, R., Khoshnood, K., Jariwala-Freeman, et al. Hepatitis in Used Syringes: The Limits of Sensitivity of Techniques to Detect Hepatitis B Virus (HBV) DNA, Hepatitis C Virus (HCV) RNA, and Antibodies to HBV Core and HCV Antigens. Journal of Infectious Diseases, 173, pp. 997-1000, 1996.

Drug Use Patterns and Attitudes toward Intervention in Reducing the Transmission of HIV

In Miami, Florida, where Needle Exchange Programs (NEPs) are illegal, other strategies are necessary to reduce the spread of HIV among IDUs. Researchers examined data from studies of IDUs in Miami and other cities and report that IDUs inject frequently, averaging more than 1,000 injections per year, per person. While almost all IDUs feel that it is important to clean needles and to use a needle only one time, many do not take these precautions. In addition, the authors describe how the context of injection is important for understanding HIV risks. Drug use patterns, IDU attitudes toward interventions, and the cultural contexts in which risky behaviors occur each affect the potential for reducing the transmission of HIV and must be considered in the planning of HIV risk reduction interventions. McCoy, C.B., Metsch, L.R., Page, J.B., McBride, D.C., et al. Injection Drug Users Practices and Attitudes toward Intervention and Potential for Reducing the Transmission of HIV. Medical Anthropology, In Press.

Correlates of Emotional Distress Among HIV Youths

The level of emotional distress and the impact of stress and personal resources on distress were examined among 149 HIV+ youths ages 14-23. These youths (who were relatively healthy) reported levels of emotional distress and self-esteem similar to uninfected adolescents. Positive coping styles were more common than negative coping styles among youths living with HIV. Social support from parents, friends, and romantic partners was high, but these support persons often engaged in sexual and substance use risk acts. Controlling for youths' physical health status, increased emotional distress was associated with significantly lower self-esteem, higher stress, and negative coping styles. Social support did not mediate emotional distress among HIV+ youths. Rotheram-Borus, J.J., Murphy, D., Reid, H., et al., Correlates of Emotional Distress Among HIV Youths: Health Status, Stress, and Personal Resources. Annals of Behavioral Medicine, 18(1), pp. 16-23, 1996.

Psychosocial Predictors of AIDS Risk Behavior

Baseline assessments of personal and social resources, threat appraisal processes, coping styles, and barriers to risk reduction as predictors of sexual and drug use behaviors were evaluated among a sample of 714 African American and 691 Latino homeless women. Based on theoretical perspectives of the Comprehensive Health Seeking and Coping Paradigm and Health Belief Models, causal modeling was conducted. Findings revealed active coping was associated with fewer sexual AIDS risk behaviors for African-American and Latino women and less drug use behavior among African American women. High threat appraisal and avoidant coping predicted drug use behavior in both groups. Self-esteem and social resources were inversely associated with emotional disturbance for both groups. Lower self-esteem predicted more barriers to condom use among Latinos. Implications of these findings point to important cultural differences that should guide educational and outreach efforts of practitioners and social scientists. Nyamathi, A., Stein, J., Brecht, M. Psychosocial Predictors of AIDS Risk Behavior and Drug Use Behavior in Homeless and Drug Addicted Women of Color. Health Psychology, 14, pp. 265-273, 1995.

Predictors of Maintained High-Risk Behaviors

Demographic, cognitive, psychosocial and behavioral factors associated with maintained high risk AIDS behaviors were assessed two to four weeks after completing an AIDS education program in a sample of 942 crack users and 767 women who had multiple partners. Maintainers of multiple sexual partners more often reported needle sharing and a sex partner who shot drugs. Maintainers of crack were more likely to be African-American, age 32 or older, and report having a sex partner who shot drugs. Further, women who maintained risky drug and sexual behaviors reported the least improvement in concerns, depression, affective coping, distress, appraisal of threat, self esteem, and social support. Implications of these findings point to the need for studies investigating the effectiveness of providing risk education within a comprehensive health promotion and resource supplementation program addressed to the couple as a unit. Nyamathi, A., Bennett, C., Leake, B. Predictors of Maintained High-Risk Behaviors Among Impoverished Women. Public Health Reports, 110, pp. 600-606, 1995.

Intervening with Adolescent Girls Living with HIV

Young women who are HIV seropositive have special needs for interventions to reduce the negative consequences of their infection for themselves, for their children, partners, and families. This chapter reviews the challenges posed by HIV to these young women and outlines intervention programs designed to reduce long-term negative social, behavioral, and mental health consequences of HIV. Rotheram Borus, M.J., Murphy, D.A., Miller, S., et.al. Intervening with Adolescent Girls Living with HIV. In A. O'Leary and L. S. Jermmott (Eds.), Women and AIDS: Coping and Care, Plenum Press, pp. 87-108, New York, 1996.

Network Membership Affects Individuals' Sex Risks

In a recent study of peer group influence and the social context of risk behaviors, researchers discovered that alcohol and crack use by drug network members was positively associated with reports of multiple sex partners and alcohol use by the index subjects. Similarly, the degree of crack use by network members was positively associated with the numbers of casual sex partners reported by index subjects. Latkin, C.A., Mandell, W., and Vlahov, D. The Relationship Between Risk Network Patterns of Crack Cocaine and Alcohol Consumption and HIV-Related Sexual Behaviors among Adult Injection Drug Users: A Prospective Study. Drug and Alcohol Dependence, In Press.

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National Institute on Drug Abuse

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September, 1996

Research Findings

Epidemiology, Etiology and Prevention Research

Executive Cognitive Functioning and Aggressive Behavior in Boys at High Risk for Substance Abuse

Deficiencies in executive cognitive functioning (ECF), defined as self regulation of goal-directed behavior, have been linked to antisocial personality disorder, substance use disorders, conduct disorder, attention deficit hyperactivity disorder, and other problems. To assess the relationship between ECF deficiencies and aggressive behavior and the interactive effects of ECF and family history of substance abuse, researchers at the Center for Education and Drug Abuse Research (CEDAR) collected multiple measures of executive cognitive functioning (ECF) and aggressive behavior from 291 10-12-year-old boys with and without a family history of substance abuse/dependence. Factor analysis of the ECF measures indicated loading on one factor. ECF was related to aggressive behavior even controlling for IQ and socio-economic status. Aggressive behavior also was related to the interaction of ECF and family history of substance abuse/dependence. These results suggest that programs to prevent and treat violent behavior in high risk groups should incorporate training in ECF's, including planning, attention, abstract reasoning, judgment, learning from experience, and cognitive self-monitoring. Giancola, P.R., Martin, C.S., Tarter, R.E., Pelham, W.E., and Moss, H.B. Executive Cognitive Functioning and Aggressive Behavior in Preadolescent Boys at High Risk for Substance Abuse/Dependence. Journal of Studies on Alcohol, 57: pp. 352-359, 1996.

Cognitive Deficits Associated with Drug Use in Adolescents

Scheier and Botvin used longitudinal data to model the relationships between several cognitive skills and drug use over time. A small but significant association was found between drug use and weak cognitive and affective self-management strategies in early adolescence; this relationship became stronger over time. The exacerbation of these cognitive weaknesses with increased drug use may contribute to impaired social, emotional, and psychological growth in late adolescence. As the authors note in their comment on a study of cognitive effects of heavy marijuana use, deficits in cognitive efficacy may actually precede and perhaps predispose to problematic drug use. Weaknesses in cognitive skills, and learning disabilities, may be undetected factors which underlie recognized risk factors such as low self-esteem, academic failure and school dropout; as such, further longitudinal studies and modeling, and perhaps early identification and intervention, are needed. Scheier, L.M. and Botvin, G.J. Effects of Early Adolescent Drug Use on Cognitive Efficacy in Early-Late Adolescence: A Developmental Structural Model. Journal of Substance Abuse, 7(4), pp. 379-40, 1995. Scheier, L.M. and Botvin, G.J. Cognitive Effects of Marijuana (letter). JAMA, 275(20), p. 1547, 1996.

Familial Factors in Female Drug Abuse/Dependency

Extending their research with males, Cadoret et al. studied genetic and environmental factors leading to drug abuse and dependency in female adoptees. Antisocial personality in a biologic parent was strongly related to the development of conduct disorder in female offspring; conduct disorder was associated with aggressive behavior, and both conduct disorder and aggression were strongly predictive of later drug abuse/dependence in the adoptees. Drug abuse/dependence was in turn correlated significantly with alcohol abuse/dependence. Environmental factors in the adoptive home were also found to be significant. Disturbed adoptive parenting contributed significantly to the development of aggression in the adoptees, which in turn resulted in increased risk of drug abuse/dependence. This relationship was complicated, however, by a finding suggesting selective (non-random) placement; adoptees from a biologic background of antisocial personality were less likely to be placed in a disturbed adoptive home. The environmental factors were thought to act independently of the genetic, thus offering an important avenue for preventive intervention through reducing aggressiveness early in life. Cadoret, R.J., Yates, W.R., Troughton, E., Woodworth, G., and Stewart, M.A. An Adoption Study of Drug Abuse/Dependency in Females. Comprehensive Psychiatry, 37 (2), pp. 88-94, 1996.

Identifying Adolescents at Risk of Escalating Their Substance Use

To assess risk factors for escalation of substance use, researchers at Yeshiva University grouped adolescents according to substance use patterns over three assessments and then examined variables differentiating the groups. The four groups--nonusers, minimal experimenters, late starters, and escalators--were identified through cluster analysis of changes in cigarette, alcohol, and marijuana use among a cohort of 1,184 eighth and ninth graders enrolled in public schools in Westchester County, NY. By modeling group differences based on variables from stress-coping theory, problem behavior theory, and peer-association theory, the researchers identified first-assessment measures predictive of subsequent escalation in substance use. Compared to nonusers and minimal experimenters, late starters and escalators had higher life stress, lower parental support, lower academic competence, more deviant attitudes, and more nonadaptive modes of coping; they also were higher in parental and peer substance use. Escalators scored lower on behavioral competence, positive control, and positive esteem. In contrast to the often cited study by Shedler and Block (1990), this study found that substance use experimenters, compared to nonusers, had higher stress, more maladaptive coping, more deviance-prone attitudes, lower levels of parental support, and lower levels of self control. Findings support the idea that some people enter adolescence with less parental support and more life stress, have less adaptive patterns of coping and competence, and tend to gravitate to groups of peer substance users. To the extent that these factors prevail and are not offset, these adolescents become involved in a network of active users. The experience-regulating function of substance use becomes more salient and they are primed to continue substance use at increasing rates. Wills, T.A., McNamara, G., Vaccaro, D. and Hirky, A.E. Escalated Substance Use: A Longitudinal Grouping Analysis from Early to Middle Adolescence. Journal of Abnormal Psychology, 105(2), pp. 166-180, 1996.

Effectiveness of School-Based Drug Prevention Programs

Effectiveness of different types of drug prevention was examined in a meta-analysis of 120 school-based programs in grades 5 through 12 that evaluated success on self-reported drug use measures. Hypothesis tests using Weighted Least Squares regressions were conducted on an a priori classification scheme that was based on program content and its delivery. Two major types of programs were identified: Interactive and Non-Interactive. Six other factors related to program effectiveness (sample size, targeted drug, type of control group, special populations, type of leader, and attrition) were included as covariates. The Interactive programs achieved significant changes on knowledge, attitudes and drug use, whereas the Non-Interactive programs affected only knowledge. The larger Interactive programs were less effective although still significantly superior to the Non-Interactive programs which suggests implementation failures. The clinically significant superiority of Interactive programs was observed for all adolescents, including various minority populations, and was equal for tobacco, alcohol, marijuana and illicit drugs. Tobler, N.S. and Stratton, H. Effectiveness of School-Based Drug Prevention Programs: A Meta-Analysis of the Research. The Journal of Primary Prevention, In Press.

Fatal Consequences of Cocaine and Opiate Use: Accidental Fatal Drug Overdoses in New York City: 1990-1992

Cocaine, often with opiates (predominantly heroin) and ethanol, caused almost 75% of accidental fatal drug overdoses in New York City from 1990 through 1992. This study assessed 1,986 cases in that period using data collected by the Office of the Chief Medical Examiner. This study excluded intentional (suicidal) fatal drug overdoses. Cocaine with opiates caused 752 (37.9%) deaths. Cocaine without opiates caused 629 (31.7%) deaths while opiates without cocaine caused 503 (25.3%) deaths. Drugs other than cocaine or opiates, predominantly benzodiazepines and antidepressants, caused 102 (5.1%) deaths. The highest cocaine overdose rates were found among African-American and Latino males. Rates of opiate overdose without cocaine did not differ in regard to race/ethnicity except for low rates among Asians. Males had higher overdose rates than women for all classes of drugs. The highest rates for cocaine and/or opiates were found among victims 35-44 years of age. The rates of overdose from cocaine and opiates increased from 1990-1992. A marked increase of cocaine overdoses in 1991 was followed by a slight decrease in 1992. The rates of overdoses from drugs other than cocaine or opiates showed no increase over time. Cocaine is the leading cause of accidental drug overdoses, unlike in the early 1980's when opiates prevailed as a cause of death. African-American and Latino males may be particularly susceptible to cocaine overdoses because of their exposure to crack in poor neighborhoods. Tardiff, K., Marzuk, P.M., Leon, A.C., Hirsch, C.S., Stajic, M., Portera, L., Hartwell, N., Accidental Fatal Drug Overdoses in New York City: 1990-1992. The American Journal of Drug and Alcohol Abuse, 22 (3), 1996.

Personality-Environment Constellations and Alcohol Use: A Process-Oriented Study of Intraindividual Change During Adolescence

Within an interactionist and process-oriented perspective, the salience of documented risk and protective factors in contributing to intraindividual changes in alcohol use behaviors and negative consequences of use during adolescence was tested. Participants (N=870) were from a longitudinal study of normal adolescent development, they were 12 or 15 years old at the first test and were retested twice at 3-year intervals (92% longitudinal retest rate). Person-environment constellations comprising high impulsivity, disinhibition, and deviant peer group associations, and to a lesser extent, low parental control, most strongly influenced high-risk developmental trajectories of use intensity and problems. Personality and environmental risk factors acted as mutual catalysts of alcohol use behaviors and consequences; that is, their co-occurrence increased the likelihood of sustained movement along problematic developmental trajectories. Pandina, R. Personality-Environment Constellations and Alcohol Use: A Process-Oriented Study of Intraindividual Change During Adolescence. Psychology of Addictive Behaviors, 9 (1), pp. 23-35, 1995.

High School Students Who Use Crack and Other Drugs

The distinguishing characteristics of adolescents who have reached different stages of drug use, in particular the highest stage represented by crack, were studied in a representative sample of students in grades 7 to 12 from 53 New York State schools (N = 7,611). Students were classified in six mutually exclusive, cumulative categories of drug use: nonusers; alcohol and/or cigarette users only; marijuana users only; users of illicit drugs other than marijuana but neither cocaine nor crack; cocaine but not crack users; and crack users. Students who use illicit drugs show deficits in school performance, quality of family relationships and health, and increased psychological symptoms. Compared with nonusers, illicit drug users are more delinquent and more actively involved with their peers and live in social environments in which the perceived use of drugs by parents and other adolescents is more extensive. Crack users exhibit the lowest level of psychosocial functioning of any drug-using group. Delinquency and extent of perceived peer drug use consistently increase with each higher stage of use. There are stage-specific characteristics and common characteristics (delinquent participation, peer drug use) throughout the developmental sequence of drug use. Despite declines over the last two decades in the prevalence of the use of different drugs, young people who use drugs display characteristics over historical time similar to those of young drug users 20 years ago. Kandel, D.B., Davies, M. High School Students Who Use Crack and Other Drugs. Archives of General Psychiatry, 53, pp. 71-80, 1996.

Pathological Gambling Among Methadone Patients

Participation in various forms of gambling activities was assessed to establish the prevalence of pathological gambling in a sample of patients (N=117) enrolled in a large methadone maintenance treatment program in New York City.

Respondents were interviewed with a protocol, that incorporates the South Oaks Gambling Screen, a validated, reliable instrument that offers a convenient means for screening populations of drug misusers, as well as general populations, for pathological gambling. Gambling was a common part of the regular activities of many methadone patients, Fifteen percent of a sample of methadone patients had some problem with gambling, and an additional 16% were probable pathological gamblers. Heroin and alcohol were the substances most likely to be used by the pathological gamblers-just prior to or while gambling; marijuana and cocaine were the substances next most likely to be used when gambling. About one-quarter had engaged in some type of crime or hustling activity to pay gambling debts or get money to be able to gamble; all of these individuals participated in multiple gambling-related criminal/hustling activities. These data suggest that a significant proportion of heroin addicts enrolled in methadone treatment programs may be pathological gamblers. For these individuals, pathological gambling may accompany and reinforce continued drug dependence, interfere with treatment engagement, and be a factor in relapse, yet it is likely that the vast majority of methadone patients who are pathological gamblers have not received and are not receiving treatment for their gambling pathology. Few pathological gamblers had ever asked someone for help with a gambling problem or had ever been to Gamblers Anonymous or a therapist for help with a gambling problem. Spunt, B.J., Lesieur, H., Hunt, D., Cahill, I. Pathological Gambling Among Methadone Patients. International Journal of the Addictions, 30 (8), pp. 929-962, 1995.

Contributions of Mothers and Fathers to Cigarette Smoking in Adolescence

There is a significant dose-related association between maternal smoking and children's smoking, especially among daughters. This finding has been obtained in a study of similarity on cigarette smoking among mothers, fathers, and young adolescents (mean age = 12.6 years) in a sample of 201 triads in which each respondent was interviewed independently. Both maternal smoking and quality of parent-child interaction affect lifetime smoking by the child, but only maternal smoking affects current smoking. Their maternal role modeling effect is stronger for daughters than for sons and persists with the inclusion in the model of perceived smoking by the adolescent's close friends. The observed familial concordance on smoking between parent and child cannot disentangle environmental from genetic effects. Intervention and prevention practices targeted toward preventing or reducing cigarette smoking among children tend to target the child's life skills, knowledge, attitudes about smoking, and resistance skills toward peer pressure. The investigation points to another important and neglected focus of intervention, namely, the smoking behavior of the youth's parents in early adolescence. Kandel, D.B., Wu, P. The Contributions of Mothers and Fathers to the Intergenerational Transmission of Cigarette Smoking in Adolescence. Journal of Research on Adolescence, 52, pp. 225-252, 1995.

Cigarette Use Among Migrant and Nonmigrant Mexican American Youth: A Socialization Latent-Variable Model

A self-report survey of cigarette use among 1,373 Mexican American 10th and 12th graders from migrant and non-migrant families in Southern California shows that children of migrant families use tobacco at about the same level as children of non-migrants. The strongest risk factor for tobacco use for Mexican American youth is having peers who use tobacco. Family tobacco use increases risk except among female children of migrant workers. Protective factors include having a family that shows a high level of caring and that closely monitors behavior, having good school adjustment and having a strong religious identification. Mexican American children who experiment with tobacco are likely to have already tried tobacco prior to the 11th grade. Rates for daily use continue to increase so tobacco addiction continues to grow through the 11th and 12th grades. Swaim, R.C., Oetting, E.R., Casas, M.J. Cigarette Use Among Migrant and Nonmigrant Mexican American Youth: A Socialization Latent Variable Model. Health Psychology, 15(4), pp. 269-281, 1996.

Children with Learning Disabilities in Need of Targeted School-Based Smoking Prevention Programs

NIDA prevention research grantees from the University of North Carolina conducted a study to assess whether children with learning disabilities should be included in school-based smoking prevention programs and whether the existing programs are appropriate for this special population. A sample was taken of 1,740 3rd and 5th grade children. Measures obtained included: initiation of smoking, peer pressure, level of self-esteem, and negative orientation towards school and each was significantly associated with smoking by all children; those with and without

learning disabilities. Current smoking prevention curricula should address issues relevant to children with learning disabilities; however, additional research is needed to identify the special needs of these children and determine the type of smoking prevention program most likely to be effective with them. Robertson, S.B. and Jackson, C. Initiation of Cigarette Smoking Among Children With and Without Learning Disabilities. Journal of Developmental and Behavioral Pediatrics, In Press.

Substance Involvement Among Juvenile Murders

Substance involvement among incarcerated juvenile offenders was evaluated. Patterns of substance involvement among juvenile offenders were compared with patterns found in older offenders. Irrespective of age group, close to one-third of all homicide perpetrators reported that they were affected by alcohol prior to the offense. In every age group, 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 in 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. Juvenile offenders were generally less substance involved than all but the oldest group of offenders. Almost all of the juveniles who were substance involved prior to the homicide attributed the homicide to the effects of those substances. Narrative accounts suggest that substances (almost always alcohol) escalated impulsive, spontaneous, violent, outbursts. Implications for the interpretation of self-reports about substance use provided by murderers were also discussed. Fendrich, M., et al. Substance Involvement Among Juvenile Murderers: Comparisons with Older Offenders Based on Interviews with Prison Inmates. The International Journal of the Addictions 30 (11), pp. 1363-1382, 1995.

Mechanisms of Noncompletion in Ethnographic Research on Drugs

Case files from two longitudinal ethnographic field studies of drug users were reviewed in order to examine mechanisms of noncompletion. Two general mechanisms, including investigator initiated termination and subject initiated withdrawal were explored. Subjects were terminated when patterns of incoherent or inconsistent responses were detected in interviews; subjects were also terminated when they stole from the field site or when they were jailed or hospitalized. The findings suggest that the initial phases of interviewing served as an important subject screening period for the researchers conducting the interviews. Most noncompletion in both studies fell under the category of subject initiated withdrawal. Analyses suggested that respondents who dropped out reported significantly less drug involvement and somewhat less extensive criminal involvement than those who completed the study. Women who dropped out were more likely to be married than women who completed the study. Men who dropped out were less likely to reside in shelters for the homeless than men who remained in the study. The studies' behavioral findings sharply contrast with findings from studies of attrition in conventional panel research on drug use. Implications for research on hidden populations were discussed. These findings suggest some important limitations in ethnographic research and underscore the importance of systematic descriptive accounts of noncompletion across a range of ethnographic studies. Fendrich, M., et al. Mechanisms of Noncompletion in Ethnographic Research on Drugs: Results from a Secondary Analysis. Journal of Drug Issues, 26 (1), pp. 23-44, 1996.

Pattern Reliability of Narcotics Addicts' Self-Reported Data

Pattern reliability, or the invariance of relationships among variables was investigated in this study. The consistency of theoretical constructs reflected by measures taken at two separate occasions can be tested using confirmatory factor analysis. Self-report data were obtained from 323 narcotics addicts in two face-to-face interviews conducted in 1974/75 and 1985/86. Through the testing of the invariance of measurement and structural models, pattern reliability was confirmed in one of the models developed. Explication of pattern reliability offers an alternative means of assessing validity of self-report data. Chih-Ping C., Yih-Ing H., & Anglin, M. D. Pattern Reliability of Narcotics Addicts' Self-Reported Data: A Confirmatory Assessment of Construct Validity and Consistency. The International Journal of the Addictions 31 (9), pp. 1189-1216, 1996.

A Three-Year Follow-Up of Drug Abuse Resistance Education (D.A.R.E.)

The longterm effectiveness of D.A.R.E. was assessed by contrasting 561 9th grade students who received the program in the 6th grade with 366 others who had not received the program. A follow-up survey assessed differences in latent variables representing central D.A.R.E. concepts such as self-esteem, resistance to peer pressure, delay of experimentation with drugs, and drug use. No significant differences were found between D.A.R.E. participants and controls. However, in general, students in both the D.A.R.E. group and the control group were doing well in terms of avoiding drugs--an encouraging outcome. The researchers concluded that D.A.R.E. could be exerting an influence in a more general way. At the time of the survey, over five-sixths of the students in the junior high schools had received the program: half of the ninth graders and all of the seventh and eighth graders. The only students in the junior high schools who had not received the program were the ninth graders in the control group. Due to diffusion, the contextual effect of this massive effort to treat every student with D.A.R.E. (plus the effects of other programs of drug education) may have created an anti-drug climate in the junior high schools. Over time, students in the control group may have caught up to those in the D.A.R.E. group. While mitigation of disadvantages does make sense, so does an interpretation that the effects wear off. It is consistent with earlier findings on maturation into the early teens in which maturation effects operate in a direction opposite to the tenets of D.A.R.E. (Dukes et al., 1995). Dukes, R., Ullman, J.B., Stein, J.A. A Three-Year Follow-Up of Drug Abuse Resistance Education (D.A.R.E.), Evaluation Review, 20, pp. 49-66, 1996.

Statistical Model for Detecting Loci for Drug Abuse and Dependence Using Affected Relative Pairs in a Genome Search

Family, twin, and adoption studies of substance abuse and dependency have demonstrated a significant role of genetic determinants. The current paper develops a general statistical model and test that can be used with traditional molecular techniques such as markers as well as the emerging GMS procedures. The model and test are designed to handle realistically complex genetic etiology and any mixture of relative types such as siblings, cousins, and grandparent-grandchildren, and also in the presence of phenocopies (i.e., misdiagnosis). Using affected pairs, the exact test controls for the elevated probability of false rejection of the null hypothesis when the entire genome is searched. This integrative model is the basis of a new research proposal written by the authors to search the human genome for the susceptibility genes underlying opioid dependency. Smalley, S.L., Woodward, J.A., Palmer, C.G.S. A General Statistical Model for Detecting Complex Trait Loci Using Affected Relative Pairs in a Genome Search. American Journal of Human Genetics, 58, pp. 844-860, 1996.

Inconsistencies in Lifetime Cocaine and Marijuana Use Reports Inconsistencies in responses to questions about lifetime cocaine and marijuana use asked of nearly 10,000 respondents from the United States in the National Longitudinal Survey of Youth in 1984 and 1988 were evaluated. Analyses showed that 14% of all responses on cocaine use and 17% of all responses on marijuana use were inconsistent in some way. 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 use disclosure. For both substances, lower level users were more likely to be inconsistent in their reports of drug use. Alternative methods for handling inconsistencies affected estimates of incidence and prevalence. Inconsistencies also varied according to respondent race/ethnicity. Implications of these findings for program evaluation were discussed. Fendrich, M. and Mackesy-Amiti M.E. Inconsistencies in Lifetime Cocaine and Marijuana Use Reports: Impact on Prevalence and Incidence. Addiction, 90, pp. 111-118, 1995.

Initiation and Maintenance of Tobacco Smoking: Changing Personality Correlates in Adolescence and Young Adulthood

Youthful smokers have been described as extroverted and peer-involved, whereas older smokers are often characterized as depressed and withdrawn. Recognizing this contradiction in personality correlates of smokers, the researchers examined cross-sectional and prospective associations between smoking and personality and social constructs assessed every four years in a sample (N = 461) originally recruited in junior high school. At Time 1, smoking was positively related to good Social Relations, Extroversion, Friends' Cigarette Use, and Cheerfulness. At Times 2-4, smoking was positively related to Depression and Friends' Cigarette Use, negatively correlated with good Social Relations, and unrelated to Extroversion. Cigarette Use was stable over time, but least stable between Times 1 and 2. Findings suggested the instability of early social smoking with peers; those who persist may smoke for tension-reduction and self-medication. Extrapolating from a use/abuse distinction, the researchers suggested that more attention should be paid to the precursors and correlates of addiction (abuse) or maintenance of the tobacco habit rather than onset since youthful experimentation may not continue. In view of the changing dynamics over time

and early instability of cigarette smoking revealed in our analyses, an effective prevention program in junior high may be quite different from one that would be appropriate in senior high school. The results suggest that learning techniques for peer-resistance might be more applicable in the junior high setting, while teaching effective and positive stress-reduction and coping skills might be more useful for high school students. Stein, J.A., Newcomb, M.D., Bentler, P.M. Initiation and Maintenance of Tobacco Smoking: Changing Personality Correlates in Adolescence and Young Adulthood. Journal of Applied Social Psychology, 26, pp. 160-187, 1996.

Self-Generated Drug Outcomes in Continuation High School Students

The perceived outcomes of drug use were studied in a sample of high risk adolescents. Participants' self generated responses provided the actual words they used to describe drug outcomes as well as associative frequency norms valuable for future research. Outcomes were compared in terms of class of outcome (positive versus negative) and class of drug (alcohol, marijuana, cigarettes, cocaine, speed, and LSD). Although the studied drugs have divergent pharmacological effects, subjects self-generated some of the same outcomes (e.g., relaxation) across some of the drugs. In addition, outcomes self-generated as positive outcomes were very rarely also self-generated as negative outcomes. Regressions revealed that self-generated responses were not predicted by ethnicity, gender, or previous drug use. Many drug use outcomes appeared to be available in memory regardless of previous drug use or other characteristics. Memory availability (memory storage) does not necessarily imply memory accessibility (i.e., ease of retrieval). Other research has recently indicated that as drug use increases in frequency, positive outcomes of drug use become more strongly associated with drug use in memory, and thoughts about potential positive outcomes (e.g., relaxation) more readily trigger drug consistent thoughts and actions. Findings from the present study and other recent studies converge on the notion that memory associations regarding drug cues and outcomes may mediate drug use decisions, although memory availability (storage) of outcomes may not have any mediational or predictive effect. Taken together, these findings have implications for interventions because programs that merely increase the availability of knowledge or skills in memory (e.g., as indicated by typical tests of knowledge) are not likely to be optimally effective, whereas interventions that make program information highly accessible from memory in high-risk settings should show stronger effects. The findings across studies also suggest that interpretations and evaluations of the mediators of program effects should take into account manipulations of cognitive processes (e.g., memory access) that are likely to vary across program conditions rather than simply the program content that labels the condition (e.g., refusal assertion versus negative consequence information). Stacy, A.W., Galaif, E., Sussman, S., Dent, C.W. Self-Generated Drug Outcomes in Continuation High School Students. Psychology of Addictive Behaviors, 10, pp. 18-27, 1996.

Prevalence of Substance Abuse and Psychiatric Disorders are High Among Incarcerated Women

In-person interviews were conducted with a near census (N=805) of women felons entering prison in North Carolina between July 1991 and November 1992. Assessments were made for eight psychiatric disorders using the Composite International Diagnostic Interview as the primary assessment measure, and 25 percent of the women were reassessed for two of these disorders for purposes of validation. Results were then compared with data from the Epidemiologic Catchment Area (ECA) Study for the North Carolina site. The researchers found the most prevalent disorders to be alcohol and drug abuse and dependence. Rates for mood disorders, antisocial personality disorders, and lifetime exposures to traumatic events were also high. Rates of disorders were found to be greater among white women than among African Americans. The researchers conclude that women prisoners have major needs for both substance abuse and mental health treatment. Jordan, B. K., Schlenger, W.E., Fairbank, J.A., and Caddell, J.M. Prevalence of Psychiatric Disorders Among Incarcerated Women. Archives of General Psychiatry, 53, pp. 513-519, 1996.

Parental Modeling Major Factor in Childrens' Risk for Early Onset of Smoking

Research to examine the relationship between smoking and anti-smoking practices in terms of socialization variables was conducted. Among 3rd and 5th grade children, it was found that early onset of smoking increases with increase of exposure to parent smoking models, and it does not matter if parents are current or former smokers; quitting by parents does not eradicate the effects of modeling. Only when parents (whether current or former smokers) engaged in
anti-smoking socialization was the rate of smoking onset significantly reduced. Jackson, C. and Henriksen, L. Do As I

Say: Parent Smoking, Anti-Smoking Socialization, and Smoking Onset Among Children. Addictive Behaviors, In Press.

Children's Early Use of Tobacco and Alcohol is related to Weak Competence Development and Socialization

Researchers at the University of North Carolina conducted cross sectional surveys to measure tobacco and alcohol use, multiple indicators of child competence, parent behaviors and parent modeling of tobacco and alcohol use. Children's tobacco and alcohol use was strongly related to low scores on child competence, both self-report and teacher rated as well as with less effective parenting behaviors and parental use of these substances. Jackson. C., Henriksen, L., Dickinson, D. and Levine, D. Early Use of Alcohol and Tobacco: Relation to Child Competence and Parental Behavior, American Journal of Public Health, In Press.

Women Who Kill in Drug Market Situations

Open ended and semi-structured interviews were used in a study with 215 women sentenced to prison in New York State for homicide, of which 19 women killed in drug market situations. The study was to explore the ways in which changing drug markets may have influenced women's involvement in lethal violence. Through qualitative analysis of the narratives offered by these women to explain their involvement in the killing, evidence was found that supports the conclusion that women will use violence, as will men, to protect or augment an economic interest in a drug market, From further analysis, however, it was concluded that even in a clearly economic context in which women are able to acquire their own economic interest, some women will kill or participate in a killing in connection with their relationship to a male business or intimate partner. That is, women who kill in the economic context of a drug market may kill for economic reasons, but the specific circumstance of involvement in a drug market does not necessarily negate the significance of gender. Brownstein, H.H., Spunt, B.J., Crimmins, S.M., Langley, S. Women Who Kill In Drug Market Situations. Justice Quarterly, 12, pp. 473-498, 1995.

Expectancy in Mediational Models of Cocaine Use

Several theoretical explanations of how expectancies may influence cocaine use were studied. Hypotheses from these approaches use trait (sensation seeking and social conformity), cognitive (expectancy), and state-like (depression and loneliness) constructs to explain cocaine use and its problem consequences. Constructs from these different approaches were compared as predictors of cocaine use among a community sample of adults. Results revealed that general and specific components of an expectancy construct predicted cocaine use independently from all other constructs. The general component of this construct represented expectancies for a variety of drugs in addition to cocaine. The specific component represented expectancies about cocaine use only. The results regarding the effects of the general component can be interpreted in terms of recent memory models of generalization processes in addictive behavior, although assessment of memory processes is needed to fully validate this contention. Another important finding involved mediational effects of expectancy. These findings suggested that expectancies may mediate the effects of certain personality constructs on cocaine use and abuse. The results contrast and integrate cognitive approaches to the explanation of drug use and other behaviors with trait and state approaches to personality. They also suggest that some form of cognitive processing of expected outcomes of drug use mediate and predict drug use behaviors. However, the measurement of cognitive processing effects through expectancy assessment does not reveal the precise form that this processing takes. Additional research is needed to specify exactly how cognitive processes predict and mediate drug use decisions. Stacy, A.W., Newcomb, M.D., and Bentler, P.M. Expectancy in Mediational Models of Cocaine Use. Personality and Individual Differences, 19, pp. 655-668, 1995.

A Theoretical Framework for Designing Effective Tuberculosis Control Strategies.

Dr. Blower and colleagues describe a theoretical framework to determine treatment levels for tuberculosis eradication, to assess the effects of noneradicating control, and to examine the global goals for controlling tuberculosis by the World Health Organization. The authors assess the effects of suboptimal control programs on the evolution of multi-drug resistant tuberculosis and define a new evaluation criterion to show how control strategies can be improved. They demonstrate that their new theoretical framework -- based on the maximum acceptable

probability of treatment failure -- can be used to build tuberculosis transmission models for developing control strategies tailored to specific environments. In particular, treatment failure rates must be lower in developing countries than in developed countries. Blower, S.M., Small, P.M., and Hopewell, P.C. Control Strategies for Tuberculosis Epidemics: New Models for Old Problems. Science, July 1996.

Assessing and Tracking Family Histories of Alcoholism

This study sought to (1) determine the rates of family history of alcoholism among a community sample, using both specific questions and structured interviews, (2) document conversions from negative (FH-) to positive (FH+) alcoholism diagnoses among parents and grandparents of subjects, and (3) investigate the concordance between interview and questionnaire methods in assessing alcoholism in family members. Method: Information concerning alcoholism among relatives of a sample of 1,201 (620 female) probands was gathered longitudinally over a 13-year period, spanning adolescence into adulthood. At Times 1 through 3 of the study, information was gleaned from personal interviews with subjects, medical health forms and information from subjects' parents, which was used to determine a "best estimate diagnosis." At Time 4, the Family History Research Diagnostic Criteria (FH-RDC) interview was used. Results: The number of subjects having an alcoholic relative increased at each test time with the largest rise occurring at Time 4. Over 80% of subjects whose parent converted to FH+ at Time 4 had previously described that parent as a heavy or problem drinker. Conclusions: The higher than previously seen escalation in FH+ status occurring at Time 4 is speculated to be the result of one or more of the following: an actual increase in the number of relatives becoming alcoholic, a newfound awareness on the part of probands about alcohol-related problems, the fact that a global judgement or single behavior observation provides an inadequate indication of familial alcoholism, or that the FH-RDC may include a more global measure of "alcohol-related problems" or "problem drinking." Johnson , V. and Bennett, M.E. Assessing and Tracking Family Histories of Alcoholism. Journal of Studies of Alcohol, 56, pp. 654-660, 1995.

The Relationship Between Work-Specific and Generalized Stress and Alcohol and Marijuana Use Among Recent Entrants to the Labor Force

This study examined changes in alcohol and marijuana use and problems in relation to the transition into full-time work, and the effects of work-related and generalized stress among a group of recent entrants to the labor force. Data were obtained from a sample of males and females who were originally interviewed when they were eighteen years old and followed up twice more at three year intervals. The authors hypothesized that those who transit into and maintain a full-time job will not increase their level of consumption if they find the job to be the "right fit." The data indicated that when age, gender, and marital status were controlled, there were few significant effects of the transition to full-time work on use measure. Data from this study provide evidence of a stronger role for generalized stress over that of work-specific stress in predicting changes in drug use in young adulthood. Pandina, R. The Relationship Between Work-Specific and Generalized Stress and Alcohol and Marihuana Use Among Recent Entrants to the Labor Force. The Journal of Drug Issues, 25 (2), pp. 237 251, 1995.

Social Support Among Impoverished Women

Types of social support, their use and efficacy were assessed in a convenience sample of 3,021 homeless and drug addicted African American and Latino women. Type of support most commonly cited was someone who listens (78%) followed by someone who provides confidence (74%), advice (74%) and understanding (73%). Almost 30% of the women reported having at least one friend or neighbor with whom they could talk. However, only 12% could count on friends or neighbors to help in changing things. Only 20% had a husband or partner to confide in and receive emotional support from but their partners were less helpful when it came to explaining things or assisting with change. Professionals, such as counselors and social workers, were most helpful in facilitating change. Implications reveal that enabling factors and barriers to the use of support from professional agencies need to be explored with a view toward designing interventions that include strengthening effective social support in different populations of homeless women. Nyamathi, A., Bennett, C., Leake, B., Chen, S. Social Support Among Impoverished Women. Nursing Research, 44, pp. 376-378, 1995.

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National Institute on Drug Abuse

Director's Report to the National Advisory Council on Drug Abuse
September, 1996

Research Findings

Intramural Research

Functional Neuroimaging Techniques Provide a Useful Tool in the Evaluation of Remission Due to Peptide T AIDS Dementia Complex

AIDS Dementia Complex (ADC) is the most common presenting neurologic manifestation of human immunodeficiency virus (HIV)-1 infection. A PET study monitored the progress of ADC in a man who completed a 12-week treatment protocol with intranasal peptide T, an octapeptide that blocks the binding of gp120, the HIV envelop protein, to the cell surface antigen CD4. Data from this patient were compared with those from a control group. From the PET images, 34 of 35 brain regions with abnormally high metabolic rates, located in the temporal and parietal lobes, showed remission after peptide T treatment. These preliminary observations suggest that functional neuroimaging is a useful tool in evaluating the response to treatment in ADC patients. Villemagne, V.L., Phillips, R.F.L., Liu, X., Gilson, S.F., Dannals, R.F., Wong, D.F., Harris, P.F., Ruff, M., Pert, C., Bridge, P. and London, E.D. Peptide T and Glucose Metabolism in AIDS Dementia Complex. J. Nucl. Med. 37: pp. 1177-1180, 1996.

Role of Extracellular Dopamine in the Initiation and Long-term Expression of Behavioral Sensitization to Cocaine

Repeated intermittent administration of cocaine sensitizes animals to the locomotor-activating effects of this agent. The neurobiochemical basis of sensitization was characterized by measuring extracellular dopamine levels in the nucleus accumbens in rats after the cessation of repeated cocaine administration. Basal dopamine levels were elevated initially following the cessation of cocaine pretreatment and declined to reach control levels by Day 22. In contrast, the dopaminergic response to cocaine was blunted initially and increased thereafter. The behavioral response to cocaine was enhanced by cocaine pretreatment and followed a different temporal pattern than did dopaminergic activity following the cessation of repeated cocaine treatment. These data suggest that behavioral sensitization is mediated by different neurobiochemical events at different times following the cessation of cocaine pretreatment. Heidbreder, C.H., Thompson, A.C., and Shippenberg, T.C. Role of Extracellular Dopamine in the Initiation and Long-Term Expression of Behavioral Sensitization to Cocaine. J. Pharmacol. Exp. Ther. 278: pp. 490-502, 1996.

A Method for Imaging Nicotinic Acetylcholinergic Receptors in the Brain Using Radiolabeled Pyridyl-7-Azabicyclo [2.2.1] Heptanes

Although nicotinic acetylcholine receptors are major excitatory neurotransmitter receptors in brain, studies of these

receptors, by noninvasive external imaging, have been limited due to a need for an appropriate radiotracer. NIDA investigators have used epibatidine, an extract from frog skin, as the basis for design of radiotracers for noninvasive imaging of nAChRs using positron emission tomography and single assessments of nAChRs as a function of chronic drug administration and withdrawal, and may prove useful in diagnosis of neurodegenerative diseases. London, E.D. Kimes, A.S., Horti, A. Dannals, R.F., and Kassiou, M. A Method for Imaging Nicotinic Acetylcholinergic Receptors in the Brain Using Radiolabeled pyridyl-7- azabicyclo [2.2.1] heptanes. US Patent application Serial No. 08/642,636. Filed, May 3, 1996.

Drug Abuse Might be Better Approached as a Disorder of the Brain. In humans, chronic cocaine abuse is associated with CNS changes, including cerebrovascular events, EEG abnormalities, vasculitis, seizures, and decrements in neurobehavioral performance. The acute administration of cocaine is associated with psychotic episodes and paranoid states while withdrawal from the drug is often associated with depressed mood. The mechanistic basis of these behavioral states is not known. Given the structural and functional changes associated with cocaine use, we propose that the chronic heavy use of cocaine may result in a neuropsychiatric syndrome associated with neuropsychological changes that are not obvious during routine clinical evaluation. This syndrome might have deleterious effects on therapeutic interventions in drug abusers. A neurobehavioral approach, comprised of a thorough neurological and psychiatric examination, neuropsychological testing, and imaging studies, would provide a rational basis for cognitive and/or pharmacological therapies. Cadet, J.L., and Bolla, K.I. Chronic Cocaine Use as a Neuropsychiatric Syndrome: A Model for Debate. Synapse 22: pp. 28-34, 1996.

The Neurotoxic Effects of Stimulants Involves the Production of Free Radicals

Methamphetamine (METH) has long-lasting neurotoxic effects on the nigrastriatal dopamine (DA) system of rodents. METH-induced neurotoxicity is thought to involve release of DA in presynaptic DA terminals, which is associated with increased formation of oxygen-based free radicals. We have recently shown that METH-induced striatal DA depletion is attenuated in transgenic (Tg) mice that express the human CuZn-superoxide dismutase (SOD) enzyme. DIR investigators used receptor autoradiographic studies of DA uptake sites to evaluate the effects of several doses of METH on striatal DA terminals of Non-Tg as well as of heterozygous and homozygous SOD-Tg mice. In Non-Tg mice, METH decreased striatal DA uptake sites in a dose-dependent fashion. The loss of DA terminals caused by METH was attenuated in a gene dosage-dependent fashion, with the homozygous mice showing the greatest protection. Female mice were somewhat more resistant than male mice against these deleterious effects of METH. These results provide further evidence for a role of superoxide radicals in the long-term effects of METH. They also suggest the notion of a gender-specific handling of oxidative stress. Hiroshi, H., Ladenheim, B., Carlson, E., Epstein, C., and Cadet, J.L. Autoradiographic Evidence for Methamphetamine-Induced Striatal Dopaminergic Loss in Mouse Brain: Attenuation in CuZn-Superoxide Dismutase Transgenic Mice. Brain Research 714: pp. 95-103, 1996.

GBR12909 Decanoate Derivative Produced a Long-Acting Decrease in Cocaine- Maintained Responding in Rhesus Monkeys

The selective DA reuptake inhibitor GBR 12909 has been shown to decrease cocaine-maintained behavior without affecting similar levels of food-maintained behavior in monkeys, an effect analogous to that expected of a medication designed to treat human cocaine abuse. In the current study, we extended this effect by developing a decanoate ester of a hydroxylated analog of GBR 12909 (5, DBL 583). Within several days of administration, active doses of 5 had decreased cocaine-maintained responding more than 80%, without affecting control (food-maintained) responding. The effect lasted almost thirty days after a single injection, and was followed by a return of responding to control levels. These results suggest that a similar formulation, if proven safe for human use, should be tested as a potential medication for cocaine abuse. Glowa, J. R., Fantegrossi, W.E., Lewis, D.B., Matecka, D.M., Rice, K.C., and Rothman, R.B.

Serotonin-4 Receptor Antagonists Reverse Cocaine-Induced Cardiac Arrhythmia

The effect of 5-HT antagonists GR113808A and GR125487D were examined in cocaine induced cardiac arrhythmia in the rat. Pre-and post i.v treatment with the 5-HT4 receptor antagonists GR113808A and GR125487D reversed cocaine induced arrhythmia without altering cardiovascular function. The results of this study indicate that 5-HT4 antagonist can reverse cocaine-induced arrhythmias. The clinical implication of this study is clear: 5-HT4 antagonists

may be useful in the treatment of acute cocaine induced cardiotoxicity, and may also be useful in reversing cocaine's CNS effects. Further study is needed to understand the exact mechanism of this phenomena. Ohuoha, D.C., Schindler, C.W., and Rothman, R.B.

Effect of Dopamine Receptor Antagonists on Cocaine Subjective Effects: A Naturalistic Case Study

Schizophrenic patients on neuroleptic medications abuse cocaine and report cocaine-induced euphoria. This study was undertaken to provide better clinical characterization of these phenomena by administering the POMS and a custom designed questionnaire. A group of heavy cocaine users who were not mentally ill served as the control group. The results clearly suggest that schizophrenic patients report cocaine-induced euphoria and post-use craving despite being treated with therapeutic doses of haloperidol or fluphenazine. The responses of the control group were similar to that of the schizophrenic group except that the latter subjects reported a greater degree of anxiety. These results suggest that blockade of D2 receptors is not sufficient to block cocaine-induced subjective effects in humans. Ohuoha, D.C., Maxwell, J.A., Thomson, L.E., Cadet, J.L., and Rothman, R.B.

Cocaine Cross-Sensitization to Dopamine Uptake Inhibitors: Unique Effects of GBR12909

Repeated administration of cocaine will cross-sensitize the locomotor response to a variety of psychomotor stimulants. The ability of cocaine to cross-sensitize the locomotor effects of other psychomotor stimulants provides information relevant to the pharmacological mechanisms underlying the sensitization process. The purpose of the current experiment was to investigate the ability of cocaine to cross-sensitize the locomotor effects of several dopamine uptake blockers with unique pharmacological profiles. Cocaine (40 mg/kg, IP) or saline was administered prior to a locomotor session on day one. On day 2, a full dose-effect curve was established for the locomotor effects of cocaine, RTI-55, mazindol, and GBR12909. Previous exposure to cocaine significantly affected locomotor activity and stereotopy-like behavior produced by cocaine, mazindol, RTI-55, and GBR12909. However, GBR12909 was unique in that the maximal stimulant effect and slope of the dose-effect curve was significantly depressed and the stereotopy-like behavior was unchanged. Thus, despite the similarity of these compounds in their ability to inhibit dopamine uptake, cocaine-induced sensitization did not generalize to GBR12909. This study further demonstrates the unique pharmacology of GBR12909 and supports the further study of this compound as a potential treatment medication for cocaine abuse. Elmer, G.I., Brockington, A., Gorelick, D.A., Carroll, F.I., Rice, K.C., Matecka, D., Goldberg, S.R., and Rothman, R.B.

Evidence for Alterations in Presynaptic Serotonergic Function During Withdrawal from Chronic Cocaine in Rats

The effects of repeated cocaine administration on serotonin (5-hydroxytryptamine, 5-HT) function were investigated by comparing the corticosterone response to 5-HT receptor agonists in cocaine-treated and vehicle-treated rats. Male rats were fitted with indwelling jugular catheters and received cocaine (15 mg/kg i.p., b.i.d.) or saline for 7 days. Rats were challenged with either saline, the 5-HT releaser fenfluramine (1.2 mg/kg i.v.). the 5-HT1a receptor agonist 8-OH-DPAT (50 mg/kg i.v.). or the 5-HT1c receptor agonist DOI (100 mg/kg i.v.) 42 h and 8 days after the final chronic treatment. Repeated blood samples were withdrawn immediately before and at 15, 30 and 60 min after acute challenge injections. All 5-HT receptor agonists increased plasma corticosterone, but the fenfluramine-induced increase in corticosterone was significantly attenuated in cocaine-treated rats withdrawn for 42 h. This blunted response to fenfluramine exhibited only partial recovery when examined at 8 days post-chronic treatment. Corticosterone responses to 8-OH-DPAT and DOI were not affected by cocaine exposure. Our data suggest that chronic cocaine produces deficits in presynaptic 5-HT function and alterations in 5-HT neurotransmission which may underlie the dysphoria experienced by abstinent cocaine users. Neuroendocrine challenge tests should be performed in human addicts to evaluate potential 5-HT dysfunction associated with cocaine abuse. Baumann, M.H., Becketts, K.M., and Rothman, R.B.

Effects of Intravenous Cocaine on Plasma Cortisol and Prolactin in Human Cocaine Abusers

The aim of the present work was to examine the cortisol and prolactin responses to acute cocaine administration in

human cocaine users. Each subject served as its own control during intravenous saline placebo and cocaine (40 mg) infusion sessions. Cocaine significantly elevated plasma cortisol but did not affect prolactin. The rise in cortisol coincided with an increase in heart rate and blood pressure after cocaine. In agreement with studies in animals our data suggest that cocaine activates the hypothalamic-pituitary-adrenal axis in humans. However, based on the well-known importance of dopamine as a prolactin-inhibiting factor the failure of cocaine to suppress prolactin in the present study raises questions concerning the role of dopamine in the mechanism of acute cocaine action in humans. Baumann, M.H., Gendron, T.M., Becketts, K.M., Henningfield, J.E., Gorelick, D.A., and Rothman, R.B.

Development of Novel, Potent and Selective Dopamine Reuptake dors through Alteration of the Piperazine Ring of GBR 12935 and GBR 12909.

The design, synthesis and biological evaluation of compounds related to the dopamine (DA) uptake inhibitors GBR 12395 (1) and GBR 12909 (2), directed towards the development and identification of new ligands interacting with high potency and selectivity at the dopamine transporter (DAT) is reported. The substitution of the piperazine ring in the GBR structure with other diamine moieties resulted in the retention of the high affinity of new ligands for the DAT. Some of the modified GBR analogs (e.g. 8, 10, (-)-49 or (-)-50) displayed substantially higher selectivity (4732- to 694-fold) for the DA versus the serotonin (5-HT) reuptake site than the parent compounds. The bis(p-fluoro) substitution in the diphenylmethoxyethyl fragment slightly increased the affinity of the ligands at the DA reuptake site but reduced their selectivity at this site (e.g. 9 and 8, 11 and 10 or 17 and 16, respectively). Congeners, such as the series of mono-and symmetrically disubstituted piperazine and trans-2,5-dimethylpiperazine, which lack the diphenylmethoxyethyl substituent ("left" fragment of GBR molecule), lost the affinity for the DAT, yet exhibited very high potency for binding to the sigma receptors (e.g. 28). The chiral pyrrolidine derivatives of GBR 12935, (-)-49 and (+)-49, exhibited an enantioselectivity ratio of 181 and 146 for the inhibition of DA reuptake and binding to the DAT, respectively. Matecka, D., Rothman, R.B., Radesca, L., de Costa, B.R., Dersch, C.M., Partilla, J.S., Pert, A., Glowa, J.R., Wojnicki, F.H.E., and Rice, K.C.

A Continuum Model of Central Dopamine-Serotonin Interactions: Studies with Amphetamine

Dopamine (DA) neuronal activity is modulated by serotonin (5-HT) in a complex manner. In the present work, investigators examined the relationship between DA and 5-HT function by testing a series of amphetamine analogs in neurochemical and behavioral assays. In vivo microdialysis was performed in the nucleus accumbens of awake rats. Phentermine, chlorphentermine, fenfluramine, or a mixture of phentermine plus fenfluramine (PHEN/FEN), was administered locally through the probe and by ip injection. Phentermine preferentially elevated extracellular DA whereas fenfluramine elevated 5-HT. Chlorphentermine and PHEN/FEN produced concurrent increases in DA and 5-HT. These agents were tested for their ability to release preloaded [3H]DA and [3H]5-HT from rat brain synaptosomes; the relative potencies and DA/5-HT selectivity ratios determined in vitro were similar to in vivo findings. Phentermine produced robust locomotor activation in mice, but fenfluramine and chlorphentermine did not. Interestingly, coadministration of fenfluramine antagonized the stimulant effects of phentermine. Our data support historical literature that suggests DA and 5-HT neuronal systems can be viewed as opposing forces along a continuum, with the net behavioral state being defined by the sum total of these forces. Shifting the balance in favor of DA is expressed as behavioral activation whereas shifting the balance in favor of 5-HT results in behavioral inhibition. Baumann, M.H., Ayestas, M.A., Dersch, C.M., and Rothman, R.B.

Characterization of a Novel Cocaine Binding Site Identified with [125I]RTI-55 in Membranes Prepared from Human, Monkey and Guinea Pig Caudate

[125I]RTI-55 is a cocaine analog with high affinity for dopamine (DA) and serotonin (5-HT) transporters. Quantitative ligand binding studies revealed a novel high affinity [125I]RTI-55 binding site assayed under 5-HT transporter (SERT) conditions which has low affinity for almost all classic biogenic amine transporter ligands, including high affinity 5-HT transporter inhibitors such as paroxetine, but which retains high affinity for cocaine analogs. This site, termed SERTsite2 for its detection under 5-HT transporter conditions (not for an association with the SERT) occurs in monkey caudate, human caudate and guinea pig caudate membranes, but not in rat caudate membranes. SERTsite2 is distinguished from the DA transporter (DAT) and SERT by several criteria, including a distinct ligand-selectivity profile, the inability to detect SERTsite2 in cells stably expressing the cloned human DAT, insensitivity to irreversible ligands which inhibit [125I]RTI-55 binding to the DAT and SERT, and an anatomical distribution distinct from the

SERT. Perhaps the most striking finding about SERTsite2 is that a wide range of representative antidepressant agents have very low affinity for SERTsite2. The affinity of cocaine for this site is not very different from the concentration cocaine achieves in the brain at pharmacological doses. Viewed collectively with the observation that ligands with high affinity for SERTsite2 are mostly cocaine analogs, these data lead us to speculate that actions of cocaine which differ from those of classic biogenic amine uptake inhibitors may be mediated in part via SERTsite2. Rothman, R.B., Silverthorn, M.L., Glowa, J.R., Matecka, D., Rice, K.C., Carroll, F.I., Partilla, J.S., Uhl, G.R., Vandenbergh, D.J., and Dersch, C.M.

Changes in Cocaine Metabolism Alter the Acute Behavioral Effects of Cocaine

Scientists in the Pharmacotherapy Section, Treatment Branch, in collaboration with colleagues in the Behavioral Pharmacology & Genetics Section, Preclinical Pharmacology Laboratory, and the National Institute on Aging Gerontology Research Center, recently completed a study showing that changes in cocaine metabolism could significantly alter the acute behavioral effects of cocaine. Rats were injected IV with a cocaine dose that substantially increased their motor activity over a 2-hour period. Separate groups of rats were pretreated with either butyrylcholinesterase (BChE), a major cocaine-metabolizing enzyme, or cymserine, a specific inhibitor of BChE. Rats pretreated with BChE had significantly less of an increase in motor activity than those pretreated with saline, while those pretreated with cymserine had more of an increase. These findings suggest that speeding up cocaine metabolism can reduce acute behavioral effects of cocaine, and could have potential therapeutic benefits. Gorelick, D.A., and Schindler, C.W.

Distinctive Pharmacological Mechanisms of Cocaine Tolerance and Sensitization

Sari Izenwasser of the DIR's Psychobiology Section has found evidence that tolerance and sensitization to cocaine are mediated by distinctive pharmacological mechanisms. When cocaine is injected on a daily basis, sensitization occurs, whereas continuously infused cocaine leads to tolerance in laboratory animals. Rats treated with cocaine pumps showed large increases in locomotor activity, compared to saline controls, after the pumps were implanted and partial tolerance to this effect developed over the course of five days. Activity levels dropped to saline levels shortly after the pumps were removed. Rats receiving a challenge injection of cocaine showed significant elevations in locomotor activity which were greater in rats that were not exposed to cocaine. The cocaine dose-effect curve was shifted to the right compared to saline controls in these subjects. When the rats were injected again on the next day their activity levels were increased even further showing sensitization. Despite this sensitization the cocaine-exposed rats were still tolerant compared to the saline controls. These findings indicate that tolerance and sensitization can exist simultaneously, implying a mediation by distinctive neuronal mechanisms.

Central Role of mu Receptor in Morphine Effects

At the International Narcotics Research Committee (INRC) Dr. George Uhl of the NIDA-IRP presented data on "knockout" transgenic mice deficient in the morphine-preferring mu opiate receptor. These mice, developed and tested in his laboratory by Drs. Sora and Miner, display increased sensitivity to painful stimuli without morphine. They also show no morphine analgesia. These results provide, for the first time, dramatic demonstration of the central role that the mu receptor, whose cDNA and gene was cloned by Dr. Uhl's laboratory (as well as others) in 1993 plays in morphine effects and even on day-to-day nociception.

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National Institute on Drug Abuse

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

September, 1996

Program Activities

Program Announcements/RFAs

B/START: Behavioral Science Track Awards for Rapid Transition--NIDA

This RFA (Number: RFA 96-005) underscores NIDA's commitment and interest in expanding the scope of basic behavioral sciences research in drug abuse. NIDA invited newly independent investigators to submit applications for small-scale, exploratory (i.e., pilot) research projects related to NIDA's basic behavioral sciences mission. The applications underwent rapid review; the funding status of applications will be determined before the end of the fiscal year. Basic science (mostly laboratory) applications were encouraged in cognitive and perceptual processes, social processes and motivational factors in drug abuse.

Craving in Drug Abuse and Addiction

The objective of this Request for Applications (RFA 97-001) is to encourage the investigation of craving from multiple biobehavioral, clinical, and medications development perspectives to further our understanding of and treatment for drug abuse and addiction. Approximately 40 applications were received in July in response to this announcement.

The Treatment Research Branch, Division of Clinical and Services Research has issued two new addenda to the Behavioral Therapies Development Program Announcement (PA-94 078). The first, which appeared in the NIH Guide (Vol. 25, No. 16) on May 17, 1996, encourages research on the development and testing of assessment instruments and brief behavioral therapies for drug abuse and dependence and related HIV/AIDS risk behaviors for patients that are seen in office-based and other health care settings. The second, published August 9, 1996 (Vol. 25, No. 27), encourages Stage 1 research on the development of new and innovative behavioral interventions for the treatment of drug addicts and the prevention or reduction of HIV risk behaviors in drug abuse treatment populations. The translation of basic behavioral science research into creative new behavioral therapies for drug addicts is the ultimate goal of this addendum.

NIDA's AIDS Program

NIDA's Office on AIDS published an advertisement in the July 28 issue of Science which featured AIDS research and profiled important HIV/AIDS discoveries in recent years. The NIDA advertisement encouraged investigators to undertake research on drug abuse-related aspects of HIV/AIDS.

DC*MADS Data Files and Documentation

Public use data files and documentation for two components of the Washington, D.C. Metropolitan Area Drug Study (DC*MADS) are now available on diskettes from the NTIS. One is for the Study of the Household and Nonhousehold Populations (#PB96-502271GEI) and the second is for the Study of Drug Use and Pregnancy (#PB96-502109GEI). Both can be ordered from NTIS by calling (703) 487-4650.

Small Business Innovation Research Award

NIDA's MDD has awarded a $700,000 Small Business Innovation Research award to ImmuLogic Pharmaceutical Corporation (Waltham, Massachusetts) to complete preclinical development of a vaccine to treat cocaine dependence. Results of ImmuLogic's early vaccine work in animals has received attention in national and trade press, and was presented at CPDD. The vaccine links a protein to cocaine, resulting in a molecule which induces antibody formulation. Once titers reach a certain level, cocaine's ability to cross the blood brain barrier is diminished. The award will expedite completion of preclinical design and testing of the vaccine with the hope that clinical trials could begin in 1997.

Medications to Prevent Cocaine Dependence Relapse

The Philadelphia VA MDRU has recently screened 6 medications for potential usefulness in preventing relapse to cocaine dependence. One of these, propranolol, seemed so promising in two open studies that a controlled double blind study has recently been instituted.

NIDA/VA Medications Development Research Units (MDRU) Meeting

On June 18-19, the NIDA/VA Medications Development Research Units held their second quarterly meeting in Washington, D.C. June 18 was a general session meeting consisting of a scientific component. The scientific discussions were focused on study design issues and review of cocaine infusion methods. Four NIDA grantees presented data and/or applications of pharmacokinetic/pharmacodynamic cocaine profiles to cocaine infusion methods. Presenters were: Suzette Evans, Ph.D. (Columbia University); George Bigelow, Ph.D. (Johns Hopkins University); Reese Jones, M.D. (UCSF) and Charles O'Brien, M.D., Ph.D. (University of Pennsylvania). On June 19 the subcommittees conducted meetings in the following areas: compound identification; protocol review; pharmacokinetics; design/methods; data management; and psychosocial/behavioral therapies.

Cocaine Clinical Trials Database

The MDD Cocaine Clinical Program has refined the Cocaine Clinical Trials Database and presented the database as a poster at CPDD. The database summarizes data from MDD sponsored clinical trials which have been completed and analyzed.

Multi-Center Protocols at MDRUs

Four clinical multi center protocols at the new Medications Development Research Units (MDRUs, located in Department of Veterans Affairs medical centers) with bupropion, nefazadone, fenfluramine and methylphenidate are in the final stages of revision. All have IRB approvals and patient enrollment is anticipated by October 1, 1996.

Supplements to VA MDRU Studies

Two supplemental studies within the VA MDRU program were approved and funded, one involving human hepatic metabolic pathways to predict potential toxic interaction with medications for cocaine dependence, the other involving PET imaging of dopamine system ligands in cocaine dependent patients.

Multi-Site Trial of Buprenorphine

Paul Fudala, Ph.D. (VA Cooperative Studies Program and University of Pennsylvania) is co-directing with MDD, NIDA (Peter Bridge, M.D.) a multi-site trial of buprenorphine combined with naloxone.

On-Site Reviews of In-Vitro Screening Contracts

MDD utilized expert consultants for on-site reviews of two of its in vitro screening contracts. A contract focusing on the dopamine transporter is located at Oregon Health Sciences University and was visited by Drs. Michael Kuhar, Gary Rudnik, Ken Johnson, Zdenek Pristupa, Deborah Mash, Beth Hoffman, and Maarten Reith. The screening contract at SRI focusses on a variety of other targets and incorporates functional assays to identify compounds as either agonists or antagonists at specific receptor sites. SRI was visited by Drs. Dmitri Grigoriadis, Bob Luedtke, and Richard Mailman.

Structure Activity Relationship (SAR) Committee

On April 5, the MDD Cocaine Treatment Discovery Team formed a Structure Activity Relationship (SAR) Committee in response to the recommendations of expert consultants for an increased role of SAR in drug discovery. The role of the committee is to strategically evaluate compounds in the database to recommend and facilitate rapid testing and to maximize cost-effectiveness of the CTDP testing program. The Committee has focused on classifying all compounds in the data base to evaluate physico-chemical relationships to:
recommend compounds for in vitro testing (BAT)
request from chemists additional synthesis of compounds targeted for further testing.
correlate in vitro results with physico-chemical features
and recommend compounds to proceed to animal testing based correlations.

Incorporate all data into one database and reporting software.

Obtain computer modeling resources for structural and energy relations to biological activity (presently done manually-at best approximation).

Health Services Research Resource Center

NIDA's Health Services Research Resource Center has accomplished several tasks, including the development of annotated bibliographies to support research in the areas of treatment effectiveness, financing, alternative delivery systems, cost-benefit and cost-effectiveness analysis, costs and benefits of treatment, and economics of drug treatment.
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National Institute on Drug Abuse

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Congressional Affairs

Appropriations

The FY 1997 President's request for NIH is $12.406 billion, an increase of $467 million (or 3.9 percent) over the FY 96 appropriation. Of this, $310 million is included for construction of the Clinical Research Center (CRC). The President's request also asks for a consolidated appropriation for the Office of AIDS Research.

Senate FY 97 NIH Appropriations Hearing

On June 18, 1996, the Senate Appropriations Subcommittee on Labor, HHS, and Education [Sen. Arlen Specter (R-PA), Chairman] held a hearing to consider the President's FY1997 budget request for NIH and the programs and policies of the agency. In opening remarks, Sen. Specter noted that "few activities of government provide greater promise for improving the quality, and reducing the costs, of health care for all Americans than our investment in medical research supported by the National Institutes of Health..." However, he noted that last year NIH was singled out for special treatment in the appropriations process and that he wished that other programs had been treated as well, and named several. Pointing to the $819 million increase provided for NIH in the House Subcommittee mark-up for FY 1997, he said that while the Senate is a great supporter of NIH, he did not want this to turn into a "bidding war," because "every dollar to NIH comes from other programs."

Dr. Varmus opened his testimony with a brief statement describing support for investigator initiated research and the proposed CRC as the agency's two highest priorities. Among major issues discussed at the hearing were the importance of sharing of scientific information, mental health coverage under the health insurance reform bill, and the consolidated AIDS budget. Noting the differences in the House and Senate perspective on Office of AIDS Research funding, Sen. Specter asked why it is important to allocate the funds to OAR and requested that Dr. Varmus provide more information for the record.

House-Passed Labor-Health and Human Services-Education Appropriations Bill (HR 3755):
On July 11, 1996, by a vote of 216-209, the House passed the appropriation bill to fund NIH for FY 97. The House bill includes $12.747 billion for NIH, $90 million of which is for the new CRC. This is $819 million over the agency's FY 96 appropriation. For NIDA the House-passed figure is $487.341 million, an increase of $21.016 million over the amount requested and $29.229 million over the comparable 1996 appropriation.

Excerpts from the House Appropriations Committee Report [HRpt 104-659]

For NIDA (in part)

"Neuroscience.--The Committee recognizes that neuroscience research has fundamentally changed our understanding of addiction and that this understanding provides the foundation for new kinds of treatments. NIDA has made progress in identifying the neurobiological bases of addiction, including craving, which is one of the major factors that can precipitate relapse. NIDA-supported researchers have also made substantial progress in identifying potential anti-cocaine medications. NIDA-supported researchers have made great strides in understanding the brain's opiate system and its role in addiction. The Committee considers neuroscience research a top priority and encourages NIDA to continue its research efforts in this area.

"Medication development.--Basic research has now progressed to the point where at least six molecular targets have been identified, allowing researchers to strategically focus research on anti-addiction medications. The Committee urges NIDA to continue research aimed at developing effective medications for the treatment of addictions, particularly for cocaine. The Committee is pleased that NIDA has issued a program announcement to encourage expedited transition of ground-breaking research from advanced preclinical findings to applied clinical applications. The Committee recognizes this is a valuable tool in advancing the discovery and development of medications for cocaine addiction.

"Behavioral science research.--The Committee understands that behavioral research is important to solving problems of drug abuse and addiction, and that behavioral interventions are the most frequently administered treatments for drug addiction in some cases, the only available treatment. The Committee commends NIDA for its basic and clinical behavioral science activities aimed at better identifying those at risk for drug abuse and developing effective approaches for breaking the cycle of addiction. The Committee also encourages NIDA's HIV/AIDS initiatives because of the increasing link between HIV infection and drug use and related behaviors.

"Social work research.--The Committee supports NIDA's research on families and drug abuse, behavioral and psychosocial treatment research and health services. The Committee also supports NIDA's efforts to increase the number of social work researchers conducting drug abuse research.

"Information dissemination.--The Committee believes that disseminating research findings in a timely manner is an important component of the NIH mission. Therefore, the Committee is pleased to learn of NIDA's "town meetings" with educators, health care providers, State and local anti-drug coalitions, and civic organizations to disseminate research findings and foster information exchange.

AIDS Research (in part)

"The Committee intends that the [NIH] funds allocated for AIDS should be spent in a manner fully consistent with the AIDS research plan developed by the Office of AIDS Research and expects the Director of NIH to use the full authority of his office to ensure that this occurs. The Committee has provided the Director of the Office of AIDS Research, jointly with the Director of NIH, transfer authority to reallocate up to three percent of funds designated for AIDS research among Institutes, subject to normal reprogramming procedures. The Committee encourages NIH to use this authority whenever it believes that an adjustment in the allocation of AIDS funding between Institutes is appropriate to achieve scientific objectives or to facilitate promising research efforts.

"The Committee wants to make clear that it continues to support the Office of AIDS Research (OAR), its leadership, and its coordinated budget planning process and that it expects the individual institutes, centers and divisions to fully cooperate with OAR's work. The Committee has provided funding for the OAR within the Office of the Director and intends that the OAR will maintain its current structure and responsibilities, including the allocation of an emergency discretionary fund.

"Last year, the number of AIDS cases passed the 500,000 mark. AIDS is now the leading cause of death for Americans between the ages of 25 and 44. The disease is spreading most rapidly among African Americans and other at-risk minority populations, adolescents, and women. Therefore, the Committee urges the OAR to carefully monitor these changes and ensure that the research plan includes objectives and strategies to respond to demographic changes in a timely fashion. NIH is also strongly encouraged to strengthen and to include the direct participation of African Americans and other minorities in its AIDS/HIV research, research training, and outreach activities. The

Committee expects the NIH to report on its progress in achieving this objective during next year's appropriations hearings.

Third Party Payments

"... NIH is authorized to collect third party payments for the cost of clinical services that are incurred in National Institutes of Health research facilities and that such payments shall be credited to the National Institutes of Health Management Fund: ... all funds credited to the NIH Management Fund shall remain available for one fiscal year after the fiscal year in which they are deposited...

Forward Funding for R29s and R01s

"Opportunities for new investigators.--The Committee understands that NIH would intend to use a portion of the funding increase to provide forward funding for a select group of first-time applicants for investigator-initiated research project grants (R-29s) and first-time R01 investigators. In the case of R-29 awards, the full five years of support would be provided; first-time R01 awards would be provided the recommended period of support. The Committee applauds NIH's plan, recognizing that it would provide a much-needed boost to the next generation of researchers, who face daunting competition for research funding. It would also insulate them from year-to-year fluctuations in grant support. The Committee will watch this experiment with interest to see if it has broader applicability for other components of the grant pool."

FY 97 Budget Resolution [HJRES 178]

The House and Senate agreed to HConRes 178, the FY 1997 federal budget, on June 7. The conference report [HRpt. 104-612] recommends maintenance of the 1996 increases in funding for NIH and assumes priority funding the agency at $11.95 billion in budget authority. Included under Section 431 is a sense of the Senate that "amounts appropriated for the NIH should provide funding for additional research on an anti-addiction drug to block the craving for illicit addictive substances."

NIH Revitalization Act of 1996

On July 17, 1996, the Senate Labor and Human Resources Committee marked up and approved, as amended, S. 1897, the NIH Revitalization Act of 1996 (with all Committee members voting in the affirmative). Several amendments were approved by voice vote by the Committee, including an amendment to establish a pediatric research initiative (Sens. DeWine and Kennedy); one which would increase diabetes related research (Sen. Simon) and a program for research and training relating to Parkinson's disease (Sen. Wellstone). An amendment offered by Sen. Faircloth (for himself and Sen. Harkin) was not voted on by the Committee. It would have required the Secretary to establish a National Center for Pain Research in NIH. Sen. Kassebaum expressed concern about the wording of the amendment and agreed to work with Sen. Faircloth on the appropriate language before the legislation is brought to the Senate floor for a vote. One day earlier, on July 16, Sen. Orrin Hatch (R-UT) had introduced S. 1955 to establish a National Center for Pain Research in NIH.

SAMHSA Reauthorization

H.R. 3847, the Drug Abuse Prevention and Treatment Consolidation and Reorganization Act, was introduced on July 18 by Representative Joe Barton (R-TX) to consolidate and reorganize SAMHSA. It would create a new Drug Abuse

Prevention and Treatment Administration which would be headed by an Administrator to be appointed by the President with the consent of the Senate. The DHHS Secretary would have the authority to appoint an Associate Administrator for Substance Abuse Prevention and an Associate Administrator for Substance Abuse Treatment. The new agency would be authorized an appropriation of "such sums as may be necessary" for fiscal years 1996 through 2002. Any programs not transferred to this new agency would be transferred to HRSA.

Other Bills of Interest

Health Insurance Reform Becomes Law

HR 3103 - The Health Insurance Portability and Accountability Act of 1996. On August 1, the House agreed to the conference report (HRpt 104-736) and sent the measure to the Senate. On August 2, the Senate agreed to the conference report, clearing the measure for the President, who signed the bill into law on August 21. Among other things, the legislation provides for increased portability of group health plans; genetic information will not be considered a preexisting condition in the absence of a diagnosis of the conditions related to such information; and discrimination against participants and beneficiaries based on health status are prohibited.

Welfare Reform Becomes Law

The House and Senate agreed to the conference report on the Welfare Reform legislation, H.R. 3734. The President signed the bill August 22. The bill includes a provision making individuals convicted of a drug-related felony ineligible for AFDC and food stamps. No other public benefits would be denied and pregnant women and individuals in treatment would remain eligible for these benefits but would lose eligibility after giving birth or leaving treatment. Family members of those denied benefits would still receive their AFDC and food stamp allocations. States could exempt those effected by the law by passing State legislation.

In the first session of the 104th Congress, an early version of welfare reform legislation [H.R. 4] included language which would have provided authorization of appropriations specifically for NIDA's medications development activities and for SAMHSA's substance abuse block grant. This provision was dropped in later versions of the bill, but a portion of the language was swept into P.L. 104-121, Senior Citizens Right to Work Act, which includes an authorization of appropriations for an additional $50 million for SAMHSA's Substance Abuse Block Grant.

Mental Health Parity

The Mental Health Parity Act of 1996, S.2031, was introduced by Sen. Pete Domenici (R-NM) on August 2. The purpose of the bill is to provide health plan protection for individuals with mental illnesses. Specifically, the legislation would provide parity for lifetime and annual financial caps for mental health insurance coverage. Similar language in the health insurance reform legislation was dropped before final passage.

Animal Research

The animal rights community observed June 18 - 24 "World Animal Awareness Week." Related to preparations for the week, there were several bills introduced in the Congress on issues ranging from "family pet protection" to "consumer products testing," in addition to a number of other bills relating to primate research facilities and other matters related to research animals that came before the Congress for other reasons. The future for most of these animal welfare bills is uncertain. Recent animal welfare bills include S. 1477, "FDA Performance and Accountability Act," introduced by Sen. Kassebaum (R-KS) Chair, Senate Labor and Human Resources Committee, on December 13, 1995. The bill was passed by the Senate on June 20, 1996. Another recently introduced bill is H.R. 3393, "Animal Welfare Act, Amendment (Family Pet Protection Act of 1996)" introduced by Rep. Fox (R-PA) on May 7. Provisions of the bill would ban research facilities from obtaining dogs or cats from dealers who do not breed and raise animals themselves, and implement strong requirements that would effectively restrict research facilities from obtaining unwanted municipal pound animals. It would also disallow private animal shelters from voluntarily making animals available for research and limit individuals to donating no more than one animal to a research facility. On the same

day Rep. Canady (R-FL) introduced his version of a pet theft bill, H.R. 3398, "Animal Welfare Act, Amendment."

In addition, two draft bills have brought special attention. First, the Department of Agriculture prepared a draft bill amending the Animal Welfare Act. Among other provisions, this proposal would place greater restrictions on the sale and purchase of research animals by laboratories and research institutions. Second, the "National Chimpanzee Sanctuary Act," has been circulating among some Congressional offices. The purpose of this bill is to provide a national retirement sanctuary for chimpanzees that will assure long-term care for chimpanzees currently housed in laboratories and other facilities.

Methamphetamine

On July 17, Sen. Orrin Hatch (R-UT) introduced S. 1965, the Comprehensive Methamphetamine Control Act of 1996. The purpose of the Hatch bill is to crack down on precursor chemicals while balancing the need to maintain availability of drugs such as pseudoephedrine for legitimate purposes. Sen. Hatch said he remains unconvinced that legitimate products purchased at the retail level are a significant source of precursor drugs for the manufacture of methamphetamine. He included several provisions to limit the potential diversion of legitimate products at the retail level to methamphetamine labs and said that he will monitor the situation very closely. If the data show that retail products containing pseudoephedrine and phenylpropanolamine are contributing to the problem of methamphetamine abuse, he said he will revisit the issue in the 105th Congress. Earlier this session, Sens. Grassley (R-IA) and Feinstein (D-CA) introduced S. 1607, the Methamphetamine Control Act of 1996, for similar purposes.

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National Institute on Drug Abuse

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International Activities

NIDA Director Dr. Alan I. Leshner met with Sir George Alleyne, Director, Pan American Health Organization, and PAHO staff in early August. The meeting, which included Dr. Zili Sloboda, Director, DEPR, and Dr. Patricia Needle, Acting Director, International Program, focused on presentation of NIDA's research portfolio and international activities, and the exploration of further collaboration with PAHO on drug abuse and related research in the Americas.

The **"International Conference on Neurochemistry and Pharmacology of Drug Addiction and Alcoholism"** was held in St. Petersburg, Russia, in June. Dr. Alan Leshner presented a plenary session on the neurobiology of drug abuse. In the workshop on Developing International Cooperation in Drug Abuse Research, Dr. Timothy Condon, Director, OSPC, provided an overview of the NIDA organization and basic science research portfolio, and Dr. Patricia Needle discussed funding mechanisms and opportunities for international cooperation. NIDA grantees Charles R. Schuster, Edward Sellers, Joseph Justice, and Boris Tabakoff presented research papers in a program coordinated by Dr. Robert Balster. Dr. Edvin Zvartau of the Institute of Pharmacology, Pavlov Medical University, was the conference organizer. At the opening ceremony of the conference, NIDA Director Leshner and Nicolai Yaitsky, Rector, Pavlov Medical University, signed documents in an Exchange of Letters agreeing to promote collaboration in the fields of biomedical and behavioral research related to drug abuse and drug-related HIV/AIDS. Funding for U.S. participation was provided by U.S. Department of State and by NIDA.

Dr. Svetlana Dambinova, Institute of the Human Brain, Russian Academy of Sciences and President, Russian Society for Neurochemistry, visited NIDA during July to discuss a range of possibilities for research collaboration with Dr. Leshner and with Drs. Edythe London and Dr. George Uhl of NIDA's Division of Intramural Research.

"Building International Research in Drug Abuse: Opportunities and Challenges," was sponsored by the International Program as a satellite CPDD meeting. Sixty-five researchers, including NIDA-trained visiting scientists and foreign fellows from 21 countries, met to present research from outside the U.S.; to explore development of a network for collaborative research; and to report on the status of drug abuse research and policy issues in world regions.

NIDA hosted the Peruvian Minister of Health Mariano Costa, Alejandro Vassilaqui, Executive Director of CEDRO (Peru's Center for Information and Education for the Prevention of Drug Abuse), and Ms. Maria Teresa Hart of the Embassy of Peru for a joint discussion on drug abuse issues in Peru and opportunities for closer collaboration between our two countries on research on the prevention and treatment of drug abuse, specifically cocaine. Dr. Donald Vereen, OD, chaired the meeting, which was attended by staff of DEPR (Zili Sloboda, Nicholas Kozel), DCSR (Henry Francis, Sander Genser), International Program (Patricia Needle) and Dr. Arlene Fonaroff, Program Officer for the Americas, Fogarty International Center.

Dr. Zili Sloboda, Mr. Nicholas Kozel, and Ms. Moira O'Brien, all of DEPR, attended the third meeting of the **International Drug Abuse Epidemiology Work Group (IDAEWG)** which was held at the World Health Organization (WHO) Headquarters in Geneva, Switzerland on July 2-4, 1996. The purpose of the meeting was to

provide a forum for representatives from epidemiology surveillance networks from around the world to present and discuss the most current epidemiologic data on drug abuse; to discuss development of an infrastructure for identifying and promoting epidemiologic and other drug abuse research; and to link research findings to community and public health policy. Recent increases in marijuana use noted in the United States were paralleled in Canada. This observation led to an OP-ED article in the Washington Post on August 22nd by Dr. David Musto of Yale University, renowned drug abuse historian. Heroin, cocaine, and marijuana still predominate much of the world with much local variation pointing out the significance of such a global network such as the IDAEWG. A summary of the meeting is currently being prepared by WHO and NIDA.

Mr. Nicholas Kozel, DEPR, cochaired the **South Asian Multi-City Epidemiology Work Group meeting** held in Colombo, Sri Lanka on July 30 - August 1. The South Asian Work Group is composed of researchers from Bangladesh, India, Nepal, Pakistan, Sri Lanka and Turkey and is one of a series of regional programs being developed to provide assessment and surveillance of drug abuse with the objective of integrating these regional data into a global perspective. The program is funded by the U.S. Department of State and is coordinated by staff of NIDA and the Universiti Sains Malaysia. The Asian Work Group is modeled after NIDA's Community Epidemiology Work Group. Indirect indicators and other measures of drug abuse show that the primary drugs of abuse in the region include heroin, buprenorphine, cannabis, codeine, tranquilizers and sedative-hypnotics.

Dr. Zili Sloboda, DEPR, attended a meeting in Munich on August 19-22 sponsored by the European Union. The focus of the meeting was the development of planning and evaluation guidelines for prevention and a conference on evaluation scheduled for January 1997. The conference will include plenaries and workshops on the state-of-the-science in Europe and the United States in the areas of outcome evaluation, epidemiology and prevention, and issues such as mediating variables, instrumentation, barriers to evaluation and the role of the mass media.

Dr. Robert Battjes, Deputy Director, DCSR, spoke at the opening plenary session of the **18th World Conference of the World Federation of Therapeutic Communities**, in St. Petersburg, Russia, September 8-13. His presentation was entitled **"Adolescent Drug Abuse: Treatment Implications."** In addition to Dr. Battjes' participation, NIDA also provided travel awards for international research presentations at the Conference.

Dr. Chiiko Asanuma of the Etiology and Clinical Neurobiology Branch, Division of Clinical and Services Research, was an invited speaker at the **Colloquium on New Perspectives in Posterior Association Cortex** held at the annual meeting of the Neuropsychology Association of Japan on September 13, 1996 in Sapporo, Japan. While in Japan, Dr. Asanuma visited the School of Medicine at Nihon University in Tokyo, where she gave a seminar on her research.

Dr. Steven W. Gust, Acting Director of NIDA's Office on AIDS participated in the **XI International Conference on AIDS** held in Vancouver in July, and presented a poster on HIV/AIDS Research at NIDA.

Katherine Davenny of the Clinical Medicine Branch, Division of Clinical and Services Research, presented a poster at the **XI International Conference on AIDS**, held in Vancouver, July 1996, where she discussed NIDA's ongoing AIDS research program.

Richard H. Needle, Ph.D., M.P.H. of CRB/DEPR presented a research poster on **"Injection Drug Users' Networks, the Injection Process, and Multiperson Use of Drug Injection Equipment and Paraphernalia,"** at the **XI International AIDS Conference** in Vancouver, July 7-12. The poster was also developed by Susan Coyle, Ph.D. and Helen Cesari, M.S. Results were presented from a multisite observational study of drug injection networks in six U.S. cities and Puerto Rico. The research was conducted as a collaborative effort by NIDA grantees from each site as well as Steve Jones, M.D., from the Centers for Disease Control and Prevention.

Arthur Hughes, Chief, ERB/DEPR, presented papers and participated in the **Pompidou Group European Monitoring Centre for Drugs and Drug Addiction meeting** June 10-14, 1996, in Strausbourg, France.

Dr. Frank Tims, DCSR, was an invited speaker at the 3rd International Congress of the Worldwide Hungarian Medical Academy in Pecs, Hungary, July 4-6. His topic was **"Contemporary Drug Issues."**

Dr. Frank Tims was an invited participant and speaker in a symposium on **"Drug Abuse and the Criminal Justice System: A Creative Partnership for Change,"** in Ottawa, Canada. The symposium was jointly sponsored by the Canadian Bar Association and the Portage Programs for Dependencies, and was convened to consider implications and strategies for implementation of Bill C-41, which is designed to greatly increase diversion of substance abusing offenders. He presented a paper entitled, **"Costs and Cost-Benefits of Treatment."**

Dr. Jean Lud Cadet, DIR, was invited to present a paper entitled, **"Methamphetamine Causes Apoptosis in Immortalized Neural Cells"** at the European Society for Neurochemistry in Groningen, The Netherlands, June 1996.

Dr. Steven Grant, DIR, presented a paper entitled, **"Positron Emission Tomographic Studies of Cerebral Glucose Metabolism in Stimulant and Opiate Addiction"** at the XXth Collegium Internationale Neuropsychopharmacologium (CINP) Congress, Melbourne, Australia, June 23-27, 1996.

Dr. Toni Shippenberg, DIR, presented a paper entitled, **"Are Muscarinic Cholinergic Systems Involved in the Development or Expression of Behavioral Sensitization to Cocaine,"** at the European Behavioral Pharmacology Society, Sardinia, Italy, May 1996.

Waldemar Oliveros, M.D., M.P.H. from Panama visited NIDA's Division of Epidemiology and Prevention Research on July 9, 1996. Dr. Oliveros just completed his M.P.H. at John Hopkins University's Department of Mental Hygiene. He has a strong interest and background in prevention and has deÿ prevention intervention trial (PIT) for children entering elementary school in the 6.5 to 8.5 age range.

The Philadelphia VA's findings on the usefulness of naltrexone in former heroin addicts currently on Federal probation were presented at the meeting of the **International Congress of Neuropsychopharmacology (CINP)** held in Melbourne, Australia in June 1996.

NIDA will support travel for researchers Dr. Garo Basmadjian and Dr. Claire Advokat to attend the **"International Symposium on the Application of the Theory of Metabolic Regulation to Pain," to be held in late September in Armenia.**

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Meetings/Conferences

NIDA co-sponsored the **Conference On Drug Abuse (CODA)** with the American Psychological Association, Science Directorate, as a satellite conference to APA's 104th Convention in Toronto, Ontario, August 9-13, 1996. The goal of CODA was to highlight the best in drug abuse and addiction research. The conference included approximately 100 coordinated drug abuse research activities including a special address by Dr. Alan Leshner, 16 keynote speeches, 5 continuing education training workshops, a reception, several grant application training workshops, program initiative workshops and other special programs as well as drug abuse symposia, paper, and poster sessions. The CODA Steering Committee worked with a contractor to develop a colorful site on the NIDA homepage. The site served as a useful tool for sharing information about the August Conference. A link was also created to the APA home page.

NIDA's Office of Science Policy and Communications organized a "Town Meeting" co-sponsored by NIDA and the Ohio Department of Alcohol and Drug Addiction Services, **"Strengthening Communities Through Prevention,"** in Columbus, on May 9, 1996. The meeting brought together local and state policy makers and professionals in the alcohol and drug abuse field to learn about effective, community-based prevention strategies/models from leading researchers.

On June 27-28, 1996 a CPDD satellite meeting on the **"Use, Abuse, and Sequelae of Methamphetamine Abuse with Implications for Prevention, Treatment and Research"** was held in San Juan, Puerto Rico. The meeting was sponsored by SAMHSA in collaboration with NIDA. Dr. Jerry Frankenheim, DBR and Dr. Dorynne Czechowicz, DCSR, presented information on NIDA's current portfolio of methamphetamine research. Dr. Frank Vocci, Acting Director, MDD, presented on medication development for psychostimulant abuse. NIDA funded grantees presented on the epidemiology of methamphetamine abuse and implications for prevention approaches; basic pharmacology and mechanisms of action; medical complications; treatment and prevention research. The NIDA representatives also participated in workgroup discussions of Basic Pharmacology and Mechanisms of Action; Medical complications and Management; and Treatment and Prevention. A report of the meeting, including the workgroup discussions, is being prepared by Dr. Scott Lucas, the methamphetamine meeting Chair.

A **Hispanic Research Conference** sponsored by NIDA was held as a satellite meeting at CPDD on June 21-22, 1996 in Puerto Rico. Presentations included sessions on patterns of drug abuse for Mexican-Americans and Puerto Ricans, recruiting and retaining Hispanic subjects in drug abuse and AIDS research, drug treatment careers among Hispanic populations, and social support and drug use.

NIDA's Hispanic Work Group met on June 20, 1996 in Puerto Rico. A highlight of the meeting was a panel presentation by young researchers who discussed the obstacles and supports encountered in developing research careers.

NIDA's Special Populations Office and the State University of New York at Old Westbury sponsored a Special Populations Research Development Workshop on **"Morphine and Nitric Oxide"** in Melville, L.I., NY on June 5-7, 1996. Approximately 20 faculty and trainee attendees took part in lectures and hands-on demonstrations of various imaging processing and analyses of nitric oxide, including computer-assisted microscopy, and learned about applications of these techniques in biomedical research.

NIDA's Special Populations Office sponsored a panel at the **National Medical Association's Convention** in Chicago on July 30, 1996. The panel focused on drug abuse in physicians.

NIDA's African American Researchers and Scholars Meeting was held in New Orleans on July 28, 1996. Participants discussed improving drug abuse research in African American communities, and on increasing involvement by African American and other ethnic minority researchers in research supported by NIDA and NIH.

A NIDA- and ORMH-supported conference on **"Creating Partnerships and Collaborations between Minority Populations Researchers, Community-Based Drug Abuse Treatment and Research Programs"** was held July 29-August 1, 1996 in New Orleans, LA. About 200 participants attended plenaries, workshops, and poster sessions on community-based research, collaboration between researchers, research institutions and community-based organizations, and technical assistance sessions on developing competitive research proposals.

NIDA's Special Populations Office cosponsored the American Psychological Association's **"Diversity Project 2000 Summer Institute 1996"** in Toronto on August 7-10, 1996. Twenty-five ethnic minority students from U.S. community colleges and their faculty sponsors attended this mentoring and leadership building program, which oriented students to career and higher education opportunities in psychology. As part of the Institute, NIDA presented a one-day program which focused on NIDA and NIH research programs, careers in psychology, and preparation for careers in drug abuse research.

NIDA's Services Research Branch sponsored a health services research seminar, **"Financing and Costs of Drug Treatment,"** June 19 in the Parklawn Building. The seminar included presentations by NIDA-funded investigators Drs. Richard Frank, Constance Horgan, Dennis McCarty, and Michael French. Dr. Cartwright of the Services Research Branch chaired the session and presented a paper entitled "Drug Abuse Treatment Costs: Findings from a New Methodology".

On September 8-14 and in collaboration with the University of Miami, NIDA sponsored a workshop entitled **"Andean Region Drug Abuse Epidemiology Methods and Research Development"** in Miami, Florida. The workshop was co-chaired by Mario De La Rosa, Ph.D., of the Office of Special Populations, Moira O'Brien of DEPR, and J. Bryan Page, Ph.D., of the University of Miami. NIDA Deputy Director Richard A. Millstein, who had met with members of the planning committee last year in Rockville, gave the opening address to the researchers from Colombia, Venezuela, Peru, Ecuador, Bolivia, and Chile.

Robert Heimer, Ph.D., of Yale University was invited by NIDA, under the auspices of CRB/DEPR and the Office on AIDS, to present a lecture entitled **"New Rigs for Old: Virologic and Molecular Epidemiologic Underpinnings of Needle/Syringe Exchange,"** held on the NIH campus on June 19. Dr. Heimer described his evaluation research to determine the effects of New Haven's Needle Exchange Program (NEP) on the spread of HIV. Using polymerase chain reaction and EIA, he and colleagues have demonstrated that the New Haven NEP has slowed the spread of HIV among IDUs by at least one third. Dr. Heimer also described their current work to elaborate the unobtrusive needle testing and syringe tracking methods used to assess NEP effects on the spread of HIV in order to determine transmission patterns of acute and chronic hepatitis infections.

The Behavioral Sciences Research Branch held a **Question and Answer Session on Training and Funding Opportunities in the Basic Behavioral Sciences of Drug Abuse** at the College on Problems of Drug Dependence meeting in San Juan, Puerto Rico in June 1996.

Alan I. Leshner, Ph.D. and Dr. Timothy Condon co-chaired the first annual **NIDA Training Directors Meeting** in Rockville, MD, May 1, 1996. Forty-two of NIDA's forty-four training directors were able to attend. During the morning session, NIDA staff briefed the Training Director's on current trends, opportunities and policies. In the afternoon, participants broke into work groups and focused on evaluating current training strategies and developing creative responses to emerging trends in the field. NIDA Deputy Director Richard Millstein and NIDA's Division Directors also attended.

NIDA Deputy Director Richard A. Millstein presented at and moderated an all-day symposium on drug abuse research findings held June 1, 1996 in Honolulu, Hawaii as a pre-conference satellite to the **1996 NASADAD Annual Meeting**. Attendees were nearly 50 state alcohol and drug abuse program directors and their staff and local Hawaiian scientists and legislators.

NIDA Deputy Director Richard A. Millstein presented historical context remarks at the **20th anniversary meeting of**

the National Institute on Drug Abuse Community Epidemiology Work Group, held in New York City June 4-7, 1996.

NIDA Deputy Director Richard A. Millstein presented a keynote address on findings from drug abuse prevention research at the **Cornell University Medical College Institute for Prevention Research's Conference on Multi-Ethnic Drug Abuse Prevention Research Findings and Implications for Practice**, June 6 - 7, 1996, in New York City.

NIDA Deputy Director Richard A. Millstein represented NIH Director Dr. Harold Varmus and NIDA Director Dr. Alan I. Leshner at the **National Leadership Forum on Preventing Substance Abuse and HIV** held August 14-16, 1996 in Tampa, Florida. The Forum responded to the request of President Clinton at the December 6, 1995 White House Meeting on AIDS that CDC "convene a meeting of state and local people involved in both public health and drug prevention to develop an action plan that integrates HIV prevention and substance abuse prevention." Federal sponsors in addition to CDC were SAMHSA, HRSA, the Office of National AIDS Policy, the Office of National Drug Control Policy, and NIDA/NIH. National organizations co-sponsoring the meeting included NASADAD, the Association of State and Territorial Health Officials, the National Alliance of State and Territorial AIDS Directors, Join Together, the Partnership for a Drug-Free America, the National Prevention League, and the Community Anti Drug Coalitions of America.

Dr. Steven Gust, Acting Director of NIDA's Office on AIDS presented an **"Overview of HIV/AIDS Research at the NIDA, NIH"** and presented a NIDA/OoA poster session at the June CPDD Conference held in San Juan Puerto Rico.

Dr. Gust held a training session on NIDA research grants and research training opportunities in the area of drug abuse-related HIV/AIDS in May at the University of Minnesota.

Ms. J.C. Comolli of NIDA's Office on AIDS attended a July 31 meeting at the **Office of National Drug Control Policy (ONDCP)** with representatives from the National Alliance of State and Territorial AIDS Directors (NASTAD), and staff from the Office on National AIDS Policy and the HHS Office of Planning and Evaluation. NASTAD requested the meeting to present findings from the States on ways to reduce the spread of infectious diseases related to drug use and to present areas of collaboration at the state and local level.

Dr. Lula Beatty, Director of NIDA's Special Populations Office, was a panelist discussing federal initiatives and opportunities in violence and drug abuse prevention at the annual convention of the **Association of Black Psychologists** in Chicago on August 2, 1996.

Dr. David Johnson, DBR, BNRB, represented NIDA at a meeting entitled **"Exploring Alternatives to Abstinence for Nicotine Dependence"** sponsored by the Robert Wood Johnson Foundation in Newark, NJ on May 23, 1996.

Dr. Tom Aigner, DBR, BNRB, represented NIDA at the **XVI Congress of the International Primatological Society** in Madison, WI on August 11-16, 1996.

Dr. Jaylan S.Turkkan, Chief of the Behavioral Sciences Research Branch, Division of Basic Research, chaired the **Federal Funding Poster Session** at the San Francisco annual meeting of the **American Psychological Society** (June 29- July 2, 1996).

Dr. Jaylan Turkkan and Dr. Timothy Condon held a breakfast roundtable entitled **"Cents and Sensibility: How to Support Your Career in Drug Abuse Research"** at the American Psychological Society Meeting in San Francisco in July, 1996. They discussed research training and early research career support opportunities such as fellowships, career development awards, and the newly initiated NIDA B/START program.

Dr. Jaylan Turkkan gave a presentation as discussant in a symposium entitled **"Laboratory Models of Drug Abuse"** at the American Psychological Association annual meeting in Toronto, Canada in August. She also chaired a lecture session given by Dr. Robert Balster entitled "Scientific Perspectives on Inhalant Abuse".

Dr. David Shurtleff chaired a lecture session at the American Psychological Association given by Dr. Thomas Coates **"Drug Abuse and HIV Transmission: What's Needed to Protect the Next Generation"**.

Dr. Cora Lee Wetherington hosted a NIDA hospitality suite event at the American Psychological Association annual meeting in Toronto, Canada entitled **"Drug Abuse, Women and Gender Differences: Research Opportunities at NIDA".**

Dr. Lynda Erinoff co-chaired a symposium at the College on Problems of Drug Dependence entitled **"Using Molecular Biological Tools to Explore Behavior".**

Dr. Cora Lee Wetherington was a discussant in a symposium entitled **"Drugs of Abuse and Gender Differences"** at the College on Problems of Drug Dependence meeting in San Juan, Puerto Rico.

On May 13, Dr. Frank Vocci presented at a Loyola University of Chicago sponsored symposium entitled **Cocaine and the Amphetamines: Effects on Brain and Behavior**. The title of Dr. Vocci's presentation was: **"Neurobiological Advances in the Pharmacology of Cocaine: Implications for Medications Development."**

On May 18, Joel Egertson, Senior Advisor to the Director, Medications Development Division, gave a presentation entitled **"Expanding Drug Abuse Treatment: We're All In This Together"** at the Maryland Addictions Directors Council (MADC) Conference on **"Coping with Change: Getting a Grip"** in Ocean City MD. Mr. Egertson discussed the work of the NIDA medications development program, and the role of pharmacotherapy in drug abuse treatment in an environment of managed care and cost containment in health care.

On June 5, Dr. Peter Cohen presented a seminar (organized by MDD) with Mercedis Serabian, Ph.D., on **"Regulatory and Ethical Issues in the Development of an Anti-Cocaine Vaccine."**

On June 19-22, Dr. Peter Cohen participated in the **Eighth Annual Bioethics Summer Retreat,** Copper Mountain, Colorado. Discussions included: "Screening Pregnant Women and Babies for HIV Infection: Privacy and its Limits" and "Perinatal AIDS: Maternal/Fetal Conflict".

On June 24, Drs. James Hill and Frank Vocci co-chaired a workshop at the College on Problems of Drug Dependence meeting in San Juan, Puerto Rico. The purpose of the workshop was to illustrate new statistical methods used in the evaluation of urine testing for illicit drugs as an efficacy marker for potential pharmacotherapies. Dr. K.-Y. Liang of Johns Hopkins University spoke of his longitudinal analysis methods and their application to the evaluation of illicit drug use in urine data in clinical trials involving new medications.

On June 24, Dr. Peter Bridge of MDD served as a discussant at the CPDD session on **Substance Abuse Medication Development and HIV Infection.**

On June 27, Dr. Frank Vocci presented the approaches to development of a medications for cocaine dependence to a satellite meeting on methamphetamine abuse. The meeting was co sponsored by CSAT and CPDD.

On August 12, Dr. Frank Vocci served as a discussant at a session entitled, **"Current Trends in the Pharmacotherapy of Opiate Abuse"** at the American Psychological Association meeting in Toronto, Canada.

Dr. Joseph Frascella, Chief of the Etiology and Clinical Neurobiology Branch, Division of Clinical and Services Research served as a moderator for the oral research presentations at the recent meeting, **"Building International Research in Drug Abuse: Opportunities and Challenges"** at the CPDD meeting in San Juan, Puerto Rico, on June 22, 1996.

Dr. Frascella was a faculty participant in the **"NIDA Special Populations Research Training Workshop on Morphine and Nitric Oxide"** held in Melville, New York, June 5 - 7, 1996. He gave a seminar entitled **"Neuroscience Research at NIDA"** as well as a seminar entitled **"Critical Aspects of the Grant Process."**

Dr. Mac Horton of the Etiology and Clinical Neurobiology Branch, Division of Clinical and Services Research, presented a workshop on **"Neuropsychology of Drug Abuse: Assessment, Residual Effects and Ecological Validity"** to the Psychology Staff and interns at Crownsville State Hospital Center, Crownsville, Maryland, on May 17, 1996.

Dr. Horton attended the **104th American Psychological Association Annual Convention** in Toronto, Canada, August 8-13, 1996 and chaired a Symposium on **"Neurobiological and Neuropsychological Assessment of Drug Abuse"**, a Poster Session on **"Applied Research on Addictions,"** and an Invited Address by George De Leon, Ph.D, on "Therapeutic Community: Advances in Research and Practice."

Dr. Harold Gordon presented a paper at the **104th American Psychological Association Annual Convention** in Toronto, Canada, August 8-13, 1996 entitled, **"Environmental and Biological Interactions: Etiologies of Drug Abuse and Violence,"** which summarized data by NIDA grantees and others suggesting some common biological and environmental factors underlying both drug abuse and violent behavior. Dr. Gordon also chaired an Invited

Address by Jack Henningfield, Ph.D, of NIDA's Division of Intramural Research on "Public Policy Foundation: Up in Smoke--Nicotine Research Travails."

On July 10, 1996 Dr. Dorynne Czechowicz, TRB, DCSR represented NIDA at an **Institute of Medicine Planning Workshop on Attention Deficit Hyperactivity Disorder: Issues of Definition, Diagnosis, and Management** which was held at the National Academy of Sciences, Washington, D.C. Federal representatives from NIDA, NIMH, NICHD, and the Department of Education Office of Special Education Programs participated in discussions of Federal Interests and Research Priorities.

Drs. Elizabeth Rahdert and Lisa Onken of the Division of Clinical and Services Research participated in the Annual Convention of the American Psychological Association (APA), held August 9-13, 1996, in Toronto, Canada. Dr. Rahdert organized and participated in the continuing education (C.E.) workshop entitled **"Adolescent Drug Abuse Treatment Strategies"** and the NIDA Child and Adolescent Workgroup hospitality suite hour entitled **"Research and Clinical Applications in Child and Adolescent Drug Abuse: Dialog and Resources."** She also chaired the symposium **"Assessment Associated with Adolescent Drug Abuse Treatment"** and served as the discussant on the symposium **"Recent Findings on Adolescent Drug Abuse and Protective Factors."** Dr. Onken organized and chaired the C.E. workshop entitled **"Drug Addiction Treatment: Clinical Applications of Recent Research Advances."**

Mr. Thomas Vischi and Dr. William S. Cartwright assisted in the planning of the Secretary's national conference, **"Access and Opportunity: A National Leadership Conference on Managed Behavioral Health Care,"** May 14 and 15, 1996, Arlington, VA.

Dr. Frank Tims chaired a NIDA symposium, **"Managed Care Research and Institutional Change,"** in conjunction with the annual meeting of the Association for Health Services Research in Atlanta, August 9. The symposium presented research on the implementation and impact of financing drug treatment services through managed care arrangements. Dr. William Cartwright served as a discussant in that symposium.

Dr. Bennett Fletcher attended the American Psychological Association meeting in Toronto August 9-13. He presented two papers, **"A Brief History of Treatment Outcome Research in the United States"** and **"Drug Abuse Treatment and Services: Reducing Violence in the Community"** (co-authored with Dr. Peter Delany), and also served as a discussant in a symposium presenting recent NIDA-funded research on treating special populations in therapeutic communities.

Timothy P. Condon, Ph.D., NIDA's Associate Director for Science Policy, and Theresa Levitin, Ph.D., Deputy Director, OEPR co-chaired a **Grant Writing Workshop** for young researchers at the College on Problems of Drug Dependence annual meeting in San Juan, Puerto Rico, April 23, 1996. Participants saw a "mock IRG" review and received a resource guide of information, contacts and selected articles.

Dr. Timothy Condon was invited to address the **American Psychological Society's (APS) Annual Board Meeting**, June 29 1996, during APS's 8th Annual Convention in San Francisco, California, June 29-July 2, 1996. He discussed NIDA's research portfolio and research training efforts.

At the Conference On Drug Abuse in Toronto, August 12, 1996, Drs. Condon, Levitin, and Turkkan hosted a grant writing workshop. Dr. Condon also co-hosted a session entitled **"Seeking NIDA Funding on the Neurobiological Basis of Drug-Related Behavior"** with Dr. Harold Gordon, DEPR. In addition, Ms. Carolyn Mosher, OSPC hosted a workshop on **"NIDA's Innovative Science Education Program".**

Dr. Condon was invited to address the Annual Meeting of the American Academy of Child and Adolescent Psychiatry's (AACAP) standing Research Workgroup, on August 14, 1996, in Washington, D.C. He spoke about NIDA's research portfolio, research training, and efforts to recruit child and adolescent psychiatrists into drug abuse and addiction research.

Dr. Cora Lee Wetherington, NIDA's Women's Health Coordinator, co-chaired a session, **"Drugs of Abuse and Gender Differences"** at the annual CPDD meeting in San Juan. She also served as the discussant for the symposium.

Dr. Cora Lee Wetherington hosted a hospitality hour, **"Drug Abuse, Women, and Gender Differences: Research Opportunities at NIDA"** at the NIDA/APA organized Conference on Drug Abuse at the annual meeting of the American Psychological Association in Toronto.

Drs. Zili Sloboda, William Bukoski and Rebecca Ashery represented NIDA's Division of Epidemiology and Prevention Research at the **Society for Prevention Research** meeting held in San Juan, Puerto Rico. In conjunction with this meeting Dr. Ashery also held a small meeting with experts in the field to examine the issue of child monitoring for family prevention intervention.

At the NIDA/American Psychological Association Science Directorate co-sponsored Conference on Drug Abuse (Toronto, Ontario, August 9-13, 1996) Meyer Glantz, Ph.D. of DEPR chaired several sessions of etiology researchers to explore more formal efforts to integrate and facilitate the activities and community of etiology researchers. Several initiatives were proposed and these will be explored further and developed by NIDA's Resiliency and Risk/ Etiology Workgroup during the coming year. Included is an increased presence and involvement of etiology research in the activities and mission of the Society for Prevention Research.

Richard H. Needle, Ph.D., M.P.H., presented highlights from the research portfolio of the Community Research Branch, DEPR for the August 2, 1996 inaugural of the new location of the National Development and Research Institutes, Inc. in New York City. NDRI moved from Beach Street to the Two World Trade Center.

Richard H. Needle, Ph.D., M.P.H., appeared on a WORLDNET broadcast to Latin America on August 8 which focused on **"Illegal Narcotics and AIDS: Ties that Bind."** Dr. Needle, along with Dr. Larry Bruni, a Washington-area physician known for his work with HIV-positive patients, engaged in an interactive, question-and-answer discussion with overseas panelists from Peru, Ecuador, and Barbados. The WORLDNET Dialogue program was the seventh in a series on Narcotics Issues that have been produced by the U.S. Information Agency Television and Film Service. Prior programs have addressed the environmental impact of cocoa production, the economic impact of money laundering in Latin America, drug prevention programs for youth, and drug abuse prevention and treatment for the general population.

Dr. Richard H. Needle, Ph.D., M.P.H., gave a presentation on research priorities in community based prevention of the risk behaviors associated with drug abuse, HIV/AIDS, and other infectious diseases, at the **Institute for Health Care Policy at Georgetown University Medical Center** in Washington, D.C., on August 12.

Dr. Leslie Cooper, ERB/DEPR, recently served as the Co-Chair for the **Healthy People 2000 Progress Report Sub-Workgroup for Priority Area 14 (Maternal and Infant Health) on Substance Abuse**. She also served as an active member of the Healthy People 2000 Progress Review for the Black Americans Sub-Workgroups for both Research and Health Services.

Dr. Coryl Jones, ERB/DEPR, has participated in the steering committees for several national efforts focused on child abuse and on domestic violence. One of the results will be the National Conference on Child Abuse and Neglect to be held in Washington, DC, September 16-21, 1996. Another activity is the coordinating committee of agencies providing research support on child abuse and on domestic violence.

Mario De La Rosa, Ph.D., formerly with CRB/DEPR and now with NIDA's Office of Special Populations, gave two presentations at the NIDA-sponsored Hispanic Drug Abuse and AIDS Research Conference, held in conjunction with the annual meeting of the College on Problems of Drug Dependency in San Juan, Puerto Rico in June. One presentation was on **"The Role of Social Support Systems in Drug Use Behavior of Hispanics,"** and the second was on **"The State of Drug Abuse Research among Hispanics."**

Susan Coyle, Ph.D., of CRB/DEPR represented NIDA at the **American Sociological Association's 5th Annual Research Support Forum**. The forum, held August 17-18 during ASA's annual meeting in New York City, included a poster session for participants to talk one-on-one with Federal program officials about research priorities, research grant application procedures, and specific areas of research interest and concern.

Peter Hartsock, Ph.D., served on the **Advisory Committee for the National Council on International Health's Annual Conference** in Washington, D.C., June 9-12. The theme of the conference was new and emerging infectious diseases (EREIDs). In recognition of the
increasing health threat and global importance of EREIDs, Vice President Albert Gore and DHHS Secretary Donna Shalala released a Presidential Decision Directive at the conference that pledged additional Federal support for new research in this area.

Mario De La Rosa, Ph.D., of NIDA's Office of Special Populations, gave a presentation on **"Developing a Conceptual Model to Understand the Drug Use/Crime Relationship"** at the American Psychological Association annual

meeting in Toronto, Canada on August 11, 1996.

Dr. Edythe D. London, DIR, presented a paper entitled, **"Cocaine-Related Cues Elicit Craving and Activate Cortical Circuits Relevant to Episodic Memory"** at the 51st annual meeting of the Society of Biological Psychiatry, New York, NY, May 1-5, 1996.

Dr. Edythe D. London presented a lecture entitled, **"Correlation of Cue-Elicited Cocaine Craving with Metabolic Activation in Prefrontal Cortex and Medial Temporal Lobe"** at the annual meeting of the College on Problems of Drug Dependence, San Juan, PR, June 22-27, 1996.

Dr. Monique Ernst, DIR, presented papers entitled, **"Influence of Sex and Age on Brain Glucose Metabolism in Control and ADHD Adults"** and "**Low Dopamine Activity in Lesch-Nyhan Disease. An 18F-fluorodopa PET Study"** at the Annual Meeting of the Society for Nuclear Medicine, Denver, CO, June 1996.

Dr. Alexis Thompson, DIR, presented a paper entitled, **"Evidence that Kappa-Opioid Agonists Induce Long-Term Alterations in Dopamine Uptake and Release"** at the International Narcotics Research Conference, Long Beach, CA, July 21-26, 1996.

Dr. Alexis Thompson presented a paper entitled, **"Interaction of Kappa-Opioid Agonists with Cocaine: Characterization by Quantitative Microdialysis"** at the annual meeting of the College on Problems of Drug Dependence, San Juan, PR, June 22-27, 1996.

Dr. Bruce Vaupel, DIR, presented a paper entitled, **"Rate of Morphine Administration Affects Subjective Responses of Experienced Heroin Users"** at the International Narcotics Research Conference, Long Beach, CA, July 21-26, 1996.

Dr. Ronald Herning, DIR, presented a paper entitled, **"Electrophysiological Findings in Substance Abuse"** at the 3rd annual Psychiatric Electrophysiological Association in Miami, FL, May 1996.

Dr. Tsung Ping Su, DIR, presented a paper entitled, **"Delta Opioid Peptide, DADLE, Attenuates METH-Induced DA Neurotoxicity in Mice"** at the 1996 International Narcotics Research Conference, Long Beach, CA, July 21-26, 1996.

Dr. Jean Lud Cadet, DIR, presented a paper entitled, **"Methamphetamine Induces Apoptosis in Neural Cells"** at the annual meeting of the College on Problems of Drug Dependence, San Juan, PR, June 22-27, 1996.

Dr. Karen Bolla, DIR, presented a paper entitled, **"Differential Effects of Withdrawal on Neurocognitive Functioning in Cocaine and Cocaine and Alcohol Abusers"** at the annual meeting of the College on Problems of Drug Dependence, San Juan, PR, June 22-27, 1996.

Dr. Ronald Herning presented a paper entitled, **"Gender Differences in Cocaine Dependence: Preliminary Neuropsychiatric Findings"** at the annual meeting of the College on Problems of Drug Dependence, San Juan, PR, June 22-27, 1996.

Dr. Hema Mann, DIR, presented a paper entitled, **"Multidrug Resistant (mdrla) Knockout Mice are Differentially Affected by Methamphetamine (METH) in Methylenedioxy-Methamphetamine (MDMA)",** at the annual meeting of the College on Problems of Drug Dependence, San Juan, PR, June 22-27, 1996.

David A. Gorelick, M.D., Ph.D., Chief, Treatment Branch, DIR, gave grand rounds at the Neurology Service, West Los Angeles VA Medical Center, on Aug. 16, 1996. His topic was **"Neurologic Consequences of Cocaine Use."**

Jonathan L. Katz, DIR, was invited to present a paper entitled **"Dopamine Uptake Inhibitors, Agonist Efficacy and Cocaine Abuse Treatments"** as part of a symposium: Agonist Efficacy, Drug Dependence, and Medications Development at the Annual meeting of the College on Problems of Drug Dependence.

Sari Izenwasser, DIR, was invited to give a series of lectures to graduate students in the Department of Pharmacology at George Washington University School of Medicine.

Sari Izenwasser was selected to present a paper entitled **"Regulation of Dopamine D2 Receptor Function by k-opioid Agonists: Biochemical and Neurochemical Studies"** as part of a symposium: Opioid-Dopamine

Interactions at the International Narcotics Research Conference.

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Media and Education Activities

Press Conferences

Press Conference on the Partnership for a Drug-Free America's National Heroin Campaign. On June 17, 1996, Dr. Alan Leshner joined Gen. Barry McCaffrey, Director of the Office of National Drug Control Policy, and Richard Bonnette, PDFA President and CEO in a press conference to release the PDFA's new national heroin campaign. Dr. Leshner's statement focused on the dangers of heroin use and the importance of research as a part of the President's comprehensive drug strategy.

Press Conference to Announce the Findings from the 1995 National Household Survey on Drug Abuse and the 1995 Drug Abuse Warning Network. On August 20, 1996, NIDA Deputy Director, Richard A. Millstein participated in a DHHS press conference to announce the findings of the 1995 National Household Survey on Drug Abuse and the 1995 Drug Abuse Warning Network. DHHS Secretary Donna Shalala, ONDCP Director, Gen. Barry McCaffrey, and SAMHSA Administrator, Nelba Chavez, released the findings at a Boys and Girls Club in Washington, D.C.

Media Advisories

May 1996: NIDA-Funded Project--BEEMNET--Highlights Brain Awareness Week. NIDA joined dozens of other Federal and private-sector sponsors in educational activities to mark Brain Awareness Week, May 12-18. The NIDA-funded BEEMNET (Brain Exchange Electronic Mentorship Network) was one unique project featured during Brain Awareness week, organized by the Society for Neuroscience and consisting of more than 100 events across the U.S., Canada and Mexico to educate the public about the impact of neuroscience research on health and human potential.

May 2, 1996: NIDA Seminar to Help With Drug Abuse Prevention in Communities Throughout Ohio. NIDA and the Ohio Department of Alcohol and Drug Addiction Services sponsored a one-day seminar, "Strengthening Communities through Prevention: Applying Research to Policies and Programs." The event, held Thursday, May 9 focused on state-of-the-art approaches to prevention of alcohol and other drug abuse.

May 6, 1996: Messing with Your Head: Cocaine Found to Affect Endorphin Gene in Brain. A quote from Dr. Leshner was included in this news release from the Rockefeller University reporting that the effects of the addictive drug cocaine result, in part, from altering the activity of a gene in the brain. The study by Dr. Mary Jeanne Kreek and

colleagues was published in the May issue of *Molecular Brain Research*.

June 7, 1996: New Research May Explain Mechanisms of Abnormalities in Offspring Prenatally Exposed to Cocaine. University of Massachusetts researchers, funded by NIDA, have reported findings of experiments that provide strong evidence that cocaine interacts directly with specific cocaine receptors in the fetal rat brain. The study authored by Lauren Shearman, Lucille Collins, and Jerrold Meyer appeared in the June issue of the Journal of Pharmacology and Experimental Therapeutics.

June 19, 1996: What Can Your Listeners Do About Alcohol and Drug Abuse? A quote from Dr. Leshner was included in this media Advisory from Join Together announcing that Dr. Leshner and Dr. David Rosenbloom, director of Join Together, were available for press interviews while in San Antonio, TX for a Conference: What We Need to Take the Lead: Local Public Policy Matters.

August 2, 1996: ImmuLogic Awarded SBIR Grant to Develop Cocaine Vaccine. A quote from Dr. Leshner was included in this news release from ImmuLogic Pharmaceutical Corporation announcing it has received a Phase II Small Business Innovation Research (SBIR) grant from NIDA to complete preclinical development of the Company's therapeutic vaccine to treat cocaine abuse.

Other Press Activity

May 1996, Columbus, OH. Dr. Leshner was interviewed by the Columbus Dispatch for an article that appeared the day prior to the NIDA Town meeting in Ohio. While in Ohio, Dr. Leshner held an editorial board meeting with editors of the Columbus Dispatch. Clips from Dr. Leshner's speech were up linked through satellite to television stations throughout the State.

May 17, 1996: McCaffrey, Leshner Address COG Substance Abuse Symposium. A quote from Dr. Leshner was included in the press release issued by the Council of Governments announcing that Dr. Leshner and General Barry McCaffrey would be addressing attendees at the Council of Government's Regional Substance Abuse Symposium.

Letter to the Editor: On June 25, 1996, The Washington Post Health Magazine published a letter to the Editor from Dr. Leshner commenting on the May 7 article "The Detoxification Conundrum." Dr. Leshner's letter corrects and clarifies misinformation given in the article and presents issues of drug addiction that were not addressed in the article.

June 12, 1996, Dr. Leshner participated in an international broadcast for WORLDNET with Latin American Officials addressing the drug problem. The program is one of a series of programs on Narcotics Issues For Latin American And Caribbean Networks. The program was interactive with panelists in Peru, Ecuador, and Barbados.

June 22-27: College on Problems of Drug Dependence. Dr. Leshner was interviewed by several local media outlets during the CPDD Conference. The local English and Spanish dailies carried stories on the Conference and included quotes from Dr. Leshner.

On-Camera Interview - On July 17, Dr. Leshner was interviewed on camera for an ABC News segment on a Nature article on the effects of nicotine and similarity to other addictive drugs. The segment aired on the ABC World News Tonight, July 17.

August 9-13, 1996: Conference on Drug Abuse. There was a significant media presence at the APA/CODA conference. Dr. Leshner was interviewed by a Toronto Radio station following his presentation. Stories appearing in the Toronto daily papers listed drug abuse among key issues being discussed at the conference.

Dr. Alan I. Leshner published recent research findings leading to the development of an anti cocaine medication in his article, **"Molecular Mechanisms of Cocaine Addiction, "** in the *New England Journal of Medicine*, 335, pp. 128-129 (July 11), 1996.

Dr. Alan I. Leshner authored a guest editorial for the new journal *Molecular Psychiatry* 1, pp. 168 169, 1996. Dr. Leshner's editorial, **"Drug Abuse and Addiction Research: Implications for the Field of Psychiatry"** introduced

articles written by three NIDA-supported researchers.

Dr. Alan I. Leshner prepared an Op-Ed piece, **"Drug Abuse and Addiction: Roles for the Professional Psychologist"**, for the "Viewpoint" section of the *National Psychologist*, an independent bimonthly newspaper which circulates to over 25,000 practitioners nationwide.

On August 13, 1996, the *New York Times'* science section carried an article devoted to the biological basis of craving and featured the work of a number of NIDA grantees.

NIDA Exhibits

NIDA has exhibited at the following meetings/conferences over the last several months:

American Psychiatric Association
May 4-9, 1996
New York, NY

NIDA/Ohio Dept. Of Alcohol and Drug Addiction Services
Strengthening Communities Through Prevention:
Applying Research to Policies and Programs
May 9, 1996
Columbus, OH

National Institutes of Health
Employee Health Fair
May 14-15
Bethesda, MD

Council of Governments
Regional Substance Abuse Symposium
May 17, 1996
Washington, D.C.

Association for Health Services Research
13th Annual Meeting
June 9-11, 1996
Atlanta, GA

American Nurses Association
Biennial Convention
June 15-17, 1996
Washington, D.C.

Association for Health Services Research
13th Annual Meeting
June 9-11, 1996
Atlanta, GA

College on Problems of Drug Dependence
Fifty-Eighth Annual Scientific Meeting
June 22-27, 1996
San Juan, Puerto Rico

100th Annual Convention and Exhibition
National Parent Teachers Association (PTA)
June 22-25, 1996
Washington, D.C.

American Psychological Society
Eighth Annual Convention
June 29 - July 2, 1996
San Francisco, CA

XI International Conference on AIDS
July 7-12, 1996
Vancouver, BC Canada
(Provided publications and other materials for the NIH exhibit)

20th Annual Conference on Addiction Treatment
National Association of Alcohol and Drug Abuse Counselors
July 24-27, 1996
Minneapolis, MN

American Psychological Association
NIDA Conference on Drug Abuse
August 9-13, 1996
Toronto, Canada

National Conference on Treatment Initiatives
National Treatment Consortium, Inc.
August 18-20, 1996
Bethesda, MD

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Publications

Kuhar, M.J., and Pilotte, N.S. **Neurochemical Changes in Cocaine Withdrawal**. SAMHSA TIPS, 17: pp. 260-264, 1996

Cohen, Peter. **How Shall They Be Known? *Daubert v. Merrell Dow Pharmaceuticals and Eye-witness Identification***. Pace Law Review 16: pp. 237-283, 1996.

Cohen, Peter. **Single vs. Multiple Sites and Mechanisms of Inhaled Anesthetics.** Anesthesia and Analgesia 83: p. 205, 1996.

Planned Meetings

Dr. Tom Aigner will be representing BNRB, DBR as a co-chair of a NIDA-sponsored satellite symposium to the **Society for Neuroscience annual meeting** in Washington, DC on November 16, 1996. Entitled **"What Can Cognitive Neuroscience Tell Us About Drug Abuse Disorders?"**, the meeting was organized by the Behavioral Neurobiology Branch (DBR) and the Etiology and Clinical Neurobiology Branch (DCSR).

A conference entitled **"The Science of Self-Report: Implications for Research and Practice**", to be co-chaired by Dr. Jaylan Turkkan will be held November 7-8, 1996, at the Masur Auditorium, on the NIH campus in Bethesda, MD. The goal of this conference is to discuss recent developments in the scientific study of self report. Research to be presented demonstrates that there are many conditions where self-reports are likely to be biased, for example, when memory processes prevent the accurate retrieval of information. Exciting new approaches to improving self-report data will be presented.

Mario De La Rosa, Ph.D., Office of Special Populations, will be chairing a joint **NIDA/NIH Office of Minority Research meeting** in Washington, D.C. on September 26-27. The meeting is entitled **"Drug Abuse Research with Minority Populations: Methodological and Theoretical Issues and Concerns."**

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Staff Highlights

Staff Changes

Timothy P. Condon, Ph.D. was appointed to the positions of Associate Director for Science Policy, NIDA, and Director of NIDA's Office of Science Policy and Communications (OSPC). In these roles, Dr. Condon oversees the Institute's science planning, policy, congressional and communications activities and coordinates NIDA's research training and science education programs.

Barry Hoffer, M.D., Ph.D., a neuropharmacologist from the University of Colorado's Health Sciences Center joined NIDA in early September as the new Scientific Director and head of the Institute's Intramural Research Program at the Addiction Research Center.

Harry W. Haverkos, M.D. has moved to the Intramural Research Program at the Addiction Research Center to become more fully involved in hands-on AIDS-related research activities.

Steven W. Gust, Ph.D. has been appointed Acting Director, Office on AIDS (OoA).

Bennett Fletcher, Ph.D., has been selected to serve as the Acting Chief of the Services Research Branch, DCSR.

David McCann, Ph.D., was selected as Chief of the Pharmacology and Toxicology Branch, MDD in March 1996.

Mr. Tom Vischi of the Services Research Branch, DCSR, is on extended detail to the Assistant Secretary for Planning and Evaluation to continue work on managed care issues.

J.C. Comolli, R.N., M.B.A., joined the OoA in June, and Lynda Erinoff, Ph.D. joined the office in September.

Naimah Weinberg, M.D., joined NIDA's Epidemiology Research Branch, Division of Epidemiology and Prevention Research, in May, 1996. Most recently, Dr. Weinberg was staff psychiatrist at Kennedy Krieger Institute in Baltimore, and assistant professor in the division of child psychiatry at Johns Hopkins Medical Institutions. She is a board-certified child psychiatrist, with clinical training from the University of Michigan, and post-doctoral work in epidemiology and public mental health at Johns Hopkins School of Hygiene and Public Health.

Hari H. Singh, Ph.D., joined the Basic Neurobiology & Biological Systems Research Branch, Division of Basic Research, on December 11, 1995. Currently, he is serving as the program officer on NIDA's Drug Supply and Analytical Services Support Program. Dr. Singh obtained his Ph.D. in chemistry and has worked at several research institutes/universities.

Dr. Singh's expertise is in medicinal chemistry, analytical chemistry, and biomedical sciences. Prior to coming to NIDA, he worked for the Food & Drug Administration and the U.S. Consumer Product Safety Commission.

Jonathan D. Pollock, Ph.D., joined NIDA in July as a program officer in the Basic Neurobiology and Biological Systems Research Branch. Dr. Pollock was an assistant scientist at Purdue University. He did his doctoral work in the laboratory of Eric R. Kandel at Columbia University College of Physicians and Surgeons where he received his Ph.D. in October of 1985. He did post-doctoral work at Caltech in the laboratory of Mark Tanouye and at the University of Utah in the laboratory of Mario Capecchi. His expertise is in the areas of the molecular basis of synaptic plasticity, transgenic animals, and mouse genetics. He has published papers that have appeared in Nature Genetics, the Journal of Biological Chemistry, and the Journal of Neuroscience as well as commentaries that have appeared in The World and I, the magazine of the Washington Times, and in The New York Times.

Jane Acri, Ph.D. has been selected to join the Pharmacology and Toxicology Branch of the Medications Development Division as a Health Scientist Administrator. Dr. Acri is currently working in the Neuroimaging/Drug Action Section of the Division of Intramural Research. She will be concentrating her efforts within the MDD preclinical Cocaine and Opioid Treatment Discovery Programs.

Avraham Forman, Deputy Chief of the Public Information Branch, OSPC, retired on August 30, 1996 after 30 years with the Commissioned Corps and 17 years at NIDA.

Frank Tims, Ph.D., formerly the Chief of DCSR's Services Research Branch, retired from Federal Service effective August 30, 1996.

Jamie Chriqui, OSPC, left NIDA in late July 1996 for a position in the private sector.

Awards

NIH Director's Award Recipients

Khursheed Asghar, Ph.D., DEPR
In recognition of his leadership, dedication, and outstanding effort in managing the review of multiple, high priority new initiatives and a record-breaking number of grant applications.

Helen Cesari, M.S., CRB, DEPR
In recognition of her outstanding leadership, resourcefulness, and extraordinary contribution to the development of NIDA's extramural HIV prevention program.

Suzanne M. Cole, MASB, OPRM
In recognition of her substantial contributions in improving and enhancing the administrative processes for the National Institute on Drug Abuse.

Timothy P. Condon, Ph.D., OSPC
In recognition of his outstanding leadership in expanding the infrastructure for drug abuse research training and in establishing new relationships between NIDA and the scientific community-at-large.

Jurij Mojsiak, Ph.D., MDD
In recognition of his role in the review and implementation of the NIDA funded Medications Development Research Units at DVAMCs focused on the development of pharmacologic treatments for cocaine dependence.

Chanvadey Nhim, MASB, OPRM
In recognition of her exemplary performance and many contributions in support of the administrative activities of the National Institute on Drug Abuse.

Commissioned Corps Outstanding Service Medal

Rebecca S. Ashery, D.S.W., PRB, DEPR
In recognition of her exceptional contributions to the field of drug abuse in the areas of community and prevention research, AIDS education, technology transfer, and women's issues.

Betty Tai, Ph.D., MDD
In recognition of her continuous leadership in the establishment of a Clinical Cocaine Treatment Program.

Other Honors/Awards

NIDA Director Dr. Alan I. Leshner has been elected as an Honorary Fellow of the American Psychiatric Association.

Dr. Naimah Weinberg, ERB, DEPR, was nominated to the editorial board of the Journal of the American Academy of Child and Adolescent Psychiatry. She has been reappointed to the Substance Abuse Committee of the American Academy of Child and Adolescent Psychiatry.

Dr. Toni Shippenberg, DIR, received the Joseph Cochin Young Investigator Award for outstanding research in the field of drug abuse at the annual meeting of the College on Problems of Drug Dependence, San Juan, PR, June 22, 1996.

Dr. Alexis Thompson, DIR, received a travel award from the International Narcotics Research Conference to attend their annual meeting in Long Beach, CA, July 21-26, 1996.

Over the last several months, **Dr. George Uhl, DIR,** served on search committees for two NIH institutes (NIDA and NCHGR) and was appointed to the program committee, Society for Neuroscience, and the Scientific Advisory Board, American Parkinson's Disease Association (in recognition of his work on monoamine transporters possibly important for neurodegeneration).

Dr. Lula Beatty, Director of NIDA's Special Populations Office, has been appointed to the NIH Extramural Associates Advisory Board to serve a three-year term.

Dr. Mac Horton has been appointed the 1997 Program Committee Chairperson for the Division of the Psychology of Addictive Behaviors of the American Psychological Association.

Grantee Honors

In June 1996, **Charles O'Brien, M.D., Ph.D.** of the Philadelphia VA M.D. Program was awarded the Burlingame Award by the Institute of Living - Hartford, CT for achievements in research and education in the area of mental health.

Dr. Nicholas Bodor, Professor of Medicinal Chemistry, Center for Drug Discovery, University of Florida, a NIDA grantee, was awarded THE 1996 LEO FRIEND AWARD. This award, sponsored by the I & EC Division of the American Chemical Society (ACS), is given annually in memory of Leo Friend, the father of CHEMTECH. Every year, one article published in CHEMTECH is chosen as the "most significant in advancing the chemical-related sciences and/or technology to enhance public good". Dr. Bodor is the 21st recipient of the Leo Friend award. The manuscript written by Bodor that was selected for the award is "Design of Biologically Safer Chemicals". Dr. Bodor is one of the pioneers in the development of innovative methodologies for targeted drug delivery.

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