
National Institute on Drug Abuse
Director's Report
to the
National Advisory Council on Drug Abuse
February, 1997

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National Institute on Drug Abuse**Director's Report to the National Advisory Council on Drug Abuse****February 1997**

Research Findings

Basic Research

Brain Substrates of Cocaine Addiction

Dr. Nora Volkow and her colleagues at the Brookhaven National Laboratory examined the rate of clearing of cocaine and methylphenidate in the brains of baboons. They found a dramatic difference between the two drugs, with cocaine being cleared much more rapidly than methylphenidate. Since cocaine tends to induce binging behavior whereas methylphenidate does not, Volkow and her colleagues postulate that (a) it may be the rapid uptake of these two (dopamine transporter inhibiting) drugs that gives rise to the initial pleasurable experience, and that (b) the extremely rapid clearing of cocaine sets the stage for the binging behavior exhibited by addicts. Drs. Volkow and colleagues also identified novel longer-term changes induced by cocaine withdrawal in addicts. A transient increase in the metabolic activity within the orbitofrontal cortex, in the thalamus, and in the striatum occurs within 2p;4 weeks following detoxification, whereas a longer-term (1p;4 month) depression in metabolic activity is seen in these identical brain regions. The authors propose that the early secondary activation (effects seen within 2p;4 weeks) seen in drug addicts might account for the dramatic difference in brain functioning known to exist between the occasional drug user and the cocaine addict. Volkow, N.D., Ding, Y.-S., Fowler, J. S., & Wang, G.-J. Cocaine Addiction: Hypothesis Derived from Imaging Studies with PET. *J. Addictive Diseases*, 1996.

Neuronal Plasticity Following Chronic Cocaine

A recent paper by Dr. Ann Graybiel and her colleagues at MIT (*Neuron* 17: pp. 147-156, 1996) showed that repeated cocaine administration to rats is accompanied by network-level changes in the expression of the Fos-Jan family of proteins in the basal ganglia that occur with the known time course of behavioral sensitization to the drug. These findings suggest an enduring functional reorganization of circuits in the basal ganglia following extended cocaine administration that might underlie the stereotyped behaviors typical of a sensitized animal. These same basal ganglia circuits are known to connect to cortical regions that have been implicated in humans with an altered metabolic activity associated with abnormal repetitive behavioral patterns.

Distribution of Mu and Kappa Opioid Receptors

NIDA grantees Dr. Howard Fields and Dr. Zhizhong Pan (University of California, San Francisco) have recently made significant gains in both opioid pharmacology and pain research. Dr. Fields, a pioneer in pain research, first described midbrain "on" cells (that turn on analgesia) and "off" cells (that turn off analgesia). Understanding how these cell types work is essential in our understanding of how the nervous system controls pain. At the 1996 Society for Neurosciences meeting, Drs. Fields and Pan presented data showing that mu, but not kappa, opioid receptors are located upon "on" cells; whereas kappa, but not mu, opioid receptors are located upon "off" cells. These differences help to explain why mu and kappa opioid-receptor activation have different effects on pain even though both mu- and kappa-opioid receptors are coupled to G proteins and act by modifying potassium channels. Understanding the functional neural basis of the analgesic effects of opioids will allow researchers to better target these neural systems through pharmacological means.

Drugs of Abuse and Neuronal Effects

Prenatal cocaine exposure has the potential to produce abnormal development of the nervous system and cause behavioral dysfunction. Levitt and colleagues (Jones et al., *Cerebral Cortex*, 6: pp. 431-445, 1996) examined the effects of cocaine on prenatal development by administering intravenous cocaine to pregnant rabbits. Their analysis of neural development centered on two regions of the cerebral cortex, the anterior cingulate and primary visual cortex, in which dopamine afferents, a target of cocaine, are differentially distributed. All postnatal rabbits exposed to cocaine prenatally displayed normal features of cortical organization such as lamination patterns, cytoarchitectonic differentiation, and cortical thickness. However, the structure and organization of dendrites in the cingulate cortex but not the primary visual cortex were altered. Less than fifty percent of the apical dendrites in cocaine-exposed animals extended into the layers II and III of the cortex as compared to control animals. The dendrites of exposed animals course through the cortex in an irregular and wavy manner instead of being straight and bundled. These data suggest that exposure to cocaine in utero can produce long lasting morphological changes affecting specific brain regions. The study also suggests that structural changes following prenatal cocaine exposure may also be found in the cingulate cortex of humans.

Chronic Morphine Induces Visible Changes in the Morphology of Mesolimbic Dopamine Neurons

Mesolimbic dopamine neurons arising from the ventral tegmental area (VTA) of the midbrain play an important role in opiate mediated reward and addiction. Previous work has shown that chronic exposure to opiates produce biochemical adaptations in this brain region. In a recent paper (Skclair-Tavron, et al., *Proceedings of the National Academy of Sciences*, 93: pp. 11202-11207, 1996), Dr. Eric Nestler and colleagues report that these biochemical changes are associated with morphological changes in VTA dopamine neurons. Chronic morphine treatment resulted in 25% reduction on average in the area and perimeter of VTA neurons. The opioid antagonist, naltrexone, or infusion of brain-derived growth factor prevented the structural changes from occurring in VTA dopamine neurons. In contrast, chronic morphine did not affect the size of non-dopaminergic neurons or change the number of dopamine neurons in the VTA. These data suggest structural changes in dopamine neurons produced by chronic morphine exposure may be related to the specific behavioral features of addiction, and lead to new approaches for the treatment of addictive disorders.

Anabolic Steroids & Sexual Behavior

NIDA supported research reports that different anabolic-androgen steroid (AAS) compounds have quite distinct effects on male sexual behavior. For example, administration of the 17 alpha-methylated compounds had the most deleterious effects in intact male rats; while, the 19-nortestosterone esters had minimal effects on sexual behavior at any dose. The individual AAS effects in male rat copulatory behavior were closely related to their effects on serum testosterone levels. In castrated male rats, in general the alpha-methylated compounds were relatively ineffective in maintaining sexual behavior. These findings suggest that examination of individual compounds is necessary as it provides a strong foundation for analysis of the physiological and behavioral responses to AAS combinations typically administered by human users. Clark, A.S., Harrold, E.V. & Fast, A.S., *Hormone & Behavior*, In Press; Clark, A.S. & Fast, A.S., *Behavioral Neuroscience*, 110, pp. 1-9, 1996.

Other recent findings in female rats also demonstrate disruption of estrous cyclicity and reproductive behavior when different AAS compounds are administered for a short-term at levels commonly used by humans. Blasberg, M.E. Langan, C.J. & Clark, A.S., *Physiology & Behavior*, In Press.

Mediation of Supersensitization of Adenylyl Cyclase via G

Dr. Zvi Vogel, a NIDA grantee, has reconstituted the ability of opioids to modulate adenylyl cyclase (AC) activity in COS-7 cells. COS-7 cells cotransfected with AC type V (AC-V) and -opioid receptor cDNAs display acute opioid inhibition of AC-V activity. Prolonged exposure to -opioid receptor agonists leads to a time-dependent development of supersensitization of AC-V, which is gradually lost following withdrawal of the agonist. The supersensitization can be prevented by pertussis toxin pretreatment, indicating the involvement of Gi/o proteins, or by co-transfection with scavengers of G dimers, indicating a role for G in AC supersensitization. Contrary to several other G-dependent signal transduction mechanisms (e.g. MAP kinase), AC-V supersensitization is not affected by the Ras dominant negative mutant N17-Ras. AC-V is localized in brain areas which are involved in reward pathways and drug addiction.

Elucidation of the precise mechanism of AC supersensitization should pave the way to a better understanding of and the design of strategies for preventing opioid abuse. Avidor-Reiss, T., ...and Vogel, Z., *J. Biol. Chem.*, 271: pp. 21309-21315, 1996.

Interactions Between Ifenprodil and the NMDA Receptor(NR)2B Subunit of the N-methyl-D-Aspartate (NMDA) Receptor

Dr. Michael Gallagher and colleagues, using chimeric NR2A/NR2B subunits co-expressed with NR1A, have localized a

determinant for high affinity ifenprodil interaction to a single amino acid (Arg-337). Ifenprodil had also previously been thought to be an antagonist at the polyamine site. Experiments with chimeric and mutant receptors have shown that Arg-337 is independent of NR2B-specific polyamine stimulation. Furthermore, it was shown that polyamine stimulation depends on the expression of NR1 splice variants, whereas high affinity ifenprodil inhibition is independent of NR1 isoform expression. These studies provide evidence that ifenprodil and polyamines interact at discrete sites on the NR2B subunit. Gallagher, M.J. Huang, H., Pritchett, D.B., and Lynch, D.R., *J. Biol. Chem.* 271: pp. 9603-9611, 1996.

The mapping of the binding of distinguished determinants for ifenprodil within the N-terminus of the NR2B subunit is significant in that (1) it helps to understand how the amino terminal segment of the NR2B subunit interacts with the ion channel in an allosteric fashion and (2) it also has direct applications to the development of new pharmacological agents at NMDA receptors.

Novel Receptor Mechanisms for Heroin and Morphine-6-Glucuronide Analgesia

NIDA grantee Dr. Gavril W. Pasternak of Sloan-Kettering Memorial Cancer Center and Cornell University Medical College and his research team have obtained evidence, using a number of different paradigms, indicating that heroin actions are most likely not mediated through the same receptors as morphine. This finding is echoed by Dr. James M. Fujimoto's observations (another NIDA grantee) that morphine, 6-monoacetylmorphine (6-MAM) (both are active metabolites of heroin), and heroin are found to exhibit unique receptor selectivities at both spinal and supra-spinal levels as well as in different mouse strains.

The rapid metabolism of heroin to 6-MAM and its slower conversion to morphine has led many to believe that heroin and morphine act through the same receptors and that the differences between them are due to their pharmacokinetics. Dr. Pasternak and his team now present evidence strongly implying that heroin and two potent drugs, fentanyl and etonitazine, act through a unique receptor mechanism similar to morphine-6-glucuronide which is readily distinguished from morphine. Heroin, 6-MAM and morphine-6-glucuronide show no cross tolerance to morphine in a daily administration paradigm, implying distinct receptors. Strain differences also reveal differences among the drugs. CXBK mice, which are insensitive to morphine, retain their sensitivity to heroin, 6-MAM, morphine-6-glucuronide, fentanyl and etonitazine. Antisense mapping of the opioid receptor MOR-1 reveals that oligodeoxynucleotide probes against exon 2, which are inactive against morphine analgesia, block morphine-6-glucuronide, heroin, fentanyl and etonitazine analgesia. Finally, an antisense probe targeting Gi1 blocks both heroin and morphine-6-glucuronide, but not morphine analgesia. These results indicate that heroin, 6-MAM, fentanyl and etonitazine all can produce analgesia through a novel analgesic system which is similar to that activated by morphine-6-glucuronide. Rossi, G.C., Brown, G.P., Leventhal, L., Yang, K. and Pasternak, G.W. *Neuroscience Letter*, 216: pp.1-4, 1996.

Catalytic Antibodies

In a continuing effort to develop catalytic antibodies for the hydrolysis of cocaine, researchers at the Seattle Biomedical Research Institute have prepared synthetically a new cocaine transition state analog, which potentially may be metabolically more stable than previous analogs, particularly at the C2 position, and which will exhibit a useful immunogenic "lifetime", after linking the analog to an immunogenic protein. Berkman, C. E., Underiner, G. E., and Cashman, J. R. *Journal of Organic Chemistry*, 61, pp. 5686-5689, 1996.

Methadone and Hair Analysis

An analytical method has been described for the determination of methadone, and its two major metabolites, utilizing a gas chromatography/ mass spectrometry procedure, and validated in human and animal hair samples. The method may prove usable in detection and pharmacokinetic studies. Wilkins, D.G., Nagasawa, P.R., Gygi, S. P., Foltz, R. L., and Rollins, D. *Journal of Analytical Toxicology*, 20, pp. 355-361, 1996.

Dopamine Transporter Ligands

A series of substituted diphenylmethoxyethyl piperidines have been synthesized, and shown to be effective as potent ligands in terms of binding to the dopamine transporter, as compared to the known inhibitor GBR 12909. They also demonstrate selectivity for the dopamine as compared to the serotonin transporter. Such compounds have a potential in treating cocaine addiction. Dutta, A., Coffey, L. L., and Reith, M. E. *Journal of Medicinal Chemistry*, In Press.

Peptide Delivery to the Brain

A recent report describes the delivery of the pentapeptide DADLE to the brain, based on reacting the N-terminal amino acid with a nicotinoyl proline, and converting the C-terminus to a lipophilic ester for transport across the blood brain barrier. The nicotinoyl group is metabolically oxidized after transport to a lipid insoluble salt, which serves to "lock" the peptide in the brain, and the proline serves as a site designed for peptidase cleavage, releasing the

esterified DADLE, and finally DADLE itself after lipase cleavage.

The DADLE delivered in this fashion showed analgesic activity in animals, which was reversed by administration of naloxone. Bodor, N., Prokai, L., Prokai-Tatrai, K. *Journal of Medicinal Chemistry*, 39, pp. 4775-4782, 1996.

Dopamine D1, D2, Beta2-Adrenergic and Serotonin 5-HT1B Receptors Exist as Dimers

NIDA grantee Philip Seeman and his coworkers at the University of Toronto, Canada obtained direct physicochemical evidence that dopamine D2 and D1, beta2 adrenergic and serotonin 5-HT1B receptors exist as dimers: Immunoblots of crude membranes from human caudate nucleus revealed that the dopamine D2 dimer exists as the predominant species. The G-protein coupled receptor (GPCR) dimers were stable in SDS and under reducing conditions indicating that dimerization was not attributed to covalent disulfide bonds. Incubation of the GPCR dimers with receptor-specific peptides derived from the putative transmembrane domains, or incubation under high temperatures or low pH resulted in the dissociation of dimers to monomers. Dopamine D2 transmembrane peptides were unable to dissociate dopamine D1 receptor dimers or serotonin 5-HT1B receptor dimers, suggesting that receptor dimers are formed by specific intermolecular noncovalent interactions involving transmembrane regions. Exposure of living D2 expressing cells (D2/cells) to glutaraldehyde resulted in a conversion of receptor monomers to dimers due to the irreversible cross-linking of receptor monomers. D2 dimers and monomers were labeled by benzamide antagonists whereas only monomers were labeled by butyrophenone antagonists, which explains the discrepancy in receptor densities estimated by these ligands in PET studies. Furthermore, dopamine exposure of D2/cells mediated an increase in cell surface D2 monomers and dimers involving the translocation of intracellular receptors. These results indicate that D2 and other G protein-coupled receptors exist as receptor dimers and that dimers play a functional role in the response to agonist exposure. These findings have important implications for neurological diseases since it is known that demolition of dimerization of the androgen receptor through mutation is one of the causes of Reifenstein syndrome in humans. *Biophys. Biochem. Res. Comm.*, Vol 227, pp. 200-204, 1996. Dr. Michael Gallagher and colleagues, using chimeric NR2A/NR2B subunits co-expressed with NR1A, have localized a determinant for high affinity ifenprodil interaction to a single amino acid (Arg-337). Ifenprodil had also previously been thought to be an antagonist at the polyamine site. Experiments with chimeric and mutant receptors have shown that Arg-337 is independent of NR2B-specific polyamine stimulation. Furthermore, it was shown that polyamine stimulation depends on the expression of NR1 splice variants, whereas high affinity ifenprodil inhibition is independent of NR1 isoform expression. These studies provide evidence that ifenprodil and polyamines interact at discrete sites on the NR2B subunit. Gallagher, M.J. Huang, H., Pritchett, D.B., and Lynch, D.R., *J. Biol. Chem.* 271: pp. 9603-9611, 1996.

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Research Findings

Behavioral Research

Decreasing Preferences for Cocaine Dr. Marilyn Carroll and her colleagues at the University of Minnesota Medical School, Minneapolis MN evaluated the effects of the opioid partial agonist buprenorphine (0.1 mg/kg) and concurrent access to either water or a glucose plus saccharin (G+S) solution in rats self-administering i.v. cocaine (0.4 mg/kg per infusion). Data obtained indicate that (1) the presence of an alternative non-drug reinforcer significantly reduced cocaine self-administration, (2) buprenorphine selectively decreased cocaine, but not water or G+S, self-administration; (3) the decrease in cocaine infusions by buprenorphine was greatest on the first day of buprenorphine administration; and (4) expressed as a percentage of baseline conditions, the combination of buprenorphine and G+S produced a greater decrease in cocaine self-administration than either buprenorphine or G+S alone. These results suggest that combined treatment with buprenorphine and concurrent access to a sweetened solution is a more effective strategy for reducing cocaine self-administration than either strategy alone. Comer S.D. et al., *Psychopharmacology*, 125, pp. 355-360, 1996.

Increasing Preferences for Cocaine and Lidocaine Dr. John Falk at Rutgers University has found, in a preference test with rats, that oral cocaine during a schedule-induced polydipsia procedure was not preferred over water. However, after pairing a glucose + saccharin (g+s) solution with cocaine and then fading out the g+s solution, the cocaine did become preferred over water. Interestingly, this g+s pairing procedure also produced a preference for lidocaine, which is not an abused drug. (*Drug and Alcohol Dependence*, 40, pp. 241-247, 1996). In a follow-up study Dr. Falk found that these drug preferences that developed after pairing with sweet tastes were maintained even when drug concentrations were raised to bitter tasting levels. (*Behavioural Pharmacology*, In Press). Previous studies in the literature indicating that oral drug preference established under similar pairing-and-fading methods now warrant re-examination given that the present research suggests that drug preference established via these methods may indeed not reflect pharmacologically reinforcing properties of the substance. These data additionally suggest that humans may continue to use a drug more because of its prior pairing with other reinforcing events (e.g., social reinforcers) than because of its pharmacologic properties.

Smoking and Menstrual Cycle Researchers at the University of Michigan have found in healthy women smokers that the effects of nicotine administered intranasally did not vary across menstrual cycle phase. This held true for both physiological and behavioral (subjective report) dependent measures. Marks et al., *J Substance Abuse*, In Press.

ADHD, Smoking and Novelty Seeking It is known that adults with Attention Deficit Hyperactivity Disorder (ADHD) smoke at nearly twice the rate as the general population. Based on these findings, researchers at the University of Michigan asked whether ADHD patients score higher on a standardized test of novelty-seeking (Cloninger's TPQ). They compared subgroups defined by smoking status, and also compared groups that lacked the ADHD diagnosis. Findings showed that among subjects who were smokers, ADHD patients began smoking at a much earlier age and scored higher on the novelty scale than non-ADHD. The data showing early age of smoking onset suggest prevention targeting for youth diagnosed with ADHD. Downey et al., *J Substance Abuse*, 8, pp. 129-135, 1996.

Job Skills Training Program using a Voucher-Based Reinforcement System Researchers at the Johns Hopkins School of Medicine recently evaluated the use of vouchers as incentives to unemployed methadone patients to stay in a job skills training program. Volunteers were given vouchers with monetary value which could be exchanged for goods and services for attending two-hour computer entry training classes. The classes were conducted over a 16 week period. As part of the study design, the value of the vouchers were escalated across weeks and then de-escalated, with additional titration of the value of the vouchers according to class attendance. Five of seven participants completed all phases of the study. In the escalating value condition, attendance rates were above 90%. Four of five volunteers stopped attending class in the descending pay condition when voucher values fell to \$6-\$9 per class. Volunteers later positively rated the classes they attended. These data indicate that a voucher-based system can sustain attendance of chronically unemployed substance abusers in prolonged job skills training programs. Silverman et al., *Drug and Alcohol Dependence*, 41, pp. 197-207, 1996.

Assessment of Buprenorphine's Physical Dependence Potential Researchers at the Johns Hopkins School of Medicine recently examined the physical dependence produced by maintaining opioid-dependent volunteers on a clinically relevant dose of buprenorphine. Eight volunteers were maintained on 8 mg/day sublingual buprenorphine, during which they received placebo, i.m. naloxone, and p.o. naltrexone 14 hours after their daily buprenorphine dose. Both naloxone and naltrexone precipitated withdrawal as indicated by changes in physiological, and subject- and observer-rated measures. These results indicate that buprenorphine maintenance produces physical dependence. These results will be important in guiding the formulation of combination agonist/antagonist medications for transitioning opioid abusers from buprenorphine to antagonist maintenance. Eissenberg et al., *Journal of Pharmacology and Experimental Therapeutics*, 276, pp. 449-459, 1996.

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Research Findings

Clinical and Services Research

Cigarette Smoking and Brain Monoamine Oxidase A Inhibition Dr. Joanna Fowler and colleagues at the Brookhaven National Laboratory compared brain monoamine oxidase A (MAO A) in nonsmokers and in smokers with [¹¹C]clorgyline and positron emission tomography. Results revealed that tobacco smoke exposure was associated with a significant reduction in brain MAO A. These findings are similar to results obtained by this group showing a reduction of brain MAO B in smokers. Because MAO A inhibitors are effective antidepressants, the authors suggest that MAO A inhibition should be considered as a potential contributing factor in the high rate of smoking in depression as well as in the development of more effective strategies for smoking cessation. Fowler, J.S., Volkow, N.D., Wang, G.-J., Pappas, N., Logan, J., Shea, C., Alexoff, D., MacGregor, R. R., Schyler, D.J., Zezulkova, I., & Wolf, A.P. Brain Monoamine Oxidase A Inhibition in Cigarette Smokers. *Proc. Natl. Acad. Sci.*, 93, pp. 14065-14069, 1996.

Smoking Increases Dose-Dependent [3H]-Nicotine Binding in Human Postmortem Brain

Dr. Sherry Leonard has demonstrated in human postmortem brain a significant increase in [3H]-nicotine binding in subjects who had life-long smoking histories until death. However, binding in life-time smokers who had quit at least two months prior to death did not differ from subjects who never smoked. Increased binding was observed in both hippocampus and thalamus and due to an increase in receptor number (B_{max}), with no change in receptor affinity (K_d). Furthermore, among those who had life-long smoking histories, the number of binding sites was correlated with degree of smoking, as measured by average number of packs per day. Similar dose-dependent increases in brain nicotinic receptor numbers have been reported in rodents; this is the first reported in humans. The results suggest that increases in nicotinic receptor levels in the human brain may underlie nicotine tolerance and addiction in smokers. Breese, C.R., Marks, M.J., Logel, J., Adams, C.E., Sullivan, B. Collins, A.C., & Leonard, S. Effect of Smoking History on [3H]-Nicotine Binding in Human Postmortem Brain. *J Pharm Exp Ther*, In Press.

Linkage of 7-nicotinic Receptor to a Neurophysiological Deficit in Schizophrenia

Using a genome-wide linkage analysis, an auditory suppression deficit seen in most schizophrenic patients and many of their (non-schizophrenic) relatives, was linked to a dinucleotide polymorphism at chromosome 15q14, the site of the 7-nicotinic receptor. The deficit has to do with an abnormal suppression or gating of the evoked response to the second of paired auditory stimuli. This is one of several physiological markers that are associated with schizophrenic diagnosis. In rodents the deficit is normalized by selective stimulation of the 7-nicotinic receptor; high doses of nicotine in schizophrenics demonstrates similar normalization. Smoking is highly prevalent in schizophrenic patients, and it has been hypothesized that they may be self-medicating a neurophysiological deficit. These data support this notion, demonstrating a genetic link. Freedman, R., Coon, H., Mules-Worsley, M., Orr-Urtreger, A., Olincy, A., Davis, A., Polymeropoulos, M., Holik, J., Hopkins, J., Hoff, M., Rosenthal, J., Waldo, M.C., Reimherr, F., Wender, P., Yaw, J., Young, D.A., Breese, C.R., Adams, C., Patterson, D., Adler, L.E., Kruglyak, L., Leonard, S., & Byerley, W. Linkage of a Neurophysiological Deficit in Schizophrenia to a Chromosome 15 Locus. *Proceedings of the National Academy of Science*, January 21, 1997.

Smoking Has a Differential Effect on Cognitive Performance and Electrophysiological Measures Depending

on Task Difficulty Post-smoking response times improved (decreased) for simple "oddball" tasks, both auditory and visual, but only in smokers whose breath carbon monoxide levels did not change substantially after smoking. This was accompanied by an increase in P300 amplitudes in the visual condition only. However, smokers as a group (i.e., pooled for carbon monoxide changes) did not significantly differ in performance before and after smoking. By contrast, post-smoking response times worsened for a memory task for memory sets of 6 items. There was a concomitant decrease in P300 amplitudes and latency. These results suggest that cigarette smoking may have enhancing effects for simple tasks, but is detrimental to more complex tasks reflected both in cognitive performance and electrophysiological responses. Ilan, A.B., & Polich, J. The Effects of Smoking on ERPs in Simple and Demanding Tasks. *Psychophysiology*, 33, S47 (presented at the meetings of the Society for Psychophysiological Research, Vancouver, B.C., Canada), 1996.

LSD Effects on Brain Dr. Henry David Abraham of the Butler Hospital in Providence, RI recently published an article entitled "LSD-Like Panic from Risperidone in Post-LSD Visual Disorder" in the *Journal of Clinical Psychopharmacology*. Dr. Abraham found that there was an unanticipated worsening of visual symptoms and induction of panic anxiety in patients, who had taken LSD 4-20 years ago, given risperidone, an antagonist of the serotonin-2 receptor. The exacerbation of visual disturbances and flashback-like experiences suggests that LSD could act as an excitotoxin at serotonin-2 receptor, cause dysfunction of inhibitory cortical interneurons and result in disinhibition of visual processors.

Neuropsychological Functioning in Cocaine Abuse NIDA-funded researcher Dr. Tony L. Strickland, Ph.D., of Charles R. Drew University of Medicine & Science and the University of California at Los Angeles (UCLA) School of Medicine, presented preliminary findings from his ongoing NIDA-funded research study on neurobehavioral functioning among cocaine abusers at the National Academy of Neuropsychology Sixteenth Annual Meeting on November 1, 1996. The focus of this paper was on neuropsychological effects of chronic cocaine use following sustained abstinence. Subjects included 37 males and 34 female freebase cocaine abusers with verifiable abstinence of between 5 and 18 months. The sample was 72% African-American and 28% Euro-American with similar representation by gender. Statistical analyses revealed significant impairment on measures of attention-concentration, memory, academic achievement, with visuospatial, motor, language and executive functioning measures less consistently impaired. Interestingly, despite a substantial gender disparity in cocaine exposure, women appeared no more impaired on neuropsychological measures than men. Curiously, greater cocaine exposure did not appear to result in greater neuropsychological impairment. An abstract of the paper will be published in the journal *Archives of Clinical Neuropsychology*.

Beneficial Effects of Thiamine on Recognition Memory and P300 in Abstinent Cocaine Dependent Patients Researchers evaluated the effects of thiamine versus placebo on memory task performance and event-related electroencephalographic potentials in 8 abstinent cocaine dependent patients. Patients orally ingested 5 g of thiamine and 5 g of a lactose placebo on two separate days scheduled approximately one week apart. The order of administration was randomized. Double blind procedures were followed. Approximately three hours after ingesting the capsules, patients completed Stemberg's (1975) memory scanning task during which performance and event-related potentials (P300) were recorded simultaneously. Thiamine was found to significantly improve recognition accuracy and P300 amplitude, at the midline parietal (Pz) electrode. The improvement was most reliable under conditions of increased memory load. These preliminary findings justify a further examination of the relationship between thiamine's hypothesized effects on central nervous system cholinergic function, and the direct and indirect effects of cocaine alone. Eston, C. and Bauer, L. *Psychiatry Research*, In Press.

The Effects of Anabolic Steroids on Driving Performance as Assessed by the Iowa Driver Simulator Perry and his colleagues at the University of Iowa studied the effects of physiologic (100 mg/wk) and supraphysiologic (250 and 500 mg/wk) doses of testosterone cypionate (TC) on automobile driving using the Iowa Driver Simulator. Six normal subject volunteers were studied off TC and on TC once steady-state concentrations were achieved after at least three weeks of dosing. Despite the administration of supraphysiologic TC doses an increase in aggressive driving behavior was not detected. Likewise, corresponding psychometric testing using the Buss-Durkee Hostility Inventory to assess aggression was unable to detect any change in aggression in the test subjects. Aggressive driving behavior may be increased by testosterone administration as reported by others, but according to the authors, the drug itself may not be responsible for these effects. Since altered driving behavior may be multifactorial in nature, supraphysiologic doses greater than 500 mg/wk and a semi-controlled research environment may be necessary to produce these effects. Ellingwood V.L., Perry P.J., Yates W.R., MacInode W.R., Watson G., Arndt S., and Holman T.L., *American Journal of Drug and Alcohol Abuse*, In Press.

Evidence for a Sex-Specific Residual Effect of Cannabis on Visuospatial Memory

Pope and his colleagues at Harvard Medical School used a novel computerized battery of neuropsychological tests of

attention to assess residual cognitive impairment in marijuana users. They compared 25 college students who were heavy marijuana smokers (who had smoked a median of 29 days in the last 30 days) with 30 students who were light smokers (who had smoked a median of 1 day in the last 30 days). All subjects were tested after a supervised period of abstinence from marijuana and other drugs lasting at least 19 hours. Although there were no significant differences between the overall heavy and light smokers on the four subtests of attention, marked and significant differences were found between heavy- and light-smoking women on the subtest examining visuospatial memory. On this test, subjects were required to examine a 6x6 "checkerboard" of squares in which certain squares were shaded. The shaded squares were then erased and the subject was required to indicate with the mouse which squares had formerly been shaded. Increasing numbers of shaded squares were presented at each trial. The heavy-smoking women remembered significantly fewer squares on this test, and they made significantly more errors than light-smoking women. These differences persisted despite different methods of analysis and consideration of possible confounding variables. The authors suggest that it may be important to study the residual effects of marijuana on men and women separately, particularly since women have been greatly under-represented in previous studies in this area. Pope, H.G. Jr., Jacobs, A., Mialet, J.P., Yurgelun-Todd, D., and Gruber, S. *Psychotherapy and Psychosomatics*, In Press.

Abnormal Cerebral Metabolism in Polydrug Abusers During Early Withdrawal: a 31P MR Spectroscopy Study

Mendelson and his colleagues (Harvard Medical School) performed phosphorus magnetic resonance spectroscopy (31P MRS) at 1.5 T on nine polysubstance abusing men. All nine patients met DSM-III-R criteria for concurrent cocaine and heroin dependence, were neurologically normal, were negative for the human immunodeficiency virus, and had normal clinical brain MRI scans. Patients were scanned 2-7 days after admission to a drug treatment unit. Eleven age-matched control subjects also were studied. The ISIS localized phosphorus spectra were obtained from a 5-cm thick axial brain slice and a 100-cc white matter volume. In the brain slice, the phosphorus metabolite signal expressed as a percentage of total phosphorus signal was 15% higher for phosphomonoesters, 10% lower for nucleotide triphosphates (beta-NTP), and 7% lower for total nucleotide phosphates in polydrug abusers compared with those in controls. Phosphodiesteres, inorganic phosphate, phosphocreatine, total phosphorus, pH, and free magnesium concentration were unchanged. None of these parameters correlated with the methadone dose or the number of days abstinence. Single photon emission computed tomographic imaging of a subgroup of the patients revealed abnormal cerebral perfusion in 80% of the patients scanned. These data suggest that cerebral high energy phosphate and phospholipid metabolite changes result from long term drug abuse and/or withdrawal and that these changes can be detected and studied by 31P MRS. Christensen, J.D., Kaufman, M.J., Levin, J.M., Mendelson, J.H., Holman, B.L., Cohen, B.M., and Renshaw, P.F., *Magnetic Resonance Medicine*, 35(5): pp. 658-663, May 1996.

Divergent Effects of Cocaine on Cytokine Production by Lymphocytes and Monocyte/Macrophages Acute intravenous administration of cocaine in humans resulted in increased production of tumor necrosis factor alpha (TNFA) in lymphocytes but decreased production in macrophages. Transmigration of "memory" T lymphocytes was inhibited by cocaethylene in an in vitro model of the blood-brain barrier (BBB) composed of human brain microvascular cells and human fetal astrocytes. Added cocaethylene and TNFA significantly increased the permeability of the model BBB to HIV-1 in a time-and concentration-dependent manner. Fiala, M., Gan, X-H., Newton, T., Chiapelli, F., Shapshak, P., Kermani, V., Kung, M.A., Diagne, A., Martinez, O., and Graves, M. *Advances in Experimental Medicine and Biology*, 4(2): pp. 145-156, 1996.

Problem-Service "Matching" in Addiction Treatment

McLellan his colleagues have conducted a study to identify specific patient problems and to match professional services to those problems in four drug abuse treatment programs. Ninety-four new patients from an Employee Assistance Program entered treatment and were randomly assigned to either: Standard Treatment - patients were treated in the usual manner; or Matched Services - patients received at least three professional sessions directed at their significant employment, family, or psychiatric problems. Matched patients stayed in treatment longer, were more likely to complete treatment, and had better post treatment outcomes than patients receiving treatment as usual in these programs. The strategy of matching appropriate services to patients' specific treatment problems was clinically and administratively practical, attractive to patients, and responsible for a 20-30% increase in effectiveness. McLellan, A.T., Grissom, G.R., Zanis, D., Randall, M., Brill, P., and O'Brien, C.P. *Problem-Service "Matching" In Addiction Treatment: A Prospective Study in Four Programs*, *Arch. Gen Psychiatry*, In Press.

Risk Reduction Approach for Discharged Methadone Patients

In a study of discharged methadone patients, Zanis, McLellan, Alterman, and Cnaan randomly assigned methadone patients discharged 1 year earlier to either a standard referral condition (n=14) or an enhanced outreach counseling intervention (n=27) to determine if these high-risk patients could be re-engaged into treatment. Two weeks following the intervention, 17 (63%) of the patients assigned to the enhanced outreach condition and 1 (7%) of the patients in

the standard condition had reenrolled in treatment. The authors conclude that this strategy may be an effective risk reduction approach for discharged methadone patients. It may also have further implications for outreach efforts. Zanis, D.A., McLellan, A.T., Alterman, A.I., & Cnaan, R.A. American Journal of Psychiatry, 153: pp. 1095-1096, 1996.

Effect of Maternal Substance Abuse on the Cost of Neonatal Care

Norton and his colleagues recently reported on a study of the effects of maternal substance abuse on the costs to neonatal care in 54 Maryland hospitals in 1991. Investigators controlled for individual hospital effects and correlated observations within hospitals. The findings suggest that exposure to drugs in newborns resulted in significantly higher total hospital charges at almost double those of non-exposed newborns ($p < .01$). The results demonstrated a consistent pattern of effects on charges, mortality, and resource use in the hospital of drug-exposed newborns due, in part, to longer lengths of stay and higher intensity care per day. Exposure to alcohol was found to be much less significant. The investigators suggest that their results confirm the policy concern that maternal substance abuse has severe consequences for the baby's health and that these cost are often borne by others. Norton, E.C., Zarkin, G.A., Calingaert, B. & Bradley, C.J. The Effect of Maternal Substance Abuse on the Cost of Neonatal Care, Inquiry, 33: pp. 247-257, 1996.

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National Institute on Drug Abuse**Director's Report to the National Advisory Council on Drug Abuse****February 1997**

Research Findings

AIDS Research

Reducing HIV Risk Behaviors in IV Drug Users Dr. Kelly Avants from Yale University has developed a treatment manual for an intervention, Risk Reduction Therapy (RRT), specifically for HIV-seropositive injection drug users who may not benefit from standard treatment interventions due to cognitive deficits related to HIV and chronic drug use. Though the manual is currently being refined, evaluation of the therapy has occurred in the context of two open label pharmacotherapy trials with HIV-seropositive cocaine- and opioid-dependent patients. One trial investigated bupropion (150 mg/day) plus RRT. Another trial investigated lamotrigine (300 mg/day) plus RRT. Results have been compared to standard treatment (methadone plus standard skills training group). Promising results have been found for both pharmacotherapies plus RRT. Cocaine use, opiate use, cocaine craving, depression, and ASI drug severity scores decreased significantly only for patients receiving the specialized Risk Reduction Program; patients receiving standard treatment showed no significant improvement.

Drug Abuse Among Gay-Bisexual Young Men at Risk for HIV/AIDS The Personal Experience Screening Questionnaire (PESQ) was developed as a brief self-report screening tool for use with adolescents (12-18 years) to identify those who should be referred for a complete chemical dependency evaluation. Winters and colleagues reported on a study designed to assess the utility of the PESQ in a sample of 500 male adolescents and young adults (13-21 years of age) who had sex with men or who otherwise considered themselves to be gay or bisexual regardless of self-reported sexual behavior. All subjects were participating in an HIV prevention program. Study results indicated the PESQ has good internal consistency reliability and convergent validity in this population. Nearly 20% of the subjects met PESQ criteria for needing further drug abuse evaluation and drug use severity was highly associated with subject reports of risky sexual behaviors (e.g., drug use during sex; engaging in unprotected sex; having multiple sex partners). The findings suggest the importance of screening for illicit drug use in gay-bisexual young men who have concerns about HIV/AIDS and provide support for the use of the PESQ to accomplish this aim. Winters et al., *Assessing Drug Abuse among Gay-Bisexual Young Men*. *Psychology of Addictive Behaviors*, 10(4): pp. 228-236, 1996.

Successful Adherence to Observed Prophylaxis and Treatment of Tuberculosis Among Drug Users in a Methadone Program Incomplete antituberculous chemoprophylaxis and treatment are major causes of the resurgence of tuberculosis (TB) among drug users. A study of directly observed prophylaxis and treatment among drug users is ongoing in a methadone program in New York City. Participants are patients in a methadone treatment program with an on-site primary care clinic where patients are screened for TB infection through PPD testing and for active TB on clinical grounds confirmed by mycobacteriologic culture. No material incentives for directly observed treatment were offered to eligible participants and methadone dosing was not contingent upon participation. Directly observed chemoprophylaxis for TB infection was accepted by 88% (90/102) of eligible patients; 75% (9/12) of patients with identified active TB accepted directly observed medication. The majority of patients were HIV infected (57%) and the majority continued active substance abuse (88%) during TB therapy. Patients were administered

more than 5 weekly doses of anti-TB therapies during more than 80% of 4740 patient weeks, with >80% adherence and treatment completion. HIV infection and active substance abuse were not associated with diminished adherence. These results indicate that successful adherence to and completion of anti-TB therapy can be attained by drug users in drug treatment, despite ongoing substance use and lack of material incentives. M. Gourevitch et al., *J Addictive Med*, 15: pp. 93-104, 1996.

Viral Infections in Short-term Injection Drug Users: The Prevalence of Hepatitis C, Hepatitis B, Human Immunodeficiency, and Human T-lymphotropic Viruses A study of the prevalence and correlates of four blood-borne viral infections was performed among illicit drug users with up to 6 years of injecting history. Data for hepatitis C (HCV), hepatitis B (HBV), HIV, and human T-lymphotropic virus types I and II (HTLV I/II) were analyzed in 6 sequential cohorts defined by duration of drug injection among patients enrolled in a long-term cohort study of HIV and other infectious diseases. Overall seroprevalence of HCV, HBV, HIV and HTLV I/II was 76.9%, 65.7%, 20.5%, and 1.8% for those injecting for up to 6 years. Among those injecting for one year or less, rates were 64.7% for HCV, 49.8% for HBV, 13.9% for HIV and 0.5% for HTLV I/II. Among the newest initiates (one year or less), HCV and HBV were associated with injecting variables in the prior 6 months (injection frequency once or more daily, any cocaine injection, use of non-sterile needles), and duration of injection >6 months: HIV was associated with sexual variables (high number of sex partners, never married, homosexual or bisexual orientation). The high rates of HCV, HBV, and HIV infections among short-term injectors emphasizes the need to target both parenteral and sexual risk reduction interventions early. Garfein, R., Vlahov, D., Galai, N., et al., *Am J Pub Health*, 86: pp. 655-661, 1996.

Outreach, Referral, and Assistance Improve Treatment Entry and Retention A study was conducted to assess the effect of client characteristics and community interventions on treatment entry and retention, and to evaluate the relative effectiveness of treatment, compared to other interventions, in reducing drug use and crime among out-of-treatment opiate injectors. Data were analyzed for 2,973 opiate injectors from 15 cities participating in NIDA's Cooperative Agreement for AIDS Community-Based Outreach Intervention Research Program (CA). The IDUs were randomly assigned to NIDA's standard or enhanced interventions, and had participated in both baseline and 6-month follow-up behavioral risk assessments. IDUs who entered treatment and those who did not reduced drug use at follow up. However, those who remained in treatment for at least 90 days reported significantly greater reductions in drug injection and crack smoking (corroborated by urinalysis), and were less likely to have been arrested, compared to IDUs who did not enter treatment. Treatment entry and retention were associated with the enhanced intervention plus active treatment referral and assistance (e.g., scheduling intake, providing transportation, and waiving admission fees); IDUs contacted by community outreach workers were also more likely to have entered treatment than subjects lacking outreach-facilitated interventions. The results show that substance abuse treatment can reduce drug use, risk for HIV infection, and arrests among not-in-treatment IDUs. Treatment entry and retention are improved by outreach worker-facilitated interventions, active referral, and assistance with the treatment entry process. Booth, R., Crowley, T., and Zhang, Y. *Substance Abuse Treatment Entry, Retention, and Effectiveness: Out-of-Treatment Opiate Injection Drug Users*. *Drug and Alcohol Dependence*, 42: pp. 11-20, 1996.

Protective Effect Against HIV Infection Linked to Participation in Syringe Exchange Meta-analytic techniques were used to examine whether participation in syringe exchange programs leads to individual-level protection against incident HIV infection. HIV incidence data from injecting drug users were combined for three studies: the Syringe Exchange Evaluation (n=280); the Vaccine Preparedness Initiative Cohort (n=133 continuing exchangers, n=188 non-exchangers); and very-high-seroprevalence cities in the National AIDS Demonstration Research (NADR) program (n=1029). HIV incidence among continuing exchangers in the Syringe Exchange Evaluation was 1.58 per 100 person-years at risk (95% CI 0.54, 4.65) and among continuing exchange users in the Vaccine Preparedness Initiative, it was 1.38 per 100 person-years at risk (95% CI 0.23, 4.57). Incidence among non-users of the exchange in the Vaccine Preparedness Initiative was 5.26 per 100 person-years at risk (95% CI 2.41, 11.49) and in the NADR cities, 6.23 per 100 person-years at risk (95% CI 4.4, 8.6). When the data were pooled, not using the syringe exchanges was associated with a hazard ratio of 3.35 (95% CI 1.29, 8.65) for incident HIV infection compared with using the exchanges. The findings indicate that an individual-level protective effect against HIV infection is associated with participation in syringe exchange programs. Des Jarlais, D.C., Marmor, M., Paone, D., et al. *HIV Incidence among Injecting Drug Users in New York City Syringe-Exchange Programmes*. *Lancet*, 348: pp. 987-991, 1996.

The Value of Combining Qualitative and Quantitative Methods in AIDS Prevention Research Ethnographers working with injection drug users in U.S. AIDS prevention projects have found that drug users generally prefer not to use each other's needles and do not conceive of needle "sharing" (transfer) as a key dimension of their identity. These findings to date have been based on qualitative ethnographic methods. Drug injector values toward needle transfer were operationalized, and a questionnaire was administered to 276 active injectors recruited in 1993 at the Dayton/Columbus, Ohio site participating in NIDA's Cooperative Agreement. Results from the questionnaire confirmed the qualitative evidence: 96% of the respondents disagreed with the statement: "When shooting up with other

people, I feel like I have to use the same outfit everyone else uses." Only 16.3% perceived new needles were inaccessible, while 72.8% feared carrying needles because of drug paraphernalia laws. This study demonstrates the value of combining qualitative and quantitative methods in AIDS prevention research. Carlson, R.G., Siegal, H.A., Wang, J., and Falck, R.S. Attitudes toward Needle "Sharing" among Injection Drug Users: Combining Qualitative and Quantitative Research Methods. *Human Organization*, 55 (3): pp. 361-369, 1996.

Risk Acts, Health Care and Medical Adherence Among HIV+Youths in Care Over Time 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 14-23 who had lifetime high risk sexual and substance abuse behaviors. When current risk behaviors were assessed twice over two 3-month periods, almost a third had been sexually abstinent. Among youths who were currently sexually active, most had multiple sexual partners and used condoms (72%-77% sexual acts protected). Use of drugs was substantial: alcohol (63%), marijuana (41%), hard drugs (36%), and injecting drugs (12%), and remained relatively consistent over 3 months. Youths were relatively healthy and attended about one third of their medical appointments. While all youths were linked to adolescent AIDS programs, unhealthy behavior and risk acts remained common. More effective and intensive intervention appears required. Rotheram-Borus, M.J., Murphy, D., Coleman, C., Kennedy, M., Reid, H., Cline, T., Birnbaum, J.M., Futterman, D., Levin, L., Schneir, A., Chabon, B., O'Keefe, Z., and Kipke, M. Risk Acts, Health Care and Medical Adherence Among HIV+Youths in Care Over Time. *AIDS and Behavior*, In Press.

Improving the Understanding and Effectiveness of HIV Risk Interventions for Drug Users.

Fen Rhodes and Kevin Malotte provide a review of modes of HIV transmission among IDUs and crack users, behavioral research and collaborative studies, needle exchange programs, and community-based HIV intervention approaches. They describe details of NIDA's Cooperative Agreement as implemented in Long Beach, California, and show that relatively brief interventions which incorporate HIV testing have proven efficacy in reducing drug-related risks, but are less so in reducing sexual risk behaviors. By contrast, research to date suggests that more intensive, longer-term interventions have been disappointing in demonstrating any incremental effectiveness beyond that of brief interventions. An intervention-oriented model of behavior change which adheres to a well-defined set of principles for designing interventions holds great promise for improving HIV intervention effectiveness and power. Rhodes, F. and Malotte, K. HIV Risk Interventions for Active Drug Users: Experience and Prospects. In: Oskamp, S. and Thompson, S. (Eds.), *Understanding and Preventing HIV Risk Behavior: Safer Sex and Drug Use*. Thousand Oaks, California: Sage Publications, pp. 207-236, 1996.

Measures Identified to Explain Variation in HIV Seroprevalence Rates Across Cities.

By analyzing the national database from NIDA's Cooperative Agreement, Isaac Montoya and John Atkinson identified subsets of behavioral variables which would, within three subgroups of drug users, distinguish 16 Cooperative Agreement cities by HIV seroprevalence levels. Baseline interview and HIV serostatus data from 4,595 heterosexual non-crack-using IDUs, 4,187 noninjecting crack users, and 2,203 crack-using IDUs in the 16 cities were used to classify the sites according to high, medium, and low HIV seroprevalence levels. Among non-crack-using IDUs, high seroprevalence rate sites were associated with males, African Americans or Hispanics, frequency of injection (particularly of cocaine), and eastern geographic location. Among noninjecting crack users, sites were distinguished by the frequency of sex-for-money exchanges, number of sexual partners, local seroprevalence rates among IDUs, and location. Among crack-using IDUs, the sites were distinguished by frequency of sex-for-drug exchanges and again by location, significantly correlated with the eastern U.S. This analysis demonstrates that subsets of behavioral variables can be used to explain variance in HIV seroprevalence rates within drug user groups and across cities. Further analysis of these and other data may help to predict whether cities may be facing higher rates, especially since the regional differences found here are likely related to differences in the time of HIV introduction. Montoya, I.D., and Atkinson, J.S. Determinants of HIV Seroprevalence Rates Among Sites Participating in a Community-Based Study of Drug Users. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*, 13: pp. 169-176, 1996.

Behavioral Settings and Personal Network Characteristics as Correlates of Needle Sharing.

Social and environmental factors were examined as possible correlates of needle sharing in a sample of 330 drug users who participated in an HIV prevention study in Baltimore, Maryland. The respondents were administered a survey on two occasions 5.2 months apart. Higher total network density, larger drug network size, and injecting at friends' residences were positively associated with reports of sharing needles that had been cleaned with bleach. Sharing of needles that had not been disinfected with bleach was positively associated with reports of injecting in semipublic areas (streets, rooftops, parks, cars, public bathrooms, and abandoned buildings). These data support ecological and resource models of needle sharing and suggest the potential utility of network-oriented strategies for reducing needle sharing among IDUs. Latkin, C., et al. People and Places: Behavioral Settings and Personal Network Characteristics as Correlates of Needle Sharing. *Journal of Acquired Immune Deficiency Syndromes and Human*

Retrovirology, 13: pp. 273-280, 1996.

Evaluating Outreach Services Using Both Qualitative and Quantitative Techniques

The development of effective HIV interventions requires rigorous evaluations that, to date, have been noticeably lacking in the field. In particular, assessments of HIV prevention efforts have considered interventions as "black boxes," with little attention to the actual services delivered. This paper presents issues related to evaluating outreach interventions, and recommends an evaluation strategy to measure the delivery of outreach services, using both quantitative and qualitative techniques. Booth, R.E. and Koester, S.K. Issues and Approaches to Evaluating HIV Outreach Interventions. *Journal of Drug Issues*, 26(3): pp. 525-539, 1996.

Reaching and Enrolling At-Risk Drug Users for Prevention Studies

The St. Louis EachOneTeachOne (EOTO) is a NIDA-funded Cooperative Agreement project aimed at examining rates of HIV risk behaviors and studying HIV risk reduction interventions among out-of-treatment IDUs and crack users. This paper describes findings related to the effect of street outreach on HIV risk behavior involvement, including (1) men reported more HIV risk behaviors than did women, but there were no racial/ethnic differences; (2) women street contacts were largely ineligible to enroll in EOTO, but the program was able to enroll women; and (3) actual EOTO enrollees, compared with street contacts and eligible street contacts, engaged in fewer HIV risk behaviors. These results imply that strategies in addition to street outreach may be needed to enlist more individuals, particularly whites and women who are engaging in the highest risk drug and sexual behaviors. Cunningham, R.M., Cottler, L.B., and Compton, W.M. Are We Reaching and Enrolling At-Risk Drug Users for Prevention Studies? *Journal of Drug Issues*, 26(3): pp. 541-560, 1996.

Outcomes of an AIDS Prevention Program for African American and Latino IDUs

This paper discusses preliminary outcomes from a community-based AIDS prevention program for drug users participating in the NIDA-funded Cooperative Agreement in Hartford, Connecticut. The efficacy of two culturally targeted, enhanced interventions, one for African Americans and one for Puerto Ricans, was compared with the NIDA standard. The data suggest that attendance in culturally targeted enhanced interventions may increase the likelihood of positive program outcome, including drug-related risk reduction for some populations. However, subgroups of IDUs, such as extremely high risk injectors or persons who drop out before initiating or completing the program, appear to require different intervention approaches. Weeks, M.R., Himmelgreen, D.A., Singer, M., et al. Community-Based AIDS Prevention: Preliminary Outcomes of a Program for African American and Latino Injection Drug Users. *Journal of Drug Issues*, 26(3): pp. 561-590, 1996.

The Efficacy of Network-Based Risk Reduction Programs in Mid-Sized Towns

Three HIV and drug abuse intervention approaches were compared in two mid-sized towns: an intensive outreach program using indigenous outreach workers providing reinforcement of an HIV risk reduction program; a low intensity outreach program combined with a more intensive office-based HIV risk reduction program, and the NIDA standard intervention. A total of 579 drug users participated in the study. Each of the enhanced interventions were effective in reducing both drug-related and sexual risks for HIV transmission in active drug users. The intensive outreach combined with office intervention and the intensive office intervention without outreach reinforcement each produced significant reductions in sexual risk taking in active drug users, beyond the reductions found in the standard intervention. Gender differences were also found, with intensive outreach having a significant effect on the reduction of sexual risk behaviors of men but not of women, and the more intensive office-based risk reduction program significantly related to improvement in the sexual risk behavior of women but not of men. Trotter, R.T., Bowen, A.M., Baldwin, J.A., and Price, L. The Efficacy of Network-Based HIV/AIDS Risk Reduction Programs in Mid-Sized Towns in the U.S. *Journal of Drug Issues*, 26(3): pp. 591-605, 1996.

Assessing Intervention Efficacy From Change Profiles of Unprotected Sex Among Drug Users

Over 700 active drug users recruited in East Harlem to participate in an AIDS prevention program were interviewed on 2 occasions 6 months apart to assess relative changes in HIV-related risk behaviors as a result of participation in the NIDA standard and an enhanced intervention. The number of unprotected sex acts reported in the 30 days prior to each interview reflected five distinct patterns of risk over time (i.e., a decrease, an increase, remaining at low risk, remaining at high risk, or no sexual activity at either time). Bivariate and multivariate analyses indicated that (1) compared to persons at high levels of unprotected sex at follow-up, those who remained at low level or decreased were more likely to be HIV positive; and (2) age, living alone, and having a stable source of income were also significant predictors of risk pattern. Sexual risk pattern was not associated with type of risk reduction intervention (standard or enhanced) nor with drug treatment between baseline and follow up. These findings suggest that knowledge of HIV serostatus can contribute to or has an effect on risk-behavior change. The findings also have implications for improving the design and implementation of behavioral interventions to address sexual risks as well as drug-related risks from injecting drugs and the smoking crack cocaine. Beardsley, M., Goldstein, M.F., Deren, S.,

and Tortu, S. Assessing Intervention Efficacy: An Example Based on Change Profiles of Unprotected Sex Among Drug Users. *Journal of Drug Issues*, 26(3): pp. 635-648, 1996.

Effective Facilitation into Drug Treatment Does Not Affect Retention

Seven hundred thirty-eight active IDUs were recruited to participate in the NIDA Cooperative Agreement in Portland, Oregon from September 1992 to June 1994. HIV-negative IDUs were randomly assigned to the NIDA standard intervention or the enhanced intervention; those assigned to the latter group also received interventions designed to facilitate entry into drug treatment or self-help. For the 266 IDUs in the enhanced intervention who participated in both the baseline and follow up assessments, initial attendance at drug treatment or self-help was increased by the procedures designed to facilitate treatment entry. However, clients tended to drop out of both after an average of only four assisted sessions, and their outcomes were no different from those clients who attended no sessions at all; i.e., they were no more likely to stop injecting than IDUs who went to no sessions. The incentive (a \$10 food coupon following each of the first four sessions) may have motivated clients to attend the first four sessions, but the intrinsic value of the drug treatment or self-help program may not have been sufficient to continue. Twenty-four percent of the IDUs ceased injecting drugs in the 30 days prior to the 6-month follow-up interview and, after adjusting for confounders, the data showed this to be significantly associated with attendance at five or more drug treatment or self-help sessions. IDUs who continued to inject also showed a reduction in needle sharing from baseline to follow up. Other factors associated with attending five or more drug treatment or self-help sessions were living with children under age 18, not residing in a regular place at the time of the baseline interview, and having a high school education. This study indicates that effective facilitation into drug treatment does not, in and of itself, increase the likelihood that clients will continue in the treatment program or cease their drug injecting or needle use behavior. Drug treatment and self-help programs need to address the ambivalence held by a large percentage of active drug users toward entering and continuing in drug treatment. He, H., Stark, M., Fleming, D., et al. Facilitation into Drug Treatment or Self-Help Among Out-of-Treatment IDUs in Portland: You Can Lead a Horse to Water, But... *Journal of Drug Issues*, 26(3): pp. 649-661, 1996.

Enhanced Treatment Adds to Behavior Improvement Beyond Standard HIV Intervention

At the Detroit site of NIDA's Cooperative Agreement, two outreach interventions were compared on effectiveness in decreasing the AIDS-related high risk behaviors of 539 active IDUs and crack cocaine users not in treatment. Half of the drug users were assigned to NIDA's standard intervention, and half to the enhanced intervention, a nursing intervention called Personalized Nursing LIGHT Model. An optional component of this intervention was a weekly "Tuesday Group," when care givers and clients would meet as a group to discuss client concerns and provide peer support and encouragement. Follow-up evaluations indicated a dose-response relationship, with participants in the enhanced intervention plus weekly Tuesday Group showing significantly more improvement in reducing their use of drugs and in engaging in unprotected sex, followed by clients in the enhanced only, then by clients in the standard intervention. The findings show the importance of positive peer support and encouragement, group counseling, and consistent, planned opportunities to participate in group sessions for reducing drug use and sexual risk behaviors, and for preventing relapse. Andersen, M.D., Hockman, E.M., and Smereck, G. Effect of a Nursing Outreach Intervention to Drug Users in Detroit, Michigan. *Journal of Drug Issues*, 26(3): pp. 619-634, 1996.

Simulating the Complex Dynamics of HIV Transmission in IDUs

Although the use of mathematical modeling as a tool for studying HIV transmission is well established, it is also problematic. The assumptions of the classical epidemiological model may not be appropriate in modeling the spread of HIV because homogeneous mixing and susceptibility to infection cannot be assumed. Using the General Purpose Simulation System, which is based on concepts of system analysis, a hypothetical cohort of IDUs was created, drawing from a common needle supply. Following the introduction of an index case, the HIV infection rate was followed over 5 simulated years to examine effects from systematic variation in the frequency of injection with contaminated needles and needle-cleaning behavior. While simplifying assumptions (specifically "other things being equal") were used in these models, greater complexity can be introduced (e.g., by specifying variable probabilities of passing contaminated needles and by including effects of sexual risks behaviors and more variable in and out migration mixing patterns). Nonetheless, the preliminary model captures the essential characteristics of an IDU system and the dynamics of HIV transfer within this group. Atkinson, J. A Simulation Model of the Dynamics of HIV Transmission in Intravenous Drug Users. *Computers and Biomedical Research*, 29: pp. 338-349, 1996.

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National Institute on Drug Abuse**Director's Report to the National Advisory Council on Drug Abuse****February 1997**

Research Findings

Epidemiology, Etiology and Prevention Research

Monitoring The Future Results from the 1996 Monitoring the Future Study were released on December 19, 1996 (Lloyd Johnston, et al). Following are the most significant findings:

Between 1995 and 1996 **use of cigarettes and marijuana** *increased* notably among 8th and 10th graders. In addition, **fewer of these students expressed negative perceptions of marijuana use**. For 8th and 10th grade students, these changes replicate recent trends that began in the early 1990s. However, for seniors, this year's data indicate that the rate of increase of use has slowed and that attitudes are improving somewhat, with many differences in use and attitudes between 1995 and 1996 being non-statistically significant. Unless noted otherwise, all changes presented below are statistically significant.

Illicit Drug Use

- Use of marijuana/hashish continued to climb, especially among 8th and 10th graders. Between 1995 and 1996, lifetime, past year, past month, and daily marijuana use *increased* among 8th and 10th graders, while only lifetime use *increased* among 12th graders. Since 1992 past year marijuana use has increased in all three grades and in virtually all demographic and geographic subdomains surveyed. (i.e., gender, census region, population density, and race/ethnicity). The only exception was no change among Hispanic Americans in 12th grade.
- Driven in large part by the rise in marijuana, lifetime, past year, and past month use of any illicit drug increased among 8th and 10th graders.
- Past month use of hallucinogens decreased among 12th graders between 1995 and 1996, as did past month use of LSD among 10th and 12th graders.
- Lifetime use of cocaine in any form increased for 10th graders while past year use increased for 12th graders. Use of crack for all recency periods remain unchanged among all three grades.
- Lifetime, past year, and past month use of tranquilizers increased for 8th graders while lifetime use increased for 10th graders.
- Heroin use did not change among seniors, 10th, and 8th graders.
- Use of stimulants for any recency period did not change among any grades.

Perceived Harmfulness and Availability

- The percentage of 10th graders reporting "great risk" in trying marijuana once or twice or in smoking the drug occasionally decreased. Among 8th graders, the percent reporting "great risk" in regular marijuana use decreased from 73.0 percent in 1995 to 70.9 percent in 1996. The percent of seniors reporting "great risk" in regular marijuana use decreased steadily from 78.6 percent in 1991 to 60.8 percent in 1995, and remain unchanged at 59.9 percent in 1996.

- The perceived risk (percentage reporting "great risk") of smoking a pack or more of cigarettes per day remain unchanged among all three grades.
- The perceived risk of trying inhalants once or twice or using them regularly, increased among 8th and 10th graders.
- The perceived risk of taking one or two drinks once or twice each weekend decreased for 8th graders and increased for 12th graders. Also the perceived risk of taking one or two drinks nearly every day decreased among 8th graders.
- The percentage reporting that marijuana was "fairly easy" or "very easy" to get increased among 8th and 10th graders. The perceived availability of amphetamines and steroids decreased among seniors.

Alcohol Use

- As in past years, alcohol continues to be used at unacceptably high levels. Notably, however, daily drinking and "being drunk" during the past month increased among 8th graders.

Cigarette Use

- Between 1995 and 1996, past month cigarette use increased from 19.1 to 21.0 percent among 8th graders and from 27.9 to 30.4 percent among 10th graders. Daily smoking increased from 16.3 to 18.3 percent among 10th graders. Among subgroups in 10th grade, increases occurred for males and females, whites, and those with college plans.
- Since 1991, past month smoking has increased from 14.3 to 21.0 percent for 8th graders, 20.8 to 30.4 percent for 10th graders, and 28.3 to 34.0 percent for 12th graders.
- From 1995 to 1996, smoking _ pack or more per day increased among 8th and 10th graders.

Cannabinoid Receptor Gene (CNR1): Association with IV Drug Use David Comings at the City of Hope (Duarte, CA) and colleagues compared individuals who were homozygous for 5 or more triplet repeats (of AAT) in the cannabinoid receptor gene (CNR1) with individuals who were either heterozygous, or homozygous for less than 5 repeats. The sample was selected from an inpatient Addiction Treatment Unit (ATU) and hospital or university controls. While there was no greater frequency of homozygous > 5 repeat genes in controls versus ATU subjects, there was a significantly (nearly twice) greater number of these homozygotes among subjects in the ATU who took drugs intravenously. This difference prevailed regardless of the drug of choice: amphetamine, cocaine, or heroin. Using a factor analysis to combine diagnostic questions, the first two factors consisted of questions primarily associated with drug dependence (Factor 1) or alcohol dependence (Factor 2). Those homozygous for > 5 repeats had a significantly higher Factor 1 (drug dependency) score than the other genotypes, but there was no difference between the genotypes on the Factor 2 (alcohol dependence) score. Comings, D.E., Muhleman, D., Gade, R., Johnson, J. P., Verde, R., Saucer, G, MacMurray, J. *Cannabinoid Receptor Gene (CNR1): Association with IV Drug Use, Molecular Psychiatry, In Press.* In a related study, male subjects of the ATU with the homozygous > 5, > 5 genotype had significantly lower amplitudes of the P300 evoked potential, especially in the frontal lobe leads compared to the heterozygote (> 5, < 5) or < 5, <5 homozygote genotypes. Lowered P300 amplitudes have been associated with subjects with substance dependence or their off-spring. Johnson, J. P., Muhleman, D., MacMurray, J., Gade, R., Verde, R., Ask, M., Kelley, J., and Comings, D.E. *Association between the Cannabinoid Receptor Gene (CNR1) and the P300 Event-related Potential. Molecular Psychiatry, In Press.* The authors hypothesize that the varying lengths of the triplet repeats affects gene regulation and that the magnitude of the effect is dependent upon the length of the repeats. These studies report behavioral outcomes (greater IV drug use and lowered P300 amplitudes) for homozygotes with >5 repeats.

The Relationship Between Childhood Maltreatment and Delinquency This study analyzed data from the Rochester Youth Development Study to investigate the relationship between childhood maltreatment and later adolescent involvement in delinquency. A significant relationship was found between child maltreatment and later delinquency, even when controlling for other factors. It appears that more extensive maltreatment was related to higher rates of delinquency. The majority of maltreated youth however demonstrated resilience in terms of serious delinquency. The findings point to further research needs on which to base the design of interventions. Smith, C. and Thornberry, T.P. *The Relationship Between Childhood Maltreatment and Adolescent Involvement in Delinquency. Criminology, 33(4), pp. 451-481, 1995.*

Perception of Friends' Drug Use among Urban Schoolchildren Linked to Own Prior Use Relations between adolescents' substance use and perceptions of their friends' substance use were examined cross-sectionally and

longitudinally in a predominantly African American school district. Students in the 4th and 5th grades were surveyed and tracked for 4 consecutive years. Cross-sectional samples included 3,073, 5,955, 7,701 and 6,616 students in years 1 to 4 respectively. The longitudinal sample included 1,802 students surveyed every year. Self-reported substance use of friends and classmates also was assessed. Perceived friends' substance use had a stronger association with the child's own prior substance use than with the friend's self reported substance use in every year. Perceived family use and classmates' self reported use also made independent contributions to regression models. Longitudinal structural equation analyses indicated that perceived friends' use is more likely to be a product of an adolescent's previous substance use than a precursor of subsequent substance use. Findings contradict prevailing theories on the influence of peers on substance use. Perceived use by peers instead derived from one's own prior use. Iannotti, R.J., Bush, P.J., and Weinfurt, K.P. Perception of Friends' Use of Alcohol, Cigarettes, and Marijuana among Urban Schoolchildren: A Longitudinal Analysis. *Addictive Behaviors*, 21(5), pp. 615-632, 1996.

Trends Among American Indian Youth Dr. Frederick Beauvais of Colorado State University reported that Indian youth residing on reservations continue to show very high rates of drug use compared to their non-Indian peers. Although overall drug use has decreased from its high levels of the 1970's and 1980's, heavy involvement with drugs is reported by about 20 percent of Indian adolescents, a proportion that has not changed since 1980. These findings are based on cross-sectional school survey data of 8th-12th grade Indian youth covering the 20 years from 1975 through 1994. The school survey is augmented by a special study of dropouts to permit adjustment of estimates to represent the total population of Indian youth. The investigator concludes that Indian youth, particularly dropouts, remain at high risk for drug use and abuse. Similar trends for these youth and their non-Indian counterparts suggest that prevention strategies effective with other youth can be effective with Indian youth. Beauvais, F. Trends in Drug Use Among American Indian Students and Dropouts, 1975-1994. *American Journal of Public Health*, 86(1), pp. 1594-1598, Nov., 1996.

Determinants of Drug Abuse in Urban Black Youth This study examined the role of cognitive efficacy, personal anomie, and general deviance in predicting substance use in a sample of urban black youth. The study also examined the reliability and construct validity of measurement of these three factors in adolescents. The findings underscore the primacy of deviance in predicting drug use for minority youth, and the need to incorporate affective influences into current interventions strategies. Scheier, L.M. and Botvin, G.J. Purpose of Life, Cognitive Efficacy, and General Deviance as Determinants of Drug Abuse in Urban Black Youth. *Journal of Child & Adolescent Substance Abuse*, 5(1), pp. 1-26, 1996.

Identifying High-Risk Youth: Prevalence and Patterns of Adolescent Drug Abuse Newcomb (1995) reviewed the literature on drug abuse epidemiology and etiology in regard to identifying youth at high risk. Data from both national and local samples were presented indicating disturbing upward trends in use of illicit drugs among teenagers. Numerous risk and protective factors were delineated as reflecting four biopsychosocial domains including biogenetic, intrapersonal, social, and socio-cultural influences. New analyses were presented that incorporated multiple risk and protective factors into cumulative indices and both the direct and moderating effects of these on drug use and abuse were evaluated. Newcomb extended this etiological approach to understanding drug use and abuse among ethnically-diverse teenagers. Both similarities and differences in risk and protection exposure and impact on drug use were emphasized. This information was discussed in regard to common versus unique approaches to drug abuse prevention among adolescents from ethnically-diverse backgrounds. In both chapters, drug use is characterized as an important aspect or symptom of general deviance that cannot be studied, predicted, or prevented in isolation from the fabric of other types of deviance. Newcomb, M.D. Identifying High-Risk Youth: Prevalence and Patterns of Adolescent Drug Abuse. In E. Rahdert and D. Czechowicz, (Eds.), *Adolescent Drug Abuse: Clinical Assessment and Therapeutic Interventions*, pp. 7-38, 1995. National Institute on Drug Abuse, Rockville, MD.

Alcohol Sensitivity and Smoking History in Men and Women Many studies have found genetic effects to contribute to alcoholism risk in both men and women. Based on preliminary evidence for shared genetic risk between smoking and drinking problems, a re-analysis of alcohol challenge data on 412 Australian twins was performed to explore the possibility that smoking may diminish or moderate the intoxicating effects of alcohol. The authors found history of smoking to be strongly associated with self-reported intoxication after alcohol challenge in women (women: $r = -0.44 + 0.08$; men: $r = -0.21 + 0.08$), comparable with self-reported average weekly consumption of alcohol, which was more strongly associated in men (women: $r = -0.37 + 0.07$; men: $r = -0.54 + 0.06$). Structural equation model fitting indicated a strong association between heavy drinking and smoking, but the association between smoking and post-alcohol intoxication remained even when the effects of heavy drinking were controlled for. These results prompt the question of whether smoking cigarettes directly influences the transition from moderate to excessive use of alcohol by diminishing feelings of alcohol intoxication. Madden, P.A.F., Heath, A.C., Stamer, G.A., Whitfield, J.B., and Martin, N.G. *Alcoholism: Clinical and Experimental Research*, 19(5), October, 1995.

Fatal Consequences of Cocaine and Opiate Use Cocaine, often with opiates (predominantly heroin) and ethanol, caused almost three-fourths of accidental fatal drug overdoses in New York City in 1990 through 1992. This study assessed all 1986 cases in that period using data collected in the Office of 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. There was a less pronounced but steady increase of opiate overdoses over that period of time. There was a marked increase of cocaine overdoses in 1991 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. This points to the urgency of targeting drug treatment and police interventions to these high risk areas. 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.

Reciprocal Relationships among Drug Use, Peers, and Beliefs This study examines the assumptions of interactional theory which posits a reciprocal relationship among drug use, association with drug using peers, and beliefs about drug use. Five waves of longitudinal data from the Rochester Youth Development Study were analyzed. Results largely supported the hypotheses, although the effect from drug use to peer drug use was slightly larger than from peer use to drug use. The effects of beliefs on drug use was relatively weak although the two variables were reciprocally related. These findings have important implications for theory development and intervention strategies. Krohn, M.D., Lizotte, A.J., Thornberry, T.P., Smith, C., and McDowall, D. *Reciprocal Causal Relationships among Drug Use, Peers, and Beliefs: A Five-wave Panel Model*. *Journal of Drug Issues*, 26(2), pp. 405-428, 1996.

Substance Use and Suicide Attempts among Runaway and Homeless Youth Researchers at RTI examined how youth suicide attempts are associated with youth and familial substance use among a nationally representative sample of runaways and homeless youth (RHY) residing in shelters, and a multi-city, purposive sample of RHY found on the street. Analyses revealed that, after controlling for key demographic characteristics, youth who had used substances, (particularly sedatives, hallucinogens, and inhalants), were much more likely than those who had not used substances to have attempted suicide. In addition, after controlling for their own substance use, youth with family members who had used substances were twice as likely as those without such family members to have ever attempted suicide. This study suggests the importance of developing and focusing suicide prevention efforts on RHY known to have used substances and to have substance-using family members. Greene, J.M. and Ringwalt, C.L. *Youth and Familial Substance Use's Association with Suicide Attempts among Runaway and Homeless Youth*. *Substance Use and Misuse*, 31(8), pp. 1041-1058, 1996.

Immediate Impact of Thirty-Two Drug Abuse Prevention Activities Among Students at Continuation High Schools Continuation (i.e. alternative) versus comprehensive (i.e. regular) high schools form a natural demarcation of youth who are at relatively high or low risk for substance abuse in the State of California. Those teenagers who are unable to remain in the regular school system for reasons including substance use are transferred to a continuation high school. Generic comprehensive social influence drug abuse prevention activities are less likely to be effective for use with these at risk youth. Thus, both classroom and self-instruction (main mode of instruction at continuation high schools) versions of 16 activities derived from different theoretical sources were tested and ranked on immediate outcome variables. Students from six continuation high schools were provided with a pretest-activity-posttest "component study" protocol. The scores on perceived quality ratings were standardized and averaged to permit easy comparisons across lessons. While yielding similar knowledge changes, students who received the health educator led activity consistently reported higher scores on perceived quality. Social influence-oriented lessons, in general, were rated relatively low perceived quality. The present approach assisted in selection of the lessons with the greatest overall immediate impact. Sussman, S., et.al. *Immediate Impact of Thirty-Two Drug Abuse Prevention Activities Among Students at Continuation High Schools*. *International Journal of the Addictions*, In Press.

Substance Abuse Disorders Among Runaway and Homeless Youth This study used systematic sampling methods to recruit a sample of 432 homeless youth from both service and natural 'hang-out' sampling sites in Hollywood. The interview procedures relied on participants' self-reports. According to DSM-III criteria, 71% of the respondents were classified as having an alcohol and/or illicit drug abuse disorder. Age and gender were not significantly associated with risk of having an alcohol or drug abuse disorder. The cumulative length of time a youth

spent without a consistent place to live was found to be positively associated with the risk for a diagnosis with either disorder. Kipke, M.D., Montgomery, S.B., Simon, T., Iverson, E.F. *Substance Use & Misuse*, 32, pp. 7-8, 1997.

Results indicated extremely high prevalences of mental health problems among homeless youth as compared with corresponding rates of mental health problems found among housed youth in previous studies. Prevalence of mental health problems differed by age and ethnicity. African-Americans were at lower risk of suicidal thoughts and self-injurious behavior than were youth of other ethnicities. Older youth and females were at increased risk of depressive symptoms and younger youth were at increased risk of self-injurious behavior. Risk factors for drug abuse disorder included ethnicity other than African-American, homelessness for one year or more, suicidality, self-injurious behavior, depressive symptoms, and low self-esteem. The study suggests the need for street-based and non-traditional mental health services targeted toward these youth. Unger, J.B., Kipke, M.D., Simon, T.R., Montgomery, S.B., and Johnson, C.J. *Homeless Youth in Los Angeles: Prevalence of Mental Health Problems and the Relationships Between Mental Health and Substance Abuse Disorders*. *American Journal of Community Psychology*, In Press.

The histories of the youths were examined in terms of violence, perpetration of violence and fear of violence in association with gender, ethnicity, age, and length of time homeless. Respondents reported having experienced a wide range of violent events and attacks. Levels of exposure to violence were similar for males and females. However, females were more likely to report having been sexually assaulted and less likely to have used a knife to attack or stab someone. There were differences between ethnic groups on some exposure measures. Exposure to violence was positively associated with cumulative length of time homeless, and inversely associated with age. Kipke, M.D., Montgomery, S., Simon T. and Iverson E. *Homeless Youth and their Exposure to and Involvement in Violence while Living on the Streets*. *Journal of Adolescent Health*, In Press.

Prevention of Steroid Use in Adolescent Athletes A randomized prospective trial involving 31 football teams in the Portland, Oregon area was recently conducted. Seven hundred two adolescent football players received seven weekly 50-minute class sessions delivered by coaches and student team leaders addressing anabolic androgenic steroid (AAS) effects, sports nutrition, and strength training alternatives to AAS use, drug refusal role play, and anti-AAS media messages. Seven weight room training sessions were taught by research staff. Compared with 804 players from control schools, the experimental subjects at 9- or 12-month follow-up had increased understanding of AAS effects, greater belief in personal vulnerability to the adverse consequences of AAS, improved drug refusal skills, less belief in AAS-promoting media messages, increased belief in the team as an information source, improved perception of athletic abilities and strength training self-efficacy, improved nutrition and exercise behaviors, and reduced intentions to use AAS. *Effects of a Multi-Dimensional Anabolic Steroid Prevention Intervention. The Adolescent Training and Learning to Avoid Steroids (ATLAS) Program*. Goldberg, L., Elliott, D., Clarke, D.N., MacKinnon, D.P., Moe, E., Zoref, L., Green, C., Wolf, S.L., Greffrath, E., Miller, D.J., and Lapin, A. *JAMA*, 276 (19), pp. 1-9, November 20th, 1996.

Effects of Chronic Cocaine Use on Physical Health The effects of chronic cocaine use by the late twenties on physical health by the mid thirties was studied in a longitudinal cohort from the general population. Among males, chronic cocaine use increased physical health problems, when controlling for possible confounding factors. Poor health also contributed to continued cocaine use. Chronic users experienced the most adverse consequences. Chen, K., Scheier, L.M., and Kandel, D.B. *Effects of Chronic Cocaine Use on Physical Health: A Prospective Study in a General Population Sample*. *Drug and Alcohol Dependence*, 43, pp. 23-37, 1996.

Polydrug Use and DSM-IV Alcohol Abuse and Dependence among Youth In a study of 176 adolescent drinkers with diagnoses of alcohol abuse (n=57) or alcohol dependence (n=61) or no alcohol diagnosis (n=58) based on a modified form of the Structured Clinical Interview for the DSM, researchers at CEDAR, the Center for Education and Drug Abuse Research at the University of Pittsburgh, investigated patterns of polydrug use, particularly combinations involving alcohol with other drugs. Lifetime histories of alcohol and other drug use were assessed, and frequency of use of specific alcohol-drug combinations was determined. Subjects with alcohol abuse and dependence diagnoses reported using greater numbers of illicit drugs than subjects without an alcohol diagnosis; recent polydrug use was higher among those with these diagnoses. Patterns of age of onset of psychoactive substance use followed those observed by prior researchers (i.e., alcohol, followed by marijuana, followed by other drugs). The most common alcohol-drug combination was alcohol with marijuana (reported by 58 percent of the sample), followed by alcohol with hallucinogens (16 percent). Frequency and extent of polydrug use increased with age and increased with increasing levels of behavioral under control and negative emotionality. Martin, C.S., Kaczynski, N.A., Maisto, S.A., and Tarter, R.E. *Polydrug Use in Adolescent Drinkers with and without DSM-IV Alcohol Abuse and Dependence*. *Alcoholism: Clinical and Experimental Research*, 20(6), pp. 1099-1108, 1996.

Nicotine Withdrawal In Women Associations between self-report symptom profiles for nicotine withdrawal,

personality (TPQ, EPQ-R), lifetime history of psychopathology, and smoking history were examined in data obtained from 553 female adult Australian twins (246 regular smokers), aged 32-48, who had participated in a telephone interview survey that included lifetime assessments of smoking history, nicotine dependence and withdrawal. 202 respondents were from high-risk pairs where either the respondent or the respondent's cotwin had reported a lifetime history of alcohol dependence; 351 were from control pairs. Latent class analysis was used to identify subtypes ('classes') of smokers reporting similar withdrawal symptom profiles. Three major classes were identified which appeared to represent a continuum from mild to severe nicotine withdrawal. Smokers from the severe withdrawal class were best characterized by hands shaking and by the prominence of depressive features during withdrawal. There were marked increases in lifetime alcohol dependence rates as a function of severity class. In contrast, significantly elevated rates of major depression, conduct disorder, and anxiety disorder were observed only among smokers from the most severe withdrawal class. With the exception of Neuroticism, personality factors were more closely related to the initiation of regular smoking than to the development of withdrawal symptoms. Madden, P.A.F., Bucholz, K.K., Dinwiddie, S.H., Slutske, W.S., Bierut, L.J., Statham, D.J., Dunne, M.P., Martin, N.G., Heath, A.C., and Phil, D. Addictions, In Press.

Development of a School-Based Drug Abuse Prevention Curriculum for High-Risk Youths This paper presents the rationale for and the description of the empirical curriculum development process in Project Towards No Drug Abuse (Project TND). First, the target population is described, continuation high-school youths who are at high risk for drug abuse. The rationale for developing a classroom-based curriculum tailored for them is also provided. Second, a brief description is provided of state-of-the-art generic social influences drug abuse prevention programming, which has been found to be the most effective among young adolescents. There is a need to consider other prevention activities, particularly those that include motivational variables, to maximize prevention efforts among higher-risk youths. Third, five types of curriculum development studies are discussed that led to a curriculum that is being implemented with continuation high-school students at schools in five counties in southern California. Finally, the contents of the final curriculum product is provided which consist of motivation, skills-training, and decision-making components. Sussman, S. Development of a School-Based Drug Abuse Prevention Curriculum for High-Risk Youths. *Journal of Psychoactive Drugs*, Vol. 28(2), April-June 1996.

Key Qualities for Achieving a 96.6 Percent Follow-Up Rate in a Study of Drug Abusers. The St. Louis Effort to Reduce the Spread of AIDS Study (ERSA) aimed to reduce the spread of HIV among St. Louis' most vulnerable drug-using population while improving drug abuse treatment. As part of ERSA, researchers utilized a three-stage tracking strategy to follow out-of-treatment drug abusers for an 18-month longitudinal study. There were 479 ERSA subjects interviewed at baseline who were eligible for reinterview at the terminal 18-month interview; at follow-up, 454 persons had a complete interview (96.6%). The three-stage tracking strategy, consisting of phone tracking, systems tracking (using private and public databases, such as national credit information, social service data, and criminal justice data), and field tracking (visits by members of the research team to residents and "hang outs") -- coupled with patience, persistence, enthusiasm, creative team work, time, and money for remuneration (to the individual, the family, and as a bonus) -- were instrumental in achieving the 96.6% follow-up rate. Two particular qualities stood out from the others: persistence (not giving up) and creative team work. The researchers identified an experienced and enthusiastic staff who could work together as the most important factor for achieving the study goals. In addition, when the hard-to-reach respondents were compared on the basis of gender, race, age, education, psychiatric status, and employment status to those less difficult to find, only employment status was associated with being hard-to-reach. Cottler, L.B., Compton, W. M., Ben-Abdallah, A., et al. Achieving a 96.6 Percent Follow-Up Rate in a Longitudinal Study of Drug Abusers. *Drug and Alcohol Dependence*, 41: pp. 209-217, 1996.

A General Statistical Model for Detecting Complex Trait Loci 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. In the case of opioid dependency, using family studies and epidemiological data, the estimates of the heritability of opioid dependency is as high as 80 to 90%. These family studies justify the more detailed search of the human genome for the existence and exact location for susceptibility genes underlying opioid dependency. Such searches already have been undertaken for alcoholism. The search of the human genome for susceptibility genes is a difficult and expensive process that requires elaborate and powerful statistical methods to deal with the high dependency among DNA segments and the large number of such segments. Novel molecular techniques such as Genomic Mismatch Scanning (GMS) are emerging and promising to reduce the expense of the full genome search. But the statistical methods appropriate to the newer molecular techniques also must be developed. 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. 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.

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National Institute on Drug Abuse
Director's Report to the National Advisory Council on Drug Abuse
February 1997

Research Findings

Intramural Research

Activation of Memory Circuits During Cue-Elicited Cocaine Craving

Evidence accumulated over more than 45 years has indicated that environmental stimuli can induce craving for drugs of abuse in individuals who have addictive disorders. However, the brain mechanisms that subserve such craving have not been elucidated. Here, a positron emission tomographic study shows increased glucose metabolism in cortical and limbic regions implicated in several forms of memory when human volunteers who abuse cocaine were exposed to drug-related stimuli. Correlations of metabolic increases in the dorsolateral prefrontal cortex, medial temporal lobe (amygdala) and cerebellum with self-reports of craving suggest that a distributed neural network, which integrates emotional and cognitive aspects of memory, links environmental cues with cocaine craving. Identifying patterns of brain activation correlated with cocaine craving can direct future investigations in the mechanism of and therapeutic interventions for craving associated with drug addiction. Grant, S., London, E.D., Newlin, D.B., Villemagne, V.L., Liu, X., Contoreggi, C., Phillips, R.L., Kimes, A.S., Margolin, A. *Proc. Natl. Acad. Sci.*, 93: pp. 12040-12045, 1996.

Subjective and Cardiovascular Effects of Nicotine in Human Volunteers

The subjective and cardiovascular effects of intravenous nicotine were assessed in smokers and nonsmokers. Both smokers and nonsmokers manifested significant increases in systolic and diastolic blood pressure and heart rate 1 min after administration of single doses of nicotine (0.75 or 1.5 mg). The most prominent difference between groups was the increase in heart rate was greater and more sustained in nonsmokers than in smokers. Nonsmokers and smokers also differed in subjective self-reports. In response to items on visual analogue scales indicative of positive effects (e.g., "good effects," "like drug," "use again," and "feel energetic"), smokers, but not nonsmokers, reported high scores after nicotine injection. In addition, responses on the MBG and LSD subscales of the Addiction Research Center Inventory indicated that smokers experienced positive subjective effects after the test doses, whereas nonsmokers experienced disorientation. The fact that intravenous nicotine was not associated with positive subjective effects in nonsmokers indicates that repeated exposure is required to establish positive reinforcing effects of nicotine. Soria, R., Stapleton, J.S., Gilson, S.F., Sampson-Cone, A., Henningfield, J.E., and London, E.D. *Psychopharmacology* 128: pp. 221-226, 1996.

PPBP[4-Phenyl-1-(4-phenylbutyl) piperidine] Decreased Brain Injury Following Transient Focal Ischemia in Rats.

Sigma-receptor ligands have been hypothesized to be therapeutically beneficial in the setting of focal cerebral ischemia. Previous studies in the cat were extended to the rat to test if intravenous administration of the potent sigma receptor ligand 4-phenyl-1-(4-phenylbutyl) piperidine (PPBP) initiated half-way through a 2 h period of transient focal ischemia and continuing for 23 h would decrease postischemic brain infarction volume occurring over 22 h of reperfusion in unanesthetized animals. The infarction volume of cerebral cortex (saline, 39Å6%; PPBP, 21Å7% of the ipsilateral hemisphere) and striatum (saline, 68Å6%; PPBP, 33Å8% of the ipsilateral striatum) was smaller in rats treated with PPBP than in rats treated with saline. Thus, PPBP effectively decreases brain injury from

transient focal ischemia, when administered after the onset of ischemia and during reperfusion, and suggests sigma-receptors may influence the progression of injury in ischemic border regions. Takahashi, H., Kirsch, J.R., Hashimoto, K., London, E.D., Koehler, R.C., Traystman, R.J. *Stroke* 27: pp. 2120-2123, 1996.

Methamphetamine-Induced Neurotoxicity

These papers show that METH can cause increase in AP-1 binding activity. This activation is secondary to the production of superoxide radicals because transgenic mice that overexpress superoxide dismutase show much less of a response. These results are consistent with previous findings that showed that AP-1 activation is dependent on cellular redox status. These papers also identify a role for AP-1 in the neurodegeneration of the dopaminergic system of mice. Methamphetamine-Induced Neurotoxicity is Associated with Increased Striatal AP-1 DNA-binding Activity in Mice. Sheng, P., Ladenheim B., Moran T.H., and Cadet J.L. *Molecular Brain Res.* 42: pp., 171-174, 1996; AP-1 DNA Binding Activation by Methamphetamine Involves Oxidative Stress. Sheng P., Wang X-B., Ladenheim B., Epstein C., and Cadet J.L. *Synapse* 24: pp. 213-217, 1996.

Neuroadaptive Changes Following Chronic Cocaine Administration

This paper shows that chronic cocaine self-administration causes increases in the number of dopamine uptake sites in the striatum, nucleus accumbens, and the ventral tegmental areas. The use of the cocaine analog GBR-12909 reduced self-administration. Moreover, GBR-12909 caused a reversal of the biochemical changes caused by cocaine. These results indicate that GBR-12909 might be an important drug in the treatment arsenal being built against cocaine addiction. Differential Reinforcing Effects of Cocaine and GBR-12909: Biochemical Evidence for Divergent Neuroadaptive Changes in the Mesolimbic Dopaminergic System. Tella S.R., Ladenheim B., Andrews A.M., Goldberg S.R., and Cadet J.L. *Journal of Neuroscience*, 16: pp. 7416-7427, 1996.

Neurotoxicity of 2'-N^h3-MPTP

These studies show that superoxide radicals are involved in the neurotoxicity of 2'-N^h3-MPTP. These results extend the role of free radicals to the neurodegeneration of serotonergic and noradrenergic systems in rodent brains. Transgenic mice with high levels of superoxide dismutase activity are protected from the neurotoxic effects of 2'-N^h3-MPTP on serotonergic and noradrenergic nerve terminals. Andrews A.M., Ladenheim B., Epstein C.J., Cadet J.L., and Murphy D.L. *Molecular Pharmacology* 50: pp. 1511-1519, 1996.

PD-128,907--A Selective D3 Dopamine Receptor Agonist with an Atypical Antipsychotic Profile

The Drug Development Group of the Behavioral Pharmacology and Genetics Section of NIDA IRP was the first group to report a common subjective effect pattern for cocaine and agonists selective for dopamine D3 receptors. D3 receptors have also become a focus of drug abuse researchers due to the reports from Koob's group that this site may be a target for cocaine abuse therapeutics. In the process of discovery of a selective antagonist for the abused drug, phencyclidine (PCP), we have found a selective D3 agonist with an atypical antipsychotic profile like that of the prototype, clozapine. PD-128,907(4aR,10bR-(+)-trans, 3,4,4a,10b-tetrahydro-4-n-propyl-2H,5H[4,3-b]-1,4-oxazin-9-ol) blocked behavioral effects of dizocilpine [(+)-MK-801], a PCP-like antagonist of the NMDA receptor-associated ion channel. Blockade occurred at doses of PD-128,907 that did not affect spontaneous locomotor activity. Like clozapine, PD-128,907 blocked the stereotyped behavior produced by dizocilpine but had minimal effects against apomorphine-induced stereotypies. The dizocilpine-blocking effects of PD-128,907 were not observed with the inactive, minus isomer of PD-128,907. Importantly, PD-128,907, like clozapine, lacked cataleptic effects, predicting an absence of chronic neurological problems associated with typical antipsychotic drugs (e.g., haloperidol). These data are the first to document a common mode of action of a D3 receptor ligand with PCP blockade and psychosis and suggest novel treatment approaches in both areas. Blockade of dizocilpine-induced behaviors may be a valuable preclinical screening device for novel pharmacological therapies for schizophrenia. The comorbidity of psychosis and drug abuse makes these findings additionally compelling. This work was presented at the annual meeting of the American College of Neuropsychopharmacology in December, 1996.

Marjolein Beekman from the University of Groningen, The Netherlands has been a guest scientist working on this project for the past 5 months. She comes from the medicinal chemistry group that synthesized the most selective drug, to date for D3 receptors. Future research will be directed toward definitive identification of D3 receptors as the target for this novel effect. Based upon the linkage with psychosis and with our previous findings on commonalities in the pharmacology of cocaine and D3 receptor ligands, further work will be expanded to identify a role for these compounds in the control of psychomotor stimulant (cocaine, methamphetamine) abuse and toxicity.

Genotype-Dependent Differences in Morphine Self-Administration

The objective of the behavior genetic work in the Behavioral Pharmacology and Genetics Section of the Preclinical Pharmacology Laboratory has been to characterize the behavioral and neural substrates that determine individual differences in the efficacy of morphine as a reinforcer and vulnerability to opioid-reinforced behavior. The specific

hypothesis has been that a significant relationship exists between individual differences in mesolimbic-opiate receptor concentration and the efficacy of morphine as a primary reinforcer. In collaboration with Dr. J.L. Cadet of the Molecular Neuropsychiatry Section of the Neuroscience Branch, behavior genetic and neuroanatomical techniques were used to investigate the relationship between regional -opiate receptor concentration and morphine-reinforced behavior. Inherited differences in regional -opiate receptor concentration (genetically engineered and naturally occurring) was used as a means to manipulate regional concentrations of the -opiate receptor. Intravenous morphine self-administration behavior was investigated in two sets of genetically engineered mice that overexpress the -opiate receptor, two commonly used recombinant inbred strains with high and low opiate receptor concentration and two commonly available inbred strains. Multivariate analysis of the relationship between -opiate receptor concentration in specific neuroanatomical regions and self-administration behavior suggest that -opiate receptor concentration in the amygdala can account for 64% of the variance (r^2) in self-administration behavior. When -opiate receptor concentration in amygdala, the shell of the nucleus accumbens and ventral tegmental area were considered jointly, these regions accounted for 98% of the variance (r^2) in self-administration behavior across genotype. These results suggest that -opiate receptor concentration in one or more regions of the mesolimbic system are predictive of genotype-dependent differences in morphine self-administration behavior and provide a significant step towards identifying specific neural regions involved in the neurobiological substrates underlying vulnerability to opioid addiction.

Additive Interactions of Caffeine and Nicotine

Nicotine and caffeine are two of the most widely used licit drugs in society, and they are repeatedly consumed together. Epidemiological reports indicate a correlation between coffee drinking and tobacco smoking and a possible explanation is provided by laboratory studies that indicate these two heavily used drugs interact additively. In a series of studies in the Behavioral Pharmacology and Genetics Section of the Preclinical Pharmacology Laboratory, we have shown that acute or chronic caffeine exposure can alter the reinforcing and other behavioral properties of nicotine. Rats consuming caffeine in their drinking water acquired i.v. nicotine self-administration faster and reached higher levels of intake than controls. Rats trained to discriminate nicotine from saline failed to generalize to other psychomotor stimulant drugs when they were chronically exposed to caffeine during training. Squirrel monkeys showed increases in nicotine self-administration responding and a marked potentiation of other behavioral effects of nicotine after acute or chronic caffeine exposure. Thus, caffeine exposure can markedly alter the reinforcing, discriminative and stimulant properties of nicotine. Such an interaction could be part of the pharmacological basis for nicotine usage and relapse to usage after cessation. Results of this research were presented at the College on Problems of Drug Dependence meeting in June, 1996 and the Society for Neuroscience meeting in November, 1996.

Methamphetamine-Associated Neurotoxicity

Investigators in the Behavioral Pharmacology and Genetics Section and the Molecular Neuropsychiatry Section of NIDA's IRP have been conducting a series of studies on methamphetamine self-administration and associated neurotoxicity in rats and monkeys. D-methylamphetamine (methamphetamine) and its stereoisomer l-methylamphetamine have been shown to have amphetamine-like abuse liability in rats and monkeys using operant drug-discrimination and intravenous self-administration procedures. Both isomers of methylamphetamine, and l-deprenyl (selegiline), whose major metabolite is l-methylamphetamine, had dose-dependent, d-amphetamine-like, discriminative-stimulus properties in rats and monkeys. Both d- and l-methylamphetamine maintained high rates of self-administration behavior in monkeys and rats. In rats, after 97 d-methylamphetamine self-administration sessions, with total intake of d-methylamphetamine over the 97 sessions ranging from 68 to 116 mg/kg, there were neuroadaptive changes in dopamine uptake sites in the caudate and a small decrease in dopamine transporter levels with corresponding upregulation of dopamine D1 receptors in the nucleus accumbens. There was an indication that opioid systems may be important in the mediation of methamphetamine's reinforcing effects since there was marked upregulation of -opioid receptors in the nucleus accumbens, substantia nigra compacta, ventral tegmental area, prefrontal cortex, anterior caudate and different hippocampus regions. Further studies in rats are underway using yoked control groups of rats that passively receive injections of either methamphetamine or saline whenever test rats self-administer injections of methamphetamine.

Potential Utility of l-deprenyl in Treating Stimulant Abuse

l-deprenyl has been suggested as a potential treatment agent for various types of psychomotor stimulant abuse. l-deprenyl failed to maintain self-administration behavior in monkeys and treatment with l-deprenyl before experimental sessions failed to alter either the discriminative-stimulus actions of d-amphetamine or d-methylamphetamine in rats or monkeys or the self-administration of either d- or l-methylamphetamine in monkeys. Thus, although l-deprenyl had amphetamine-like, discriminative-stimulus properties, it did not appear to have methamphetamine-like reinforcing properties in rats or monkeys and was ineffective in altering established patterns of methamphetamine self-administration behavior. It is possible, however, that l-deprenyl treatment would ameliorate the neurotoxicity seen with extended administration or self-administration of high doses of

methamphetamine.

Development of Compound that Binds Irreversibly to the Dopamine Transporter

The Psychobiology Section of NIDA's IRP has developed a drug that binds irreversibly to the dopamine transporter. The drug was derived from a compound that binds to the dopamine transporter and inhibits dopamine uptake but does not have cocaine-like behavioral effects. It is believed that the parent compound acts primarily through a low-affinity binding site on the dopamine transporter, although that is highly speculative. The characterization of the in vitro pharmacology of the compound that binds irreversibly is currently in progress. Studies will more fully characterize the drug in order to assess its suitability for functional characterization of the roles of the high- and low-affinity sites on the dopamine transporter.

Human Pharmacokinetics of Intravenous, Sublingual and Buccal Buprenorphine

Buprenorphine is a potent opioid analgesic used in the treatment of moderate to severe pain. At higher doses it has demonstrated potential for treating heroin dependence. Collaborative efforts between scientists from NIDA's IRP and the Armed Forces Institute of Pathology were undertaken to investigate buprenorphine pharmacokinetics by different routes of administration at dosages approximating those used in opioid dependence studies. Six healthy male subjects who were non-dependent but had a history of heroin use were administered buprenorphine in a cross-over design study by intravenous (1.2 mg), sublingual (4.0 mg) and buccal (4.0 mg) routes of administration. Plasma samples were collected up to 96 hours and assayed for buprenorphine and norbuprenorphine by negative chemical ionization tandem mass spectrometry. Plasma concentrations of buprenorphine and norbuprenorphine were analyzed by nonlinear regression analysis with standard non-compartmental methods. Buprenorphine bioavailability by the sublingual and buccal routes was estimated as 51.4% and 27.8%, respectively, although there was considerable inter-subject variability by both routes of administration. The terminal elimination half-lives were longer for the sublingual and buccal routes than the intravenous route. The extended elimination half-lives may be due to a shallow depot effect by sequestration of buprenorphine in the oral mucosa. Norbuprenorphine mean peak plasma concentrations were less than 1 ng/mL and were highly variable between different routes of administration and subjects. The terminal elimination half-life of norbuprenorphine was longer than buprenorphine.

Cocaine Disposition in Meconium from Newborns of Cocaine-Abusing Mothers and Urine of Adult Drug Users

The analysis of meconium for cocaine and other metabolites has proven to be a reliable method for the detection of fetal cocaine exposure. Better sensitivity and a larger gestational window of detection have been demonstrated for meconium testing as compared to neonatal urine testing. Cocaine and cocaine metabolites have been identified in meconium including benzoylecgonine, ecgonine methyl ester, cocaethylene, norcocaine, benzoynorecgonine, and m-hydroxybenzoylecgonine. The origin of these metabolites, whether maternal or fetal, has not been established. This study was conducted to compare the disposition of cocaine and metabolites in meconium from cocaine exposed fetuses to that of urine from cocaine abusers. Meconium specimens were obtained from 6 neonates of mothers positive for cocaine use by urinalysis and/or self-report during pregnancy. Urine specimens were obtained from 17 adult female and 17 adult male cocaine users enrolled in a treatment program. Specimens were analyzed by GC-MS for cocaine and 12 related analytes. The following analytes were identified and measured in meconium and urine: anhydroecgonine methyl ester; ecgonine methyl ester; ecgonine ethyl ester; cocaine; cocaethylene; benzoylecgonine; norcocaine; norcocaethylene; benzoynorecgonine; m- and p-hydroxy-cocaine; and m- and p-hydroxybenzoylecgonine. In addition, both m- and p-hydroxy-benzoylecgonine were found to exhibit approximately equal crossreactivity with benzoylecgonine in the EMIT and TDx assays. The presence of p-hydroxybenzoylecgonine in meconium suggested that this newly identified metabolite, like m-hydroxybenzoylecgonine, might serve as a valuable marker of fetal cocaine exposure during pregnancy. The presence of cocaine and anhydroecgonine methyl ester in meconium was attributed to transfer across the placenta from the mother. However, the origin of the hydrolytic and oxidative metabolites of cocaine could not be established since they were also identified in urine specimens of adult, female cocaine users and could have arisen in meconium from either fetal or maternal metabolism.

Melanin and Lipids on Cocaine Binding to Caucasoid and Africoid Hair

Although the mechanism(s) of drug deposition in hair are unknown, there is evidence which suggests that the amount and type of melanin present is a major factor in determining how much drug enters hair following exposure. Divided hair specimens (N=7) from male and female Caucasoids (black/brown and blond colored) and Africoids (black colored) were exhaustively extracted to remove lipid components (lipid-extracted hair). Separate portions were bleached to denature or alter melanin content. Experiments with radiolabeled cocaine were performed on untreated, lipid-extracted and bleached portions of hair from different groups. Cocaine binding was significantly higher ($p < 0.01$) to male Africoid hair compared to other groups. The amount of drug binding was similar among specimens from female Africoids and male and female black/brown Caucasoids. The lowest amount of binding was observed with

blond, female Caucasoid specimens. Binding experiments also revealed that specific cocaine binding generally did not differ significantly between lipid-extracted hair and untreated hair, but bleaching of most hair specimens resulted in significant ($p < 0.01$) decreases in specific binding compared to untreated hair. In separate experiments with cocaine-treated hair specimens, digested samples were evaluated to determine if removal of the insoluble melanin fraction from soluble hair components provided a means of normalization of drug content and elimination of color bias. Removal of the insoluble melanin fraction was not effective in removal of significant amounts of cocaine indicating that the digestion process released bound cocaine into the digest solution. Overall, these experiments suggested that lipids in hair play a minor role in drug binding, whereas melanin functions as a major binding site for cocaine. Natural (ethnic) or artificial differences (bleaching) in melanin content may determine the extent of cocaine entrapment in hair after drug exposure. Further, digestion of hair samples with removal of insoluble melanin failed to be effective in removal of hair color bias.

Phentermine Pretreatment Antagonizes the Cocaine-Induced Rise in Mesolimbic Dopamine

Coadministration of phentermine and fenfluramine has been used to treat cocaine dependence. Patients who relapse while receiving this treatment report diminished subjective effects of cocaine. Due to the importance of mesolimbic dopamine (DA) in mediating cocaine reinforcement, we hypothesized that phentermine might attenuate the effects of cocaine on DA transmission. We examined this proposal directly using *in vivo* microdialysis methods in the nucleus accumbens of awake rats. Rats were pretreated with saline or phentermine (1 mg/kg, iv) and then challenged with cocaine (3 mg/kg, iv). Phentermine alone caused a modest increase in DA, and phentermine pretreatment substantially reduced the cocaine-induced rise in extracellular DA. Alternately, phentermine did not alter the stimulatory effect of cocaine on 5-HT. Our findings suggest that phentermine may antagonize the subjective effects of cocaine in humans via a DA mechanism. Rothman, R.B., Ayestas, M., and Baumann, M.H. *Neuroreport*, In Press.

Sustained Decrease in Cocaine-Maintained Responding in Rhesus Monkeys with 1-[2-[bis-(4-fluorophenyl)methoxy]ethyl]-4-[3-hydroxy-3-phenylpropyl] piper-aziny] decanoate, a Long-Acting Ester Derivative of GBR 12909

The selective DA reuptake inhibitor GBR 12909 previously has been shown to decrease cocaine-maintained responding without affecting similar levels of food-maintained responding in monkeys, an effect analogous to that expected of a medication designed to treat human cocaine abuse without adverse effect. In the current study, we extended this type of effect by developing a decanoate ester of a hydroxylated analog of GBR 12909 (compound 5). Within several days of the administration of an active dose of 5, cocaine-maintained responding had decreased more than 80% while food-maintained responding was unaffected. This selective effect on cocaine-maintained responding lasted almost thirty days with a single injection, and was followed by a return to control levels of responding. 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. *J. Med. Chem.* 39(24): pp. 4689-4691, 1996.

Serotonin-4 Receptor Antagonists Reverse Cocaine-Induced Cardiac Arrhythmia

The effect of 5-HT₄ 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. Pretreatment with 2mg/kg of either drug increased the dose of cocaine required to induce arrhythmia by 168 and 286 percent respectively. This effect was dose dependent. The antagonists were ineffective when given intraperitoneally in rats. The results of this study indicate that 5-HT₄ antagonist can reverse cocaine-induced arrhythmias.

The clinical implication of these findings 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. Submitted to *NeuroReport*.

Therapeutic Potential of Enhancing Cocaine Metabolism

Scientists from the Preclinical Pharmacology, Clinical Pharmacology, and Treatment Branches of the Division of Intramural Research, in collaboration with scientists at the Drug Development Program of the Gerontology Research Center of NIA, recently completed a study providing the first experimental demonstration that enhancing the metabolism of cocaine could significantly reduce the acute behavioral effects of a cocaine challenge. Cocaine metabolism in rats was increased several-fold by IV administration of exogenous butyrylcholinesterase (extracted from horse serum), the major cocaine-metabolizing enzyme in primates. Thirty minutes later, the rats were challenged with IP cocaine or saline and their locomotor activity measured for 2 hours. The rats receiving enzyme pretreatment had a significantly blunted response to cocaine (i.e., less of an increase in distance traveled and stereotypy) compared to those receiving saline pretreatment. Rats receiving only butyrylcholinesterase had the same locomotor activity as those receiving saline, indicating that the enzyme by itself did not influence this behavior. These

findings, presented at the Society for Neuroscience annual meeting in November 1996, suggest that enhancement of cocaine metabolism by increasing metabolizing enzyme activity may have therapeutic potential.

Chronic Cocaine Exposure Influences Mu-Opiate Receptor Function

Scientists from the Treatment Branch, Division of Intramural Research, in collaboration with scientists at the Johns Hopkins Medical Institutions, recently published a study showing that chronic, heavy cocaine users have increased mu-opiate receptor binding in selected brain areas, and that this increased binding correlates with self-reported cocaine craving. Binding was measured by positron emission tomography (PET) scanning using ¹¹C-carfentanil, a potent synthetic mu-opioid agonist drug. This finding is the first confirmation in humans of the previously reported finding in animals that chronic cocaine exposure influences mu-opiate receptor function, and suggests a possible mechanism for the reported therapeutic effect of buprenorphine, a partial mu-opioid agonist, in reducing cocaine use by cocaine addicts in treatment. *Nature Medicine*, 2: pp. 1225-1229, 1996.

Cocaine Use Early In Treatment Predicts Outcome In A Behavioral Treatment Program

To evaluate baseline drug use as a predictor of treatment outcome, cocaine use (qualitative and quantitative urinalysis and self-report) during baseline was compared in methadone patients who had <5 weeks of abstinence (n = 10) during a 12-week experimental voucher-based cocaine abstinence reinforcement treatment. Baseline cocaine use was evaluated at the first and last clinic visit and first and last week of baseline and as a mean across the 5-week baseline; treatment response was calculated as a mean across 12-weeks of treatment. Those who had successful outcomes (Abstainers) used significantly less cocaine in the 5-week baseline than those with less successful outcomes (Nonabstainers). Differences in cocaine use were not evident in the first baseline visit or week, but Abstainers used significantly less cocaine in the last visit and week of baseline compared to Nonabstainers. Cocaine use during baseline provided critical predictors of response to the experimental treatment.

Assessment of Cocaine Use With Quantitative Urinalysis

Measures of cocaine use are pivotal both in treatment and in clinical trials of new cocaine abuse treatments. Current qualitative urinalysis methods of monitoring cocaine use may over-detect frequency of use because of carryover from previous cocaine administrations, masking effective treatments and decreasing the sensitivity of clinical trials. This study assessed the value of quantitative urinalysis and a newly developed measure of cocaine use. Urine specimens collected in a cocaine dosing study in non-treatment-seeking subjects (N=5) and a clinical trial of a behavioral treatment for cocaine abuse (N=37) were analyzed for the cocaine metabolite, benzoylecgonine (BE), with qualitative and quantitative methods. Pharmacokinetic criteria ("New Use" rules) were developed and applied to quantitative data to identify occasions of new cocaine use. Results were compared to known cocaine administrations in the laboratory study and to self-reported drug use, qualitative urinalysis and treatment response for subjects in the treatment trial. New Use criteria correctly identified cocaine administrations in the cocaine dosing study in all but a small number of specimens. In the clinical trial, urine BE concentrations and estimated New Uses were more sensitive to differences in cocaine use in statistical analyses than qualitative urinalysis. Interpretation of quantitative urinalysis with New Use rules appears to be a useful method for monitoring treatment outcome and may be more accurate than traditional qualitative urinalysis in estimating frequency of cocaine use. Methamphetamine-Associated Neurotoxicity Investigators in the Behavioral Pharmacology and Genetics Section and the Molecular Neuropsychiatry Section of NIDA's IRP have been conducting a series of studies on methamphetamine self-administration and associated neurotoxicity in rats and monkeys. D-methylamphetamine (methamphetamine) and its stereoisomer l-methylamphetamine have been shown to have amphetamine-like abuse liability in rats and monkeys using operant drug-discrimination and intravenous self-administration procedures. Both isomers of methylamphetamine, and l-deprenyl (selegiline), whose major metabolite is l-methylamphetamine, had dose-dependent, d-amphetamine-like, discriminative-stimulus properties in rats and monkeys. Both d- and l-methylamphetamine maintained high rates of self-administration behavior in monkeys and rats. In rats, after 97 d-methylamphetamine self-administration sessions, with total intake of d-methylamphetamine over the 97 sessions ranging from 68 to 116 mg/kg, there were neuroadaptive changes in dopamine uptake sites in the caudate and a small decrease in dopamine transporter levels with corresponding upregulation of dopamine D1 receptors in the nucleus accumbens. There was an indication that opioid systems may be important in the mediation of methamphetamine's reinforcing effects since there was marked upregulation of μ -opioid receptors in the nucleus accumbens, substantia nigra compacta, ventral tegmental area, prefrontal cortex, anterior caudate and different hippocampus regions. Further studies in rats are underway using yoked control groups of rats that passively receive injections of either methamphetamine or saline whenever test rats self-administer injections of methamphetamine.

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National Institute on Drug Abuse**Director's Report to the National Advisory Council on Drug Abuse****February, 1997**

Program Activities

Program Announcements/RFAs

Drug Use, Sexual Risk Behaviors, and HIV in Men

The Community Research Branch, Division of Epidemiology and Prevention Research, in collaboration with the Division of Clinical and Services Research, has issued a new Program Announcement (PA-96-074) to encourage research aimed at understanding and preventing drug abuse and HIV in drug using men who have sex with men (DU MSM). DU MSM use drugs by injection and/or non-injection, and they engage in same-gender sex regardless of self-identified sexual orientation. Because DU MSM may engage in high risk drug and sex practices, and may have multiple partners and networks, they are an important HIV risk group not only in and of themselves, but also in their potential to bridge HIV transmission between heterosexual IDUs and non-IDU MSM. This new program initiative underscores NIDA's commitment to and interest in supporting epidemiological and HIV prevention research on this understudied and dual risk group.

Neurobiological Substrates of Cognitive Functioning in Drug Abuse

The Division of Clinical and Services Research and the Division of Basic Research have issued a joint RFA (DA-98-001) on the "Neurobiological Substrates of Cognitive Functioning in Drug Abuse." The emphasis is on bridging the gap between the fields of cognitive neuroscience and addiction research. The application receipt date is June 13, 1997, and the Institute contacts are Chiiko Asanuma, Ph.D. for human studies, and Thomas Aigner, Ph.D. for animal studies.

Young Investigators: B/START

NIDA launched the Behavioral Science Track Awards for Rapid Transition (B/START) program in order to fund small pilot projects submitted by new investigators. Eight B/START applications were funded in the first cohort. B/START is planned to be an ongoing program.

Discovery of Novel Pharmacotherapies for Cocaine Dependence

The Medications Development Division issued RFA DA-97-003 entitled "Discovery of Novel Pharmacotherapies for Cocaine Dependence," to encourage applications containing medicinal chemistry and preclinical pharmacology to design, synthesize and test compounds leading to the identification of candidates for advanced preclinical and clinical evaluation as potential pharmacotherapies for cocaine dependence. Applications under the R01 and R29 mechanisms are requested with a letter of intent date of February 13, 1997 and an application receipt date of March 13, 1997.

NIDA Role in Grants under NIH RFA on Domestic Violence

The 15-agency consortium for the NIH RFA on Domestic Violence resulted in 10 awards totalling more than \$1.5 million. Although participating agencies including CDC and NIJ are collaborators, NIDA is now the lead agency for management and scientific administration. Dr. Donald Vereen, OD is the NIDA representative to the NIH consortium;

Dr. Coryl Jones DEPR/ERB is the scientific program official; and Catherine Mills OPRM/GMB is the Grants Management Official. This group of awards includes studies of children of battered women, post-rape psychopathology, homicide in violent intimate relationships, partner violence among Native American Women, PTSD among cocaine-dependent women, elder abuse, emotions and self cognitions of maltreated children, and preventive interventions for adolescents. Although violence and victimization within the family were the focus of the RFA, drug and alcohol abuse emerged as a key factor in the predisposing situations.

Centers for AIDS Research (CFAR)

NIDA's Office on AIDS has worked closely with the Division of AIDS, NIAID to develop a multi-Institute program announcement, PA-98-AI-011, "Centers for AIDS Research (CFAR)" which will support cores (P30-mechanism) to provide infrastructure and promote basic, clinical, behavioral and translational AIDS-related research at institutions that receive significant funding from multiple NIH Institutes. The objective is to enhance collaboration and coordination of all AIDS and AIDS-related investigators at an institution.

Multi-Institute Program Announcement

NIDA's Office on AIDS worked with NIMH to develop a multi-Institute Program Announcement, PA-97-010, "HIV-1 Infection of the Central Nervous System" that was announced in the NIH Guide to Contracts and Grants, December 20, 1996.

Supplements for the Study of Drug Abuse and HIV/AIDS

NIDA, through its Office on AIDS, published a notice in the NIH Guide announcing the availability of funds to supplement existing NIH research project grants. The funds would be used to study issues related to drug abuse with a focus on HIV/AIDS issues. Awards are to be made available through both administrative and competing mechanisms. One of the goals of this announcement is to encourage grantees who have not traditionally focused their research in the AIDS arena to do so. Eligibility is also extended to current AIDS focused/related projects. The current areas of NIDA's AIDS effort include the following: Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, Behavioral and Social Science Research, Information Dissemination, Research Mentoring and Career Development and International Research Collaboration. Inquiries should be directed to Steven Gust, Ph.D., Acting Director, Office on AIDS.

Other Activities

Buprenorphine and Buprenorphine/Naloxone Clinical Trials

The Medications Development Division has started two clinical trials to provide the data necessary to support NDAs for two products for the treatment of opiate dependence. The first product is a buprenorphine tablet, the second a buprenorphine combined with naloxone tablet. As of January 10, there were 132 subjects enrolled in these studies.

MDD Ad Hoc Consultants Meeting

The Medications Development Division held a two day (Nov. 14-15) ad hoc consultant's meeting to review clinical and preclinical information relating to clinical targets for cocaine and opiate medications development. The review provided valuable insights for use in developing protocols for potential testing within the Division's clinical program, and for examining compounds currently in various preclinical development stages.

MDD Clinical Trials Database

The Medications Development Division has developed a Clinical Trials Database (covering cocaine and opiates). The database covers all NIDA funded trials which are completed and those on-going trials for which data was reported. A poster on the database was presented at the ACNP meeting in December.

Implementation Plan for AIDS Research Evaluation

The Office of AIDS Research (OAR) at NIH has led a cross-Institute activity to develop an Implementation Plan in response to the Report of the NIH AIDS Research Program Evaluation Task Force. This plan was developed in conjunction with the NIDA Office on AIDS and NIDA staff served on the committees that drafted the report. This plan summarizes ongoing and future activities of the Institutes in response to the recommendations of the Program Evaluation Task Force and will be used by the OAR and the NIH Institutes to guide HIV/AIDS research in the future. The report is in the final stages of review before presentation to the OAR Advisory Council on March 14.

NIDA Pain Workgroup

NIDA's Pain Interest Group, which has been informally meeting during the past year recently gained official workgroup status. The goals of this workgroup, chaired by David Thomas, Ph.D., DBR, include fostering communication within NIDA on the topic of pain; facilitating the field of pain research by sponsoring meetings and workshops; and promoting NIDA's positive role in pain research.

NIDA Genetics Workgroup

A Genetics workgroup has recently been established at NIDA to study genetic research approaches for understanding drug abuse vulnerability and neuroadaptation. The workgroup will build on recent advances in genetic research of complex diseases; the human genome project; and identification of gene alleles for specific diseases to study the application of these techniques to drug abuse research. The workgroup is co-chaired by Jonathan D. Pollock, Ph.D, DBR, and Naimah Z. Weinberg, M.D., DEPR.

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National Institute on Drug Abuse**Director's Report to the National Advisory Council on Drug Abuse****February, 1997**

Congressional Affairs

I. 104TH Congress

Congressional interest in overall NIH research priorities, activities, and funding continued throughout the 104th Congress. By the close of the 104th Congress on October 4, 1996, a total of 7,991 bills had been introduced, of which 2,486 were related to health and medicine. Some 240 of these bills were related to medical research and development and the subject of diseases and conditions in humans. Although many of these bills received limited or no action, 12 bills (excluding appropriations) were enacted that have some impact on NIH programs. These included bills such as the Paperwork Reduction Act, The Biotechnology Process Patents Protection Act, and the Federal Reports Elimination and Sunset Act. In addition, provisions regarding parity for insurance coverage for mental health conditions (specifically excluding substance abuse or chemical dependency) is included in language in the Department of Defense Appropriations Act for FY 1997, which became the vehicle for passage of the Omnibus Consolidated Appropriations Act of 1997 (P.L. 104-208).

Several bills specifically relating to drug abuse received considerable attention late in the second session. The Rohypnol Control Act (HR 4137) established new criminal penalties for anyone who attempts to use a controlled substance to reduce a victim's resistance to sexual assault. The bill provides for up to 15 years in prison for possession of the drug flunitrazepam. The bill was signed into law on October 13, 1996 to become P.L. 104-305.

On October 3, 1996, President Clinton signed into law the Comprehensive Methamphetamine Control Act (PL 104-237), introduced by Senator Joseph Biden (D-DE). The bill was designed to help authorities respond quickly to an upsurge in methamphetamine use. The law lets authorities seize chemicals used to make the drug. It also increases penalties for trafficking in the chemicals and for possessing equipment to make the drug.

Senator Biden introduced the Pharmacotherapy Development Act on September 3, 1996. The intent of the bill was to create financial incentives to encourage pharmaceutical companies to develop and market anti-addiction medications and to develop a partnership between private industry and the public sector in order to encourage the active marketing and distribution of new medicines. The bill, which did not pass before the 104th Congress adjourned, has been reintroduced as part of another bill in the 105th Congress.

Appropriations -- FY 1997

The Congress determined that it would not be possible to pass all 13 of the regular FY 1997 appropriations bills individually before adjournment. Therefore, negotiators pieced together an omnibus spending bill that included appropriations for the Departments of Commerce, Justice, State (H.R. 3814); Defense (H.R. 3610); Foreign Operations (H.R. 3540); Interior (H.R. 3662); Labor, HHS, Education (H.R. 3755); and Treasury-Postal Service (H.R. 3756). The bill, which took the number of the Department of Defense bill, H.R. 3610, passed the House on

September 28 by a vote of 370-37, cleared the Senate on September 30 by a vote of 84-15, and was signed by the President on the same day. Included in the measure is funding for each of the agencies, including NIH, as well as major legislative language affecting immigration law, banking law, and Federal personnel law.

For NIH, and the remainder of the agencies covered by the FY 1997 Labor, HHS, Education Appropriation, this meant there would be a mechanism for resolution of the House-passed bill with the Senate Committee version, since the Senate had not passed H.R. 3755, the FY 1997 Labor, HHS, Education appropriations bill.

The House Committee Report language [HRpt. 104-659] was included in the September 1996 Director's Report. The Senate Committee Report language [SRpt. 104-368] is as follows:

Neuroscience. The Committee applauds NIDA for its recent breakthroughs in research on drug abuse and addiction. 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. Research supported by NIDA has made tremendous progress in identifying the neurobiological bases of all aspects of addiction, including craving, which is one of the major factors that can precipitate relapse. Among the most remarkable accomplishments of the past year was the successful immunization of animals against the psycho stimulant effects of cocaine. NIDA-supported researchers have also made substantial progress that is critical in directing their efforts to identify potential anticocaine medications. The Committee expects that neuroscience research will continue to be a top priority and encourages NIDA to continue its research efforts in this area."

Medications. As a result of NIDA's research program, basic research now has progressed to the point where at least six molecular targets have been identified, now allowing NIDA to strategically focus its research on antiaddiction medications. The Committee commends NIDA for progress in medications development and urges NIDA to continue research aimed at developing effective medications for the treatment of addictions, particularly for cocaine. The Committee is pleased to note 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 an extremely valuable tool in advancing the discovery and development of medications for cocaine addiction."

Methamphetamine. Methamphetamine represents the most commonly used synthetic drug in the United States. The Committee is concerned that there is mounting evidence of a growing methamphetamine epidemic, which bears the potential of becoming a truly national epidemic. The Committee recognizes NIDA's strong history of funding research on amphetamines and methamphetamine; however, there is an urgent need at present for attention to treatments of human populations, particularly those in the Western United States, including rural populations, and those who have been infected with HIV. A most pressing priority is the development of effective pharmacological treatments for methamphetamine abusers, in conjunction with behavioral treatments and prevention efforts. The Committee encourages NIDA to continue this critical research area as well as develop new mechanisms to expedite research on methamphetamine."

Research Centers. The Committee commends NIDA for encouraging applications for comprehensive research center grants to support research training, continuing education for health care professionals, dissemination of information to the public, and conduct of both basic and clinical research. The Committee notes that in fiscal year 1996, NIDA supported two new research centers and looks forward to NIDA's continuing commitment to this approach. The Committee strongly encourages NIDA to support multi disciplinary comprehensive approaches to underserved populations including minorities, rural populations, children, women, and those already infected with HIV and at an elevated risk for HIV. The Committee hopes that such centers will be representative of the varying regional epidemiological profiles of drug problems in the United States; including consideration of methamphetamine abuse in at least some of the centers."

Behavioral Research. The Committee understands that behavioral research is essential to solving problems of drug abuse and addiction, and that behavioral and psychosocial interventions are the most frequently administered treatments for drug addiction and in some cases, are the only available treatment. The Committee commends NIDA for expanding both its basic and clinical behavioral science activities in order to better identify who may be at risk for falling victim to drugs, and to develop effective approaches for breaking the cycle of addiction. Of particular interest is NIDA's behavioral therapies development program, which applies the same controlled evaluation process as is used in evaluating new medications to the assessment of behavioral therapies. The Committee also commends NIDA's initiatives in the fight against AIDS/HIV because of the increasing link between HIV infection and drug use and related behaviors.

The Committee understands that NIDA is in the process of expanding innovative community-based epidemiological and ethnographic research in relation to HIV transmission and prevention. The Committee encourages NIDA to continue to place high priority in this area of research, particularly with regard to documentation of the growing methamphetamine epidemic in the West, Midwest, and South.

The Committee notes that NIDA has initiated the B/START program to increase the supply of young investigators in behavioral science. The Committee is pleased to see that NIDA has initiated this program, which invites newly independent investigators to submit applications for small scale pilot research projects related to the behavioral science mission."

Treatment and Prevention. Drug abuse treatment and prevention techniques must be grounded in research in order to be effective with patients, providers, and insurers. The Committee urges NIDA to continue its efforts to strengthen the scientific basis for treatment and prevention interventions, and recommends that NIDA conduct research on ways to prevent drug use, interrupt the progression of drug abuse, reduce the likelihood of relapse, and lessen the adverse health and social consequences of drug abuse."

Social Work Services. The Committee commends NIDA's support for research on families and drug abuse, behavioral and psychosocial treatment research, and health services. The Committee also applauds NIDA for its initial effort to increase the number of social work researchers conducting drug abuse research, and encourages NIDA to expand these efforts in fiscal year 1997."

Information Dissemination. The Committee believes that disseminating research findings in a timely manner is essential to the mission of NIH. Therefore, the Committee commends NIDA for hosting a series of town meetings with educators, health care providers, State and local antidrug coalitions, and civic organizations to disseminate research findings and foster information exchange."

Advanced Instrumentation. The Committee understands that magnetic resonance imaging holds great promise for enhancing understanding of mental illness. The Committee encourages the Institute to support advanced instrumentation projects related to the study, diagnosis, and treatment of mental disorders."

Medical Applications of Marijuana. During the fiscal year 1997 budget hearings, the Committee received testimony regarding the possible therapeutic applications of marijuana on certain medical conditions. Furthermore, the Committee was advised that while research on the therapeutic use of marijuana has been conducted on disorders, such as HIV wasting syndrome, multiple sclerosis, glaucoma, and on relieving the side effects of chemotherapy, further research is needed to conclusively answer questions of efficacy, particularly in comparison with existing conventional therapies."

"The Committee understands that the NIH currently is supporting studies on the effects of marijuana on human performance and health. However, no studies are being supported, or marijuana provided, for trials examining its possible therapeutic benefit. The Committee encourages the Institute to review its policy with regard to support of studies examining possible medical benefits of marijuana, which have Food and Drug Administration approval to ensure that the scientific questions of the medical applications can be investigated and resolved.

Conference Report and Bill

Following are the major features of the conference report affecting NIH (House Report 104-863):

Budget: NIH was appropriated \$12,747,203,000, the same amount as the House-passed level, which is an increase of \$370.6 million over the President's request, \$332.6 million over the Senate Committee reported level, and \$819.6 million, or 6.9 percent, over the comparable FY 1996 level.

Advanced Instrumentation: The conferees concur with the Senate report language regarding the promise magnetic imaging may hold for treating drug abuse and mental illness and are supportive of extramural clinical research in this area.

AIDS: The conference agreement does not contain a separate appropriation for the Office of AIDS Research (OAR). The agreement does contain a general provision that directs that the funding for AIDS research as determined by the Directors of the NIH and OAR be allocated directly to the OAR for distribution to the Institutes consistent with the AIDS research plan. The Directors of NIH and OAR have indicated that they expect to allocate \$1,501,720,000 for

AIDS research. The conference agreement also includes a general provision permitting the Directors of NIH and the OAR to shift up to 3 percent of AIDS research funding between Institutes and Centers if needs change or unanticipated opportunities arise. The conference agreement also provides an earmark of \$35,589,000 for the operations of OAR within the OD appropriation.

1 Percent Transfer: The NIH Director continues to keep the 1 percent transfer authority.

Administrative Costs: The conference report notes concurrence with House report language regarding the definition of administrative costs and the restriction of FY 1997 administrative costs to the FY 1996 level. House language directed that, beginning in the FY 1998 Congressional Justification, for reporting purposes, NIH should use the definition of administrative costs included in P.L. 99-158, which means Aexpenses incurred for the support of activities relevant to the award of grants, contracts, and cooperative agreements and expenses incurred for general administration of the scientific programs and activities of the National Institutes of Health. The Committee expressed intent that NINR, FIC, NLM, and the CC be included in this definition.

Third Party Payments: The bill authorizes NIH to collect third party payments for the cost of clinical services that are incurred in National Institutes of Health research facilities and that such funds shall be credited to the National Institutes of Health Management Fund. The bill further provides that the funds credited to the management fund are to be available for 1 fiscal year after the fiscal year for which they are deposited.

SBIR: The Conferees deleted a provision that was in the House bill regarding SBIR grants. The Conferees encourage NIH to convene a conference to discuss further improvements (in the SBIR program) that can be made to address the quality concerns raised by some in the biomedical community.

The following shows FY 97 funding levels for the NIH Institutes.

NCI-----	\$2,382,532,000
NHLBI-----	1,433,001,000
NIDR-----	195,997,000
NIDDK-----	815,982,000
NINDS-----	726,746,000
NIAID-----	1,257,234,000
NIGMS-----	998,470,000
NICHD-----	631,703,000
NEI-----	332,735,000
NIEHS-----	308,819,000
NIA-----	486,047,000
NIAMS-----	257,111,000
NIDCD-----	188,422,000
NINR-----	59,743,000
NIAAA-----	212,004,000
NIDA-----	489,375,000
NIMH-----	701,585,000
NCCR-----	415,145,000
NCHGR-----	189,657,000
FIC-----	26,586,000
NLM-----	151,103,000
OD-----	287,206,000
NIH Total-----	\$12,747,203,000

II. Looking Ahead - The 105TH Congress

Although Republicans maintained control of the House and the Senate as a result of the November 5 election, changes in Committee leadership and rosters as a result of retirements and/or election defeats are expected in a number of cases. It is not yet clear what impact these changes will have on interest in NIH or NIDA research issues. However, NIH reauthorization legislation, the subject of action in the 101st through 104th Congresses, is certain to be taken up again in the 105th as selected NIH authorities expired in FY 1996. Also in need of reauthorization are authorities of NIDA, NIAAAA, and NIMH to bring these institutes onto the same schedule as that of other NIH entities.

Drug abuse related issues are expected to be of particular interest to Congress this session. Specifically the areas of needle exchange research, legalization of drugs, drug testing (particularly hair testing), medications development, and purported medical uses of marijuana are likely to be the subject of Congressional briefings and hearings during the first session. Continued congressional interest is also expected in areas relating to AIDS, genetic privacy, biomedical ethics, technology transfer, and emerging infections.

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National Institute on Drug Abuse**Director's Report to the National Advisory Council on Drug Abuse****February, 1997**

International Activities

NIDA Director, Dr. Alan Leshner, traveled to Istanbul in November to present two lectures at the **Third International Bakirköy Days** hosted by Bakirköy State Hospital for Psychiatric and Neurological Diseases. The topics of his presentations were "**Neuroscientific Advances in Drug Abuse**" and "**The Health Impact of Drug Abuse.**" Dr. Leshner also held research discussions with staff of Bakirköy's Alcohol and Drug Addiction Treatment and Research Center.

The 1996-97 Hubert H. Humphrey Fellows in Drug Abuse made their annual orientation visit to NIDA on December 6. NIDA program staff Drs. Roger Brown, DBR, Betty Tai, MDD, Bennett Fletcher, DCSR, James Colliver, Richard Needle and William Bukowski, all of DEPR, and Lula Beatty, Office of Special Populations, made presentations on their respective research program portfolios to provide the Humphrey Fellows with an introduction to the broad range of drug abuse research being conducted by NIDA. The Fellows remarked on the value of this information in planning their program affiliations and in developing research plans for implementation on return to their home countries.

NIDA and several other NIH institutes hosted a delegation from the Georgian Republic for meetings organized by the Fogarty International Center. The Georgians report a growing problem with drug abuse by youth in their country and are interested in collaboration on drug abuse research, particularly methadone maintenance treatment and HIV prevention strategies. Delegation member Dr. Gela Lezhava, Director of the Georgian Research Institute on Addiction and former Minister of Health, met with several division directors and visited the Intramural Research Program in Baltimore.

NIDA's International Program sponsored an international satellite meeting on "**Building International Research in Drug Abuse,**" at the June 1996 CPDD meeting in San Juan, Puerto Rico. This meeting, supported by the U.S. Department of State, provided an opportunity for drug abuse researchers from around the world to share their research and to explore potential areas for collaboration. Dr. Joseph Frascella, DCSR, participated in candidate selection for the meeting and served as a moderator for the research presentations session at the meeting. Proceedings of the meeting have recently been prepared and distributed to participants; additional copies are available through the NIDA International Program. Building on the success of 1996, there will be a second international satellite meeting in Nashville in June 1997.

The International Program now has an International Home Page available within the Home Page. Information on NIDA's goals for the further development of international drug abuse research and information dissemination are contained at this site, as well as material on the NIDA/INVEST and the NIDA/Hubert H. Humphrey Training Fellowships. The International Home Page also contains up-to-date details on International Meetings, NIDA travel awards available to international scientists and copies of the three most recent INVEST Letters.

The International Program and Division of Epidemiology and Prevention Research coordinated NIDA's substantial contribution to the U.S.-Mexico White Paper being developed for the Office of National Drug Control Policy, in preparation for high level meetings with Mexican government officials and for future bilateral collaboration in drug abuse demand reduction activities. The paper includes reports on epidemiological trends in the United States, findings of prevention and treatment interventions specifically applicable to Hispanic culture and language, and NIDA and NIH

international research opportunities available to Mexican scientists and policy makers in drug abuse.

Dr. Frank Tims, DCSR, 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. Dr. Tims presented a paper entitled **"Costs and Cost Benefits of Treatment."** The symposium was jointly sponsored by the Canadian Bar Association and the Portage Programs for Dependencies.

Dr. Tims also was an invited speaker at the **3rd International Congress of the Worldwide Hungarian Medical Academy** in Pecs, Hungary during July. He spoke on **"Contemporary Drug Issues."**

In September, Dr. Yng-Shiuh Sheu, DCSR, assisted the Psychotropic and Narcotic Drugs Unit, Mental Health, World Health Organization and its Expert Committee on Drug Dependence in preparing medical and scientific reviews on seven psychoactive substances. These substances were reviewed by WHO because they were being considered for international control under the 1961 Single Convention and 1971 Convention on Psychotropic Substances. Compounds reviewed by the Expert Committee in October, 1996 were alprazolam, diazepam, ephedrine, nicotine (gum, patches, nasal spray, and inhaler), remifentanyl, dihydroetorphine, and sumatriptan.

Drs. Robert Battjes and Jack Blaine, DCSR, represented NIDA at the **Steering Committee Meeting of the WHO/NIH Joint Project on the Assessment and Classification of Disabilities** on December 10th-11th in Rockville, MD. The Steering Committee reviewed progress on the work of this cooperative agreement including the data analysis and publications being prepared from the recently completed Substance Use Disorders Reliability and Validity Study as well as the development of disablement assessment instruments and the planned cross-cultural applicability research study on disablement.

Dr. Jack Blaine, DCSR, participated as a research collaborator in the investigators meeting held in Antalya, Turkey on September 28-October 1 from the Substance Use Disorders Reliability and Validity Study being conducted as part of the WHO/NIH Joint Project on the Assessment and Classification of Disabilities. While in Turkey, Dr. Blaine visited the Alcohol and Drug Addiction Treatment and Research Center (AMATEM), of the Bakirköy State Hospital for Psychiatric and Neurological Diseases in Istanbul on October 2-4. He made a presentation on treatment of heroin addiction and met with clinical and research staff at AMATEM to provide technical assistance in treatment of drug addiction and to explore opportunities for binational research cooperation.

Dr. Richard Needle, Chief, Community Research Branch, DEPR, participated in the Fifth Annual HIV Epidemiology Research Meeting sponsored by Health Canada in Toronto during December. Dr. Needle met with Canadian and other international researchers to discuss cross-cutting issues associated with the epidemiology of HIV, current Canadian research prevention and intervention efforts, and future research directions, including opportunities for collaborative efforts.

Dr. Peter Hartsock, Community Research Branch, DEPR, in collaboration with colleagues at NIAID, the Fogarty Center, and the Russian Institute of Pure Biochemicals, organized the first U.S.-Russian Conference on Emerging and Reemerging Infectious Diseases (EREIDs), which was held in St. Petersburg, Russia, Dec. 8-11, 1996. The purpose of the conference was to stimulate U.S.-Russian cooperative research efforts in EREIDs. The conference was supported by the Civilian Research and Development Foundation (CRDF) of the former Soviet Union. NIH contributed \$1 million through the Fogarty Center to the CRDF, with additional financial support from the NIH Office of AIDS Research, as did the Russian Ministry of Science and Technology and the Russian Ministry of Health.

Arthur Hughes, ERB/DEPR presented a paper entitled **"The Epidemiology and Social Context of Amphetamines, MDMA, and other Psychostimulant Use in the United States"** at the WHO Meeting on Amphetamines, MDMA and Other Psychostimulants, held November 12-15, 1996 in Geneva, Switzerland.

Dr. James Colliver, DEPR, represented NIDA at the semiannual meeting of the Pompidou Group of substance abuse epidemiologists November 25 and 26 at the Council of Europe in Strasbourg, France. He presented information on recent drug use trends in the United States and on the activities of the International Drug Abuse Epidemiologic Work Group. The Pompidou group includes representatives from cities in nations in the European Union, eastern bloc countries of the former Soviet Union, and selected other locations.

On December 12, 1996, Dr. James Colliver was interviewed on World Net Television's Dialogue program which focused on the methods of measuring drug use. World Net TV is part of the U.S. Information Agency, and its programming is transmitted by satellite to viewers in 140 countries. The show was broadcast live in Spanish and English, and questions came from panelists in Peru, Paraguay, and Jamaica.

Dr. Derrick S. Binns visited the Division of Clinical and Services Research and the Prevention Research Branch, DEPR on November 6, 1996. Dr. Binns is a clinical psychologist with the National Drug Commission of Bermuda.

On September 12, 1996 nine individuals from Brazil, Belize, Honduras, Bahamas, Trinidad and Tobago, Barbados, Jamaica, and Honduras were briefed by DEPR staff Nicholas Kozel and Dr. Larry Seitz on the latest results in prevention intervention research.

Dr. Peter Cohen, MDD made a presentation entitled "**Science and Law as Alternative Approaches to Reality**" to the **Department of Anaesthetics, Manchester Royal Infirmary, United Kingdom, November 1996.**

Dr. Peter Cohen, MDD made a presentation entitled "**Personal Injury/Medical Negligence: An American Perspective**" to a group of private practice attorneys in the United Kingdom, November 1996.

Dr. Alexis Thompson, IRP, presented papers entitled, "**Characterization of Striatal Dopamine in the Mouse Using Conventional and Quantitative Microdialysis Methods,**" and "Effects of Psychostimulants on Striatal Dopamine in Mice Using Quantitative Microdialysis" at the 7th International Conference on In Vivo Methods, Santa Cruz de Tenerife, Spain, October 1996.

Dr. Steven R. Goldberg, IRP, presented a talk on "**Methamphetamine Administration and Associated Neurotoxicity**" as an invited symposium participant at the 11th Meeting of the Society for Neurochemistry, Groningen, The Netherlands in July, 1996.

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National Institute on Drug Abuse**Director's Report to the National Advisory Council on Drug Abuse****February, 1997**

Meetings/Conferences

NIDA organized a "**Town Meeting**" in St. Louis, Missouri entitled "**Understanding Drug Abuse and Addiction: Myths Vs. Reality**" on October 29. Dr. Leshner and NIDA researchers discussed ways that state policy makers, organizations, schools and communities can utilize the latest scientific research to assess state and local drug problems and develop programs to meet these needs.

In conjunction with the St. Louis Town Meeting, a community meeting was held with parents, teachers, and community leaders at the **Kirkwood School** in Kirkwood, Missouri, on October 29, to discuss the current state of scientific knowledge on drug abuse and addiction.

NIDA recently sponsored a trans-NIH symposium entitled "**Unique Contributions of Nonhuman Primate Research to Neuroscience**" on November 15, as a satellite symposium to the Society for Neuroscience Meeting in Washington, D.C. The symposium explored the role of nonhuman primates in neuroscience research; the unique contributions made through the use of primates in neuroscience research; and current areas of neuroscience research in which there is a critical need for primate research. The symposium featured an outstanding cadre of scientists, including a nobel laureate. Other participating institutes included: NIAAA, NIMH, NINDS, NIA, NCRR, NICHD, NEI, and NIDCD.

On November 16, 1996, a Satellite Symposium on "**Cognitive Functions and Drug Abuse**" was held at the annual Society for Neuroscience meeting in Washington D.C. The purpose of this symposium was to explore advances in cognitive neuroscience and in addictions research with the goal of identifying common scientific challenges and opportunities for synergistic interactions between these fields. Leading researchers in both areas of research discussed topics of mutual interest, such as the formation of different types of memory in different regions of the brain and the factors that influence memory formation in these brain regions, as well as the brain circuits that are activated during cocaine craving. Following Dr. Alan I. Leshner's opening address, Dr. Stephen R. Zukin delivered introductory remarks. The morning session included presentations from Drs. Nora Volkow, Mortimer Mishkin, Edythe London, and Steven Petersen, and was chaired by Dr. Zukin. The afternoon session, chaired by Dr. Steven J. Grant, included presentations from Drs. James McGaugh, Barry J. Everitt, P. Read Montague, Bruce R. Rosen, and Michael Gazzaniga. The organizers of this meeting were Drs. T. Aigner, C. Asanuma, R. Brown, J. Frascella, S.J. Grant, A.I. Leshner, K. Skinner, and S.R. Zukin.

NIDA's Special Populations Office co-sponsored the **Minorities in Neuroscience Forum** that was held November 19, 1996 in Washington, DC as part of the Society for Neuroscience Annual Meeting. The work of minority supplement recipients was highlighted in a poster session, and attendees included NIDA training directors, high school students, and college and university students interested in drug abuse research.

NIDA hosted its **Third Annual Constituent Conference** on November 25-26 at the Lansdowne Conference Center in Lansdowne, Virginia. Dr. Alan Leshner presented the "Report Card" highlighting specific actions taken by NIDA in response to constituent group recommendations. Laurie Flynn, Executive Director of the National Alliance for the Mentally Ill addressed the participants concerning the recent success of the mental health community in obtaining

parity through legislation.

On December 2-3, 1996 NIDA's Office of Science Policy and Communications held a regional meeting in San Francisco entitled "Methamphetamine: Abuse, Treatment, and Prevention." The meeting was opened by Congresswoman Nancy Pelosi and brought together scientists, practitioners, policy makers, and the community to discuss the most current research on the growing problem of methamphetamine abuse in the western United States.

Dedication of the NIDA Brain Imaging Center took place on December 16, 1996. General Barry McCaffrey, Director, Office of National Drug Control Policy, Dr. Harold Varmus, Director, National Institutes of Health (NIH), and Dr. Ruth L. Kirschstein, Deputy Director, NIH, joined Dr. Alan Leshner, Director, National Institute on Drug Abuse (NIDA), Dr. Barry Hoffer, Director, Division of Intramural Research, Mr. Richard Millstein, Deputy Director, NIDA, and Dr. Roy Pickens, Chief, Clinical Neurogenetics Section in a tour of the facility, scientific presentations, and the Center dedication. A state-of-the-art Exact HR+ Positron Emitting Tomography (PET) scanner (Siemens) and a RDS-111 cyclotron (Computers Technology Incorporated) are the primary instruments, which will permit the acquisition of high resolution PET images of the brain using fluorine-18, carbon-11 and oxygen-15 labeled tracers. This capability will permit the neuroanatomical exploration and identification of physiological and cognitive substrates underlying drug abuse in humans, and has the potential to provide new directions for the development of pharmacological and behavioral therapies. Dr. Edythe London is the director of the new Brain Imaging Center.

A meeting of the NIDA Scientific Review Group (SRG) Chairpersons and additional representatives was held on January 6 at NIH. NIDA Director, Dr. Alan Leshner, provided a State of the Institute report and discussed developments in the integration of NIDA's peer review structure into the broader NIH structure. He also requested input from the SRG members on several peer review issues that are under discussion by the Peer Review Oversight Group (PROG), particularly the rating criteria. Dr. Wendy Baldwin, NIH Deputy Director for Extramural Research, also attended and discussed activities of the PROG, which she chairs. Dr. Elvira Ehrenfeld, newly appointed Director, Division of Research Grants (DRG), also met with the group. She noted that she is looking forward to working with NIDA. There was a positive dialogue between the NIH leadership and the NIDA SRG members.

A meeting on "Measurements in Family Prevention Intervention" held on October 13-15, 1996 in Salt Lake City was sponsored by the Prevention Research Branch and chaired by Dr. Rebecca Ashery. The meeting explored family functioning and parenting instruments that would be useful to researchers in the field.

On December 3-4, Drs. Robert Battjes and Lisa Onken, DCSR, chaired a NIDA meeting entitled "Treatment Readiness: Factors Influencing Entry and Engagement." The meeting brought together ethnographers who are studying drug abusers perspectives on treatment, researchers who focus on motivation to change, and researchers studying alternative treatment approaches. It was designed to clarify factors that impact acceptability and accessibility of treatment and also to consider directions for future research that will lead to improved recruitment strategies, treatment approaches, and more acceptable treatment environments.

The Behavioral Science Working Group hosted a master-class lecture (L.E.A.D.E.R.S.) by Dr. Steven Hursh entitled "Behavioral Economics, A Conceptual Framework for Drug Abuse Research, Intervention and Policy."

As part of NIDA's HBCU initiative, a technical assistance meeting was held with faculty and staff from HBCUs on September 9-12, 1996 in Washington, DC.

NIDA's Special Populations Office co-sponsored the 4th Annual Conference on Psychopharmacology, Psychopathology, Substance Abuse and Culture on October 10-12, 1996 in Los Angeles, CA.

With support from the NIH Office of Research on Minority Health, a meeting was held October 9, 1996 in Los Angeles, CA, to develop strategies for promoting collaborative research between majority and minority institutions. The meeting was coordinated and chaired by Dr. Tony Strickland and attended by NIDA grantees and interested minority investigators and institutions.

A NIDA-sponsored Policy Workshop on Research Development For Hispanic Drug Abuse Researchers was held in Washington, D.C. January 27-28, 1997. The meeting was chaired by Dr. Mario De La Rosa.

On November 21-22, 1996, Howard University Research Center sponsored a meeting of faculty and staff from HBCUs who are forming a consortium to research substance abuse and other health issues of women on Black college campuses. This is a joint project with CSAP and the National Black Women's Health Project.

As part of NIDA's HBCU initiative, a technical assistance meeting for HBCUs was held December 16 -19, 1996 in Washington, DC.

Dr. Alan Leshner, Director, NIDA, was keynote speaker and co-chaired a day-long Institute on adolescent substance abuse and treatment at the American Academy of Child and Adolescent Psychiatry Annual Meeting held in Philadelphia on October 24 - 25, 1996.

Richard A. Millstein, Deputy Director, NIDA, spoke at and moderated the session "Effective Drug Treatment- What Works" at the Fourth Annual Conference on Psychopathology, Psychopharmacology, Substance Abuse and Culture held in Los Angeles, CA on October 11, 1996.

Richard A. Millstein and Dr. William Bukoski, DEPR, presented on NIDA prevention research at the Center for Substance Abuse Prevention (CSAP) senior staff meeting held in Rockville, MD on October 23, 1996. CSAP senior staff then presented to NIDA senior staff in December. Development of an MOU between NIDA and CSAP is currently being pursued to formalize discrete areas of cooperation and collaboration.

Richard A. Millstein represented NIDA at the presentation of the Dana Foundation Awards for Pioneering Achievements in Health and Education on November 6, 1996 in New York, NY.

Richard A. Millstein served as a panelist at a special presentation on the integration of peer review entitled "New Directions in Neuroscience Grant Review at NIH--A Discussion with the Directors" at the Society for Neuroscience Annual Meeting held in Washington, DC on November 18, 1996.

Richard A. Millstein spoke at the NIDA Minority Fellows Forum, "Neuroscience Research in Drugs of Abuse" at the Society for Neuroscience Annual Meeting in Washington DC on November 19, 1996.

Richard A. Millstein spoke at the symposium, "NIDA: The Next Generation," a satellite to the Society for Neuroscience Annual Meeting held in Washington DC on November 20, 1996.

Richard A. Millstein presented to the Hubert Humphrey Fellows in Rockville, MD on December 6, 1996.

Dr. Timothy Condon, Associate Director for Science Policy, and Director, OSPC, chaired a Grant Writing Workshop with Dr. Vince Smeriglio, DCSR and Dr. Naimah Weinberg, DEPR, at the American Academy of Child and Adolescent Psychiatry Annual Meeting held in Philadelphia on October 24 - 25, 1996. The aim of the workshop was to encourage attending psychiatrists interested in a career in drug abuse and addiction research.

Dr. Joseph Frascella, Chief of the Etiology and Clinical Neurobiology Branch, DCSR, attended the Winter Brain Conference in Breckenridge, Colorado, January 25-February 1, 1997. He represented NIDA on two panels that discussed issues related to the integration of the neurosciences at the DRG.

Dr. Meyer Glantz presented a paper entitled "Women and Substance Abuse" at the American Psychological Association - 1996 Women's Health Conference, Washington, D.C., September 1996. The paper explored some of the unique characteristics of women substance abusers, particularly those related to comorbidity.

Richard H. Needle, Ph.D., M.P.H., DEPR, gave a seminar entitled "Community-Based HIV Epidemiology and Prevention Research: 1987-1997" at the Centers for Disease Control and Prevention (CDC) on September 18, 1996. He described risk factors and rates of HIV seroprevalence among out-of-treatment injection drug users and crack smokers from NADR to NIDA's CA; research findings on the efficacy of interventions designed to prevent, eliminate, or reduce HIV risk behaviors; and future directions in community-based HIV research.

Richard H. Needle, Ph.D., M.P.H., served as discussant for a session entitled "Ethnographic Investigation: Drug Abusers Perspectives on Treatment," at DCSR's December 3-4 review meeting on "Treatment Readiness: Factors Influencing Entry and Engagement." Five ethnographers whose research NIDA supports gave presentations for the session, including Drs. Koester, Carlson, Dunlap, Murdoch, and Bourgois.

Helen Cesari, M.S., Community Research Branch, DEPR, provided an overview of the Drug- Using Men Who Have Sex with Men Multi-Site Study at the Centers for Disease Control and Prevention (CDC) on September 18. CRB/DEPR initiated this collaborative study with CDC's Division of STD/HIV Prevention to address the increasing incidence of HIV among DU MSM. Following the overview, Sherry Deren, Ph.D., NDRI, described the study methods and interview data, Robert Trotter, Ph.D., Northern Arizona University (NAU), provided a discussion of preliminary findings from the

network analysis, Fen Rhodes, Ph.D., California State University Long Beach, reviewed the themes, issues, and implications stemming from the multi-site focus groups, and Robert Trotter, Ph.D., NAU, concluded with a presentation on findings from the focus group transcript analyses.

Elizabeth Lambert, M.Sc., DEPR, and Helen Cesari, M.S., DEPR, co-authored a presentation entitled "Understanding HIV-Related Risks among Men Who Use Drugs and Have Sex with Men: The Role of Multi-Site Research." This was the first of six presentations in a session on DU MSM, held at the 95th annual meeting of the American Anthropological Association, November 20-24, in San Francisco. Presentations were also given by Michelle Wood (of the Long Beach site), Michael Stark (Portland, Oregon), Russel Falck (Dayton/Columbus, Ohio), and Michelle Shedlin (New York, NY).

Arnold Mills, M.S.W., CRB, DEPR, coordinated the National Technical Assistance Workshop and Annual Meeting for Faculty and Staff from Historically Black Colleges and Universities (HBCUs) participating in the Drug Abuse Research Technical Assistance Project (DARTAP), held September 9-12, 1996 in Bethesda, MD.

Arnold Mills, M.S.W., CRB, DEPR, gave an invited presentation on December 11, 1996 to faculty and staff of the Georgia Prevention Institute, Medical College of Georgia, Paine College, Augusta State University, and the Augusta Veterans Administration Hospital. The presentation, on NIDA's HIV/AIDS prevention research program, was in response to the medical college's interest in establishing a family-focused research program which would emphasize drug abuse and HIV/AIDS prevention research.

Moira O'Brien, ERB, DEPR, represented NIDA at an ONDCP interagency work group to develop a joint U.S./Mexico Drug Abuse Threat Assessment Paper for the U.S. Mexico bilateral High Level Contact Group on Drug Control.

Moira O'Brien, ERB, DEPR, participated in the Measurement Issues for Family Prevention Meeting in Salt Lake City, Utah, October 14, 1996 and gave a presentation on NIDA and World Health Organization collaboration in the development of comparable, cross culturally applicable epidemiologic instruments for drug abuse prevalence assessment.

Dr. Coryl Jones, ERB, DEPR was a discussant in several sessions exploring the role of drug abuse in child abuse and neglect and the seminar on Federal research initiatives at the National Conference of Child Abuse and Neglect, Washington, DC, September 16-19, 1996.

Dr. James Colliver, DEPR, presented information on adolescent drug use at a meeting on the President's Initiative on Youth, Drugs, and Driving, held November 14, 1996. Along with NIDA, representatives from DOT, NHTSA, FHWA, Dept of Ed., SAMHSA, DOJ, and ONDCP were present. Arthur Hughes, ERB/DEPR attended a subsequent meeting held on December 4, 1996. These meetings were held to discuss issues in a variety of areas (e.g., epidemiology, pharmacology, drug testing, State laws, treatment, and prevention) and to propose recommendations on the initiative to reduce teenage driving under the influence of illicit drugs.

Dr. Rita Liu, OEPR, was an invited speaker at a meeting held in Hong Kong in December 1996. Dr. Liu gave a special topic presentation on the NIH Peer Review system to the attendants of the "Orientation Workshop on Opioid Research Across the Strait." The meeting was also attended by NIDA grantees Drs. Horace Loh, Lei Yu, I.K. Ho, and Ji-Sheng Han.

Dr. Jerry Frankenheim presented an invited seminar, "Methamphetamine: America's Newest Drug Problem" at the University of Mississippi Medical Center, Jackson MS on October 14, 1996. He also led a discussion of pharmacology/neuroscience/drug abuse research career opportunities with students at the Medical Center.

Dr. Jaylan S. Turkkkan, Chief of the Behavioral Sciences Research Branch, was a discussant in a symposium organized by NIDA's Intramural Research Program entitled "Neurocognitive Approaches to Craving for Abused Drugs" at the 30th Annual Association for Advancement of Behavior Therapy (AABT) convention in NYC, November 1996.

Dr. Jaylan S. Turkkkan gave a lecture entitled "Psychological Sciences at the Turn of the Century" at the annual meeting of the Pavlovian Society in Baltimore, December 1996.

Dr. Jaylan S. Turkkkan represented NIDA at two nicotine-related meetings: the first was the executive meeting of the Society for Research on Nicotine and Tobacco (November 1996) in Washington, DC. The second was a trans-NIH planning group around tobacco and smoking-related research and initiatives (Dr. Peter Greenwald, NCI, Chairman. December 1996).

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

Dr. Sander Genser, CMB, DCSR, attended the Annual Meeting of the American Academy of Addiction Psychiatry in San Francisco and co-hosted with Dr. Jack Blaine, TRB, DCSR, a luncheon session on the NIDA Research Program.

Dr. Peter Delany, SRB, DCSR, attended the Annual Meeting of the National Association of Social Workers (NASW) and met with officials of NASW and the Institute for the Advancement of Social Work Research (IASWR) to discuss research trends and opportunities at NIDA.

Dr. Peter Delany, SRB, DCSR, helped plan and presented a paper entitled "Evaluating Your Practice: Answering So What?.." at the Uniformed Services Social Work Conference, in Cleveland, Ohio. This was the largest inter-service conference for social work professionals.

Dr. Mac Horton, ECNB, DCSR, gave a presentation entitled "Funding Opportunities at the National Institute on Drug Abuse"; chaired the session devoted to Disorders of Childhood and Adolescence; and presented a talk during the session on "Neuropsychological Assessment of Adult Attention Deficit Disorder," at the Fourth Annual Conference on Psychopathology, Psychopharmacology, Substance Abuse, and Culture, in Los Angeles, California, October 10-12, 1996

Dr. Horton presented a talk on "Research Opportunities at NIDA" at the 16th Annual National Academy of Neuropsychology Conference in New Orleans, Louisiana on November 1, 1996.

Dr. Frank Vocci, Acting Director, MDD, presented Grand Rounds at the Department of Psychiatry, New York University Medical Center, October 24, 1996. Dr. Vocci's topic was "Approaches to the Development of Medications for the Treatment of Cocaine Dependence."

Dr. Frank Vocci, MDD, was a discussant at a December 11, 1996 scientific session of the American College of Neuropsychopharmacology, San Juan, Puerto Rico. The session was entitled "Evolving Molecular Targets for Cocaine Pharmacotherapy" and showcased NIDA-sponsored research funded through various mechanisms. Dr. Barbara Fox, Dr. Eric Nestler, Dr. George Uhl, and Dr. Thomas Kosten presented on the development of a cocaine vaccine; potential medications aimed at the dopamine transporter; altering or reversing long-term intracellular changes; and clinical approaches to medications development, respectively.

Dr. Peter Cohen, MDD, participated with the Substance Abuse and Mental Health Services Administration as a member of two resource panels developing Treatment Improvement Protocols (TIPs) entitled Substance Abuse Among Older Americans, and Case Management for Substance Abuse Treatment.

Dr. Lula Beatty, Chief, Special Populations Office (SPO), chaired a panel on the need for research on drug abuse and other health issues of Black women on Black college campuses at a meeting of HBCU administrators and foundation representatives sponsored by CSAP on September 16, 1996 in Washington, DC.

Dr. Lula Beatty, SPO, moderated a panel on drug abuse in women at the American Psychological Association's women's conference on September 19, 1996 in Washington, DC.

Dr. Lula Beatty, SPO, was a panelist on a federal panel to discuss NIDA research needs and funding opportunities with scholars funded under CSAP's high risk program on September 20, 1996 in Washington, DC.

Dr. Lula Beatty, SPO, moderated two panels at the 4th Annual Psychopharmacology, Psychopathology, Substance Abuse and Culture Conference held on October 10-12, 1996 in Los Angeles, CA.

Dr. Lula Beatty, SPO, presented an overview of research with minority populations for the Humphrey Fellows on December 5, 1996 as part of a visit coordinated by NIDA's International Office.

Dr. Lula Beatty, SPO, was the keynote speaker for the MARC program at Temple University on December 21, 1996.

Dr. Mario De La Rosa, SPO, chaired a joint NIDA/NIH Office of Minority Research meeting in Washington, D.C. on September 26-27. The meeting was entitled "Drug Abuse Research with Minority Populations: Methodological and

Theoretical Issues and Concerns." Twenty scientists presented information and data regarding the development and application of more effective methods to recruit and retain minority persons in drug abuse research studies.

Dr. Monique Ernst, IRP, presented papers entitled, "Functional Brain Imaging in ADHD," and "MAOIs in ADHD," at the 43rd Annual Meeting of the American Academy of Child and Adolescent Psychiatry, Philadelphia, October 1996.

Dr. Steven Grant, IRP, gave a presentation entitled, "Activation of Memory Circuits During Cue-Elicited Cocaine Craving," at the Nuclear Magnetic Resonance Center, Massachusetts General Hospital, Boston, MA, October 1996.

Dr. Edythe London, IRP, presented a lecture entitled, "Interactions of Nicotine with Specific Receptors and Circuits in Brain," at the 9th National Conference on Nicotine Dependence sponsored by the American Society of Addiction Medicine, Washington, D.C., November 1996.

Dr. Edythe D. London, IRP, presented a lecture entitled, "Activation of Memory Circuits During Cocaine Craving: PET Studies" at the NIDA Satellite Symposium, "What Can Cognitive Neuroscience Tell Us About Drug Abuse Disorders?" at the Annual Meeting of the Society for Neuroscience, Washington, D.C., November 1996.

Dr. Steven Grant, IRP, co-chaired the NIDA Satellite Symposium, "What Can Cognitive Neuroscience Tell Us About Drug Abuse Disorders," at the Annual Meeting of the Society for Neuroscience, Washington, D.C., November 1996.

Dr. Katherine Bonson, IRP, presented a paper entitled, "Regulation of 5-HT₂ Receptors by Chronic DOM, DOI, Ritanserin or DOM plus Ritanserin: Behavioral Evidence," at the Annual Meeting of the Society for Neuroscience, Washington, D.C., November 1996.

Dr. Monique Ernst, IRP, presented a paper entitled, "PET with [fluorine-18]fluorodopa in Autism," at the Annual Meeting of the Society for Neuroscience, Washington, D.C., November 1996.

Dr. Steven Grant, IRP, presented a paper entitled, "Activation of Memory Circuits During Cue-Elicited Cocaine Craving," at the Annual Meeting of the American Association for Behavioral Therapy, New York City, NY, November 1996,

Dr. Steven Grant, IRP, presented a paper entitled, "PET Studies in Cocaine Craving," at the symposium entitled, "NIDA: The Next Generation," at the Annual Meeting of the Society for Neuroscience, Washington, D.C., November 1996.

Dr. Xiang Liu, IRP, presented a paper entitled, "Reduced Volume of Prefrontal Lobe in Polysubstance Abusers: A Magnetic Resonance Imaging Study" at the Annual Meeting of the Society for Neuroscience, Washington, D.C., November 1996.

Dr. John Matochik, IRP, presented a paper entitled, "Cerebral Metabolic Effects of Triiodothyronine in Adults with Resistance to Thyroid Hormone," at the Annual Meeting of the Society for Neuroscience, Washington, D.C., November 1996.

Dr. Evan Morris, IRP, presented a paper entitled, "Can Positron Emission Tomography Detect Changes in Intrasynaptic Dopamine? Computer Simulations Can Optimize the Experimental Design," at the Annual Meeting of the Society for Neuroscience, Washington, D.C., November 1996.

Dr. Masamitsu Takagishi, IRP, presented a paper entitled, "Effects of Low Dose Mecamylamine on Regional Cerebral Glucose Metabolism in Rats Receiving Chronic Nicotine," at the Annual Meeting of the Society for Neuroscience, Washington, D.C., November 1996.

Dr. Alexis Thompson, IRP, presented a paper entitled, "Delta-Opioid Receptor Blockade Prevents Sensitization to the Conditioned Reinforcing Effects of Morphine," at the Annual Meeting of the Society for Neuroscience, Washington, D.C., November 1996.

Dr. Bruce Vaupel, IRP, presented a paper entitled, "Inhibition of Constitutive but not Inducible Nitric Oxide Synthase Attenuates Signs of Morphine Withdrawal," at the Annual Meeting of the Society for Neuroscience, Washington, D.C., November 1996.

Dr. Edythe London, IRP, co-chaired a symposium entitled, "Controversies in Nicotine and Tobacco Smoking Actions," at the 35th Annual meeting of the American College of Neuropsychopharmacology, San Juan, PR, December 1996.

Dr. Robert Phillips, IRP, made an oral presentation entitled, "PET Imaging: New Frontiers in Diagnosing Drug Addiction and Functional Brain Disorders," at a symposium of the Idaho Neurological Institute, St. Adolphus Hospital, Boise, Idaho, December 1966.

Drs. Charles Schindler and Steven Goldberg, IRP, organized and participated in a symposium on the "Motivational Factors in Drug Abuse" at the 1996 meeting of CPDD.

Dr. Amy Newman, IRP, presented a lecture entitled "In Search of a Cocaine-Abuse Therapeutic: New Clues from an Old Drug" as part of the NIH Director's Seminar Series.

Dr. David A. Gorelick, IRP, attended the Eighth International Catecholamine Symposium (held Oct., 1996 in Asilomar, CA) as co-chair of a session on drug abuse, and gave an invited presentation on "The Rate Hypothesis and Agonist Substitution Approaches to Cocaine Abuse Treatment."

Mann H., Hirata H., Ladenheim B., Moran T.H., and Cadet J.L. "Multidrug Resistant (mdrla) Knockout Mice are Differentially Affected by Methamphetamine (METH) and Methylenedioxy-methamphetamine (MDMA)" was presented at the Society for Neuroscience annual meeting held November 16-21, 1996.

Cadet J.L., Ordonez S., and Ordonez J. "Methamphetamine Causes Superoxide Generation and Apoptosis in Neural Cells" was presented at the Society for Neuroscience annual meeting held November 16-21, 1996.

Hirata H., and Cadet J.L. "Kainate-Induced Neurotoxicity is Attenuated in SOD-TG Mice" was presented at the Society for Neuroscience annual meeting, November 16-21, 1996.

Herning R.I., Better W., and Cadet J.L. "Blood Flow in Cocaine Dependence" was presented at the Society for Neuroscience annual meeting held November 16-21, 1996.

Tsao L-I, Ladenheim B. Cadet, J.L., and Su T-P. "Delta Opioid Peptide [D-ALA2, D-LEU5]-Enkephalin (DADLE) Attenuates Methamphetamine (METH)-Induced Neurotoxic Damage to Dopaminergic Neurons in Mice" was presented at the Society for Neuroscience annual meeting held November 16-21, 1996.

Sheng P., Ladenehim B., Moran T.H., Wang C.-B., and Cadet J.L. "Methamphetamine- Induced Neurotoxicity is Associated with Prolonged Increase in Striatal AP-1 DNA-Binding in Mice" was presented at the Society for Neuroscience annual meeting held November 16-21, 1996.

Ladenheim B., Hirata H., and Cadet J.L. "Differential Regulation of Mu Receptors by Methamphetamine in p53 Knock-Out Mice" was presented at the Society for Neuroscience annual meeting held November 16-21, 1996.

McCoy M.T., and Cadet J.L. "Induction of Bclxs and Bclxl by Methamphetamine in Immortalized Neural Cells" was presented at the Society for Neuroscience annual meeting held November 16-21, 1996.

Cadet, J.L. "Cell Cycle and Apoptosis" was presented at the 3rd Annual Meeting of the Oxygen Society held in Miami Beach, Florida on November 21-25, 1996.

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Media and Education Activities

NIDA recently collaborated with *Scholastic Magazine* to produce a set of science education materials for elementary school students. The materials, which include a classroom poster, an eight page teaching guide and a take home guide for parents, provide information on inhalants, nicotine and marijuana. The materials were mailed to 73,000 third through sixth grade teachers and 2.3 million students in November.

Press Conferences

NIDA Director, Dr. Alan Leshner was joined by NIH Director, Dr. Harold Varmus, ONDCP Director, General Barry McCaffrey for the **dedication of NIDA's Brain Imaging Center** on December 16. Principals were interviewed by CNN and Associated Press following the ribbon cutting ceremony.

Press Conference to release findings from the **1996 Monitoring the Future Study**. On December 19, Dr. Leshner joined DHHS Secretary Donna Shalala, Transportation Secretary Frederico Pena, Education Secretary, Richard Riley, ONDCP Director, General Barry McCaffrey, and Dr. Lloyd Johnston for the release of the 1996 Monitoring the Future Study which showed continued increases in drug and cigarette use among young people.

Media Advisories

September 19: Effective Drug Abuse Prevention Programs Released at National Conference of Researchers and Practitioners. Secretary Donna Shalala and ONDCP Director General McCaffrey joined Dr. Leshner for NIDA's National conference on Prevention.

October 7: Chronic Morphine Use Produces Visible Changes in Brain. Study by scientists at Yale University School of Medicine provides the first direct evidence that long-term, chronic opiate exposure is associated with structural changes in both the size and shape of specific neurons in the brain. The study was published in the October 1 issue of the Proceedings of the National Academy of Sciences.

October 10: Scientists Discover New Brain System that Counters Effects of Opioid Drugs. NIDA funded researchers at the Oregon Health Sciences University have discovered a neuronal system in the brain that modulates and opposes the action of the brain's own opioid system. These findings appeared in the October 3 issue of Neuroscience.

October 11: Early Pregnancy Halted By Chemicals in Marijuana. NIDA funded researchers at the University of Kansas have determined a link between activation of the biological receptors that respond to cannabinoids, the

psychoactive ingredients in marijuana and abrupt interruption of pregnancy at a very early stage.

The research reported in the October issue of *Biology of Reproduction*, suggests that exposure of embryos to the cannabionoids can often prevent the embryos from attaching to the uterine wall.

October 14: Scientists Identify Brain Systems Involved in Drug Craving. Researchers at NIDA and Yale University have identified major areas of the brain activated during drug craving by cocaine addicts. Using PET, scientists visualized changes in the brain triggered by environmental cues that are associated with past experiences of using drugs and that lead to drug craving, even when no drug is available. The study is published in the October 15 issue of the *Proceedings of the National Academy of Sciences*.

October 18: NIDA Town Meetings in St. Louis Area Present Latest Scientific Findings About Drug Abuse and Addiction. On October 28 and 29, NIDA held two town meetings hosted by Dr. Leshner, to present the latest scientific information available to prevent and treat drug abuse and addiction.

October 31: New Action-Oriented Drug Education Materials Now Available to Parents, Teachers and Students. NIDA and Scholastic Inc. have joined forces to help parents, teachers, and students arm themselves with knowledge in the fight against drug abuse. A classroom poster and teaching guide, and a 4 page parent take home guide provide important science based information about drug abuse and addiction to more than 73,000 third through sixth grade teachers and 2.3 million students. The materials were included in the November 1 issue of *Scholastic News*.

November 19: New Drug Prevention Program Helps Student Athletes Avoid Steroids Use. NIDA announced a new drug prevention and education program called ATLAS (Adolescents Training and Learning to Avoid Steroids) which demonstrated that students in the program had enhanced health behaviors, reduced factors that encourage steroid use, and lower intent to use steroids. The study results were published in the November 20 issue of the *Journal of the American Medical Association*.

November 22: NIDA Names New Scientific Director. NIDA Director announced the appointment of Barry J. Hoffer, M.D., Ph.D., as Scientific Director and Director of NIDA's Division of Intramural Research.

November 27: Methamphetamine Abuse, Consequences and Solutions Topics of Regional Conference In San Francisco. NIDA held a two-day conference in San Francisco on methamphetamine abuse, its resulting consequences and solutions to the problem on December 2-3 at the Laurel Heights Conference Center of the University of California-San Francisco.

November 29: New Brain Studies Yield Insights Into Cocaine Binging and Addiction. NIDA funded scientists at Brookhaven National Laboratory have identified some of the unique properties of cocaine that account for the binging pattern of use exhibited by cocaine addicts. The study shows that repeated and frequent activation of the dopaminergic system by cocaine results in an abnormal state in one of the brain's neural circuits. This study is published in the winter 1996 issue of the *Journal of Addictive Diseases*.

OTHER PRESS ACTIVITY

San Francisco Editorial Board Meetings - On December 3, Dr. Leshner held an editorial board meeting with editors of the *San Francisco Chronicle*. On December 4, Dr. Leshner held an editorial board meeting with editors of the *San Francisco Examiner*.

Methamphetamine Meeting, San Francisco, CA - While in San Francisco, Dr. Leshner conducted several interviews on NIDA's research on methamphetamine abuse.

St. Louis Editorial Board Meeting - On October 29, Dr. Leshner held an editorial board meeting with editors of the *St. Louis Dispatch*. Dr. Leshner was also interviewed for stories in the *Dispatch* and local papers about his two presentations in St. Louis.

Secretary's Marijuana Prevention Initiative Support - In support of the Secretary's initiative, NIDA conducted meetings in Fairfax County, Virginia schools and in Montgomery County, Maryland schools. Dr. Alan Leshner spoke at each meeting to encourage the attendees and media to reach large numbers of the population with the message that "there is clear scientific evidence that marijuana is a dangerous drug that can impair learning and affect memory, perception, judgment, and complex motor skills such as those needed to drive." The meetings were attended by community leaders, parents, law enforcement officials, students, and educators. They were carried live on local cable;

segments were used on CNN; and the Washington Post did a major article in its Week Ender Magazine.

NIDA Exhibits

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

COSSMHO 11th Biennial Health and Human Services Conference on Drugs

September 9-12, 1996

Santa Fe, New Mexico

National Conference on Drug Abuse Prevention Research

September 19-20, 1996

Washington, D.C.

National Nurses Society on Addictions

October 2-5, 1996

Orlando, Florida

Psychopathology, Psychopharmacology, Substance Abuse and Culture

October 10-12, 1996

Los Angeles, California

American Academy of Child and Adolescent Psychiatry Annual Meeting

October 22-27, 1996

Philadelphia, Pennsylvania

Society for the Advancement of Chicanos and Native Americans in Science

October 24-27, 1996

Washington, D.C.

NIDA Town Meeting

October 28-29, 1996

St. Louis, Missouri

Association of Medical Education and Research in Substance Abuse

November 7-9, 1996

Reston, Virginia

National Association of Social Workers

November 13-16, 1996

Cleveland, Ohio

Community Anti-Drug Coalitions of America

November 14-16, 1996

Washington, D.C.

American Indian Science and Engineering Society

November 14-17, 1996

Salt Lake City, Utah

Society for Neuroscience Annual Conference

November 16-17, 1996

Washington, D.C.

American Public Health Association

November 17-21, 1996

New York, New York

NIDA Third Annual Constituent Conference

November 25-26, 1996
Leesburg, Virginia

American Academy of Addiction Psychiatry
December 6-7, 1996
San Francisco, California

American Society for Cell Biology
December 7-11, 1996
San Francisco, California

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Planned Meetings

The NIDA Neuroscience Consortium and NIDA-B, the Molecular, Cellular and Chemical Neurobiology Research Review Subcommittee, are co-sponsoring a workshop on February 11, 1997 entitled **"Knockouts and Transgenic Animals: Implications for Drug Abuse Research."** Speakers and their topic are: Alcino Silva, Ph.D., Cold Spring Harbor Laboratory, Gene targeting: novel window on learning and memory; Mark Mayford, Ph.D., UC San Diego, Regulated genetic control of synaptic plasticity: learning and memory; Rene Hen, Ph.D., Columbia, Targeting addictive behavior: the knockout approach; George Uhl, M.D., Ph.D., NIDA Intramural Research Program, Transgenic mice provide novel insights into cocaine, amphetamine, and morphine actions; and Eric Nestler, M.D., Ph.D., Yale, Understanding addiction: tools to manipulate genes in the brain. The aim of the workshop is to inform committee members, NIDA staff, and NIH staff about recent advances in transgenic technology and its application to drug abuse research. The workshop is scheduled to be held from 1:00 to 5:00 pm in the Potomac Room of the Parklawn Building.

On February 11-13, 1997, the NIH Office of Medical Applications of Research, in conjunction with several NIH Institutes, will convene a consensus development conference to address several questions about what is known about interventions to reduce behaviors related to HIV transmission. Several presentations will be made on interventions to reduce risks related to drug abuse, including outreach to out-of-treatment IDUs by Dr. Richard Needle, Chief, Community Research Branch, DEPR.

NIDA's Neuroscience Consortium has organized a workshop for high school teachers entitled **"The Biology of Addiction: Your Brain on Drugs"** to be held on March 17, 1997 from 7:00 to 9:00 pm at the Natcher Auditorium on the NIH campus in Bethesda, Maryland. This workshop is being organized in recognition of **Brain Awareness Week** (March 17-23). The featured speaker will be NIDA Director, Dr. Alan Leshner. Dr. Leshner will discuss the latest research on biological mechanisms underlying drug abuse and addiction, and current strategies for its prevention and treatment. There will be opportunities for teachers to ask questions and engage in discussions with Dr. Leshner and other NIDA staff. In addition, free teaching materials will be available.

NIDA's Behavioral Science Working Group in conjunction with the American Psychological Society (APS) will be sponsoring an all-day satellite conference at the APS Convention entitled **"Cognitive Science Research: More Than Thinking About Drug Abuse."** The meeting will be held on May 23, 1997 at the Washington Hilton. Dr. Alan Leshner, NIDA Director, will open the meeting which will feature many distinguished cognitive scientists. There will be an emphasis on the role of cognitive science in understanding the problem of drug abuse and addiction. Invited speakers will focus on topics such as animal cognition, the effects of drugs of abuse on cognitive ability, information processing, social cognition, and cognitive aspects of drug treatment and therapy. The meeting will provide opportunities for active interchanges between speakers and attendees for discussing cognitive science and drug abuse issues. The meeting will be open to the public and APS Convention attendees.

To highlight scientific advances and research opportunities in the field of drug abuse research on AIDS, NIDA's Office on AIDS has worked closely with the College on Problems of Drug Dependence (CPDD) to develop a number of AIDS-related symposia for the CPDD annual meeting in Nashville, June 14-19, 1997. In addition, the Office on AIDS sought

to stimulate submission of AIDS-related abstracts to CPDD through mailings to NIDA grantees, participants in the 1995 Scottsdale CPDD Satellite Meeting, and attendees at neuroAIDS and neuroimmunology meetings sponsored by NIH. Over 35 abstracts were submitted for NIDA sponsorship to CPDD.

Publications

National Conference on Marijuana Use: Prevention, Treatment, and Research Highlights, NIH Publication #96-4106, NCADI #BKD928.

Highlights from the Conference held in July 1995. Discusses the extent of the problem, consequences, prevention, and treatment of marijuana abuse. Dispels myths and provides science-based information on the drug.

Epidemiologic Trends in Drug Abuse: Community Epidemiology Work Group June 1996: Volume I Highlights and Executive Summary, NIH Publication #96-4126, NCADI #BKD211.

Summarizes the data discussed at the June 1996 meeting of the Community Epidemiology Work Group, which assessed recent drug abuse trends and pinpoints populations at risk in the U.S. and abroad.

Epidemiologic Trends in Drug Abuse: Community Epidemiology Work Group June 1996: Volume II: Proceedings, NIH Publication #96-4127.

Summarizes the data discussed at the June 1996 meeting of the Community Epidemiology Work Group, which assessed recent drug abuse trends and pinpoints populations at risk in the U.S. and abroad.

National Survey Results From the Monitoring the Future Study, 1975-1995, Volume I: Secondary School Students, NIH Publication #97-4139, NCADI #BKD213.

The two-volume monograph reports the results of the 21st national survey of drug use and related attitudes among American high school seniors, the 16th such survey of American college students, and the 5th such survey of 8th and 10th grade students.

Evaluating the Efficacy of HIV Prevention Among Drug Users: Models, Methods, and Measures. The Journal of Drug Issues, Summer 1996 (vol. 26, number 3), edited by E. Czajkoski and Guest Editor, Merrill Singer, is devoted to the topic of evaluating the efficacy of HIV prevention among drug users: models, methods, and measures. Contributors to the special issue were all recent or current researchers participating in NIDA's Cooperative Agreement for AIDS Community-Based Outreach/Intervention Research Program. Guest Editor Merrill Singer and Richard H. Needle, Ph.D., M.P.H., Chief, Community Research Branch, provide the introduction on **"Preventing AIDS Among Drug Users: Evaluating Efficacy"** which describes the history and objectives of NIDA's Cooperative Agreement program and points to its new directions toward a second wave of even more effective HIV prevention models.

Dr. Peter Cohen of MDD authored **"Off-Label" Use of Prescription Drugs: Legal, Clinical, and Policy Considerations.** European Journal of Anaesthesiology, In Press.

Cadet J.L., Sheng P., Epstein C., and Hirata H. **Nitric Oxide and Superoxide Radicals as Mediators of Toxicity of Amphetamine Analogs.** In: Free Radicals in Brain Physiology and Disorders. Academic Press, Chpt. 33, pp. 441-448, 1996.

Pushpa V. Thadani & Conference Participants. **NIDA Conference Report on Cardiopulmonary Complications of "Crack" Cocaine Use: Clinical Manifestation and Pathophysiology,** CHEST, 110, pp. 1072-1076, 1996.

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Staff Highlights

Staff Changes

In December 1996, **Robin I. Kawazoe**, Deputy Director, OSPC, began a detail to the NIH Office of the Director, Office of Science Policy. Among the issues Robin will be working on are health services research and managed care, as well as planning, policy coordination, and intergovernmental affairs. This detail is a wonderful opportunity for Robin to gain a broad perspective of science policy and planning across NIH as well as to represent NIH to the Department and in other forums.

Bennett W. Fletcher, Ph.D. was appointed Chief of the Services Research Branch, Division of Clinical and Services Research.

Susan Y. Azeka, M.S.W., joined OSPC in August as NIDA's Planning and Evaluation Officer. Prior to joining NIDA, she was a licensed social worker with a geriatric mental health treatment program in DC.

Shayna Steinger, M.I.A., joined OSPC in September from the National Aeronautics and Space Administration. She is a graduate of the Presidential Management Internship program and will serve as Special Assistant to the Director, OSPC.

Monica Jones, formerly of DRG/NIH, joined NIDA in September as a Program Assistant.

Jane Smither Holland joined the OSPC staff in October as a Program Analyst. She will act as Constituent Relations coordinator and will assist in Congressional affairs activities. She is a former Aide to Congressman E. (Kika) de la Garza of Texas who retired at the end of the 104th Congress.

Beverly Wyckoff Jackson joined NIDA as the Chief of the Public Information Branch, OSPC, in November. She has been in the health and science communications business for many years, having headed up the public affairs departments of Children's National Medical Center and the American Psychological Association, in addition to founding a public relations firm specializing in social science and health issues. Most recently she helped develop the public information program for the National Campaign to Prevent Teen Pregnancy.

Lucinda L. Miner, Ph.D., joined OSPC in November as Deputy Research Training Coordinator. Prior to joining the Science Policy Branch, Dr. Miner was the Acting Chief of the Molecular Genetics Section of NIDA's Intramural Research Program. Dr. Miner received a Ph.D. in Psychology with a specialty in Behavioral Genetics in 1986 from the University of Colorado and conducted postdoctoral work in the Molecular Neurobiology and Genetics Program at the University of Pittsburgh before coming to NIDA in 1992.

John Boren, Ph.D., retired from Federal service effective November 23, 1996. He was recently Program Officer in the Treatment Research Branch, DCSR, and formerly Chief, Clinical and Behavioral Pharmacology Branch, DBR/DCR.

Yng-shiuh Sheu Ph.D. retired from Federal service effective January 4, 1997. Dr. Sheu worked at NIDA for seventeen years as a pharmacologist responsible for reviewing the abuse liability of psychoactive drugs. He frequently served as an advisor to the World Health Organization in assessing the abuse liability of selected psychoactive drugs.

Richard Sackett, Public Information Branch, OSPC retired from Federal service on December 31, 1996 after 20 years at NIDA.

Staff Honors and Awards

NIDA Director's Awards

John Hamill, OPRM (EEO Award)

Nikki Zangwill, OPRM

Information Resources Management Branch, OPRM:

Linda Katzper

Constance Latsko

Marguerite Lewis

Tina McDonald-Bennett

Joseph Reckley

Dan Tick

Mona Brown, OSPC (EEO Award)

Robin Kawazoe, OSPC

Patricia Thomas, OSPC

Niki Turner, OSPC

Bennett Fletcher, Ph.D., DCSR (Commissioned Officer Award)

Women's Interagency HIV Study Group:

Katherine Davenny, M.P.H., DCSR

Vincent Smeriglio, Ph.D., DCSR

Coryl Jones, Ph.D., DEPR (30 year service)

Nicholas Kozel, DEPR (30 year service)

Melanie Pickett, DEPR

Fay Polcak, IRP (30 year service)

C. Jamie Biswas, Ph.D., MDD

Minority Recruitment and Training Program Staff:

Mary Affeldt, Administrative Services Branch, IRP

Brain Alston, Neuroscience Branch, IRP

Micha Brown, Administrative Services, IRP

Lula Beatty, Special Populations Office, OD

Jean Lud Cadet, Ph.D., Neuroscience Branch, IRP

Beverly Cepl, Clinical Pharmacology Branch, IRP

Lena Eads, Administrative Services, IRP

Stephen Heishman, Ph.D., Clinical Pharmacology Branch, IRP

Jack Henningfield

Angela McLeod, Neuroscience Branch, IRP

Richard Millstein, OD

Fay Polcak, Administrative Services Branch, IRP

Kathleen Wilson, Administrative Services Branch, IRP

NIDA EEO Advisory Committee: (EEO Group Award)

Mona Brown, Public Information Branch, OSPC

Paul Coulis, Ph.D., Clinical Medicine Branch, DCSR

Carol Cushing, Regulatory Affairs Branch, MDD
Anne Gupman, Molecular Neurobiology Branch, DIR
Rick Harrison, Contracts Review Branch, OEPR
Arthur Horton, Ph.D., Etiology and Clinical Neurobiology Branch, DCSR
Davey Jones, Management Analysis and Services Branch, OPRM
Jagitsing Khalsa, Ph.D., Clinical Medicine Branch, DCSR
Theresa Kopajtic, Molecular Neurobiology Branch, DIR
Arnold Mills, Community Research Branch, DEPR
Rao Rapaka, Ph.D., Basic Neurobiology and Biological Systems Res. Branch, DBR
Nancy Soulen, J.D., Science Policy Branch, OSPC
Jewell Webb, Program and Financial Management Branch, OPRM
Nikki Zangwill, Contracts Management Branch, OPRM

Conference on Drug Abuse Steering Committee

Lula Beatty, Ph.D., Special Populations Office, OD
Tim Condon, Ph.D., OD, OSPC
James Colliver, Ph.D., Epidemiology Research Branch, DEPR
Meyer Glantz, Ph.D., OD, DEPR
Harold Gordon, Ph.D., Etiology and Clinical Neurobiology Branch, DCSR
Stephen Heishman, Ph.D., Clinical Pharmacology Branch, DIR
Arthur Horton, Ph.D., Etiology and Clinical Neurobiology Branch, DCSR
Teri Levitin, Ph.D., OD, OEPR
Robin Macker, M.P.H., Science Policy Branch, OSPC
Carolyn Mosher, M.P.A., Science Policy Branch, OSPC
Joan Nolan, Public Information Branch, OSPC
Lisa Onken, Ph.D., Treatment Research Branch, DCSR
Elizabeth Rahdert, Ph.D., Treatment Research Branch, DCSR
David Shurtleff, Ph.D., Behavioral Sciences Research Branch, DBR
Jaylan Turkan, Ph.D., Behavioral Sciences Research Branch, DBR

Other Awards

Peter Cohen, M.D., J.D., MDD was awarded first prize (Surgery) in the British Medical Association Medical Book Competition, November 26, 1996. Dr. Cohen and his co-author Dr. Thomas E.J. Healy shared this honor for their book entitled **Wylie and Churchill- Davidson's A Practice of Anaesthesia**, Sixth Edition.

Mario R. De La Rosa, Ph.D., SPO, was featured in the American Association for the Advancement of Science publication entitled "**Making a Difference: Minorities in Substance Abuse**" as one of twenty-one minority scientists in the United States who have made significant contributions to the substance abuse field.

Meyer D. Glantz, Ph.D. Associate Director for Science, DEPR, has been elected as a Fellow of the American Psychological Association.

Arthur MacNeill Horton, Ph.D., DCSR, was presented with a Recognition Award "For Your Commitment Toward Development of Substance Abuse Research on Underserved Populations", on October 10, 1996 by the Program Committee of the Fourth Annual Conference on Psychopathology, Psychopharmacology, Substance Abuse, and Culture in Los Angeles, California.

Sari Izenwasser, Ph.D., IRP, received a travel award from the International Narcotics Research Conference to attend its annual meeting.

Edythe London, Ph.D., IRP, received the Dean's Recognition Award for Outstanding Alumni of the College of Natural and Mathematical Sciences, Towson State University, Towson, MD, November 1966.

Richard H. Needle, Ph.D., M.P.H., Chief of the Community Research Branch, DEPR, received the 1996 award from the American Anthropological Association's Commission on AIDS Research and Prevention. The award is for "outstanding leadership, vision, and commitment in supporting and significantly furthering anthropological research on substance abuse and AIDS."

Jaylan S. Turkkan, Ph.D., was elected as Fellow of the American Psychological Society.

Cora Lee Wetherington, Ph.D., was elected Fellow of Division 28, Psychopharmacology and Substance Abuse, of the American Psychological Association.

Grantee Honors

Stephen Higgins, Ph.D., Associate Professor of Psychiatry and Psychology at the University of Vermont and NIDA grantee, has won the 1996 Dan Anderson Research Award. The award, sponsored by the Butler Center for Research and Learning at Hazelden, recognizes the distinguished contribution of a researcher who has advanced the scientific knowledge of addiction recovery. Dr. Higgins' work has concentrated on improving treatment approaches to cocaine addiction.

Robert G. Carlson, Ph.D., Associate Professor, Wright State University School of Medicine, was awarded the Steven Polgar Award for "state of the art excellence" in Medical Anthropology by the Society for Medical Anthropology, at the American Anthropological Association's 95th annual meeting in San Francisco. The award was presented to Dr. Carlson in recognition of his outstanding article, "**The Political Economy of AIDS Among Drug Users in the United States: Beyond Blaming the Victim or Powerful Others,**" published in *American Anthropologist*, 98(2): pp. 266-278, 1995.

Three NIDA investigators -- **Dennis McCarty, Richard Frank, and Constance Weisner**, served as members of the Institute of Medicine's Committee on Quality Assurance and Accreditation Guidelines for Managed Behavioral Health Care. IOM's report, **Managing Managed Care: Quality Improvement in Behavioral Health**, was published in November 1996. Drs. McCarty and Weisner were also co-editors (with others) of the report, which sought to develop a framework to guide the development, use, and evaluation of performance indicators, accreditation standards, and quality improvement mechanisms. **Thomas McLellan**, Director of the Drug Abuse Treatment Evaluation Center, co-authored a Commission paper: "**Can the Outcome Research Literature Inform the Search for Quality Indicators in Substance Abuse Treatment?**"

Dr. Murray Goodman, a NIDA grantee and professor, Department of Chemistry, University of California, San Diego, was selected as the recipient of the Ralph F. Hirschman Award in Peptide Chemistry sponsored by Merck Research Laboratories. The award will be presented at the 213th ACS National Meeting in San Francisco, CA. Dr. Goodman, over many years, designed and synthesized novel hormones, opioids, antibiotics and neurotransmitters. Under his NIDA grant Dr. Goodman synthesized a number of novel opioid peptides and the molecules were analyzed by spectroscopy, x-ray diffraction and computer simulations. He proposed structure-bioactivity relationships for a series of opioid peptides and peptidomimetics.

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