Director's Report to the National Advisory Council on Drug Abuse - September, 2003

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Director's Report to the National Advisory Council on Drug Abuse - September, 2003

Research Findings - Basic Research

Effect of Buproprion on Nicotine Self-Adminstration in Rats

This study investigated the effects of bupropion, which inhibits monoamine uptake and nicotine acetylcholine receptor (AChR) function, on nicotine self-administration in rats. The effects of bupropion were compared with methamphetamine and apomorphine, which do not affect nAChR function. The specificity of bupropion's effects on nicotine self-administration, sucrose-maintained responding and amphetamine self-administration were also investigated. Bupropion produced a biphasic dose-response pattern at both doses (0.01 and 0.02 mg/kg/inf) of nicotine. Low doses of bupropion increased nicotine self-administration while high doses decreased self-administration. A similar pattern of responding was produced with methamphetamine challenges. Apomorphine had no effect at low doses, but reduced nicotine self-administration at high doses. The low dose of bupropion appeared to be selective, as it did not alter responding for sucrose and amphetamine. The high dose of bupropion, however, appeared to be non-specific, since it also dose-dependently decreased responding for sucrose and amphetamine. The investigators conclude that the increase in nicotine self-administration produced by low doses of bupropion is likely due to inhibition of dopamine and norepinephrine transporters combined with inhibition of nAChRs. Rauhut, A.S., Neugebauer, N., Dwoskin, L and Bardo, M.T. Effect of Bupropion on Nicotine Self-administration in Rats. Psychopharmacology (online publishing: June2003).

Silent Antagonist of Anandamide Receptor

The cannabinoid analog abnormal cannabidiol [abn-cbd; (-)-4-(3-3,4-*trans-p*-menthadien-[1,8]-yl)-olivetol] does not bind to CB1 or CB2 receptors, yet it acts as a full agonist in relaxing rat isolated mesenteric artery segments. Vasorelaxation by abn-cbd is endothelium-dependent, pertussis toxin-sensitive, and is inhibited by the BKCa channel inhibitor charybdotoxin, but not by the nitric-oxide synthase inhibitor *N*_-nitro-L-arginine methyl ester or by the vanilloid VR1 receptor antagonist capsazepine. The cannabidiol analog O-1918 does not bind to CB1 or CB2 receptors and does not cause vasorelaxation at concentrations up to 30 _M, but it does cause concentration-dependent (1-30_M) inhibition of the vasorelaxant effects of abn-cbd and anandamide. In anesthetized mice, O-1918 dose-dependently inhibits the hypotensive effect of abn-cbd but not the hypotensive effect of the CB1 receptor agonist (-)-11-OH-_9-tetrahydrocannabinol dimethylheptyl. In human umbilical vein endothelial cells, abn-cbd induces phosphorylation of p42/44 mitogen activated protein kinase and protein kinase B/Akt, which is inhibited by O-1918, by pertussis toxin or by phosphatidylinositol 3 (PI3) kinase inhibitors. These findings indicate that abn-cbd is a selective agonist and that O-1918 is a selective, silent antagonist of an endothelial "anandamide receptor," which is distinct from CB1 or CB2 receptors and is coupled through Gi/Go to the PI3 kinase/Akt signaling pathway. Offertáler, L., Mo, F.M., B‡tkai, S., Liu, J, Begg, M., Razdan R.K., Martin, B.R., Bukoski, R.D. and Kunos, G. Selective Ligands and Cellular Effectors of a G Protein-Coupled Endothelial Cannabinoid Receptor. Molecular Pharmacology, 63, pp. 699-705, 2003.

FAAH Inhibition

The available extracellular concentration of the endogenous cannabinoid anandamide is regulated, in part, by uptake into neurons and glia where it is degraded by the fatty acid amide hydrolase (FAAH), among other enzymes. Inhibitors of FAAH can be considered as indirect cannabinoid receptor agonists, but without the common side effects of traditional agonists such as THC. Thus, FAAH inhibitors are useful

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pharmacological tools and have potential as pharmaceutical agents. Previously investigated classes of FAAH inhibitors include: palmitylsulfonyl fluoride, organophosphorous pesticides, the anesthetic propofol, alpha-keto esters and amides, and fatty acid sulfonyl fluorides. In a collaborative study with the University of Urbino, Dr. Daniele Piomelli has recently reported on the preparation, modeling, and pharmacological testing of a new class of FAAH inhibitor, which are alkylcarbamic acid aryl esters. Several of these compounds displayed nanomolar or low micromolar IC50 inhibitory values toward FAAH activity, without affecting acetylcholinesterase or butylcholinesterase activity, and without appreciable binding to the CB1/CB2 receptors. In general, ester or urea analogs of these compounds were not effective as inhibitors, and replacement of oxygen with sulfur (resulting in a thiocarbamate) was also not successful. The use of molecular modeling has suggested that carbamates with a meta-substituted aryl group possess a curvature which somewhat resembles the "bent" or "U-shape" adopted by fatty acids such as arachidonic acid in binding to different proteins. To date, these carbamates exhibit little in-vivo cannabimimetic effects (such as catalepsy, reduced body temperature, or stimulation of feeding), but they do show potential as anxiolytic agents in rodent models. Tarzia, G., Duranti, A., Tontini, A., Piersanti, G., Mor, M., Rivara, S., Plazzi, P., Park, C., Kathuria, S., and Piomelli, D. Journal of Medicinal Chemistry, 46, pp. 2352-2360, 2003.

Methamphetamine Neurotoxicity and Neurokinin Receptors

Methamphetamine (METH), a long lasting derivative of d-amphetamine, is an addictive substance and is known to cause extensive dopaminergic (DA) neural degeneration in the central nervous system. As METH also augments striatal Substance P (SP) levels, a neuropeptide intimately involved in postsynaptic actions of DA in striatum region of brain, Dr. Jing Yu and associates at Hunter College CUNY speculated that SP plays a role in METH-induced DA toxicity and neural damage in the striatum. To test this hypothesis, they designed studies to assess the effects of concurrent administration of METH and selective non-peptide neurokinin-1 (NK-1) receptor antagonists on several markers of DA terminal toxicity in the mouse striatum. Their studies demonstrate for the first time that pharmacological blockade of NK-1 receptors is protective against neurochemical toxicity of striatal DA terminals induced by METH. Their results also provide evidence that tachykinins, particularly SP, acting through NK-1 receptors, play a crucial role in the pathogenesis of nigrostriatal DA terminal degeneration induced by METH. This finding could lead to novel therapeutic strategies to offset drug addictions as well as in the treatment of a number of other disorders such as, Parkinson's and Hunting's diseases. Yu, J., Cadet, J.L. and Angulo, J.A. Neurokinin-1 (NK-1) Receptor Antagonists Abrogate Methamphetamine-induced Striatal Dopaminergic Neurotoxicity in the Murine Brain. Journal of Neurochemistry, 83, pp. 613-622, 2002.

Gene Therapy Increases the Efficacy of Morphine Analgesia

Li-Yen Mae Huang of the University of Texas Medical Branch and her colleagues have been investigating the use of gene therapy to make pain treatments more effective. Specifically, she injected adeno-associated viral (AAV) vectors encoding mu-opioid receptor cDNA into the dorsal root ganglia (DRG) or sciatic nerves of rats. This resulted in a substantial long-term increase in the number of mu-opioid receptors identified in DRG neurons, many of which relay pain signals. In rats with this treatment, morphine was much more effective at producing analgesia, and there was a decrease in the tolerance typically seen with repeated morphine administration. This treatment might provide a novel way to make opioid treatments more effective, allowing smaller doses to be used, and decreasing the incidence of side effects. Yanping, Y.X., Gu, Y., Li, G., and Huang, L.M. Efficiencies of Transgene Expression in Nociceptive Neurons Through Different Routes of Delivery of Adeno-Associated Viral Vectors, Human Gene Therapy, 14, pp. 897-906, 2003.

Targeting the Purinergic Neuromodulator -- A Potential Therapeutic Strategy to Reduce Withdrawal from Opiates

While neuromodulators are known for their roles in normal brain function, much less is documented about their function in the addicted brain. Studies have suggested that the neuromodulator adenosine is involved in drug addiction and withdrawal. Recently, Dr. Williams' work suggests that chronic exposure to morphine may alter adenosine metabolism in the nucleus accumbens. His lab examined the effects of chronic morphine treatment (subcutaneous implantation of morphine pellets in rats for one week) on the ability of adenosine to inhibit excitatory postsynaptic currents in the medium spiny neurons of the nucleus accumbens. Although the treatment did not alter the level of adenosine-mediated tonic inhibition of excitatory synapses in the nucleus accumbens, it did induce a leftward shift in the adenosine dose-response

curve, indicating an increase in the sensitivity of synaptic currents to exogenously applied adenosine. This shift was not due to a change in adenosine receptors or their effectors, because chronic morphine treatment had no effect on the dose-response relationship of a non-metabolized adenosine receptor agonist. When adenosine transport was blocked, it eliminated the shift of the adenosine dose-response curve induced by chronic morphine. These data suggest that the increase in the sensitivity of nucleus accumbens synapses to the inhibitory effects of adenosine may be due to a decrease in adenosine transport. The identification of these changes in the adenosine system after chronic drug exposure may help identify new therapeutic strategies aimed at reducing the symptoms of withdrawal from opiates. Brundege, J.M. and Williams, J.T. Increase in Adenosine Sensitivity in the Nucleus Accumbens following Chronic Morphine Treatment. Journal of Neurophysiology, 87, pp. 1369-1375, 2002.

Counter-Regulation of Serotonin Release by GABAergic and Glutamatergic Inputs is Modulated by Morphine

Dysregulation of serotonin (5-HT) levels in the nucleus accumbens (NAc) plays a role in opiate addiction and withdrawal symptoms. Dr. Tao's work previously showed that release of 5-HT is regulated in a counter-balanced manner by glutamatergic and GABAergic inputs to 5-HT neurons. Activation of glutamate receptors enhances 5-HT release while activation of the GABA receptors does the opposite. This counter-regulation is, in turn, modulated by opioids. For example, in the dorsal raphe nucleus (DRN) -- whose 5-HT neurons are afferent to the NAc -- release of 5-HT is tonically induced by endogenous opioid peptide via delta receptors and enhanced by exogenous morphine via activation of both mu and delta receptors. These effects are mediated by opioid receptors on both GABAergic and glutamatergic inputs to 5-HT neurons in the DRN, as release is increased after blockade of GABAA receptors and decreased after blockade of glutamate receptors. However, local infusion of morphine into the DRN inhibits both glutamate and GABA release, which suggests that the overall impact of opioids on 5-HT release depends on the balance of GABAergic and glutamatergic afferents. In this study, the investigators used microdialysis to characterize the effects of systemic morphine on 5-HT release in the rat. Their first aim was to determine whether opioids alter 5-HT release in the NAc locally (by modulating DRN afferents) or, alternatively, by effects on 5-HT neurons within the DRN. They found that the morphine-induced increase of 5-HT was blocked or attenuated when antagonists to either opioid, GABAA, GABAB, or glutamate receptors were locally infused into the DRN, but not when infused into the NAc. Thus the site of regulation appears to be only within the DRN. A second aim was to further characterize the GABA/glutamate counter regulation of 5-HT release. Their results indicate that morphine inhibits GABA release more than glutamate release, thus the net effect of morphine is to increase 5-HT efflux. Further studies are needed to determine how the counter-regulation system is affected when brain homeostasis is altered by chronic exposure to drugs of abuse or stress. Tao, R. and Auerbach, S.B. GABAergic and Glutamatergic Afferents in the Dorsal Raphe Nucleus Mediate Morphine-induced Increase in Serotonin Efflux in the Rat CNS. Journal of Pharmacology and Experimental Therapeutics, 303, pp. 704-710, 2002.

Ofloxacin as a Reference Marker in Hair of Various Colors

Diana Wilkins and her colleagues, proposed that the administration of a reliable marker substance to human subjects may enhance the ability to identify drug use and treatment compliance in drug treatment programs. The goal of the study was to determine if an oral dose of the antibiotic, Ofloxacin (OFLX) could be used as a marker substance to establish reference points with respect to time in hair of various colors. Male and female subjects (n=32) between 18 and 40 years of age received 800 mg of OFLX as a divided oral dose on a single day. Subjects were restricted from cutting their hair or performing chemical treatments. Hair was collected (by cutting) before, and at weeks 4, 5, 6, and 7 after OFLX administration. Subjects were classified as having black (n=5), brown (n=13), blonde (n=8), or red (n=6) hair. Hair was segmented into 3.0 cm segments prior to chemical digestion, extraction, and analysis by HPLC. At 7 weeks, the OFLX concentrations in the first 3.0 cm of hair closest to the scalp were as follows: 30.6±8.5 (black), 6.0±1.8 (brown), 3.5±1.6 (blonde), and 1.4±0.3 (red). A similar pattern was found in hair collected at weeks 4-6. Quantitative eumelanin (EUM) hair concentrations for each subject were also determined by HPLC. A strong relationship between OFLX concentration at 7 weeks and EUM was noted. For six subjects, the authors determined the intra-subject variability of OFLX incorporation into individual hair strands. Four strands from each subject were cut into 2-mm segments and analyzed. OFLX appeared in segments 1-10 at week 5 (the first centimeter of hair). OFLX appeared in segments 2-20 at week 7 (first and second centimeter of hair). The maximum OFLX concentration (the "band"

of drug) and location was then determined for each strand. The maximum OFLX concentration was measured in segments 2-5 at week 5 for all subjects (within the first centimeter of hair length). The maximum OFLX concentration was measured in segments 3-8 at week 7 (within the first and second centimeter of hair). This was consistent with a growth rate of less than 1.0 cm/month, although considerable inter-subject variability was found. No significant axial diffusion of OFLX along the hair shaft beyond the first 3.0 cm of hair was noted. Despite a strong effect of hair color, these data suggest that OFLX may be a suitable marker substance for hair, allowing subjects to serve as their own "controls." Wilkins, D.G., Mizuno, A., Borges, C.R., Slawson, M.H., and Rollins, D.E. Ofloxacin as a Reference Marker in Hair of Various Colors, Journal of Analytical Toxicology, 27, pp. 130-136, 2003.

Navigated Laser Capture Microdissection as an Alternative to Direct Histological Staining for Proteomic Analysis of Brain Samples

Advances in biology often arise as a result of advances in technology. A relatively new technology is laser capture microdissection (LCM). This technique uses a laser to dissect individual cells or cell clusters such as a brain nucleus from tissue slices. In this study, the researchers were interested in analyzing the protein from the microdissected sample using the proteomic technologies, two-dimensional electrophoresis (2-DE) and mass spectrometry. It had previously been demonstrated that histological stains used to visualize cells can interfere with 2-DE analysis of proteins. Therefore, in these studies, the researchers set out to examine an approach called "navigated LCM" as an alternative to LCM of stained tissue. The navigated LCM uses an adjacent, stained tissue slice to navigate dissection of the unstained tissue slice. Navigated LCM requires that the tissue slice to be dissected be fixed with 70% ethanol and cleared with xylene. Three major questions had to be answered. When compared to manually dissected, unstained, unfixed tissue: Does navigated LCM affect total protein recovery? Does navigated LCM affect 2-DE protein spot resolution? Does navigated LCM affect protein identification or protein coverage by mass spectrometry? Examining brain tissue slices, the researchers found no significant difference between manually dissected, unstained, unfixed tissue and the navigated LCM, ethanol-fixed tissue in terms of protein recovery, 2-DE resolution or protein identification and coverage by mass spectrometry. This demonstrates that the ethanol fixation had no significant effect on protein analysis and that navigated LCM could be used for proteomics analysis of brain nuclei regardless of size, shape or location. This approach could be used to perform proteomics analysis of changes in protein expression in specific brain regions associated with disease or pharmacological treatment. Mouledous, L., Hunt, S., Harcourt, R., Harry, J., Williams, K.L., and Gutstein, H.B. Proteomics, 3, pp. 610-615, 2003.

Naltrexone Response in Alcohol-dependent Patients is Associated with a Functional Polymorphism of the m-Opioid Receptor Gene

Naltrexone, which primarily blocks the endogenous m-opioid receptor, is prescribed to treat alcohol dependence and narcotic addiction. Two specific polymorphisms in exon 1 of the mu-opioid receptor gene have been shown to have potential functional relevance. Therefore, David Oslin and colleagues examined the hypothesis that there may be an association between these polymorphisms and treatment responses to naltrexone. A total of 82 patients who were randomized to naltrexone and 59 who were randomized to placebo were genotyped for the two variants (Asn40Asp and Ala6Val). The association between genotype and drinking outcomes was measured over 12 weeks of treatment. Subjects with one or two copies of the Asp40 allele who were treated with naltrexone had significantly lower rates of relapse ($p=0.04$) and a longer time to return to heavy drinking ($p=0.04$) than those homozygous for the Asn40 allele. Abstinence rates and relapse rates did not differ between the two genotyped groups among those assigned to placebo. Unfortunately, the number of subjects in the study was too small to examine the effects of the Ala6Val variant. However, the findings for the Asn40Asp variant suggest that genotyping of the m-opioid receptor may be useful for identifying patients who are most likely to respond to naltrexone. Oslin, D.W., Berrettini, W., Kranzler, H.R., Pettinati, H., Gelernter, J., Volpicelli, J.R., and O'Brien C.P. A Functional Polymorphism of the m-Opioid Receptor Gene is Associated with Naltrexone Response in Alcohol-Dependent Patients. Neuropsychopharmacology, 28, pp. 1546-1552, 2003.

A Developmental Role for Nicotinic Acetylcholine Receptors (NAChr) in Modulation of Passive Avoidance Behavior

Chronic nicotine exposure exerts multiple effects on the developing brain that likely contribute to subsequent impaired function as adults. High affinity nicotinic cholinergic receptors are expressed normally throughout the brain and are thought to be involved

in the development and function of synaptic activity. Because of the extensive distribution of these receptors, however, efforts to determine a definitive role for nAChRs and/or the underlying anatomical regions have been problematic. Dr. Marina Picciotto and her colleagues at Yale studied passive avoidance behavior, a test of fear associated learning, in transgenic mice with inducible expression of the ß2 subunit of the AChRs in corticothalamic projection neurons. They found that nicotine-induced changes in neurotransmission through AChRs during development were associated with impaired passive avoidance learning as adults. King, S., Marks, M., Grady, S., Calderone, B., Koren, A., Muhkin, A., Collins, A., and Picciotto, M. Conditional Expression in Corticothalamic Efferents Reveals a Developmental Role for Nicotinic Acetylcholine Receptors in Modulation of Passive Avoidance Behavior. Journal of Neuroscience, 23(9), pp. 3837-3843, 2003.

Repeated Nicotine Administration Enhances Cocaine-Seeking in Rats

Drugs with high abuse liability such as psychostimulants, opioids, nicotine or alcohol are likely to be co-administered, and the use of one drug may trigger craving and relapse for another drug. Dr. Greg Mark and his colleagues at the Oregon Health and Science University School of Medicine studied the effects of acute and chronic nicotine treatment on the self-administration of cocaine in rats. Acute, subcutaneous injection of nicotine 3 minutes before access to cocaine resulted in an inverted U-shaped dose-response function (low nicotine doses increased and high doses decreased the number of cocaine infusions). Repeated nicotine administration with the high dose before each daily session significantly increased the number of cocaine infusions by the 8th day of nicotine exposure. In addition, in sessions where responding no longer led to cocaine infusions, i.e. extinction, injections of nicotine caused a reinstatement of the previously reinforced responding. Dr. Mark concluded that nicotine facilitates cocaine reinforcement, can contribute to the transition from moderate drug taking to an escalation of drug intake, and may trigger relapse to drug taking. Bechtholt, A.J. and Mark, G.P. Enhancements of Cocaine-Seeking Behavior by Repeated Nicotine Exposure in Rats. Psychopharmacology, 162, pp. 178-185, 2002.

A Conditional Deletion of the NR1 Subunit of the NMDA Receptor in Adult Spinal Cord Dorsal Horn Reduces NMDA Currents and Injury-induced Pain

In order to determine the importance of the NMDA receptor (NMDAR) in pain hypersensitivity after injury, Dr. Charles Insturrisi and his research team at the Weill Medical College of Cornell University selectively deleted the NMDAR1 (NR1) subunit in the lumbar spinal cord of adult mice by the localized injection of an adenoassociated virus expressing Cre recombinase into floxed NR1 mice. NR1 subunit mRNA and dendritic protein were reduced by 80% in the area of the virus injection, and NMDA currents, but not AMPA currents, were reduced 86-88% in lamina II neurons. The spatially-restricted NR1 knockdown did not alter heat or cold paw-withdrawal latencies, mechanical threshold, or motor function. However, injury-induced pain produced by intraplantar formalin is reduced by 70%. These results demonstrate conclusively that the postsynaptic NR1 receptor subunit in the lumbar dorsal horn of the spinal cord is required for central sensitization, the central facilitation of pain transmission produced by peripheral injury. South, S.M., Kohno, T., Kaspar, B.K., Hegarty, D., Vissel, B., Drake, C.T., Ohata, M., Jenab, S., Sailer, A.W., Malkmus, S., Masuyama, T., Horner, P., Bogulavsky, J., Gage, F.H., Yaksh, T.L., Woolf, C.J., Heinemann, S.F., and Inturrisi, C.E. A Conditional Deletion of the NR1 Subunit of the NMDA Receptor in Adult Spinal Cord Dorsal Horn Reduces NMDA Currents and Injury-induced Pain. Journal of Neuroscience, 23, pp. 5031-5040, 2003.

Endogenous RGS Protein Action Modulates Mu-Opioid Signaling through G_o: Effects on Adenyly cyclase, Extracellular Signal-Regulated Kinases, and Intracellular Calcium Pathways

RGS (regulators of G protein signaling) proteins are GTPase-activating proteins (GAP) for the G_ subunits of heterotrimeric G proteins and act to regulate signaling by rapidly cycling G protein. RGS proteins may integrate receptors and signaling pathways by physical or kinetic scaffolding mechanisms. To determine whether this results in enhancement and/or selectivity of agonist signaling, Dr. John Traynor and his research team at the University of Michigan have prepared C6 cells stably expressing the mu-opioid receptor and either pertussis toxin-insensitive or RGS- and pertussis toxin-insensitive G_o. They have compared the activation of G protein, inhibition of adenylyl cyclase, stimulation of intracellular calcium release, and activation of the ERK1/2 MAPK pathway between cells expressing mutant G_o that is either RGS-insensitive or RGS-sensitive. The mu-receptor agonist DAMGO and partial agonist morphine were much more potent and/or had an increased maximal effect in inhibiting adenylyl cyclase and in activating MAPK in cells expressing RGS-insensitive

G_o. In contrast, mu-opioid agonist increases in intracellular calcium were less affected. The results are consistent with the hypothesis that the GAP activity of RGS proteins provides a control that limits agonist action through effector pathways and may contribute to selectivity of activation of intracellular signaling pathways. Clark, M.J., Harrison, C., Zhong, H., Neubig, R.R., and Traynor, J.R. Endogenous RGS Protein Action Modulates Mu-Opioid Signaling through G_o: Effects on Adenylyl Cyclase, Extracellular Signal-Regulated Kinases, and Intracellular Calcium Pathways. Journal of Biological Chemistry, 278, pp. 9418-9425, 2003. Epub Jan 10, 2003.

Differential Mechanisms of Morphine Antinociceptive Tolerance Revealed in Arrestin-2 Knock-Out Mice

Morphine induces antinociception by activating μ opioid receptors (μORs) in spinal and supraspinal regions of the CNS. Arrestin-2 (arr2), a G-protein-coupled receptor-regulating protein, regulates the μOR in vivo. Dr. Laura Bohn and her colleagues at the Duke University Medical Center previously showed that mice lacking arr2 experience enhanced morphine-induced analgesia and do not become tolerant to morphine as determined in the hot-plate test, a paradigm that primarily assesses supraspinal pain responsiveness. To determine the general applicability of the arr2-μOR interaction in other neuronal systems, they tested arr2 knockout (arr2-KO) mice using the warm water tail-immersion paradigm, which primarily assesses spinal reflexes to painful thermal stimuli. In this test, the arr2-KO mice had greater basal nociceptive thresholds and markedly enhanced sensitivity to morphine. Interestingly, however, after a delay onset, they do ultimately develop morphine tolerance, although to a lesser degree than the wild-type (WT) controls. In the arr2-KO but not WT mice, morphine tolerance could be completely reversed with a low dose of the classical protein kinase C (PKC) inhibitor chelerythrine. These findings provide in vivo evidence that the μOR is differentially regulated in diverse regions of the CNS. Furthermore, although arr2 appears to be the most prominent and proximal determinant of μOR desensitization and morphine tolerance, in the absence of this mechanism, the contributions of a PKC-dependent regulatory system become readily apparent. Bohn, L.M., Lefkowitz, R.J., and Caron, M.G. Differential Mechanisms of Morphine Antinociceptive Tolerance Revealed in Arrestin-2 Knock-Out Mice. J Neurosci., 22(23), pp. 10494-10500, December 1, 2002.

The Cystine-Glutamate Exchanger: A Neurobiological Mechanism Underlying Cocaine Relapse

Repeated cocaine abuse can lead to cocaine addiction, which is often characterized as a compulsive pattern of continued drug taking despite potential harm. For many years NIDA supported researchers have studied this phenomenon in animals using the drug self-administration model in which animals are trained to press a response lever to receive an intravenous injection of cocaine. With this procedure, the animal continues to escalate its drug taking over several days. In extinction conditions, when the drug is no longer provided for lever responding, drug-seeking behavior declines. However, self-administration can be reinstated by administering a priming injection of the drug itself, exposing the animal to environmental cues associated with drug taking, or exposing the animal to a stressor. Because many of these same factors have often been reported to lead to drug abuse relapse, this reinstatement procedure is thought to model drug abuse relapse in human addicts. Through the reinstatement model much has been learned about the changes in brain function (i.e., neuroadaptations) and neural substrates that are thought to be involved in drug-seeking behavior and relapse to drug use. Although it has been known for quite some time that dopamine release in the nucleus accumbens (NAc) is associated with the reinforcing effects of cocaine, it has become evident that this is not the only neurotransmitter or substrate involved in drug addiction or relapse. In particular, increased glutamate neurotransmission in the NAc has been shown to mediate drug-seeking behavior, and withdrawal from cocaine reduces glutamate levels in the NAc. Further detailed investigation of this neurotransmitter and it role in cocaine relapse has been extensively studied by Dr. Peter Kalivas and his colleagues at Medical University of South Carolina. Their recent research has shown that reduction in glutamate brought about by repeated administration of cocaine results from modulation of the cystine/glutamate exchanger, which is found throughout the brain. The exchanger normally helps maintain appropriate glutamate levels in the brain. As cystine is brought into the neuronal cells for glutathion synthesis, glutamate is taken out to help maintain glutamate neurotransmission and glutamatergic tone among neurons in the brain. Through a series of experiments, the investigators concluded that cocaine administration cause a long lasting reduction in glutamate by reducing the activity of the cystine/glutamate exchanger. Cystine administered directly to the NAc restored this exchange and returned the reduced amount of extracellular glutamate caused by

cocaine to normal levels. Similarly, administrating N-acetylcysteine systemically, a cystine pro-drug, elevated glutamate in the brains of rats that had been repeatedly administered cocaine and were experiencing cocaine withdrawal. Furthermore, and most importantly, when N-acetylcysteine was administered to rats after withdrawal from repeated cocaine administration, this cystine pro-drug successfully blocked cocaine-induced reinstatement (relapse). These results indicate that repeated abuse of cocaine and cocaine withdrawal compromises glutamatergic tone in the brain and this effect is mediated through the cystine/glutamate exchanger. How cocaine affects the exchanger to reduce glutamate is not clear and will need further investigation. This research, however, does identify the cystine/glutamate exchanger as a neurobiological mechanism that is affected by repeated cocaine administration and possibly linked to drug abuse relapse. Further investigation of this neurobiological mechanism and cocaine-induced neuroadaptation could lead to exciting new leads for pharmacotherapies for treating cocaine addiction and relapse. Baker, D.A., McFarland K., Russell, L.W., Shen, H., Tang,X.C., Toda, S. and Kalivas, P.W. Neuroadaptations in the Cystine-Glutamate Exchange Underlie Cocaine Relapse. Nature Neurosci., 6, pp. 743-749, 2003.

Methylphenidate (Ritalin") and MDMA ("Ecstasy") Adolescent Exposure in Mice: Long-Lasting Consequences on Cocaine-induced Reward and Psychomotor Stimulation in Adulthood

The consequences of methylphenidate and MDMA abuse during adolescence on vulnerability to subsequent drug abuse and relapse in adulthood are unknown. To investigate this question, researchers administered methylphenidate, MDMA or saline to adolescent (26 day old) mice for 7 days. After one month (62 days old; when mice are considered 'adults'), the three groups of mice received cocaine injections for 4 or 5 days to determine their sensitivity to the rewarding and psychomotor stimulating effects of cocaine in adulthood. The rewarding effect of cocaine was determined in the conditioned place preference paradigm, and cocaine-induced psychomotor stimulation was determined by measuring locomotion. They found that cocaine induced the same magnitude of place preference in the control and MDMA groups, suggesting that exposure to MDMA did not alter the acquisition of the rewarding effect of cocaine. The methylphenidate group developed lower place preference, suggesting that exposure to methylphenidate diminished the acquisition of the rewarding effect of cocaine. In the locomotor activity studies, the methylphenidate group showed enhanced sensitivity to cocaine compared to the saline and MDMA groups. To investigate their response to challenge cocaine injection following cocaine withdrawal (a measure for drug relapse), mice remained drug free for 14 days and were re-tested in response to a low dose of cocaine. This low dose of cocaine induced very high place preference response as well as pronounced locomotor stimulation in the methylphenidate and MDMA pre-exposed groups, but not in the saline group. These findings demonstrate that (1) adolescent exposure to methylphenidate or MDMA ultimately elicits similar consequences in response to cocaine during adulthood and (2) the sensitized or heightened response to cocaine is expressed primarily after withdrawal from the initial exposure to cocaine. Thus, although the initial responses to cocaine of the drug pre-exposed mice were not always different from those of the saline pretreated mice, the methylphenidate and MDMA pre-exposed subjects ultimately developed significantly higher sensitivity to both the rewarding and psychomotor stimulating effects of cocaine after the withdrawal period from cocaine. The implications of these findings for human adolescent exposure to methylphenidate and MDMA should be cautiously regarded. However, these results suggest that although methylphenidate and MDMA pre-exposed subjects may not be more prone to initiate drug use, they may exhibit greater vulnerability than unexposed subjects to drug relapse after drug use has been initiated. Achat-Mendes, C., Anderson, K.L., and Itzhak, Y. Methylphenidate and MDMA Adolescent Exposure in Mice: Long-Lasting Consequences on Cocaine-induced Reward and Psychomotor Stimulation in Adulthood. Neuropharmacology, 45, pp. 106-115, 2003.

Mu-Opioid Receptors Mediate Immunosuppression Induced by Chronic Restraint Stress

Psychological stress is associated with immunosuppression in both humans and animals. Although it was well established that psychological stressors stimulate the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, resulting in the release of various hormones and neurotransmitters, the mechanisms underlying these phenomena are poorly understood. In this study, the investigators used mice with a genetic knockout of the mu-opioid receptor knockout (MORKO) to examine whether the mu-opioid receptor mediates the immunosuppression induced by restraint stress. Their results showed that wild-type (WT) mice subjected to chronic

12-h daily restraint stress for 2 days exhibited a significant decrease in splenocyte number with a substantial increase in apoptosis and CD95 (Fas/APO-1) expression of splenocytes. The effects were essentially abolished in MORKO mice. Furthermore, inhibition of splenic lymphocyte proliferation, IL-2, and IFN-gamma production induced by restraint stress in WT mice was also significantly abolished in MORKO mice. Interestingly, both stressed WT and MORKO mice showed a significant elevation in plasma corticosterone and pituitary proopiomelanocortin mRNA expression, although the increase was significantly lower in MORKO mice. Adrenalectomy did not reverse restraint stress-induced immunosuppression in WT mice. These data clearly established that the mu-opioid receptor is involved in restraint stress-induced immune alterations via a mechanism of apoptotic cell death, and that the effect is not mediated exclusively through the glucocorticoid pathway. Wang, J.H., Charboneau, R., Barke, R.A., Loh, H.H., and Roy, S. Mu-Opioid Receptor Mediates Chronic Restraint Stress-Induced Lymphocyte Apoptosis. Journal of Immunology, 169, pp. 3630-3636, 2002.

Stress-Induced Suppression of the Immune System after Withdrawal from Chronic Cocaine

Recent evidence suggests that withdrawal from cocaine shares similarities to the stress response. In this study, the investigators examined whether withdrawal from chronic cocaine produces immune system alterations and whether the hypothalamic-pituitary-adrenal axis is involved. Male Sprague-Dawley rats received daily cocaine injections (10 mg/kg i.p.) for or saline for 7 days, followed by 2 h, 1, 2, 4, 6, and 14 days of withdrawal. Proliferation responses of peripheral blood lymphocytes to concanavalin A were significantly suppressed and persisted for up to 6 days during withdrawal from chronic cocaine. Flow cytometric analysis revealed no significant differences in the immunophenotype of blood lymphocytic populations of T cells, B cells, or monocytes at 2 or 6 days of withdrawal from cocaine. Consistent with the suppression in cellular immunity observed in the in vitro response, the in vivo delayed-type hypersensitivity response was also significantly decreased in cocaine withdrawing animals. Plasma corticosterone levels were significantly elevated after cessation of cocaine but returned to basal values by 2 days of withdrawal. The suppressive effects of cocaine withdrawal were no longer observed in either adrenalectomized animals or those treated with the glucocorticoid receptor antagonist mifepristone (RU486), when administered during the first 2 days of withdrawal. These data argue that repeated exposure to cocaine followed by withdrawal leads to an activation of the neuroendocrine stress response, which alters cellular immunity during the initial withdrawal phase and may contribute to an increased susceptibility to infection. Avila, A.H., Morgan, C.A., and Bayer, B.M. Stress-Induced Suppression of the Immune System after Withdrawal from Chronic Cocaine. Journal of Pharmacology and Experimental Therapeutics, 305, pp. 290-297, 2003.

Dual Infection Processes and Opiates

An aspect of disease that is often overlooked are problems associated with multiple infections. However, a recent paper describes experiments examining the effects of opiates on the growth of two disease viruses in culture. Infection of injection drug users (IDUs) with the human T-cell leukemia viruses (HTLVs) or HIV is considerably higher than in the non-IDU population. Also, coinfection with HIV-1 and HTLV type 1 (HTLV-1) occurs more frequently. There is little or no information on the effects of opiates (i.e., morphine) on HTLV infection alone or on coinfection of HTLV-1-infected cells with HIV-1. Therefore, the authors analyzed the in vitro effects of morphine on HIV or HTLV infection alone as well as on dual infection with both viruses. Morphine decreased the in vitro levels of interferon-gamma (IFN-gamma) and IL-2 during single infections, and this effect was reversed by the addition of the opioid antagonist naloxone. In contrast, treatment with morphine resulted in a 31% and 36% increase in IFN-gamma and IL-2 levels, respectively, during dual infection. In addition, naloxone had an apparent additive effect on the morphine-associated enhancement of IFN-gamma and IL-2 expression in the dual-infection model. Despite the high levels of IFN-gamma expression, the viability of the coinfected cells in the presence of morphine was maintained. Importantly, morphine treatment was associated with augmented viral reverse transcription activity in dually infected cultures, apparently to the benefit of HTLV-1. If a similar putative morphine-induced advantage for HTLV-1 production also occurs during in vivo coinfection, opiates such as morphine could contribute to the observed increased rate of HIV-1/HTLV-1 infection in the IDU population in a more direct fashion than was previously believed. Nyland, S.B., Cao, C.H., Bai, Y., Loughran, T.P., and Ugen, K.E. Modulation of Infection and Type 1 Cytokine Expression Parameters by Morphine during in vitro Coinfection with Human T-cell Leukemia Virus Type I and HIV-1. Journal of Acquired Immune Deficiency

Syndromes, 32, pp. 406-416, 2003.

A Contingent Payment Model of Smoking Cessation

This study characterized nicotine withdrawal during a 5-day period. Smokers were assigned to one of two contingent monetary groups or a control group. Subjects provided CO samples 3 times/day (morning, afternoon, evening), with completion of subjective questionnaires following the evening sampling. Subjects in the contingent groups had significantly lower CO and salivary cotinine levels, regardless of amount paid. Subjects in the contingent groups reported increased withdrawal symptoms, including increased anxiety and restlessness, hunger, and desire to smoke. The investigators concluded that contingent payment procedures may provide an effective method for studying nicotine withdrawal in smokers. Heil, S.H., Tidey, J.W., Holmes, H.W., Badger, G.J. and Higgins, S.T. A Contigent Payment Model of Smoking Cessation: Effects on Abstinence and Withdrawal. Nicotine and Tobacco Research, 5(2), pp. 205-213, 2003.

Director's Report to the National Advisory Council on Drug Abuse - September, 2003

Research Findings - Behavioral Research

Neurotoxicity Produced by High Dose METH may Enhance Subsequent Psychostimulant Reinforcement

NIDA-grantee, Dr. Michael Bardo, and colleagues at the University of Kentucky have followed up on earlier studies investigating the behavioral consequences of a neurotoxic regimen of methamphetamine (METH) treatment in the rat. They note that previous investigations showing decreases in central dopamine (DA) are paralleled by deficits in active avoidance, balance beam performance, and the Morris water maze task. Animals treated with such a dosing regimen also have decreased locomotor activity in response to acute METH. However, the functional consequences of high dose METH treatment in central transmitter systems that subserve drug reward are presently unknown. To address this question, the researchers treated rats with four injections of D-METH HCl (10 mg/kg each), separated by 2 hours between injections. In the first neurochemical study, rats were sacrificed 15 days later and it was determined that DA was significantly depleted in the nucleus accumbens (NAS) and striatum; and serotonin (5-HT) was significantly depleted in the NAS, striatum and prefrontal cortex. In the second study, locomotor response to challenge doses of 0.1, 0.3 or 1.0 mg/kg METH, and the development of a conditioned place preference (CPP) to this stimulant, was assessed at 5 days post high-dose treatment. Unlike previous reports in the literature, locomotor activity measured during four conditioning sessions in the CPP apparatus was no different for animals previously treated with neurotoxic doses of METH or with saline. Rats treated with saline before the CPP training was begun developed a preference for the side of the box paired with 1.0 mg/kg METH. However, rats that underwent a neurotoxic dosing schedule with high-dose METH prior to CPP also showed a significant place preference to the side paired with a lower METH dose (0.3 mg/kg). These findings suggest that the neurochemical alterations induced by neurotoxic doses of METH enhance sensitivity to the drug's rewarding properties, when assessed using responses to incentive motivational stimuli (i.e., the environmental cues previously paired with drug). The authors suggest that an upregulation of DA receptors (compensatory to DA terminal loss), or depletion in 5-HT systems that are inhibitory on central reward systems, may be responsible. Further investigation is needed to extend these findings to other models of drug reinforcement per se, and explore the underlying mechanism responsible for this behavioral effect. Gehrke, B.J., Harrod, S.B., Cass, W.A. and Bardo, M.T. The Effect of Neurotoxic Doses of METH on METH-Conditioned Place Preference in Rats. Psychopharmacology, 166, pp. 249-257, 2003.

Perinatal Lead Exposure and Relapse to Drug-Seeking Behavior in the Rat: A Cocaine Reinstatement Study

Prior work published by Dr. Jack Nation and his colleagues at Texas A&M University has shown that perinatal lead exposure enhances cocaine-induced locomotor sensitization. He now reports that perinatal lead exposure enhances cocaine reinstatement, measured in a paradigm that is regarded to be a preclinical model of drug-seeking and relapse. Female rats were gavaged with either 0 or 16 mg lead prior to mating and this exposure procedure was continued through gestation and postnatal day 21. At postnatal day 120, male offspring were trained to self-administer cocaine. Following acquisition of steady-state responding, cocaine restatement was assessed over a 5-hour session in which cocaine self-administration occurred during the first hour, extinction via replacement of cocaine with saline occurred in hours 2-4, followed by a priming i.p. injection of either 0.00, 5.00, 10.00, or 20.00 mg/kg cocaine with assessment of drug-induced reinstatement in hour 5. During hour 5, both the lead-exposed and non-lead-exposed rats exhibited a dose-related increase in saline

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responding, indicative of "drug-seeking" behavior elicited by environmental cues previously paired with drug reward. The lead-exposed group, however, exhibited more saline responding than the non-lead-exposed group following priming doses of 5.00 and 10.00 mg/kg. These results indicate that low levels of lead exposure during gestation and lactation are associated with enhanced vulnerability to cocaine relapse in response to reintroduction of the drug cue. In the same paper, Dr. Nation cites unpublished data from his research program showing that adult rats with a history of perinatal lead exposure self-administer more low-dose cocaine than non-lead-exposed rats. The mechanism underlying perinatal lead exposure's effects on cocaine sensitivity and vulnerability in adulthood is not known, but Dr. Nation suggests that it could be mediated by lead's direct effects on maternal behavior or by lead's direct effects on the pups which then modulate maternal behavior. Such early pup/dam behavioral interactions could alter motivational circuits expressed in adulthood as enhanced cocaine vulnerability. In view of human data indicating that lead exposure during pregnancy and lactation can produce significant developmental and neurological abnormalities, the present data are particularly important, especially given that 1999 survey data shows approximately 70% of inner-city children have "unsafe" blood lead levels and that this percentage is even higher for urban minority children. Nation, J.R., Cardon, A.L., Heard, H.M., Valles, R., and Bratton, G.R. Perinatal Lead Exposure and Relapse to Drug-Seeking Behavior in the Rat: A Cocaine Reinstatement Study. Psychopharmacology, 168, pp. 236-243, 2003.

The Effects of Alprazolam and Buspirone in Light and Moderate Female Social Drinkers

Benzodiazepines are prescribed to women almost twice as often as men. Additionally, women are more likely than men to become dependent on sedatives. Ongoing laboratory-based research by Dr. Suzette Evans and her colleagues at Columbia University is investigating sub-populations of women who may be at risk for anxiolytic abuse. One such population is moderate social drinkers. Several laboratory-based studies have shown a relationship between the positive reactions to the anxiolytic diazepam (a benzodiazepine) and degree of alcohol use. Those studies, however, did not examine data separately for females nor did they control for a family history of alcoholism. In the present study, Dr. Evans and her colleagues compared the subjective and cognitive/motor performance reactions to the anxiolytic benzodiazepine alprazolam (0.25, 0.50, 0.75 mg) in 14 female light social drinkers who consumed four drinks per month and 14 female moderate social drinkers who consumed 36 drinks per month. All subjects were non-drug abusing, without substance abuse problems, and had no first- or second-degree family history of alcoholism. Buspirone (5, 10, 15 mg), a non-benzodiazepine anxiolytic of low abuse liability and minimal performance effects, was studied as a comparison drug. The researchers found that the two anxiolytics produced similar cognitive/motor impairment. The impairment was dose-related for alprazolam, but not buspirone. Both anxiolytics produced greater "Drug Liking" and "Good Drug Effect" in moderate drinkers than in light drinkers. The moderate drinkers, but not the light drinkers, however, also reported more positive reactions to the placebo. These data suggest that female social drinkers may be more likely have enhanced psychoactive drug expectancies and to report positive subjective reactions that can contribute to vulnerability for addiction. Evans, S.M. and Levin, F.R. The Effects of Alprazolam and Buspirone in Light and Moderate Female Social Drinkers. Behavioural Pharmacology, 13, pp. 427-439, 2002.

Beta-Endorphin and Enkephalin Knock-Out Mice Show a Selective Reduction in Incentive Motivational Value of Food Rewards

Dr. Malcolm Low and colleagues have recently published an elaborate series of NIDA-funded investigations to determine how endogenous opioids modulate natural rewards. They tested groups of mice who were either B-end (beta-endorphin) deficient, met- and leu-enkephalin deficient, double knock-out, or male wild-type in progressive ratio (PR) procedures to obtain "normal", "sweet", or "fat" food pellets for bar press responses in an operant chamber. All three knock-out groups responded significantly less for food reward than their wild-type counterparts, when maintained on ad libitum feeding conditions. Thus, break-points (the number of operant responses an animal is "willing" to make to earn a food reward) were significantly less for these three knock-out groups. While there was a gradient for food preference of these three types of pellets, there was no difference in preference over the four groups. By contrast, when tested in PR procedures at 75-85% of their previous free-feeding body weights, all four groups responded for the three types of pellets with break-points that were not significantly different. The authors conclude that these endogenous opioid systems play a role in incentive motivational properties of food, or

the hedonic quality of the food, rather than being important for caloric regulation or homeostatic balance. This was true even with three different food rewards that differ in palatability. In additional experiments, the Principal Investigator (PI) also was able to show that knock-out mice could work just as hard for food on a FR schedule (hence, were not motorically impaired), did not make more inappropriate responses on the inactive lever than their wild-type controls (thus, learned the operant task), and in a similar one-hour test session, all groups continued to bar press at an equivalent rate for food and consumed pellets throughout the session (suggesting that knock-out groups did not satiate sooner). Because PR schedules use an extinction criterion as an endpoint, the PI also conducted an independent assessment of resistance to extinction. In this study, he found that all four groups showed the same extinction curve when responding under a PR schedule. These separate control studies strengthen the investigators' interpretation of differences between knock-out and wild-type mice during PR operant testing under food satiation conditions. Thus, these endogenous opioid systems seem to be important for appetitive aspects of behavior directed toward food rewards, rather than for consummatory behaviors per se. Hayward, M.D., Pintar, J.E. and Low, M.J. Selective Reward Deficit in Mice Lacking B-Endorphin and Enkepahlin. J. Neurosci., 22, pp. 8251-8258, 2002.

Effects of THC on Behavioral Measures of Impulsivity in Humans

Drugs of abuse have been associated with poorly controlled, maladaptive behaviors that have been described as impulsive. Research on the effects of drugs of abuse on impulsive behavior has been hampered, in part, because there is no universally accepted measure of impulsivity. The purpose of the present study was to examine the effects of THC on four behavioral measures of impulsivity in male and female recreational marijuana users. The four tasks were: The Stop task, which measures the ability to inhibit a prepotent motor response; a Go/No-Go task, which involves reward/punishment conflict and the ability to inhibit a punished response; a Delay Discounting task, which measure the value of delayed or uncertain reinforcers; and a Time Estimation task, which measures alterations in time perception. Subjects also completed mood questionnaires and general measures of performance. Results indicated that THC produced increases in euphoria and responses on the marijuana scales of the ARCI (Addiction Research Center Inventory). In addition, THC increased impulsive responding on the Stop task, but had no effect on the Go/No-Go task or the Delay Discounting task. THC decreased patterns of impulsive responding on the Time Estimation task. There were no effects of gender alone or in interaction with the four tasks. There were no significant correlations among the four measures of impulsivity, suggesting that multiple processes underlie impulsive behavior, and that THC affects some, but not all, of these processes. These findings emphasize the importance of using multiple measures when investigating impulsive behavior. To say that drugs of abuse affect impulsivity, without specifying how impulsivity is measured, may not give an accurate or meaningful description of the drug's effects. Mcdonald, J., Schleifer, L., Richards, J.B., and deWit, H. Effects of THC on Behavioral Measures of Impulsivity in Humans. Neuropsychopharmacology, 28, pp. 1356-1365, 2003.

Repeated Exposure to Nicotine Facilitates Reward-Related Learning

Repeated exposure to drugs of abuse causes neuroadaptive changes in brain circuits that may comprise the neurobiological substrate for incentive-motivational processes and reward-related learning. Drug-induced alterations may contribute to the process of drug addiction because the combination of enhanced incentive motivation (i.e., increased salience of drug-associated cues), and increased stimulus control over behavior by drug-associated cues, can drive compulsive drug-seeking and drug-taking. The present study investigated the effects of repeated exposure to nicotine on the acquisition and performance of a Pavlovian discrimination task. Water deprived rats were trained to associate a light/tone CS (conditioned stimulus) with the presentation of a water reward in 15 consecutive sessions. Approach to the CS and the water served as the measure of learning. Separate groups of rats were repeatedly treated with nicotine (0.35 mg/kg, s.c.) either (1) prior to the onset of training, (2) after each daily training session, or (3) both prior to onset of training and after each daily training session. Results indicated that all nicotine treatment schedules increased discriminative approach behavior. This work demonstrates that systemic nicotine administration facilitates appetitively motivated stimulus-reward learning in the rat, and suggests that nicotine augments the control over behavior by reward-associated stimuli. These results contribute to understanding nicotine abuse and addiction since smoking-related cues elicit craving and can trigger relapse during nicotine abstinence. Olausson, P., Jentsch, J.D., and Taylor, J.R. Repeated Nicotine Exposure Enhances Reward-Related Learning in the Rat. Neuropsychopharmacology, 28, pp. 1264-1271, 2003.

Prolonged Deficits in Associative Learning for Natural Rewards Following Opiate Withdrawal

Opiate abuse has been associated with cognitive deficits in human addicts. To determine if prior opiate exposure alters the ability to learn, Dr. Glenda Harris and Dr. Gary Aston-Jones tested animals during morphine withdrawal in several learning tasks for food reward. The first experiment involved learning to press a bar for food. During a 2-week period after withdrawal, morphine-abstinent rats were significantly slower at learning an escalating fixed-ratio response for food reward compared to placebo-treated animals. In another experiment, morphine-abstinent rats withdrawn 2 or 5 weeks were tested for their ability to associate a highly palatable food reward with a specific environment using a place-conditioning paradigm. At 2 weeks post-withdrawal, morphine-abstinent rats did not show any significant place preference for a food they readily consumed, while placebo-treated rats readily learned to prefer the food-paired environment. At 5 weeks post-withdrawal, abstinent rats developed significantly less preference for food-associated cues, but more preference for morphine-associated cues, compared to placebo-treated animals. The results of these two experiments indicate that, during protracted abstinence, animals are slower to learn to respond for food reward, and slower to learn about environmental cues that predict food reinforcement, while at the same time they readily learn about cues that are predictive of morphine reward. To determine whether the learning deficits of withdrawn animals was limited to the positive reinforcement of natural rewards, animals from the first experiment were also trained in a conditioned suppression paradigm (two tone-shock pairings given in the operant box). Morphine-withdrawn animals were not impaired in this aversive conditioning, and in fact showed greater retention than control animals. The results of these experiments are consistent with hypotheses implicating post-withdrawal dysregulation of hedonic processing as a factor that may compromise the ability of former addicts to overcome their addictions. Harris, G.C. and Aston-Jones, G. Altered Motivation and Learning Following Opiate Withdrawal: Evidence for Prolonged Dysregulation of Reward Processing. Neuropsychopharmacology, 28, pp. 865-871, 2003.

Rats in Withdrawal from Amphetamine Show Increased Impulsivity and Impaired Inhibitory Control

Impulsivity is thought to contribute to relapse to drug abuse. The prefrontal cortex (PFC) is involved in the inhibitory control of impulsive behavior, and the dopaminergic input to PFC is critical for this function. A previous collaborative electrophysiological study from the laboratories of Drs. Frank White and Marina Wolf at the Chicago Medical School showed that the inhibitory effect of dopamine on the firing rate of medial PFC neurons was reduced in rats following repeated amphetamine treatment. They have followed up with a behavioral study to determine if impulsivity is increased after amphetamine treatment. They used a behavioral task called differential reinforcement for low rates of responding (DRL30), in which rats are trained to inhibit a nose poke response for 30 seconds, after which a nose poke results in food reward. An inactive hole was also provided to assess non-specific effects on overall nose poking behavior. After training, the rats received 5 days of daily saline or amphetamine injections. Following 3 days of withdrawal, performance on the DRL30 task was tested for 9 days. Throughout the 9 days, nose poking by amphetamine-withdrawn animals was elevated compared to saline controls, significantly so on withdrawal days 3, 6, and 7. On the first day of post-withdrawal testing, but not on subsequent days, previously amphetamine- treated animals also nose poked more often in the inactive hole. Amphetamine pretreatment also increased the number of times rats nose poked before the 30 seconds were up; that is, made a greater number of responses that were not reinforced in this paradigm. Therefore, previous drug treatment significantly reduced "training efficiency," defined as the percent of nose pokes that result in reward. The DRL task has been used in a wide variety of studies and is thought to reveal a specific aspect of impulsiveness, termed inhibitory control -- the ability to inhibit or delay a voluntary behavior. The results of this experiment, combined with the previous results, suggest that this aspect of impulsivity is increased during amphetamine withdrawal as a result of disruption of dopamine function in the medial PFC. Peterson J.D., Wolf M.E., and White F.J. Impaired DRL 30 Performance During Amphetamine Withdrawal. Behavioural Brain Research 143, pp. 101-108, 2003.

Cannabinoid Exposure Alters Vocal-Motor Learning in a Songbird

Song learning in birds is an established model system that has been used to study the neurobiology of critical period learning and sensori-motor development. Song is learned in two stages: first, a young bird memorizes the song of an adult "tutor" and

then later, during a period equivalent to adolescence, it begins to vocalize and practices its song until it is a near match to the tutor song. At that point, the song becomes "crystallized" and is usually produced in a highly stereotyped manner for the rest of the bird's life. Dr. Ken Soderstrom has been exploiting this system to investigate the role of endocannabinoids and the effects of exogenous cannabinoids in this well-defined type of learning. Previously, Dr. Soderstrom and his co-investigator, Dr. Frank Johnson found that the CB1 cannabinoid receptor is densely expressed in areas of the songbird brain known to be involved in song learning and production. Now they have shown that daily cannabinoid exposure at modest doses during the adolescent period alters song learning, while the same treatment has no effect on already-learned song in the adult. They compared the songs of pairs of birds that had been exposed to the same tutor and then either injected with the cannabinoid agonist WIN55212-2 or vehicle for 50 days. Vehicle-treated birds developed a normal song with, on average, about 8 different syllable types sung in stereotyped motifs. In contrast, the adult songs of birds treated with WIN55212-2 had an average of only about 6 song syllables, contained abnormally repeated notes, and were less stereotyped than the songs of vehicle-treated birds, even though they were no longer being exposed to cannabinoid agonist. The altered vocal learning in the cannabinoid-treated animals may be the result of effects on neural development, mechanisms of learning, or both. These effects of cannabinoids on coordinated perceptual-motor learning may be parallel to their effects on striatal processes in mammals. The songbird model, for which the brain structures and behavioral contingencies of song learning are well-characterized, may provide insight into the neural mechanisms of endocannabinioids and the disruptive effects of marijuana on specific types of learning. Soderstrom, K. and Johnson, F. Cannabinoid Exposure Alters Learning of Zebra Finch Vocal Patterns. Developmental Brain Research, 142, pp. 215-217, 2003.

Director's Report to the National Advisory Council on Drug Abuse - September, 2003

Research Findings - Treatment Research and Development

Effect of Smoking Reduction on Later Cessation: A Pilot Experimental Study

It is unclear whether reducing the number of cigarettes in smokers not trying to quit increases or decreases the likelihood of future quitting. Investigators at the University of Vermont conducted a pilot study in which smokers not currently interested in quitting (n=67) were randomized to two groups. Experimental participants received behavioral treatment and NRT (choice of gum, patch, or inhaler) to reduce smoking by 50% over 4 weeks, followed by brief advice to quit. Usual-care participants receive only brief advice to quit and NRT if they decided to quit. The results suggest that adding a reduction option neither increases nor undermines interest in cessation. Higher than expected rates of attempted cessation and quitting in the usual-care group suggest that recruited smokers had above average motivation to quit. Thus, a replication test in a less-motivated group of smokers is needed. Carpenter, M.J., Hughes, J.R. and Keely, J.P. Nicotine and Tobacco Research, 5(2), pp. 155-162, April 2003.

Ethnic Differences in Smoking Withdrawal Effects Among Adolescents

At the University of Memphis, smoking withdrawal effect information was collected from 75 adolescents making a quit attempt during a school-based smoking cessation program. A strong need to smoke was the most common withdrawal effect, followed by irritability and difficulty concentrating. Most participants experienced two or more withdrawal effects during the quit attempt, and withdrawal effects were evident in those smoking less than daily. Significant ethnic differences were found, with African Americans reporting significantly fewer withdrawal effects than Caucasians. After controlling for smoking frequency, African Americans were still less likely to report irritability, difficulty concentrating, and restlessness. Participants who chose to use nicotine replacement during the quit attempt were more likely to report difficulty concentrating, restlessness, and feeling miserable. Reidel, B.W., Robinson, L.A., Klesges, R.C. and McLain-Allen, G. Addictive Behaviors, 28(1), pp. 129-140, 2003.

Correlates of Substance Use Disorder Among Psychiatric Outpatients: Focus on Cognition, Social Role Functioning and Psychiatric Status

Dr. Kate Carey and her colleagues at Syracuse University conducted this study that compared psychiatric outpatients who were never, former, and current substance abusers on psychiatric, social, and cognitive functioning. Fifty-six outpatients with schizophrenia spectrum and bipolar disorders volunteered to complete diagnostic and social role function interviews, self-report inventories, and neuropsychological tests. Multinomial logic regression analyses indicated that current and former substance abusers reported greater subjective feelings of distress than those who never abused substances. Contrary to expectations, however, both groups of substance abusers performed better on nonverbal cognitive tests compared with those who never abused. Differences in social functioning were also observed: former abusers demonstrated better instrumental role functioning than those who never abused substances. These findings challenge assumptions about the additive effects of comorbid disorders on cognitive and social functioning. Carey, K.B., Carey, M.P., and Simons, J.S. Journal of Neurological and Mental Disorders, 191(5), pp. 300-308, May 2003.

Comparative Profiles of Women with PTSD and Comorbid Cocaine or Alcohol Dependence

Drs. Back, Sonne, Killeen, Dansky, and Brady, at the Medical University of South

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Carolina examined the differences in substance abuse severity, trauma history, posttraumatic stress disorder (PTSD) symptomatology and psychiatric comorbidity among treatment-seeking women (N=74) with PTSD and either comorbid cocaine or alcohol dependence. Women in the cocaine/PTSD group, compared with the alcohol/PTSD group, demonstrated greater occupational impairment (e.g., greater severity on the employment subscale of the Addiction Severity Index, less monthly income, fewer days worked in the past month), more legal problems (e.g., greater number of months incarcerated and arrests for prostitution), and greater social impairment (e.g., fewer number of close friends, less likely to be married). Women in the alcohol/PTSD group evidenced higher rates of exposure to traffic accidents, other situations involving serious injury, and other stressful life events. Rates of major depression and social phobia were higher among the alcohol/PTSD group than the cocaine/PTSD group. Women in the alcohol/PTSD group scored higher on the CAPS avoidance, hyperarousal, and total subscale scores. These findings enhance our understanding of the substance-specific profiles of women with PTSD and comorbid substance use disorders, and may have important implications for the design of treatment interventions for substance abusing women with co-occurring psychiatric disorders. Back, S.E., Sonne, S.C., Killeen, T., Dansky, B.S., and Brady, K.T. American Journal of Drug and Alcohol Dependence, 29(1), pp. 169-189, 2003.

Cognitive Impairment, Retention, and Abstinence Among Cocaine Abusers in Cognitive-Behavioral Treatment

In this study Dr. Efrat Aharonovich and her colleagues at Columbia University examined the relationship between cognitive impairment and two treatment outcomes, cognitive-behavioral therapy completion and drug abstinence among cocaine dependent individuals involved in a clinical trial that consisted of once weekly individual, manualized cognitive-behavioral therapy plus medication (either gabapentin or placebo). Cognitive-behavioral therapy (CBT) depends on adequate cognitive functioning in patients, but prolonged cocaine use may impair cognitive functioning. In this study 18 carefully screened non-depressed cocaine dependent patients in a psychopharmacological clinical trial were administered the MicroCog computerized battery to assess cognitive performance at treatment entry. T-tests were used to compare cognitive functioning between completers (patients remaining in treatment at least 12 weeks) and dropouts. The results indicated that the treatment completers demonstrated significantly better cognitive performance at baseline than patients who dropped out of treatment. Abstinence from cocaine use also appeared to be related to cognitive functioning, as patients with high cognitive proficiency scores had significantly more negative urines than patients with low cognitive proficiency scores. Cognitive domains that significantly distinguished between treatment completers and dropouts were attention, mental reasoning and spatial processing. This study provides preliminary evidence that impairments in cognitive functioning may impede the ability of chronic cocaine abusers to benefit from cognitive-behavioral therapy. Aharonovich, E., Nunes, E., and Hasin, D. Drug and Alcohol Dependence, 71(1), July 2003.

Data Entry Productivity Improved by Increasing Reinforcer Magnitude

Conrad Wong, Ken Silverman and colleagues at The Johns Hopkins University examined data entry productivity in drug abusers participating in the therapeutic workplace program, a behavioral treatment program which requires submission of a drug free urine in exchange for entry into a employment environment. Using an ABA reversal design, these investigators examined the effects of reinforcement magnitude on a group of people who had not responded well to monetary reinforcement for data entry productivity. Of six participants tested, four showed the highest rates of responding in the high magnitude reinforcement condition. The two participants with the lowest overall response rates, showed less robust changes to the magnitude manipulation. These findings suggest that therapeutic workplace productivity may be improved by increasing reinforcer magnitude. Wong, C.J., Sheppard, J.M., Dallery, J., Bedient, G., Robles, E., Svikis, D. and Silverman, K. Effects of Reinforcer Magnitude on Data-Entry Productivity in Chronically Unemployed Drug Abusers Participating in a Therapeutic Workplace, Experimental and Clinical Psychopharmacology, 11 (1), pp. 46-55, 2003.

Contingency Management Intervention Helps People with Antisocial Personality Disorder

Richard Rawson and colleagues at UCLA Integrated Substance Abuse Programs examined the retention of methadone maintained drug abusers with and without Antisocial Personality Disorder (ASP) in four treatment conditions: standard methadone maintenance, contingency management, cognitive behavioral therapy,

and cognitive behavioral therapy plus contingency management and found a strong effect of treatment condition on outcome for those with antisocial personality disorder. This effect was largely due to a strong response to the contingency management interventions by individuals with ASP who were more likely to abstain from cocaine use when reinforced for abstinence with a voucher. These findings suggest that interventions like contingency management that provide timely reinforcement for treatment participation may be an efficacious way to engage individuals with ASP. Messina, A., Farabee, D. and Rawson, R. Treatment Responsivity of Cocaine-dependent Patients with Antisocial Personality Disorder to Cognitive-Behavioral and Contingency Management Interventions. Journal of Consulting and Clinical Psychology, 17 (3), pp. 320-329, 2003.

Pregnant Women With Drug-Using Partners Have Poorer Treatment Outcomes

Hendree Jones and a colleague at Johns Hopkins University School of Medicine surveyed pregnant women enrolled in a comprehensive treatment program for addiction regarding their male partners and found that 50% of their partners used drugs. Additionally, results showed that male drug-using partners had more unemployment, current legal involvement and less education than drug-free partners. Additionally, male drug-using partners were less likely to be supportive of the pregnant woman's recovery efforts and more likely to give them money to buy drugs. Treatment retention data indicated that women with drug-using partners are retained in treatment for a shorter time. Findings suggest treatments that target the drug-using male partners may improve treatment outcomes for women with such partners. Tuten, M. and Jones H.E. A Partner's Drug-Using Status Impacts Women's Drug Treatment Outcome. Drug and Alcohol Dependence, 70 (1), pp. 327-330, 2003.

Wives of Substance-Abusing Men are at Risk of Exposure to HIV

Dr. Fals-Stewart and colleagues at the Research Institute on Addictions and the San Diego VA Medical Center assessed the HIV risk behaviors of 144 men in treatment for substance abuse and their wives. Almost all wives (96%) reported having sexual intercourse with their husbands during the year before treatment, and of these, 78% reported not regularly using condoms during intercourse. Of all husbands in the study, 40% reported engaging in risky behaviors, including having unprotected sex with a partner other than their wives, and/or engaging in risky needle practices. Almost three-fourths of wives (71%) reported they were not aware of their husbands' risky behaviors, and so unknowingly were at indirect risk for HIV. These results suggest the need for effective HIV risk reduction strategies for married couples in which husbands abuse drugs. Fals-Stewart, W., Birchler, G.R., Hoebbel, C., Kashdan, T.B., Golden, J., and Parks, K. An Examination of Indirect Risk of Exposure to HIV among Wives of Substance-abusing Men. Drug and Alcohol Dependence, 70, pp. 65-76, 2003.

Behavioral Family Counseling Improves Naltrexone Adherence and Substance Abuse Outcomes

Dr. Fals-Stewart at the Research Institute on Addictions and Dr. O'Farrell at Harvard University studied the impact of Behavioral Family Counseling on naltrexone adherence and substance abuse among 124 opioid-dependent men and their family members. All patients were prescribed 50mg/day naltrexone, and a platform treatment of weekly individual and group counseling. Patients were randomly assigned to either Behavioral Family Counseling (in which a family member participated by observing and reinforcing the patient's ingestion of naltrexone), or to Treatment-As-Usual (in which patients attended individual sessions weekly with a counselor to discuss compliance with the naltrexone). Men receiving BFC had significantly higher naltrexone adherence, treatment attendance, and rates of abstinence than men receiving TAU. This study adds to the evidence that behavioral treatments involving family members can improve outcomes of pharmacological treatments for drug abuse. Fals-Stewart, W. and O'Farrell, T.J. Behavioral Family Counseling and Naltrexone for Male Opioid-Dependent Patients. Journal of Consulting and Clinical Psychology, 71, pp. 432-442, 2003.

Latent Cognitive Abilities of Drug-Abusing Patients and Associated Risk Factors

Dr. Fals-Stewart at the Research Institute on Addictions and Dr. Bates at Rutgers conducted a study to clarify the latent structure of the neuropsychological abilities of drug-abusing patients. Using the results of a battery of 15 neuropsychological screening instruments, an exploratory factor analysis was conducted on 329 patients

entering drug abuse treatment, and followed with a confirmatory factor analysis with a subsequent 258 patients entering treatment. A multi-factor solution fit the data best, with four factors emerging: Executive Functioning, Verbal Ability, Speed, and Memory. Drug-related factors associated with scores in these four domains included number of years of substance use disorders, years of regular alcohol use, and percentage of days of heavy drinking in the past year. The results of this study contribute methodological tools for further studying cognitive functioning among drug-abusing patients, and suggest potential risk factors for key aspects of cognitive functioning for this population. Fals-Stewart, W. and Bates, M.E. The Neuropsychological Test Performance of Drug-Abusing Patients: An Examination of Latent Cognitive Abilities and Associated Risk Factors. Experimental and Clinical Psychopharmacology, 11, pp. 34-45, 2003.

Cognitive Behavior Group Therapy (CBT) and Psychoeducation Group Therapy (PET) for Adolescent Substance Abusers

A total of 88 adolescents were randomly assigned to 8 weeks of CBT or PET for treatment of substance abuse. On average, adolescents in both treatment groups significantly improved in terms of drug use, based on self reported use (Teen-Addiction Severity Index) and objective urinalysis. While there were no significant overall differences between 3-month and 9-month drug outcomes for adolescents in CBT or PET, variables such as age and the presence of comorbid Conduct Disorder predicted differential success in treatment. These findings highlight the need for additional refinement of CBT group therapy for adolescent drug abuse, and the importance of including mediation and moderation analyses in treatment studies. Kaminer, Y., Burleson, J.A. and Goldberger, R. Cognitive-behavioral Coping Skills and Psychoeducation Therapies for Adolescent Substance Abuse. Journal of Nervous and Mental Disease, 190, pp. 737-745, 2002.

Gambling Behavior in Adolescent Substance Abusers

Dr. Kaminer and colleagues from the University of Connecticut assessed the gambling behavior of 97 adolescents receiving outpatient treatment for substance use disorders. In this sample, 34% had never gambled, 57% were classified as non-pathological gamblers, 8% were identified as "in transition" gamblers, and 1% met criteria for pathological gambling. Adolescent boys were more likely to gamble than girls, and younger age of onset of gambling behavior was associated with being female, history of suicide attempts, more symptoms of Cluster B personality disorders, and other factors. Importantly, none of the gambling adolescents had ever been referred for treatment. While these findings suggest that the prevalence of gambling behavior among substance abusing adolescents is similar to a non-substance abusing population, they also suggest that identification and treatment of problematic gambling behavior is not being adequately addressed for this population. Kaminer, Y., Burleson, J.A.and Jadamec, A. Gambling Behavior in Adolescent Substance Abusers. Substance Abuse, 23, pp. 191-198, 2002.

Identifying Active Ingredients of Double Trouble in Recovery Self-Help Groups

Dr. Magura of the National Development and Research Institute and colleagues conducted a study of potential active ingredients in self-help groups for substance abusing adults with co-morbid psychiatric disorders (Double Trouble in Recovery). These researchers interviewed members of 24 DTR groups at baseline and then re-interviewed participants 12 months later. Of the three ingredients hypothesized to be important elements of self-help treatment--the therapeutic value of assuming a helper role, reciprocal learning among group members, and provision of emotional support--both the helper role and reciprocal learning were related to drug abuse outcomes, but emotional support was unrelated to outcomes. These results suggest areas of emphasis for self-help treatments in order to streamline treatment and maximize success. Magura, S., Laudet, A.B., Mahmood, D., Rosenblum, A., Vogel, H.S. and Knight, E.L. Role of Self-Help Processes in Achieving Abstinence Among Dually Diagnosed Persons. Addictive Behaviors, 28, pp. 399-413, 2003.

Mediators of Abstinence Outcomes for Double Trouble in Recovery Self-Help Groups

Dr. Magura of the National Development and Research Institute and colleagues compared several mediation models of treatment outcome. Specifically, the researchers tested the degree to which two common factors (internal locus of control and sociability) and two treatment-specific factors (spirituality and instillation of hope) mediated the relationship between 12-step group affiliation and outcomes (drug use

and health promoting behavior). Interviews with members of 24 DTR self-help groups at baseline and at 12-month follow-up revealed that internal locus of control and sociability mediated the relationship between 12-step affiliation and both outcomes, whereas spirituality and the instillation of hope mediated only the relationship between 12-step affiliation and health promoting behavior. The authors argue that these results suggest an explanation for the effectiveness of 12-step self-help treatments that may be more acceptable to addiction and mental health professionals because of its roots in well-documented social learning principles. Magura, S., Knight, E.L., Vogel, H.S., Mahmood, D., Laudet, A.B. and Rosenblum, A. Mediators of Effectiveness in Dual-Focus Self-Help Groups. The American Journal of Drug and Alcohol Abuse, 29, pp. 301-322, 2003.

Brief Strategic Family Therapy (BSFT) and Group Therapy for Treating Adolescent Behavior Problems and Substance Abuse

Dr. Santisteban and colleagues at the University of Miami tested the relative efficacy of BSFT and group therapy among 126 Hispanic adolescents referred for treatment for behavior problems. BSFT cases showed significantly greater pre- to post-intervention improvement in parent reports of adolescent conduct problems and delinquency, adolescent reports of marijuana use, and observer ratings and self reports of family functioning. Adolescents participating in BSFT showed significantly greater improvement in adolescent conduct problems and delinquency, marijuana use, and family functioning. Further, more adolescents in group therapy had deteriorations in behavior problems, drug use, and family functioning. These results extend prior findings on the efficacy of family interventions to a sample of Hispanic adolescents. Santisteban, D.A., Coatsworth, J.D., Perez-Vidal, A., Kurtines, W.M., Schwartz, S.J., LaPerierre, A. and Szapocznik, J. Journal of Family Psychology, 17, pp. 121-133, 2003.

Error-Rate-Related Caudate and Parietal Cortex Activation During Decision-Making

Dr. Martin Paulus and colleagues at the University of California, San Diego used fMRI during performance of a two-choice prediction task to investigate the relationship between error-rate related behavioral changes during decision-making and activation patterns in the caudate and parietal cortex. Activation in the caudate and parietal cortex was related to success-rates. At low error rates, participants utilized success-related behavioral strategies by decreasing switching responses and increasing response predictability, which were associated with activation changes in the caudate and parietal cortex. Therefore, less response switching and increased response predictability during decision-making can be directly related to the degree of activation in the caudate and posterior parietal cortex. Verney, S.P., Brown, G.G., Frank, L. and Paulus, M.P. Neuroreport, 14(7), pp. 923-928, May 2003.

Cognitive Efficiency in Stimulant Abusers With and Without Alcohol Dependence

Dr. Sara Nixon and colleagues at the University of Oklahoma investigated whether concurrent stimulant and alcohol abuse had a synergistic effect on cognitive ability. The study sample included detoxified men and women who met criteria for dependence of (a) alcohol only (ALC)m stimulants only (STIM) (n = 15), and both alcohol and stimulants (A/STIM) along with age- and education-matched community controls. Subjects were tested in a cognitive battery that included tasks that measured visual spatial skills, problem solving and abstraction, short-term memory, cognitive flexibility, and gross motor speed were administered to participants. For each test, both speed and accuracy were assessed and an efficiency ratio (accuracy/time) was derived. An overall performance index of cognitive efficiency was calculated from the average of these efficiency ratios. Controls performed statistically significantly better in relation to the A/STIM and STIM groups ($p < 0.01$), but not the ALC group. Individual comparisons revealed that the ALC group performed significantly better than the STIM group, although the ALC group did not differ from either the control or A/STIM groups (p£ 0.05). These findings suggest that the cognitive effects of chronic stimulant abuse are not additive with those of alcohol abuse. That is, singly addicted stimulant abusers demonstrated similar or greater neurocognitive impairments than individuals who abuse alcohol and stimulants concurrently. The reason for this pattern is speculative but may be attributed to alcohol's opposing actions on cerebrovascular effects brought on by stimulant abuse. Lawton-Craddock, A., Nixon, S.J. and Tivis, R. Alcoholism-Clinical and Experimental Research, 27(3), pp. 457-464, March 2003.

Multinuclear Magnetic Resonance Spectroscopy of High-Energy Phosphate

Metabolites in Human Brain Following Oral Supplementation of Creatine-Monohydrate

Dr. Perry Renshaw and colleagues at McLean Hospital, Harvard Medical School investigated whether treatment for cocaine dependence would improve cerebral energy metabolism in the frontal lobes of cocaine abusers. Relative concentrations of phosphocreatine (PCr) and creatine (Cr) were used as markers for cerebral energy metabolism. Relative PCr and Cr levels were derived from T-2 relaxation times in 1H Magnetic Resonance Spectroscopy (1H-MRS). Cocaine dependent (CD) subjects were studied before and after 8 weeks of cocaine dependence treatment. At baseline, left frontal lobe ratios of PCr/Cr were 0.406+/-0.081 in CD subjects and 0.411+/-0.016 in comparison subjects. After treatment, these ratios increased 14.3% (0.464 vs. 0.406; p=0.006) in CD subjects, remaining unchanged in comparison subjects (2.9%, 0.399 vs. 0.411; p=0.480). At baseline, PCr levels of non-responders were 17.8% lower (0.375 vs. 0.442; p=0.042) than those of responders, defined as 25% decrease in urine cocaine metabolites. After treatment, CD subjects had increased PCr levels: 18.4% (0.444 vs. 0.375; p=0.035) for non-responders and 10.4% (0.488 vs. 0.442; p=0.092) for responders. These results are consistent with decreased cerebral metabolism during treatment, measured as increased PCr. This is the first report using H-1 MRS T-2 relaxometry to measure a change in human brain energetics. Lyoo, I.K., Kong, S.W., Sung, S.M., Hirashima, F., Parow, A., Hennen, J., Cohen, B.M. and Renshaw, P.F. Psychiatry Res., 123(2), pp. 87-100, June 2003.

Early-Onset Cannabis Use and Cognitive Deficits: What is the Nature of the Association?

Drs. Harrison Pope, Deborah Yurgelun-Todd, and colleagues at McLean Hospital, Harvard Medical School investigated whether individuals who initiate cannabis use at an early age, when the brain is still developing, might be more vulnerable to lasting neuropsychological deficits than individuals who begin use later in life. The study sample included both heavy cannabis users (n=122) and subjects (n=87) with minimal cannabis exposure. All subjects underwent a 28-day period of abstinence from cannabis, monitored by daily or every-other-day observed urine samples. Early-onset cannabis users were compared with late-onset users and with controls, using linear regression controlling for age, sex, ethnicity, and attributes of family of origin. Early-onset users (who began smoking before age 17) differed significantly from both the late-onset users (who began smoking at age 17 or later) and from the controls on several measures, most notably verbal IQ (VIQ). Few differences were found between late-onset users and controls on the test battery. However, after adjusting for VIQ, virtually all differences between early-onset users and controls on test measures ceased to be significant. The findings indicate that early-onset cannabis users exhibit poorer cognitive performance than late-onset users or control subjects, especially in VIQ, but the cause of this difference cannot be determined from the present data. The difference may reflect (1) innate differences between groups in cognitive ability, antedating first cannabis use; (2) an actual neurotoxic effect of cannabis on the developing brain; or (3) poorer learning of conventional cognitive skills by young cannabis users who have eschewed academics and diverged from the mainstream culture. Pope, H.G., Gruber A.J., Hudson, J.I., Cohane, G., Huestis, M.A. and Yurgelun-Todd D. Drug And Alcohol Dependence, 69(3), pp. 303-310, April 2003.

Influence of Acetylcholine Levels on the Binding of a SPECT Nicotinic Acetylcholine Receptor Ligand [I-123]5-I-A-85380

Dr. Giles Tamagnan and colleagues at Yale School of Medicine used SPECT imaging to determine whether increases in acetylcholine (ACh) levels induced by an acetylcholinesterase inhibitor, physostigmine, inhibit in vivo binding of [I-123]5-iodo-3-(2(S)-2-azetidinyl-methoxy) pyridine (5-I-A-85380), ligand for the high-affinity type nicotinic ACh receptor (nAChR). Baboons were used for seven studies with a bolus plus constant infusion equilibrium paradigm. After achieving equilibrium at 5 h, physostigmine (0.02 (n=1), 0.067 (n=3), and 0.2 (n=3) mg/kg) was administered intravenously and data were acquired for up to 8 h. To confirm equilibrium conditions, [I-123]5-I-A-85380 plasma levels were measured in four studies, including all studies with 0.2 mg/kg physostigmine. Prior to physostigmine administration, thalamic activities were stable, with changes of 1.1%/h or less, except in one study with a gradual increase of 4.2%/h. Thalamic activities were decreased by 15% in one study with 0.067 mg/kg and 14-17% in all studies with 0.2 mg/kg physostigmine administration (P=0.009). In these studies with 0.2 mg/kg physostigmine administration, [I-123]5-I-A-85380 plasma levels showed a transient or a sustained increase after physostigmine administration that would have increased thalamic activities. These results suggest that elevated ACh levels induced by physostigmine

can effectively compete in vivo with [I-123]5-I-A-85380 binding at nAChRs. However, decreased thalamic activities could have been caused by other mechanisms, including internalization of the receptor with an associated decreased affinity for radioligand. Fujita M., Al-Tikriti, M.S., Tamagnan, G., Zoghbi, S.S., Bozkurt, A., Baldwin, R.M. and Innis R.B. Synapse, 48(3), pp. 116-122, June 2003.

Arterial Spin Labeling Perfusion fMRI with Very Low Task Frequency

Dr. John Detre and colleagues at the University of Pennsylvania investigated whether arterial spin labeling (ASL) perfusion contrast MRI was superior to the more commonly used blood oxygenation level-dependent (BOLD) contrast for studies involving slow or low frequency neural activation. Drug administration studies and exposure to videotape stimuli in cue-reactivity studies would be examples of slow or low-frequency events that are difficult to study with BOLD fMRI because baseline drift effects result in poor sensitivity for detecting slow variations in neural activity. On the other hand, drift effects are minimized in arterial spin labeling (ASL) perfusion contrast, primarily as a result of successive pairwise subtraction between images acquired with and without labeling. Recent data suggest that ASL contrast shows stable noise characteristics over the entire frequency spectrum, which makes it suitable for studying low-frequency events in brain function. The present study investigated the relative sensitivity of ASL and BOLD contrast in detecting changes in motor cortex activation over a spectrum of frequencies of experimental design, where the alternating period between the resting state and activation is varied from 30 s up to 24 hr. The results demonstrate that 1) ASL contrast can detect differences in motor cortex activation over periods of minutes, hours, and even days; 2) the functional sensitivity of ASL contrast becomes superior to that of BOLD contrast when the alternating period between the resting state and activation is greater than a few minutes; and 3) task activation measured by ASL tends to have less intersubject variability than BOLD contrast. The improved sensitivity of the ASL contrast for low task frequency and longitudinal studies, along with its superior power for group analysis, is expected to extend the range of experimental designs that can be studied using fMRI. Wang, J.J., Aguirre, G.K., Kimberg, D.Y., Roc, A.C., Li, L. and Detre J.A., Magnetic Resonance In Medicine, 49(5), pp. 796-802, May 2003.

Cognitive Effects of the Dopamine Receptor Agonist Pergolide

Dr. Mark D'Esposito of University of California, Berkeley investigated the effects of dopamine agonists on human cognitive performance. The effects of a single dose of pergolide on a variety of cognitive tests, including tests of memory and of frontal/executive function were tested in young healthy subjects. Across this battery of tasks, the only tasks reliably affected by pergolide were delayed response tasks. Across four variants, the authors observed that the effect of pergolide was more beneficial for subjects with greater working memory capacities. Kimberg D.Y. and D'Esposito M., Neuropsychologia, 41(8), pp. 1020-1027, 2003.

Temporal Prediction Errors in a Passive Learning Task Activate Human Striatum

Dr. Gregory Berns and colleagues at Emory School of Medicine and Baylor School of Medicine used fMRI to investigate whether the striatum participates in processing information about the predictability of rewarding stimuli. The present study sought to determine whether the striatum primarily processes information about stimuli that are unpredictable in character (what stimulus arrives next), unpredictable in time (when the stimulus arrives), or unpredictable in amount (how much arrives). Using a passive conditioning task and fMRI in human subjects, the authors found that positive and negative prediction errors in reward delivery time correlated with BOLD changes in human striatum, with the strongest activation lateralized to the left putamen. For the negative prediction error, the brain response was elicited by expectations only and not by stimuli presented directly; that is, striatal activation occurred when juice was expected but not delivered rather than when nothing was expected and nothing delivered. McClure, S.M., Berns, G.S., and Montague, P.R., Neuron 38(2), pp. 339-346, April 2003.

Sex-Related ERP Differences in Deviance Detection

Dr. Geoffery Potts and colleagues at Rice University used dense sensor array (128 channel) event-related potential recordings (ERPs) to examine the effect of sex on neural mechanisms of auditory mismatch detection. ERPs of 32 right-handed subjects (16 males) were recorded to frequent (85%, 880 Hz) and infrequent (15%, 1480 Hz) tones. There were no sex differences in mismatch negativity (80-180 ms), however, the fronto-central P2 (180-260 ms) was less positive in males ($F=12.56$, $P<0.005$)

and the N2 (260-340 ms) was more negative in males ($F=6.28$, $P<0.05$). The increased negativity in males spanning the P2 and N2 may index a top-down process of attention bias towards novelty. This result supports the hypothesis of an adaptive, sexually dimorphic processing of novel events in humans. Nagy, E., Potts, G.F. and Loveland, K.A., International Journal of Psychophysiology, 48(3), pp. 285-292, June 2003.

Orbitofrontal Cortex Dysfunction in Abstinent Cocaine Abusers

This NIDA supported study tested for structural (i.e., tissue composition) abnormalities that could underlie the cognitive deficits in executive function seen in cocaine abusers. To determine white and gray matter densities, voxel-based morphometry of T1-weighted brain scans were evaluated in cocaine abusers and non-drug user controls. There were no group differences in frontal cortex white matter; however, gray matter density in the cocaine users was significantly reduced in the frontal, medial and lateral orbitofrontal and middle/dorsal cingulate gyrus in the right hemisphere cortices. The results corroborate and extend previous findings of defective frontal cortical activation (indexed by cerebral blood flow) in cocaine abusers to include other brain areas not previously described. Bolla, K.I., Eldreth, D.A., London, E.D. Kiehl, K.A., Mouratidis, M., Contoreggi, C., Matochik, J.A., Kurian, V., Cadet, J-L., Kimes, A.S., Funderburk, F.R., and Ernst, M. Orbitofrontal Cortex Dysfunction in Abstinent, Cocaine Abusers Performing a Decision-Making Task. NeuroImage, 19(3), pp. 1085-1094, July 2003.

Frontal Cortical Tissue Composition in Abstinent Cocaine Abusers

Cocaine abusers exhibit impairment of executive cognitive functions that are mediated by the frontal cortex. This work tested for structural (i.e., tissue composition) abnormalities that may underlie such performance deficits. Abstinent for 20 days, cocaine abusers ($n = 14$) and a non-drug-using comparison group ($n = 11$) underwent magnetic resonance imaging (T1-weighted scans of the brain). Gray matter and white matter tissue densities were determined and results demonstrated cocaine abusers had significantly lower gray matter tissue density than did the non-drug users in 10 of 13 small volumes analyzed in the frontal cortex. No group differences were found in white matter density of the frontal cortex. These results extend previous findings of defective frontal cortical activation (indexed by cerebral blood flow) in cocaine abusers to include abnormalities in gray matter tissue density in the same frontal cortical regions. Matochik, J.A., London, E.D., Eldreth, D.A., Cadet, J-L, and Bolla, K.I. Frontal Cortical Tissue Composition in Abstinent Cocaine Abusers: A Magnetic Resonance Imaging Study. NeuroImage, 19(3), pp. 1095-1102, July 2003.

Predictor of Cocaine's Euphoric Effects

This study evaluated the association between negative affective symptoms during initial abstinence and euphorigenic response to experimentally administered cocaine. Cocaine-dependent individuals, after achieving 5 days of abstinence in a hospital setting, were administered 40mg of cocaine intravenously on the fifth day of abstinence, and were asked to rate the subjective effects produced by the drug. The associations between irritability, self-reported depression, and the subjective ''high'' produced by cocaine were evaluated. Increased levels of irritability and depression were significantly positively correlated with heightened response to experimentally administered cocaine as indexed by self-reported subjective ''high.'' The positive association between irritability and subjective ''high'' remained after controlling for self-reported depressive symptoms. The opponent process model predicts that increased levels of negative affect should be associated with administered euphoric response to cocaine; however, the opposite was observed. If these findings are replicated in a larger sample, then it may be necessary to reconsider the applicability of the opponent process model to cocaine addiction in humans. Newton, T.F., Kalechstein, A.D., Tervo, K.E., and Ling, W. Irritability Following Abstinence from Cocaine Predicts Euphoric Effects of Cocaine Administration. Addictive Behaviors, 28(4), pp. 817-821, June 2003.

Methamphetamine Dependence is Associated with Neurocognitive Impairment in the Initial Phases of Abstinence

This study documented the association between neurocognitive impairment and methamphetamine (METH) dependence in a sample of 27 METH dependent individuals who achieved 5 to 14 days of continuously monitored abstinence and in 18 control subjects. METH-dependent individuals performed significantly worse than control subjects on neurocognitive measures sensitive to attention/psychomotor speed, on

measures of verbal learning and memory, and on executive systems measures sensitive to fluency. These findings are the first to demonstrate that METH dependence is associated with impairments across a range of neurocognitive domains in a sample of users whose abstinence was continuously monitored with the use of urine screening. Kalechstein, A.D., Newton, T.F., and Green. M. Methamphetamine Dependence is Associated with Neurocognitive Impairment in the Initial Phases of Abstinence. Neuropsychiatry Clinical Neuroscience, 15, pp. 215-220, May 2003.

Self-Regulated Dosing of Morphine Resulted in Increased Total Consumption in a Rat Model

Kreek and associates at Rockefeller University provided an experimental session whereby rats could increase their dosage of morphine by choosing a lever that delivered a larger amount of morphine that increased if the rat persisted in choosing that lever. The comparison group could experience only a fixed amount with every selection. However, while there was an increase in total consumption, there was not an increase in rate. This pattern is a good model for dose escalation in the human situation where rate does not increase but total consumption does. In addition, [35S]GTP_S binding was significantly lower in the self-escalating group of rats, suggesting receptor desensitization following morphine stimulation. Kruzich, P.J., Chen, A.C.H., Unterwald, E.M. and Kreek, M.J. Synapse, 47, pp. 243-249, 2003.

Relapse was Significantly Reduced with Buprenorphine and Relapse-Prevention Therapy in Treatment-Seeking Heroin Addicts

Dr. Kakko and other investigators working with Mary Jeanne Kreek in Sweden focused on patients who would not qualify for methadone treatment in Sweden. Accordingly, patients could be ethically randomized into buprenorphine and placebo groups (20 each) and followed for one year. Both groups received relapse-prevention therapy. All of the subjects in the placebo group dropped out of treatment after drug use was demonstrated by urinanalysis. By contrast, only 25% dropped out of the buprenorphine group, most of whom had drug-free urines throughout the period. In addition, the treatment group members who were still participating were assessed for improvement in addiction severity and found to have significantly improved. The results suggest that buprenorphine and intensive psychosocial treatment is safe and highly efficacious to add to the arsenal of potential treatments for heroin dependence. Kakko, J., Svanborg, K.D., Kreek, M.J., and Heilig, M. The Lancet, 361, pp. 662-668, 2003.

Depression is Not Necessarily Counter-Indicative for Smoking Cessation

Dr. Hitsman and colleagues at Brown University completed a meta-analysis study to determine if smokers with a lifetime history of depression are less likely to be successfully treated to quit smoking than those who have no history of depression. Fifteen studies of 2,984 smokers published between 1966-2000 included assessments of both history of depression and smoking cessation outcome. Only two of thirteen studies showed a significant association between history of depression and abstinence of three months or less; only one of twelve showed that history of depression was associated with abstinence of six months or more. In addition, the depression-abstinence association did not differ between females and males at either time point. Hitsman, B., Borelli, B., McCargue, D.E., Spring, B., and Niaura, R. Journal of Consulting and Clinical Psychology, 71(4), pp. 657-663, 2003.

Up- and Down-Regulation of Genes in Rat Caudate Putamen After Binge Cocaine Administration

Using microarrays in triplicate (deemed far superior to single arrays) investigators at Rockefeller University demonstrated 21 up-regulated genes that were immediate early genes for transcription factors, effecter proteins, and a number of phosphatases. Down-regulation was seen for 17 genes including many associated with energy metabolism in mitochondria. Also found was a differential expression of somatostatin receptor (SSTR2) (not know to be cocaine-response, as well as the clock gene Per2. Yuferov, V., Kroslak, T., LaForge, K.S., Zhou, Y.H., Ho, A., and Kreek, M.J. Synapse, 48, pp. 157-169, 2003.

Sex Differences were Found in Limbic Responsiveness Using a Procaine Challenge and Assessed by SPECT

Dr. Adinoff and colleagues at University of Texas Southwestern Medical Center administered procaine by slow intravenous infusion to healthy female and male volunteers (controls for other studies) and compared the resultant stimulation to saline infusion. In between group comparisons of the relative increases in regional

cerebral blood flow, females had a significantly greater increase in the left amygdala while males had a significantly greater increase in the left insula and marginally greater increase in the right insula. In both instances, the significant increase was relative since both males and females had significant increases following procaine relative to saline -- for females the increase was considerable greater in the amygdala while in males it was in the insula. Subjective differences to the procaine were assessed but were not found to be different between the sexes. This study is among the first to demonstrate differential limbic responsiveness to pharmacological challenge. It remains to be demonstrated whether this reflects the differential emotional responses often reported in the literature. Adinoff, B., Devous, M.D., Sr., Best, S.E., Chadler, P., Alexander, D., Payne, K., Harris, T.S., and Williams, M.J. NeuroImage,18, pp. 697-706, 2003.

The Fetal Brain has a Different Pattern of Expression of Cannabinoid Receptor mRNA Compared to Adult

Yasmin Hurd at Karolinska Institute and colleagues at SUNY, Downstate have for the first time determined the expression of the cannabinoid receptor in the fetal (20 week) brain. While the adult brain showed high expression throughout the brain, expression in fetal brain was much more heterogeneous. The highest concentration was in the limbic structures of the hippocampus and amygdala. It is not clear what this might mean functionally; it is speculated that these might be the most vulnerable to prenatal exposure. Wang, X., Dow-Edwards, D., Keller, E., and Hurd, Y.L. Neuroscience, 118, pp. 681-694, 2003.

Preliminary Evidence for Linkage to Chromosomes 3 and 9 for Substance Dependence

Vulnerability M. Stallings and colleagues working in T. Crowley's center at the University of Colorado have performed a genome-wide search in treatment-referred adolescent volunteers. A phenotype was defined as the average number of dependence symptoms (total number for all illicit substances divided by the number of substances). Analyses revealed Lod "peaks" at 3q24-25 and 9q34 that are not far from locations reported previously by other researchers. A number of candidate genes are associated with these areas; it will remain for future work to replicate these results and assess the functionality of these candidate genes. Stallings, M.C., Corley, R.P., Hewitt, J.K., Krauter, K.S., Lessem, J.M., Mikulich, S.K., Rhee, S.H., Smolen, A., Young, S.E., and Crowley, T.J. Drug and Alcohol Dependence, 70, pp. 295-307, 2003.

Haplotypes at the OPRM1 Locus are Associated with Susceptibility to Substance Dependence

In the laboratory of Joel Gelernter at Yale University, a technique that investigated the relationship between various substance dependence profiles and gene variants revealed a significant associated between the allele -2044A (and haplotypes containing this allele) and patients with "alcohol plus opioid" dependence. This was true, however, only in European Americans. There was no difference between African American patients and controls, possibly reflecting frequency differences between these groups for the -2044A allele of the μ-opiate receptor gene (OPRM1). Whether these differences are "true" will depend on future studies with a greater number of subjects. For the time being, these data suggest that in European Americans, the OPRM1 may play a role in the pathophysiology of a diagnosis-specific form of substance dependence. Luo, X., Kranzler, H.R., Zhao, H., and Gelernter, J. American Journal of Medical Genetics Part B (Neuropsychiatric Genetics), 120B, pp. 97-108, 2003.

Stress Increases Cocaine Craving as well as HPA Axis and Sympatho-Adreno-Medullary Responses

Rajita Sinha of Yale University and colleagues measured physiological, hormonal, and subjective responses to cocaine-related and stress-related imagery in treatment-seeking individuals. Both stress and cocaine images induced activation of the hypothalamic-pituitary-adrenal axis determined by increases in plasma of ACTH, cortisol, prolactin as well as norepinephrine and epinephrine. Pulse rate and blood pressure also increased. These were largely correlated with increases in subjective ratings of craving and, to a lesser extent, anxiety. These data suggest that stress is a factor in inducing craving in recovering cocaine dependence and that stress and drug reward systems overlap with possible implications for treatment. Sinha, R., Talih, M., Malison, R., Cooney, N., Anderson, G.M. and Kreek, M.J. Psychopharmacology, (Epub ahead of print), July 4, 2003.

Attenuated Adrenocortical and Blood Pressure Responses to Psychological

Stress in Ad Libitum and Abstinent Smokers

Dr. al'Absi and colleagues examined the effects of ad libitum smoking and abstinence on adrenocortical and cardiovascular responses to acute psychological stress in dependent cigarette smokers. They evaluated differences among abstinent smokers, smokers who continued to smoke at their normal rate, and nonsmokers in salivary cortisol concentrations, systolic and diastolic blood pressure (BP), heart rate (HR), and mood reports. Measurements were obtained during rest and in response to acute psychological stress (public speaking) in one session (stress session) and during continuous rest in a control session. Thirty-eight smokers (21 women) and 32 nonsmokers (18 women) participated. Smokers were assigned to either abstain from smoking the night prior to and the day of each session, or to continue smoking at their normal rate before each session. All groups showed significant stress-induced changes in BP and HR. Smokers, regardless of their assigned condition, showed attenuated systolic BP responses to the public-speaking stressor when compared to nonsmokers. While resting cortisol levels were greater among smokers than nonsmokers, no cortisol response to the acute stressor was demonstrated in either ad libitum or abstinent smokers. These results indicate that chronic smoking diminishes adrenocortical and cardiovascular responses to stress, and that short-term abstinence does not correct these alterations. al'Absi, M., Wittmers, L.E., Erickson, J. et al. Attenuated Adrenocortical and Blood Pressure Responses to Psychological Stress in Ad Libitum and Abstinent Smokers. Pharmacol. Biochem. Behav., 74, pp. 401-410, 2003.

Nicotine Withdrawal and Depressive Symptomatology during Short-Term Smoking Abstinence: A Comparison of Postmenopausal Women Using and Not Using Hormone Replacement Therapy

This study investigated whether taking medications for transdermal hormone replacement therapy (HRT) influenced smoking-cessation variables in postmenopausal women undergoing short-term abstinence from cigarettes. Women were recruited into two groups according to their pre-enrollment medication status--those currently on HRT (n = 17) or those not on HRT (n = 13). The HRT group had their previous medication replaced with a standard 0.1 mg estradiol transdermal system and 2.5 mg of Cycrin daily. After 2 weeks of medication adjustment, participants continued smoking as usual for 1 week, at which time baseline measurements were taken. Participants were then instructed to quit smoking for the remaining 2 weeks. They were provided with smoking-cessation counseling and monitored for abstinence. Data were collected during five clinic visits on all dependent measures: Minnesota Nicotine Withdrawal Scale, Beck Depression Inventory (BDI) scale, Profile of Mood States, Motor Speed Tasks, and Reaction Time Test. Contrary to our hypothesis, the exogenous hormone use did not have a differential effect on most of the dependent variables during the first 2 weeks of smoking abstinence. One exception was depressive symptomatology: the BDI change scores (week 2 - baseline) differed significantly for the HRT and non-HRT groups ($p = .045$), with women in the HRT group experiencing an increase in depressive symptomatology. This finding, though preliminary, may have clinical implications for postmenopausal women who attempt to quit smoking while on HRT, particularly since depressed mood following abstinence is associated with a relapse to smoking. Allen, S.S., Hatsukami, D.K. and Christianson, D. Nicotine Withdrawal and Depressive Symptomatology During Short-Term Smoking Abstinence: A Comparison of Postmenopausal Women Using and Not Using Hormone Replacement Therapy. Nicotine. Tob. Res., 5, pp. 49-59, 2003.

"Outer-Directed Irritability": A Distinct Mood Syndrome in Explosive Youth With a Disruptive Behavior Disorder?

A sample (N = 20) of disruptive youth (aged 10-18 years) entering a divalproex treatment study of temper and irritable mood swings was compared to normal controls (N = 18) on measures of aggression/irritability directed against others (externalizing symptoms) and on aggression/ irritability against self, anxiety, and depression (internalizing symptoms). All patients met DSM-IV criteria for a disruptive behavior disorder (oppositional defiant disorder of conduct disorder) in addition to research criteria. "Outer-directed irritability" most clearly distinguished patients from controls (effect size 4.1) and did not correlate with other mood measures. Patients and controls showed no to minimal differences on internalizing symptoms. Disruptive behavior disordered children and adolescents characterized by outer-directed irritability exist, can be identified, and should be further investigated, especially since they are potentially treatable. Donovan, S.J., Nunes, E.V., Stewart, J.W. et al. "Outer-Directed Irritability": A Distinct Mood Syndrome in Explosive Youth with a Disruptive Behavior Disorder? J. Clin. Psychiatry, 64, pp. 698-701, 2003.

Lack of Effect of 5HT(3) Antagonist in Mediating Subjective and Behavioral

Responses to Cotinine

This study determined whether granisetron, a 5HT(3) receptor antagonist, would enhance the efficacy of the nicotine patch. Subjects were randomly assigned to one of the three granisetron conditions (N=43 for 2 mg/day; N=43 for 1 mg/day; N=42 for 0 mg/day) and asked to take the assigned medication daily during 15 days of tobacco abstinence. Because the investigators were interested in interactions between cotinine and serotonin, all groups were also treated with a 21-mg nicotine patch. Assessments of withdrawal symptoms were made for 1 week during baseline smoking and several times during the experimental period. There was a near but non-significant difference among groups on a measure of tobacco withdrawal and no significant differences on global measures of drug effects or physiological measures. The data do not strongly support the hypothesis that 5HT(3) agonism is the mechanism by which cotinine offsets the effects of nicotine. Hatsukami, D.K., Jensen, J., Brauer, L.H. et al. Lack of Effect of 5HT(3) Antagonist in Mediating Subjective and Behavioral Responses to Cotinine. Pharmacol. Biochem. Behav., 75, pp. 1-7, 2003.

Efficacy of Nicotine Patch in Smokers with a History of Alcoholism

One hundred fifteen smokers with a history of alcohol dependence (median of 5 years previously) were randomly assigned to either a 21-mg nicotine patch or placebo in a trial designed to be as similar as possible to a prior study that examined smokers with no history of alcoholism. Both studies were of heavy smokers with similar levels of nicotine dependence; thus, any differences in trials would be due to a history of alcohol problems per se. In the current trial, adjusted prolonged smoking abstinence in those with a history of alcohol dependence was higher in the active than the placebo group at end-of-treatment (28% vs. 11%; odds ratio, 3.2; $p = 0.04$) and at 6-month follow-up (24% vs. 6%; odds ratio, 4.9; $p = 0.02$). Among subjects not lost to follow-up, none reported drinking problems or increases in craving for alcohol. Smoking abstinence was not lower and the odds ratio for nicotine patch therapy was not greater in smokers with a history of alcohol dependence than in smokers with no such history. Heavy smokers with a history of alcoholism benefit from nicotine patch treatment. A history of alcohol problems after a period of stable sobriety does not appear to influence smoking outcomes or response to nicotine replacement. Although no smokers relapsed to alcohol use, a trial that follows up all subjects is needed to verify this. Hughes, J.R., Novy, P., Hatsukami, D.K. et al. Efficacy of Nicotine Patch in Smokers with a History of Alcoholism. Alcohol Clin. Exp. Res., 27, pp. 946-954, 2003.

Desipramine and Contingency Management for Cocaine and Opiate Dependence in Buprenorphine Maintained Patients

To test the efficacy of combining CM with these medications the investigators designed a 12-week, randomized, double blind, four cell trial evaluating DMI (150 mg/day) or placebo plus CM or a non-contingent voucher control in 160 cocaine abusers maintained on buprenorphine (median 16 mg daily). Cocaine-free and combined opiate and cocaine-free urines increased more rapidly over time in those treated with either DMI or CM, and those receiving both interventions had more drug-free urines (50%) than the other three treatment groups (25-29%). Self reported opiate and cocaine use and depressive and opioid withdrawal symptoms showed no differences among the groups and symptom levels did not correlate with urine toxicology results. Lower DMI plasma levels (average 125 ng/ml) were associated with greater cocaine-free urines. DMI and CM had independent and additive effects in facilitating cocaine-free urines in buprenorphine maintained patients. The antidepressant appeared to enhance responsiveness to CM reinforcement. Kosten, T., Oliveto, A., Feingold, A. et al. Desipramine and Contingency Management for Cocaine and Opiate Dependence in Buprenorphine Maintained Patients. Drug Alcohol Depend., 70, pp. 315-325, 2003.

Bupropion Treatment for Cocaine Abuse and Adult Attention-Deficit/Hyperactivity Disorder

Eleven patients who met DSM-IV diagnostic criteria for cocaine dependence and adult ADHD were entered into a 12-week single-blind trial of divided daily doses of bupropion (BPR). All patients received weekly individual standardized relapse prevention therapy. Treatment compliance and retention were good. Patients reported significant reductions in attention difficulties, hyperactivity and impulsivity. Self-reported cocaine use, cocaine craving, and cocaine positive toxicologies, also decreased significantly. In a previously published trial, 12 patients who met similar diagnostic criteria for adult ADHD and cocaine dependence were entered into a 12-week trial of divided daily doses of sustained-release methylphenidate (MPH). Improvements observed on BPR were similar to, and did not differ from those

previously observed with MPH. These preliminary data suggest that BPR may be as effective as sustained-release MPH, when combined with relapse prevention therapy, for cocaine abusers with adult ADHD. However, a future study directly comparing BPR to MPH in a double-blind placebo-controlled trial is needed. Levin, F.R., Evans, S.M., McDowell, D.M. et al. Bupropion Treatment for Cocaine Abuse and Adult Attention-Deficit/Hyperactivity Disorder. J. Addict. Dis., 21, pp.1-16, 2002.

Effect of Maternal Smoking on Fetal Catecholamine Concentrations at Birth

Pregnant women who were self-identified as smokers (>/=10 cigarettes per day throughout pregnancy) or nonsmokers were recruited for study participation. Maternal blood was collected for cotinine concentrations. Umbilical artery cord blood was collected at delivery for arterial pH and catecholamine concentrations. Cord blood was obtained from 51 subjects, including 21 smokers and 30 nonsmokers. Median epinephrine concentrations [304 pg/mL versus 597 pg/mL (Mann-Whitney U = 170; p = 0.006)] and median norepinephrine concentrations [3148 pg/mL versus 6558 pg/mL (Mann-Whitney U = 191; p = 0.006)] were significantly lower in smokers compared with nonsmokers, respectively. After controlling for gestational age, route of delivery, and arterial pH, log-transformed epinephrine concentrations between smokers and nonsmokers were statistically significant (p = 0.03), with a similar trend for log-transformed norepinephrine concentrations (p = 0.07). Analyses of the data using cotinine <20 ng/mL to classify nonsmokers also showed differences in epinephrine concentrations between groups (p = 0.02). These results are consistent with results from animal studies showing that catecholamine concentrations may be affected by prenatal nicotine exposure. Further studies are needed to validate these findings and to examine the specific mechanism by which these differences may arise. Oncken, C.A., Henry, K.M., Campbell, W.A. et al. Effect of Maternal Smoking on Fetal Catecholamine Concentrations at Birth. Pediatr. Res., 53, pp. 119-124, 2003.

Psychiatric and Substance Dependence Comorbidities, Sexually Transmitted Diseases, and Risk Behaviors Among Methamphetamine-Dependent Gay and Bisexual Men Seeking Outpatient Drug Abuse Treatment

This article describes psychiatric and substance dependence comorbidities, lifetime rates of infectious disease, and reported high-risk sexual behaviors for methamphetamine-dependent, gay and bisexual men at entry to outpatient drug abuse treatment in Los Angeles. A total of 82 participants met criteria for lifetime depressive disorders; 44 participants met criteria for lifetime anxiety disorders. Compared to those without psychiatric diagnoses, significant differences were observed in lifetime prevalence of sexually transmitted infections among those who have generalized anxiety disorder (higher rates of genital gonorrhea), specific phobia and major depressive disorder (higher rates of oral gonorrhea), social phobia (higher rates of syphilis) and bipolar disorder, type I (higher rates of HIV). Differences in infectious disease prevalence did not correspond to significantly different rates of high-risk sexual behaviors. Findings indicate that gay and bisexual men seeking outpatient treatment for methamphetamine dependence are likely to experience psychiatric comorbidity and to have high rates of infectious disease, including HIV, syphilis and gonorrhea. Shoptaw, S., Peck, J., Reback, C.J. et al. Psychiatric and Substance Dependence Comorbidities, Sexually Transmitted Diseases, and Risk Behaviors among Methamphetamine-Dependent Gay and Bisexual Men Seeking Outpatient Drug Abuse Treatment. J. Psychoactive Drugs, 35, Suppl 1, pp. 161-168, 2003.

Selegiline Enhances Smoking Cessation Rates in Nicotine-Dependent Cigarette Smokers

Since dopaminergic mechanisms appear to be involved in nicotine dependence, the investigators from the Yale Medical School examined the safety and efficacy of the monoamine oxidase B inhibitor selegiline hydrochloride and compared with placebo for smoking cessation in nicotine-dependent cigarette smokers. Forty subjects with DSM-IV nicotine dependence were randomized to selegiline hydrochloride (5 mg p.o. twice daily) or placebo in an 8-week trial. Outcome measures included smoking cessation rates, treatment retention, and medication side effects. Selegiline hydrochloride statistically significantly increased end point prevalence smoking cessation rates and smoking cessation rates during the last 4 weeks of the trial in comparison with placebo. Six-month follow-up smoking cessation rates were also greater for the selegiline group than for placebo. Treatment retention was similar between drug and placebo groups, and selegiline hydrochloride was well tolerated in cigarette smokers. George, T.P., Vessicchio, J.C., Termine, A., Jatlow, P.I., Kosten, T.R. and O'Malley, S.S. A Preliminary Placebo-Controlled Trial of Selegiline Hydrochloride for Smoking Cessation. Biol Psychiatry. 53(2), pp.136-143, January 15,

2003.

Neuroleptic Olanzapine Worsens Cocaine Treatment Outcome

Evidence suggests dopaminergic and serotonergic involvement in the reinforcing effects of cocaine. Olanzapine, which blocks dopamine D2 receptors, as well as serotonin receptors 5HT2A and 5HT2C, was anticipated to reduce the euphoric effects of cocaine and to attenuate cocaine craving. Therefore, it was tested for its ability to reduce cocaine use in cocaine dependent patients. Thirty patients received either olanzapine (10 mg/day) or identical placebo in a 12-week, double blind, placebo controlled, pilot trial. Outcome measures included treatment retention, qualitative urine benzoylecgonine tests, cocaine craving, clinical global impression scores, and results from the addiction severity index. Treatment retention was slightly, but significantly, better in the placebo-treated subjects and placebo-treated subjects were more likely to be abstinent from cocaine during the trial compared to olanzapine-treated subjects. Olanzapine was not superior to placebo in any outcome measure. The results do not support the usefulness of olanzapine for the treatment of cocaine dependence. Kampman, K.M., Pettinati, H., Lynch, K.G., Sparkman, T. and O'Brien, C.P. A Pilot Trial of Olanzapine for the Treatment of Cocaine Dependence. Drug Alcohol Depend., 70(3), pp. 265-273, June 5, 2003.

Modafinil Blunts Cocaine Euphoria

Modafinil, a novel medication for the treatment of narcolepsy, is now being studied as a potential treatment for cocaine dependence. The neurotransmitter actions of modafinil appear to be opposite to cocaine-induced neuroadaptations affecting GABA, dopamine and glutamate circuits. Safety of modafinil was tested in combination with intravenous cocaine (30 mg). Seven subjects received a baseline cocaine infusion. Three subsequent cocaine infusions were administered after subjects received 4 days of low dose modafinil (200 mg/day), high dose modafinil (400 mg/day), or placebo in randomized double-blind sequences. The results showed that co-administering modafinil and a single dose of intravenous cocaine is not associated with medical risk in terms of blood pressure, pulse, temperature, or electrocardiogram measures. Modafinil pretreatment did not intensify cocaine-induced craving, but significantly blunted cocaine euphoria. The results suggest that modafinil may potentially be an effective medication for the treatment of cocaine dependence. Dackis, C.A., Lynch, K.G., Yu, E., Samaha, F.F., Kampman, K.M., Cornish, J.W., Rowan, A., Poole, S., White, L. and O'Brien, C.P. Modafinil and Cocaine: A Double-Blind, Placebo-Controlled Drug Interaction Study. Drug Alcohol Depend. 70(1), pp. 29-37, May 1, 2003.

Buspirone Attenuates the Objective and Subjective Opiate Withdrawal Symptoms

Effectiveness of buspirone in attenuating opiate withdrawal symptoms in heroin addicts and methadone-maintained patients was examined in twenty hospitalized male chronic opiate users. For the first five days, patients received doses of methadone that were decreased to 30 mg and were maintained on this dose for the following three days. Methadone was then discontinued, and patients were randomly assigned to buspirone or placebo treatment from day nine to seventeen. The buspirone dose was 15 mg on day nine and 30 mg from day ten to day seventeen. Treatment was double-blind. Withdrawal symptoms were measured with the Objective Opiate Withdrawal Scale (OOWS) and the Subjective Opiate Withdrawal Scale (SOWS). Buspirone-treated patients had significantly lower scores on the OOWS on days thirteen ($p=.040$), fourteen ($p=.025$), fifteen ($p=.035$), and seventeen ($p=.035$). They also had lower scores on the SOWS on days sixteen ($p=.050$). Rose, J.S., Branchey, M., Wallach, L. and Buydens-Branchey, L. Effects of Buspirone in Withdrawal from Opiates. Am J Addict.,12(3), pp. 253-259, May-June 2003.

Low Plasma Cholesterol Levels are Associated with Greater Rates of Relapse in Detoxified Cocaine Addicts

Recent studies suggest an association of low plasma levels of cholesterol with various psychiatric disorders. The investigators explored relationships between cholesterol levels and relapse rates in a group of cocaine addicts who had undergone inpatient detoxification. The total cholesterol levels of 38 cocaine addicts were determined while they were hospitalized. Drug use was subsequently assessed 3, 6, and 12 months after patients were discharged from the hospital. Comparisons of the cholesterol levels of relapsers and nonrelapsers by analyses of covariance with age and weight as covariates revealed significantly lower cholesterol values in patients who relapsed at 3 months ($p =.046$), 6 months ($p =.030$), and 12 months ($p =.019$) after discharge. Buydens-Branchey, L. and Branchey, M. Association Between Low

Plasma Levels of Cholesterol and Relapse in Cocaine Addicts. Psychosom Med. 65(1), pp. 86-91, January-February, 2003.

Director's Report to the National Advisory Council on Drug Abuse - September, 2003

Research Findings - Research on AIDS and Other Medical Consequences of Drug Abuse - AIDS Research

Psychological Burden in the Era of HAART: Impact of Selenium Therapy

Shor-Posner and her colleagues at the University of Miami conducted a randomized, double-blind, placebo-controlled selenium therapy (200g/day) trial in HIV+ drug users to determine the impact of nutritional (selenium) chemo-prevention on levels of psychological burden (anxiety, depression, and mood state) in HIV/AIDS. Psychosocial measures (STAI-State and Trait anxiety, BDI-depression, and POMS-mood state), clinical status (CD4 cell count, viral load), and plasma selenium levels were determined at baseline and compared with measurements obtained at the 12-month evaluation in 63 participants (32 men, 31 women). Results showed that the majority of the study participants reported elevated levels of both State (68%) and Trait (70%) anxiety. Approximately 25% reported overall mood distress (POMS >60) and moderate depression (BDI > 20). Psychological burden was not influenced by current drug use, antiretroviral treatment, or viral load. At the 12-month evaluation, participants who received selenium reported increased vigor ($p = 0.004$) and had less anxiety (State, $p = 0.05$ and Trait, $p = 0.02$), compared to the placebo-treated individuals. No apparent selenium-related affect on depression or distress was observed. The risk for state anxiety was almost four times higher, and nearly nine times greater for trait anxiety in the placebo-treated group, controlling for antiretroviral therapy, CD4 cell decline (> 50 cells) and years of education. The authors concluded that selenium therapy may be a beneficial treatment to decrease anxiety in HIV+ drug users who exhibit a high prevalence of psychological burden. Shor-Posner, G., Lecusay, R., Miguez, M.J., Moreno-Black, G., Zhang, G., Rodriguez, N., Burbano, X., Baum, M.and Wilkie, F. Psychological Burden in the Era of HAART: Impact of Selenium Therapy, Int'l. J. Psychiatry in Medicine, 33, pp. 55-69, 2003.

The Association of Hepatitis C Prevalence, Activity, and Genotype with HIV Infection in a Cohort of New York City Drug Users

Factors associated with serum HCV antibody, HCV RNA level, and HCV genotype were assessed in 557 current and former drug users. Additional assays included HIV antibody, CD4+ lymphocyte counts, HIV viral loads, and hepatitis B markers. Seventy-five percent of subjects were anti-HCV positive, of whom 75% had detectable HCV RNA (median, 5.04 x 10(5) IU/mL; range, 1020-15.7 x 10(6)). On multivariate analysis HCV seropositivity was associated with history of drug injection, HIV seropositivity, and increased age and inversely with drug snorting. Among anti-HCV-positive persons, detectable HCV RNA was independently associated with HIV seropositivity, male gender, and history of injection and inversely associated with hepatitis B surface antigen positivity. Among persons with detectable HCV RNA, higher levels were independently associated with higher HIV viral load, increased age, and genotypes 2a and 2b. These findings demonstrate an association of HCV RNA level with HIV viral load, independent of the level of immunosuppression. However, a substantial degree of the person-to-person variability in the prevalence and level of detectable HCV RNA remains unexplained. Strasfeld, L., Lo, Y., Netski, D., Thomas, D.L. and Klein, R.S. J Acquir Immune Defic Syndr. 33(3), pp. 356-364, July 1, 2003.

Prevalence of and Risk Factors for Viral Infections Among Human Immunodeficiency Virus (HIV)-Infected and High-Risk HIV-Uninfected Women

Viruses that can persist in the host are of special concern in immunocompromised populations. Among 871 human immunodeficiency virus (HIV)-infected and 439 high-

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risk HIV-uninfected women, seroprevalences of cytomegalovirus, hepatitis B virus, hepatitis C virus, and herpes simplex virus types 1 and 2 and prevalence of human papillomavirus DNA in cervicovaginal lavage fluids were all >50% and were 2-30 times higher than prevalences in the general population. Prevalences were highest among HIV-infected women, of whom 44.2% had >or=5 other infections, and were relatively high even among the youngest women (age 16-25 years). In multivariate analyses, viral infections were independently associated not only with behaviors such as injection drug use and commercial sex but also with low income, low levels of education, and black race. Disadvantaged women and women who engage in high-risk behaviors are more likely to be coinfected with HIV and other viruses and, thus, may be at high risk of serious disease sequelae. Stover, C.T., Smith, D.K., Schmid, D.S., Pellett, P.E., Stewart, J.A., Klein,,R.S., Mayer, K., Vlahov, D., Schuman, P. and Cannon, M.J. HIV Epidemiology Research Study Group. J Infect Dis., 187(9), pp. 1388-1396, May 1, 2003. Epub April 15, 2003.

Clinical and Immunologic Progression in HIV-Infected US Women Before and After the Introduction of Highly Active Antiretroviral Therapy

The objective of this study was to examine factors associated with clinical and immunologic HIV disease progression in a cohort of US women. Data from a prospective, longitudinal, case-control study of HIV-infected women followed every 6 months for 7 years in four urban clinical centers in the United States were analyzed. Participants were 648 HIV-infected women who did not have AIDS at time of entry into the study. Structured clinical and behavioral interviews, protocol-directed physical examinations, CD4 lymphocyte counts, plasma HIV RNA, and infectious pathogen serologies were performed. With 2304 women-years of follow-up, 46.1% of the women developed AIDS; however, 93.3% of the diagnoses were based on CD4 counts dropping to <200 cells/mm3. Only 10.6% of the women with CD4 counts <200 cells/mm3 developed an opportunistic infection. Baseline CD4 count was the strongest predictor of subsequent clinical progression. Illicit substance use, multiple pregnancies, demographic variables, and other infections were not associated with progression. Among women with CD4 counts >500 cells/mm3 at baseline, those who were anemic or had hepatitis C were more likely to progress to AIDS. By the end of the study, only 52% of the participants were on highly active antiretroviral therapy (HAART). Despite underutilization of HAART in this multicenter cohort of urban women, opportunistic infections were uncommon, despite CD4 declines. Mayer, K.H., Hogan, J.W., Smith, D., Klein, R.S., Schuman, P., Margolick, J.B., Korkontzelou, C., Farzedegan, H., Vlahov, D. and Carpenter, C.C. HIV Epidemiology Research Study (HERS) Group. J Acquir Immune Defic Syndr. 33(5), pp. 614-624, August 15, 2003.

Home Intervention for Mothers and their Drug-Exposed Infants

This longitudinal randomized cohort study assessed the effects of a home intervention and ongoing maternal drug use on developmental outcomes of drug-exposed infants. Participants included 108 low-income, inner-city, drug-exposed children and their biological mothers (control, 54; intervention, 54). Results suggest that, compared to control infants, intervention infants had significantly higher Bayley Scales of Infant Development (BSID) Mental Development Index (MDI), and BSID Psychomotor Developmental Index (PDI) scores during the first 18 months post partum. Furthermore, ongoing maternal drug use was associated with worse developmental outcomes for both groups. Schuler, M.E., Nair, P., and Kettinger, L. Drug Exposed Infants and Developmental Outcome: Effects of a Home Intervention and Ongoing Maternal Drug Use. Archives of Pediatrics & Adolescent Medicine, 157, pp. 133-138, 2003.

Increased Density of Neurons Containing NADPH Diaphorase and Nitric Oxide

Synthase in the Cerebral Cortex of Patients with HIV-1 Infection and Drug Abuse To determine whether nitrogen monoxide (nitric oxide; NO) synthase (NOS) and NADPH diaphorase (NDP) co-containing cerebrocortical neurons (NOSN) are affected in patients infected with human immunodeficiency virus type 1 (HIV 1) with and without associated intake of drugs of abuse, authors examined the temporal neocortex of 24 individuals: 12 HIV-1 positive (including 3 drug users, 9 non-drug users) and 12 HIV-1 negative (including 6 drug users and 6 non-drug users). Histochemical labeling for NDP-an enzymatic domain co-expressed in the NOS enzyme was employed to visualize NOSN. Drug abuse and HIV-1 infection cause independently an increase in NOSN density, but combined they result in up to a 38-fold increase in NOSN density, suggesting that the combination of these factors induces NOS expression powerfully in neurons that normally do not synthesize NDP/NOS. This is associated with an increase in the proportion of NOSN displaying dystrophic changes, indicating that NOSN undergo massive degeneration in association with NOS synthesis induction. The

increase in density of NOSN in HIV-1 infected drug abusers may be among the important sources of NO mediating cerebrocortical dysfunction, and the degeneration of NOS containing local circuit neurons in patients with HIV-1 infection or drug abuse may underlie in part their neuropsychiatric manifestations. Kuljis, R.O., Shapshak, P., Alcabes, P., Rodr'guez, de la Vega, P., Fujimura, R. and Petito, C. Journal of NeuroAIDS. 2(3), pp. 19-36, 2002.

The Role of Macrophase/Microglia and Astrocytes in the Pathogenesis of Three Neurologic Disorders: HIV Associated Dementia, Alzheimer's Disease, and Multiple Sclerosis

Macrophage/microglia (M∅) are the principal immune cells in the central nervous system (CNS) concomitant with inflammatory brain disease and play a significant role in the host defense against invading microorganisms. Astrocytes, as a significant component of the blood -- brain barrier, behave as one of the immune effecter cells in the CNS as well. However, both cell types may play a dual role, amplifying the effects of inflammation and mediating cellular damage as well as protecting the CNS. Interactions of the immune system, M∅, and astrocytes result in altered production of neurotoxins and neurotrophins by these cells. These effects alter the neuronal structure and function during pathogenesis of HIV-1 associated dementia (HAD), Alzheimer disease (AD), and multiple sclerosis (MS). HAD primarily involves subcortical gray matter, and both HAD and MS affect sub-cortical white matter. AD is a cortical disease. The process of M∅ and astrocytes activation leading to neurotoxicity share similarities among the three diseases. Human Immunodeficiency Virus (HIV)-1 infected M∅ are involved in the pathogenesis of HAD and produce toxic molecules including cytokines, chemokines, and nitric oxide (NO). In AD, M∅s produce these molecules and are activated by _-amyloid proteins and related oligopeptides. Demyelination in MS involves M∅ that become lipid laden, spurred by several possible antigens. In these three diseases, cytokine chemokine communications between M∅ and astrocytes occur and are involved in the balance of protective and destruction actions by these cells. This review describes the role of M∅ and astrocytes in the pathogenesis of these three progressive neurological diseases, examining both beneficent and deleterious effects in each disease. Minagar, A., Shapshak, P., Fujimura R., Ownby, R., Heyes, M., and Eisdorfer, C. Journal of the Neurological Sciences, 202, pp. 13-23, 2002.

Brain Macrophage Surface Marker Expression with HIV-1 Infection and Drug Abuse: A Preliminary Study

The goal of this study was to determine the heterogeneity of surface marker expression of macrophages in the temporal lobe of patients who died with AIDS who were also drug abusers (DAs). Authors studied the expression of macrophage surface markers CD11c, CD14, CD68, and HLA-DR and T cell surface markers CD4 and CD8. The macrophage is the prime locus for HIV-1 associated pathology, the most frequently infected cell in the brain, and has the highest virus load compared to other cells. The current authors previously described the heterogeneity of macrophage surface maker expression and performed morphometric analysis in peripheral nerves of patients who died from AIDS compared to HIV-1 negative individuals and showed that the HIV-related neuropathy in AIDS is a multifocal process. It is similarly important to determine the expression of macrophage surface markers in brain. Temporal lobe tissue was selected for this preliminary study because authors previously found elevated HIV-1 proviral DNA load and inflammatory processes in this neuroanatomic location for subjects who died with AIDS. There is a high prevalence of drug abuse in Miami, Florida, associate with AIDS that may interactively affect HIV-associated pathology. Temporal lobe tissue was examined from 17 HIV-1-seropositive patients (4 with drug abuse and 13 without drug abuse) and 11 HIV-seronegative individuals (5 with drug abuse and 6 without drug abuse). Standard immunohistochemistry utilized alkaline phosphatase conjugate secondary antibody and fuchsin substrate. Authors found that HIV-1 infection and the interaction of HIV-1 infection and drug abuse produced changes in macrophage surface marker expression. Macrophage surface markers, CD11c, CD14, CD68, and HLA-DR, and T-cell marker CD4 were increased with statistical significance due to HIV-1 infection (all $p<.001$) whereas CD8 remained unchanged. Changes due to drug abuse alone were not significant. Interaction of drug abuse and HIV-infected individuals showed increased expression of CD68 ($p=.011$), HLA-DR ($p=.001$), CD4 ($p=.027$), and CD8 ($p=.016$). The authors concluded that drug abuse and HIV-1 infection are factors that differentially and interactively result in multiple macrophages surface marker effects. In HIV-1 infected individuals, drug abuse stimulates surface marker expression. Since brain macrophage surface markers do not change uniformly as a result of drug abuse and HIV infection, these cells may be heterogeneous and contain sub-types (sub-

sets). It remains to be determined which macrophage sub-types may be most pathognomic for pathology. Shapshak, P., Stewart, R.V., Rodriguez de la Vega, P., Dom'nguez, B., Fujimura, R., Segal, D.M., Sun, N.C.J., Delgado, S. and Petito, C. Journal of NeuroAIDS, 2(3), pp. 37-50, 2002.

HIV and Hepatitis C Virus Risk in New and Longer-Term IDUs in Oslo, Norway

Research has focused on understanding injecting drug use initiation in the era of HIV/AIDS. However, differences between new and longer-term injecting drug users (IDUs) have not received as much attention. This study examined injecting initiation experience, risk and risk reduction practices, and self-reported HIV and hepatitis C virus (HCV) testing practices and infection among new (injecting < or =4 years) and longer-term IDUs. Data from 3 cross-sectional surveys in 1992, 1994, and 1997 of syringe exchange program (SEP) users in Oslo, Norway, were used. Approximately one fifth of IDUs were new injectors. New IDUs were increasingly indistinguishable from longer-term IDUs in terms of socio-demographics, risk practices, and HIV and HCV testing. The prevalence of HIV infection remained low (5%); in contrast, approximately two thirds of all SEP users reported being HCV-infected. Known HCV infection status had no impact on syringe sharing; most HCV-infected SEP users reported sharing syringes, regardless of the duration of injecting. The only variable associated with HCV infection was injecting < or =4 years (adjusted odds ratio = 0.2; 95% confidence interval = 0.1-0.4). Increased similarity in age between new and longer-term IDUs may have contributed to the rapid spread of HCV infection by facilitating mixing patterns between HCV-infected and -susceptible IDUs. Miller, M., Mella, I., Moi, H. and Eskild, A. HIV and Hepatitis C Virus Risk in New and Longer-Term Injecting Drug Users in Oslo, Norway. JAIDS, 33(3), pp. 373-379, July 1, 2003.

Staphylococcus Aureus Colonization in a Community Sample of HIV+/- Drug Users

HIV-infected individuals, especially those with a history of injecting drug use, are at high risk of S. aureus infection. Moreover, the use of antimicrobial agents for opportunistic infections may increase nasal colonization by antimicrobial-resistant S. aureus in this population and, subsequently, levels of infection with multidrug-resistant S. aureus in the community. From February 1999 and March 2000, 500 subjects from a community-based cohort of drug users completed an interview and underwent a physical exam. Risk factors for colonization by S. aureus were examined, the antibiotic susceptibility profiles of all strains were determined, and DNA strain analysis was performed. One hundred twenty (24%) subjects had positive S. aureus nasal cultures. Only HIV infection and homelessness were associated with S. aureus colonization. Ten (8%) isolates were methicillin-resistant S. aureus. Methicillin-resistant S. aureus isolates were found more frequently among HIV-infected than HIV-uninfected respondents (14% vs. 3%, P=0.04). Among those colonized and HIV infected, the mean number of resistant isolates was higher for those currently reporting antibiotic use (5.0 vs. 2.3, P<0.001) and for those with CD4+ counts

Intervention Response Rates Among Drug-Using Women

Injection drug users (IDUs) who also smoke crack may be at greatest risk for infection with HIV as well as other blood-borne and sexually transmitted infections and in most need of positive behavioral changes. In this study, researchers randomly assigned 333 women (aged 18-59 years) to one of two enhanced gender- and culturally specific HIV intervention conditions or to the NIDA standard condition. Of primary interest were baseline risk and intervention response rates among three groups of drug users--IDUs who did not smoke crack, IDUs who did smoke crack, and crack smokers who did not inject. Using univariate and multivariate methods, including generalized estimating equations, the study found that the intervention produced positive behavioral changes over time, but that response rates varied according to drug-using group. Women in the crack smoking IDU group were found to be less responsive to the intervention than women in the other drug-using groups, and participants in the crack smoking only group were less responsive than those in the IDU only group. These findings indicate that there is a continuing need to develop and target improved, effective interventions to particular subgroups of high-risk individuals who may be most resistant to change. Sterk, C., Theall, K. and Elifson, K. Who's Getting The Message? Intervention Response Rates Among Women Who Inject Drugs and/or Smoke Crack Cocaine. Prev Med., 37(2), pp. 119-128, August 2003.

Migration and HIV Risk Behaviors: Puerto Rican Drug Injectors in New York City and Puerto Rico

Researchers compared injection-related HIV risk behaviors of Puerto Rican current

injection drug users living in New York City and in Puerto Rico who also had injected in the other location with those who had not. They recruited 561 Puerto Rican IDUs in New York and 312 in Puerto Rico. Of the former, 39% were newcomers, having previously injected in Puerto Rico; of the latter, 14% were returnees, having previously injected in New York. Risk behaviors were compared within each sample between those with and without experience injecting in the other location. Newcomers reported higher levels of risk behaviors than other New York IDUs. Newcomer status (adjusted OR= 1.62) and homelessness (adjusted OR = 2.52) were significant predictors of shooting gallery use; newcomer status also predicted paraphernalia sharing (adjusted OR = 1.67). Returnee status was not related to these variables. These findings underscore the importance of targeting HIV intervention services to reach mobile populations who move between environments characterized by high-risk and low-risk behaviors. Deren, S., Kang, S.Y., Colon, H., Andia, J., Robles, R., Oliver-Velez, D. and Finlinson, A. Migration and HIV Risk Behaviors: Puerto Rican Drug Injectors in New York City and Puerto Rico. Amer J Public Health, 93, pp. 812-816, 2003.

HIV Prevalence, Risk Behaviors, and High-Risk Sexual and Injection Networks Among Young Women Injectors Who Have Sex With Women

Women who inject drugs and have sex with women constitute 20% to 30% of American women IDUs. Compared with other women IDUs, this group has higher prevalence and incidence of HIV, and a greater likelihood of engaging in high-risk injection and sexual practices with men. In this study, researchers examined HIV risk among women who inject drugs and have sex with women, and compared their social situations, injection and social networks, and behaviors with those of other young women IDUs. A sample of 803 women IDUs was recruited from 5 U.S. cities between July 1997 and March 1999, of which 274 reported having had sex with a woman in the past 6 months or identifying as lesbian or bisexual. Compared to the other women IDUs, those who had sex with women were more likely to have been recently homeless, to have ever been institutionalized in a mental health facility, and to have been incarcerated. They were more likely to receive most of their income from selling sex than from other sources. Women who inject drugs and have sex with women were more likely to have injected drugs with a person who was HIV positive, and to be positive for hepatitis B and HIV (but not hepatitis C, chlamydia, or gonorrhea), in high prevalence but not low prevalence sites. They were also more likely to have engaged in receptive syringe sharing, and to have shared rinse water. These differences cannot be accounted for by their greater involvement in sex work. The findings show that sexual identity and sex between women are important in studies of women drug users, and may help explain variations in homelessness, institutionalization, behavior, networks, and infection rates. Friedman, S.R., Ompad, D., Maslow, C., Young, R., Case, P., Hudson, S., Diaz, T., Morse, E., Bailey, S., Des Jarlais, D., Perlis, T., Hollibaugh, A. and Garfein, R. HIV Prevalence, Risk Behaviors, and High-Risk Sexual and Injection Networks Among Young Women Injectors Who Have Sex With Women. Amer J Public Health, 93, pp. 902-906, 2003.

Rapid Assessment of the HIV/AIDS Crisis in Racial and Ethnic Minority Communities: An Approach for Timely Community Interventions

In 1998, the US Department of Health and Human Services, in collaboration with the Congressional Black Caucus, created a new initiative to address the disproportionate ongoing HIV/AIDS crisis in racial/ethnic minority populations. The initiative included deploying technical assistance teams through the Office of HIV/AIDS Policy. The teams introduced rapid assessment and response (RARE) methodologies and trained minority communities in their use. The first 3 eligible cities (Detroit, Miami, and Philadelphia) focused assessments in small geographic areas, using multiple methodologies to obtain data. The data indicate that high-risk drug and sexual behavior result in local and commuter mixing of risk groups and produce concurrent and sequential exposure to multiple and overlapping HIV transmission risk among bridge populations. RARE is a useful strategy for rapidly obtaining local data about changes in an epidemic in small geographic areas. It helps to focus on persons at risk in specific environments. It also provides a mechanism to link assessment data to the rapid deployment of new intervention strategies based on site- and culture-specific risk taking. Needle, R.H., Trotter, R.T., Singer, M., Bates, C., Page, B., Metzger, D., and Marcelin, L. Rapid Assessment of the HIV/AIDS Crisis in Racial and Ethnic Minority Communities: An Approach for Timely Community Interventions. Amer J Public Health, 93, pp. 970-979, 2003.

Failure to Return for HIV Posttest Counseling in an STD Clinic Population

Researchers assessed the extent of and characteristics associated with failure to

return (FTR) for HIV posttest counseling in persons undergoing an HIV test during their visit to a sexually transmitted disease (STD) clinic. The study population included all 101 newly diagnosed HIV-infected subjects and 411 matched HIV-uninfected subjects, identified over a 5-year period in a publicly funded STD clinic in the southeastern United States. Overall, 55% of subjects failed to return for their test results. HIV testing history, demographic characteristics, and STD diagnosis were associated with FTR. Of clients testing HIV-positive, 58% failed to return. A median of 12 days was required for disease intervention specialists (DIS) to locate HIV-infected subjects who failed to return. Clients with a history of drug use, including injection drug use, were unlikely to return for their posttest counseling appointment (66% vs 34% for those without a history of drug use; p=.02). FTR was least likely among MSM and clients who engaged in other high-risk behaviors (sex for drugs or money, sex with an IDU, sex with an HIV+ contact or recipient of blood products). This study found that the proportion of persons returning for HIV antibody test results is low among patients tested while seeking STD services. Considerable time and effort is required to find and notify those subjects testing HIV-positive who fail to return. To maximize the potential benefit of counseling and testing, interventions need to be designed to target those at highest risk of not returning. Hightow, L., Miller, W., Leone, P., Wohl, D., Smurzynski, M., and Kaplan, A. Failure to Return for HIV Posttest Counseling in an STD Clinic Population. AIDS Educ Prev., 15(3), pp. 282-290, June 2003.

Drug-Scene Roles and HIV Risk Among Puerto Rican Injection Drug Users in East Harlem, New York and Bayamon, Puerto Rico

This article describes and compares distributions of drug-scene roles, frequency of engaging in role behaviors, and relationships of roles, high-risk behaviors, and sexual partnerships among Puerto Rican injection drug users in New York and Puerto Rico. For this study, 561 street-recruited injection drug users in East Harlem, New York, and 312 in Bayamon, Puerto Rico were asked the number of days (in the last 30) in which they earned money or drugs in each of seven drug-scene roles; and about behaviors and egocentric risk partner characteristics in the last 30 days. East Harlem subjects were more likely to get resources by selling drugs and syringes, and buying drugs for someone else; Bayamon subjects were more likely to be "hit doctors," buy needles for others, operate a shooting gallery, or escort others to shooting galleries. All roles were part-time except shooting gallery management in East Harlem. About 27% of respondents at each site engaged in two or more roles. Many roles were associated with increased odds of injecting more than twice a day, receptive syringe sharing, distributive syringe sharing, receptive paraphernalia sharing, and having a drug-injecting sex partner. Drug-scene role structures vary between cities. Most roles are part-time pursuits. Role-holders have higher-risk behaviors and sexual partnerships than other drug injectors. Although further research is needed, drug-scene role-holders should be targeted for interventions to affect their own risk and their communications with others. Friedman, S., Kang, S., Deren, S., Robles, R., Colon, H., Andia, J., Oliver-Velez, D. and Finlinson, A. Drug-Scene Roles and HIV Risk among Puerto Rican Injection Drug Users in East Harlem, New York and Bayamon, Puerto Rico. J Psychoactive Drugs, 34(4), pp. 363-369, October-December 2003.

Violence, Homelessness, and HIV Risk Among Crack-Using African-American Women

This study compares the characteristics of out-of-treatment, homeless, crack-using African-American women with those who are not homeless to determine what risks and protective factors differentiate the two groups. From 1999 to 2001, researchers interviewed and serologically tested 683 out-of-treatment, African-American crack-using women (of whom 219 were categorized as homeless). They examined risk factors (adverse childhood experiences, psychological distress, physical health, violence and victimization, drug use, and risky sex behaviors) as well as protective factors (marital status, education, public assistance, and the responsibility of caring for children). Overall, both groups of women started crack use in their mid-twenties and started drug use with alcohol in their teenage years, though differed significantly on each risk factor examined. Logistic regression analysis found that variables associated with increased odds of being homeless are physical abuse before age 18, crack runs greater than 24 hours, income less than 500 dollars in the last 30 days, depression, and current cigarette smoking. Protective factors found are marital status, living with children under 18, having had a physical in the past year, and receiving money from welfare in the last 30 days. Being sexually assaulted in the past 90 days was marginally associated with homelessness in the model. These findings, specific to crack-using African-American women, suggest that not only do these women overall report painful histories and currently stressful lives, but homeless women are more

likely than women who are not homeless to have experienced childhood abuse and are more involved with drug use. Interventions designed for these women need to consider gender, cultural, and contextual issues that not only incorporate aspects of risk reduction related to violence, alcohol use, and comorbid conditions, but also linkages that will address housing issues, education, and skills for independence. Wechsberg, W., Lam, W., Zule, W., Hall, G., Middlesteadt, R. and Edwards, J. Violence, Homelessness, and HIV Risk Among Crack-Using African-American Women. Subst Use Misuse, 38(3-6), pp. 669-700, February-May 2003.

Methamphetamine Use Among HIV-Positive Men Who Have Sex With Men

This study compared the social and behavioral characteristics of binge users and non-binge users of methamphetamine (meth) in a sample of 90 HIV-positive men who have sex with men. Forty-one participants (46%) self-identified as a binge user. Meth binges ranged from 2 to 33 days (mean = 5.6), and average consumption was 3.1 grams. Binge users were significantly more likely than non-binge users to be ethnic minority and to have lower education. The two groups did not differ in terms of the total amount of meth used in the past 30 days; however, binge users reported significantly more social difficulties, more mental and physical health problems, and more sexual risk behaviors as compared with non-binge users. These findings, though preliminary, have implications for drug treatment approaches and the development of behavioral interventions. Semple, S., Patterson, T. and Grant, I. Binge Use of Methamphetamine Among HIV-Positive Men Who Have Sex With Men: Pilot Data and HIV Prevention Implications. AIDS Educ Prev, 15(2), pp. 133-147, April 2003.

HIV Risk Behaviors Among Older American Drug Users

Despite increasing numbers of Americans older than 50 years of age, little is known about the impact of HIV/AIDS on aging drug users. The current study assesses the drug-related and sex-related HIV risk behaviors of older and younger injection drug users and crack smokers. Structured interview responses from 1508 out-of-treatment active drug users older than 50 years of age were compared with those of 1515 out-of-treatment active drug users who were 50 years old or younger. Comparisons were also made within the older cohort to examine differences in risk behaviors between crack smokers and nonsmokers, men and women, and users older than 60 years of age and those in their 50s. Results indicated that although older drug users (older than 50 years of age) were less likely to have had sex in the prior month, those who did were as risky as their younger counterparts with regard to sex-related risk behaviors. They were, however, significantly less risky in their needle sharing practices than those 50 years old or younger. Among the older cohort, those who smoked crack were extremely risky. Men older than 50 years of age were riskier than women older than 50 years of age; however, users older than 60 years of age were no less risky than those in their 50s. The findings show that interventions designed for older drug users should focus on sex risk behaviors, especially among those who smoke crack. Kwiatkowski, C. and Booth, R. HIV Risk Behaviors Among Older American Drug Users. JAIDS, 33 (Supplement 2), S131-S137, June 1, 2003.

Late-Onset Crack Users: An Emergent HIV Risk Group

This article explores late-onset crack use among midlife and older adults as an emerging risk factor for HIV infection. Most research on illicit drug use and HIV infection/AIDS has focused on younger drug users, typically those who inject. The initiation into crack use during later adulthood challenges this narrow view. The analysis the authors present was drawn from qualitative and quantitative data collected as part of their ongoing research on illicit drug use. The subsample consisted of 27 men who began using crack at the age of 50 or older and 40 women who started using crack at the age of 35 or older. The findings suggest a typology of late-onset users with differing forms of HIV risk and prevention needs. The authors end the article with recommendations for effective HIV risk reduction programs for late-onset crack users. Johnson, W. and Sterk, C. Late-Onset Crack Users: An Emergent HIV Risk Group. JAIDS, 33 (Supplement 2), S229-S232, June 1, 2003.

Safer Sex by Type of Relationship Following an HIV Intervention Among Women

Predictors of increased male condom use were investigated following a recent, gender-specific HIV intervention among African-American women. Data were analyzed from 138 women (aged 18 to 59), recruited from inner-city Atlanta neighborhoods. Predictors of condom use with steady and casual paying partners were examined separately. Increased condom use with steady partners was associated with drug-using status, intervention assignment, sexual relationship

characteristics, age at first condom use, and HIV testing history. An increased ability to communicate openly and honestly with one's sex partner was another partner-specific factor that predicted increased condom use over time. Condom use with casual paying partners was associated with having sex while high and the frequency of crack cocaine use. Personalized norms regarding condom use were not salient factors in predicting increased rates of condom use with either partner type. These findings indicate the continued need to consider sex in the context of drug use, and reveal the importance of measuring such influences and all antecedents of condom use separately for steady vs. casual sexual relationships. Theall, K., Sterk, C. and Elifson, K. Male Condom Use by Type of Relationship Following an HIV Intervention Among Women Who Use Illegal Drugs. J Drug Issues, pp. 1-28, 2003.

Religiosity and HIV Risk Behavior Among "At Risk" Women

During the past decade, increased attention has been given to the role that religious and faith-based organizations can play in enhancing health behaviors. In this study, researchers examined the role that religiosity plays in women's involvement in HIV risk behaviors. They analyzed data from an intergenerational drug use study with 250 mother/daughter dyads, collected from August 1997 to August 2000 in Atlanta, Georgia. Three measures of religiosity were used: frequency of attending worship services, belief in the role of religion in influencing personal behavior, and an interaction term that combined these 2 variables. They found that religiosity was a strong predictor of women's involvement in HIV-related risky behaviors, even when the effects of other demographic/background variables, childhood maltreatment experiences, psychosocial measures, experiences and relationships with other persons, exposure to substance abusers, and condom related beliefs and attitudes were considered. The more frequently women attended worship services and the more influential they perceived their religion to be on their behaviors, the less involved they tended to be in HIV-related risky behaviors. Elifson, K., Klein, H., and Sterk, C. Religiosity and HIV Risk Behavior Involvement Among 'At Risk' Women. J Religion and Health, 42(1), pp. 47-65, Spring 2003.

Perceived Temptation To Use Drugs And Actual Drug Use Among Women

Much research has been conducted to examine the relationship between various psychological and psychosocial factors and substance use/abuse. Where as such topics as depression, bipolar disorder, anxiety, self-esteem, optimism/pessimism, coping, and stress/tension have been studied fairly extensively others have received much less attention. One such understudied psychosocial factor is perceived level of temptation to use drugs under specified circumstances. This research is based on a study of 125 adult women drug users residing in the Atlanta, Georgia metropolitan area, interviewed between August l997 and August 2000. Street outreach efforts were used to identify potential study participants, with further expansion of the sample done via targeted sampling and ethnographic mapping procedures. The present study examines 16 specific items assessing temptations to use drugs. After describing which circumstances people think will be most likely to bring about greater illegal drug usage, the authors compare perceptions to actual drug use behaviors. Multivariate analyses are conducted to examine the role that perceived temptations to use drugs play in predicting actual drug use when the effects of demographic variables, background experiences, childhood maltreatment experiences, other psychosocial measures, and exposure to substance abusers are taken into account. A multivariate model explaining nearly one-half of the variance in actual drug abuse is derived, and retained several of the temptations-to-use-drugs items. Klein, H., Elifson, K.W. and Sterk, C.E Journal of Drug Issues, pp. 161-192, 2003.

Effectiveness Of A Risk Reduction Intervention Among African American Women Who Use Crack Cocaine

The primary objective of this study was to evaluate the effectiveness of an HIV intervention for African American women who use crack cocaine. Two hundred sixty-five women (aged 18-59 years) were randomly assigned to one of two enhanced intervention conditions or to the national institute on drug abuse standard condition. A substantial proportion of women reported no past 30-day crack use at 6-month follow-up (100%-61%, $p < .001$). Significant ($p < .05$) decreases in the frequency of crack use; the number of paying partners; the number of times vaginal, oral, or anal sex was had with a paying partner; and sexual risks, such as trading sex for drugs, were reported over time. Significant ($p < .05$) increases in male condom use with sex partners were observed, as well as decreases in casual partners' refusal of condoms. Findings suggest that combined components of our culturally appropriate, gender-tailored intervention may be most effective at enhancing preventive behavior among similar populations. Sterk, C.E., Theall, K.P. and Elifson, K.W. AIDS Education and

Prevention, 15(1), pp. 15-32, 2003.

HIV Risk Reduction Among African-American Women Who Inject Drugs: A Randomized Controlled Trial

A community-based HIV intervention for African-American women who are active injection drug users (IDUs) was evaluated. Seventy-one women (aged 20-54 years) were randomly assigned to one of two enhanced gender- and culturally specific intervention conditions or to the NIDA standard condition. Substantial decreases ($p < .001$) were found in the frequency of drug use and the frequency of drug injection as well as in the sharing of injection works or water and the number of injections. Trading sex for drugs or money, having sex while high, as well as other sexual risk behaviors were also reduced significantly. Furthermore, women in both enhanced intervention conditions were more likely to reduce their drug-using and sexual risk behaviors than were women in the standard condition. Results indicate the value of including additional components in interventions designed to reduce the risk of infection with HIV among women who inject drugs. Sterk, C.E., Theall, K.P., Elifson, K.W., and Kidder, D., AIDS and Behavior, 7(1), pp. 73-85, March 2003.

Increased Glial Metabolites Predict Increased Working Memory Network Activation in HIV Brain Injury

Deficits in attention and working memory are common in HIV-1+-infected individuals, but the pathophysiology of these deficits is poorly understood. Modern neuroimaging techniques, such as proton magnetic resonance spectroscopy (1H MRS) and functional MRI (fMRI), can assess some of the processes underlying HIV brain injury. To evaluate the model that attentional deficits in early HIV brain disease are related to brain inflammation, 1H MRS and fMRI were performed by researchers at Brookhaven National Laboratory in 14 HIV+ subjects with AIDS dementia complex stage 1 or less. Increasing attentional load on three working memory tasks was assessed with fMRI, and the concentrations of brain metabolites were measured with 1H MRS in the frontal gray and white matter, and basal ganglia. Metabolite concentrations were correlated with fMRI blood oxygenation level-dependent (BOLD) signals. Several positive correlations were observed between the BOLD signal strength in the working memory network (posterior parietal cortex and lateral prefrontal cortex) and the concentrations of frontal white matter and basal ganglia metabolites that are predominant in glial cells. In contrast, BOLD signals in the working memory network were not correlated with the concentration of N-acetyl compounds or with metabolite concentrations in the frontal gray matter. These findings are consistent with previous results that mild HIV brain injury is associated with increased glial activation without major involvement of neuronal abnormalities. Ernst, T., Chang, L. and Arnold, S. NeuroImage, 19(4), pp. 1686-1693, 2003.

Working Memory Deficits in HIV-Positive Polydrug Abusers

HIV-seropositive (HIV+) individuals are often plagued by working memory (WM) deficits that can be exacerbated by manipulating a variety of task parameters, such as increasing memory load or information complexity. Researchers at UIC investigated the role of timing in HIV-associated WM defects by varying the amount of time required to maintain information online while holding memory load and information complexity constant. Fifty HIV+ and 35 HIV-seronegative (HIV-) polydrug abusers abstinent at testing and well matched on demographic variables were tested. The HIV- group outperformed the HIV+ group across all stimulus-response time delays. HIV-associated WM defects are not critically dependent on the amount of time stimulus representations must be maintained and might be attributed to impaired encoding or retrieval of stimulus representations. Martin, E.M., Pitrak, D.L, Rains, Niles, R., Grbesic, S. Pursell, K, Nunnally, G. and Bechara, A. Delayed Nonmatch-to-Sample Performance in HIV-Seropositive and HIV-Seronegative Polydrug Abusers. Neuropsychology, 17, pp. 283-288, April 2003.

Director's Report to the National Advisory Council on Drug Abuse - September, 2003

Research Findings - Research on AIDS and Other Medical Consequences of Drug Abuse - Non-AIDS Research

Welfare and Work Outcomes after Substance Abuse Treatment

Employment and welfare outcomes are investigated for women who received both welfare and substance abuse treatment in Florida from 1994 to 1999. By linking information from three statewide administrative databases, the authors identify 4,236 women who meet both criteria. Over the study period, there was a significant increase in the proportion of women moving from welfare to work. Predictors of post treatment employment include demographic characteristics, treatment related characteristics, and working during the month of admission. Both completion of treatment and length of time in treatment are associated with employment. Metsch, L.R., Pereyra, M., Miles, C. and McCoy, C.B. Social Service Review, 77(2), pp. 2003.

Met and Unmet Need for Dental Services Among Active Drug Users in Miami, Florida

This study considers both met and unmet need for dental services among chronic drug users in Miami, Florida, and compares them with non-drug users recruited from the same neighborhoods (N=1,479). Three primary findings emerged: (1) dental problems are among the most frequently reported health problems, (2) drug use is independently associated with need for dental services, and (3) injection drug use is independently associated with increased odds of unmet need for dental services. These findings suggest that policies that increase access to dental services for drug user and other disadvantaged groups are needed. These services could be integrated into existing behavioral health programs already targeting active drug users. Metsch, L.R., Crandall, L., Wohler-Torres, B., Miles, C., Chitwood, D.D., and McCoy, C.B. The Journal of Behavioral Health Services & Research (JBHSR), 29(2), pp. 176-188, 2002.

Hepatitis C Virus Infection Among Noninjecting Drug Users in New York City

The prevalence of hepatitis C virus (HCV) infection among noninjecting drug users has been reported to be higher than in the general population, but the reasons for this observation remain unclear. Noninjecting drug users aged 15-40 years and who used drugs for no longer than 10 years were enrolled in the study. The participants were interviewed about risk behaviors and had specimens drawn for serological testing. Of 276 enrolled, 4.7% were infected with HCV. Drug users who had ever sniffed or snorted heroin in combination with cocaine were significantly more likely to be infected with HCV compared with those who never sniffed or snorted heroin with cocaine. No other drug use or sexual risk behaviors were found to be associated with HCV infection. These findings suggest that sniffing or snorting heroin with cocaine may explain the increase frequently found in HCV infection among noninjectors, but further studies are necessary. Koblin, B.A., Factor, S.H., Wu, Y. and Vlahov, D. J Med Virol.,70(3), pp. 387-390, July 2003.

Hepatitis C Virus Infection and Incident Type 2 Diabetes

Although hepatitis C virus (HCV) infection is more common among adults with type 2 diabetes, it is uncertain whether HCV precedes the development of diabetes. Thus, we performed a prospective (case-cohort) analysis to examine if persons who acquired type 2 diabetes were more likely to have had antecedent HCV infection when enrolled in a community-based cohort of men and women between the ages of 44 and 65 in the United States (Atherosclerosis Risk in Communities Study [ARIC]). Among 1,084 adults free of diabetes at baseline, 548 developed diabetes over 9 years of follow-up evaluation. Incident cases of diabetes were identified by using fasting glucose and

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medical history and HCV antibodies were assessed at baseline. A priori, persons were categorized as low-risk or high-risk for diabetes based on their age and body mass index, factors that appeared to modify the type 2 diabetes-HCV infection incidence estimates. The overall prevalence of HCV in this population was 0.8%. Among those at high risk for diabetes, persons with HCV infection were more than 11 times as likely as those without HCV infection to develop diabetes (relative hazard, 11.58; 95% confidence interval, 1.39-96.6). Among those at low risk, no increased incidence of diabetes was detected among HCV-infected persons (relative hazard, 0.48; 95% confidence interval, 0.05-4.40). In conclusion, pre-existing HCV infection may increase the risk for type 2 diabetes in persons with recognized diabetes risk factors. Additional larger prospective evaluations are needed to confirm these preliminary findings. Mehta, S.H., Brancati, F.L., Strathdee, S.A., Pankow, J.S., Netski, D., Coresh, J., Szklo, M. and Thomas, D.L. Hepatology, 38(1), pp. 50-56, July 2003.

The Effect of HAART and HCV Infection on the Development of Hyperglycemia Among HIV-Infected Persons

The objective of this study was to examine the prevalence and incidence of hyperglycemia among HIV-infected patients by hepatitis C virus (HCV) infection and type of highly active antiretroviral therapy (HAART). A retrospective cohort analysis was performed of 1,230 persons on their first HAART regimen who had at least 1 random glucose measurement before and during antiretroviral therapy. The prevalence of hyperglycemia and the incidence of hyperglycemia were compared among persons with and without HCV infection while on a protease inhibitor (PI)-containing HAART regimen, a non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimen, or a regimen that contained both a PI and an NNRTI. Hyperglycemia was defined as either 2 random glucose levels > 11.1 mM (200 mg/dL) or documentation of the diagnosis of diabetes in the medical record. The prevalence of hyperglycemia was significantly higher in HCV-coinfected (5.9%) than HCV-uninfected persons (3.3%, P = 0.02). Among persons receiving HAART, both HCV co-infection (adjusted relative hazard [ARH], 2.28; 95% CI, 1.23-4.22) and PI use (ARH, 5.02; 95% CI, 1.39-18.16) were independent risk factors of developing hyperglycemia. The incidence of hyperglycemia was highest among HCV-coinfected persons receiving a PI (5.6 cases per 100-person years) and only 1 person who was neither HCV-infected nor receiving a PI developed hyperglycemia. In this urban HIV cohort, the risk of hyperglycemia was increased in HCV-coinfected patients and those prescribed a PI. Mehta, S.H., Moore, R.D., Thomas, D.L., Chaisson, R.E. and Sulkowski, M.S. J Acquir Immune Defic Syndr. 33(5), pp. 577-584, August 15, 2003.

Differential Effects on Cognitive Functioning in 13- to 16-Year-Olds Prenatally Exposed to Cigarettes and Marijuana

The ongoing effects of prenatal cigarette and marijuana exposure were explored in a study conducted by Fried and colleagues. Assessments were carried out in the areas of general intelligence, achievement, memory, and aspects of executive functioning. Maternal cigarette smoking during pregnancy was categorized into nonsmoking, light, and heavy ($16 mg nicotine/day), while maternal average marihuana use across pregnancy was categorized into two groups: no use plus infrequent/ moderate use, and heavy use ($6 joints/week). After controlling for confounding variables, the strongest relationship between maternal cigarette use and cognitive variables was seen with overall general intelligence and aspects of auditory functioning. Prenatal marijuana exposure was negatively associated with tasks that required visual memory, analysis, and integration. The areas that appear vulnerable to prenatal exposure to either cigarettes or marijuana are the same that were identified at earlier ages, and these two drugs continue to differentially impact varying aspects of cognition. Fried, P., Watkinson, B., and Gray, R. Differential Effects on Cognitive Functioning in 13- to 16-Year-Olds Prenatally Exposed to Cigarettes and Marijuana. Neurotoxicology and Teratology, 25, pp. 427-436, 2003.

Influence of Prenatal Cocaine Exposure on Early Language Development

Researchers at the University of Miami have recently reported effects of prenatal cocaine exposure on early language development. The Miami Prenatal Cocaine Study prospectively enrolled 476 African-American infants categorized as cocaine-exposed or non-cocaine exposed. The Bayley Scales of Infant Development were administered at 4, 8, 12, 18, and 24 months. At 3 years, the Clinical Evaluation of Language Fundamentals-Preschool was administered. Information was also collected from the primary caregiver at the time of child assessment. Prenatal substance exposure was measured by the number of cigarettes smoked, number of marijuana cigarettes smoked, number of drinks of beer, wine, or hard liquor, and number of cocaine lines or rocks recorded in increments of usual daily dose, usual days per week, and number

of weeks used. Longitudinal analyses indicated evidence for a subtle, consistent pattern of cocaine-associated deficits in language functioning over the six intervals assessed during the first three years of life. This association remained stable after considering prenatal exposure to other substances, and important social-environmental factors. The investigators suggest that these subtle deficits may have important ramifications for long-term academic and social adaptation, especially when considered within the broader context of additional potential risk factors. Morrow, C.E., Bandstra, E.S., Anthony, J.C., Ofir, A.Y., Xue, L., and Reyes, M.B. Influence of Prenatal Cocaine Exposure on Early Language Development: Longitudinal Findings from Four Months to Three Years of Age. Developmental and Behavioral Pediatrics, 24(1), pp. 39-50, 2003.

Cannabis Withdrawal Syndrome

Budney and his colleagues at the University of Vermont have presented an excellent overview of the scientific and clinical literature on cannabis abstinence effects providing a critical examination of extant data relevant to determining the validity and significance of a cannabis withdrawal syndrome. They have reviewed briefly the animal laboratory literature followed by more detailed discussion of human laboratory and clinical studies. Converging evidence from the basic laboratory to the clinic indicates that a reliable withdrawal syndrome follows discontinuation of chronic, heavy use of cannabis or THC. Common symptoms are primarily emotional and behavioral, although appetite change, weight loss, and physical discomfort are also frequently reported. The onset and time course of these symptoms appear similar to that of other substance withdrawal syndromes. Their magnitude and severity appears substantial suggesting that the syndrome has clinical importance. They have proposed criteria for cannabis withdrawal syndrome, have discussed limitations of existing research, and identified areas for future basic and clinical research on marijuana. Budney, A., Hughes, J.R., Moore, B.A. and Vandrey, R. A Review of the Validity and Significance of the Cannabis Withdrawal Syndrome, Archives of General Psychiatry, August 2003.

Chronic Pain Among Patients in MMTP and Residential Treatment Facilities

Little is known about the prevalence and characteristics of chronic pain among patients with different types of chemical dependency. In this study, researchers estimated the prevalence and examined the characteristics of chronic severe pain in chemically dependent populations receiving methadone maintenance or inpatient residential treatment. Participants included representative samples of 390 patients from 2 methadone maintenance treatment programs (MMTPs) and 531 patients from 13 short-term residential substance abuse treatment (inpatient) programs, all in New York State, surveyed in late 2000 and early 2001. The main outcome measures were prevalence of chronic severe pain, defined as pain that persisted for more than 6 months and was of moderate to severe intensity or that significantly interfered with daily activities. Thirty-seven percent of MMTP patients and 24% of inpatients experienced chronic severe pain, and 80% of MMTP patients and 78% of inpatients reported pain of any type or duration during the past week. Among those with chronic severe pain, 65% of MMTP patients and 48% of inpatients reported high levels of pain-related interference in physical and psychosocial functioning. Among MMTP patients, correlates of chronic pain in a multivariate model were age, chronic illness, lifetime psychiatric illness, psychiatric distress, and time in treatment. Among inpatients, the correlates of chronic pain were race, drug craving, chronic illness, and psychiatric distress. Among those with chronic severe pain, inpatients were significantly more likely than MMTP patients to have used illicit drugs, as well as alcohol, to treat their pain complaint (51% vs 34%, $p = .005$) but were less likely to have been prescribed pain medications (52% vs 67%, $p = .01$). Chronic severe pain is prevalent among patients in substance abuse treatment, especially MMTP patients. Pain is associated with functional impairment and correlates of pain vary with the population. Self-medication for pain with psychoactive drugs appears especially problematic among substance users who enroll in drug-free treatment programs. Substance abuse treatment programs need to develop comprehensive and structured pain management programs. Rosenblum, A., Joseph, H., Fong, C., Kipnis, S., Cleland, C. and Portenoy, R. Prevalence and Characteristics of Chronic Pain Among Chemically Dependent Patients in Methadone Maintenance and Residential Treatment Facilities, JAMA, 289(18), pp. 2370-2378, 2003.

Chronic Drug Use and Reproductive Health Care among Low-Income Women in Miami

In this study, researchers interviewed a stratified, network-referred sample of chronic drug-using women (CDUs) and socially and ethnically similar women who were not

CDUs about reproductive health issues. Women who were not CDUs were significantly more likely to report a regular source of health care than CDUs. About one third of each group reported experiencing reproductive health problems (other than pregnancy) in the 12 months preceding their interview. Chronic drug users were twice as likely to report that these problems remained untreated. Measures of use of preventive services (physical exam, breast exam, pelvic exam, family planning visit) consistently showed lower use by CDUs. A higher proportion of women who were not CDUs reported pregnancies in the 12 months preceding interview. The 32 pregnant CDUs were much less likely to have received prenatal care than the 42 pregnant women who were not CDUs. For women who reported a pregnancy in the year preceding interview, logistic regression analysis showed a strong and robust negative effect of being a CDU on receiving prenatal care even when the effects of having a usual source of care and having third-party coverage were controlled. Crandall, L., Metsch, L., McCoy, C., Chitwood, D. and Tobias, H. Chronic Drug Use and Reproductive Health Care among Low-Income Women in Miami, Florida: A Comparative Study of Access, Need, and Utilization, J Behav Health Serv Res., 30(3), pp. 321-331, July-September 2003.

Director's Report to the National Advisory Council on Drug Abuse - September, 2003

Research Findings - Epidemiology and Etiology Research

Community Epidemiology Work Group

The 54th meeting of the Community Epidemiology Work Group (CEWG), chaired by Moira O'Brien, DESPR, was held in St. Louis, Missouri on June 24-27, 2003. The CEWG is composed of researchers from 21 metropolitan areas of the United States who meet semiannually to report on patterns and trends of drug abuse in their respective areas, emerging drugs of abuse, vulnerable populations and factors that may place people at risk of drug abuse and negative health and social consequences. Reports are based on a variety of drug abuse indicator data such as morbidity and mortality information, treatment data and local and State law enforcement data. Additional sources of information include criminal justice, correctional, medical and community health data, local and State survey information, and findings from qualitative research studies.

Polysubstance abuse is proliferating across CEWG areas. The abuse of an array of licit and illicit substances used in a variety of combinations is contributing to emergency department admissions and deaths. DAWN ED estimates for the first half of 2002 show that 71 percent of cocaine mentions represented multidrug episodes, as did 53 percent of the heroin mentions, 74 percent of the marijuana mentions and 54 percent of the methamphetamine mentions. Among DAWN drug-involved death mentions across 20 CEWG areas in 2001, the vast majority of deaths involving cocaine (83 percent), heroin (89 percent), methamphetamine (92 percent) and marijuana mentions (78 percent) involved more than one drug.

Methamphetamine abuse and production continue at high levels in Hawaii, west coast CEWG areas, and some southwestern areas. Abuse and manufacture of methamphetamine continue to move eastward, especially to rural areas. Methamphetamine ED mention rates in the first half of 2002 continued to be highest in west coast areas and parts of the southwest with San Francisco leading with 24 per 100,000 followed by San Diego (11), Phoenix (10), Seattle (9) and Los Angeles (8).

Marijuana indicators were mixed. Rates of marijuana ED mentions increased significantly between the first halves of 2001 and 2002 in Miami, Newark, Phoenix and San Diego but decreased in Chicago, San Francisco and Seattle. Although the proportion of primary marijuana treatment admissions in CEWG areas was high in 2002, there was little change from 2001.

Cocaine/Crack emergency department mention rates in the first half of 2002 were particularly high in Baltimore, Miami, Atlanta, Philadelphia and Chicago ranging between 120 and 140 per 100,000.

Heroin abuse indicators were relatively stable in 2002, but continued at high levels in Boston, Chicago, Detroit, Newark, Philadelphia and San Francisco.

Other Opiate abuse indicators continue to trend upward reflecting the increasing popularity of oxycodone and hydrocodone products reported by several CEWG members. Oxycodone ED mentions increased 110 percent between the first halves of 2001 and 2002 in San Francisco where ethnographic observers concurred that the use of oxycodone is on the rise. Hydrocodone ED mentioned increased nearly 79 percent between the first halves of 2001 and 2002 in Minneapolis/ St. Paul.

MDMA (methylenedioxymethamphetamine) indicators are stable or declining in most CEWG areas. MDMA ED mentions decreased in 11 CEWG areas from the first and/or second half of 2001 to the first half of 2002, with a significant increase reported only

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in New Orleans. The highest number of MDMA ED mentions in the first half of 2002 were in Philadelphia, Miami, San Francisco, Atlanta, Los Angeles and New York City.

Phencyclidine (PCP) indicators increased in five CEWG areas: Los Angeles, Philadelphia, Phoenix, Washington, D.C. and Texas. In Washington D.C., criminal justice sources report an increase in PCP availability and use. In Los Angeles, there was an 11 percent increase in PCP-related arrests from 2001 to 2002.

Lysergic Acid Diethylamide (LSD) indicators have been declining sharply in most CEWG areas. This is consistent with the declines in prevalence of LSD use reported by the most recent national surveys, the Monitoring the Future study (2002) and Household Survey on Drug Abuse (2001).

Student Drug Testing and Rates of Illicit Drug Use

Investigators at the University of Michigan conducted a study of the association between school drug testing practices and rates of drug use. They combined data from the 1998 through 2001 Monitoring the Future surveys, yielding a base of around 30,000 8th grade students in 260 schools, 23,000 10th grade students in 227 high schools, and 23,000 12th grade students in 235 high schools from across the nation. School drug testing policies and practices were determined from questionnaires administered to school administrators, and student drug use was ascertained from self-administered questionnaires. At each grade level studied, the investigators found virtually identical rates of drug use in the schools that have drug testing and the schools that do not. For example, in 12th grade, 36% of those in non-testing schools reported having used marijuana in the twelve months prior to the survey, versus 37% in the schools that did test. Additional analyses showed that in high schools that tested athletes, marijuana and other drug use by male athletes was not significantly different from use among male athletes in the great majority of high schools that do not test their athletes. The authors acknowledge that with only cross-sectional data they could not make definitive causal interpretations regarding the effects of drug testing; it is conceivable, for example, that the schools that instituted drug testing initially had higher use, and that drug testing reduced those levels. While the results are not conclusive, they indicate a lack of evidence for a preventive effect from student drug testing as it is commonly practiced. Yamaguchi, R., Johnston, L.D., and O'Malley, P.M. The Relationship Between Student Illicit Drug Use and School Drug-Testing Policies. Journal of School Health, 73(4), pp. 159-164, 2003.

Genetic and Environmental Factors for Drug Use Disorders in Males

This study examines whether genetic and shared environmental risk factors for substance use disorders render individuals vulnerable to use of specific substances or to substance use and related disorders in general. Data for this population-based study comes from interviews with 1196 male twin pairs determined by birth registry. Six categories of drug use and abuse/dependence were included in the models: cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates. Several important findings were reported. First, it appears from these models that one common genetic factor strongly influences the risk for both use and abuse/dependence for all substances; that is, individuals appear to be genetically vulnerable to drug abuse in general, rather than to a specific drug. This has important implications for efforts to locate genes for drug abuse vulnerability. Second, shared environmental influences also appeared largely non-specific; thus, family or peer environmental factors do not appear strongly determinative of which drug an individual uses or becomes dependent on. Third, it then appears that an individual's personal (non-shared environmental) experiences are largely responsible for determining which drug an individual uses. Both of these latter points have important implications for preventive interventions. Kendler, K.S., Jacobson, K.C., Prescott, C.A. and Neale, M.C. Specificity of Genetic and Environmental Risk Factors for Use and Abuse/Dependence of Cannabis, Cocaine, Hallucinogens, Sedatives, Stimulants, and Opiates in Male Twins. American Journal of Psychiatry, 160, pp. 687-695, 2003.

Neurobehavioral Disinhibition in Childhood Predicts Substance Use Disorder

This longitudinal study determines the extent to which boys at high-average-risk (n=47) and low-average-risk (n=65) for substance use disorder (based upon family-history of illicit drug abuse) differ on a construct of neurobehavioral disinhibition (based upon measures of affect, behavior, and neurocognition), evaluates the capacity of neurobehavioral disinhibition to predict substance use frequency at age 16, and demonstrates the utility of neurobehavioral disinhibition in predicting substance use disorder at age 19. The neurobehavioral disinhibition score significantly discriminated boys at high average risk from those at low average risk at ages 10-12.

Neurobehavioral disinhibition at age 16, in conjunction with substance use frequency and risk status group, predicted substance use disorder at age 19 with 85% accuracy and accounted for 50% of the variance in Drug Use Screening Inventory overall problem density score. Neurobehavioral disinhibition was a stronger predictor of substance use disorder (odds ratio = 6.8) than substance consumption frequency (odds ratio = 3.2). Results are consistent with the notion that neurobehavioral disinhibition is a component of a liability to develop substance use disorder. Tarter, R.E., Kirisci, L., Mezzich, A., Cornelius, J.R., Pajer, K., Vanyukov, M., Gardner, W., Blackson, T. and Clark, D. Neurobehavioral Disinhibition in Childhood Predicts Early Age At Onset of Substance Use Disorder. American Journal of Psychiatry, 160(6), pp. 1078-1085, 2003.

A Twin Study of Neuropsychological Consequences of Stimulant Abuse

Previous studies document neuropsychological deficits associated with stimulant abuse, but findings are inconsistent. This study identified 50 twin pairs (aged 40-51 yrs) in which only 1 member had heavy stimulant abuse (cocaine and/or amphetamines) ending at least 1 year before the evaluation. Subjects were administered an extensive neuropsychological test battery organized into the following 5 functions: attention, executive functioning, motor skills, intelligence, and memory. Multivariate tests showed that abusers performed significantly worse than nonabusers on functions of attention and motor skills. Within each of these functions, univariate tests showed that abusers performed significantly worse on certain tests of motor skills and attention. In contrast, abusers performed significantly better on one test of attention measuring visual vigilance. Within the abuser group, higher levels of stimulant use were largely uncorrelated with neuropsychological test scores, although a few significant correlations indicated better functioning with more stimulant use. This study demonstrates that deficits in attention and motor skills persist after 1 year of abstinence from stimulant use and raises hypotheses regarding relative strengths on a vigilance task among abusers. Toomey, R., Lyons, M.J., Eisen, S.A., Xian, H., Chantarujikapong, S., Seidman, L.J., Faraone, S.V. and Tsuang, M.T. A Twin Study of Neuropsychological Consequences of Stimulant Abuse. Archives of General Psychiatry, 60(3), pp. 303-310, 2003.

Parent-Child Conflict and Childhood Externalizing Disorders

The authors sought to examine the relationship between parent-child conflict and externalizing disorders (attention deficit-hyperactivity disorder, or ADHD, oppositional defiant disorder, or ODD, and conduct disorder, or CD), which can confer increased risk for later substance use disorders. Data were gathered from 808 same-sex 11-year-old twin pairs from a population-based sample, and their mothers. Resulting models suggest that parent-child conflict acts as a common factor increasing vulnerability for multiple childhood disorders. This offers an important target for preventive interventions, perhaps of multiple disorders. Moreover, analyses found that common genetic and environmental factors appear to underlie the externalizing childhood disorders and the parent-child conflict. Thus, such genetically-informed studies can help disentangle genetic and environmental influences, and clarify productive preventive approaches. Burt, A., Krueger, R.F., McGue, M., and Iacono, W. Parent-Child Conflict and the Comorbidity Among Childhood Externalizing Disorders. Archives of General Psychiatry, 60, pp. 505-513, 2003.

Heterogeneity in Progression from Abuse to Dependence

The purpose of this study was to examine progression from drug abuse to drug dependence across alcohol, cannabis, cocaine, and opiates. Retrospective data were reanalyzed from the DSM-IV Substance Use Disorders Working Group. Participants (n=1,226) were interviewed with the Composite International Diagnostic Interview-Substance Abuse Module. Results consistently suggest that a progression generally occurs from abuse to dependence for alcohol and cannabis, but not for cocaine or opiates. Regarding the timing of onset of abuse/dependence, cocaine and opiate use disorders onset closely in time irrespective of the length of time from first use. Moreover, more cocaine users experienced a disorder (85%) compared to users of cannabis (58%) or opiates (64%). Results suggest considerable heterogeneity in the course of drug disorders, and highlight the need for more research on nosologic, environmental, and genetic contributions to the transitions to dependence. Ridenour, T.A., Cottler, L.B., Compton, W.M., Spitznagel, E.L. and Cunningham-Williams, R.M. Is There a Progression from Abuse Disorders to Dependence Disorders? Addiction, 98, pp. 635-644, 2003.

HIV and AIDS Risk Behaviors in Juvenile Detainees

Detained youth may be at especially high risk for contracting HIV and AIDS. This study reports on the rates of HIV and AIDS sexual and drug risk behaviors among a group of juvenile detainees participating in the Northwestern Juvenile Project. Participants in this longitudinal study included 1829 youth (age 10-18) initially arrested and detained between 1995 and 1998 at the Cook County Juvenile Temporary Detention Center in Chicago, Ill. The random sample was stratified by gender, race/ethnicity, age, and charge severity. Information related to HIV and AIDS risk behavior was collected on 800 participants from the larger study. Results indicate 95% of the detained youth report engaging in 3 or more sexual and drug risk behaviors, and 65% report engaging in 10 or more risk behaviors. More than 90% of the males were sexually active; 61% had more than one sexual partner in the last three months. Significantly more males than females report engaging in the sexual risk behaviors examined in this study. No significant gender differences were found in the self-report data related to drug risk behaviors. Regarding race/ethnicity: African American males report engaging in significantly more sexual risk behaviors, although non-Hispanic Whites and Hispanics report participating in more drug risk behaviors. Among females, significantly more non-Hispanic Whites than African Americans or Hispanics report engaging in sexual risk behaviors, while Non-Hispanic Whites and Hispanics report participating in more drug risk behaviors. Over 50% of juveniles age 10-13 report engaging in both sexual and drug risk behaviors. These findings highlight the importance of developing effective sexual and drug-related HIV/AIDS risk reduction interventions for youth in the juvenile justice system. Teplin, L.A., Mericle, A.M., McCelland, G.M., and Abram, K.M. HIV and AIDS Risk Behaviors in Juvenile Detainees: Implications for Public Health Policy. American Journal of Public Health, 93(6), pp. 906-912, 2003.

Race/Ethnic Differences in the Effects of Cumulative Adversity on Drug Dependence in Young Adults

This study assesses the effects of cumulative exposure to stressors as a risk factor for drug dependence, and evaluates whether race/ethnic differences in exposure to stressful events contributes to race/ethnic differences in prevalence of drug dependence. Data were analyzed cross-sectionally from a community survey of lifetime adverse experiences and substance and psychiatric disorders among young adults. Data were collected between 1997-2000 in Miami-Dade County, Florida. The sample size is 1,803 former Miami-Dade Public School students, 93% of whom were between ages 19 and 21 when interviewed. Males and females of Cuban origin, other Caribbean basin Hispanics, African-Americans, and non-Hispanic Whites are equally represented. Drug dependence disorder was assessed by DSM-IV criteria using the Composite International Diagnostic Interview, and a 41-item checklist of lifetime exposure to major and potentially traumatic experiences were used to measure cumulative adversity. Both measures include age at time of first occurrence. The lifetime rate of drug dependence disorder (total 14.3%) did not vary significantly ($p>.05$) by socioeconomic group. The rate for males (17.6%) was significantly greater than female rate (10.9%). The African-American rate (6.5%) was dramatically lower than non-Hispanic White (17.0%), Cuban (18.1%) and non-Cuban Hispanic (16.0%) rates despite their dramatically higher exposure to adversity. Twenty eight of 33 individual adversities were associated with the subsequent onset of drug dependence ($p<.05$). Cumulative lifetime exposure was greatest for males and for African-Americans, and was inversely associated with socioeconomic level. Multivariate discrete-time event history analysis revealed significant independent effects of distal (>1 year earlier) and proximal (previous year) exposure to adverse events ($p<.05$), controlling for childhood conduct disorder, ADHD, and prior psychiatric disorder. Lifetime cumulative exposure to distant as well as more recent adversity predicts risk of subsequent drug dependence, though it does not explain ethnic group differences in risk. Implications are that distal and proximal stressful events should both be included when measuring stress exposure. Turner, R.J. and Lloyd, D. Cumulative Adversity and Drug Dependence in Young Adults: Racial/Ethnic Contrasts. Addiction, 98, pp. 305-315, 2003.

The Deterrence Hypothesis Reexamined: Sports Participation and Substance Use Among Young Adults

The widely held notion that sports participation reduces subsequent risk of substance use is evaluated with longitudinal survey data of a representative sample of 1,172 youth when they were in their preteen and young adult years. Unlike previous inquiries into the deterrence hypothesis, the present study controls for other major factors previously found to be predictive of alcohol and drug use, such as family structure and stress exposure. Results of analyses revealed that contrary to the deterrence hypothesis, playing high school sports does not appear to be a protective

factor that lowers one's involvement in young adult alcohol or drug use--with one exception. Subgroup analyses revealed that among blacks, the greater the extent of high school sports participation the less the risk of substance use. In direct contradiction to the deterrence hypothesis, playing high school sports was found to be positively associated with alcohol use for whites, even in the context of other major predictors of alcohol use. Further analyses revealed that the positive association between sports participation and alcohol use appeared to exist only for white males. These findings cast doubt about the contention that playing high school sports is protective against alcohol and illegal substance use. Eitle, D., Turner, R.J. and McNulty Eitle, T. The Deterrence Hypothesis Reexamined: Sports Participation and Substance Use Among Young Adults. Journal of Drug Issues, 33, pp. 193-222, 2003.

Maternal Correlates of Toddler Insecure and Dependent Behavior

The present study was designed to examine the relationship between characteristics of mothers' and toddlers' insecure and dependent behavior. Two hundred fifty-four 2-year-old toddlers and their mothers were studied using a structured questionnaire administered to the mothers in their homes. The extent to which insecure and dependent behavior is related to the domains of maternal personality traits, maternal drug use, maternal child rearing, and parental marital relations was assessed. Using Pearson correlations and hierarchical multiple regression analyses, the maternal child-rearing and maternal personality domains were found to have a direct effect on the toddlers' insecure and dependent behavior. The maternal child-rearing domain also served as a mediator for the domains of the parents marital/partner relations, maternal personality attributes, and maternal drug use. There was also evidence suggesting an indirect effect of maternal personality attributes on the toddlers insecure and dependent behavior, which is mediated by the domain of maternal child-rearing practices. Implications for the prevention of insecure and dependent behavior in toddlers are discussed. Brook, J.S., Brook, D.W., and Whiteman, M. Maternal Correlates of Toddler Insecure and Dependent Behavior. Journal of Genetic Psychology, 164(1), pp.72-87, 2003.

BIS/BAS Levels and Psychiatric Disorder: An Epidemiological Study

Behavioral inhibition and behavioral activation levels have been theorized to relate to a broad range of psychopathologies. To date, however, studies have focused on a single diagnosis, and the measures used to assess different psychopathologies have varied greatly. This study assessed how levels of behavioral inhibition and behavioral activation relate to lifetime diagnoses of depression, anxiety, drug abuse and dependence, alcohol abuse and dependence, attention deficit hyperactivity disorder, and conduct disorder. A representative community sample of 1,803 individuals between the ages of 19 and 21 in the Miami area was surveyed with the Composite International Diagnostic Interview and the Behavioral Inhibition and Behavioral Activation Scales (BIS/BAS; Carver & White, 1994). Results supported the role of BIS as a vulnerability factor for depression and anxiety and for BAS Fun-Seeking for drug abuse and non-comorbid alcohol diagnoses. Goals in understanding BIS and BAS are described, including the need for prospective studies with a broader array of behavioral indices. Johnson, S.L., Turner, R.J. and Iwata, N. BIS/BAS Levels and Psychiatric Disorder: An Epidemiological Study. Journal of Psychopathology and Behavioral Assessment, 25, pp. 25-36, 2003.

Protective Effect of Social Self-Efficacy on the Link between Maltreatment and Internalizing Problems

Data were collected on 305 maltreated and 195 nonmaltreated children from low-income families (aged 5-12 yrs) who were assessed on perceived social self-efficacy and evaluated by camp counselors on internalizing and externalizing symptomatology. Younger (<8 yrs) maltreated children exhibited inflated levels of perceived self-efficacy in conflictual peer interactions compared to younger nonmaltreated children. Younger maltreated children with higher levels of social self-efficacy showed significantly less internalizing behaviors compared to younger maltreated children with lower levels of social self-efficacy. For older children (>8 yrs), regardless of maltreatment status, higher levels of perceived social self-efficacy in conflict situations were related to lower levels of internalizing symptomatology. Kim, J. and Cicchetti, D. Social Self-Efficacy and Behavior Problems in Maltreated and Nonmaltreated Children. Journal of Clinical Child and Adolescent Psychology, 32(1), pp. 106-117, 2003.

Antisocial Behavior Impairs Emotion Regulation among Cocaine-Using Women

This study examined the relation between deficits in affect regulation and adult antisocial behavior (ASB) in a sample of 80 inner-city crack/cocaine-using women. Retrospective narrative early memories were coded for two components of affect regulation, affect tolerance and affect expression, using the Epigenetic Assessment Rating Scale. Analyses compared the affect regulation measures among primary crack/cocaine-using women with and without ASB, as measured by the adult criteria of antisocial personality disorder. Findings revealed that women with ASB had significantly poorer capacity for affect tolerance and affect expression than women without ASB. Litt, L.C., Hien, D.A.and Levin, D. Psychology of Women Quarterly, 27(2), pp. 143-152, 2003.

Emotion-Focused Coping as a Mediator of Maternal Cocaine Abuse and Antisocial Behavior

This study examined the links between maternal drug use and antisocial behavior in a case-control study of 279 inner-city mothers in 3 comparison groups: drug abusers, (n = 112), depressed mothers (n = 73), and nonsubstance abusing controls (n = 94). Using hierarchical regression techniques and mediational analyses controlling for ethnicity, current depression, and family history of substance abuse, support was provided for an emotion-focused coping style as a link between addictive and antisocial behavior. These results highlight the importance of focusing on emotion regulation models in the prevention and treatment of violence in drug-abusing women. Hien, D.A. and Miele, G.M. Emotion-Focused Coping as a Mediator of Maternal Cocaine Abuse and Antisocial Behavior. Psychology of Addictive Behaviors, 17(1), pp. 49-55, 2003.

The Validity of Analyses Testing the Etiology of Comorbidity between Two Disorders: A Review of Family Studies

This study examined the validity of family prevalence analyses in testing alternative comorbidity models. Across 42 family studies, three comorbidity models were tested: the alternate forms model, the correlated liabilities model, or the three independent disorders model. Results from data simulations suggest that some analyses may be valid tests of the alternate forms model (i.e., two disorders are alternate manifestations of a single liability), but that none of the analyses are valid tests of the correlated liabilities model (i.e., a significant correlation between the risk factors for the two disorders) or the three independent disorders model (i.e., the comorbid disorder is a third, independent disorder). Rhee, S.H., Hewitt, J.K., Corley, R.P. and Stallings, M.C. The Validity of Analyses Testing the Etiology of Comorbidity between Two Disorders: A Review of Family Studies. Journal of Child Psychology & Psychiatry and Allied Disciplines, 44(4), pp. 612-636, 2003.

Buffering Effects of Religiosity on Substance Use

This research tested the hypothesis that religiosity buffers the impact of life stress on adolescent substance use. Data were from a sample of 1,182 participants surveyed on 4 occasions between 7th grade and 10th grade. Cross-sectional results showed an inverse relation between religiosity and substance use (cigarette smoking, alcohol use, heavy drinking, marijuana use). Longitudinal analyses using latent growth modeling indicated that the impact of negative life events on both initial level of substance use and rate of growth in substance use was reduced among individuals scoring high on religiosity. Wills, T.A., Yaeger, A.M., and Sandy, J.M. Buffering Effect of Religiosity for Adolescent Substance Use. Psychology of Addictive Behaviors, 17, pp. 24-31, 2003.

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Research Findings - Prevention Research

Limited Transfer of Research to Practice in School-based Substance Use Prevention

This study compared current substance use prevention practices in schools against standards of evidence-based prevention strategies for "effective content" and "effective delivery." Respondents were lead school staff that taught substance use prevention from 1998-1999 in a national sample of public and private schools that included middle school grades (N=1,795). Results indicate that most providers (62.25%) taught effective content, but few used effective delivery (17.44%), and fewer still used both effective content and delivery (14.23%). Those who taught evidence-based programs (e.g., Life Skills Training, Project ALERT), however, were more likely to implement both effective content and delivery, as were those teachers who were recently trained in substance use prevention and were comfortable using interactive teaching methods. These findings indicate that in the past, transfer of research knowledge to practice about school-based substance use prevention programming has been limited. Ennett, S.T., Ringwalt, C.L., Thorne, J., Rohrbach, L.A., Vincus, A., Simons-Rudolph, A., and Jones, S. A Comparison of Current Practice in School-Based Substance Use Prevention Programs with Meta-analytic Findings. Prevention Science, 4(1), pp. 1-14, 2003.

Sampling of High Risk-Related Populations

Adaptive sampling, where the sampling design adapts based on observations made during the survey, is particularly useful to substance use researchers when the population of interest is rare, unevenly distributed, hidden, or hard to reach. Examples of such populations are injection drug users, individuals at high risk for HIV/AIDS, and young adolescents who are nicotine dependent. By contrast, conventional sampling designs are based entirely on a priori information, and are fixed before the study begins. In the present article several adaptive sampling designs are discussed. Link-tracing designs such as snowball sampling, random walk methods, and network sampling are described, along with adaptive allocation and adaptive cluster sampling. It is stressed that special estimation procedures taking the sampling design into account are needed when adaptive sampling has been used. These procedures yield estimates that are considerably better than conventional estimates. For rare and clustered populations adaptive designs can give substantial gains in efficiency over conventional designs, and for hidden populations, link-tracing and other adaptive procedures may provide the only practical way to obtain a sample large enough for study objectives. Thompson, S. K. and Collins, L.M. Adaptive Sampling in Research on Risk-Related Behaviors. Drug and Alcohol Dependence, 68(1), pp. 57-67, 2002.

Sensation-Seeking Moderates Peer Influences on Marijuana and Cigarette Use

The interactions of sensation seeking with peer influence variables on marijuana and cigarette use were examined. Using survey data from 3,127 eighth graders in 20 U.S. middle schools, authors found that peer pressure and perceived peer marijuana use had a relatively small effect on low sensation-seekers and a much greater effect on high sensation seekers. In addition, aspirations inconsistent with marijuana use appeared protective for high sensation-seekers. These findings suggest that moderate and high sensation-seekers should be the primary audience for substance use prevention efforts directed toward younger adolescents. Reinforcing the perceptions that substance use is inconsistent with personal aspirations might counterbalance the

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vulnerability sensation-seeking youth to peers. Slater, M.D., Sensation-Seeking as a Moderator of the Effects of Peer Influences, Consistency with Personal Aspirations, and Perceived Harm on Marijuana and Cigarette Use Among Younger Adolescents. Substance Use & Misuse 38(7), pp. 865-880, 2003.

Self-Fulfilling Prophecies and Underage Drinking

This research examined whether mothers' expectations about their children's drinking behavior influenced their children's alcohol use through self-fulfilling prophecies and examined factors moderating this influence. The researchers defined self-fulfilling prophecies as expectations that lead to their own fulfillment (Merton, 1948). Longitudinal survey data were used from a study of 505 mother-child dyads living in the rural Midwest who participated in a prevention program. The investigators constructed a measure of the "inaccurate" portion of mothers' expectations by regressing mother's expectation for her child's future alcohol use on a composite score of valid predictors of the child's substance use (such as child's gender, family income, and child's past alcohol use) then creating residuals reflecting the accuracy of the mother's expectation. The investigators found that the inaccurate portion of mother expectations predicted children's future alcohol use after accounting for relevant control variables. Moderation analyses indicated that the self-fulfilling effect of mother expectations was stronger among high self-esteem children and when mother expectations were positive. These findings suggest that mothers have a small but significant self-fulfilling effect on their children's future alcohol use. Madon, S., Guyll, M., Spoth R.L., Cross, S.E., and Hilbert, S.J. The Self-fulfilling Influence of Mother Expectations on Children's Underage Drinking. Journal of Personality and Social Psychology, 84(6), pp. 1188-1205, 2003.

Life Skills Training Program Outcomes in a Rural, Midwest Youth Population

The purpose of this study is to extend earlier research by evaluating the effect of the Life Skills Training (LST) school-based preventive intervention on substance initiation and two related constructs, expectancies and refusal intentions, in a rural, Midwestern sample. The 15-session LST program (which is based on social cognitive/learning theory and problem behavior theory) was implemented during classroom periods by trained teachers using interactive teaching techniques. All seventh-grade students in 24 participating schools were recruited for participation in the study, and a total of 847 students were included in the growth curve analysis. The pretest, posttest, and follow-up assessments were conducted during the fall of the seventh grade, the spring of seventh grade, and the spring of eighth grade, respectively. The intervention significantly slowed the rate of increase in substance initiation and significantly slowed the rate of decrease in refusal intentions in both males and females. Notably, a stronger intervention effect was detected for females with regard to the rate of decrease in refusal intentions. Trudeau, L., Spoth, R., Lillehoj, C., Redmond, C., and Wickrama, K.A.S. Effects of a Preventive Intervention on Adolescent Substance Initiation, Expectancies, and Refusal Intentions. Prevention Science, 4(2), pp. 109-122, 2003.

Mixture Models for Nonignorable Dropout in Longitudinal Data

Random-coefficient pattern-mixture models (RCPMM's) have been proposed for longitudinal data when dropout is thought to be nonignorable. An RCPMM is a random-effects model with summaries of dropout time included among the regressors. The basis of every RCPMM is extrapolation. This article reviews RCPMM's, describes various extrapolation strategies, and shows how analyses may be simplified through multiple imputation. Using simulated and real data, it shows that alternative RCPMM's that fit equally well may lead to very different estimates for parameters of interest. The authors also show that minor model misspecification can introduce biases that are quite large relative to standard error, even in fairly small samples. For many scientific applications, where the form of the population model and nature of the dropout are unknown, interval estimates from any single RCPMM may suffer from undercoverage because uncertainty about model specification is not taken into account. Demirtas, H. and Schafer, J.L. On the Performance of Random-Coefficient Pattern-Mixture Models for Nonignorable Dropout. Statistics in Medicine, 21, pp. 1-23, 2003.

Communication of Prevention Program Requirements to School Program Implementers

The Department of Education promulgated the "Principles of Effectiveness" and required school districts that received support from the Safe and Drug-Free Schools and Community initiative to: 1) base drug and violence prevention programming on

needs assessment data; 2) develop measurable program goals and objectives; 3) implement programs for which there is research evidence of effectiveness, and 4) periodically evaluate programs relative to their goals and objectives. This paper reports on the extent of national awareness of these Principles of Effectiveness, and plans for their implementation among public school districts and schools in the year following their announcement. Results of a mail survey of a national sample of public and private schools' lead staff who taught substance use prevention in the 1998-1999 school year (n=1,795) showed that baseline levels of awareness for these requirements were low in both school districts and schools. Results also suggest the need for greater communication about the principles to school districts and, in turn, the need for greater communication between district and school-levels substance use prevention staff to produce better adherence to these principles. Simons-Rudolph, A.P., Ennett, S.T., Ringwalt, C.L., Rohrbach, L.A., and Vincus, A.A. The Principles of Effectiveness: Early Awareness and Plans for Implementation in a National Sample of Public Schools and Their Districts. Journal of School Health, 73, pp. 181-185, 2003.

Outcomes from the Child Development Project

The Child Development Project is a longitudinal, multisite study that examines the development of aggressive behavior disorders in children and adolescents. Families were recruited in two cohorts in 1987 and 1988 at three sites: Nashville, TN, Knoxville, TN, and Bloomington, IN. The original sample included 585 youths and their families. Results from several recent secondary data analyses are presented:

Neighborhood Structure, Parenting Processes, and Externalizing Behaviors

Associations among neighborhood structure, parenting processes, and the development of externalizing behavior problems were examined among youth age 11 to 13. Hierarchical linear modeling revealed that less parental monitoring was associated with more externalizing behavior problems at age 11, and more unsupervised time spent out in the community and less positive parental involvement were associated with increases in externalizing behavior at ages 12 and 13. The decrease in externalizing levels associated with more parental monitoring was significantly more pronounced when youths lived in neighborhoods with more residential instability. Beyers, J.M., Bates, J.E., Pettit, G.S. and Dodge, K.A. Neighborhood Structure, Parenting Processes, and the Development of Youths' Externalizing Behaviors: A Multilevel Analysis. American Journal of Community Psychology, 31, pp. 35-53, 2003.

Social Rejection and Antisocial Behavior

With a series of ANOVA models and path analysis, this paper examined the relationship between social rejection and growth in antisocial behavior over time. Several findings of note were reported. First, early peer rejection predicted growth in aggression over time. Second, early aggression moderated the effect of rejection, such that rejection exacerbated antisocial development only among children initially disposed toward aggression. Third, social information processing patterns were found to mediate partially the effect of early rejection on later aggression. Dodge, K.A., Lansford, J.E., Salzer Burks, V., Bates, J.E., Pettit, G.S., Fontaine, R. and Price, J.M. Peer Rejection and Social Information-Processing Factors in the Development of Aggressive Behavior Problems in Children. Child Development, 74, pp. 374-393, 2003.

Father Absence and Risk for Early Sexual Activity and Teenage Pregnancy

The impact of father absence on early sexual activity and teenage pregnancy was investigated in longitudinal studies in the United States and New Zealand. In both studies girls were studied prospectively from age 5 until age 18. Results from both datasets revealed that greater exposure to father absence was strongly associated with elevated risk for early sexual activity and adolescent pregnancy. After controlling for important covariates, there was a stronger and more consistent relationship between father absence and early sexual activity and teenage pregnancy than on other behavioral and mental health problems or academic achievement. Ellis, B.J., Bates, J.E., Dodge, K.A., Fergusson, D.M., Horwood, L.J., Pettit, G.S. and Woodward, L. Does

Father Absence Place Daughters at Special Risk for Early Sexual Activity and Teenage Pregnancy? Child Development, 74, pp. 801-821, 2003.

Parents' Monitoring-Relevant Knowledge and Adolescents' Delinquent Behavior

This study examined relationships between parental knowledge and adolescent delinquent behavior over a period of 4 years beginning at age 14. Results showed that parental monitoring-relevant knowledge was negatively correlated with delinquent behaviors at baseline and increases over time in such knowledge were negatively correlated with increases in parent-reported delinquent behavior. Reciprocal correlations may indicate that low levels of parental knowledge predict increases in delinquent behavior and that high levels of delinquent behavior predict decreases in knowledge. Laird, R.D., Pettit, G.S., Bates, J.E. and Dodge, K.A. Parents' Monitoring-Relevant Knowledge and Adolescents' Delinquent Behavior: Evidence of Correlated Developmental Changes and Reciprocal Influences. Child Development, 74, pp. 752-768, 2003.

Effects, Message Sensation and Cognition Value

An experimental study was designed to investigate the influence of message strategies on cognitive processing and changes in attitudes, behavioral intentions, and behavior in relation to marijuana use. Researchers created a measure of message cognition value (MCV) and evaluated anti-marijuana messages designed to vary on cognition value as well as sensation value. Three hundred and thirty eight 18-20 year old college students viewed four anti-marijuana public service announcements four times over a four-week period in a lab setting. They completed instruments measuring the need for sensation (NFS) and need for cognition (NFC), cognitive processing attitudes toward marijuana use, intention to use marijuana, and self-reported marijuana use. There was partial support for a main effect of message sensation value (MSV) on changes in attitude, intention and behavior but limited support for an interaction of MSV with NFS on attitude change. Additionally, a significant main effect for message cognition value (MCV) indicates that high cognition value messages led to greater recall than low cognition messages but there was no interaction effect of MCV with NFC. Cognitive processing and message cognition value did not affect attitude, behavioral intentions or behavior regarding marijuana use. Based on these findings, designing messages high in both sensation value and cognition value should be the goal of prevention campaigns. Harrington, N.G., Lane, D.R, Donohew, L., Zimmerman, R.S., Norling, G.R., An, J.H., Cheah, W.H., McClure, L., Buckingham, T., Garofalo, E., and Bevins, C.C. Persuasive Strategies for Effective Anti-Drug Messages, Communication Monographs 70(1), pp.16-38, 2003.

Theory in the Design of Effective Communication

The usefulness of two integrating theories for the development of effective health campaigns is illustrated. The integrative model of behavioral prediction focuses on changing beliefs about the consequences (costs and benefits), perceived norms, and self-efficacy regarding a particular behavior. These, in turn, shape intentions to perform the behavior that underlies action. The model can help explain why some members of a target population are performing the behavior and others are not and this understanding points to the beliefs that need to be addressed in a theory-based communication. For example, if people have not formed the desired intention, an intervention should be directed at changing attitudes, norms or self- efficacy. However, if people have the desired intention but are not acting on it, the intervention should be directed at skill building or removing environmental constraints. Media priming theory focuses on strengthening the association between a belief and its outcomes, such as attitude and intention toward performing the behavior. An effective communication campaign increases the association between beliefs that are consonant with recommended behavior and the more proximal determinants of that behavior. The message strategy should be to identify and target attitudes, norms or beliefs consonant with the desired behavior. The theories are complementary and the article shows how together they provide guidance for selecting beliefs to target in an intervention, namely those that both change beliefs and strengthen the association between the belief and attitude and/or intention. Fishbein, M. and Yzer, M. Using Theory to Design Effective Health Behavior Interventions. Communication Theory 13(2), pp. 64-183, 2003.

Using Beliefs About Consequences in Message Design

Improving health communications campaigns through message design is illustrated

with findings on messages targeted at adolescent marijuana use. The Integrated Model of Behavior holds that a primary determinant of behavior is the person's intention to perform it; intention, in turn, is a function of the person's attitude, normative pressure and self-efficacy to perform the behavior. These are functions of underlying beliefs about the outcomes of performing the behavior. Based on a sample of 1,175 adolescents from middle and high schools around Philadelphia, the researchers explored 36 behavioral beliefs (i.e., positive and negative consequences that a person thinks will happen to him or her) related to regular marijuana use, and compared the responses of high and low risk youth. They found substantial differences between the groups with respect to the likelihood of an effect but far less difference between the risk groups in the value they place on a behavioral belief related to use. For example, high-risk youth do not believe that marijuana use leads to stronger drugs but low risk youth do; both groups agree that that is a negative outcome. The findings suggest campaign designers use the IM to test for the acceptability of behavioral beliefs; test a comprehensive group of beliefs; focus on the beliefs of the high risk subgroup; select beliefs that are already accepted to change. Capella, J.N., Yzer, M. and Fishbein, M. Using Beliefs about Positive and Negative Consequences as the Basis for Designing Message Interventions for Lowering Risky Behavior. pp. 210-219 in Romer, D. (Ed.) Reducing Adolescent Risk. Thousand Oaks, CA: Sage, 2003.

Lessons From a Successful Participatory Action Research Model

This article describes the use of Participatory Action Research (PAR) in the development of the Drug Resistance Strategies Project. PAR requires the direct participation of the community under study and emphasizes social change to solve problems. Through the use of focus groups with teachers and students and the field-testing of products, investigators learned valuable lessons that were translated directly into programmatic design features. Student feedback led to an emphasis on grade 7, the selection of core strategies for drug resistance, the program specific graphic material, and video production (which was undertaken by students). Feedback from teachers was directly used for development of learning objectives and materials as well as practical implementation concerns. Teachers were included in the research team and given ownership of the lessons. The success of this model is inferred in part from positive program outcomes such as a favorable shift in social norms and reduced alcohol and/or drug use among program participants. Gosin, M.N., Dustman, P.A., Drapeau, A.E., and Harthun, M.L. Participatory Action Research: Creating an Effective Prevention Curriculum for Adolescents in the Southwestern US. Health Education Research, 18(3), pp. 363-379, 2003.

Stimulating Adoption of Empirically Supported Treatments in Clinical Settings

Drawing on their experiences implementing the Incredible Years Parent-Training Program and several other empirically supported treatments in a children's mental health center, recommendations and guidelines for future program adoption were developed based on suggestions about effective methods for adopting empirically supported treatment programs in mental health centers. Data were collected through surveys and qualitative interviews with the clinicians and administrators following their implementation of the Incredible Years Program. Successful program implementation hinges on the representation, support, and joint involvement of clinicians, administrators, and an "innovator" who acts as a champion and advocate for the program adoption process. Adoption is fostered by: developing a collaborative working group, making the decision process clear, pilot testing, and garnering organizational commitment for the use of empirically supported treatments. A detailed list of role specific recommendations is offered for each of the three collaborative workgroup participants: the innovator, the clinician, and the administrator. Schmidt, F. and Taylor, T.K. Putting Empirically Supported Treatments Into Practice: Lessons Learned in a Children's Mental Health Center. Professional Psychology, 33, pp. 483-489, 2002.

The Timing and Spacing of Observations in Longitudinal Studies

The impact of the temporal design (i.e., the sampling of times of measurement), can affect the statistical and substantive conclusions drawn from longitudinal biomedical and social science research. For a study of a given duration, if observations are spaced too far apart the resulting data can support misleading conclusions, whereas if observations are spaced relatively close together, a much more veridical picture of the process of interest is provided. These ideas are applied to several types of analyses including correlation and regression analyses, where a variable measured at one time is used to predict a variable measured at a later time; growth curve analyses; and analyses involving stage-sequential processes. The authors argue that

longitudinal designs should relate the choice of timing and spacing of observations in longitudinal studies to characteristics of the processes being measured. In addition, consideration of the possible effects of measurement design on results of statistical analyses may aid in their interpretation. New approaches involving intensive data collection with much shorter measurement interval, such as Ecological Momentary Assessment, are promising but costly and are not suitable for every research question. Collins, L.M. and Graham, J.W. The Effect of the Timing and Spacing of Observations in Longitudinal Studies of Tobacco and Other Drug Use: Temporal Design Considerations. Drug and Alcohol Dependence, 68(1), pp. 85-96, 2002.

Review of the Communities That Care Youth Survey

Risk and protective factors predictive of adolescent problem behaviors such as substance abuse and delinquency are promising targets for preventive intervention. Community planners should assess and target risk and protective factors when designing prevention programs. This paper describes the development, reliability and validity of a self-report survey designed for adolescents 11 to 18 that measures an array of risk and protective factors across multiple ecological domains as well as adolescent problem behaviors. This instrument can be used to assess the epidemiology of risk and protection in youth populations and to prioritize specific risk and protective factors in specific populations as targets for preventive interventions. Arthur, M.W., Hawkins, J.D., Pollard, J.A., Catalano, R.F., and Baglioni, A.J. Measuring Risk and Protective Factors for Substance Use, Delinquency, and Other Adolescent Problem Behaviors: The Communities That Care Youth Survey. Evaluation Review, 26(6), pp. 575-601, 2002.

Cost Analysis of Prevention Programs

Fast Track is a multiyear, multicomponent intervention targeted to children at risk for emotional and behavioral problems. This article does not show a definitive cost analysis of the program, but it presents various ways of conceptualizing this analytic approach. The components of the Fast Track intervention include a universal prevention within schools, selective prevention provided to families of children identified as high risk during kindergarten screening, and individualized selective support provided to high-risk children and families based on criterion-referenced assessments over time. The cost analysis process involves identifying the resources involved, measuring their use, and valuing the resources used in dollar terms. The resulting cost estimates include both the direct and morbidity-related costs of the intervention, such as the costs of services provided to children with emotional and behavioral problems. In many cases, such costs are actually reduced by a prevention program, and if so, this provides an opportunity for a cost offset. This type of economic analysis generally results in a range of estimates calculated for each competing assumption or set of figures. Supplemental analysis can be used to examine variation in the impact of the intervention for children with different problem severity levels. The key question to be answered by such cost analysis is whether the direct costs of a prevention program are offset by reductions in the other, morbidity-related costs, such as the subsequent use of expensive services. Foster, E.M., Dodge, K.A. and Jones, D. Issues in the Economic Evaluation of Prevention Programs. Applied Developmental Science, 7, pp. 76-86, 2003.

Assessing Reliability of Substance Use Measures

Latent class models can be used to identify classes of individuals and to assess the psychometric reliability of categorical items. The latent class model is a categorical latent variable model used to identify homogeneous classes of respondents such that class membership accounts for item responses. The assessment of measurement reliability comes directly from the estimates of the model. Although not based on classical test theory, the reliability assessment procedures described answer the same question--that is, how consistent or dependable is measurement? The goal is to identify reliable indicators of a characteristic by examining measurement error and the inter-relatedness of the items. Methods for estimating the reliability of individual items as well as sets of items are presented. These methods are illustrated with data on cigarette smoking from a national sample of adolescents. By using the procedures described, researchers are able to determine: (1) which classes of people are measured well and which are not; (2) which items perform well and which do not; and (3) whether items need to be altered or added in order to measure and identify particular classes better. Flaherty, B.P. Assessing Reliability of Categorical Substance Use Measures with Latent Class Analysis. Drug and Alcohol Dependence, 68(1), pp. 7-20, 2002.

Using Theory to Design Evaluations of Communication Campaigns

A general theory about media campaign effects is presented to illustrate the use of theory in the evaluation of communication campaigns, highlight a theory of campaign effects, and demonstrate its implications for evaluation design using the National Youth Anti-Drug Media Campaign (NYAMC). Campaign exposure effects may operate through individual, social or institutional paths. Such effects also may require substantial levels of exposure through multiple channels over long periods of time in order to accumulate measurable changes. Thus, the design of responsive evaluations depends on selecting appropriate units of analysis and comparison groups, measuring lagged effects, selecting samples able to detect subgroup effects, and analytic strategies consistent with both the underlying theoretical model and the theory of effects. The ongoing evaluation of the NYAMC illustrates such an evaluation strategy and the need for complex evaluation design to detect its effects. Hornik, R and Yanovitzky, I. Using Theory to Design Evaluations of Communication Campaigns: The Case of the National Youth Anti-Drug Media Campaign. Communication Theory, 13(2), pp. 204-224, 2003.

Director's Report to the National Advisory Council on Drug Abuse - September, 2003

Research Findings - Services Research

Costs and Benefits of Addiction Treatment

Little information is available on the client and treatment characteristics that contribute to treatment costs and benefits. This study analyzed data from a sample of treatment clients from the Chicago Target Cities Project to develop estimation techniques and to determine predictors of treatment cost, benefit, and net benefit. The Chicago Project was a quasi-experimental evaluation study of 2,862 individuals in various addiction treatment facilities. Economic analyses were conducted in two stages. First, the authors estimated cost and benefit during the 6-month follow-up, using previously published methods, and then used these measures to compute average cost, benefit, net benefit, and benefit-cost ratio. Second, the authors statistically examined the distributions of cost, benefit, and net benefit and selected empirical models for handling non-normal data. These models were then estimated to identify the predictors of cost, benefit, and net benefit. Results indicate that the average (per client) cost of all treatment services from baseline to follow-up was $1,943. The average treatment benefit was $8,268, leading to an average net benefit of $6,325 and a benefit-cost ratio of 4.26. Findings from a robust regression suggest that (1) age, race, age at first drug use, treatment modality, and some treatment characteristics were significantly related to treatment cost, and (2) education, age at first drug use, some scores on the Addiction Severity Index, some types of treatment, and resistance to continuing care were related to treatment benefit and net benefit. In conclusion, for the average individual, the net benefit (benefit-cost ratio) of treatment was significantly greater than zero (one). Furthermore, cost and benefit were significantly related to certain client and program characteristics. Future studies may find these empirical models useful when investigating the predictors of the costs and benefits of addiction treatment. Salome, H.J., French, M.T., Scott, C., Foss, M. and Dennis, M. Investigating Variation in the Cost and Benefits of Addiction Treatment: Econometric Analysis of the Chicago Target Cities Project. Evaluation and Program Planning, 26, pp. 325-118, 2003.

Utilization and Cost Impact of Integrating Substance Abuse Treatment and Primary Care

This study examined the impact of integrating medical and substance abuse treatment on health care utilization and cost. Patients participated in a randomized clinical trial in which they were assigned to one of two treatment modalities: (1) an Integrated Care model where primary health care was provided with substance abuse treatment within the unit, and (2) an Independent Care model where medical care was provided in the HMO's primary care clinics independently from substance abuse treatment. There were no statistically significant differences between the two treatment groups over time for the full, randomized cohort. However, among the subset of patients with substance abuse related medical conditions, Integrated Care patients had statistically significant decreases in hospitalization rates, inpatient days and Emergency Room use. Total medical costs per member-month declined significantly from $431.12 to $200.03. Among Independent Care patients with substance abuse related medical conditions, there was a downward trend in inpatient days and Emergency Room costs, but no statistically significant decrease in total medical cost. Findings for the full sample suggest that integrating substance abuse treatment with primary care may not be necessary or appropriate for all patients. However, it may be beneficial to refer patients with substance abuse related medical conditions to a provider also trained in addiction medicine given that there appear to be large cost impacts of providing integrated care for such patients. Parthasarathy, S., Mertens, J., Moore, C., and Weisner, C. Utilization and Cost Impact of Integrating

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Substance Abuse Treatment and Primary Care. Medical Care, 41(3), pp. 357-367, 2003.

The Value of Intensive Services for High-Risk Offenders

Tests of the importance of service matching have had varying results, yet little attention has been given to testing the hypotheses about outcomes for clients based on differing risks to recidivate. The authors tested the "risk principle" (i.e., treatment services should target the specific factors that increase risk of recidivism for each client) and "responsivity principle" (i.e., treatment services should be consistent with the abilities and learning style of each individual offender) using a sample of clients from one site of a four-site randomized block experimental design study examining the effectiveness of traditional criminal justice supervision vs. a systemic case management model in which the management and organization of treatment and criminal justice supervision services are part of an integrated care plan. Findings from a preliminary examination of official and self-report data from this site suggest the importance of the risk and responsivity concepts in providing substance abuse treatment, particularly for high-risk clients. Because of the relatively low statistical power of the tests used in this exploratory analysis, many observed relationships were not statistically significant. Nonetheless, the delivery of criminal justice supervision with a continuing care intervention improves treatment participation and retention. Those in the high-risk treatment group experienced fewer overall arrests within one-year of randomization into the study. Thanner, M.H. and Taxman, F.S. Responsivity: The Value of Providing Intensive Services to High-Risk Offenders. Journal of Substance Abuse Treatment, 24(2), pp. 137-147, 2003.

Employment Intervention for Drug Abusing Offenders

An examination of 500 participants at drug court entry who consented to participate in the Kentucky project revealed that less than half worked full-time before entering Drug Court; participants averaged 3.7 jobs in the five years before entering drug court; and the longest full-time job held averaged 4.3 years with 80.4 days of employment at a legal job in the six months before entering Drug Court. Most participants reported their last or usual occupation as a service worker or as a laborer. Participants reported transportation, job placement and job training as the types of employment help they most needed, which reinforced the finding that almost half (41%) reported employment problems in the six months before entering Drug Court. These findings highlight the importance of developing employment interventions that can assist drug abusers involved in the criminal justice system. Future project studies will examine differences in participants who are randomized into the enhanced employment intervention when compared with those who are randomized into Drug Court as usual. Leukefeld, C., Smiley McDonald, H., Staton, M., Mateyoke-Scrivner, A., Hopper, H., Webster, J.M., Logan, T.K., Hiller, M. and Garrity, T. An Employment Intervention for Drug Abusing Offenders. Federal Probation, April 2003.

Psychological Distress, Employment, and Drug Use among Female Welfare Recipients

In this study, the authors examined the relationship over time among work experience, psychological distress, and illegal substance use in a sample of 534 women receiving Temporary Assistance for Needy Families. Study participants were interviewed at intake and at 4-month intervals for a period of 2 years. Each interview recorded the number of hours worked in the previous 4 months and the use of powder cocaine, crack cocaine, heroin, or methamphetamines during the same period. To measure the extent of psychological distress, participants completed the personal adjustment problems subscales of the Multidimensional Addictions and Personality Profile at intake and at 1-year intervals. A path model was analyzed to assess the temporal effects of employment, drug use, and emotional and psychological distress. Results suggest a cycle in which employment at one time period can reduce the likelihood of drug use in the following period, which, in turn, can lead to improvement in levels of distress. This improvement can lead to an increase in the number of hours worked and further improvement in distress levels. Atkinson, J.S., Montoya, I.D., Whitsett, D.D., Bell, D.C. and Nagy, C.W. The Relationship Among Psychological Distress, Employment, and Drug Use Over Time in a Sample of Female Welfare Recipients. Journal Of Community Psychology, 31(3), pp. 223-234, 2003.

Little Change During 1990s in Availability of Comprehensive Services in Outpatient Drug Abuse Treatment

Research suggests that comprehensive medical and psychosocial services that are essential to high quality addiction treatment, declined in the 1980s. To determine whether this downward trend in the availability of comprehensive services continued in the 1990s, the researchers analyzed data from a national panel study of outpatient substance abuse treatment units in 1990 (n=481), 1995 (n=618), and 2000 (n=745). Response rates exceeded 85%. Regarding the availability of comprehensive services, including physical examinations, routine medical care, mental health services, financial counseling, and employment counseling, administrators reported whether any substance abuse treatment client received the service in the past year. The reported availability of comprehensive services changed little during the 1990s, with the exception of physical examinations (reported availability increased from 1990 to 1995) and financial counseling (reported availability decreased from 1990 to 1995). These findings highlight the continuing need to monitor access to comprehensive services and other markers of program quality in addiction treatment over time. Friedmann, P.D., Lemon, S.C., Durkin, E.M., and D'Aunno, T.A. Trends in Comprehensive Service Availability in Outpatient Drug Abuse Treatment. Journal of Substance Abuse Treatment, 24(1), pp. 81-88, 2003.

Accessibility of Addiction Treatment: Results from a National Survey of Outpatient Substance Abuse Treatment Organizations

This study examined organization-level characteristics associated with the accessibility of outpatient addiction treatment. Program directors and clinical supervisors from a nationally representative panel of outpatient substance abuse treatment units in the United States were surveyed in 1990, 1995, and 2000. Accessibility was measured from clinical supervisors' reports of whether the treatment organization provided "treatment on demand" (i.e., average wait time of < 48 hours for treatment entry), and of whether the program turned away any patients. In multivariable logistic models, provision of "treatment on demand" increased two-fold from 1990 to 2000, while reports of turning patients away decreased nonsignificantly. Private for-profit units were twice as likely to provide "treatment on demand," but seven times more likely to turn patients away than public programs. Conversely, units that served more indigent populations were less likely to provide "treatment on demand" or to turn patients away. Methadone maintenance programs were also less likely to offer "treatment on demand," but more likely to turn patients away. Although the provision of timely addiction treatment appears to have increased throughout the 1990s, accessibility problems persist in programs that care for indigent patients and in methadone maintenance programs. Friedmann, P.D., Lemon, S.C., Stein, M.D., and D'Aunno, T.A. Accessibility of Addiction Treatment: Results from a National Survey of Outpatient Substance Abuse Treatment Organizations. Health Services Research, 38, pp. 887-903, 2003.

Prevalence of Hepatitis C in a Drug Using and Non-using Welfare Population

Drug use is a primary route for the transmission of the hepatitis C virus (HCV), and a substantial proportion of welfare recipients have been shown to be substance abusers. Despite the fact that HCV symptoms may inhibit welfare recipients' ability to seek and maintain employment, federal legislation has imposed limits on the number of months individuals may receive welfare benefits and has mandated most recipients to participate in a 'work activity' in exchange for benefits. In this study, researchers sought to assess the prevalence of HCV in recipients of Temporary Assistance to Needy Families (TANF), and the effects of HCV antibody seropositivity on employability. Participants were 380 individuals participating in a longitudinal study of employment patterns among TANF recipients in Houston, TX. Participants were interviewed about welfare receipt, employment, and drug use at intake into the study and at 4-month intervals for one year. They also received a one-time blood draw to test for the presence of HCV antibodies by enzyme-linked immunoassay. Overall, 12% of participants tested positive for the presence of HCV antibodies, with a significantly greater proportion of chronic drug users (31%) than non-drug users (4%) testing positive. Those who tested positive for hepatitis C had significantly lower rates of employment. Future research should focus more closely on the impact of HCV infection in obtaining employment for welfare recipients. Montoya, I.D., Atkinson, J.S., Lichtiger, B., and Whitsett, D.D. Prevalence of Hepatitis C in a Drug Using and Non-Using Welfare Population. Health Policy, 64(2), pp. 221-228, 2003.

Provision of Hepatitis C Education in Drug Treatment Programs

Using a nationwide sample of 434 drug treatment programs, the researchers report the results of a logistic regression analysis that differentiates programs providing HCV education to all of their patients versus programs that do not. Fifty-four percent of the programs provide HCV education to all patients. Programs are about four and a half

times as likely to provide HCV education to all patients if they dispense methadone; almost four times as likely to provide this service if they educate most of their staff about HCV; twice as likely if they are residential; and almost twice as likely if they conduct HIV testing on-site. Thus, in spite of the high prevalence of hepatitis C among drug users, only about half of the drug treatment programs in the United States educate all of their patients about hepatitis C. Drug-free outpatient programs, especially those without a medical orientation, need to take proactive steps to provide critically needed HCV education to all of their patients. Astone, J., Strauss, S.M., Vassilev, Z.P., and Des Jarlais, D.C. Provision of Hepatitis C Education in a Nationwide Sample of Drug Treatment Programs. Journal of Drug Education, 33(1), pp. 107-117, 2003.

Screening for Sexually Transmitted Infections in Substance Abuse Treatment Programs

The authors evaluated the prevalence of two sexually transmitted infections (STIs)--chlamydia and gonorrhea--in clients at a methadone maintenance program and a residential detoxification program. Data collection included urine specimens for chlamydia and gonorrhea ligase chain reaction testing and assessment of sexual, substance abuse, and STI histories. Of 700 subject assessments, 490 occurred among detoxification clients and 210 in methadone maintenance clients. Chlamydia trachomatis was detected in 5/700 (0.9, 5% CI = 0.1-1.8%) and Neisseria gonorrhoeae in none. All chlamydia-infected subjects were recruited from the detoxification program. Subjects reported high risk sexual behavior: 17% reported commercial sex exchange, and 22% reported inconsistent condom use with multiple sex partners during the prior 2 months. Study results suggest that routine screening among younger substance abusers and in communities with high prevalence should be considered. Liebschutz, J.M., Finley, E.P., Braslins, P.G., Christiansen, D., Horton, N.J., and Samet, J.H. Screening for Sexually Transmitted Infections in Substance Abuse Treatment Programs. Drug and Alcohol Dependence, 70(1), pp. 93-99, 2003.

On-Site Primary Medical Care at Addiction Treatment Programs Can Improve Outcomes

This secondary data analysis examined whether the availability of primary medical care on-site at addiction treatment programs or off-site by referral improves patients' addiction severity and medical outcomes, compared to programs that offer no primary care. The original study involved a prospective cohort of patients admitted to a purposive national sample of substance abuse treatment programs. Administrators at 52 treatment programs and 2,878 patients completed treatment intake, discharge, and follow-up interviews. After controlling for treatment modality, geographic region, and multiple patient-level characteristics, patients who attended programs with on-site primary medical care experienced significantly less addiction severity at 12-month follow-up compared with patients who attended programs with no primary medical care. However, on-site care did not significantly influence medical severity at follow-up. Referral to off-site primary care exerted no detectable effects on addiction severity or medical severity. It appears then that on-site primary medical care can improve addiction-related outcomes but not necessarily the health --related outcomes of substance treatment patients. Friedmann P.D., Zhang Z., Hendrickson J., Stein, M.D., and Gerstein, D.R. Effect of Primary Medical Care on Addiction and Medical Severity in Substance Abuse Treatment Programs. Journal of General Internal Medicine, 18(1), pp. 1-8, 2003.

Multidisciplinary Clinic Links Substance Abusers with Medical Care

In response to an increasing need for pragmatic approaches to the integration of medical care and substance abuse treatment, the authors assessed the effectiveness of a novel multidisciplinary clinic for linking patients in a residential detoxification program to primary medical care. Patients undergoing in-patient detoxification from alcohol, heroin, or cocaine, who had no primary care physician, entered into a randomized controlled trial. The intervention consisted of a clinical evaluation within the detoxification unit of the Health Evaluation and Linkage to Primary Care (HELP) clinic by a nurse, social worker, and physician, plus facilitated referral to an off-site primary care clinic. The primary outcome was attendance at a primary care appointment within 12 months. Secondary outcomes assessed over 24 months were addiction severity; health-related quality of life, utilization of medical and addiction services, and HIV risk behaviors. Of the 470 participants enrolled, 235 were randomized to the HELP clinic intervention. Linkage to primary medical care occurred in 69% of the intervention group compared to 53% in the control group, a statistically significant difference. The HELP clinic, a multidisciplinary clinic located in a detoxification program, effectively linked alcohol- and drug-dependent individuals to

primary medical care. This intervention utilized a "reachable moment," the period of addiction care, as a window of opportunity for linking substance abusers to medical care. The HELP clinic did not significantly affect secondary outcomes. Samet, J.H., Larson, M.J., Horton, N.J., Doyle, K., Winter, M., and Saitz, R. Linking Alcohol- and Drug-Dependent Adults to Primary Medical Care: A Randomized Controlled Trial of a Multidisciplinary Health Intervention in a Detoxification Unit. Addiction, 98(4), pp. 509-516, 2003.

Drug-Use Initiation and Conduct Disorder among Adolescents in Drug Treatment

This study investigated effects of drug-use initiation and conduct disorder (CD) among 1,031 adolescents who participated in the Drug Abuse Treatment Outcomes Studies for Adolescents (DATOS-A) sponsored by the National Institute on Drug Abuse (NIDA). The mean age of first drug use was 12.7 (S.D.=2.2), 57% met DSM-III-R criteria for CD, and earlier initiators were more likely to have CD. About 78% of the adolescents with CD reported that their first CD symptom occurred prior to drug-use initiation. The proportions of adolescents who had prior treatment were similar (about 28%) across all groups, but earlier initiators reported a greater number of treatment episodes and younger ages at their first treatment. Conduct disordered adolescents revealed greater problems prior to DATOS-A treatment, but they appeared to be more motivated and ready for treatment. Although adolescents with CD still showed worse outcomes after treatment, the impact of CD appeared to lessen when pretreatment differences were controlled. To a lesser extent, adolescents who began using drugs at earlier ages had greater alcohol and drug use and other problems at intake, but their treatment outcomes appeared to be similar to later initiators. There were few significant interaction effects of initiation and CD. Findings from this study highlight the importance of better understanding the progression of drug use, treatment utilization, and psychiatric comorbidity among adolescents with substance abuse problems. Hser, Y.I., Grella, C.E., Collins, C., and Teruya, C. Drug-Use Initiation and Conduct Disorder Among Adolescents in Drug Treatment. Journal of Adolescence, 26(3), pp. 331-345, 2003.

Gender Identity, Ethnicity, Acculturation, and Drug Use Among Adolescents in the Southwest

This article presents the findings of a survey completed by 1,351 predominantly Mexican-American middle school students residing in a large urban center in the U.S. Southwest. The study explored associations between drug use attitudes and behaviors and biological sex, gender identity, ethnicity and acculturation status. Based on the concepts of machismo and marianismo that have been used to describe Mexican populations, four dimensions of gender identity were measured: aggressive masculinity, assertive masculinity, affective femininity and submissive femininity. In explaining a variety of indicators of drug use behaviors and anti-drug norms, biological sex alone had limited explanatory power, while gender identity--often regardless of biological sex--was a better predictor. Aggressive masculinity was generally associated with higher risk of drug use, while the other three gender identity measures had selected protective effects. However, the impact of gender identity was strongly mediated by acculturation. Less acculturated Mexican-American students reported lower aggressive masculinity scores than non-Latinos. Less acculturated Mexican-American girls reported both the lowest aggressive masculinity scores and the highest submissive femininity scores. More acculturated Mexican-American students, along with the less acculturated Mexican-American boys, did not appear to be following a polarized approach to gender identity (machismo and marianismo), as was expected. The findings suggest that some aspects of culturally prescribed gender roles can have a protective effect against drug use behaviors and attitudes, possibly for both girls and boys. Kulis, S. Marsiglia, F.F., and Hurdle, D. Gender Identity, Ethnicity, Acculturation and Drug Use: Exploring Differences among Adolescents in the Southwest. Journal of Community Psychology, 31(2), pp. 167-188, 2003.

Effects of Ethnic Pride and Biculturalism on Drug Use Norms of Urban American Indian Adolescents

This study examined how strength of ethnic identity, multiethnic identity, and other indicators of biculturalism relate to the drug use norms of urban American Indian middle school students. Following the focus theory of norms, different categories of norms that may impact drug use are distinguished. Regression analysis of self-reports by 434 American Indian 7th graders attending middle schools in a large southwestern U.S. city show that those with a more intense sense of ethnic pride adhere more strongly to certain anti-drug norms, while those with negative feelings toward their

ethnic or racial heritage have more permissive norms toward drug use. Compared to multi-ethnic American Indian students, those claiming only an American Indian identity report less certainty that they would refuse potential drug offers. Those who speak a language other than English with family and friends at least occasionally report that fewer of their friends are drug users. While American Indian students with better grades in school hold consistently stronger anti-drug norms, there are few differences by gender, socioeconomic status, or age. Kulis, S., Napoli, M. and Marsiglia, F.F. Ethnic Pride, Biculturalism, and Drug Use Norms of Urban American Indian Adolescents in the Southwest. Social Work Research, 26(2), pp. 101-112, 2002.

Self-Reported Health Status Among Treated Methamphetamine Users

Little research has examined how drug abuse is related to general health status over the long term among young and middle-aged adults. The authors investigated how self-reported health status is related to prolonged methamphetamine use in a diverse sample of 350 methamphetamine users, ages 18 to 52, who have been treated for drug abuse. Using retrospective data, the authors investigated how prolonged methamphetamine use in younger and older age groups is related to two self-reported measures of current health status: overall health, and presence of a health condition that began after starting illegal drug use. The authors controlled for the effects of drug use history, social and demographic factors, and other early experiences (e.g., early sexual abuse) that might pose obstacles to good health later in life. They found that having a current health condition is predicted by greater age and by more prolonged methamphetamine use, especially among younger adults. Early sexual abuse predicts both measures of poor health. Current health status is predicted by several measures of drug use history and early experiences, but by fewer social and demographic factors. The results suggest that reduction of methamphetamine use among younger people is important in promoting their later health and that methamphetamine treatment services could be improved by a greater understanding of how early experiences influence later health. Greenwell, L., and Brecht, M.L. Self-Reported Health Status Among Treated Methamphetamine Users. American Journal Of Drug And Alcohol Abuse, 29(1), pp. 75-104, 2003.

The Role of Chronic Drug Use in Serious Injuries and Trauma

The authors estimated the differential risks of serious injury or trauma for a community-based sample of 926 chronic drug users (CDU) and a matched comparison group of 553 nondrug users (NDUs). The authors also estimated whether CDUs and NDUs differed in their utilization of health care services for serious injury or trauma. Data were collected in 1996 and 1997 through community outreach activities in Miami-Dade County, Florida. Analyses estimated the effects of drug use on (1) any lifetime serious injury or trauma, (2) any serious injury or trauma during the past 12 months, and (3) utilization of health care services for serious injury or trauma. All analyses were gender specific and the models were estimated with a measure of problematic alcohol use in addition to CDU. Female CDUs experienced significantly more serious injury, trauma, or both (both lifetime and past year) than nonusers, but drug use status did not predict serious injury or trauma (lifetime and past year) for males. Regardless of gender, conditional on experiencing any serious injury or trauma during the past year, CDUs and NDUs did not differ in their utilization of health care services. The elevated risk for serious injury or trauma for female CDUs renders these individuals vulnerable to severe medical problems. Specific training in substance abuse issues may be necessary if health care providers are to identify, engage, knowledgeably serve, and refer CDUs for appropriate services. Zavala, S.K., and French, M.T. Dangerous to Your Health - The Role of Chronic Drug Use in Serious Injuries and Trauma. Medical Care, 41(2), pp. 309-322, 2003.

Stabilization Programs Reduce Homeless Persons' Substance Use After Detoxification

This study examined whether homelessness predicted earlier resumption of substance use after detoxification, and sought evidence concerning the impact of post-detoxification stabilization programs among homeless and non-homeless individuals. Kaplan-Meier plots and proportional hazards models were used to determine association between homelessness, stabilization program use, and recurrent substance use in a prospective cohort of 470 persons entering inpatient detoxification. Among the 254 persons available at 6 months, 76% reported recurrent substance use. Homeless persons not using stabilization programs experienced the highest hazard of return to substance use after detoxification, Hazard Ratio (HR) 1.26, 95% CI (0.88,1.80). Homeless persons using these programs had the lowest rate of return to substance use HR 0.61, 95% CI (0.40,0.94). A similar impact of stabilization

programs was not seen among non-homeless participants. Post-detoxification stabilization programs may slow the "revolving door" phenomenon of relapse after detoxification among homeless persons. Kertesz, S.G., Horton, N. J., Friedmann, P.D., Saitz, R., and Samet, J.H. Slowing the Revolving Door: Stabilization Programs Reduce Homeless Persons' Substance Use After Detoxification. Journal of Substance Abuse Treatment, 24(3), pp. 197-207, 2003.

Community Referral Sources and Entry of Treatment-Naive Clients into Outpatient Addiction Treatment

This study assessed the association of sources of client referral with enrollment of treatment-naive clients. Data from the 1995 (n=618) and 2000 (n=745) waves of the National Drug Abuse Treatment Survey, a panel study of outpatient substance abuse treatment units (OSAT), were analyzed. Enrollment of treatment-naive clients was defined as the percentage of OSAT clients who entered treatment in the past 30 days with no prior treatment for substance abuse. A generalized estimating equation model simultaneously assessed the association of each referral source with the dependent variable, while controlling for potential confounding and accounting for correlation of unit-level responses over time. In the multivariable model, OSAT units with a greater proportion of treatment-naive clients had received more referrals from employee assistance programs and the criminal justice system, and fewer referrals from mental health agencies. No effect of referral from medical or social service agencies was observed. These results highlight the role of coercive community institutions in treatment outreach efforts to persons in earlier phases of the "addiction career." Friedmann, P.D., Lemon, S.C., Stein, M.D., and D'Aunno, T.A. Community Referral Sources and Entry of Treatment-Naive Clients into Outpatient Addiction Treatment. The American Journal of Drug and Alcohol Abuse, 29(1), pp.105--115, 2003.

General Psychiatrists Consult Addiction Psychiatrists for Diagnostic Information and Aftercare Recommendations

Researchers reviewed the records of 381 consecutive substance abuse consultations completed by the Substance Abuse Consultation Service (SACS) of McLean Hospital to ascertain the most frequent reasons why general psychiatrists consulted the SACS, and the clinical characteristics of patients for whom consultation was sought. The most frequent reasons for consultation were to make aftercare recommendations (66%) or to make (20%) or clarify (6%) a diagnosis of substance use disorder. Mood disorders were the most prevalent co-occurring psychiatric disorder, and alcohol use disorders were the most prevalent substance use disorder. Findings indicate the potential utility of a substance abuse consultation service in a psychiatric hospital. Greenfield, S.F., Hennessy, G., Sugarman, D.E. and Weiss, R.D. What General Psychiatrists Ask Addiction Psychiatrists: A Review of 381 Substance Abuse Consultations in a Psychiatric Hospital. American Journal on Addictions, 12(1), pp. 18-28, 2003.

Baseline Health Status and Psychiatric Symptoms Predict Subsequent Health Status of Patients in Substance Abuse Treatment

This study examined the predictors of self-reported health status at follow-up in the Drug Abuse Treatment Outcomes Study (DATOS), a longitudinal study of drug abuse treatment programs and patients in 1991-1993. Baseline and follow-up interviews of 2,966 patients in 75 programs were performed. Follow-up assessment was targeted to occur 12 months after treatment terminated; longterm methadone patients in treatment for the entire 12-month period were interviewed 24 months after intake. A composite measure, developed through principal component analysis, assessed health status. A multivariate hierarchical linear regression model adjusted for independent identified baseline predictors of health status at follow-up. Poor physical health status (including the composite measure, comorbid conditions, and pain) and greater severity of psychiatric symptoms at baseline were the strongest predictors of poor health status at follow-up. Other predictors of worse health status included older age, public insurance coverage, and employment. The authors conclude that baseline health status and psychiatric symptoms predict the subsequent health status of patients in substance abuse treatment as in other clinical populations. Future research should examine whether early identification and treatment of physical and mental health problems among patients in addiction treatment programs might remediate their adverse effects on longterm health status outcomes. Friedmann, P.D., Lemon, S.C., Anderson, B.J., and Stein, M. D. Predictors of Follow-up Health Status in the Drug Abuse Treatment Outcome Study (DATOS). Drug and Alcohol Dependence, 69(3), pp. 243-251, 2003.

Change in Smoking Status Following Substance Abuse Treatment

The impact of change in smoking status on 12-month substance abuse treatment outcomes was examined among an HMO population seeking substance abuse treatment. Of the 749 participants who entered the study at baseline, 87% (649) were retained at the 12-month follow-up. At treatment entry, 395 participants were smokers, and 254 were nonsmokers. At follow-up, 13% of the 395 baseline smokers reported quitting smoking; 12% of the 254 baseline nonsmokers reported starting/relapsing to smoking. Those who quit smoking were less likely to be diagnosed as alcohol dependent compared to those who remained smokers. Those who started/resumed smoking were more likely to be diagnosed as both alcohol and drug dependent at treatment entry compared to all other groups. Total days abstinent from alcohol and illicit drugs was greatest for individuals who quit smoking (adjusted M = 310.6) or who were nonsmokers (adjusted M = 294.7) and lowest for those who started/resumed smoking (adjusted M = 246.6) or remained smokers (adjusted M = 258.2), even after controlling for demographic (i.e. age, income), psychosocial (ASI psychiatric severity), and other treatment characteristics (length of treatment stay, prescribed bupropion) that were associated with days abstinent at 12 months. Self-initiated smoking cessation does not appear to be detrimental to substance abuse treatment outcomes, and may be beneficial. Starting/resuming smoking after entering substance abuse treatment may be a clinical marker for individuals at greater risk of relapse. Future studies may want to measure the smoking status of all participants at all time points in order to include this higher-risk group of substance using smokers. Kohn, C.S., Tsoh, J.Y., and Weisner, C.M. Changes in Smoking Status among Substance Abusers: Baseline Characteristics and Abstinence from Alcohol and Drugs at 12-month Follow-Up. Drug And Alcohol Dependence, 69(1), pp. 61-71, 2003.

A New Look at Treatment Duration and Outcomes

Researchers used longitudinal data from the National Treatment Improvement Evaluation Study to examine whether there is a minimum retention threshold, continuous, or non-linear relationship between the duration of addiction treatment and improvement in drug use. Researchers conducted baseline and one-year follow-up interviews with 4,005 clients in 62 treatment units representing four different treatment modalities: methadone maintenance, outpatient non-methadone, short-term residential, and longterm residential. Controlling for multiple factors, treatment duration had a positive linear relationship with improved primary drug use among methadone clients and an inverted-U-shaped relationship with improved overall and primary drug use for outpatient and longterm residential clients. Improvement with longer duration was greatest for long-term residential clients. This finding contradicts previous arguments for a sharp retention threshold for onset of treatment effects, showing instead smooth curves relating treatment duration to improvements in methadone maintenance, outpatient non-methadone, and long-term residential modalities. The relationships were linear for treatment durations typically observed in single treatment episodes. However, unusually long retention in outpatient non-methadone and longterm residential units appeared steadily less predictive of improvement. Zhang, Z., Friedmann, P.D., and Gerstein, D. R. Does Retention Matter? Treatment Duration and Improvement in Drug Use. Addiction, 98(5), pp. 673-684, 2003.

Director's Report to the National Advisory Council on Drug Abuse - September, 2003

Research Findings - Intramural Research

Development and Plasticity Section, Cellular Neurobiology Research Branch

Platelet-derived Growth Factor-producing Cells Immortalized from Rat Mesencephalon with SV40 Large T Antigen Transduced by an AAV Vector Adeno-associated virus (AAV) can infect a wide variety of mammalian cell types and is capable of infecting both dividing and non-dividing cell populations. Here IRP investigators report the construction of a recombinant AAV vector which expresses the SV40 large T protein (AAV-T) and the use of this vector to immortalize primary cells from embryonic rat mesencephalon. The AAV-T vector was constructed by introducing the BamH1 fragment of the pCMV/SVE/Neo plasmid containing T antigen and SV40 regulatory elements into the JM48 plasmid containing the inverted terminal repeats of AAV. Neuronal cultures from E-12 rat mesencephalon were grown in defined media supplemented with basic fibroblast growth factor. These cells were infected with the AAV-T vector. A cell line (designated RMAT) and six subclones were established from these cultures through multiple passages. This cell line was immunoreactive for SV40 large T antigen and the cytoskeletal proteins nestin and vimentin. Morphological differentiation and expression of neurofilament 160 kDa were induced by exposure to dibutyrl cyclic AMP. Immunoassays performed to measure endogenous production of growth factors showed that RMAT cells produced high levels of platelet-derived growth factor (PDGF). AAV may be a useful vector for the transduction of oncogenes to produce cell lines. Phillips, A.W., Zhang, P., Truckenmiller, M.E., Keir, S.D., Bouvier, M., Tornatore, C., and Freed, W.J. Restorative Neurology and Neuroscience, 21, pp. 1-10, 2003.

Analysis of Microarray Data Using Z-score Transformation High-throughput cDNA microarray technology allows for the simultaneous analysis of gene expression levels for thousands of genes and, as such, rapid, relatively simple methods are needed to store, analyze, and cross-compare basic microarray data. The application of a classical method of data normalization, Z score transformation, provides a way of standardizing data across a wide range of experiments and allows the comparison of microarray data independent of the original hybridization intensities. Data normalized by Z score transformation can be used directly in the calculation of significant changes in gene expression between different samples and conditions. IRP investigators used Z scores to compare several different methods for predicting significant changes in gene expression including fold changes, Z ratios, Z and t statistical tests. The authors conclude that the Z score transformation normalization method accompanied by either Z ratios or Z tests for significance estimates offers a useful method for the basic analysis of microarray data. The results provided by these methods can be as rigorous and are no more arbitrary than other test methods, and, in addition, they have the advantage that they can be easily adapted to standard spreadsheet programs. Cheadle, C., Vawter, M.P., Freed, W.J., and Becker, K.G. Journal of Molecular Diagnostics, 5, pp. 73-81, 2003.

Cellular Pathobiology Unit, Development and Plasticity Section, Cellular Neurobiology Research Branch

Intracellular Dynamics of Sigma-1 Receptors (sigma1 binding sites) in NG108-15 Cells Sigma-1 receptors bind diverse kinds of psychoactive compounds including cocaine, and translocate upon stimulation by these compounds. However, the exact intracellular localization and dynamics of sigma-1 receptors have been unclear. IRP scientists recently found that sigma- 1 receptors specifically localize on cholesterol-enriched loci on the endoplasmic reticulum membrane that function as neutral lipid storage sites (i.e., ER lipid droplets or ER-LD) from which neutral lipids

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bud out to form cytosolic lipid droplets (c-LD). By combining immunocytochemistry and real-time monitoring of enhanced yellow fluorescent protein (EYFP)-tagged sigma-1 receptors (Sig-1R-EYFP) in living cells, authors characterized the sigma-1 receptor translocation in this study. (+) Pentazocine, a selective sigma-1 receptor agonist, causes a significant decrease of sigma-1 receptors in ER-LD and a diffused distribution of sigma-1 receptors over the entire endoplasmic reticulum reticular network in NG108- 15 cells. In the presence of sigma-1 receptor agonists, Sig-1R-EYFP move out from ER-LD and slide along the endoplasmic reticulum network toward nuclear envelope and the tip of neurites. Fluorescence recovery after photobleaching (FRAP) analysis demonstrates that Sig-1R- EYFP on endoplasmic reticulum reticular network are highly mobile compared to those in ER-LD. A sucrose gradient fractionation study shows that (+)pentazocine shifts sigma-1 receptors from ER-LD membranes to higher- density membranes. These results indicate that sigma-1 receptors localize on ER-LD and upon stimulation translocate on continuous endoplasmic reticulum reticular network toward peripheries of cells. Because sigma-1 receptors specifically target ER lipid storage sites and compartmentalize neutral lipids therein, these results suggest that sigma-1 receptors' dynamic translocation might affect lipid transport and distribution in neuronal cells. Hayashi, T. and Su, T.P. Journal of Pharmacology and Experimental Therapeutics, 306, pp. 726-733, 2003.

Sigma-1 Receptors (sigma1 binding sites) Form Raft- like Microdomains and Target Lipid Droplets on the Endoplasmic Reticulum: Roles in Endoplasmic Reticulum Lipid Compartmentalization and Export The brain sigma-1 receptors can bind neurosteroids and psychotropic drugs including neuroleptics and cocaine and are implicated in schizophrenia, depression and drug dependence. In this study, IRP investigators found that sigma-1 receptors specifically target lipid storage sites (lipid droplets) on the endoplasmic reticulum by forming a distinct class of lipid microdomains. Both endogenously expressing sigma-1 receptors and transfected C-terminally EYFP-tagged sigma-1 receptors (Sig-1R-EYFP) target unique "ring-like" structures associated with endoplasmic reticulum reticular networks in NG108-15 cells. The "ring- like" structures contain neutral lipids and are enlarged by the oleate treatment, indicating that they are endoplasmic reticulum-associated lipid droplets (ER-LD). Sigma-1 receptors colocalize with caveolin-2, a cholesterol-binding protein in lipid rafts on the ER-LD, but not with ADRP, a cytosolic lipid droplet (c-LD) specific protein. When the double-arginine ER retention signal on the N-terminus of sigma-1 receptors is truncated, sigma-1 receptors no longer exist on ER-LD, but predominantly target c-LD which contain ADRP. Sigma-1 receptors on ER-LD form detergent-resistant raft-like lipid microdomains, the buoyancy of which are different from those of plasma membrane lipid rafts. (+)Pentazocine causes sigma-1 receptors to disappear from the microdomains. N-terminally EYFP-tagged Sigma-1 receptors (EYFP-Sig-1R) failed to target ER-LD. EYFP-Sig-1R- transfected cells showed an unrestricted distribution of neutral lipids all over the endoplasmic reticulum network, decreases in c-LD and cholesterol in plasma membranes, and the bulbous aggregation of endoplasmic reticulum. Thus, sigma-1 receptors are unique endoplasmic reticulum proteins that regulate the compartmentalization of lipids on the endoplasmic reticulum and their export from the endoplasmic reticulum to plasma membrane and c- LD. Hayashi, T. and Su, T.P. Journal of Pharmacology and Experimental Therapeutics, 306, pp. 718-725, 2003.

Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Functional Tolerance and Blockade of Long-term Depression at Synapses in the Nucleus Accumbens after Chronic Cannabinoid Exposure The rewarding properties of the psychoactive constituents of marijuana, termed "cannabinoids," may reflect actions on synaptic transmission in the nucleus accumbens (NAc). Excitatory and inhibitory synapses are acutely inhibited by cannabinoids in the NAc, and endogenous cannabinoids play a critical role in the expression of long-term depression (LTD) of excitatory cortical afferents in this structure. To examine the impact of repeated cannabinoid exposure on synaptic processes in the NAc, rat brain slices were prepared for electrophysiological recordings following a 7 day treatment of the animals with vehicle solution, Delta9-tetrahydrocannabinol (THC), or the cannabinoid agonist WIN55,212-2. Extracellular glutamatergic postsynaptic potentials and whole-cell GABAergic IPSCs were concentration-dependently inhibited by WIN55,212-2 in slices from naive or vehicle-treated animals. However, the sensitivity to WIN55,212-2 was diminished in chronic agonist-treated animals. Cross-tolerance to the inhibitory effect of the mu-opioid agonist DAMGO was also observed. Endocannabinoid-mediated LTD was initiated via electrical stimulation (5 min, 10 Hz) of glutamatergic afferents to the NAc and was completely blocked by the cannabinoid receptor antagonist SR141716A in vehicle-treated animals. LTD was not observed in brain slices from rats chronically treated with Delta9-THC or WIN55,212-2. These data

demonstrate that repeated exposure to cannabinoid agonists blocks synaptic plasticity in the NAc and reduces the sensitivity of GABAergic and glutamatergic synapses to both cannabinoids and opioids. Hoffman, A.F., Oz, M., Caulder, T., and Lupica, C.R. Journal of Neuroscience, 23, pp. 4815-4820, 2003.

Drugs of Abuse and Striatal Synaptic Plasticity Drug addiction can take control of the brain and behavior, activating behavioral patterns that are directed excessively and compulsively toward drug usage. Such patterns often involve the development of repetitive and nearly automatic behaviors that we call habits. The striatum, a subcortical brain region important for proper motor function as well as for the formation of behavioral habits, is a major target for drugs of abuse. Here, IRP scientists review recent studies of long-term synaptic plasticity in the striatum, emphasizing that drugs of abuse can exert pronounced influences on these processes, both in the striatum and in the dopaminergic midbrain. Synaptic plasticity in the ventral striatum appears to play a prominent role in early stages of drug use, whereas dopamine- and endocannabinoid-dependent synaptic plasticity in the dorsal striatum could contribute to the formation of persistent drug-related habits when casual drug use progresses towards compulsive drug use and addiction. Gerdeman, G.L., Partridge, J.G., Lupica, C.R., and Lovinger, D.M. Trends in Neuroscience, 26, pp. 184-192, 2003.

Beta-Funaltrexamine, a Gauge for the Recognition Site of Wildtype and Mutant H297Q mu-opioid Receptors The antagonist beta-funaltrexamine (beta-FNA), known to bind covalently to mu-opioid receptors by a two-step, doubly discriminating sequence, was used as a sensitive gauge to compare wildtype to mutant H297Q mu-opioid receptors. IRP researchers addressed whether this mutation, which enhances the intrinsic activities of alkaloid mu-receptor agents, affects both the reversible and covalent phases of beta-FNA binding. Such altered binding serves as a reporter for the dimensions and topography of the receptor's recognition site. Using the voltage-clamped Xenopus oocyte expression system with coexpressed GIRK potassium channels, we found that beta-FNA blocked the wildtype and mutant H297Q receptors both reversibly and irreversibly, indicating overall conserved tertiary structure in the mutant. The mutant H297Q receptor, however, was more resistant to both phases of blockade, indicating some disturbance of the mutant H297Q receptor recognition site. Beta-FNA acted as a partial agonist at the mutant H297Q receptor expressed in both oocytes, as measured by the activation of GIRK channels, and in COS-7 cells assayed by GTPgamma(35)S binding. Beta-FNA showed no activity at the wildtype receptor expressed in oocytes, but surprisingly induced binding of GTPgamma(35)S in transfected COS-7 cells. Thus, the topography of the mutant H297Q receptor recognition site is sufficiently conserved to allow the selective binding of beta-FNA, but the decrease in binding affinity and increase in efficacy in oocytes demonstrates clear differences from the wildtype receptor. Spivak, C.E., Beglan, C.L., Zollner, C. and Surratt. C.K. Synapse, 49, pp. 55-60, 2003.

Effects of Extracellular Sodium on mu-opioid Receptors Coupled to Potassium Channels Coexpressed in Xenopus Oocytes Wild-type or mutant H297N or H297Q of the mu-opioid receptor were co-expressed with the inwardly rectifying potassium channel GIRK1 in oocytes from Xenopus laevis. Under voltage clamp, pairs of concentration response curves were generated using the agonist normorphine in a bathing medium containing 38.5 mM sodium or an identical medium in which the sodium was replaced by an equimolar concentration of choline. The maximum currents were greater in the presence of sodium by about 30% at wild-type receptors and by about 100% at the mutant receptors. The EC(50) values tended to increase somewhat as well, though these differences reached statistical significance only for the mutant H297Q. Flame photometry detected no change in the intracellular sodium or potassium concentrations of oocytes, suggesting that the effect of sodium was solely extracellular. Thus sodium, long known for its effects on in vitro ligand binding at mu-opioid receptors, also affects overall transduction as revealed in the Xenopus oocyte model of a complete, living cell system. Oz, M. and Spivak, C.E. Pflugers Archives, 445, pp. 716-720, 2003.

Molecular Neuropsychiatry Research Branch

Frontal Cortical Tissue Composition in Abstinent Cocaine Abusers: A Magnetic Resonance Imaging Study Cocaine abusers exhibit impairment of executive cognitive functions that are mediated by the frontal cortex. This work tested for structural (i.e., tissue composition) abnormalities that may underlie such performance deficits. Research participants were cocaine abusers (n = 14) abstinent for 20 days and a non-drug-using comparison group (n = 11), who underwent magnetic resonance imaging (T1-weighted scans of the brain). Gray matter and white matter

tissue densities were determined using voxel-based morphometry with small volume correction based on a priori hypotheses derived from functional imaging of the same subjects. Cocaine abusers had significantly lower gray matter tissue density than did the non drug users in 10 of 13 small volumes analyzed in the frontal cortex [bilateral anterior cingulate gyrus (infragenual and perigenual regions) and medial orbitofrontal cortex and the lateral orbitofrontal cortex and middle/dorsal cingulate gyrus in the right hemisphere]. No group differences were found in white matter density of the frontal cortex. These results extend the authors' previous findings of defective frontal cortical activation (indexed by cerebral blood flow) in cocaine abusers to include abnormalities in gray matter tissue density in the same frontal cortical regions. + Neuroimage, 19, pp. 1095-102, 2003.

Orbitofrontal Cortex Dysfunction in Abstinent Cocaine Abusers Performing a Decision-making Task Cocaine abusers demonstrate faulty decision-making as manifested by their inability to discontinue self-destructive drug-seeking behaviors. The orbitofrontal cortex (OFC) plays an important role in decision-making. In this preliminary study IRP investigators tested whether 25-day-abstinent cocaine abusers show alterations in normalized cerebral blood flow (rCBF) in the OFC using PET with (15)O during the Iowa Gambling Task (a decision-making task). This task measures the ability to weigh short-term rewards against long-term losses. A control task matched the sensorimotor aspects of the task but did not require decision-making. Cocaine abusers (N = 13) showed greater activation during performance of the Iowa Gambling Task in the right OFC and less activation in the right dorsolateral prefrontal cortex (DLPFC) and left medial prefrontal cortex (MPFC) compared to a control group (N = 13). Better Iowa Gambling Task performance was associated with greater activation in the right OFC in both groups. Also, the amount of cocaine used (grams/week) prior to the 25 days of enforced abstinence was negatively correlated with activation in the left OFC. Greater activation in the OFC in cocaine abusers compared to a control group may reflect differences in the anticipation of reward while less activation in the DLPFC and MPFC may reflect differences in planning and working memory. These findings suggest that cocaine abusers show persistent functional abnormalities in prefrontal neural networks involved in decision-making and these effects are related to cocaine abuse. Compromised decision-making could contribute to the development of addiction and undermine attempts at abstinence. Bolla, K.I., Eldreth, D.A., London, E.D., Kiehl, K.A., Mouratidis, M., Contoreggi, C., Matochik, J.A., Kurian, V., Cadet, J.L., Kimes, A.S., Funderburk, F.R. and Ernst, M. Neuroimage, 19, pp. 1085-1094, 2003.

EEG Deficits in Chronic Marijuana Abusers During Monitored Abstinence: Preliminary Findings Cognitive, cerebrovascular, and psychiatric impairments have been documented with chronic marijuana users. To better understand the nature and duration of these neurocognitive changes in marijuana abusers, IRP scientists recorded the resting EEG of 29 abstinent chronic marijuana abusers and 21 control subjects. The marijuana abusers were tested twice: the first evaluation occurred within 72 hours of admission to the inpatient research unit; the second evaluation occurred after 28 to 30 days of monitored abstinence. A three-minute period of EEG was recorded during resting eyes-closed conditions from eight electrodes (F(3), C(3), P(3), O(1), F(4), C(4), P(4), and O(2)). The artifacted EEG was converted to six frequency bands (delta, theta, alpha(1), alpha(2), beta(1), and beta(2)) using a fast Fourier transform. During early abstinence, absolute power was significantly lower ($p < 0.05$) for the marijuana abusers than for the control subjects for the theta and alpha(1) bands. These reductions in theta and alpha(1) power persisted for 28 days of monitored abstinence. These EEG changes, together with cerebral blood flow deficits, might underlie the cognitive alterations observed in marijuana abusers. Additional research is needed to determine how long these deficits persist during abstinence and if treatment with neuroprotective agents may reverse them. Herning, R.I., Better, W., Tate, K. and Cadet, J.L. Annals of the New York Academy of Sciences, 993, pp. 75-78, 2003.

Methylenedioxymethamphetamine (MDMA, Ecstasy) Neurotoxicity: Cellular and Molecular Mechanisms Methylenedioxymethamphetamine (MDMA, Ecstasy) is a very popular drug of abuse. This has led to new intense concerns relevant to its nefarious neuropsychiatric effects. These adverse events might be related to the neurotoxic effects of the drug. Although the mechanisms of MDMA-induced neurotoxicity remain to be fully characterized, exposure to the drug can cause acute and long-term neurotoxic effects in animals and nonhuman primates. Recent studies have also documented possible toxic effects in the developing fetus. Nevertheless, there is still much debate concerning the effects of the drug in humans and how to best extrapolate animal and nonhuman primate data to the human condition. Herein, IRP researchers review the evidence documenting the adverse effects of the drug in

some animal models. The authors also discuss possible mechanisms for the development of MDMA neurotoxicity. Data supporting deleterious effects of this drug on the developing fetus are also described. Much remains to be done in order to clarify the molecular and biochemical pathways involved in the long-term neuroplastic changes associated with MDMA abuse. Lyles, J. and Cadet, J.L. Brain Research Review, 42, pp. 155-168, 2003.

Molecular Neurobiology Section, Molecular Neurobiology Branch

New Findings for Human Dopamine Transporters DAT is a principal site for cocaine reward, yet its human variants and regulation have not been well understood. In the first of these two reports, IRP scientists have described large functional effects of DAT variants found in humans, including a nearly dominant-negative effect that causes efffects on the mutant and on wildtype DAT coexpressed with mutant DAT. In the second, the authors followed up on their initial descriptions of DAT regulation by phosphorylation by elucidating specific DAT sites that are required for phosphoregulation mediated by distinct pathways. Lin, Z. and Uhl, G.R. Pharmacogenomics Journal, 3, pp. 159-168, 2003; Lin, Z., Zhang, P.W., Zhu, X., Melgari, J.M., Huff, R., Spieldoch, R.L. and Uhl, G.R. Journal of Biological Chemistry, 278, pp. 20162-20170, 2003.

Effects of Gene Variants on Reward Derived from Addictive Substances Mouse models are helping to elucidate effects of gene variants on reward elicited by addictive substances. These models can assist in understanding effects of human allelic variants in drug reward. The human BDNF locus is near markers identified in other studies of human drug abuse vulnerability. IRP scientists have also identified human allelic variants at the DAT and VMAT2 locus that influence addiction vulnerabilities. These papers describe effects of mouse models of these human allelic variants on reward elicited by stimulants and ethanol. They also describe the limitations of acute drug reward models for fully understanding effects of human allelic variants that influence vulnerability to drug dependence in humans. Hall, F.S., Sora, I. and Uhl, G.R. Neuropsychopharmacology, 28, pp. 620-628, 2003.

Gene Expression Changes with Behaviorally-Relevant Doses of Amphetamine Studying changes in gene expression provides a good window for enhancing understanding of the neuroadaptations that drug exposure causes in the brain, including those important for addiction. Little information has been available concerning the constellations of genes whose expression is changed by acute- and chronic administration of rewarding and sensitizing doses of amphetamine, although work reported after this paper was submitted describes changes that follow neurotoxic amphetamine doses. The surprisingly-widespread changes in acutely- and chronically regulated genes described here provide a powerful indication of the widespread impact that stimulant administration has on the brain. Sokolov, B.P., Polesskaya, O.O. and Uhl, G.R. Journal of Neurochemistry, 84, pp. 244-252, 2003.

Psychobiology Section, Medications Discovery Research Branch

The Validity of the Reinstatement Model of Craving and Relapse to Drug Use Several types of models used in psychopharmacology are described as conforming to definitions of formal-equivalence, correlational, and functional-equivalence models. The means of validation of each of these types of models are described. The "reinstatement" model is evaluated with regard to which type of model it is, and whether its validity has been adequately established. This assessment is conducted within the context of both preclinical and clinical research and findings. It is concluded that the model is used differently by various investigators, and thus has characteristics of each type. It is further concluded that the model possesses some face validity, as it has some similarity in form to relapse. However, the model falls short of being an established valid model when more rigorous criteria of predictive and functional validity are applied. Several areas for further research are illuminated through this analysis. Katz, J.L. and Higgins, S.T. Psychopharmacology, 168, pp. 21-30, 2003.

Medicinal Chemistry Section, Medications Discovery Research Branch

Dual Probes for the Dopamine Transporter and s1 Receptors: Novel Piperazinyl alkyl-bis-(4'-fluorophenyl)amine Analogues as Potential Cocaine-Abuse Therapeutic Agents Both dopamine uptake inhibitors and s1 receptor antagonists have been implicated as potential pharmacotherapeutics for the treatment of cocaine abuse. While the dopamine uptake inhibitors may share with cocaine neurochemical mechanisms underlying reinforcing properties, s1 antagonists have been shown to attenuate some behavioral actions and toxic side effects

associated with cocaine overdose. Rimcazole, a s1 receptor antagonist that binds to the dopamine transporter (DAT; Ki =224 nM), is not behaviorally cocaine-like and attenuates some of the behavioral actions of cocaine. In order to determine the roles of both DAT and s1 receptors in the behavioral actions of rimcazole, a series of analogues was synthesized. Initial studies identified two analogues that showed high to moderate affinities for both DAT and s-1 receptors and failed to show cocaine-like discriminative stimulus (DS) effects. A second series of bis-(4'-fluorophenyl)amine analogues have now been prepared in which the most potent DAT compound, (Ki=8.5 nM) was selective over serotonin transporter (SERT/DAT=94), norepinephrine transporter (NET/DAT=63) and s1 receptor binding (s1/DAT =44). In addition, two other analogues showed superior selectivity for DAT over SERT (170- and 140-fold, respectively) and DAT over NET (219- and 190-fold, respectively) but were essentially equipotent at DAT and s1 receptors. Comparative Molecular Field Analysis studies at both DAT and s1 receptors were performed to examine structural requirements for optimal binding at these two targets as well as to assess differences between them. Behavioral evaluation of analogues with varying affinities for both DAT and s1 receptors may provide a novel approach toward designing medications for cocaine abuse. Cao, J., Kulkarni, S.S., Husbands, S.M., Bowen, W.D., Williams, W., Kopajtic, T., George, C. and Newman, A.H. Journal of Medicinal Chemistry, 46, pp. 2589-2598, 2003.

N-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butyl, butenyl and butynyl}arylcarboxamides as Novel Dopamine D3 Receptor Antagonists The dopamine D3 receptor subtype has been targeted as a potential neurochemical modulator of the behavioral actions of psychomotor stimulants, such as cocaine. Previous synthetic studies provided structural requirements for high affinity binding to D3 receptors, which included a 2,3-dichloro-phenylpiperazine linked to an arylamido function via a butyl chain. To reduce lipophilicity of these agents and further investigate optimal conformation, a second series of 15 novel ligands was designed that included heteroaromatic substitution and unsaturated alkyl linkers. These compounds were synthesized and evaluated for binding at rat D3 and D2 receptors stably expressed in Sf9 cells. D3 binding affinities ranged from Ki = 0.6 - 1080 nM, with a broad range of D3/D2 selectivities (2-97). The discovery of potent, selective and bioavailable D3 receptor ligands will provide essential molecular probes to elucidate the role D3 receptors play in the psychomotor stimulant and reinforcing effects of cocaine. Newman, A.H., Cao, J., Bennett, C.J., Robarge, M.J., George, C., Freeman, R. and Luedtke, R. Bioorganic Medicinal Chemistry Letters, 13, pp. 2179-2183, 2003.

Neurobiology of Relapse Section, Behavioral Neuroscience Research Branch

Molecular Neuroadaptations in the Accumbens and Ventral Tegmental Area During the First 90 Days of Forced Abstinence from Cocaine Self-administration in Rats Cocaine self-administration is associated with a propensity to relapse in humans and reinstatement of drug seeking in rats after prolonged withdrawal periods. These behaviors are hypothesized to be mediated by molecular neuroadaptations within the mesolimbic dopamine system. However, in most studies of drug-induced neuroadaptations, cocaine was experimenter-delivered and molecular measurements were performed after short withdrawal periods. In the present study, rats were trained to self-administer intravenous cocaine or oral sucrose (a control non-drug reward) for 10 days (6-h/day) and were sacrificed following 1, 30, or 90 days of reward withdrawal. Tissues from the accumbens and ventral tegmental area (VTA) were assayed for candidate molecular neuroadaptations, including enzyme activities of cAMP-dependent protein kinase (PKA) and adenylate cyclase (AC), and protein expression of cyclin-dependent kinase 5 (cdk5), tyrosine hydroxylase (TH) and glutamate receptor subunits (GluR1, GluR2, and NMDAR1). In the accumbens of cocaine-trained rats, GluR1 and NMDAR1 levels were increased on days 1 and 90, while GluR2 levels were increased on days 1 and 30, but not day 90; PKA activity levels were increased on days 1 and 30, but not day 90, while AC activity, TH, and cdk5 levels were unaltered. In the VTA of cocaine-trained rats, NMDAR1 levels were increased for up to 90 days, while GluR2 levels were increased only on day 1; TH and cdk5 levels were increased only on day 1, while PKA and AC activity levels were unaltered. Cocaine self-administration produces long-lasting molecular neuroadaptations in the VTA and accumbens that may underlie cocaine relapse during periods of abstinence. Lu, L., Grimm, J.W., Shaham, Y. and Hope, B.T. Journal of Neurochemistry, 85, pp. 1604--1613, 2003.

The Reinstatement Model of Drug Relapse: History, Methodology and Major Findings The reinstatement model is currently used in many laboratories to investigate mechanisms underlying relapse to drug seeking. Here IRP investigators

review briefly the history of the model and describe the different procedures that have been used to study the phenomenon of reinstatement of drug seeking. The results from studies using pharmacological and neuroanatomical techniques to determine the neuronal events that mediate reinstatement of heroin, cocaine and alcohol seeking by acute priming injections of drugs, drug-associated cues and environmental stressors are summarized. In addition, several issues are discussed, including (1) the concordance between the neuronal mechanisms involved in drug-induced reinstatement and those involved in drug reward and discrimination, (2) the role of drug withdrawal states and periods in reinstatement of drug seeking, (3) the role of neuronal adaptations induced by exposure to drugs in relapse, and (4) the degree to which the rat reinstatement model provides a suitable preclinical model of relapse to drug taking. The data derived from studies using the reinstatement model suggest that: the neuronal events that mediate drug-, cue- and stress-induced reinstatement of drug seeking are not identical; that the mechanisms underlying drug-induced reinstatement are to some degree different from those mediating drug discrimination or reward; and that the duration of the withdrawal period following cocaine and heroin self-administration has a profound effect on reinstatement induced by drug cues and stress. Finally, there appears to be a good correspondence between the events that induce reinstatement in laboratory animals and those that provoke relapse in humans. Shaham, Y., Shalev, U., Lu, L., de Wit, H. and Stewart, J. Psychopharmacology, 168, pp. 3-20, 2003.

Chemistry and Drug Metabolism Section, Clinical Pharmacology & Therapeutics Research Branch

Reliability and Validity of the Tobacco Craving Questionnaire This study documented the initial reliability and validity of the Tobacco Craving Questionnaire (TCQ), a new multidimensional questionnaire to assess tobacco craving. Current cigarette smokers (n = 213) not attempting to reduce or quit smoking completed the 47-item TCQ and other forms assessing demographics, tobacco and other drug use history, quit attempts, and current mood. Exploratory factor analyses and structural equation modeling indicated that a four-factor solution best described the item structure. Factor subscales derived from the 17-items with significant loadings had low to high internal consistencies and inter-item correlations and exhibited low to moderate, positive intercorrelations. Factor scales were significantly correlated with single-item measures of craving, current mood, and daily cigarette smoking. Results indicated that four specific constructs characterized craving for tobacco: 1) emotionality, smoking in anticipation of relief from withdrawal or negative mood; 2) expectancy, anticipation of positive outcomes from smoking; 3) compulsivity, an inability to control tobacco use; and 4) purposefulness, intention and planning to smoke for positive outcomes. These preliminary data suggest that the TCQ is a reliable and valid instrument for assessing tobacco craving in individuals not attempting to reduce or quit smoking. Heishman, S.J., Singleton, E.G. and Moolchan, E.T. Nicotine and Tobacco Research, 5, pp. 1-10, 2003.

Director's Report to the National Advisory Council on Drug Abuse - September, 2003

Program Activities

New NIDA PAs and RFAs

On June 16, NIDA issued a new Program Announcement (PA) entitled **Women, Gender Differences and Drug Abuse (PA-03-139)**. This PA encourages gender-based drug abuse research that explores the mechanisms, origins, and consequences of drug abuse, and that develops and assesses gender-based prevention and treatment interventions and services. It also encourages the study of female-specific issues in all areas of drug abuse.

On July 7, 2003, NIDA issued a Program Announcement (PA) entitled **Behavioral Science Track Award for Rapid Transition (B/START) -- NIDA (PAR-03-146)**. This PA is a reissuance of PAR-01-014, issued November 8, 2000 in the NIH Guide. Through this PA, NIDA seeks to facilitate the entry of beginning investigators into the field of behavioral science research. NIDA invites newly independent investigators to submit applications for small-scale, exploratory, or pilot research projects related to NIDA's behavioral science mission.

On July 22, 2003, NIDA issued a Program Announcement (PA) entitled **Molecular Genetics of Drug Addiction Vulnerability (PA-03-155)**. This PA seeks investigator-initiated applications for research projects that identify chromosomal loci and genetic variation in genes and haplotypes that are associated with increased vulnerability to addiction or dependence on stimulants (e.g., cocaine and amphetamine), narcotics (e.g., opiates), nicotine, benzodiazepines, barbiturates, cannabis, hallucinogens, and/or multiple drugs of abuse in human beings.

On July 22, 2003, NIDA issued a Program Announcement (PA) entitled **SBIR/STTR Phase II Continuation Awards (PA-03-154)**. This PA provides up to another three years of support to small businesses for drug development by providing a second stage of Phase II Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) funding. A recipient of an NIH SBIR/STTR Phase I and Phase II award normally receives under $1 million, and less than three years of support. Although Phase I and Phase II SBIR/STTR support is sufficient for initial discovery efforts (e.g., compound synthesis and some in vitro and in vivo preclinical pharmacological testing), it is not adequate to support either the kind of developmental work needed for compliance with the Food and Drug Administration's requirements for an investigational new drug (IND), or for clinical trials. This PA specifically invites applications for the competing continuation of previously funded Phase II SBIR and STTR grants, to take existing, promising pharmacological treatment agents for drug and nicotine abuse and dependence through the next step of drug discovery and development.

On May 23, 2003, NIDA issued an RFA entitled **Centers for the Development of Medications to Treat Drug Dependence DA-04-003** to solicit applications for funding research centers called Medication Development Units (MDUs) directed towards the identification, evaluation and development of safe and effective medications for the treatment of cocaine, methamphetamine, club drug, opiate, and cannabis related disorders, including substance use (abuse and dependence) and substance-induced disorders such as substance withdrawal and intoxication. Letter of Intent Receipt Date for this RFA: September 15, 2003; Application Receipt Date: October 14, 2003.

PAs/RFAs Issued With Other NIH Components or Agencies

On May 19, 2003, NIDA, in collaboration with NIAAA, issued a Program

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Announcement (PA) entitled **Behavioral Therapies Development Program (PA-03-126)**. Through this PA, NIDA and NIAAA are seeking research grant applications on the development of behavioral treatments for drug and alcohol abuse and dependence. This PA reaffirms NIDA's and NIAAA's continued and ongoing commitment to major programs of research on behavioral therapies.

On June 6, 2003, NIDA, in collaboration with NIMH and NICHD, issued a Program Announcement (PA) entitled **Women's Mental Health in Pregnanacy and the Postpartum Period (PA-03-135)**. In this PA, research on women's mental health in relation to pregnancy and the postpartum period is encouraged including epidemiological, diagnostic, clinical, and intervention research on postpartum depression and psychosis.

On May 16, 2003, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement (PA) entitled **Global Health Research Initiative Program for New Foreign Investigators (PAR-03-118)**. This PA is intended to promote productive re-entry of NIH-trained foreign investigators from low-income countries into their home countries as part of a broader program to enhance the scientific research infrastructure in developing countries, to stimulate research on a wide variety of high priority health-related issues in these countries, and to advance NIH efforts to address health issues of global import.

On May 12, 2003, NIDA, in conjunction with numerous other NIH components, issued a Program Announcement (PA) entitled **Innovations in Biomedical Computational Science and Technology: SBIR/STTR Initiative (PAR-03-119)**. Participating Institutes and Centers of NIH invite applications for innovative research in biomedical computational science and technology to promote the progress of biomedical research. This PA will utilize the SBIR and STTR mechanisms but will be run in parallel with a PA of identical scientific scope (PAR-03-106) that will utilize the traditional research project grant (R01) or the phased innovation award (R21/R33).

On June 4, 2003, NIDA, in conjunction with a number of other NIH Institutes and the National Science Foundation (NSF), issued a Program Announcement (PA) entitled **Tools for Collaborations that Involve Data Sharing (PA-03-134)**. This PA invites proposals to develop collaborative tools and techniques that creatively manage and analyze large amounts of data that are generated during research and need to be shared among several (or many) groups.

On July 11, 2003, NIDA, in collaboration with numerous other NIH Institutes and Centers, issued a Program Announcement (PA) entitled Biobehavioral Pain Research (PA-03-152). The purpose of this PA is to inform the scientific community of the interests of the various institutes at the NIH and to stimulate and foster a wide range of basic and clinical studies on pain as they relate to the missions of these Institutes.

On August 7, 2003, NIDA, in collaboration with NIMH, NIAAA, NIA and NCI issued a Program Announcment (PA) entitled **Research on the Reduction and Prevention of Suicidality (PA-03-161)**. Through this PA the participating NIH Institutes invite grant applications for research that will reduce the burden of suicidality (deaths, attempts, and ideation). The intent of this PA is to intensify investigator-initiated research on this topic, to attract new investigators to the field, and to increase interdisciplinary approaches to developing effective strategies to reduce suicidality.

On July 1, 2003, NIDA, in collaboration with the National Human Genome Research Institute (NHGRI) and the NIH Office of Rare Diseases (ORD), issued an RFA entitled **Mentored Patient-Oriented Research Career Development Award with Emphasis on the Application of Genomic or Proteomic Technologies (K23) (HG-03-006)**. The purpose of this K23 award is to support the career development of clinicians who intend to engage in patient-oriented research that involved the application of the knowledge, tools, technologies and approaches of genomics and proteomics to the study of diseases in an effort to develop effective therapeutic interventions. This award will provide support for three to five years of supervised study and research for clinically trained professionals who plan to become independent, productive, clinical investigators focusing on patient-oriented research. Application Receipt Dates for this RFA: October 20, 2003; October 20, 2004; and October 20, 2005.

On August 20, 2003, NIDA, in collaboration with NIMH, issued an RFA entitled **Developing Translational Research on Mechanisms of Extinction Learning (RFA-MH-04-005)**. Through this RFA, NIMH and NIDA hope to foster collaborations between basic and clinical researches who are focusing their research interests on extinction mechanisms. The goal of this RFA is to promote the development of

innovative pilot projects that incorporate multidisciplinary approaches to the study of extinction learning and to accelerate the development of novel pharmacological, behavioral, and cognitive therapies for anxiety and drug disorders that are marked by deficits in extinction learning and/or the inability to consolidate safety signals. Letter of Intent Receipt Date for this RFA: November 18, 2003. Application Receipt Date: December 18, 2003.

On August 6, 2003, NIDA, in collaboration with NIMH and NIAAA, issued an RFA entitled **Developing Centers on Interventions for the Prevention of Suicide (DCIPS) (RFA-MH-04-003)**. The purpose of this RFA is to establish core support for building research infrastructure for the study of preventive and treatment interventions for suicidality (severe ideation, attempts, deaths) related to mental health, substance use disorders (SUDs) and alcohol use disorders (AUDs). Letter of Intent Receipt Date for this RFA: October 17, 2003. Application Receipt Date: November 18, 2003.

On May 22, 2003, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Human Subjects Research Enhancements Program (HSREP) (OD-03-007)**. The purpose of this initiative is to provide short-term interim support for institutional activities that will strengthen oversight of human subjects research at institutions that receive significant NIH support for clinical research. Application Receipt Date for this RFA: July 11, 2003.

On May 30, NIDA, in collaboration with several other NIH components and the Agency for Healthcare Research and Quality (AHRQ) issued an RFA entitled **Research on Research Integrity (NS-04-001)**. The purpose of this RFA is to foster empirical research on societal, organizational, group and individual factors that affects, both positively and negatively, integrity in research. Letter of Intent Receipt Date for this RFA: October 14, 2003. Application Receipt Date: November 14, 2003.

On July 14, 2003, NIDA, in collaboration with a number of other NIH components, issued an RFA entitled **Research on Mind-Body Interactions and Health (OD-03-008)**. Through this RFA, participating Institutes, Centers and Offices invite applications in support of research on mind-body interactions and health. "Mind-body interactions and health" refers to the relationships among cognitions, emotions, personality, social relationships and health. Letter of Intent Receipt Date for this RFA: November 17, 2003. Application Receipt Date: December 17, 2003.

On August 5, 2003, NIDA and several other NIH components issued an RFA entitled **International Bioethics Education and Career Development Award (RFA-TW-04-001)**. This RFA invites applications to develop or expand current graduate level curricula and training opportunities in international bioethics related to performing research involving human subjects in low- and middle-income nations. Letter of Intent Receipt Date for this RFA: November 17, 2003. Application Receipt Date: December 16, 2003.

Other Program Activities

Aging and Drug Abuse Workgroup

A new NIDA workgroup has been formed under the leadership of Drs. Timothy Condon and Susan Weiss, with participants from each Division, to focus on issues related to aging and drug abuse. The overall goal is to determine how NIDA should support and encourage research that addresses the questions of how a history of drug abuse might affect the aging process, and whether drug abuse will emerge as a significant problem in the aging baby-boomer generation. The workgroup has reviewed NIDA's portfolio in this area and is in the process of planning a workshop tentatively titled: Preparing for the 21st Century: How Serious a Problem will Drug Abuse be in the Elderly Population? The workgroup has and will continue to collaborate with other NIH Institutes (NIMH, NIA, NIAAA) in this endeavor.

CTN Protocol Update

Wave 1 Protocols:

- Five CTN studies have closed enrollment, five other studies are open and enrolling. A total of 4,745 patients have been screened with 2,282 of those enrolling in the trials. Other studies as listed below are starting in the next few months.
- Protocol CTN-0004 (Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse) is actively enrolling at sites across 3 states. A total of 455 participants have enrolled in this study so far. Three of the five

participating sites have reached their targeted enrollment of 100 clients.

Wave 2 Protocols:

- CTN 0011 (A Feasibility Study of a Telephone Enhancement Procedure - TELE - to Improve Participation in Continuing Care Activities) began enrollment in January 2003. A total of 199 patients in four sites have enrolled in the last six months. This is a feasibility study and will be carried out at four sites across three nodes. Participation is at 55% of the targeted enrollment of 360.
- Protocol CTN 0008 (Baseline Survey) has been actively collecting survey information in all 17 Nodes since January 2002.
- Protocol CTN 0009 (Smoking Cessation Treatment With Transdermal Nicotine Replacement Therapy in Substance Abuse Rehabilitation Programs) started enrolling April 9, 2003. This study will be carried out at 12 Community Treatment Programs across 7 Nodes. Twenty participants have been enrolled in the last two months at 2 sites. The other 10 sites will be enrolling once IRB approvals are finalized.
- Protocol CTN 0003 (Bup/Nx: Comparison of Two Taper Schedules) began enrollment June 30, 2003. This study will be carried out at 11 sites across 8 nodes. The targeted enrollment is 480 participants.
- CTN 0010 (Buprenorphine/Naloxone Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults) began enrollment on July 17, 2003. This is the first adolescent protocol in the CTN. This study will be carried out at 5 CTP sites across 4 nodes. The targeted enrollment is 240 adolescent/ young adult participants.
- Protocol CTN 0012 (HIV/AIDS, Hep C, and Infections Screening in Substance Abuse Treatment Programs) was approved for implementation. The protocol training was held at the Albuquerque Steering Committee Meeting in March 2003. This is a survey to be conducted in all CTPs across all 17 nodes. This was initiated and data has begun to be collected.

Wave 3 Protocols:

- The third wave of protocols are progressing and some are near implementation.
- Protocol CTN 0021(Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse) has been approved. Protocol and therapist training were held July 21-23, 2003 in Miami, FL. Enrollment began in August 2003. This is the first Spanish only protocol in the CTN. It will be conducted at 6 bi-lingual sites across 5 nodes.
- Protocol CTN 0013 (Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome in Pregnant Substance Abusers) has been approved for implementation. Training was held in July 2003, and MET test cases are enrolling now. Once the test cases are reviewed and the therapists certified, enrollment will begin.
- Protocol CTN 0014 (Brief Strategic Family Therapy for Adolescent Drug Abusers (BSFT)) has been approved by NIDA. Therapist training and implementation will take place in waves. The first wave of 5 sites received protocol training on August 18, 2003. Pilot family cases will be recruited in September 2003. BSFT will be implemented at 13 sites across 10 nodes plus Puerto Rico. This intervention is the first CTN study to target adolescents and their families.
- Three HIV protocols (CTN 0017 HIV and HCV Intervention in Drug Treatment Settings, CTN 0018 HIV/STD Safer Sex Skills Groups for Men in Methadone Maintenance or Drug Free Outpatient Programs, and CTN 0019 HIV/STD Safer Sex Skills Groups for Women in Methadone Maintenance or Drug Free Outpatient Programs) were reviewed at the April 2003 Data and Safety Monitoring Board (DSMB) Meeting. Sites are being finalized for those protocols. They will be carried out at numerous sites across the Network. It is expected that these will start enrolling in January 2004.
- Protocol CTN 0020 (Job Seekers Training for Patients with Drug Dependence) was also reviewed at the April 2003 Data Safety and Monitoring Board Meeting. This study is expected to be launched in the

Spring of 2004.

Wave 4 Protocols:

- The fourth wave of new protocols was submitted for review by the Protocol Review Board on August 13-14, 2003.
  These protocols include: CTN 0022 (Family Management Skills for Drug Involved Women in Treatment); CTN 0023 (12-Step Facilitation as an Intervention to Increase 12-Step Involvement and Improve Outcomes Among Substance Dependent Individuals); CTN 0024 (Reducing HIV Risk Behavior Among Adolescents in Community Based Substance Abuse Programs); CTN 0025 (Community Reinforcement and Family Training (CRAFT)); and CTN 0026 (Treatment of Depression in Adult Substance Abusers with Escitalopra).

Summer Research with NIDA Program

Flair Lindsey, NIDA Special Populations Office, coordinated the seventh annual Summer Research with NIDA program. The program allowed high school and undergraduate students to engage in drug abuse research with NIDA grantees for 8-10 weeks during the summer. In 2003, 72 students and 25 grantees participated in the program.

NIDA's New and Competing Continuation Grants Awarded Since May 2003

Alexander, Jeffrey A. -- University of Michigan at Ann Arbor
Drug Abuse Treatment System Survey

Anderson, Rachel L. -- University of Iowa
Integrating Rural Health Services for Adolescents

Arnsten, Julia H. -- Yeshiva University
Efficacy and Cost of HAART DOT In Methadone Clinics

Arria, Amelia M. -- University of Maryland
The Natural History and Consequences of Ecstasy Use

Aston-Jones, Gary S. -- University of Pennsylvania
Role of Extended Amygdala In Opiate and Cocaine Abuse

Ator, Nancy A. -- Johns Hopkins University
Functional Analysis of GABAergic Sedative/Anxiolytics

Baum, Marianna K. -- Florida International University
HIV Disease, Drug Abuse, & Nutrient Therapy In Botswana

Bechara, Antoine -- University of Iowa
Changes In Addictive Behaviors After Brain Lesions

Benowitz, Neal L. -- University of California San Francisco
Pharmacokinetics and Pharmacodynamics of Nicotine

Berns, Gregory S. -- Emory University
The Neurobiology of Uncertainty

Berridge, Kent C. -- University of Michigan at Ann Arbor
Cue-Triggered Reward Seeking

Bibb, James A. -- University of Texas South West Medical Center/Dallas
The Role of Cdk5 in Addiction

Blank, Michael B. -- University of Pennsylvania
HIV Prevention Program Among Substance Abusing SMI

Blough, Bruce E. -- Research Triangle Institute
Potential Treatment Medications for Drug Abuse

Bolla, Karen I. -- Johns Hopkins University
Sleep Disturbance In Marijuana Withdrawal

Booth, Robert E. -- University of Colorado Health Sciences Center
Reducing HCV/HIV Risks Comparing Two Interventions

Bradberry, Charles W. -- Yale University
CNS Consequences of Chronic Cocaine Self-Administration

Branch, Marc N. -- University of Florida

Behavioral Determinants of Cocaine Tolerance

Brooner, Robert K. -- Johns Hopkins University
Services Research: Psychiatric Comorbidity In Drug Abuse

Budney, Alan J. -- University of Vermont & State Agricultural College
Clinical Significance of Marijuana Withdrawal

Bukstein, Oscar G. -- University of Pittsburgh at Pittsburgh
Home Based Treatment For Drug Use In Early Adolescents

Capaldi, Deborah M. -- Oregon Social Learning Center, Inc.
Adjustment Problems and Substance Use In 3 Generations

Castillo, Pablo -- Yeshiva University
Presynaptic Forms of Long-Term Plasticity In The CNS

Chavkin, Charles -- University of Washington
Opioid Mediation of Stress-Potentiated Cocaine Response

Cinciripini, Paul M. -- University of Texas MD Anderson Cancer Center
A Mood Management Intervention For Pregnant Smokers

Clatts, Michael -- National Development & Research Institutes
Male IDUs In Viet Nam: Ethno-Epidemiology of HIV Risk

Colby, Suzanne M. -- Brown University
Smoking Versus Alternative Reinforcers In Adolescents

Correia, Christopher J. -- Auburn University at Auburn
Behavioral Treatment For College Student Cigarette Use

Cowan, Ronald L. -- Vanderbilt University
High-Field Functional MRI of Human Euphoria

Cox, Brian M. -- Henry M. Jackson Fnd. For The Advancement of Military Medicine
N/Ofq Expression and Neural Injury

Cunningham, Kathryn A. -- University of Texas Medical Branch, Galveston
Targeted Proteomics of Stress and Addiction

Dakof, Gayle A. -- University of Miami
"Engaging Moms." An Intervention For Family Drug Court

Dallery, Jesse -- University of Florida
A Home-Based Behavioral Treatment For Cigarette Smoking

Dallery, Jesse -- University of Florida
Impulsivity and Relapse Prevention In Smoking

Dallman, Mary F. -- University of California San Francisco
Chronic Stress Intensifies Incentive Relativity

Davis, Betsy -- Oregon Research Institute
Preventing Drug Abuse In American Indian Children

Delaney-Black, Virginia -- Wayne State University
Consequences of Prenatal Cocaine Exposure In Adolescence

Deutsch, Dale G. -- State University New York Stony Brook
Anandamide and the Fatty Amide Hydrolase (FAAH)

Dobs, Adrian S. -- Johns Hopkins University
Cognitive Consequences of Endocrine Dysfunction In IDU

Donny, Eric C. -- Johns Hopkins University
Effects of Chronic Exposure To Smoking Stimuli

Duvauchelle, Christine L. -- University of Texas Austin
Cocaine & Brain: Progressive Changes In Behavior/DA/Fos

Espy, Kimberly A. -- Southern Illinois University Carbondale
Prenatal Tobacco Exposure: Perinatal and Genetic Risks

Fals-Stewart, William S. -- State University of New York at Buffalo
Parent Training and Couples Therapy for Drug Abuse

Faw, Leyla -- Fordham University
Fidelity of Residental Treatment for Teen Drug Abuse

Fishbein, Diana H. -- Research Triangle Institute
Neurocognitive Function In Russian Heroin Addicts

Foltin, Richard W. -- New York State Psychiatric Institute
Laboratory Analysis of Cocaine Abstinence

Friedman, Theodore C. -- Charles R. Drew University of Medicine & Science
HPA Axis Activation and Nicotine Use

Friedman, Theodore C. -- Charles R. Drew University of Medicine & Science
Chronic Nicotine's Activation of the HPA Axis

Furr-Holden, Carolyn D. -- Pacific Institute for Research and Evaluation
Using Randomized Incidents In Prevention Research

Galizio, Mark -- University of North Carolina Wilmington
Drugs of Abuse and Complex Behavior

Garner, Craig C. -- Stanford University
Sap97 Isoforms In Trafficking Synaptic Glur1

Gerbert, Barbara -- University of California San Francisco
Prevention for Prenatal Health

Gibelman, Margaret -- Yeshiva University
Educating for Responsible Research Conduct

Gold, Paul E. -- University of Illinois Urbana-Champaign
Stress Effects on the Balance Between Memory Systems

Gruber, Staci A. -- Mc Lean Hospital, Belmont, MA
Frontal Neural Mechanisms and Risk for Substance Abuse

Haller, Deborah L. -- St. Luke's-Roosevelt Institute for Health Sciences
Drug Treatment for Transplant Candidates

Halliday-Boykins, Colleen A. -- Medical University of South Carolina
Substance Outcomes For Youth In Psychiatric Crisis

Hargreaves, Kenneth M. -- University of Texas Health Sciences Center San Antonio
Peripheral Mechanisms of Opioid Analgesia

Hawkins, J. David -- University of Washington
Science-Based Prevention: Testing Communities That Care

Hecht, Michael L. -- Pennsylvania State University-University Park
Drug Resistance Strategies Minority Project

Henriksen, Steven J. -- Scripps Research Institute
Drugs of Abuse and Neuroaids: Proteome Activity Profiles

Herzog, David B. -- Massachusetts General Hospital
Substance Use Disorders In Women With Anorexia/Bulimia

Hillard, Cecilia J. -- Medical College of Wisconsin
Brain Endocannabinoids and Chronic Stress

Hook, Vivian -- Buck Institute for Age Research
Proteomics/Genomics of Opiate Analgesia and Addiction

Hopfer, Christian J. -- University of Colorado Heallth Sciences Center
A Family Study of Substance Use & Conduct Disorder

Hough, Lindsay B. -- Albany Medical College of Union University
Non-Opioid Analgesics Derived From Improgan

Howell, Leonard L. -- Emory University
Transitional States In Drug Addiction

Iacono, William G. -- University of Minnesota Twin Cities
Twin Family Study of Vulnerability To Substance Abuse

Ingersoll, Karen S. -- Virginia Commonwealth University

Development of Cart For HIV Adherence and Cocaine Abuse

Izenwasser, Sari -- University of Miami
Neurochemical Consequences of Drugs In Adolescent Rats

Jacobs, Barry L. -- Princeton University
Marijuana & Cytokine Actions On Rat Brain Mitogenesis

Janda, Kim D. -- Scripps Research Institute
A New Protein-Based Approach For Cocaine Abuse Treatment

Janda, Kim D. -- Scripps Research Institute
Catalytic Antibodies As Therapy For Drug Addiction

Kahler, Christopher W. -- Brown University
Improving Smoking Cessation Outcomes In Heavy Drinkers

Kaldor, John M. -- National Centre/HIV Epidemiology/Clincal Research
Longitudinal Cohort of Newly Acquired HCV Infection

Kauer, Julie A. -- Brown University
Synaptic Plasticity In The VTA Studied In Vivo

Kilts, Clinton D. -- Emory University
Cocaine Dependence and Cognitive Control of Behavior

Kinlock, Timothy W. -- Friends Research Institute, Inc.
Methadone Maintenance For Prisoners

Kinnunen, Taru -- Harvard University School of Medicine
Exercise and Nicotine Replacement for Female Smokers

Kipke, Michele D. -- Children's Hospital Los Angeles
YMSM Drug Use, Sexual Risk & Health Promoting Behaviors

Kohlenberg, Barbara S. -- University of Nevada Reno
Reducing Felt Stigma In SUD

Landau, Emmanuel M. -- Mount Sinai School of Medicine of New York University
Translational Control of LTP

Lankenau, Stephen E. -- Columbia University Health Sciences
Ketamine Injection and HIV Risk Among High Risk Youth

Larson, Mary J. -- New England Research Institutes, Inc.
E-Technology To Enhance Addiction Counselor Helping

Laruelle, Marc A. -- New York State Psychiatric Institute
PET Imaging of Serotonin Transmission In MDMA Users

Latimer, William W. -- Johns Hopkins University
Youth Drug Abuse Family and Cognitive-Behavioral Therapy

Latkin, Carl A. -- Johns Hopkins University
RCT of Russian IDU Peer Network HIV Prevention Intervention

Latkin, Carl A. -- Johns Hopkins University
A Network & Dyad HIV Prevention Intervention For IDUs

Lee, Margaret T. -- Brandeis University
Adolescent Substance Abuse Performance Measures

Lejuez, Carl W. -- University of Maryland
Distress Tolerance and Early Smoking Lapse

Levine, Eric S. -- University of Connecticut School of Medicine and Dentistry
Cannabinoid Modulation of Cortical Synaptic Transmission

Liddle, Howard A. -- University of Miami
Training Clinicians In Empirically Based Family Therapy

Linehan, Marsha M. -- University of Washington
Evaluation of Dialectical Behavior Therapy (DBT)

London, Edythe D. -- University of California Los Angeles
Early Methamphetamine Abstinence: fMRI and Cognition

Lukas, Ronald J. -- St. Joseph's Hospital And Medical Center
Molecular Bases for Effects of Nicotine

Lyons, David M. -- Stanford University
Early Chronic Stress and Prefrontal Development

Mackinnon, David P. -- Arizona State University
Estimating Mediation Effects In Prevention Studies

Mackler, Scott A. -- University of Pennsylvania
Nac-1 A Cocaine Regulated mRNA In The Rat Brain

Mael, Fred A. -- American Institutes for Research
Organizational Culture & Quality of Drug Abuse Treatment

Malan, Thomas P. -- University of Arizona
Non-Addicting Cannabinoid Medications

Marmorstein, Naomi R. -- Rutgers The State University of New Jersey, New Brunswick
Child Psychopathology and Risk for Drug Use Disorders

Martin, Catherine A. -- University of Kentucky
Modafinil and Nicotine In Adolescents: Phase I Trial

Marzilli, Thomas S. -- University of West Florida
The Influence of Nicotine on Fractionated Reaction Time

Mash, Deborah C. -- University of Miami
CNS Mechanisms In Cocaine Related Sudden Death

Massey, Catherine J. -- Slippery Rock University of Pennsylvania
Psychosocial Correlates of Smoking In College Students

Matuszewich, Leslie -- Northern Illinois University
Impact of Stress on Cocaine Withdrawal Behaviors

Mccallion, Philip -- State University of New York at Albany
Child Welfare, Drug Abuse and Intergenerational Risk

Mcfarland, Bentson H. -- Oregon Health & Science University
Standardized Patients As Drug Abuse Treatment Clients

Meredith, Gloria E. -- Finch University of Health Sciences/Chicago Medical School
Mechanisms Underlying Reward-Related Synaptogenesis

Morikawa, Hitoshi -- University of Texas Austin
Calcium Signaling In the Reward Circuit & Drug Addiction

Morse, Gene D. -- State University of New York At Buffalo
TDM & Drug Interactions In HIV-infected Substance Abusers

Murphy, Sheigla B. -- Scientific Analysis Corporation
An Exploratory Study Of Ecstasy Distribution

Nemoto, Tooru -- University of California San Francisco
Drug Use and HIV Risk Behaviors Among Transgenders

Nestler, Eric J. -- University of Texas South West Medical Center, Dallas
Molecular Neurobiology of Drug Addiction

Nichols, Tracy R. -- Weill Medical College of Cornell University
Gender Differences In Preventing Adolescent Drug Use

Nyamathi, Adeline M. -- University of California Los Angeles
HBV Prevention For Homeless At-Risk For HBV/HCV/HIV

Ozechowski, Timothy J. -- Oregon Research Institute
Assessing Clinical Skills In Functional Family Therapy

Pasternak, Gavril W. -- Sloan-Kettering Institute for Cancer Research
Synthesis & Pharmacology of Novel Opiates and Systems

Patkar, Ashwin A. -- Thomas Jefferson University
Serotonin and Cocaine Dependence: Treatment Implications

Petry, Nancy M. -- University of Connecticut School of Medicine and Dentistry
Training Therapists To Administer Contingency Management

Pomerleau, Ovide F. -- University of Michigan at Ann Arbor
Candidate Genes for Smoking In Related and Unrelated Individuals

Poundstone, Katharine E. -- Johns Hopkins University
A Dynamic Multilevel Analysis of Substance Use and HIV

Pugatch, David -- Miriam Hospital
HIV Rapid Testing for Young Substance Users

Ramsey, Susan E. -- Rhode Island Hospital, Providence, RI
Preventing Depression In MMT Patients on Interferon

Rao, Yi -- Washington University
Signal Transduction In Axonal and Neuronal Guidance

Ring, Huijun Z. -- SRI International
Cytochrome P450 Polymorphism and Nicotine Metabolism

Rogers, Thomas J. -- Temple University
HIV Infection and Opioid-Induced Immunoregulation

Rohrbach, Louise A. -- University of Southern California
Diffusion of Project Towards No Drug Abuse (TND)

Roy, Sabita -- University of Minnesota Twin Cities
Mu Opioid Receptor and Immune Function

Rush, Craig R. -- University of Kentucky
Human Cocaine Discrimination

Sanna, Pietro P. -- Scripps Research Institute
Role of Proteoglycans In Cocaine Dependence

Santa Ana, Elizabeth J. -- State University of New York at Albany
Efficacy of Group Motivational Interviewing

Schoenbaum, Geoffrey M. -- University of Maryland Baltimore Professional School
Lasting Effects of Cocaine Use On Corticolimbic Funciton

Shaw, Susan J. -- Hispanic Health Council
Community Organizations In Syringe Exchange In Springfield, MA

Sherman, Steven J. -- Indiana University Bloomington
Social Psychological Factors In Teen and Adult Smoking

Sholomskas, Diane E. -- Applied Behavioral Research
Randomized Trial of Novel Approaches to CBT Training

Siegal, Harvey A. -- Wright State University
Reducing Barriers to Drug Abuse Treatment Services

Siegel, Karolynn -- Columbia University Health Sciences
HIV-Infected IDU Living With HCV Coinfection

Slesnick, Natasha --University of New Mexico Albuquerque
Treatment Outcome With Runaway Adolescents

Sofuoglu, Mehmet -- Yale University
Progestrone and the Effects of Nicotine

Sopori, Mohan -- Lovelace Biomedical & Environmental Research
Nicotine & Immunopathogenesis of Cryptococcal Meningitis

Spealman, Roger D. -- Harvard University School of Medicine
Nonhuman Primate Models Of Speedball Abuse

Stone, Laura S. -- University of Minnesota Twin Cities
G-Protein Coupled Receptor Oligomerization In The CNS

Surratt, Christopher K. -- Duquesne University
Dopamine Transporter Structure-Function Studies

Tomasi, Dardo -- Brookhaven Science Associates-Brookhaven National Laboratory

"Acoustic Interference on Attention In HIV Patients"

Undie, Ashiwel S. -- University of Maryland Baltimore Professional School
Signaling Mechanisms In Dopamine Receptor Synergism

Unger, Vinzenz M. -- Yale University
Tools for Membrane Protein Structure Determination

Varas-Diaz, Nelson -- University of Puerto Rico, Rio Piedras
AIDS Stigma and Health Professionals In Puerto Rico

Velasquez, Mary M. -- University of Texas Health Sciences Center Houston
A Transtheoretical Model Group Therapy for Cocaine

Wald, Anna -- University of Washington
Treatment of Acute Hepatitis C In Injection Drug Users

Waldron, Holly B. -- Oregon Research Institute
Transitional Treatment for Adolescents In Family Therapy

Wechsberg, Wendee M. -- Research Triangle Institute
Woman Focused HIV Prevention With African-Americans

Weed, Michael R. -- Johns Hopkins University
Aids & Drug Abuse: Tremor and Motor Control In Macaques

Weisner, Constance M -- University of California San Francisco
Course of Problems In Adolescent Drug Treatment Intakes

Whistler, Jennifer L. -- Ernest Gallo Clinic and Research Center
G Protein Coupled Receptor Trafficking and Opiate Drugs

White, Tara L. -- Brown University
Imaging Individual Differences In Amphetamine Effects

Williams, Mark L. -- University of Texas Health Sciences Center Houston
Positive Choices Research Project

Wohl, David A. -- University of North Carolina Chapel Hill
HIV+ Prison Releases To Access To HIV Care and Services

Wong, Mamie M. -- Wested
Clients Who Seek On-Line Drug Treatment

Woods, James H. -- University of Michigan st Ann Arbor
Narcotic Drug and Opioid Peptide Basic Research Project

Wu, Ping -- Columbia University Health Sciences
PTSD and Substance Use/Abuse In Youth

Yamamoto, Bryan K. -- Boston University Medical Campus
Chronic Stress and MDMA Neurotoxicity

Yang, Xiaowei -- Bayessoft
Transition Model for Incomplete Longitudinal Binary Data

Zhan, Chang-Guo -- University of Kentucky
Redesign of Butyrylcholinesterase for Cocaine Metabolism

Ziedonis, Douglas M. -- Univ. of Med. and Dentistry,NJ-Robert Wood Johnson Med Sch
Treatment of Addiction To Nicotine In Schizophrenia

Zvolensky, Michael J. -- University of Vermont & State Agricultural College
Panic and Smoking Cessation

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Extramural Policy and Review Activities

Receipt, Referral, and Review

NIDA received 1162 applications, including both primary and dual assignments and the Loan Repayment Program applications, for which the Office of Extramural Affairs (OEA) managed the programmatic referral process during this council cycle. Of these, NIDA received the primary assignment on 753 applications.

OEA arranged and managed 22 review meetings in which 387 applications were evaluated. OEA's reviews included applications in chartered, standing review committees; applications in conflict-of-interest with standing committees; and submissions to special initiatives. In addition, OEA's Contracts Review Branch (CRB) arranged and managed eight contract proposal reviews and ten concept reviews. The CRB also took responsibility for, and completed, 58 Loan Repayment Program application reviews included in the total of 387 noted above.

NIDA's chartered committees consist of NIDA-E (Treatment Review Committee), NIDA-F (Health Services Review Committee), NIDA-L (Medications Development Committee), and NIDA-K (Training Committee). In addition to holding meetings of each of these committees, OEA staff held three Special Emphasis Panels to review applications in conflict with the chartered committees. Special Emphasis Panels were also constituted for the Minority Institutions Drug Abuse Research Development Program (MIDARP), Centers applications (2 panels), a Program Project, Behavioral Science Track Award for Rapid Transition (B/START), Conference Grants, and Cutting Edge Basic Research Awards (CEBRA). Seven Special Emphasis Panels reviewed RFA submissions, and a final panel was constituted for the Loan Repayment Program.

OEA managed the following RFA reviews:

- DA 03-001: Diffusion of HIV Infection through Sexual Risk Behaviors of Drug Users
- DA03-002: Enhancing HIV Vaccine Efficacy in High-Risk Drug Users
- DA03-003: Improving Behavioral Health Services and Treatment for Adolescent Drug Users
- DA03-008: Transdisciplinary Prevention Research Centers
- DA03-010: Translating Tobacco Addiction Research into Treatment
- DA03-012: Drug Abuse and HIV Prevention in Youth
- DA03-015: Immunotherapy for Addition Treatment: SBIR/STTR Initiative

Completed Reviews from the Contracts Review Branch since the last Council are as follows:

- N01DA-3-7736: Synthesis and Distribution of Drugs of Abuse and Related Compounds
- N44DA-3-7709: Virtual Reality -- Enhanced Therapy System for Treating Joint Pain
- N01DA-3-8839: Receptor Profiling and/or Compound Liability Screening
- N44DA-3-1109: Inside Out! The Human Board Game (SBIR Phase II)
- N01DA-3-8840: GMP Synthesis of Bulk Drug Substances
- N44DA-3-5519: Web-based Games to Support Drug Abuse (SBIR Phase II)

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- N01DA-4-5524: DESPR Clinical Data Management & Support
- N01DA-4-7737: Quantitation of Drugs of Abuse by GC/MS

Concept Reviews

- N43DA-4-7739C: Development of Novel Approaches in Human Development
- N43DA-4-7744C: Virtual Reality for the Neurobiological Study of Drug-Brain and Behavior Interactions and Drug Abuse Treatment
- N43DA-4-5526C: Develop New Technologies for Screening & Assessing Drug Abuse and Matching Patients with Appropriate Treatment
- N43DA-4-5527C: Develop Screening and/or Assessment Tools for Multi-Problem Youth
- N43DA-4-5528C: New Technologies for Epidemiology Research
- N43DA-4-7742C: Discovery of New Chemical Probes
- N43DA-4-7740C: Efficient in vivo Delivery System for siRNA
- N43DA-4-7741C: Nanoscience-based Design of Therapies for Substance Abuse Treatment
- N43DA-4-7743C: Reagents to Identify Transcription Factors that Define Neural Cell Types
- N43DA-4-8843C: Design, Evaluation, and Integration of Image Analysis Methods to Facilitate Clinical Neuroimaging

Extramural Outreach

Drs. Teri Levitin, Director, OEA; Mark Green, Chief, Clinical, Epidemiological, and Applied Sciences Review Branch; and Mark Swieter, SRA, Basic Sciences Review Branch, presented a workshop at the annual College on Problems of Drug Dependence in June 2003. Their presentation, "What's New at NIH/NIDA and How Could it Affect You?" provided an update on extramural policies and procedures.

Dr. Swieter participated in a grantwriting workshop at the College on Problems of Drug Dependence, along with Drs. Cindy Miner and David Shurtleff of NIDA and Dr. Scott Lukas.

Dr. Rita Liu, Associate Director for Receipt and Referral, OEA, represented NIDA in Boston at the June 2003 meeting of the Environmental Genome Project symposium, "Genes, Environment, and Disease".

Dr. Teri Levitin represented NIDA at the annual meeting of the American Psychological Society in Atlanta, GA.

Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued through the summer. Topics addressed have included stimulating creativity among grantees, special grant mechanisms for innovative research and junior investigators, and policy updates. The symposium series is organized and hosted by Dr. Mark Swieter.

Other Activities

The OEA has continued to assist in meeting requirements related to the President's Management Agenda objective regarding competitive sourcing, with staff involved in various aspects of the NIH competition of grants support functions.

Dr. William C. Grace, Deputy Director, OEA, participated in a focus group providing feedback to NIH on the effects of implementing modular grant policies.

Dr. Grace served on an NIH-wide committee developing a new mechanism for supporting development of clinical trials.

Dr. Teri Levitin represented NIDA on the NIH High-Risk Research Roadmap Working Group as part of the roadmap activities initiated by Dr. Zerhouni.

Dr. Teri Levitin served on an NIH-wide committee on review criteria for clinical research/ clinical trials applications.

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Congressional Affairs

FY 2004 Appropriations

On July 10, 2003, the House of Representatives passed the FY 2004 Labor, Health and Human Services and Education Appropriations (L/HHS) bill (HR 2660). The vote was 215-208. For the National Institutes of Health, the bill would provide the President's budget request, $27.7 billion, which would be a $681 million increase over FY 2003. The Senate recessed for its August break without considering the bill, but agreed by unanimous consent that HR 2660 would be the first item on its agenda when it resumes business on Tuesday, September 2, 2003. The floor manager is Senator Arlen Specter (R-PA). The Senate bill (S 1356), had $445 million less to allocate than the House Labor, Health and Human Services and Education Appropriations bill.

Senate Committee Report (108-81) Language for NIDA:

Appropriations, 2003 $961,721,000
Budget estimate, 2004 995,614,000
Committee recommendation 997,614,000

The Committee recommends an appropriation of $997,614,000 for the National Institute on Drug Abuse [NIDA], the same as budget request. The fiscal year 2003 appropriation was $961,721,000. The comparable numbers for the budget estimate include funds to be transferred from the Office of AIDS Research.

Mission - Created in 1974, NIDA supports about 85 percent of the world's biomedical research in the area of drug abuse and addiction. The Committee commends NIDA for demonstrating through research that drug use is a preventable behavior and that addiction is a treatable disease. NIDA's basic research plays a fundamental role in furthering knowledge about the ways in which drugs act on the brain to produce dependence, and contributes to understanding how the brain works. In addition, NIDA research identifies the most effective pharmacological and behavioral drug abuse treatments. NIDA conducts research on the nature and extent of drug abuse in the United States and monitors drug abuse trends nationwide to provide information for planning both prevention and treatment services. An important component of NIDA's mission is also to study the outcomes, effectiveness, and cost benefits of drug abuse services delivered in a variety of settings and to assure dissemination of information with respect to prevention of drug abuse and treatment of drug abusers.

Adolescent Decision Making and Drug Abuse - The Committee recognizes that the scientific understanding gained by the support of behavioral and cognitive research will lead to improved treatment and prevention of drug abuse and addiction. The Committee encourages NIDA to support more research on adolescent decision making, including the cognitive, behavioral and social processes involved in initiating and continuing drug use.

Asian Americans and Pacific Islanders - The Committee notes that there is a lack of relevant research and culturally competent service programs to address the increased incidence of substance use and abuse among Asian American and Pacific Islander youth and adults. The Committee urges the Director of NIH and the Administrator of SAMHSA to increase their collaborative efforts to address the critical need for substance abuse research regarding these populations.

Drug Abuse and HIV Interventions - Women, youth, and minorities account for a growing proportion of new AIDS cases in the United States, and increasing numbers

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of cases are emerging in rural and smaller urban areas. Therefore, the Committee encourages NIDA to support research to develop and test developmentally and contextually appropriate drug abuse-related HIV prevention interventions or intervention components to reach the broad youth population.

Homeless Populations and Drug Abuse - The Committee recognizes that homeless adults and youth have disproportionate rates of drug use disorders. The Committee encourages NIDA to accelerate more research on homeless populations, especially those that suffer from alcohol, drug abuse and/or mental disorders, and their ability to access services and treatment.

Information Dissemination - The Committee urges NIDA to use both the existing National Drug Abuse Treatment Clinical Trials Network infrastructure and the new prevention infrastructures that are currently being established as part of NIDA's new Prevention Research Initiative, to ensure that findings are put into practice in communities across the country. The Committee is pleased that NIDA and SAMHSA/CSAP are already having discussions to make this a reality.

Methamphetamine Abuse - The Committee continues to be concerned with the rate of methamphetamine abuse across the Nation. The problem is especially acute in Iowa and other Midwestern States. The Committee again urges NIDA to expand its research on improved methods of prevention and treatment of methamphetamine abuse.

New Targets for Medications Development - The Committee is pleased that NIDA research continues to lead to new discoveries about the brain. Recent advances have revealed new targets for medications development. The Committee urges NIDA to continue to support this important research to unravel the complexity of the brain and identify new systems, molecules, proteins, and genes that can be useful in developing new and better medications to treat drug abuse and addiction.

Prevention Research - The Committee is pleased that NIDA has launched a multi-component National Prevention Research Initiative that will involve partners at the State and local levels. The committee urges NIDA to expand this initiative to test the effectiveness of new and existing science-based prevention approaches in different communities, while also identifying the core components of effective drug abuse prevention, so that they can be easily adapted to meet local needs.

Relapse - The Committee encourages NIDA to continue its support of behavioral research that can further our understanding about the underlying cognitive, emotional, and behavioral factors that lead to drug abuse relapses.

Stress - The Committee encourages NIDA to continue to explore the effects of stress and its relationship on the initiation of drug use and the role that stress plays in triggering relapse to drug use. Such research may lead to development of more effective prevention and treatment, particularly for those who suffer from mental disorders as well as substance abuse.

Tobacco Addiction - The Committee recognizes the central role that NIDA research has played in paving the way for developing effective treatments for addiction to nicotine. The Committee is pleased with NIDA's participation with other NIH Institutes in activities to more rapidly translate tobacco addiction research into new treatments. The Committee urges NIDA to accelerate its efforts in these areas, particularly research that focuses on prevention of adolescents from starting to smoke.

Translational Research - The Committee applauds NIDA's efforts to support behavioral science research that provides insight into drug abuse and addiction, especially in the field of tobacco and nicotine addiction. Behavioral and cognitive studies are needed to examine the forerunners and consequences of nicotine use and the nature of the nicotine addiction process, including both genetic and environmental risk factors for nicotine abuse. The Committee encourages NIDA to continue its innovative approaches to move basic behavioral science into clinical application.

Treatments for Adolescent Drug Abusers - The Committee continues to see adolescent drug abuse as a major public health concern and recognizes the need for developing more treatments that are tailored to the unique needs of adolescent drug abusers.

House Committee Report (108-188) Language for NIDA:

The Committee provides $995,614,000 for the National Institute on Drug Abuse (NIDA), which is $33,893,000 above the fiscal year 2003 comparable level and the

same as the budget request.

Mission.--NIDA-supported science addresses questions about drug abuse and addiction, which range from its causes and consequences to its prevention and treatment. NIDA research explores how drugs of abuse affect the brain and behavior and develops effective prevention and treatment strategies; the Institute works to ensure the transfer of scientific data to policy makers, practitioners, and the public.

Bills of Interest

[For the full text and additional information about any bill, go to the Library of Congress website at http://thomas.loc.gov]

HR 2086 - On May 14, 2003, Mark Souder, R-Ind, introduced HR 2086, a bill that would reauthorize the Office of National Drug Control Policy (ONDCP) and related programs through fiscal 2008. House floor action is expected following the August 2003 recess.

Selected provisions:

- **HR 2086** would clarify that the ONDCP Director has the authority to prohibit the certification of any budget request that failed to meet certain conditions.
- The bill would require agencies that deal with drug control, including NIDA, to submit reprogramming or transfer requests for $1 million or more to the ONDCP Director for review. This amount is down from the $5 million under current law.
- The legislation would authorize $195 million annually for fiscal 2004 and 2005 and $210 million annually for fiscal 2006 through 2008 to carry out a National Youth Anti-Drug Media Campaign.
- The Partnership for a Drug Free America would serve as the primary outside strategic adviser to the campaign.
- The bill would require the ONDCP Director to designate an independent entity to evaluate the campaign's effectiveness using specified criteria.
- The measure would require the ONDCP Director to submit an annual report to Congress evaluating the strategy and success of the media campaign in the previous year.

HR 1863 - On April 29, 2003, Rep. Michael Rogers (R-MI) introduced HR1863, the National Pain Care Policy Act of 2003. The bill would declare adequate pain care research, education, and treatment as national public health priorities. It was referred to the House Energy and Commerce Committee. The bill would, in part, establish in the NIH a National Center for Pain and Palliative Care Research. The Center would be headed by a Director appointed by the Director of NIH. The Center would have an advisory council known as "The National Pain and Palliative Care Research Center Advisory Board. Membership of this Board would include voting and non-voting members. The Director, NIDA, would be among the non-voting members.

HR 2507 -- On June 18, 2003, Rep. Darlene Hooley (D-OR) introduced HR 2507, the Conquering Pain Act of 2003. While the majority of the legislation would address services and insurance coverage, there is a provision that would require NIH to convene a national conference to discuss the translation of pain research into the delivery of health services, including mental health services, to chronic pain patients and those in need of end of life care. The Secretary DHHS would be required to use unobligated amounts appropriated for DHHS to convene the conference. On April 29, 2003, Rep. Rogers (R-MI) introduced HR 1863, the National Pain Care Policy Act of 2003. The only similarity between the two is that there is a requirement for a conference on pain in both bills.

HR 2989 -- On July 30, 2003, Rep. Istook, (R-OK) introduced the Transportation-Treasury-Independent Agencies Appropriations for FY 2004. The bill provides a total of $89.3 billion, $2.7 billion (3%) more than the FY 2003 level and $3.4 billion (4%) more than proposed by the administration. This is the first time the House has considered a bill funding both the Transportation and Treasury departments. When the House and Senate Appropriations committees reorganized to create a new subcommittee for homeland security, the subcommittees on Transportation and Treasury-Postal Service were combined into one in order to keep the total number of subcommittees at 13.

Drug-Related Programs & Activities

The bill appropriates $29 million for salaries and expenses for the Office of National Drug Control Policy (ONDCP), and $40 million for the office's Counterdrug Technology Assessment Center. The amount provided for the office is 10% more than current funding, while the center's appropriation is 16% less than FY 2003. The measure provides $226 million for the High Intensity Drug Trafficking Areas (HIDTA) Program, through which assistance is provided to federal, state and local law enforcement units operating in those areas most adversely affected by drug trafficking that have been designated as HIDTAs. The amount provided is 1% more than current funding and $20 million (10%) more than requested. The increase above the administration's request would permit the continued funding of all existing HIDTA programs at their FY 2003 funding level, as well as the expansion of some of those areas and funding of several new areas. The bill also appropriates $230 million - 4% more than current funding but $20 million (8%) less than requested - for other federal drug control programs, which were previously known as the "Special Forfeiture Fund". The total includes $150 million for the National Youth Anti-Drug Media Campaign and $70 million for the Drug Free Communities Support Program.

Federal Employees

The measure also provides for a 4.1% pay raise for civilian federal employees - equal to the pay raise for the military - and it continues for FY 2004 language from previous appropriations acts that ban federal employee health plans from paying for abortions, require those health plans to provide coverage for contraceptives, and prohibit implementation of a regulation allowing banks to enter the real estate business. The bill also requires all federal agencies to submit to Congress at the end of each calendar year an annual report that details actions taken by the agency to contract out agency tasks to the private sector.

S 189 -- On June 19, 2003, the Senate Committee on Commerce, Science, and Transportation reported S.189, the 21st Century Nanotechnology Research and Development Act, to create in statute a National Nanotechnology Program. As reported the bill would direct the President to establish a National Nanotechnology Program and a National Coordination Office to 1) establish goals and priorities for evaluating Federal nanotechnology research and development 2) authorize NSF, as the lead agency, along with the Dept. of Energy, NASA, NIH, NIST, EPA DoJ, DHS, and the Dept of Agriculture to develop and support research and development programs in nanotechnology and related sciences; and 3) provide for coordination of Federal nanotechnology activities. In particular NIH would be authorized $70 million for FY 2004 and increasing amounts through FY 2008. A similar but not identical bill HR 766, the Nanotechnology Research and Development Act of 2003, passed the House on May 7, 2003. The NIH was not mentioned in that bill.

S 1278 - On June 18, 2003, Senator Ron Wyden (D-OR) introduced S 1278, the Conquering Pain Act of 2003. The bill would amend the Public Health Service Act to provide for a public response to the public health crisis of pain. It was referred to the Senate Committee on Health, Education, Labor and Pensions (HELP).

Meetings and Briefings

NIDA Director, Dr. Nora Volkow, had courtesy visits with several Members of Congress. On July 8, 2003, she met with Congressman Ciro Rodriguez (D-TX). On July 9, 2003, she met with Congressman David Wu (D-OR), and on July 24, 2003, she met with Congressman Patrick Kennedy (D-RI). Dr. Timothy Condon, Associate Director, NIDA, accompanied Dr. Volkow for her meeting with Rep. Kennedy.

Dr. Eric Moolchan, Clinical Investigator and Director, Teen Tobacco Addiction Research Clinic, NIDA IRP, participated with Dr. Jack Henningfield, Johns Hopkins Medical School, in briefing Senate staff on tobacco addiction and treatment on Thursday, July 30, 2003. The briefing was arranged by staff from the Senate HELP Committee.

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International Activities

The eighth annual **NIDA International Forum**, Building International Research: Emerging Drug Trends and Patterns in Drug Abuse around the World, was held in conjunction with the College on Problems of Drug Dependence (CPDD) Annual Meeting from June 13--19, 2003, in Miami, Florida. The Forum, which grew from 65 participants representing 26 countries in 2001 to 180 participants from 49 countries and territories in 2003, has been very successful in allowing scientists from around the world to exchange information and establish collaborative drug abuse research projects, and remains an integral part of the NIDA International Program. The Forum was chaired by Dr. Steven W. Gust, International Program, and featured remarks by NIDA Director Dr. Nora Volkow, and Dr. M. Patricia Needle, OSPC. Updates on emerging and changing drug abuse patterns in Asia, Europe, Australia, and North America were provided by Dr. Kamran Diaz, United Nations Office on Drugs and Crime; Dr. Vladimir Poznyak, World Health Organization; Dr. Louisa Degenhardt, National Drug and Alcohol Research Center, University of New South Wales, Australia; Mr. Balasingam Vicknasingam, National Center for Drug Research, University Sains Malaysia; and Dr. James Hall, Up Front Drug Information Center, Miami. In a special workshop on journal publishing chaired by Dr. Robert Balster, Editor-in-Chief of the *Journal of Drug and Alcohol Dependence*, Dr. Ian Stolerman, Co-Editor of the *Journal of Drug and Alcohol Dependence* and Dr. Kerstin Stenius, President of the International Society of Addiction Journal Editors, offered insights and tips on how to publish scientific papers in international journals. Members of two binational research teams discussed their differing models of successful international collaboration: Dr. Walter Ling, University of California, Los Angeles, and Dr. Phunnapa Kittirattanapaiboon, Suanprung Psychiatric Hospital, Chiang Mai, Thailand; and Dr. George Woody, University of Pennsylvania, and Dr. Edwin Zvartau, Pavlov Medical University, St. Petersburg, Russia.

As part of its Southern African Initiative, NIDA cosponsored a meeting, **Research Collaborations Across Continents: Drug Abuse, Health Disparities, HIV and Other Health-Related Consequences**, held July 1-3, 2003, in Cape Town, South Africa. Other cosponsors included the U.S. Department of State, the Medical Research Council of South Africa, and the World Health Organization. Participants included drug abuse researchers, clinicians, community representatives, and students from the United States and Southern Africa. Several NIDA staff members made presentations, moderated sessions, and served as rapporteurs, including Dr. Leslie Cooper, DESPR, who organized and co-chaired the scientific meeting; Dr. Donald Vereen, OD; Dr. M. Patricia Needle, OSPC; and Dr. Jacques Normand, CAMCODA. Ms. Pamela Goodlow, Special Populations Office, coordinated the travel awards and poster presentations. NIDA grantees who presented included: Dr. James Anthony and Dr. William Latimer, Johns Hopkins University; Dr. Dorothy Browne, Morgan State University; Dr. David Brook and Dr. Judith Brook, Mount Sinai School of Medicine; Dr. Ronald Braithwaite, Emory University; Dr. Murelle Harrison, Southern University; Dr. Gary King, Pennsylvania State University, Dr. Alexandros Makriyannis, University of Connecticut; Dr. Neo Morajele, Medical Research Council of South Africa; Dr. Perry Renshaw and Dr. Deborah Yurgelun-Todd, Harvard University; Dr. Kathy Sanders-Phillips, Howard University; Dr. Wendee Wechsberg, RTI International; Dr. Constance Weisner, University of California, San Francisco; and Dr. Frank Wong, George Washington University. The primary goal of the NIDA Southern Africa Initiative is to stimulate binational collaborative drug abuse research between the United States and Southern Africa that focuses on reducing drug abuse, addiction, and drug-associated adverse behavioral, social, and health consequences such as violence and infectious diseases (including hepatitis C, HIV/AIDS, and pulmonary diseases). The Southern African

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Initiative integrates drug abuse research in the areas of epidemiology, early interventions, clinical, prevention, treatment, or health services.

One of the 2003-2004 **NIDA INVEST Fellows** has begun his research. Zhijun Li, M.D., China, is working with Xiao-Fang Yu, M.D., D.Sc., Johns Hopkins University, studying RNA clearance of the hepatitis C virus using specimens collected from a cohort of Chinese injection drug users. Dr. Li is the Deputy Director and chief physician of the AIDS Center at the Guangxi Centers for Disease Control and Prevention, which conducts HIV/AIDS and sexually transmitted infection surveillance, prevention, control, and research in the Chinese province. The other 2003-2004 NIDA INVEST Fellow, Pajulo Marjaterttu, M.D., Ph.D., Finland, will arrive later this year to work with Linda C. Mayes, M.D., at Yale University School of Medicine. INVEST Research Fellows also participate in an orientation program at NIDA and receive travel support to attend scientific meetings. Fellows and their mentors jointly develop a collaborative research proposal for implementation in the Fellows' home country.

The four 2002-2003 **Hubert H. Humphrey Drug Abuse Research Fellows** supported by NIDA have completed their professional affiliations with NIDA grantees. Dr. Amit Chakrabarti, India, worked with Dr. Janet Neisewander, Arizona State University, to examine the role of 5-HT systems in incentive motivation for cocaine. Dr. Winston De La Haye, Jamaica, worked with Dr. James Anthony, Johns Hopkins University, to establish a collaborative school surveillance survey modeled on Dr. Anthony's collaborations with several Latin American researchers. Dr. Ye Swe Htoon, Myanmar, worked with Dr. David Celetano, Johns Hopkins University, on epidemiological studies of, and local responses to, production, trafficking, and use of narcotics and methamphetamines in northern Thailand and Myanmar border areas. Mr. Alisher Latypov, Republic of Tajikistan, worked with Dr. Steffanie Strathdee, Johns Hopkins University, on gathering epidemiological data, evaluating drug abuse intervention programs, and writing grant proposals. NIDA sponsors the competitive, 10-month Fellowships in cooperation with the U.S. Department of State, the Institute of International Education, and The Johns Hopkins University. Through a combination of academic courses and professional experience, Fellows learn about NIDA - supported drug abuse research and the application of research to the development of prevention programs, treatment protocols, and government policy.

NIDA provided travel awards to support the participation of 11 scientists at the **American Psychological Association Conference**, held August 7-10, 2003, in Toronto, Canada. The NIDA-supported participants included: Josefina Alvarez, Ph.D., DePaul University; Susan Budney, Ph.D., Cornell University Weill Medical College; Christopher Cronin, Ph.D., Saint Leo University; Mark K. Greenwald, Ph.D., Wayne State University School of Medicine; Kerry Grohman, Ph.D., Research Institute on Addictions, Buffalo, New York; Matthew W. Johnson, M.A., University of Vermont; Danica K. Knight, Ph.D., Texas Christian University; Juliet Lee, Ph.D., Pacific Institute Prevention Research Center; Maria Mouratidis, Psy.D., Yale University; Amy L. Odum, Ph.D., University of New Hampshire; and Brian J. Piper, M.S., University of Massachusetts.

NIDA provided support for the I**nternational Society for Neurochemistry Satellite Meeting** held July 29 - August 1, 2003, in Kyoto, Japan. The 150 attendees from 14 countries focused on cellular and molecular mechanisms of drugs of abuse and neurotoxicity. NIDA Division of Intramural Research scientists Michael Baumann, Ph.D., F. Scott Hall, Ph.D., and George Uhl, M.D., Ph.D., presented research results during the conference. NIDA supported the participation of the following researchers at the conference: Dr. Michael Kuhar, Emory University; Dr. Glen Hansen, University of Utah; Dr. Francesco Fornai, University of Pisa, Italy; Dr. Valentina Bashkatova, Institute of Pharmacology, Moscow, Russia; Mr. Frederica Pereira, University of Coimbra, Portugal; and Dr. Jo Lewohl and Ms. Nina Foley, University of Queensland, Brisbane, Australia.

Visitors from 15 different countries visited NIDA as part of the Department of State's "Narcotics Demand Reduction Efforts" program. Meeting with the group from NIDA were, Dr. Steve Gust, International Program, OSPC, Dr. Cindy Miner, OSPC, Dr. Katherine Davenny, CAMCODA, Drs. Ivan Montoya and Cece McNamara, DTR&D, and Dr. Shakeh Kaftarian, DESPR. The 15 countries represented by the group were, Afghanistan, Cyprus, Czech Republic, Jamaica, Kazakhstan, Lithuania, Laos, Namibia, New Zealand, Romania, Saudi Arabia, Serbia/Montenegro, Trinidad & Tobago, United Kingdom and Zambia.

Drs. Peter Bootsma and Dirk Ruwaard from the Royal Netherlands Embassy visited NIDA on June 24, 2003. Dr. Bootsma is the outgoing Counselor for Health and Welfare at the Embassy. Dr. Ruwaad will be replacing him in that position. Dr. Steve

Gust and Dale Weiss of the International Program, OSPC, met with Dr. Bootsma and Dr. Ruwaard. Discussions centered around the duties of the Counselor at the Embassy and ways to develop further collaborations between NIDA and The Netherlands.

Jesús Antonio Pérez de Arróspide, Juan Carlos Melero and Jorge Melguizo from Spain, Margarita María Sánchez from Colombia, and Julio Calzada from Uruguay, visited NIDA on July 15, 2003. Their visit was sponsored by the International Development Bank and the Spanish National Plan on Drugs and was focused on presenting the work of EDEX, the school-based drug abuse prevention program titled "The Adventure of Life." EDEX has disseminated this program to 20 different organizations in 16 countries. EDEX representatives discussed possibilities for program evaluation with Dr. Steve Gust International Program, OSPC; Dr. Patricia Needle, OSPC, and Drs. Larry Seitz and Susan Martin, DESPR.

NIDA, along with the Fogarty International Center (FIC), NIAAA and NICHD hosted a Department of State sponsored "Communication Strategies for Promoting Health: Russia" program on July 22, 2003. The purpose of the program was to examine a number of themes and institutions relating to the United States experience with health advertising campaigns. Meeting with the Russian group was Dr. Steve Gust, International Program, OSPC; Jan Lipkin, OSPC; Dr. Jack Stein, DESPR; Natalie Tomitch, Program Officer for Russia, Newly Independent States, and Central & Eastern Europe, FIC; Isabel Ellis, NIAAA; and Dr. John McGrath, NICHD.

Eight International Clinical, Operational and Health Services Research and Training Award (ICOHRTA) recipients from Peru and two summer minority trainees all currently at Johns Hopkins University visited NIDA on July 24, 2003. Dr. Steve Gust, International Program, OSPC; Dr. Vince Smeriglio, CAMCODA; Dr. Cece McNamara, DTRD; and Dr. Susan Martin, DESPR, met with the group to present current NIDA research projects and to discuss ways to form future research collaborations.

Dr. William Corrigall, DNBR, organized a workshop at the World Conference on Tobacco or Health in Helsinki, August 3-8, 2003. The workshop, entitled "Translating the Science of Nicotine Addiction into Practice", included presentations on "NIDA's Agenda in Translating Nicotine and Tobacco Research" (Bill Corrigall), "Development of Medications for Smoking Cessation "(Frank Vocci), and "Genetic Variation in Drug Metabolizing Enzymes and the Risks for Smoking and Cessation" (Rachel Tyndale, Toronto).

Dr. William Corrigall, DNBR, was the discussant in the research panel on "Transdisciplinary Approaches to Etiology, Prevention and Treatment" at the World Conference on Tobacco or Health in August 2003.

Dr. Timothy P. Condon, Associate Director, NIDA, presented "Nicotine Addiction: The Neurobiological Underpinnings of Smoking Behavior," at the 2003 World Conference on Tobacco or Health (WCTOH) in Helsinki, Finland, on August 6, 2003.

Dr. Timothy P. Condon, Associate Director, NIDA, presented "The Basics: Writing a Credible Research Grant Application," and conducted an afternoon practicum at the NIDA sponsored WCTOH Pre-Conference Symposium: Funding for Global Tobacco/Nicotine Research/Grant-Writing for Success on August 3, 2003, in Helsinki, Finland.

Dr. Frank Vocci, Director, DTR&D, traveled to three European countries to meet with pharmaceutical firms between June 26 and July 3, 2003. He was accompanied by Drs. Bill Corrigall, Jane Acri, Ahmed Elkashef, and David McCann. The group interacted with GlaxoSmithKline Pharmaceuticals in Verona, Italy, the Novartis Institute for Biomedical Research in Basel, and Solvay Pharmaceuticals in Amsterdam, Netherlands.

As an invited speaker, Dr. Jag Khalsa of CAMCODA delivered a talk on: Drug abuse, neuroAIDS Research, and Brain Banking Issues and International Collaborations at NIDA at the annual meeting of XV International Congress of Neuropathology, September 14-18, 2003, Turin, Italy. This is a follow-up to the NIDA/NINDS-sponsored International Conference on Brain Banking, April 2002, the proceedings of which are being published in the Journal of Neuropathology.

Dr. Wilson Compton, Director, DESPR, presented a paper at the July 2003 World Psychiatric Association Section Meeting in Paris, France on "Developing a Public Health Drug Abuse Research Program".

Dr. Meyer Glantz, DESPR, presented a paper at the July 2003 World Psychiatric Association Section Meeting in Paris, France written by the Analytic Unit of the

Division of Epidemiology, Services and Prevention Research. The paper, entitled "Twenty Years of Adolescent Drug Use: Comparing Multiple Sources" was written by Meyer Glantz, Ph.D., James Colliver, Ph.D., Marc Brodsky, M.S., Bennett Fletcher, Ph.D. Published and publicly available data from the MTF, NHSDA, YRBSS, NCS, ADHealth, NLSY, NSPY, NELS and NSAUS studies were used to create variables that are comparable across the studies for age and drug use by adolescents in the years 1975 through 2001.

Drs. Elizabeth Robertson and Shakeh Kaftarian, both of DESPR, met with Dr. Olivia McLeod, Director of Substance Abuse Prevention Programs of the United Kingdom, on June 20, 2003 to discuss substance abuse prevention research methods and programs in both countries.

Dr. Gianluigi Tanda, IRP, presented a paper at a meeting in Stockhom, Sweden on "Monitoring Molecules in Neuroscience." The title of his paper was: "A Microdialysis Study of the Effects of 4-Cl-BZT on Mesostriatal, Mesocortical and Mesolimbic Dopamine Transmission: Comparison with Cocaine's Effects."

Drs. Lisa Onken, DTR&D, and David Shurtleff, DNBR, organized and co-chaired a symposium: "Stress Anxiety and Drug Abuse" at the 111th annual meeting of the American Psychological Association in Toronto, Canada.

Dr. Cora Lee Wetherington, NIDA's Women & Gender Research Coordinator, chaired the symposium, "Substance Abuse Prevention, Treatment, and Service Delivery for Adolescent Girls," American Psychological Association, August 7-10, 2002, Toronto, Canada. The symposium was co-organized by Drs. Beverly Pringle and Redonna Chandler, DESPR.

Drs. Cora Lee Wetherington & David Shurtleff, DNBR, co-chaired a symposium, "Adolescence and Nicotine Addiction -- Basic and Clinical Research Perspectives," at the annual meeting of the American Psychological Association, August 7-10, 2003, Toronto, Ontario, Canada.

At the invitation of the American Embassy in Mexico and the Mexican state of Quintana Roo, Ana Anders, Senior Advisor on Special Populations, made a presentation at Mexico's First International Congress on the Prevention and Treatment of Addiction Among Children on May 6-9, 2003 in Cancun, Mexico.

Ana Anders met with researchers at the FILIUS Institute of University of Puerto Rico to discuss substance abuse prevention on May 14-15, 2003.

John Rotrosen, M.D. (NY Node PI) and Paul Wakim, Ph.D., CCTN, co-chaired a CTN workshop entitled, "Challenges in Multi-Site Community Effectiveness Trials," at the 3rd Joint International Conference of the International Society for Clinical Biostatistics and the Society for Clinical Trials (ISCB/SCT) on July 22, 2003 in London, England.

Betty Tai, Ph.D., Director CCTN, co-chaired and presented a CTN Symposium on "The National Drug Abuse Clinical Trials Network (CTN): Emerging Roles of Practitioners in Drug Abuse Research," at the American Psychological Association conference in Toronto, Canada, on August 7, 2003.

Betty Tai, Ph.D., addressed the Tenth International Conference on Treatment of Addictive Behaviors meeting held in Heidelberg, Germany, September 4-8, 2003. The meeting theme was "From Research to Practice and Back Again". Dr. Tai also joined panel members, Bill Miller, Everett Rogers, and Tom McLellan for a round table discussion: What Does It Take for Evidence-Based Treatments to be Adopted in Practice?

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Meetings/Conferences

On May 22 and 23, 2003, the Division of Epidemiology, Services, and Prevention Research hosted a meeting entitled **The Heterogeneity of Drug Abuse**. The purpose of the meeting was to bring together diverse researchers to discuss and identify ways to better describe, discriminate, and predict the nature and course of drug use disorders so as to offer more precise phenotypic indicators of underlying genetic and environmental risk. The meeting summary will be made available, and plans are underway to disseminate papers derived from this meeting in a special issue of a peer-reviewed journal.

A NIDA-sponsored workshop entitled **Developing Behavioral Treatments for Drug Abusers with Cognitive Impairments**, organized and co-chaired by Debbie Grossman, DTR&D, Herb Weingartner, DNBR, and Lisa Onken, DTR&D was held on June 4-5, 2003 in Gaithersburg, MD.

NIDA's Division of Epidemiology, Services, and Prevention Research (DESPR) sponsored a seminar on **Family-Provider Partnerships for Treating Youth with Comorbid Substance Abuse and Mental Health Disorders** on June 6, 2003 in Tulsa, Oklahoma. The seminar was conducted as part of the *Systems of Care Community Meeting*, sponsored by the Center for Mental Health Services and the Center for Substance Abuse Treatment, of the Substance Abuse and Mental Health Services Administration. The seminar, organized by Dr. Beverly Pringle, featured the following three NIDA grantees who presented findings from their research: Dr. Craig Anne Heflinger of Vanderbilt University, Dr. Howard Liddle of the University of Miami, and Dr. Kim Mueser of Dartmouth College.

NIDA sponsored a 3-day meeting titled **Neuronal Nicotinic Receptors and Ligands: Targets for Medications** on June 12-14, 2003 in Bal Harbor, Florida, prior to the meeting of the College of Problems of Drug Dependence. The meeting, chaired by Drs. Bill Corrigall and Rao Rapaka, DNBR and Dr. Frank Vocci, DTR&D, was translational in nature, in that its purpose was to introduce medicinal chemists to the biology of the nicotinic cholinergic receptor, in order to advance the synthesis of new molecular species to target the receptor. Presentations by national and international experts in receptors biology, molecular modeling and chemistry, coupled with an active audience of more than 100 people contributed to the success of the meeting. NIDA is following up recommendations from the meeting with concrete steps, specifically to examine the feasibility of establishing a compound database and repository, and encouraging collaborative research interactions.

During CPDD, Dr. Vocci and Dr. Ahmed Elkashef, DTR&D, were co-chairs of a workshop entitled **Analysis of Clinical Trials Involving Substance Abuse Populations: Strategies for Missing Data** on June 16, 2003.

NIDA's Women & Gender Research Group sponsored Women and Gender Junior Investigator Travel Awards at the annual meeting of the College on Problems of Drug Dependence, June 14-19, 2003, Bal Harbour, FL. A total of 77 applications were submitted and 31 awards were made.

NIDA's Women & Gender Research Group sponsored the "Focus on Women and Gender Differences: Mini-Program" book at the annual meeting of the College on Problems of Drug Dependence, June 14-19, 2003, Bal Harbour, FL.

In June 2003, Drs. Wilson Compton, DESPR, and David Shurtleff, DNBR, organized and co-chaired a symposium at the annual meeting of the College on Problems of Drug Dependence entitled **Linking Basic And Applied Research: Finding New**

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Solutions Through Multidisciplinary Drug Abuse Research in Bal Harbour, FL.

NIDA's National Hispanic Science Network Summer Research Training Institute was held in June 2003 at the University of Houston, Houston TX. A number of NIDA staff gave presentations on a variety of topics including the following: NIDA Deputy Director, Mr. Richard A. Millstain gave two talks entitled "Bringing the Power of Science to Bear on Drug Abuse and Addiction" and "Funding Mechanisms at NIH: What You Need To Know"; Ana Anders, Senior Advisor on Special Populations, presented at a session on June 21-23; Dr. Cece McNamara, DTR&D, presented an overview of Treatment Research and Development on June 24, 2003; and Dr. Joseph Frascella, DTR&D, gave a presentation entitled "Grant Writing: Some Strategies for Success" on June 27, 2003.

NIDA's Division of Epidemiology, Services, and Prevention Research (DESPR) held a research agenda-setting seminar on **Primary Care and Drug Abuse** on July 17-18, 2003. The seminar, organized by Drs. Jerry Flanzer and Jack Stein, brought together researchers and service providers to review what is known about current linkages among drug abuse treatment and prevention services and primary care systems and to develop a research agenda for examining the role that primary health care services can play in the early identification, prevention, and ongoing treatment of drug use problems.

On July 24-25, 2003, NIDA convened the first of three meetings of the **Health Services Research Blue Ribbon Task Force** in Gaithersburg, Maryland. The purpose of the Task Force is to conduct a comprehensive review of NIDA's existing health services research portfolio and to provide recommendations for future research at NIDA within the context of facilitating the rapid transfer of research to practice. This Blue Ribbon Task Force was developed at the request of the NIH Director, Dr. Elias Zerhouni. The Task Force is co-chaired by Drs. A. Thomas McLellan and Constance Weisner, both members of the National Advisory Council on Drug Abuse. Representatives from other agencies, including the Office of National Drug Control Policy (ONDCP) and the Substance Abuse and Mental Health Services Administration (SAMHSA), are also members of the working group.

On August 19-20, NIDA sponsored the **Clinical Trials Network (CTN) Workgroup** in Gaithersburg, Maryland. The objectives of this workgroup are to review the current and future scope of the CTN's research portfolio and to identify research strengths, gaps, and opportunities for drug abuse and addiction research. Dr. David Rosenbloom, National Advisory Council on Drug Abuse member, chairs the Workgroup.

On September 7, 2003, NIDA co-hosted a **Single State Agency Directors' Meeting** at the Westin Westminster, Westminster, Colorado in order to provide an overview of the CTN and create a forum to exchange important strategies for States as research findings are disseminated into practice.

NIDA hosted **Blending Clinical Practice & Research: Forging Partnerships in the Rocky Mountain States to Enhance Drug Addiction Treatment** at the Westin Westminster, Westminster, Colorado, September 8-9, 2003. This conference provided an opportunity for clinicians and researchers to examine cutting-edge findings about drug use and addiction and their application to clinical practice.

Dr. Tom Kresina, CAMCODA, participated in a workgroup entitled "A Working Group on the Use of Directly Observed Therapy and Other Community Based Efforts to Get HAART to Those Who Aren't Getting It" at Tufts University, Boston, February 2003. The Tufts Nutrition Collaborative, the Lifespan/Brown/Tufts Center for AIDS Research, NIDA/Center for AIDS and Other Medical Consequences of Drug Abuse (CAMCODA), and the Centers jointly sponsored this workgroup for Disease Control and Prevention. Over 70 people attended the workgroup. Investigators at Brown and The Miriam Hospital collaborated with Greg Lucas, M.D. at Johns Hopkins and Alice Tang, Ph.D. The workgroup focused on four different models of providing antiretroviral therapy among active substance users in the United States, and two different adherence models providing antiretroviral therapy in the developing world, specifically Haiti and South Africa. Lessons learned in these projects were emphasized and a very active discussion focused on engaging substance users into HIV related medical care and retaining them within the context of adherence to antiretroviral medications. The importance of preventing the emergence of resistant HIV was among the key points emphasized at the conference. The proceedings of this workgroup are being prepared as a special supplement in the Clinical Infectious Diseases (CID) journal.

Dr. Henry Francis and Dr. Tom Kresina, CAMCODA, co-sponsored with Meharry

Medical College in Atlanta and organized a meeting on bioethics entitled "Issues, Ethics, and You: A Community Discussion of HIV/AIDS and Substance Abuse, Research and Treatment", Atlanta, June 23-24, 2003. The objectives of the meeting were to: (1) identify ethical challenges in developing and maintaining partnerships among government, academic, clinical, and community-based organizations working on various aspects of HIV/AIDS and substance abuse; (2) identify ethical complexities facing a collaborative effort to address the issues in HIV/AIDS and substance abuse research and treatment; and (3) recognize regulatory and practical issues in the inclusion of minorities and underserved populations in HIV/AIDS and substance abuse.

CTN Meetings

National Steering Committee Meetings were held in Fort Lauderdale, Florida, June 19-21, 2003.

- The CTN Executive Committee met on June 19 and June 20 in Fort Lauderdale. The EC discussed the following: NIDA-CTN partnership with ATTCs; potential buprenorphine liver toxicity study; CTN page in upcoming NIDA Notes; and protocol related issues.
- The CTP Caucus met on June 19 in Fort Lauderdale. The group heard reports on how the CTN Nodes are moving to incorporate consumers into CTN activities. Several new protocols were reviewed and discussed. A member from Dr. Paul Roman's grant which is studying the CTN presented some initial findings and answered questions regarding future activities.
- The Portfolio Coordinating Committee met on June 20, 2003. The members finalized the revised protocol review process and addressed issues regarding selection of Community Treatment Programs for studies in the CTN.
- The Operations Coordinating Committee met on June 20, 2003. Among the topics covered were the review and approval of the DMAS executive summary and recommendation of DMAS dated 6/12/03 to "require more than one data acquisition for the CTN".
- The External Affairs Coordinating Committee met on June 20, 2003. The group heard reports from several subcommittees. It was announced that NIDA Notes will include a regular column on the CTN. Upcoming publications and guidelines for dissemination were also addressed.
- The Executive Committee met on July 14, 2003, in Bethesda, Maryland, to develop the CTN roadmap for the next five years.
- Other groups met during the June Steering Committee Meeting such as the CTN Common Assessment Battery, Behavior Therapy Interest Group, the Treatment Matching Interest Group, and a combined Minority and Gender Interest Group Meeting.

The CTN Protocol Review Board met in Bethesda, Maryland, on August 13-14, 2003 to review the fourth wave of new protocols.

Dr. Cindy Miner, Deputy Director, OSPC, presented the keynote address at the Chief Resident Immersion Training Program (CRIT) in Brewster, Massachusetts on May 15th, 2003.

Dr. Cindy Miner, Deputy Director, OSPC, unveiled the grand prize artwork from the *"Heads Up: Real News About Your Drugs and Your Body"* poster contest at the Scholastic Headquarters in New York, New York on May 16, 2003.

Dr. Cindy Miner, Deputy Director, OSPC, Dr. David Shurtleff, DNBR, Mark Swieter, OEA, and Dr. Scott Lucas, McLean Hospital presented a Grant Writing Workshop at the College on Problems of Drug Dependence (CPDD) Annual Meeting in Bal Harbour, Florida on June 16, 2003.

Dr. Cindy Miner, Deputy Director, OSPC, presented "Science to Service: Blending Research and Practice" at the District of Columbia 2003 Summer Institute at Gallaudet University on July 16, 2003.

Dr. Cindy Miner, Deputy Director, OSPC, participated in a plenary session "Addiction is a Brain Disease: Blending Research and Practice" at the 4th Annual Arizona Summer Institute in Sedona, Arizona on July 24, 2003.

Dr. Suman Rao, OSPC, presented at the American Psychiatric Institute for Research and Education, 8th Annual Research Colloquium for Junior Investigators, as part of the American Psychiatric Association annual meeting, which was held on May 18, 2003 in San Francisco, California.

Dr. Suman Rao, OSPC, presented "NIH Research Funding Opportunities: Overview and Suggestions" at the Society for Prevention Research annual meeting on June 12, 2003 in Washington, D.C.

Dr. Suman Rao, OSPC, organized and coordinated the 2003 NIDA Tutorials at the College on Problems of Drug Dependence (CPDD) annual meeting on June 14, 2003 in Bal Harbour, Florida.

Dr. Suman Rao, OSPC, organized and coordinated both the 2003 NIDA Grant Writing Workshop and Training Mixer at the College on Problems of Drug Dependence (CPDD) annual meeting on June 17, 2003 in Bal Harbour, Florida.

Dr. Suman Rao and Monica Jones, OSPC, participated in the 5th Annual NIH/SBIR/STTR Conference held on June 2-3, 2003 at the Natcher Conference Center, NIH. Drs. Pushpa Thadani, DNBR, and Larry Seitz, DESPR, participated in the 1-on-1 sessions. This conference served as an opportunity for the SBIR/STTR community to talk with NIH staff about new/emerging interests at NIH, the application, review and award process as well as to discuss their innovative ideas.

Dr. Lula Beatty, Chief, Special Populations Office (SPO), participated in a panel at CPDD on June 17, 2002 in Bal Harbour, Florida. She presented a talk entitled "NIDA's Programs to Train and Support Racial/Ethnic Minority Drug Abuse Researchers."

Dr. Lula Beatty presented a session on drug abuse research opportunities to the NIH EARDA program participants on June 24, 2003 in Rockville, Maryland.

Dr. Lula Beatty participated as a faculty advisor in a research development seminar for racial/ethnic investigators sponsored by the Minority Fellowship Program, American Psychological Association, on July 17, 2003 in Washington, D.C.

Dr. Lula Beatty presented a session on NIH funding mechanisms at a workshop for minority investigators in HIV prevention research sponsored by the NIH Office on AIDS on July 26-27, 2003 in Atlanta, Georgia.

Ana Anders presented information on NIDA's National Hispanic Science Network to faculty from the Hispanic Association of Colleges and Universities on July 31, 2003 in Bethesda, Maryland.

Ana Anders participated in a meeting of CSAP's Hispanic Initiative Steering Committee on August 4-6, 2003 in Miami, Florida.

Drs. Karen Skinner and Herbert Weingartner from DNBR, and Bill Bukoski from DESPR, were invited discussants at the NIH Bioengineering Consortium Symposium "Catalyzing Team Science" held June 23 and 24, 2003 at the Natcher Conference Center.

Dr. Cora Lee Wetherington, NIDA's Women & Gender Research Coordinator, chaired the session, "Sex/Gender Differences" at the Building Interdisciplinary Research Careers in Women's Health 3rd Annual Program Directors' Meeting, sponsored by the NIH Office of Research on Women's Health, July 7-8, 2003, Bethesda, MD.

Dr. Cora Lee Wetherington, NIDA's Women & Gender Research Coordinator, gave the keynote address at the Alcohol & Drug Problems Association of North America (ADPA) national women's conference, September 14 --16, 2003, Buffalo, NY.

Dr. Frank Vocci, Director, DTR&D, attended the CSAT sponsored workshop: Methadone Associated Mortality: A National Assessment Workshop in Arlington, VA on May 8-9, 2003.

Dr. Frank Vocci attended the BIO meeting in Washington, DC. On June 23, 2003, Drs. Vocci and Corrigall from NIDA, and Dr. Robert Lipsky of NIAAA spoke at a session on unmet needs for medications in addictions and how to interact with the Federal government.

Dr. Vocci traveled to Eli Lilly and Company in Indianapolis, Indiana on August 27, 2003. While at Eli Lilly and Company, he presented Grand Rounds on August 28, 2003.

On May 27, 2003, Dr. Cece McNamara, DTR&D, presented a talk on Behavioral

Therapies highlighting Contingency Management Interventions to a group of visitors to the State Department interested in drug abuse research.

Dr. Cece McNamara attended the Annual Meeting on the College on Problems of Drug Dependence in Bal Harbour, Florida to update the Contingency Management Working Group on the current Contingency Management Grant Portfolio and discuss future initiatives and directions with the Working Group.

Dr. Steven Grant represented NIDA on the trans-institute Cognitive Neuroscience Consortium during the planning and conduct of the conference on Executive Function held as a satellite to the annual meeting of the Organization for Human Brain Mapping in New York City, June 15-17, 2003.

Dr. Joseph Frascella, DTR&D, participated in the ONDCP/CTAC meeting to define a developmental plan to improve technological tools for substance abuse research in San Diego, CA, July 7-9, 2003.

Mr. Robert L. Walsh, DTR&D, gave presentations on HIPAA to the Methamphetamine Clinical Trials Group's site physicians, and research personnel, at the Bupropion Study Initiation Meeting on May 22, and 23, 2003, in San Diego, California.

Dr. Roberta Kahn, Ms. Ann Montgomery and Mr. Robert Walsh participated in the RPR 102681 Study Initiation Meeting held on July 9, 2003 in the Clinical Pharmacology Unit at the Uniformed Services University of the Health Sciences (USUHS), Bethesda, Maryland.

On June 19, 2003 at the CPDD meeting in Bal Harbour Florida, Dr. Jane B. Acri presented a poster entitled "NIDA Medications Discovery Programs I: Efficacy-Related Testing" and Dr. David McCann presented a poster entitled "NIDA Medications Discovery Programs II: Safety-Related Testing."

Drs. William Corrigall, DNBR, and Ivan Montoya, DTR&D, participated in a series of work group meetings on "Addressing Tobacco Dependence among Smokers with Mental Illness or Addiction" sponsored by the Robert Wood Johnson Foundation.

Dr. Ivan Montoya, DTR&D, presented at the Society for Research on Nicotine and Tobacco meeting in New Orleans, LA, the results of a study examining the prevalence of nicotine problems in patients seen in routine psychiatric practice and comparing the sociodemographic, clinical, and health care characteristics of psychiatric patients with and without nicotine problems.

Dr. Ivan Montoya, DTR&D, was invited to present at the seventh annual meeting of the National Hispanic Medical Association in Washington DC on. The topic of his presentation was "Hispanic Drug Abuse Research."

Dr. Ivan Montoya, DTR&D, organized and chaired two symposia at the American Association for the Treatment of Opioid Dependence Conference in Washington, D. C. April 13-16, 2003. One was entitled "Treatment of Opioid-Dependent Adolescents" and the other "Treatment Needs of Pregnant Women Receiving Methadone Treatment."

Dr. Wilson Compton, Director, DESPR, presented at a training workshop lead by Dr. Bill Bukoski at the College on Problems of Dependence Annual Meeting held in Bal Harbour, FL in June 2003.

In May 2003, Dr. Wilson Compton participated in meetings at the American Psychiatric Association Annual Meeting in San Francisco on preparing for DSM-V.

Dr. Kevin Conway, DESPR, presented a paper entitled "Familial/Genetic Vulnerability in Drug Abuse Epidemiology" at the Annual Meeting of the Society for Epidemiologic Research held in Atlanta, Georgia, on June 14, 2003.

Dr. Yonette Thomas, DESPR, presented a paper entitled "The Social Epidemiology of Drug Abuse: Bringing Social Environment into Focus" at the Annual Meeting of the Society for Epidemiologic Research held in Atlanta, Georgia, on June 14, 2003.

Dr. Moira O'Brien, DESPR, gave a presentation, "Assessing Drug Abuse Patterns and Trends: Drug Abuse Surveillance and Research at the National and Local Levels," for the Society for Epidemiologic Research Meeting, in Atlanta, Georgia, June 12-14, 2003.

Dr. Lynda Erinoff, DESPR, was the discussant for a panel on "Drug Studies Focusing on Racial and Ethnic Populations: Giving More Attention to Minorities" held July 29, 2003 at the National Institute of Justice's Annual Conference on Criminal Justice

Research and Evaluation.

Dr. Moira O'Brien, DESPR, chaired the meeting of the NIDA Community Epidemiology Work Group, in St. Louis, Missouri, June 24-27, 2003.

On May 22 and 23, 2003 Dr. Elizabeth Robertson, DESPR, provided technical assistance to the Wyoming Division of Substance Abuse in developing program and evaluation plans for a state-wide wilderness-based drug abuse prevention program intervention. The meeting was sponsored by The Daniels Fund Wyoming and was held in Jackson Hole, WY.

On June 12, 2003, Dr. Elizabeth Robertson was a panelist on "A Framework for Understanding Evidence in Prevention Research and Programs" and a discussant on a paper titled, "Can Sequential Experimentation Hasten the Progress of Prevention Science?" at the 11th Annual Society for Prevention Research meeting held in Washington, DC.

On June 14, 2003 Drs. Elizabeth Robertson (NIDA) and Belinda Sims (NIMH) co-hosted a symposium titled "The Impact of Universal Interventions on High-risk Populations, at the 11th Annual Society for Prevention Research meeting held in Washington, DC. Symposium presenters were Richard Spoth and Max Guyll, Iowa State University; Mark Greenberg, Chi-Ming Kam and Carol Kusche, Pennsylvania Statue University; Mark Lipsey, Vanderbilt University; and C. Hendricks Brown, University of South Florida.

Dr. Elizabeth Robertson participated in the OBBSR planning committee for an NIH conference on Designs for Translational and Effectiveness Research at the Community Level. This committee met on August 20, 2003.

Dr. Susan Martin participated in a meeting on Positive Youth Development sponsored by the Annenberg School of Communication in Philadelphia on May 28-30, 2003.

Dr. Susan Martin presented, "Dissemination of Scientific Findings from a NIDA Perspective: Bridging the Gaps between Research and Practice," on June 12, 2003 at the annual meeting of the Society for Prevention Research in Washington D.C.

Dr. Aria Crump, DESPR, presented a talk titled "NIH Data and Safety Monitoring in Prevention Research" on June 12, 2003 at the Annual Meeting of the Society for Prevention Research in Washington, D.C.

Drs. Aria Crump, Bill Bukoski, Kathleen Etz, Susan Martin, Shakeh Kaftarian, and Eve Reider of DESPR participated in a meeting held by the Early Career Preventionist Network of the Society for Prevention Research on June 12, 2003. The meeting was designed to provide early career investigators with opportunities to make contacts with staff from NIH and other federal partners to develop prevention research studies.

Drs. Eve Reider, NIDA, and Belinda Sims, NIMH, organized a symposium for Society for Prevention Research annual meeting on June 13 in Washington D.C., titled "Long-Term Impact of Prevention Interventions on Health Risking Behaviors." The symposium focused on the long-term outcomes of prevention interventions conducted by J. David Hawkins, University of Washington, David Olds, University of Colorado, and Irwin Sandler, Arizona State University.

Drs. Aria Crump, Kathleen Etz, Elizabeth Robertson, and Eve Reider of DESPR held a roundtable discussion, "Can Prevention Studies Inform Etiological Research? A Case Study Involving Gender Effects in Prevention Research," on June 13, 2003 at the Society for Prevention Research Meeting in Washington, D.C.

Dr. Aria Crump of DESPR collaborated with Dr. Cheryl Boyce of NIMH to present a New Investigators' Informational Forum on June 13, 2003 at the Annual Meeting of the Society for Prevention Research in Washington, D.C.

Drs. Shakeh Kaftarian and Elizabeth Robertson presented a poster at the Society for Prevention Research titled, "From Research to Practice: What Helps and Hinders Program Selection, Implementation and Institutionalization," on June 13, 2003, in Washington, D.C.

Dr. Aria Crump attended the Family Research Consortium Fifth Annual Summer Institute, a forum for intellectual exchange among family researchers that was held in Santa Ana Pueblo, New Mexico June 26-29, 2003.

Drs. Shakeh Kaftarian and Aria Crump attended the Scientific Advisory Panel Meeting of the National Community Anti-Drug Coalitions Institute (CADCA) on July 10-11,

2003 in Washington D.C., and participated in discussions related to multi-site evaluations of coalitions.

Dr. Jack Stein, DESPR, presented "Drug Dependence Blending Adolescent Treatment Research and Practice: Update from the National Institute on Drug Abuse" during the Center for Substance Abuse Treatment's Satellite Session: From Science to Services: Effective Practices for Substance Abuse Treatment, at the Annual Scientific Meeting of The College on Problems of Drug Dependence, in Bal Harbour, Florida, on June 14, 2003.

Dr. Jack Stein participated in a roundtable discussion on research opportunities at the annual meeting of the Society for Adolescent Substance Abuse Treatment Effectiveness, in Bal Harbour, Florida, on June 15, 2003.

Dr. William S. Cartwright, DESPR, delivered a paper, "Applied Economic Research in Behavioral Health Care" at the International Health Economics 4th World Congress, Global Health Economics: Bridging Research and Reforms in San Francisco June 15th - 18th, 2003.

Dr. William S. Cartwright presented "Economic Impact of Substance Abuse Treatment and Benefits of Treatment" at the Drug Free Workforce Conference in Washington DC on July 10, 2003. The conference was sponsored by the Department of Labor to examine improving productivity and other employment outcomes through substance abuse prevention, intervention, treatment, and recovery. Dr. Thomas Hilton served on the conference planning committee.

Dr. Jerry Flanzer, DESPR, presented a paper on "Drug Abuse Health Services Research: AIDS and the Elderly" at the AIDS, Substance Abuse, and Elderly Conference sponsored by the School of Social Work at Columbia University, in New York on March 8, 2003.

Edward Nunes, M.D. (Lead Investigator and Node PI) and Paul Wakim, Ph.D., chaired a CTN workshop titled "From Efficacy to Effectiveness in the Design of Multisite, Community-Based Clinical Trials for Drug Abuse" at the College on Problems of Drug Dependency (CPDD) Meeting June 14-19, 2003, in Bal Harbour, Florida.

Betty Tai, Ph.D., Director, CCTN, co-chaired with Raye Litten, Ph.D., from NIAAA, a pre-meeting symposium at the Research Society on Alcoholism meeting in Fort Lauderdale on June 21, 2003. This signified the first step of NIDA/NIAAA collaboration in translating research into practice.

Dr. Jonathan Katz, IRP, was the keynote speaker at the thirteenth annual "Training in Behavioral Pharmacology of Drug Dependence Summer Retreat" held by the University of Vermont in Burlington. The title of his talk was "Drug Discovery Research on Cocaine Dependence."

Dr. Amy Newman, IRP, was invited to present a seminar in the Department of Physiology & Neuroscience, Medical University of South Carolina, Charleston, SC in June 2003.

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Media and Education Activities

Press Releases

May 2, 2003 -- **NIDA NewsScan #22**

- Real-Time Monitoring of Dopamine Activity in Brain Helps Explain How Environmental Cues Contribute to Cocaine Relapse
- Starting Marijuana Use in Mid-Teens or Younger May Result in Cognitive Impairment Later in Life But Reasons are Unclear
- Study Finds Lobeline Reduces Self-Administration of Methamphetamine in Rats
- Sigma Receptors Play Role in Cocaine-Induced Suppression of Immune System

May 8, 2003 -- **NIDA Announces 7th Annual "PRISM" Award Winners**. Val Kilmer, Neve Campbell, Bernie Mac, John Spencer, Tim Matheson and Noah Wyle received ***PRISM Awards*** for individual performances in film and television at the ***7th Annual PRISM Awards*** ceremony which was held May 8 in Hollywood. This is the first time that actors have been recognized for outstanding performances since the award show's inception. Presented by the Entertainment Industries Council, Inc. (EIC), in partnership with The Robert Wood Johnson Foundation (RWJF) and the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health, Department of Health and Human Services, the ***7th Annual PRISM Awards*** recognize accurate depictions of drug, alcohol and tobacco use and addiction in television, feature film, music and comic book entertainment.

May 23, 2003 -- **NIDA NewsScan #23**

- PRISM Award Winners Announced in Hollywood Ceremony
- Treatment for Cocaine Addiction May Reduce HIV Risk
- Study Finds Link Between Inflammatory Protein and Heart Disease Among Cocaine Users
- HIV Patients Who are Older, Free of Cognitive Deficits, and Do Not Abuse Drugs Comply Better with Medication Schedules
- Immigrant Status and Country of Origin Important in Compiling Smoking Prevalence Statistics
- Behavioral Treatment May Reverse Brain Changes that Occur with Cocaine Use and Help Prevent Relapse

June 13, 2003 -- **Scientists Gather to Discuss Advances in Drug Abuse Research**. More than 1,000 scientists met June 14-19 in Bal Harbour, Florida, at the Sixty-fifth Annual Meeting of the College on Problems of Drug Dependence (CPDD) to discuss their latest findings on drug abuse and addiction.

July 11, 2003 -- **NIDA NewsScan #24**
Special Issue of NewsScan Focuses on NIDA Funding News

- NIDA to Fund Medication Development Units
- NIDA Seeks New Funding Solicitations for Proteomics Research
- Behavioral Therapies Program (PA-03-126)
- Women Gender Differences and Drug Abuse (PA-03-139)

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- Cutting Edge Basic Research Awards (PAR-03-017)

July 30, 2003 -- **NIDA NewsScan #25**

- New Vaccine Reduces Behavioral Effects of Nicotine
- Drugs of Abuse and Stress May Cause Similar Changes in the Brain
- Patients Pay Greater Portion of Costs for Substance Abuse and Mental Health Treatment Than for Medical Services in Many Managed Care Plans
- Individuals With Medical Conditions Related to Alcohol or Drug Abuse Benefit From Integrating Medical and Substance Abuse Treatment
- Genetics, Shared Environment Have Little Impact on Choice of Commonly Abused Drugs
- College on Problems of Drug Dependence Publishes Position Statement on Opioid Use and Abuse
- Methamphetamine Abuse May Cause Functional Abnormalities in the Brain

August 11, 2003 -- **New Compound That Acts on Peripheral Receptors May Be Promising Treatment for Some Nerve Pain**. A new study in mice and rats showed that a compound which acts on a specific type of cell receptor outside the central nervous system decreases the animals' pain responses. But the researchers caution that studies investigating the safety and efficacy of this compound in humans have yet to be done. The scientists hope this approach may lead to the development of pain-relief drugs that lack the debilitating central nervous system side effects limiting the effectiveness of currently available pharmaceuticals.

Articles of Interest

May 1, 2003, *Psychiatric Times*--"Bringing New Medications to the Treatment of Addiction" -- Article by Frank Vocci, PhD.

June 22, 2003, *London Times*--"Genetic Addiction: Is There a Cure?" -- Interview with Nora D. Volkow, M.D.

July 4, 2003, *Science*-- "New Head of Drug Institute is Wired for Action" -- Interview with Nora D. Volkow, M.D.

August 19, 2003, *New York Times*-- "A Scientist's Lifetime of Study Into the Mysteries of Addiction" -- Interview with Nora D. Volkow M.D.

August 21, 2003, *Washington Post*- "Revolutionary Thinker" -- Interview with Nora D. Volkow, M.D.

Dr. Ivan Montoya, DTR&D, was interviewed for the Spanish-speaking TV channel Telemundo on public health issues concerning the development and use of the nicotine vaccine.

Educational Activities

As part of its ongoing commitment to provide schools with science-based information about drug abuse and addiction, NIDA is mailing a host of innovative classroom materials developed for elementary, middle school, and high-school students and teachers to hundreds of schools across the United States. The initiative entitled *NIDA Goes Back-to-School* will raise awareness on NIDA's classroom materials, which provide accurate, science-based information about drugs and their health effects, as well as making learning and science fun for children and adolescents. The first mailing is expected to begin in September 2003.

NIDA for Teens Website -- NIDA has launched the brand new website www.teens.drugabuse.gov that focuses on the science of drug abuse and addiction. Features include the latest research findings on drugs of abuse, personal stories from teens, publications, and activities for students.

To bring awareness about the effects of drug use on the most vulnerable populations -- children and adolescents -- as they returned to school, Community Anti-Drug Coalitions of America (CADCA) partnered with the National Institute on Drug Abuse (NIDA) to release, *"Practical Theorist 5: Marijuana Abuse: Using Science for an Effective Community Response."* The release of the Practical Theorist coincided with the presentation of CADCA's Humanitarian of the Year Award to P. Anthony Ridder, Chairman and CEO of Knight Ridder, Inc. Mr. Ridder was recognized for his commitment to CADCA's Drug Free-Kids Campaign, which seeks to improve the lives

of youth by raising corporate America's awareness of substance abuse issues and community efforts to keep youth drug free. The award ceremony took place on Sept. 16, 2003, at the Andrew W. Mellon Auditorium in Washington, D.C.

Exhibits/Conferences

September 2003: Hispanic Heritage Month Event
September 8-9, 2003: NIDA Blending Clinical Practice and Research
September 14-17, 2003: National Association of Alcoholism and Drug Abuse Counselors
September 23-25, 2003: Latino Behavioral Health Institute
October 2003: NIH Share the Health: An Exposition of Health Resources from NIH to its Neighbors
October 2-5, 2003: Society for Advancement of Chicanos and Native Americans in Science
October 14-19, 2003: American Academy of Child & Adolescent Psychiatry
October 15-18, 2003: Annual Biomedical Research Conference for Minority Students
October 18-21, 2003: Hispanic Association of Colleges and Universities
November 4-8, 2003: American Society of Human Genetics
November 5-8, 2003: Joint Meeting of the Association for Medical Education and Research in Substance Abuse and the International Nurses Society on Addictions
November 8-11, 2003: Society for Neuroscience Annual Conference
November 15-19, 2003: American Public Health Association
November 20-23, 2003: American Indian Science and Engineering Society
November 22-24, 2003: Employee Assistance Professionals Association Annual Conference
December 9-12, 2003: National Conference on Tobacco or Health 2003

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Planned Meetings

NIDA is sponsoring a mini-convention, on **Frontiers in Addiction Research** which is comprised of 8 satellite symposia at the Society for Neuroscience 33rd Annual Meeting on November 7, 2003 in New Orleans, Louisiana. This convention will bring together an exciting group of participants from a wide array of scientific disciplines to share advances and discuss future directions in the neuroscience of drug abuse related areas.

The National Institute on Drug Abuse (NIDA) is organizing a special research-based track **Integrating the Science of Addiction into Psychiatric Practice** to include a number of symposia, workshops, forums, and invited speakers, at the Annual Meeting of the American Psychiatric Association (APA) May 1-6, 2004 in New York City. This is the second time NIDA has collaborated with APA to produce a major track at the APA meeting where the attendance runs at about 20,000. The first NIDA series with APA in 1998, "Drug Addiction: A Treatable Disease" was extremely popular, well attended and provided attendees with an opportunity to hear first hand about new advances, and prevention and treatment approaches that may not be published until months or years later. The program also provided an opportunity for medical students, residents, fellows, and faculty to meet both formally and informally with addiction specialists and researchers to discuss opportunities for pursing research careers in the substance abuse area. For these reasons, and because numerous science advances have been made in understanding the brain substrates and contributing factors that lead to comorbidity between drug abuse and mental illness, there is renewed need for this special series that focuses on drug abuse.

A National CTN Steering Committee Meetings is planned for January 26-28, 2004 in Tucson, Arizona.

A National meeting, adjunct with the January 2004 CTN Steering Committee Meeting, is planned to address challenges and opportunities in treating addicted patients with co-morbid infectious disease. Recommendations are expected from this meeting to guide the research portfolio development.

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Publications

NIDA Publications

Drug Use Among Racial/Ethnic Minorities
NIH Pub. No. 03-3888
NCADI #BKD180
The Drug Use Among Racial/Ethnic Minorities 2003 is a revised updated publication, which draws together data from multiple sources to address the issue of substance use and related consequences of drug use for minority subgroups within the United States. The publication includes the most recent data available in the public domain at the time of the report on drug use among racial/ethnic minorities.

NIDA NOTES: Articles that Address Research on Club Drugs
NCADI #0060
New collection features NIDA NOTES articles originally published from 1996 through 2002. Topics include: the effects of ecstasy and methamphetamine on the brain and body; prenatal exposure to ecstasy; research aimed at reversing methamphetamine's neurotoxic effects; the epidemiology of club drug use; NIDA's initiatives to control the use of club drugs, and LSD, PCP, GHB, and ketamine.

NIDA NOTES: Articles that Address Research on Marijuana
NCADI #NN0058
New collection features NIDA NOTES articles originally published from 1995 through 2002. Topics include: long-term cognitive impairments in heavy marijuana users; evidence that chronic marijuana users experience withdrawal upon quitting; the influence of genes and the environment on drug abuse vulnerability; the body's natural THC-like compounds; epidemiology, prevention, and treatment.

Serie de Reportes De Investigaci—n Alucin—genos Y Drogas Disociativas (Research Report Series: Hallucinogens and Dissociate Drugs)
NIH Pub. No. 03-4209(S)
NCADI #PHD876S
Outlines the mechanisms by which hallucinogens work and details their effects and their dangers. Includes review of such drugs as LSD, PCP, and ketamine.

Principios para la Prevenci&oacte:n del VIH en las Poblaciones de Usarios de Drogas: Una guia basada en la investigación (Principles of HIV Prevention in Drug-Using Populations: A Research-Based Guide)
NIH Pub. No. 03-4733(S)
NCADI #BKD440S
The guide describes principles that characterize effective HIV/AIDS prevention in drug users. As an important contribution to NIDA's expanding prevention toolbox, this Guide will prove useful to community planners, policymakers, and medical practitioners as they develop and implement comprehensive HIV/AIDS prevention programs to prevent the spread of HIV and other infections among drug users and their sexual partners.

Brief Strategic Family Therapy for Adolescent Drug Abuse
NIH Pub. No. 03-4751
NCADI #BKD481
An essential tool for mental health professionals and other drug abuse treatment practitioners who deal with adolescent drug abuse. NIDA's first treatment manual in a series describes Brief Strategic Family Therapy (BSFT), a short-term intervention strategy for treating adolescent drug abusers. BSFT targets associated conduct

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problems in adolescent drug users by basing the treatment intervention within the context of family dynamics.

National Survey Results on Drug Use From the Monitoring the Future, 1975-2002: Volume I, Secondary School Students
NIH Pub. No. 03-5375
NCADI #483
Reports on the prevalence of drug use among students in 8th-, 10th-, and 12th grades. Trends are analyzed to understand the changing drug abuse problem and to formulate appropriate prevention and treatment policies.

National Survey Results on Drug Use From the Monitoring the Future, 1975-2002: Volume II, College Students and Adults Ages 19-40
NIH Pub. No. 03-5376
NCADI #BKD486
Reviews trends in drug use by populations based on gender, college plans, regions of the country, population density, race/ethnicity, and parents' education. Trends are analyzed to understand the changing drug abuse problem and to formulate appropriate prevention and treatment policies.

Epidemiologic Trends in Drug Abuse -- Community Epidemiology Work Group, Volume I- December 2002
NIH Pub. No. 03-5364
NCADI #
This report provides an ongoing assessment of drug abuse in major metropolitan areas of the United States with the purpose of keeping both public and private sector policymakers and researchers informed with current and accurate data.

Epidemiologic Trends in Drug Abuse -- Community Epidemiology Work Group,

Volume II -- December 2002
NIH Pub. No. 03-5365
This report provides an in-depth analysis of the epidemiologic trends and special reports for a limited audience made up primarily of drug abuse researchers who utilize this volume to identify potential areas for further research.

Preventing Drug Use Among Children and Adolescents: A Research-Based Guide for Parents, Educators, and Community Leaders, Second Edition
NIH Pub. No. 03-4212A
NCADI # PHD1023A
This second edition of the "Red Book" includes updated principles, new questions, new program information, and expanded references and resources based on the latest findings from NIDA-funded prevention research. The 16 fundamental prevention principles, derived from research on effective prevention programs, are outlined. Discussions include key factors that place youth at risk for drug abuse, guidance for planning drug abuse prevention programs in the community, applying the prevention principles to programs, and describing the core elements of effective prevention programs.

Preventing Drug Use Among Children and Adolescents -- A Research-Based Guide for Parents, Educators, and Community Leaders, Second Edition, In Brief
NIH Pub. No. 03-4212B
NCADI # PHD1023B
This "In Brief" version provides highlights from the "Red Book" -- Preventing Drug Use Among Children and Adolescents: A Research-Based Guide for Parents, Educators, and Community Leaders, Second Edition. It presents the updated prevention principles, an overview of program planning, and critical first steps for those learning about prevention. This shortened version therefore can serve as an introduction to research-based prevention for those new to the field of drug abuse prevention.

Science & Practice Perspectives, Vol. 2, No. 1
2003 * Journal * NCADI #M
NIDA's peer-reviewed journal brings together scientific investigators and clinical practitioners to present and discuss ideas for improving drug abuse treatment and research. The issue features:
Researcher --written reviews: Douglas B. Marlowe proposes integrating substance abuse treatment with criminal justice supervisions for economical use of resources and for levels of monitoring appropriate to clients' drug use and criminal justice histories. Paula D. Riggs presents current knowledge of treatment of adolescents with both substance abuse and psychiatric disorders, offering practical advise for history

taking and identifying areas requiring further investigation.
Clinician-written perspectives: James R. Sharp and colleagues tell why and how their inpatient programs treat nicotine addiction as uncompromisingly as addiction to any other drug of abuse. Gregory S. Brigham describes the integration of 12-step treatment and empirically-based therapy at his community-based facility in Ohio.
And: Panel discussions examine and expand the ideas and implications of each review and perspective article.
Plus: Nancy M. Petry and Michael J. Bohn discuss their experiences with low-cost contingency management. A striking visual captures brain activity during cue-induced craving. A continuing education (CE) quiz offers counselors an opportunity to earn two NAADAC-certified CE hours.

NIDA INVEST Letter, Spring -- Summer 2003
The main article in this issue summarized the 11 programs to address the international impact of drug abuse and addiction that are cosponsored by NIDA and the National Institutes of Health Fogarty International Center. Other features focused on the interaction of drug abuse, HIV infection, and progression to AIDS and announced a Global Forum for Health Research request for proposals to identify research capacity in low- and middle-income countries. Dr. James Smith, Wake Forest University School of Medicine and a member of the NIDA Advisory Council International Subcommittee, wrote the inaugural edition of "From the Field," a column by NIDA grantees to address the way international collaboration has influenced their drug abuse research. In the "Fellow Profile," former NIDA INVEST Fellow, Dr. Eli Lawental, Israel, discussed his training and research career. Other articles on Fellowship activities announced the appointment of Zhijun Li, M.D., China, and Pajulo Marjaterttu, M.D., Ph.D., Finland, as the 2003-2004 NIDA INVEST Fellows; reported on the orientation program and grant process workshop for current INVEST and Humphrey Fellows; and memorialized former NIDA Hubert H. Humphrey Fellow Dr. Viswananthan S. Mani, India, who died of a heart attack in February 2003.

NIDA NOTES

NIDA Notes, Volume 17, Issue No. 5
NIH Pub. No. 03-3478
The lead article discusses a study by Dr. Thomas Dishion of the Oregon child and Family Center. Dr. Dishion found that preventive interventions that put high-risk youths into groups could, under certain circumstances, produce worse rather than better behavior.

Other articles include the first study to clearly show an association between cocaine exposure before birth and cognitive impairments in toddlers. Researchers at Case Western Reserve University found that nearly twice as many cocaine-exposed children scored in the mental retardation range of a test that assesses mental development compared to unexposed children. Also described is a study that found that monkeys that became dominant developed higher brain dopamine levels and were significantly less inclined to self-administer cocaine than subordinate monkeys--a finding that may have implications for understanding the interaction between environmental factors and drug abuse vulnerability in humans. Monitoring the Future (MTF) survey results are reported showing that from 2001 to 2002 the use of MDMA (ecstasy), marijuana, and cigarettes declined among 8th-, 10th-, and 12th-graders.

NIDA Notes, Volume 17 Issue No. 6
NIH Pub. No. 03-3478
The lead article discusses recent research on nicotine's effects on the brain/s reward system. In the Director's Column, Dr. Glen R. Hanson discusses NIDA's research partnership with the National Institute of Mental Health for investigating the roles of neurochemical receptors in mood disorders and nicotine addiction. Also discussed is Translating Tobacco Addiction Research to Treatment, a NIDA initiative that supports the development of new treatment and prevention options. Other articles on NIDA-funded research address cocaine's effect on blood components and the link to heart attack and stroke, middle schools' selection and implementation of drug prevention programs, the use of vouchers to reward naltrexone treatment for heroin-dependent patients, and sex differences in the success of strategies to reduce drug-seeking. News articles note Dr. Nora D. Volkow's appointment as the new NIDA Director and the addition of eight new Advisory Council members.

NIDA Notes, Volume 18 Issue No. 1
NIH Pub. No. 03-3478
In the Director's Column, Dr. Nora D. Volkow discusses NIDA's commitment to expand research to increase understanding of factors contributing to dual addiction to drugs and alcohol and to provide insight into the development of effective treatment

interventions that will address both problems. To meet this research need, NIDA and the National Institute on Alcohol Abuse and Alcoholism have issued a joint program announcement to spur studies to evaluate the efficacy of current drug and alcohol treatment medications and new pharmacological treatment for dually addicted patients.

Simultaneous treatment of posttraumatic stress disorder (PTSD) and cocaine abuse is the focus of the lead story. The article discusses findings that exposure therapy can be safely and effectively combined with substance abuse counseling to reduce PTSD symptoms and cocaine use in some patients.

In other research findings, a new animal study stimulating human exposure to cocaine found that prenatal exposure to cocaine might cause long-term changes in short-term memory. Other research addressed in this issue examines how medications to treat ADHD help protect children with this disorder from later drug abuse, and notes ethnic and gender variations in the co-occurring psychiatric disorders seen in adolescent substance abusers. The Tearoff page announces the upcoming release of the Brief Strategic Family Therapy Manual, the latest in the Therapy Manuals for Drug Addiction series.

CTN PUBLICATIONS

During the months April -- July 2003, nine editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN.

"Quality Assurance & You; A Guide to Conducting High Quality Research in the CTN" was approved and printed for distribution to the clinical trial sites.

Three new brochures for the Suboxone (Buprenorphine/Naloxone) Taper: A Comparison of Taper Schedules protocol (CTN 0003) have been written and approved for printing and distribution.

A clinician brochure written for the Smoking Cessation Treatment With Transdermal Nicotine Replacement Therapy in Substance Abuse Rehabilitation Programs protocol (CTN 0009) was approved and distributed to the clinical trial sites.

Three new brochures for the Buprenorphine/Naloxone-Facilitated Rehabilitation for Opioid Dependent Adolescent/Young Adults protocol (CTN 0010) have been approved and distributed to the clinical trial sites.

Two new brochures for the Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome in Pregnant Substance Users protocol (CTN 0013) have been approved and distributed to the clinical trial sites. Two new brochures (patient and clinician) written for the Women's Treatment for Trauma and Substance Use Disorders protocol (CTN 0015) were approved for printing and distribution to the clinical trial sites.

OTHER PUBLICATIONS

A Life Sciences issue entitled "Stimulants and Other Drugs of Abuse and their Effects on Neuropeptides and the Peptidergic Systems" was published as a special Proceedings volume. It appeared as Vol 73, Issue 6, Pages 641-822, 27 June 2003. This issue resulted from a NIDA Workshop On Neuropeptides, held June 27-28, Marco Island, Florida and chaired by Dr. Rao Rapaka. Guest Editors for the special issue were Dr R. S. Rapaka and Dr. F. Porreca.

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Director's Report to the National Advisory Council on Drug Abuse - September, 2003

Staff Highlights

Staff Honors and Awards

2003 NIDA Director's Award Recipients

Individual Awards

Jagjitsingh H. Khalsa, Ph.D., CAMCODA
Carmen Rosa, M.S., CCTN
Paul Wakim, Ph.D., CCTN
Elaine Solano, DESPR
Lynda Erinoff, Ph.D., DESPR
Moira O'Brien, M. Phil, DESPR
Christine Colvis, Ph.D., DNBR
William Corrigall, Ph.D., DNBR
Adele B. Roman, M.S.N, R.N., DNBR
Barbara H. Herman, Ph.D., DTR&D
Ivan D. Montoya, M.D., M.P.H., DRT&D
Liza D. M. Gorgon, DTR&D
Nora Chiang, Ph.D., DTR&D
Robert Walsh, DTR&D
Annie Joseph, OEA
Rita Liu, Ph.D., OEA
William C. Grace, Ph.D., OEA
David L. Anderson, OSPC
Juanita Nelson, OSPC
Sheryl A. Massaro, OSPC
Suman Rao, Ph.D., OSPC

Group Awards

"CTN Data Integrity and Human Subject Protection Team"
"DESPR Support Staff"
Ann Hutzler
Roxie Brown
"Roger Brown Memorial and Symposium Coordinating Committee"
Beth Babecki, DNBR
Dave Thomas, DNBR
Rita Liu, OEA
Suzanne Cole, OPRM
Charlie Sharp, DNBR
Nancy Pilotte, DNBR
Joe Frascella, DTR&D
Cathrine Sasek, OSPC
Rick Harrison, OEA
Minda Lynch, DNBR
Susan Volman, DNBR
"The Office of the Medical Director -- IRP"
Carlo S. Contoreggi, M.D.
Michelle K. Leff, M.D.
"NIDA Budget Office"
Donna Jones
Jewell Webb
Carol Cornwell

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Lawrence Raigrodski
Gloria Lester
Miriam Jackson
"Management Analysis and Services Branch"
Suzanne Cole
Sharon Goon
Bridget McDonald
Chanvadey Nhim
Donna Tolson
Dave Daubert
Davy Jones
Montrue Nelson
Traci Pelan

2003 NIDA EEO Award Recipients

Elizabeth B. Robertson, Ph.D., DESPR
Thomas Hilton, Ph.D., DESPR
Flair Lindsey, SPO
Aria Davis Crump, Sc.D., DESPR
Barry J. Hoffer, M.D., Ph.D., IRP
Richard A. Millstein, J.D., OD

Dr. Mu-Fa Zou, IRP, received a Staff Recognition Award in August 2003.

On July 25,2003, **Ms. Pamela Oliver**, NIDA EEO Office, received the "Outstanding EEO Counselor" Award from the NIH Office of Equal Opportunity and Diversity Management.

Dr. Richard Hawks, Deputy Director, DTR&D, received the J. Michael Morrison Award from the College on Problems of Drug Dependence, at the Plenary and 2003 Awardees Program, June 15, 2003, Bal Harbour, Florida.

Dr. Frank Vocci, Director, DTR&D, received the Distinguished Service Award from the College on Problems of Drug Dependence, at the Plenary and 2003 Awardees Program, June 15, 2003, Bal Harbour, Florida.

Dr. Lisa Onken, DTR&D, has been selected by the American Psychological Association to receive the Meritorious Research Service Commendation, in recognition of her efforts to bridge basic and clinical science, and for creating NIDA's Behavioral Therapies Development Program.

CAPT. Steve Oversby, DTR&D was awarded "The Outstanding Unit Citation", as a member of the CCRF, by Surgeon General Carmona.

Dr. Rao S. Rapaka, DNBR, was elected as the Vice-Chair elect, for the Section of "Drug Design and Discovery", American Association of Pharmaceutical Scientists (AAPS). He will become Chair-elect 2004, and Chair by 2005. This section of AAPS includes, in addition to drug discovery, medicinal chemistry and natural products.

Gary Fleming, Chief of NIDA's Grants Management Branch, OPRM, received an Excellence in Leadership Award from the NIH Vision Steering Committee at a ceremony held June 6, 2003.

The following NIDA Grants Management personnel also recently received awards from the NIH Grants Management Community:

Diana Haikalis -- Excellence in Leadership Award
Deborah Wertz -- Special Recognition Award
Debra Battle-Dudley -- Letter of Appreciation
Catherine Mills -- Letter of Appreciation
Daisey Parker -- Letter of Appreciation

Current and former members of the Division of Treatment Research and Development (Peter Bridge, Nora Chiang, Lee Cummings, Dorynne Czechowicz, Joel Egertson, Liza Gorgon, Charles Grudzinskas, Richard Hawks, Susan Herbert, Moo Park, James Terrill, and Frank Vocci) along with Timothy Condon and Mary Mayhew from NIDA's Office of Science Policy and Communication, received the Secretary's Award for Distinguished Service for their roles in the NIDA/FDA/SAMHSA Buprenorphine Work Group at a ceremony held at DHHS headquarters, June 11, 2003.

Dr. Jerry Flanzer, DESPR, has been appointed Co-chair of the Social Work Section of

the International Council of Alcohol and Addiction.

Dr. Amy Newman, IRP, was asked to serve on the 2nd NIH Task Force on the Status of Women Scientists by Dr. Michael Gottesman, Deputy Director, NIH.

Dr. Mu-Fa Zou, IRP, received a Staff Recognition Award in August 2003.

Dr. Toni Shippenberg, IRP, was appointed to Adjunct Associate Professor, Pharmacology & Experimental Therapeutics, University of Maryland School of Medicine, 2003-2004.

Dr. Toni Shippenberg, IRP, was elected to serve on the Executive Board of the International Research Conference for a 3 year term, 2003.

Staff Changes

Jennifer Wong, Ph.D. joined the Regulatory Affairs Branch in the Division of Treatment Research and Development on July 27, 2003 as a Health Scientist Administrator. Dr. Wong received her Ph.D. in physiology from the University of Tennessee - Memphis. Before coming to NIDA, Dr. Wong was a Regulatory Compliance Specialist at Technical Resources International in Bethesda, Maryland.

Steve Oversby, Psy.D., FPPR, joined the MRGB, DTR&D as a Health Scientist Administrator in May 2003. Steve graduated from California State University, Hayward, and is an RN with Board Certifications in Addictions, as well as a Licensed Professional Addictions Counselor, and a Licensed Clinical Psychologist. Currently Steve is a student in the Prescribing Psychologist's Register (PPR) Psychopharmacology Program. Steve joined the U.S. Public Health Service in 1987, and has had a wide range of professional experience. Steve brings to the DTR&D one year of NIDA CCTN experience, ten years of dual diagnosis counseling, and two years of Substance Abuse Program Development with the D.C. Department of Mental Health.

Elizabeth Ginexi, Ph.D. joined the Prevention Research Branch (PRB) at NIDA in July 2003. Her work has emphasized the application of innovative longitudinal data analysis methods to advance research on mental health and substance abuse prevention among families and youth. Prior to coming to NIDA, she worked at Westat, a contract research firm in Rockville, MD, where she participated in the development and implementation of several large-scale drug abuse treatment and prevention evaluations funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the Substance Abuse and Mental Health Services Administration (SAMHSA). Prior to working at Westat, Dr. Ginexi played a major role in data collection, data management, and analysis for several large longitudinal field studies involving mental health preventive interventions and services research. She received her doctoral degree in Applied Social Psychology at the George Washington University (GWU). She received postdoctoral training under two Public Health Service Grant National Research Service Awards, one at Children's National Medical Center and the GWU Center for Family Research, and the other at the Center for Mental Health Policy at Vanderbilt University.

Drs. Kevin Conway and **Yonette Thomas** were appointed Deputy Branch Chiefs for the Epidemiology Research Branch. Each will be responsible for overseeing two separate but interrelated streams of science and administration. Dr. Conway will be responsible for *Emerging ERB Science*, which includes the promotion of new areas of ERB science, spearheading initiatives that crosscut ERB program areas, and executing pending ERB scientific activities. Dr. Thomas will be responsible for *Existing ERB Science*, which consists of reviewing and integrating the current ERB science, communicating ERB science to NIDA and the broader scientific community, and cultivating relationships with outside universities and organizations to attract new investigators.

Jessica Campbell, Ph.D. joined NIDA's Division of Epidemiology, Prevention and Services Research (DESPR) as a Health Scientist Administrator in July 2003. Dr. Campbell comes to DESPR from the Human Development Unit of NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse (CAMCODA). Her work in CAMCODA focused on the development of children growing up in drug abusing environments and the health and developmental consequences of prenatal exposure to drugs and drug abuse by high-risk youth. Dr. Campbell came to NIDA in August 2000 as an Executive Branch Fellow, sponsored by the American Association for the Advancement of Science (AAAS) and the Society for Research in Child Development (SRCD). Prior to joining NIDA, Dr. Campbell completed a Postdoctoral Research Fellowship at the National Institute of Child Health and Human Development (NICHD),

where she was involved with a longitudinal study of early child-care effects on children's social, emotional, and cognitive development. She received her doctoral degree in Human Development and Family Studies at the University of North Carolina - Greensboro. Dr. Campbell will serve as the Program Director for Child Development Research within the Epidemiology Research Branch of DESPR.

Arnold Mills was appointed Acting Chief, Epidemiology Research Branch, DESPR on July 13, 2003.

Robin Mackar was named Acting Chief of OSPC's Science Policy Branch on August 24, 2003.

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Grantee Honors

Dr. James Anthony of the Johns Hopkins University has been included in the roster of Highly Cited Scientists, compiled by the Institute for Scientific Information, which publishes Science Citation Index and Social Science Citation Index. The award is based on being in the upper 1/2 of 1% of researchers in the social sciences general category, in terms of citation of one's work by peers.

Kathleen Carroll, Ph.D., Yale University, was elected the President of Division 50 of the American Psychological Society for the coming year.

Dr. Renee Cunningham-Williams of Washington University was awarded the Eli Robins/ Samuel Guze Award in 2002 at the annual meeting of the American Psychopathological Association (APPA) in New York.

Dr. Craig Anne Heflinger, Senior Research Associate in the Center for Mental Health Policy at Vanderbilt University, was named Fellow of the Robert Penn Warren Center for the Humanities: Medicine, Health, and Society, for 2003-2004 at Vanderbilt University. Dr. Heflinger received two additional awards: a Peabody College Principal Investigator Contribution Award, May 2003; and The Invisible Child Award, from the Tennessee Voices for Children (a local affiliate of the Federation of Families for Children's Mental Health) for "the person who has done the most to bring children's mental health problems into the open so that they are recognized, appropriately treated and understood," May 2003.

Dr. Carl G. Leukefeld, Chair of the Department of Behavioral Science at the University of Kentucky, and Director of the Center on Drug and Alcohol Research, was awarded the Knee/Wittman Lifetime Achievement Award by the National Association of Social Workers Foundation for his exemplary contribution to health and mental health practice over the course of his career.

Two NIDA-supported researchers, **Dr. Tom McLellan**, University of Pennsylvania, and **Dr. William Miller**, University of New Mexico, were among the 5 winners of this year's Robert Wood Johnson Foundation "Innovator's Combating Substance Abuse" Award. This national award was established in 2000 and amounts to a $300,000 grant to be used by the awardees in the field of substance abuse.

Dr. Drake Morgan, Wake Forest University School of Medicine, was awarded the Wyeth Young Psychopharmacologist Award from the American Psychological Association in August 2003.

In May, the winner of the American Association for Marriage and Family Therapy "Outstanding Research Publication Award" for 2003 was announced **as J.D. Coatsworth, H. Pantin, and J. Szapocznik**, University of Miami, for their publication, "Familias Unidas: A Family-Centered Ecodevelopmental Intervention to Reduce Risk for Problem Behavior Among Hispanic Adolescents".

Maxine Stitzer, Ph.D, Johns Hopkins University, was awarded the 2003 CPDD Marian Fischman Award, which recognizes the careers of successful female scientists. The award was presented at the annual CPDD meeting in June 2003.

Dr. George Woody, University of Pennsylvania, was voted unanimously to receive the University Council (the supreme legislative body of Pavlov) "Doctor Honoris Causa" Award. He will be honored at a ceremony in Russia in the Fall of 2003.

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