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

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

## Research Findings - Basic Research

### MDMA ("Ecstasy") Inhibits Rats' Response to Stress

MDMA is known to damage forebrain serotonin neurons. Since the integrity of the central serotonergic system is important for some neurochemical responses to acute stress, neurochemical responses during immobilization stress were measured in male rats that had been administered a neurotoxic dosing regimen of MDMA 7 days earlier. In vivo microdialysis was used to assess extracellular dopamine and serotonin in the dorsal hippocampus and prefrontal cortex during 1 hour of immobilization stress. In saline- treated control rats, serotonin in the hippocampus and serotonin and dopamine in the prefrontal cortex were increased during immobilization stress. Rats pretreated with MDMA, however, showed blunted neurotransmitter responses in the hippocampus and the prefrontal cortex. In the MDMA pretreated rats, basal serotonin levels in the hippocampus, but not the prefrontal cortex, were lower compared to saline-pretreated controls. Stress-induced increases in plasma corticosterone and body temperature were not affected by the pretreatment condition. These findings suggest that depletion of serotonin stores in terminal regions with MDMA compromises the ability of the serotonergic neurons to activate central systems that respond to stressful stimuli. This altered responsiveness may have implications for long-term functional consequences of MDMA abuse as well as the interactions between the serotonergic system and stress. Matuszewich, L., Filon, M.E., Finn, D.A. and Yamamoto, B.K. Altered Forebrain Neurotransmitter Responses to Immobilization Stress Following 3,4-methylenedioxymeth-amphetamine. Neuroscience, 110, pp. 41-48, 2002.

### Superoxide Free Radical May Play Role in PCP Effects and in Schizophrenia

Kenneth M. Johnson's group previously showed that repetitive administration of PCP to rats in the perinatal period results in cortical apoptosis (cell death) and a long-lasting deficit in sensorimotor gating. Because these changes are blocked by olanzapine, an atypical antipsychotic agent, the researchers suggested that the effects of perinatal PCP could be used to model certain aspects of schizophrenia. Studies of PCP and NMDA-induced cell death suggested that superoxide could play a role in the pathway leading to cell death after PCP administration. The purpose of the current study was to determine whether the in vivo administration of M40403, a superoxide dismutase mimetic agent (which destroys superoxide), could prevent PCP-induced cortical apoptosis and/or deficits in prepulse inhibition (PPI). Deficits in PPI indicate deficits in sensorimotor gating, and decreased PPI is a clinical sign of schizophrenia. Perinatal rat pups were administered 10 mg/kg PCP on postnatal (PN) days 7, 9, and 11, with or without treatment with 10 mg/kg M40403. Pups were either killed on PN 12 for analysis of various apoptotic markers, or they were assessed for PPI on PN 24 to 26. Treatment with M40403 2 and 24 hours after each PCP treatment prevented PCP-induced increases in indicators of apoptosis in the dorsolateral frontal cortex and in the olfactory cortex. PCP-induced proapoptotic changes in Bax and Bcl-XL (regulators of apoptosis) were also prevented by M40403 treatment. This regimen did not prevent the deficit in PPI caused by PCP treatment, but when the treatment regimen was extended through PN 23, M40403 completely prevented the PCP-induced deficit in PPI. These data suggest that perinatal PCP treatment leads to long-lasting changes in the pathway(s) leading to cell death and behavioral deficits, and that the superoxide radical plays a critical role in the underlying mechanism. Wang, C., McInnis, J., West, J.B., Bao, J., Anastasio, N., Guidry, J., Ye, Y., Salvemini, D., and Johnson, K.M. Blockade of Phencyclidine-induced Cortical Apoptosis and Deficits in Prepulse Inhibition by M40403, A Superoxide Dismutase Mimetic. J. Pharmacol. Exp. Ther., 305, pp. 266-271, 2003.

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### Importance of Nonpharmacological Factors in Nicotine Self-administration

This paper reviews the work of the authors' laboratory and focuses on factors that influence nicotine self-administration. Nicotine dose, by itself, is not sufficient to explain the high rates of self-administration that is seen in animals and humans. It is concluded that although the direct pharmacological effects of nicotine are important, other factors such as environmental stimuli and conditioned reinforcement also influence rates of self-administration. The authors suggest that nicotine's principle function is to magnify the salience of other reinforcers. The interaction between therapeutic strategies targeting the direct effects of nicotine and those of the associated stimuli and contexts should be studied. Caggiula, A.R., Donny, E.C., Chaudhri, N., Perkins, K.A., Evans-Martin, F.F., and Sved, A.F. Importance of Nonpharmacological Factors in Nicotine Self-administration. Physiology & Behavior, 77, pp. 683-687, 2003.

### Rat Strain Differences in Nicotine Self-administration Using an Unlimited Access Paradigm

A 23 hour unlimited access paradigm was used in which several strains of rat (including inbred Lewis rats, inbred Fisher 344 rats, and outbred Holzman rats) lever pressed for nicotine. The ability for each strain to learn and maintain operant nicotine self-administration (0.03 and 0.0075 mg/kg, iv) at several FR schedules (FR1 to FR5) was measured. Rat strains differed both in sensitivity to nicotine dose and ability to maintain different schedules of reinforcement. This work suggests that the Lewis rats are genetically more susceptible to nicotine addiction. Brower, V.G., Fu, Y., Matta, S.G., and Sharp, B.M. Rat Strain Differences in Nicotine Self-administration Using an Unlimited Access Paradigm. Brain Research, 930, pp. 12-20, 2002.

### Delta Receptor Antagonism

Past efforts in the design of peptide ligands active at opioid receptors have recognized the utility of introducing structural constraints which will limit the available number of conformations which the peptide can adopt, based on single bond rotations about the bonds beta and gamma (C-2 and C-3) to the alpha carbon (C-1) of a particular amino acid. In this respect, modification of the dipeptide Tyr-Tic (tyrosine-tetrahydroisoquinoline) has been of interest, since this sequence is a minimum length peptide which still retains opioid receptor binding. It has been previously determined that methylating the beta carbon and dimethylating the aromatic ring of tyrosine produced four isomers of beta-methyl-2'-6'-dimethyl Tyr-L-Tic, of which only the 2S,3R isomer showed potent binding at the delta receptor (IC50 of 9 nM), and a very high selectivity ratio relative to the mu receptor. The low energy conformation of this molecule is believed to position the substituted phenolic group trans to the C(alpha)-amino bond. In a recombinant in-vitro cell system (Chinese hamster ovary) overexpressing the human delta receptor, this dipeptide behaved as an inverse agonist, as shown by a concentration dependent reduction in GTPgammaS35 binding. In this functional assay, agonists increased the binding of labeled GTP above baseline activity, and an antagonist produced only baseline activity with increasing concentration. In order to test the dipeptide further, the same GTPgammaS35 assay was performed using mouse brain membrane, where the level of delta receptor is likely lower than in the CHO cell expression system. In the membrane, the response was one of neutral antagonism rather than inverse agonism, i.e., the peptide did not alter the baseline activity of GTP binding by the receptor. Additionally, the dipeptide displayed antagonism of deltorphin II (delta receptor) antinociception, but not DAMGO (mu receptor) antinociception, when pre-administered in-vivo by icv injection, using the mouse tail-flick assay. When administered by itself, the dipeptide did not produce a nociceptive response, in either the tail-flick or radiant heat paw-withdrawal assays. Ligands of the type described above, showing selective in-vivo inhibition of the delta opioid receptor, have significance both as pharmacological tools, as well as leads for the development of agents which can prevent the side effects of mu analgesics. Hosohata, K., Varga, E.V., Alfaro-Lopez, J., Tang, X., Vanderah, T.W., Porreca, F., Hruby, V.J., Roeske, W.R., and Yamamura, H.I. (2S,3R)_-Methyl2'6'-dimethyltyrosine-L-tetrahydroisoquinoline-3-carboxylic acid [(2S,3R)TMT-L-Tic-OH] Is a Potent, Selective _-Opioid Receptor Antagonist in Mouse Brain. Journal of Pharmacology and Experimental Therapeutics, 304, pp. 683-688, 2003.

### Transcellular Transport of a Highly Polar 3+ Net Charge Opioid Tetrapeptide

Oligopeptides are generally thought to have poor permeability across biological membranes. Recent studies, however, suggest significant distribution of [Dmt1]DALDA (Dmt-D-Arg-Phe-Lys-NH2; Dmt is 2,6-dimethyltyrosine), a 3+ net charge opioid peptide, to the brain and spinal cord after subcutaneous administration.

Peptide transporters (PEPT1 and PEPT2) play a major role in the uptake of di- and tripeptides across cell membranes, but their ability to transport tetrapeptides is not clear. The purpose of this study was to determine whether [Dmt1]DALDA can translocate across Caco-2 cell monolayers and whether PEPT1 plays a role in the uptake process. Dr. Szeto and her colleagues showed that [3H][Dmt1]DALDA can readily translocate across Caco-2 cells, with a permeability coefficient estimated to be 1.24-10-5 cm/s. When incubated with Caco-2 cells, [3H][Dmt1]DALDA was detected in cell lysates by 5 min. The internalization of [Dmt1]DALDA was confirmed visually with a fluorescent [Dmt1]DALDA analog (H-Dmt-D-Arg-Phe-dns Dap-NH2; dnsDap is dansyl-L-diaminopropionic acid). The uptake of [3H][Dmt1]DALDA was concentration-dependent but temperature- and pH-independent. Treatment with diethylpyrocarbonate (DEPC) inhibited [14C]glycine-sarcosine uptake but increased [3H][Dmt1]DALDA uptake 34-fold. These findings suggest that PEPT1 is not involved in [Dmt1]DALDA internalization. [Dmt1]DALDA uptake was also observed in SH-SY5Y, human embryonic kidney 293, and CRFK cells, and was independent of whether the cells expressed opioid receptors. The efflux of [3H][Dmt1]DALDA from Caco-2 cells was temperature dependent and was inhibited by DEPC, but was not affected by verapamil, an inhibitor of P-glycoprotein. These data show transcellular translocation of a highly polar 3+ charge tetrapeptide and suggest that [Dmt1]DALDA may not only distribute across the blood-brain barrier but also it may even have reasonable oral absorption. Zhao, K., Luo, G., Zhao, G-M., Schiller, P.W., and Szeto, H.H. Importance of Nonpharmacological Factors in Nicotine Self-administration. J. Pharmacol. Exp. Ther., 304, pp. 703-715, 2003.

### Anabolic-Androgenic Steroids (AAS) & Aggression

In a recent study, Dr. Richard Melloni and his associates examined the effects of chronic AAS exposure during adolescent development on the arginine vasopressin (AVP) V1A receptor system regulating offensive aggression. They undertook this study because clinical and basic research have demonstrated a positive correlation between long-term use of AAS and negative behavioral effects including increased aggressive behavior. Studies also report increased hypothalamic AVP and facilitation of offensive aggression in male Syrian hamsters following repeated AAS exposure. Findings from this study show for the first time that exposure to high-dose of AAS during adolescent development can dramatically increase the binding of AVP V1A receptors in intact animals. These findings are significant as they demonstrate that increases in offensive aggression resulting from adolescent AAS exposure correlate directly with increases in AVP V1A receptor binding activity in several key areas of the hamster brain implicated in aggressive responding, but not in others. From a neuroanatomical standpoint, these data implicate enhanced AVP neural signaling via AVP V1A receptor in these aggression areas as potential neural substrates for adolescent AAS-facilitated offensive aggression. DeLeon, K.R., Grimes, J.M. and Melloni, Jr., R.H. Repeated Anabolic-Androgenic Steroids Treatment during Adolescence Increases Vasopressin V1A Receptor Binding in Syrian Hamsters: Correlation with Offensive Aggression, Hormones & Behavior, 42, pp. 182-191, 2002.

### An Analysis of the Binding of Cocaine Analogues to the Monoamine Transporters Using Tensor Decomposition 3-D QSAR

The conformation and alignment of cocaine analogues bound to the monoamine transporter proteins were explored using the tensor decomposition 3-D QSAR method. It was proposed from these calculations that the bound conformation of these ligands to the three transporter proteins has the 3-beta aryl substituent in a conformation in which the aryl group is orthogonal or approximately orthogonal to the propane ring. Based upon these results, rigid and semi rigid tropane analogues were designed, synthesized, and their affinities for the monoamine transporters were determined. Appell, M., Dunn III, W.J., Reith, M.E.A., Miller, L. and Flippen-Anderson, J.L. An Analysis of the Binding of Cocaine Analogues to the Monoamine Transporters Using Tensor Decomposition 3-D QSAR. Bioorganic and Medicinal Chemistry, 10, pp. 1197-1206, 2002.

### Opiates and HIV Infection: Role of Chemokines

The HIV virus attacks lymphocytes and macrophages by linking to a chemokine receptor, which introduces the virus into the cell. For several years, opiates have been shown to alter chemotaxis through inhibition of chemokine action and thereby modulate HIV function in vitro. This review clarifies how opiates can stimulate or inhibit this basic immune system. The analgesic property of opiates has been known since ancient times. Only recently has an appreciation of the broad effects of opioids on the inflammatory response emerged. Acting largely through mu-, kappa- and delta-opioid G protein-coupled receptors on T lymphocytes and macrophages, cognate

ligands modulate many activities of these cells, including cytokine production. In addition to acting as chemotactic stimuli, opioids can, through the process of heterologous cross-desensitization, act as stop signals in leukocyte trafficking. When administered into the central nervous system, certain chemokines can cross-desensitize to the analgesic effect of opioids. Thus, opioids should be considered members of the cytokine family - future research on opioids could yield new therapies for inflammatory and infectious diseases, including HIV-1 infection. Rogers, T.J., Peterson, P.K. Opioid G Protein-coupled Receptors: Signals at the Crossroads of Inflammation. Trends Immunol., 24, pp. 116-121, 2003.

A related article explores the mechanism of this activity. Morphine alters the production of chemokines and the receptors to stimulate the increase in HIV infection. Injection drug use, remains a significant risk for acquiring HIV infection. The mechanisms by which morphine enhances HIV infection of human immune cells are largely unknown. This study was designed to determine the possible mechanisms by which morphine upregulates HIV infection of human blood monocyte-derived macrophages (MDM). Morphine significantly enhanced HIV R5 strain infection of MDM but had little effect on X4 strain infection. The macrophage-tropic R5 strain envelope-pseudotyped HIV infection was markedly increased by morphine, whereas murine leukemia virus envelope-pseudotyped HIV infection was not significantly affected. Furthermore, morphine significantly upregulated CCR5 receptor expression and inhibited the endogenous production of beta-chemokines in MDM. The opioid receptor antagonist naltrexone blocked the effects of morphine on the production of beta-chemokines. It is concluded that opiates enhance HIV R5 strain infection of macrophages through the downregulation of beta-chemokine production and upregulation of CCR5 receptor expression and may have an important role in HIV immunopathogenesis. Guo, C.J., Li, Y., Tian, S., Wang, X., Douglas, S.D., and Ho, W.Z. Morphine Enhances HIV Infection of Human Blood Mononuclear Phagocytes through Modulation of Beta-Chemokines and CCR5 Receptor. J. Investigative Med., 50, pp. 435-442, 2002.

### In Vivo Activation of a Mutant µ-opioid Receptor by Antagonist: Future Direction for Opiate Pain Treatment Paradigm that Lacks Undesirable Side Effects

It had been previously discovered that :-opioid receptor in which serine 196 has been changed to an alanine (S196A), could be activated by receptor antagonists in vitro. That is to say that receptor antagonists such as naloxone and naltrexone caused the activation of G-protein coupled inward rectifying potassium channel 1 (GIRK1) when it was co-expressed in Xenopus oocytes with the mutant :-opioid receptor. In this study, investigators wanted to know whether this mutant receptor could be used to elicit the analgesic effects seen with opioids without the negative side effects such as dependence and tolerance. In order to do this, they introduced the mutant receptor into mice using a knock-in strategy and tested the analgesic effects. They found that in mice that have two copies of the mutant receptor, homozygous mutant mice, naloxone and naltrexone produced antinociceptive (painkiller) effects similar to those of partial agonists. In their evaluation of tolerance development, they found that the homozygous mutant mice treated chronically with morphine for 72 hours had a 37-fold increase in the 50% effective dose (ED50) of morphine. This is actually greater tolerance than is seen in wild type mice. However, tolerance to naltrexone was not observed in the homozygous mutant mice. When the investigators examined the development of dependence using agonist, morphine or naltrexone, they found that the homozygous mutant mice did develop some symptoms of dependence, but these were much less severe than what is seen in wild type animals and morphine. The ability of a receptor antagonist to elicit an antinociceptive effect without development of tolerance in these mutant mice represents an alternative approach to pain treatment paradigms. Law, P-Y., Yang, J.W., Guo, X., and Loh, H.H. In Vivo Activation of a Mutant _-opioid Receptor by Antagonist: Future Direction for Opiate Pain Treatment Paradigm that Lacks Undesirable Side Effects. Proc. Natl. Acad. Sci. U.S.A., 100(4), pp. 2117-2121, February 18, 2003.

### Dimerization of Morphine and Orphanin FQ/Nociceptin Receptors: Generation of a Novel Opioid Receptor Subtype

Although orphanin FQ/nociceptin (OFQ/N) receptors are a member of the opioid receptor family of receptors, they bind traditional opioids with very poor affinity. In this study Dr. Pasternak and his research team demonstrate that mu opioid receptors can physically associate with OFQ/N receptors, resulting in a complex with a unique binding selectivity profile. Immunopre-cipitation of epitope-tagged OFQ/N receptors co-precipitates mu receptors. When the two receptors were co-expressed in CHO

cells, [3H]OFQ/N retained its high binding affinity for its receptor. However, co-expression of the two receptors increased by up to 250-fold the affinity of a series of opioids in [3H]OFQ/N binding assays. This enhanced affinity was limited to agonists with high affinity for mu receptors. Selective kappa(1) and delta opioids did not lower binding. Despite the dramatic increase in affinity for the opioid agonists in co-expressing cells, the opioid antagonists naloxone and diprenorphine failed to compete [3H]OFQ/N binding. These findings suggest possible functionally significant interactions between OFQ/N and mu receptors, an observation consistent with the co-expression of mu and OFQ/N receptors in the dorsal horn of the spinal cord, the hippocampal formation, and the caudate/putamen and may help explain the reports of functional interactions between OFQ/N and opioids. Biochem. Biophys. Res. Commun. 297(3), pp. 659-663, September 27, 2002 Erratum in: Pan, Y.X., Bolan, E., and Pasternak, G.W. Dimerization of Morphine and Orphanin FQ/Nociceptin Receptors: Generation of a Novel Opioid Receptor Subtype. Biochem. Biophys. Res. Commun. 298(3), p. 456, November 1, 2002.

### Genetic Dissociation of Opiate Tolerance and Physical Dependence in Delta-Opioid Receptor-1 and Preproenkephalin Knock-Out Mice

Previous experiments have shown that mice lacking a functional delta-opioid receptor (DOR-1) gene do not develop analgesic tolerance to morphine. Here Drs. Pintar and Pasternak and their colleagues report that mice lacking a functional gene for the endogenous ligand preproenkephalin (ppENK) show a similar tolerance deficit. In addition, they found that the DOR-1 and ppENK knock-outs as well as the NMDA receptor-deficient 129S6 inbred mouse strain, which also lacks tolerance, exhibit antagonist-induced opioid withdrawal. These data demonstrate that although signaling pathways involving ppENK, DOR, and NMDA receptor are necessary for the expression of morphine tolerance, other pathways independent of these factors can mediate physical dependence. Moreover, these studies illustrate that morphine tolerance can be genetically dissociated from physical dependence, and thus provide a genetic framework to assess more precisely the contribution of various cellular and molecular changes that accompany morphine administration to these processes. Nitsche, J.F., Schuller, A.G., King, M.A., Zengh, M., Pasternak, G.W., and Pintar, J.E. Genetic Dissociation of Opiate Tolerance and Physical Dependence in Delta-Opioid Receptor-1 and Preproenkephalin Knock-out Mice. J. Neurosci. 22(24), pp. 10906-10913, December 15, 2002.

### Identification of a Signaling Network in Lateral Nucleus of Amygdala Important for Inhibiting Memory Specifically Related to Learned Fear

Post-traumatic stress disorder is a comorbid disorder that commonly occurs with substance abuse. Conditioned fear may be an excellent model for post-traumatic stress disorder and phobias. The lateral nucleus of the amygdala has been implicated as a central site within the brain mediating conditioned fear. Following fear conditioning the synaptic connections that feed into the lateral nucleus of the amygdala from the cortex and thalamus are greatly enhanced. In a recent paper that appeared in the December 2002 issue of Cell, Dr. Vladim Bolshakov, a NIDA grantee, in collaboration with Dr. Eric Kandel and his colleagues have identified gastrin releasing peptide and the gastrin releasing peptide receptor as important molecular mechanisms in this pathway regulating changes in synaptic strength in the lateral nucleus during fear conditioning. They report that gastrin releasing peptide is highly expressed in the lateral nucleus of the amygdala and in neurons that send projections into the lateral nucleus. When gastrin releasing peptide is secreted, the peptide acts on the gastrin releasing peptide receptors located on GABA inhibitory interneurons. The binding of the gastrin releasing peptide to its receptor excites GABA excitatory interneurons in the lateral nucleus. Mice lacking the gastrin releasing peptide receptor showed that tonic inhibition in the lateral nucleus was decreased while long term potentiation (LTP) of the cortico-amygdala pathway is enhanced. Long term memory for fear to both contextual and auditory cues was found to be increased. The enhancement of long-term memory is specific to fear conditioning because animals showed normal amounts of anxiety in behavioral tests that examine anxiety in mice and the mice showed no deficits on spatial memory tasks. This work demonstrates the potential of gastrin releasing peptide and receptor as important therapeutic targets for the treatment of phobia and post-traumatic stress disorder. Shumyatsky, G.P., Tsvetkov, E., Malleret, G., Vronskayaa, S., Hatton, M., Hampton, L., Battey, J., Dulac, C., Kandel, E., and Bolshakov, V. Identification of a Signaling Network in Lateral Nucleus of Amygdala Important for Inhibiting Memory Specifically Related to Learned Fear, Cell. 11(6), pp. 905-918, December 13, 2002.

### Active Heroin Administration Induces Specific Genomic Responses in the

### Nucleus Accumbens Shell

The shell of the nucleus accumbens (NAc) is a brain region important for reward by mediating retrieval of learned associations affecting goal-directed behavior. Dr. Anton N.M. Schoffelmeer and his colleagues studied the genomic response in the rat NAc after long-term withdrawal of active and passive heroin administration. Using different cohorts of rats with a history of heroin or cocaine exposure, they validated and examined a set of 40 transcripts that is down-regulated in the NAc shell after long-term cessation of heroin self-administration by real-time quantitative PCR. They found that active, but not passive administration induces long-term genomic responses in the NAc shell. These down-regulated transcripts comprise a large functional diversity of proteins involved in basic cellular processes such as neuronal growth, apoptosis, signal transduction, neuropeptide synthesis and release, transcription, translation, and cell metabolism. These data indicate that cellular processes are still affected long after extinction of heroin self-administration. Combined with the integral role of the NAc shell with the limbic system, the authors suggest that long-lasting changes in cellular functional may change synaptic transmission in related brain structures. They also point out that these genomic changes outlast simple pharmacological effects of the drugs themselves. Taken together, drug-seeking behavior may be a direct result of altered genetic and cellular networks. Jacobs, E.H., Spijker, S., Verhoog, C.W., Kamprath, K., DeVries, T.J., Smit, A.B., and Schoffelmeer, A.N.M. Active Heroin Administration Induces Specific Genomic Responses in the Nucleus Accumbens Shell. FASEB J, 16(14), pp. 1961-1963, 2002.

### Guiding GABAergic Neurons

Understanding the cellular and molecular consequences of prenatal drug exposure requires a foundation in developmental neurobiology. During drug exposure, the normal differentiation and positioning of neurons can be altered in a myriad of ways. Still, NIDA-sponsored research is dissecting out the complexities of these processes. A substantial number of cortical GABAergic interneurons are born in the basal telencephalon and migrate tangentially to reach their final destination in the neocortex and hippocampus. To accomplish this, they must interpret multiple guidance cues encountered through their trajectory. Previous work had demonstrated that the basal telencephalon contains a repulsive activity for tangentially migrating cells, whereas the cerebral cortex contains an attractive activity. While the repulsive membrane proteins Slit1, Slit2, and Netrin1 are all good candidates to act as repulsive cues in the basal telecephalon, whether they are necessary for the entirety of repulsive cues was unknown. Using a combination of explants and Slit1, Slit2 and Netrin mutant mice, the lab of John Rubenstein was able to address this issue directly. In brief, their experiments demonstrate that whereas Slit1 and Slit2 are not necessary for tangential migration of interneurons to the cortex, these proteins regulate neuronal migration within the basal telencephalon by controlling cell positioning close to the midline. As such, these results argue that both attractive and repulsive activities direct interneuron migration to the cortex, and that distinct factors control distinct choice points along the way. As a result, a complex group of guidance cues are likely to be vitally involved in GABAergic development. Marin, O., Plump, A., Flames, N., Sanchez-Camacho, C., Tessier-Lavigne, M., and Rubenstein, J. Directional Guidance of Interneuron Migration to the Cerebral Cortex Relies on Subcortical Slit1/2-Independent Repulsion and Cortical Attraction. Development, 130, pp. 1889-1901, 2003.

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

## Research Findings - Behavioral Research

### Self-Administration of Heroin Leads to Alterations in Immune Function in Rats

The high incidence of bacterial, viral and fungal infections among human heroin abusers suggests that heroin use might alter infectious disease resistance. Previous work from Dr. Lysle's laboratory has demonstrated that heroin alters the induction of nitric oxide, a molecule known to regulate immune responses and resistance to infection. The present study was designed to investigate whether environmental stimuli paired with heroin administration alter the expression of inducible nitric oxide synthase (iNOS), an enzyme responsible for nitric oxide production. On three conditioning days, 48 hr apart, the experimental group received an injection of heroin (1 mg/kg) immediately prior to being placed for 1 hr in an environmental chamber that served as the conditioned stimulus. An unpaired control group was treated the same way except that the heroin injections and placement in the chamber were separated by 12 hr. A saline control group received an injection of saline before being placed in the environmental chamber. Six days after the third conditioning session, all rats were re-exposed to the conditioning chambers in the absence of heroin. Immediately after this 1 hr exposure, they were injected with lipopolysaccharide (LPS) to induce iNOS expression. Six hr later, the animals were euthanized and the production of nitric oxide was determined by measuring iNOS mRNA and protein in spleen, liver and lung. The results indicated that exposure to the conditioned stimulus on the test day in the experimental group produced a significant reduction in the expression of iNOS mRNA and protein in spleen, liver and lung. Control procedures indicated that this effect was due to conditioning processes. This study provides the first evidence that heroin-induced alteration of iNOS expression can be conditioned and suggests that environmental stimuli associated with drug abuse may modulate infection susceptibility. Lysle, D.T., and Ijames, S.G. Heroin-associated Environmental Stimuli Modulate the Expression of Inducible Nitric Oxide Synthase in the Rat. Psychopharmacology, 164, pp. 416-422, 2002.

### Mechanisms of Neural Plasticity Underlying Behavioral Sensitization

Drug addiction involves persistent functional changes in the brain circuits underlying motivated behavior that are responsible for protracted craving, drug seeking and relapse. The present study investigated the role of the phosphatidylinositol 3 kinase (PI3K) signal transduction pathway in long lasting behavioral sensitization to cocaine in rats. Based upon previous research on long-term potentiation (LTP), it was hypothesized that PI3K is required for the expression but not the induction of behavioral sensitization to cocaine. Two experiments were conducted. In Experiment 1, two groups of rats were injected IP for 5 consecutive days with cocaine (15 mg/kg) or its saline vehicle. Half of each group received an ICV injection of either the reversible PI3K inhibitor LY294002 or its DMSO vehicle 20 min before each cocaine or saline injection. Sensitization to cocaine induced locomotor activity was observed in the group given cocaine/DMSO, but not in the group given cocaine/LY294002. Ten days later all animals were challenged with cocaine in the absence of LY294002. Both cocaine groups, those pretreated with DMSO as well as those pretreated with LY294002 showed a sensitized locomotor response to cocaine on this test. These results suggest that PI3K activity is not necessary for the induction of cocaine sensitization, but is necessary for its expression. Experiment 2 provided a further test of this hypothesis. As in the first experiment two groups were pretreated with either cocaine or saline, but without the ICV LY294002 or its vehicle. Then ten days after the last injection, those rats that showed behavioral sensitization were randomly assigned to one of two groups. One group was given LY294002 prior to being challenged with

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cocaine; the other was given DMSO before the cocaine challenge. The first group did not show locomotor sensitization to the cocaine injection, whereas the second group did. One week later, cocaine was administered again to both groups without LY294002 pretreatment and now both groups showed a sensitized locomotor response to cocaine. This result confirms the hypothesis that LY294002 reversibly blocks the expression of behavioral sensitization to cocaine and indicates that PI3K activity is necessary for the expression but not the induction and persistence of sensitization. The similarity between the role of PI3K in LTP and in cocaine-induced behavioral sensitization suggests that similar synaptic mechanisms underlie both phenomena. Izzo, E., Martin-Fardon, R., Koob, G., Weiss, F., and Sanna, P.P. Neural Plasticity and Addiction: PI3-kinase and Cocaine Behavioral Sensitization. Nature Neuroscience, 5(12), pp. 1263-1264, 2002.

### Prescription Opioid Non-Medical Use and Abuse: Task Force Position Statement

A College on Problems of Drug Dependence Task Force, chaired by NIDA grantee James Zacny has issued a position paper on prescription opioid non-medical use and abuse. Non-medical use and abuse of prescription opioids are on the rise in the United States, illicit use of several widely prescribed opioids has increased disproportionately more than licit use, and the prevalence of prescription opioid abuse appears to be similar to that of heroin and cocaine abuse. The task force noted that policy decisions about prescription opioid non-medical use and abuse must take a balanced approach so that strategies developed to prevent and reduce diversion of prescription opioids do not deter physicians from prescribing high efficacy opioids when necessary for pain management. While acknowledging that the science related to the abuse of prescription opioids is limited, the task force recommended a number of actions that should be taken by scientists working with appropriate governmental, non-governmental and industry representatives: 1] Initiate a national forum to review the extant taxonomy of terms related to the non-medical use and abuse of prescription opioids and their impact on policy; 2] Initiate a comprehensive assessment of non-medical use and abuse of prescription opioids, including an assessment of its magnitude and demographics, and its impact on public health and safety; 3] Initiate a comprehensive assessment of opioid use and risk of abuse in patients with pain; 4] Initiate research programs to assess the abuse liability of prescription opioids, developing comparative data fur currently used agents; 5] Initiate the development of targeted prevention programs after identifying those sub-populations that are at risk for prescription opioid abuse; 6] Initiate the development of controlled clinical trials to assess treatments for prescription opioid abuse in different sub-populations; 7] Initiate a broad educational program on the proper prescribing of opioids for pain coordinated with pain experts and substance abuse experts. Zacny, J., Bigelow, G., Compton, P., Foley, K., Iguchi, M., and Sannerud, C. College on Problems of Drug Dependence Taskforce on Prescription Opioid Non-Medical Use and Abuse: Position Statement. Drug and Alcohol Dependence, 69, pp. 215-232, 2003.

### Predicting Choice Behavior Between Cocaine and Food in Monkeys

Drug abuse can be thought of as a maladaptive, habitual choice of a drug over non-drug reinforcers. An understanding of the factors that determine the choice to self-administer a drug, therefore, will help us understand drug abuse and perhaps how to treat and prevent it. The matching law, a mathematical expression that accurately predicts response choice between alternative reinforcers, has successfully modeled choice behavior. Basically, the matching law predicts that one response is chosen over an alternative response in direct proportion to the reinforcement available for the two responses. Fro example, if food is twice as likely to occur for choosing response A over response B, the matching law correctly predicts that response A will occur twice as often as response B. The generalized matching law has provided a good fit to experimental data across a variety of species, behaviors and reinforcers. However, there have been few tests of the matching law that have pitted a drug against a non-drug alternative. Dr. Woolverton and his colleagues investigated whether the matching law provides a good fit to experimental data involving a choice between cocaine and food. Thus, four male rhesus monkeys pressed one lever for food and another lever for cocaine (0.025 and 0.05 mg/kg per injection) over a number of sessions that varied the frequency of reinforcement. Results indicated that the matching law provided a good account of the data. As with studies involving food only, monkeys showed undermatching, i.e., they responded less for the alternative with the greater reinforcement frequency than predicted by the matching law. In addition, there was a bias toward food when it was pitted against the lower dose of cocaine but a bias away from food when it was pitted against the higher dose of cocaine. These results suggest that the matching law can reliably describe the

relationship between relative rate of reinforcement and behavior in the choice between a drug and a non-drug reinforcer. A quantitative model of choice like the matching law may eventually be useful for predictions of drug choice as typified in drug-abuse situations. Anderson, K.G., Velkey, A.J., and Woolverton, W.L. The Generalized Matching Law as a Predictor of Choice Between Cocaine and Food in Rhesus Monkeys. Psychopharmacology, 163, pp. 319-326, 2002.

### Gonadectomy Has Opposite Effects on the Antinociceptive Effects of Opioids in Male and Female Rats

Greater sensitivity of males than females to the antinociceptive effects of mu opioids has been reported from clinical research, and is paralleled by findings from animal research with non-human primates and rodents. The basis for this sex difference is not fully accounted for by either pharmacokinetic factors, mu opioid binding affinity or receptor density. In an effort to examine the role of gonadal hormones, researchers at the University of North Carolina at Chapel Hill directly manipulated hormone levels via gonadectomy in F344 rats, which typically display relatively large sex differences in opioid antinociception, and in Sprague Dawley rats, which typically exhibit small differences. Given evidence that the magnitude of sex difference in opioid nociception is inversely related to the relative effectiveness of the opioid, the researchers examined the effects of both high-efficacy mu opioids (morphine and etorphine) and low-efficacy mu opioids (buprenorphine and dezocine) as well as mixed-action opioids with low efficacy at both mu and kappa opioid receptors (butorphanol and nalbuphine). Consistent with prior research, the researchers found greater opioid antinociception in intact males than intact females, with larger sex differences occurring with the less-effective opioids and in the F344 strain. In both strains, gonadectomy resulted in a decrease in opioid antinociception in males and an increase in females. The smallest effects were seen with high efficacy mu opioids, i.e., the magnitude of the decrease in males and the increase in females was inversely related to the relative effectiveness of the opioid. NIDA-grantee Theodore Cicero and colleagues (Cicero et al., 2002; May 2003 Director's Report) have shown that shortly after birth gonadectomy in males decreases morphine's antinociception effect, while in females the combination of gonadectomy-plus-testosterone increases morphine's antinociception effect -- reflecting the organizational effects of sex hormones in the early development of the rat brain. Taken together, these studies provide evidence that sex differences in opioid antinociception are due in part to the dual role played by gonadal hormones in sexual differentiation of the brain and in the acute response to opioids in adulthood. Terner, J.M., Barrett, A.C., Grossell, E., and Picker, M.J. Influence of Gonadectomy on the Antinociceptive Effects of Opioids in Male and Female Rats. Psychopharmacology, 163, pp.183-193, 2002.

### Differential Subjective Effects of D-amphetamine by Gender, Hormone Level and Menstrual Cycle Phase

Prior research by Dr. Harriet de Wit and colleagues at the University of Chicago has shown that women report higher positive subjective effects of d-amphetamine in the follicular phase of the menstrual cycle when estrogen levels are high relative to progesterone than in the luteal phase when both hormones are high. She has also shown that exogenous administration of progesterone can produce moderate decreases in mood states. Thus, to further understand the role of estrogen and progesterone in producing the menstrual cycle modulation of the subjective effects of amphetamine and to examine possible sex differences, Dr. de Wit and her colleagues compared the subjective responses to d-amphetamine in males and females and also examined in women the correlation between these responses and endogenous levels of estrogen and progesterone during the follicular phase. Consistent with her prior study, the positive subjective responses, e.g. euphoria, feeling "high," and wanting more drug, were higher in the follicular phase than the luteal. Further, subjective responses of women during the follicular phase did not differ from men, but were lower than men during the luteal phase. In the follicular phase, these stimulant effects were inversely related to salivary levels of progesterone, but were only weakly positively correlated with salivary estradiol. These data point to the role of the menstrual cycle in understanding sex differences in the subjective response to d-amphetamine and point to the role of progesterone in understanding variations in amphetamine responsivity among women. These findings have important implications for understanding the role the menstrual cycle in the use and escalation of d-amphetamine abuse as well as its role in treatment. White, T.L., Justice, A.J., and de Wit, Harriet. Differential Subjective Effects of D-amphetamine by Gender, Hormone Level and Menstrual Cycle Phase. Pharmacology, Biochemistry and Behavior, 73, pp. 729-741, 2002.

### Influence of Estrus Cycle and Estradiol on Behavioral Sensitization to Cocaine in Female Rats

Several studies have shown that sensitization of locomotor response to cocaine and amphetamine is greater in females that males. Prior research by Dr. Kathryn Cunningham and colleagues at the University of Texas Medical Branch has shown that the acute locomotor response to cocaine in female rats is highest during proestrus when estrogen levels are highest. In a recent study, she examined the role of the estrus cycle in cocaine sensitization of the locomotor response. Following 5 days of twice daily injections of cocaine or saline and a three-day withdrawal period, the expression of locomotor sensitization was assessed via a challenge injection of cocaine. Compared to the saline group, sensitization of the locomotor response in the cocaine group was observed only in the diestrus phase when estrogen levels are lowest. In a second study, the researchers examined whether the presence or absence of estradiol would affect the development and expression of cocaine-induced locomotor sensitization. An ovariectomized group and an ovariectomized group given estradiol replacement were each given twice daily injections of cocaine for five days, and then were given a challenge injection of cocaine 3, 13, and 34 days after this treatment. During the five days of twice daily cocaine injections, the two groups developed similar levels of sensitization. After 3 days of withdrawal, neither group exhibited sensitization to the cocaine challenge, but after 13 and 34 days, both groups exhibited progressive sensitization. Again the estradiol-treated rats did not exhibit greater sensitization than the non-estradiol-treated rats. These data point to a role of the estrus cycle in the acute locomotor response to cocaine in females, but do not implicate estradiol in cocaine sensitization of the locomotor response. Sell, S.L., Thomas, M.L., and Cunningham, K.A. Influence of Estrous Cycle and Estradiol on Behavioral Sensitization to Cocaine in Female Rats. Drug and Alcohol Dependence, 67, pp. 281-290, 2002.

### Synapses in Different Brain Areas are Modified by Self-administered Morphine as Compared to Experimenter-administered Drug

From studies on animal models of drug addiction it is becoming increasingly clear that drugs of abuse can have different behavioral and neurobiological effects depending on whether they are administered passively, by the experimenter, or self administered. Further understanding of these differences will help uncover causal connections between particular neurobiological alterations and the behavioral effects of drugs of abuse. Terry Robinson and his colleagues have been investigating the ability of drugs to remodel connections in the brain by altering the density of synaptic spines on neuronal dendrites. In a recent study, they compared the long-term effects of experimenter- versus self-administered morphine on dendritic spine morphology. In most brain regions (medial frontal cortex, occipital sensory cortex, and nucleus accumbens), spine density decreased irrespective of mode of administration. However, in the CA1 and dentate gyrus regions of the hippocampus, only self-administered morphine decreased spine density, while in parietal sensory cortex only experimenter-administered morphine was effective. In orbital frontal cortex, by contrast, both treatments increased spine density, but self-administration had a much greater effect. The results indicate that morphine has a persistent (at least 1 month) effect on spine density in many brain regions and on many different cell types, but the effect is specific and varies as a function of both brain region and mode of administration. The ability of morphine to remodel synaptic inputs in a regionally specific manner may account for the many different long-term sequelae of opioid use, including impairments of cognitive function. The different effects of experimenter- versus self-administered drug suggest that some neuronal changes do not result simply from the drug's molecular actions, and they help identify brain areas and mechanisms that may be particularly involved in linking external cues and motivational states with drug taking. Robinson, T.E., Gorny, G., Savage, V.R., and Kolb, B. Widespread but Regionally Specific Effects of Experimenter- versus Self-administered Morphine on Dendritic Spines in the Nucleus Accumbens, Hippocampus, and Neocortex of Adult Rats. Synapse, 46, pp. 271-279, 2002.

### A Variety of Pharmacological Classes of Drugs of Abuse, or Stress, Trigger a Common Synaptic Adaptation that May Contribute to Cross Sensitization between Drugs and Stress

A previous collaborative study between the laboratories of Antonello Bonci and Robert Malenka showed that a single dose of cocaine altered the response of dopaminergic neurons in the VTA to glutamatergic inputs from the prefrontal cortex. Altered synaptic transmission was evident as an enhanced synaptic current through AMPA receptors relative to current through NMDA receptors, which is an established

hallmark of long-term potentiation (LTP). In a new study, they found a similar effect with other addictive substances -- amphetamine, morphine, nicotine, and ethanol -- some of which have very different initial molecular mechanisms from cocaine. They also observed an enhanced AMPA:NMDA response ratio after animals were subjected to acute stress (forced swimming). As a control, they tested two psychoactive compounds, the antidepressant fluoxetine and carbamazepine (commonly used to treat seizure disorders and bipolar disorder), neither of which affected excitatory synapses in the VTA. The stress-induced potentiation could be blocked with the glucocorticoid antagonist RU-486, which did not block the response to cocaine, indicating that the cocaine effect was not simply mediated by the stress of injection. The results of these experiments suggest that plasticity at excitatory synapses on dopamine neurons may be a key early neural adaptation contributing to addiction and its interactions with stress, and thus may be an attractive therapeutic target for reducing the risk of addiction. Saal, D., Dong, Y., Bonci, A., and Malenka, R.C. Drugs of Abuse and Stress Trigger a Common Synaptic Adaptation in Dopamine Neurons. Neuron, 37, pp. 577-582, 2003.

### A Likely Neurobiological Substrate for Increased Maternal Aggression Produced by Chronic Cocaine Administration During Gestation

Females of most mammalian species aggressively protect their offspring from potential harm. Maternal aggressive behavior by lactating female rats consists of a characteristic set of postures, threats and attacks used to protect the young from intruders in the nest area. This behavior is generally adaptive, but previous research by Josephine Johns has shown that, following chronic gestational cocaine administration, rat dams can become so aggressive that they leave their young unprotected and vulnerable, or even cause injury to their offspring during interactions with an intruder. Dr. Johns has previously observed a decrease in oxytocin levels in the amygdala of rats chronically treated with cocaine during gestation. This observation, together with other evidence, led to her hypothesis that heightened aggressiveness in these animals might be caused by the deficit of oxytocin in the amygdala. To test the hypothesis, she implanted dams with bilateral cannulae into the central nucleus of the amygdala and infused them with an oxytocin antagonist (OTA) or vehicle 4 hours before testing. Maternal aggressive behavior was compared among drug-na•ve dams infused with OTA, control animals infused with vehicle, and chronic cocaine-treated dams infused with vehicle only. Drug na•ve animals infused with OTA behaved significantly more aggressively towards intruders compared to control animals, and at a level comparable to that of the cocaine-treated animals. The results suggest that disruption of oxytocin activity in the central amygdala may be sufficient to selectively increase maternal aggressive behavior. To further test her hypothesis that this mechanism could account for the behavior of cocaine-treated animals, Dr. Johns plans to determine whether oxytocin infusions in these animals will reverse their abnormal aggressiveness. Cocaine abuse by human mothers is correlated with a high incidence of child neglect and abuse. Dr. Johns' research on the neurobiological substrates of these behaviors in an animal model may help identify possible therapeutic targets. Lubin, D.A., Elliott, J.C., Black, M.C., and Johns, J.M. An Oxytocin Antagonist Infused Into the Central Nucleus of the Amygdala Increases Maternal Aggressive Behavior. Behavioral Neuroscience, 117, pp. 195-201, 2003.

### Serotonergic Receptor Substrates for the "Reinforcing" Effects of 3,4-methylenedioxy-methamphetamine (MDMA, "ecstasy")

The drug ecstasy produces subjective effects that resemble both psychostimulants, like amphetamine, and hallucinogenics, like LSD. In human subjects, some of these subjective effects arise from activation of central dopamine (DA) transmitter systems, and other effects appear more closely linked with stimulation of the neurotransmitter, serotonin (5-HT). Unlike the classic hallucinogenic drugs, which act primarily at 5-HT2a receptors, MDMA is self-administered in animal models. However, it is unknown whether dopaminergic or serotonergic substrates mediate these effects. Recently, investigators from the laboratories of Drs. James Woods and Gail Winger trained four rhesus monkeys to self-administer i.v. S(+)-MDMA and R(-)-MDMA and pretreated these animals with either a 5-HT2 antagonist (ketanserin) or a 5-HT2a antagonist (MDL100907) prior to the session. Dose response determinations (range=0.001-0.3 mg/kg/injection) were made for both enantiomers and the racemic mixture of MDMA. The same animals were also tested with 0.01 mg/kg/injection cocaine and 0.0003-0.003 mg/kg/injection methamphetamine. All animals self-administered racemic MDMA and both of the stereoisomers, generating inverted U dose response curves. However, none of the doses maintained injection rates as high as seen for cocaine or the 0.003 dose of methamphetamine. When animals were pretreated with the serotonin receptor antagonists, cocaine responding was not significantly affected by

0.1 mg/kg pretreatment with either drug. And while both antagonists produced shifts in the inverted U function for (+)-MDMA these effects were also not significant. However, with (-)-MDMA, the 0.1 mg/kg dose of either antagonist significantly suppressed self-administration. Due to subject variability in self-administration response rates, this suppression was statistically significant only at 0.03(-)-MDMA for both pretreatments. Several interesting observations were made in this study. First, self-administration of MDMA was highly variable across animals - much more so than for the comparison drug, cocaine. Secondly, while further studies are needed to assess relative reinforcement (e.g., choice procedures), in the doses tested, cocaine was a more potent reinforcer of operant behavior. And lastly, in agreement with a growing body of literature to support the role of serotonergic substrates in drug reinforcement (e.g., interacting DA-5HT systems), it appears that 5-HT2a receptors may be important for ecstasy's hedonic or rewarding properties. Fantegrossi, W.E., Ullrich, T., Rice K.C., Woods, J.H. and Winger, G. 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") and its Stereoisomers as Reinforcers in Rhesus Monkeys: Serotonergic Involvement. Psychopharmacology, 161, pp. 356-364, 2002.

### Sucrose and the Development of Conditioned Place Preference with Fentanyl and Amphetamine: The Role of Reinforcement History?

Animals who consume palatable foods and fluids show altered behavioral responses to drugs of abuse; (e.g., more pronounced opiate-induced antinociception and anorexia). However, providing palatable solutions either preceding, or concomitant with availability of self-administration, attenuates drug intake. Conditioned place preference (CPP) is a paradigm used to assess incentive motivational value of an environment previously paired with a drug reward. When environmental cues are paired with the positive effects of drugs, these cues take on reinforcing properties of their own by virtue of classically conditioned associations with the subjective drug experience. In CPP, these reinforcing properties are measured by time spent in proximity of the cues, or what some have called "approach responding" to the drug-associated environment. Recently, Dr. Robin Kanarek and colleagues have examined the ability of sucrose availability to alter the establishment of CPP with an opiate, fentanyl, and the psychostimulant, amphetamine. All rats in this study were fed rat chow, but some groups also had access to a 32% (w/v) sucrose solution 24 hr per day. They then underwent conditioning with 0.004 or 0.016 mg/kg fentanyl paired with the non-preferred side of a CPP apparatus and were tested in the drug free state to see if side preferences had shifted as a result of the association with drug. Collapsing across chow-only and chow+sucrose groups, there was a significant increase of time spent in the high dose-paired side compared to baseline times before the drug conditioning. However, when data were examined separately for the two groups, only the sucrose drinking animals showed a significant CPP. Interestingly, sucrose drinking rats also showed greater antinociceptive effects of fentanyl when assessed with tail-flick measures of analgesia, indicating a greater sensitivity to opiate effects. When a separate set of animals was tested for CPP to 0.33 or 1.00 mg/kg amphetamine, collapsed groups showed a significant shift in time spent on the drug-paired side at both doses. But again, only the sucrose-drinking rats showed a significant CPP when groups were analyzed separately. In fact, at the lower dose, sucrose-drinking rats spent double the amount of time in the drug-associated environment compared to chow-only animals. The investigators suggest that sucrose may enhance the rewarding effects of both drugs by increasing dopamine release in the nucleus accumbens, or perhaps via actions upon endogenous opioid systems. In light of previous observations that sucrose attenuates drug self-administration, this CPP finding suggests that: (1) less drug is needed to produce reinforcement in self-administration when sucrose is available; and (2) sucrose intake stimulates central reward systems, which sums with the reinforcing effects of these drugs in CPP. Vitale, M.A., Chen, D. and Kanarek, R.B. Chronic Access to a Sucrose Solution Enhances the Development of Conditioned Place Preferences for Fentanyl and Amphetamine in Male Long-Evans Rats. Pharmacol. Biochem. Behav., 74, pp. 529-539, 2003.

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

## Research Findings - Treatment Research and Development

### Brief Interventions for Smoking Cessation in Alcoholic Smokers

Dr. Rohsenow and colleagues conducted a 2 X 2 randomized controlled trial with alcoholic smokers comparing Motivational Interviewing (MI) to Brief Advice (BA). Treatments were provided in a single session or with two booster sessions 1 week and 4 weeks after the first session. The MI session was approximately 50 minutes and included personalized feedback and setting stage-specific goals. BA was approximately 10 minutes and involved direct brief advice to quit smoking along with assistance in obtaining needed information or help. All participants were given free access to NRT on request. Preliminary results show that more patients were abstinent at 1 month in BA (35%) than in MI (13%) with a trend for more abstinence at 6 months (13% vs. 2%). Neither treatment type affected alcohol or drug use outcomes. BA takes approximately one eighth of the time that MI does yet is significantly more effective in motivating smoking cessation. Providing booster sessions of either treatment results in better long-term quit rates. Rohsenow, D.J., Monti, P.M., Colby, S.M., and Martin, R.A. Alcoholism: Clinical and Experimental Research, 26(12), pp. 1950-1951, December 2002.

### Depressive Symptoms and Readiness to Quit Smoking Among Cigarette Smokers in Outpatient Alcohol Treatment

Researchers at Brown Medical School examined whether length of alcohol abstinence and depressive symptoms were related to motivational readiness to consider smoking cessation among patients in alcohol treatment. Participants were adults (N= 253) enrolled in a smoking cessation trial. A significant interaction of days since last drink and depressive symptoms was found. Results showed that a greater number of days since last drink was associated with greater readiness, but only among patients with a low depression score. The findings suggest that alcoholic smokers with low depressive symptoms are more receptive to quitting after sustained alcohol abstinence. Hitsman, B., Abrams, D.B., Shadel, W.G., Niaura, R., Borrelli, B., Emmons, K.M., Brown, R.A., Swift, R.M., Monti, P.M., Tohsenow, D.J., Colby, S.M. Psychology of Addictive Behaviors, 16(3), pp. 264-268, 2002.

### Computer and Manual Self-Help Behavioral Strategies for Smoking Reduction: Initial Feasibility and One-Year Follow-Up

Researchers examined the feasibility of two self-help behavioral interventions to reduce and maintain a 50% reduction in smoking among those unable or unwilling to quit, and to evaluate the impact of smoking reduction on subsequent quit attempts. Ninety-three smokers who desired to reduce rather than quit smoking were randomly assigned to either computerized scheduled gradual reduction (CSGR) or to a manual-based selective elimination reduction (SER). Both groups produced significant reductions in smoking (approximately 10 cigarettes per day, during the 7-week treatment phase), which were maintained over one year. The CSGR group reported greater mean percent reductions in smoking from pre- to post-treatment (37% for CSGR, 20% for SER) and a greater percentage of subjects meeting the 50% reduction goal (30% for CSGR, 16% for SER) compared to the SER group. The results of this study lend support to the feasibility of self-help behavioral interventions to produce sustained reductions in smoking rates without apparent negative impact on subsequent quit attempts. Riley, W., Jerome, A., Behar, A., and Weil, J. Nicotine & Tobacco Research, Supplement 2, pp. S183-S188, 2002.

### A History of Depression and Smoking Cessation Outcomes Among Women Concerned About Post-Cessation Weight Gain

## Index

Drs. Levine, Marcus, and Perkins at the University of Pittsburgh School of Medicine sought to document the prevalence of depression history among weight-concerned women smokers, and evaluate its effect on treatment outcome. They also evaluated the impact of baseline depressive symptoms and cessation-related changes in symptoms. Two hundred and nineteen women were classified as depression history positive (MDD+; 52%) or negative (MDD-) and received a group-based smoking cessation treatment. Findings showed that although MDD+ women were significantly more nicotine dependent, rates of continuous abstinence did not differ between MDD+ and MDD- women. However, MDD+ women were more likely to drop out of treatment prior to quitting. Irrespective of depression history, depressive symptoms were associated with abstinence. Women who reported an increase in depressive symptoms from pre- to post treatment were significantly less likely to be abstinent post treatment, suggesting that depressive symptoms are more predictive of outcome than previous disorder. Levine, M.D., Marcus, M.D., and Perkins, K.A. Nicotine & Tobacco Research, 5(1), pp. 69-76, 2003.

### African Americans and Caucasians Have Need for Different Services Ancillary to Treatment

Nancy Petry and colleagues at the University of Connecticut Health Center found several important differences between a cohort of non-Hispanic Caucasians and African Americans seeking outpatient treatment for cocaine problems on the Addiction Severity Index. African Americans had similar years of education but lower incomes than Caucasians. Caucasians were a few years older. Although the groups began first use of drugs and regular use at similar ages (21 and 27 years respectively) Caucasians were more likely to use injection drugs and African Americans were more likely to present with a drug positive urine at intake. In terms of drug related problems, African Americans were more likely to have employment problems but less likely to have family, psychiatric, legal or alcohol problems. These findings suggest the two groups might benefit from tailored treatment approaches to address these needs. For example, African Americans might benefit from treatments with employment as a focus. Petry, N.M. A Comparison of African American and Non-Hispanic Caucasian Cocaine-Abusing Outpatients. Drug and Alcohol Dependence, 69(1), pp. 43-49, 2003.

### Drug Avoidance Activities Predict Treatment Outcome

Richard Rawson and colleagues at UCLA Integrated Substance Abuse Programs examined the post-treatment behavior of drug abusers who received either Cognitive Behavioral Therapy (CBT) or Voucher Based reinforcement for clean urines, i.e., Contingency Management (CM) and found that regardless of treatment condition assignment, individuals who reported engaging in Drug Avoidance Activities (DDAs) most frequently had higher levels of abstinence at treatment end and 12 months after treatment. Those exposed to CBT reported engaging in a larger number of DAAs and doing DDAs more frequently. This suggests the importance of engaging frequently in a range of strategies to avoid drugs rather than relying on a single strategy. This study lends support to the idea that one mechanism of action of CBT may be increasing use of coping skills. Farabee, D. Rawson, R. and McCann, M.A. Adoption of Drug Avoidance Activities Among Patients in Contingency Management and Cognitive-behavioral Treatments. Journal of Substance Abuse Treatment, 23(4), pp. 343-350, 2002.

### Pregnant Homeless Women More Challenged Upon Treatment Entry

Hendree Jones and colleagues at Johns Hopkins University School of Medicine found a number of important differences when they compared housed and homeless pregnant women at substance abuse treatment entry. Homeless pregnant women reported spending more money on cocaine and alcohol than pregnant women with permanent residences. They experienced three times the number of medical problems, and received only 65% of the social service income of the housed group. Significantly greater rates of psychopathology were observed including greater lifetime rates of anxiety and depression, histories of suicidal thoughts and attempts, and higher lifetime incidence of emotional, physical, and sexual abuse. Homeless pregnant women also left treatment at greater rates. Results suggest treatment programs may need special interventions to treat and engage homeless pregnant women. Tuten, M., Jones, H.E., and Svikis, D.S. Comparing Homeless and Domiciled Pregnant Substance Dependent Women on Psychosocial Characteristics and Treatment Outcomes. Drug and Alcohol Dependence, 69(1), pp. 95-99, 2003.

### Concurrent Treatment for Alcohol and Tobacco Dependence: Are Patients

### Ready to Quit Both?

Drs. Stotts, Schmitz, and Grabowski, at the University of Texas, Houston, examined mechanisms involved in changing both alcohol and tobacco use concurrently using the trans-theoretical model measures of change. One hundred and fifteen alcohol and tobacco dependent outpatients entering a dual- substance dependence program were compared on baseline measures of motivation, self-initiated change activities, and self-efficacy associated with each substance use behavior. Motivation to change each behavior was also examined as a potential predictor of retention in treatment. Results indicated that patients reported high self-efficacy to abstain and lower temptation to use alcohol relative to cigarettes. Change activities were also initiated at higher levels for drinking compared with smoking. An interaction between drinking and smoking motivation for change was found in the prediction of treatment retention; those with higher motivation for changing their alcohol use and lower motivation to quit smoking remained in treatment longer, while those who were higher in motivation for changing both behaviors dropped out the earliest. Overall, participants in this dual-dependence program were more confident and active in changing their alcohol use. Initiating cessation of both behaviors equally and simultaneously may prove difficult for this population. Stotts, A., Schmitz, J., and Grabowski, J. Drug and Alcohol Dependence, 69, pp. 1-7, January 2003.

### A Partner's Drug Using Status Impacts Women's Drug Treatment Outcome

Drs. Michelle Tuten and Hendree Jones at Johns Hopkins University School of Medicine examined the role that male sexual partners play in the treatment outcome of drug dependent pregnant women. Pregnant women enrolled in a comprehensive treatment program with drug free or drug using male sexual partners completed a relationship survey and were compared on partner and psychosocial variables. Compared with male drug free partners, male drug using partners had more unemployment and more current legal involvement, less education, were less likely to be supportive of the pregnant woman's recovery efforts and were more likely to give them money to buy drugs. Male drug free partners also had fewer medical, dental, legal, and transportation needs than male drug using partners. Data from treatment retention suggests that women with male drug using partners are retained in a comprehensive treatment for a shorter time than women with male drug free partners. A male partner's drug using status should be considered when treating pregnant drug dependent women. Tuten, M. and Jones, H., Drug and Alcohol Dependence, pp. 1-4, March 2003.

### Concurrent Validity of a Brief Self-Report Drug Use Frequency Measure

Dr. O'Farrell of Harvard University, and Drs. Fals-Stewart and Murphy of SUNY Buffalo RIA, developed and tested a self-report measure of the illicit drug use frequency (DUF). Male alcoholic patients in treatment and a community sample of male and female participants without identified drug or alcohol use disorders completed the DUF. All participants also completed the Timeline Followback (TLFB) and consented to collaterals providing information about participants' drug and alcohol use. The DUF showed good concurrent validity, with high correlations between self-reports of drug use on the DUF and TLFB, and between participant and collateral reports of the use and frequency of use of illicit drugs. This study suggests that the Drug Use Frequency measure provides accurate drug use data, relative to other accepted methods of assessing drug use. O'Farrell, T.J., Fals-Stewart, W. and Murphy, M. Addictive Behaviors, 28(2), pp. 327-337, March 2003.

### Past Anabolic-Androgenic Steroid Use Among Men Admitted for Substance Abuse Treatment: An Under Recognized Problem?

Dr. Roger Weiss, along with colleagues from McLean Hospital and Harvard University, assessed prior use of anabolic-androgenic steroids (AAS) among 223 male substance abusers admitted for treatment. Participants with likely AAS experience participated in semi-structured interviews that included questions about whether AAS had helped to introduce participants to other drugs. Twenty-nine participants reported prior AAS use, only 4 of which were recorded on physicians' admission evaluations. Significantly more men reported past AAS use whose primary drug of choice was opioids (25%) compared to men reporting primary use of other drugs (5%). Some men with AAS experience also reported buying opioids from the same person who had sold them AAS, that AAS was the first drug they had ever self-administered by injection, and that AAS use was associated with severe aggressiveness. This study highlights the potential association between AAS use and other drug use, particularly opioid dependence. Kanayama, G., Cohane, G.H., Weiss, R.D. and Pope, H.G. Journal of Clinical Psychiatry, 64(2), pp. 156-160, May 2003.

### Gender Differences Found with a Novel Cognitive-Behavioral Approach for Treatment-Resistant Drug Dependence

Many opiate-dependent patients continue illicit drug use despite the application of treatments that combine methadone administration, weekly counseling, and contingency reinforcement strategies. Dr. Pollack and colleagues tested a novel cognitive-behavioral treatment (CBT) designed to reduce illicit drug use among patients receiving methadone treatment. The CBT was a modification of a treatment designed to treat benzodiazepine dependence in patients with panic disorder, which was now focused to reduce sensitivity to interoceptive cues associated with drug craving and trained alternative responses to these cues. Twenty-three methadone maintenance patients were randomly assigned to either this novel CBT program or a program of increased counseling, such that the two programs of treatment were equated for therapist contact, assessment time, and contingency-reinforcement strategies. The new program was associated with significantly greater reductions in illicit drug use for women, but not for men measured by percentage of negative urine drug screens. The (CBT) program offered advantages to women who attended the treatment on the order of a very large (d = 1.00) effect size. Contrary to expectations, results indicated that intensified counseling with existing providers tended to offer better outcome than CBT-IC for men in our program (d = 0.89). Pollack, M.H., Penava, S.A., Bolton, E., Worthington III, J.J., Lanka, G., Farach Jr., F.J. and Otto, M.W. Journal of Substance Abuse Treat, 23(4), pp. 335-342, December 2002.

### Bupropion Enhances Smoking Cessation in Schizophrenic Smokers

Schizophrenic patients have high rates of cigarette smoking compared with the general population. The investigators compared sustained-release (SR) bupropion with placebo for smoking cessation in patients with schizophrenic disorders. Thirty-two subjects meeting DSM-IV criteria for schizophrenia or schizoaffective disorder and nicotine dependence were randomized to bupropion SR (BUP, 300 mg/day) or placebo (PLA). Outcomes included treatment retention, smoking abstinence rates, expired breath carbon monoxide (CO) levels, psychotic symptoms, and medication side effects. Bupropion significantly increased prevalence smoking abstinence rates compared with placebo. The results suggest that 1) BUP enhances smoking abstinence rates compared with PLA in nicotine-dependent schizophrenic smokers; 2) BUP is well-tolerated and safe for use in these patients; and 3) atypical antipsychotics may enhance smoking cessation outcomes with BUP. George, T.P., Vessicchio, J.C., Termine, A., Bregartner, T.A., Feingold, A., Rounsaville, B.J. and Kosten, T.R. A Placebo Controlled Trial of Bupropion for Smoking Cessation in Schizophrenia, Biol. Psychiatry, 52(1), pp. 53-61, July 1, 2002.

### Triple HIV Therapy May Increase the Rate of Methadone Metabolism

There is a belief among methadone patients that triple therapy for HIV reduces methadone potency. This cross-sectional study compared the rate of methadone metabolism (peak-trough blood levels) in two groups of methadone-maintained patients, AIDS patients receiving triple therapy (N = 17), and HIV patients without triple therapy (N = 19). These preliminary findings suggest that triple therapy may increase the rate of methadone metabolism, though further studies are warranted. Akerele, E.O., Levin, F., Nunes, E., Brady, R. and Kleber, H. Effects of HIV Triple Therapy on Methadone Levels, Am. J. Addict.,11(4), pp. 308-314, Fall 2002.

### Attrition is a Serious Problem for Naltrexone Maintenance: Previous Methadone Therapy Worsens Outcome

Treatment of opiate dependence with naltrexone has been limited by poor compliance. Behavioral Naltrexone Therapy (BNT) was developed to promote adherence to naltrexone and lifestyle changes supportive of abstinence, by incorporating components from empirically validated treatments, including Network Therapy with a significant other to monitor medication compliance, the Community Reinforcement Approach, and voucher incentives. In an uncontrolled Stage I trial (N = 47), 19% completed the 6-month course of treatment. Retention was especially poor in the sub-sample of patients who were using methadone at baseline (N = 18; 39% completed 1 month, none completed 6 months), and more encouraging among heroin-dependent patients (N = 29; 65% completed 1 month, 31% completed 6 months). Thus, attrition continues to be a serious problem for naltrexone maintenance, although further efforts to develop interventions such as BNT are warranted. Rothenberg, J.L., Sullivan, M.A., Church, S.H., Seracini, A., Collins, E., Kleber, H.D. and Nunes, E.V. Behavioral Naltrexone Therapy. An Integrated Treatment for Opiate Dependence. J. Subst. Abuse Treat., 23(4) pp. 351-360,

December 2002.

### Naltrexone Increases the Reinforcing Effects of Oral THC

Studies in animals suggest that opioid antagonists block the reinforcing effects of cannabinoids These studies in humans investigated how naltrexone modulates (1) the subjective and physiological effects of oral THC in comparison to methadone, (2) the reinforcing effects of oral THC, and (3) plasma levels of oral THC. Pretreatment with naltrexone significantly increased many of the "positive" subjective effects of oral THC ratings of Good Drug Effect and Capsule Liking. Naltrexone did not alter plasma THC levels. These studies demonstrate that naltrexone increases the subjective effects of oral THC. Thus, oral THC's effects are enhanced rather than antagonized by opioid receptor blockade in heavy marijuana smokers. Haney, M., Bisaga, A. and Foltin, R.W. Interaction Between Naltrexone and Oral THC in Heavy Marijuana Smokers. Psychopharmacology (Berl), 166(1), pp. 77-85, May 2003.

### An NMDA Receptor Antagonist Produces Some Stimulant-like Subjective Effects

This study investigated the discriminative stimulus, subjective (e.g. "Good Drug Effect"), psychomotor performance, and cardiovascular effects (e.g. blood pressure) of oral methamphetamine following acute oral memantine (a non-competitive NMDA antagonist) in humans. Initially, participants were trained to discriminate 10 mg methamphetamine from placebo using a standard two-response procedure (drug versus placebo). Then, the effects of memantine (0, 40 mg) on methamphetamine discrimination were examined across several methamphetamine doses (0, 5, 10, 20 mg) using a novel-response procedure (drug versus placebo versus novel). Following placebo pretreatment, 10 mg methamphetamine produced 99% methamphetamine-appropriate responding and placebo produced 75% placebo-appropriate responding. Following memantine pretreatment, participants responded as if they had been given a novel compound, although memantine did not significantly alter most subjective-effects ratings following methamphetamine. Memantine alone produced "positive" subjective effects and novel drug-appropriate responding. These data indicate that the memantine-methamphetamine combination produced novel discriminative stimulus effects and that memantine produced some stimulant-like subjective effects. Hart, C.L., Haney, M., Foltin, R.W. and Fischman, M.W. Effects of the NMDA Antagonist Memantine on Human Methamphetamine Discrimination. Psychopharmacology (Berl), 164(4), pp. 376-384, December 2002.

### Oral Delta (9)-THC Does Not Alter Self-administration of Marijuana

Agonist therapies have been demonstrated to be effective for the treatment of substance use disorders. This study evaluated the influence of oral Delta (9)-THC maintenance on choice to self-administer smoked marijuana. During this 18-day residential study, 12 healthy research volunteers received one of three doses of oral Delta (9)-THC capsules (0, 10, 20 mg q.i.d.) for 3 consecutive days, followed by 3 consecutive days of matching placebo. Each morning, except on days 6, 12, and 18, participants smoked the 'sample' marijuana cigarette (1.8% Delta (9)-THC w/w) and received a $2 voucher. Following the sample, volunteers participated in a four-trial choice procedure during which they had the opportunity to self-administer either the dose of marijuana they sampled that morning or to receive the $2 voucher. Relative to placebo Delta (9)-THC maintenance, participants' choice to self-administer marijuana was not significantly altered by either of the two active Delta (9)-THC maintenance conditions. Some 'positive' subjective drug-effect ratings following the sample marijuana cigarette were reduced. The effects of smoked marijuana on psychomotor task performance were only minimally affected by oral Delta (9)-THC maintenance. The data indicate that participants' choice to self-administer marijuana was unaltered by the oral Delta (9)-THC dosing regimen used in the present investigation. Hart, C.L., Haney, M., Ward, A.S., Fischman, M.W. and Foltin, R.W. Effects of Oral THC Maintenance on Smoked Marijuana Self-Administration. Drug Alcohol Depend., 67(3), pp. 301-309, August 1, 2002.

### Cardiovascular and Subjective Effects of Smoked Cocaine Vary as a Function of Menstrual Cycle Phase

Few studies have systematically determined whether the response to cocaine in human females is related to hormonal fluctuations at different phases of the menstrual cycle. The goal of this study was to investigate the responses to repeated doses of smoked cocaine in women during two phases of the menstrual cycle using a within-subject design. Eleven non-treatment seeking female cocaine smokers were administered smoked cocaine during the follicular and mid-luteal phases of the

menstrual cycle. The order of menstrual cycle phase was counterbalanced across women and the order of cocaine doses was randomized. During each phase, there were four cocaine administration sessions. During each session, participants could smoke up to six doses of cocaine (either 0, 6, 12, or 25 mg cocaine base, depending on the session) at 14-min intervals. Results obtained showed that the number of cocaine doses administered did not vary between the follicular and luteal phases. After cocaine administration, heart rate and several ratings - such as "good drug effect", "high", "stimulated", and "drug quality ratings" - were increased more during the follicular phase than the luteal phase, although, for some measures, these effects varied based on the cocaine dose. Further, dysphoric mood during the luteal phase was improved after cocaine administration. These results indicate that the cardiovascular and subjective effects of repeated doses of smoked cocaine are complex and vary as a function of menstrual cycle phase and cocaine dose. Evans, S.M., Haney, M. and Foltin, R.W. The Effects of Smoked Cocaine During the Follicular and Luteal Phases of the Menstrual Cycle in Women. Psychopharmacology (Berl), 159(4), pp. 397-406, February 2002.

### Maternal Vaccination Against Nicotine Reduces Nicotine Distribution to Fetal Brain in Rats

This study examined whether vaccination of female rats prior to pregnancy would reduce the distribution to fetal brain of a single nicotine dose administered during gestation. Female rats immunized with a nicotine conjugate vaccine received a single dose of nicotine 0.03 mg/kg i.v. on gestational day 16-22. Five minutes later, vaccinated rats had substantially higher bound and lower unbound serum nicotine concentration, and lower brain nicotine concentration than controls. Fetal brain nicotine concentration was reduced by 43% in vaccinated rats, comparable to the reduction in the maternal brain nicotine concentration. The whole fetus nicotine concentration was not altered by vaccination. A similar experiment was performed in which pregnant rats were passively immunized with rabbit nicotine-specific IgG 7 or 21 mg/kg just prior to nicotine dosing. The effects of passive immunization on nicotine distribution in the mother were IgG dose-related and the higher dose reduced nicotine distribution to fetal brain by 60%. These data suggest that vaccine effects on nicotine distribution to serum and brain are similar in pregnant female rats to those previously reported in adult males. Vaccination of female rats prior to pregnancy, or passive immunization during pregnancy, can reduce the exposure of fetal brain to a single dose of maternally administered nicotine. Keyler, D.E., Shoeman, D., LeSage, M.G., Calvin, A.D. and Pentel, P.R. Maternal Vaccination Against Nicotine Reduces Nicotine Distribution to Fetal Brain in Rats. J Pharmacol Exp Ther., February 11, 2003 [epub ahead of print].

### Contingent Monetary Reinforcement of Smoking Reductions, With and Without Transdermal Nicotine In Outpatients with Schizophrenia

This study investigated the effects of contingent monetary reinforcement (CM) for smoking reduction, with and without transdermal nicotine, on cigarette smoking in individuals with schizophrenia. Fourteen outpatients participated in each of 3 conditions: (a) CM combined with 21 mg transdermal nicotine, (b) CM combined with placebo patch, and (c) noncontingent reinforcement combined with placebo patch. Each condition lasted 5 days. Carbon monoxide levels were measured 3 times daily, and nicotine withdrawal symptoms were measured once daily in each condition. Results indicated that CM reduced smoking but that 21 mg transdermal nicotine did not enhance that effect. These results offer further evidence supporting the efficacy of CM for reducing smoking among people with schizophrenia, but higher doses of nicotine replacement therapy, or another pharmacotherapy, may be needed to enhance that effect. Tidey, J.W., O'Neill, S.C. and Higgins, S.T. Contingent Monetary Reinforcement of Smoking Reductions, With and Without Transdermal Nicotine, in Outpatients with Schizophrenia. Exp Clin Psychopharmacol., 10(3), pp. 241-247, August 2002.

### Acute Effects of "Advance": A Potential Reduced Exposure Product for Smokers

This study examined the acute effects of "Advance", a potential reduced exposure product (PREP) for smokers marketed as a means to reduce exposure to toxic gases and tobacco specific nitrosamines. A Latin square ordered, three condition, laboratory based, crossover design with 20 smokers of light or ultra-light cigarettes (15 or more cigarettes/day) was employed. In each 2.5 hour condition, participants completed an 8-puff smoking bout from their own brand, "Advance", or an unlit cigarette (that is, sham smoking) every 30 minutes for a total of four bouts. Subject rated measures of tobacco/nicotine withdrawal; carbon monoxide (CO), and heart rate; plasma nicotine

concentrations. Relative to own brand, "Advance" produced similar withdrawal suppression and heart rate increase, lower CO boost, and higher plasma nicotine concentrations. In conclusion, PREPs for smokers need to be evaluated using a comprehensive strategy that includes empirical examination of acute and long-term effects. Adequate withdrawal suppression and potentially lower concentrations of CO associated with "Advance" use are positive factors, although higher nicotine concentrations do not constitute "reduced exposure". Overall, longer exposure periods are necessary to determine carcinogen delivery. PREP evaluation is complex and should be completed objectively. Breland, A.B., Evans, S.E., Buchhalter, A.R. and Eissenberg, T. Acute Effects of "Advance": A Potential Reduced Exposure Product for Smokers. Tobacco Control, 11(4), pp. 376-378, December 2002.

### Evaluating Acute Effects of Potential Reduced-exposure Products for Smokers: Clinical Laboratory Methodology

The study of smoke constituent exposure, and any resulting harm reduction from a potential reduced-exposure product (PREP), involves preclinical, clinical, and epidemiological research. The purpose of this study was to evaluate a clinical laboratory model for assessing the acute effects of PREPs for smokers. Philip Morris' Accord and R.J. Reynolds' Eclipse were used as examples. Twenty overnight-abstinent smokers (> 15 'light' or 'ultra-light' cigarettes/day) participated in 4 Latin-square ordered, 2.5-hr sessions in which they completed an 8-puff smoking bout every 30 minutes. Sessions were separated by at least 24 hours and differed by product used: own brand, denicotinized tobacco cigarettes, Accord, or Eclipse. Tobacco withdrawal and carbon monoxide (CO) were assessed before and after smoking, heart rate was assessed before and during smoking, and puff volume, duration, and interpuff interval were assessed while subjects smoked. Blood was sampled at the beginning and end of each session. Relative to normal cigarettes, Accord was less effective at suppressing withdrawal and produced minimal CO boost despite the fact that, when using Accord, subjects took bigger and longer puffs. Eclipse suppressed withdrawal fully and increased CO boost by approximately 30%. Own brand, Accord, and Eclipse, but not denicotinized cigarettes, increased plasma nicotine concentration. Taken together, these results suggest that neither Accord nor Eclipse is likely to be an effective reduced-exposure product for smokers and that this clinical laboratory model is valuable. Breland, A.B., Buchhalter, A.R., Evans, S.E. and Eissenberg, T. Evaluating Acute Effects of Potential Reduced-Exposure Products for Smokers: Clinical Laboratory Methodology. Nicotine Tob. Res., 4 Suppl 2, pp. 131-140, 2002.

### A Liquid Chromatographic-Electrospray Ionization-tandem Mass Spectrometric Method for Determination of Buprenorphine, its Metabolite, Norbuprenorphine, and a Co-formulant, Naloxone, that is Suitable for In Vivo and In Vitro Metabolism Studies

The authors report the development and validation of a liquid chromatographic-electrospray ionization-tandem mass spectrometric method for determination of the anti-abuse medication, buprenorphine, its primary metabolite, norbuprenorphine, and a proposed co-formulant, naloxone. The method uses deuterated internal standards and a simple liquid-liquid extraction. Mass spectrometry employed selected reaction monitoring of the transitions of m/z 468 to 396 for buprenorphine, 472 to 400 for [2H4]buprenorphine, 414 to 101 for norbuprenorphine, 423 to 110 for [2H9]norbuprenorphine, 328 to 310 for naloxone, and 345 to 327 for its internal standard, [2H3]naltrexone. The method was accurate and precise across the dynamic range of 0.1 to 10 ng/ml. All analytes were stable in human plasma stored at room temperature for up to 24 h and after three freeze-thaw cycles. Reconstituted extracts were stable at -20 degrees C for up to 3 days. In human subjects receiving a sublingual tablet of 8 mg buprenorphine and 2 mg naloxone, buprenorphine and norbuprenorphine were detected for up to 24 h with respective maximum concentrations at 1 and 1.5 h. Maximal concentrations ranged from 2.2 to 2.8 and 1.5 to 2.4 ng/ml for buprenorphine and norbuprenorphine, respectively (i.e., approximately 6 nM). The method detected norbuprenorphine formation in human liver microsomes incubated with 5-82 nM buprenorphine, which encompasses the therapeutic plasma concentration range. When cDNA-expressed P450s were incubated with 21 nM buprenorphine, norbuprenorphine formation was detected for P450s 3A4, as previously described, but also for 3A5, 3A7, and 2C8. Buprenorphine utilization generally exceeded norbuprenorphine formation, suggesting that P450s 2C18, 2C19, 2D6, and 2E1 may also be involved in buprenorphine metabolism to other products. These results suggest this method is suitable for both in vivo and in vitro studies of buprenorphine metabolism to norbuprenorphine. Moody, D.E., Slawson, M.H., Strain, E.C., Laycock, J.D., Spanbauer, A.C. and Foltz, R.L. A Liquid Chromatographic-Electrospray Ionization-tandem Mass Spectrometric Method for Determination of

Buprenorphine, Its Metabolite, Norbuprenorphine, and a Co-formulant, Naloxone, that is Suitable for In Vivo and In Vitro Metabolism Studies. Anal Biochem., 306(1), pp. 31-39, July 1, 2002.

### An Investigation of Predictors of Nicotine Abstinence in a Smoking Cessation Treatment Study of Smokers with a Past History of Alcohol Dependence

This study examined predictors of nicotine abstinence at 12-week follow-up among 85 smokers with a past history of alcohol dependence enrolled in a smoking cessation trial. Length of alcohol abstinence at time of enrollment and longest previous period of smoking abstinence were significantly associated with smoking status at follow-up. Multiple logistic regression with these variables entered as predictors suggested that longest previous period of smoking abstinence partially mediated the relationship between length of alcohol abstinence at enrollment and smoking status at follow-up. Additional research is warranted to identify predictors of nicotine abstinence and smoking relapse in this population and to understand the factors that mediate the relationship between length of alcohol abstinence at enrollment and smoking outcome. Kalman, D., Tirch, D., Penk, W. and Denison, H. An Investigation of Predictors of Nicotine Abstinence in a Smoking Cessation Treatment Study of Smokers with a Past History of Alcohol Dependence. Psychol Addict Behav., 16(4), pp. 346-349, December 2002.

### A Clinical Approach to Integrating Treatment for Adolescent Depression and Substance Abuse

This study provides a preliminary, but empirically derived, clinical treatment algorithm which could be useful as a starting point to help clinicians structure an integrated approach to the treatment of depression in adolescents with SUD. Adolescents with substance use disorders (SUD) commonly suffer from co-occurring major depression (MDD), which impairs psychosocial functioning, contributes to the severity of substance abuse, and interferes with effective engagement in substance treatment. Because the magnitude of the public health impact and the clinical complexity of adolescents with comorbid disorders are so great, it is important to at least begin to derive a more standardized clinical treatment algorithm to guide our approach to integrated treatment from the current empirical base. Riggs, P.D. and Davies, R.D. A Clinical Approach to Integrating Treatment for Adolescent Depression and Substance Abuse. J Am Acad Child Adolesc Psychiatry., 41(10). pp. 1253-1255, October 2002.

### A Preliminary Placebo-Controlled Trial of Selegiline Hydrochloride for Smoking Cessation

This study assessed the safety and efficacy of the monoamine oxidase B inhibitor selegiline hydrochloride compared with placebo for smoking cessation in nicotine-dependent cigarette smokers. Forty subjects with DSM-IV nicotine dependence were randomized to: 1) selegiline hydrochloride (5 mg p.o. twice daily) or 2) placebo in an 8-week trial. Outcome measures included smoking cessation rates, treatment retention, and medication side effects. Selegiline hydrochloride increased trial end point (week 8) 7-day point prevalence smoking cessation rates (selegiline hydrochloride, 9/20 [45.0%]; placebo, 3/20 [15.0%], odds ratio = 4.64, 95% CI, 1.02-21.00, p <.05), and smoking cessation rates during the last 4 weeks of the trial (selegiline hydrochloride, 6/20 [30.0%]; placebo, 1/20 [5.0%], odds ratio = 8.14, 95% CI, 0.88-75.48, p =.07) in comparison with placebo. Six-month follow-up 7-day point prevalence smoking cessation rates were reduced compared with trial end point (selegiline hydrochloride, 4/20 [20.0%]; placebo, 1/20 [5.0%], odds ratio = 4.75, 95% CI, 0.48-46.91, p =.18). Treatment retention was similar between drug and placebo groups (p =.13), and selegiline hydrochloride was well tolerated in cigarette smokers. This preliminary study suggests that selegiline (10 mg/day) is safe for use and enhances smoking cessation rates compared with placebo in nicotine-dependent 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, 2002.

### Patients' Views on Smoking Cessation and Tobacco Harm Reduction during Drug Treatment

The investigators conducted focus groups and interviews among 78 patients from five Methadone Maintenance Treatment (MMT) sites. Measures included a written survey and open-ended questions on (a) motivation for quitting, (b) what quit methods worked and what didn't work, and (c) interest in smoking reduction and nicotine maintenance as an alternative to complete cessation. Discussions were audiotaped,

transcribed, and coded using computer-based qualitative software; inter-observer reliability was 83%. Successful quitters used in general a combination of quit methods such as prayer, nicotine gum, keeping busy, quitting 'one day at a time,' nicotine patches, deep breathing, and avoidance of triggers. Nicotine craving, rather than withdrawal, was cited as the biggest challenge to staying quit. Some current smokers feared quitting smoking would divert them from their goal of quitting illicit drug use or tapering off MMT. Current smokers were interested in smoking reduction as an alternative to quitting; however, those who had tried but failed to reduce smoking preferred complete cessation. Nicotine maintenance was favored by only a few participants with major health problems who did not believe they would be able to quit. Findings suggest combination pharmacotherapy could help patients control withdrawal and acute episodes of craving. Patients have a number of skills from coping with illicit drug dependence that are useful in combating nicotine dependence. Behavioral methods and short-term pharmacotherapy to help patients reduce tobacco exposure should be explored. Richter, K.P., McCool, R.M., Okuyemi, K., Mayo, M.S. and Ahluwalia, J.S. Patient's Views on Smoking Cessation and Tobacco Harm Reduction during Drug Treatment. Nicotine and Tobacco Research, S139-S136, 2002.

### African American Smokers Interested In and Eligible for a Smoking Cessation Clinical Trial: Predictors for not Returning for Randomization

The investigators compared 287 enrolled African American smokers who did not return for randomization, to the 500 who returned and were randomized to participate in a clinical trial for smoking cessation in African Americans. Analyses were conducted to identify variables associated with not returning for randomization. Univariate comparisons found the nonrandomized group to be significantly different from those randomized. Logistic regression showed younger age, less readiness to quit, having been proactively recruited, lacking a regular source of health care, believing that they will be smoking in 6 months, less church attendance, and a lower literacy level to be jointly related with not returning for randomization. In conclusion, African American participants who did not return for randomization into a clinical trial were different from those who did. Better understanding of these factors may allow researchers to target recruitment efforts resulting in enhanced accrual in clinical trials and increased efficiency. Ahluwalia, J.S., Richter, K.P., Mayo, M.S., Ahluwalia, H.K., Choi, W.S., Schmelzle, K.H. and Resnicow, K. African American Smokers Interested In and Eligible for a Smoking Cessation Clinical Trial: Predictors for Not Returning for Randomization. Annals of Epidemiology, 12, pp. 206-212, 2002.

### Smoking Reduction Practices Among African American Smokers

A survey was conducted of 484 African American smokers classified as occasional, light, moderate, and heavy smokers to examine sociodemography, smoking characteristics, and eight smoking reduction strategies, including intentional limiting of smoking, smoking less than half of a cigarette, setting a daily limit for smoking, changing cigarette brand, reducing number of cigarettes, smoking only on some days, switching to a lighter tar cigarette, and not inhaling deeply. Compared to moderate and heavy smokers, occasional and light smokers were more likely to have engaged in most of these strategies. Smokers who used >/= 4 strategies on average smoked 11 cigarettes per day (cpd), compared to 14 cpd and 18 cpd for those who used 1 to 3 strategies and no strategies respectively ($p < .0001$). After analyses controlled for age, gender, and education, the number of smoking reduction strategies utilized was a significant predictor of smoking 10 or fewer cigarettes per day. This study provides evidence that African American smokers who engaged in multiple smoking reduction strategies smoked fewer cigarettes per day. Smokers not interested in quitting but willing to reduce their smoking should be encouraged to utilize a variety of smoking reduction strategies. Okuyemi, K.S., Richter, K.P., Ahluwalia, J.S., Mosier, M.C., Nazir, N. and Resnicow, K. Smoking Reduction Practices Among African American Smokers. Nicotine and Tobacco Research, 4 Suppl 2:S167-S173, 2002.

### Effects of Smoking Cessation on Reduction of Hormone Profiles and Bone Turnover in Postmenopausal Women

A prospective study was conducted to evaluate the impact of smoking cessation on hormonal concentrations, sex hormone-binding globulin (SHBG) and markers of bone turnover in postmenopausal women. Sixty-six women who were either users or non-users of estrogen replacement therapy (ERT) were randomly assigned, using a weighted randomization scheme, to smoking cessation (SC) or to smoking cessation after 6 weeks of monitoring (wait-list control group, WLC). The study measured hormones [estrone, estradiol, testosterone, parathyroid hormone, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS) and androstenedione] and SHBG, markers of bone turnover [procollagen peptide (PINP),

bone alkaline phosphatase (BAP), and osteocalcin (OC), N- and C-terminal collagen cross-links (NTx and CTx)], and cotinine, at baseline and again at 6 weeks in women who reported smoking cessation and in women randomized to the WLC group. Analyses included 20 subjects who quit or significantly reduced their smoking and 18 subjects in the WLC group. After controlling for differences in age and ERT use between groups, we found a significant change in SHBG in the SC vs. the WLC group (-8% vs. +5%, respectively; p = 0.01), and in DHEA (-18% vs. -5%, respectively; p = 0.04), but not in other hormonal concentrations. Authors also noted a significant change in NTx in the SC vs. WLC group (-5% vs. +56%, respectively, p = 0.01), but not in other markers of bone turnover. Percentage changes in SHBG and NTx were correlated with changes in plasma cotinine (r = 0.48; p = 0.004 and r = 0.36; p = 0.04, respectively). Six weeks of smoking abstinence produces reductions in SHBG and NTx. This may partly explain how smoking contributes to osteoporosis in postmenopausal women. Oncken, C., Prestwood, K., Cooney, J.L., Unson, C., Fall, P., Kulldorff, M. and Raisz, L.G., Nicotine Tob. Res., 4(4), pp. 451-458, November 2002.

### Effect of Maternal Smoking on Fetal Catecholamine Concentrations at Birth

Catecholamine concentrations in the fetal umbilical artery cord blood from the offspring of smokers were compared to the offspring of nonsmokers. 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., Kuhn, C.M., Slotkin, T.A. and Kranzler, H.R. Effect of Maternal Smoking on Fetal Catecholamine Concentrations at Birth. Pediatr Res. 53(1), pp. 119-124, January 2003.

### Severe, Demyelinating Leukoencephalopathy in AIDS Patients on Antiretroviral Therapy

Dr. Grant and his team at the University of California, San Diego used clinical and neuroimaging findings to test a hypotheses regarding the pathogenesis for a severe form of demyelinating HIV-associated leukoencephalopathy in AIDS patients who fail highly active antiretroviral therapy (HAART). Each patients entered into the study had a detailed neuromedical, neuropsychological, neuroimaging and post-mortem neuropathological examination. Immunocytochemical and PCR analyses were performed to determine brain HIV levels and to exclude other viruses. Seven recent autopsy cases of leukoencephalopathy in antiretroviral-experienced patients with AIDS were identified. Clinically, all were severely immunosuppressed, six (86%) had poorly controlled HIV replication despite combination antiretroviral therapy, and five (71%) had HIV-associated dementia. Neuropathologically, all seven had intense perivascular infiltration by HIV-gp41 immunoreactive monocytes/macrophages and lymphocytes, widespread myelin loss, axonal injury, microgliosis and astrogliosis. The extent of damage exceeds that described prior to the use of HAART. Brain tissue demonstrated high levels of HIV RNA but evidence of other pathogens, such as JC virus, Epstein-Barr virus, cytomegalovirus, human herpes virus type-8, and herpes simplex virus types 1 and 2, was absent. Comparison of the stages of pathology suggests a temporal sequence of events. In this model, white matter damage begins with perivascular infiltration by HIV-infected monocytes, which may occur as a consequence of antiretroviral-associated immune restoration. Intense infiltration by immune cells injures brain endothelial cells and is followed by myelin loss, axonal damage, and finally, astrogliosis. Taken together, the findings provide evidence for the emergence of a severe form of HIV-associated leukoencephalopathy. This condition warrants further study and increased vigilance among those who provide care for HIV-infected individuals. Langford, T.D., Letendre, S.L., Marcotte, T.D., Ellis, R.J., McCutchan, J.A., Grant, I., Mallory, M.E., Hansen, L.A., Archibald, S., Jernigan,

T., Masliah, E. and the HNRC Group. Severe, Demyelinating Leukoencephalopathy in AIDS Patients on Antiretroviral Therapy. AIDS, 16(7), pp. 1019-1029, 2002.

### Expression of Stromal Cell-Derived Factor 1a Protein in HIV Encephalitis

Dr. Grant and colleagues during further investigation of encephalopathy, analyzed the patterns of stromal cell-derived factor 1 (SDF-1) expression in brains from HIV-positive patients. Evidence suggested that in neuronal cells, SDF-1 might play a role in neuroprotection and neurite extension in response to HIV infection. In all cases analyzed, SDF-1 immunoreactivity was primarily present in astroglial cells. Patients with HIV encephalitis (HIVE) showed intense somato-dendritic neuronal SDF-1 immunoreactivity, while HIVE negative patients with neurodegeneration had a significant decrease in neuronal SDF-1 immunoreactivity. Neuronal cells treated with SDF-1 displayed increased neurite outgrowth. Similarly, neurons treated with HIV-Tat, which induced SDF-1 expression, also showed neurite outgrowth. Tat-mediated neurite outgrowth was blocked by anti-SDF-1 antibody. These results suggest that SDF-1 may play a role in the neuronal response to HIV in the brains of AIDS patients. Langford, D., Sanders, V.J., Mallory, M., Kaul, M., and Masliah, E. Expression of Stromal Cell-Derived Factor 1a Protein in HIV Encephalitis. Journal of Neuroimmunology, 127, pp. 115-126, 2002.

### The Functional Impact of HIV-Associated Neuropsychological Impairment in Spanish-Speaking Adults: A Pilot Study

Among English-speaking adults, HIV-associated neuropsychological (NP) impairments have been associated with problems in everyday functioning, including the ability to function at work and drive an automobile. Latinos account for a disproportionate number of HIV/AIDS cases nationwide, and a significant segment of this population is primarily Spanish speaking. This research team had previously developed an assessment that evaluates English-speakers on a variety of instrumental activities of daily living. In this pilot study, Spanish-language translations of the functional battery to investigate the cultural relevance of such measures were used. Additionally, the relationships between NP status and ability to perform important, everyday tasks in HIV-infected Spanish-speakers was explored. Sixteen HIV-infected monolingual Spanish-speaking adults received comprehensive, Spanish language NP testing and functional assessments included the following domains: Medication Management, Cooking, Finances, Shopping, and Restaurant Scenario. Results revealed that most of the functional tasks appeared culturally relevant and appropriate with minor modifications. NP-impaired participants were significantly more functionally impaired compared to NP-normals (88% vs. 13%, $p < .01$). Performances on the functional assessment and the NP battery were also related to indicators of real world functioning, including employment status and quality of life. These results, though preliminary, suggest that Spanish language functional assessments are potentially valid tools for detecting everyday functioning deficits associated with NP impairments in HIV-infected Spanish-speakers. Rivera Mindt, M., Cherner M., Marcotte, T.D., Moore, D.J., Bentley, H., Esquivel, M.M., Lopez, Y., Grant, I., Heaton, R.K., and the HNRC Group. The Functional Impact of HIV-Associated Neuropsychological Impairment in Spanish-Speaking Adults: A Pilot Study. Journal of Clinical and Experimental Neuropsychology, 25(1), pp. 122-132, 2003.

### Decision Making by Methamphetamine-Dependent Subjects Is Associated with Error-Rate-Independent Decrease in Prefrontal and Parietal Activation

Dr. Martin Paulus and colleagues at the University of California, San Diego used fMRI to investigate how success or failure influences subsequent decision-making. Results from a previous investigation, in which methamphetamine-dependent subjects (MD) adopted a more consistent win-stay/lose-shift response pattern than normal comparison subjects (NC), implied that MD are more influenced by success. This study examined whether varying the degree of success and the degree of predictability differentially affected MD's decision making. Fourteen MD individuals were compared with 14 NC individuals while performing the two-choice prediction task at three success rates and the two-choice response task. Win-stay/lose-shift consistent responses by MD subjects relative to NC subjects were independent of success rate. Whereas NC showed success-related patterns of neural activation in the orbitofrontal, dorsolateral prefrontal, and parietal cortex, brain activation in MD was highest when the outcome was most unpredictable. Irrespective of success, MD showed less task-related activation in orbitofrontal cortex (Brodmann's area [BA] 10), dorsolateral prefrontal cortex (BA 9), anterior cingulate (BA 32), and parietal cortex (BA 7). These results are consistent with the hypothesis that MD decision-making is characterized by more rigid stimulus-response relationships, which may be due to a shift from processing "success" toward processing the degree of stimulus

"predictability." Paulus, M.P., Hozack, N., Frank, L., Brown, G.G. and Schuckit, M.A. Biological Psychiatry 53(1), pp. 65-74, January 2003.

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

Dr. Harrison Pope and colleagues at McLean Hospital investigated whether individuals who initiate cannabis use at an early age might be more vulnerable to lasting neuropsychological deficits than individuals who begin use later in life. After 28 days of monitored abstinence from cannabis, 122 long-term heavy cannabis users and 87 comparison subjects with minimal cannabis exposure were given a battery of neuropsychological tests. Comparison of early onset cannabis users with late-onset users and with controls was controlled for age, sex, ethnicity, and attributes of family of origin. The 69 early-onset users (who began smoking before age 17) differed significantly from both the 53 late onset users (who began smoking at age 17 or later) and from the 87 controls on several measures, most notably verbal IQ (VIQ). Few differences were found between late-onset users and controls on the test battery. After controlling for VIQ, virtually all differences between early-onset users and controls on test measures ceased to be significant. Although early-onset cannabis users exhibit poorer cognitive performance than late-onset users or control subjects, especially in VIQ, 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, Jr., H.G, Gruber, A.J., Hudson, J.I., Cohane, G., Huestis, M.A., and Yurgelun-Todd, D. Drug and Alcohol Dependence 699(3), pp. 303-310, April 2003.

### Characterization of Effects of Mean Arterial Blood Pressure Induced by Cocaine and Cocaine Methiodide on BOLD Signals in Rat Brain

Dr. F. Luo and colleagues at the Medical College of Wisconsin used functional magnetic resonance imaging (fMRI) in rats to determine whether cocaine analogue that does not pass the blood-brain barrier (cocaine methiodide, CM) can produce a global increase in blood oxygenation level-dependent (BOLD) contrast. Cocaine methiodide is a quaternary derivative of cocaine that shares the same cardiovascular effects of cocaine, but does not penetrate the blood-brain barrier (BBB). Both CM (with doses of 2.5 and 7.5 mg/kg) and cocaine (with doses of 1.25 and 5.0 mg/kg) induced a robust increase 30-80% in mean arterial blood pressure (MABP). In contrast, CM only produced scattered, weak, and transient BOLD signals in a few voxels of the rat brain. Furthermore the CM-induced BOLD signals were not dose-dependent. In contrast, the administration of cocaine induced dose-dependent biphasic BOLD signals that were consistent with pharmacologically induced cerebral vascular constriction and neuronal activity in the mesolimbic systems of the rat brain. These results confirm that the BOLD-weighted fMRI method can be extended to map drug-induced neuronal activity, and that the potential confounding factors of MABP changes have little effect on the interpretation of drug-induced BOLD signal changes. Luo, F., Wu, G., Li, Z., and Li, S.J. Magnetic Resonance in Medicine 49(2), pp. 264-270, May 2003.

### Central Beta-Adrenergic Modulation of Cognitive Flexibility

Dr. David Beversdorf and colleagues at Ohio State University investigated whether noradrenergic modulation of cognitive flexibility in normal humans is a centrally or peripherally mediated phenomenon. Prior research had shown that administration of propranolol (beta-adrenergic antagonist) but not ephedrine (beta-adrenergic agonist) lead to better performance on a task requiring cognitive flexibility, the anagram task. However, these drugs have both peripheral and central beta-adrenergic effects. In the present study the effects of propranolol (peripheral and central beta-blocker) were compared to nadolol (peripheral beta-blocker) and placebo on anagram task performance. Solution latency scores for each subject were compared across the drug conditions. Anagram solution latency scores after propranolol were significantly lower than after nadolol. This suggests a centrally mediated modulatory influence of the noradrenergic system on cognitive flexibility. Beversdorf, D.Q.,White, D.M., Chever, D.C., Hughes, J.D., and Bornstein, R.A. Neuroreport, 139(18), pp. 2505-2507, December 2002.

### Loss of Striatal Vesicular Monoamine Transporter Protein (VMAT2) in Human Cocaine Users

Dr. Karley Little at the University of Michigan investigated whether cocaine use leads

to damage to dopamine nerve terminals. Vesicular monoamine transporter (VMAT2) protein in the striatum was used as an indirect marker of the integrity of dopamine terminals. Post-mortem striatal samples from human cocaine users retrieved at autopsy were compared to striatal samples from age-, sex-, and postmortem interval-matched comparison subjects. Immunoblot assays were performed by using a highly specific VMAT2 antibody, striatal radioligand binding to VMAT2 was assessed with dihydrotetrabenazine ([(3)H]DTBZ), and dopamine levels were determined employing high-performance liquid chromatography. Interviews with family members and friends were used to obtain information regarding drug use and potential psychiatry dysfunction. Cocaine users displayed a marked reduction in VMAT2 immunoreactivity as well as reduced [(3)H]DTBZ binding and dopamine levels. It did not appear that the reduction in VMAT2 immunoreactivity was related to ethanol use, but dopamine levels were lower in subjects with only ethanol diagnoses. Subjects who may have had co-morbid mood disorders displayed a trend towards greater loss of VMAT2 immunoreactivity. These results indicate that human cocaine users lose VMAT2 protein, which might reflect damage to striatal dopamine fibers. These neuronal changes could play a role in causing disordered mood and motivational processes in more severely dependent patients. Little, K.Y., Krolewski, D.M., Zhang, L., and Cassin, B.J. American J Psychiatry, 160(1), pp. 47-55, January, 2003.

### The Orbitofrontal Cortex in Methamphetamine Addiction: Involvement in Fear

Dr. Rita Goldstein and colleagues at Brookhaven National Laboratory examined whether cerebral metabolism measured with PET in the orbitofrontal gyrus in methamphetamine abusers was related to personality measures of inhibitory control. Tellegen's Multidimensional Personality Questionnaire (MPQ) harm avoidance (fear) scale and the constraint superfactor were used as the personality measures of inhibitory control. Cerebral rate of glucose metabolism in the orbitofrontal gyrus was measured at rest in 14 recently abstinent methamphetamine-dependent subjects and 22 comparison subjects. Higher MPQ scores were associated with higher relative orbitofrontal gyrus metabolism in the methamphetamine-dependent subjects. There was a tendency towards a negative association for the comparison subjects. These results suggest that stable personality predispositions related to inhibitory control are associated with basal activity in the orbitofrontal cortex. These findings further implicate this region in the core characteristics of drug addiction. Goldstein, R.Z., Volkow, N.D., Chang, L., Wang, G.J., Fowler, J.S., Depue, R.A., and Gur, R.C. NeuroReport 13(17), pp. 2253-2257, December 2002.

### Brain Dopamine Associated with Eating Behaviors in Humans

Dr. Nora Volkow and colleagues at the Brookhaven National Laboratory and SUNY Stony Brook investigated the role of the neurotransmitter, dopamine, in food motivation. Ten healthy, nonobese subjects were administered the Dutch Eating Behavior Questionnaire (DEBQ) to measure attitudes toward food (i.e., Restraint, Emotionality, and Externality). These subjects were also scanned (using positron emission tomography) during neutral stimulation (baseline) and during food stimulation. Results revealed that a different pattern of correlations between dopamine (DA) measures and Restraint and Emotionality factors of the DEBQ. Restraint was correlated with DA changes with food stimulation (higher restraint, greater responsivity); emotionality was negatively correlated with baseline D2 receptors (higher emotionality, lower D2 receptors; whereas externality was not correlated. The correlations were significant in the dorsal striatum but not in the ventral striatum. These results indicate that DA in the dorsal striatum is involved with the restraint and emotionality components regulating eating behaviors, and further, these two dimensions reflect different neurobiologic processes. Volkow, N.D., Wang, G.J., Maynard, L., Jayne, M., Fowler, J.S., Zhu, W., Logan, J., Gatley, S.J., Ding, Y.S., Wong, C., and Pappas, N. Brain Dopamine is Associated with Eating Behaviors in Humans. International Journal of Eating Disorders, 33, pp. 136-142, 2003.

### Methylphenidate's Cardiovascular Effects Associated with Increased Dopamine in Brain and Epinephrine in Plasma

Dr. Nora Volkow and colleagues evaluated the cardiovascular effects of methylphenidate to assess the role of dopamine (DA) in their mediation. This association was evaluated in humans using positron emission tomography and [11C]raclopride, a DA D2 receptor radioligand that competes with endogenous DA for occupancy of the D2 receptors, to assess changes in brain DA after different doses of intravenous methylphenidate in 14 healthy subjects. Cardiovascular (blood pressure and heart rate) and catecholamine (plasma epinephrine and norepinephrine) were measured to assess their relationship to methylphenidate-induced changes in brain

DA. Results revealed that methylphenidate administration significantly increased heart rate, systolic and diastolic blood pressure, and epinephrine concentration in plasma. The blood pressure increases were significantly correlated with methylphenidate-induced increases of DA in striatum and of plasma epinephrine levels. Additionally, methylphenidate-induced DA increases in striatum were correlated with increases of epinephrine in plasma. For those subjects that did not show an increased DA response to methylphenidate, no changes in blood pressure or plasma epinephrine were observed. These results are consistent with the hypothesis that methylphenidate-induced increases in blood pressure are due, in part, to its central dopaminergic effects. They also suggest that methylphenidate's pressor effects may be mediated, in part, by DA-induced increases in peripheral epinephrine. Volkow, N.D., Wang, G.J., Fowler, J.S., Molina, P.E., Logan, J., Gatley, S.J., Gifford, Ding, Y.S., A., Wong, C., Pappas, N., Zhu, W., and Swanson, J.M. Cardiovascular Effects of Methylphenidate in Humans are Associated with Increases of Dopamine in Brain and of Epinephrine in Plasma. Psychopharmacology, 166, pp. 264-270, 2003.

### Substance Abuse-Related P300 Differences in Response to an Implicit Memory Task

Dr. N. Ceballos and colleagues at the University of Oklahoma examined the P300 component of the event-related potential as an electrophysiological index of cognitive efficiency in alcoholics and controls. They predicted that, if alcohol-related impairment in cognitive efficiency was due to inability to ignore irrelevant stimuli, alcoholics would experience less negative priming than normal controls. They used a negative priming paradigm in which sets of novel shapes were presented: two overlapping green and red shapes on the left and a single white shape on the right. Participants were instructed to ignore the red shape, but to determine whether the green shape was the same as or different from the white shape. On primed trials, previously red (to be ignored; i.e., irrelevant) shapes became green (relevant) shapes in a second component of the task. Participants who were capable of ignoring irrelevant stimuli were expected to experience more difficulty in the primed condition. Both amplitude and latency were measured in response to each trial condition. Controls exhibited increased P300 amplitude and latency in response to negatively primed trials whereas alcoholics did not demonstrate this pattern. These findings were consistent with the prediction of alcohol-related cognitive inefficiency. Ceballos, N.A., Nixon, S.J. and Tivis, R. Progress In Neuropsychopharmacology & Biological Psychiatry 27(1), pp. 157-164, May 2003.

### The Multi-Source Interference Task: Validation Study with fMRI in Individual Subjects

Dr. G. Bush and colleagues at the Massachusetts General Hospital used BOLD fMRI in normal human subjects to test a novel cognitive task designed to reliably and robustly activate the dorsal Anterior Cingulate (dACC). Existing tasks used to probe dACC function, such as the classic Stroop Task, require group-averaging techniques to obtain significant dACC activation in functional neuroimaging studies. Development of a task that can be used to discern dACC activation within individuals will improve imaging studies of neuropsychiatric disorders. By combining aspects of tasks that involve cognitive interference (Stroop, Eriksen and Simon) with factors known to increase dACC activity, the Multi-Source Interference Task (MSIT) was developed that was expected to maximally tax dACC function. FMRI responses and performance data were compared between interference and control trials in 8 normal subjects. Significant dACC activation was observed in all eight individuals and in the group-averaged fMRI data. In addition to dACC activation, group data also showed activation of other regions including dorsolateral prefrontal, pre-motor, and parietal cortices, connected to the dACC. The MSIT's reaction time interference effect (overall mean 312+/-61 ms) was up to 10 times greater than that of its component predecessors and temporally stable over hundreds of trials. The robustness, reliability and stability of the neuroimaging and performance data should make the MSIT a useful task with which to study normal human cognition and psychiatric pathophysiology. Bush, G., Shin, L.M., Holmes, J., Rosen, B.R., and Vogt, B.A. Molecular Psychiatry, 8(1), pp. 60-70 2003.

### Simultaneous EEG and fMRI of the Alpha Rhythm

Dr. R. Goldman and colleagues at the University of California, Los Angeles used a combination of fMRI and EEG to determine the source of alpha rhythms in normal humans. The alpha rhythm in the EEG is 8-12 Hz activity present when a subject is awake with eyes closed. Simultaneous EEG and fMRI were used to make maps of regions whose MRI signal changed reliably with modulation in posterior alpha activity in 11 normal subjects as they rested with eyes closed. Increased alpha power was

correlated with decreased MRI signal in multiple regions of occipital, superior temporal, inferior frontal, and cingulate cortex, and with increased signal in the thalamus and insula. These results are consistent with animal experiments and point to the alpha rhythm as an index of cortical inactivity that may be generated in part by the thalamus. These results also may have important implications for interpretation of resting baseline in fMRI studies. Goldman, R.I., Stern, J.M., Engel, J., and Cohen, M.S. NeuroReport, 13(18), pp. 2487-2492, December 2002.

### Hallucinogen Persisting Perception Disorder: What Do We Know After 50 Years?

Drs. John Halpern and Harrison Pope at McLean Hospital reviewed the literature between 1955 and 2001 on 'Flashbacks' following use of hallucinogenic drugs. Flashbacks have been reported for decades; they are recognized in DSM-IV as 'Hallucinogen Persisting Perception Disorder (Flashbacks)', or HPPD. The review analyzed 20 quantitative studies between 1955 and 2001. Many of these studies were performed before operational criteria for HPPD were published in DSM-III-R, so they are difficult to interpret in the light of current diagnostic criteria. Overall, (1) the term 'flashbacks' is defined in so many ways that it is essentially valueless; (2) most studies provide too little information to judge how many cases could meet DSM-IV criteria for HPPD; and consequently (3) information about risk factors for HPPD, possible etiologic mechanisms, and potential treatment modalities must be interpreted with great caution. HPPD appears to be a genuine but uncommon disorder, sometimes persisting for months or years after hallucinogen use. It is reported most commonly after illicit LSD use, but less commonly with LSD administered in research or treatment settings, or with use of other types of hallucinogens. There are case reports, but no randomized controlled trials, of successful treatment with neuroleptics, anticonvulsants, benzodiazepines, and clonidine. Although it may be difficult to collect large samples of HPPD cases, further studies are critically needed to augment the meager data presently available regarding the prevalence, etiology, and treatment of HPPD. Halpern, J. and Pope, Jr., H.G. Drug and Alcohol Dependence 69(2), pp. 109-119, March 2003.

### Progress in Developing D3 Dopamine Receptor Ligands as Potential Therapeutic Agents for Neurological and Neuropsychiatric Disorders

Drs. R. Luedtke and R. Mach of Wake Forest University reviewed recent advances in the biochemistry and pharmacology of the D3 receptor from the molecular to the behavioral level and medicinal chemistry approaches toward developing D3-selective ligands. Evidence was presented showing an alteration in D3 receptor function as playing an important role in the etiology of a variety of CNS disorders, including schizophrenia, Parkinson's disease, and substance abuse. Also discussed were the recent developments in attempting to map the ligand-binding domains of the D2 and D3 receptors. Luedtke, R.R. and Mach, R.H. Pharmaceutical Design 9(8), pp. 643-671, 2003.

### Haplotypes at the OPRM1 Locus are Associated with Susceptibility to Substance Dependence in European Americans

Drs. Gelernter, Kranzler and associates at Yale and University of Connecticut compared eight single nucleotide polymorphisms (SNPs) for the gene encoding the _-opioid receptor (OPRM1) in two groups of Americans of European and African heritage. There was a significantly greater frequency in the European American group diagnosed with "alcohol+opioid" dependence compared to a matched group for the -2044A allele (-2044C/A mutation). This suggests this allele may play a role in the physiology of substance abuse for this group. There were no differences in frequency for this or any other allele between the African American patients and comparison group. Also, there were significant differences in frequencies of the alleles studied between the two heritage groups. If the mutation confers susceptibility it is apparently diagnosis- and population-specific. Luo, X., Kranzler H.R., Zhao H., and Gelernter, J. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, published online April 10, 2003.

### Electrical Response of Retinal Blue Cones May be a Neurobiological Marker to Dopamine Function in Cocaine-Dependent Patients

Using the observation that dopamine in the retina plays an important role in electroretinogram (ERG) amplitudes, Alec Roy and colleagues assessed cone response to blue light in abstinent cocaine-dependent patients and compared this response to concentrations of homovanillic acid (HVA; metabolite of dopamine) in the cerebrospinal fluid (CSF). There was significantly less HVA in the CSF of patients

whose ERG amplitude was less than 0.5 µV. This cut-off is considerably below amplitudes of controls (~1.0 µV) and determined in previous work to divide the cocaine patients in approximately two equal groups. Further supporting the grouped data, there was a significant correlation ($r = .57$; $p < .05$) between the CSF HVA concentrations and blue cone amplitude. These results suggest that the non-invasive measure of an ERG of cones to blue flash are a neurobiological marker of dopaminergic function in abstinent cocaine patients. Roy A., Roy M., Berman J., Gonzalez B. Psychiatry Research, 117, pp. 191-195, 2003.

### Cocaine Abusers Have an Over-Expression of α-synuclein in Dopamine Neurons

Mash and colleagues at the University of Miami assessed post-mortem brains of chronic cocaine abusers who died a sudden death. In particular, increases of α-synuclein protein and mRNA levels were found in the substantia nigra (SN) and ventral tegmental area (VTA) but not the hippocampus. Also of interest, there was no elevation in the SN and less elevation in the VTA in the subset of cocaine abusers who exhibited excited delirium (who exhibit bizarre and violent behavior just prior to death). There was no increase in α-synuclein. It is speculated that over-expression of α-synuclein may occur as a protective response to changes in dopamine turnover and oxidative stress resulting from cocaine abuse. Mash, D.C., Ouyang, Q., Pblo, J., Basile, M., Izenwasser, S., Liberman, A., and Perrin, R. The Journal of Neuroscience, 23(7), pp. 2564-2571, April 1, 2003.

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

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

### Drug Use Patterns and STIs among Young Adults in a High-Risk Neighborhood of NYC

Researchers sought to examine whether and how drug users, particularly IDUs and crack smokers, may be a core group for some sexually transmitted infections (STIs). They conducted a cross-sectional survey on drug use and assays for HIV, hepatitis B and C, syphilis, gonorrhea, and other sexually transmitted infections among 363 young (18-24) adults in an impoverished New York City minority neighborhood with major drug markets. They found that hepatitis C and HIV were concentrated among IDUs and that herpes, syphilis, and hepatitis B increased among women in relation to "hardest drug ever used." These findings suggest that using harder drugs (defined in increasing order of hardness as no drug use, marijuana use, non-injected heroin or cocaine use, crack smoking and injection drug use) is associated with some but not all of these STIs. The findings underscore the importance of targeted HIV prevention efforts to reduce unsafe sex and drug use among high-risk youth. Friedman, S.R., Flom, P.L., Kottiri, B.J., Zenilman, J., Curtis, R., Neaigus, A., Sandoval, M., Quinn, T. and Des Jarlais, D. Drug Use Patterns and Infection with Sexually Transmissible Agents Among Young Adults in a High-Risk Neighborhood in New York City. Addiction, 98, pp. 159-169, 2003.

### HIV Risk Behaviors in African American Drug Injector Networks

Researchers examined the mechanism by which "partnership-level" variables (the mix of characteristics of individuals who inject drugs together) affect the incidence of HIV risk behaviors, including receptive syringe sharing, and facilitate or impede the spread of HIV. They analyzed data on injection partnerships (pairs of individuals who inject together) using a network sample of 401 African American IDUs in Washington, DC. Drug injectors tended to select injection partners of the same gender and similar age, but risk behaviors were most common in partnerships between individuals who were dissimilar in gender and age. Partners who had a sexual relationship, injected drugs frequently together, smoked crack cocaine regularly, injected speedball regularly, and/or had close social ties were more likely to engage in risky injection practices than otherwise similar partners. These factors accounted for the association between the gender-age mix of the partnership and injection risk behavior. These findings show that, among African American IDUs in Washington, DC, partnership-level variables have a critical role in the transmission of HIV. Johnson, R.A., Gerstein, D.R., Pach, A., Cerbone, F., and Brown, J. HIV Risk Behaviors in African-American Drug Injector Networks: Implications of Injection-Partner Mixing and Partnership Characteristics. Addiction, 97, pp. 1011-1024, 2003.

### Depression and HIV Risk Behavior Among Seattle-Area IDUs and Young MSM

Psychological depression has been identified as a condition that may influence HIV risk behavior among IDUs and men who have sex with men (MSM). Researchers analyzed data from the Center for Epidemiological Studies Depression Scale (CES-D) for two Seattle studies involving 1,228 IDUs and 429 MSM. They found that 47% of IDUs had CES-D scores > 23, and that a high score was significantly associated with injection with a syringe used by another IDU (adj OR=1.4) but not other injection risk behavior. Among MSM, CES-D scores > 16 were related to reporting 3 or more sex partners in the last 6 months but not to other sexual risk behavior. These findings indicate that psychological depression may influence certain HIV risk behavior in young MSM and IDUs, and that interventions addressing depression should be

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considered for these populations. Perdue, T., Hagan, H., Thiede, H., and Valleroy L. Depression and HIV Risk Behavior Among Seattle-Area IDUs and Men Who Have Sex with Men. AIDS Educ & Prev, 15(1), pp. 81-92, 2003.

### Effectiveness of an HIV Intervention Among African American Women Who Use Crack

Researchers evaluated 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 NIDA standard condition. A substantial proportion of women reported no past 30-day crack use at 6-month follow-up (100%-61%, $p<.001$). Significant decreases in the frequency of crack use; the number of paying partners, the number of times unsafe sex occurred with a paying partner; and sexual risks, such as trading sex for drugs, were reported over time. Significant increases in male condom use with sex partners were also observed, as well as decreases in casual partners' refusal of condoms. These findings suggest that combined components of the culturally appropriate, gender-tailored HIV intervention are likely to be most effective in enhancing preventive behavior among similar high risk populations. Sterk, C., Theall, K., and Elifson, K. Effectiveness of a Risk Reduction Intervention Among African American Women Who Use Crack Cocaine. AIDS and Behavior, 15(1), pp. 15-32, 2003.

### HIV Risk Reduction Among African American Women Who Inject Drugs

Researchers evaluated a community-based HIV intervention for African American women who are active IDUs. 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, and other sexual risk behaviors were also reduced significantly. 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., Theall, K., Elifson, K., and Kidder, D. HIV Risk Reduction Among African American Women Who Inject Drugs: A Randomized Controlled Trial. AIDS and Behavior, 7(1), pp. 73-86, 2003.

### Feasibility of Referring Drug Users from a Needle Exchange Program (NEP) to an Addiction Treatment Program

This study evaluated program entry, retention, and early treatment response of NEP attendees referred to a drug treatment program using LAAM. Of 163 referrals, 114 (70%) entered the program, and 84% were retained for at least 90 days. Comparing baseline and follow-up visits after 1 month, there were significant reductions in the Addiction Severity Index subscale scores for drug and alcohol use and legal situation. A 31% and 22% reduction in heroin-and cocaine-positive urine tests, respectively, was observed ($p<.001$). Although LAAM is no longer considered a first line treatment for heroin addiction, these results demonstrate the feasibility of utilizing long-acting agonist therapies such as LAAM to treat opioid dependence among NEP attendees. Kuo, I., Brady, J., Butler, C., Schwartz, R., Brooner, R., Vlahov, D., and Strathdee, S. Feasibility of Referring Drug Users from a NEP into an Addiction Treatment Program: Experience with a Mobile Treatment Van and LAAM Maintenance. J Subst Abuse Treat, 24, pp. 67-74, 2003.

### Readiness for Cessation of Drug Use Among Recent Needle Exchange Program (NEP) Attenders vs Nonattenders

It has been shown that NEPs represent a bridge to drug abuse treatment, but that many NEP attenders have more severe drug problems and may be less ready to reduce their drug use than other drug users. In this study, researchers investigated the relationship between NEP attendance and readiness for cessation of drug use in a community-based sample of IDUs that have participated in semiannual interviews and HIV testing since 1988-1989. A total of 288 IDUs completed a questionnaire on readiness for cessation of drug use, which was assessed with a validated scale of problem drug use and intention to quit, based on the "stages of change" model. Thirty percent of respondents attended the NEP in the past month. Stage of change in readiness for cessation of drug use did not differ between NEP attenders and nonattenders. Similar proportions of persons recently attending and not attending the NEP were classified as ready to stop drug use (about 30%). In multivariate analysis,

readiness for cessation of drug use was associated with speedball injection and previous enrollment in drug treatment but not with NEP attendance. NEP attenders, although exhibiting characteristics consistent with more severe drug dependence, were as motivated for cessation of drug use as were nonattenders. These findings suggest that formal collaboration between NEPs and drug treatment programs could increase the proportion of IDUs in treatment. Henerdson, L., Vlahov, D., Celentano, D., and Strathdee, S. Readiness for Cessation of Drug Use Among Recent Attenders and Nonattenders of a Needle Exchange Program. J Acquir Immune Defic Syndr, 32(2), pp. 229-237, 2003.

### HIV Knowledge and Risk Behaviors Among Pakistani and Afghani Drug Users in Quetta

Researchers studied HIV knowledge and risk behaviors among Pakistani and Afghani drug users between July 2001 and November 2001. Of 959 drug users, all were male and the majority used heroin. Most were Pakistani (84.8%), 14.9% were Afghani, and 0.3% were Iranian. Relative to Pakistani drug users, a higher proportion of Afghanis reported no formal education, homelessness, and unemployment ($p<.001$). Afghanis were significantly more likely to have used an opiate as their first illicit drug, to have ever injected, to report needle sharing, or to report a drug user in their family. None of the sexually active Afghanis had ever used a condom compared with 5.0% of the Pakistanis. Only 4.3% of Afghans had ever heard of HIV/AIDS compared with 18.3% of Pakistanis ($p<.001$). Extremely low levels of HIV/AIDS awareness and high HIV risk behaviors were evident among drug users in Quetta, among whom Afghanis were especially vulnerable. Interventions to prevent transition to injection, drug treatment, and needle exchange are urgently required to prevent blood-borne infections. Zafar, T., Brahmbhatt, H., Imam, G., Hassan, S., and Strathdee, S. HIV Knowledge and Risk Behaviors Among Pakistani and Afghani Drug Users in Quetta, Pakistan. J Acquir Immune Defic Syndr, 32, pp. 394-398, 2003.

### Norms, Social Networks, and HIV Risks Among Urban Disadvantaged Drug Users

This study sought to examine the relationship between condom use, norms, and social network characteristics among a sample of economically impoverished individuals at risk for acquiring and transmitting HIV. Participants were 1051 individuals from a drug using community in the USA. Eighty percent were current drug users; 17% were HIV seropositive. Reported condom use was strongly associated with peer norms about condom use (friends talking about condoms, encouraging condom use, and using condoms). Women were less likely than men to report that their friends used condoms. Injection drug use was negatively associated with peer norms about condom use, while church attendance and network characteristics were positively associated with condom-promoting norms. Network research and methodologies are useful for identifying specific ties that promote condom use norms in a population. The findings of the study have implications for norm change interventions among disadvantaged communities at high risk for HIV/AIDS. Latkin, C., Forman, V., Knowlton, A., and Sherman, S. Norms, Social Networks, and HIV-Related Risk Behaviors Among Urban Disadvantaged Drug Users. Social Science and Medicine, 56, pp. 465-476, 2003.

### Psychological Distress and Progression to AIDS in a Cohort of IDUs

Researchers investigated whether psychological distress was independently associated with more rapid progression to AIDS among HIV-infected IDUs. They followed a cohort of IDUs in Baltimore from 1988 to 1999, of which a total of 451 IDUs met the eligibility criteria of being HIV+ but AIDS-free at baseline. Of the 451 participants, 76.3% were male and 95.8% were African American; the median age at enrollment was 34 years. The cumulative incidence of AIDS within 2 years of baseline was 7.1%. In multiple regression analysis, distress was associated with more rapid time to AIDS. The strongest association was observed among IDUs with the lowest CD4 counts ($<200 \times 106$ /L). Psychological distress was independently associated with shorter time to AIDS among HIV-infected IDUs, especially among those with the lowest CD4 cell counts, but was not predictive of mortality in this cohort. Further study of the effects of psychological distress on AIDS progression within this population is warranted. Golub, E., Astemborski, J., Hoover, D., Anthony, J., Vlahov, D., and Strathdee, S. Psychological Distress and Progression to AIDS in a Cohort of IDUs. J Acquir Immune Defic Syndr, 32, pp. 429-434, 2003.

### Overcoming Barriers to HIV Testing

Researchers sought to determine strategies to overcome barriers to HIV testing

among persons at risk. They developed a survey that elicited testing motivators, barriers, and preferences for new strategies among 460 participants at a needle exchange program, three venues for men who have sex with men, and a STD clinic. Barriers to testing included factors influenced by individual concern (fear and discrimination); by programs, policies, and laws (named reporting and inability to afford treatment); and by counseling and testing strategies (dislike of counseling, anxiety waiting for results, and venipuncture). The largest proportions of participants preferred rapid testing strategies, including clinic-based testing (27%) and home self-testing (20%); roughly equal proportions preferred oral fluid testing (18%), urine testing (17%), and standard blood testing (17%). One percent preferred home specimen collection. Participants who had never tested before were significantly more likely to prefer home self-testing compared with other strategies, and African Americans were significantly more likely to prefer urine testing. These findings suggest that strategies for improving acceptance of HIV counseling and testing include: information about access to anonymous testing and early treatment; expanding options for rapid testing, urine testing, and home self-testing; providing alternatives to venipuncture; making pretest counseling optional; and allowing telephone results disclosure may encourage more persons to learn their HIV status and take steps necessary to reduce their risk behaviors and prevent spread of the infection. Spielberg, F., Branson, B., Goldbaum, G., Lockhart, D., Kurth, A., Celum, C., Rossini, A., Critchlow, C., and Wood, R. Overcoming Barriers to HIV Testing: Preferences for New Strategies Among Clients of a Needle Exchange, a Sexually Transmitted Disease Clinic, and Sex Venues for MSM. J Acquir Immune Defic Syndr, 32(3), pp. 318-327, 2003.

### Case Reporting of Acute HBV and HCV Among IDUs

Researchers examined the relationship between hepatitis B (HBV) and hepatitis C (HCV) incidence and case reporting of HBV and HCV in Seattle IDUs to determine the extent to which public health surveillance systems may undercount or misrepresent cases of hepatitis in IDUs. They compared names of participants in a Seattle IDU cohort study who acquired HBV or HCV infection over a 12-month follow-up period to a database of persons with acute HBV and HCV reported to the health department surveillance unit over the same time period. Of 2,208 IDUs enrolled in the cohort study that completed a follow-up visit, 63/759 acquired HBV infection, 53/317 acquired HCV infection, and 3 acquired both HBV and HCV. Of 113 cohort participants who acquired HBV or HCV, only 2 (1.5%) cases were reported; both had acute HBV. The upper 95% confidence interval for case reporting of HCV in the cohort was 5.7%, and for HBV, it was 7.5%. In this study, very few IDUs who acquired HBV or HCV infection were reported to a public health hepatitis surveillance system, raising questions regarding the limitations of community surveillance data to characterize viral hepatitis epidemiology in that population group. Because the majority of study participants who acquired HBV or HCV infection were apparently asymptomatic, they would not have met CDC surveillance case definition. This suggests that alternate methods of hepatitis case finding in IDUs may be needed to monitor incidence in the community. These findings suggest that dependence of routine communicable disease surveillance systems on both access to clinical services and individual clinicians' reporting behavior may lead to under-reporting of IDUs among hepatitis cases, particularly in the case of HCV infection. To the degree that surveillance system data are used to estimate the relative burden of hepatitis diseases borne by drug injectors, there may be under allocation of prevention and care resources. Hagan, H., Snyder, N., Hough, E., Yu, T., McKiernan, S., Boase, J., and Duchin, J. Case Reporting of Acute Hepatitis B and C Among Injection Drug Users. J Urban Health, 79(4), pp. 579-585, 2002.

### Service Needs Among IDUs: Needle Exchange and Methadone Maintenance

In this study, researchers compared the prevalence of perceived and unmet needs of HIV-negative IDUs not receiving drug treatment (n=251) and those recruited from a methadone maintenance program (n=312) in 1998. Researchers studied self-reported needs for 6 community services (medical, mental health, housing, income assistance, alcohol treatment, and drug treatment). Respondents reported the highest levels of need for mental health and housing services. Ninety-four percent of out-of-treatment IDUs reported having at least one medical or psychosocial need compared to 62% of methadone clients ($p<.001$). Across all reported service needs, at least 69% of respondents in both cohorts reported their needs were unmet. While HIV-infected drug users receive assistance through the Ryan White CARE Act, these findings suggest that seronegative drug users may benefit from similar community services. Stein, M. and Friedmann, P. Need for Medical and Psychosocial Services Among IDUs: A Comparative Study of Needle Exchange and Methadone Maintenance. Amer J on

Addictions, 11, pp. 262-270, 2002.

### HIV+ Drug Users Unaware of Their Status: Who Gets Tested, Who Returns for Results

Researchers analyzed a subset of data collected from out-of-treatment HIV+ drug users (N=1,544) who participated in the NIDA-funded Cooperative Agreement for AIDS Community-Based Outreach/Intervention Research Study. They identified socio-demographic characteristics and drug use and sexual risk behaviors that differentiate HIV+ individuals who had obtained HIV testing in the past and those who had not and, among those who had been tested, what differentiates individuals who had returned to obtain their test results and those who had failed to return. In total, 33.4% of persons who tested HIV+ indicated that they had never been tested for HIV before. Persons who were HIV+ and more likely to have been tested in the past were: female, identified as gay or lesbian, had a history of arrests, were ever in drug treatment, had no IDU sex partner in the past month, and ever had a STD. Among HIV+ persons who reported prior HIV testing, 24.1% never returned for their test results. Persons who were HIV+ and more likely to return to obtain a past HIV test results were: not Hispanic, domiciled (not homeless), married, and recruited in a low HIV prevalence site. These findings suggest that out-of-treatment drug users who do not have contact with institutional systems (e.g., corrections) may need to be targeted for testing through hospital emergency rooms or outreach efforts. Efforts must also be made to shorten the interval between testing and providing test results so that transient individuals may obtain these results before moving on. Clearly, more needs to be done to improve interventions to encourage drug users to obtain HIV testing and counseling and to return for their test results. Strauss, S., Deren, S., Rindskoph, and Falkin, G. HIV-Positive Out-of-Treatment Drug Users Who Are Unaware of Their HIV Status: Predictors of Who Gets Tested and Who Returns for Test Results. J Drug Issues, pp. 1017-1032, Fall 2002.

### Anemia in HIV-Infected Drug Abusing Women

Risk factors for anemia and cumulative incidence of anemia were examined in a longitudinal cohort study of 622 injection drug users (IDUs) (8885 visits) in Baltimore, Maryland, from 1988 to 2000. At enrollment, 19.6% subjects were anemic (16.1% of men and 30.5% of women, P<0.0001) and 8.4% had microcytic anemia (6.7% of men and 14.0% of women, P=0.006). Cumulative incidence of anemia was 82.2% (87.9% of men and 100% of women, P<0.0001) during a median of 7.5 years follow-up. Factors associated with anemia included age (per 5 year increase, odds ratio (OR)=1.22; 95% confidence interval (CI): 1.10,1.36), female gender (OR=1.62; 95% CI: 1.16, 2.27), CD4+ lymphocyte count <200 cells/microl (OR 1.85; 95% CI: 1.52, 2.24), weight loss (OR 1.55; 95% CI: 1.26, 1.91), oral thrush (OR 1.53; 95% CI: 1.21, 1.94), Mycobacterium avium complex infection (OR 1.30; 95% CI: 1.04, 1.64), and zidovudine use (OR 1.24; 95% CI: 1.04, 1.48). Higher body mass index (OR 0.92; 95% CI: 0.88, 0.95) and marijuana use (OR 0.75; 95% CI: 0.61, 0.92) were associated with a lower risk of anemia. The cumulative incidence of anemia is high among IDUs, and women are at highest risk of anemia, Semba, R.D., Shah, N., and Vlahov, D., Risk Factors and Cumulative Incidence of Anemia Among HIV-infected Injection Drug Users, Int. J. STD AIDS, 13(2), pp. 119-123, 2002.

### Contextual Factors and Other Correlates of Sexual Risk of HIV Among African American Crack-Abusing Women

This study examined differences in contextual factors, substance use, sexual risk behaviors, and comorbid histories between African American, out of treatment crack abusing women who had either a single sexual partner or multiple partners. Bivariate analysis indicated that women with multiple partners were more likely than women with a single partner to be homeless, financially dependent, and to have histories of sexual, physical, and emotional abuse. Women with multiple partners reported higher levels of depression, anxiety and more symptoms of posttraumatic stress disorder. In multiple logistic regression analysis, being unemployed, difficult childhood, and number of days of crack use in the previous 30 days, longer crack runs, and more frequent unprotected fellatio were associated with increased odds of having multiple sexual partners. Being married or living as married was associated with decreased odds of having multiple sexual partners. The importance of assessing contextual and historical factors and implications for future research is discussed. Roberts, A.C., Wechsberg, W.M., Zule, W. and Burroughs, A.R. Contextual Factors and Other Correlates of Sexual Risk of HIV Among African American Crack-Abusing Women. Addictive Behaviors, 28, pp. 523-536, 2003.

### Women, AIDS, and Protective Factors

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, 683 out-of-treatment, African American crack-using women (of whom 219 were categorized as homeless) were interviewed and serologically tested. Risk factors that were examined include adverse childhood experiences, psychological distress, physical health, violence and victimization, drug use, and risky sex behaviors. Protective factors that were examined include 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. Logistic regression analysis found that 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 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. 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.M., Lam, W.K., Zule, W., Hall, G., Middlesteadt, R., and Edwards, J. Violence, Homelessness, and HIV Risk Among Crack-Using African American Women. Substance Use and Misuse, 38(3-6), pp. 671-701, 2003.

### Effectiveness of Risk Reduction Interventions in Drug-Abusing Women

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. Effectiveness of a Risk Reduction Intervention Among African American Women Who Use Crack Cocaine. AIDS Education and Prevention, 15(1), pp. 15-32. May 2003.

### High Risk Sexual Behaviors among Heroin Sniffers Who Have No History of Injection Drug Use: Implications for HIV Risk Reduction

The purpose of this paper was to assess sexual behaviors which place heroin sniffers (HSs) at high risk for HIV infection. A stratified network-based sample was used to recruit HSs who had no history of injection drug use from the streets of South Florida, USA. HSs displayed a high HIV seroprevalence rate of 12.1%; women (18.1%) were more likely than men (8.7%) to test positive for HIV. Both men and women HSs engaged in considerable high-risk sex behavior, including high-risk sex for money or drugs exchange behavior. The use of crack cocaine was associated with increased sex for money or drugs exchange behavior among women. The need for intervention programs targeted toward HSs is discussed. Sanchez, J., Comerford, M., Chitwood, D.D., Fernandez, M.I. and McCoy, C.B. AIDS Care, 14(3), pp. 391-398, June 2002.

### Behavioral Problems in HIV-Infected Children

In an effort to increase understanding of previously-reported behavioral problems among HIV-infected children, investigators have analyzed data from the Women and Infants Transmission Study (WITS), a large multi-site, longitudinal study of maternal-infant HIV infection and the health and developmental outcomes of the children. The analyses examined influences of HIV infection, drug exposure, and family characteristics on behavioral outcomes of 307 children born to HIV-positive mothers (96 HIV-infected and 211 seroreverters). The age range of behavioral outcome assessment was 3 to 8 years. Analyses indicated a high prevalence of behavioral problems in this sample, but the multivariate analyses did not find an association between either HIV status or prenatal drug exposure and poor behavioral outcomes. The strongest associations with increased behavioral problems involved demographic characteristics. Mellins, C.A., Smith, R. and O'Driscoll, P., et al. High Rates of Behavioral Problems in Perinatally HIV-Infected Children Are Not Linked to HIV Disease. Pediatrics, 111, pp. 384-393, 2003.

### Factors Affecting Cognitive Functioning in a Sample of Human Immunodeficiency Virus-Positive Injection Drug Users

Dr. Margolin and colleagues at Yale University examined the specific contribution of the multiple factors contributing to cognitive functioning among injection drug users that may affect engagement in, and response to, addiction and HIV-related interventions. The current study examined the independent contributions to neuropsychological test performance of premorbid educational attainment, medical and psychiatric history, long- and short-term drug use, in a sample of 90 HIV-positive injection drug users dually addicted to heroin and cocaine. Assessments were by laboratory, observation, and self-report measures, and plasma HIV-1 RNA viral load and CD4+ count. Fully 88% of the sample showed evidence of impairment on the test battery selected to assess processes associated with successful engagement in the treatment of substance abuse and HIV, such as learning and memory of verbal information, capacity to solve new problems and deal with more than one stimulus at a time, visual-motor coordination, and visual tracking and cognitive flexibility. In addition to drug use, independent predictors of test performance were HIV viral load, educational attainment, and premorbid medical and psychiatric problems. Findings underscore the multiplicity of factors that contribute to cognitive impairment in HIV-positive drug -abusing individuals in addition to drug use. Margolin, A., Avants, S.K., Warburton, L.A., and Hawkins, K.A. AIDS Patient Care STDS, 16(6), pp. 255-267, 2002.

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

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

### Family-Based Treatment For Drug Abuse

Dr. Howard Liddle and colleagues at the University of Miami's Center for Treatment Research on Adolescent Drug Abuse (CTRADA) conducted a comprehensive review of the status of family-based treatment for drug abuse in 1995 and concluded that this modality offered a "promising, but not definitive" approach to treating drug abuse among adolescents and adults. Less than a decade later, significant progress can be seen in the treatment of drug abuse problems using family-based approaches, particularly with adolescents. Family-based treatments are currently recognized as among the most effective approaches for adolescent drug abuse. Family-based treatment of adult drug abuse problems has also advanced in important ways with the recent systematic application and testing of engagement techniques and behavioral couples therapy approaches. The current review characterizes and discusses the developmental status of this subspecialty and outlines areas in which continued research attention is needed. Rowe, C.L. and Liddle, H.A. Journal of Marital and Family Therapy, 29(1), pp. 97-120, January 2003.

### Consequences and Costs of Closing a Publicly Funded Methadone Maintenance Clinic

Dr. Pierre Alexandre and colleagues examined the economic consequences and related costs of closing the Central Methadone Clinic (CMT), a long-established substance abuse treatment program in Miami, Florida, on May 31, 1997. Economic consequences were determined through comparative analysis of patient status at baseline and one year following treatment cessation for Miami clients, relative to a comparison group in Jacksonville, Florida that had continued access to a publicly funded methadone treatment clinic. Outcome measures included health-care utilization, addiction treatment, employment income, and crime. Bivariate and multivariate analyses were conducted to estimate differences in consequences and related costs. Total cost as well as the cost for each category (except for addiction treatment) was statistically similar for both groups. The researchers concluded that clients at the CMT did not generate significant economic consequences/costs for taxpayers or society in general during the year following closure relative to clients at a comparison clinic. Alexandre, P.K., Salome, H.J., French, M.T., Rivers, J.E. and McCoy, C.B. Social Science Quarterly, 83(2), pp. 519-536, June 2002.

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

Dr. Lisa Metsch and colleagues examined both met and unmet need for dental services among chronic drug users in Miami, Florida, and compared 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 users 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.C., Chitwood, D.D. and McCoy, C.B. Journal of Behavioral Health Services Research, 29(2), pp. 176-88, May 2002.

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### Mass Vaccination for Smallpox More Effective Than Alternatives

With support from NIDA, and in response to requests for assistance from the National Academy of Sciences (NAS) and Fogarty International Center, AIDS modelers embedded a traced vaccination approach in a smallpox disease transmission model to estimate the number of cases and deaths that would result from an attack in a large urban area. They demonstrated that mass vaccination results in both far fewer deaths and much faster epidemic eradication over a wide range of disease and intervention policy parameters, including those believed most likely, and that mass vaccination similarly outperforms starting with traced vaccination and switching to mass vaccination only if required. Kaplan, E., Craft, D., and Wein, L. Emergency Response to a Smallpox Attack: The Case for Mass Vaccination. Proceedings of the National Academy of Sciences, 99, pp. 10395-10440, 2003.

### Emergency Response to an Anthrax Attack

NIDA researchers developed a mathematical model that included atmospheric dispersion, age-dependent dose response, disease progression, and queuing systems for antibiotic distribution and hospital care to compare various emergency responses in the event of an airborne anthrax attack. They demonstrated the need for extremely aggressive and timely use of oral antibiotics by all asymptomatics in the exposure region, for the creation of surge capacity for supportive hospital care, and for the use of federal and military resources and nationwide network of medical volunteers. Wein, L.M., Craft, D.L., and Kaplan, E.H. Emergency Response to an Anthrax Attack. Proceedings of the National Academy of Sciences, 100(7), pp. 4346-4351, 2003.

### Drugs and Firearms Deaths in New York City

Firearm deaths remain among the leading causes of mortality in the United States. Changing law enforcement activities, incarceration, drug use, and socioeconomic conditions may have played roles in the declining rates of firearm deaths during the 1990s. Using records from the Office of the Chief Medical Examiner, we analyzed the role of drugs in firearm deaths in New York City between 1990 and 1998. Positive drug toxicology was present in over half of all firearm death victims during this time. Cocaine, cannabis, opiates, and alcohol accounted for almost all of these deaths with drug-positive toxicology. There were decreases in cocaine-and alcohol-positive toxicology for firearm deaths in New York City starting in the early 1990s; there was a more gradual decrease in heroin-positive toxicology for firearm deaths. Cannabis-positive toxicology for firearm deaths increased in the early part of the 1990s and then decreased starting in the mid-1990s. Although the disparities between minority and white firearm death rates narrowed during this time, minorities remained about three times more likely to be victims of fatal firearm violence than whites in 1998. The highest firearm death rates were among African American and Latino male decedents, with a larger proportion of Latinos testing cocaine or opiate positive, while a larger proportion of African Americans tested cannabis positive. These results suggest a complex role of drugs in firearm-related deaths, Galea, S., Ahern, J., Tardiff, K., Leon, A.C., and Vlahov, D. Drugs and Firearm Deaths in New York City, 1990-1998. J Urban Health, 79(1), pp. 70-86, March 2002.

### Maternal Smoking During Pregnancy

University of Chicago researchers have reported on fluctuations in women's cigarette smoking during pregnancy, with special attention to implications for the design of clinical interventions and for research on the effects of fetal exposure to cigarettes. Data were analyzed from two independent projects, the National Health Interview Survey 1991 Pregnancy and Smoking Supplement (N=1426), and the Family Health and Development Project, the latter a small (N=60), prospective, clinic-based study. A substantial portion of the women in the large study showed a pattern of repeated cessation and relapse. In the smaller sample, fluctuations in smoking intensity were also substantial. While 48% quit or reduced smoking when they learned of their pregnancy, more than half changed smoking intensity multiple times. The investigators conclude that simple measures of smoking during pregnancy may lead to underestimation of possible fetal impact, and that brief smoking cessations early in pregnancy are likely to be inadequate for many women. Pickett, K.E., Wakschlag, L.S., Dai, L., and Leventhal, B.L. Fluctuations of Maternal Smoking During Pregnancy. Obstetrics and Gynecology, 101, pp. 140-147, 2003.

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

## Research Findings - Epidemiology and Etiology Research

### Community Epidemiology Work Group

The 53rd meeting of the Community Epidemiology Work Group (CEWG), chaired by Nicholas Kozel, DESPR, was held in Miami, Florida on December 10-13, 2002. 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.

**Cocaine/Crack** continues to be the predominant illicit drug in most CEWG areas, despite declining indicators in recent years. There were reports in seven areas that powder cocaine was more available and cheaper in street markets than in past years.

**Heroin** abuse indicators increased among young White and suburban populations in several CEWG areas. White powdered heroin from South America is the predominant type available in areas east of the Mississippi River, while black tar is the predominant type in areas on the west side.

**Other Opiate** abuse indicators continue to trend upward, with increased use of controlled substances reported in almost all CEWG areas. Oxycodone, hydrocodone, and methadone abuse indicators increased in most CEWG areas. Research efforts are underway in some areas to assess the extent to which these drugs are diverted to illicit markets and are being abused.

**Methamphetamine** abuse indicators remained high in Hawaii, all west coast CEWG areas, and Phoenix. Abuse of the drug has continued to spread to Denver, Detroit, and Minneapolis/St. Paul, and there is increased evidence that it is spreading to populations in east coast areas (e.g., Atlanta, Miami, New York City, and Washington DC).

**Marijuana** abuse indicators continued to increase in 10 CEWG areas. In 2001, high proportions of clients entering treatment programs in Minneapolis/St. Paul (49.2 percent), Colorado (40.6), New Orleans (37.5), Seattle (34.4), St. Louis (33.3), Hawaii (28.6), Texas (26.0), Illinois (25.9), San Diego (25.9), and New York (25.2) were primary marijuana abusers.

**MDMA (methylenedioxymethamphetamine)** abuse continues to spread to different populations, and is being sold around schools and street corners in urban, suburban, and rural communities. Increasingly, pills and capsules marketed as "ecstasy" contain other drugs (e.g., amphetamines, methamphetamine, phencyclidine [PCP], ketamine) with or without MDMA.

**Benzodiazepine** abuse indicators have been increasing in most CEWG areas. Alprazolam (Xanax) is reportedly widely used by cocaine/crack, heroin, and polydrug-abusing populations.

### Illicit Drug Escalation Associated with Early-Onset Cannabis Use in a Twin Sample

This study examined whether the association between early cannabis use and

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subsequent progression to use of other drugs and drug abuse/dependence persists after controlling for genetic, shared environmental influences, and other risk factors. Data come from a cross-sectional survey (conducted between 1996 and 2000) among an Australian national volunteer sample of 311 young adult monozygotic and dizygotic same-sex twin pairs discordant for early cannabis use (i.e., before age 17). Findings indicate early cannabis use is associated with increased risk of other drug use, alcohol dependence, and drug abuse/dependence. Controlling for known risk factors (early-onset alcohol or tobacco use, parental conflict/separation, childhood sexual abuse, conduct disorder, major depression, and social anxiety) had only negligible effects on these results. The authors interpret these results as being consistent with the "gateway theory" of drug use. The major strength of this study is the twin design, which assumes that twins share the same environment and family experiences, and that monozygotic pairs share the same genetic risk. Limitations include the cross-sectional design and unmeasured but potentially important environmental effects that are unique (i.e., nonshared) to marijuana using twins such as peer and social contexts in which cannabis is used. Lynskey, M.T., Heath, A.C., Bucholz, K.K., Slutske, W.S., Madden, P.A. F., Nelson, E.C., Statham, D.J., and Martin, N.G. Journal of the American Medical Association, 289, pp. 427-433, 2003.

### Racial/Ethnic and Gender Differences in the Incidence and Onset Age of DSM-IV Alcohol Use Disorder Symptoms among Adolescents

Several investigators have questioned the validity of the DSM-IV Alcohol Use Disorders criteria for diagnosing alcohol use problems among teenagers, with specific concerns about their utility across different subgroups. In the current study, authors examined whether particular racial/ethnic or gender subgroups varied in the incidence and onset age of Alcohol Use Disorder symptoms. Members of a sample composed of 1,045 community-dwelling "drinkers" (59.4% male; 13.8% black, 21.2% foreign-born Hispanic, 30.7% U.S.-born Hispanic and 33.6% non-Hispanic white) were interviewed retrospectively using the Composite International Diagnostic Interview. The first occurrence of each DSM-IV symptom in a participant was examined by race/ethnicity and gender. Discrete-time event history analysis compared onset patterns from ages 14 through 20 years. The cumulative incidence of Alcohol Abuse and Alcohol Dependence diagnoses, as well as one alcohol abuse symptom and four dependence symptoms, varied by race/ethnicity. The incidence of both diagnoses, as well as two alcohol abuse symptoms, varied by gender. Event history analysis revealed no significant subgroup variation in first onset patterns for only three of the eleven symptoms. Racial/ethnic variation, but not gender variation, was significant for three symptoms, and both racial/ethnic variation and gender variation was significant for the remaining five symptoms. Study authors' findings indicate that most of the DSM-IV Alcohol Use Disorder symptoms, when applied to adolescents, demonstrate significant subgroup variation in incidence and onset age patterns. These results speak to the urgent need for additional research concerning the nosology and diagnosis of alcohol use problems among younger drinkers, especially among specific racial/ethnic and gender subgroups. Wagner, E.F., Lloyd, D.A., and Gil, A.G. Journal of Studies on Alcohol, 63, pp. 609-619, 2002.

### Genetic and Environmental Risk Factors for Drug Problems in Adoptees

Applying survival analysis methodology to age-of-onset data from an adoption study (N=196), authors present evidence that risks for both drug use and drug problems (DSM abuse or dependence) are elevated when combined antisocial personality (ASP) and substance abuse is present in the same biological parent. It is increased not only in comparison to adoptees with no known biological risk, but also when compared to adoptees with a biological background for only substance problems or only ASP. Neither of these later groups showed a statistically higher risk when compared with controls. Among adoptees with recurrent drug use, adolescent aggressivity is also elevated when the combined substance abuse/ASP biological diathesis is present. Statistical control for aggressivity diminished but did not eliminate the predictive significance of the combined biological diathesis for drug problems. The authors also verify, using more refined methodology, our previous reports of gender and adverse adoptive environmental influences on drug-related outcomes in these subjects. A biology-environment interaction could not be documented since power to do so was rather low. The authors argue that the observed biological associations are broadly consistent with generalization to other substances of an alcoholism phenotype similar to Cloninger's Type II or Babor's Type B. Langbehn, D.R., Cadoret, R.J., Caspers, K., Troughton, E.P., and Yucuis, R. Genetic and Environmental Risk Factors for the Onset of Drug Use and Problems in Adoptees. Drug and Alcohol Dependence, 69(2), pp. 151-67, 2003.

### Serotonergic Gene Variant and Family History of Antisocial Personality and Alcoholism Associated with Risk of Externalizing Problems

This genetic association study examined the relation between polymorphisms of the serotonin-transporter-linked promoter region (5HTTLPR) and externalizing behaviors (aggression, conduct disorder, and attention deficit disorder) in a sample of 87 adoptees at risk for externalizing and substance abuse by virtue of parental family history of antisociality and/or alcoholism. Results failed to show main effects between 5HTTLPR status and externalizing problems, but indicated several interactions between 5HTTLPR status and family history. The LL variant of 5HTTLPR was associated with an increased risk of externalizing in offspring of antisocial parents, whereas the SS or SL variants were associated with increased risk of externalizing in offspring of alcoholics. The gender of the adoptee also interacted with 5HTTLPR status, as an increased risk of externalizing was observed in males with LL and in females with SS or SL. Results indicated an interaction between this serotonergic gene and other forms of genetic diathesis (antisocial personality and alcoholism), thereby suggesting that epistasis (gene-by-gene interactions) may be involved in the etiology of externalizing problems. Cadoret., R., Langbehn, D., Caspers, K., Troughton, E.P., Yucuis, R., Sandhu, H.K., and Philibert, R. Associations of the Serotonin Transporter Promoter Polymorphism with Aggressivity, Attention Deficit, and Conduct Disorder in an Adoptee Population. Comprehensive Psychiatry, 44(2), pp. 88-101, 2003.

### Adolescent Drug Use, Abuse, and Dependence: Epidemiology and Heterogeneity of Symptom Expression by Drug Type and Gender

This study evaluates symptom profiles based on DSM-IV abuse and dependence criteria for tobacco, alcohol and marijuana, including a gender comparison. Participants are 3,072 adolescents (12-18 years) drawn from three community-based family samples in Colorado. Age trends suggest that substance use is a developmental phenomenon, which increases almost linearly from early to late adolescence. Substance use disorders are less common than experimentation in adolescence, but approximately 1 in 4 adolescents in the oldest cohorts meets criteria for abuse for at least one substance, and 1 in 5 meets criteria for substance dependence. By age 18, nearly one in three adolescents report daily smoking and 8.6% meet criteria for tobacco dependence. Although alcohol is the most commonly abused substance (10%), a slightly larger proportion of adolescents meet criteria for dependence on marijuana (4.3%) than alcohol (3.5%). Males more frequently meet criteria for dependence on alcohol and marijuana in late adolescence, while females are more often nicotine dependent. A comparison of abuse and dependence symptom profiles shows variability across substances, and suggests that manifestations of a subset of symptoms are gender specific. Young, S.E., Corley, R.P., Stallings, M.C., Rhee, S.H., Crowley, T.J. and Hewitt, J.K. Substance Use, Abuse, and Dependence in Adolescence: Prevalence, Symptom Profiles and Correlates. Drug and Alcohol Dependence, 68(3), pp. 309-322, 2002.

### Psychiatric and Substance Use Disorders in South Florida: Racial/Ethnic and Gender Contrasts in a Young Adult Cohort

Prevalence rates of psychiatric and substance use disorders among young adults in South Florida are presented. Unique aspects of the study include the large sample size, its ethnic diversity, and the fact that a substantial proportion of Hispanic participants were foreign born. This study builds on a previous cohort study of students who entered middle school in 1990. A random subsample of this representative cohort (N = 1803) was interviewed between 1998 and 2000 when most were between 19 and 21 years of age. Disorders were assessed through computer-assisted personal interviews utilizing the DSM-IV version of the Michigan Composite International Diagnostic Interview. More than 60% of the sample met lifetime criteria for 1 or more study disorders, and 38% did so within the preceding year. Childhood conduct and major depressive and alcohol abuse disorders were the most prevalent. Although rates of affective and anxiety disorders in females were double that in males, this gender difference disappeared when attention-deficit/hyperactivity disorder, conduct disorders, and antisocial personality disorders were also considered (46.6% vs. 45.7% for females vs. males, respectively). Substantially lower rates were observed among African Americans for depressive disorders and substance abuse and dependence. Among Hispanics, rates tend to be lower among the foreign-born in comparison with their US-born counterparts, particularly for the substance disorders. The documented presence of psychiatric and substance disorders in middle and high school populations emphasizes the importance of prevention efforts in school settings. Research on the origins of ethnic and nativity

differences is called for. Turner, R.J., and Gil, A.G., Archives of General Psychiatry, 59, pp. 43-50, 2002.

### Drug Use and the Risk of Major Depressive Disorder, Alcohol Dependence, and Substance Use Disorders

The Children in the Community Study is a prospective longitudinal study investigating the association between early drug use (childhood, adolescence, and early 20's) and later psychiatric disorders (in the late twenties). Utilizing data from a community-based sample of 736 adults (50% female) from upstate New York, the subjects were interviewed at mean ages of 14 years, 16 years, 22 years, and 27 years. Psychiatric disorders, measured by age-appropriate versions of the University of Michigan Composite International Diagnostic Interview (UM-CIDI), and participant drug use were assessed. Adolescent and young adult tobacco use was significantly associated with an increased risk of alcohol dependence and substance use disorders (SUDs) at mean age 27, but not with new episodes of major depressive disorder (MDD). Earlier alcohol use significantly predicted later MDD, alcohol dependence and SUDs in the late twenties, as did early marijuana use and other illicit drug use. Except for the effect of tobacco use on MDD, early drug use was significantly related to later psychiatric disorders, even after statistically controlling for age, gender, parental education, family income, and prior episodes of MDD and SUDs. Results suggest that early drug use is associated with and predicts later psychiatric disorders. Preventive implications stem from the importance of studying a range of psychiatric disorders in the context of substance use assessed over a wide age range. Brook, D.W., Brook, J.S., Zhang, C., Cohen, P. and Whiteman, M. Drug Use and the Risk of Major Depressive Disorder, Alcohol Dependence, and Substance Use Disorders. Archives of General Psychiatry, 59, pp. 1039-1044, 2002.

### Zygosity Diagnosis in the Absence of Genotypic Data: An Approach Using Latent Class Analysis

This study applies a latent class analyses for zygosity diagnosis in the absence of genotypic data using secondary data from a young adult Australian twin cohort (N = 2094 complete pairs and 519 singleton twins from same-sex pairs with complete responses to all zygosity items). The application of latent class analysis (LCA), fitting a 2-class model, yields results showing good concordance with traditional methods of zygosity diagnosis, but with certain important advantages. These include the ability, in many cases, to assign zygosity with specified probability on the basis of responses of a single informant, and the ability to quantify the probability of misassignment of zygosity, allowing prioritization of cases for genotyping as well as identification of cases of probable laboratory error. Out of 242 twins (from 121 like-sex pairs) where genotypic data were available for zygosity confirmation, only a single case was identified of incorrect zygosity assignment by the latent class algorithm. Zygosity assignment for that single case was identified by the LCA as uncertain (probability of being a monozygotic twin only 76%), and the co-twin's responses clearly identified the pair as dizygotic (probability of being dizygotic 100%). Findings highlight the application of LCA for zygosity assignment or confirmation in the absence of genotypic data, or as a safeguard against sample duplication. Heath, A.C., Nyholt, D.R., Neuman, R., Madden, P.A., Bucholz, K.K., Todd, R.D., Nelson, E.C., Montgomery, G.W., and Martin. N.G. Zygosity Diagnosis In The Absence of Genotypic Data: An Approach Using Latent Class Analysis. Twin Research, 6(1), pp. 22-26, 2003.

### Meta-analysis Finds Childhood Stimulant Therapy Associated with Reduced Risk for Later Drug Use Disorders

This study used meta-analytic techniques to address the question as to the long-term impact of childhood stimulant therapy for attention deficit hyperactivity disorder on the risk for developing subsequent substance use disorders (SUD). Five studies were identified with long-term outcomes of medicated and unmedicated subjects. Overall results found a reduction in risk for SUD in individuals treated with stimulants; a greater protective effect was found in studies that followed subjects into adolescence than into adulthood. The authors note several possible confounding factors that may temper these findings, in particular the naturalistic (non-randomized) nature of the treatment samples; there may be significant differences between treated and untreated subjects on important variables such as family history of SUD, severity of illness, and comorbidity. Thus, while this study may provide some reassurance, further study of this important public health question is needed. Wilens, T.E., Faraone, S.V., Biederman, J. and Gunawardene, S. Does Stimulant Therapy of Attention-Deficit/Hyperactivity Disorder Beget Later Substance Abuse? A Meta-Analytic Review of the Literature. Pediatrics, 111(1), pp. 179-185, 2003.

### Comorbid Depression and Conduct Disorder Associated with Increased Risk for SUD

Using data from a sample of 17 year old twins, subjects with a history of major depressive disorder and/or conduct disorder or neither were selected and school success and substance dependence examined. The combination of disorders was found to be particularly associated with school behavior problems, nicotine and drug dependence for both males and females. These findings, which are similar to those reported by other groups, point to a need to assess youth for both internalizing and externalizing disorders and awareness of the increased risk associated with their co-occurrence. Marmorstein, N.R. and Iacono, W.G. Major Depression and Conduct Disorder in a Twin Sample: Gender, Functioning, and Risk for Future Psychopathology. Journal of the American Academy of Child and Adolescent Psychiatry, 42(2), pp. 225-233, 2003.

### Personal Competence Skills, Distress, and Well-Being as Determinants of Substance Use in a Predominantly Minority Urban Adolescent Sample

Several previous studies have investigated the relationship between psychological distress and substance use among youth. However, less research has investigated the potentially protective role of psychological well-being on adolescent substance use, and the extent to which personal competence skills may promote well-being. The present study examined personal competence skills, psychological distress and well-being, and adolescent substance use over a three-year period in a predominantly minority sample of urban students (N = 1,184) attending 13 junior high schools in New York City. Structural equation modeling indicated that greater competence skills predicted less distress and greater well-being over time. While psychological well-being was associated with less subsequent substance use, distress did not predict later substance use. Findings indicate that competence skills promote resilience against early stage substance use in part by enhancing psychological well-being, and suggest that school-based prevention programs should include competence enhancement components in order to promote resilience. Griffin, K.W., Botvin, G.J., Scheier, L M., Epstein, J.A., and Diaz, T. Prevention Science, 3, pp. 23-33, 2002.

### Positive Impact of Competence Skills and Psychological Wellness in Protecting Inner-city Adolescents from Alcohol Use

Research has shown that competence enhancement prevention programs for substance use are effective in reducing alcohol use and other problem behaviors. However, less is known about the mechanisms by which high competence helps youth avoid negative outcomes. This study explored whether greater competence is associated with increased levels of psychological wellness that in turn deters subsequent alcohol use. Specifically, 1,459 students attending 22 middle and junior high schools in New York City completed surveys that included measures of competence (decision making, self-efficacy), psychological wellness, and alcohol use. Students completed surveys at baseline, 1-year follow-up, and 2-year follow-up. Data collectors administered the questionnaire following a standardized protocol during a regular 40-min class period. On the basis of a longitudinal structural equation model, adolescents who were highly competent reported greater psychological wellness, which was then associated with less drinking. These findings highlight the potential of alcohol prevention programs designed to enhance competence and psychological wellness. Epstein, J.A., Griffin, K.W. and Botvin, G.J. Positive Impact of Competence Skills and Psychological Wellness in Protecting Inner-city Adolescents from Alcohol Use. Prevention Science, 3, pp. 95-104, 2002.

### Earlier Marijuana Use and Later Problem Behavior in Colombian Youth

The study examined the relationship between earlier adolescent marijuana use and later adolescent behavioral problems. A community-based sample of Colombian adolescents was interviewed in 1995-1996 and 1997-1998. The time 2 (T2) sample consisted of 1151 males and 1075 females. The psychosocial measures assessed adolescent problem behavior, the peer and sibling social network, and ecological/ environmental stress and cultural domains. Logistic regression analyses included controls on demographic and time 1 (T1) dependent measures. The findings suggest that T1 adolescent marijuana use was associated with increased risks for T2 adolescent difficulty at work or school, violent experiences, peer marijuana use, and sibling marijuana problems. This study provides important evidence in this cohort of the specific relationship between T1 adolescent marijuana use and (T2) adolescent problem behavior in a society in which drug use, crime, violence, and low educational attainment are pervasive. Similar findings have been shown in previous research with U.S. adolescents. The findings suggest that early adolescent marijuana use is

associated with an increase in problem behavior during later adolescence. Brook, J.S., Brook, D.W., Rosen, Z. and Rabbitt, C.R. Earlier Marijuana Use and Later Problem Behavior in Colombian Youth. Journal of the American Academy of Child and Adolescent Psychiatry, 42 (4), pp. 1-8, 2003.

### Marijuana Use Among the Adolescent Children of High-Risk Drug-Abusing Fathers

This study examines marijuana use among children of male drug abusers. Subjects were 83 African-American and European-American male drug abusers (the majority of whom were injection drug users) and their children. Thirty-one of the fathers were HIV-positive and 52 were HIV-negative. Using logistic regression analyses, the authors explored cross-sectionally the relationship between four psychosocial domains (i.e., paternal attributes, adolescent problem behaviors, father-adolescent relations, and the environment) and adolescent marijuana use. The father's use of illegal drugs and his failure to cope adaptively predicted adolescent marijuana use, while a close father-child bond predicted less adolescent marijuana use. Adolescent problem behaviors predicted an increased likelihood of marijuana use. Furthermore, hierarchical regression analysis demonstrated that the adolescent's problem behavior mediated the associations between the father-adolescent relationship as well as environmental factors with adolescent marijuana use. Reducing the risk factors and enhancing the protective factors within each of the domains could help reduce marijuana use among the adolescent children of drug-abusing fathers. Moreover, if a father is a drug abuser, it is important to help him establish a close bond with his child in order to help attenuate the influence of his drug use on the child's marijuana use. Brook, D.W., Brook, J.S., Richter, L., Whiteman, M. and Arencibia-Mireles, O. Marijuana Use Among the Adolescent Children of High-Risk Drug-Abusing Fathers. The American Journal on Addictions, 11, pp. 95-110, 2002.

### Tobacco Use as a Predictor of Illicit Drug Use and Drug-Related Problems in Colombian Youth

To examine the extent to which personality and peer factors mediate the relationship between early cigarette use and later illicit drug use, as well as associated drug use problems, in a population of Colombian adolescents. A longitudinal study (2-year interval), using face-to-face structured interviews was begun in 1996 using a community-based sample, randomly selected from census data in three cities in Colombia, South America. The participants were 2,837 adolescents with a mean age of 15.0 (SD +/- 1.6) years at time 1 (T1). Males comprised 52% of the sample and 65% resided with two parents. Approximately 78% (N = 2,226) completed the second structured interview 2 years later (T2). The main outcome measures were marijuana use, other illicit drug use, and associated drug use problems at T2. Three series of logistic regressions were conducted. The odds of marijuana use (adjusted odds ratio [AOR] = 1.64-2.01; confidence interval [CI]: 1.11-2.94), other illicit drug use (AOR = 1.77-2.49; CI: 1.03-4.19), and associated drug use problems (AOR = 2.25-3.47; CI: 1.45-5.26) at T2, was increased two- to three-fold among adolescents reporting cigarette use at T1, with control on the demographic, personality, and peer factors, as well as T1 drug use variables. Earlier adolescent cigarette smoking was directly associated with later marijuana use, other illicit drug use, and problems with drug use. Siqueira, L.M. and Brook, J.S. Tobacco Use as a Predictor of Illicit Drug Use and Drug-related Problems in Colombian Youth. Journal of Adolescent Health, 32, pp. 50-57, 2003.

### Early and Mid-adolescence Risk Factors for Later Substance Abuse by African Americans and European Americans

This study examined the relationship between risk factors experienced during adolescence by African Americans and European Americans and DSM-IV alcohol dependence and marijuana abuse or dependence in early adulthood. The authors followed a cohort of adolescents from 1990-91 (grades 6 and 7) to 1998-2000 (ages 19-21), evaluating risk factors during early adolescence as predictors of DSM-IV alcohol dependence and marijuana abuse and dependence. African Americans had higher exposure to school, family structure, delinquency, and psychosocial factors. School factors and drug-use modeling of peers and family were the most important risk factors for marijuana abuse or dependence for both European and African Americans. Personal, familial, and social context factors during early adolescence affect adult drug-use problems, particularly for African Americans. Levels of drug use are lower among African Americans, but exposure to risks is higher and there are clear differences in the long-range impact of risk factors. These findings highlight the importance of developing and timing appropriate prevention efforts. Gil, A., Vega, W., and Turner, R.J. Public Health Reports, 117, Supplement 1:S15-S29, 2002.

### Risk and Protective Factors of Adolescent Drug Use: Implications for Prevention Programs

The first purpose of this chapter is to identify the risk and protective factors related to adolescent drug use. The framework is derived from the family interactional theory. Operating within a developmental framework, the authors explore the interrelations of risk factors related to drug use. In addition, they elucidate the protective factors that mitigate adolescents' vulnerability to drug use. A second goal of the chapter was to elucidate the implications of etiological research for prevention, treatment, public policy, and research. In so doing, authors build heavily on a number of the major studies that have been conducted in the last decade. Finally, they present several prevention programs that have successfully incorporated the findings of etiological research into their prevention programs. Brook, J.S., Richter, L.and Whiteman, M. In Z. Sloboda and W.J. Bukoski (eds.), Handbook of Drug Abuse Prevention: Theory, Science and Practice, pp. 265-287, New York: Plenum, 2003.

### Coping in Adolescent Children of HIV-Positive and HIV-Negative Substance Abusing Fathers

This study examines the coping techniques of adolescents whose fathers are at risk for contacting the HIV virus or have the HIV virus. Adolescent coping is an important aspect of the adolescent's vulnerability or resilience to drug use and abuse and associated problems. The data for this study was taken from an epidemiological study of fathers who are substance abusers and their adolescent offspring. Adolescents were asked questions regarding their ability to cope with the knowledge that their fathers have AIDS or may contract it. Adolescent adaptive coping was found to be positively related to the adolescents' conventionality, intrapersonal and interpersonal adjustment, and infrequent or no use of marijuana. Adolescent adaptive coping was also associated with paternal adaptive coping, a close father-child bond, and under some conditions, less paternal drug use. Furthermore, for every additional psychosocial risk factor beyond a minimal number, there is a doubling in the odds ratio of the adolescent using maladaptive techniques of coping. Knowledge of such relationships helps guide intervention and policy procedures for adolescents who are at risk because their fathers are HIV-positive or may contract HIV. Brook, D.W., Brook, J.S., Arencibia-Mireles, O., Whiteman, M., Pressman, M. and Rubenstone, E. Coping in Adolescent Children of HIV-Positive and HIV-Negative Substance Abusing Fathers. The Journal of Genetic Psychology, 163 (1), pp. 5-23, 2002.

### Alcohol Use in Adolescents Whose Fathers Abuse Drugs

This study examined the interrelation of several domains, including father attributes, father-child relations, peer influences, environmental factors, and youth personality, as they related to adolescent alcohol use. Several aspects of the father-child relationship were also examined as possible protective factors against adolescent drinking. Subjects consisted of 204 HIV-positive and HIV-negative drug-abusing fathers and their adolescent children between the ages of 12 and 20. Data were collected via individual structured interviews of both the fathers and the youth. Results indicated that several items from each domain were related to adolescent drinking, and that an affectionate father-child bond had a protective effect. Moreover, hierarchical regression analyses demonstrated that the youth's personality mediated between all other domains and adolescent alcohol use. There was also a direct effect of peer influences on adolescent drinking. Findings extend the literature on the specific mechanisms which link parental substance use with adolescent alcohol use in a high-risk population. Brook, D.W., Brook, J.S., Rubenstone, E. and Zhang, C. Alcohol Use in Adolescents Whose Fathers Abuse Drugs. Journal of Addictive Diseases, 22, pp. 11-33, 2003.

### Intergenerational Transmission of Risks for Problem Behavior

The intergenerational transmission of risk factors for problem behaviors was examined across three generations. Two hundred fifty-four 2-year-old toddlers, one or two of their parents, and one grandmother of each toddler were studied. Grandmothers and parents were individually interviewed. Data were analyzed for the male and female toddlers combined. Correlations and hierarchical multiple regression analyses were performed. Findings indicate that the grandmother-parent relationship, parental personality attributes, marital harmony, and drug use and the parent-toddler relationship, predict the toddlers' behavior. The investigation provides evidence for a longitudinal, intergenerational process whereby the grandmother-parent relationship and the parents' personality and behavioral attributes are transmitted across generations through their association with the parent-child relationship. Brook, J.S., Balka, E.B., Whiteman, M. and Zheng, L. Intergenerational Transmission of Risks for

Problem Behavior. Journal of Abnormal Child Psychology, 30(1), pp. 65-76, 2002.

### Maladaptive Parenting and the Association Between Parental and Offspring Psychiatric Disorders

A longitudinal study was conducted to investigate the role of maladaptive parental behavior and the association between parent and offspring psychiatric disorders. Psychosocial and psychiatric interviews were carried out in a representative community sample of 593 biological parents and their offspring from two counties in the state of New York in 1975, 1983, 1985-86, and 1991-93. In 1975, the mean age of offspring was 6 years. Maladaptive parental behavior was assessed in 1975, 1983, and 1985-86. Parent and offspring psychiatric symptoms were assessed in 1983, 1985-86, and 1991-93. Maladaptive parental behavior substantially mediated a significant association between parental and offspring psychiatric symptoms. Parents with psychiatric disorders had higher levels of maladaptive behavior in the household than did parents without psychiatric disorders. Maladaptive parental behavior, in turn, was associated with increased offspring risk for psychiatric disorders during adolescence and early adulthood. Most of the youths that experienced high levels of maladaptive parental behavior during childhood had psychiatric disorders during adolescence or early adulthood, independent of whether or not their parents had psychiatric disorders. In contrast, the offspring of parents with psychiatric disorders were not at increased risk for psychiatric disorders unless there was a history of maladaptive parental behavior. Maladaptive parental behavior is associated with increased risk for the development of psychiatric disorders among the offspring of parents with and without psychiatric disorders. Maladaptive parental behavior appears to be an important mediator of the association between parental and offspring psychiatric symptoms. Johnson, J.G., Cohen, P., Kasen, S., Smailes, E. and Brook, J.S. Maladaptive Parenting and the Association Between Parental and Offspring Psychiatric Disorders. Zeitschrift fŸr Psychosomatische Medizin und Psychotherapie, 48, pp. 396-410, 2002.

### Adolescent Substance Use Related to Risky Sex Behaviors in Early Adulthood

This study examined the developmental relationship between adolescent substance use and risky sexual behavior in young adulthood. A sample of 808 children was surveyed at age 10 and followed prospectively to age 21 years. Different trajectory groups were identified, including binge-drinking, cigarette smoking, marijuana use, and the use of other illicit drugs. Membership in these groups significantly predicted risky sexual behavior at age 21, after other substance use and early measures of sexual behavior were controlled. Early binge-drinkers had significantly more sex partners than non-binge drinkers. Late onset binge-drinkers and marijuana users had significantly more sex partners and were less likely to use condoms consistently than those who did not binge drink or use marijuana. Experimenters in cigarette smoking, who did not escalate smoking, were more likely to use condoms consistently than nonsmokers. In contrast, the use of other illicit drugs in adolescence did not predict risky sexual behavior at age 21. Guo, J., Chung, I., Hill, K.G., Hawkins, J.D., Catalano, and Abbott, R.D. Developmental Relationships Between Adolescent Substance Use and Risky Sexual Behavior in Young Adulthood. J. of Adolescent Health, 31(4), pp. 354-362, 2002.

### Peers Continue to Influence Substance Use in Young Adulthood

This study included data from 294 young adults, ages 19-25, and both a same- and an opposite-gender best friend or mate collected across three annual assessments. The similarity to and influence of the peer on the young adult's substance use were explored. The authors found a similarity across time between both peers and the young adult in cigarette use, alcohol use, binge drinking and, in most cases, marijuana use. In prospective analyses, peer use predicted young adult cigarette use, binge drinking and problem use by the young adults. Results were generally consistent across gender and for both same- and opposite-gender peers. Andrews, J.A., Tildesley, E. Hops, H. and Li, F. The Influence of Peers on Young Adult Substance Use. Health Psychology, 21(4), pp. 349-357, 2002.

### Academic Beliefs and Behaviors Related to Increased Cigarette and Marijuana Use

This study examined substance use between 10th and 12th grades in a predominantly African American sample of 785 adolescents from an urban environment. Psychological distress, academic factors, and perceptions of parents and peers were used to examine 10th-grade substance use and changes in use. Results indicated that low achievement and motivation, high truancy, and perceptions of peer substance use

were associated with higher 10th-grade substance use. Growth curve analyses revealed that adolescents who perceived negative school attitudes among peers were more likely to increase their cigarette and marijuana use. Among high-achieving students, low motivation was a risk factor for increased cigarette use. Bryant, A.L., and Zimmerman, M.A. Examining the Effects of Academic Beliefs and Behaviors on Changes in Substance Use Among Urban Adolescents. J. of Educational Psychology, 94 (3), pp. 621-637, 2002.

### High School Failure Predicted by Deviance, Academic Competence and Tobacco Use

This study explored whether general (vs. specific) deviance and academic competence mediated the relationships between structural strain factors (gender, ethnicity and socioeconomic status (SES)) and 12th grade high school failure. Independent variables of structural strain and mediational variables of drug use, sexual involvement, school trouble, delinquency, and academic performance were assessed in a sample of 754 8th graders and used to predict 12th-grade high school dropout and number of missed months of school in 12th grade (reflecting a latent construct of High School Failure). High school failure was directly predicted by earlier General Deviance, poor Academic Competence, low Family SES, and tobacco use. All ethnic and gender differences in high school failure were mediated by deviance and academic ability or accounted for by Family SES discrepancies. Newcomb, M.D., Abbott, R. D., Catalano, R. F., Hawkins, J. D., Battin-Pearson, S. and Hill, K. Mediational and Deviance Theories of Late High School Failure: Process Roles of Structural Strains, Academic Competence, and General Versus Specific Problem Behaviors. J. of Counseling Psychology, 49(2), pp. 172-186, 2002.

### Negative Affectivity and Drug Use in Adolescent Boys: Moderating and Mediating Mechanisms

Using data from the Center on Education and Drug Abuse Research, this investigation examined the relation between negative affectivity and drug use in adolescent boys. In Study 1, 311 boys (15-17 years old) completed inventories of negative affectivity, positive affectivity, constraint, delinquency, peer delinquency, and drug use. Negative affectivity was positively related to drug use, but only for individuals exhibiting high peer delinquency or low constraint. Study 2 examined mechanisms for this relation by following up 143 of the participants at ages 17-20 years. Delinquency and peer delinquency mediated the relation between negative affectivity and later drug use. These findings suggest that the relation between negative affectivity and drug use is best understood within the context of other drug use risk factors. Shoal, G.D. and Giancola, P.R. Negative Affectivity and Drug Use in Adolescent Boys: Moderating and Mediating Mechanisms. Journal of Personality and Social Psychology, 84(1), pp. 221-233, 2003.

### Epidemiology of Gambling Participation in the United States

This study examined demographic patterns of gambling participation in the U.S. using a national telephone survey with 2,630 representative U.S. residents aged 18 or older. The sample as weighted for analysis was 48% male, 12% black, and 11% Hispanic. Respondents were questioned on 15 types of gambling: how often they played and how much they won or lost. Eighty-two percent reported having gambled in the past year. Lottery was the most commonly played game, while casino gambling accounted for the largest extent of gambling involvement. Men and women were equally likely to gamble in the past year, but men gambled more frequently and had larger wins and losses, particularly on sports betting and games of skill. Black respondents were less likely to report having gambled in the past year, but blacks who gambled did so more heavily than other racial groups. Blacks and Hispanics were more likely than average to be pathological gamblers. The rate of past year gambling declined with age, but extent of gambling involvement among gamblers did not vary with age. Rates of participation in most forms of gambling increased with socioeconomic status, but higher socioeconomic status gamblers had lower rates of pathological gambling, and lower extent of gambling involvement, particularly for lottery. New Englanders gambled more heavily than other Americans. Comparison with past studies showed an increase in overall gambling participation in the U.S., and large increases in rates of participation in lottery and casino gambling. Welte, J.W., Barnes, G.M., Wieczorek, W.F., Tidwell, M.C., and Parker, J. Gambling Participation in the U.S.--Results from a National Survey. J. Gambling Studies, 18(4), pp. 313-337, 2002.

### Effects of Alcohol Misuse on Gambling Patterns in Youth

This study hypothesized that alcohol misuse would predict a pattern of increased youth gambling or a pattern of stable high gambling after controlling for key sociodemographic, socialization and individual factors. Data were analyzed from two longitudinal studies of youth living in a western New York metropolitan area. Respondents' gambling at two times over the course of 12-18 months was classified into one of five gambling pattern groups, representing flat-low, increasing, flat-medium, flat-high and decreasing levels of gambling. Alcohol misuse among males predicted increasing gambling over time or a pattern of stability of high rates of gambling even after controlling for socioeconomic status, race, age, impulsivity and parental monitoring in the family study. Higher parental monitoring and lower alcohol misuse were significant in predicting a decreasing pattern of gambling among males in the male delinquency study. For females in the family study, alcohol misuse predicted an increasing pattern of gambling only when other factors such as high impulsivity or low parental monitoring were present. Results are consistent with the notion that gambling and alcohol misuse are prevalent among youth and may be part of a common problem behavior syndrome. Barnes, G.M., Welte, J.W., Hoffman, J.H., and Dintcheff, B.A. Effects of Alcohol Misuse on Gambling Patterns in Youth. Journal of Studies on Alcohol, 63(6), pp. 767-775, 2002.

### Intimate Partner Violence and Substance Abuse Among Minority Women

This study describes the rates of lifetime and current intimate partner violence (IPV) among women awaiting care in an emergency department and explores the association between IPV and having a substance abuse problem, after controlling for demographic factors and history of childhood victimization. Face-to-face interviews were conducted with 143 low-level triaged women recruited from an inner-city emergency department. Nearly one-half reported ever experiencing IPV, and over 18% reported IPV during the year before the interview. Participants who were physically abused by their partner during the past year (15%, n = 21) were more likely than nonabused women (85%, n = 122) to report more alcohol-related problems on the Alcohol Use Disorders Identification Test (AUDIT) (4.9 vs. 2.4) and more drug-related problems on the Drug Abuse Severity Test (DAST) (3.0 vs. 1.3). In addition, sexually abused women (6%, n = 9) had higher AUDIT scores (6.4 vs. 2.5) than their counterparts (94%, n = 134). The findings have implications for how the intersecting public health problems of IPV and substance abuse should be taken into consideration in research and patient care protocols in emergency departments. El-Bassel, N., Gilbert, L., Witte, S., Wu, E., Gaeta, T., Schilling, R. and Wada, T. Intimate Partner Violence and Substance Abuse Among Minority Women Receiving Care from an Inner-City Emergency Department. Women's Health Issues, 13(1), pp. 16-22, 2003.

### Two-Dimensional Nature of Psychopathy in Adjudicated Youths

This study sought to clarify the nature of two dimensions associated with psychopathic traits (a callous/unemotional factor [C/U] and an impulsivity/conduct problems factor [I/CP]) with social-cognitive problems in incarcerated adolescents. One hundred sixty-nine male and female adjudicated youths were recruited for participation. Self-report measures and archival data were used to assess psychopathic traits, emotional distress, behavioral dysregulation, social-cognitive processes, and delinquency severity. Analyses demonstrated that the I/CP factor is associated with increased levels of dysregulated behavior, while the C/U dimension is related to deficits in empathy. The two factors exhibited differential relations with measures of emotional distress and fearfulness. C/U traits were associated with an increased focus on the positive aspects of aggression and a decreased focus on the negative aspects of hostile acts. Findings remained after controlling for demographic characteristics, abuse history, intellectual abilities, and delinquency severity. Results provide support for the two-dimensional nature of psychopathy in youths and suggest that C/U traits are associated with lower emotional distress and a specific social information-processing pattern. Pardini, D.A., Lochman, J.E., and Frick, P.J. Callous/Unemotional Traits and Social-Cognitive Processes in Adjudicated Youths. Journal of the American Academy of Child and Adolescent Psychiatry, 42(3), pp. 364-371, 2003.

### Minnesota Twin Family Study Focuses on Substance Abuse and Related Problems

As part of a special issue of the journal Twin Research, the authors provide an overview of their study, to which NIDA has contributed significant support. This is a large longitudinal study of twins and parents, with a parallel study of adoptive and biologically related siblings and their parents. Subjects participate in an intensive assessment battery including physiologic measures of endophenotype,

psychopathology and personality, cognition, and environmental factors. DNA is being collected for future candidate gene studies. Numerous findings regarding behavioral undercontrol, heritability, environmental protective factors, personality and substance abuse, and psychophysiologic markers of risk have been published. The principal researchers have fostered the research development of many junior investigators, and they outline opportunities for collaborations with other research groups. Iacono, W.G. and McGue, M. Minnesota Twin Family Study. Twin Research, 5(5), pp. 482-487, 2002.

### Overview of the National Comorbidity Survey

This chapter presents an overview of the research program associated with the U.S. National Comorbidity Survey (NCS). This research program includes the baseline NCS, the NCS-2, and NCS-R, the NCS-A, and the WMH2000. The baseline NCS (1990-1992) was the first nationally representative mental health survey in the Unites States to use a fully structured research diagnostic interview to assess the prevalences and correlates of DSM-III-R disorders, including substance use disorders. The NCS-2 is a 10-year follow-up of the baseline NCS designed to study patterns and predictors of mental and substance use disorders, and to evaluate the effects of primary mental disorders in predicting the onset and course of secondary substance use disorders. Carried out in conjunction with the NCS-2, the NCS-R is a replication of the baseline NCS with a new nationally representative sample of 10,000 respondents, and the NCS-A is a survey of a nationally representative sample of 10,000 adolescents. Finally, the WMH2000 is a centralized cross-national analysis of World Mental Health surveys administered to nationally representative samples from 28 countries. Kessler, R.C. and Walters, E. The National Comorbidity Survey. In M.T. Tsuang and M. Tohen (Eds.) Textbook in Psychiatric Epidemiology (2nd Ed.), pp. 343-361, 2002.

### Exploring a Source of Deviance-Producing Strain for Females: Perceived Discrimination and General Strain Theory

While the oppression of women has been held by many feminist criminologists to be at the core of female crime, little research had explored the link between discrimination, generally, and gender-based discrimination, specifically, and female deviance. Using the framework of general strain theory (GST), this study used a sample of young adult females to explore whether self-reported measures of discrimination experiences were related to self-reported criminal activity and/or diagnoses of substance use disorders. Results indicated that a measure of major discrimination that included gender discrimination was a significant predictor of both crime and substance use disorders. Results indicated that a measure of major discrimination that included gender discrimination was a significant predictor of both crime and substance use disorders. These findings were interpreted as being supportive of GST and previous scholarship by other feminist criminologists. Eitle, D.J., Journal of Criminal Justice, 30, pp. 429-442, 2002.

### Exposure to Community Violence and Young Adult Crime: The Effects of Witnessing Violence, Traumatic Victimization, and Other Stressful Life Events

Evidence has accumulated that young people in America are witness to considerable violence at home and in the community. This study is the first to examine the association between witnessing community violence and criminal behavior in a representative sample of young adults. In addition, the authors consider whether receiving traumatic news, witnessing domestic violence, experiencing accidents, and being the direct victim of domestic and community-based violence are independently associated with young adult crime. The results indicate that recent exposure to violence in the community along with a history of receiving traumatic news, direct victimizations in the community, recent life events, and associations with criminal peers increase the risk for young adult criminal offending. The implications of these results are discussed. Eitle, D. and Turner, R.J. Journal of Research in Crime and Delinquency, 39, pp. 214-237, 2002.

### Perceived Discrimination, Social Stress and Depression in the Transition to Adulthood: Racial Contrasts

We consider the association between racial discrimination and depression in a relatively comprehensive assessment of general social stress. Data for this investigation come from a sample of Miami-Dade County young adults; the present analyses are limited to African American and white non-Hispanic respondents. Findings indicate that perceptions of discrimination are strongly related to psychological distress. Surprisingly, however, these perceptions contribute almost

nothing to an understanding of the origins of racial differences in depression. It appears that differences in lifetime adversity and in exposure to recent and chronic stressors capture those variations in personal history and circumstance which are linked to and arise from social disadvantage and which are relevant to mental health. Variations in these more general forms of social stress account for observed racial differences in depressive symptomatology. Taylor, J., and Turner, R.J. Social Psychological Quarterly, 65, pp. 213-225, 2002.

### Race/Ethnicity and Depressive Symptoms In Community-Dwelling Young Adults: A Differential Item Functioning Analysis

To examine variations in the manifestation of depressive symptomatology across racial/ethnic groups, analyses of differential item functioning (DIF) on the Center for Epidemiologic Studies Depression Scale (CES-D) were separately conducted for representative samples of young adults in the following groups: African-Americans (n = 434), Hispanics born in the US (n = 493), and Hispanics born outside the US (n = 395). Non-Hispanic whites (n = 463) were employed as the reference group in all analyses. The effects of gender and age were controlled. DIF analyses indicated that: (1) about half of the CES-D items functioned differently among non-Hispanic whites compared to each of the other racial/ethnic groups; (2) the manifestation of symptoms seemed to be similar for both Hispanic groups, except for low positive affect; (3) African-Americans tended to favor somatic symptoms over affective (depressive) symptoms; (4) Immigrant Hispanics appeared to inhibit the expression of positive affect, and thus more high scorers on the total CES-D were observed within this subgroup. In contrast, no differences were observed when only negative items were considered. The use of positive affect items might artifactually induce spurious differences among people who were born outside the United States or North America. Turner, R.J., Lloyd, D.A. and Iwata, N. Psychiatry Research, 110, pp. 281-289, 2002.

### Ethnographic Analysis of African-American Women's Pathways to Involvement in Drug Distribution

This is an exploratory ethnographic analysis to address the question of "What factors in Black women's backgrounds lead them towards crack (and other drug) sales as a primary economic activity in adulthood?" There is considerable overlap in women's pathways to involvement in drug distribution, including positive exposure to the local level informal economy during childhood, the historical positioning of Black women as producers and consumers within the informal sector, the impact of structural and cultural disinvestment, drug use, and early recruitment to and participation in street life. While drug use was a crucial variable in determining their subsequent involvements in distribution activities, this study indicates that most women sellers were engaged in lawbreaking prior to regular involvement in illicit drug use. All of the women acquired an early start in street life and an early introduction into the ways of making "fast" money. For these women, street life is a critical variable that mediates involvement in drug distribution. The study suggests that it was not merely the involvement of the domestic network or kinship group in extra-legal and illegal activities, but rather the lack of social and economic infrastructure and the absence of legitimate opportunity structures and employment at the neighborhood level that led African-American women to seek alternative avenues of income generation. Maher, L., Dunlap, E. and Johnson, B. Black Women's Pathways to Involvement in Illicit Drug Distribution and Sales: An Exploratory Ethnographic Analysis in Drugs and Crime Deviant Pathways, edited by S. Brochu, C. da Agra, and M-M. Cousineau, Ashgate, pp. 167-193, 2002.

### Youth Report and Census Measures of Neighborhood Context Show Correspondence

This study sought to determine whether survey data could be used to measure neighborhood context. Using a non-representative sample of youth, the consistency was explored between measures of neighborhood disadvantage/disorganization developed from the national census and from surveys of youth given the same year. Results showed strong correspondence between the contemporaneous measures, suggesting that survey data can be used to measure neighborhood factors. Herrenkohl, T.I., Hawkins, J.D., Abbott, R.D. and Guo, J.J. Correspondence Between Youth Report and Census Measures of Neighborhood Context. Community Psychology, 30(3), pp. 225-233, 2002.

### Childhood Factors Predict Offense Trajectories

Using data from a longitudinal study of youth followed since 1985, this study

identified childhood predictors of different offense trajectories. Five offense trajectories were identified including nonoffenders, late onsetters, desisters, escalators, and chronic offenders. Results indicated that among initial nonoffenders at age 13, late onsetters were distinguished from non-offenders by individual factors such as aggressive behavior and/or being anxious/depressed measured at ages 10 and 12. Among youth already delinquent at age 13, escalators were distinguished from desisters by peer, school, and neighborhood factors. Chung, I., Hill, K.G., Hawkins, J.D., Gilchrist, L.D. and Nagin, D.S. Identifying and Predicting Offending Trajectories among Poor Children. J. of Research in Crime and Delinquency, 39(1), pp. 60-90, 2002.

### Gender and Ethnic Differences in Students' Smoking, Drinking and Illicit Drug Use

Researchers affiliated with Monitoring the Future at the University of Michigan examined ethnic differences in licit and illicit drug use among American 8th, 10th and 12th grade students over the period from 1972 through 2002, with a particular focus on girls. The study used cross-sectional data from the large, ethnically diverse, nationally representative MTF samples of 8th, 10th and 12th graders including 40,416 8th grade girls and 37,977 8th grade boys; 35,451 10th grade girls and 33,188 10th grade boys; and 33,588 12th grade girls and 31,014 12th grade boys. Across ethnic groups, drug use was found to be highest among Native American girls and lowest among black and Asian American girls. Trend data suggested that there have been important changes in girls' drug use over time and girls' and boys' drug use patterns are converging. The authors concluded that drug use is widespread among American adolescent girls and that further research is needed to determine whether risk and protective factors identified in the past, using predominantly white samples, are also applicable to drug use among non-white girls. Wallace, J.M., Bachman, J.G., O'Malley, P.M., Schulenberg, J.E., Cooper, S.M. and Johnston, L.D. Gender and Ethnic Differences in Smoking, Drinking and Illicit Drug Use Among American 8th, 10th and 12th Grade Students, 1976-2000. Addiction, 98(2), pp. 225-234, 2003.

### Relational and Physical Victimization Within Adolescent Friendships

This study examines relational and physical forms of victimization within dyadic relationships such as friendships. Results showed that boys were more physically victimized by their friends than were girls. Girls were more relationally than physically victimized by their friends. Friend victimization was related to adjustment difficulties for both boys and girls; however, friend physical victimization was particularly related to boys whereas friend relational victimization was particularly related to girls. Crick, N.R. and Nelson, D.A. Relational and Physical Victimization Within Friendships: Nobody Told Me There'd Be Friends Like These. Journal of Abnormal Child Psychology, 30(6), pp. 599-607, 2002.

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

## Research Findings - Prevention Research

### Comprehensiveness of Substance Use Prevention Programs in U.S. Middle Schools

This study assessed how current practice in middle school substance use prevention programs compares to seven recommended guidelines adapted from the Centers for Disease Control and Prevention's guidelines for school-based tobacco use prevention programs. Substance use prevention practice was analyzed using data from a 1999 mailed survey of a nationally representative sample of 1,496 public and private schools with middle school grades that reported having a substance use prevention program. An estimated 64 percent of schools met four or more of the recommendations for school-based substance use prevention practice; 4 percent met all seven recommendations. Of the seven, schools were most likely to report having and enforcing substance use prevention policies (84 percent), and least likely to report training teachers in substance use prevention (18 percent). More recommendations were implemented by schools with the following characteristics than by those without them: they were public, had larger enrollments, greater perceived availability of resources, greater school board and parental support for substance use prevention, and had hired a school substance use prevention coordinator. Additional resources may be needed to increase the prevalence of comprehensive substance use prevention programs in U.S. middle schools. Wenter, D.L., Ennett, S.T., Ribisl, K., Vincus, A.A., Rohrbach, L., Ringwalt, C.L., and Jones, S.M. Journal of Adolescent Health, 30(6), pp. 457-464, 2003.

### Outcomes of the Minnesota DARE PLUS Project

In the past, the Drug Abuse Resistance Education (DARE) has been the most widely used drug use prevention program in elementary schools. Several evaluations have shown the program's lack of effectiveness; other evaluations of the DARE curriculum have reported short-term changes in cigarette smoking that have been modest in size. The Minnesota DARE PLUS Project was designed to capitalize on the successful elements of DARE and also provide additional, complementary components based on state-of-the-art prevention strategies. DARE PLUS curriculum focuses on middle/junior high school level, and is designed to reduce tobacco, alcohol and marijuana use, and violent behavior among 7th and 8th grade students. The evaluation study of DARE PLUS involved 24 middle and junior high schools in Minnesota that were matched on socio-economic measures, drug use, and size, and were randomly assigned to three conditions: 1) DARE; 2) DARE PLUS, and 3) delayed DARE PLUS control. The principal outcomes of the study were measured by self-administered questionnaires. Differences between the three conditions were tested using a three-level, linear, random coefficients model. DARE PLUS was found to significantly improve the DARE middle/junior high curriculum, and was an effective intervention for reducing alcohol, tobacco, and multi-drug use and victimization among adolescent boys. However, DARE PLUS did not demonstrate similar effects among adolescent girls. The gender differences in outcomes need further exploration. Perry, C.L., Komro, K.A., Veblen-Mortenson, S., Bosma, L.M., Farbakhsh, K., Munson, K.A., Stigler, M.H., and Lytle, L.A. A Randomized Controlled Trial of the Junior High DARE and DARE PLUS programs. Archives of Pediatrics and Adolescent Medicine, 157, pp. 178-184, 2003.

### Positive Support for the Theoretical Model in the Coping Power Program

This study tests the contextual social-cognitive model, which has served as the basis for the Coping Power program. That program involves an indicated preventive

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intervention with at-risk preadolescent boys at the time of transition from elementary to middle school. The contextual social-cognitive (CSC) model assumes that (a) aggressive children have distortions in their social-cognitive appraisals and deficiencies in their social problem solving skills and (2) their parents have deficiencies in parenting behaviors. To test this model, particularly the assumption that changes in CSC processes can impact later adolescent outcomes and that these outcomes are mediated through intervention-produced changes at one-year post-intervention follow up, 183 boys were identified as being at risk on the basis of fourth grade and fifth grade teachers' ratings of children's aggressive and disruptive behaviors. Subsequently, the interventions were delivered at the end of elementary school and the beginning of middle school. The intervention effect on delinquency, substance use, and school behavior outcomes was at least partially mediated through intervention-produced changes in the child and parent variables that were targets for the intervention. These analyses testing the model at one-year follow up assessment provided unique support for the assumptions in the CSC model. Changes in the mediating processes, even among high-risk boys, have a meaningful impact on later negative outcomes. Lochman, J.E., and Wells, K.C. Contextual Social-Cognitive Mediators and Child Outcome: A Test of the Theoretical Model in the Coping Power Program. Development and Psychopathology, 14(4), pp. 945-967, 2002.

### Effects of The Coping Power Program

This study evaluates the effects of both a universal and an indicated preventive intervention. Children were identified as being at risk on the basis of 4th-grade teachers' ratings of children's aggressive and disruptive behaviors. Interventions were delivered during the 5th- and 6th-grade years. Children were randomly assigned to the Coping Power (indicated) intervention, the universal intervention, the combined Coping Power plus universal intervention, or a control condition. The Coping Power program included child and parent components. Results indicated that all three intervention conditions produced relatively lower rates of substance use at post-intervention than did the control condition. The interventions also produced effects on three of the four predictor variable domains: children's social competence and self-regulation and parents' parenting skills. Lochman, J.E., and Wells, K.C. The Coping Power Program at the Middle-School Transition: Universal and Indicated Prevention Effects. Psychology of Addictive Behaviors, 16(4), pp. S40-S54, 2002.

### Three-Year Outcomes of the Early Risers Longitudinal Prevention Trial

This study evaluated the effects of participation following a 3-year preventive intervention trial targeting elementary school children with early-onset aggressive behavior. The Early Risers intervention model includes two core components: CORE, a coordinated set of school-centered interventions that target key developmental domains underlying risk and protection in young children and FLEX, a risk-adjusted family-focused intervention delivered through home visitation to foster parenting skills. Intent-to-treat analyses revealed that compared with controls, program participants showed greater gains in social skills, academic achievement, and parent discipline, with mean scores in the normative range on the latter two constructs. As-intended participation in the FLEX Family Program, which included separate parent and child education and skills-training groups, was associated with improved parent discipline practices and gains in children's social skills, with level of child aggression moderating gains in academic achievement. Recommended level of FLEX family support contact time was associated with gains in academic achievement, concentration problems, and social skills, with parents of severely aggressive children showing greater reductions in parent distress. August, G.J., Hektner, J.M., Egan, E.A., Realmuto, G.M. and Bloomquist, M.L. The Early Risers Longitudinal Prevention Trial: Examination of 3-Year Outcomes in Aggressive Children with Intent-to-Treat and As-Intended Analyses. Psychology of Addictive Behaviors, 16(4), pp. S27-S39, 2002.

### Findings from the Raising Healthy Children Social Development Intervention

This study examined results of a comprehensive, multifaceted longitudinal school-based prevention program called Raising Healthy Children (RHC). RHC focuses on enhancing protective factors with the goal of promoting positive youth development, reducing identified risk factors and preventing adolescent problem behaviors. Participants included 938 first or second graders who were enrolled in 10 area schools in the Pacific Northwest and randomly assigned to the RHC or control condition. Analyses were conducted 18 months after implementation and focused on academic and behavioral outcomes in the school environment. Results using hierarchical linear modeling showed that RHC students, compared to their peers who did not receive the intervention, had significantly higher teacher-reported academic performance and a stronger commitment to school. RHC students showed a significant decrease in

antisocial behaviors and an increase in social competency compared to control peers. Regression results from parent-reported outcomes also showed that RHC students had higher academic performance and a stronger commitment to school. Catalano, R.F., Mazza, J.J., Harachi, T.W., Abbott, R.D., Haggerty, K.P. and Fleming, C.B. Raising Healthy Children Through Enhancing Social Development in Elementary School: Results after 1.5 years. Psychology of Addictive Behaviors 16(2), pp. 129-134, 2003.

### Peer Influence and Prevention of Problem Behavior

Research shows that deviant peer influence is related to the escalation of various problem behaviors such as substance use, delinquent behavior and violence. The goal of this research was to examine the effects of a family-centered prevention strategy on deviant peer affiliation. The investigators hypothesized that the Adolescent Transitions Program (ATP) would significantly reduce growth in deviant peer affiliation from the beginning of sixth grade to the beginning of ninth grade and that the reduced growth in deviant peer involvement would be correlated with the intensity of the parents' contact with the intervention. The Adolescent Transitions Program involves a 6-week classroom curriculum for all intervention youth, a Family Check-Up component to improve the family management in families identified by a teacher as potentially at-risk, and additional preventive strategies, such as family therapy and brief consultations, for families with motivation and need for assistance. This intervention was administered through a "Family Resource Center" at the school. Six hundred seventy-one youth and their families were recruited to participate from a diverse metropolitan community. Using latent growth analysis, the growth in deviant peer involvement for intervention youth was reliably less than that of the control group. In addition, the results showed that the extent to which parents accessed the family resource center mediated growth in deviant peer affiliation. Dishion, T.J., Bullock, B.M., and Granic, I. Pragmatism in Modeling Peer Influence: Dynamics, Outcomes, and Change Processes. Development and Psychopathology, 14, pp. 969-981, 2002.

### Test of the Early-Starter Model of the Development of Serious Conduct Problems

The Fast Track prevention trial was used to test hypotheses from the Early-Starter Model of the development of chronic conduct problems. The researchers randomly assigned 891 high-risk first-grade boys and girls (51 percent African American) to receive or not receive the long-term Fast Track preventive intervention. After four years, outcomes were assessed through teacher ratings, parent ratings, peer nominations, and child self-report. The positive effects of assignment to intervention were evident in teacher and parent ratings of conduct problems, peer social preference scores, and association with deviant peers. Assessments of proximal goals of intervention (e.g., reduced hostile attributional bias, harsh parental discipline, and aggressive behavior at home and school; improved problem-solving skills and pro-social behavior), collected after third grade were found to partially mediate these effects. The findings are interpreted as consistent with developmental theory. Bierman, K.L., Coie, J.D., Dodge, K.A., Greenberg, M.T., Lochman, J.E., McMahon, R.J., and Pinderhughes, E.E. Using the Fast Track Randomized Prevention Trial to Test the Early-Starter Model of the Development of Serious Conduct Problems. Development and Psychopathology, 14, pp. 925-943, 2002.

### Generalizability of the Social Development Model

The social development model is a theory of behavior that has proven useful in explaining the etiology of delinquency, violence, and substance use among adolescents as well as early antisocial behavior among preadolescents. To test the model's generalizability across gender and income groups, a section of the model representing prosocial influences in the etiology of problem behavior was compared for girls and boys and for children from low-income families and non low-income families. Using a sample of 851 elementary school-aged youth from the Raising Healthy Children study, multiple group structural equation modeling was used to assess differences across groups in both measurement of model constructs and hypothesized structural paths between constructs. For both sets of comparisons, overall similarity was found in both measurement and structural models, indicating the robustness of the social development model for different groups. While some studies of differences in the effects of social/interactional variables on problem behavior in adolescence have shown differences by gender and ethnicity, these findings indicate that generally the protective paths from early social skills and family socialization to problem behavior in the elementary school period appear to operate in much the same way in different gender and income groups. Fleming, C.B., Catalano,

R.F., Oxford, M.L., and Harachi, T.W. A Test of Generalizability of the Social Development Model Across Gender and Income Groups with Longitudinal Data from the Elementary School Development Period. Journal of Quantitative Criminology, 18(4), pp. 423-439, 2002.

### Protective Aspects of American Indian Culture

American Indian youth have notably high rates of use of alcohol and certain illicit substances, yet prevention efforts for this population have been limited. This study examines whether and in what ways differences in ethnic and cultural identities among American Indian youth relate to their drug use norms. Four hundred thirty-four seventh graders from a large southwestern U.S. city who self-identified as American Indian provided self-reports of their norms in use of alcohol, tobacco, marijuana, and other drugs as well as the strength of their ethnic self-identities. Regression analysis indicated that ethnic pride was predictive of some anti-drug norms. For example, students who had a more intense sense of ethnic pride were more likely to report that it was not OK for someone their age to use alcohol, cigarettes, or marijuana. Intragroup ethnic diversity and speaking English only at home and with friends were unrelated to drug norms when other predictors were controlled, and there were 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. Social Work Research, 26(2), pp. 101-112, 2002.

### Parent Figure Transitions, Delinquency, and Drug Abuse

Children of substance abusing parents have an elevated risk for experiencing disruptions in household composition, including changes in primary caretakers. This study investigated whether changes in caretakers, also called "parent figure transitions" predicted the likelihood of delinquency and drug use among a sample of youth with parents receiving methadone treatment for opiate addiction. A sample of 67 youth was derived from the Focus on Families program, a family-based intervention study to prevent substance abuse in children of opiate-addicted parents. For this analysis, 67 children ages 9-14 were interviewed (mean age=11.4 years at baseline; 13.8 years at final interview). Controlling for baseline delinquency, child characteristics, family conflict, parental depression, and parent criminal history, a greater number of parenting disruptions during the longitudinal study period was associated with a higher probability of delinquent behavior. Gender moderated the effect of parent figure transitions in a parallel analysis for drug use. After accounting for baseline drug use and other confounders, only adolescent females had a higher likelihood of drug use as the number of family disruptions increased. A subgroup of youth who experienced tremendous family instability and had no single consistent parent figure during the study were at extreme risk for delinquent behavior. Keller, T.E., Catalano, R.F., Haggerty, K.P., and Fleming, C.B. Parent Figure Transitions and Delinquency and Drug Use Among Early Adolescent Children of Substance Abusers. American Journal of Drug and Alcohol Abuse, 28(3), pp. 399-427, 2002.

### Alienation, Aggression and Sensation Seeking Predict Adolescent Use of Violent Media Content

Use of violent media content by adolescents has become an even greater matter of concern following the Columbine shootings. This study examined predictors of various types of self-reported use of violent media content by 8th graders (N=3,127) from 20 schools around the U.S. Hierarchical regression analyses indicate that gender, sensation seeking, aggression, and frequency of Internet use make relatively strong contributions to explaining the use of media content based on a composite measure of use of violent media content (i.e., use of action films, video/computer games, and violence-oriented Internet site use), as well as on a measure of violent website content use. Alienation variables contribute significantly, albeit modestly, to variance explained in the use of violence-oriented websites but not the composite measure. Alienation from school and family also appears to partially mediate effects of sensation seeking and aggression on use of violent Internet content. These findings suggest the relative importance of traits such as sensation seeking and aggressiveness in predicting use of violent media content in general. In addition, youth who feel alienated from school or family may turn to antisocial media content, particularly websites, as alternatives to antisocial peer groups. However, from a social policy perspective, focusing on such websites may be less effective than intervention strategy directed at alienation factors including schools and family relationships. Slater, M.D. Alienation, Aggression and Sensation Seeking as Predictors of Adolescent Use of Violent Film, Computer and Website Content. Journal of Communication 53(1), pp. 105-121, 2003.

### Leisure Time Motivation Scale for Adolescents

Understanding and measuring motivation can be important in developing and testing prevention interventions for youth. A new self- report measure of adolescent free-time motivation based on self-determination theory (Ryan & Deci, 2000) has been developed. The scale measures five forms of motivation (amotivation, external, introjected, identified, and intrinsic motivation), and is appropriate for use with young adolescents (ages 12-15). Using confirmatory factor analysis, examination of each of the motivation subscales indicated minimally acceptable levels of fit. The test of the overall model without modification was also minimally acceptable. The deletion of two items improved the fit and provided preliminary evidence of the validity of the overall scale. However, future replication of this finding is needed. Baldwin, C.K., and Caldwell, L.L. Leisure Time Motivation Scale for Adolescents. Journal of Leisure Research, 35, pp. 129-151, 2003.

### Adding Missing-Data-Relevant Variables to FIML-Based Structural Equation Models

Conventional wisdom in missing data research dictates adding variables to the missing data model when those variables are predictive of (a) missingness and (b) the variables containing missingness. However, it has recently been shown that adding variables that are correlated with variables containing missingness, whether or not they are related to missingness, can substantially improve estimation (by reducing bias and increasing efficiency). Including large numbers of these "auxiliary" variables is straightforward for researchers who use multiple imputation. However, what is the researcher to do if one of the full-information maximum likelihood (FIML) structural equation model (SEM) procedures is the analysis of choice? This article suggests two models for SEM analysis with missing data, and presents simulation results to show that both models provide estimation that is clearly as good as analysis with the expectation maximization (EM) algorithm, and by extension, multiple imputation. One of these models, the saturated correlates model, also provides good estimates of model fit. Graham, J.W. Adding Missing-Data-Relevant Variable to FIML-Based Structure Models. Structural Equation Modeling, 10(1), pp. 80-100, 2003.

### Mediation Designs for Tobacco Prevention Research

This article describes research designs and statistical analyses to investigate how tobacco prevention programs achieve their effects on tobacco use. A theoretical approach to program development and evaluation useful for any prevention program guides the analysis. The theoretical approach focuses on action theory for how the program affects mediating variables and on conceptual theory for how mediating variables are related to tobacco use. Information on the mediating mechanisms by which tobacco prevention programs achieve effects is useful for the development of efficient programs and provides a test of the theoretical basis of prevention efforts. Examples of the potential mediating mechanisms are described including mediated effects through attitudes, social norms, beliefs about positive consequences, and accessibility to tobacco. Prior research provides evidence that changes in social norms are a critical mediating mechanism for successful tobacco prevention. Analyses of mediating variables in single group designs with multiple mediators are described as are multiple group randomized designs which are the most likely to accurately uncover important mediating mechanisms for successful tobacco prevention. More complex dismantling and constructive designs also are described and illustrated using current findings from tobacco research. Mediation analysis for categorical outcomes and more complex statistical methods are discussed. MacKinnon, D.P., Taborga, M.P., and Morgan-Lopez, A.A. Drug and Alcohol Dependence, 68, pp. 69-83, 2002.

### A Comparison of Methods to Test Mediation and Other Intervening Variable Effects

A Monte Carlo study compared 14 methods to test the statistical significance of the intervening variable effect. An intervening variable (mediator) transmits the effect of an independent variable to a dependent variable. The commonly used R.M. Baron and D.A. Kenny approach has low statistical power. Two methods based on the distribution of the product and two difference-in-coefficients methods have the most accurate Type I error rates and greatest statistical power except in one important case in which Type I error rates are too high. The best balance of Type I error and statistical power across all cases is the test of the joint significance of the two effects comprising the intervening variable effect. Tests of the intervening variable effect are useful because they examine processes by which variables are related. In clinical and community research, such tests are critical for the elucidation of how prevention and treatment programs work. MacKinnon, D.P., Lockwood, C.M., Hoffman, J.M., West,

S.G., and Sheets, V. A Comparison of Methods to Test Mediation and Other Intervening Variable Effects. Psychological Methods, 7(1), pp. 83-104, 2002.

### Preventive Intervention Implementation in Rural Schools

Interactive prevention programs (i.e., characterized by dynamic instructional processes such as engaging students in classroom discussions, role-plays, and games) have been proven to be more effective in decreasing student problem behaviors than didactic practices. While almost all rural schools provide some programming to address student behavior problems, minimal attention has been paid to the unique features of rural schools that are particularly relevant to training teachers in the delivery of interactive preventive interventions. This paper describes teacher evaluation of a training based on a model proposed by Tortu and Botvin (1989) and the process of implementing the interactive intervention components of the Capable Families and Youth Prevention Project. This study involves the recruitment of thirty-six schools from communities in a rural Midwestern state for a test of the efficacy of school-based and school-based plus family-based substance abuse prevention programs. Teachers who participated in a two-day training completed an evaluation immediately after the training and upon completion of the classroom implementation. Results showed that teachers were confident about their ability to deliver the program following both training and classroom implementation. Lillehoj, C.J., Spoth, R., and Trudeau, L. Rural Teacher Training. Rural Educator, 24(1), pp. 3-12, 2002.

### Factors Associated with Regular Marijuana Use Among High School Students: A Long-Term Follow-up Study

The present study investigated whether several behavioral and psychosocial factors measured during early adolescence predicted regular marijuana use 6 years later in a sample of high school students. As part of a school-based survey, 7th-grade students (N=1132) reported levels of alcohol, tobacco, and marijuana use, and were assessed on several domains of psychosocial functioning potentially relevant in the etiology of marijuana use. When students were followed-up in the 12th grade, 14% smoked marijuana on a regular basis (once or more per month). Findings indicated that early cigarette smoking, alcohol use, and alcohol intoxication predicted later regular marijuana use. For boys, early marijuana use increased the odds for later regular marijuana use. Cigarette smoking by friends and siblings during early adolescence also increased the likelihood of later monthly marijuana use. The findings suggest that early prevention programs for adolescent alcohol, tobacco, and/or other drug use may have important preventive effects in terms of potentially more serious levels of marijuana involvement later in adolescence and early adulthood. Griffin, K.W., Botvin, G.J., Scheier, L.M. and Nichols, T.R. Factors Associated with Regular Marijuana Use among High School Students: A Long-Term Follow-up Study. Substance Use & Misuse, 37, pp. 225-238, 2002.

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

## Research Findings - Services Research

### The Effect of Primary Medical Care on Addiction and Medical Severity in Substance Abuse Treatment Programs

Researchers performed secondary analysis of data from a prospective cohort study of patients admitted to a purposive national sample of substance abuse treatment programs to examine 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. 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 either addiction severity or medical severity. These findings indicate that on-site primary medical care improves substance abuse treatment patients' addiction-related outcomes, but not necessarily their health-related outcomes. Friedmann, P.D., Zhang, Z., Hendrickson, J., Stein, M.D., and Gerstein, D.R. The Effect of Primary Medical Care on Addiction and Medical Severity in Substance Abuse Treatment Programs. Journal of General Internal Medicine, 18, pp. 1-8, 2003.

### Effects of Management Practices on Retaining Counseling Staff at Substance Abuse Treatment Centers

The annual turnover rate for drug abuse treatment counselors in a national study of 345 private treatment organizations was 18.5%. Significantly higher than such high-turnover occupations as teachers (13%) and nurses (12%), employee withdrawal presents a significant disruptive factor to continuity of care in drug abuse treatment. Results indicated that increasing counselor autonomy, providing rewards for strong job performance, and establishing a creative and innovative work environment can reduce counselor turnover. Knudsen, H.K., Johnson, J.A., and Roman, P.M. Retaining Counseling Staff at Substance Abuse Treatment Centers: Effects of Management Practices. Journal of Substance Abuse Treatment, 24, pp. 1-7, 2003.

### Role of Treatment Completion and Length of Stay on Employment and Crime in Outpatient Drug-free Treatment

Length of stay in treatment has been found to be a significant predictor of positive post-treatment outcomes, such as decreases in unemployment and crime. However, length of stay may be an incomplete predictor of successful treatment. The objective of this study was to examine the effect that treatment completion and length of stay have on post-treatment employment and crime for patients in outpatient drug-free treatment, the largest treatment modality in the United States. Data are from the National Treatment Improvement Evaluation Study and include 986 adults enrolled in outpatient drug-free programs across the United States. Findings suggest that treatment completion and length of stay are significantly related to post-treatment employment. Holding length of stay constant, the occurrence of employment at follow-up among patients who complete their planned treatment is almost 2 times that of patients who do not complete treatment. However, treatment completion did not have a statistically significant effect on the probability of post-treatment crime. Although the results of this study are mixed, the findings suggest that greater attention should be placed on evaluating the importance of both length of stay and treatment completion in treatment outcome studies. Zarkin G.A., Dunlap L.J., Bray

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J.W. and Wechsberg W.M. The Effect of Treatment Completion and Length of Stay on Employment and Crime in Outpatient Drug-free Treatment. Journal of Substance Abuse Treatment, 23(4), pp. 261-271, 2002.

### Effects of HIV Prevention Services in Correctional Drug Treatment Programs

This study evaluated receipt of HIV prevention services in correctional substance abuse treatment programs and examined their impact on short-term risk behaviors. The authors performed a secondary analysis of the National Treatment Improvement Evaluation Study, a prospective cohort study conducted during 1993 to 1995. The sample included 1,223 adult non-HIV-positive inmates, enrolled in nine correctional substance abuse treatment programs. A composite index modeled after the validated Risk Assessment Battery measured HIV risk behavior at treatment entry and at 12-month follow-up. Overall, most inmates received HIV prevention services while in treatment. Controlling for potential confounders, HIV prevention services were significantly associated with reduced risk behavior among inmates who were out of custody at follow-up, but no such association was observed among those still in custody. Analyses suggest that HIV prevention services are beneficial in reducing risk behavior among incarcerated individuals whose discharge is expected in the near future. Ballard Lubelczyk, R.A., Friedmann, P.D., Lemon, S.C., Stein, M.D., and Gerstein, D. The Effects of HIV Prevention Services in Correctional Drug Treatment Programs: Do They Change Risk Behaviors? AIDS Education and Prevention, 14, pp. 117-125, 2002.

### Mental Health Problems and Sexual Abuse Among Adolescents in Foster Care: Relationship to HIV Risk Behaviors and Intentions

Adolescents in foster care present with multiple psychosocial and mental health problems that individually are associated with increased risk for HIV infection. However, few studies have examined the interrelationships among these problems and HIV risk behaviors in this population. This study examined the sexual abuse histories and mental health problems among 343 youths in foster care to determine their association with HIV-risk behaviors and behavioral intentions. Results indicated that 25% reported internalizing behaviors (withdrawn, somatic complaints, depressed), and 28.3% reported externalizing behaviors (delinquent and aggressive behaviors). Of the sample, 37% reported some form of prior sexual abuse. Multivariate analyses using simultaneous entry of variables indicated that controlling for demographic variables and behavioral intentions, externalizing behaviors showed the strongest relationship with HIV risk behaviors. Likewise, in the multivariate model, it was most strongly associated with behavioral intentions. Moreover, there was a significant race by gender interaction with Caucasian females engaging in more risky behaviors than their male counterparts, and youths of color. Auslander, W.F., McMillen, J.C., Elze, D., Thompson, R., Jonson-Reid, M., and Stiffman, A. Mental Health Problems and Sexual Abuse Among Adolescents in Foster Care: Relationship to HIV Risk Behaviors and Intentions. AIDS & Behavior, 6(4), pp. 351-359, 2002.

### Mental Health and Addiction Problems Among American Indian Youth

This study examined the addiction and mental health service use of American Indian adolescents. The Diagnostic Interview Schedule and the Service Assessment for Children and Adolescents were used to ask Southwestern American Indian youth about their mental health needs, substance use, and service configurations. Seventy-nine percent had mental health or addiction problems, with half meeting criteria for at least one diagnosis. One in 4 youth met criteria for drug dependence/abuse or conduct disorder, 1 in 5 for depression, and 1 in 8 for alcohol dependence/abuse. Most youth received treatment services from a combination of providers. Youth meeting more diagnostic criteria were increasingly likely to use service configurations with adults, nonspecialist professionals, and specialists, respectively. Regardless of disorder, youth were least likely to use configurations with traditional healers or specialists, and there was little difference in rates of use between the two. The lack of services from specialist providers was potentially offset by use of an extensive range of informal adults, nonspecialist professionals, and peers. Since informal helpers, peers, and nonspecialist providers, but not specialists, are providing the bulk of services to these adolescents, they must be given support and skills so they can function effectively. Stiffman, A.R., Striley, C.W., Brown, E., Limb, G., and Ostmann, E. American Indian Youth: Who Southwestern Urban and Reservation Youth Turn To for Help with Mental Health or Addictions. Journal of Child & Family Studies, 12, pp. 319-333, 2003.

### Cost Sharing by Managed Care Plans for Substance Abuse and Mental Health Treatment

Recent initiatives to improve private insurance coverage for substance abuse and mental health in the United States have mostly focused on equalizing coverage limits to those found in general medical care. Federal law does not address cost sharing (co-payments and coinsurance), which may also deter needed care or impose significant financial burdens on enrollees. This article reports on cost sharing requirements for outpatient care in a nationally representative sample of managed care plans in 1999. Levels of cost sharing are substantial, with around 40 percent of products requiring co-payments of $20 or more and another 15 percent requiring coinsurance of 50 percent. Cost sharing for outpatient substance abuse treatment is very similar to that for mental health. Compared to general medical care, at least 30 percent of products impose higher cost sharing for substance abuse and mental health treatment. Future parity initiatives should be examined for how they address differences in cost sharing as well as limits. Hodgkin, D., Horgan, C.M., Garnick, D.W., and Merrick, E.L. Cost Sharing for Substance Abuse and Mental Health Services in Managed Care Plans. Medical Care Research and Review, 60(1), pp. 101-116, 2003.

### Behavioral Health Quality Management Activities within Managed Care Organizations

This study analyzes managed care organizations' (MCOs') use of behavioral health quality management activities using nationally representative survey data. Four hundred and thirty four MCOs in 60 market areas were surveyed regarding their use of four behavioral health quality management activities: patient satisfaction surveys, clinical outcomes assessment, performance indicators, and practice guidelines. Chi(2) tests and logistic regression were used to determine effects of product type (HMO, PPO, point-of-service) and behavioral health contracting arrangement (specialty contract, comprehensive contract including general medical and behavioral health, internal provision). Three-quarters of products used patient satisfaction surveys (70.1%), performance indicators (72.7%), and practice guidelines (73.8%) for behavioral health. Under half (48.9%) assessed clinical outcomes. Most commercial managed care products use patient satisfaction surveys, performance indicators, and practice guidelines for behavioral health, whereas clinical outcomes assessment is less common. Product type and contracting arrangements significantly affect use of these activities. Merrick, E.L., Garnick, D.W., Horgan, C.M., and Hodgkin, D. Quality Measurement and Accountability for Substance Abuse and Mental Health Services in Managed Care Organizations. Medical Care, 40(12), pp. 1238-1248, 2002.

### Cost Analysis of Cannabis Youth Treatment Approaches

The present study conducted an economic cost analysis of several outpatient adolescent treatment approaches. The Cannabis Youth Treatment (CYT) study evaluated five structured treatments for cannabis-using adolescents. Using the Drug Abuse Treatment Cost Analysis Program (DATCAP), the economic cost of each site-specific treatment was determined. The average economic costs of the five types of outpatient treatments ranged from $837 to $3334 per episode, and varied by both direct factors (e.g. hours of treatment, treatment retention) and indirect factors (e.g. cost of living, staff level, case-load variation). These adolescent treatment cost estimates are examined in terms of their calculation, variability by condition, variability by site within condition and comparability with previous DATCAP results from outpatient drug-free programs for adults. Future research will integrate treatment outcomes and costs to complete cost-effectiveness and benefit-cost analyses of the five therapies. French, M.T., Roebuck, M.C., Dennis, M.L., Diamond, G., Godley, S.H., Tims, F., Webb, C. and Herrell, J.M. The Economic Cost of Outpatient Marijuana Treatment for Adolescents: Findings from a Multi-site Field Experiment. Addiction. 97, Suppl 1, pp. 84-97, 2002.

### Costs and Benefits of Methadone Treatment: Crime Cost Savings

Longer lengths of stay in methadone treatment have been associated with greater treatment benefits such as reductions in heroin use and criminal activity. This paper examines monetary returns from investments in longer-term methadone treatment for opioid users who participated in NIDA's Drug Abuse Treatment Outcome Studies (DATOS). Part 1 focuses on crime cost savings for discharged patients (patients who left their index DATOS treatment program before completing 1 year of treatment) and continuing patients (those who continued in treatment for 1 year or longer). Subjects were 394 methadone patients from 8 medium to large cities and 16 programs; overall 37% were women, 33% African American, with an average age of 37.2. Greater lengths of stay in methadone treatment were associated with greater crime cost savings. Results showed that methadone treatment provides significant returns on treatment investments for both continuing and discharged patients. However, greater net economic benefits were realized from continuing patients. Flynn, P.M., Porto, J.V.,

Rounds-Bryant, J.L., and Kristiansen, P.L. Costs and Benefits of Methadone Treatment in DATOS - Part 1: Discharged Versus Continuing Patients. Journal of Maintenance in the Addictions, 2(1/2), pp. 129-149, 2003.

### Costs and Benefits of Methadone Treatment: Gender Differences

This paper examines the role played by patient gender in affecting the cost savings of outpatient methadone treatment (OMT) in NIDA's Drug Abuse Treatment Outcome Studies (DATOS). Subjects were 144 women and 250 men from 8 cities and 16 programs. Female subjects were 30% African American, 43% Caucasian, and 26% Hispanic with an average age of 35.5 years. Male subjects were 35% African American, 40% Caucasian, and 24% Hispanic with an average age of 38 years. Women had greater reductions in crime costs than men. Greater net economic benefits to society were accrued by women than men. Results suggest that males might benefit from longer stays in methadone treatment. Flynn, P.M., Porto, J.V., Rounds-Bryant, J.L., and Kristiansen, P.L. Costs and Benefits of Methadone Treatment: Gender Differences for Discharged and Continuing Patients. Journal of Maintenance in the Addictions, 2(1/2), pp. 151-169, 2003.

### Building Bridges Between Research and Practice in Drug Abuse Treatment

The slowness with which most treatment innovations enter the field of drug abuse treatment has been a long and persistent complaint in the field. Dr. James Sorensen and his co-authors recently published an edited book of papers addressing ways to promote and exemplify collaboration in the substance abuse field. Chapter authors examine what field-developed treatments have attracted research attention, what research-developed treatments have been readily adopted into the field, and what is needed to bring researchers and practitioners into accord. By working together, researchers and practitioners can identify and develop promising scientific protocols, use the most rigorous standards to test them, and put into practice treatments that prove to be most effective. Drug Abuse Treatment through Collaboration: Practice and Research Partnerships that Work. Sorensen, James L., Rawson, Richard A. , Guydish, Joseph, and Zweben, Joan E. (Eds). Ways to Build Bridges Between Research and Practice in Drug Abuse Treatment. Washington, DC, US: American Psychological Association. xxii, 326 pp., 2003.

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

## Research Findings - Intramural Research

### Development and Plasticity Section, Cellular Neurobiology Research Branch

**Transcriptional Profiling in the Human Prefrontal Cortex: Evidence for Two Activational States Associated with Cocaine Abuse** CNS-focused cDNA microarrays were used to examine gene expression profiles in dorsolateral prefrontal cortex (dlPFC, Area 46) from seven individual sets of age- and post-mortem interval-matched male cocaine abusers and controls. The presence of cocaine and related metabolites was confirmed by gas chromatography-mass spectrometry. Sixty-five transcripts were differentially expressed, indicating alterations in energy metabolism, mitochondria and oligodendrocyte function, cytoskeleton and related signaling, and neuronal plasticity. There was evidence for two distinct states of transcriptional regulation, with increases in gene expression predominating in subjects testing positive for a metabolite indicative of recent 'crack' cocaine abuse and decreased expression profiles in the remaining cocaine subjects. This pattern was confirmed by quantitative polymerase chain reaction for select transcripts. These data suggest that cocaine abuse targets a distinct subset of genes in the dlPFC, resulting in either a state of acute activation in which increased gene expression predominates, or a relatively destimulated, refractory phase. Lehrmann, E., Oyler, J., Vawter, M.P., Hyde, T.M., Kolachana, B., Kleinman, J.E., Huestis, M.A., Becker, K.G., and Freed, W.J. Pharmacogenomics, 3, pp. 27-40, 2003.

**5-Hydroxytryptamine 1A Receptor Activation Protects Against N-Methyl-D-aspartate-induced Apoptotic Cell Death in Striatal and Mesencephalic Cultures** Apoptosis and glutamate-mediated excitotoxicity may play a role in the pathogenesis of Parkinson's disease (PD) and toxic effect of drugs of abuse such as amphetamines. We investigated whether stimulation of the 5-hydroxytryptamine 1A (5-HT1A) receptor attenuates N-methyl-D-aspartate- (NMDA) and 1-methyl-4-phenylpyridinium (MPP(+))-induced apoptotic cell death. A brief exposure (20 min) of M213-2O striatal cells to NMDA or glutamate produced a delayed increase in caspase-3 activity and DNA fragmentation. NMDA-induced caspase-3 activity and DNA fragmentation were almost completely blocked by the 5-HT1A agonists 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT) and (R)-5-fluoro-8 hydroxy-2-(dipropylamino)-tetralin (R-UH-301). Similarly, increases in caspase-3 activity and DNA fragmentation in rat primary mesencephalic neurons after exposure to NMDA and glutamate were almost completely inhibited by 8-OH-DPAT. This neuroprotective effect of 8-OH-DPAT was reversed by WAY 100635. Furthermore, 8-OH-DPAT and blocked apoptotic cell death in primary mesencephalic neurons that were exposed to the toxin MPP(+). Together, these results suggest that 5-HT1A receptor stimulation may be a promising pharmacological approach in the development of neuroprotective agents. Madhavan, L., Freed, W.J., Anantharam, V., and Kanthasamy, A.G. Journal of Pharmacology and Experimental Therapeutics, 304, pp. 913-923, 2003.

**Nerve Growth Factor-induced Neurite Sprouting in PC12 Cells Involves Sigma-1 Receptors: Implications for Antidepressants** One theory concerning the action of antidepressants relates to the drugs' ability to induce an adaptive plasticity in neurons such as neurite sprouting. Certain antidepressants are known to bind to sigma-1 receptors (Sig-1R) with high affinity. Sig-1R are dynamic endoplasmic reticulum proteins that are highly concentrated at the tip of growth cones in cultured cells. In this study, IRP researchers tested the hypotheses that Sig-1R might participate in the neurite sprouting and that antidepressants with Sig-1R affinity may promote the neuronal sprouting via Sig-1R. The prototypic Sig-1R agonist (+)-pentazocine [(+)PTZ], as well as the Sig-1R-active antidepressants imipramine and fluvoxamine, although ineffective by themselves, were found to enhance the nerve

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growth factor (NGF)-induced neurite sprouting in PC12 cells in a dose-dependent manner. A Sig-1R antagonist N,N-dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]-ethylamine monohydrochloride (NE100) blocked the enhancements caused by these Sig-1R agonists. In separate experiments, IRP investigators found that NGF dose and time dependently increased Sig-1R in PC12 cells. Chronic treatment of cells with (+)PTZ, imipramine, or fluvoxamine also increased Sig-1R. These latter results suggested that NGF induces the neurite sprouting by increasing Sig-1R. Indeed, the overexpression of Sig-1R per se in PC12 cells enhanced the NGF-induced neurite sprouting. Furthermore, antisense deoxyoligonucleotides directed against Sig-1R attenuated the NGF-induced neurite sprouting. When taken together, these results indicate that Sig-1R plays an important role in the NGF-induced neurite sprouting and that certain antidepressants may facilitate neuronal sprouting in the brain via Sig-1R. Takebayashi, M., Hayashi, T., and Su, T.P. Journal of Pharmacology and Experimental Therapeutics, 303(3), pp. 1227-1237, 2002.

**Chronic [D-Ala(2), D-Leu(5)]enkephalin Treatment Increases the Nerve Growth Factor in Adult Mouse Brain** The delta opioid peptide [D-Ala(2), D-Leu(5)]enkephalin (DADLE) has been shown to enhance the survival of dopaminergic neurons. Here, IRP scientists found that chronic treatment with DADLE caused a significant increase in nerve growth factor (NGF) in the hippocampus and the midbrain of adult albino Swiss (CD-1) mice, but not in the striatum or frontal cortex. Glia-derived neurotrophic factor (GDNF) was not significantly affected. Thus, the neuroprotective action of DADLE may be mediated in part by NGF. Hayashi, T., and Su, T.P. European Journal of Pharmacology, 464, pp. 237-239, 2003.

### Molecular Neuropsychiatry Section, Cellular Neurobiology Research Branch

**Methadone Treatment Induces Attenuation of Cerebrovascular Deficits Associated with the Prolonged Abuse of Cocaine and Heroin** Opiate replacement therapy has been useful in reducing heroin use and in keeping patients in treatment programs. However, neuropsychological and neurophysiological effects of this treatment regimen have not been evaluated systematically. To determine whether methadone treatment reduces the magnitude of cerebral blood flow alternations in polysubstance (heroin and cocaine) abusers, IRP scientists compared blood flow parameters in control subjects (n=26), polysubstance abusers (n=28) maintained on methadone for 24 weeks, and polysubstance abusers (n=22) who were not seeking treatment. Blood flow velocity was recorded from the anterior and middle cerebral arteries using transcranial Doppler sonography on an outpatient visit. The pulsatility index, a measure of cerebrovascular resistance, was significantly ($p<0.05$) increased in both groups of polysubstance abusers compared to control subjects. Increased pulsatility in the two groups of substance abusers suggests constriction of the small cortical arteries. Nevertheless, the methadone-maintained polysubstance abusers had significantly lower pulsatility values than the nontreatment substance-abusing group. These findings suggest that maintenance on methadone might have significant beneficial neurovascular effects on this population of patients. Herning, R.I., Better, W.E., Tate, K., Umbricht, A., Preston, K.L., and Cadet, J.L. Neuropsychopharmacology, 28, pp. 562-568, 2003.

### Preclinical Pharmacology Section/Behavioral Neuroscience Branch

**Glutamate mGlu5-Adenosine A2A-Dopamine D2 Receptor Interactions in the Striatum: Implications for Drug Therapy in Neuropsychiatric Disorders and Drug Abuse** There is growing evidence for the existence of not only homomeric, but also functional heteromeric receptor complexes, particularly involving G protein coupled receptors (GPCRs). These include adenosine A2A-dopamine D2 and adenosine A2A-glutamate mGlu5 receptor complexes. The role of these receptor complexes in receptor function seems to be multiple, involving hetero-modulation of ligand recognition, signalling and trafficking. The preferential localization of A2A-D2 and A2A-mGlu5 receptor complexes is in the dendritic spines of striatopallidal GABAergic neurons. Results obtained from behavioral and in vivo microdialysis experiments have shown an important role of mGlu5-A2A-D2 receptor interactions in the modulation of the function of the striatopallidal GABAergic neurons. The striatopallidal GABAergic neurons play a key role in the pathophysiology of basal ganglia disorders, like Parkinson's disease, and comprise a common pathway for the rewarding effects of opiates and psychostimulants and for the antipsychotic effects of neuroleptics. The formation of receptor complexes modifies the single receptor transducing characteristics and leads to the appearance of "emergent properties". Thus, the study of mGlu5-A2A-D2 receptor interactions in the striatum reveals new properties of these GPCRs and gives indications for a new rational approach for drug therapy in neuropsychiatric disorders and drug addiction. Ferre, S., Ciruela, F., Woods, A.S.,

Canals, M., Burgueno, J., Marcellino, D., Karz-Kubicha, M., Hope, B.T., Morales, M., Popoli, P., Goldberg, S.R., Fuxe, F., Luis, C., Franco, R. and Agnati, L. Curr. Med. Chem.-Central Nervous System Agents, 3, pp. 1-26, 2003.

**Second-order Schedules of Drug Self-administration in Animals** On a second-order schedule, a subject responds according to one schedule (the unit schedule) for a brief presentation of a stimulus such as a light. Responding by the subject on this unit schedule is then reinforced according to another schedule of reinforcement. Second-order schedules of drug injection allow the study of more complex behavioral sequences than do simple schedules and may more accurately reflect the human drug-abuse situation. Much of the early work in this area used primates as subjects and focused on the behavioral variables controlling responding. It was shown that long sequences of behavior could be maintained on second-order schedules with relatively infrequent injections of drug and that the second-order, brief-stimulus presentations were critical to the acquisition and maintenance of responding. Also, the continued presentation of the brief stimulus in extinction often led to prolonged extinction behavior. These studies clearly showed that environmental stimuli greatly influence drug self-administration behavior under second-order schedules. The focus of much of the more recent work with second-order schedules has been on the evaluation of pharmacological treatments for drug addiction, both as antagonist and substitution therapies. Both types of potential therapies have shown promise in these preclinical models of addictive behavior. The recent extension of second-order self-administration studies to rats as subjects has facilitated the investigation of neural mechanisms involved in this behavior. While this use of second-order schedules is a relatively recent phenomenon, significant contributions have already been made in identifying neural mechanisms critical to second-order schedule drug self-administration. This active area of research holds great promise for delineating specific brain regions critical to different aspects of drug addiction. Schindler, C.W., Panlilio, L.V. and Goldberg S.R. Psychopharmacology, 163, pp. 327-344, 2002.

### Cognition and Pharmacology Section, Neuroimaging Research Branch

**Cognitive Mechanisms of Nicotine on Visual Attention** Nicotine is known to improve performance on a range of cognitive tasks, notably attention and to a lesser extent, working memory in both humans and animals, which could contribute to smoking maintenance by improving concentration. As such, understanding nicotine's neurobiological and cognitive mechanisms may help explain both its addictive properties and potential therapeutic applications. To this end, functional magnetic resonance imaging (fMRI) was used to determine the neural substrates of nicotine's effects on a sustained attention (rapid visual information-processing) task. Task performance activated specific bilateral frontal, parietal, thalamic, occipital and cerebellar regions previously associated with sustained attention and working memory, with additional strong task-induced activations in the anterior insula and caudate. Decreased activation in left frontal, anterior and posterior cingulate, insula and left parahippocampal regions were also seen. Along with subtle behavioral deficits, mildly abstinent smokers showed less task-induced brain activation in the parietal cortex and caudate than did non-smokers. Application of a 21 mg nicotine patch to smokers improved task performance in smokers and increased task-induced BOLD activation in attention-related areas bilaterally including the parietal cortex, thalamus and caudate, while nicotine induced a generalized increase in occipital cortex activity. The nicotine patch also prevented the decline in mood ratings that followed task performance in smokers with placebo patch. Nicotine administration further deactivated some of the brain regions deactivated by the task, suggesting that nicotine improves attention in smokers by enhancing activation in areas traditionally associated with visual attention, arousal and motor activation in order to specifically focus attentional resources on task demands. Lawrence, N.S., Ross, T.J. and Stein, E.A. Neuron, 36, pp. 539-548, 2002.

### Neuropsychopharmacology Section, Behavioral Neuroscience Research Branch

**Dopamine D3 Receptor Antagonists as Potential Anti-craving and Anti-relapse Medications for Treatment of Addiction** IRP investigators have determined that acute blockade of the dopamine D3 receptor in the rat brain (which is neuroanatomically restricted to the mesolimbic dopamine system, implicated in drug-induced reward and drug-seeking behavior) dose-dependently attenuates cocaine-enhanced brain-stimulation reward, acquisition of cocaine-induced conditioned cue preference, expression of cocaine-induced conditioned cue preference, acquisition of heroin-induced conditioned cue preference, expression of heroin-induced conditioned cue preference, and cocaine-triggered relapse to cocaine-seeking behavior in animals

pharmacologically detoxified and behaviorally extinguished from their intravenous cocaine-taking behavior. These findings suggest that dopamine D3 receptor antagonists are worthy of further investigation as potential anti-craving and anti-relapse medications for the treatment of drug abuse. Ashby, C.R. Jr., Paul, M., Gardner, E.L., Heidbreder, C.A., and Hagan, J.J. Synapse, 48, pp. 154-156, 2003.

**Anatomically Focal Mild Electrical Stimulation of the Brain Triggers Drug-seeking Behavior, A Way to Map the "Relapse" Circuits of the Brain** Brain IRP scientists have determined that anatomically focal mild electrical stimulation of specific sites deep within the brain triggers relapse to drug-seeking behavior in animals pharmacologically detoxified and behaviorally extinguished from their intravenous drug-taking behavior. In this way, they have begun to anatomically map out the "relapse" circuits of the brain. They have also determined that these "relapse" circuits of the brain correspond to the brain areas that are activated in humans during drug-craving. They have further determined that these "relapse" circuits in the brain use the brain chemical glutamate as their synaptic transmitter. These findings suggest that compounds acting on the glutamate neurotransmitter system of the brain are worthy of further investigation as potential anti-craving and anti-relapse medications for the treatment of drug abuse. Hayes, R.J., Vorel, S.R., Spector, J., Liu, X., and Gardner, E.L. Psychopharmacology, electronic publication ahead of print, January 24, 2003 [PMID 12545331].

### Neurobiology of Relapse Section, Behavioral Neuroscience Research Branch

**Time-dependent Increases in Brain-derived Neurotrophic Factor (BDNF) Protein Levels Within the Mesolimbic Dopamine System Following Withdrawal from Cocaine: Implications for Incubation of Cocaine Craving** Using a rat model of drug craving, IRP scientists found that the responsiveness to cocaine cues progressively increases or incubates over the first 60 days of cocaine withdrawal. Here investigators studied whether alterations in BDNF protein levels within the mesolimbic dopamine system are associated with this incubation phenomenon. BDNF is involved in synaptic plasticity and was found to enhance responding for cues associated with natural rewards. Rats were trained to lever-press for intravenous cocaine or oral sucrose for 6-hours/day for 10 days; each earned reward was paired with a tone-light cue. Resumption of lever-pressing behavior was then assessed on days 1, 30 or 90 of reward withdrawal. First, resistance to extinction was assessed during 6 hours wherein lever presses were not reinforced and the cue was absent. Second, cue-induced reinstatement was assessed after extinction during 1 h wherein responding led to cue presentations. Other rats were sacrificed without testing on days 1, 30, and 90 of reward withdrawal and BDNF and nerve growth factor (NGF) protein levels were measured in the ventral tegmental area (VTA), accumbens and amygdala. Lever pressing during extinction and cue-induced reinstatement tests of cocaine craving progressively increased following cocaine withdrawal. Time-dependent changes also were observed during the tests for sucrose craving, with maximal responding on day 30. BDNF, but not NGF, levels in the VTA, accumbens and amygdala progressively increased following cocaine, but not sucrose, withdrawal. Time-dependent increases in BDNF levels may lead to synaptic modifications that underlie enhanced responsiveness to cocaine cues after prolonged withdrawal periods. Grimm, J.W., Lu, L., Hayashi, T., Su, T.P., Hope, B.T. and Shaham, Y. The Journal of Neuroscience, 23, pp. 742-747, 2003.

### Treatment Section, Clinical Pharmacology & Therapeutics Research Branch

**Effects of Opioid Detoxification on Withdrawal and Pain in Hospitalized Heroin-Dependent AIDS Patients** With the growing role of intravenous drug use in the transmission of HIV infection, HIV-infected patients frequently present with comorbid opioid dependence. Yet, few empirical evaluations of the efficacy and consequences of opioid detoxification medications in medically ill HIV-infected patients have been reported. In a randomized, double blind clinical trial, IRP scientists evaluated the impact of three medications on the signs and symptoms of withdrawal and on pain severity in heroin-dependent HIV-infected patients (N=55) hospitalized for medical reasons on an inpatient AIDS service. Patients received a 3-day pharmacologic taper with intramuscular buprenorphine (n=21), oral clonidine (n=16), or oral methadone (n=18). Observer- and subject-rated opiate withdrawal scores decreased significantly following the first dose of medication and overall during treatment. Among all 55 subjects, self-reported and observer-reported pain decreased after treatment (on average OOWS scores declined 5.6 units and SOWS declined 4.77 units $p<0.001$ for both) with no indication of increased pain during medication taper. There were no significant differences of pain decline and other measures of withdrawal between the 3 treatment groups. Supplemental morphine

was administered as medically indicated for pain to 45% of the patients; only 34% of men versus 62% of women received morphine ($p < .05$). These findings suggest buprenorphine, clonidine, and methadone regimens each decrease opioid withdrawal in medically ill HIV-infected patients. No differences between effectiveness of these treatment regimens were detected. Umbricht, A., Leslie, J.M., Tucker, M.J., Hoover, D.R., Chaisson, R.E. and Preston, K.L. Drug and Alcohol Dependence, 69, pp. 263-272, 2003.

**Abstinence Reinforcement Maintenance and One-Year Follow-Up in Methadone Maintenance Patients** Relapse to drug use is often seen when contingencies designed to reduce drug use are discontinued. IRP scientists tested a stepdown maintenance contingency and 1-year follow-up in 110 patients who had completed the contingency management trial targeted to decreasing their opiate use. In this study participants were rerandomized to receive vouchers and take-home methadone doses contingent on providing opiate-negative urine specimens (N=55) or noncontingently (N=55) for 12 weeks. Follow-up interviews were conducted at 3, 6, and 12 months after study participation. Patients who received the maintenance contingency following an 8-week induction contingency had better outcomes than those who received noncontingent incentives in either the maintenance or induction phases of the trial. Good outcome at follow-up was predicted by enrollment in methadone maintenance after the study. Significantly more participants in the maintenance contingency group transferred directly to another methadone program. These findings support the therapeutic value of extending the duration of contingency management and long-term methadone maintenance. Preston, K.L., Umbricht, A. and Epstein, D. Drug and Alcohol Dependence, 67, pp. 125-137, 2002.

**Cognitive-Behavioral Therapy Plus Contingency Management for Cocaine Use in Methadone-Maintenance Patients: Emergent Effects One Year Later?** This project assessed methods for decreasing HIV-risk behaviors in substance abusers, and assessed the safety and efficacy of pharmacological and behavioral treatments for opioid dependence in those already infected with HIV. Contingency management (CM) rapidly reduces cocaine use, but its effects subside after treatment. Cognitive-behavioral therapy (CBT) produces reductions that emerge 6-12 months after treatment ends. Combined, the 2 treatments might be complementary. In a 2x2 design, 193 cocaine-using methadone-maintained outpatients were randomly assigned to 12 weeks of group therapy (CBT or a control condition) and voucher availability (CM contingent on cocaine-negative urines, or noncontingent vouchers). As part of the CBT treatment, patients were taught 1) to identify and seek out sources of reinforcement that do not carry risks of HIV; and 2) to develop adaptive problem-focused and emotion-focused coping responses to general and drug-specific stressors that might otherwise trigger HIV-risk behaviors. Follow-up visits occurred 3, 6, and 12 months after study exit. The primary outcome measure was cocaine-negative urines. During treatment, the initial effect of CM was apparently dampened by CBT. Posttreatment, there were signs of additive benefits, significant in 3 vs. 12-month contrasts. Former CBT participants were also more likely to acknowledge cocaine use and its effects, and to report more employment. The treatment outcome data have been published. Data on HIV risk behaviors are currently being analyzed. Epstein, D., Hawkins, W., Covi, L., Umbricht, A. and Preston, K.L. Psychology of Addictive Behaviors, 17, pp. 73-82, 2003.

**Urinary Elimination of Cocaine Metabolite in Chronic Cocaine Users During Cessation** In an earlier study, IRP investigators showed that chronic cocaine use by active illicit users produced a longer plasma half-life than expected based on acute low-dose cocaine studies. In this study urinary excretion patterns of cocaine metabolites such as benzoylecgonine (BE) equivalents from 18 of the same individuals, housed for up to 14 days on a closed research unit, were evaluated. In addition, the investigators evaluated whether creatinine normalization of BE equivalents increased mean detection time and reduced mean within-subject variability. All urine voids (N=953) were individually assayed; BE equivalents were determined semi-quantitatively by immunoassay. Compared to the concentration found in first void after admission, BE equivalents decreased to approximately 33%, 8%, and 4% at 24, 48, and 72 hours, respectively. Mean + SD (range) time to first negative specimen (BE equivalents <300 ng/mL) was 43.6 + 17.1 (16-66) hours. BE equivalents fluctuated considerably across successive specimens; 69% of participants tested positive at least once after testing negative, and the mean time to last positive specimen was 57.5 + 31.6 (11-147) hours after the first specimen. Thus, mean cocaine metabolite detection times were consistent with prolonged elimination, with 63% of participants testing positive longer than the expected 48-hour window of detection after admission to the unit. Mean time to last positive after last use of cocaine, known by self-report only, was approximately 81 + 34 [range 34 - 162]

hours. Creatinine normalization, with the cutoff of 300 ng BE equivalents/mg creatinine, increased detection time: mean time to first negative specimen was 54.8 + 20.7 (20-100) hours, and mean time to last positive specimen was 88.4 + 51.0 (35.6-235) hours. Compared to the concentration found in the first void after admission, BE equivalents/creatinine decreased to approximately 56%, 6%, and 5% at 24, 48, and 72 hours. However, creatinine normalization did not reduce the fluctuation of BE equivalents across successive specimens. Thus, creatinine normalized values may be useful when the goal is to maximize the probability or duration of cocaine metabolite detection, but may be less useful in determining whether an individual has used cocaine since a previous specimen collection. Preston, K.L., Epstein, D.H., Cone, E.J., Wtsadik, A.T., Huestis, M.A. and Moolchan, E.T. Journal of Analytical Toxicology, 26, pp. 393-400, 2002.

**A Dose-response Study of Cognitive Behavioral Therapy in Cocaine Abusers** In order to evaluate the effect of frequency of counseling sessions, IRP scientists studied retention, cocaine use and craving, and psychiatric symptoms of 68 cocaine-dependent outpatients randomly assigned to twice weekly, once weekly, or biweekly sessions in a 12-week treatment program that utilized manual-based, individual cognitive behavioral psychotherapy. All participants were tested and monitored twice a week. Retention was comparable among treatment groups, and improvement was found regardless of counseling frequency. Cocaine use (urine toxicology and self-report), cocaine craving (VAS), and total psychiatric symptoms (SCL-90) decreased by modest but statistically significant ($p<0.05$) amounts in all treatment groups. Findings suggest that cognitive behavioral therapy is effective in reducing cocaine use even if a less intensive schedule is used. Covi, L., Hess, J.M., Schroeder, J.R. and Preston, K.L. Journal of Substance Abuse Treatment, 23, pp. 191-197, 2002.

**Does Cannabis Use Predict Treatment Failure in Methadone-maintenance Patients?** It is unclear whether cannabinoid-positive urine specimens in heroin-dependent outpatients predict other drug use or impairments in psychosocial functioning, and whether such outcomes are better predicted by cannabis-use disorders than by cannabis use itself. IRP scientists have completed retrospective analyses of three clinical trials conducted in an urban outpatient methadone clinic. Each trial included a behavioral intervention (contingency management) for cocaine or heroin use during methadone maintenance, lasted 25-29 weeks, and had follow-up evaluations at 3, 6, and 12 months posttreatment. Data were pooled across trials where appropriate. Four hundred and eight polydrug abusers meeting methadone-maintenance criteria were categorized as nonusers, occasional users, or frequent users of cannabis based on thrice-weekly qualitative urinalyses. Cannabis-use disorders were assessed with the Diagnostic Interview Schedule III-R. Outcome measures included proportion of cocaine- and opiate-positive urines and the Addiction Severity Index (at intake and follow-ups). Cannabis use was not associated with retention, use of cocaine or heroin, or any other outcome measure during or after treatment. The analyses employed had a power of .95 to detect an r2 of .11 between cannabis use and heroin or cocaine use; the r2 we detected was less than .03 and nonsignificant. A previous finding that cannabis use predicted lapse to heroin use in heroin-abstinent patients did not replicate in the current sample. However, cannabis-use disorders were weakly associated with psychosocial problems at posttreatment follow-up. Cannabinoid-positive urines need not be a major focus of clinical attention during treatment for opiate dependence, unless patients report symptoms of cannabis-use disorders. Epstein, D.H. and Preston, K.L. Addiction, 98, pp. 269-279, 2003.

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

## Program Activities

### New NIDA PAs and RFAs

On February 6, 2003, NIDA issued a Request for Applications (RFA) entitled **Neuroimaging the Effects of Drugs of Abuse on the Development of the Human Nervous System (RFA-04-002)**. This RFA is designed to encourage research that takes advantage of the rapidly evolving methodology of neuroimaging to further our understanding of the consequences of drug exposure, abuse and addiction on the developing human brain. Neuroimaging is progressing rapidly and new techniques are continually being developed and refined providing a window into the structural, neurochemical and functional neurobiology of the nervous system. Research that addresses the effects of drug exposure during development, spanning the continuum of development from in utero exposure through the transition to adulthood, is greatly needed. This announcement seeks to encourage investigators experienced in the field of drug abuse, as well as researchers from the spectrum of disciplines that investigate neurobiological and neurobehavioral aspects of typical and atypical development, to apply their knowledge and expertise to the complexities of the effects of drugs of abuse on the developing human brain.

On April 28, 2003, NIDA issued an RFA entitled **NIDA Neuroproteomics Research Centers (NIDA NPRCs) (DA-04-004)**. These Centers should be built around scientific themes that address questions relevant to the mission of NIDA. The Centers will support already existing neuroscience research, provide training in proteomics technologies and develop new proteomics technologies. The objective of this program is to provide technical and administrative support for proteomics Centers in order to increase the accessibility of the Centers to neuroscience researchers at institutions with a demonstrated need for such a resource, to develop new or improve existing proteomics technologies that would be applied to the analysis of tissues of the nervous system and promote sharing of information with the scientific community. Letter of Intent Receipt Date for this RFA is September 24, 2003; Application Receipt Date is October 24, 2003.

### PAs and RFAs Issued With Other NIH Components/Agencies

On February 20, 2003, NIDA, in collaboration with a number of other NIH Institutes, the Centers for Disease Control and Prevention (CDC) and the United States Agency for International Development (USAID), issued a Program Announcement (PA) entitled **Planning Grants to Organize Programs for International Clinical, Operational, and Health Services Research Training for AIDS and Tuberculosis (PAR-03-073)**. This PA, which replaces PA-02-022, published in the NIH Guide on November 28, 2001, provides extended support for training to foster collaborative, multidisciplinary research in developing country sites where HIV/AIDS, TB or both are significant problems. This program is an integral and critical component of a comprehensive global strategy of the NIH and Department of Health and Human Services (DHHS) to address the needs of the millions suffering from HIV/AIDS, tuberculosis, and related conditions in resource-limited nations.

On March 27, 2003, NIDA, in collaboration with a number of other NIH components, issued a Program Announcement entitled **Centers for AIDS Research: D-CFAR, CFAR (PAR-03-089)**. This PA, which replaces PAR-00-054, published in the NIH Guide on February 9, 2000, invites applications for center core grants (P30) to support Centers for AIDS Research: standard CFARs (CFAR) and Developmental CFARs (D-CFAR). CFAR cores provide infrastructure and promote basic, clinical, behavioral and translational AIDS research activities at institutions that receive

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significant AIDS funding from multiple NIH Institutes or Centers. CFARs foster synergy and improve coordination of research, support emerging research opportunities, and promote economy of scale through resources shared by multiple independent laboratories.

On March 31, 2003, NIDA, in collaboration with the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Aging (NIA), and the National Institute of Environmental Health Sciences (NIEHS), issued a Program Announcement entitled **Gene Discovery for Complex Neurological and Neurobehavioral Disorders (PAS-03-092)**. The goal of this PA is to promote the identification of susceptibility genes for complex neurological and neurobehavioral disorders. For this PA, complex disorders are defined as those caused by the interaction of multiple genes, or by a combination of genetic and environmental risk factors. Many of these disorders are relatively common and clinically heterogeneous. Projects focusing on any phase of the gene discovery process, from initial patient ascertainment to positional cloning, are appropriate. Novel approaches, including the use of intermediate phenotypes that potentially underlie complex disorders, are also encouraged.

On April 7, 2003, NIDA, in collaboration with numerous other NIH and DHHS components, issued a Program Announcement entitled **Research on Children Exposed to Violence (PAR-03-096)**. This PA invites grant applications that will enhance our understanding of children exposed to domestic violence, community violence, and war/terrorism. This PA is designed to develop new knowledge in these areas and in the definition, identification, epidemiology, prevention, etiology, effects, early intervention, and mechanisms of violence exposure.

On April 17, 2003, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement **entitled Innovations in Biomedical Computational Science and Technology (PAR-03-106)**. Through this PA, participating Institutes and Centers of NIH invite applications for innovative research in biomedical computational science and technology to promote the progress of biomedical research. As defined here, biomedical computing or biomedical information science and technology includes database design, graphical interfaces, querying approaches, data retrieval, data visualization and manipulation, data integration through the development of integrated analytical tools, and tools for electronic collaboration, as well as computational and mathematical research including the development of structural, functional, integrative, and analytical models and simulations.

On April 18, 2003, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement entitled **NIH Small Research Grant Program (R03) (PA-03-108)**. This announcement redefines the NIH Small Grant (R03) mechanism, and extends its use to investigator-initiated applications at the participating Institutes and Centers. The R03 award supports small research projects that can be carried out in a short period of time with limited resources.

On April 18, 2003, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement entitled **NIH Exploratory/Developmental Research Grant Award (R21) (PA-03-107)**. This announcement redefines the NIH Exploratory/Developmental Research Grant Award (R21) mechanism, and extends its use by participating NIH components as an investigator-initiated mechanism. The R21 is intended to encourage exploratory and developmental research projects by providing support for the early and conceptual stages of these projects.

On February 12, 2003, NIDA, along with a number of other NIH Institutes, issued an RFA entitled **Clinical Research Education and Career Development (CRECD) in Minority Institutions (RR-03-007)**. CRECD awards are intended to support the development and implementation in minority institutions of curriculum-dependent programs to train selected doctoral and postdoctoral candidates in clinical research leading to a Master of Science in Clinical Research or Master of Public Health in a clinically relevant area. A successful program will result in an accredited master's degree program and will produce well-trained clinical researchers who can lead clinical research projects. The Letter of Intent receipt date for this RFA was March 31, 2003; Application Receipt Date was April 29, 2003.

### Other Program Activities

#### Increased Focus on "Relapse Models" within DTR&D's Contract Infrastructure for Medications Discovery

A competitive renewal of NIDA's contract to support behavioral pharmacology studies

for the Opiate Treatment Discovery Program was awarded to Virginia Commonwealth University in February of 2003, with increased support for the evaluation of potential medications in heroin self-administration relapse models and decreased support for work in opiate-dependent monkeys. This change reflects a continuing shift of resources toward addressing the relapse prevention aspect of opiate addiction treatment. Within the Cocaine Treatment Discovery Program, a separate contract (also with VCU) supports the evaluation of potential medications in cocaine self-administration relapse models. On April 10, 2003, in San Diego (prior to the Experimental Biology meeting), Drs. David McCann and Jane Acri, both of DTR&D, co-chaired a consultants meeting to review related contract progress and to discuss future directions of these efforts. A highlight of the meeting was the presentation of data - obtained during protocol development efforts - showing a striking interaction between stress and conditioned cues, two triggers to the reinstatement of drug seeking behavior that are usually considered in isolation. The unpublished findings have impacted protocols used for compound evaluations under NIDA's contracts and, when reported to the field, will likely stimulate increased research on the interactions between stress and conditioned cues. VCU contract scientists include Drs. Patrick Beardsley, Keith Shelton, Charlie Cook, and Louis Harris.

### Preclinical Methods for Evaluating Compounds with Potential for Treating Methamphetamine-Induced Cognitive Impairment

On April 29, 2003, in Rockville, Dr. Nathan Appel, DTR&D, chaired a consultants meeting entitled, "Preclinical Methods for Evaluating Compounds with Potential for Treating Methamphetamine-Induced Cognitive Impairment." The purpose of the meeting was to review preclinical models of methamphetamine-induced cognitive impairment that NIDA might employ in contract-supported efforts to evaluate potential medications. Dr. Sara Simon discussed how cognitive impairment as a consequence of methamphetamine abuse is manifested in patients and how it has been studied in clinical experiments. NIDA grantees Drs. Victoria Luine, John Marshall, and Charles Voorhees presented their work on the effects of methamphetamine on cognitive impairment in rats. A group of listening consultants, primarily experts on preclinical models of cognitive impairment and drug screening from major pharmaceutical companies and academe provided feedback to NIDA that will help plan and develop a preclinical program to evaluate potential drug candidates for treating methamphetamine-induced cognitive impairment. The meeting organizers were Dr. Appel, Mr. Hirsh Davis, DTR&D, and Dr. Jerry Frankenheim, DNBR.

### National Drug Abuse Treatment Clinical Trials Network (CTN) Protocol Update

- **Protocols CTN 0006** and **CTN 0007** have closed enrollment. Over 800 patients were randomized across 20 community treatment programs in 9 states.
- **Protocol CTN 0004** (Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome in Subjects Seeking Treatment for Substance Abuse) is actively enrolling at 6 sites across 3 states. A total of 358 participants have enrolled in this study so far.
- **Protocol CTN 0011** (A Feasibility Study of a Telephone Enhancement Procedure - TELE - to Improve Participation in Continuing Care Activities) began enrollment in January 2003. Over 150 patients in two sites have been enrolled in the last three months.
- **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.
- **Protocol CTN 0010** (Buprenorphine/Naloxone Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults) and Protocol CTN 0021(Motivational Enhancement Treatment to Improve Treatment Engagement and Outcome for Spanish-Speaking Individuals Seeking Treatment for Substance Abuse) are in the final stages of approval before being launched in the CTN. Enrollment is expected to begin in Second Quarter 2003.
- **Protocol CTN 0012** (Infections Screening in Substance Abuse Treatment Programs) is in the final stages of approval. The protocol training was held at the Albuquerque Steering Committee Meeting in March 2003. The trial is expected to begin in April or May 2003.

- Protocols in the third wave have been submitted and are in various stages of development and review. **Protocol CTN 0013**, Motivational Enhancement Therapy to Improve Treatment Utilization and Outcome in Pregnant Substance Abusers, has been approved for implementation. Final IRB approvals are being obtained. Enrollment is expected to start in May or June of 2003. 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 Data and Safety Monitoring Board (DSMB) Meeting. Protocol **CTN 0020**, Job Seekers Training for Patients with Drug Dependence, was also reviewed at the April DSMB. These studies are expected to be launched in the summer or fall of 2003.
- Five new research concepts have been approved for further development into protocols. The protocol teams and Lead Investigators were approved at the Steering Committee Meeting on October 23, 2002. First versions of the protocols are expected July 1, 2003.
- The CTN Design and Analysis Workgroup and the Dissemination Subcommittee are developing guidance on the implications of releasing data to clinics that participate in CTN clinical trials prior to completion of the trial and publication of the data. While acknowledging the desirability of releasing data to clinics as soon as possible in the process, the document will provide guidance on the minimum standards necessary for protecting the integrity of clinical trials and data analyses, and will address some of the issues surrounding different types of preliminary analyses that a Lead Investigator may perform, and which represent opportunities for early release of data to participating clinics.

### Neuroscience Perspectives Tutorial Series

Dr. Herbert Weingartner, DNBR, designed a tutorial series (Neuroscience Perspectives) for all of NIDA staff. The series meets on the first and third Tuesday of each month from 2:00-3:00pm in the NIDA conference room.

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

**Aharonovich, Efrat** -- New York State Psychiatric Institute
*Cognitive Deficits: Treatment Outcome In Cocaine Abusers*

**Aldrich, Jane V.** -- University of Kansas Lawrence Affinity Labels for Opioid Receptors

**Anagnostaras, Stephan G.** -- Emory University
*Memory Processes Governing Psychostimulant Sensitization*

**Andersen, Susan L.** -- McLean Hospital
*Translational Imaging of Methylphenidate Exposure*

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

**Bannon, Michael J.** -- Wayne State University
*Cocaine-Binding Dopamine Transporter: Molecular Biology*

**Bayer, Barbara M.** -- Georgetown University
*Lymphocyte Activity During Stress: Effects of Morphine*

**Bennett, Larry W.** -- University of Illinois at Chicago
*Jane Addams Substance Abuse Research Collaboration*

**Bergman, Jack** -- McLean Hospital, Belmont, MA
*Behavioral Effects and Abuse of Dopaminergic Drugs*

**Borchardt, Ronald T.** -- University of Kansas Lawrence
*Cyclic Prodrugs of Opioid Peptides*

**Bracken, Michael B.** -- Yale University
*Paraxanthine and Reproductive Effects of Caffeine*

**Broman, Clifford L.** -- Michigan State University
*Race and Family Factors In Adolescent Drug Use*

**Brook, Judith S.** -- Mount Sinai School of Medicine
*Drug Use and Problem Behaviors In Minority Youth*

**Carr, Kenneth D.** -- New York University School of Medicine
*CNS Mechanisms That Modulate Reward*

**Caudle, Robert M.** -- University of Florida
*Targeted Cholera Toxin for Treatment of Hyperalgesia*

**Dey, Sudhansu K.** -- Vanderbilt University
*Endocannabinoid Signaling During Early Pregnancy*

**Dorn, Lorah D.** -- University of Pittsburgh at Pittsburgh
*Smoking and Metabolic Complications In Adolescent Girls*

**Dym, Martin** -- Georgetown University
*A New Approach To Generate Transgenic Animals*

**Ettenberg, Aaron** -- University of California Santa Barbara
*Mechanisms of Opiate and Stimulant Drug Reinforcement*

**Fleckenstein, Annette E.** -- University of Utah
*Psychostimulants and Monoamine Transporters*

**Flynn, Patrick M.** -- Texas Christian University
*Organizational and Resource Assessments for Treatment Providers*

**Gabuzda, Dana H.** -- Dana-Farber Cancer Institute
*Monocyte Viral Reservoirs In HIV-1 Dementia*

**Gahring, Lorise C.** -- University of Utah
*Cholinergic Modulation of Inflammatory CNS Cytokines*

**Gilchrist, Lewayne D.** -- University of Washington
*Tandem Risk: Outcomes for Children of Teen Mothers*

**Glennon, Richard A.** -- Virginia Commonwealth University
*Chemical/Behavioral Studies On Hallucinogenic Agents*

**Goeders, Nicholas E.** -- Louisiana State University Health Sciences Center, Shreveport
*Environmental Influences On Cocaine Self-Administration*

**Goldsamt, Lloyd A.** -- National Development & Research Institutes
*Behavioral Aspects of HIV/HBV/HCV Risks In New Injectors*

**Grabowski, John** -- University of Texas Health Sciences Center, Houston
*Pharmacotherapy For Cocaine Dependence*

**Grace, Anthony A.** -- University of Pittsburgh at Pittsburgh
*Stress-Induced Alterations In Amygdala-LC Interactions*

**Grimm, Jeffrey W.** -- Western Washington University
*Incubation of Craving: Neural Substrates*

**Heimer, Robert** -- Yale University
*Syringe Exchange Based Hepatitis B Vaccination of IDU's*

**Herzog, Thaddeus A.** -- H. Lee Moffitt Cancer Center & Research Institute
*Stage Versus Continuum Models For Smoking Cessation*

**Hjelmstad, Gregory O.** -- Ernest Gallo Clinic and Research Center
*Plasticity of Kappa Opioid Function In Reward Circuitry*

**Howells, Richard D.** -- University of Medicine and Dentistry of New Jersey, Newark
*Purification and Mass Spectrometry of Opioid Receptors*

**Hruby, Victor J.** -- University of Arizona
*New Modalities for Treatment of Pain and Drug Abuse*

**Hser, Yih-Ing** -- University of California, Los Angeles
*Readiness for Implementation of Research To Practice*

**Hussey, Jon M.** -- University of North Carolina, Chapel Hill
*Child Maltreatment and Later Drug Use*

**Javitch, Jonathan A.** -- Columbia University Health Sciences
*Dopamine Transporter: Substrate & Cocaine Binding Sites*

**Kaplan, Howard B.** -- Texas A&M University System
*Drug Abuse and Other Deviant Adaptations: Two Generations*

**Kelley, Ann E.** -- University of Wisconsin, Madison
*Plasticity and Learning In A Corticostriatal Network*

**Knapp, Pamela E.** -- University of Kentucky
*Opioids Modulate Oligodendrocyte Development & Function*

**Koek, Wouter** -- University of Texas Health Sciences Center, San Antonio
*Neuropharmacology of GHB Discrimination*

**Largaespada, David A.** -- University of Minnesota, Twin Cities
*Transposon Mediated Insertional Mutagenesis In Mice*

**Laudet, Alexandre** -- National Development & Research Institutes
*12-Step As Aftercare: Predictors and Effectiveness*

**Lester, Henry A.** -- California Institute of Technology
*Biogenic Amine Transporters-Structure/Function*

**Liguori, Anthony** -- Wake Forest University Health Sciences
*Motivation and Attention In Marijuana Use and Withdrawal*

**Luthar, Suniya S.** -- Columbia University Teachers College
*Substance Abuse Among Suburban Youth: Prospective Study*

**Lysle, Donald T.** -- University of North Carolina, Chapel Hill
*Opioid-Induced Immune Alterations: Sex Differences*

**Mackler, Scott A.** -- University of Pennsylvania
*NAC-1 A Cocaine Regulated mRNA In the Rat Brain*

**Margolin, Arthur** -- Yale University
*Spiritual Self-Reevaluation Therapy for HIV+ Drug Users*

**Markman, Arthur B.** -- University of Texas, Austin
*Effects of Goal Activation on Competing Goals*

**Matta, Shannon G.** -- University of Tennessee Health Sciences Center
*Gestational Drugs and Nicotine Self-Administration*

**McCaffrey, Daniel F.** -- Rand Corporation
*Causal Effects of Community-Based Treatments for Youths*

**McGehee, Daniel S.** -- University of Chicago
*Nicotinic Modulation of the Mesoaccumbens DA System*

**McLaughlin, Jay P.** -- University of Washington
*Endogenous Opioid Mediation of Stress and Drug Reward*

**Melloni, Richard H.** -- Northeastern University
*Adolescent Anabolic Steroids, Vasopressin and Aggression*

**Menard, Scott W.** -- University of Colorado at Boulder
*Inhalant Abuse Across Generations In A National Sample*

**Mendelson, Jack H.** -- McLean Hospital, Belmont, MA
*Neurobiology of Nicotine: Hormones and Behavior*

**Miller, Bonnie C.** -- University of Texas SW Medical Center, Dallas
*Opioid Receptors On T Cell Subsets*

**Moeller, Frederick G.** -- University of Texas Health Sciences Center, Houston
*Serotonin, Drug Use and MDMA Induced Deficits*

**Morgan, Michael M.** -- Washington State University
*Cellular Mechanisms of Opioid Tolerance*

**Morrell, Joan I.** - Rutgers, The State University of New Jersey, Newark
*Maternal Rat Preferences for Pups Versus Cocaine*

**Nagarkatti, Prakash S.** -- Virginia Commonwealth University

*Cannabinoid-Induced Apoptosis In T Cell Regulation*

**Neaigus, Alan** -- National Development & Research Institutes
*Hiv Risk and Neighborhood Networks of New IDUs*

**Nichols, David E.** -- Purdue University West Lafayette
*Stereochemical Aspects of Hallucinogenesis*

**Olsen, George D.** -- Oregon Health & Science University
*Mu Opioid Receptor Regulation In Neonatal Brainstem*

**Pappas, George D.** -- University of Illinois at Chicago
*Analgesic Effects of Adrenal Chromaffin Cell Transplants*

**Peterson, Phillip K.** -- Minneapolis Medical Research Foundation, Inc.
*Modulation of Cell-Mediated Immune Function by Opiates*

**Piasecki, Thomas M.** -- University of Missouri, Columbia
*Ecology Momentary Assessment of College Smoking*

**Picciotto, Marina R.** -- Yale University
*Galanin-Opiate Interactions*

**Pickel, Virginia M.** -- Weill Medical College of Cornell University
*Em-Transmitter Interactions of Striatal Opioid Neurons*

**Pierce, R.C.** -- Boston University Medical Campus
*mPFC, N. Accumbens and Reinstatement of Cocaine Seeking*

**Ramaswami, Mani** -- University of Arizona
*Fos, Jun and Control of Synaptic Plasticity*

**Reggio, Patricia H.** -- Kennesaw State University
*Molecular Determinants for Cannabinoid Activity*

**Schafer, William R.** -- University of California, San Diego
*Analysis of Touch Response and Habituation In C. Elegans*

**Strathdee, Steffanie A.** -- Johns Hopkins University
*Incidence of HIV Infection In A Cohort of IV Drug Users*

**Takahashi, Traci A.** -- University of Washington
*Hospital Care IDUs With Soft Tissue Infections*

**Tapert, Susan F.** -- Veterans Medical Research Foundation, San Diego
*fMRI and Cognition In Adolescent MDMA and Cannabis Users*

**Tashkin, Donald P.** -- University of California, Los Angeles
*Cocaine Smoking Effects On Lung Immunity and Host Defense*

**Terman, Gregory W.** -- University of Washington
*Modulation of Spinal Cord LTP by Kappa Opioids*

**Toll, Lawrence** -- SRI International
*Computational Approach To Neuropeptides and Drug Abuse*

**Van Bockstaele, Elisabeth J.** -- Thomas Jefferson University
*Very Low Naltrexone Treatment of Opiate Withdrawal*

**Vaughan, Roxanne A.** -- University of North Dakota
*Affinity Labeling the Dopamine Transporter Active Site*

**Vaughan, Roxanne A.** -- University of North Dakota
*Phosphorylation and Regulation of Dopamine Transporters*

**Wagner, John J.** - North Dakota State University
*Cocaine-Induced Metaplasticity In the Hippocampus*

**Wakschlag, Lauren S.** -- University of Chicago
*Prenatal Smoking and Patterns of Youth Problem Behavior*

**Wang, Qiang** -- University of Missouri, Kansas City
*Metabotropic Glutamate Regulation of Amphetamine Action*

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

**Winger, Gail** -- University of Michigan at Ann Arbor
*Behavioral Economic Analysis of Polydrug Abuse*

**Witte, Susan S.** -- Columbia University New York Morningside
*Defining Fatherhood Among Drug Dependent Men*

**Wolf, Marina E.** -- Finch University of Health Sciences, Chicago Medical School
*Dopamine and Glutamate Receptor Interactions*

**Wu, Li-Tzy** -- Research Triangle Institute
*Inhalant Use/Dependence: Incidence and Comorbidity*

**Xie, Xiang-Qun** -- University of Connecticut, Storrs
*Advanced Isotope Aided NMR For Cb2 Structural Study*

**Yeomans, David C.** -- Stanford University
*In Vivo Genetic Manipulation of Neuronal Excitability*

**Zarkin, Gary A.** -- Research Triangle Institute
*Three Methods for Costing Methadone Treatment Services*

**Zhan, Chang-Guo** -- Columbia University Health Sciences
*Redesign of Butyrylcholinesterase for Cocaine Metabolism*

**Zhdanova, Irina V.** -- Boston University Medical Campus
*Cocaine-Induced Behaviors In Larval Zebrafish*

**Zhu, Hong** -- University of Mississippi Medical Center
*Neuronal Mechanisms of Opioid Action*

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

## Extramural Policy and Review Activities

### Reviews

NIDA received 972 grant applications, including both primary and dual assignments, 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 682 applications. OEA arranged and managed 18 review meetings in which 317 applications were evaluated. (Others were reviewed by the Center for Scientific Review). 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 four contract proposal review meetings, ten Small Business Innovation Research reviews, and two concept reviews. CRB staff are currently in the process of managing the reviews of fifty-eight Loan Repayment Program applications.

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. Two Special Emphasis panels were constituted for reviews of program project applications, and another was held to review unsolicited center grants. A meeting was held for a single application on a topic that did not fit into other committees.

Reviews were held for RFAs, including, "Chronic Stress and Its Relation to Drug Abuse and Addiction," " Guidance for Behavioral Treatment Providers: Research on Knowledge and Skill Enhancement," and "The Impact of Child Psychopathology and Childhood Interventions on Subsequent Drug Abuse."

The remaining panels were for the reviews of Behavioral Science Track Award for Rapid Transition-NIDA (B/START; 2 panels), Imaging Science Track Award for Rapid Transition (I/START), Cutting Edge Basic Research Awards, and Conference Grant mechanisms.

The completed review activities of the Contracts Review Branch are given below.

### Concept Reviews

- NO1DA-3-5524c: DESPR Clinical Data Management & Support
- NO1DA-4-7737c: Quantitation of Drugs of Abuse by Gas Chromatography/Mass Spectrometry

### Concept Proposals

- NO1DA-3-8829: Analytical Chemistry Resources Center for Medications Development
- NO1DA-3-8823: Rodent and Monkey Test for NIDA Medications Development Program
- NO1DA-3-1202: Logistics Support for NIDA's Contracts Review Branch/OEA
- NO1DA-3-8831: Assessment of Potential Cocaine Treatment in Non-Human Primates

### SBIR Reviews

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- N43DA-3-1112: Development of Science Education Materials Related to the Use of Animals
- N43DA-3-8832: Design, Synthesis, Preclinical Testing and Scale up of Novel Treatment Agents for Stimulant Abuse
- N43DA-3-5522: Worksite Based Health Promotion for Youth
- N43DA-3-5523: Develop New Technologies for Drug Abuse Prevention Delivery
- N43DA-3-5521: Measurement Modules for Psychiatric Comorbidity Evaluation
- N43DA-3-7733: Synthesis of New Chemical Probes
- N43DA-3-7734: Virtual Reality for Treatment of Pain or Drug Addiction
- N43DA-3-7735: Technologies for Proteomic Analysis in the Nervous System
- N43DA-3-4402: Development of Testing Technology to Support Delivery of Linked Drug Abuse Treatment and Primary Medical Care
- N43DA-3-8835: Pharmacovigilance Database for Anti-Addiction Medications

### Extramural Outreach

On February 25, 2003, Dr. Teresa Levitin, Director, OEA, participated in a workshop, "Peer Review of Education Research Grant Applications: Considerations, Implications and Future Directions" sponsored by the National Research Council Committee on Research in Education.

In March 2003, Dr. William Grace, Deputy Director, OEA, presented two talks at Binghamton University's Destination Discovery Research Symposium. The first was an update on NIH funding priorities and changes at NIH; the second was a discussion of peer review procedures at NIH.

Dr. Mark Swieter, SRA, Basic Sciences Review Branch, spoke on the grants enterprise at a meeting of the NIDA INVEST and Humphrey fellows in April 2003 when they met at the NIH campus. He participated in a panel presentation and discussion of "The Changing Scene of Funding for Neuroscience Training" at the annual meeting of the Association of Neuroscience Departments and Programs in Washington DC in May 2003.

### Staff Training and Development

The OEA Symposium Series provides staff training and a forum for sharing of ideas and information. Topics addressed have included the NIH policies on data sharing, the Health Insurance Portability and Accountability Act (the "Privacy Rule"), and data safety and monitoring. In addition, Dr. Cindy Miner spoke on activities of NIDA's Office of Science Policy and Communications. The symposium series is organized and hosted by Dr. Mark Swieter.

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

## Congressional Affairs

*(Prepared April 16, 2003)*

### FY 2003 Appropriations

On February 13, 2003, both the House and Senate approved a $397.4 billion FY 2003 omnibus spending bill. On February 20, 2003, the President signed into law H.J.Res.2, the Consolidated Appropriations Resolution, 2003, as P.L. 108-7. This legislation provides funding for FY 2003 for the 11 appropriations bills that had not been completed in the 107th Congress. The bill provides $27.2 billion for NIH, a $3.8 billion increase over FY 2002, and completes the doubling of the NIH budget over 5 years.

The NIH funding also includes a $100 million transfer by NIAID to the International Global Fund to Fight AIDS, Tuberculosis and Malaria.

### The Conference Report [Conf. Rpt. 108-10 to accompany HJ Res 2] includes the following language of special interest to NIDA:

NIH/NIDA: "The conference agreement includes $968,013,000 for NIDA as proposed by the Senate instead of $912,489,000 as proposed by H.R. 246.

The conferees commend NIDA for its partnership with the ONDCP, particularly the ongoing support NIDA provides to the sites established by the Counterdrug Technology Assessment Center (CTAC). The conferees encourage the continuation and expansion of NIDA funding for these research centers where CTAC has likewise committed resources."

OFFICE OF NATIONAL DRUG CONTROL POLICY:
*"Special Forfeiture Fund (Including Transfer of Funds)*
The conferees agree to provide $223,200,000 ÉÉ This includes $150,000,000 for the National Youth Anti-Drug Media Campaign, $60,000,000 for the Drug-Free Communities Support Program, $3,000,000 for the Counterdrug Intelligence Executive Secretariat, $2,000,000 for the Performance Measures Development, $6,400,000 for the US Anti-Doping Agency, $1,000,000 for the National Drug Court Institute, and $800,000 for dues to the World Anti-Doping Agency. The conferees provide that $2,000,000 of Drug Free Communities Funds shall be used to make a grant directly to the Community Anti-Drug Coalitions of America to establish and maintain the National Community Anti-Drug Coalition Institute as proposed by the Senate, instead of no provision as proposed by the House."

*"National Youth Anti-Drug Media Campaign"*
The conferees are deeply disturbed by the lack of evidence that the National Youth Anti-Drug Media Campaign has had any appreciable impact on youth drug use. With the funds provided for FY 2003, expenditures on the Media Campaign will be over $1,000,000,000 since the program's inception in FY 1998. While the evaluation conducted under the auspices of the NIDA has shown that the Media Campaign has had a slight sporadic impact on the attitudes of parents, it has had no significant impact on youth behavior. While the conferees are aware of surveys, such as MTF, that show recent declines in youth drug use, the NIDA study was undertaken to measure the specific impact of the Media Campaign, not simply to gauge general trends. The conferees have not included a provision requiring ONDCP to spend a certain amount on media buys for the Media Campaign as proposed by the House. The conferees expect ONDCP to allocate not less than the amount provided in FY 2002 to support the non-advertising public communications activities of the Media Campaign.

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The Director has inaugurated certain changes in the direction of the Media Campaign, such as producing new ads demonstrating the link between drug use and terrorism and other criminal activity, as well as an intensive anti-marijuana campaign launched in the fall of 2002 and a shift in the youth age group focus of the campaign. The conferees are hopeful that these and other changes will result in the achievement of the campaign's goal of reducing youth drug use. The conferees intend to rely on the scientifically rigorous NIDA study to gauge the ultimate impact of the campaign. If the campaign continues to fail to demonstrate effectiveness, then the Committees will be compelled to reevaluate the use of taxpayer money to support the Media Campaign."

*U.S. Anti-Doping Agency*
"The conferees include $6,400,000 for the U.S. Anti-Doping Agency (USADA). Within this amount, the conferees include $500,000 for the development of a school-based program for educating young athletes on the risks associated with dietary supplements. Not only are certain supplements banned from use by USADA, many supplements contain steroid precursors (which the body metabolizes into testosterone), such as androstenedione, androstendiol, and DHES. Studies have shown that these steroid precursors are being used by young athletes as performance-enhancing drugs at an alarming rate, even as early as the grade school level. The conferees believe that an education program is therefore necessary to make your young athletes aware of the risks associated with certain dietary supplements."

## FY 2004 APPROPRIATIONS

The President released his FY 2004 budget request on February 3, 2003. The program level for the NIH is $27.893 billion, an increase of $549 million over the FY 2003 Amended President's Budget. For NIDA, the FY 2004 figure is $996 million. When adjusted for one-time facilities costs in FY 2003, the total available for NIH non-biodefense research programs increases by 4.3 percent. The NIH President's Budget request to the Labor/Health and Human Services/Education Appropriations Subcommittee is $27.664 billion.

## BILLS OF INTEREST - 108TH CONGRESS

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

S. 8 - "The Educational Excellence for All Learners Act of 2003" would fully fund education reform, as called for in the "No Child Left Behind Act," and would increase authorized funding for the Safe and Drug Free Schools and Communities Program by $50 million to $700 million in FY 2004. Committees: Senate Health, Education, Labor and Pensions.

S. 22 - The Senate Democratic Caucus, led by Senate Minority Leader Daschle (D-SD), introduced legislation, "The Justice Enhancement and Domestic Security Act of 2003," that would authorize additional resources for drug and alcohol education, prevention and treatment programs. Committees: Senate Judiciary.

H.R. 207 - On January 7, 2003, Reps. Sweeney (R-NY) and Osborne (R-NE) introduced the bill "To amend the Controlled Substances Act with respect to the placing of certain substances on the schedules of controlled substances, and for other purposes." The bill would allow certain steroid precursors to be placed in a schedule as controlled substances. It would also authorize the Director of ONDCP to "undertake education programs at the grade and high school levels to highlight harmful effects of steroids and steroid precursor use by youths." There is authorized to be appropriated for such programs $10,000,000 for fiscal year 2004, $15,000,000 for fiscal year 2005, and $17,500,000 for fiscal year 2006. Committees: House Education and the Workforce, House Energy and Commerce, House Judiciary.

HR 811 - "Student Medical Access Raising Test Scores Health Act" or "SMARTS Health Act" was introduced February 13, 2003 by Rep. E.B. Johnson, (D-TX). The bill would authorize the Secretary of HHS to make demonstration grants to promote the well being and educational achievement of children through school-based health programs. The Secretary would coordinate the program with various Social Security and Medicaid programs, with programs of SAMHSA, HRSA, CDC, AHRQ, NIH, and the National Center on Minority Health and Health Disparities. Committees: House Education and the Workforce, House Energy and Commerce.

HR 844 - "National Center for Social Work Research Act" introduced February 13, 2003, by Rep. Rodriguez (D-TX). The bill would amend the PHSA to provide for establishment of a National Center for Social Work Research. A companion measure

(S73) was introduced in the Senate January 7, 2003, by Senator Inouye, D-HI. Committees: House Energy and Commerce.

HR 1599 - A bill to amend the Office of National Drug Control Policy Reauthorization Act of 1998 to ensure that adequate funding is provided for certain high intensity drug trafficking areas, was introduced April 3, 2003, by Rep. Cummings (D-MD). Committees: House Energy and Commerce, House Government Reform.

HR 1717 - A bill to amend the Controlled Substances Act to provide an affirmative defense for the medical use of marijuana in accordance with the laws of the various states was introduced April 10, 2003, by Rep. Farr (D-CA). Committees: House Energy and Commerce, House Judiciary.

On March 25, 2003, Dr. Henry (Skip) Francis, Director, Division of AIDS and Other Medical Consequences of Drug Abuse, NIDA, participated in a Congressional Briefing sponsored by Members of the Congressional Black Caucus [Rep. Donna Christian-Christensen (D-V.I.) and Rep. Edolphus Towns (D-NY)] and the National AIDS Treatment Advocacy Project. Advocates, community leaders, congressional representatives and their staff, attended the briefing designed to raise awareness about HCV and HIV/HCV co-infection. Dr. Francis addressed the relationship between drug abuse and HCV.

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## International Activities

On May 2, 2003, NIDA Director, Dr. Nora Volkow met with Mr. Gonzalo Robles Orozco, Government Delegate for the Spanish National Plan Against Drugs, the lead government official on drug policy and programs in Spain. Also in attendance were Mr. Javier Sagredo, currently at OAS/CICAD (Organization of the Americal States, Interamerican Commission on Control of Drug Abuse) and Drs. Richard Millstein, Timothy Condon, Steven Gust, Donald Vereen, and Patricia Needle. Topics of the discussion included the recent creation of the Instituto Nacional de Investigación y Formación sobre Drogas (National Drug Research and Training Institute) in Spain October 2002, and shared interest in developing a collaboration between the two countries. Plans were discussed for a bilateral workshop on research collaboration in the fall of 2003 and the signing of a letter of agreement between NIDA and Plan Nacional.

NIDA supported a one-day pre-conference, Global Initiatives in Tobacco Research held on February 19, 2003 before the **Society for Research on Nicotine and Tobacco** (SRNT) meeting in New Orleans. The pre-conference explored opportunities for expanding global research capacity, collaboration, and training through a keynote address by Dr. Kenneth E. Warner, University of Michigan, four plenary sessions, and a poster session. The four plenary sessions focused on current research, the interaction of research and tobacco control efforts, ways SRNT can facilitate research, and funding opportunities supported by NIDA, the National Cancer Institute, the Fogarty International Center, the Centers for Disease Control and Prevention, the American Cancer Society, and Canada's Research for International Tobacco Control. Dr. Steven W. Gust, International Program, OSPC, presented NIDA's mission, organization, and funding mechanisms during the meeting. Among the participants were grantees in the Fogarty Center's International Tobacco and Health Research and Capacity Building Program, which is partially supported by NIDA.

NIDA sponsored a workshop, Building Research Collaboration with the United States, at the **First European Congress on Addictive Disorders**, organized March 26 - 29, 2003 in Alicante, Spain by the Sociedad Espa–ola de Toxicomanias. The conference was designed to promote collaborations between clinicians and researchers across Europe and to facilitate consensus on a European level about the problems of substance use and treatments. Presenters included drug abuse clinicians and researchers from 12 European nations, the United States, the European Monitoring Centre for Drugs and Drug Addiction, and the World Health Organization. The NIDA workshop was organized by Dr. M. Patricia Needle, International Program, OSPC, and focused on the Institute's International Program mission, NIDA funding mechanisms to support collaborative research, and the U.S. National Institutes of Health grants process.

NIDA supported a symposium, Sex Differences in Addiction With Emphasis on Nicotine, at the **5th Neurochemistry Winter Conference**, held April 5-10, 2003 in Sšlden, Austria, by the University of Innsbruck. Drs. Minda Lynch (DNBR) and Steven Gust organized the NIDA symposium, which featured presentations by Dr. Sakire Pogun, Ege University School of Medicine, Turkey; and NIDA grantees Dr. Marilyn E. Carroll, University of Minnesota; Dr. Rosemarie M. Booze, University of South Carolina; and Dr. Anthony R. Caggiula, University of Pittsburgh. In addition to providing travel support for the four presenters, NIDA supported the participation of four recipients of the Young Investigator Award: Ms. Allyson McCormick, University of Washington; Dr. Amy Ramsey Mohn, Duke University; Dr. Etienne Sibille, Columbia University; and Dr. Andrew Tryba, University of Chicago.

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NIDA supported the participation of seven international researchers at the **American Association for the Treatment of Opioid Dependence Conference** April 13-16, 2003 in Washington, D.C., and the pre-conference forum of the European Opiate Addiction Treatment Association. NIDA-supported participants included Dr. Michael Arieli, Israel; Dr. Ray Baker, Canada; Dr. James Bell, Australia; Dr. Emilia Figueroa, Mexico; Dr. Peter Hickey, Canada; Dr. Alexander Kantchelov, Bulgaria; and Dr. Besnik Juca, Albania.

Two researchers have been selected as the **2003 WHO/NIDA/CPDD International Traveling Fellows**: Anna Maria Azevedo Simoes, M.D., M.S., Ph.Dc., Brazil; and Lan Ma, Ph.D., China. The fellowships are co-sponsored by NIDA, the World Health Organization, and the College on Problems of Drug Dependence (CPDD) to support the participation of international researchers in the NIDA International Forum and the CPDD Annual Scientific Meeting. The Fellowship also supports brief research visits by the Fellows with NIDA grantees in the United States. Dr. Simoes is the Principal Investigator of a study funded by the STD/AIDS National Coordination - Brazilian Ministry of Health to evaluate the feasibility and validity of using an Audio Computer Assisted Self Interview (A-CASI) to assess HIV risk behavior among Brazilian drug users. Study participants receive pre- and post-test counseling, and researchers assess the prevalence of HIV, hepatitis, and syphilis infection among individuals entering treatment at the State Center for Treatment and Rehabilitation of Addicts in Rio de Janeiro. NIDA grantee Dr. David Metzger, University of Pennsylvania, is a consultant to the project and co-author of the study. He and Dr. Simoes have collaborated since her 1997-1998 Hubert H. Humphrey Drug Abuse Research Fellowship, when she spent her six-week professional affiliation at the University of Pennsylvania Center for Studies of Addiction. For her Fellowship professional visits, Dr. Simoes will meet with Dr. Metzger and Dr. Don DesJarlais, Beth Israel Medical Center, New York. Dr. Ma researches the mechanisms of opioid addiction and opioid signaling as Associate Director of the National Laboratory of Medical Neurobiology, Fudan University Medical Center, Shanghai. She earned her Ph.D. at the University of North Carolina at Chapel Hill, and was named a 1993-1995 Miles Scholar by the Bayer Corporation. During 2002, Dr. Ma's research appeared in *Neuropharmacology*, 43, pp. 809-816; *Psychopharmacology*, 159, pp. 125-132; and the *Journal of Neuroscience*, 22, pp. 1914-1921. She will spend her research visits discussing collaborative research in the mechanisms of opioid signal transduction with Dr. Yavin Shaham, IRP; the neurobiology of relapse to opioid seeking with Dr. Jai B. Wang, University of Maryland; and the regulation of gene expression in the brain by chronic opioid administration and withdrawal with Dr. H.H. Loh, University of Minnesota.

**The 2002-2003 INVEST Research Fellows attended a NIDA orientation program** on April 3-4, 2003 in Baltimore and Bethesda, MD. The four INVEST Fellows are Dr. Isabelle Husson, France, who is working with Dr. Barry E. Kosofsky, Massachusetts General Hospital; Dr. Yilang Tang, China, whose mentor is Dr. Joseph F. Cubells, Yale University School of Medicine; Dr. Patricia Obando, Costa Rica, who is working with Dr. Edward L. Murrelle, Virginia Commonwealth University; and Dr. Tamo Nakamura, Japan, whose mentor is Dr. Anthony A. Wright, University of Texas. The four met with the following scientists at the NIDA Intramural Research Program in Baltimore: Drs. David Epstein, Marilyn Huestis, Eric Moolchan, Tom Ross, Elliot Stein, and David Gorelick. At NIDA headquarters, the Fellows met with Drs. Steven W. Gust and M. Patricia Needle, both of NIDA's International Program, as well as their mentors' project officers: Dr. Husson with Dr. Robert Riddle, DNBR; Dr. Tang with Dr. Harold Gordon, DTR&D; Dr. Nakamura with Dr. Paul Schnur, DBNR; and Dr. Obando with Dr. Cecilia McNamara, DTR&D. The 2002-2003 Hubert H. Humphrey Drug Abuse Research Fellows joined the INVEST Fellows for a seminar, Introduction to the NIH Research Grant Process. Presenters included Dr. Needle, Dr. Mark Swieter, Office of Extramural Affairs; Dr. David Thomas, DNBR; and Natalie Tomitch, Fogarty International Center. The participating Humphrey Fellows included: Ms. Maria Ametemben, Indonesia; Dr. Amit Chakrabarti, India; Dr. Meen Chhetri, Nepal; Dr. Ye Swe Htoon, Myanmar; Dr. Rastislav Lacko, Slovakia; and Dr. Asad Sabr, Saudi Arabia.

NIDA has selected two scientists as **2003-2004 INVEST Research Fellows**: Pajulo Marjaterttu, M.D., Ph.D., Finland, and Zhijun Li, M.D., China. Dr. Marjaterttu is a professor of child psychiatry at the University of Tempere and a senior physician in the department of infant psychiatry at Tempere University Hospital. Her current research explores psychological characteristics of early motherhood among substance-addicted mothers in residential treatment in Finland. She will spend her fellowship at Yale University School of Medicine working with Linda C. Mayes, M.D., to learn new research techniques for studying parenting among substance-using mothers and to identify substance-abuse treatment methods for parenting women.

Drs. Marjaterttu and Mayes hope to collaborate on developing prenatal interventions for substance-addicted pregnant women. Dr. Marjaterttu earned her medical degree at the University of Turku. 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. He will spend his fellowship at Johns Hopkins University working with Xiao-Fang Yu, M.D., D.Sc., to strengthen his lab research and data analysis skills, to study RNA clearance of the hepatitis C virus using specimens collected from a cohort of Chinese injection drug users, and to enhance the existing collaborative relationship with Dr. Yu. Dr. Li earned his Medical Degree at Guangxi Medical College and a Master of Science degree from University College Medical School, London, United Kingdom.

NIDA and the U.S. Department of State have selected nine researchers as **2003-2004 Hubert H. Humphrey Drug Abuse Research Fellows**. The two agencies cosponsor competitive, 10-month awards that provide academic training at Johns Hopkins University and six-week professional affiliations with NIDA-supported researchers. Awardees include:

- Ana Djordevic, M.D., Serbia and Montenegro, is a psychiatric resident specializing in drug abuse prevention and treatment. She established a school-based prevention program coordinated with a public education effort, and a separate prevention program targeted to at-risk children and adolescents.
- Reminder Kaur, M.B.B.S., M.P.M., Malaysia, is a psychiatrist in charge of the substance abuse clinic at Kuala Lumpur Hospital, where she has conducted clinical trials on the efficacy of buprenorphine in opiate detoxification and trains healthcare professionals.
- Natalia Lishchenko, M.D., Ukraine, teaches pediatrics at Ternopil State Medical Academy, conducts research on preventing drug and alcohol abuse among children and adolescents, practices pediatric medicine at the Ternopil Region Children's Clinical Hospital, and advises the local public health department.
- Boris Lobodov, M.D., Russia, directs the Center for Prevention and Treatment of Addictive Diseases at the Central District of Voronezh Clinic. He has conducted research on risk factors for addiction and established Web-based prevention programs for adolescents.
- David Otiashvili, M.D., Georgia, treats alcohol- and opioid-abuse patients at the Tbilisi Research Institute on Addiction, and studies the effects of rapid detoxification on neurophysiologic and hormonal systems.
- Riza Sarasvita, Indonesia, coordinates the provision of psychological services and supervises research at Fatmawati Drug Dependence Hospital in Jakarta. She is conducting a study of HIV/AIDS among Indonesian injection drug users and represents Indonesia on the Regional United Nations Task Force on IDU and HIV Vulnerability.
- Vladimir Stempliuk, Brazil, is completing his master's degree in science at Sao Paulo University School of Medicine, where he conducts research in epidemiology, teaches drug treatment courses, and provides drug abuse prevention services through community-based organizations.
- Chenghua Tian, M.D., Ph.D., China, is a psychiatrist and director of Scientific Research Management at the Peking University Institute of Mental Health, where he focuses on the prevention, education, treatment, and rehabilitation of alcohol abuse and alcoholism. He is an editor of the *Chinese Journal of Mental Health*.
- Tomas Zabransky, M.D., Ph.D., Czech Republic, is a researcher at the National Drug Commission, where he is responsible for building research capacity, establishing a data collection and monitoring system, and studying opiate agonist treatment protocols. He advises the Czech Parliament on drug issues, works on Czech Republic - European Union efforts, and serves on the scientific advisory boards of two professional journals, the Czech journal *Adictology* and Florida State University's *Journal of Drug Issues*.

NIDA provided travel support for a February 28, 2003 meeting at Institute headquarters between staff from the Prevention Research Branch, DESPR, Visiting Scholar Dr. Irina Pervova, Russia; and NIDA grantees Drs. Ed Smith and Linda Caldwell, Pennsylvania State University.

Dr. Suman Rao, OSPC, and Dr. Jim Colliver, DESPR met with two visitors from India on February 26, 2003. The visitors were Mr. Shankar Jiwal, Zonal Director, South Zone Narcotics Control Bureau, and Mr. Vivek Ranjan, Deputy Narcotic Commissioner, Central Bureau of Narcotics. The discussions centered on epidemiology, community work and training materials.

A "Business of Advertising" group from Belarus, sponsored by the Department of State's International Visitor Program visited NIDA on February 20, 2003. This is a Freedom Support Project for Belarus. The project is intended to give advertising professionals from Belarus the opportunity to gain a first-hand view of the management, policies and best practices of the business of advertising in the United States. The program is to show how advertising influences business development and affects the success of government agencies and non-governmental organizations. The NIDA representatives that met with the group were Ms. Jan Lipkin and Ms. Dale Weiss, both of OSPC.

Dr. Leslie Cooper, DESPR, and Ms. Dale Weiss, OSPC visited the South African Embassy on March 13, 2003. The purpose of the visit was to meet with Health Minister Nobayeni Dladla. Discussions included the upcoming NIDA South African Initiative meeting in Cape Town, South Africa on July 1-3, 2003, and other opportunities for NIDA to collaborate with researchers in South Africa.

Dr. Timothy P. Condon, Associate Director, NIDA, and Dr. Steve Gust, Dr. Patricia Needle and Ms. Dale Weiss, International Program, OSPC visited the Bureau for International Narcotics and Law Enforcement Affairs (INL), U.S. Department of State on January 21, 2003. Dr. Condon provided an overview of NIDA, and a brief tutorial of how drugs of abuse affect the brain. The audience, members of the INL Policy and Coordination and Latin American branches, asked many questions and were appreciative of the information presented.

A group of 11 Latin Americans visited NIDA on April 15, 2003. The visit was part of a program titled, "U.S. Drug Control Policy and Demand Reduction Efforts", sponsored by the U.S. Department of State. Countries from Latin America represented by the group were, Argentina, Chile, Colombia, Costa Rica, Guatemala, Paraguay, Peru and Venezuela. NIDA representatives speaking to the group were: Dr. Jag Khalsa, CAMCODA, Dr. Cathrine Sasek, OSPC, Dr. Jackie Kaftarian, DESPR, and Ms. Ana Anders, Office of Special Populations.

Dr. Meyer Glantz presented a discussion of drug abuse etiology and DESPR's research programs to a visiting delegation from the European Drug Demand Reduction Group on January 28, 2003. The delegation included representatives from Austria, The European commission, Greece, Italy, The Netherlands, Spain, the United Kingdom, and the U.S. Department of State and the National Association of Drug Court Professionals. The presentation discussed findings from research in the United States and the group discussion focused on the application of those findings to other countries.

Dr. Shakeh J. Kaftarian facilitated several meetings for the purpose of initiating scientific collaborations between a Woodrow Wilson fellow (Dr. Irina Pervova of Russia) and three NIDA investigators (Dr. Lawrence Scheier of University of Nevada and Drs. Ed Smith and Linda Caldwell of Penn State University). The above-mentioned meetings, which started in January 2003, have culminated into a collaborative activity between Drs. Pervova and Scheier, and will continue until arrangements are made between Drs. Pervova, Smith and Caldwell for another scientific collaboration.

Dr. Eliot Stein, IRP, presented a talk at a conference entitled, fMRI Experience V. at the Institute of Psychiatry, King's College, London in March 2003.

Dr. Peter Hartsock participated in the first organizational meeting at St. Petersburg State University (Russia) to plan development of the former Soviet Union's first school of public health. Meeting participants included deans from St. Petersburg State and Pavlov Medical University and NIDA grantees from various institutions around the U.S. including Johns Hopkins and Yale. Major emphasis in the new school will be upon research as well as teaching.

Drs. Peter Hartsock and Jacques Normand, both of CAMCODA, participated in a Fogarty International Center ICHORTA planning meeting involving NIDA/CAMCODA grantees (St. Petersburg, Russia, January 24-26, 2003). NIDA is a major player in the ICHORTA program, which deals with AIDS and TB. Drug abuse is the major driver of AIDS in Russia and AIDS, in turn, is the major driver of multi-drug resistant TB in that country.

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

## Meetings/Conferences

On February 10-11, 2003 NIDA sponsored a meeting entitled **Stem Cells: Opportunities for Drug Abuse Research?** The purpose of this meeting was to link drug abuse research to stem cell research; to explore the opportunities afforded by stem cell research; and to guide future NIDA research directions in this area of endeavor. The target audiences were developmental neuroscientists inside and outside NIH; neuroscientists in general, and drug abuse researchers with a particular interest in this line of work.

NIDA (Drs. Bill Corrigall, Frank Vocci) NCI (Dr. Scott Leischow) and NIAAA co-sponsored a one day pre-meeting workshop at the Society for Research on Nicotine and Tobacco (SRNT) Meeting on February 19, 2003, entitled, **"Smoking Cessation Pharmacotherapy: Accelerating Discovery to Delivery"**. Dr. Bill Corrigall chaired the Discovery of Targets section. Speakers in the discovery section included Drs. Caryn Lerman, Marina Picciotto, Julie Staley, and Daniel McGehee. Speakers in the Development of Medications section included Drs. John Hughes, Charles Grudzinskas, Paul Pentel, and Frank Vocci. The Delivery and Demand for Medications section was chaired by Dr. Scott Leischow. Speakers included Drs. Saul Schiffman, Sue Curry, Richard Hurt, and Scott Leischow.

On March 12, 2003, to commemorate *Brain Awareness Week*, NIH held a symposium entitled **Stress and the Brain: Developmental, Neurobiological, and Clinical Implications**. NIDA was the lead Institute coordinating this effort. The symposium highlighted basic and clinical scientific findings related to the various ways that stress can impact the brain, the body, and ultimately, peoples' lives. The speakers included NIDA Director Designee, Dr. Nora Volkow (Brookhaven National Laboratory), and Drs. Stephen Suomi (NICHD), Steven Maier (University of Colorado), Joseph LeDoux (New York University), and Kathleen Brady (Medical University of South Carolina). The topics of discussion were: environmental factors that impact addiction; the influence of early rearing on behavioral development; interactions between the immune system and the brain; the neurobiology of fear and emotion; and the role of trauma in mental health and substance abuse disorders.

On April 3-4, 2003 NIDA's Division of Epidemiology, Services and Prevention Research sponsored a conference entitled **What Do Schools Really Think About Prevention Research? Blending Research and Reality** in Bethesda, Maryland. This meeting provided a forum for discussing the challenges inherent in both conducting prevention research and implementing research-based prevention programs in schools. Researchers, practitioners (e.g., school administrators, principals, teachers), and Federal agency representatives explored their differing perspectives on these issues. The agenda included individual and panel presentations, and interactive workgroups. Program attendees were encouraged to fully participate in the dialogue.

On April 14, 2003, a NIDA sponsored workshop on **Smoking Cessation in Opioid Dependent Patients** was held at the meeting of the American Association for the Treatment of Opioid Dependence, in Washington, D.C. The workshop provided information on: the prevalence of cigarette smoking among opiate dependent individuals in the U.S.; behavioral and/or pharmacological treatments for nicotine dependence in opiate dependent patients; and approaches to relapse prevention. This workshop was organized by Dr. Dorynne Czechowicz and Dr. Ivan Montoya, both of DTR&D.

The Services Research Branch of the Division of Epidemiology, Services, and Prevention Research co-sponsored a services research conference, entitled, **Beyond**

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**the Clinic Walls: Expanding Mental Health, Drug & Alcohol Services Research Outside the Specialty Care System**. Over 250 individuals participated in the conference, which included 4 preconference workshops, 30 oral presentations, and 60 posters. Co-sponsored by NIDA, NIMH, and NIAAA, it was the first multi-institute services research conference ever to be held by NIH, and, as such, represents a new commitment to collaborative efforts among these three institutes to strengthen the research base underlying care for addictions and mental health problems. Abstracts from the conference presentations will be published on the NIMH homepage (www.nimh.nih.gov).

On March 27-28, 2003, a workshop was held on **Drug Use and Suicidal Behavior**. The workshop covered the epidemiology of suicidal behavior associated with drug use in adults and adolescents, treatment of suicidal drug users, prevention of suicide in adults and adolescents, and genetic and neurobiological approaches to understanding suicidal behavior, impulsivity, and aggression. Participants identified research gaps and suggested both new studies and ways of adding components to existing studies that would further our understanding of drug abuse and suicidal behavior and improve our ability to prevent and treat suicidal behavior in drug using populations.

NIDA's Office of Science Policy and Communications sponsored an **Advisory Panel** meeting on April 29, 2003 for the **Effectiveness of NIDA's Public Information Publications**. The meeting brought together experts to review the overall research design and the individual study methodologies. Participants included: Dr. David Rosenbloom (Boston University), Nancy Petry (University of Connecticut), Tom Valente (University of Southern California), Carol Schechter (Academy for Educational Development) and Ednita Wright (Cornell University). NIDA staff included: Drs. Timothy Condon, Cindy Miner and Denise Pintello.

On May 14-15, 2003, NIDA hosted **Foundations and Innovations in the Neuroscience of Addiction**, a 2-Day scientific meeting in honor of Dr. Roger Brown. For more than 20 years, Roger was instrumental in fostering the development of cutting edge neuroscience research in the area of drug abuse and addiction. The programs he helped stimulate and develop have made seminal contributions to our current understanding of neurobiology substrates for reinforcing effects of drugs of abuse, the transition to compulsive, uncontrollable patterns of use, and events that trigger relapse. Nobel laureate Dr. Arvid Carlsson, with whom Roger studied, delivered the keynote address. Other senior scientists contributing to these landmark developments presented a historical context for major accomplishments in this field. In addition, presentations from over 20 prominent investigators studying motivation and reward, cognition, neurotoxicity, pain and analgesia, and neuroplasticity highlighted contemporary findings from cutting edge research in the neuroscience of drug abuse and addiction.

**National CTN Steering Committee Meetings - Miami, FL**
The following meetings were held in Miami, Florida, January 25-30, 2003.

- The CTN Regulatory Affairs Subcommittee conducted a meeting on January 29, 2003.
- The CTN Quality Assurance Subcommittee held a meeting on January 30, 2003.
- A Buprenorphine Interest Group Meeting was held to discuss a pending liver safety study proposed by a drug company.
- The CTP Caucus met on January 26, 2003. The group reviewed a list of study priorities generated by the CTPs and developed a nomination process for the Eileen Pencer Lecture Series to be held at NIDA's Blending Meeting in September 2003.
- The Portfolio Coordinating Committee met on January 27, 2003. Members addressed the evaluation of Wave 4 Lead Investigators (LI) and teams, and requested supporting materials from LIs.
- The Operations Coordinating Committee met on January 27, 2003, to review and approve the final LI Report template for the LI monthly reports to the OCC and the Report to SC template. The Committee also reviewed progress on the GCP Competency Course and the proposed *CTN Guidebook*.
- The External Affairs Coordinating Committee met on January 27, 2003. The members reviewed the findings from the Criminal Justice Interest Group's assessment of criminal justice clients undergoing treatment throughout the Network. The group discussed how the CTN can develop

and support a cadre of new researchers and clinicians for future studies. The Dissemination Subcommittee reported on a planning meeting set for March 18-19, 2003 to discuss joint SAMSHA, CSAT, NIDA and CTN approaches.

- The Executive Committee met on January 26 and January 29, 2003. The committee addressed the following: a proposition for close-out meetings for protocols; node performance objectives and critical indicators; a draft of CTN By-Laws; a policy on Lead Investigator qualifications; and a proposal for a formal strategic plan for the CTN.
- Several other interest groups met in Miami at the Steering Committee Meeting including: Behavioral Therapy Interest Group (IG), Co-Occurring Disorders IG, Minority IG, Treatment Matching IG, and Gender IG.
- The Baseline Protocol (CTN 0008) leaders met with staff from the three new nodes and conducted a training session on the active protocol.
- The Family Management Skills Concept Team met in Miami and worked on drafting the first version of this new protocol.
- The Design and Analysis Workgroup met on January 26, 2003 to discuss outcome measures in addiction clinical trials; CONSORT guidelines; and lessons learned from the protocol reviews by D&A, PRB and DSMB.

**National CTN Steering Committee Meetings - Albuquerque, NM**

The CTN By-Laws were reviewed and approved by the entire Steering Committee. The following meetings were held in Albuquerque, New Mexico, March 23-28, 2003.

- The CTN Training Subcommittee conducted a meeting March 26-27, 2003. The meeting focused on discussing new roles and responsibilities of the TSC, developing a strategic plan for the rest of the year, reviewing current SOPs, developing mechanisms for better communication between trainers, developing a mechanism for ongoing review and update of training materials and finalizing the content of a training tracking system through review of new Training Schedule Grid and an old Documentation & Evaluation system.
- A Buprenorphine Interest Group Meeting was held on March 23, 2003 to continue discussing a buprenorphine liver safety study proposed by a drug company.
- The Portfolio Coordinating Committee met on March 24, 2003. Members had made recommendations to the SC on March 5, 2003 with regards to the Wave 4 LI and Team qualifications. All teams were approved, with the stipulation that the more junior investigators had the full support and mentorship of their Node PIs. PCC also finalized the protocol development and review flowchart, and endorsed the protocol monitoring template for monitoring the progress and development of Wave 4 protocols towards NIDA approval.
- The Operations Coordinating Committee met on March 24, 2003, to review the progress and problems in the current CTN protocols and presented guidelines that will address slow LI response to protocol tasks with step-wise interventions.
- The External Affairs Coordinating Committee met on March 24, 2003. Two invited speakers gave presentations: Wilson Compton, Ph.D, Director of NIDA's DESPR, presented on the CJ-DATS program. Dr. Cecilia McNamara reviewed research on training community providers in behavioral treatments. Other topics included a summarization of dissemination activities, future publications, CTP access to data prior to publication, and an outside request for support from the Research Liaison Group.
- The Executive Committee met March 23, 25-26, 2003 while in New Mexico. The group considered the following: a joint liver safety study of buprenorphine with a drug company; UCLA IRB comments on the planned CTN 0003 buprenorphine study; NIH Roadmap for Action developed by NIH Director Elias Zerhouni, M.D; CTN's research agenda; and the first draft of the CTN Strategic Plan.
- Several other interest groups met including: Behavioral Therapy Interest Group (IG), Co-Occurring Disorders IG, Minority IG, Gender IG, Smoking IG, Adolescent IG, Homelessness IG, and the Spirituality Research IG.
- The CTP Caucus met on March 23, 2003 for their first all day meeting.

- Three protocol groups held meetings to train staff or kick off their protocols: CTN 0012 (Infections Screening in Drug Abuse Treatment Programs), CTN 0015 (Women's Treatment for Trauma and Substance Use Disorders), and CTN 0021 (MET for Spanish Speakers).
- The Family Management Skills Concept Team met to continue working on drafting the first version of this new protocol.
- The Data Management and Analysis Subcommittee met on March 27-28, 2003 to discuss the possible centralization of data management activities and Data Management Centers performance evaluation. Other important topics included the review of a series of Lead Node guidelines, policies and reporting templates. There were also workgroup and breakout discussions of systems validation, external system review, the handling of missing data, logic language standardization, CONSORT reporting requirements, and a substantial new implementation of SOP/Guideline review and revision procedures.
- The Design and Analysis Workgroup met on March 23, 2003 to go over the presentations that will be made in June at the CPDD meeting and in July at the ISCB/SCT meeting.
- The Design and Analysis Workgroup met on March 26, 2003 to discuss how the CTN can capitalize on data on minority populations already collected by the CTN; possible alternative methods (other than urine test) for assessing drug use; and ways to shorten time to dissemination.
- The CTN LI workshop was conducted on March 27, 2003 and was well received and appreciated by CTN investigators. This workshop's focus was on protocol development. Dr. Lynda Powell gave an excellent presentation of Clinical Trial Methodology, particularly as applied to clinical trials involving behavioral interventions. CCTN staff gave presentations on all the essential components of a good protocol. The CCTN Guidance on Data and Safety Monitoring Plan, and details on Adverse Event Monitoring for CTN Trials, were also presented. A preview of what is needed for protocol implementation was also given.

NIDA was a cosponsor of the Dr. Lonnie E. Mitchell National HBCU Substance Abuse Research Conference held April 2-4, 2003 in Baltimore, MD. The conference theme was **"Reaching Beyond Our Traditional Roles: A Call to Action for HBCU and the Faith Community."** Dr. Lula Beatty, Chief of NIDA's Special Populations Office, participated as an expert panelist during the Town Hall meeting and as moderator of a session on NIDA's HBCU U24 Programs. Approximately 500 persons attended the Conference, about one third of whom were students.

NIDA was a sponsor of the **First Annual Cyber Therapy Conference** held January 19-21, 2003 in San Diego, California. This meeting focused on recent advances in the use of computer-human interfaces (e.g. virtual reality technologies, remote therapeutics) in the treatment of disease. Dr. David Thomas, DNBR, gave a presentation titled, "Progress and Opportunities in Virtual Reality Research at the National Institute on Drug Abuse." Dr. Nathan Appel, DTR&D, made a presentation titled, "Funding Opportunities Available at NIDA."

NIDA's Women & Gender Research Group sponsored the symposium, **Drug Abuse as a Gender Issue**, at the American Society for Pharmacology & Experimental Therapeutics (ASPET) meeting, April 11-15, 2003 in San Diego, CA. The co-chairs were Linda P. Dwoskin, University of Kentucky and Kathleen M. Kantak, Boston University and the speakers were Suzette M. Evans, Columbia University, Marlene A. Wilson, Ph.D., University of South Carolina School of Medicine, Kathleen Brady, Medical University of South Carolina, Marilyn E. Carroll, University of Minnesota, Sharon Allen, University of Minnesota, and Nadia Chaudhri, University of Pittsburgh.

NIDA sponsored a Special Events Program at the Society for Research in Child Development Biennial Meeting in Tampa, FL, April 24 - 27, 2003. This program included two components. The first was a "Career Opportunities Program," which featured a Mentoring Program, a poster and discussion hour focusing on child and adolescent research support at NIDA, and a NIDA Exhibit Booth. The second component featured 2 scientific symposia titled "Substance Use and Cycles of Youth Homelessness and Street Life: Antecedents, Epidemiology, and Transitions" and "Adolescent Decision Making and Drug Abuse." Members of the Child and Adolescent Workgroup that participated in the planning of the events and/or represented NIDA at the conference include Drs. Jessica Campbell, Kevin Conway, Aria Crump, Kathleen Etz, Teresa Levitin, Nicolette Borek, Anthony Salandy, and Vincent Smeriglio.

As part of the **CCTN Classroom Series**, on March 21, 2003, Dr. Richard Rawson, UCLA Department of Psychiatry, presented on "Outpatient Treatments for Substance Use Disorders: An Update".

The second workshop for Safety Monitoring in CTN Trials was held on March 17, 2003, in Bethesda, MD, including NIDA, NIAAA, and NIMH colleagues. The purpose was to discuss standards for safety monitoring in behavioral and medication clinical trials in the CTN and to share and collaborate with our partner institutes. Dr. Belinda Seto also presented an update on the NIH Roadmap for a more global NIH clinical enterprise.

The CTN Data and Safety Monitoring Board met April 24, 2003, in Bethesda, Maryland. The group reviewed 4 new protocols.

Dr. Timothy P. Condon, Associate Director, NIDA, presented "Why NIDA Supports the Parent Corps," at the Parent Corps Conference in Atlanta, Georgia, on January 30, 2003.

Dr. Timothy P. Condon, Associate Director, presented "The Substance Abuse Factor: Putting Practice into Action," at the Grantmakers In Health's Annual Meeting on February 21, 2003 in Los Angeles, California.

Dr. Timothy P. Condon presented "Addiction as a Brain Disease: Implications for Drug Addiction Treatment," at the Region X American Society of Addiction Medicine Conference on Addiction on March 28, 2003 in Kissimmee, Florida.

On February 14, 2003, Dr. Cathrine Sasek, Acting Chief, SPB, OSPC, participated in a workshop at the AAAS meeting in Denver, Colorado on the development of NIDA's high school curriculum supplement, "The Brain, Understanding Neurobiology Through the Study of Addiction." Dr. Sasek presented an overview of NIDA's science education program, as well as a description of the process whereby the curriculum supplement was developed and how scientists can become more involved in science education.

On May 16, 2003, Dr. Cindy Miner and Sheryl Massaro, both of OSPC, participated in an award ceremony at Scholastic, Inc. headquarters in New York, to honor the winner of a nationwide poster contest Scholastic began in November 2002, featuring artwork and messages based on the information provided in articles highlighting NIDA science. The winning poster, from more than 1,000 entries, was from Ania Lisa Etienne of Mark Twain Public School in Brooklyn, NY. Ms. Etienne's poster relates to snorting cocaine, with the theme "You can't sniff away your sorrows." The poster will be professionally rendered and distributed to schools in November 2003.

Dr. Lula Beatty, Chief, Special Populations Office, was the keynote speaker at Career Day at Southern University in Baton Rouge, LA on February 26, 2003.

Dr. Lula Beatty presented a session on minority and health disparities research at NIDA to the minority committee at the Clinical Trials Network meeting on January 25, 2003 in Miami, FL.

Dr. Lula Beatty was a speaker at a faculty development session in the School of Social Work, Florida International University on January 27, 2003 in Miami, FL.

Dr. Lula Beatty attended the Multicultural Summit on January 23-25, 2003 in Los Angeles, CA, where she participated in meetings of the Society on the Psychology of Women.

Dr. Lula Beatty presented a session on Funding Opportunities at NIH for a workshop for minority investigators sponsored by the NIH Office on AIDS Research on April 4, 2003 in Washington, DC.

Dr. Lula Beatty presented information on NIDA's programs to staff and faculty at Bowie State University on March 5, 2003 in Bowie, MD.

Dr. Lula Beatty was a keynote speaker at Hampton University's 25th Annual Conference on the Black Family on March 21, 2003 in Hampton, VA.

Dr. Betty Tai, Director, CCTN, presented CTN's experience in blending research and practice to the Texas Commission on Alcohol and Drug Abuse Best Practices Conference in Austin, TX on February 20, 2003.

Dr. Betty Tai, Director, CCTN, led a workshop at the American Association for the Treatment of Opioid Dependence (AATOD) April 13-16, 2003 in Washington, DC, entitled, "Overview of the National Drug Abuse Treatment Clinical Trials Network."

Dr. Frank Vocci, Director, DTR&D, attended a 2-day Buprenorphine Consensus

Meeting on March 7-8, 2003. The meeting was sponsored by The American Academy of Addiction Psychiatry, the Robert Wood Johnson Foundation, and the Center for Substance Abuse Treatment.

Dr. Frank Vocci represented NIDA and spoke at a dinner sponsored by Reckitt-Benckiser Pharmaceuticals on March 16, 2003. The theme of the meeting was "History in the Making" and Dr. Vocci spoke about the treatment of narcotic dependence in the US from 1914 to 2002.

Dr. Frank Vocci gave a seminar at Purdue Pharma in Stamford, Connecticut on April 16, 2003, entitled, "Addiction is a Brain Disease: A Conceptual Framework from a Neural Systems Perspective".

Dr. Cece McNamara, DTR&D, presented a talk on NIDA's Behavioral Therapy Development Portfolio highlighting the Stage III portfolio relevant to therapist training as well as a discussion on the NIDA funding mechanisms to train clinicians in research methods at the CTN Extramural Affairs Committee Meeting in Albuquerque, New Mexico on March 23, 2003.

Dr. Lisa Onken, DTR&D, gave a talk on the Stage Model of behavioral treatment research as conceptualized in the Behavioral Therapies Development Program announcement to the NIAAA treatment review committee in Bethesda, MD on February 27, 2003. NIAAA is now partnering with NIDA on this program of research.

Dr. Lisa Onken presented a talk on behavioral treatment research at NIDA to the Behavioral Pharmacology Research Unit at the Bayview campus of Johns Hopkins University in Baltimore, MD on March 13, 2003.

Dr. Steven Grant, DRT&D, represented NIDA at a conference on Computational Modeling of Dopamine Function held at Rutgers University in Newark, New Jersey on March 28, 2003.

Dr. Steven Grant represented NIDA at the annual meeting of the Cognitive Neuroscience Society in New York City on March 29-April 1, 2003.

On February 21, 2003, Dr. Ivan Montoya 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. The results suggest that during routine clinical practice, psychiatrists tend to under-report patients who smoke and under-treat their smoking problem and that psychiatric patients with nicotine problems have more psychosocial stressors than those who do not. The results have important public health implications because psychiatrists can play a very significant role in the reduction of smoking among psychiatric patients.

Dr. Ivan Montoya presented at a workshop in the seventh annual meeting of the National Hispanic Medical Association held in Washington DC on March 22, 2003. The topic of his presentation was "Hispanic Drug Abuse Research." He examined representation of Hispanics in drug abuse research, Hispanic issues in science, and Hispanic community in drug abuse clinical trials. He provided some analysis of the gaps in those areas and discussed with participants possible recommendations.

Dr. Naresh Chand, DTR&D, presented "Perspectives on Research Opportunities: Basic and Clinical Priorities- GBR 12909 As A New Research Tool for the Understanding of the HERG Assay" and discussed the usefulness of this assay for the evaluation of the cardiac drug safety in early drug discovery and development at the North American Society of Pacing and Electrophysiology (NASPE) Meeting, Washington, D.C., May 14, 2003.

On April 29-30, 2003 in Bethesda, Maryland, the Behavioral Treatment Development Branch conducted a state-of-the-science meeting on Group Therapy Research. Participants discussed the achievements in the area, and the challenges to moving the field forward.

Dr. Wilson Compton, Director, DESPR, chaired a symposium at the American Psychopatho-logical Association Meeting held in New York City, March 6-8, 2003. The symposium was entitled "Synapses, Neuroplasticity and Psychiatry" and included presentations by Drs. Nora Volkow, Steve Hyman and Eric Kandel.

Dr. Wilson Compton presented to the external affairs committee of the Clinical Trials Network on Services Research and the Criminal Justice Drug Abuse Treatment Studies, March 24, 2003, Albuquerque, New Mexico.

Drs. Wilson Compton, Elizabeth Robertson and Bill Bukoski, all of DESPR, organized and attended a planning meeting with the Department of Education's Institute for Education Sciences on "Advancing Supply and Demand for Rigorous, Relevant Research on Education, Drug Abuse, and Social Issues", Washington, DC, April 17, 2003.

Drs. Jack Stein and Wilson Compton, both of DESPR, worked with NIMH and NIAAA to develop and implement a technical assistance workshop for SAMHSA grantees who wished to learn more about submitting grants to NIH. This workshop took place on April 24, 2003 in Rockville, MD.

Drs. Wilson Compton and Shakeh Kaftarian were invited by the Robert Wood Johnson Foundation to attend the final grantee meeting of the Fighting Back Grant Program in Chicago, IL on March 2-4, 2003. At the meeting reports were presented on the final national evaluation of Fighting Back and lessons learned from the program.

On February 12, 2003, Drs. Elizabeth Robertson, DESPR, and Suman Rao, OSPC, presented a workshop at the annual meeting of the Community Anti-Drug Coalitions of America held at the Omni Shoreham Hotel in Washington, DC. The title of the presentation was "NIDA's 2003 Prevention Principles: Using Research to Address Community Needs."

Dr. Eve Reider, DESPR, participated in the "Fact-Finding Forum on Student Drug Testing: A Review of Legal, Scientific, and Implementation Issues." The U.S. Department of Education and the National Institute on Drug Abuse convened this one-day meeting on February 19, 2003 at the Omni Shoreham Hotel in Washington, D.C.

Dr. Eve Reider participated in "Creating Communities that Monitor the Well-Being of America's Children and Adolescents," a meeting that was convened by the Society for Prevention Research and held February 27-28th, 2003 at the Hilton Eugene in Eugene, OR.

Dr. Susan Martin, DESPR, represented NIDA at a Workshop on Health Literacy sponsored by the Office of Disease Prevention and Health Promotion of the U.S. Department of Health and Human Services on April 2, 2003 at NIH in Bethesda, Maryland.

Dr. Jack Stein, Chief, Services Research Branch, DESPR, recently served on the executive committee for *Beyond the Clinic Walls: Expanding Mental Health, Drug and Alcohol Services Research Outside the Specialty Care System*, which was held in Washington D.C., March 10-12, 2003. He moderated two plenary sessions: *Welfare to Work and Missing Work: The Potential of Workplace Platforms for Alcohol, Drug, and Psychiatric Intervention and Prevention*.

Dr. Jack Stein facilitated a 1.5 day meeting with representatives from NIDA's Clinical Trials Network (CTN) Dissemination Subcommittee and CSAT's Addiction Technology Transfer Centers (ATTCs) to determine a process for transferring research findings into drug treatment programs.

William Cartwright, Ph.D., Services Research Branch, DESPR, served on the executive committee for *Beyond the Clinic Walls: Expanding Mental Health, Drug and Alcohol Services Research Outside the Specialty Care System*, which was held in Washington D.C., March 10-12, 2003. He moderated a panel on "Alcohol, Drug, and Mental Health Services in the Justice System" and organized a plenary session on "Welfare to Work."

Redonna Chandler, Ph.D., Services Research Branch, DESPR, participated in a panel presentation on technology transfer issues for drug abusing offenders in the criminal justice system at the Academy of Criminal Justice Sciences annual meeting in Boston, MA, March 2003.

Jerry P. Flanzer, Ph.D., Services Research Branch, DESPR gave a presentation entitled "Directions for Services for HIV, Drug Use, and Aging", at a conference on Illicit Drug Use and HIV Risk Among Older Adults: Implications for Intervention and Prevention, sponsored by the Columbia University School of Social Work, Interchurch Center, in New York, March 2003.

Dr. Jerry Flanzer also spoke about the science-community partnership aspects of ongoing research at the inauguration of a health services study concerning the implementation of Proposition 36, the Substance Abuse Alternative to Incarceration Act, at UCLA, March 2003.

Beverly Pringle, Ph.D., Services Research Branch, DESPR, recently served on the executive committee for *Beyond the Clinic Walls: Expanding Mental Health, Drug and Alcohol Services Research Outside the Specialty Care System*, which was held in Washington D.C., March 10-12, 2003. She moderated a panel on "School Based Services for Alcohol, Drug, and Mental Health Problems".

Drs. Laurence Stanford and Joseph Frascella, both of DTR&D, gave a presentation entitled Some Strategies for Successful Grant Writing and Review Considerations at Marist College in Poughkeepsie, NY on March 8, 2003.

Dr. Joseph Frascella participated in the 10th Annual Undergraduate and Graduate Research Symposium held on the Morgan State University campus in Baltimore, MD on April 17, 2003.

Dr. Herb Weingartner, DNBR, was a keynote speaker at the Leadership forum of the National Science Teachers Association (NSTA) Meeting, March 26-28, 2003, Philadelphia PA.

Dr. Cora Lee Wetherington, NIDA's Women & Gender Research Coordinator, served as NIDA representative on the steering committee for the NCI-led meeting, "Women, Tobacco, & Cancer: An Agenda for the 21st Century," held February 3-5, 2003 in Houston, Texas. She also co-organized and co-chaired (with Gary Swan, and Ovide Pomerleau) the agenda-planning breakout group, "Addiction -- Addressing the Biology and Behavior of Addiction" which included Drs. Karen Ahijevych, Jan Blalock, Rosemarie Booze, Bill Corrigall, Dorothy Hatsukami, David Kalman, Denise Kandel, Taline Khroyan, Francis Leslie, Wendy Lynch, Pam Madden, Sherry Mills, Scott Rogers, and Teri Franklin.

Dr. Cora Lee Wetherington served on the advisory board for the report, "The Formative Years: Pathways to Substance Abuse Among Girls and Young Women Ages 8-22", prepared by the National Center on Addiction and Substance Abuse (CASA) at Columbia University and released at a press conference at the National Press Club, Washington, February 5, 2003.

Dr. Cora Lee Wetherington gave a talk entitled "Sex Differences in Nicotine Dependence," at The American University, April 7, 2003, as a guest lecturer in the course, "Psychology of Women."

Dr. Jean Lud Cadet, IRP, gave a talk in the Department of Neurology at the Mount Sinai Hospital in New York on March 26, 2003 entitled, "Cellular and Molecular Bases of Methamphetamine-induced Neuronal Apoptosis: Evidence from Gene Expression Studies."

On February 3, 2003 Mr. Noble Jones, CAMCODA, made a presentation to the staff and doctoral students of the Morgan State University Drug Abuse Research Program (DARP) in Baltimore, MD. The title of the presentation was "Ethical Dilemmas Faced by Researchers in Conducting Field Research With Injection Drug Users."

Dr. Peter Hartsock, CAMCODA, participated in the first meeting of a national smallpox advisory group established by former Surgeon General C. Everett Koop held in Washington, D.C., February 27, 2003. Dr. Hartsock presented on NIDA/CAMCODA's large-scale AIDS modeling program whose methodology development has applied to other emerging and reemerging infectious diseases such as smallpox which pose possible biowarfare as well as public health threats.

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

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

## Media and Education Activities

### Press Releases

January 23, 2003 - **Nora D. Volkow Named New Director of NIH's National Institute on Drug Abuse (NIDA).** National Institutes of Health Director Elias A. Zerhouni, M.D., announced the appointment of Nora D. Volkow, M.D., as the new director of the NIH's National Institute on Drug Abuse (NIDA). Dr. Volkow is currently Associate Director for Life Sciences at Brookhaven National Laboratory (BNL), Director of Nuclear Medicine at BNL, and Director of the NIDA-DOE Regional Neuroimaging Center at BNL. She is also Professor at the Department of Psychiatry, SUNY-Stony Brook, and Associate Dean for the Medical School at SUNY-Stony Brook. Coverage of this release appeared in *Wall Street Journal, Psychiatric News, Substance Abuse Letter, Science Magazine, Join Together Online, Drug Week,* and *Alcoholism and Drug Abuse Weekly.*

Nabi Biopharmaceuticals, a company in Rockville, MD, which presently has NIDA grant funding for the development of a nicotine vaccine (NicVAX™), issued a press release on February 19, 2003, to announce the completion of a Phase I safety trial, and the enrollment in a Phase I/Phase II clinical trial in smokers, ex-smokers and non-smokers, in the Netherlands. The purpose of the present trial is to evaluate the safety and immunogenicity of NicVAX. Additional clinical trials are planned to begin later this year in the United States.

February 19, 2003 - **NIDA NewsScan #19**

- Studies Show Bidis and Smoking Products Are No Safer Than Conventional Cigarettes
- Selegiline Hydrochloride May Help Smokers Quit
- Quitting Smoking Offers Psychological Benefits; Unsuccessful Attempts May Change Perceptions of Health Risk
- Parental Smoking, Behaviors, and Attitudes May Be Associated with Adolescent Smoking
- Study Finds Short-Term Benefit from Both Antidepressant Therapy and Counseling in Smoking Cessation

As a result of NewsScan promotion, coverage appeared in *Time Magazine, Health and Medicine Week, Los Angeles Times, Family Practice News,* and *Pain & Central Nervous System Week.*

February 21, 2003 - **Stress and the Brain will be the Focus of NIH Symposium during Brain Awareness Week, March 10-16, 2003.** The National Institutes of Health (NIH), in recognition of *Brain Awareness Week,* sponsored a scientific symposium. The meeting focused on the various ways that stress can impact the brain, body, and ultimately, peoples' lives. *Brain Awareness Week* is a nationwide effort, organized by the Dana Alliance for Brain Initiatives, to promote the public and personal benefits of brain research.

March 5, 2003 - **NIDA NewsScan #20**

- Stimulant Treatment of Children with ADHD Reduces Subsequent Substance Abuse
- Women Who Abuse Drugs Are At High Risk For Serious Injury or Trauma

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- Cocaine Use May Alter Brain Cells, Play Role in Depression
- Study Links Ecstasy Use with Changes in Cardiovascular Function

As a result of NewsScan promotion, coverage appeared in *Los Angeles Times, Orlando Sentinel, Mental Health Weekly Digest,* and *Heart Disease Weekly*.

March 26, 2003 - **NIDA Hosts Two-Day Neuroscience Symposium to Honor the Late Dr. Roger Brown.** NIDA organized the symposium, "Foundations and Innovations in the Neuroscience of Addiction," dedicated to the memory of Dr. Roger Brown, Associate Director of Neuroscience in the Division of Neuroscience and Behavioral Research at the National Institute on Drug Abuse (NIDA).

April 4, 2003 - **NIDA Hosts Blending Clinical Practice and Research: Forging Partnerships in the Rocky Mountain States to Enhance Drug Addiction Treatment.** This two-day conference brings together clinicians and researchers to examine cutting-edge scientific findings about drug use and addiction and their application to clinical practice.

April 9, 2003 - **NIDA NewsScan #21**

- Study of Twins Reveals That Changes in Attention and Motor Skills Persist at Least a Year after Heavy Stimulant Abuse
- Environmental Cues Associated with Heroin Use May Decrease Immune Function
- Increased Depression During Treatment May Make It Harder for Women to Quit Smoking
- Concurrent Use of Tobacco and Marijuana May Hamper Cigarette Smoking Cessation Efforts
- Pain Control Bandage Now Available for Clinical Use

### Articles of Interest

February 1, 2003, *Counselor Magazine*--"NIDA is Making Progress in Developing Medications to Treat Stimulant Addiction " -Article by Frank Vocci, Ph.D.

February 25, 2003, *JAMA*--"Public Health Implications of Excessive Alcohol Consumption" -Editorial by Glen R. Hanson Ph.D, D.D.S, and Ting-Kai Li, M.D.

March 24, 2003, *Los Angeles Times*--"Recycled for Rehab" -Interview with Frank Vocci, Ph.D.

April 1, 2003, *Counselor Magazine*--"Survey Shows Decrease in Teen Use of Ecstasy, Marijuana, and Cigarettes" -Article by Glen R. Hanson, Ph.D., D.D.S.

April 11, 2003, *USA Today*--"Scientists Find Clues to Cocaine's Hold on Addicts" -Interview with Roy Wise, Ph.D.

Dr. Frank Vocci, Director, DTR&D, was interviewed by Peter Landers for an article on medications to treat addictions that ran in the Wall Street Journal on February 20, 2003.

Dr. Frank Vocci was interviewed by Mark Elliott of Toronto radio CFRB on April 4, 2003 on Lofexidine and other treatments for opiate addiction.

Dr. Frank Vocci was interviewed by Shari Roan for an article on pharmacotherapies for cocaine dependence that ran in the LA Times on March 24, 2003.

Dr. Frank Vocci was interviewed by Mignon Fogarty in February 2002 for an article on the nicotine vaccine to run in The Scientist.

Dr. Frank Vocci was interviewed by Stephen Cotler of the Los Angeles Weekly on March 27, 2003 for an article about buprenorphine as a treatment for opiate addiction.

Dr. Frank Vocci was interviewed by Duncan McCue of the Canadian Broadcasting Company on April 2, 2003 for a segment on Ibogaine as a potential addiction treatment.

Dr. Frank Vocci was interviewed by Bob Holmes on February 14, 2003 for an article on Ibogaine to run in the New Scientist.

### Educational Activities

David Shurtleff, Ph.D., DNBR, and Sheryl Massaro, OSPC, represented NIDA at the National Press Club on March 13, 2003 for the kickoff of National Inhalants and Poisons Awareness Week (NIPAW), with SAMHSA and the National Inhalants Prevention Coalition (NIPC). NIDA continues to reach audiences with several products. In March, magazines such as Junior Scholastic and Science World, targeting middle school and early high school students, carried an article on inhalants as part of NIDA's collaborative series with Scholastic Magazines, Inc., **Heads Up: Real News About Drugs and Your Body.** Scholastic also worked closely with NIPC in producing the article. As in 2002, to coincide with the 2003 NIPAW, NIDA produced two post cards featuring graphics from the NIPC website, and distributed 240,000 of the cards in surf, ski and skate shops nationwide. Mind Over Matter, a seven-part series including a segment on inhalants, encourages young people in grades 5 through 9 to learn about the neurobiological effects of drugs. The **Research Report Series on Inhalants** presents information on the types of inhalants, the consequences of their use, who is abusing inhalants, and how to recognize inhalant abuse. All materials can be downloaded from NIDA's website, www.drugabuse.gov.

NIDA has reached the end of Year 1 in its 2-year collaboration with Scholastic Magazines, Inc. Magazines such as Junior Scholastic and Science World, targeting middle school and early high school students, have carried articles on inhalants, ecstasy, marijuana, and nicotine as part of the **Heads Up: Real News About Drugs and Your Body** series. The last articles for year 1, on heroin and steroids, were distributed to schools nationwide. The second year's lineup will include articles on the health effects of a variety of stimulants and hallucinogens, and on the abuse of medications. The magazines are distributed to 1.7 million students nationwide, with a reach of 6.8 million.

Over 200 middle-school and high-school students from Virginia, Maryland, Washington, D.C., and North Carolina attended the **Brain Awareness Week** activities held at the National Museum of Health and Medicine on March 12 and 13, 2003. NIDA sponsored **"Who Wants to be a NIDA Neuroscientist,"** which is designed to generate student interest in brain research and to teach students about the brain and the effects of drug use. Dr. Glen Hanson, Acting Director, NIDA, delivered a plenary session on drugs and the brain to local students. Other participating NIDA staff included Anna Staton, Drs. Denise Pintello, Cathrine Sasek, David Thomas, Jane Acri, Cynthia Kleppinger, Rita Liu, and Betty Tai.

On May 8, 2003, Dr. Nora Volkow, Dr. Timothy P. Condon and Beverly Jackson represented NIDA at the 7th Annual PRISM Award Celebration in Los Angeles. The PRISM Awards are sponsored by the Entertainment Industries Council (EIC), NIDA, and the Robert Wood Johnson Foundation. These awards recognize the efforts of the entertainment industry to accurately depict drug, alcohol and tobacco addiction. Winning entries this year included the feature film *"Skins;"* episodes of *"ER"*, the *"Young and the Restless"* and *"Ozzie and Drix"*; the NBC news production *"Sudden Impact: The Ripple Effects of Drunk Driving,"* the Bernie Mac Show *"Sweet Home Chicago"*, and the Ricki Lake Show episode *"Ephedra: Miracle Supplement or Deadline Drug?"* MTV original movie *"Wasted"*; and biographical episodes of VH1's Behind the Music *"Aerosmith"* and The E! True Hollywood Story, *"Andy Dick"*. Singer Kenny Chesney won for music entry, *"The Good Stuff."* The PRISM Awards television special premiered May 15, 2003 on Capitol Hill prior to the national airing on the FX network on May 25, 2003.

### Exhibits/Conferences

March 10-16, 2003: Brain Awareness Week
March 20-23, 2003: National Student Assistance Conference
March 21-25, 2003: American Counseling Association Annual Convention
March 27-30, 2003: National Science Teachers Association
April 2-5, 2003: Lonnie E. Mitchell Historic Black Colleges and Universities Substance Abuse Conference
April 11-15, 2003: Experimental Biology 2003
April 13-16, 2003: American Association for the Treatment of Opioid Dependence
April 16-18, 2003: Association of Minority Health Professions School Annual Symposium on Career Opportunities in Biomedical Sciences
April 24-27, 2003: Society for Research in Child Development Biennial Meeting
May 1-4, 2003: American Society of Addiction Medicine
May 17-22, 2003: American Psychiatric Association
May 27-31, 2003: American College Health Association
May 29 - June 1, 2003: American Psychological Society
June 14-19, 2003: College on Problems of Drug Dependence

June 20-22, 2003: National Congress of Parents and Teachers Association
June 22-25, 2003: BIO 2003 Annual Convention
June 27-29, 2003: Academy Health Annual Research Meeting
July 15-19, 2003: Association on Higher Education and Disability
July 27-30, 2003: 2003 National HIV Prevention Conference
July 30 - August 3, 2003: National Black Nurses Association
August 7-10, 2003: American Psychological Association Annual Convention

Dr. Eliot Stein, IRP, was interviewed for and his research was highlighted in the New York Times Television Science episode on Addictions.

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

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## Planned Meetings

Drs. Lisa Onken, DTR&D, Vincent Smeriglio, CAMCODA, and Joseph Frascella, DTR&D, are organizing a 2-day meeting entitled **Neurobiology of Treatment: Recovery of Brain Structure and Function through Behavioral Treatments** to be held in Bethesda in May 29-30, 2003.

NIDA will hold a 3-day meeting prior to the 2003 College on Problems of Drug Dependence in June 2003. The purpose of the meeting is to review the biology of neuronal nicotinic receptors and to encourage the medicinal chemistry field to work in the area to develop new ligands that can be useful for a variety of purposes, ranging from research tools to treatment. The meeting will occur June 12-14, 2003 in Bal Harbor, Florida.

Edward Nunes, M.D. (LI Node PI) and Paul Wakim, Ph.D, will chair 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 scheduled for June 14-19, 2003, in Bal Harbour, Florida.

A 3-day meeting on Executive Function will be held in June 2003 as a satellite symposium to the Human Brain Mapping annual meeting in New York City. The meeting was organized by the NIH Cognitive Neuroscience Consortium, and is co-sponsored by NIDA, NINDS, NIMH, NIA, and NIAAA. Dr. Steven Grant, DTR&D, participated in the organization of this meeting.

The Services Research Branch of the Division of Epidemiology, Services, and Prevention Research will host a research meeting July 17-18, 2003 on the role of primary care in substance abuse treatment. The purpose of the meeting will be to develop a new agenda for supporting health services research that examines how the primary health care system can enhance the early identification, treatment, and long-term management of drug abuse and addiction problems.

National CTN Steering Committee Meetings are planned for the following dates and locations: June 20-21, 2003, in Fort Lauderdale, FL; and September 10-12, 2003, in Denver, CO.

John Rotrosen, M.D., CTN NY Node PI and Paul Wakim, Ph.D., CCTN, will co-chair 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) scheduled for July 22, 2003 in London, England.

A CTN Symposium on "The National Drug Abuse Clinical Trials Network (CTN): Emerging Roles of Practitioners in Drug Abuse Research," will be presented at the American Psychological Association conference in Toronto, Canada, on August 7, 2003.

Drs. Cora Lee Wetherington and David Shurtleff, DNBR organized and will chair a symposium, "Adolescence and Nicotine Addiction: Basic and Clinical Research Perspectives" for the annual meeting of the American Psychological Association in Toronto, August 8-10, 2003.

NIDA will host **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 will

provide an opportunity for clinicians and researchers to examine cutting-edge findings about drug use and addiction and their application to clinical practice.

Dr. Susan Volman, DNBR, will chair a symposium entitled "Functional Changes in Synaptic Transmission and Drug Abuse" at the Society for Neuroscience annual meeting, November 2-8, 2003 in New Orleans, LA. The symposium will focus on the mechanisms and implications of drug-induced alterations of synaptic transmission, particularly long-term potentiation (LTP) and long-term depression (LTD), through which drugs of abuse usurp or interrupt the mesolimbic and mesocortical neural pathways involved in reinforcement learning and reward processing. The speakers, all of whom are NIDA investigators, will be: Julie A. Kauer, Brown University, "Amphetamine Modulates Synaptic Plasticity in the Ventral Tegmental Area;" Daniel S. McGehee, University of Chicago, "Synaptic Modulation by Nicotine in Brain Reward Areas;" Mark J. Thomas, University of Minnesota, "Synaptic Plasticity in the Mesolimbic Dopamine System: Role in Behavioral Sensitization to Psychostimulants;" and Patricio O'Donnell, Albany Medical College, "Effects of Repeated Methamphetamine on Information Processing in the Nucleus Accumbens."

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

## Publications

**National Survey Results on Drug Use - Overview of Key Findings 2002**
**NIH Pub. No. 03-5374**
This publication provides a concise review of the findings of the Monitoring the Future Study and comparison of data from previous years.

**Problems of Drug Dependence 2002: Proceedings from the 64th Annual Scientific Meeting of the College on Problems of Drug Dependence**
**NIH Pub. No. 03-5339**
This publication summarizes the activities of the most recent meeting of the nation's most influential drug abuse professionals and measures progress in a variety of areas. It also discusses outcomes of symposia, meetings, and presentations, and provides abstracts of current research.

**NIDA INVEST Letter, Winter 2003** - This issue introduces newly appointed NIDA Director Dr. Nora D. Volkow, and announces the NIDA Supplement Program (PAS-03-023) to fund international collaborative research on drug abuse and addiction. Other stories profile former NIDA INVEST Fellow Dr. Irena Martin-Kleiner, Croatia, and focus on the NIDA International Forum, to be held June 13-19, 2003 in conjunction with the College on Problems of Drug Dependence Annual Scientific Meeting in Miami, Florida.

### NIDA NOTES

**NIDA NOTES, Volume 17, Issue 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 can, 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 when a group of monkeys were moved from isolation to cages with other monkeys and developed social hierarchies, the 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. The finding that youths' opportunities to experiment with drugs in later drug use is also discussed.

**NIDA NOTES, Volume 17, Issue 6**
**NIH Pub. No. 03-3478**

The lead article discusses recent research on nicotine's effects on the brain's reward system. Adding to their knowledge of how nicotine directly stimulates this reward system, researchers have discovered that nicotine also indirectly stimulates two types of neurons that intensify the pleasure from smoking and makes it last longer.

In the Director's Column, Dr. Glen R. Hanson discusses NIDA's continued commitment

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to nicotine research. The column notes NIDA's research partnership with the National Institute of Mental Health to identify and develop pharmacological compounds for use in investigating the roles of specific 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 four new Advisory Council members. The Tearoff page discusses Monitoring the Future findings of dramatic declines in adolescents' smoking in 2002.

### CTN Publications

Eight editions of the CTN Bulletin Board were distributed this period. The Bulletin Board is an electronic report on the activities of the various protocol teams and subcommittees of the CTN.

The CTN brochure "Successfully Including Women in Clinical Trials" was translated into Spanish and distributed throughout the Network.

The CTN brochure, "What is the CTN?" was revised and translated into Spanish.

Two new patient brochures written for the Smoking Cessation Protocol (CTN 0009) have been approved and printed for distribution to the clinical trial sites.

A revised CTN Directory was approved and printed during this period.

- Three new brochures for the TELE Protocol (CTN 0011) have been written and approved for printing and distribution.
- A pre-printed rolodex card was approved for the CTN and was distributed to node staff at the Albuquerque meeting in March 2003.

### Other Publications

Ashby, C.R. Jr., Paul, M., Gardner, E.L., Heidbreder, C.A., and Hagan, J.J. Acute Administration of the Selective D3 Receptor Antagonist SB-277011A Blocks the Acquisition and Expression of the Conditioned Place Preference Response to Heroin in Male Rats. Synapse, 48, pp. 154-156, 2003.

Carlezon, W.A., Jr., and Wise, R.A. Unmet Expectations: The Brain Minds. Nature Medicine, 9(1), pp. 15-16, 2003.

Chefer, V., Zakharova, I., and Shippenberg, T.S. Enhanced Responsiveness to Novelty and Cocaine is Associated with Decreased Basal Dopamine Uptake and Release in the Nucleus Accumbens: Quantitative Microdialysis in Rats under Transient Conditions. Journal of Neuroscience, 23, pp. 3076-3084, 2003.

Cheng, D.T., Knight, D.C., Smith, C.N., Stein, E.A. and Helmstetter, F.J. Functional MRI of Human Amygdala Activity during Pavlovian Fear Conditioning: Stimulus Processing Versus Response Extinction. Behavioral Neuroscience, 117, pp. 3-10, 2003.

Hayes, R.J., Vorel, S.R., Spector, J., Liu, X., and Gardner, E.L. Electrical and Chemical Stimulation of the Basolateral Complex of the Amygdala Reinstates Cocaine-Seeking Behavior in the Rat. Psychopharmacology, electronic publication ahead of print, January 24, 2003 [PMID 12545331].

Herning R.I., Better, W.E., Tate, K., Umbricht, A., Preston, K.L., and Cadet, J.L. Methadone Treatment Induces Attenuation of Cerebrovascular Deficits Associated with the Prolonged Abuse of Cocaine and Heroin. Neuropsychopharmacology, 28(3), pp. 562-568, 2003.

Ikemoto, S., and Witkin, B.W. Locomotor Inhibition Induced by Procaine Injections into the Nucleus Accumbens Core, But Not the Medial Ventral Striatum: Implication for Cocaine-induced Locomotion. Synapse, 47, pp. 117-122, 2003.

Kiyatkin, E.A., and Brown, P.L. Naloxone Depresses Cocaine Self-administration and Delays its Initiation on the Following Day. NeuroReport - Neuropharmacology & Neurotoxicology, 14(2), pp. 251-255, 2003.

Sharan, N., Chong, V.Z., Nair, V.D., Mishra, R.K., Hayes, R.J., and Gardner, E.L. Cocaine Treatment Increases Expression of a 40 kDa Catecholamine Regulated Protein in Discrete Brain Regions. Synapse, 47, pp. 33-44, 2003.

Windels, F. and Kiyatkin, E.A. Modulatory Action of Acetylcholine on Striatal Neurons: Microiontophoretic Study in Awake, Unrestrained Rats. Journal of Neuroscience, 17, pp. 613-622, 2003.

Xi, Zheng-Xiong and Stein, E.A. Opiate Self-administration. In: Z.Z. Pan (ed.). Methods in Molecular Biology/Biotechnology/Medicine. Opioid Research: Methods and Protocols. Humana Press, 2002.

Xi, Zheng-Xiong and Stein, E.A. GABAergic Mechanisms of Opiate Reinforcement. Alcohol and Alcoholism, 37, pp. 485-494, 2002.

Zapata, A., Chefer, V., Shippenberg, T.S. Behavioral Sensitization and Enhanced Dopamine Response in the Nucleus Accumbens after Intravenous Cocaine Self-administration in Mice. European Journal of Neuroscience, 17, pp. 590-596, 2003.

Simons-Morton, B.G. and Crump, A.D. Association of Parental Involvement and Social Competence with School Adjustment and Engagement Among Sixth Graders. Journal of School Health, 73(3), pp. 121-126, 2003.

Vocci, F. NIDA is Making Progress in Developing Medications to Treat Stimulant Addiction. Counselor, 4(1), pp. 42-48, 2003.

Brook, D.W., Brook, J.S., Pahl, T. and Montoya I. The Longitudinal Relationship Between Drug Use and Risky Sexual Behaviors Among Colombian Adolescents. Arch Pediatr Adolesc Med. 156(11), pp. 1101-1107, November 2002.

DiPaula, B.A., Schwartz, R., Montoya, I.D., Barrett, D. and Tang, C. Heroin Detoxification with Buprenorphine on an Inpatient Psychiatric Unit. J Subst Abuse Treat., 23(3), pp. 163-169, October 2002.

Brook, D.W., Brook, J.S., Rosen, Z., Montoya, I. Correlates of Marijuana Use in Colombian Adolescents: A Focus on the Impact of the Ecological/Cultural Domain. J Adolesc Health, 31(3), pp. 286-298, September 2002.

The proceedings of the symposium "Cannabinoids: Chemistry and Biology" appeared as special issues, Nos. 1-2 of the Journal "Chemistry and Physics of Lipids". These special issues were edited by Rao. S. Rapaka, A. Makriyannis and H.H.O. Schmid. CPL, 121(1-2), December 31, 2002.

Dr. Herbert Weingartner, DNBR, published a paper "Psychopharmacology of Human Memory" (with Val Curran), in Handbook of Memory Disorders, Baddley, Kopelman, & Wilson (Eds.), John Wiley Press, 2002.

Dr. Rao Rapaka, DNBR, organized a symposium on "Structural Biology and Structural Genomics/Proteomics" the proceedings of which have been published as special volumes by the following two journals:

1. Biopolymers: Peptide Science, 66(5), December 2002-January 2003.
2. The Journal of Peptide Research, 60(6), December 2002.

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

## Staff Highlights

### Staff Honors and Awards

**Dr. Betty Tai**, Director of the CCTN, has been nominated for the Innovators Award, a national program supported by The Robert Wood Johnson Foundation, for her innovative work in the substance abuse field. Five Innovators Awards are made each year in the form of a $300,000 grant in the field of substance abuse research.

**Dr. Lula Beatty**, Director of NIDA's Special Populations Office, received a distinguished alumni award from the National Association for Equal Opportunity in Higher Education (NAFEO), the member association of black colleges and universities, in recognition of her achievements as a graduate of Lincoln University (PA). The award was presented on April 12, 2003 at NAFEO's annual convention in Washington, D.C.

**Dr. Lula Beatty** received an NIH plain language award for her participation in an NIH group that developed guidance on involving the community in research.

**Dr. Toni Shippenberg**, Chief, Integrative Neuroscience Section, Behavioral Neuroscience Branch, IRP, was appointed to the Editorial Board of Neuropsychopharmacology effective January 1, 2003.

**Drs. Melissa Racioppo**, and **Cece McNamara**, both of DTR&D, won first prize in the category Best Campaign Event in the 2002 Combined Federal Campaign Communication (CFC) Contest for the Washington D.C. area. Drs. Racioppo and McNamara won for NIDA's "Contributor Appreciation Day" in which individuals who contributed to the CFC campaign from NIDA received tangible reinforcers including cakes and cookies from a local vendor, as well as a chance to draw for prizes from a fishbowl as a thank you for participation. This motivational incentive event was adapted from a NIDA grantee's behavioral treatment intervention, Lower Cost Contingency Management, currently under study. NIDA met its CFC goal in 9 weeks.

### Staff Changes

**Nora D. Volkow, M.D.** joined NIDA as its new Director on May 1, 2003. Dr. Volkow comes to NIDA from Brookhaven National Laboratory (BNL) where she was Associate Director for Life Sciences, Director of Nuclear Medicine and Director of the NIDA-Department of Energy Regional Neuroimaging Center. She was also Professor at the Department of Psychiatry, State University of New York (SUNY) at Stony Brook and Associate Dean for the Medical School at SUNY-Stony Brook. Dr. Volkow received her M.D. from the National University of Mexico, Mexico City and performed her residency in psychiatry at New York University. Much of Dr. Volkow's research has focused on elucidating mechanisms underlying the reinforcing, addictive and toxic properties of drugs of abuse in the human brain. She was the first to use imaging technology to study the neurochemical changes in the human brain that occur during drug addiction. She has also used imaging to investigate the effects of stimulant drugs with respect to both their rewarding as well as their therapeutic actions and to measure changes in neurotransmitter systems that occur with aging and their functional significance. Dr. Volkow has authored or co-authored more than 280 peer-reviewed publications, three edited books and more than 50 book chapters and non-peer reviewed manuscripts. She has received many prestigious awards for her research, and has been elected to membership in the Insitute of Medicine of the National Academy of Sciences. In 2000, Dr. Volkow was named "Innovator of the Year" by *US News and World Report*.

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**Dr. Eliane Lazar-Wesley** joined OEA as a Health Scientist Administrator/Scientific Review Administrator in February 2003. Prior to coming to NIDA, Dr. Lazar-Wesley was with the U.S. Patent Office where she examined patent applications in biotechnology. She completed a Ph.D. in molecular biology at the Universite Louis Pasteur, conducted research at the Centre National de la Recherche Scientifique and then obtained a Fogarty fellowship at the National Cancer Institute. She has also worked as a senior staff fellow at NIAAA.

**Karla Moras, Ph.D.** joined the Center for the Clinical Trials Network in March 2003. Prior to this she had been with DTR&D's Behavioral Treatment Development Branch since September 2002. Dr. Moras came to NIDA from the University of Pennsylvania School of Medicine, Department of Psychiatry. While at Penn, she was involved in NIDA's multi-site Cocaine Collaborative Study of behavioral treatments for cocaine dependence. She also was the Principal Investigator of two NIMH grants: an Independent Scientist Award (K02) and a Treatment Development Grant (R21) for medication resistant unipolar depression. Dr. Moras has done research on psychodiagnostic assessment methods, including the reliability and validity of the DSM-III-R criteria. Currently, she is president of the international Society for Psychotherapy Research (SPR) and previously served as president of the North American Regional Chapter of the SPR. She received the Society's Early Career Contribution Award in 1994.

**Mary Ann Chutuape Stephens, Ph.D.** recently joined the Behavioral Treatment Development Branch of DTR&D as a Health Scientist Administrator. Dr. Stephens started at NIDA in June 2000 as a Special Expert at the Center for the Clinical Trials Network, where she facilitated development of randomized controlled trials of behavioral treatments in community-based settings. She was also the Center's representative on dissemination activities involving the Network and other government agencies. Prior to joining NIDA, Dr. Stephens served as Project Director for a NIDA-funded substance abuse treatment research clinic at the Johns Hopkins University School of Medicine, where she was an Assistant Professor in the Department of Psychiatry and Behavioral Sciences. Her research focused on behavioral and pharmacotherapy trials for the treatment of opioid, cocaine and benzodiazepine dependence. Dr. Stephens received her Ph.D. in Behavioral Sciences from the University of Chicago.

On May 1, 2003, **Lucinda (Cindy) Miner, Ph.D.** was appointed as Deputy Director, Office of Science Policy and Communications (OSPC). She has been serving as the Acting Deputy Director, OSPC since January 2003. Cindy received her Ph.D. in psychology from the University of Colorado in 1986. She came to NIDA in 1992 to work in the Intramural Research Program in Baltimore. At the IRP, Cindy worked in the Molecular Neurobiology Branch and helped to establish the Molecular Genetics Section and served as its first Acting Chief. In 1996, Cindy joined the Science Policy Branch, OSPC to help coordinate NIDA's research training program. In 2000, Cindy was promoted to Chief of the Science Policy Branch, OSPC, which, among many things, coordinates the legislative, research planning and evaluation activities of the Institute. During her career, Cindy has published numerous papers and book chapters on the genetic and biochemical bases of addiction.

**Beverly Pringle, Ph.D.,** has been selected to serve as Deputy Chief of the Services Research Branch, Division of Epidemiology, Services, and Prevention Research.

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## Grantee Honors

**Dr. Ronald T. Borchardt**, University of Kansas Department of Pharmaceutical Chemistry, will receive the 2003 Smissman Bristol Myers-Squibb award of the American Chemical Society Division of Medicinal Chemistry.

**Drs. Denise Hallfors** and **Dionee Godette** were winners of the 11th annual Douglas S. Leathar Award for their article, "Will the 'Principles of Effectiveness' Improve Prevention Practice? Early Findings from a Diffusion Study," (Health Education Research, 17(4), pp. 461-470, 2002). The article focuses on a major policy initiative meant to make public health practice, at least in the school health setting, more evidence-based. The authors informed their study using the diffusion of innovation perspective, providing the field with important data on the factors that facilitate and hinder program implementation.

**Drs. Patti Chamberlain** and **John Reid**, Oregon Social Learning Center, Eugene, Oregon, were selected to be Fellows in the Academy of Experimental Criminology.

Investigators from the University of Southern California's Transdisciplinary Drug Abuse Prevention Research Center received the following honors and awards:

> **C. Anderson Johnson** was Guest Professor of Peking University's School of Public Health; **C. Anderson Johnson** and **Peggy Gallagher** received a Citation of Recognition from the Society of Behavioral Medicine; **Stanley Azen** received a Certificate of Appreciation for Advancing Occupational Therapy Research; **Lourdes Baezconde-Garbani** was awarded for contributions in advancing Latino Health through research at the 1st National Hispanic/Latino Conference on Prevention and Control in Washington, D.C., and in advancing Latino Health through research advocacy at the National Hispanic/Latino Cancer Network and the National Latino Council on Alcohol and Tobacco Prevention.

The distinguished title of Regents Professor has been conferred on **Dr. Howard Kaplan** of the Department of Sociology at Texas A&M University. Previously, Dr. Kaplan was named Distinguished Professor of Sociology and the Mary Thomas Marshall Professor of Liberal Arts, all lifetime honors. Dr. Kaplan has been a NIDA grantee since 1980 and is the recipient of a Senior Scientist Award.

**Faye Taxman, Ph.D.**, faculty member of the University of Maryland, College Park, was awarded the University of Cincinnati Research Award by the American Probation and Parole Association (APPA) and Researcher of the Year Award from the Maryland Department of Public Safety and Correctional Services.

**Kenneth Winters, Ph.D.**, Associate Professor at the University of Minnesota, has been named Associate Editor of *Psychology of Addictive Behaviors*, and Chair of the Technical Advisory Network for the Mentor Foundation (for international drug abuse prevention).

**Dr. A. Thomas McLellan**, Co-PI from the CTN Delaware Valley Node at the University of Pennsylvania, was honored with a lifetime achievement award from the British Medical Society in London, England, in March 2003.

On February 19, 2003, **Dr. Edward Kaplan**, William N. and Marie A. Beach Professor of Management Sciences and Professor of Public Health, Yale School of Management, New Haven, Connecticut, was inducted into the National Academy of Engineering (one

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of the three parts of the National Academy of Sciences) in recognition of his NIDA-supported research in advanced mathematical modeling of the HIV/AIDS epidemic, assessing the public health impact and cost effectiveness of AIDS interventions, and bringing engineering perspectives to the design of public health policies.

**Dr. Howard Liddle**, University of Miami Center for Treatment Research on Adolescent Drug Abuse, was recently awarded the 2002 Recognition Award for Distinguished Contributions to Substance Abuse Research for Special Populations at the Ninth Annual Conference on Behavior, Clinical Neuroscience, Substance Abuse and Culture.