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Research Findings - Basic Research

Endocannabinoids Facilitate the Induction of LTP in the Hippocampus

The hippocampus is an important site in the memory process. Long-term potentiation (LTP) of neural activity, which is one type of neuronal plasticity, is commonly used in the study of the neuronal basis of memory and to assess effects of pharmacological agents. The interaction of glutamate and GABA systems plays an important role in the memory process and LTP. Alger and his colleagues characterized a cannabinoid-mediated generation of LTP, induced by depolarization-suppression of inhibition (DSI type of disinhibition). They found that following burst depolarization of the principal neurons in the hippocampus, the GABAergic IPSCs are suppressed for a short period of time. As a consequence of the disinhibition, they showed that a weak stimulus, which would not usually induce LTP, was capable of inducing NMDA-dependent LTP if it was applied soon after a preceding depolarizing pulse (conditioning stimulus), or under conditions in which the GABA receptor was blocked. The cannabinoid receptor activation, apparently through presynaptic interneurons, was necessary and sufficient for the DSI type of disinhibition/LTP in hippocampus. When it was blocked, the weak testing stimulus train failed to induce the DSI-mediated LTP, even though the hippocampus is still capable of generating LTP in response to standard (stronger) pulses. It is known that hippocampus neurons *In Vivo* often fire in bursts independently, and a burst of action potentials in a single cell can induce DSI. The DSI-mediated LTP is likely to be restricted in space for the short travel distance of released endocannabinoid. Such targeted LTP could underlie behavioral learning. Dr. Alger's work reveals two distinct types of LTP that are correlated with GABA and glutamate systems respectively. Exogenous cannabinoids will globally activate cannabinoid receptors, including those on the excitatory synapse and disrupt the exquisite temporal and special pattern of coding and recall mediated by endocannabinoids, and may contribute to the learning and memory deficiencies associated with cannabinoid drug abuse. Nature Neurosci., 5(8), pp. 723-724, 2002.

Cannabinoids Reduce Tolerance to Opioids

NIDA-grantee Dr. Sandra P. Welch of Virginia Commonwealth University and her colleagues have examined the interactions of cannabinioids and opioids in producing analgesia. Chronic exposure to opioids, such as morphine, results in a tolerance to the analgesic properties of the opioid. There is a concomitant decrease in opioid receptors (where morphine primarily acts) in the brain and spinal cord. Dr. Welch has found that tetrahydrocannabinol (THC) administration in mice reduced morphine-induced analgesic tolerance. Further, THC eliminated the down regulation of opioid receptors seen after chronic morphine administration. These data help to identify a mechanism of opioid tolerance, as well as demonstrate the interaction of cannabinioids and opioids at both the behavioral and cellular levels. Cichewicz, D.L., Haller, V.L., and Welch, S.P. Changes in Opioid and Cannabinoid Receptor Protein following Short-Term Combination Treatment with Tetrahydrocannabinol and Morphine, The Journal of Pharmacology and Experimental Therapeutics, 297, pp. 121-127, 2001.

Slower Metabolism and Reduced Intake of Nicotine: Ethnic Differences

In the United States, about 90% of lung cancer cases are attributable to cigarette smoking. The incidence of lung cancer can, therefore, be taken as a population

marker of cigarette-related disease. Considerable ethnic differences are seen in the prevalence of lung cancer. The lowest rates of lung cancer are seen in Asians and Latinos, with higher rates in whites and the highest rates in African-Americans. Ethnic differences in nicotine metabolism might, in part, explain ethnic differences in cigarette consumption and/or nicotine intake per cigarette and resultant tobacco-related cancer risk. Dr. Benowitz and colleagues compared the rate of nicotine metabolism and intake of nicotine per cigarette smoked among smokers of different ethnicities. Healthy volunteers, including Chinese-Americans, Latinos, and whites, received simultaneous infusions of deuterium-labeled nicotine and cotinine, a metabolite of nicotine. From blood and urine measurements, the disposition kinetics and the daily intake of nicotine from smoking were determined. Total and non-renal clearance of nicotine and cotinine and metabolic clearance of nicotine via the cotinine pathway were similar in Latinos and whites and statistically significantly lower in Chinese-Americans. Intake of nicotine per cigarette by Chinese-Americans was statistically significantly lower than that of Latinos. Among all the participants, there was a statistically significant positive correlation between nicotine clearance and daily intake of nicotine from cigarettes. The lower nicotine (and, therefore, tobacco smoke) intake per cigarette and the fewer cigarettes smoked per day, which may result, in part, from slower clearance of nicotine, may explain lower lung cancer rates in Chinese-Americans. Lower lung cancer rates among Latinos compared with whites, given their similar nicotine intake per cigarette, is probably due to smoking fewer cigarettes. The results with Chinese-Americans may have implications for dosing with nicotine medications to aid smoking cessation in Chinese-American smokers and perhaps in other Asian smokers. Benowitz, N.L., Perez-Stable, E.J., Herrera, B., and Jacob III, P. Slower Metabolism and Reduced Intake of Nicotine From Cigarette Smoking in Chinese-Americans. Journal of the National Cancer Institute, 94(2), pp. 108-115, 2002.

Biphalin Update

Biphalin is an opioid peptide first reported in 1991, which has a dimeric or "bivalent" enkephalin structure. It was designed as one of a class of compounds containing two pharmacophoric regions within one molecule, in this case separated by a two-atom hydrazide bridge. Biphalin possesses high affinity (nanomolar) for both the mu and delta receptors, and a lower affinity for the kappa receptor. It has been found to be more potent than morphine as an antinociceptive agent when given intracerebroventricularly to rats, and equipotent with morphine when given intraperitoneally. Interest in biphalin has persisted in part because of its diminished symptoms of dependence produced in the rat. Biphalin has limited ability to cross the blood brain barrier. However, this is somewhat enhanced by halogenation with chlorine, fluorine, or iodine on the phenyl rings of the phenylalanines present in the molecule. I-125-labeled biphalin has been shown to accumulate in the nucleus accumbens, the choroid plexus, and the pituitary, following intravenous injection. In recent work, Dr. Victor Hruby and his associates have reported new findings. The first is the crystal structure of biphalin sulfate, indicating a folded structure existing for both halves of the molecule. Specifically, amino acids 1-4 exhibited a random coil structure in the solid phase, and could be overlapped with the same four amino acid residues of the delta ligand DADLE. There was also overlap seen between some of the backbone atoms and the tyrosine group of TIPP-NH2 (a mu ligand) and corresponding atoms in residues 5-8 of biphalin. Secondly, because previous studies have shown that the minimum structural requirement for mu and delta activity in biphalin is the presence of one lipophilic amino acid beyond the hydrazide bridge, replacement of phenylalanine in position five with a dansyl group has been carried out, in order to produce a ligand with multiple receptor activity and fluorescence properties. The dansyl derivative of biphalin showed comparable mu/delta binding, antinociceptive properties in the rat model, and strong fluorescence emission at 600 nm, which may render this compound useful for pharmacokinetic studies. Misicka, A., Lipkowski, A., Kosson, D., Kosson, P., Lachwa-From, M., Brodzik-Bienkowska, A., and Hruby, V. Life Sciences. 70, pp. 893-897, 2002; Flippen-Anderson, J., Deschamps, J., George, C., Hruby, V., Misicka, A., and Lipkowski, A. J. Peptide Research, 59, pp. 123-133, 2002.

Control of Synaptic Strength by Glial TNFalpha

The role of glia in synaptic plasticity has largely been ignored despite the fact that glia comprises 90 percent of all the cells in the brain. The Laboratories of Mark Von Zastrow of UCSF, Michael Beattie and Robert Malenka in the March 22, 2002 issue of Science show that glia control synaptic strength by releasing tumor necrosis factor alpha (TNFalpha). They found that application of media from glia cells increased the number of AMPA glutamate receptors and the frequency of spontaneous transmitter release of hippocampal neurons in culture. The increase in the number of AMPA

receptors and the increase in the spontaneous transmitter release could be blocked by adding a TNFalpha antibody or the TNF receptor to the culture medium, which absorb TNF from the media and prevents TNF from activating receptors on neurons. In addition, an inhibitor of TNFalpha release from glia also blocked the increase in the number of AMPA receptors and the increase in spontaneous transmitter release. Similar results were found in hippocampal slice preparations where the number of AMPA receptors and the frequency of spontaneous transmitter release was decreased by blockers of TNFalpha. These results suggest that TNFalpha may play a role in forms of synaptic plasticity such as long-term potentiation which involves increased insertion of AMPA receptors into the post-synaptic membrane. It may also explain how TNFalpha may contribute to neural injury by increasing the number of AMPA receptors. Beattie, E.C., Stellwagen, D., Morishita, W., Bresnahan, J.C., Ha, B.K., Von Zastrow, M., Beattie, M.S., and Malenka, R.C. Control of Synaptic Strength by Glial TNFalpha. Science, 295(5563), pp. 2282-2285, 2002.

Brain-Derived Neurotrophic Factor is Essential for Opiate-Induced Plasticity of Noradrenergic Neurons

Withdrawal from chronic opiates is associated with increased firing of noradrenergic neurons in the locus coereleus. Withdrawal symptoms can be blocked by treating animals with clonidine, an alpha 2-adreneric agonist that decreases the firing of noradrenergic neurons in the locus coereleus. Biochemically, the increase in electrical impulses of locus coerelus neurons is associated with increased activity of the cAMP pathway and increased synthesis of tyrosine hydroxylase, the rate-limiting enzyme in norepinephrine synthesis. Exactly what regulates the processes of adaptation of noradrenergic neurons to chronic opiate treatment is not well understood. Brain Derived Neurotrophic Factor (BDNF) supports the survival of noradrenergic Locus Coereleus neurons and plays a significant role in synaptic plasticity. To test the role of BDNF in regulating adaptation of Locus Coereleus neuron to opiates, Dr. Akbarian generated a conditional knockout of the BDNF gene in which the gene was deleted in the adult mouse but not during development. Dr. Akbarian reports in the May 15, 2002 issue of the Journal of Neuroscience that deletion of the BDNF gene significantly attenuated opiate withdrawal without affecting tolerance. Deletion of BDNF blocked the upregulation of adenylyl cyclase, the enzymes responsible for cAMP synthesis, and induction of tyrosine hydroxylase. This report is consistent with work of Marc Caron's laboratory on beta-arrestin and work by Rafael Maldonado, Julie Blendy, and Gunter Schutz that found that the biochemical pathways regulating withdrawal are different from those regulating tolerance to opiates. It remains to be determined whether BDNF contributes to compulsive drug seeking behavior and relapse in the absence of physical dependence. Akbarian, S., Rios, M., Liu, R.J., Gold, S.J., Fong, H.F., Zeiler, S., Coppola, V., Tessarollo, L., Jones, K.R., Nestler, E.J., Aghajanian, G.K., Jaenisch, R. Brain-derived Neurotrophic Factor is Essential for Opiate-induced Plasticity of Noradrenergic Neurons. J. Neurosci., 22(10), pp. 4153-4162, May 15, 2002.

Modulation of Postendocytic Sorting of G Protein-Coupled Receptors

Ligand-induced endocytosis contributes to the physiological regulation of a wide variety of signaling receptors. Many G protein-coupled receptors (GPCRs) are endocytosed by a mechanism involving receptor phosphorylation, interaction with beta-arrestins, and concentration in clathrin-coated pits. However, the functional consequences of GPCR endocytosis through this conserved cellular mechanism are diverse. Trafficking of internalized GPCRs by a rapid recycling pathway restores the complement of functional receptors in the plasma membrane and promotes resensitization of receptor-mediated signal transduction. In contrast, the sorting of internalized GPCRs to lysosomes promotes proteolytic down-regulation of receptors, leading to a prolonged attenuation of cellular signal transduction. Furthermore, the postendocytic sorting of certain GPCRs can itself be regulated under physiological condition.

Mu Opioid Receptors

(MORs) and delta opioid receptors (DORs) are structurally homologous GPCRs that mediate the actions of endogenously produced opioid neuropeptides and exogenously administered opiate drugs. Both receptors are endocytosed via clathrin-coated pits after agonist-induced activation, phosphorylation, and association with cytoplasmic beta-arrestin. However, it has been known that DOR, but not MOR, exhibits down-regulation and was rapidly proteolyzed after agonist-induced endocytosis. Moreover, DORs were found to concentrate in the perinuclear region of the cells and colocalized with the endosome and lysosome while MORs were localized in vesicles distributed

throughout the cytoplasm that failed to colocalize with endosome and lysosome. Drs. Whistler and von Zastrow and their research team at the University of California and University of Lund, Sweden, using various cellular and molecular approaches, have identified a previously unknown protein with human, rat, and murine homologs that binds preferentially to the cytoplasmic tail of the DOR as a candidate heterotrimeric GTP binding protein (G protein)-coupled receptor-associated sorting protein (GASP). Disruption of the DOR-GASP interaction through receptor mutation or overexpression of a dominant negative fragment of GASP inhibited receptor trafficking to lysosomes and promoted recycling. The GASP family of proteins (noncovalent interactions with GPCRs), along with ubiquitinylation (covalent modification of GPCRs), may modulate lysosomal sorting and functional down-regulation of a variety of G protein-coupled receptors. Such complexity in postendocytic sorting machinery might be critical for generating the remarkable diversity and specificity with which signaling receptors are regulated in multicellular organisms.Whistler, J.L., Enquist, J., Marley, A., Fong, J., Gladher, F., Tsuruda, P., Murray, S.R. and von Zastrow, M. Modulation of Postendocytic Sorting of G Protein-Coupled Receptors. Science, 297(5581), pp. 615-620, July 26, 2002.

Potentiation of Opioid Analgesia in Dopamine2 Receptor Knock-out Mice: Evidence for a Tonically Active Antiopioid System

Dopamine (DA) systems are intimately involved with opioid actions. Pharmacological studies suggest an important modulatory effect of dopamine and its receptors on opioid analgesia. Dr. Gavril Pasternak and his research team at the Memorial Sloan-Kettering Cancer Center have now examined these interactions in a knock-out mouse model in which the D2 receptor has been disrupted. Loss of D2 receptors enhances, in a dose-dependent manner, the analgesic actions of the mu analgesic morphine, the kappa1 (k1) agonist U50,488H and the k3 analgesic naloxone benzoyl-hydrazone. The responses to the delta opioid analgesic [d-Pen2, d-Pen5]enkephalin were unaffected in the knock-out animals. Loss of D2 receptors also potentiated spinal orphanin FQ/nociceptin analgesia. Antisense studies using a probe targeting the D2 receptor revealed results similar to those observed in the mouse knock-out model. The modulatory actions of D2 receptors were independent of final sigma receptor systems because the final sigma agonist (+)-pentazocine lowered opioid analgesia in all mice, including the D2 knockout group. Thus, D2 receptors represent an additional, significant modulatory system that inhibits analgesic responses to mu and kappa opioids. King, M.A., Bradshaw, S., Chang, A.H., Pintar, J.E., and Pasternak, G.W. Potentiation of Opioid Analgesia in Dopamine2 Receptor Knock-Out Mice: Evidence for a Tonically Active Antiopioid System. J Neurosci., 21(19), pp. 7788-7792, October 1, 2001.

(1R)-2-[3R,4S)-3-Methyl-4-(N-phenyl-N-propionylamino) piperidin-1-yl]-1-phenylethyl p-bromobenzoate and N-{(3R,4S)-1-[(2S)-2-(4-bromo-phenyl)-2-hydroxyethyl] -3-methyl-piperidin-4-yl} -N-phenylacrylamide

Two brominated derivatives (both titled compounds) of the potent opioid, cis-b-hydroxy-3-methylfentanyl (ohmefentanyl) were studied and their absolute configuration were determined to assign the proper configuration of two of these stereoisomers and the compounds have the same stereochemistry at two of the three asymmetric C atoms. Ohmefentanyl is an extremely potent analgesic exhibiting high selectivity for the m-opioid receptor. It is one of the 'super potent' analogs of fentanyl that is more potent in producing antinociception than was predicted on the basis of its m-receptor affinity. With three asymmetric C atoms, the compound has eight possible stereoisomers. Four, two pairs of optical isomers, of the eight possible steroisomers would have cis arrangements of the substituents on C3 and C4. When the two pairs were separated, one pair was found to be 5.3 times more potent than the other and 6300 times more potent than morphine. The more active pair was referred to as ohmefentanyl. A second sample, designated as RTI-4614-4 was determined to be a mixture of all four cis isomers and was shown to be 25,000 times more potent than morphine. In view of the differing activities and isomeric compositions of ohmefentanyl and RTI-4614-4, it was clearly necessary to resolve ohmefentanyl into its four stereoisomers. Therefore two brominated derivatives of ohmefentanyl (titled compounds) were synthesized (Brine et al., J. Med. Chem., 38, 1547, 1995) to resolve the stereochemistry of ohmefentanyl. In this paper the absolute configuration of these two bromo-derivatives are reported. This study will help in the design of new opioid ligands for further development of better opioid therapies. Deschamps, J.R., George, C. and Flippen-Anderson, J.L. Acta Cryst., C58, pp. o362-o364, 2002.

Decreased Expression of the Transcription Factor NURR1 in Dopamine Neurons of Cocaine Abusers

NURR1 affects the transcriptional regulation of the dopamine transporter (DAT), a cocaine-sensitive gene. In this study, investigators looked at the postmortem brains of individuals who had died from cocaine overdoses and compared these to drug-free controls that were closely matched for age, sex, postmortem interval, and tissue pH. The investigators first confirmed that the NURR1 gene was expressed in the same regions of the brain as the phenotypic marker of dopamine neurons, the DAT gene. They observed NURR1 mRNA within almost every mid-brain dopamine cell. When they compared the NURR1 mRNA and protein levels in the ventral tier of the substantia nigra of cocaine abusers versus control tissue, they found very low levels of NURR1 in the cocaine abusers. Since other studies have shown that NURR1 regulates DAT expression *In Vitro*, they examined the level of DAT mRNA in the ventral tier dopamine cells and found that the level of DAT mRNA in cocaine abusers was 70-75% of the level observed in the control tissue. However, VMAT2, a distinct transporter protein expressed in high abundance in dopamine neurons, but not known to be regulated by NURR1, was unaltered in the tissue of cocaine abusers. This suggests that the decrease in NURR1 and DAT expression observed in cocaine abusers is gene-specific and not a general pathologic process within the dopamine neurons. Since DAT is a major site of action for cocaine in the brain, cocaine-induced decreases of DAT transcription could represent an important component of the compensatory mechanisms that occur as a result of chronic drug exposure. Bannon, M.J., Pruetz, B., Manning-Bog, A.B., Whitty, C.J., Michelhaugh, S.K., Sacchetti, P., Granneman, J.G., Mash, D.C., and Schmidt, C.J. Proc Natl Acad Sci, 99(9), pp. 6382-6385, April 30, 2002.

Synapses are Fundamental in Processing Information within the Central Nervous System

One of the hallmarks of synaptic transmission is its plasticity: neural activity channeled through synapses modulates the efficacy of subsequent transmission. Temporally correlated activity may also modulate neuronal networks by creating and eliminating synapses. Such use-dependent plasticity may provide a cellular mechanism for the encoding of persistent memories. Dr. Yukiko Goda and her colleagues at the University of California at San Diego have pioneered the technique of photoconductive excitation of individual neurons cultured on a silicon chip and demonstrated that activity-dependent morphological synaptic plasticity occurs by video-imaging GFP-actin at individual synapses. A single tetanus transiently moved presynaptic actin toward and postsynaptic actin away from the synaptic junction. Repetitive spaced tetani induced glutamate receptor-dependent stable restructuring of synapses. The presynaptic actin redistributed and new puncta indicative of active synapses were formed within 2 hours. Their results indicate that activity-dependent presynaptic structural plasticity facilitates the formation of new active presynaptic terminals. These data are among the first to be reported as a result of NIDA's CEBRA (Cutting Edge Basic Research Award) mechanism, which focuses on innovative science. Colicos, M.A., Collins, B.E., Sailor, M.J., and Goda, Y. Remodeling of Synaptic Actin Induced by Photoconductive Stimulation. Cell, 107, pp. 605-616, 2001.

Synaptic Mechanisms Explain Nicotine's Prolonged Effects

Scientists studying nicotine's effects on the brain have faced a puzzling question: Why do dopamine (DA) cells projecting from the ventral tegmental area (VTA) to the nucleus accumbens continue to release dopamine for more than an hour *In Vivo*, after even a single exposure to nicotine, when the nicotinic acetylcholine receptors (nAChRs) on those cells desensitize rapidly? Now, investigators at the University of Chicago report that this phenomena can be explained by examining the system of inhibitory and excitatory neurons providing inputs to the VTA dopamine neurons. Drs. Huibert D. Mansvelder, J. Russel Keath, and Daniel S. McGehee undertook a series of electrophysiological studies examining the GABAergic and glutamatergic inputs to the VTA dopamine neurons. They report that each cell type is modulated by a different type of nicotinic receptor. "7 type receptors on the excitatory glutamatergic inputs mediate enhancement of glutamatergic transmission during exposure to nicotine, and desensitize less than the nicotinic receptors on the GABAergic neurons. The nicotinic receptors on the GABAergic neurons appear similar to those on the dopamine neurons themselves, and likely contain "4 and $2 subunits, according to the investigators. Initially, nicotine activates these receptors, but then they rapidly desensitize. As a result, the inhibitory input to the dopamine neurons becomes suppressed, leading to disinhibtion of the dopamine neurons. The receptors on the GABAergic neurons

remain desensitized for a longer period of time than those on the glutamatergic neurons. The net effect of these different receptor behaviors on various synaptic inputs in the system is thus a shift toward excitation of the dopamine neurons which persists for some time. Indeed, as the Chicago research team points out: "If the DA neuron is depolarized sufficiently, the enhancement of glutamatergic transmission can induce a long-term potentiation of these inputs, as we reported previously." The investigators also looked at the role of endogenous acetylcholine (ACh) inputs. Their findings supported the idea that desensitization of nAChRs by nicotine or chronic ACh can reduce the excitatory drive on the GABAergic neurons. Again, this action effectively disinhibits the dopamine neurons and increases their excitability. Thus, different nAChR's with different spatial and temporal responses located on different cell types constitute components of a system whose behavior leads to the release of dopamine, which, in turn, appears correlated with the reinforcing properties of nicotine. This work was supported by the Netherlands Organization for Scientific Research, the National Institute on Drug Abuse, the National Institute of Neurological Disorders and Stroke, and the Brain Research Foundation. Mansvelder, H.D., Keath, J.R. and McGehee, D.S. Synaptic Mechanisms Underlie Nicotine-Induced Excitability of Brain Reward Areas, Neuron, 33, pp. 905-919, March 14, 2002.

Coordinated Release of ATP and GABA May Offer Novel Synaptic Flexibility to Hypothalamic Circuits

Adenosine triphosphate (ATP) is recognized as the major energy source within cells; however it also can serve as a neurotransmitter, in a process called "purinergic" transmission. (Adenine is a purine.) As a neurotransmitter, ATP interacts with a family of receptors generally known as P2X receptors. Although these receptors are expressed throughout the central nervous system, little is known about them, because of difficulties in detecting small amplitude synaptic currents, and because of a lack of P2X receptor antagonists. One brain region which expresses P2X receptors prominently is the hypothalamus. NIDA grantee Dr. Lorna Role undertook the task of determining if P2X receptor expression underlies a significant contribution of ATP to synaptic transmission in the hypothalamus. Through electrophysiological *In Vitro* studies on neurons from the lateral hypothalamus, she found evidence for robust and reliable action potential-dependent ATP P2X receptor-mediated purinergic transmission in preparations of embryonic chick neurons and in preparations of neurons from postnatal mice; moreover, based on recordings from pairs of pre- and postsynaptic neurons, she found that postsynaptic currents mediated by ATP and GABAA receptors originate from coordinated release of ATP and GABA from individual neurons. From her findings, Dr. Role proposes that the GABA and ATP may be stored within the same synaptic vesicle. Dr. Role notes that GABA is the primary inhibiting neurotransmitter in the hypothalamus, and that inhibitory circuits in the lateral hypothalamus may play an important role in feeding. During development, however, GABA can exert depolarizing effects on neurons. Dr. Role suggests that during development, the coordinate release of ATP and GABA may provide important synergy for excitatory influences on the developing synapses. At mature synapses, according to Dr. Role, activation of GABAA receptors may enhance calcium influx through P2X receptors. Thus, the coordinated release of the two transmitters may serve as a means for synaptic tuning of hypothalamic circuits in developing versus mature animals. Understanding lateral hypothalamic circuits is crucial because they integrate autonomic and limbic information, and are important in behavioral arousal. This work demonstrates the importance of examining the effects of multiple systems simultaneously and the properties of the systems at different temporal stages. Young-Hwan, J. and Role, L.W. Coordinated Release of ATP and GABA at *In Vitro* Synapses of Lateral Hypothalamic Neurons, The Journal of Neuroscience, 22(12), pp. 4794-4804, June 12, 2002.

cAMP Mediated Transcription Mapping during Morphine Withdrawal

cAMP response element binding protein (CREB) is a genetic transcription factor which recognizes the cAMP-response element (CRE) promoter site. A variety of stimuli can lead to CREB activating the transcription of target genes. For example, chronic opiate exposure upregulates CREB in the locus ceruleus (LC) of the brain. This has long been of interest since CREB also has been implicated in long term synaptic processes associated with learning and memory. But does morphine dependence actually influence transcription mediated by the CRE response element? To answer this question, Dr. Eric Nestler of the University of Texas Southwestern Medical Center and a team of investigators studied morphine dependent transgenic animals containing a marker to tell if and where transcription occurred during naltrexone precipitated

withdrawal. The transgenic animals contained a genetic construct in which a "reporter" is made in such a way that it is under the control of CRE-consensus elements. In other words, they used the "reporter" molecule, beta-galactosidase, as a visual indicator for CRE-mediated transcription. They also used cell markers to identify specific neuronal cell populations where changes in gene expression occurred. They observed changes in gene transcription in several brain regions consistent with expected physiological effects, such as those concerned with arousal, reward, mood, and affective responses. For example, they found morphine withdrawal affected expression of beta-galactosidase in a mixed population of cells in the nucleus accumbens. The authors suggest that CRE-mediated transcription during withdrawal may be a homeostatic mechanism responding to molecular adaptations which developed during chronic opiate exposure. Observing such transcription also may serve as a marker of neuronal plasticity during withdrawal, according to the research team. Shaw-Lutchman, T.Z., Barrot, M. Wallace, T., Gilden, L., Zachariou, V., Impey, S., Duman, R.S., Storm, D. and Nestler, E.J. Regional and Cellular Mapping of cAMP Response Element-mediated Transcription during Naltrexone-precipitated Morphine Withdrawal. Journal of Neuroscience, 22(9), pp. 3663-3672, May 1, 2002.

Chemokines as Modulators of Pain

Chemokines are recently studied peptides interacting with glia and neurons in the brain and also on blood leukocytes. It has been known for awhile that opioids inhibit the chemotactic activity of these chemokines, thus impacting on their neuroimmune functions. This group has focused on the chemotaxis of peripheral blood monocytes. Herein they find that opioids activate chemokine receptors in these cells leading to immunosuppression. They postulate this crosstalk between these two receptors may also lead to desensitization of the opioid receptors so that chemokines build up in inflammatory states. Further studies should elucidate the basic mechanism of how opioids and chemokines function together in pain or inflammatory processes. The chemokines use G protein-coupled receptors to regulate the migratory and proadhesive responses of leukocytes. Based on observations that G protein-coupled receptors undergo heterologous desensitization, they have examined the ability of chemokines to also influence the perception of pain by cross-desensitizing opioidGprotein-coupled receptors function *In Vitro* and *In Vivo*. The authors found that the chemotactic activities of both m- and d-opioid receptors are desensitized following activation of the chemokine receptors CCR5, CCR2, CCR7, and CXCR4 but not of the CXCR1 or CXCR2 receptors. Furthermore, they also found that pretreatment with RANTES/CCL5, the ligand for CCR1, and CCR5 or SDF-1a /CXCL12, the ligand for CXCR4, followed by opioid administration into the periaqueductal gray matter of the brain results in an increased rat tail flick response to a painful stimulus. Because chemokine administration into the periaqueductal gray matter inhibits opioid-induced analgesia, the authors propose that the activation of proinflammatory chemokine receptors down-regulates the analgesic functions of opioid receptors, and this enhances the perception of pain at inflammatory sites. Szabo, I., Chen, X.H., Xin, L., Adler, M.W., Howard, O.M.Z., Oppenheim, J.J., and Rogers, J. Heterologous Desensitization of Opioid Receptors by Chemokines Inhibits Chemotaxis and Enhances the Perception of Pain. PNAS, 99, pp. 10276-10281, 2002.

Inhibition of Morphine-potentiated HIV-1 Replication in Peripheral Blood Mononuclear Cells with the Nuclease-resistant 2-5A Agonist Analog, 2-5A(N6B)

The compound, 2-5AN6B is a nuclease-resistant 2-5A agonist analog. In these studies using morphine-treated peripheral blood mononuclear cell cultures researchers found that 2-5AN6B, but not AZT or saquinavir completely reversed morphine-induced potentiation of HIV-1 infection. Treatment of peripheral blood mononuclear cell cultures with 2-5AN6B increased RNase L activity in control peripheral blood mononuclear cell cultures, in morphine-treated peripheral blood mononuclear cell cultures and in morphine-treated, HIV-1-infected peripheral blood mononuclear cells. The researchers also found that 2-5AN6B enhanced expression of both IFN-" and IFN-(. The increased expression of IFN-(was associated with a significant increase in expression of RANTES and monocyte chemotactic protein-1, chemokines that may inhibit HIV-1 infection by blocking viral attachment to CCR2 and CCR5 co-receptors. By adding 2-5AN6B to the cultured morphine-treated peripheral blood mononuclear cells, the researchers were able to reverse the morphine-potentiated HIV-1 infection of the cells. Homan, J.W., Steele, A.D., Martinand-Mari, C., Rogers, T.J., Henderson, E.E., Charubala, R., Pfleiderer, W., Reichenbach, N.L., and Suhadolnik, R.J. J Acquir Immune Defic Syndr.,30(1), pp. 9-20, May 1, 2002.

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Research Findings - Behavioral Research

Research Implicates the Basolateral Amygdala (BLA) in Heroin Relapse

Researchers at the Medical University of South Carolina discovered that similar to cocaine relapse, stimuli (i.e., environmental cues) paired with heroin infusions can induce drug abuse relapse in a rodent model. In this experiment, rats were trained to press a lever to deliver intravenous heroin infusions. The heroin infusions were also paired with a change in the environment. That is, heroin infusions were paired with the presentation of a tone and a light stimulus. After rats learned to press the lever to receive heroin infusions, they were put under an "extinction" phase in which lever pressing resulted in the delivery of saline and not heroin. During this "extinction" phase responding on the lever decreased. Later, when rats were exposed to the tone and light stimuli previously paired with heroin they began to press the lever to infuse heroin, although heroin was not actually available. This phenomenon is referred to as "cue-induced" relapse. Similarly, if rats were administered a small "priming" dose of heroin following the "extinction" phase they also began to press the lever for heroin. This phenomenon is referred to "drug-induced relapse." The researchers further showed that the BLA was an important brain region for both drug- and cue-induced relapse in animals trained to self-administer this opiate drug. The BLA has previously been shown to be important for learning and in motivated behavior. These researchers showed when they inactivated this brain region temporarily with tetrodotoxin neither the cues nor the drug itself induced relapse after heroin rewarded responding had been extinguished. In the past, this same group of researchers has shown that cocaine itself does induce relapse if the BLA is inactivated. These results suggest that the BLA is an important component of the neural circuitry that underlies cue- and heroin-induced relapse. Furthermore these results suggest that different neural circuits may be critical for cocaine-induced relapse relative to heroin-induced relapse. Fuchs, R.A. and See, R.E. Psychopharmacology, 160, pp. 425-433, 2002.

Neurobiological Stress Systems Play a Role in Relapse Triggered by Drug-related Environmental Cues

Dr. Nicholas Goeders and his colleagues at the Louisiana State University Health Sciences Center in Shreveport, LA, have been studying the role of central stress systems (specifically, the hypothalamo-pituitary-adrenal axis) in drug abuse and addiction. He employs an animal model of drug self-administration with cocaine and has previously reported that corticosterone (CORT) is crucial for acquisition, and is involved in continued drug taking during maintenance. Also, the CORT synthesis inhibitor, ketoconazole, reduces 'reinstatement' to drug-seeking behavior. In the reinstatement paradigm, animals are trained to self-administer drug, and then put into extinction where their responses produce no consequences (i.v. infusions of cocaine are not delivered). Eventually, animals stop making drug-seeking responses during this extinction. Then, several different manipulations can be used to 'reinstate' drug-seeking behavior - that is, responses made on the operant lever that previously delivered cocaine. One manipulation is to provide environmental cues previously paired with cocaine during self-administration. These cues serve to signal drug reward and also take on secondary reinforcing properties of their own, thereby activating incentive motivational systems that direct behavior. For example, animals will make responses just to receive presentation of these cues - which become conditioned stimuli (CS). These experimental observations parallel reports from human drug abusers, where drug-paired stimuli induce emotional responses of arousal and

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anticipation, and elicit positive, 'drug-like' reports that may define human craving. In a recent report, Dr. Goeders used response-contingent cues to reinstate cocaine-seeking behavior and examined the effects of ketoconazole pretreatment in this animal model of relapse. In his study, extinguished rats reinstated responding on the drug-associated lever, just to gain access to CS previously associated with cocaine. Thus, this behavior is driven by the incentive motivational properties of the CS. Pretreatment with the CORT synthesis inhibitor ketoconazole abolished CS-induced reinstatement of responses on the cocaine lever, and a similar result was obtained by pretreating animals with a corticotropin-releasing hormone (CRH) receptor antagonist (specifically, for the CRH1 site, CP-154,526). Parallel findings with the direct receptor antagonist provide additional evidence that the HPA axis is involved in reinstatement triggered by a drug-associated CS, since activation of CRH receptors on the pituitary trigger the adrenals (through ACTH) to release CORT. Ketoconazole also decreased the rise in plasma CORT that was seen in vehicle-pretreated rats, during reinstatement (thus, reinstatement activated the HPA axis). In the present study, inhibition of CORT synthesis, or blockade of pituitary receptors that ultimately promote CORT activation, diminished the ability of an incentive motivational CS to reinstate cocaine directed behavior. Reductions of plasma CORT at the same time suggest that this attenuation in the ability of conditioned incentive stimuli to drive drug seeking may result from a blunting of CS-induced activation in the HPA axis. Goeders, N.E., and Clampitt, D.M. Potential Role for the Hypothalamo-Pituitary-Adrenal Axis in the Conditioned Reinforcer-induced Reinstatement of Extinguished Cocaine Seeking in Rats. Psychopharmacol., 161, pp. 222-232, 2002.

Dopamine D2 Receptors May Act as a "Brake" on Escalation of Cocaine Self-administration

Recent findings from human neuroimaging studies, and from non-human primates housed in a social colony, implicate basal ganglia Dopamine D2 receptor substrates both in the subjective, pleasurable response to psychostimulant drugs and to the vulnerability to begin self-administration. A recent report from Dr. S. Barak Caine and colleagues at McLean Hospital, Harvard Medical School, also implicates this substrate specifically in high dose cocaine reinforcement. Dr. Caine used a creative experimental approach where converging evidence from C57BL/6 D2 knock-out mice was evaluated along with pharmacologic probes of the D2 system in mice and in outbred rats. When D2 knock-outs were allowed to make operant responses to receive food, their rate of responding was lower than their wild type counterparts. However, in a cocaine self-administration procedure, these knock-outs took significantly more cocaine, with heterozygous animals responding at rates between those of the wild types and homozygous (knock-out) mice. A dose-response analysis revealed that knock-out mice took more cocaine only at the higher doses offered (i.e., 1.0 and 3.2 mg/kg/injection). When self-administering cocaine doses <1.0 mg/kg/injection, their response rates were no different than the other groups. When challenged with a D2 antagonist (eticlopride), wild type and heterozygous mice showed significant increases in their cocaine intake (as is usually seen with D2 antagonist treatment in cocaine self-administration studies), but the antagonist was without effect in the D2 knock-outs. Outbred rats showed a similar rightward shift in dose response function for cocaine self administration when pretreated with a more selective D2 antagonist (L-741,626). In this case, rats showed significantly greater self-administration of cocaine for doses of 3.2 mg/kg/injection, and less self-administration with lower doses (i.e., 0.3 mg/kg/injection). By contrast, drug intake was not increased following pretreatment with either a selective D3/D4 antagonist, or a D3 antagonist. Collectively, these findings implicate a D2 receptor substrate as critically important in modulating the intake of high doses of cocaine. Since continued cocaine use has been observed to progress to increasingly greater drug intake (i.e., higher doses per administration), these receptors may play an important role in escalation or transition to higher dose patterns of use. Caine, S.B., Negus, S.S., Mello, N.K., Patel, S., Bristow, L., Kulagowski, J., Vallone, D., Saiardi, A., and Borrelli, E. Role of Dopamine D2-like Receptors in Cocaine Self-administration: Studies with D2 Receptor Mutant Mice and Novel D2 Receptor Antagonists. J. Neurosci., 22, pp. 2977-2988, 2002.

Escalation Schedule Produces Changes in Central Reward Systems that May Drive Compulsive Drug-taking

NIDA-funded investigators Drs. George Koob and Athina Markou from the Scripps Research Institute, in collaboration with Drs. Serge Ahmed and Paul Kenny, recently provided evidence that repeated binge cycles of cocaine self-administration in the rat produce a persistent dampening of central reward mechanisms indexed by intra-

cranial self-stimulation (ICSS). These researchers trained animals to self-administer cocaine over 12 daily sessions that were either one or six hours long. Six hours of self-administration availability has been previously shown to be associated with escalated drug intake in this model. ICSS thresholds, as a measure of reward sensitivity, were assessed 17-22 hours after each daily self-administration session. On these test days, animals made a discrete response to receive reinforcing electrical stimulation delivered to the posterior lateral hypothalamus and thresholds were measured from current-intensity profiles. Over 12 days, rats in the long access group (LgA) showed increased ICSS reward thresholds, whereas those in the one hour exposure group (short access, ShA) and others who did not self-administer cocaine had stable thresholds. Over the course of these 12 days, there was also a significant escalation in number of cocaine injections per drug self-administration session in LgA animals only. In fact, the authors report a high correlation between the slope of reward thresholds and the slope of this escalated drug self-administration for the LgA group. Daily cocaine intake was also positively correlated with daily ICSS thresholds from LgA rats, and ICSS thresholds continued to be elevated for eight days following this long access testing (i.e., during subsequent days when LgA rats were switched to a ShA procedure). All animals were also assessed for acute effects of cocaine on ICSS thresholds at the end of the 12 days of self-administration. Cocaine normally lowers reward thresholds for ICSS and this measure has been proposed as an index for a drug's central reinforcing effects. However, because reward thresholds remained elevated for LgA rats over the 12 days, an acute cocaine probe did not lower ICSS thresholds in these animals to as great an extent as seen in the other groups. These observations suggest that central reward systems are blunted over the course of escalation to excessive cocaine intake and that continued drug-seeking and drug-taking, in the face of a newly established reward "set point" in the system, may represent an attempt to recapture previous reinforcing effects of the drug. Ahmed, S.H., Kenny, P.J., Koob G.F., and Markou A. Neurobiological Evidence for Hedonic Allostasis Associated with Escalating Cocaine Use. Nature Neurosci., 5, pp. 625-626, 2002.

Acute Marijuana Produces Deficits in Adaptation to Changing Reinforcement Contingencies

Acute administration of delta9-THC (THC, the active pharmacological component of marijuana) impairs performance on a variety of different learning tasks and in human subjects decreases rate of "working" to receive experimenter delivered rewards. Drs. Scott Lane and Don Cherek recently tested human marijuana users in a laboratory-based study to measure sensitivity to reinforcement frequency. Subjects of this study presented with clean urine samples for THC and were tested on three to four multiple random interval operant schedules each day to earn monetary rewards. On drug days, all subjects were tested immediately following smoked THC for one session of a concurrent random interval schedule that offered two response choices and required them to continue to switch to a "least preferred" option over the course of the session in order to maximize money earned. That is, if volunteers preferred one option over the other the overall amount of money earned decreased. THC was self-administered by smoking one of four doses: One placebo cigarette, one-half of a 1.77% (w/w) THC cigarette plus one-half of a placebo cigarette, one 1.77% THC cigarette, and 3.58% THC cigarette. Doses were tested in counter-balanced order. Under placebo conditions, subjects switched between the two response option and maximized monetary gain. However, this pattern of behavior decreased as a function of THC dose. Behavioral differences were noted between placebo versus 3.58% THC, and placebo versus 1.77% THC conditions. Thus, after smoking a cigarette with these THC doses, subjects allocated more responses to the decreasing option, and switched less despite diminishing monetary returns. Differences were not attributable to overall decreases in response rates. Adaptive response strategies on this task require the volunteers to discriminate a change in reinforcement frequency and to shift their responses to the higher frequency option. These findings reveal that an acute dose of self-administered THC results in an insensitivity to changing reward frequency. The authors suggest that this impairment might be manifest as a deficit in adaptability to changing environmental or social demands. Whether the observed behavior can be attributed to blunted central reinforcement processes, an inability to shift responses, or impaired learning and memory processes remains to be determined. Lane, S.D., and Cherek D.R. Marijuana Effects on Sensitivity to Reinforcement in Humans. Neuropsychopharmacol., 26, pp. 520-529, 2002.

Sensitization Produced by d-amphetamine Increases "Willingness" to Work for Drug

When animals are treated repeatedly with a psychostimulant, such as cocaine or amphetamine (amp), they show greater locomotor activation to a subsequent acute challenge of these drugs and enhanced dopamine (DA) release in the nucleus accumbens (NAS). This sensitization process has been linked to a substrate in the ventral tegmental area (VTA -- the cell body region for the mesocorticolimbic DA projection system). Animals pretreated with psychostimulants also more readily acquire self-administration behavior for these drugs. But we know little about what the phenomenon of sensitization has to do with features of addiction such as escalation in use, transition to compulsion, or "willingness to work" to obtain drug. Dr. Paul Vezina at the University of Chicago has addressed this question by testing amp sensitized rats in an operant procedure that requires them to make progressively more and more bar press responses, over the course of a session, to obtain an infusion of drug. When compared to animals receiving saline during a pre-exposure phase, rats repeatedly treated with amp (amp pre-exposed) responded the same under a requirement of 10 responses per amp infusion. However, when subjected to increasing response requirements under a progressive ratio (PR) operant schedule to receive i.v. amp, rats pre-exposed to amp emitted threefold to fivefold more responses to receive drug. This effect was observed over a range of self-administered amp doses, and in animals that had been pre-exposed to amp via an intraperitoneal route of administration, or via direct amp infusion into the VTA. When measuring concomitant DA release from the NAS in these groups, the investigator found greater DA efflux from amp pre-exposed rats. Over the session, DA became depleted in saline pre-exposed animals and they stopped responding for drug. However, at the same time, and under the same increasing response demands, DA continued to be released in amp pre-exposed rats. The last study in this series addressed the question of relapse, using a reinstatement procedure where animals are withdrawn (i.e., bar presses no longer result in delivery of drug) and receive a 'priming' injection of amp to stimulate drug-seeking behavior. In this procedure, amp pre-exposed (thus, 'sensitized') animals emitted more drug seeking bar press responses and had a significantly greater DA efflux in response to the amp prime than saline pre-exposed rats. Collectively, these findings implicate previously observed behavioral and neurochemical changes, that are signatures for psychostimulant-induced sensitization, are evident during drug maintenance and relapse phases of the addictive process. Vezina, P., Lorrain, D.S., Arnold, G.M., Austin, J.D., and Suto, N. Sensitization of Midbrain Dopamine Neuron Reactivity Promotes the Pursuit of Amphetamine. J. Neurosci., 22, pp. 4654-4662, 2002.

Acute Cocaine Alters Oxytocin Levels in the Medial Preoptic Area and Amygdala in Lactating Rat Dams

Child abuse and neglect are strongly correlated with drug abuse in women. Prior research by Dr. Josephine Johns at the University of North Carolina at Chapel Hill, using an animal model of maternal neglect, has shown that chronic cocaine treatment during pregnancy and acute cocaine treatment in postpartum dams both increase maternal neglect, defined as the disruption of pup-directed maternal behavior. Chronic cocaine during pregnancy also increases postpartum maternal aggression toward intruders, but does so to the extent that pups are injured. On the other hand, acute cocaine treatment after partuition decreases the protection of pups from intruders. In humans, lower levels of the peptide oxytocin (OT) and cocaine use in pregnancy have been associated with general feelings of anger and hostility and difficulty in establishing infant attachment. Dr. Johns rodent work has shown that chronic gestational cocaine treatment reduces OT in the medial preoptic area (MPOA) on postpartum day 1 (PPD1), a time at which maternal behavior disruptions were observed, and in the amydala on PPD6 when increases in maternal aggression were observed. OT is a peptide that is associated with sexual behavior, onset of maternal behavior, and maternal aggression in rats. Dr. Johns has now extended these prior findings by showing that acute cocaine treatment during lactation also alters OT. Thirty mg/kg cocaine delivered on PPD1 resulted in a significant reduction of OT in the MPOA, consistent with the effect of gestational cocaine on OT. On PPD6, cocaine resulted in significant increases in OT levels in the amygdala, in contrast to the reduction in OT in the amydala previously observed on PP6 following gestational cocaine. Future work by Dr. Johns will explore the role of OT in chronic and acute cocaine effects on maternal behavior. Elliot, J.C., Lubin, D.A., Walker, C.H. and Johns, J.M. Acute Cocaine Alters Oxytocin Levels in the Medial Preoptic Area and Amygdala in Lactating Rat Dams: Implications for Cocaine-induced Changes in Maternal Behavior and Maternal Aggression. Neuropeptides, 35(2), pp. 127-134, 2001.

Methadone-Cocaine Combinations are Preferred Over These Drugs Alone in Rhesus Monkeys

Methadone maintenance effectively decreases opioid use, increases retention in drug treatment programs, reduces criminal behavior, and slows the spread of HIV. These benefits of maintenance, however, are often undermined by concurrent cocaine use. While cocaine use is problematic among methadone maintenance patients, and while concurrent use of heroin and cocaine ("speedball") is prevalent among drug addicts, little laboratory research has been devoted to the study of opiate-cocaine combinations. Dr. Richard Meisch and his colleagues at the University of Texas Health Science Center have developed an animal model of oral self-administration using the rhesus monkey that permits assessment of choice between the combination of heroin and cocaine and the component drugs alone. When given concurrent access to the combination and one of the component drugs, subjects typically preferred the combination. In cases where the two options were equally preferred, the researchers found that increasing the response requirement (cost) for these options resulted in a shift to preference for the cocaine-heroin combination. Further investigations with this animal model could have implications for the use of methadone in the treatment of comorbid opiate and cocaine dependence. Wang, N.S., Brown, V.L., Grabowski, J., and Meisch, R.A. Reinforcement by Orally Delivered Methadone, Cocaine, and Methadone-Cocaine Combinations in Rhesus Monkeys: Are the Combinations Better Reinforcers? Psychopharmacology, 156, pp. 63-72, 2001.

Context Dependence of Amphetamine-induced Psychomotor Sensitization Involves Inhibitory As Well As Excitatory Processes

Behavioral sensitization - a progressive and long-lasting increase in drug-induced motor responses - is observed when repeated doses of psychostimulant drugs are administered to an animal. This phenomenon is of interest because the underlying neuroadaptations are thought to contribute to addiction and to persistent brain changes that may be involved in relapse. Under some circumstances, sensitization is "context dependent:" an increased response to a challenge dose of a drug occurs only in the environment where the repeated doses were previously given, whereas a challenge dose in other environments produces a smaller response (i.e., similar to what is observed in drug-na•ve animals). A new study by Anagnostaras et al. reveals that context specificity depends, in part, on inhibition of sensitization in the unfamiliar context, rather than on facilitation of drug-induced responses in the familiar context. In the present study, animals with unilateral (6-hydroxydopamine-induced) dopamine depletions were given repeated doses of d-amphetamine (AMPH) in group-specific environments, and rotational behavior was used as the measure of psychomotor activation. Some animals then received electroconvulsive shock (ECS) in their drug-associated environment. Since ECS produces retrograde amnesia, it was expected that upon return to this previously drug-paired environment, memories evoked of the drug experience would be vulnerable to disruption by the shock procedure. Surprisingly, animals given ECS and, later, a challenge dose in the same drug-paired environment continued to show sensitization. However, animals given ECS in their drug-paired environment and then tested in a different environment, where they had never before received AMPH, now showed a robust sensitization. These results, in conjunction with previous findings, indicate that repeated psychostimulant administration sensitizes the neural substrate that mediates a non-associative, unconditioned responses to these drugs, but that the behavioral expression of sensitization can be blocked in contexts where the drug is not expected. By these processes, drug-associated contexts can come to gain powerful associative control over behavioral sensitization, and perhaps also over craving and relapse. Anagnostaras, S.G., Schallert T., and Robinson T.E. Memory Processes Governing Amphetamine-induced Psychomotor Sensitization. Neuropsychopharmacology, 26, pp. 703-715, 2002.

Mood, Stress, and Physiological Reactivity in Withdrawal from Nicotine

A recent study by NIDA investigator Dr. M. al'Absi and colleagues was designed to evaluate the effects of short-term abstinence from smoking on psychophysiological activity and mood changes during rest and following behavioral challenge. Subjective reports indicate that abstinence from smoking leads to anxiety, depression, restlessness, irritability and distractibility that may produce impairments in cognitive performance. These symptoms are reported to occur within 4-24 hr after smoking cessation and may contribute to relapse risk. Moreover, withdrawal symptoms after abstinence may be exacerbated by stressors and subsequently may then contribute to early relapse. The current study investigated the effects of short-term abstinence (18-21 hours) from smoking on psychophysiological activity and responses to brief behavioral challenges evaluated by withdrawal symptoms in male and female habitual

smokers (mean years smoking = 4; mean number cigarettes/day = 19.5). Thirty habitual smokers (15 women and 15 men) participated in two sessions conducted after abstinence and after ad lib smoking (in counterbalanced order). Saliva cotinine concentrations and expired carbon monoxide were measured in both conditions. A subset of the sample (8 men and 8 women) provided saliva samples after 18 hr abstinence and after ad lib smoking while outside the laboratory setting (ambulatory controls). Abstinence produced significant withdrawal symptoms in all participants, with women reporting greater desire to smoke than men. Participants showed greater systolic BP responses to a behavioral challenge (fast-paced mental arithmetic tasks) in the abstinence condition than in the control condition. They also showed worse cognitive performance on the challenges in the abstinence than in the ad-lib condition. Salivary cotinine was greater in the ad lib than the abstinence condition, confirming the effectiveness of the abstinence manipulation. Men had greater salivary cortisol levels than women and both men and women showed the expected decline in cortisol levels across time. However, there were no differences in cortisol levels as a function of abstinence or ad lib smoking conditions in either the laboratory or ambulatory measurements. These results show that abstinence alters mood, performance and BP responses, but not adrenocortical responses, seen upon acute challenge. It is possible that these changes contribute to stress-related vulnerability to smoking relapse. On the other hand, absence of effects of abstinence on salivary cortisol production during the ambulatory measurements and in response to the laboratory challenges does not support the hypothesis that abstinence is associated with enhanced adrenocortical activity. al'Absi , M., Amunrud, T., and Wittmers, L.E. Psychophysiological Effects of Nicotine Abstinence and Behavioral Challenges in Habitual Smokers. Pharmacology, Biochemistry and Behavior, 72, pp. 707-716, 2002.

Self-administration of Heroin Alters Immune Function More than Passive Administration

There is considerable evidence that opioids such as morphine induce immunomodulation. Morphine has been shown to induce dose-dependent, naltrexone-reversible suppression of natural-killer cell activity, proliferation of lymphocytes, anti-body production and the production of interferon. Morphine has also been shown to reduce the stimulated production of nitric oxide. In contrast to what is known about morphine, there is very little information available about heroin's immunomodulatory effects. Yet, the high incidence of bacterial, viral and fungal infections among human heroin abusers suggests that heroin use might alter infectious disease resistance. Nitric oxide has been shown to play a critical role in immune processes including resistance to infectious disease. The enzyme responsible for producing nitric oxide is nitric oxide synthase (NOS) and previous work from Dr. Lysle's laboratory has demonstrated that a single heroin injection reduces lipopolysaccharide (LPS)-induced expression of inducible NOS (iNOS) mRNA in spleen, liver and lung. The purpose of the present study was to extend the investigation of heroin's effects on LPS-induced iNOS expression using a self-administration paradigm. A typical triadic design was used: Animals in the self-administration group learned to lever press for infusions of heroin, in 2-hr sessions; each animal in the second group was yoked to an animal in the self-administration group and received a passive infusion of heroin whenever the first group self-administered heroin; each animal in the saline control group was yoked to an animal in the self-administration group and received a passive infusion of saline whenever the first group self-administered heroin. The experiment sought to determine [1] whether animals would self-administer a sufficient quantity of heroin to induce alterations in the expression of iNOS; and [2] whether self-administration of heroin would have different immunomodulatory consequences from the same dose of heroin infused passively. Heroin self-administration lasted 16 days. Following the last training session, animals were injected with LPS and euthanized 6 hr later. The production of nitric oxide was determined by measuring iNOS mRNA protein in spleen, liver and lung. In addition, accumulation of nitrite/nitrate was measured in plasma. Results indicated that animals acquired self-administration that leveled off at approximately 26 lever presses per animal during the 2 hr session. The mean dose of heroin thus administered was 1.59 mg/kg per animal in each session. The biochemical assays indicated that heroin administered in this manner induced significant, widespread reductions in the expression of iNOS in spleen, lung and liver, as well as in the accumulation of plasma nitrite/nitrate. Moreover, there was a trend toward greater reductions in nitric oxide production by self-administering animals compared to yoked controls receiving heroin in six out of seven measures, but only one achieved statistical significance (iNOS mRNA expression in the liver). The importance of nitric oxide as an antimicrobial agent, as well as its role in immune system regulation, makes it a critical molecule to understand. The demonstration that animals will self-administer sufficient quantities of heroin to induce widespread iNOS

expression may have implications for the increased incidence of infectious diseases among heroin abusers. Lanier, R.K., Ijames, S.G., Carrigan, K.A., Carelli, R.M., and Lysle, D.T. Self-Administration of Heroin Produces Alterations in the Expression of Inducible Nitric Oxide Synthase. Drug and Alcohol Dependence, 66, pp. 225-233, 2002.

Drug Onset Cues Elicit Compensatory Conditioned Responses that Mediate Morphine Tolerance

Recent evidence from many laboratories indicates that associative learning processes are important for regulating some aspects of drug addiction. In particular, Pavlovian conditioning mechanisms have been hypothesized to mediate drug tolerance. According to this analysis, cues present at the time of drug administration come to function as conditioned stimuli (CSs) capable of contributing to subsequent behavioral reactivity to drug administration. The direct effect of the drug constitutes the unconditioned stimulus (UCS), which prior to any learning elicits unconditioned responses (UCRs) that compensate for drug-induced disturbances. After paired presentations of the CS and UCS, drug compensatory responses come to be elicited by pre-drug cues (i.e., CSs). These conditioned compensatory responses (CCRs) mediate the development of tolerance by counteracting the drug effect. For example, in rats tolerant to the analgesic effect of morphine, presentation of a drug-associated CS, in the absence of morphine administration, elicits a CCR of hyperalgesia. Although many drug associated CSs are exteroceptive, another source of drug associated CSs can be found in the early, drug-onset cues (DOCs) that precede and signal later, maximal drug effects. The present experiments evaluated the contribution of DOCs to morphine tolerance in rats. It was hypothesized that DOCs would elicit CCRs in the form of hyperalgesia. In these experiments, rats were made tolerant to a 5mg/kg infusion of morphine and tested for pain sensitivity using tail flick responses to radiant heat as a measure of analgesia. Drug infusions were gradual - each infusion was about 30 min in duration. When rats displayed tolerance to analgesic effects of the drug, they were tested with a probe morphine infusion, consisting of the first 10% of the morphine infusion used during tolerance development; i.e., 0.5 mg/kg infused over a period of 3 min. In three experiments, Siegel and his colleagues demonstrated that DOCs indeed elicit hyperalgesia. Thus, a small dose of a drug can serve as a cue for a larger dose of that drug and can function as CSs to elicit CCRs that contribute to tolerance. Recognition that associations formed to interoceptive effects of early drug onset can contribute to drug effects has important implications for theories of tolerance. Expanding our understanding of drug-paired associations to interoceptive drug cues may also inform the design of conditioning-based treatments for drug addiction, which are based on extinguishing associations between predrug exteroceptive cues and the drug administration. The present success of learning based treatment approaches may be limited by the fact that they do not include explicit extinction of such DOCs. Sokolowska, M., Siegel, S., and Kim, J.A. Intraadministration Associations: Conditional Hyperalgesia Elicited by Morphine Onset Cues. Journal of Experimental Psychology: Animal Behavior Processes, 28(3), pp. 309-320, 2001.

Anti-opioid Peptide Appears to Mediate Conditioned Compensatory Responding and Morphine Tolerance in Rats

As described above, Pavlovian conditioning mechanisms have been hypothesized to mediate drug tolerance: Cues present at the time of drug administration come to serve as conditioned stimuli (CSs) that can be observed in the absence of drug administration. After paired presentations of a CS and drug (the unconditioned stimulus, UCS), drug compensatory responses (CCRs) come to be elicited by pre-drug cues (i.e., CSs). These CCRs then mediate the development of tolerance by counteracting the drug's unconditioned effect. For example, in rats tolerant to the analgesic effect of morphine, presentation of drug-associated CSs elicit a CCR of hyperalgesia. The present experiment examined conditioned CCRs to morphine in the form of early drug onset cues to evaluate the hypothesis that this CCR of hyperalgesia can be related to an increase in brain cholecystokinin (CCK) activity. According to this hypothesis, blocking CCK activity should block the expression of behavioral hyperalgesia and tolerance. CCK was of interest because of its potential role as an endogenous "anti-opioid peptide." Two experiments were conducted using tail-flick latency to evaluate this hypothesis. In Experiment 1, rats received eight daily gradual intravenous infusions of either morphine (5 mg/kg) or saline during the tolerance acquisition phase. On a subsequent test, all rats received an injection of a "probe" morphine infusion (the putative CS), which consists of the approximately first one-tenth of the usual morphine infusion. Prior to this probe infusion, half of the animals

in morphine and saline-treated groups received an injection of vehicle and half were injected with the CCK2 receptor antagonist, PD135,158. Analgesia was evident in rats given morphine and across days, tolerance developed to morphine analgesia. On the test day, morphine tolerance was still evident in the morphine treated rats that had been pretreated with saline, but in those morphine animals pretreated with the CCK antagonist, tolerance was significantly attenuated. That is, the CCK antagonist blocked the expression of the CCR and tolerance. Experiment 2 was conducted like Experiment 1, except that on the test day, the same morphine dose as used during tolerance development was administered (5 mg/kg), preceded by either saline or PD135,158. Thus, whereas Experiment 1 was an assessment of the CCK antagonist's effectiveness in attenuating the CCR, Experiment 2 investigated the CCK antagonist's ability to attenuate the display of tolerance seen with the full dose. The results indicated that morphine treated animals were tolerant to morphine analgesia, but that analgesic tolerance was significantly attenuated in animals tested under PD135,158. Together, these results suggest that a CCK2 receptor antagonist attenuates both the expression of opiate tolerance and the conditioned compensatory response hypothesized to mediate such tolerance. Kim, J.A. and Siegel, S. The Role of Cholecystokinin in Conditional Compensatory Responding and Morphine Tolerance in Rats. Behavioral Neuroscience, 115, pp. 704-709, 2001.

Gender and Phenotype Interact Differently in the Vulnerability to Acquire Heroin or Cocaine Self-administration

Rats that have high preference for sweet-tasting solutions have been shown to acquire self-administration of amphetamine, ethanol, and morphine more rapidly than rats with low preference. Dr. Marilyn Carroll and colleagues sought to extend this observation to cocaine and heroin i.v. self-administration using male and female rats selectively bred for high (HiS) or low (LoS) preference for saccharin. They report that for cocaine, in females, but not males, the HiS subjects met an acquisition criterion of 100 cocaine infusions during 6-hr sessions over 5 consecutive days more rapidly than LoS subjects. In both phenotype groups, females met the criterion more rapidly than males and a higher percentage of females met the criterion for acquisition within 30 days. For heroin, phenotype had no effect on acquisition of self-administration, for which the criterion was 20 infusions during 6-hr sessions over 5 consecutive days; however, females in both phenotype groups acquired more quickly than males, and in the HiS group, females administered more infusions than males. The cocaine subjects were subsequently tested under a progressive ratio schedule whereby successive cocaine infusions requires more and more bar presses until responding ceases, i.e., a breakpoint occurs. The breakpoint was unaffected by phenotype, but was larger in females than males. This work indicates that both saccharin-preference phenotype and sex are determinants of acquisition of drug self-administration; however, sex appears to be a stronger factor than saccharin-preference phenotype. Carroll, M.E., Morgan, A.D., Lynch, W.J., Campbell, U.C., and Dess, N.K. Intravenous Cocaine and Heroin Self-administration in Rats Selectively Bred for Differential Saccharin Intake: Phenotypes and Sex Differences. Psychopharmacology, 161, pp. 304-313, 2002.

Prescription Medications Interact to Alter the Subjective Effects of Phencylidine

Dr. Robert Balster at the Medical College of Virginia has been studying the discriminative cue properties of the dissociative anesthetic, phencylidine (PCP) and characterized the receptor profile for subjective effects of this drug in an animal model. Some second generation tetracycline antibiotics, (such as doxycycline and minocycline), have been noted to have NMDA antagonist-like effects in regard to their CNS side effects and neuroprotective properties. NMDA is a glutamatergic receptor and channel blockade at this site has been associated with subjective effects of PCP on drug discrimination procedures in the rat. These investigators recently published that minocycline and doxycycline did not substitute for PCP in rats trained to discriminate PCP from saline. This finding suggests that the antibiotics may bind at a different site on the receptor complex than does PCP. However, both drugs shifted PCP dose response curves for discriminative cue effects to the left, indicating a potentiation of PCP's subjective effects in this animal model. While the authors suggest that the mechanism of this enhancement may be via inhibition of nitric oxide synthases, the interesting observation at the behavioral level is that prescription drug medications - in clinically used dose ranges - may significantly alter the subjective effects of drugs of abuse. This is especially noteworthy in that these tetracyclines have no known abuse liability themselves and are not recognized as having psychotropic effects. Munzar P., Hua L., Nicholson K.L., Wiley J.L., and Balster R.L. Enhancement of the Discriminative Stimulus Effects of Phencyclidine by the

Tetracycline Antibiotics Doxycycline and Minocycline in Rats. Psychopharmacol., 160, pp. 331-336, 2002.

Director's Report to the National Advisory Council on Drug Abuse - September, 2002

Research Findings - Treatment Researchand Development

Ethnic Differences in Comorbidity Among Substance Abusing Adolescents Referred to Outpatient Therapy

Dr. Michael Robbins and colleagues at the University of Miami examined differences in psychiatric comorbidity between African-American and Hispanic substance-abusing adolescents referred for outpatient therapy. Study participants included 167 substance-abusing adolescents and their family members who completed an intake assessment. As part of the intake assessment, adolescents and parents were administered the Diagnostic Interview Schedule for Children-Predictive Scales to screen for the presence of nine psychiatric diagnoses representing both externalizing and internalizing disorders. In this study both African-American and Hispanic youths presented with high-above-threshold symptom rates of co-occurring disorders. However, both adolescents and parents reported that Hispanic youths (78.3% and 83.9%, respectively) demonstrated greater rates of externalizing than African-American youths (65.2% and 70.1%, respectively). African-American youth (40%) reported significantly more symptoms of agoraphobia than Hispanic youths (19.5%). The results of this study have implications for understanding the development of substance abuse across ethnic groups and for developing treatment approaches that are sensitive to the needs of each group. Robbins, M.S., Kumar, S., Walker-Barnes, C., Feaster, D., Briones, E. and Szapocznik, J. Journal of the American Academy of Child and Adolescent Psychiatry, 41(4), pp. 394-401, April 2002.

Gender Differences in Psychiatric Comorbidity Among Adolescents with Substance Use Disorders

As part of a Stage I behavioral therapy development project, Dr. William Latimer at Johns Hopkins University examined gender differences in the rates of psychiatric disorders among 135 adolescents with one or more psychoactive substance use disorders. Consistent with expectations, male adolescents exhibited a higher rate of ADHD and Conduct Disorder than did females, and females exhibited a higher rate of Major Depressive Disorder than did males. Unexpectedly, rates of ADHD and Conduct Disorder were fairly high among females, despite being significantly lower than for males, and rates of dysthymia, "double depression" (i.e., major depression and dysthymia), and bipolar disorder were equivalent between genders. This study helps to identify common gender differences-and similarities-in comorbidities among adolescent substance abusers, one key to developing effective screening, assessment, and treatment interventions. Latimer, W.W., Stone, A., and Winters, K.C. Experimental and Clinical Psychopharmacology, 10, pp. 310-315, August 2002.

Gambling Behavior in Adolescent Substance Abuse

Dr. Yifrah Kaminer and colleagues at the University of Connecticut assessed gambling behavior among adolescents in outpatient substance abuse treatment. Of 97 adolescents assessed via diagnostic interviews and self-report, 34% had never gambled; 57% participated in social or nonpathological gambling; 8% were considered at-risk or transition gamblers; and 1% met criteria for pathological gambling. Compared to studies of adolescents without drug abuse disorders, this treatment population exhibited similar or lower gambling behavior. While a strong connection has been reported between gambling and drug abuse among adults, this study suggests that this connection may develop after adolescence, and sets the stage for further studies of the etiology and treatment of both disorders. Kaminer, Y.,

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Burleson, J.A., and Jadamec, A. Substance Abuse, 23, pp. 191-198, 2002.

Urine Toxicology Samples in Cocaine Treatment Trials: How Many Need to Be Tested?

Investigators Delucchi and colleagues at the University of California San Francisco empirically evaluated how often urine sample should be conducted for cocaine testing by examining the weekly variation in cocaine metabolite (benzoylecgonine-BE) concentration between pairs of weekly urine samples from a clinical trial of a treatment for cocaine dependence. Twice weekly samples were collected and agreement between pairs was estimated for quantitative and qualitative measures of BE. Results indicate substantive intra-week variation with correlations never exceeding 50% and approximately 20% disagreement among samples that used cutoff values in place of quantitative levels. Group averages over time however, were much more stable. Findings suggest a single quantitative measure may not be representative but when collected several weeks over several individuals a representative picture of the group's behavior emerges. These findings suggest at least 2 samples per week may be needed to accurately represent the cocaine use of an individual. Delucchi, K.L., Batki, S.L., Moon, J., Jacob, P., and Jones, R.T. Journal of Addictive Diseases, 21, pp. 17-26, 2002.

Depression and Stages of Change for Smoking in Psychiatric Outpatients

Investigators Acton, and colleagues at the University of California San Francisco examined psychiatric outpatients on measures of depression and various transtheoretical model constructs related to smoking and thoughts about abstinence from smoking. Those who had never smoked showed lower rates of diagnosed major depressive disorder (MDD). Participants in early stages of change did not show more MDD or depressive symptoms, but did report more negative thoughts about quitting. This study suggests psychiatric outpatients seeking mental health treatment may be amenable to smoking cessation interventions and interventions that are matched to the readiness to change are likely to be important. Acton, G.S, Prochaska, J.J., Kaplan, A.S., Small, T. and Hall, S. Addictive Behaviors, 26, pp. 621-631, 2001.

The Feasibility of Enhancing Psychiatric Outpatients' Readiness to Change Their Substance Abuse

Dr. Kate Carey and colleagues at Syracuse University evaluated the feasibility and acceptability of a brief motivational intervention for 22 outpatients with severe and persistent mental illness and drug use problems. The intervention consisted of four individual sessions that were guided by the therapeutic principles of motivational interviewing. The median time for completion of the intervention was 28 days. Preliminary results demonstrate the feasibility of the motivational intervention in this population. It was possible to retain psychiatric outpatients in the intervention, and the patients reported positive perceptions of the intervention. Readiness to change and involvement in treatment increased between the pre-intervention and post intervention assessments. However, many of the post intervention gains were not been maintained at 3-month follow-up. Preliminary findings from this Stage I behavioral development study support the feasibility and acceptability of a 4 session motivational intervention for use with persons who have serious and persistent mental illness and a substance use disorder. Karey, K.B., Carey, M.P., Maisto, S.A., and Purnine, D.M., Psychiatric Services, 53(5), pp. 602-608, May 2002.

Cognitive-Behavioral Treatment of Bipolar Disorder and Substance Abuse: A Preliminary Randomized Study

Dr. Joy Schmitz and colleagues at the University of Texas evaluated the feasibility and potential efficacy of cognitive-behavioral therapy (CBT) in conjunction with pharmacotherapy for patients diagnosed with bipolar disorder and substance use disorder. In this study 46 randomly assigned outpatients received up to 12 weeks of medication monitoring (MM) plus individual CBT (MM + CBT) or medication monitoring only. Sixty percent of the subjects in the medication monitoring plus the cognitive-behavioral therapy group completed treatment compared with 33% of the subjects in the medication monitoring only group, with session attendance also significantly higher in the combined treatment group (MM + CBT). The two groups did not differ in substance use outcomes during treatment, but there was some indication of greater improvement in the MM + CBT group with regard to outcomes related to medication compliance and mood symptoms. This study is a preliminary attempt to develop and evaluate a new, integrated treatment approach for patients with bipolar disorder who

have coexisting substance abuse. Schmitz, J.M., Averill, P.A., Sayre, S., McCleary, P., Moeller, F.G., and Swann, A. Addictive Disorders and Their Treatment, 1(1), pp. 17-24, March 2002.

Feasibility of Computerized Scheduled Gradual Reduction for Adolescent Smoking Cessation

Dr. William Riley and colleagues at PICS, Inc. conducted two small pilot studies to determine the feasibility of using a computerized (hand-held) scheduled gradual reduction approach to smoking cessation in group support and in minimal contact modalities with adolescent smokers. The results of these two small trials suggest that a computerized scheduled gradual reduction approach may be an accepted and potentially efficacious approach for smoking cessation among adolescent smokers. Riley, W., Jerome, A., Behar, A., Zack, S. Substance Use and Misuse, 37, pp. 255-63, 2002.

Impaired Autonomic Activation in Substance Dependent Individuals when Making Decisions with Negative Future Consequences

Bechara and colleagues at the University of Iowa tested the hypothesis that substance abusers who perform disadvantageously on a decision-making instrument, the gambling task (GT), have a deficit in the somatic signals that help guide their decision in the advantageous direction. Skin conductance response (SCR) was assessed as an index of somatic state activation. Forty-six substance dependent subjects, 49 normal controls, and 10 patients with ventromedial prefrontal (VM) lesions were studied. A subgroup of substance-dependent subjects showed defective performance on the GT coupled with impaired anticipatory SCR, but normal SCR to punishment, and normal acquisition of conditioned SCR to an aversive loud sound, similar to the pattern observed with the VM lesioned patients. This supports the hypothesis that the poor decision-making in some substance abusers is associated with defective somatic state activation, and may be due to a dysfunctional VM cortex. A dysfunctional VM cortex underlying the "myopia" for the future in some substance abusers may be one of the mechanisms underlying the transition from casual substance taking to compulsive and uncontrollable behavior. Bechara et al., Neuropsychologia, 40, pp. 1675-1689, 2002.

Are Decision-making Deficits in Substance Abusers Due to Myopia for the Future or Hypersensitivity to Reward?

In another study, Bechara and colleagues at the University of Iowa investigated whether the impaired performance of substance abusers on the Gambling Task (GT) is due to hypersensitivity to reward or inability to project the future consequences of choices in the present ('myopia for the future'). In order to dissociate these two possibilities, a variant version of the GT was used, in which the good decks yielded high immediate punishment but higher delayed reward, whereas the bad decks yielded low immediate punishment and lower delayed reward. Substance-dependent subjects who were not impaired on the original GT performed normally on the variant GT. Substance-dependent subjects who were impaired on the original GT showed two levels of performance on the variant GT. One subgroup (36% of the sample) performed poorly on the variant GT, and showed similar behavioral and physiological impairments to patients with ventromedial prefrontal lesions. The other subgroup (64% of the sample) performed normally on the variant task, but had abnormally large autonomic responses to reward, i.e., large SCR after receiving reward (reward SCR) and large SCR in anticipation of outcomes that yield large reward. These results suggest 3 distinct sub-groups of substance abusers with respect to decision-making abilities. One sub-population is without impairments that can be detected by any measure of the GT paradigm. Another sub-population is similar to VM patients in that they are insensitive to the future, both positive and negative. A third sub-population is hypersensitive to reward, so that the presence or the prospect of receiving reward dominates their behavior. These finding may provide a basis for predicting treatment response and potential for relapse. Bechara et al., Neuropsychologia, 40, pp. 1690-1705, 2002.

Neural Substrates of Decision Making

As decision-making is central to motivated behavior, understanding its neural substrates can help identify the deficits that characterize various maladaptive behaviors. Healthy adults (20) performed a risk-taking task during PET with 15O-labeled water. A computerized card game was used to test the ability to weigh short-term rewards against long-term losses. A control task matched all components of the

risk-taking task except for decision-making and the difference between responses to contingent and non-contingent reward and punishment. Decision-making activated orbital and dorsolateral prefrontal cortex, anterior cingulate, insula, inferior parietal cortex and thalamus predominantly on the right side, and cerebellum predominantly on the left side. In an exploratory analysis, 'guessing' produced activation of sensory-motor associative areas, and amygdala on the left side, whereas informed decision-making activated areas that subserve memory (hippocampus, posterior cingulate) and motor control (striatum, cerebellum). The findings provide a framework for future investigations of decision-making in maladaptive behaviors. Ernst et al., Decision-making in a Risk-taking Task: A PET Study. Neuropsychopharmacology, 26(5), pp. 682-691, 2002.

Evidence of Reduced Cognitive Inhibition in Methamphetamine-Dependent Individuals

Nordahl and colleagues at the University of California, Davis used a computerized single-trial version of the Stroop Test to examine selective attention and priming in methamphetamine-dependent (MD) subjects to investigate clinical observations that methamphetamine abusers are highly distractible and have difficulty focusing. Eight MD men (31.7+/-7.2 years of age) and 12 comparison subjects were tested. Relative to the comparison subjects, the MD subjects exhibited significantly greater interference despite intact priming, consistent with the distractibility they show clinically. Error rates did not differ between the groups. The dissociation between explicit attentional performance and priming effects suggests that some attentional functions are not as affected by long-term methamphetamine use as others. Salo et al., Psychiatry Res., 111, pp. 65-74, 2002.

Cognitive Function in Methamphetamine Abusers Uncovers Interactive Gender Differences

Chang and colleagues at the Brookhaven National Laboratory investigated regional cerebral blood flow (relative rCBF) and cognitive function in abstinent methamphetamine (METH) users. Twenty METH-dependent participants and 20 age- and gender-matched controls were evaluated with perfusion MRI and neuropsychological tests. Decreased relative rCBF was seen bilaterally in putamen/ insular cortices (right: -12%; left: -10%) and in the right lateral parietal brain region (-11%)in the METH users but increased relative rCBF bilaterally in the left temporo-parietal white matter (+13%), the left occipital brain region (+10%) and the right posterior parietal region (+24%). Interaction effects were observed between METH and gender in the right occipital cortex and a midline brain region; female METH users showed increased relative rCBF (+15% both regions) whereas the male METH users had decreased relative rCBF (-10% and -18%, respectively). METH users performed within normal ranges on standard neuropsychological testing; however, they were slower on tasks on the California Computerized Assessment Package, especially working memory tasks. Findings indicate that METH abuse is associated with persistent physiologic changes in the brain, and these changes are accompanied by slower reaction times on computerized measures of cognitive function. Chang et al., Perfusion MRI and Computerized Cognitive Test Abnormalities in Abstinent Methamphetamine Users. Psychiatry Research: Neuroimaging. 114(2), pp. 65-79, 2002.

Relationship Between High Risk Sex and Methamphetamine in HIV+ Men Who Have Sex with Men

Previous research has demonstrated an association between methamphetamine (METH) use and high-risk sex among HIV- men who have sex with men (MSM); however, little is known about the sexual risk behaviors of HIV+ METH-using MSM. The purpose of this study was to explore personal motivators of METH use among HIV+ MSM, and to elaborate upon the interaction between METH use and risky sex. Thematic analysis of qualitative data from 25 HIV+ MSM (aged 27-57 yrs) revealed METH use was associated with high rates of anal sex, low rates of condom use, multiple sex partners, sexual marathons, and anonymous partners. Motivations associated with METH use included: sexual enhancement and self-medication of the negative affect associated with HIV+ serostatus. A variety of treatment approaches are used to describe how client insights into motivations can be used by clinicians to promote change in drug use and sexual risk behavior. Semple et al., Motivations Associated with Methamphetamine Use among HIV+ Men Who Have Sex with Men. Journal of Substance Abuse Treatment. 22(3), pp. 149-156, 2002.

Reduced Frontal White Matter Integrity In Cocaine Dependence

Lim and colleagues at the Nathan S. Kline Institute for Psychiatric Research in Orangeburg, New York used a new magnetic resonance imaging method, diffusion tensor imaging (DTI), to investigate changes in white matter fiber tracts associated with cocaine use. Compared to 13 age-matched controls, the 12 cocaine-dependent subjects had reduced fractional anisotropy, a measure of the integrity of myelinated fiber tracts, in ventral, but not dorsal, prefrontal regions. These findings were consistent with the hypothesis that cocaine dependence involves alterations in orbitofrontal connectivity, and supplement prior studies showing metabolic and neurochemical changes in the orbitofrontal cortex in cocaine abusers. Lim et al., Biol Psychiatry, 51, pp. 890-895, 2002.

Higher Levels of CSF of Homovanillic Acid in Recently Abstinent Cocaine-dependent Patients

Alec Roy and colleagues performed lumbar punctures on 30 cocaine-dependent male patients abstinent for an average of 28 days and compared homovanillic acid levels to 69 male controls. The average concentration among the cocaine patients was about 30% higher than in the controls (33.6 ng/ml vs. 25.4 ng/ml). The distribution of levels in the patients was fairly constant over the range from 12 to 57 ng/ml; the controls had a larger range but 75% had levels less than the patients' average. There was overlap for the patients as well in as much as 30% had levels less than the controls' average. The data support increased dopamine turnover perhaps due to a dysregulated system in these recently abstinent patients. Roy et al., Am J Psychiat 159(6), pp. 1053-1055, 2002.

Relationship Between Cocaine Craving and Depressive Symptomatology

Elman and his colleagues studied the relationship between self-reported cocaine craving following cocaine administration (0.2 mg/kg, i.v.) and depressive symptoms in 33 cocaine-dependent individuals. Scores on the Hamilton Rating Scale for Depression (HRSD) were positively correlated with the intensity of cocaine-primed craving, even after controlling for baseline spontaneous craving, age, gender, frequency of use, time since last use, monetary expenditure on cocaine and Addiction Severity Index Drug Composite Score. These data support the hypothesis that depressive symptomatology affects cocaine-primed craving and that this relationship is relatively specific to symptoms defined by the HRSD and not to a number of other clinical and demographic variables. Elman et al., J Psychopharmacol., 16, pp. 163-167, 2002.

Standardized Neuropsychological Measures of Apathy and Depression in the Cocaine Abstinence Syndrome

The cocaine abstinence syndrome has been associated with a range of symptoms, including apathy and depression. Although initial studies reported high prevalence rates of "apathy/amotivation" and depression, validated rating scales of apathy were not then available. A validated measure of apathy was used to test whether newly abstinent cocaine-dependent subjects would report increased apathy compared with non-cocaine-using control subjects. Because apathy and depression are dissociable in other neuropsychiatric syndromes, testing to determine whether they were dissociable in recently abstinent cocaine-dependent subjects was also conducted. Following four days of monitored abstinence, 11 cocaine-dependent subjects and 19 non-drug-using control subjects were administered standardized tests of apathy and depression. Cocaine-dependent subjects had elevated scores on the apathy rating scale compared with the control group, but the groups did not differ in ratings of depression. These data suggest that apathy is present during the initial phases of abstinence for a subset of cocaine-dependent individuals. Kalechstein et al., Apathy Syndrome in Cocaine Dependence. Psychiatry Research. 109(1), pp. 97-100, 2002.

Neuropsychological Performance in Users of Crack-Cocaine Alone or in Combination with Alcohol

Little data exist on the neuropsychological effects of crack-cocaine dependence or crack-cocaine and alcohol dependence. This study examined cognitive function in abstinent crack dependent and crack and alcohol dependent individuals at 6 wks and 6-mo abstinence. A comprehensive neuropsychological battery, including the MicroCog computerized assessment, was administered to 20 abstinent crack dependent Ss, 37 abstinent crack and alcohol dependent Ss, and 29 normal controls. Depression was examined as a covariate, and the association between substance use

variables and neuropsychological performance was examined. Results show that the 2 substance dependent groups had similar neuropsychological profiles at 6 wks abstinent, with both groups exhibiting significant cognitive impairment in a wide range of functions compared to controls. The substance dependent groups were still impaired significantly at 6 mo of abstinence. Only mild effects of depression on neuropsychological performance were observed. The strongest predictor of brain damage associated with substance dependence in this sample was dose (particularly quantity and duration of peak dose). DiSclafani et al., Neuropsychological Performance of Individuals Dependent on Crack-Cocaine, or Crack-Cocaine and Alcohol, at 6 Weeks and 6 Months of Abstinence. Drug & Alcohol Dependence, 66(2), pp. 161-171, 2002.

Probing Brain Reward System Function In Major Depressive Disorder: Altered Response to Dextroamphetamine

Busto and colleagues at the University of Toronto tested the hypothesis that the dopaminergic component of the brain system related to reward is dysfunctional in depressed individuals. It was hypothesized that depressed individuals would exhibit an altered response to dextroamphetamine due to anhedonic symptoms. The behavioral and physiological effects of a single 30-mg dose of oral dextroamphetamine sulfate were measured using a double-blind, placebo-controlled, randomized, parallel study design. The subjects were 40 medication-free patients with depressive disorder (22 assigned to dextroamphetamine and 18 to placebo) and 36 control subjects (18 assigned to dextroamphetamine and 18 to placebo). Severity of depression as measured by the Hamilton Rating Scale for Depression was highly correlated with the rewarding effects of dextroamphetamine in the depressed group (model R(2) = 0.63; interaction P =.04). Furthermore, patients with the most severe symptoms reported rewarding effects 3.4-fold greater than controls. The results showing the presence of a hypersensitive response in the brain reward system of depressed patients may reflect a basal hypofunctional state contributing to symptoms of anhedonia. These results provide a basis for the high degree of co-morbidity between stimulant abuse and depression. Busto et al., Arch Gen Psychiatry, 59, pp. 409-416, 2002.

Dopamine Transport Function is Elevated in Cocaine Users but Not Those with Excited Delirium

Mash and colleagues have assessed dopamine transporter (DAT) function in the post-mortem brain tissue of individuals with chronic cocaine abuse. These results are consistent with previous studies indicating adaptive increases in DAT-binding site density. By contrast, levels of dopamine uptake were not elevated in victims of excited cocaine delirium. These individuals experience paranoia and marked agitation prior to death. It is speculated that these symptoms may result from an uncompensated increase in dopamine without increased re-uptake at the pre-synapse. Mash et al., J Neurochem., 81, pp. 292-300, 2002.

Potentially Functional Polymorphism in the Promoter Region of Prodynorphin Gene May be Associated with Protection Against Cocaine Dependence or Abuse

Mary Jeanne Kreek and her associates studied the promoter region of the prodynorphin gene that has been shown to contain one, two, three, or four copies of a 68-base pair tandem repeat. It has been shown that this opioid peptide plays a modulating role in the effects of cocaine (among other drugs). Three or four copies of the repeat were shown to increase the transcription activation. Accordingly, this area was analyzed in cocaine abusers and in dependent patients and compared to ethnic-matched controls. It was discovered that the Relative Risk for the greater number of tandem repeats (3 + 4) was significantly low, suggesting that possession of one of these alleles was a protective factor in cocaine abuse or dependence. The number of patients was too small for a completely separate analysis for each ethnic group, though the risk in African American subjects was strong enough to demonstrate a significant effect. Chen et al., Am J Med Genet (Neuropsychiat Genet) 114, pp. 429-435, 2002.

Measures of Impulsivity, Aggression, and Sensation-seeking were Confirmingly Higher in Cocaine-dependent Individuals but Neither These Characteristics Nor the Patients Themselves were Distinguished by Polymorphisms of the Serotonin Transporter

In another study, Patkar and associates investigated several personality measures in 44 patients seeking treatment for cocaine dependence as well as gene variants in the serotonin transport. The results showed much higher scores for nearly all scales of the Buss-Durkee and for the Disinhibition and Thrill/adventure subscales of the Sensation Seeking (SSS) inventory. There was a modest difference for the Barratt Impulsivity (BIS) inventory, especially the Cognitive Subscale. Two different polymorphisms were examined and neither has variants that were related to any of the personality measures even though it had been shown that many of these measures were heritable. Patkar et al., Psychiatric Res, 110, pp. 103-115, 2002.

Effects of Smoked Marijuana on Brain Perfusion and Cognition

O'Leary and colleagues at the University of Iowa used PET imaging to assess the effects of smoked marijuana on brain activation related to cognitive performance. Regional cerebral blood flow (rCBF) was imaged before and after smoking of marijuana in 12 recreational marijuana users in a double-blinded, placebo study design. The subjects performed an auditory attention task while being imaged. Smoking marijuana did not significantly alter mean behavioral performance on the attention task. Despite dramatic increases in heart rate and blood pressure following smoking of marijuana, there was no change in global cerebral blood flow. Marijuana increased rCBF predominately in "paralimbic" regions such as the orbital and medial frontal lobes, insula, temporal poles, and anterior cingulate, as well as in the cerebellum. Activations in these areas most likely reflect marijuana's mood-related effects. Reduced rCBF was observed in temporal lobe auditory regions, in visual cortex, and in brain regions that may be part of an attentional network (parietal lobe, frontal lobe and thalamus). These rCBF decreases may be the neural basis of perceptual and cognitive alterations that occur with acute marijuana intoxication. Most intriguingly, there was no significant rCBF change in the nucleus accumbens or other reward-related brain regions, or in basal ganglia or hippocampus, which have a high density of cannabinoid receptors. O'Leary et al., Neuropsychopharmacology, 26, pp. 802-816, 2002.

Effects of Frequent Marijuana Use on Memory-Related Regional Cerebral Blood Flow

In another study, O'Leary and colleagues at the University of Iowa used PET imaging of regional cerebral blood flow (rCBF) to examine changes in memory-related brain activation in frequent marijuana users after 26 hours of monitored abstinence. During initial learning, marijuana users, relative to control subjects, required an average of 2.7 more presentations to learn a word list to criterion and 3.1 more presentations during subsequent relearning. In single-trial recall, marijuana users recalled 23% more items than control subjects from the end of a list, but 19% less from the middle, suggesting that marijuana users have an increased reliance on short-term memory. Memory-related blood flow in marijuana users, relative to non-using control subjects, was decreased in the prefrontal cortex, increased in regions of cerebellum, and exhibited altered lateralization in the hippocampus. These findings indicate that during early abstinence marijuana users differed most in brain activity related to episodic memory encoding. O'Leary, et al., Pharmacol. Biochem. Behav., 72, pp. 237-250, 2002.

Increased Number of Opioid Receptors on Erythrocytes of Opioid Abusers

Patkar and associates assayed for mu opioid receptors on erythrocytes in opioid-dependent subjects. Overall there were significantly more in the dependent subjects but the distribution was bimodal where one subgroup has very high levels and the other was indistinguishable from normal subjects. Those with high levels showed distortions of the erythrocytes, suggesting a cause for the high prevalence of anemia in these subjects. Zeiger et al., Addict Biol., 7(2), pp. 207-217, 2002.

Buprenorphine Maintenance and Opioid Drug-Seeking Behavior in Humans

Greenwald and colleagues at Wayne State University contrasted the effects of daily versus alternating-day administration of high versus low buprenorphine doses on the choice of, and operant responding for, hydromorphone versus money. Fourteen heroin-dependent outpatients were maintained under four buprenorphine sublingual tablet dose conditions using a double-blind, within-subject, randomized crossover design. All participants received: buprenorphine doses of 2mg daily; 4 mg/placebo on alternating days; 16 mg daily; and 32 mg/placebo on alternating days for 2 weeks for

each drug condition. In test sessions, participants chose between money ($2/choice) and drug (1/8 of total hydromorphone, 4 or 24 mg, i.m. in different sessions) alternatives using an eight-trial, non-independent progressive ratio schedule (FR 100, 200,12,800). The drug dose and money amount earned was delivered after the end of the 2.5-h work period. Hydromorphone 24 mg was more reinforcing than 4 mg. Higher versus lower average buprenorphine doses (regardless of daily versus alternate-day schedule) significantly decreased hydromorphone 24 mg choice and increased money choice. Baseline heroin craving questionnaire scores predicted drug choice, and craving scores were significantly decreased by high-dose buprenorphine. These results demonstrate that high-dose buprenorphine attenuates opioid drug-seeking behavior, heroin craving self-reports and increased sensitivity to alternative reinforcement. These beneficial effects were retained when high-dose buprenorphine was administered on alternate days. Greenwald et al., Psychopharmacology, 160, pp. 344-352, 2002.

Perfusion Deficits in Cocaine and Alcohol Dependent Individuals

Cocaine abuse has been associated with widely distributed areas of significant cerebral blood flow (CBF) reductions or hypo-perfusion as well as CBF hyper-perfusion, but these perfusion abnormalities have not been examined using newer technologies such as statistical parametric mapping (SPM). These areas of abnormal CBF may be more likely among those who abuse cocaine and alcohol together. Using SPECT with HMPAO for CBF, investigators compared proportional scaling (PS) to histogram normalization (HEQ) in SPM among 20 controls and 32 recently abstinent cocaine abusers. The cocaine abusers were separated into two groups (12 cocaine plus alcohol abusers and 20 cocaine alone abusers) and both groups compared to the 20 controls for brain areas of hypo- and hyper-perfusion. Sensitivity to hypo-perfusion was greater with HEQ than PS. Hypo-perfused areas were more likely in the 12 alcohol plus cocaine abusers than in the 20 cocaine alone abusers or 20 controls, and hyper-perfused areas were significantly more likely among the cocaine abusers than controls. The type of CBF abnormality varied by brain location with hypo-perfusion significantly more likely in occipital and temporal cortex or cerebellum and hyper-perfusion more likely in frontal and parietal cortex. These abnormalities in brain perfusion are consistent with previous non-SPM approaches that showed more hypo-perfusion in cocaine abusers than controls and appear to reflect vasospasm and potential compensations in cerebral blood flow. Gottschalk, P., and Kosten, T. Cerebral Perfusion Defects in Combined Cocaine and Alcohol Dependence. Drug Alcohol Depend., 68(1), pp. 95., September 2, 2002.

Buproprion Enhances Smoking Abstinence in Nicotine-Dependent 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. They also examined how antipsychotic class predicts smoking cessation outcomes with bupropion. 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 trial endpoint 7-day point prevalence smoking abstinence rates compared with placebo [BUP,8/16 (50.0%), PLA, 2/16 (12.5%); chi(2) = 5.24, df = 1, $p < .05$], and reduced CO levels during the trial [Medication x Time interaction; $Z = 3.09$, $p < .01$]. Positive schizophrenia symptoms were not altered by BUP, but negative symptoms were significantly reduced. Atypical antipsychotic drug treatment enhanced smoking cessation responses to BUP. Major side effects were dry mouth, gastrointestinal symptoms, headache, and insomnia. These 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.

Deficits in Sensory Gating and Attention May be Associated with Increased Proneness to Developing Psychotic Symptoms During Cocaine Use

Factors increasing vulnerability of a cocaine user to develop psychotic symptoms are unknown. Deficits in sensory gating and attention, such as those occurring in idiopathic psychosis, might represent experimentally tractable factors contributing to vulnerability to cocaine-induced paranoia. Severity of cocaine-induced paranoid symptoms was assessed with the Cocaine Experience Questionnaire (CEQ) in 30 abstinent cocaine-dependent individuals. Sensory gating was assessed in a paired-click auditory evoked potential paradigm (S1 and S2) using the S2/S1 attenuation ratio of the P50 evoked response as the primary outcome measure. The Wender-Utah Rating Scale (WURS) for attention deficit was also administered. Subjects were divided into those with high CEQ scores (n = 10) and those with low CEQ scores (n = 20). The mean P50 ratios were significantly higher for the high CEQ subjects compared with the low CEQ group ($F = 4.6$, $p < .04$). The WURS did not correlate with the total CEQ but correlated with the CEQ Severity subscale, $r = .432$, $p < .02$. The data suggest that deficient P50 sensory gating and attention deficits may be associated with increased proneness to developing psychotic symptoms in the context of cocaine use. Boutros, N.N., Gelernter, J., Gooding, D.C., Cubells, J., Young, A., Krystal, J.H., and Kosten, T. Sensory Gating and Psychosis Vulnerability in Cocaine-dependent Individuals: Preliminary Data. Biol Psychiatry, 51(8), pp. 683-686, April 15, 2002.

Heavy MDMA Users Show Increased Impulsivity

Moeller and associates assessed heavy (> one use/week; > 50 uses total), infrequent (< one use/week; < 30 uses total), and non-users of MDMA on a performance measure of impulsivity and on the Barratt Impulsiveness Scale. Heavy (but not infrequent) users had increased impulsivity on the Barratt and more commission errors as well as fewer correct responses on the performance measure. The performance measure required subjects to view quickly-presented five-digit numbers and determine if successive numbers were the same or different. Not only were the heavy users worse for errors as a group, but their errors were significantly correlated with the amount of self-reported MDMA use. The correlation was especially strong ($r = .69$; $p < .003$) for the performance measure when a memory element was introduced. While this study is limited by a small sample size, and the possibility of confounding effects of other drugs, it is suggestive that MDMA use is associated with impulsivity warranting further study. Moeller, F.G., Dougherty, D.M., Steinberg, J.L., Swann, A.C., Silverman, P.B., Ruiz, P., Barratt, E.S. Heavy "Ecstasy" Use is Associated With Increased Impulsivity. Journal of Addictive Disorders and Their Treatment, 1, pp. 47-52, 2002.

Opioid Dependence is Associated with Perturbation of HPA Axis

Alteration in noradrenergic regulation as well as alteration in the hypothalamic-pituitary-adrenal (HPA) axis have been associated with opioid dependence and acute abstinence symptoms. This double-blind, placebo-controlled study evaluated subjective, physiologic, and biochemical responses to yohimbine (.4 mg/kg, IV) in eight patients receiving methadone and compared results to those from a pool of nine healthy volunteers. All subjects were compared for panic anxiety symptom scale (PASS) scores, systolic and diastolic blood pressure, heart rate, plasma 3-methoxy-4 hydroxy-phenethylene glycol (MHPG), and cortisol. Yohimbine elicited objective and subjective opioid withdrawal and elevated craving for opioid drugs in methadone patients. Significant yohimbine effects were seen across the combined subject group for PASS, physiologic measures, MHPG, and cortisol. Methadone patients had lower baseline MHPG levels. Methadone group interactions with yohimbine were seen for systolic blood pressure and cortisol levels. Methadone-maintained patients are sensitive to the postsynaptic effects of noradrenergic-facilitating medications, experiencing greater physiologic and psychological symptoms, including an increase in craving. Medications that increase synaptic noradrenaline should be used with care in opioid-dependent patients. Stine, S.M., Southwick, S.M., Petrakis, I.L., Kosten, T.R., Charney, D.S., and Krystal, J.H. Yohimbine-induced Withdrawal and Anxiety Symptoms in Opioid-dependent Patients. Biol Psychiatry, 51(8), pp. 642-651, April 15, 2002.

Inhibition of Cortisol Synthesis Does not Reduce Cocaine or Opioid Use in Humans Maintained on Methadone

Stress plays an important role in substance abuse problems. For example, in studies with rodents stress induces reinstatement of opioid and cocaine self-administration. In addition, attenuation of the stress response by pharmacological adrenalectomy using ketoconazole, a cortisol synthesis inhibitor, reduces cocaine self-administration in rodents. In contrast, studies in primates and humans have produced conflicting

results using cortisol synthesis inhibitors for attenuating cocaine-related behaviors and subjective effects. To explore the treatment implications of these findings, ketoconazole's (600-900 mg daily) ability to reduce heroin and cocaine use was compared with placebo in 39 methadone maintained patients with a history of cocaine abuse or dependence during a 12-week double blind trial. Contrary to the predicted effects, both heroin and cocaine use increased after patients were stabilized on methadone and ketoconazole. Depressive and withdrawal symptoms improved no more with ketoconazole than with placebo treatment, and side effects were greater on ketoconazole than placebo. As reported before with methadone treatment, morning cortisol levels were significantly lower than normal values throughout the clinical trial, but were not lower with ketoconazole than placebo treatment. Thus, in agreement with the negative results from acute dosing studies in primates and humans, chronic ketoconazole treatment does not appear to reduce cocaine or opioid use in humans maintained on methadone. Kosten, T.R., Oliveto, A., Sevarino, K.A., Gonsai, K., and Feingold, A. Ketoconazole Increases Cocaine and Opioid Use in Methadone Maintained Patients. Drug Alcohol Depend, 66(2), pp. 173-180, April 1, 2002.

Effects of Oral THC Maintenance on Smoked Marijuana Self-Administration

Studies have shown that the Delta (9)-tetrahydrocannabinol (Delta (9)-THC) concentration in marijuana cigarettes is an important factor for the maintenance of marijuana self-administration. Yet the impact of oral Delta (9)-THC treatment on marijuana self-administration is unknown. Because other agonist therapies have been demonstrated to be effective for the treatment of substance use disorders, the objective of this study was to evaluate 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 QID) for 3 consecutive days, followed by 3 consecutive days of matching placebo. The order of active Delta (9)-THC administration was counterbalanced. 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 (redeemable for cash at study's end). 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: by day 3 of active oral Delta (9)-THC maintenance, participants' rating of 'Good Drug Effect' and 'High' were significantly decreased. Smoked marijuana-related total daily caloric intake was not significantly altered under any maintenance conditions. Finally, the effects of smoked marijuana on psychomotor task performance were only minimally affected by oral Delta (9)-THC maintenance. These 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.

Intravenously Administered Buprenorphine May Have Abuse Liability in Nonopioid-Dependent Individuals Who Abuse Heroin

Several sources indicate that intravenously administered buprenorphine may have significant abuse liability in humans. This study evaluated the reinforcing effects of intravenously administered buprenorphine (0, 2, and 8 mg) in detoxified heroin-dependent participants during a 7.5-week inpatient study. Participants (n = 6) were detoxified from heroin over a 1.5-week period immediately after admission. Testing subsequently occurred in three 2-week blocks. During the first week of each 2-week block, the reinforcing effects of buprenorphine were evaluated. Participants first received a dose of buprenorphine and $20 and then were given either the opportunity to self-administer the dose or $20 during choice sessions. During the second week of each 2-week block, the direct effects of heroin were measured to evaluate potential long-lasting antagonist effects of buprenorphine. Progressive ratio break-point values were significantly higher after 2 and 8 mg of buprenorphine compared with placebo. Correspondingly, several positive subjective ratings increased after administration of active buprenorphine relative to placebo. Although there were few differences in peak effects produced by 2 versus 8 mg of buprenorphine, the higher buprenorphine dose generally produced longer-lasting effects. Heroin also produced dose-related increases

in several subjective effects. Peak ratings produced by heroin were generally higher than peak ratings produced by buprenorphine. There was little evidence of residual antagonism produced by buprenorphine. These results demonstrate that buprenorphine served as a reinforcer under these conditions, and that it may have abuse liability in nonopioid-dependent individuals who abuse heroin. Comer, S.D., Collins, E.D., and Fischman, M.W. Intravenous Buprenorphine Self-administration by Detoxified Heroin Abusers. J Pharmacol Exp Ther, 301(1), pp. 266-276, April 2002.

Bupropion May be as Effective as Methylphenidate, When Combined with Relapse Prevention Therapy, for Cocaine Abusers with ADHD

There are few published studies assessing the efficacy of pharmacologic treatments for attention-deficit hyperactivity disorder (ADHD) among substance abusers seeking treatment. Eleven patients who met DSM-IV diagnostic criteria for cocaine dependence and adult ADHD were entered into a 12-week single-blind trial of divided daily doses of bupropion (BPR). All patients received weekly individual standardized relapse prevention therapy. Treatment compliance and retention were good. Patients reported significant reductions in attention difficulties, hyperactivity and impulsivity. Self-reported cocaine use, cocaine craving, and cocaine positive toxicologies, also decreased significantly. In a previously published trial, 12 patients who met similar diagnostic criteria for adult ADHD and cocaine dependence were entered into a 12-week trial of divided daily doses of sustained-release methylphenidate (MPH). Improvements observed on BPR were similar to, and did not differ from those previously observed with MPH. These preliminary data suggest that BPR may be as effective as sustained-release MPH, when combined with relapse prevention therapy, for cocaine abusers with adult ADHD. However, a future study directly comparing BPR to MPH in a double-blind placebo-controlled trial is needed. Levin, F.R., Evans, S.M., McDowell, D.M., Brooks, D.J., and Nunes E. Bupropion Treatment for Cocaine Abuse and Adult Attention-Deficit/Hyperactivity Disorder. J Addict Dis., 21(2), pp.1-16, 2002.

Addition of Naloxone to Buprenorphine May deter the Parenteral Abuse of Buprenorphine/Naloxone, but Does Not Enhance the Therapeutic Efficacy of Buprenorphine

Buprenorphine is an opioid agonist-antagonist used in the treatment of opioid dependence. Naloxone has been combined with buprenorphine to decrease the parenteral abuse potential of buprenorphine. This addition of naloxone may also confer further opioid blockade efficacy. The objective of this study was to test the opioid blockade efficacy of sublingual buprenorphine/naloxone versus buprenorphine alone and determine whether: (1) the blockade efficacy of buprenorphine/naloxone varies between the time of expected maximal and minimal effects of naloxone, (2) the blockade efficacy of buprenorphine/naloxone and buprenorphine varies as a function of maintenance dose level, and (3) there are adaptive changes over time associated with repeated daily dosing of buprenorphine/naloxone and buprenorphine. Residential subjects (n=6) were maintained on different double-blind dose levels of buprenorphine/naloxone (4/1, 8/2, 16/4, 32/8 mg) and buprenorphine (32 mg) for 6-day periods and challenged with parenteral doses of hydromorphone (12 mg) in laboratory sessions. There was no evidence of additional opioid blockade efficacy conferred by combining naloxone with buprenorphine. Higher doses of buprenorphine/naloxone provided greater blockade of hydromorphone effects. Changes over time associated with repeated daily dosing of buprenorphine/naloxone and buprenorphine were minimal. The addition of naloxone to buprenorphine may deter the parenteral abuse of buprenorphine/naloxone, but it does not enhance the therapeutic efficacy of buprenorphine. The blockade efficacy of buprenorphine/naloxone is dose related; however, doses up to 32/8 mg buprenorphine/naloxone provide only partial blockade when subjects receive a high dose of an opioid agonist. Strain, E.C., Walsh, S.L., and Bigelow, G.E. Blockade of Hydromorphone Effects by Buprenorphine/Naloxone and Buprenorphine. Psychopharmacology (Berl), 59(2), pp. 161-166, January 2002.

Gender, Family/Social Environment, and Years of Education Influence Treatment Dropouts in Addicts

Determining pre-treatment variables that predict attrition in an outpatient cocaine abuse program is critically important in efforts to enhance retention and ultimately improve client outcome. Potential predictors have been identified, such as treatment history, deviant behaviors, and level of drug use; however there is not widespread

agreement on their applicability across treatments and populations. This study examines the relationship of demographic, drug use severity, and psychosocial factors with treatment attrition and the time of dropout. One hundred and sixty-five individuals from the Houston area, seeking treatment for cocaine dependence, completed a pre-treatment assessment battery prior to starting 12 weeks of outpatient treatment. A series of regression analyses showed that treatment dropouts were more likely to be separated from their spouses, have poorer family/social functioning, have fewer years of education, and to be female. Those participants with higher education levels and those with poorer psychiatric functioning tended to remain in treatment longer. The implications of these findings are discussed. Sayre, S.L., Schmitz, J.M., Stotts, A.L., Averill, P.M., Rhoades, H.M., and Grabowski, J.J. Determining Predictors of Attrition in an Outpatient Substance Abuse Program. Am J Drug Alcohol Abuse, 28(1), pp. 55-72, 2002.

Cocaine Addicts have Decreased Cortical Gray Matter Concentration in Comparison to Controls

Structural deficiencies within limbic and prefrontal regions may contribute to the characteristic drug-seeking and drug-taking behaviors that prevail in persons dependent on cocaine. To date, a focal structural analysis of the brains of cocaine patients has not been undertaken. Investigators used voxel based morphometry in conjunction with statistical parametric mapping on the structural magnetic resonance images of cocaine-dependent (n = 13) and cocaine-naive individuals (n = 16) to assess differences between the two groups in gray and white matter concentration. Authors report a decrease in gray matter concentration in the ventromedial orbitofrontal, anterior cingulate, anteroventral insular, and superior temporal cortices of cocaine patients in comparison to controls ($p < .01$ corrected for multiple comparisons). The average percentage decrease in gray matter concentration within a region ranged from 5% to 11%. White matter concentration did not differ between groups. Authors conclude that the brains of cocaine patients are structurally dissimilar from those of nondrug-using controls. The differences were detected in regions involved in decision-making, behavioral inhibition and assignation of emotional valence to environmental stimuli and, hence, may contribute to some of the behavioral deficits characteristic of chronic cocaine users. Franklin, T.R., Acton, P.D., Maldjian, J.A., Gray, J.D., Croft, J.R., Dackis, C.A., O'Brien, C.P., and Childress, A.R. Biol Psychiatry, 51(2), pp. 134-142, January 15, 2002.

Effects of Infusion Rate of Intravenously Administered Morphine on Physiological, Psychomotor, and Self-reported Measures in Humans

The rate of onset of a drug effect is commonly believed to contribute to a drug's abuse liability. The purpose of this study was to investigate the profile of physiological, psychomotor, and self-reported effects of infusion rate (a key means of manipulating onset of drug action) of intravenously administered morphine, the prototypical analgesic with a known abuse liability in human participants. Two doses of morphine sulfate (5 and 10 mg/70 kg, i.v.) and a placebo dose (0 mg/70 kg, i.v.) were administered to healthy volunteers under three infusion rates (2 min bolus, 15 min, and 60 min). Faster infusions of morphine produced greater positive subjective effects than slower infusions on visual analog scale measures of good drug effect, drug liking, and high. Faster infusions also resulted in greater self-reported drug effects and opioid agonist effects, without producing significant physiological or psychomotor impairment. Importantly, faster rates of drug infusion produced significantly higher morphine plasma levels than slower rates, and morphine plasma levels followed a similar pattern and timing of peak effect as the self-reported effects of the drug. Moreover, morphine produced dose-dependent increases in self-reported drug effects, opioid agonist effects, and morphine plasma levels in the study. Results suggest that the pharmacokinetic properties of a drug, including the dosage administered and the rate at which it is administered may function to jointly affect the abuse liability of the drug. Marsch, L.A., Bickel, W.K., Badger, G.J., Rathmell, J.P., Swedberg, M.D., Jonzon, B., and Norsten-Hoog, C. J. Pharmacol Exp Ther., 299(3), pp. 1056-1065, December 2001.

Outcomes and Service Use Among Homeless Persons with Serious Mental Illness and Substance Abuse

This study compared baseline characteristics and clinical improvement after 12 months among 5,432 homeless persons with a diagnosis of serious mental illness with and without a comorbid substance use disorder. The results showed that clients with

dual diagnoses were worse off than those without dual diagnoses on most clinical and social adjustment measures. Clients with dual diagnoses also had poorer outcomes at follow-up on 15 (62 percent) of 24 outcome measures. However, among clients with dual diagnoses, those who reported extensive participation in substance abuse treatment showed clinical improvement comparable to or better than that of clients without dual diagnoses. On measures of alcohol problems, clients with dual diagnoses who had a high rate of participation in self-help groups had outcomes superior to those of other clients with dual diagnoses. Clients with dual diagnoses who received high levels of professional services also had superior outcomes in terms of social support and involvement in the criminal justice system. Homeless persons with dual diagnoses had poorer adjustment on most baseline measures and experienced significantly less clinical improvement than those without dual diagnoses. However, those with dual diagnoses who received extensive substance abuse treatment showed improvement similar to those without at 12 months. Gonzalez, G., and Rosenheck, R.A. Psychiatr Serv., 53(4), pp. 437-446, April 2002.

A Pilot Placebo-Controlled Study of Fluvoxamine for Pathological Gambling

The objective of this study was to evaluate the efficacy of fluvoxamine in the treatment of pathological gambling. Thirty-two patients were treated for 6 months in a double-blind, placebo-controlled study of fluvoxamine 200 mg/day. Outcome measures included reduction in money and time spent gambling per week. Longitudinal mixed effects models and completers analyses were used for estimation and hypothesis testing. Fluvoxamine was not statistically significantly different from placebo in the overall sample. However, fluvoxamine was statistically significantly superior to placebo in males and in younger patients. The power of the study was limited by the high (59%) placebo-response rate. Fluvoxamine may be a useful treatment for certain subgroups of patients with pathological gambling. Several methodological recommendations are made for future pharmacological trials of pathological gambling. Blanco, C., Petkova, E., Ibanez, A., and Saiz-Ruiz, J. Ann Clin Psychiatry, 14(1), pp. 9-15, March 2002.

The Subjective Effects of Nicotine: Methodological Issues, A Review of Experimental Studies, and Recommendations for Future Research

This paper reviews findings from placebo-controlled human experimental studies of the effects of nicotine on subjective experience. Studies are grouped according to whether participants were smokers (significantly nicotine deprived, minimally nicotine deprived) or non-smokers. Within each category, studies are also grouped according to method of nicotine administration (e.g., smoked tobacco, nasal spray) and nicotine dose. The results show that: (1) there is a linear relationship between nicotine dose and measures of drug high (e.g., rush, euphoria) in significantly nicotine-deprived smokers; (2) there appear to be few positive or negative main effects of nicotine on mood in minimally nicotine-deprived smokers; (3) nicotine has positive effects (e.g., increases head rush) and negative effects (e.g., tension) in non-smokers; (4) stronger effects of nicotine on mood emerge when individual difference variables (e.g., neuroticism) and situational contingencies (e.g., exposure to stressful stimuli) are examined. The investigator suggests additional studies with minimally nicotine-deprived smokers and non-smokers are needed to further specify the conditions under which nicotine affects mood and other subjective experience. Kalman, D. Tobacco Res., 4(1), pp. 25-70, February 2002.

Locating Nucleobase Lesions Within DNA Sequences by MALDI-TOF Mass Spectral Analysis of Exonuclease Ladders

Investigators at the University of Minnesota Cancer Center and Department of Medicinal Chemistry studied the location of carcinogen-modified nucleobases (DNA adducts) within DNA sequences as a critical factor affecting their promutagenic properties and persistence in DNA. They report the use of controlled exonuclease digestion followed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) to directly map modified nucleobases within DNA. The DNA sequence is determined by mass spectral analysis of the DNA ladders produced by sequential removal of nucleotides with either 5'-->3' or 3'-->5' exonuclease. Individual mononucleotides are identified from the mass differences between adjacent peaks corresponding to singly charged ions of the products of enzymatic cleavage. Chemically modified nucleotides are detected and identified by their molecular weight. The resolution and mass accuracy of this approach are sufficient to identify

nucleobase modifications differing in mass by as little as 2 Da. No a priori information on the DNA sequence or adduct type is required. The investigators demonstrated the general applicability of this method by sequencing synthetic oligonucleotides containing a range of nucleobase modifications: O(6)-methylguanine, peroxynitrite-induced oxidative lesions (oxaluric acid, oxazolone, cyanuric acid), and the N(2)-guanine adduct of (+,-)-7r,8t-dihydroxy-9t,10t-epoxy-7,8,9,10-tetrahydribenzo [a]pyrene. Sequence information is also obtained for DNA oligodeoxynucleotides containing O(6)-pyridyloxobutylguanine, despite the ability of this lesion to block 3'-phosphodiesterase. Tretyakova, N., Matter, B., Ogdie, A., Wishnok, J.S., and Tannenbaum, S.R. Chem Res Toxicol., 14(8), pp. 1058-1070, August 2001.

Formation of Benzo[a]pyrene Diol Epoxide-DNA Adducts at Specific Guanines within K-ras and p53 Gene Sequences: Stable Isotope-Labeling Mass Spectrometry Approach

The mutagenicity of a prominent tobacco carcinogen, benzo[a]pyrene (B[a]P), is believed to result from chemical reactions between its diol epoxide metabolite, (+)-anti-7r,8t-dihydroxy-c9,10-epoxy-7,8,9,10- tetrahydrobenzo[a]pyrene (BPDE), and DNA, producing promutagenic lesions, e.g., (+)-trans-anti-7R,8S,9S- trihydroxy-10S-(N(2)-deoxyguanosyl)-7,8,9,10-tetrahydrobenzo [a]pyrene (N(2)-BPDE-dG). Previous studies used the DNA repair enzyme UvrABC endonuclease in combination with ligation-mediated PCR (LMPCR) to demonstrate an increased reactivity of BPDE toward guanine nucleobases within codons 157, 248, and 273 of the p53 tumor suppressor gene. These sites are also "hot spots" for mutations observed in lung tumors of smokers, suggesting an involvement of B[a]P in the initiation of lung cancer. However, the LMPCR approach relies on the ability of the repair enzyme to excise BPDE-induced lesions, and thus the slowly repaired lesions may escape detection. Furthermore, BPDE-DNA adduct structure and stereochemistry cannot be determined. In the present work, the investigators performed a direct quantitative analysis of N(2)-BPDE-dG originating from specific guanine nucleobases within p53- and K-ras-derived DNA sequences by using a stable isotope labeling-mass spectrometry approach recently developed in the authors laboratory. (15)N-labeled dG was placed at defined positions within DNA sequences derived from the K-ras proto-oncogene and p53 tumor suppressor gene, the two genes most frequently mutated in smoking-induced lung cancer. (15)N-labeled DNA was annealed to the complementary strands, followed by BPDE treatment and liquid chromatography-electrospray ionization tandem mass spectrometry analysis (HPLC-ESI-MS/MS) of N(2)-BPDE-dG lesions. The extent of adduct formation at (15)N-labeled guanine was determined directly from the HPLC-ESI-MS/MS peak area ratios of (15)N-N(2)-BPDE-dG and N(2)-BPDE-dG. BPDE-induced guanine adducts were produced non-randomly along K-ras and p53 gene-derived DNA sequences, with over 5-fold differences in adduct formation depending on sequence context. N(2)-BPDE-dG yield was enhanced by the presence of 5-Me substituent at the cytosine base-paired with the target guanine nucleobase, an endogenous DNA modification characteristic for CpG dinucleotides within the p53 gene. In the K-ras-derived DNA sequence, the majority of N(2)-BPDE-dG adducts originated from the first position of the codon 12 (GGT), consistent with the large number of G --> T transversions observed at this nucleotide in smoking-induced lung cancer. On the contrary, the pattern of N(2)-BPDE-dG formation within the p53 exon 5 sequences did not correlate with the mutational spectrum in lung cancer, suggesting that factors other than N(2)-BPDE-dG formation are responsible for these mutations. The stable isotope labeling HPLC-ESI-MS/MS approach described in this work is universally applicable to studies of modifications to isolated DNA by other carcinogens and alkylating drugs. Tretyakova, N., Matter, B., Jones, R., and Shallop, A. Biochemistry, 41(30), pp. 9535-9544, July 30, 2002.

Prevalence of Cigarette Smoking in Pregnant Women Participating in the Special Supplemental Nutrition Program for Women, Infants and Children (WIC) in Minneapolis and Saint Paul, Minnesota, USA

It is important to determine the prevalence of cigarette smoking among pregnant low-income women and to evaluate their smoking cessation patterns in order to target appropriate interventions. Ethnically diverse pregnant women aged 15-45 years were recruited from Minneapolis or Saint Paul Women, Infants, and Children (WIC) clinics before their third trimester. Serum cotinine levels were assayed for 98 women and compared with self-report. The women were unaware that their smoking status would be validated. Twenty-one (21%) women had a positive serum cotinine value (>/=3 ng/mL); 16 (76%) admitted smoking within the previous 24 h before interview and five denied smoking. Of the five, four had cotinine levels that could

suggest passive smoke exposure. Thirty-seven women (38%) admitted cigarette smoking during the pregnancy but before knowing that they were pregnant; 18 (49%) of these denied current smoking at the interview and also presented with negative cotinine levels. These data suggest that some participants in WIC make a concerted effort to quit smoking when they find out they are pregnant, and are generally truthful when reporting their smoking habits during pregnancy. Ross, J.A., Swensen, A.R., and Murphy, S.E. Paediatr Perinat Epidemiol., 16(3), pp. 246-248, July 2002.

Cigarette Smoking and Lung Cancer: Chemical Mechanisms and Approaches to Prevention

Much is now known about the carcinogens in cigarette smoke, their conversion to forms that react with DNA, and the miscoding properties of the resulting DNA adducts that cause the many genetic changes known to exist in human lung cancer. The chronic exposure of pulmonary DNA to a multitude of metabolically activated carcinogens is consistent with our current understanding of cancer as a disease resulting from many changes in key genes regulating growth. This review illustrates how this solid foundation of knowledge can be used to find new ways to prevent lung cancer. Three prevention-related topics are discussed: human uptake of tobacco carcinogens as a way of assessing risk and investigating mechanisms; individual differences in the metabolic activation and detoxification of carcinogens, which may relate to cancer susceptibility; and chemo-prevention of lung cancer in smokers and ex-smokers. These new approaches are necessary as adjuncts to education and cessation efforts, which despite some success have not eliminated tobacco smoking. Hecht, S.S. Lancet Oncol., 3(8), pp. 461-469, August 2002.

Quantitation of Metabolites of 4-(methylnitrosamino)-1-(3-pyridyl) -1-butanone After Cessation of Smokeless Tobacco Use

Two major metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) were previously shown to be highly persistent in human urine after cessation of cigarette smoking. The authors hypothesized that NNK or its metabolite, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), was sequestered in the lung. In this study, the investigators further evaluated this hypothesis by quantifying the NNK metabolites, NNAL and its glucuronides (NNAL-Gluc), in urine and plasma after cessation of smokeless tobacco use, in which NNK is administered p.o. rather than by inhalation. Thirteen male nonsmokers, 11 snuff dippers and 2 tobacco chewers, in the study. Urine and plasma were obtained at baseline and at intervals 2-126 days after cessation of smokeless tobacco use. The distribution half-lives t(1/2alpha) (days) of NNAL (1.32 +/- 0.85 versus 3.35 +/- 1.86) and NNAL-Gluc (1.53 +/- 1.22 versus 3.89 +/- 2.43) were significantly shorter in smokeless tobacco users than in smokers. There were no significant differences in the terminal half-lives t(1/2beta) (days) of NNAL (26.3 +/- 16.7 versus 45.2 +/- 26.9) and NNAL-Gluc (26.1 +/- 15.1 versus 39.6 +/- 26.0) in smokeless tobacco users and smokers. Baseline levels as well as renal clearance of the NNK metabolites correlated with number of tins or pouches of smokeless tobacco consumed. Ratios of (S)-NNAL:(R)-NNAL and (S)-NNAL-Gluc:(R)-NNAL-Gluc in urine were significantly (3.1-5.7 times) higher 7 days after cessation than at baseline in both smokeless tobacco users and smokers, indicating stereoselective retention of (S)-NNAL. Collectively, the results of this study suggest that there is a receptor in the human body, possibly in the lung, for (S)-NNAL, the more carcinogenic NNAL enantiomer. These data may have considerable implications for understanding mechanisms of tumor induction by NNK. Hecht, S.S., Carmella, S.G., Ye, M., Le, K.A., Jensen, J.A., Zimmerman, C.L., and Hatsukami, D.K. Cancer Res., 62(1), pp. 129-134, January 1, 2002.

Human Urinary Carcinogen Metabolites: Biomarkers for Investigating Tobacco and Cancer

Measurement of human urinary carcinogen metabolites is a practical approach for obtaining important information about tobacco and cancer. This review presents currently available methods and evaluates their utility. Carcinogens and their metabolites and related compounds that have been quantified in the urine of smokers or non-smokers exposed to environmental tobacco smoke (ETS) include trans, trans-muconic acid (tt-MA) and S-phenylmercapturic acid (metabolites of benzene), 1- and 2-naphthol, hydroxyphenanthrenes and phenanthrene dihydrodiols, 1-hydroxypyrene (1-HOP), metabolites of benzo[a]pyrene, aromatic amines and heterocyclic aromatic amines, N-nitrosoproline, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its

glucuronides (NNAL and NNAL-Gluc), 8-oxodeoxyguanosine, thioethers, mercapturic acids, and alkyladenines. Nitrosamines and their metabolites have also been quantified in the urine of smokeless tobacco users. The utility of these assays to provide information about carcinogen dose, delineation of exposed vs. non-exposed individuals, and carcinogen metabolism in humans is discussed. NNAL and NNAL-Gluc are exceptionally useful biomarkers because they are derived from a carcinogen- 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)- that is specific to tobacco products. The NNAL assay has high sensitivity and specificity, which are particularly important for studies on ETS exposure. Other useful assays that have been widely applied involve quantitation of 1-HOP and tt-MA. Urinary carcinogen metabolite biomarkers will be critical components of future studies on tobacco and human cancer, particularly with respect to new tobacco products and strategies for harm reduction, the role of metabolic polymorphisms in cancer, and further evaluation of human carcinogen exposure from ETS. Hecht, S.S. Carcinogenesis, 23(6), pp. 907-922, June 2002.

A Population-based Study of Cigarette Smoking Among Illicit Drug Users in the United States

The investigators describe smoking patterns among illicit drug users, assess whether cigarette smoking is more prevalent among illicit drug users than it is among non-users and explore how smoking relates to level and type of drug use. The sample consisted of adult responses to the 1997 National Household Survey on Drug Abuse (n = 16,661). Multivariate analyses used SUDAAN to adjust standard errors for the sampling design and controlled for age, race, sex, education, depression, treatment history and alcohol. The results show that 71% of recent illicit drug users smoked cigarettes at least once in the past month. Their adjusted odds of being a smoker were much greater than for the general population (OR = 3.07, P < 0.0001). Their quit rate, although substantial, was half that of non-users (23% versus 56%, P=0.0001). Odds of being a smoker were higher for poly- versus monodrug users (OR = 2.35, P=0.0020) and rose with increased drug use (OR = 1.36, P=0.0374). Illicit drug users who perceived smoking to be risky were four times less likely to smoke (OR = 0.23, P=0.0008). The results suggest that although most recent illicit drug users smoke, some are able to quit. Clinicians, policy makers and user advocates should address tobacco use in drug treatment and in harm reduction interventions. Richter, K.P., Ahluwalia, H.K., Mosier, M.C., Nazir, N., and Ahluwalia, J.S. Addiction, 97(7), pp. 861-869, July 2002.

A Screening Trial of Amantadine as a Medication for Cocaine Dependence

This screening trial evaluated whether amantadine hydrochloride (100 mg bid) demonstrated sufficient clinical efficacy compared to placebo to recommend development as a pharmacotherapy for cocaine dependence. Participants were randomized to amantadine (n=34) or placebo (n=35) conditions in a 16-week, placebo-controlled, double blind trial with three times per week group counseling. Amantadine-treated participants were retained significantly longer than placebo. Based on results of a joint probability index for urine drug testing results (i.e. the proportion of cocaine-metabolite free urine samples divided by the number of participants assigned to the condition), participants assigned to amantadine were found to be significantly more likely to be cocaine abstinent on the last day of 8-weeks of treatment than participants assigned to placebo. Results at the end of 16 weeks of treatment were similar. Standard measures of urine drug testing consistently favored the amantadine condition over placebo, although not at levels of statistical significance. There was no statistical significance infrequency or severity of reported adverse events by treatment condition. Participants assigned to amantadine exhibited greater reductions in global staff ratings of cocaine dependence severity from baseline to termination compared with placebo. There were no significant differences in frequency or severity of reported adverse events by treatment condition. These results provide moderate support for further study of amantadine for the treatment of cocaine dependence. Shoptaw, S., Kintaudi, P.C., Charuvastra, C., and Ling, W. Drug Alcohol Depend., 66(3), pp. 217-224, May 1, 2002.

Director's Report to the National Advisory Council on Drug Abuse - September, 2002

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

Methamphetamine Increases Lentivirus' Ability to Replicate in Brain Tissue

A study led by Dr. Michael Podell, Ohio State University, found that exposing astrocytes infected with feline immunodeficiency virus (FIV) - a surrogate for HIV - to methamphetamine in tissue culture for two weeks increases those brain cells' ability to replicate the virus as much as 15-fold. It is known that astrocytes serve as a reservoir of chronic brain lentivirus infection. The concentration of methamphetamine the astrocytes were exposed to was equal to an average level of methamphetamine in an adult abuser's bloodstream. The paper also reports that before an astrocyte can become infected with the virus, it must be associated with a specific type of lymphocyte, or immune cell, known as a peripheral blood mononuclear cell (PBMC). Lastly, the researchers discovered that, once the virus infects the astrocytes, it mutates into a form (containing 4 amino acid substitutions in the envelope polyprotein) that no longer needs this PBMC association to reproduce. Thus, lentiviral infection of the brain in the presence of methamphetamine may result in enhanced astrocyte viral replication, producing a more rapid and increased brain viral load. Gavrilin, M.A., Mathes, L.E., and Podell, M. Methamphetamine Enhances Cell-associated Feline Immunodeficiency Virus Replication in Astrocytes. J. Neurovirol., 8(3), pp. 240-249, 2002.

Risk Networks and Racial/Ethnic Differences in HIV Among Injection Drug Users

A number of studies have found higher prevalence of HIV between African American and Puerto Rican IDUs than among White IDUs. Researchers examined how risk networks might contribute to racial/ethnic variations in HIV prevalence. They sought to determine whether African American and Puerto Rican IDUs engage in greater levels of risk behaviors than their White counterparts; the extent that racial/ethnic selectivity of risk networks explain variations in HIV prevalence; whether White IDUs who have network contacts with minority IDUs are at higher risk of HIV than their counterparts who do not have such contact; and whether racial/ethnic differences in HIV persist after adjusting for risk behaviors and network characteristics. They recruited 662 IDUs on the street in Bushwick, New York City, interviewed these individuals, and tested them for HIV. Risk behaviors and networks were analyzed to explain racial/ethnic variations in HIV. The study found that 40% of IDUs were HIV positive and that HIV prevalence was greater among Puerto Ricans (45%) and African Americans (44%) than Whites (32%). The personal sexual and drug risk networks of IDUs were predominantly racially and ethnically homogeneous. After multivariate adjustments for risk behaviors and risk networks, African American-White differences in HIV prevalence were no longer significant. Although differences between Puerto Ricans and Whites persisted, post hoc analyses suggested that network partner characteristics might explain these. Although the study was not able to fully explain the sustained high prevalence of HIV among Puerto Rican IDUs, it appears that network patterns within and between racial/ethnic groups may continue to be a key factor in the future of the epidemic. Moreover, in Bushwick, racially/ethnically discordant risk partnerships involving African American IDUs may function as potential bridges of transmission between groups. Kottiri, B.J., Friedman, S.R., Neaigus, A., Curtis, R., and Des Jarlais, D.C. Risk Networks and Racal/Ethnic

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Differences in the Prevalence of HIV Infection Among Injection Drug Uses. J Acquired Immune Deficiency Syndromes, 30, pp. 95-104, 2002.

Decreases in Self-Reported Risks and Increases in New STDs among HIV+ Adults

Researchers examined high-risk sexual behavior among HIV-positive individuals as a factor contributing to the spread of the HIV epidemic. They conducted a retrospective chart review to compare self-reported STD risk behaviors and clinic diagnoses of 191 known HIV-positive clients attending Miami-Dade STD clinics with those of 191 uninfected controls. The analysis included 130 men (68.1%) and 61 (31.9%) women. HIV-positive clients were significantly more likely than controls to be African American, to report a history of injection drug use, to be no more likely than controls to have had sex with an IDU, to be more likely to report no sexual activity in the last 2 months, or if active, to report condom use at last sexual intercourse. Two themes are discussed as emerging from this study: First, although HIV-positive STD clinic patients were more likely than controls to report fewer sexual risk behaviors, they were more likely to be diagnosed with infectious syphilis and/or gonorrhea and to have sex partners with documented gonorrhea, chlamydia, or syphilis. Second, there appears to be a subset of HIV-positive adults who represent core transmitters: they have known about their HIV positive serostatus for a long time, are more likely to have had 4 or more sex partners in the past year, are more likely to have used crack cocaine, and are more likely to be symptomatic for an STD and in need of treatment for exposure to infectious syphilis, gonorrhea or chlamydia. This subset of HIV-positive clients continues to engage in high-risk sexual behavior after their diagnosis of HIV. This group of individuals seems to be playing a key role as core transmitters of HIV and bacterial STDs in the African American community in Miami and is in need of targeted intervention. Brewer, T.H., Metsch, L.R., and Zenilman, J.M. Use of a Public STD Clinic by Known HIV-Positive Adults: Decreased Self-Reported Risk Behavior and Increased Disease Incidence. J Acquired Immune Deficiency Syndromes, 29, pp. 289-294, 2002.

Peer-Driven Intervention to Improve Drug Users' Adherence to HIV Treatment

Active drug users with HIV often have low utilization of and adherence to primary care. Combining drug treatment and primary care on-site can help to reduce these problems by creating a social support structure wherein treatment staff can monitor patient adherence while also providing encouragement and social support. Researchers conducted a 6-month feasibility study to assess an alternative support structure, called a peer-driven intervention, that serves as a functional equivalent to drug treatment for increasing drug users' adherence to HIV therapeutics. The study included 14 adult drug users receiving medical care for HIV. As a health advocate, each subject was assigned and asked to meet with another subject weekly at the project storefront to provide peer support and counseling. As a peer, each subject was assigned and asked to meet with another health advocate weekly to receive support in keeping up his/her medical care. No two subjects played both roles for one another, and advocates earned nominal monetary rewards for eliciting positive responses from their peers in keeping appointments, responding to physician referrals, picking up prescriptions on time and attending weekly meetings with the advocate. Although this study was small, it suggested that it is possible to harness peer pressure of drug users to promote positive behavioral changes. In particular, the results indicate that an alternative social support structure to drug treatment is feasible for increasing active drug users' adherence to medical care. Broadhead, B., Heckathorn, D., Altice, F., van Hulst, Y., Carbone, M., Friedland, G., O'Connor, P., and Selwyn, P. Increasing Drug Users' Adherence to HIV Treatment: Results of a Peer-Driven Intervention Feasibility Study. Social Sci and Medicine, 55, pp. 235-246, 2002.

Selection Effect of Needle Exchange in Anchorage, Alaska

Researchers examined participation bias (selection bias) as a potential threat to validity in studies that attempt to evaluate the effects of needle exchange programs (NEPs). They focused on IDUs who were randomly assigned to a needle exchange condition in a 2-arm randomized clinical trial of needle exchange. Time to follow-up between the experimental NEP condition (n=296; median = 261 days) and pharmacy sales conditions (n=304; median=256 days) was not significantly different. Within the NEP condition, a similar analysis comparing time to follow-up between IDUs who used the NEP (n=65, median=199 days) and those who refrained from using the NEP (n=231, median=286 days) was highly significant. Moreover, within the NEP condition, follow-up rates differed between those who used the NEP and those who

did not. Of drug users randomly assigned to an NEP, the ones who actually used the NEP had higher levels of drug use. Predictors of who used the NEP were consistent with other studies reporting bias in a nonrandomized study of IDUs who use a voluntary NEP. This study found that there is an inherent selection bias among IDUs who use NEPs; that is, IDUs who use NEPs engage in higher frequency drug use and higher levels of other risk behaviors compared to IDUs who do not use NEPs, Moreover, IDUs who used both the NEP and the pharmacy to obtain sterile syringes injected significantly more often than other IDUs. This indicates that it is need, rather than compliance, that leads to the use of multiple sources of syringes. Fisher, D.G., Reynolds, G.L., and Harbke, C.R. Selection Effect of Needle Exchange in Anchorage, Alaska, 79(1), pp. 128- 135, 2002.

Localized vs Citywide Trends in the AIDS Epidemic Among IDUs in New York City

Researchers examined trends over phases of the AIDS epidemic among injection drug users in New York City, which accounts for almost 25% of the AIDS cases among IDUs in the U.S. They sought to determine whether recent declining trends in AIDS among IDUs were localized within boroughs of the city or generalized across the boroughs. Two methods were used: (1) the compilation and analysis of existing data on historical AIDS case rates, recent HIV sero- prevalence, and HIV prevention service levels by borough and (2) a qualitative study (key informant interviews and focus groups) in two communities (Staten Island and Rockaway, Queens) an hour from Manhattan where services are less accessible. Findings indicated that (1) epidemiological differences in risk behaviors and in services existed from early in the epidemic (i.e., before 1984), (2) HIV prevention services have been and continue to be concentrated in Manhattan; and (3) the long-term concentration of prevention programs in Manhattan appears to be related to the greater number of new infections associated with IDU and female heterosexual transmission in the Bronx and Brooklyn compared to Manhattan since 1984. This study suggests that the AIDS epidemic in New York City among IDUs and their sexual partners may have been shaped by the long-term, unequal geographic distribution of HIV prevention and outreach services in the City's boroughs. It also suggests that enhancing access to services for IDUs in the boroughs outside Manhattan will be needed to sustain declining trends in AIDS cases among IDUs throughout the boroughs of the City. Rockwell, R., Deren, S., Goldstein, M.F., Friedman, S.R., and Des Jarlais, D.C. Trends in the AIDS Epidemic Among New York City's Injection Drug Users: Localized or Citywide? J Urban Health, 79(1), pp. 136-146, 2002.

The First Decade of High Prevalence of HIV Among Injecting Drug Users in Bangkok

In order to examine the long-term structure of the HIV epidemic among IDUs in Bangkok, researchers conducted annual surveys on HIV seroprevalence at drug use treatment clinics of the Bangkok Metropolitan Administration (BMA) from 1987 onward, as well as risk behavior surveys with IDUs in 1989, 1993, and 1997. They also conducted a large cohort study to measure HIV incidence among clients of the BMA clinics from 1995 to 1998. Findings indicate that HIV prevalence rose rapidly in 1988 and then remained stable at 30-40%. By the fall of 1989, more than 90% of IDUs reported reducing their injection risk behaviors (stopping or reducing injecting, not sharing injection equipment). Reduction in injecting risks was not risk elimination, however: moderate percentages of IDUs continued to report injecting with a syringe that had been used by someone else. Sexual risk behavior (i.e., without a condom) occurred most often within primary relationships. The estimated HIV incidence was moderate to high at 5.8/100 person-years at risk from 1995 to 1998. Incarceration and injecting while incarcerated were strongly associated with incident HIV infections. The researchers conclude that the HIV epidemic among IDUs in Bangkok appears to have reached a rough equilibrium. Deaths among HIV positive IDUs and the continuing entry of new injectors (most of whom are HIV negative) into the population serve to decrease HIV prevalence. The stability of the epidemic has not yet brought it under control, however: the incidence rate remains too high (5.8/100 person-years at risk). The authors describe four key lessons learned from Bangkok's experience: one is that HIV can spread very rapidly among IDUs and therefore, prevention programs should be implemented as early as possible; the second is that even after rapid HIV transmission has occurred, IDUs will change their HIV risk behaviors (both injection and sexual risks); the third is that risk reduction is not risk elimination because residual risk behavior is likely to remain even after a majority of IDUs are aware of AIDS and have taken steps to reduce their risk behaviors; and finally, a long-term perspective is needed on controlling HIV epidemics among IDUs,

especially since there seems to be a continuing entry of new injectors. Vanichseni, S., Choopanya, K., Des Jarlais, D.C., Sakuntanaga, P., Kityaporn, D., Sujarita, S., Raktham, S., Hiranrus, K., Wasi, C., Mock, P.A., and Mastro, T.D. HIV Among Injecting Drug Users in Bangkok: The First Decade. International J Drug Policy, 3, pp. 39-44, 2002.

Increased Substance Use among Residents of Manhattan, N.Y. after September 11th

Investigators examined the effects of the September 11th attacks on substance use behaviors among 988 adults in Manhattan, New York City. They conducted a random digit dial telephone survey of households and achieved an overall response rate of 64.3%. Interviews inquired about cigarette smoking, alcohol drinking, and marijuana use pre- and post- September 11th as well as demographic characteristics, other types of traumatic events that may have occurred before 9/11, and mental health status (PTSD, depression). They found that 28.8% of respondents reported increased use of any one of the 3 substances (cigarettes, alcohol, marijuana); 9.7% reported an increase in smoking; 24.6% reported an increase in alcohol consumption; and 3.2% reported an increase in marijuana use. Persons who reported an increase in cigarette use and marijuana use were significantly more likely to experience PTSD than those who did not (24.2% vs 5.6% PTSD for cigarettes; 36.0% vs 6.6% for marijuana). Depression was more common among those who increased than for those who did not increase cigarette smoking (22.1 vs 8.2%), alcohol consumption (15.5% vs 8.3%), and marijuana smoking (22.3% vs 9.4%). These results suggest a substantial increase in substance use among Manhattan residents in the acute post-disaster period after September 11th. Increased substance use may be a significant problem in the immediate aftermath of a disaster and may frequently co-occur with PTSD and depression. Vlahov, D., Galea, S., Resnick, H., Ahern, J., Boscarino, J.A., Bucuvalas, M., Gold, J., and Kilpatrick, D. Increased Use of Cigarettes, Alcohol, and Marijuana among Manhattan, New York, Residents after the September 11th Terrorist Attacks. Amer J Epidemiol., 155(110), pp. 988-996, 2002.

Needle Exchange-Based Health Services Help to Reduce Emergency Department Use

Researchers in New Haven, Connecticut examined the impact of the New Haven Community Health Care Van, a mobile needle exchange-based health care delivery system, in reducing emergency department (ED) use among out-of-treatment IDUs over the 2-year period of January 1996 to December 1998. A pre-post comparison of ED utilization was performed using linked medical records from New Haven's only two EDs. Among 373 IDUs, 117 (31%) were clients of the mobile NEP clinic and 256 had not used its services. At baseline, the mobile NEP clinic users were more frequent users of ED services ($p<.001$). After full-scale implementation of the mobile NEP clinic, mean ED utilization declined among its clients by more than 20% and increased within the non-client group. Use of the mobile NEP clinic was significantly associated with reductions in ED use; these reductions were striking because the mobile clinic was not specifically designed or intended to achieve this result. Reduced ED use appears to have resulted indirectly from other efforts of the mobile NEP clinic to improve the health status of clients and to use case management and outreach to provide continuity of care. The study's findings suggest that NEP-based health care services can reduce ED utilization among high-risk IDUs and have an important role within communities with high rates of drug use and HIV/AIDS. Pollack, H.A., Khoshnood, K., Blankenship, K.M., and Altice. F.L. The Impact of Needle Exchange-Based Health Services Emergency Department Use. J Gen Intern Med, 17, pp. 341-348, 2002.

Risk Behaviors Associated with Transition to Injection Drug Use in Young Drug Users

Researchers in Baltimore, MD sought to identify discrete high-risk circumstances occurring early on in a young drug user's life (such as age at first sexual experience, trading sex, rape or assault, high school dropout, juvenile detention) that would help determine whether such factors known to be associated with adolescent substance use and HIV were, in fact, also associated with being a recent onset IDU. An age-matched case-control analysis was performed from a cohort study in Baltimore (1997-1999) of street-recruited non-injection and injection drug users aged 15-30. Cases were IDUs injecting less than 2 years and controls were age-matched persons who used non-injection heroin, cocaine, or crack. At baseline, all were interviewed about prior year-by-year behaviors; data analysis was based on information for the year

prior to injection onset for the case and the same calendar time for the controls as well as recent behaviors for both groups. Of 270 participants, most were African American (78%), female (61%), and HIV seroprevalence was 7% at baseline. IDUs were significantly more likely than controls to be non-African American and report high school dropout, early sex trading, and recent violence victimization. Given that new injectors are at high risk for HIV and hepatitis yet difficult to reach for prevention efforts, these data suggest some categories to use to target non-injectors who are likely to transition into injection drug use. Fuller, C.M., Vlahov, D., Ompad, D.C., Shah, N., Arria, A., and Strathdee, S.A. High-risk Behaviors Associated with Transition from Illicit Non-Injection to Injection Drug Use among Adolescent and Young Adult Drug Users: A Case-Control Study. Drug and Alcohol Dependence, 66, pp. 189-198, 2001.

Cognitive and Motor Outcomes of Cocaine-Exposed Infants

Dr. Lynn Singer and colleagues at Case Western Reserve University have reported that tests of infant cognitive development at 2 years of age (Bayley Scales of Infant Development, Mental Development Index, or MDI)) showed a significant association with prenatal exposure to cocaine, after taking account of potentially confounding factors (e.g., maternal age, parity, prenatal care, maternal and current caregiver non-verbal intelligence, education, home environment quality, and maternal use of tobacco, alcohol, marijuana, and other drug use). The average difference in the developmental quotient was 6 points (82.7 for the exposed and 88.7 for the non-exposed). The average MDI score for the general population is 100. When children were grouped by developmental scores in the range of mental retardation (<70 MDI) at 2 years of age, cocaine-exposed children were almost twice as likely to be so classified - specifically 13.7% of the cocaine-exposed children relative to 7.1% of the non-cocaine-exposed children. The percentage in the exposed group is 4.89 times higher than expected in the general population. Mild delays (<80 MDI) were present in 37.6% of exposed and 20.9% of non-exposed children. No associations were found between prenatal cocaine exposure and motor development at 2 years of age (Bayley Scales of Infant Development, Psychomotor Development Index, or PDI). As noted in an accompanying editorial to this publication, this "is the only 1 of 10 peer-reviewed, adequately-controlled, large scale, prospective longitudinal studies to show an unequivocal association between toddlers' developmental scores and prenatal exposure to cocaine." These findings illustrate the importance of multiple studies on the topic, allowing for comparison across studies and potential explanations for differences in findings, which in turn may guide appropriate interventions and clinical care. Singer, L.T., Arendt, R., Minnes, S., Farkas, K., Salvator, A., Kirchner, H.L., and Kliegman, R. Cognitive and Motor Outcomes of Cocaine-Exposed Infants. Journal of the American Medical Association, 287(15), pp. 1952-1960, 2002; Zuckerman, B., Frank, D.A., and Mayes, L. Cocaine-Exposed Infants and Developmental Outcomes: "Crack Kids" Revisited. Journal of the American Medical Association, 287(15), pp. 1990-1991, 2002.

Prenatal Alcohol, Marijuana, and Tobacco Exposure: Neuropsychological Outcomes at 10 Years of Age

In a longitudinal study at the University of Pittsburgh, neuropsychological outcomes at 10 years of age have recently been reported for a sample of 593 children, who had been assessed at multiple times since birth. The mothers had been recruited into the study during pregnancy. Half of the women were African-American, and half were Caucasian. They were generally from lower socioeconomic status families, and light to moderate level users. At the 10-year follow-up, prenatal alcohol use was found to be significantly and negatively associated with performance on a test of memory and learning skills. Prenatal marijuana exposure also was negatively associated with learning and memory performance, as well as with a measure of impulsivity. These associations persisted when other predictors of learning and memory were controlled (e.g., child's intelligence level, gender, and anxiety; parents' socioeconomic level and intellectual ability). An earlier publication (2001) on this sample focused on prenatal tobacco exposure, and documented, after statistically controlling for such factors as other prenatal substance use, current tobacco use, and multiple socioeconomic covariates, an association of prenatal tobacco exposure with various outcomes at 10 years of age (i.e., deficits in verbal learning and design memory, slowed responding on a test of eye-hand coordination, reduced ability for flexible problem solving, and more impulsivity). The investigators are continuing to follow this sample into the adolescent years. Richardson, G.A., Ryan, C., Willford, J., Day, N.L., and Goldschmidt, L. Prenatal Alcohol and Marijuana Exposure: Effects of Neuropsychological Outcomes at 10 Years. Neurotoxicology and Teratology, 24, pp. 309-320, 2002; Cornelius, M.D., Ryan, C.M., Day, N.L., Goldschmidt, L., and Willford, J.A. Prenatal Tobacco Effects on

Neuropsychological Outcomes among Preadolescents. Developmental and Behavioral Pediatrics, 22(4), pp. 217-225, 2001.

Head Growth and Neurodevelopment of Infants Born to HIV-Infected Drug-Using Women

Researchers from the Women and Infants Transmission Study (WITS) continue to examine health and development outcomes of children born to HIV-positive mothers, with attention to drug use as a variable of importance. The WITS is a multi-site study of mother-infant HIV transmission and outcomes in the mothers and their children, and is collaboratively supported by three NIH Institutes (NIAID, NICHD, NIDA). Enrollment began in 1990 and has continued since that time. Macmillan et al. report on neurodevelopment and head growth during the first 30 months of life among HIV-positive and HIV-negative infants with and without in utero exposure to opiates and cocaine. Of the 1,094 infants in the analysis, 147 were HIV-positive and 383 were exposed in utero to opiates or cocaine (maternal self-report or positive urine screen). There were differences in developmental test scores and head circumference among the groups at 4 months of age (HIV+/drug negative, and HIV-/drug positive showing the lowest scores and head circumference); by 24 months of age, only HIV infection was found to be associated with decreased neurodevelopment test performance and smaller head circumference. The authors note that as the children enter their school-age years, a more detailed examination of specific developmental domains will be possible (i.e., language, attention, memory , and behavior). Macmillan, C., Magder, L.S., Brouwers, P., et al. Head Growth and Neurodevelopment of Infants Born to HIV-1-Infected Drug-Using Women. Neurology, 57, pp. 1402-1411, 2001.

Development of Thrombocytosis in HIV+ Drug Users: Impact of Antiretroviral Therapy

Miguez-Burbano et al. report for the first time thrombocytosis in 9% of the HIV+ patients receiving highly active antiretroviral therapy (HAART) being followed in a nutritional clinical trial. Patients were evaluated every 6 months during a 2-year period (1998-2000) and blood drawn for biochemical, hematological and immunological parameters. Natural killer (NK) cells were negatively correlated with platelet counts in the total cohort ($p=0.018$) and persistently elevated with antiretroviral therapy. Chronic thrombocytosis was associated with significantly lower NK percentages ($p=0.005$). Twenty-five percent of the patients with thrombocytosis developed a cardiovascular disease. Together, these results support the proposal that HAART may increase the risk of hematological dysfunction and impact the risk of cardiovascular disease. Miguez, M.J., Burbano, X., Rodriguez, A., Lecusay, R., Rodriguez, N., and Shor-Posner, G. Platelets, 12(8), pp. 456-461, 2002.

Effect of Cocaine Use on Coronary Calcium Among Black Adults in Baltimore, Maryland

Lai et al. report for the first time significantly high levels of calcium deposits in coronary arteries of African-Americans who abuse cocaine, a finding that suggests cocaine use might promote subclinical atherosclerosis. A total of 187 African-American subjects (average age of 38; 67% men; recruited from the ALIVE cohort) were enrolled in a longitudinal study to examine if subclinical atherosclerosis was related to HIV infection and cocaine use. Data showed that of the 139 participants, about 33% had detectable coronary calcium suggesting that cocaine use was independently associated with a higher coronary calcium after controlling for age and gender. The findings suggest that cocaine use may have an important effect on the natural history of subclinical atherosclerosis and that strategies to reduce drug abuse may be critical in early prevention of cardiovascular disease in the US. Lai, S., Lai, H., Meng, Q., Tong, W., Vlahov, D., Celentano, D., Strathdee, S., Nelson, K., Fishman, E.K., and Lima, J.A.C. Am J. Cardiology, 90, pp. 326-328, 2002.

Use of HIV Protease Inhibitors Is Associated with Left Ventricular Morphologic Changes and Diastolic Dysfunction

Lai and his colleagues report for the first time that treatment of HIV/AIDS with protease inhibitors is associated with serious adverse effects such as left ventricular hypertrophy and that should be taken into consideration in the analysis of cardiac structure and function in patients with HIV infection. The investigators assessed the effects of PIs (e.g., nelfinavir, indinavir, ritonavir, saquinavir) on cardiac function and structure in 98 African-American adults aged 25-45 years with HIV infection and who were being treated with antiretroviral therapy. Substance use prevalence was quite high. Echocardiographic examinations, blood pressure and other cardiac function

examinations showed that left ventricular posterior wall (LVPW) and interventricular septum (IVS) thickness were increased along with decreased LV diastolic function in HIV-infected participants on PI therapy compared with those not on PI therapy suggesting that PI therapy is associated with ventricular structural changes and thus dysfunction. Further, cardiac diastolic dysfunction was present in the absence of systolic dysfunction. Although substance use was quite common, no significant changes in cardiac effects could be attributed to any one specific drug. Meng, Q., Lima, J.A.C., Lai, H., Vlahov, D., Celentano, D., Strathdee, S., Nelson, K., Tong, W., and Lai, S. JAIDS, 30, pp. 306-310, 2002.

Mechanism of Cocaine-induced Hyperthermia in Humans

Ron Victor and his colleagues report that in humans cocaine use increases body temperature by impairing heat dissipation mechanisms. Cocaine abuse is a major cause of life-threatening cardiovascular emergencies, inlcuding hypertensive crisis, acute myocardial infarction, and ventricular arrythmias. Furthermore, lethal effects of cocaine are also related to cocaine's propensity to cause hyperthermia, the mechanism of which is unknown. Investigators conducted a randomized double-blind, placebo-controlled crossover trial to test the effects of cocaine on body temperature regulation in seven (7) healthy, 23-37 year old, men and women. The body temperature (esophageal), skin blood flow, forearm sweat rate, heart rate, EKG, mean arterial blood pressure, cutaneous vascular conductance were all measured on the participants after receiving intranasal cocaine hydrochloride (2 mg/kg bw, 10% solution) or lidocaine (2 mg/kg bw, 10% solution, as a control). See the paper for detailed methodology. Results showed: (1) that cocaine significantly augmented the progressive increase in esophageal temperature during heat stress, but it also attenuated the increase in thermal discomfort; and (2) cocaine significantly attenuated the progressive increase in cutaneous vascular conductance and sweating during heat stress. This experiment shows that cocaine impairs the perception of heat stress further confirming that cocaine acts centrally to alter thermoregulatory responses. Participants experienced less thermal discomfort with low non-euphoric doses of cocaine even though core temperature was higher than with lidocaine. Larger doses of cocaine produce intoxication, agitation, and increased locomotor activity and heat production leading to impaired heat dissipation and toxic/fatal hyperthermia, particularly in warm environments of nightclubs or at "rave parties". Craig, G., Vongpatanasin, W., and Victor, R. Ann Intern Med., 136, pp. 785-791, 2002.

Marijuana Use and Cessation of Tobacco Smoking in Adults from a Community Sample

Ford and his colleagues from Johns Hopkins University report that those adults who smoke tobacco and marijuana find it harder to give up tobacco smoking. This analysis is based on interview data from 431 adults less than 45 years of age who reported recent tobacco smoking in the 1981 baseline interview in the house-hold based Baltimore Epidemiologic Catchment Area study and were re-interviewed 13 years later. At baseline 41% of the tobacco smokers reported marijuana ever use, 27% reported monthly use, and 9% reported daily use for 2 weeks or more in the last 30 days. At follow-up 13 years later, 79% of the original 431 smokers were still smoking tobacco. The monthly users were more likley to use tobacco than non-users. Data indicate that tobacco smokers who also smoke marijuana are less likely to have stopped tobacco smoking over a period of 13 years of follow-up. Recent use of marijuana at baseline, and especially sustained daily use, was more associated with continued tobacco smoking than past use of marijuana. Authors state that difficulty in tobacco cessation might be considered one of the most important adverse effects of marijuana use. They suggest that clinicians working with patients who are trying to stop tobacco smoking may be aided by routinely assessing history of marijuana use, particularly with the recent increase in co-smoking of marijuana and tobacco. Ford, D.E., Vu, H.T., and Anthony, J.C. Drug Alc Dep, 67, pp. 243-248, 2002.

Director's Report to the National Advisory Council on Drug Abuse - September, 2002

Research Findings - Epidemiology, Etiology and Prevention Research

Child, Parent, and Peer Predictors of Early-Onset Substance Use: A Multisite Longitudinal Study

The purpose of this study was to identify kindergarten-age predictors of early-onset substance use from demographic, environmental, parenting, child psychological, behavioral, and social functioning domains. Data from a longitudinal study of 295 children were gathered using multiple-assessment methods and multiple informants in kindergarten and 1st grade. Annual assessments at ages 10, 11, and 12 reflected that 21% of children reported having initiated substance use by age 12. Results from longitudinal logistic regression models indicated that risk factors at kindergarten include being male, having a parent who abused substances, lower levels of parental verbal reasoning, higher levels of over activity, more thought problems, and lower social problem-solving skills. Children with no risk factors had less than a 10% chance of initiating substance use by age 12, whereas children with 2 or more risk factors had greater than a 50% chance of initiating substance use. Results highlight the potential preventive value of early identification of children at risk for substance use. Kaplow, J.B., Curran, P.J., and Dodge, K.A. Journal of Abnormal Child Psychology, 30(3), pp. 199-216, 2002.

Part-time Work, Social Activities, Health Behaviors, and Substance Use

University of Michigan researchers examined adolescents' part-time work intensity and its relation to participation in various activities as well as substance use. Numerous studies have found that part-time work during adolescence is associated with higher rates of cigarette, alcohol, and illicit drug use. The investigators contrasted two hypotheses regarding mechanisms underlying this observation (1) the "time trade-off perspective," and (2) "the precocious development perspective." Nationally representative data were drawn from the Monitoring the Future project from 8th, 10th and 12th grade students (overall N approximate to 380,000) to address the research questions. Work intensity was found to be linked to more time spent on unstructured social activities, and to less time spent engaged in sports, health behaviors, and school-related activities. Social time use and health behaviors were found to partially mediate the relationship between work hours and substance use. Overall, results provide evidence for a combination of both perspectives. Safron, D.J., Schulenberg, J.E., and Bachman, J.G. Part-Time Work and Hurried Adolescence: The Links Among Work Intensity, Social Activities, Health Behaviors, and Substance Use. Journal of Health and Social Behavior, 42, pp. 425-449, 2001.

Community Epidemiology Work Group

The 52nd biannual meeting of the Community Epidemiology Work Group (CEWG), chaired by Nicholas J. Kozel, was held in Philadelphia, PA on June 11-14, 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

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community health data, local and State survey information, and findings from focus groups and qualitative research studies. The following are highlights from the meeting:

Cocaine/Crack indicators remained high, with a possible resurgence in Boston, increases in Miami and New York, and decreases or stabilization in other CEWG areas.

Heroin indicators increased in Atlanta, Miami, Minneapolis, New Orleans, New York, and Philadelphia and remained high in areas such as Boston, Baltimore, and San Francisco.

Narcotic Analgesic Indicators, especially narcotic analgesics including hydrocodone and oxycodone, continue to rise. DAWN death mentions involving narcotic analgesics/ combinations peaked in 16 CEWG areas, and in 8, exceeded the death mentions for cocaine and heroin.

Marijuana indicators increased in Chicago, Honolulu, Minneapolis, New York, Philadelphia, Phoenix, St. Louis, and San Francisco, but leveled off in other CEWG areas.

Methamphetamine indicators continue to remain at elevated levels in Hawaiian, West Coast, and Southwest CEWG areas. High proportions of adult female arrestees tested methamphetamine- positive in Honolulu, San Diego, and Phoenix (45, 36, and 29 percent, respectively). Rates of DAWN ED methamphetamine/speed mentions per 100,000 population were highest in San Francisco (14) and San Diego (13).

MDMA (methylenedioxymethamphetamine or "ecstasy") indicators continue to rise in most CEWG areas and to spread beyond the young White populations frequenting "raves." Past-year use by 12th graders rose from 5.6 percent in 1998 to 8.2 percent in 2000 in the most recent Monitoring the Future Study, and large percentage increases in lifetime use are estimated from National Household Survey data. Several CEWG sites continue to report that ecstasy is often adulterated with drugs other than MDMA.

Drug Treatment as a Crime Fighting Tool

The researchers model and empirically investigate the extent to which a change in drug use that results from treatment reduces crime and whether a change in drug use is causally related to change in crime. They analyze the change in drug use and crime pre and post treatment in a multi-site data set of 3,502 inner-city drug users entering treatment. Drug treatment apparently may be an effective crime-fighting tool. Treatment reduces not only the crime of drug possession but also crime-for-profit. Bonet, M.J., Sindelar, J.L. The Journal of Mental Health Policy and Economics, 4, pp. 175-188, 2001.

Maternal Smoking During Pregnancy: Not a Stable Phenomenon

Pickett and her colleagues examined smoking fluctuation during pregnancy in the Family Health and Development Project (FHDP), a prospective study of 92 pregnant women, and the National Health Interview Survey 1991 Pregnancy and Smoking Supplement (NHIS-S), a population-based survey of women who had given birth in the previous five years. The authors examined categories of amount smoked for each month in the FHDP and fluctuations in overall smoking status across pregnancy in the NHIS-S. Fluctuations in smoking status were substantial, only 11.5% of women in the FHDP had consistent smoking status throughout pregnancy. While many women quit or reduced their smoking upon learning of their pregnancy (58%), nearly half changed smoking status multiple times. In the NHIS-S, first quit attempts were most frequent in the first trimester. Nearly 40% of women made a serious quit attempt but 44% relapsed during pregnancy. Among women who quit for >1 week, the duration of time off cigarettes varied from 1 to 2 weeks (34%) to 8+ weeks (32%). Smoking during pregnancy is a complex and variable behavior for many women. Average or one-time measures of smoking may lead to substantial misclassification of fetal exposure. The determinants of smoking fluctuation and the significance of multiple variations in dosage and timing of exposure for predicting the risk of adverse outcomes deserve further study. Pickett, K.E., Wakschlag, L.S., and Leventhal, B.L. Maternal Smoking During Pregnancy: Not a Stable Phenomenon. Society for Pediatric and Perinatal Epidemiologic Research, Paediatric and Perinatal Epidemiology, 15, A1-A38, 2001.

Genetic and Environmental Factors in Cannabis Use

This study used data from a national probability sample of twins and siblings to

replicate findings from three prior population-based twin studies regarding genetic and environmental contributions to cannabis use. Monozygotic twins showed the greatest resemblance for last year cannabis use, with significant but weaker resemblance between dizygotic twins and among siblings. Evidence was strongest for a genetic contribution and likely supportive of a family-environment role as well. The findings were consistent with the prior twin studies and thus validate use of such samples to study gene and environment contributions to understanding drug abuse. Kendler, K.S., Neale, M.C., Thornton, L.M., Aggen, S.H., Gilman, S.E., and Kessler, R.C. Cannabis Use in the Last Year in a US National Sample of Twin and Sibling Pairs. Psychological Medicine, 32, pp. 551-554, 2002.

A Novel Opioid Maintenance Program for Prisoners: Preliminary Findings

Effective post incarceration treatment for individuals with preincarceration heroin dependence is urgently needed because relapse typically follows release. This article presents first-year findings from a unique 2-year pilot study of opioid agonist maintenance treatment initiated in prison and continued in the community. Incarcerated males with preincarceration heroin dependence were randomly assigned to Levo-alpha-acetylmethadol (LAAM) maintenance or control conditions 3 months before release. Approximately 92% of eligible inmates volunteered to participate; 36 of 58 subjects who were eligible and randomly assigned to LAAM maintenance successfully initiated treatment. Twenty-eight of these continued on LAAM until release; 22 (78.6%) entered community-based maintenance treatment; and 11 (50%) remained in treatment at least 6 months post release. Changes in LAAM's labeling, because of its association with cardiac arrhythmias now makes it a second-line treatment for heroin dependence, unsuitable for treatment initiation. Nonetheless, study findings may also be applicable to methadone maintenance treatment, suggesting such treatment may be a promising means of engaging prisoners with preincarceration heroin dependence into continuing treatment. Kinlock, T.W., Battjes, R.J., Schwartz, R.P., J Subst Abuse Treat., 22(3), pp. 141-147, 2002.

Sensation Seeking, Lower Self Esteem, and Early Substance Use Associated with Early Pubertal Onset

Structured questionnaires were administered to 1,002 subjects (571 females and 431 males) who were followed from the 6th to the 10th grades and again at age 20 to investigate the relationship between early pubertal onset, substance use, sensation seeking, and self-esteem. In females, early pubertal onset was associated with greater cigarette use and lower self-esteem. In males, early pubertal onset was associated with elevated alcohol use and higher sensation seeking, with the opposite trends for late pubertal onset. Martin, C., Logan, T.K., Leukefeld, C., Milich, R., Omar, H., and Clayton, R. Adolescent and Young Adult Substance Use: Association With Sensation Seeking, Self Esteem and Retrospective Report of Early Pubertal Onset. A Preliminary Examination. International Journal of Adolescent Medicine & Health, 13(3), pp. 211-219, 2001.

Early Pubertal Maturation and Onset of Substance Use in Female Early Adolescents

Data from the National Longitudinal Study of Adolescent Health found important differences between early maturing females and their on-time and late-maturing counterparts in initiation of substance use . Twenty percent of the 7th grade females were identified as early maturers based on body changes (increased breast size and body curviness). During 7th grade, females in the early-maturing group were three times more likely to be in the most advanced group of substance users (involving alcohol use, drunkenness, cigarette use, and marijuana use) than are those in the on-time/late groups. Prevalence rates indicate that early maturers are more likely to have tried alcohol, tried cigarettes, been drunk, and tried marijuana. Prospective findings show that early developers are significantly more likely to transition out of the "No Substance Use" stage between 7th and 8th grade (47% for early developers versus 22% for on-time and late developers). In addition, early developers are more likely to advance in substance use in general, regardless of their level of use at grade 7. Lanza, S.T. and Collins, L.M. Pubertal Timing and the Onset of Substance Use in Females During Early Adolescence. Prevention Science, 3(1), pp. 69-82, 2002.

Elevated Testosterone Levels and Nicotine Use In Young Women

The relationship of testosterone levels, carbon monoxide (CO) levels, current and adolescent nicotine use, and histories of pubertal onset was examined in 30 young

adult female smokers. Subjects completed questionnaires regarding nicotine use in the 7th through 10th grades, and again at age 21 as part of a cohort study of drug use. In addition, history of pubertal onset was obtained at age 21, as were testosterone and CO levels. Testosterone levels were positively correlated with cigarette use in the last 30 days, CO levels, and cigarette use reported in the 7th and 10th grades, and negatively correlated with age of pubertal onset. Martin, C., Logan, T.K., Portis, C., Leukefeld, C.G., Lynam, D., Staton, M., Brogli, B., Flory, K., and Clayton, R.R. The Association of Testosterone with Nicotine Use In Young Adult Females. Addictive Behaviors, 26(2), pp. 279-283, 2001.

Stress and Smoking in Adolescence: A Test of Directional Hypotheses

This study conducted a comparative test of the hypotheses that (a) stress is an etiological factor for smoking and (b) cigarette smoking causes increases in stress. Participants were a sample of 1,364 adolescents, initially surveyed at mean age 12.4 years and followed at three yearly intervals. Measures of negative affect, negative life events, and cigarette smoking were obtained at all four assessments. Latent growth modeling showed negative affect was related to increase in smoking over time; there was no path from initial smoking to change in negative affect. Comparable results were found for negative life events, with no evidence for reverse causation. Wills, T.A., Sandy, J.M., and Yaeger, A.M. Health Psychology, 21(2), pp. 122-30, 2002.

Childhood Psychiatric Disorders Precede Alcohol and Opioid Dependence

This study used a retrospective design and a clinical sample of 47 adults in treatment for opioid or alcohol dependence, to evaluate the developmental relationship between substance use disorders and psychopathology. The majority of subjects reported psychopathology beginning in childhood, often prior to onset of drug use disorder. Several disorders typically onset before substance use disorder: attention deficit/hyperactivity disorder, multiple anxiety, and disruptive disorders. Depressive and bipolar disorders typically onset after substance use disorder. These findings add to the literature on child psychopathology risk factors for drug abuse, and point to possible opportunities for prevention and early intervention in childhood. Hahesy, A.L., Wilens, T.E., Biederman, J., Van Patten, S. L., and Spencer, T., Temporal Association Between Childhood Psychopathology and Substance Use Disorders: Findings from a Sample of Adults with Opioid or Alcohol Dependency. Psychiatry Research, 109, pp. 235-253, 2002.

Substance Use Outcomes of Childhood Learning Disabilities and ADHD

This preliminary study is one of very few to examine learning disabilities as a possible risk factor for substance use and related disorders. A clinic sample of 109 children with ADHD was followed into adolescence. Substance use was not predicted by childhood diagnoses of reading or math disability or by IQ/achievement discrepancy in children with ADHD. However, level of cognitive functioning may be an important predictor of later substance use disorders for children with ADHD. Children with ADHD who had higher IQs were more likely to try cigarettes, smoke daily, and have their first drink or cigarette at an early age, while children with higher reading achievement were less likely to develop alcohol disorders. Thus, this preliminary work points to possible avenues for identifying subgroups of children at increased risk for later substance abuse. Molina, B.S.G., and Pelham, W.E. Substance Use, Substance Abuse, and LD Among Adolescents with a Childhood History of ADHD. Journal of Learning Disabilities, 34, pp. 333-342, 2001.

Early Drug Use Predicted by Low Birth Weight

The authors used a prospective design and community-based sample to assess whether low birth weight predicted early drug use. A sample of 473 low birth weight and 350 normal birth weight children were assessed at ages 6 and 11. Early onset of drug use was significantly higher for low birth weight boys than for normal birth weight boys, and this finding held even when controlling for potential mediators or confounders such as IQ, externalizing disorders, ADHD, and maternal smoking. Thus, low birth weight in boys may prove to be a useful vulnerability marker for early drug use. Chilcoat, H.D., and Breslau, N. Low Birth Weight as a Vulnerability Marker for Early Drug Use. Experimental and Clinical Psychopharmacology, 10, pp. 104-112, 2002.

Four-Year Follow-Up of Multisystemic Therapy with Substance-Abusing and Substance-Dependent Juvenile Offenders

The authors examined the 4-year outcomes of an evidence-based treatment of substance-abusing juvenile offenders. Eighty of 118 substance-abusing juvenile offenders participated in a follow-up 4 years after participating in a randomized clinical trial comparing Multisystemic Therapy with usual community services. A multimethod (self-report, biological, and archival measures) assessment battery was used to measure the criminal behavior, illicit drug use, and psychiatric symptoms of participating young adults. Analyses demonstrated significant long-term treatment effects for aggressive criminal activity (0.15 versus 0.57 convictions per year) but not for property crimes. Findings for illicit drug use were mixed, with biological measures indicating significantly higher rates of marijuana abstinence for MST participants (55% versus 28% of young adults). Long-term treatment effects were not observed for psychiatric symptoms. These findings provide some support for the long-term effectiveness of Multisystemic therapy with substance-abusing juvenile offenders. Henggeler, S.W., Clingempeel, W.G., Brondino, M.J., and Pickrel, S.G. J Am Ac Child and Adoles Psychiatry, 41(7), pp. 868-874, 2002.

Meta-Analysis Finds Truancy Best Risk Indicator For Youth Substance Use

Increasingly schools are held responsible for implementing effective health promotion activities, such as drug abuse prevention efforts funded through the federal Safe and Drug-Free Schools program. Consequently, school districts use student surveys as a method for assessing trends and evaluating effects of programs on behavior. Because cost and practical concerns often preclude consistent population-based school survey sampling, risk indicators provide an essential tool in analyzing needs and selecting program evaluation measures. This paper examines three risk measures associated with substance use from among those commonly assessed by school surveys: truancy, grade point average, and recent sexual intercourse. Measures were compared using meta-analysis techniques, to assess their reliability across different survey instruments, different communities, and different points in time. Truancy was judged superior, because of its strong predictive value, particularly among younger students, and because rates can be compared to school records to assess sampling validity over time. Hallfors, D., Vevea, J.L., Iritani, B., Cho, H., Khatapoush, S., and Saxe, L. Truancy, Grade Point Average, and Sexual Activity: A Meta-Analysis of Risk Indicators for Youth Substance Use. Journal of School Health, 72(5), pp. 205-211, 2002.

Influence of Peers on Substance Use Continues Into Young Adulthood

Longitudinal data were collected from 294 young adults, ages 19-25, and a same- and opposite-gender best friend or mate across three assessments. Analysis assessed the similarity in drug use patterns between the young adult and his or her peers and the peers' influence on the young adult's drug use. Patterns of cigarette use, alcohol use, binge drinking and, in most cases, marijuana use were similar between the young adult and peers. In prospective analyses, peer use predicted young adult cigarette use, binge drinking and problem use by the young adults. Results were generally consistent across genders and for both same- and opposite-gender peers. Findings emphasize the contribution of peer influence to young adult substance use. Andrews, J.A., Tildesley, E. Hops, H. and Li, F.Z. Health Psychology, 21(4), pp. 349-357, 2002.

Peer Influence is Greater for Those Who Use Less in Earlier Adolescence

This study drew data from a national data set assessing alcohol use between the ages of 14 and 18. Results of growth mixture modeling revealed two developmental trajectories for alcohol use with significant differences in levels of use. Further analyses revealed that exposure to deviant peers had a differential effect on the alcohol use of those in the distinct groups. The prospective influence of deviant peers was greater for those adolescents who had lower initial use. Thus, the study suggests that there is heterogeneity in the developmental trajectory of adolescent alcohol use and that the influence of peers varies depending on the initial status of alcohol use and the subsequent trajectory. Li, F.Z., Barrera, M. Hops, H., and Fisher, K.J., Jouranl of Behavioral Medicine, 25(3), pp. 293-315, 2002.

Family Effects Decline While Peer Effects Increase Throughout Adolescence

This study examined the effects of sociodemographic, family and peer predictors on the developmental patterns of illicit drug initiation from ages 12-21. A diverse urban sample of 808 children was surveyed longitudinally beginning at age 10 in 1985 through age 21 in 1996. Analyses revealed that the risk for initiating illicit drug use increased steadily from the ages of 12 to 21. High family conflict, low family bonding, and high peers' antisocial activities predicted higher risk of initiation across this developmental period. The effect of family bonding began to decline after age 18, while the effect of peers' antisocial activities began to increase after age 15. Few gender and ethnic differences were found. Implications for prevention include the need to include family and peer factors in developmentally appropriate ways in interventions. Guo, J., Hill, K.G., Hawkins, J.D., Catalano, R.F., and Abbott, R.D. J. Am. Acad. Child Adolesc Psychiatry, 41(7), pp. 838-845, 2002.

Secure Attachment to Friends Predicts Fewer Problem Behaviors

Using a sample of low achieving African-American youth, this study explored how stability and change in adolescents' internal working models of their close friendships was related to functioning in multiple domains. These included psychological well-being, participation in problem behaviors, negative peer influences, school attitudes, and sexual behavior. Results indicated that adolescents with stable secure friendship orientations functioned better than those with insecure working models across all domains. The group for whom attachment status changed over time either resembled the stable-insecure group or fell between the two stable groups. The findings suggest that adolescents' friendship orientations change over time and are associated with deleterious outcomes. Further, they extend attachment theory to demonstrate the importance of secure attachment in relations with friends. Miller, A.L., Notaro, P.C., and Zimmerman, M.A. J. of Social and Personal Relationships, 19, pp. 207-233, 2002.

Relationships With Natural Mentors Associated with Resiliency

Drawing from a sample of 770 adolescents from a Midwestern city, this study found that 52% reported having a natural mentor. Those with natural mentors were less likely to use alcohol, smoke marijuana, or be involved in nonviolent delinquency, and had more positive attitudes toward school. Natural mentors had no apparent effect on anxiety or depression. Using the resiliency theory framework, natural mentors were found to have compensatory but not protective effects on school attitudes. Direct and indirect (mediated) effects were found for problem behaviors and school attitudes. This study supports the potential importance of natural mentors. Zimmerman, M.A., Bingenheimer, J.B., and Notaro, P.C. Am J of Community Psychology, 30, pp. 221-243, 2002.

A Case Study of Transmission of Conduct Norms for Drug Abuse, Sexual Violence, and Violence Across Four Generations of African-American Women

This case report ethnographic study describes how conduct norms for drug abuse, sexual exploitation, and violence are transmitted across generations in severely distressed households in inner-city New York through abuse, neglect, and negative role models. Young girls growing up in these households learn to accept violent physical and sexual assault, substance abuse and sales, and unstable households as effective conduct norms. The continual assault on young girls often leads to mortification of self, characterized by acceptance of their situation and socialization to these behaviors in adulthood. This socialization to accept and expect abusive relationships results in their treating their children no better than they had been treated as children and maintains the intergenerational transmission process of drug abuse/sales, sexual exploitation, and violence. This study suggests that addressing the problems of the inner city will necessitate, in addition to providing needed services such as improved education, policing, and job training, a cultural change in young girls growing up in distressed households. Dunlap, E., Golub, A., Johnson, B.D., and Wesley, D. Intergenerational Transmission of Conduct Norms for Drugs, Sexual Exploitation and Violence: A Case Study. Brit. J. Criminol., 42, pp. 1-20, 2002.

Family Functioning, Peer Affiliation, and Problem Behaviors in Children of Antisocial and Substance Dependent Fathers

This study examined associations between paternal substance dependence (SD), paternal antisocial personality disorder (APD), family functioning, peer environments,

and child psychopathology. Children of fathers with SD (with or without APD) faired worse than those without SD on several measures of family functioning. Children of fathers with both SD and APD demonstrated the highest levels of externalizing and internalizing psychopathology as well as greater affiliation with deviant peers, which, in turn, was associated with psychopathology. Regression models indicate that paternal substance dependence/antisocial personality disorder status and the child's affiliation with deviant peers were most robustly associated with child psychopathology. Results support a developmental model of antisocial problems that implicates dysfunctional family processes and deviant peer associations as key factors in the development of antisocial problems. Research is needed to develop interventions that effectively enhance familial functioning and healthy peer relations. Moss, H.B., Lynch, K.G., Hardie, T.L., and Baron, D.A. American Journal of Psychiatry, 159, pp. 607-614, 2002.

Adolescent Substance Use and Adulthood Antisocial Behavior

This general-population, retrospective study investigated the plausibility of causal relationships between adolescent drug and alcohol misuse and antisocial personality disorder (ADP) among subgroups who reported childhood-onset conduct problems (CP), adolescent-onset CP, or no more than one symptom of CP. Data from the Epidemiological Catchment Area Study (N = 8,724) suggested that persons with childhood-onset CP are at much greater risk for ADP than persons with adolescent-onset CP. Also, being drunk by age 18 or having a drug use-related symptom before age 18 increased AAB risk, even after controlling for CP history and substance use-related disorder in adulthood. Results implicate both early-onset behavior problems and substance use problems as potential etiologic factors in adult antisocial behavior. Ridenour, T.A., Cottler, L.B., Robins, L.N., Compton, W.M., Spitznagel, E.L., and Cunningham-Williams, R.M. Journal of Abnormal Psychology, 111, pp. 144-155, 2002.

Meta-Analysis of Genetic and Environmental Influences on Antisocial Behavior

A meta-analysis of 51 twin and adoption studies was conducted to estimate the magnitude of genetic and environmental influences on antisocial behavior. The best fitting model included moderate proportions of variance due to additive genetic influences (.32), nonadditive genetic influences (.09), shared environmental influences (.16), and nonshared environmental influences (.43). The magnitude of familial influences (i.e., both genetic and shared environmental influences) was lower in parent-offspring adoption studies than in both twin studies and sibling adoption studies. Age and assessment method, but not gender, were significant moderators of the magnitude of genetic and environmental influences on antisocial behavior. Rhee, S.H., and Waldman, I.D. Psychological Bulletin, 128(3), pp. 490-529, 2002.

Early Onset Delinquency and Substance Dependence

This study used an epidemiological twin sample to examine delinquency subtypes in relation to the development of substance dependence. Alcohol, nicotine, and cannabis dependence symptoms were examined in 36 early-onset delinquent, 86 late onset delinquent, and 25 non-delinquent boys over a six year span from ages 11 to 17. Early onset delinquents showed earlier onset and faster rate of increase in cannabis and nicotine dependence, and both delinquent groups showed more rapid increase in alcohol dependence symptoms. Identifying subtypes at greater risk holds potential for early targeted interventions. Taylor, J., Malone, S., Iacono, W.G., and McGue, M. Development of Substance Dependence in Two Delinquency Subgroups and Nondelinquents From a Male Twin Sample. Journal of the American Academy of Child and Adolescent Psychiatry, 41, pp. 386-393, 2002.

Labor Supply of Poor Residents in Metropolitan Miami, Florida: The Role of Depression and the Co-Morbid Effects of Substance Use

A unique set of survey data was collected between 1996-1997 in crime-ridden and low-income neighborhoods of Miami-Dade County, Florida. A targeted sampling strategy was used to recruit chronic drug users (including injection drug users) and non-drug users to examine local health care delivery system characteristics in relation to the population of substance users. The final analysis sample included 1,274 adults aged 18 to 65. Depression significantly decreased the probability of being employed. Specifically, depression reduced the probability of employment by an average of 19 percentage points in both modes, from a sample average of 43 percent of the non-depressed to 24 percent for the depressed. Estimates from the Tobit models revealed

that depression also significantly reduced the number of weeks worked. The findings also showed that the effects of depression on employment and annual weeks worked may be overestimated if the analysis does not account for the comorbid influence of substance use. Alexandre, P.K., and French, M.T. The Journal of Mental Health Policy and Economics, 4, pp. 161-173, 2001.

The Relationship Between Sexual and Physical Abuse and Substance Abuse Consequences

The authors examined the relationship between a history of physical and sexual abuse and drug and alcohol related consequences. Data came from 359 male and 111 female subjects recruited from an inpatient detoxification unit. The Inventory of Drug Use Consequences measured negative life consequences of substance use. Eighty-one percent of women and 69% of men reported past physical/sexual abuse, starting at a median age of 13 and 11, respectively. Physical and sexual abuse was associated with more substance abuse consequences. For men, age 17 or younger, age at first abuse was significantly associated with more substance abuse consequences than an older age at first abuse, or no abuse. For women, the association of abuse with substance use consequences was similar across all ages. Liebschutz, J., Savetsky, J.B., Saitz, R., Horton, N.J., Lloyd-Travaglini, C., and Samet, J.H. Journal of Substance Abuse Treatment, 22, pp.121-128, 2002.

New Ways to Handle Multivariate Linear Mixed-Effects Models With Missing Values

This article presents new computational techniques for analyzing multivariate longitudinal or clustered data with missing values which will benefit prevention researchers. Current methodology for analyzing linear mixed-effects models can accommodate imbalance or missing data in a single response variable, but it cannot handle missing values in multiple responses or additional covariates. A multivariate extension of a popular linear mixed-effects model is used to create multiple imputations of missing values for subsequent analyses by a straightforward and effective Markov chain Monte Carlo procedure. A new EM algorithm for parameter estimation that converges more rapidly than traditional EM algorithms is derived. Schafer, J.L. and Yucel, R. M. Computational Strategies for Multivariate Linear Mixed-Effects Models With Missing Values. Journal of Computational and Graphical Statistics, 11(2), pp. 421-442, 2002.

New Measurement Models for Dynamic Regimes

A dynamic intervention regime is a list of rules for how the level of intervention will be tailored over time to an individual's changing problem severity. In general, individuals who receive the highest level of intervention are the persons with the greatest problem severity and need. Thus, there is planned selection of the intervention dose. In addition to the planned selection, staff judgment results in unplanned selection of the intervention level. The methodology presented in this article allows the estimation of a mean response to a dynamic intervention regime under the assumption of sequential randomization. Murphy, S.A., Van Der Laan, and Robins, J.M. Marginal Mean Models for Dynamic Regimes. Journal of the American Statistical Association, 96, pp. 1410-1423, 2002.

Gender Differences in Relation Between Social Processes and Adolescent Sexual Behavior

This study examined gender-specific contextual and socioeconomic predictors of the timing of first intercourse among low achieving African-American youth. This three year longitudinal sample was comprised of 558 African-American high school students. For women, the significant predictors of timing of intercourse include age, mother's education, time with mother, and involvement in church activities. For males, the significant factors were school achievement, an interaction between living in an intact family and time with father, participation in family decision-making, and neighborhood poverty level. Males and females are differently affected by social control processes and neighborhood poverty plays a significant role in young African-American males' sexual behavior. Ramirez-Valles, J., Zimmerman, M.A., and Juarez, L. Youth and Society, 33(3), pp. 418-441, 2002.

School-Based vs. Family and School Based Prevention Outcomes

This study evaluated the effects of combining family and school-based competency-training intervention components on substance initiation . Thirty-six rural schools

were randomly assigned to 1 of 3 conditions: (a) the classroom-based Life Skills Training (LST) program and the Strengthening Families Program for Parents and Children 10-14, (b) LST only, and (c) a control condition. Outcomes were examined one year post intervention, using a substance initiation index of lifetime use of alcohol, cigarettes, and marijuana and rates of use of individual substances. Intervention-control contrasts showed significant effects for both the combined and LST-only interventions on the substance initiation index and on marijuana initiation. The combined intervention students had lower substance initiation rates than the LST-only students, however differences between the two intervention conditions were significance only for the new alcohol user rate. Relative reduction rates for alcohol initiation were 30% for the combined intervention and 4% for LST only. These preliminary results suggest that the family-focused interventions may be particularly important in preventing the initial transition into alcohol use. Spoth, R.L., Redmond, C., Trudeau, L., and Shin, C. Longitudinal Substance Initiation Outcomes for a Universal Preventive Intervention Combining Family and School Programs. Psychology of Addictive Behaviors, 31, pp. 129-134, 2002.

Alcohol and Gambling Pathology among U.S. Adults: Prevalence, Demographic Patterns and Comorbidity

This study was designed to determine the prevalence and demographic distribution of problem gambling, pathological gambling, alcohol abuse and alcohol dependence in the United States, and to examine the co-occurrence of gambling pathology and alcohol pathology in the United States. A representative sample (N = 2,638) of U.S. adults age 18 and older was surveyed in the year 2000 using computer-assisted telephone interviewing. Gambling pathology and alcohol dependence were assessed by the South Oaks Gambling Screen (SOGS) and the Diagnostic Interview Schedule (DIS). Current pathological gambling had an overall prevalence of 1.3% as measured by the DIS and 1.9% as measured by the SOGS, with a higher prevalence among minorities and lower socioeconomic status (SES) respondents. Current pathological gambling and alcohol dependence were correlated, and the highest correlation was found among higher SES respondents. These epidemiologic data indicate that the prevalence of current pathological gambling in the United States is higher than previously estimated, with minorities and lower SES Americans have higher than average rates. Welte, J., Barnes, G., Wieczorek, W., Tidwell, M.C., and Parker, J. Journal of Studies on Alcohol, 62(5), pp. 706-712, 2001.

Adolescent Binge-Drinking Trajectories and Substance Abuse in Adulthood

This study describes binge-drinking trajectories from adolescence to early adulthood in 238 children of alcoholics and 208 controls. Mixture modeling identified three trajectory groups of drinkers: early-heavy (early onset, high frequency), late-moderate (later onset, moderate frequency), and infrequent (early onset, low frequency). The early-heavy group was characterized by parental alcoholism and antisociality, peer drinking, drug use, and (for boys) high levels of externalizing behavior, but low depression. The infrequent group was elevated in parent alcoholism and (for girls) adolescent depression, whereas the nonbinger and late-moderate groups showed the most favorable adolescent psychosocial variables. All three drinking trajectory groups raised risk for later substance abuse or dependence compared with the nonbingers, with the early-heavy group at highest risk. Chassin, L., Pitts, S.C., and Prost, J. Journal of Consulting and Clinical Psychology, 70(1), pp. 67-78, 2002.

Most Rape Victims Express Rape-Related HIV Risk Concerns

A sample of 62 recent rape victims who had received post-rape medical care were interviewed an average of 6 weeks after being raped to assess fear or concern about contracting HIV as a result of rape. Fifty-seven of the 62 women (91.9%) reported some degree of initial fear or post-rape concern about contracting HIV; and 45 of the 62 women (72.6%) reported that they were extremely fearful or concerned about contracting HIV. Women who were extremely fearful or concerned about contracting HIV were more likely to have been raped by a stranger. Reported fear/concern was not simply a function of current intensity of intrusive or avoidance symptoms of post-traumatic stress disorder. Fifty-one women (82.3%) wanted more information about HIV at post-rape medical treatment visits. Resnick, H., Monnier, J., Seals, B., Holmes, M., Nayak, M., Walsh, J., Weaver, T.L., Acierno, R., and Kilpatrick, D.G. Rape-Related HIV Risk Concerns Among Recent Rape Victims. Journal of Interpersonal Violence, 17(7), pp. 746-759, 2002.

Patterns of Assault In a Sample of Recent Rape Victims

Intimate partner assault patterns are not well understood in recent rape victims. In an effort to examine these patterns, 47 rape victims seeking care from a forensic medical examination facility were sampled across three assessment points (6 weeks post-assault, 3 months post-assault, and 6 months post-assault). Index rape, prior rape and physical assault, and new rape and subsequent physical assault were classified by victims' relationships to their perpetrators. At the initial medical exam, 17 women had been past victims of domestic violence. Six women were victims of intimate partner violence during the 6 months after the index rape. Monnier, J., Resnick, H.S., Kilpatrick, D.G., Seals, B., and Holmes, M. Violence against Women, 8(5), pp. 585-596, 2002.

The Relationship Between Distress and Resource Loss Following Rape

Rape is a prevalent traumatic stressor, with an estimated 12 million U.S. adult women reporting the experience of rape in their lifetimes. It has been identified as a risk factor for development of a range of negative mental health and physical health outcomes. Previous studies have demonstrated that women who are victims of interpersonal violence experience subsequent disruption in resources (e.g., unemployment, reduced income, divorce) following victimization. The present study examined the impact of resource loss on violent crime victims. Subjects were 57 women over the age of 18 who were recent victims of rape. Results indicate that psychological distress is followed by increased resource loss for rape victims. These results suggest that distress may be an underlying mechanism for resource loss in victims of sexual assault. Monnier, J., Resnick, H.S., Kilpatrick, D.G., and Seals, B. Violence & Victims, 17(1), pp. 85-92, 2002.

Alcohol and Drug Use among College Students

Monitoring the Future (MTF) researchers at the University of Michigan reported on the extent of alcohol use and other drug use among American college students. MTF plus four additional data sources were examined to estimate recent levels of alcohol and other drug use among college students: Harvard School of Public Health College Alcohol Study (CAS), the Core Institute (CORE), Monitoring the Future (MTF), National College Health Risk Behavior Survey (NCHRBS) and National Household Survey on Drug Abuse (NHSDA). Alcohol use rates were found to be very high among college students; approximately two of five American college students were heavy drinkers, defined as having had five or more drinks in a row in the past 2 weeks. Alcohol use is higher among male than female students. According to race/ethnicity, white students are highest in heavy drinking, black students are lowest and Hispanic students are intermediate. Use of alcohol--but not cigarettes, marijuana and cocaine--is higher among college students than among noncollege age-mates. Longitudinal data show that, while in high school, students who go on to attend college have lower rates of heavy drinking than do those who will not attend college. Both groups increase their heavy drinking after high school graduation, but the college students increase distinctly more and actually surpass their nonstudent age-mates. Trend data from 1980 to 1999 show some slight improvement in recent years. The authors concluded that, despite improvements in the past 20 years, colleges need to do more to reduce heavy alcohol use among students. O'Malley, P.M. and Johnston, L.D. Epidemiology of Alcohol and Other Drug Use among American College Students. Journal of Studies on Alcohol, Supplement 14, pp. 23-39, 2002.

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Research Findings - Services Research

A Synthesis of Welfare Reform Policy and Its Impact on Substance Users

The purpose of this study was to provide an overview of welfare reform and its impact on the substance-abusing recipient. Factors relevant to transitioning welfare recipients into the workplace, such as transportation and childcare, have special ramifications for the drug-using population. These individuals require treatment for their addictions in order to become employable. The issue of concern is that recipients may be deterred from seeking benefits by various provisions of welfare reform legislation and turn instead to other sources (including illicit activities) for sustenance. Welfare caseloads have been dropping over the past two years. However, the number of substance abusers continues to rise. Montoya, I.D. and Atkinson, J.S. Am J Drug Alcohol Abuse, 28(1), pp. 133-146, 2002.

Benefit-Cost Analysis of Addiction Treatment: Methodological Guidelines and Empirical Application Using the DATCAP and ASI

This study provides detailed methodological guidelines for using the Drug Abuse Treatment Cost Analysis Program (DATCAP) and Addiction Severity Index (ASI) in a benefit-cost analysis of addiction treatment. A representative benefit-cost analysis of three outpatient programs was conducted to demonstrate the feasibility and value of the methodological guidelines. Procedures are outlined for using resource use and cost data collected with the DATCAP. Techniques are described for converting outcome measures from the ASI to economic (dollar) benefits of treatment. Finally, principles are advanced for conducting a benefit-cost analysis and a sensitivity analysis of the estimates. DATCAP was administered at three outpatient drug-free programs in Philadelphia, PA, for 2 consecutive fiscal years (1996 and 1997). The ASI was administered to a sample of 178 treatment clients at treatment entry and at 7-months post-admission. The DATCAP and ASI appear to have significant potential for contributing to an economic evaluation of addiction treatment. The benefit-cost analysis and subsequent sensitivity analysis all showed that total economic benefit was greater than total economic cost at the three outpatient programs, but this representative application is meant to stimulate future economic research rather than justifying treatment per se. This study used previously validated, research-proven instruments and methods to perform a practical benefit-cost analysis of real-world treatment programs. The study demonstrates one way to combine economic and clinical data and offers a methodological foundation for future economic evaluations of addiction treatment. French, M.T., Salome, H.J., Sindelar, J.L., and Mclellan, A.T. Health Services Research, 37(2), pp. 433-455, 2002.

Integration and its Discontents: Substance Abuse Treatment in the Oregon Health Plan

In this article the authors examined the impact managed care had on access to integrated substance abuse treatment and physical care services for Medicaid clients. Managed care practices of 7 health plans serving Medicaid clients in the state of Oregon were explored between 1996 and 1998. Results indicated the original vision of integrating substance abuse treatment services with physical care for enrollees evolved into a multi-layered, carved-out approach. Factors working against integration included changes in the administration and management of the chemical dependency benefit, financial losses by health plans, and lack of training and

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incentives for physicians to refer clients to substance abuse treatment. Laws, K.E. and McFarland, B.H. Health Aff, 21(4), pp. 284-289, August 2002.

The Impact of Withdrawals By Medicaid Managed Care Plans on Behavioral Health Services

In 1991, there were 9.5 percent of Medicaid enrollees in some form of managed care, but by 1999, this stood at 55.6 percent with 17.8 million enrollees. The authors examined the impact when managed care plans decide to abandon the state Medicaid market. There is concern for those mental health and substance abuse patients who would have to adjust to a new approach to their care management, and continuity of care may also be threatened. Three case studies of Missouri's integrated, Oregon's carve out, and New Jersey's fee-for-service programs are discussed. These cases suggest that carve-outs and fee-for-service arrangements offer some protection against disruption to treatment when a managed care plan exits the Medicaid market. Huskamp, H.A., Garnick, D.W., Hanson, K.W., and Horgan, C. Psychiatric Services, 52(5), pp. 600-602, 2001.

Measuring Perceptions of Innovation Adoption in Drug Abuse Prevention

A 17-item scale was administered to 107 Safe and Drug Free Schools (SDFS) coordinators in 12 states as a part of a larger investigation examining the diffusion of a federal drug prevention policy. The scale was based on theory, previously validated measures, expert review, and pre-testing with SDFS coordinators. Factor analysis revealed three underlying constructs representing relative advantage/compatibility, complexity and observability. Each construct was correlated with a district's adoption of the drug prevention policy. The relative advantage/compatibility construct was especially useful in assessing policy adoption. This scale has the potential to be easily adapted for use in understanding the adoption of other health education interventions. Measuring Perceptions of Innovation Adoption: The Diffusion of a Federal Drug Prevention Policy. Pankratz, M., Hallfors, D., and Cho, H. Health Education Research, 17(3), pp. 315-326, 2002.

Cost-Effectiveness and Cost Benefit Analyses of Family-Focused Prevention

Cost-benefit and cost-effectiveness analyses of two, brief, universal family-focused interventions were conducted to assess their value for preventing alcohol use disorders. The interventions were the Iowa Strengthening Families Program (ISFP), a seven-session intervention with parents and students together, and Preparing for the Drug Free Years (PDFY), a five-session intervention focusing primarily on parents. Both interventions included instruction on parenting skills designed to support family-related protective factors and reduce family-related risk factors for substance use. Thirty-three rural schools in 19 contiguous counties were blocked on school size and randomized to ISFP, PDFY, or minimal contact control conditions. During in-home assessments, students provided self-reported data on alcohol use from which age of alcohol-use onset was calculated. Analysis involved assumptions based on expected alcohol disorder rates given alcohol initiation data in the three conditions. ISFP demonstrated a cost-effectiveness of $12,459 per case prevented, a benefit-cost ratio of $9.60 per $1 invested, and a net benefit of $5,923 per family. PDFY demonstrated a cost effectiveness of $20,439 per case prevented, a benefit-cost ratio of $5.85 per $1 invested, and a net benefit of $2,697 per family. Universal family skills training interventions have the potential to delay the onset of alcohol use and reduce societal costs of alcohol disorders. Spoth, R.L., Guyll, M., and Day, S.X. Universal Family-Focused Interventions in Alcohol-Use Disorder Prevention: Cost Effectiveness and Cost-Benefit Analyses of Two Interventions. Journal of Studies on Alcohol, 63, pp. 219-228, 2002.

Factors Associated with Adolescent Alcohol Treatment Service Use

The authors used data from the National Household Survey on Drug Abuse to examine factors associated with adolescents' use of alcohol treatment services. The majority of adolescents reporting problems related to alcohol use did not receive treatment. Among those receiving treatment, white adolescents were more likely to do so than non-white adolescents. Problems in home, school, or other settings, or associated drug use and poor health were more predictive of receiving alcohol treatment. The authors call for improved service delivery to meet the needs of adolescents with alcohol problems, as many are not receiving treatment. Wu, P.,

Hoven, C.W., Tiet, Q., Kovalenko, P., and Wicks, J. Factors Associated with Adolescent Utilization of Alcohol Treatment Services. American Journal of Drug and Alcohol Abuse, 28, pp. 353-369, 2002.

Varieties of Centralized Intake: The Portland Target Cities Project Experience

The authors examined the influence of a centralized intake system on client outcomes of alcohol and drug use, and legal and psychiatric problems as measured by the Addiction Severity Index. Data was collected at baseline, six month, and twelve month intervals following intake and compared for clients experiencing two different models of centralized intake. Centralized intake clients were more likely than provider intake clients to have legal problems, and those legal problems became fewer over time. Clients from in-jail intake, including pretreatment services and accompanied placement, showed greater initial and lower subsequent prevalence of drug, psychiatric, and legal problems than the clients of freestanding centralized intake. For all clients, higher psychiatric composite scores were powerful predictors of problems in alcohol, drug, medical, and legal areas. McFarland, B.H. and McCamant L. J of Psychoactive Drugs, 34(1), pp. 75-86, March 2002.

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Research Findings - Intramural Research

Cellular Neurophysiology Section, Cellular Neurobiology Research Branch

Effects of Cerebral Ischemia in Mice Deficient in Persephin

Persephin (PSP), a recently cloned member of the transforming growth factor superfamily (TGF) and glial cell line-derived neurotrophic factor (GDNF) subfamily, is distributed throughout the nervous system at extremely low levels and is thought to function as a survival factor for midbrain dopaminergic and spinal motor neurons *In Vivo*. Here IRP investigators report that mice lacking PSP by homologous recombination show normal development and behavior, but are hypersensitive to cerebral ischemia. A 300% increase in infarction volume was observed after middle cerebral artery occlusion. The authors found that glutamate induced Ca2+ influx, thought to be a major component of ischemic neuronal cell death, can be regulated directly by the Persephin protein (PSP) and that PSP can reduce hypoxia/reperfusion cell death *In Vitro*. Neuronal cell death can be prevented or markedly attenuated by administration of recombinant human PSP *In Vivo* before ischemia in both mouse and rat models. Taken together, these data indicate that PSP is a potent modulator of excitotoxicity in the central nervous system with pronounced neuroprotective activity. Our findings support the view that PSP signaling can exert an important control function in the context of stroke and glutamate-mediated neurotoxicity, and also suggest that future therapeutic approaches may involve this novel trophic protein. Agulnick, A.D., Haughey, N., Chang, C.-F., Zhang, Y., Backman, C., Morales, M., Mattson, M.P., Wang, Y., Westphal, H., and Hoffer, B.J., PNAS, 99, pp. 9521-9526, 2002.

Development and Plasticity Section, Cellular Neurobiology Research Branch

Analysis of Gene Expression in Schizophrenia Using DNA Microarrays

IRP investigators describe experiments performed by their group and others, in which DNA microarrays were employed to probe samples from human postmortem brain tissue to examine gene expression differences in schizophrenia. Genes for which decreases in expression were identified fell into two categories. First, decreases in the expression of genes related to presynaptic, glutamatergic, and GABAergic function have been identified. Secondly, preliminary studies have identified changes in gene expression that are suggestive of cellular stress or sub-lethal injury. The authors therefore suggest the following hypothesis. An underlying deficit in trophic, developmental, or regulatory processes in schizophrenia places stress on certain sub-populations of neurons. As a result of this cellular stress, these neurons down-regulate neurotransmitter and synaptic function. This impaired neurotransmitter and synaptic function may be directly related to the symptoms of schizophrenia. The authors suggest that an underlying defect, which has not yet been identified, may impair or stress the function of certain neurons, and is ultimately responsible for the pathophysiology of schizophrenia. Further microarray experiments with larger cohorts of subjects, and pooling of results across laboratories may lead to further insights into defects in gene expression in schizophrenia and eventually to pharmacological

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treatments based on these defects. Freed, W.J., Hyde, T.M., Kleinman, J.E., Becker, K.G., and Vawter, M.P. Trends in Evidence Based Neuropsychiatry, 4, pp. 48-57, 2002.

Gene Expression Profiling in Drug Abuse

Recent advances in the use of microarrays for massive parallel screening for gene expression provides an opportunity to develop an understanding of complex processes of brain function on the genomic and molecular level. Microarrays involve the use of libraries of hybridization targets, arrayed on a fixed surface, to measure gene expression for many genes simultaneously in cells or tissue samples. Both small and large scale arrays are commercially available from a number of sources. In addition, IRP investigators have developed a specialized "neuroarray" comprised of 1152 cDNAs selected for relevance to brain function. The authors used the neuroarray to examine differences in gene expression in postmortem tissue from human subjects who had abused cocaine. Subsequent animal studies of chronic cocaine administration may help to determine the degree to which brain adaptations seen in human subjects can be modeled in animal studies. Understanding the process through which drugs of abuse produce adaptations in brain function may help to identify methods for intervening to influence drug addiction. Freed, W.J., Lehrmann, E., Hyde, T.M., Kleinman, J.E., Vawter, M.P., and Becker, K. Proceedings of the ONDCP International Technology Symposium entitled "Counterdrug Research and Development: Technologies for the Next Decade", 1, pp. 119-131, 2001.

Behavioral, Hormonal and Histological Stress Markers of Anxiety-separation in Postnatal Rats are Reduced by Prepro-thyrotropin-releasing hormone 178-199

IRP scientists investigated in the present study whether systemic injections of prepro-thyrotropin-releasing-hormone 178--199 (PPTRH 178--199) in postnatal 3-days old rat pups can provide ameliorative effects in a model of anxiety-separation disorder. The pups were individually separated from their mother and placed in a novel environment. PPTRH 178--199-treated animals started exploring the novel environment in a significantly shorter time and elicited significantly less distress vocalizations than control animals. PPTRH 178--199-treated animals also had markedly lower serum adrenocorticotropic hormone and corticosterone compared to control animals. Furthermore, we observed a significant increase in PPTRH 178--199 immunoreactive cell bodies in the hypothalamus of PPTRH 178--199-treated animals compared to controls, suggesting that the peptide crossed the blood--brain barrier. PPTRH 178--199 treatment can help to reduce behavioral and hormonal disturbances associated with anxiety-separation situations. Stahl, E.E., Redei, E., Wang, Y., and Borlongan, C.E. Neuroscience Letters, 321, pp. 85-89, 2002.

T155g-immortalized Kidney Cells Produce Growth Factors and Reduce Sequelae of Cerebral Ischemia

Fetal rat kidney cells produce high levels of glial-derived neurotrophic factor (GDNF) and exert neuroprotective effects when transplanted into the brain in animal models of Parkinson's disease and stroke. The purpose of the present experiment was to produce kidney cell lines that secrete GDNF. Genes encoding two truncated N-terminal fragments of SV40 large T antigen, T155g and T155c, which does not code for small t antigen, were used. T155g was transduced into E17 cultured fetal Sprague-Dawley rat kidney cortex cells using a plasmid vector, and T155c was transduced with a plasmid and a retroviral vector. Sixteen clones were isolated from cultures transfected with the T155g-expressing plasmid. No cell lines were obtained with T155c. Four clones produced GDNF at physiological concentrations ranging from 55 to 93 pg/ml of medium. These four clones were transplanted into the ischemic core or penumbra of rats that had undergone middle cerebral artery occlusion (MCAO). Three of the four clones reduced the volume of infarction and the behavioral abnormalities normally resulting from MCAO. Blocking experiments with antibodies to GDNF and platelet-derived growth factor (PDGF) suggested that these growth factors contributed only minimally to the reduction in infarct volume and behavioral abnormality. These cell lines may be useful for intracerebral transplantation in animal models of brain injury, stroke, or Parkinson's disease. Dillon-Carter, O., Johnston, R.E., Borlongan, C.V., Truckenmiller, M.E., Coggiano M., and Freed, W.J., Cell Transplantation, 11, pp. 251-259, 2002.

AF5, a CNS Cell Line Immortalized with an N-Terminal Fragment of SV40 Large T: Growth, Differentiation, Genetic Stability and

Gene Expression

Central nervous system progenitor cells that are self-renewing in culture and also differentiate under controlled conditions are potentially useful for developmental studies and for cell-based therapies. IRP investigators characterized growth and plasticity properties and gene expression in a rat mesencephalic cell line, AF5, that was immortalized with an N-terminal fragment of SV40 large T (T155g). For over 150 population doublings in culture, the growth rate of AF5 cells remained steady, the cells remained responsive to bFGF, and telomerase activity and telomere lengths were unchanged. While karyotype analyses revealed some chromosomal abnormalities, these were also unchanged over time; additionally, no mutations in p53 gene sequences were found, and wild-type p53 activation was normal. AF5 cells produced PDGF, TGFbeta1, TGFbeta2, and bFGF. Similar to primary progenitor cells, AF5 cells retained their plasticity in culture; they could be propagated in an undifferentiated state as "neurospheres" in serum-free media or as adherent cultures in serum-containing media, and they differentiated when allowed to become confluent. Adherent subconfluent actively growing cultures expressed a marker for immature neurons, nestin, while few cells expressed the mature neuronal cell marker betaIII-tubulin. Confluent cultures ceased growing, developed differentiated morphologies, contained few or no nestin-expressing cells, and acquired betaIII-tubulin expression. Global gene expression was examined using a 15,000 gene microarray, comparing exponential growth with and without bFGF stimulation, and the differentiated state. The AF5 cell line exhibited stable genetic and growth properties over extended periods of time, while retaining the ability to differentiate *In Vitro*. These data suggest that the AF5 cell line may be useful as an *In Vitro* model system for studies of neural differentiation. Truckenmiller, M.E., Vawter, M.P. Zhang, P., Conejero-Goldberg, C., Dillon-Carter, O., Morales, N., Cheadle, C., Becker, K.G., and Freed, W.J. Experimental Neurology, 175, pp. 318-337, 2002.

Psychobiology Section, Medications Discovery Research Branch

Comparison of Interactions of D1-like Agonists, SKF 81297, SKF 82958 and A-77636, with Cocaine: Locomotor Activity and Drug Discrimination Studies in Rodents

Recent data suggest that dopamine (DA) D1-like receptor full agonists may be potential pharmacotherapeutic agents for treating cocaine abuse. The structurally novel isochroman D1-like agonist, A-77636, was compared to those obtained with the better investigated benzazepine D1-like dopamine agonists, SKF 82958 and SKF 81297. Each D1-like agonist produced a dose-related decrease in the cocaine-induced stimulation of locomotor activity. Each of the D1-like agonists partially substituted for the subjective effects of cocaine, with maximal substitution approximating 49, 35, and 24% for SKF 81297, SKF 82958, and A-77636, respectively. Both SKF 82958 and SKF 81297 shifted the cocaine dose-effect curve to the left. In contrast, A-77636 either did not affect the cocaine dose-effect curve or shifted it to the right. All three agonists produced similar effects on cocaine-induced locomotor activity, however the discriminative-stimulus effects of cocaine were affected differently by the D1 agonists. These results suggest fundamental differences in the actions of these D1 agonists. Because A-77636 consistently attenuated the present effects of cocaine, it may prove more useful than the others as a pharmacotherapy to treat cocaine abuse. Chausmer, A.L. and Katz, J.L. Psychopharmacology, 159, pp. 145-153, 2002.

Synthesis and Biological Evaluation of 2-substituted 3-tolyltropane Derivatives

A series of eight 2-substituted 3-tolyltropane derivatives were synthesized and the *In Vitro* and *In Vivo* biological activities as dopamine uptake inhibitors were determined. From the *In Vitro* structure-activity data it is apparent that a tolyl group in the 2-position, independent of the stereochemical attachment to the tropane ring system provided compounds that exhibit high affinity binding at the DAT. Although a slight stereochemical preference in binding affinity at the DAT was observed for the 2b-(R)-alcohol over the 2b-(S)-isomer, no significant differences in behavioral effects were observed. Furthermore, despite a relatively low potency of one compound for the inhibition of dopamine uptake compared to its affinity for the DAT, its behavioral profile did not vary significantly from cocaine. These data indicate that a behavioral characterization of compounds is a critical feature of efforts to discover pharmacological treatments for cocaine abuse. Xu, L., Izenwasser, S., Katz, J.L.,

Kopajtic, T., Klein-Stevens, C., Zu, N., Lomenzo, S.A., Winfield. L. and Trudell, M.L. Journal of Medicinal Chemistry, 45, pp. 1203-1210, 2002.

Structure-activity Relationships at Monoamine Transporters for N-substituted Benztropines: Synthesis and Comparative Molecular Field Analysis (CoMFA)

The dopamine transporter (DAT) has been implicated as the primary molecular site of action of psychostimulant drugs of abuse. The development of structure-activity relationships of dopamine uptake inhibitors and comparing their effects models of cocaine abuse has provided insight into the complex relationships between structure, binding, and behavioral activity. Understanding the molecular interactions of the DAT with different ligands, will assist in developing effective medications for cocaine abuse. A molecular modeling study using CoMFA was performed on a set of 76 benztropine analogs. The models provided insight into the structural features for optimal binding to the DAT, which was used to design more selective compounds. The role of pharmacokinetics also entered into the design of the new compounds. Previously, potent analogs in the benztropine series were also highly lipophilic, rendering them unreasonable candidates as medications. Hence, in this study, heteroatom substitutions were used in order to retain high DAT affinity but reduced lipophilicity. A series of 10 novel N-substituted analogues were designed, synthesized and evaluated for binding at DAT, the serotonin and norepinephrine transporters, and muscarinic M1 receptors, in rat brain. Most of the analogues showed high DAT affinity (12-50 nM) and selectivity for DAT over other sites. Furthermore, reduced cLogD values suggested that decreased lipophilicity could be achieved while retaining favorable binding profiles. Future studies will further improve our understanding of the importance of physiochemical properties in the behavioral actions of these molecules. This information is essential for devising an efficacious medication strategy for cocaine addiction. Kulkarni, S.S., Kopajtic, T., Katz, J.L. and Newman, A.H. Presentation at the 2002 Gordon Conference on Medicinal Chemistry, New London, NH, August 4-9, 2002.

Intravenous Cocaine-induced Activity in A/J and C57BL/6J Mice: Behavioral Sensitization and Conditioned Activity

The purpose of this study was to develop a methodology for studying i.v. cocaine-induced activity in the mouse, which allows within-session determination of the dose-response function for a rapid characterization of activity in subjects that may be extremely valuable and in short supply (i.e. genetically engineered mice). The stimulant effects of i.v. cocaine (3-25 mg/kg) were investigated both acutely and following repeated treatments. Cocaine produced a dose-dependent increase in measures of motor activity, and repeated cocaine treatment resulted in the development of behavioral sensitization. In summary, these data extend to the i.v. route of administration previous observations on cocaine-induced activity and conditioned activity and allow an assessment of cocaine induced activity without handling of subjects. Mead, A.N., Katz, J.L. and Rocha, B.A. Neuropharmacology, 42, pp. 976-986, 2002.

Cocaine-induced Locomotor Activity and Cocaine Discrimination in Dopamine D4 Receptor Mutant Mice

The role of dopamine D4 receptors in the behavioral effects of cocaine, including its locomotor stimulant and interoceptive discriminative-stimulus effects was investigated using dopamine D4 receptor knockout (DA D4R KO) and wild-type (WT) mice. The mice were trained in daily sessions to discriminate IP injections of saline from cocaine (10 mg/kg). Responses on one of two response keys intermittently produced a food pellet; one response was reinforced in sessions following cocaine injection (10 mg/kg), and the other response was reinforced in sessions following saline injection. Each twentieth response produced a food pellet (fixed-ratio, or FR 20 schedule of reinforcement). Horizontal locomotor activity was also assessed in each genotype. Each genotype acquired the discrimination of 10 mg/kg cocaine in a comparable number of training sessions. Tested doses of 1.0 - 10.0 mg/kg of cocaine produced dose-related increases in the percentage of drug-appropriate responses. The dose-effect curve for cocaine was significantly shifted to the left approximately 2.5-fold in the DA D4R KO mice (ED50 value = 0.50 mg/kg) compared to their WT littermates (ED50 value = 2.6 mg/kg). Cocaine did not significantly alter response rates across the dose range tested. In addition, cocaine was more a potent stimulator of locomotor activity in the DA D4R KO mice compared to WT littermate mice. The present results on the stimulation of activity and interoceptive/subjective effects of cocaine are

consistent with the previously reported disregulation of dopamine synthesis in DA D4R KO mice, and further suggest a role of the DA D4R in vulnerability to stimulant abuse. Katz, J.L., Chausmer, A.L., Elmer, G.I., Rubinstein, M., Low, M.J. and Grandy D.K. Presentation at the Dopamine 2002. Satellite Symposium of the IUPHAR Congress, Portland OR, July, 10-14, 2002.

Cocaine-induced Locomotor Activity and Cocaine Discrimination in Dopamine D2 Receptor Mutant Mice

Dopamine D2-like antagonists block several effects of cocaine, including its locomotor stimulant and interoceptive discriminative-stimulus effects. Because these compounds generally lack selectivity among the D2-like dopamine receptors, the specific roles of the subtypes remain unclear. Dopamine D2 receptor knockout (DA D2R KO), heterozygous (HET) and wild-type (WT) mice were used to study the role of D2 dopamine receptors in the effects of cocaine. DA D2R KO, HET and WT mice were treated with cocaine (1-10 mg/kg) or vehicle and their horizontal locomotor activity was assessed. The mice were also trained to discriminate IP injections of saline from cocaine (10 mg/kg) using a 2 response-key food-reinforcement (FR 20) procedure. Both DA D2R KO and HET mice showed reduced levels of locomotor activity compared to WT mice. Cocaine dose-dependently stimulated activity in each genotype, with the highest level of activity induced in the DA D2R WT mice, and all three genotypes acquired the discrimination of 10mg/kg cocaine. Raclopride dose-dependently shifted the cocaine dose-effect curve to the right in DA D2R WT and HET mice. However in DA D2R KO mice raclopride was inactive as an antagonist. The present data indicate an involvement of D2 dopamine receptors in the locomotor-stimulating effects and the interoceptive discriminative-stimulus effects of cocaine in WT subjects. However, the D2 receptor is not necessary for the effects, suggesting redundant dopaminergic mechanisms for the discriminative-stimulus interoceptive effects of cocaine. Chausmer, A.L., Elmer, G.I., Rubinstein, M., Low, M.J., Grandy, D.K. and Katz, J.L. Psychopharmacology, Published online: 17 July 2002 [DOI 10.1007/s00213-002-1142-y].

Medicinal Chemistry Section, Medications Discovery Research Branch

Three Generations of N-substituted Benztropine Analogues as Potential Medications for Cocaine Abuse

A series of novel dopamine uptake inhibitors, based on benztropine (BZT), have been synthesized and evaluated as potential medications for cocaine-abuse. Structure-activity relationships revealed structural features for optimal dopamine transporter (DAT) affinity and selectivity. Several first generation N-substituted 4',4"-diF-BZTs (NH, N-methyl, N-allyl, N-butyl and N-butylphenyl) were evaluated in animal models of cocaine abuse. None of these compounds was found to be as efficacious as cocaine, in stimulating locomotor activity in mice. Furthermore, only the N-methyl analogue demonstrated full generalization to the cocaine discriminative stimulus, in rats trained to discriminate 10 mg/kg cocaine from saline, at a pretreatment time of 90 min. The other N-substituted analogues were not recognized as being cocaine-like, regardless of pretreatment time. The lack of cocaine-like actions, despite potent dopamine uptake inhibition, suggested that sub-optimal pharmacokinetics, due to high lipophilicity, may be confounding the behavioral actions of these compounds. Hence, a second generation of N-substituted analogues (N-cyclopropylmethyl, N-N-indole-3-ethyl, 2'-aminoethyl, (S)-2"-amino-3"-methyl-n-butyl) were evaluated. These compounds demonstrated higher DAT binding affinities and greater selectivity compared to the first generation of analogs. These compounds also had lower lipophilicities, as measured by cLogD values. Behavioral evaluation of these compounds and comparisons to cocaine, as well as the design of a third generation of N-substituted analogues are presented. Newman, A.H., Kulkarni, S., Kopajtic, T., O'Callaghan, M. and Katz, J.L. Presentation at the Dopamine 2002 Satellite Symposium of the IUPHAR Congress, Portland OR, July, 10-14, 2002.

[3-cis-3,5-Dimethyl-1-piperazinyl) alkyl]-bis-(4'-fluorophenyl) Amine Analogs as Dual Probes for the Dopamine Transporter and Sigma1 Receptors

Rimcazole, a sigma1 receptor antagonist that binds to the DAT (Ki =224), is not behaviorally cocaine-like and attenuates some of the behavioral actions of cocaine. In order to determine the roles of both DAT and sigma1 receptors in the behavioral

actions of rimcazole, a series of analogs was synthesized. Two analogs (SH 3-24 and 3-28) showed high to moderate affinities for both DAT and sigma1 receptors and failed to show cocaine-like discriminative stimulus (DS) effects. Further, a potentiation of cocaine's DS effects was not observed, unlike with other DAT inhibitors, suggesting a potential role of sigma1. Another series of bis-(4'-fluorophenyl)amine analogs were prepared in which the most potent DAT compound, JJC-2-010 (Ki = 8.5 nM) was highly selective over sigma1 receptor binding (DAT/sigma1>100). CoMFA studies at both DAT and sigma1 receptors were performed to examine structural requirements and differences. Behavioral evaluation of analogs with varying affinities for both DAT and sigma1 receptors may provide direction toward designing medications for cocaine abuse. Cao, J., Kulkarni, S.S., Bowen, W., Williams, W., Kopajtic, T., Katz, J.L. and Newman A.H. Presentation at the 2002 American Chemical Society, Boston, MA, August, 2002.

SAR comparison of (S)-2-substituted-3a-[bis (4'-fluorophenyl)methoxy] tropanes and (R)-2-substituted-3a- (3,4-dichlorophenyl)tropanes at the DAT

Extensive SAR have been developed around two classes of tropane-based dopamine transporter (DAT) ligands. Significant chemical modification at the 2-position in the cocaine class is well tolerated, although the substituent must be in the R-configuration. In the benztropine class, a substituent need not be in the 2-position to bind to the DAT with high affinity. However, if a substituent (ex. COOMe) is placed in the 2-position it must be in the S-configuration, in order to bind. This opposing enantioselectivity suggests that these tropane-based DAT inhibitors may not access identical binding domains. In order to further investigate these disparities, a series of (S)-2a-carboalkoxy-4,4'-difluorobenztropines and their identically (R)-2-substituted-3a-(3,4-dichlorophenyl) tropanes were prepared and evaluated for binding at the DAT, SERT, NET, and muscarinic receptors. SAR suggest that identical 2-position substituents on the tropane rings of these two classes of compounds confer differing binding affinities and selectivities for the DAT, which may be exploited toward the discovery of a cocaine-abuse pharmaco- therapeutic. Zou, M-.F., Kopajtic, T., Katz, J.L. and Newman, A.H. Presentation at the 2002 American Chemical Society, Boston, MA, August, 2002.

Synthesis and Evaluation of a Novel Series of 2-chloro-5- ((1-methyl-2- (S)-pyrrolidinyl) methoxy)-3-(2-(4-pyridinyl)vinyl) pyridine Analogues as Potential Positron Emission Tomography Imaging Agents for Nicotinic Acetylcholine Receptors

Reportedly, 2-[(18)F]fluoro-A-85380, 1, a promising radiotracer for imaging the nicotinic acetylcholine receptor (nAChR) by positron emission tomography (PET) in humans, exhibits slow penetration through the blood-brain barrier (BBB) due to its low lipophilicity. A ligand for nAChRs with greater lipophilicity than that of 1 would be potentially more favorable for PET imaging of nAChR due to its faster penetration through the BBB. Herein, a novel series of compounds has been developed based on the high affinity ligand for nAChRs, 2-chloro-5-((1-methyl-2-(S)-pyrrolidinyl)methoxy)-3-(2-(4-pyridinyl)vinyl)pyridine, 3b. The *In Vitro* binding affinities for the new series were found to be in the range of K(i) = 9-331 pM. A molecular modeling study showed differences in the comformational profiles and the electronic properties of these compounds, which provides further insight into the structure-activity relationships at nAChR. Lipophilicities of the compounds 3b-6b have been found to be substantially higher than that of 1. As a result, compounds 3b-6b might exhibit a faster penetration through the BBB than the less lipophilic 1. The N-methyl derivatives 3b and 6b demonstrated very high affinities at nAChRs (K(i) = 28 and 23 pM, respectively) and will be targets for development of (11)CH(3)-labeled derivatives as radiotracers for PET imaging of nAChRs. Brown, L.L., Kulkarni, S., Pavlova, O.A., Koren, A.O., Mukhin, A.G., Newman, A.H., and Horti, A.G. Journal of Medicinal Chemistry, 45, pp. 2841-2849, 2002.

Director's Report to the National Advisory Council on Drug Abuse - September, 2002

Program Activities

New NIDA PAs and RFAs

On May 30, 2002, NIDA issued a Program Announcement entitled **Genetic Epidemiology of Substance Abuse Disorders (PA-02-112)**. The purpose of this announcement is to stimulate epidemiologic studies of substance use disorders (SUDs, drug abuse and dependence). Previous studies using twin, adoption and family approaches indicate that genetic factors substantially influence the risk for SUDs. Building on these findings, new studies are needed to refine SUD phenotypes for future molecular genetic studies, clarify gene-environment interactions, refine nosology and thus improve treatment matching, and expand findings to understudied populations. Also needed are longitudinal and developmental studies, more advanced statistical and analytic approaches to complex disorders and traits, and new methodological approaches to address challenges such as the equal environment assumption, the definition of affected and unaffected status, and changes in adoption patterns and family configuration.

On September 9, 2002, NIDA issued a new Program Announcement entitled **Economic Evaluation of Drug Abuse Treatment and Prevention Services for HIV/AIDS (PA-02-164)**. Through this PA, applications are sought that employ the methods of economic analysis to pressing problems in the financing and delivery of HIV/AIDS services and drug abuse treatment and/or prevention services.

PAs and RFAs Issued With Other NIH Components/Agencies

On May 1, 2002, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement entitled **Research on Ethical Issues in Human Studies (PA-02-103)**. This PA replaces OA-99-079. The purpose of this announcement is to solicit research addressing the ethical challenges of involving human participants in research in order to inform and optimize protections for human participation in research.

On May 16, 2002, NIDA, in collaboration with numerous other NIH components issued a Program Announcement entitled **Structural Biology of Membrane Protein SBIR/STTR Announcement (PA-02-108)**. The purpose of this announcement is to encourage researchers to solve the structures of membrane proteins at atomic resolution and to develop the tools needed to solve these structures.

On May 29, 2002, NIDA, in collaboration with numerous other NIH Institutes, issued a Program Announcement entitled **Genetic Architecture, Biological Variation, and Complex Phenotypes (PA-02-110)**. This announcment updates PA-98-078 and is intended to solicit applications for new studies on genetic variation and the architecture of complex phenotypes. It restates the interest of a number of NIH Institutes in studies of the underlying causes and architecture of complex phenotypes, including human diseases. It is motivated by the volume and complexity of biological data that are being generated and by the understanding that complex phenotypes involve many genetic components that evolve in a variety of environments.

On July 2, 2002, NIDA along with many other NIH components, issued a Program Announcement entitled **Bioengineering Nanotechnology Initiative (PA-02-125)**. This PA, which supercedes PA-00-018 and was issued as an initiative of the trans-NIH Bioengineering Consortium (BECON), invites grant applications for Small Business Innovation Research (SBIR) projects on nanotechnologies useful to biomedicine.

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On July 10, 2002, NIDA, in collaboration with numerous other NIH Institutes, issued a Program Announcement entitled **Mentored Quantitative Research Career Development Award (PA-02-127)**. This PA, which supercedes PA-99-087, was issued in an effort to advance research relevant to the mission of NIH which includes basic biomedical, clinical biomedical, bioengineering, bioimaging, and behavioral research. Participating Institutes solicit applications for the Mentored Quantitative Research Career Development Award (K25). The K25 mechanism is meant to attract to NIH-relevant research those investigators whose quantitative science and engineering research has thus far been focused primarily on questions of health and disease.

On July 18, 2002, NIDA, in collaboration with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Deafness and Other Communication Disorders (NIDCD), issued a Program Announcement entitled **Collaborative Neurological Sciences (CNS) Award (PAR-02-130)**. The purpose of the CNS Award is to encourage collaborative research investigations among scientists at minority institutions and grantees from leading research laboratories that have NIH or equivalent grant support to conduct neuroscience research. It is envisioned that funding from the CNS Award will lead to joint research efforts and publications, shared research instrumentation and resources, exchange of research techniques, and other scientific activities to enhance the research capabilities of applicants at minority institutions to successfully compete for independent research funding during the performance period of award.

On July 26, 2002, NIDA, in collaboration with several other NIH components, issued a Program Announcement entitled **Continued Development and Maintenance of Bioinformatics and Computational Biology Software (PA-02-141)**. The goal of this PA is to support the continued development, maintenance, testing, and evaluation of existing software. The proposed work should apply best practices and proven methods for software design, construction and implementation to extend the applicability of existing bioinformatics/computational biology software to a broader biomedical research community.

On August 2, 2002, NIDA, numerous other NIH Institutes, and the Trans-NIH Zebrafish Coordinating Committee issued a joint Program Announcement entitled **Tools for Genetic Studies in Zebrafish (PAR-02-142)**. This PA is intended to encourage investigator-initiated applications for research designed to exploit the power of mutagenesis screening in zebrafish in order to detect and characterize genes, pathways, and phenotypes of interest in development and aging, organ formation, behavior, and disease processes. Applications that propose to advance the technologies associated with such phenotyping are also welcome. A secondary goal of this PA is to ensure that tools developed under this initiative are widely available to the research community.

On August 9, 2002, NIDA, in collaboration with numerous other NIH components, issued a Program Announcement entitled **Novel Approaches to Enhance Animal Stem Cell Research (PA-02-147)**. The purpose of this PA is to encourage the submission of applications for research to enhance animal stem cells as model biological systems. Research to isolate, characterize and identify totipotent and multipotent stem cells from nonhuman biomedical research animal models, as well as to generate reagents and techniques to characterize and separate those stem cells from other cell types is encouraged. Innovative approaches to the problems of making multipotent stem cells available from a variety of nonhuman sources, and to creating reagents that will identify those stem cells across species and allow for separation of multipotent stem cells from differentiated cell types, will be stressed.

On August 16, 2002, NIDA, in collaboration with the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute of Mental Health (NIMH) issued a Program Announcement entitled **Services and Intervention Research With Homeless Persons Having Alcohol, Drug Abuse, or Mental Disorders (PA-02-150)**. This PA encourages research that will expedite the dissemination, implementation, and adoption of effective treatment and prevention efforts for homeless persons with ADM disorders. Interdisciplinary research teams and research partnerships with providers and consumers across multiple systems in community settings are strongly encouraged. Such settings may include but are not limited to shelters and food programs, parole and correctional settings, non-traditional or ad hoc service settings, or street-based, transitional, and special housing programs.

On May 9, 2002, NIDA, in collaboration with the Office of Research Integrity, the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Nursing Research (NINR) issued an RFA entitled **Research on Research**

Integrity (NS-03-001). The purpose of this program is to foster empirical research on the institutions, processes, and values that affect integrity in research. The sponsoring agencies are particularly interested in studies that will inform policy making at DHHS, NIH, and research institutions, with the goal of fostering appropriate attention to integrity in publicly funded research programs. Letter of Intent Receipt Date for this RFA: October 15, 2002; Application Receipt Date: November 15, 2002.

On June 20, 2002, NIDA, a number of other NIH components and the Canadian Institutes of Health Research (CIHR)/Institute of Neurosciences, Mental Health and Addiction (INMHA) with the International Development Research Centre (IDRC) jointly issued an RFA entitled **Stigma and Global Health Research Program (TW-03-001)**. The purpose of this initiative is to stimulate investigator-initiated research on the role of stigma in health, and on how to intervene to prevent or mitigate its negative effects on the health and welfare of individuals, groups, and societies world-wide. Collaborative interdisciplinary applications are particularly encouraged. Letter of Intent Receipt Date for this RFA: October 14, 2002; Application Receipt Date: November 14, 2002.

On July 26, 2002, NIDA, the National Institute of Mental Health (NIMH) and the National Institute of Nursing Research (NINR) jointly issued an RFA entitled **HIV Prevention in Treatment Settings: U.S. and International Priorities (MH-03-006)**. The purpose of this RFA is to solicit research grant applications that will address some of the research gaps that currently exist in basic, behavioral science, medical and policy areas that are needed to develop enhanced HIV prevention strategies in treatment settings. Letter of Intent Receipt Date for this RFA: September 27, 2002; Application Receipt Date: October 29, 2002.

On July 31, 2002, NIDA and the National Institute of Mental Health (NIMH) jointly issued an RFA entitled **Development of Tools for the Assessment of Depression (MH-03-002)**. This RFA invites research applications that apply recent advances in affective science, basic behavioral science, and measurement theory to the development of an instrument or assessment battery to assess depression. The instrument must be psychometrically sound, time-efficient, and suitable for tracking changes in symptoms and functioning as a repeated measure over time or in response to therapeutic intervention. Letter of Intent Receipt Date for this RFA: September 15, 2002; Application Receipt Date: October 15, 2002.

On August 27, 2002, NIDA and NIMH jointly issued an RFA entitled **National Cooperative Drug Discovery Groups for the Treatment of Mood Disorders and Nicotine Addiction (MH-03-008)**. The purpose of this RFA is to establish a program to accelerate innovative drug discovery, the development of pharmacologic tools for basic and clinical research in mood disorders or nicotine addiction, and, in the case of mood disorders, the development and validation of models for evaluating novel therapeutics. The partnership between NIMH and NIDA in this initiative is logical given the likelihood that there are targets in common and overlap in the expertise that can be brought to bear on the discovery and development. An additional purpose of this RFA is to establish long-term partnerships between NIH, academia, and industry that will advance the development and testing of fundamentally new, rationally designed medications and treatments for mental disorders and drug addiction. Letter of Intent Receipt Date for this RFA: October 25, 2002; Application Receipt Date: November 26, 2002.

On August 28, 2002, NIDA, in collaboration with NIMH issued an RFA entitled **Exploratory/Developmental Translational Grants for Borderline Personality (MH-03-001)**. In this RFA, NIDA and NIMH extend their translational research initiatives to borderline personality disorder research, inviting exploratory/developmental R21 applications for new, innovative translations of basic science theories, methods and findings to clinical research concerning borderline personality disorder, its features, and its relationship to co-occurring disorders, e.g., depression, post traumatic stress disorder, and drug dependence. Letter of Intent Receipt Date for this RFA: January 13, 2003; Application Receipt Date: February 12, 2003.

Other Program Activities

Phase III Trial of Lofexidine Hydrochloride Discontinued

The placebo arm of a Phase III multi-center double-blind trial of lofexidine hydrochloride (trade name BritLofex) as a medication to treat opiate withdrawal was discontinued after an interim analysis by the Central Department of Veterans Affairs Data Safety Monitoring Board showed overwhelming efficacy for the BritLofex arm of

the study. The efficacy of BritLofex over placebo was statistically and clinically significant. BritLofex is a non-opiate, non-dependence producing alpha 2 adrenergic agonist compound used to manage withdrawal symptoms in patients during opiate detoxification. The study was conducted under a Clinical Trial Agreement between NIDA (DTR&D) and Britannia Pharmaceuticals, Ltd. Participating clinical sites were the UCLA Integrated Substance Abuse Program, the New York Psychiatric Institute, and the Philadelphia Veterans Affairs Medical Center. The company is actively pursuing future product development plans. If BritLofex were approved by the FDA, it would be the first non-opiate detoxification agent available in the U.S.

NIDA Guidelines for Developing Data and Safety Monitoring Plans

Dr. Ivan Montoya of the DTR&D led an initiative to prepare and implement the NIDA guidelines for developing data and safety monitoring plans for NIDA grantees who are conducting, or planning to conduct, clinical trials. This initiative was in response to new NIH policies on data and safety monitoring in NIH supported clinical trials. The guidelines have been posted on the NIDA website at http://www.nida.nih.gov/Funding/DSMBSOP.html.

Targets for High-Throughput Screening in Cocaine Treatment Discovery

On June 7, 2002, in Quebec City (prior to the CPDD meeting), Dr. David McCann (DTR&D) chaired a consultants meeting entitled "Targets for High-Throughput Screening in Cocaine Treatment Discovery." Dr. Friedbert Weiss presented the case for pursuing CRF-1 and Neuropeptide Y ligands, Dr. Michael Kuhar for CART peptide receptor ligands, Dr. Mark Epping-Jordan for mGluR5 antagonists, and Dr. Elliott Richelson for Neurotensin agonists. In addition, Drs. James Bibb, William Freeman and David Self presented the results of recent studies evaluating the effects of cocaine on gene expression, with a focus on identifying new targets for medication discovery. A group of listening consultants - primarily leaders in target identification within major pharmaceutical companies - provided feedback to NIDA. The consultants expressed the greatest enthusiasm for pursuit of CRF-1 antagonists and/or mGluR5 antagonists in future NIDA library screening efforts. The meeting organizers were Dr. McCann, Dr. Jane Acri (DTR&D) and Dr. David Thomas (DNBR).

Translationally Oriented Approaches, Devices, and Strategies (TOADS) Workgroup

Drs. Ro Nemeth-Coslett (DTR&D) and Dave Thomas (DNBR) formed and co-chair the new NIDA workgroup, "Translationally Oriented Approaches, Devices, and Strategies" (TOADS) whose purpose is to promote the development and application of state-of-the-art technologies that are being used successfully in other disciplines (e.g., virtual reality) for the purposes of studying, preventing and treating drug abuse, as well as related NIDA programmatic areas (e.g., pain). To explore the exciting possibilities of applying new approaches, devices and/or strategies to problems of substance abuse, many areas of expertise are clearly needed. TOADS, therefore, draws on a multidisciplinary trans-Institute effort in the strong belief that cooperation and interaction between various NIDA staff are essential for the proposed aims to be realized. Basic research-oriented individuals will be invaluable in the assessment of the effectiveness of applying the various technologies to models of drug abuse and clinically oriented NIDA staff will be needed to evaluate the clinical utility of the new technologies as primary, adjunctive or complimentary preventive or treatment interventions.

CTN Protocol Update

- For protocols CTN 0001 - 0007, over 1,500 patients have been enrolled in these studies.
- A Spanish version of protocol CTN 0004, Motivational Enhancement Therapy, is being developed for Spanish speaking subjects throughout the CTN. Five community treatment programs across five nodes have signed up for this study.
- Protocol CTN 0008 (Baseline Survey) began enrollment in January 2002.
- Protocols CTN 0010 (Buprenorphine/Naloxone Facilitated Rehabilitation for Opioid Dependent Adolescents/Young Adults) and CTN 0011 (A Feasibility Study of a Telephone Enhancement Procedure - TELE - to Improve Participation in Continuing Care Activities) have received approval and will begin enrollment early this fall.
- Two new protocols are in the final stages of approval before being launched in the CTN. These are CTN 0009 (Smoking Cessation

Treatment in Substance Abuse Programs) and CTN 0012 (Infections Screening in Substance Abuse Treatment Programs).

- The third wave of protocols has been submitted and is in various stages of development and review. These will be launched in the fall or winter of 2002. By the end of 2002, it is projected that twenty protocols will be actively enrolling patients throughout the CTN.
- A fourth wave of protocol concepts was reviewed by the CTN Steering Committee in August 2002.

Evaluation of the National Youth Anti-Drug Media Campaign: Fourth Semi-Annual Report of Findings

The National Youth Anti-Drug Media Campaign (the Campaign) was funded by the Congress to reduce and prevent drug use among young people both directly, by addressing youth and indirectly, by encouraging their parents and other adults to take actions known to affect youth drug use. The major intervention components include television, radio, and other advertising, complemented by public relations efforts including community outreach and institutional partnerships. The goals of the evaluation are to determine: 1) if there is change in the behaviors, attitudes and beliefs targeted by the campaign and 2) if such change can be attributed to the Campaign. The findings summarized below are from the fourth Evaluation report; the first three waves of data collection involved enrolling nationally representative samples of about 8,100 youth from 9 to 18 and 5,600 of their parents. The 4th wave was the first follow-up wave, including about 2100 youth from 12 to 18 and 1500 of their parents who had been originally interviewed in Wave 1. The new report covers the period from September 1999 through December 2001 and examines 1) exposure to anti-drug messages (both general exposure and specific exposure to ads played on a computer to respondents); 2) effects on parents; and 3) effects on youth.

Exposure to and Recall of Campaign Messages

Most parents and youth recalled being exposed to Campaign anti-drug messages. About 70 percent of both groups report exposure to one or more messages through all media channels every week. The average (median) youth remember seeing one television ad per week. In previous waves less than 25 percent of parents recalled seeing a TV ad every week; this increased to 40 percent in the second half of 2001. Both parents and youth reported substantial recognition of the Campaign's "anti-drug" brand phrases.

Effects on Parents

The evidence suggests a favorable Campaign effect on parents. Overall, there are favorable changes in 4 out of 5 parent belief and behavior outcome measures including talking about drugs with, and monitoring of, children. In addition, those parents who report more exposure to Campaign messages scored better on those outcomes after applying statistical control for confounders. However, there is no evidence of indirect effects on youth behavior as a result of parent exposure to the Campaign.

Effects on Youth

Thus far, there is no evidence of direct favorable Campaign effects on youth. There is no statistically significant decline in marijuana use or improvements in beliefs and attitudes about marijuana use between 2000 and 2001, and no tendency for those reporting more exposure to Campaign messages to hold more desirable beliefs.

For some outcomes, and for some subgroups of respondents, the analyses suggest the possibility that those youth with greater exposure to the specific Campaign ads during the first six months of the evaluation had less favorable outcomes over the following 18 months. This was found among youth respondents who were nonusers and aged 10 to 12 at the start of the evaluation, with regard to their intentions to use marijuana in the future and for all youth 12 to 18 for their perceived social norms about marijuana use. Girls with the highest exposure to Campaign ads at the start were more likely to initiate marijuana use than less exposed girls. This effect was not seen for boys. This unfavorable association with initiation was also significant for the youngest respondents and for the low risk respondents. Further data collection and analysis is required before any firm conclusion can be reached to support these unexpected outcomes.

The Wave 4 Report findings are interim results that reflect only the first 2 years of an evaluation and only a first follow up with 40 percent of the respondents. The full

evaluation will involve three interviews with respondents over 3 and a half years. It is possible that subsequent semi-annual reports may show different effects, including a favorable impact on youth. The Executive Summary and the full Wave 4 report are available on the NIDA website at: /initiatives/westat/Westat502/ExecSummary502.html.

2002 Summer Research With NIDA Program

The Sixth Annual Summer Research With NIDA Program, coordinated by Flair Lindsey, Special Populations Office, allowed high school and undergraduate students to engage in drug abuse research with NIDA grantees for 8-10 weeks during the summer. In 2002, 76 students and 24 grantees participated in the program.

NIDA's New and Competing Grants Awarded Since May 2002

Abood, Mary E. -- California Pacific Medical Center-Pacific Campus
Molecular Mechanisms of Cannabinoid Receptor Regulation

Allen, Richard M. -- University of Colorado at Denver
Escalating Cocaine Self-Administration: NMDA Mechanisms

Allen, Sharon S. -- University of Minnesota Twin Cities
Menstrual Phase Effects on Smoking Relapse

Atchley, Paul -- University of Kansas Lawrence
Attentional Supports of Smoking Behavior

Bailey, Susan L. -- University of Illinois at Chicago
Family Process and HIV Risk Reduction In Young IDU's

Bandstra, Emmalee S. -- University of Miami
Neurodevelopmental Outcome of In Utero Cocaine Exposure

Bentler, Peter M. -- University of California Los Angeles
Collaborative Research on Drug Abuse

Bergman, Jack -- McLean Hospital
Cocaine Addiction: Medication Strategies and Evalution

Berrettini, Wade H. -- University of Pennsylvania
Quantitative Genetics of Opiate Addiction

Beversdorf, David Q. -- Ohio State University
Cognitive Flexibility, Withdrawal, and Norepinephrine

Brauer, Lisa H. -- University of Minnesota Twin Cities
Interactions Between Progesterone and Cocaine In Women

Carroll, Frank I. -- Research Triangle Institute
Development of Ligands for Nicotinic Receptors

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Reviews

For this council cycle, the Office of Extramural Affairs arranged and managed 24 review meetings for the reviews of 398 grant applications. These reviews included applications in standing review committees, applications in conflict-of-interest with standing committees, and submissions to special initiatives. In addition, OEA's Contracts Review Branch arranged and managed 11 contract proposal review meetings and 14 concept reviews.

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 four Special Emphasis Panels to review applications in conflict with the chartered committees. Two Special Emphasis panels were constituted for reviews of specific mechanisms (unsolicited centers and conference grant applications), and 11 Special Emphasis Panels were held for the nine RFAs noted below. In addition, OEA staff managed the reviews for B/START, I/START, and Cutting Edge Basic Research Award mechanisms.

The following RFA reviews were held:

DA02-002	Inhalant Abuse: Supporting Broad-based Research Approaches
DA02-003	Expansion of the National Drug Abuse Treatment Clinical Trials Network
DA02-004	NIDA National Prevention Research Initiative (NNPRI): Community Multi-Site Prevention Trials (CMPT)
DA02-005	NIDA National Prevention Research Initiative (NNPRI): Transdisciplinary Prevention Research Centers
DA02-006	Modifying and Testing Efficacious Behavioral Therapies to Make Them More Community Friendly
DA02-008	Hepatitis C Diagnosis, Treatment, and Interaction with HIV/AIDS
DA02-009	New Approaches to Prevent HIV/Other Infections in Drug Users
DA02-010	NIDA's National Prevention Research Initiative: Using Basic Science to Develop New Directions in Drug Abuse Prevention Research
DA02-011	National Criminal Justice Drug Abuse Treatment Services Research System

The Contract Review Branch managed the following reviews:

N01DA-2-1106	NIDA's Science Meetings Logistic Support
N01DA-2-1206	NIDA's Contracts Review Logistics Support
N44DA-2-7716	Bio-Sensor Mass Spectrometry Array
N44DA-2-5512	Interactive CD-ROM Training for Prevention Providers
N44DA-2-5507	Preventing Substance Abuse with Multi-Media Life Science
N44DA-2-5511	Primary Care Adolescent Drug/Alcohol Screening Instrument
N44DA-2-5509	Automated Social Network Data Collection
N01DA-2-8822	Assessment of Potential Cocaine Treatment in Rodents
N01DA-3-8830	*In Vitro* Metabolism and Metabolite Quantification
N01DA-2-8824	Medications Development for Stimulant Dependence
N44DA-2-7716	Bio-Sensor Mass Spectrometry Array

Concept Reviews

N01DA-3-8831	Assessment of Potential Cocaine Treatment in Non-Human Primates
N01DA-3-8830	*In Vitro* Metabolism and Metabolite Quantification

SBIR Concepts

Design, Synthesis, Preclinical Testing and Scale-up of Novel Treatment Agents for Stimulant Abuse

Antibody based Therapies for Substance Abuse Treatment

Virtual Reality for the Treatment of Co-Morbid Drug Abuse and Post-Traumatic Stress

Pharmacovigilance Database for Anti-Addiction Medications

National Census of Therapeutic Community Treatment Services for Substance Abusers

Measurement Modules for Psychiatric Co-Morbidity Evaluation

Worksite Based Health Promotion for Youth

Synthesis of New Chemical Probes

Virtual Reality for Treatment of Pain or Drug Addiction

Technologies for Proteomic Analysis in the Nervous System

Development of Science Education Materials Related to the use of Animals in Research

Development of Testing Technology to Support Delivery of Linked Drug Abuse

Treatment and Primary Medical Care

Staff Training

The OEA Symposium Series, a forum for staff training and sharing of solutions to problems in extramural research administration, continued to meet monthly under the guidance of Dr. Mark Swieter, SRA, Basic Sciences Review Branch. In May, Dr. Carlos Caban, from the Office of Extramural Programs, NIH, came to discuss NIH requirements for data safety and monitoring plans, and Dr. Swieter and other NIDA staff participated in that presentation. In July, Dr. Gary Fleming, Chief, Grants Management Branch, NIDA, presented on ways to strengthen the collaborations between grants management staff and other NIDA staff.

OEA staff have been actively involved in "cross-training" activities to provide guidance on review policies and procedures for other NIDA staff who have assisted with reviews this summer. In particular, Drs. Marina Volkov, Mark Green, and Kay Nimit of the Clinical, Epidemiological, and Applied Sciences Review Branch and Dr. Mark Swieter have provided training. Drs. Kevin Conway and Rachel Schiffman provided valuable assistance beyond the usual level of program-review staff collaboration. Dr. Charles desBordes, who came under an IPA with the City College of New York, contributed to arranging and summarizing the reviews.

Extramural Activities Development

Three RFAs which made up the NIDA National Prevention Research Initiative (NNPRI) were reviewed this summer. These were developed by a cross-institute working group in which Drs. Mark Green and Marina Volkov of OEA's Clinical, Epidemiological, and Applied Sciences Review Branch actively participated to provide input on scientific issues and review perspectives.

Extramural Outreach

Dr. Teresa Levitin, Director, OEA, and Dr. Lula Beatty, Chief, Special Populations Office, organized, and Dr. Levitin chaired, a symposium entitled "National-International Health Disparities Research at NIDA" for the biennial meeting of The Society for the Psychological Study of Social Issues held in Toronto, Ontario, June 28-30, 2002.

On June 25, 2002, Dr. Mark Green, Chief, Clinical, Epidemiological, and Applied Sciences Review Branch, OEA, made a presentation about the review process to Morgan State University Students, as part of the 2002 Summer Research with NIDA Program for Underrepresented Minority Students.

Drs. Teresa Levitin, Mark Green and Mark Swieter of OEA organized and presented two workshops at the 64th annual meeting of the College on Problems of Drug Dependence in Quebec City, Quebec, June 8-13, 2002. Dr. Swieter chaired the first workshop on Monday evening, with Drs. Green and Levitin as co-chairs. This workshop was on Career Development and was attended by about 100 people. Over 35 people attended the second workshop on Tuesday evening chaired by Dr. Green and co-chaired by Drs. Swieter and Levitin. This workshop was entitled "What's New at NIDA and NIH: How Will It Affect You?"

Mr. Richard Harrison, Chief, Contracts Review Branch, OEA, gave the invocation and participated in an American Indian ceremony for the Secretary's National Leadership Summit on Eliminating Racial and Ethnic Disparities in Health, which was held July 10-12, 2002 in Washington, DC.

Mr. Eric Zatman, Contract Review Branch, OEA, met with private sector participants at the NIH Small Business Innovation Research Conference, held June 21, 2002 in Bethesda, MD.

Dr. Khursheed Asghar, Chief, Basic Sciences Review Branch, OEA, conducted reviews of medications development applications in California this July to take advantage of the availability of scientists attending meetings of the International Narcotics Research Conference and the International Cannabinoids Research Society. By making his review meeting convenient for the reviewers, he was able to recruit successfully and also attend the meetings to represent OEA to scientists there.

Dr. Mark Swieter, Basic Sciences Review Branch, OEA, gave a talk at a Grant Writing workshop organized by Dr. Cindy Miner of OSPC and represented OEA at a meeting of the NIDA Training Grant Directors.

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(Prepared September 6, 2002)

FY 2003 Appropriations

FY 2003 Senate Labor, HHS, Education Appropriation Bill (S. 2766) - and accompanying Senate Report 107-216

On July 18, 2002, the Senate Appropriations Subcommittee on Labor, HHS, Education reported out S. 2776, appropriations for the Departments of Labor, Health and Human Services, and Education for the fiscal year ending September 30, 2003. The bill includes a total of $27,192,926,000 for NIH. This represents an increase of $3,737,083,000 over the Fiscal Year 2002 level and $25,000,000 over the President's budget request. The Committee states that this appropriation will complete the historic 5-year effort to double the funding for the NIH.

Senate Report Language for NIDA:

The Committee recommends an appropriation of **$968,013,000** for the National Institute on Drug Abuse [NIDA]. This is $3,400,000 more than the budget request and $80,280,000 more than the fiscal year 2002 appropriation. The comparable numbers for the budget estimate include funds to be transferred from the Office of AIDS Research.

Mission. -- Created in 1974, NIDA supports about 85 percent of the world's biomedical research in the area of drug abuse and addiction. The Committee commends NIDA for demonstrating through research that drug use is a preventable behavior and that addiction is a treatable disease.

NIDA's basic research plays a fundamental role in furthering knowledge about the ways in which drugs act on the brain to produce dependence, and contributes to understanding how the brain works. In addition, NIDA research identifies the most effective pharmacological and behavioral drug abuse treatments. NIDA conducts research on the nature and extent of drug abuse in the United States and monitors drug abuse trends nationwide to provide information for planning both prevention and treatment services. An important component of NIDA's mission is also to study the outcomes, effectiveness, and cost benefits of drug abuse services delivered in a variety of settings and to assure dissemination of information with respect to prevention of drug abuse and treatment of drug abusers.

Collaboration with SAMHSA and other agencies. -- The Committee encourages NIDA to continue to collaborate with SAMHSA and other agencies to bridge the existing gap between research and practice. The Committee is pleased that NIDA plans to support CSAT's Addiction Technology Transfer Centers. The Committee believes that this collaborative effort will have a significant impact on how communities receive and develop the skills, systems, and necessary support to implement new research findings.

Community-friendly behavioral therapies. -- Research-based behavioral treatments are often criticized as too lengthy, costly, complex, or difficult for treatment providers to integrate with more traditional methods of care. The Committee applauds NIDA's efforts to remedy this situation by developing and bringing behavioral therapies to community treatment centers. NIDA is urged to encourage researchers to make

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behavioral treatments more "community friendly," while still maintaining their effectiveness. The Committee is pleased that NIDA has expanded the scope of its research beyond testing new treatments to include studies on financing and organizational adaptation and change. The Committee encourages NIDA to continue testing new treatments in clinical trials and supporting research on how to move effective treatments into health care systems.

Hepatitis C treatment. -- The Committee notes the high incidence of hepatitis C among the U.S. population that uses drugs. Research into the efficacy of treating such individuals for hepatitis C concurrently with drug dependency protocols such as methadone is highly recommended.

Information dissemination. -- The Committee urges NIDA to use both the existing National Drug Abuse Treatment Clinical Trials Network infrastructure and the new prevention infrastructures that are currently being established as part of NIDA's new Prevention Research Initiative to ensure that findings are put into practice in communities across the country.

Methamphetamine. -- The Committee continues to be concerned about methamphetamine abuse across the Nation, especially in the Midwest. The Committee again urges NIDA to expand its research on improved methods of prevention and treatment of methamphetamine abuse.

Nicotine. -- The Committee applauds NIDA's efforts to support a comprehensive research portfolio that has indisputably demonstrated the addictive nature of nicotine. The Committee encourages NIDA to work independently and, where possible, collaborate with other Institutes and organizations to identify and develop targets for new treatments. The Committee recognizes that treating addiction to nicotine remains among the most cost-effective approaches to reducing cancer risk.

Prevention research. -- The Committee is pleased that NIDA has launched a multi-component National Prevention Research Initiative that will involve partners at the State and local levels. The Committee urges NIDA to expand this initiative to test the effectiveness of new and existing science-based prevention approaches in different communities, while also studying how best to adapt the programs for local needs.

Stress and substance abuse. -- Stress plays a major role in the initiation and continuation of drug use, and in relapse to addiction. The Committee encourages the NIDA to increase its research portfolio on this topic as well as on post-traumatic stress disorder and substance abuse.

Translating basic research. -- NIDA's strong basic research foundation has provided great insight into the addiction process and has helped identify molecular targets for the development of medications as well as new behavioral treatment strategies. The Committee urges NIDA to use translational research to continue to rapidly bring knowledge from the lab into clinical practice.

FY 2003 House Labor, HHS, Education Appropriation Bill (HR 5320)

On September 4, 2002, the House Appropriations Chairman, C.W. "Bill" Young, introduced the FY 2003 House Labor HHS Education Appropriations bill (HR 5320). The bill, as introduced, is identical to the President's FY 03 budget request. The action was taken to fulfill a House Republican leadership commitment to take up the Labor/HHS/Education bill before any other appropriation bill. The text of the President's budget is available at w3.access.gpo.gov/usbudget.

Bills of Interest

H.R. 5005 B On July 26, 2002, the House passed with amendments H.R.5005, the Department of Homeland Security Act of 2002. Provisions would authorize the new Department to conduct basic and applied research, development, demonstration, testing, and evaluations related to chemical, biological, radiological, and other emerging terrorist threats, provided that these activities do not extend to human health-related research and development. The bill also would require the Secretary of HHS to set priorities, goals, objectives, and policies and develop a coordinated strategy for civilian human-health related R&D activities related to countermeasures for chemical, biological, radiological, nuclear, and other emerging terrorist threats. This would be done in collaboration with the Secretary for Homeland Security to ensure consistency with the Department of Homeland Security=s national policy and strategic plan. H.R.5005 was considered in the Senate on July 31, 2002, where a

cloture motion was offered to limit further consideration of the measure to 30 hours of debate.

H. R. 4775 B On July 23, 2002, the House passed the conference report for H.R. 4775, the 2002 Supplemental Appropriations Act for Further Recovery From and Response to Terrorist Attacks on the United States. The Senate passed the measure on July 24. The President signed the bill into law on August 2, 2002. (P.L. 107-206).

H.R. 3814 - "The National Center for Social Work Research Act" was introduced February 27, 2002, by Rep. Rodriguez (D-TX) for himself and Rep. Upton (R-MI). The bill was referred to the Committee on Energy and Commerce. The bill would establish a National Center for Social Work Research as part of the National Institutes of Health to conduct, support, and disseminate targeted research on social work methods and outcomes related to problems of significant social concern. As of July 26, 2002, the bill had 33 co-sponsors (27 Democrats; 6 Republicans).

H.R. 3793 - "The Health Professionals Substance Abuse Education Act" was introduced February 26, 2002, by Rep. Kennedy (D-RI). The bill was referred to the House Committee on Energy and Commerce. A companion measure, S.1966, was introduced February 26, 2002, in the Senate by Sen. Biden (D-DE). The Senate bill was referred to the Committee on Health, Education, Labor and Pensions. The bills would promote education of health professionals concerning substance abuse and addiction, authorize $3.5 million for FY 2002 through 2006, and would create an oversight committee to include the Director of the Office of National Drug Control Policy, and representatives of NIDA, NIAAA, SAMHSA, HRSA, as well as non-governmental organizations.

S. 2633 - The Senate Judiciary Committee approved a bill (S. 2633) sponsored by Joseph R. Biden Jr., (D-DE) that would include raves under a law that allows prosecutors to seek the destruction of crack houses. The bill would also require the U.S. Sentencing Commission to review federal sentencing guidelines for offenses involving the drug gamma hydroxybutyric acid (GHB).

Congressional Hearings and Visits

May 13, 2002 - NIDA staff participated in a briefing for House and Senate staff from several committees, on the NIDA evaluation of the ONDCP youth anti-drug media campaign. Hill staff included: Marcia Lee, Senate Judiciary staff; Jeff Ashford, House Appropriations Subcommittee on Treasury Postal Service; Charlie Diaz, drug policy advisor to the Speaker of the House; Dave Bucci, Mr. Portman's staff; Tony Haywood, Mr. Cumming's staff. The briefing was conducted by Drs. Peter Delany and James Colliver, NIDA and Drs. Dave Macklin and Robert Orwin, Westat.

May 14, 2002 - NIDA staff participated in a briefing for staff of the House Government Reform Subcommittee on Criminal Justice, Drug Policy and Human Resources. Drs. James Colliver and Peter Delany, NIDA conducted the briefing.

June 6, 2002 - NIDA staff participated in a briefing on the evaluation of the ONDCP Media Campaign for Walter Hearne, majority, and Mike Malone, minority staff of the House Appropriations Treasury Postal Subcommittee. Dr. Wilson Compton, Director, Division of Epidemiology, Services and Prevention Research (DESPR), and Dr. Susan Martin, project officer for the evaluation contract, conducted the briefing.

June 20, 2002 - Dr. Wilson Compton, Director, DESPR, testified at a hearing before the Subcommittee on Treasury Postal Service of House Appropriations Committee concerning the NIDA evaluation of the ONDCP Anti-Drug Youth Media Campaign.

July 23, 2002 - Dr. Glen R. Hanson, Acting Director, NIDA, briefed Rep. Patrick Kennedy (D-RI) on drug abuse research, particularly with regard to the commonalities of substance abuse and mental illness.

July 31, 2002 - Dr. Glen R. Hanson had a courtesy visit with Senator Orrin Hatch (R-UT) to discuss drug abuse research.

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International Activities

The **Seventh NIDA International Forum, Building International Research on Drug Abuse: Treatment Innovations**, was held June 13-15, 2002 in Quebec City, Canada, immediately following the Annual Scientific Meeting of the College on Problems of Drug Dependence. The 95 participants represented 27 countries and the World Health Organization, including 25 current and former NIDA Distinguished Scientists, INVEST Fellows, Visiting Scientists, Hubert H. Humphrey Drug Abuse Research Fellows, and WHO/NIDA/CPDD International Traveling Fellows. Through oral and abstract presentations, scientists reviewed advances in drug abuse treatment research. Presenters on two panels reported on international studies of heroin and methamphetamine treatment, while a third group of international researchers reviewed issues in clinical studies. A session on fellowships and research opportunities for international scientists featured presentations by Dr. Bill Dant, Institute of International Education; Dr. Aron Primarck, Fogarty International Center; and NIDA International Program Acting Director Dr. Steven Gust, who also planned the meeting. An afternoon workshop organized by Dr. Gust and Dr. Ivan Montoya, CCTN, focused on the design and implementation of drug abuse clinical trials, reviewing issues in study design, outcome measures, data analysis, data and safety monitoring, and regulatory issues. NIDA staff members and grantees who participated were: Dr. James D. Colliver, DESPR; Dr. Jennifer Schroeder, IRP; Dr. Jack Blaine, CCTN; Mr. Robert Walsh, DTRD; Ms. Dale Weiss, IP; Dr. Adam Bisaga, Columbia University; Dr. James Cornish, University of Pennsylvania; Dr. Paul Fudala, Philadelphia Veterans Affairs Medical Center; and Dr. Richard Rawson, University of California, Los Angeles.

CAMCODA staff, working with NIDA grantees and other individuals and organizations, developed seven proposals for satellite sessions for the **XIV International AIDS Conference**, held in July 2002 in Barcelona, Spain. The sessions included: 1) Youth Drug Abuse and HIV Infection in Cultural Context, organized by Jessica Campbell, Ph.D., of CAMCODA; 2) Impact of Health Disparities on HIV Interventions in Drug-Using Populations, organized by Dionne Jones, Ph.D., of CAMCODA; 3) Drug Abuse Treatment as HIV Prevention, organized by Katherine Davenny, M.P.H., of CAMCODA; 4) Effects of Drug Abuse and Sex Work on HIV Prevention Across National Borders, organized by Elizabeth Lambert, M.Sc., of CAMCODA; 5) HIV Risk Among Transgenders: The Social and Cultural Context of Substance Abuse, organized by Deborah Smith, M.D., of CAMCODA; 6) Clarifying the Controversy About Whether Drug Abuse Influences AIDS Progression, organized by Jag Khalsa, Ph.D., of CAMCODA; and 7) the Global Research Network on HIV Prevention in Drug-Using Populations, organized by the GRN Planning Committee, including Henry Francis, M.D., Helen Cesari, M.Sc., and Elizabeth Lambert, M.Sc., of CAMCODA.

Dr. Frank Vocci chaired an eighth satellite symposium on Psychostimulant Abuse and HIV Risk. Dr. Kyle Kampman spoke on "Drug Abuse Treatment as a Method of Reducing HIV Transmission among Cocaine and Alcohol-Dependent Men and Women in Philadelphia, Pennsylvania". Dr. Walter Ling spoke on "HIV Risk in Cocaine and Methamphetamine Users in Los Angeles." Dr. Mayat Htoo Razak spoke on " Amphetamine Type Stimulants (ATS) Use and Risk of HIV Infection: Public Concerns and the Public's Health". Dr. Robert Ali spoke on "Amphetamine Type Stimulants and HIV Risk Exposure in Australia". Dr. Vladimir Pozynak of the World Health organization was the discussant.

Dr. Arun Kumar Sharma, India, and Dr. Yehuda Neumark, Israel, were selected as the **2002 WHO/NIDA/CPDD International Traveling Fellows**. The awards support

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the researchers= collaborative visits with U.S. scientists and participation in two June 2002 scientific meetings, the NIDA-sponsored Building International Research on Drug Abuse: Treatment Innovations, and the College on Problems of Drug Dependence (CPDD) Annual Scientific Meeting. NIDA, the World Health Organization, and CPDD support the competitive International Traveling Fellowships. Dr. Sharma worked with Dr. Samuel Friedman, National Development Research Institute, to develop a draft research plan to study the drug-using and sexual networks of injection drug users in Delhi and determine the relationships between network variables, levels of risk behaviors, and the prevalence of HIV and other sexually transmitted diseases (STDs). An associate professor at the University College of Medical Sciences in Delhi, Dr. Sharma has conducted research on STDs, drug use, and sexual behaviors for the government of India, and has published articles in Indian medical journals. Dr. Neumark visited Dr. Robert Ballster, Medical College of Virginia, to develop plans for research on the etiology of inhalant abuse. A lecturer at Hebrew University of Jerusalem, Dr. Neumark was a NIDA-supported post-doctoral Fellow at Johns Hopkins University. He has conducted research on determinants of drug and alcohol abuse and on drug-, alcohol-, and sexual- risk behaviors of Israeli military personnel. Dr. Neumark has researched the genetic influences on alcohol consumption and metabolism in collaboration with Dr. T.K. Li, Indiana University, and has published articles in U.S. and Israeli scientific journals.

Three scientists have been selected as **INVEST Research Fellows** for 2002-2003: Dr. Tamo Nakamura, Australia; Dr. Yilang Tang, China; and Dr. Isabelle Husson, France. Each will spend a year in the United States working with a NIDA-supported scientist and receiving training in U.S. drug abuse research methods and the National Institutes of Health grant application process. Dr. Nakamura, University of New South Wales, will work with Dr. Anthony A. Wright, University of Texas Medical School at Houston to study the effects of diazepam on a visual same/different task in rhesus monkeys. Dr. Tang, Capital University of Medical Sciences, Beijing, will spend his fellowship year with Dr. Joseph F. Cubells, Yale University School of Medicine, researching the association between neuronal gene polymorphisms and cocaine-induced paranoia and psychotic symptoms. Dr. Husson, INSERM/H™pital R. DebrŽ, will work with Dr. Barry E. Kosofsky, Massachusetts General Hospital East/Harvard Medical School, conducting molecular analyses of sensitization to cocaine in adult mice exposed to cocaine in utero. Dr. Patricia Obando, Instituto sobre Alcoholismo y Farmacodependencia, IAFA, Costa Rica, who was selected as a 2001-2002 INVEST Fellow, began her fellowship in July. She is working with Dr. Dace Svikis, Virginia Commonwealth University, Richmond, VA, to study psychological dysregulation, drug abuse and social adjustment in Latin American adolescents. INVEST Research Fellows also participate in an orientation program at NIDA and receive travel support to attend scientific meetings. Fellows and their mentors jointly develop a collaborative research proposal for implementation in the Fellows' home country.

The four **Hubert H. Humphrey Drug Abuse Research Fellows** supported by NIDA during 2001-2002 each spent six weeks in a professional affiliation with a NIDA grantee. Dr. Monica Beg, Bangladesh, worked with Dr. Steffanie Strathdee, Johns Hopkins University, to develop skills in program evaluation, study design, instruments, staff training, and quality assurance for both observational and intervention studies, data management issues, and writing a draft grant proposal. Dr. Petra Exnerova, Czech Republic, interned with Michael Y. Townsend, Partnership for a Drug-Free America, to evaluate whether the nonprofit group's goals, strategies, operations, and programs could be adopted for use in the Czech Republic. Dr. Svitlana Pkhidenko, Ukraine, worked with Dr. George E. Bigelow, Johns Hopkins University, to learn more about behavioral and pharmacological effects of drug abuse and the role of psychiatric comorbidity in treatment and prognosis. She will evaluate whether clinical trials conducted by the Behavioral Pharmacology Research Unit at Hopkins could be adapted for use in Ukraine. Ms. Olga Toussova, Russia, joined Dr. David S. Metzger, University of Pennsylvania, to examine psychological factors associated with risk behaviors among drug users, counsel drug users at risk of HIV infection, conduct data analysis, and explore potential areas of future research.

Dr. Frank Vocci presented at the NIDA co-sponsored International Conference on Neuroscience and Addictions: New Developments, New Hopes, in Mexico City on June 25, 2002. His talk was titled, "New Pharmacological Treatments for Substance Dependence: Are They the Result of Advances in the Neurosciences? Can They Advance the Understanding of Dependence and Related Brain Processes?"

Dr. Don Vereen was the keynote speaker at a luncheon meeting sponsored by the Phelps Stokes Fund. The occasion was the program opening for the Multi-Regional Project on Drug Prevention, Treatment and Education. The goals of the project are to

identify the common interest among nations in combating substance abuse; to share local and national prevention strategies that have proven successful; to illustrate the roles of individuals, families, communities, schools, churches, businesses, civic groups, and organizations in dealing with substance abuse through prevention, education, treatment and research; and to provide a balanced view of the variety of methods of narcotics and substance abuse prevention, treatment, and education in the United States. Participants represented 12 different countries. In addition to Dr. Vereen, NIDA was represented by Dr. Eve Reider, DESPR, and by Dr. Steve Gust and Ms. Dale Weiss, International Program.

Drs. Steve Gust and Wilson Compton met with Dr. Wilbur Ricardo Grimson, from the Argentine Republic. Dr. Grimson is the Secretary of Programming for the Prevention of Drug Addiction and the Fight against Drug Traffic. Discussions included prevention, the Argentine socio-economic situation and its effect on drug issues and the training and exchange of professionals.

Dr. Steve Gust, International Program, Ms. Sheryl Massaro, Public Information and Liaison Branch, OSPC, Dr. Jacques Normand, DESPR, Dr. Jack Blaine, CCTN, and Dr. Vince Smeriglio, CAMCODA, met with a group of eight doctors from Uzbekistan. Information presented included dissemination techniques, epidemiology, treatment, and drug abuse and HIV/AIDS.

Dr. Steve Gust, International Program, Mr. David Anderson, Public Information and Liaison Branch, OSPC, Dr. Eve Reider, DESPR, and Dr. Peter Hartsock, and Ms. Helen Cesari, CAMCODA, met with eight visitors from Russia. The visitors were interested in, and presented information on, approaches to drug abuse prevention, approaches to HIV/AIDS prevention among intravenous drug users, establishing and running anti-drug media campaigns, and practices and concepts in diagnosing and understanding chemical dependency.

Dr. Eve Reider, DESPR, Ms. Jan Lipkin, Public Information and Liaison Branch, OSPC, and Ms. Dale Weiss, International Program met with a group of visitors from various Caribbean island nations. The group was part of a 21-day subregional project on Drug Reduction and Counter Narcotics organized to explore substance abuse in the United States, with a detailed examination of drug prevention, education, and treatment.

Dr. Melissa Racioppo, DTR&D, met with Dr. Lizbeth Barrera, a psychiatrist from Panama. Dr. Barrera was in the United States to become familiar with new and diverse therapies on drug abuse and prevention in the United States.

Drs. Elizabeth Robertson, DESPR and Jag Khalsa, CAMCODA and Ms. Dale Weiss, International Program, met with Ms. Ana Regina Noto from the Universedada Federal de S‹o Paulo, S‹o Paulo, Brazil. Discussions with Ms. Noto centered around prevention and HIV/AIDS.

Dr. William Corrigall, DNBR, presented a paper on Tobacco Addiction in a symposium focused on medications for addiction at the meeting of the Biotechnology International Organization (BIO 2002) in Toronto in June 2002. BIO is the global forum for biotechnology research and development.

Dr. Wilson Compton presented a paper on "Improving Services for Drug Abusers with Depression" at the International Federation of Psychiatric Epidemiology, Edmonton, Alberta, Canada, May 12-15, 2002.

Dr. Wilson Compton met with and presented on drug abuse prevention at NIDA on June 5, 2002 to members of Canadian Parliament, the "House of Commons Special Committee on the Non-Medical Use of Drugs." Members of Parliament included: Paddy Torsney, M.P., Carole-Marie Allard, M.P., Libby Davies, M.P., The Hon. Hedy Fry, M.P., Derek Lee, M.P., and Kevin Sorenson, M.P. Staff members included: Carole Chafe, Marilyn Pilon, Chantal Collin, Lise Tierney, Helene Regimbald, and Peter Douglas. Nicholas Dimic was present from the Canadian Embassy.

On May 17, 2002, Drs. Wilson Compton and James Colliver, DESPR, the Prevention Research Branch, Dr. Gilbert Botvin, Cornell University, and Dr. Edward Smith, Pennsylvania State University met with Ruth Joy and Paul Baker, Research Officers of the British Home Office on Drugs Strategy. The meeting was designed to provide technical assistance to Great Britain as they launch a nationwide skills-based drug abuse prevention program to be implemented through the schools. Ongoing assistance from NIDA is being provided.

Dr. Elizabeth Robertson presented at the Addictions 2002 meeting held in Einhoven, The Netherlands on September 15-17, 2002. The title of her presentation was: Re-

conceptualizing Prevention Research.

Members of the Division of Epidemiology, Services and Prevention Research (Drs. Jim Colliver, Elizabeth Robertson, Eve Reider, and Jacques Normand) met on May 6, 2002 to discuss issues of drug use and abuse with Dr. Carlo Bertorello, Italian representative to Pompidou Group and Member of the Conseil National de Recherche Institut de Physiologie Clinique de Pise, Dr. Rebecca Duane, Maya Lieble Institute, and Paolo Liebl von Schirach of the Maya Liebl Insitute.

Dr. Eve Reider met with and presented on drug abuse prevention research at NIDA on June 19, 2002 to a group of visitors from Russia, "Drug Abuse Prevention and Treatment: A Freedom Support Grant Project for Russia." Their visit was coordinated through the U.S. Department of State International Visitor Program and arranged by Meridian International Center.

On June 27, 2002, Dr. Vocci consulted with Dr. Franco Vaccarino and World Health Organization (WHO) officials and other scientists on a WHO document on neuroscience and addiction. The initial draft of the document is due this fall.

Dr. Steven Grant represented NIDA at the 2nd Biannual Motivational Neural Network meeting in Noordwijkerhout, Netherlands on June 29- July 2, 2002.

Dr. Peter I. Hartsock co-chaired the 10th International Conference on AIDS, Cancer, and Related Problems held at the University of St. Petersburg, St. Petersburg, Russia, May 25-31, 2002.

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Meetings/Conferences

The Office of National Drug Control Policy's Counter-Drug Technology Assessment Center and NIDA co-sponsored the 2002 ONDCP Demand Reduction Technology Symposium, "Technology Challenges to Support Drug Abuse Prevention and Treatment Research," in Cambridge, MA on July 8-10, 2002. Mr. Richard Millstein, Deputy Director, NIDA, presented the keynote address, "Applying Technology to Understanding Addiction." Dr. Joseph Frascella, Chief, Clinical Neurobiology Branch, DTR&D, moderated the session, "Probing the Human Brain to Find Better Treatments for Drug Abuse and Addiction." Dr. Eliot Gardner, of NIDA's Intramural Research Program was one of the 10 speakers at that session. Dr. Cindy Miner, Chief, Science Policy Branch, OSPC, moderated the session on "Genotype/Phenotype and the Vulnerability of the Human Brain to Drug Abuse." Dr. Jonathon Pollock, Chief, Genetics and Molecular Neurobiology Branch, DNBR, Dr. Elliot Stein, Chief, Neuroimaging Research Branch, Intramural Research Program, and Dr. Steven Grant of the Clinical Neurobiology Branch, DTR&D, were speakers in this session. Dr. Barry Hoffer, Director of the NIDA Intramural Research Program moderated the session, "What Are the Elements for Success?" Dr. Stein moderated the session, "How Do We Advance the Equipment Needed to Improve and Accelerate Our Research?" Drs. Frascella, Miner and Hoffer also presented their thoughts on future directions of technology in drug abuse research at the closing session.

The National Institute on Drug Abuse (NIDA) co-sponsored the 64th annual meeting of the **College on Problems of Drug Dependence (CPDD)**, in Quebec City, Quebec. More than 1,000 scientists gathered to discuss the latest research findings on drug abuse and dependence. The conference was held June 8-13, 2002 at the Hilton Hotel and the Quebec City Convention Center.

Drs. James Colliver and Meyer Glantz, DESPR, chaired a symposium at the CPDD meeting in June, 2002 in Quebec, Canada. The symposium, entitled **Longitudinal Studies of Pathways to Drug Abuse: Current Status, Emerging Findings, and Implications for Prevention**, brought together the principal investigators of several of the best designed and most comprehensive longitudinal studies of the development of drug abuse to discuss the current status of their research programs, present recent findings, identify emerging trends and patterns across studies, and highlight implications for prevention. Papers were presented by Drs. Laurie Chassin, Ralph Tarter, Thomas Wills, and Rolf Loeber, and Dr. Robert Pandina served as discussant.

On June 10, 2002 during the CPDD meeting in Quebec City, Drs. David McCann and Jane Acri (DTR&D) presented an evening workshop entitled **NIDA Medications Development Workshop: New Directions and Resources for Medicinal Chemists Targeting Biogenic Amine Transporters**. The workshop was aimed at medicinal chemists and their pharmacologist collaborators who are focusing on biogenic amine transporters (DAT, NET and/or SERT) as targets for the discovery of medications to treat drug dependence disorders. A new method for visualizing a compound's transporter selectivity, with regard to activity at the 3 different biogenic amine transporters, was presented. Using the new method for data analysis and graphing, the selectivity of marketed transporter compounds (bupropion, mazindol, etc.) and transporter compounds in clinical development (GBR-12909 and NS2359) were visualized and "gap areas" in transporter selectivity were identified. These gap areas represent transporter selectivity patterns for which there are no clinically available compounds and, therefore, they may serve to focus new medication discovery efforts. The new method was also used to visualize the selectivity patterns

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of the hundreds of novel transporter compounds that were submitted to NIDA's Cocaine Treatment Discovery Program over the past decade. Again, gap areas in transporter selectivity were identified. The theoretical pros and cons of including DAT, NET, and/or SERT inhibition activity in potential medications were discussed and the theoretical rationale (beyond "novelty") for pursuing the discovery of compounds with specific transporter selectivity patterns was presented. Finally, contract resources available to chemists (through NIDA) to support compound testing were summarized. It is hoped that this workshop will facilitate the discovery of novel transporter-directed medications for treating cocaine and other drug dependence disorders.

NIDA's Center on AIDS and Other Medical Consequences of Drug Abuse (CAMCODA) held a Working Meeting on **Strategies to Improve the Replicability, Sustainability, and Durability of HIV Prevention Interventions for Drug Users**, on May 6-7, 2002, in Chevy Chase, Maryland. The meeting brought together experts in the field of HIV prevention to exchange information on their current research on interventions to prevent HIV and other infectious diseases among drug users, their sexual partners, and other at-risk populations. Its focus was on strategies to improve the replicability, sustainability, and durability of interventions, and to address gaps and future directions in HIV prevention research in drug users and other populations at risk. Helen Cesari, M.Sc., and Elizabeth Lambert, M.Sc., of CAMCODA organized the Working Meeting, which was chaired by Wendee Wechsberg, Ph.D., of the Research Triangle Institute. Additional information about the meeting is now available on the NIDA website.

A science workshop on **Adolescent Decision Making: Proximal Processes in Adolescent Drug Abuse** organized and chaired by Drs. Kathy Etz from DESPR, Minda Lynch and Cora Lee Wetherington from DNBR, and Suman Rao from OSPC, was held in Bethesda, MD on July 19, 2002. Participants with expertise ranging from cognitive decision-making models, to neurobiological substrates engaged by affective processes, discussed high risk and pathological behaviors along a developmental continuum.

A scientific workshop entitled **Nonconscious Processes in Self-Regulation: Application to Drug Abuse and Addiction**, organized and chaired by Dr. Paul Schnur, DNBR, was held on July 22-23, 2002, at the Neuroscience Center in Rockville, MD. Participants discussed a role for learning processes in physiological and behavioral regulation, the influence of homeostatic variables, impulsivity as regulation directed to positive versus negative goals. Parallels were drawn to compulsive, excessive patterns of drug abuse and interpretations discussed in regard to automatic behaviors and nonconscious processes.

A symposium on **Drug Abuse Relapse-Behavioral and Neurobiological Perspectives**, organized and co-chaired by Dr. David Shurtleff, DNBR, and Dr. Lisa Onken, DTR&D was held on August 25,2002 at the Annual Meeting of the American Psychological Association (APA) in Chicago, IL. The participants and the titles of their presentations included: Dr. Peter Kalivas, Medical University of South Carolina, "Neural Circuitry Mediating Relapse," Dr. Rajita Sinha, Yale University, "Stress, Drug Cues and Cocaine Relapse: Neurobiological and Cognitive Correlates, " Dr. Thomas Piasecki, University of Missouri, Columbia, " Individual Differences in Smoking Withdrawal Dynamics and Smoking Relapse," and Dr. Saul Shiffman, University of Pittsburgh, "Real Time Data on Relapse."

On July 24, 2002, NIDA Acting Director, Dr. Glen Hanson and other NIDA senior staff members briefed Dr. Andrea Barthwell and the ONDCP demand reduction staff on NIDA's research programs and future directions.

A CCTN training session entitled "How to Monitor Clinical Trials for GCP Compliance" was conducted with members of the Network on August 11-12, 2002, in Seattle, Washington. A second training session will be held October 24-25, 2002, in Bethesda, MD.

Drs. Wilson Compton, Peter Delany, Elizabeth Robertson, Eve Reider, and Aria Crump of DESPR sponsored a meeting with representatives of the Casey Family Foundation, SAMHSA, and prevention researchers to provide technical assistance on the Casey/SAMHSA Starting Early Starting Smart (SESS) program. Scientists in attendance were: Margaret Burchinal, Ph.D., University of North Carolina at Chapel Hill; Nicholas Ialongo, Ph.D., Johns Hopkins University; Jill G. Joseph, M.D., Ph.D. Director, Center for Health Services and Clinical Research Children's Medical Center, George Washington University; Philip Leaf, Ph.D., Johns Hopkins University; Fred Springer, EMT Associates and Director of the SESS Data Coordinating Center; and Daniel Shaw, Ph.D., University of Pittsburgh. Casey Family Programs representatives

included: Barbara Kelly Duncan, M.Ed., Vice President, Enterprise Development; Jean McIntosh, M.S.W., Executive Vice President, Strategic Planning and Program Development; Eileen O'Brien, Ph.D., Senior Enterprise Development Specialist for Federal Partnerships; Peter J. Pecora, Ph.D., Senior Director, Research Services and Professor, University of Washington. This program was formerly sponsored by CSAP. Representatives from SAMHSA included: Michele Basen, M.P.A.; Pat Sabry, M.A; Paul Brounstein, Ph.D.; Sybil Goldman, Ph.D.; Soledad Sambrano, Ph.D..

On May 8, 2002, the Prevention Research Branch, DESPR, hosted a presentation by Dr. Mary Jane Rotheram-Borus and Mr. Mark Etzel from the University of California at Los Angeles. The title of the presentation was Prevention Programming for HIV Positive Youth. Following the presentation Dr. Rotheram-Borus met with the Street Youth Interest Group to provide technical assistance on ideas related to research on street youth.

Drs. Elizabeth Robertson, DESPR, Timothy Condon, OSPC, Eve Reider, DESPR, Jack Stein, OSPC, and Suman Rao, OSPC, provided a technical assistance workshop at the University of North Carolina Chapel Hill on May 20 and 21, 2002. The purpose of the workshop was to provide expertise in the areas of program development and evaluation for a pilot project of the National Families in Action (Ms. Sue Rusche, Director) titled The National Parent Corp. Over 20 scientists primarily from North Carolina attended along with Ms. Sue Rusche and three scientists from outside the state: Drs. Richard Catalano, University of Washington, Michael Hecht, Pennsylvania State University and Steve Sussman, USC.

A workgroup composed of representatives from several NIH Institutes met on July 23, 2002, and discussed "Safety Monitoring in Behavioral Trials". The participants discussed current regulations and guidelines; current experiences in Adverse Event reporting in behavioral trials; and next steps for the workgroup.

On April 26, 2002, the Division of Epidemiology, Services, and Prevention Research hosted a presentation by Drs. Lynne Vernon-Feagans and Martha Cox at University of North Carolina, and Dr. Mark Greenberg at Pennsylvania State University. The title of the presentation was Families Living in Rural Poverty: Environmental and Biological Influences Related to Alcohol and Drug Abuse.

On June 26, 2002, the Division of Epidemiology, Services, and Prevention Research hosted a presentation by Drs. Michael Dennis and Christy Scott on promising models for treating addiction as a chronic, relapsing condition.

Rafael de la Torre, Pharm.D., Ph.D., Head, Pharmacology Unit, IMIM, Barcelona, Spain, at the invitation of NIDA's Club Drugs Workgroup, spoke on July 26, 2002 on the Involvement of Drug Metabolism in MDMA ("Ecstasy") Pharmacology and Neurotoxicity.

Mr. Richard A. Millstein, Deputy Director, NIDA, spoke on NIDA's three RFAs comprising the NIDA National Prevention Research Initiative at the annual meeting of the Society for Prevention Research, Seattle, Washington, May 30-June 1, 2002.

Mr. Millstein chaired a symposium, "Drugs and Crime," at the annual meeting of the College on Problems of Drug Dependence, Quebec City, Quebec, Canada, June 9-13, 2002.

Mr. Millstein represented NIDA at the American Association of Immunologists' Public Service Award recognition for NIH Deputy Director, Dr. Ruth Kirschstein, Bethesda, Maryland, June 18, 2002.

Mr. Millstein met with Mr. Robert Morrison, Director of Public Policy, National Association of State Alcohol and Drug Abuse Directors (NASADAD), Ms. Lizbet Boroughs, Director of Government Relations, American Psychiatric Association, and Mr. Andrew Kessler, Director of Government Relations, American Psychological Society about opportunities for NIDA and their organizations to work collaboratively, Bethesda, Maryland, July 2, 2002.

Mr. Millstein spoke at the NIDA/CCTN-sponsored meeting on Safety Monitoring and Reporting in Behavioral Clinical Trials, Bethesda, MD, July 23, 2002. NIDA, NIMH, NIAAA, NHLBI, NIH Office of the Director and pharmaceutical company officials presented and initiated a dialogue.

Mr. Millstein presented remarks at the NIDA/CAMCODA-sponsored working meeting, "HIV/AIDS in the Caribbean," Washington, DC, August 15, 2002. Representatives of CARIB, NIDA, NIAAA, NIMH, NIH Office of AIDS Research, and Caribbean Basin

nations began a dialogue on enhancing research on drug abuse-related HIV/AIDS in this region of the world.

Mr. Millstein participated in the Clinical Review of NIDA's Intramural Research Program, Baltimore, MD, September 12-13, 2002.

Dr. Timothy P. Condon presented "Addiction as a Brain Disease: Implications for Prevention and Treatment" and discussed NIDA program initiatives with NIDA-funded investigators at the University of Kentucky, Lexington on May 24 and 25, 2002.

Dr. Timothy P. Condon presented "Addiction as a Brain Disease: Implications for Drug Abuse Treatment," on May 30, 2002 at the Substance Abuse Treatment Symposium in Sacramento, California.

Dr. Timothy P. Condon spoke at the CADCA Mid-Year Training Institute on "New Advances in Drug Prevention Research," on August 8, 2002 in Seattle, Washington.

Dr. Timothy P. Condon participated in the American Psychological Association 2002 Annual Convention, August 21-25, 2002 in Chicago, Illinois.

Dr. Timothy P. Condon presented "Drug Abuse Research Update: Communicating Science Fact, Not Science Fiction" at the Partnership for a Drug-Free America Leadership Conference in Chicago, Illinois on September 6, 2002.

Dr. Timothy P. Condon presented on substance abuse after 9/11, at The New York Academy of Medicine conference "One Year After 9/11: What Have We Learned and Where Do We Go From Here?" on September 9, 2002 in New York, New York.

Dr. Jack Stein, Deputy Director, OSPC, presented "Update on NIDA Research" at the Los Angeles Gay & Lesbian Center's Third Annual Lesbian, Gay, Bisexual and Transgender (LGBT) Health Roundtable in Los Angeles, CA on June 7, 2002.

Drs. Cindy Miner, Chief, Science Policy Branch, OSPC, and Suman Rao, OSPC, organized NIDA's Grant Writing Workshop at CPDD in Quebec City, Canada. Presentations were made by Drs. Cindy Miner, David Shurtleff, and Mark Sweiter from NIDA and Dr. Scott Lukas from McLean Hospital.

Dr. Suman Rao, OSPC, coordinated and moderated the NIDA Tutorials at CPDD in Quebec City, Canada. Speakers at the 2002 Tutorials were Nicholas Goeders, Louisiana Health Sciences Center-Shreveport, Alexandros Makriyannis, University of Connecticut, John Gatley, Brookhaven National Laboratory, and Andrew Health, Washington University School of Medicine.

Drs. Cindy Miner and Suman Rao, OSPC, organized the NIDA Training Director's Meeting for the Directors of T32 Institutional Training Grant sites from across the country. The meeting was held in Rockville, MD on September 13, 2002.

On May 6 -7, 2002, Ana Anders, Senior Advisor on Special Populations, co-chaired a meeting with the National Council of La Raza for a HRSA, CSAT and NIDA collaborative project entitled, "Sharing Success" in Washington, D.C.

On May 23, 2002, Ana Anders, along with NIDA grantee Jose Szapocznik, Ph.D., briefed Dr. Andrea Barthwell, Director of Demand Reduction, ONDCP, on the National Hispanic Science Network on Drug Abuse in Washington, D.C.

On June 10-13, 2002, Ana Anders made a presentation on Hispanic drug abuse research to health professionals at the University Menendez Pelayo in Valencia, Spain.

Ana Anders served as mentor and supervisor for a Hispanic Association of Colleges and Universities (HACU) summer intern from June - August, 2002.

On July 18, 2002, Ana Anders presented information on NIDA's Hispanic Initiative to a group of University faculty from the HACU organization at a meeting sponsored by NIMH in Bethesda, MD.

On July 23, 2002, Ana Anders presented and moderated a panel on drug research, prevention, and treatment at the National Council of La Raza annual conference in Miami, FL.

On July 30, 2002, Ana Anders presented information on NIDA's Hispanic Initiative at a conference sponsored by the University of Georgia in Athens, GA.

On August 9, 2002, Ana Anders met with a delegation of Puerto Rican scientists from the University of Puerto Rico at a NIMH sponsored meeting in Bethesda, MD.

On May 2, 2002, Dr. Donald Vereen, Acting Chief, Special Populations, was the keynote speaker at the 5th annual conference on "Counseling African American Families" in Houston, Texas.

On May 13, 2002, Dr. Donald Vereen was a speaker at a Substance Abuse and Mental Health symposium, sponsored by the Department of Psychiatry at Howard University's Medical School. The symposium was held in Washington, D.C.

On June 27, 2002, Dr. Donald Vereen was a keynote speaker at the Mississippi Mental Health Summit in Jackson, MS.

On August 4-6, Dr. Donald Vereen made two presentations and chaired a panel at the Annual Convention and Scientific Assembly of the National Medical Society in Honolulu, HI.

On May 20, 2002, Dr. Donald Vereen represented NIDA at the inaugural meeting of the State Department sponsored Campaign Against Commercial Sexual Exploitation of Children in Washington, D.C.

On May 22, 2002, Dr. Donald Vereen delivered a Grand Rounds presentation to the Maine Medical Center in Portland, Maine.

On May 29, 2002, Dr. Donald Vereen was a speaker at the 35th Anniversary conference of the Dwight Ashbury Free Clinic in San Francisco, CA.

On May 30, 2002, Dr. Donald Vereen was a keynote speaker at the National Association of Counties (NAC) annual meeting in Dallas, TX.

On June 21, 2002, Dr. Donald Vereen was a speaker at the annual convention of the Medical Association of Jamaica in Kinston, JA.

On August 19, 2002, Dr. Donald Vereen was a presenter at the Air Force Alcohol and Drug Abuse Prevention and Treatment/Demand Reduction conference in Denver, CO.

On July 8, 2002, Dr. Peter I. Hartsock represented the Department at the annual Interagency Arctic Research Policy Committee (IARPC) Seniors Meeting at the National Science Foundation, Arlington, VA. Jerry Frankenheim spoke at the University of Virginia School of Medicine, Charlottesville on MDMA - 'Ecstasy,' or 'Despair'" on June 4, 2002. This was a NIDA Club Drugs Workgroup activity.

Dr. Cora Lee Wetherington, DNBR and NIDA's Women & Gender Research Coordinator, participated in the ORWH-sponsored meeting of the principal investigators from the 12 ORWH-funded women's health centers on July 12, 2002, in Bethesda, MD. Established in response to the RFA, "Building Interdisciplinary Research Careers in Women's Health" (BIRCWH), these K12 centers provide for mentoring and protected time for research by junior faculty members wishing to pursue a program of research on women's health and gender differences. Three of these 12 BIRCWHs are co-funded by NIDA. They are located at the University of Kentucky (Emory Wilson, PI), Virginia Commonwealth University (Roy Pickens, PI), and Yale University (Carolyn Mazure, PI).

At the American Psychological Association annual meeting, Aug 22-25, 2002, in Chicago, Dr. Cora Lee Wetherington, DNBR and NIDA's Women & Gender Research Coordinator, co-chaired a session on "Prescription Opioid Abuse: The Problem Seen from Multiple Perspectives," with Dr. James Zacny from the University of Chicago. The speakers and presentation titles were as follows: Drs. Jim Zacny, "Prescription Opioids and Abuse Liability Issues;" Peggy Compton, UCLA, "Epidemiology of Prescription Opioid Abuse;" Christine A. Sannerud, DEA, Role of Governmental Agencies in Preventing Prescription Opioid Diversion; and June L. Dahl, "Impact of Opioid Abuse on Legitimate Use: Stigmatization, Opiophobia, Under-Medication." Dr. Davied Thomas, DNBR, NIDA served as the session's discussant.

At the American Psychological Association annual meeting, Aug 22-25, 2002, in Chicago, Dr. Cora Lee Wetherington, DNBR and NIDA's Women & Gender Research Coordinator, participated in the Executive Committee meeting of Division 28: Psychopharmacology and Substance Abuse. Dr. Wetherington serves as a Member-at-Large on the Executive Committee.

At the annual meeting of the Society for Behavioral Neuroendocrinology, June 26-30, 2002, in Amherst, MA, Dr. Susan Volman, DNBR, was the discussant for a symposium on Neuroendocrinology of Motivation and Reward. The keynote speaker was Dr. Barry Everitt, University of Cambridge, whose presentation was entitled "From Sexual Behavior to Drug Addiction via Associative and Motivational Systems in the Brain".

Other participants were: Dr. Lique Coolen, University of Cincinnati, "Motivating Circuits: Common Substrates for Sex and Drugs;" Dr. Jill Becker, University of Michigan "Rapid Effects of Estrogen on Dopamine Systems: Effects on Motivated Behaviors;" Dr. Elaine Hull, SUNY, Buffalo, "Sex and the Single Rat: Tales of Dopamine and Serotonin;" and Dr. Thomas Insel, Emory University, "Is Love an Addictive Disorder?"

Dr. Susan Volman, DNBR, represented NIDA at 5th International Zebrafish Development and Genetics meeting, June 12-16, 2002, in Madison, WI. With representatives from other NIH Institutes, she spoke in an information session on opportunities for funding and NIH interest in research using this model organism. Dr. Volman emphasized NIDA's encouragement of the use of zebrafish for behavioral and systems neurobiological studies.

Dr. William Corrigall, DNBR, attended a conference in Providence RI in June 2002 at which progress in the Transdisciplinary Tobacco Use Research Centers was reviewed. NIDA co-funds these centers with NCI and the Robert Wood Johnson Foundation. This meeting allowed NIDA to gain additional insights to the overall performance of the centers as they complete their 3rd year of support.

Dr. James Colliver, DESPR, gave a presentation entitled "Drugs of Abuse: Overview of Epidemiologic Patterns" at the Structural Biology and Structural Genomics/Proteomics Symposium chaired by Dr. Rao Rapaka, DNBR, May 8-10, 2002 in Bethesda, MD.

Dr. Jerry Flanzer, DESPR, presented a lecture on "The Relationship of Substance Abuse and Child Abuse and Neglect Services as Influenced by the Recent Welfare Reform Act" to the Senior staff of the Children's Bureau, Administration of Child, Youth and Families, HHS, Washington, DC, May 16, 2002.

Drs. Jerry Flanzer and Thomas Hilton, DESPR, led the drug abuse researchers caucus, June 25, 2002, and participated in the federal workshop on grantmanship on June 23, 2002 at the Academy of Health Services Research and Health Policy's Annual Conference, Hilton Hotel, Washington, D.C.

Drs. Jerry Flanzer and Peter Delany, DESPR, led a grantmanship workshop for potential principal investigators, at the National Association of Drug Court Professionals' (NADCPs') 8th Annual Drug Court Training Conference, held in Washington, DC at the Marriott Wardman Park on Connecticut Avenue, NW, June 13, 2002.

Dr. Aria Crump, DESPR, presented a paper at the Society for Prevention Research Conference in Seattle, Washington on June 1, 2002. The paper was entitled "Going Places: Persuasive Communications in the Context of a School-Based Problem Behavior Prevention Program."

Drs. Shakeh Jackie Kaftarian and Elizabeth Robertson, DESPR, organized and made a presentation at a session titled " NIDA's New Initiatives: Will they Complete the Cycle of Prevention Research to Practice?" on June 1, 2002 at the annual meeting of the Society for Prevention Research in Seattle, Washington.

Drs. Shakeh Jackie Kaftarian and Elizabeth Robertson presented a seminar at the Safe and Drug-Free Schools Program, National Technical Assistance Meeting August 5-7, 2002, at the Marriott Wardman, Washington, D.C.

On July 25, 2002, Dr. Susan Martin, DESPR, chaired a breakout group focused on Community Violence as part of a meeting on "Children's Exposure to Violence: Current Status, Gaps, and Research Priorities" organized by NICHD, cosponsored by NIDA, and held at the Georgetown Holiday Inn, Washington, D.C.

On August 8 and 9, 2002, Dr. Susan Martin convened an Expert Panel meeting entitled "The ONDCP Youth Anti-Drug Media Campaign Evaluation: Balancing Continuity and Change in the Next Iteration." Participants included research design experts Patrick O'Malley, University of Michigan, David McKinnon, University of Arizona, Joseph Schafer, Pennsylvania State University, and Steve Thompson, Pennsylvania State University; youth development and drug use specialists Steve Buca, Harvard University, Phyllis Ellickson, RAND, and Helene White, Rutgers; and persuasive communications researchers including William Crano, Claremont Graduate School, Brian Flynn, University of Vermont, Nancy Harrington, University of Kentucky, Leslie Snyder, University of Connecticut, and Jerome Williams, Howard University. After initial briefings by ONDCP Campaign staff and the current evaluators from Westat and the Annenberg School of Communications, the experts systematically reviewed all aspects of the ongoing study, and identified modifications and additions

to strengthen further study.

Dr. William Cartwright, DESPR, presented a lecture, Costs and Drug Courts, to the National Association of Drug Court Professionals' (NADCPs') 8th Annual Drug Court Training Conference, taking place in Washington, DC at the Marriott Wardman Park on Connecticut Avenue, NW, June 15, 2002.

Dr. Thomas Hilton, DESPR, presented a paper co-authored by Drs. Flanzer, Fletcher, and Cartwright, all of DESPR, entitled, "Resistance to Innovation Among US Drug Abuse Treatment Providers: When Organizational Knowledge Interferes With Organizational Learning" at the 3rd European Conference on Organizational Knowledge, Learning, and Capabilities (OKLC 2002) in Athens Greece April 4-6, 2002.

Dr. Kathy Etz, DESPR, presented a paper entitled "Developmental Science: Bridges to Drug Abuse Research" at the annual meetings for the Society for Prevention Research in Seattle, Washington on June 1, 2002.

Dr. Jack Blaine, CCTN, participated in a meeting on " Research Priorities Suggested by Providers" sponsored by the NIAAA in Bethesda on April 19, 2002.

On May 13, 2002, Dr. Betty Tai, Director, CCTN, presented an update on the NIDA CTN to the EU Demand Reduction Seminar sponsored by the White House ONDCP.

The CTN Data and Safety Monitoring Board met July 22-23, 2002. The Board reviewed the current trials for safety and scientific integrity. The meetings addressed: 1) reports on all Serious Adverse Events; 2) the trials' progress; 3) review of a new protocol; and 4) discussion of current issues.

On May 23, 2002, Drs. Ling Chin and Paul Wakim, CCTN, presented "Clinical Trials for the Layman" to NIDA personnel as part of the Director's "Science for the Layman" series.

On June 21, 2002, Dr. Janet Levy, CCTN, presented "CTN Data Management System" as part of the CCTN Classroom series.

On July 2, 2002, Dr. Betty Tai, Director, CCTN, gave a presentation on the Clinical Trials Network to representatives from NASADAD, APA, and APS.

On July 17 Jacquelyn Goldberg, J.D., gave a presentation on NCI's Central Institutional Review Board as part of the CCTN Classroom series.

Dr. Frank Vocci spoke at the CSAT sponsored Buprenorphine Stakeholders Meeting on July 26, 2002, in Bethesda. His presentation was on recent clinical trials with buprenorphine and buprenorphine/naloxone products.

Dr. Frank Vocci was a discussant at a Medications Development Symposium on the development of cocaine dependence pharmacotherapies at the American Psychological Association meeting in Chicago on August 23, 2002.

Dr. Cece McNamara, DTR&D, presented a talk entitled "Contingency Management and the Stage Model" to the Contingency Management Workgroup June 10, 2002 in Quebec City, Quebec, Canada to inform the field of NIDA's continuing interest in contingency management research.

Dr. Cece McNamara, DTR&D, gave a presentation on Drug Abuse Treatment Development Research and participated in a day long seminar for graduate students attending the NIDA sponsored National Hispanic Science Network Training Institute on Hispanic Drug Use in Houston Texas June 18, 2002.

Dr. Lisa Onken, BTDB Chief, DTR&D, gave a presentation on the Stage Model of Behavioral Treatment Development to the CSAT Targeted Capacity Expansion Grantees and Evaluators on June 25th and 28th, 2002. The BTDB branch staff attended these talks to provide technical assistance to potential grantees.

Dr. Debbie Grossman, BTDB, DTR&D, participated in the Youth Tobacco Cessation Collaborative Meeting on June 3, 2002 in Washington, D.C.

Dr. Dorynne Czechowicz, DTR&D, participated in a CSAT meeting to review Clinical Guidelines on LAAM in June, 2002.

Drs. Steven Grant, Ro Nemeth-Coslett, and Joseph Frascella of the Clinical Neurobiology Branch participated in the organization and conduct of the NIDA-sponsored meeting on "Youth, Internet, and Drugs" held in Rockville, MD on June 6, 2002.

Dr. Joseph Frascella gave a presentation entitled "NIH Grant Proposal Writing: Some Hints and Strategies" at the "National Hispanic Science Network Summer Research Training Institute on Drug Abuse" in Houston, Texas on June 23, 2002.

Dr. Jonathan L. Katz, IRP, was invited to present a paper entitled "Cocaine-Induced Locomotor Activity and Cocaine Discrimination in Dopamine D4 Receptor Mutant Mice" at Dopamine 2002, a Satellite Symposium of the IUPHAR Congress, in Portland OR, July, 10-14, 2002.

Dr. Santosh S. Kulkarni, IRP, was accepted as a poster presenter at the 2002 Gordon Conference on Medicinal Chemistry, New London, NH, August 4-9, 2002.

Dr. Amy H. Newman, IRP, was invited to present a seminar entitled "Three Generations of N-Substituted Benztropine Analogues as Potential Medications for Cocaine Abuse" at the Department of Pharmacology, University of North Texas Health Science Center at Fort Worth, July 9, 2002.

Dr. Toni S. Shippenberg, Behavioral Neuroscience Branch, IRP, chaired a symposium entitled: "Opiate Dependence and Addiction: The Neuropeptide/GABA Connection" at the 33rd International Narcotics Research Conference held July 9-14, 2002 in Pacific Grove, CA.

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Press Releases

April 8, 2002 - **NIDA NewsScan**

- Special Issue of Psychoneuroendocrinology

As a result of NewsScan promotion, coverage appeared in *USA Today, The Washington Post* and *Alcoholism & Drug Abuse Weekly*.

April 9, 2002 - **Significant Deficits in Mental Skills Observed in Toddlers Exposed to Cocaine Before Birth**. A study conducted by researchers from Case Western Reserve University in Cleveland found that children exposed to cocaine before birth were twice as likely to have significant delays in mental skills by age 2, compared to other toddlers with similar backgrounds but whose mothers had not used cocaine during pregnancy. According to the researchers it is probable that these cocaine-exposed children will continue to have learning difficulties and an increased need for special educational services when they reach school age. The study was published in the April 17, 2002 issue of the Journal of the American Medical Association. Coverage of this release appeared in *Women's Health Weekly, The Boston Herald, National Public Radio, Associated Press* and *Substance Abuse Letter*.

April 24, 2002 - **Research Yields New Insights into Molecular Control of Addiction**. In research employing fruit flies, scientists at the University of Arizona have provided new insights into how molecules may control addiction, memory formation, and brain plasticity. Their research has provided the first evidence that the molecule AP1, which helps to regulate changes in the manufacture of certain proteins in brain cells, also is required for long-term changes in the function of synapses (the connections between brain cells). This NIDA funded study was published in the April 25, 2002 issue of Nature. Coverage of this release appeared in *The Sun Herald* and *Alcoholism & Drug Abuse Weekly*.

May 1, 2002 - **Study Quantifies Cost-Benefit of Family Interventions Designed to Prevent Adolescent Alcohol Use**. Iowa State University researchers have calculated that brief family intervention programs designed to discourage teen drinking are both beneficial and cost-effective. Their study found that each dollar spent on intervention programs for adolescents was returned many times over in savings by preventing future costs associated with alcohol problems in adulthood. The research was published in the *Journal of Studies on Alcohol*. Coverage of this release appeared in *Alcoholism & Drug Abuse Weekly*.

May 10, 2002 - **6th Annual PRISM Award Winners**. "Blow," starring Johnny Depp and Penelope Cruz, received the PRISM Award in the Theatrical Feature Film category at the 6th Annual PRISM Awards[a] held May 9, 2002 at CBS Television City in Los Angeles. Other PRISM's were awarded to ABC's "My Wife and Kids" and "All My Children," Lifetime's "The Division," NBC's "Third Watch," and ABC's "Life With Judy Garland: Me and My Shadows." A PRISM also went to Ozzy Osbourne for his song "Junkie" in the Music Recording or Music Video category, one of two new categories to receive a PRISM this year. Independent films "Acts of Worship" and "Smoke and Mirrors: A History of Denial" were the recipients of the other new category, the PRISM Film Festival Award, which is presented to films that have not yet been released but are playing the festival circuit. In total, 14 winners were selected out of 56 nominees and 236 submissions. Coverage of this event appeared in *USA Today, Los Angeles*

Times, Daily Variety, Associated Press, The Hollywood Reporter, The Washington Post and *Entertainment Tonight*.

May 28, 2002 - **Substance Abuse Increases in New York City in Aftermath of September 11th**. Survey results indicate that smoking, alcohol and marijuana use increased among residents of Manhattan during the five to eight weeks after the terrorist attacks on the World Trade Center. Almost one-third of the nearly 1,000 persons interviewed reported an increased use of alcohol, marijuana, or tobacco following the terrorist attacks. The largest increase was in alcohol use. The survey results appear in the June 1, 2002 issue of the American Journal of Epidemiology. Coverage of this release appeared in *Associated Press, The New York Times, Los Angeles Times, USA Today, The Washington Post, Join Together Online, Sun-Sentinel, Reuters Health Information,* and *Alcoholism & Drug Abuse Weekly*.

May 28, 2002 - **NIDA NewsScan**

- Dopamine May Play Role in Cue-Induced Craving Distinct from Its Role Regulating Reward Effects
- Long-Term Cognitive Impairment Found in Crack-Cocaine Abusers
- Neuronal Differences in Brain Regions Involved in Decision-Making and Other Functions Observed for the First Time in Chronic Users of Cocaine
- Drug Used in Treatment of Alcoholism May Have Role in the Treatment of HIV

June 5, 2002 - **Study Reports Preliminary Findings Related to Methamphetamine**. Scientists from The Ohio State University are examining the interaction between methamphetamine use and feline immunodeficiency virus (FIV) to determine whether such research may offer insights that would aid in developing treatments for drug-using individuals who are infected with human immunodeficiency virus (HIV). In their study, published in the June issue of the Journal of Neurovirology, the researchers found that methamphetamine exposure significantly increased the replication of FIV in certain brain cells called astrocytes, suggesting that the amount of FIV also may be increased in the brain. Astrocytes comprise the largest cell population in the brain, and provide structural and physiological support for brain neurons. Coverage of this release appeared in *Time, The New York Times, The Washington Times, Nature, The Columbus Dispatch, United Press, AIDS Weekly, Washington Fax* and *Associated Press*.

June 6, 2002 - **Scientists Gather in Quebec to Discuss Drug Abuse**. More than 1,000 scientists and physicians met at the 64th annual meeting of the College on Problems of Drug Dependence (CPDD) in Quebec City, Quebec, to discuss the latest research findings on drug abuse and dependence. The conference, partially sponsored by the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health in the United States, was held June 8-13, 2002 at the Hilton Hotel and the Quebec City Convention Center.

June 24, 2002 - **NIDA NewsScan**

- *Journal of General Internal Medicine* Produces Special Issue on Substance Abuse
- Cocaine Use Linked to Poor Adherence To Antiretroviral Therapy in HIV Patients
- Physicians, Residents Report Experiencing Less Professional Satisfaction in Treating Substance-Abusing Patients
- Integrated Medical/Substance Abuse Treatment Increases Likelihood of Patients' Continuing Substance Abuse Treatment
- Needle-Exchange Program Found to Reduce Emergency Room Visits Among Intravenous Drug Users

As a result of NewsScan promotion, coverage appeared in *AIDS Weekly, Virus Weekly* and *Medical Letter on the CDC and FDA*.

July 7, 2002 - **Exposure to Hepatitis C Has No Effect on Antiretroviral Treatment Outcomes in HIV Patients**. A study of HIV-infected patients in Baltimore, Maryland, revealed that individuals seropositive for hepatitis C had similar clinical outcome measures when treated with antiretroviral drug regimens compared to seronegative patients. These findings were presented in a press conference at the XIV International AIDS Conference held in Barcelona, Spain, July 7-12, 2002.

Coverage of this release appeared in *Los Angeles Times, Newsday, United Press* and *The Advertiser*.

July 8, 2002 - **NIDA to Host Satellite Meetings on HIV & Drug Use at the XIV International AIDS Conference**. Under the auspices of the XIV International AIDS Conference held in July 2002, the National Institute on Drug Abuse (NIDA) hosted a series of satellite meetings to highlight the latest national trends and scientific findings by leading researchers on drug abuse and HIV/AIDS. Coverage of this event appeared in *The Washington Times*.

July 11, 2002 - **NIDA Launches New Publication For Researcher-Provider Dialogue**. NIDA launched Science & Practice Perspectives, a new publication that promotes a practical, creative dialogue between researchers and treatment providers. Published twice a year, the exchange of information, observations, and insights is expected to help clinicians maximize their programs and treatment outcomes, while helping researchers construct new hypotheses and design studies relevant to the needs of providers and patients. Coverage of this release appeared in *Join Together Online*.

Articles of Interest

May 1, 2002, *Reason Online* - "Hungry for the Next Fix" - Interview with Alan I. Leshner, Ph.D.

May 30, 2002, *CNN.com* - "Beefing Up While Forfeiting Health" -Interview with Dr. Linn Goldberg.

June 4, 2002, *The Washington Post* - "The Real Dope" - NIDA mentioned.

June 9, 2002, *The Washington Post* - "Breaking Out of the 12-Step Lockstep" - NIDA mentioned.

June 10, 2002, *Alcoholism & Drug Abuse Weekly* - "Study Finds Link Between Methamphetamine, HIV-Dementia" - Interview with Glen R. Hanson, Ph.D., D.D.S.

June 11, 2002, *USA Today* - "Heroin Withdrawal Drug Proves Successful" - Interview with Frank Vocci, Ph.D.

July/August 2002, *Health* - "Ecstasy for Agony" - Interview with Glen R. Hanson, Ph.D., D.D.S.

Dr. Frank Vocci has been working as a scientific consultant to BioSci Ed, a group that publishes a magazine YOUR WORLD on biotechnology for 7th to 12th grade students. An issue in the fall will be devoted to drug abuse and alcohol effects on the brain.

Dr. Frank Vocci was interviewed by Mr. Randy Schmid of the AP on June 10, 2002 on the efficacy results of the multi-center Lofexidine trial.

Dr. Frank Vocci was interviewed by Mr. Andy Coghlan of New Scientist magazine on June 12, 2002 regarding the nicotine vaccine research that NIDA is funding.

Dr. Frank Vocci was interviewed by Mr. John Keilman of the Chicago Tribune on July 3, 2002 regarding the development of buprenorphine and buprenorphine/naloxone for the treatment of opiate dependence.

Dr. Frank Vocci was interviewed by Mr. Todd Mundt of NPR on July 11, 2002 regarding the development of the nicotine vaccine.

Dr. Frank Vocci was interviewed by Ms. Kitta McPherson of the New Jersey Star Ledger on July 19, 2002 regarding the progress made in the understanding of the neurobiology of addiction and how this is influencing new directions in treatment research and medications development.

Dr. Frank Vocci was interviewed by Ms. Elaine Cooper of Better Homes and Gardens magazine on July 26, 2002 regarding the potential utility of the nicotine vaccine.

NIDA Exhibits Program

July 3-6, 2002	National Association of Alcoholism and Drug Abuse Counselors
July 7-12, 2002	XIV International AIDS Conference

July 8-12, 2002	Association of Higher Education and Disability
July 17-19, 2002	National Association of Hispanic Nurses
July 20-24, 2002	National Council of La Raza Annual Conference
August 22-25, 2002	American Psychological Association Annual Conference
September 3, 2002	NIDA CTN Annual Meeting
September 9-11, 2002	National Conference on Tobacco or Health 2002
September 24-26, 2002	Latino Behavioral Health Institute
September 26-29, 2002	Society for Advancement of Chicanos and Native Americans in Science
October 1, 2002	NIH Share the Health
October 1, 2002	Hispanic Association of Colleges and Universities
October 22-27, 2002	American Academy of Child & Adolescent Psychiatry
November 1, 2002	American Indian Science and Engineering Society
November 2-7, 2002	Society for Neuroscience Annual Conference

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On November 1, 2002 at the Society for Neuroscience Annual Meeting, Drs. Christine Colvis and Rita Liu will co-chair a symposium: **Proteomics & Mass Spectrometry in Neuroscience**. The latest in neuroproteomics, peptidomics, imaging mass spectrometry, and protein mass spectrometry, will be presented by: Dr. Richard Caprioli,Vanderbilt University, Dr. Ariel Deutch, Vanderbilt University, Dr. Lloyd Fricker, Albert Einstein College of Medicine, Dr. Seth Grant, University of Edinburgh, UK, Dr.Vivian Hook, Buck Institute for Age Research, and Dr. Amina Woods, NIDA.

On November 1, 2002 at the Society for Neuroscience Annual Meeting, Drs. Steven Grant and Herbert Weingartner will co-chair a poster session, sponsored by Neuron and NIDA: **Systems Neurobiology and Drug Abuse**. This session will feature poster presentations related to the three Friday NIDA symposia on "Proteomics & Mass Spectrometry in Neuroscience," "Mechanisms of Reward: Implications for Addiction," and "Systems Neurobiology of Drug Abuse." In addition to the poster presenters, speakers from the symposia and NIDA staff will be on hand for conversation during the poster session.

On November 1, 2002 at the Society for Neuroscience Annual Meeting, Drs. Kenny Blum, Neuron, and David Shurtleff, DNBR, will co-chair a symposium, sponsored by Neuron and NIDA: **Mechanisms of Reward: Implications for Addiction**. Current research and this symposium focus on how the reward and decision-making processes in our brains work and fail. These mechanisms involve both molecular interactions and sophisticated neural circuitry, and these different perspectives will be presented by: Dr. Gregory Berns, Emory University, Dr. Marc Caron, Duke University, Dr. Jonathan Cohen, Princeton University, Dr. Read Montague, Baylor College of Medicine, and Dr. Wolfram Schultz, University of Cambridge, UK.

On November 1, 2002 at the Society for Neuroscience Annual Meeting, Drs. Francis White, Chicago Medical School, and Rita Liu, OEA, will co-chair a symposium: **Systems Neurobiology of Drug Abuse**. Presentations will focus on mechanisms of action of psychomotor stimulants (amphetamine and cocaine), cannabinoids (marijuana), nicotine, alcohol, opiates, and natural rewards (e.g. food, water). The speakers will be: Dr. Ann Kelley, University of Wisconsin-Madison Medical School, Dr. Rafael Maldonado, University of Pompeu Fabra, Barcelona, Spain, Dr. Marina Picciotto, Yale University, Dr. Toni Shippenberg, NIDA, IRP, Dr. Friedbert Weiss, The Scripps Research Institute, and Dr. Marina Wolf, Chicago Medical School.

On November 2, 2002, at the Society for Neuroscience Annual Meeting, Dr. Yu Woody Lin, DNBR will chair a symposium: **Neuropeptides: A Role in Drug Abuse?** This symposium represents a state-of-the-art look at where neuropeptide research stands today and how it is poised to provide insights into the understanding of normal brain functions and brain functions after exposure to drugs of abuse. The speakers will be: Dr. Glen Hanson, NIDA, Dr. S. Hunt, University College London, UK, Dr. Yasmin Hurd, Karolinska Institute, Stockholm, Sweden, Dr. George Koob, The Scripps Research Institute, Dr. William Rostene, Hopital St Antoine, Paris, France, and Dr. S. Zahm, St. Louis University.

On November 2, 2002, at the Society for Neuroscience Annual Meeting, Dr. Susan Volman will co-chair a poster session: **Neurobiology of Drug Abuse: Cellular Mechanisms**. This session will feature poster presentations related to the two Saturday NIDA symposia on "Neuropeptides: A Role in Drug Abuse?" and "Synaptic Change and Addiction." In addition to the poster presenters, speakers from the

symposia and NIDA staff will be on hand for conversation during the poster session.

On November 2, 2002, at the Society for Neuroscience Annual Meeting, Drs. Jonathan Pollock, DNBR and Susan Volman, DNBR will co-chair a symposium: **Synaptic Change and Addiction**. The goal of this symposium is to present information about the molecular mechanisms controlling dendritic morphology and the relevance of these mechanisms to long-term adaptations to drugs of abuse. The speakers will be: Dr. Terry Robinson, University of Michigan, Dr. Eric Nestler, University of Texas Southwestern Medical Center, Dr. Angus Nairn, Rockefeller University, Hollis Cline, Cold Spring Harbor Laboratory, Dr. Kristen Harris, Boston University, Dr. Oswald Steward, University of California, Irvine, Dr. Morgan Sheng, Massachusetts Institute of Technology, and Dr. Kausik Si, Columbia University.

On November 5, 2002, at the Society for Neuroscience Annual Meeting, Drs Rita Liu, OEA, and Minda Lynch will co-chair a symposium: **Neurobiology of Relapse**. This program is dedicated to the memory of Dr. Roger Brown, DNBR. The current state of knowledge about brain mechanisms underlying relapse to drug addiction, future directions for research, and implications for practice will be discussed by: Dr. Glen Hanson, Acting NIDA Director, Dr. Peter Kalivas, The Medical University of South Carolina, Dr. George Koob, The Scripps Research Institute, and Dr. Jane Stewart, Concordia University. Following the symposium, there will be an opportunity to meet with NIDA staff to discuss NIDA's interests in behavioral neuroscience, integrative and cellular neurobiology, molecular neurobiology, proteomics, medications development, and other related topics. Staff will also be available to discuss "how to prepare a better grant application," training and career development mechanisms, gender research in drug abuse, and opportunities for special populations.

On November 6, 2002, at the Society for Neuroscience Annual Meeting, held at the University of Central Florida, Orlando, Florida, Drs. Pushpa Thadani, DNBR, and Donald Vereen, SPO will cochair a forum: **Minority Scholars: Research and Funding Opportunities at the National Institute on Drug Abuse**. The forum will showcase research at various training levels (undergraduate, graduate, postgraduate, and faculty) affiliated with minority or majority institutions. The speakers will be Dr. Delia Vazquez, University of Michigan Medical School and Cassandra Baskfield, Virginia Commonwealth University. There will be ample opportunities for attendees to interact with Dr. Hanson, the presenters, NIDA supported training directors and researchers, and NIDA staff, as well as to discuss various grant-funding opportunities at NIDA. The forum will be co-hosted by the University of Central Florida, Orlando, Florida.

National CTN Steering Committee Meetings are planned for the follow dates and locations: August 12-14 in Seattle, Washington; October 21-24 in Bethesda, Maryland; and January 27-29, 2003, in Miami, Florida.

The CTN Data and Safety Monitoring Board will meet, October 10-11, 2002 and January 16-17, 2003, in Bethesda, Maryland.

The CTN Protocol Review Board will meet November 5, 2002 in Bethesda, MD.

The CTN Ad-Hoc Oversight Board will convene October 29, 2002 to review and approve CTN's 4th wave of concepts.

On May 14-15, 2003, NIDA will hold a 2-day symposium in honor of Dr. Roger M. Brown at Masur Auditorium on the NIH main campus in Bethesda, MD. Numerous NIDA-supported scientists will be invited to share a remembrance of Roger and discuss many of the exciting research programs that Roger helped to foster during his tenure at NIDA. Plans are also underway to secure a publisher who will combine manuscripts of the symposium presentations into a volume dedicated to Roger's memory.

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NIDA Publications

National Survey Results of the Monitoring the Future Study 1975-2001, Volume I
NIH Pub. No. 02-5106
The annual report is the prevalence of drug use among American secondary students (specifically 8th, 10th & 12th graders). The trends are used for understanding the changing drug abuse problems and for formulating the appropriate intervention (prevention/treatment) policies.

National Survey Results of the Monitoring the Future Study 1975-2001, Volume II
NIH Pub. No. 02-5107
The annual report is the trends in use by populations based on gender, college plans, regions of the country, population density, race/ethnicity, and parents' education. The trends are used for understanding the changing drug abuse problems and for formulating the appropriate intervention (prevention/treatment) policies.

Drug Counseling for Cocaine Addiction: The Collaborative Cocaine Treatment Study Manual #4
NIH Pub. No. 02-4380
This publication describes specific behavioral/cognitive models which can be implemented in a wide range of differing drug abuse treatment settings. The manual is designed to present material in a user friendly manner to program administrators, counselors and other related service providers assuming that these targeted populations have a wide range of prior academic training and experience with the concepts and processes involved.

Asian Americans/Native Hawaiians and Other Pacific Islanders - 2003 Calendar
NIH Pub. No. 02-05173
The purpose of the calendar is to increase the audience's knowledge and awareness of the signs, symptoms, and neurophysiological, and behavioral effects of various drugs.

Research Report Series: Marijuana Abuse
NIH. Pub. No. 02-3859
This publication will discuss the consequences of use, the effects of using, and peripheral issues such as medical uses.

NIDA Science and Practice Perspectives, Vol. 1
The National Institute on Drug Abuse has developed a new publication directed towards a combined specialized audience of drug abuse researchers and practitioners. This bi-annual publication aims to enhance the practical use of research and the rapid adaptation of research-based practices in drug abuse treatment. The first issue of this publication was released in July 2002.

NIDA Notes

NIDA Notes Volume 17, Issue 2
NIH Pub. No. 02-3478
The lead article describes a study that may provide insight into why women may suffer less brain damage from chronic cocaine abuse than men. Dr. Marc Kaufman of

McLean Hospital, Harvard Medical School found that cocaine had no significant effect on cerebral blood flow during the phase of a women's menstrual cycle that precedes ovulation when levels of the female sex hormone, estrogen are at their highest. However, cocaine reduced blood flow by about 10 percent following ovulation when levels of the hormone progesterone are highest. Cocaine also reduces cerebral blood flow in men. The minimal effect of cocaine on women's brain blood volume prior to ovulation may be attributable to the protective effects of estrogen, which improves blood vessel elasticity and may counter the vasoconstrictive effects of cocaine.

The Director's Column by Dr. Glen Hanson discusses NIDA's efforts to expand and focus research on the far-reaching and complex role of gender differences in all aspects of drug addiction ranging from risk of abuse through responses to treatment.

Other articles include a 10-year study that found that high-risk sexual behavior, rather than needle sharing and other injection behaviors, is the primary predictor of HIV infection for both men and women injection drug users; genetic variations in the brain's serotonin system, which mediates mood and behavior, that may be linked to smoking initiation at an earlier age; and brief family-focused prevention programs implemented with sixth-graders and their families that produced reductions in adolescent substance abuse over a 4-year follow-up period.

NIDA Notes, Volume 17, Issue 1
NIH Pub. No. 02-3478
The front-page story reports on research that found that even though the damage to brain cells is reduced over time, the damage to cognitive and motor skills continues to be impaired. Researchers at Brookhaven National Laboratory in New York used brain-imaging techniques to measure the amount of damage and subsequent recovery of brain cells.

In the Director's Column, Dr. Glen Hanson discusses NIDA's efforts to address the dual epidemics of HIV/AIDS and substance abuse in the United States and other countries. NIDA-supported research has increased understanding of the complex role that drug abuse plays in the spread of HIV/AIDS.

Another article reports on the first large-scale study to evaluate the outcomes of adolescents in age-specific drug abuse treatment programs. The researchers found that longer stays in treatment can effectively decrease drug and alcohol use and criminal activity and improve the teens' school performance and psychological adjustments. Another article describes a program for HIV-positive youth that helps to reduce substance abuse and high-risk sexual behaviors that contribute to the spread of HIV.

The Tearoff presents the 17 science-based prevention principles from the new NIDA handbook: Principles of HIV Prevention in Drug-Using Populations. The Bulletin Board notes the publication of NIDA's latest Community Alert Bulletin: Stress and Substance Abuse; describes new radio and TV public service announcements to educate young people about the dangerous link between drug use and transmission of HIV/AIDS; and announces the publication of the latest manual in NIDA's "Therapy Manual for Drug Addiction" series.

Other Publications

Montoya, I.D., Preston, K.L., Rothman, R., and Gorelick, D.A. Open-Label Pilot Study of Bupropion Plus Bromocriptine for Treatment of Cocaine Dependence. Am J Drug Alcohol Abuse, 28(1), pp. 189-196, 2002.

Kreek, M.J. and Vocci, F. History and Current Status of Opioid Maintenance Treatments: Blending Conference Session. Journal of Substance Abuse Treatment, 23(2), pp. 93-105, 2002.

Schindler, C.W., Gilman, J.P., Bergman, J., Mello, N.K., Woosley, R.L., and Goldberg, S.R. Interactions Between Cocaine and Dopamine Agonists on Cardiovascular Function in Squirrel Monkeys. Journal of Pharmacology and Experimental Therapeutics, 300(1), pp. 180-187, 2002.

Stefanski, R., Lee, S-H., Yasar, S., Cadet, J.L., and Goldberg, S.R. Lack of Persistent Changes in the Dopaminergic System of Rats Withdrawn from Methamphetamine Self-administration. European Journal of Pharmacology, 439, pp. 59-68, 2002.

Munzar, P., Justinova, Z., Kutkat, S.W., Ferre, S., and Goldberg, S.R. Adenosinergic Modulation of the Discriminative-stimulus Effects of Methamphetamine in Rats.

Psychopharmacology, 161, pp. 348-355, 2002.

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Nine 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 Summer 2002 edition of the CTN Report, a quarterly newsletter on the CTN, was distributed in August 2002.

A poster on good clinical practice strategies entitled "Be on Target with Your Protocols!" was published and distributed to all clinical trial sites within the CTN.

Director's Report to the National Advisory Council on Drug Abuse - September, 2002

Staff Highlights

Staff Honors and Awards

On June 19, 2002, the following NIDA staff members received awards at the NIH Director's Award ceremony:

Dr. Eric Moolchan, IRP, received the NIH Director's Award of Merit "in recognition of leadership, creativity, and innovativeness in pioneering a new treatment and research program to combat teen smoking".

Dr. Sander Genser, CAMCODA, received the Distinguished Service Medal of the U.S. Public Health Service, the highest corps award, "for conspicuous bravery in saving the life of a severely injured individual".

Dr. Ahmed Elkashef, DTR&D, received the Meritorious Service Medal of the U.S. Public Health Service "in recognition of exceptional effort in conceptualizing and operating the clinical pharmacology program and the methamphetamine clinical program".

NIDA staff members **Drs. Ann Anderson, Janice Carico, Leslie Cooper, Peter Delany and Paul Na** were among the group of over 50 "world trade center and anthrax responders" who were collectively bestowed an award.

Dr. Jack Manischewitz, OPRM, received the NIH Merit Award for his contributions as a member of the NIH Office of Research on Women's Health "Reviewing Inclusion Issues Subcommittee" at an Office of the Director Honor Awards Ceremony held August 14, 2002.

NIDA staff received the following awards at the Annual Appreciation Day event held August 13, 2002:

2002 NIDA Director's Awards

Individual Awards

Ms. Amira Debbas, DNBR
Herbert Weingartner, Ph.D., DNBR
Ms. Jan Lipkin, OSPC
Ms. Patricia Thomas, OSPC
Jack B. Stein, Ph.D., OSPC
Cathrine Sasek Ph.D., OSPC
Ms. Sara Rosario, OSPC
Mark Green, Ph.D., OEA
Ms. Pamela Stokes, OEA
Ms. Roxie Brown, DESPR
Mr. David Jones, OPRM
Mr. John Hamill, OPRM
Ms. Donna Jones, OPRM
Ms. Deborah Wertz, OPRM
Jack R. Manischewitz, Ph.D., OPRM
Jagjitsingh H. Khalsa, Ph.D., CAMCODA
Vincent Smeriglio, Ph.D., CAMCODA
Nora Chiang, Ph.D., DTR&D
Carol Cushing, RN, CCTN

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Leslie A. Barnett, IRP

Group Awards

Blending Clinical Practice & Research
Jack B. Stein, Ph.D., OSPC
Tim Condon, Ph.D., OSPC
Ms. Beverly Jackson, OSPC
Ms. Blair Gately, OSPC
Ms. Niki Andrews, OSPC
Ms. Holly Buchanan, OSPC
Ms. Brenda Fogel, OSPC
Ms. Jane Holland, OSPC
Betty Tai, Ph.D., CCTN
Carol Cushing, RN, CCTN
Mary Ann Stephens-Chutuape, Ph.D., CCTN

The CEBRA Program Group
Susan Volman, Ph.D., DNBR
Ms. Jackie Porter, OEA
William Grace, Ph.D., OEA
Teresa Levitin, Ph.D., OEA

The OEA Grants Technical Assistants
Ms. Diana Souder, OEA
Ms. Annie Mathew, OEA
Ms. Marilyn Thomas, OEA
Ms. Angela Benjamin, OEA

The Prevention Initiative Workgroup
Katherine Davenny, M.P.H., CAMCODA
Vincent L. Smeriglio, Ph.D, CAMCODA
William Cartwright, Ph.D., DESPR
James D. Colliver, Jr., Ph.D., DESPR
Susan L David, M.P.H., DESPR
Peter Delany, D.S.W., DESPR
Shakeh Jackie Kaftarian, Ph.D., DESPR
Eve E. Reider, Ph.D., DESPR
Elizabeth B. Robertson, Ph.D., DESPR
Moira P. O'Brien, M.P.H., DESPR
Mark Green, Ph.D., OEA
Marina L. Volkov, Ph.D., OEA
Debra S. Grossman, M.A., DTR&D
Minda Lynch, Ph.D., DNBR
Steven J. Grant, Ph.D., DNBR
David Shurtleff, Ph.D., DNBR
Herbert Weingartner, Ph.D., DNBR
Lucinda Miner, Ph.D., OSPC
Jack B. Stein, Ph.D., OSPC
Ivan Montoya, M.D., DTR&D
Lisa S. Onken, Ph.D., DTR&D
Melissa W. Racippo, Ph.D., DTR&D
Suman A. Rao, Ph.D., OSPC

The IRMB Team
Ms. Tina McDonald-Bennett, OPRM
Ms. Marquerite Lewis, OPRM
Mr. Joe Reckley, OPRM
Mr. Michael Wright, OPRM
Mr. Berhane Yitbarek, OPRM

MASB Business Management Tech Staff
Sharon Goon, OPRM
Montrue Nelson, OPRM
Jean Yee, OPRM

Bridging Science & Culture Conference Planning Committee
Ana Anders, M.S.W., SPO
Ann Anderson, M.D., CCTN
Lula Beatty, Ph.D., SPO
Leslie Cooper, Ph.D., DESPR

Joseph Frascella, Ph.D., DTR&D
Ms. Pamela Goodlow, SPO
Dionne Jones, Ph.D., CAMCODA
Ms. Monica Jones, OSPC
Ms. Flair Lindsey, SPO
Ms. Sheryl Massaro, OSPC
Mr. Arnold Mills, M.S.W., DESPR
Amrat Patel, Ph.D., DTR&D
Ms. Rosemary Pettis, OD
Suman Rao, Ph.D., OSPC
Jack Stein, Ph.D., OSPC
Mark Swieter, Ph.D., OEA
Pushpa Thadani, Ph.D., DNBR

Equal Employment Opportunity Staff
Ms. Rosemary Pettis
Ms. Pamela Oliver

NIDA Equal Employment, Diversity amd Quality of Worklife Advisory Committee Award

Individual Award

Khursheed Asghar, Ph.D., OEA

Comissioned Corps Award

Honored for efforts and support during the WTC/Anthrax events
CAPT Leslie Cooper, DESPR
CAPT Janice Carico, IRP
LCDR Paul Na, IRP
LCDR Ann Anderson, DTR&D
Senior Nurse Officer Angela Martinelli, OSPC

Length of Service Awards

30 Years of Service

Mr. David C. Jones, OPRM
Richard L. Hawks, Ph.D., DTR&D

Employee of the Months Awardees

August 2001
James McKenzie, IRP
Michelle Scala, OPRM

September 2001
Duewa Williams, IRP

October 2001
Cindy Ambriz, IRP

November 2001
Amira Debbas, DNBR
Kandi Dillard, IRP

December 2001
Melissa Racioppo, DTRD
Christine McCray, IRP

January 2002
Pamela Oliver, OD
Patricia Ballerstadt, IRP

February 2002
Donna Inman, DTRD
Lena Eads, IRP

March 2002
Lyle Furr, OEA
Mary Pfeiffer, IRP

April 2002
Edwina Smith, DTRD
Theresa Doged, IRP

May 2002
Pat Mummaugh, OPRM
Margaret Griffin, IRP

June 2002
Eric Thorndike, IRP

July 2002
Diane French, IRP

Combined Federal Campaign Awards

Elizabeth Lambert, CAMCODA, Deputy Coordinator
Diane French, IRP
Christie Baxter, DNBR
Bryan Neccai, CAMCODA
Richard Harrison, OEA
Marc Brodsky, DESPR
Davy Jones, OPRM/MASB
Michael Wright, OPRM/IRMB
Carol Cornwell, OPRM/PFMB
Suzanne Dawkins, OPRM/CMB
Tu Phan, OPRM/GMB
Holly Buchanan, OSPC
Melissa Racioppo, DTRD
Ana Anders, OD

Dr. Jonathan L. Katz, IRP, was elected Chair of the ASPET Behavioral Pharmacology Division, [Chair-Elect, 2002-2003].

Dr. David Shurtleff, Acting Director, DNBR has been selected as one of the recipients of the American Psychological (APA) Meritorious Research Service Citation. This award was initiated this year by the APA Board of Scientific Affairs to recognize outstanding contributions in program development and research facilitation. The award will be presented at the December 2002 meeting of APA's Board of Directors.

Dr. Elizabeth Robertson, Chief, Prevention Research Branch, DESPR, was awarded the Society for Prevention Research 2002 Public Service Award on May 31, 2002 in Seattle Washington.

Dr. Jerry Flanzer, DESPR, received a special award from the National Association of Social Workers for his leadership and service as chair and board member of the Alcohol, Tobacco and other Addictions Section, 1997-2001.

Dr. Kathy Etz, DESPR, was elected to the Board of Directors for the Society for Prevention Research.

Staff Changes

Teneshia Alston joined OPRM's Contracts Management Branch as a Contract Specialist on June 30, 2002. Prior to coming to NIDA, Teneshia was with the National Heart, Lung and Blood Institute.

Allison Chausmer, Ph.D. joined the Translational Research Branch in the Division of Neuroscience and Behavioral Research on August 26, 2002 as a Health Scientist Administrator. Dr. Chausmer received her Ph.D. in Psychology at the University of California, Santa Barbara, where she specialized in Neuroscience and Behavior. After a postdoctoral fellowship at NIDA's IRP working with dopamine receptor involvement in the behavioral effects of cocaine, she complemented her training in a second fellowship at the Behavioral Pharmacology Research Unit of the Johns Hopkins School of Medicine. Dr. Chausmer's research experience with animal and human subjects will serve her well as she assumes responsibility for part of NIDA's nicotine/tobacco portfolio.

Redonna Chandler, Ph.D., joined the Division of Epidemiology, Services and Prevention Research Branch as a Social Scientist Analyst in May 2002. Redonna was trained as a psychologist and received her doctoral degree from the University of Kentucky in 1993. After completing her degree, she worked for three years on the faculty of Berea College, a small liberal arts college serving students from the

Appalachian region of the United States. For six years, prior to joining NIDA, she worked for the Bureau of Prisons coordinating residential and non-residential substance abuse treatment for federally sentenced inmates. She developed a treatment program for inmates with co-occurring disorders and worked collaboratively with the National GAINS Center and the University of South Florida developing treatment protocols and training related to dually diagnosed offenders. Areas of interest include identifying and meeting the drug treatment needs of individuals involved in the criminal justice system, unique treatment and service needs of women, developing integrative treatment systems for individuals with co-occurring disorders, and the transfer of scientific knowledge to practice. As a licensed psychologist she is an active member in the American Psychological Association and serves as the co-chair for the Committee on Training and Practice of Division 35, Society for the Psychology of Women.

Vivian Chiu joined NIDA's Office of Extramual Affairs (OEA) as a Grants Technical Assistant on June 16, 2002.

Angela Davis joined the Office of the Director of NIDA's Division of Neuroscience and Behavioral Research as an Office Automation Clerk on May 28, 2002.

Petra Exnerova, M.D., joined DESPR's Services Research Branch in June 2002 as a NIDA Fellow after completing a Humphrey fellowship in drug abuse treatment at Johns Hopkins University. Dr. Exnerova was trained as a psychiatrist and received her medical degree from Charles' University, Prague, Czech Republic in 1995. After finishing her studies, she worked in a mental hospital and outpatient clinic, where she was responsible for substance abuse treatment and prevention programs. Since 1998, she has been serving as a counselor at the Ministry of Health, where she coordinates drug policies, research and treatment programs for the Czech Republic. She extended the first methadone maintenance program and created the accreditation system for drug treatment services for her country. Dr. Exnerova will be at NIDA for 6-month lengths while she studies how NIDA applies theory -based research to the effective development of treatment and prevention programs. She is helping to develop mechanisms that will assist the establishment of a research infrastructure in the field of substance abuse in the Czech Republic to permit complementary research with US and other international scientists.

Diane Loeb joined OPRM's Contracts Management Branch as a Contract Specialist on June 30, 2002. Prior to coming to NIDA, Diane was with the Department of Commerce's National Institute of Standards and Technology (NIST).

CAPT Steve Oversby, Psy.D., R.N., joined the CCTN as a Health Scientist Administrator in May 2002. Steve graduated from California State University, Hayward, and is a Public Health RN with Board Certifications in Chemical Dependency Nursing, Psychiatric Nursing, and "Advanced Practice" Addictions Nursing. He is also a Licensed Professional Addictions Counselor, and a Licensed Clinical Psychologist. Currently Steve is a post doc. student in the Fielding Institute's Neuropsychology, and PPR's Prescription Privilege Programs. Steve brings to the CCTN ten years of recent clinical experience in dual diagnosis counseling and psychotherapy, as well as two years of dual diagnosis program development experience with the D.C. Dept. of Mental Health. Based on SAMHSA/CSAT guidelines and "Best Practice Models" in the D.C. community, Steve wrote the recovery-based Dual Diagnosis Program, which was successfully implemented by St. Elizabeth's Hospital in March 2002, using the new "Treatment Mall" concept.

Catherine Pilotte joined the Office of the Director of the Division of Treatment Research and Development (DTR&D) as an Office Automation Clerk on June 2, 2002.

Stephanie Powell joined the Office of the Director of the Division of Neuroscience and Behavioral Research (DNBR) as an Office Automation Clerk on May 28, 2002.

Beverly Pringle, Ph.D., joined DESPR's Services Research Branch as a Social Science Analyst in May 2002. Beverly completed her doctorate in clinical psychology at the University of Maryland, Baltimore County, where her research focused on distress management and preserved memory in sedated pediatric cancer patients. She trained at the Kennedy Krieger Institute and Johns Hopkins University Hospital in the field of behavioral pediatric psychology. Her research and clinical work there focused on behavioral treatments for pediatric patients and their families plus cognitive-behavioral treatments for inner city youth with multiple behavioral and emotional problems. Beverly's professional background includes work as a Senior Research Associate & Managing Director at Policy Studies Associates, Inc., where she conducted research and analysis on the organization, delivery, and effectiveness of educational

services for special populations (i.e., children living in poverty, inner-city children, American Indians, children of migrant farm workers, bilingual children). Beverly's areas of focus at NIDA include adolescents, tobacco use, women's issues, and linkages among systems of care and service.

Robert D. Riddle, Ph.D. joined the Genetics and Molecular Neurobiology Research Branch in the Division of Neuroscience and Behavioral Research on August 26, 2002 as a Health Scientist Administrator. Dr. Riddle received his Ph.D. from Northwestern University, Department of Biochemistry, Molecular Biology, and Cell Biology. Dr. Riddle's post-doctoral work at Harvard University Medical School led to the discovery of sonic hedgehog and Wnt7a as important signals in limb and neural development. Before coming to NIDA, Dr. Riddle was Assistant Professor in the Department of Cell and Developmental Biology at the University of Pennsylvania School of Medicine where he studied the molecular basis of midbrain/hindbrain formation.

SiHui Ruan joined the Office of the Director of the Division of Neuroscience and Behavioral Research (DNBR) as an Office Automation Clerk on June 2, 2002.

Ms. Susan Rubb joined NIDA's DTR&D in May 2002 as an Information Technology Management Specialist. Prior to joining NIDA, Ms. Rubb was a Senior Applications Developer for SAS Institute Inc. Prior to that she worked for Johns Hopkins University where she developed School-wide applications and also worked as a Senior Statistical Programmer in the Department of Epidemiology's Infectious Disease Program, co-authoring several papers for the MACS/Share longitudinal cohort study on HIV/AIDS. Ms. Rubb has an M.S. in Business from Johns Hopkins University with a concentration in Information Technology.

Laurence R. Stanford, Ph.D. joined NIDA's Clinical Neurobiology Branch within the Division of Treatment Research and Development as a health scientist administrator in June 2002. Previously he was a program director at the National Institute of Child Health and Human Development where he managed research programs on the neurobiological and neurobehavioral basis of mental retardation and developmental disabilities subsequent to serving as the Director of the NICHD Division of Scientific Review. Prior to coming to NIH, he was a faculty member at the Waisman Center on Mental Retardation and Human Development at the University of Wisconsin-Madison, where he conducted NIH- and NSF-funded research on the neurobiology and development of the retina and visual thalamus. Susan Weiss, Ph.D. joined the Science Policy Branch, OSPC in June 2002 as a Health Scientist Administrator. Dr. Weiss was previously the Senior Director of Research at the National Mental Health Association, and prior to that, served as the Chief, Unit on Behavioral Biology in the Biological Psychiatry Branch of the National Institute of Mental Health (NIMH). Dr. Weiss' research program at the NIMH sought to characterize the evolving nature of psychiatric and neurologic illnesses through the use of animal models, in order to help in the development of novel treatment options for patients with disorders of affect, anxiety, and substance abuse. Her research focused on the cellular and molecular changes associated with tolerance to anticonvulsant drugs, which are now used to treat affective disorders in addition to epilepsy. Dr. Weiss also studied the role of environmental factors in the behavioral and neurochemical responses to drugs of abuse. Dr. Weiss received her Ph.D. in Psychology from the University of Maryland, and her B.A. in Psychology from the State University of New York at Stony Brook.

CDR Angela M. Martinelli, DNSc, RN left NIDA in May 2002 to accept a position in the Commissioned Corps Readiness Force, Office of Emergency Preparedness as a Response Coordinator. She had been with NIDA since February 2000 serving as the Deputy Research Training Coordinator in OSPC's Science Policy Branch.

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Grantee Honors

Dr. Frank Ivy Carroll, director of Organic and Medicinal Chemistry at Research Triangle Institute in North Carolina, has received the American Chemical Society award in medicinal chemistry for 2002, in recognition of his contributions to synthetic medicinal chemistry, including the development of therapeutic agents for the treatment of cocaine addiction.

Dr. Shelly F. Greenfield, Director of Research Administration, Psychiatry Department, McLean Hospital, received several honors this past year. Dr. Greenfield was (a) elected to membership in the American College of Psychiatrists, (b) elected to Fellowship in the American Psychiatric Association, (c) appointed Vice Chair of the Council on Addictions of the American Psychiatric Association, (d) appointed Member of the American Psychiatric Association's Work Group for the Practice Guidelines for Substance Use Disorders, and (e) promoted from Deputy Editor to Co-Editor in Chief of the Harvard Review of Psychiatry.

Dr. Michael Hecht, Pennsylvania StateUniversity, received the 2001 Gerald R. Philips Award for Distinguished Applied Communication Scholarship from the National Communication Association for his NIDA-funded *Drug Resistance Strategies Project*.

The Family Services Research Center under the direction of **Dr. Scott Henggeler** of the University of South Carolina Medical College received the 2001 Families Court Award, 2001 Exemplary Substance Abuse Prevention Program Award from the Center for Substance Abuse Prevention, U.S. Department of Health and Human Services, and the Points of Light Foundation President's Award in recognition of excellence in community service directed at solving community problems.

Dr. Edward Kaplan, Yale University, was asked by the Fogarty International Center to apply the advanced mathematical modeling techniques (developed by Dr. Kaplan and his colleagues for analyzing the AIDS epidemic and related interventions), to evaluating response options for a possible smallpox attack against the U.S. This request was part of new Homeland Defense initiatives. NIDA funding supported the smallpox evaluation, which was published in the June 2002 Proceedings of the National Academy of Sciences. Dr. Kaplan also appeared on the June 8th Today Show and was in the June 8th New York Times discussing his smallpox attack response assessment. The most significant finding of Dr. Kaplan's smallpox analysis was that mass vaccination outperforms the existing policy of starting with traced vaccination and switching to mass vaccination, only if required.

A paper published by **Dr. Rae R. Matsumoto**, University of Oklahoma Health Sciences Center, in the journal Neuropharmacology (Involvement of sigma receptors in the behavioral effects of cocaine: evidence from novel ligands and antisense oligodeoxynucleotides - Neuropharmacology. 2002 Jun;42(8):1043-55) was highlighted by the journal's Editor-in-Chief as being of particular interest to the neuroscience community and selected for alert to the neuroscience community, through the journal publisher's online alerting service, Paper Reporter. Dr. Matsumoto is recipient of NIDA DA11979.

Dr. Cynthia L. Rowe, University of Miami School of Medicine, was honored by the College on Problems on Drug Dependence during the 2002 Annual Meeting in Quebec City, receiving an Early Career Investigator Award. After a NIDA-sponsored postdoctoral fellowship at the Center for Treatment Research on Adolescent Drug Abuse, Dr. Rowe was appointed Research Assistant Professor at the University of

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Miami, and continues her research on family interventions for adolescent drug abuse.

Dr. Jeffrey H. Samet, Associate Professor of Medicine and Public Health, Boston Medical Center, was promoted to Professor of Medicine and Social & Behavioral Sciences at Boston University Schools of Medicine and Public Health in 2002. He was also appointed Chief, Section of General Medicine, in the Department of Medicine at Boston University School of Medicine-Boston Medical Center in July 2002.

Dr. Linda Teplin, of Northwestern University, received the National Commission on Correctional Health Care, 2001 Bernard P. Harrison Award of Merit for her research focused on delinquent juveniles.